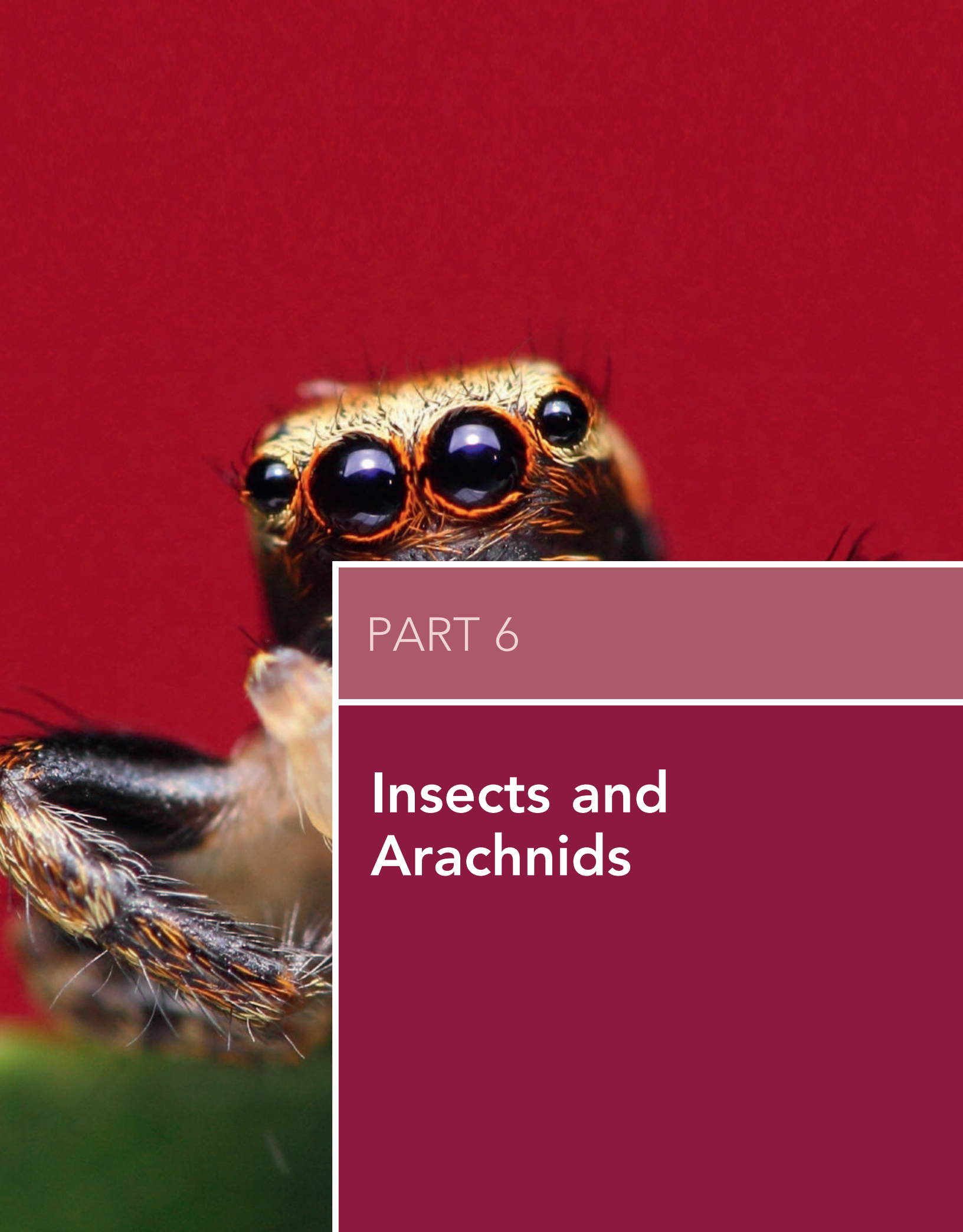


PART 6

Insects and Arachnids

CHAPTER 39

Mosquitoes and Mosquito-Borne Diseases

SEAN M. KIVLEHAN, JULIAN VILLAR, AND HEMAL K. KANZARIA

Mosquitoes are in the biologic phylum Arthropoda, class Insecta, order Diptera, and family Culicidae. There are approximately 35 genera, which include *Anopheles, Culex, Psorophora, Ochlerotatus, Aedes, Sabethes, Wyeomyia, Culiseta,* and *Haemagogus.* Worldwide there are more than 3000 species and subspecies, and in the United States alone, there are an estimated 200 different species of mosquitoes that vary in habitat and behavior.[235] In addition to transmitting the parasitic disease of malaria to 200 to 300 million people per year and thereby killing an estimated 627,000 people in 2012,[227] mosquitoes also serve as vectors for arboviruses that cause significant illness in and death of humans worldwide. Mosquitoes are also responsible for transmission of the larval nematode that causes lymphatic filariasis.

MOSQUITOES

Mosquitoes (the word is derived from the 16th-century Spanish or Portuguese word for *little fly*) have been in existence for an estimated 170 million years. They are characterized by scaled wings, long legs, and a slender body. Their size varies but rarely exceeds 15 mm (0.6 inch) in length. They weigh approximately 2 to 2.5 mg and can fly at about 1.4 to 2.6 km/hr (0.9 to 1.6 mph).

MOSQUITO ANATOMY

The mosquito has a slender body with two wings (rather than four as possessed by flies) and six long, delicate legs (Figure 39-1). Mosquito wings are covered with scales, and the body is divided into three parts, head, thorax, and abdomen. The head has two large compound eyes with many lenses angled in different directions, and two antennae. The mouth, or proboscis, resembles a downward-pointing funnel, and is used to pierce skin and suck blood (in females) or sip nectar (in males). The mouthparts include the labrum and the labium, which can be understood as upper and lower lips, respectively. The mandible and maxilla are anterior and posterior structures that form a jaw-like configuration. The maxillary palps are small, antenna-like sensory structures that detect chemicals from animals, and sensory hairs (setae) on the antennae sense vibration and motion from potential prey and other organisms.

A thin, short neck connects head to thorax, which is triangular and holds the wings. The thorax also has two pairs of spiracles, tubular structures used for gas exchange. The abdominal shape can be pointed or rounded depending on the species, and it has eight pairs of spiracles. The legs are divided into the coxa, femur, tibia, and tarsus.

The spiracles form the basis of the mosquito's tracheal system, which is finely branched so that cells are directly oxygenated. Mosquitoes have a dorsal blood vessel that extends directly from the eighth abdominal segment into the head. The heart is the portion of the blood vessel located within the thorax, and although it is not innervated, it pulses automatically at a rate of 85 beats/min.[210]

MOSQUITO LIFE CYCLE

Most species of mosquitoes have a four-stage life cycle of egg, larva, pupa, and adult. The duration of each stage depends on the mosquito species and temperature. *Culex tarsalis,* for example, has a 14-day life cycle at 20° C (68° F), and a 10-day life cycle at 25° C (77° F). The life cycle varies from 4 days to 1 month, but averages around 2 weeks, meaning that several generations can arise within a single year.[235] Most mosquitoes outside the tropics lie dormant as eggs, although some, such as the genus *Culex,* overwinter as larvae or adults.

The female mosquito usually mates once in her lifetime and stores sperm in her body. She fertilizes her eggs as she lays them, which is generally on the surface of water, often in the form of egg rafts (shown in Figure 39-2) or sometimes in groups in empty containers or jars (shown in Figure 39-3). Eggs can survive winter and hatch in the spring. They hatch into larvae (also known as wrigglers), about 1 to 2 cm (0.4 to 0.8 inch) long, that feed on microscopic animals, plant life, and in some cases other mosquito larvae. Except for the genus *Anopheles,* the larvae must come to the surface to employ their air tubes, or siphons, which supplement their gills (Figure 39-4). After molting several times, they develop into pupae (Figure 39-5), floating on the surface of the water and breathing through an air tube, now called a trumpet. While encased in the hard pupal case, they transform into adult mosquitoes. When enough pressure is created by the growing pupa, the case bursts open, releasing an adult. Once the wings harden, the mosquito can fly and live on land.[210]

MECHANISM OF MOSQUITO BITES

Mosquitoes technically do not sting, because they lack a stinger; they simply pierce the skin and suck blood. Only females of most species have sucking mouth parts that can pierce skin and thus transmit disease (Figure 39-6). Mosquitoes have evolved to feed on blood (protein) because the normal mosquito diet of nectar and fruit juices does not contain enough protein for egg development. (One genus, *Toxorhynchites,* does not suck blood, and its larvae prey on other mosquito larvae). Mosquitoes generally identify victims by scent, as well as by the carbon dioxide of exhaled breath and some chemicals found in sweat. Mosquitoes have been shown to have odor-binding receptors on their antennae that bind ammonia, lactic acid, and other carboxylic acids, stimulating their olfactory neurons and allowing them to locate their human prey.[179,198] Other risk factors for becoming mosquito prey include male gender, heavier weight, and type O blood.[84] Additionally, pregnant women and military personnel travelling to endemic areas are particularly at risk.

When mosquitoes pierce human skin, all six legs are usually positioned on the skin surface, along with the labella (part of the proboscis). The female proboscis is made up of six shafts, four of which cut and pierce skin. One serves as a conduit for blood into the mosquito, and another transports mosquito saliva into the skin. The mosquito lays the labella on the skin, which allows the maxillae of the fascicle (a bundle of feeding stylets, contained within the proboscis) to saw into the skin in an oscillatory cutting fashion. Blood is drawn up into the fascicle, which collects into the labrum held between the mandibles of the mosquito. The female mosquito usually requires about 50 seconds to insert the fascicle into the skin, and approximately 2 minutes to finish feeding. She can withdraw her fascicle in 5 seconds.[83,96]

Mosquito saliva contains a wide array of antihemostatic molecules that facilitate feeding. These molecules include vasodilators, such as amines and prostaglandins; platelet aggregation inhibitors, such as nitric oxide and apyrase; molecules that

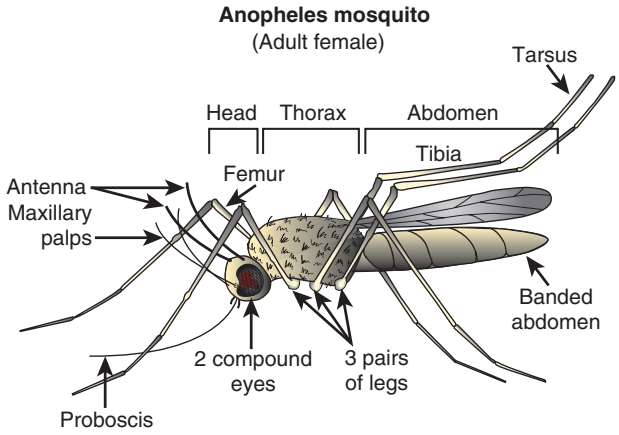


FIGURE 39-1 Anatomy of a mosquito.

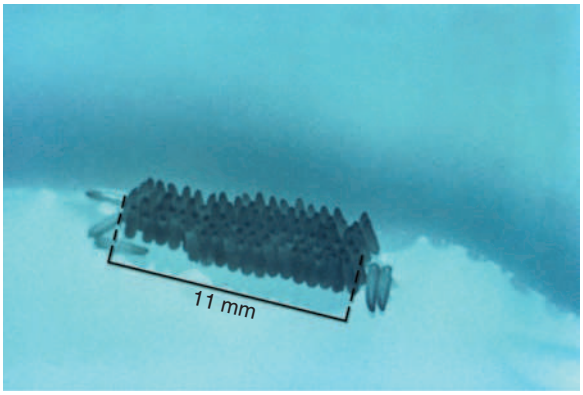


FIGURE 39-2 A *Culex* mosquito "egg raft," measuring 11 mm (0.4 inch) in length and composed of 200 to 300 eggs.

sequester adenosine diphosphate; peptides specifically targeted to integrin receptors; and anticoagulants, such as thrombin and factor Xa inhibitors. The saliva and its accompanying proteins (specifically, the 33-kilodalton F-1 protein found in mosquito saliva) that remain in human skin after feeding serve as antigens that evoke an immune response.[65,66]

Pathophysiology and Clinical Manifestations of Mosquito Bites

Humans vary in their responses to mosquito bites. Almost all experience local irritation caused by a type I immunoglobulin E (IgE)–mediated response of a soft, pale, pruritic wheal or plaque (Figure 39-7). Subsequent effects reveal which type of immune response a person has to the bite. Type I IgE responses can also create immediate hive-like skin lesions (rare), whereas type IV cell-mediated immunity causes delayed pruritic papules or

FIGURE 39-3 Eggs of *Aedes aegypti* mosquito, which transmits dengue virus.

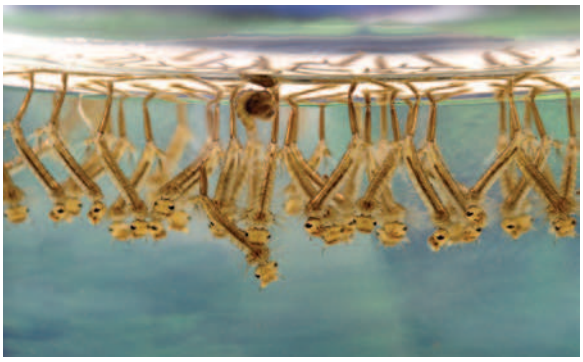


FIGURE 39-4 *Culex* larvae suspended diagonally, with siphons at the surface of the water.

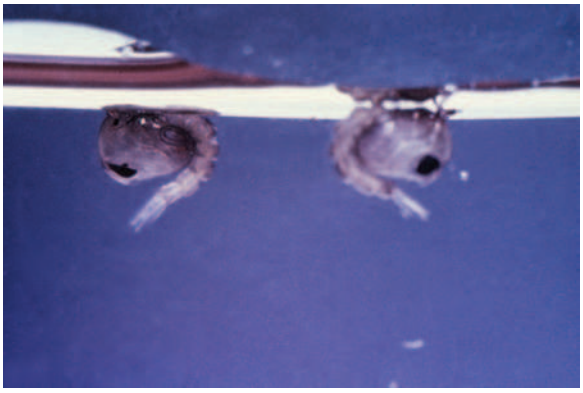


FIGURE 39-5 Pupae, where the eyes, legs, and wings are visible.

FIGURE 39-6 A female *Aedes albopictus* mosquito (a vector of the West Nile virus) becoming engorged with blood while feeding on a human.

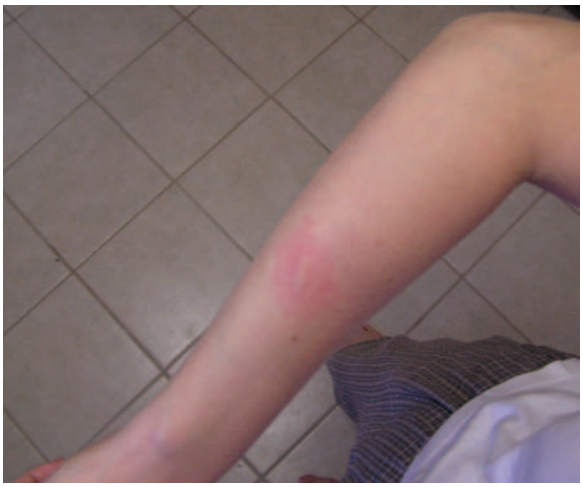


FIGURE 39-7 Urticarial plaque.

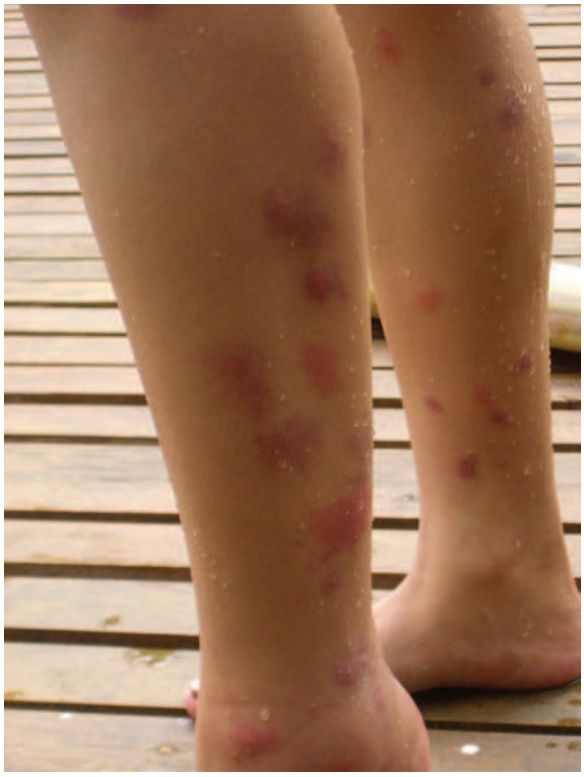


FIGURE 39-8 Mosquito bite demonstrating papular urticaria.

vesicles within 48 hours. Other type IV reactions caused by mosquito bites include blisters, bullae, and erythema multiforme or purpura, but these are rare.

One common type IV hypersensitivity response is papular urticaria, an eruption of pruritic papules measuring 3 to 10 mm (0.1 to 0.4 inch) in diameter that may be surrounded by vesicles grouped in irregular clusters (Figure 39-8). Because repeated exposures may lead to desensitization in adults, these lesions are more common in children. They begin as an erythematous wheal, lasting from 2 to 10 days, and may lead to temporary hyperpigmentation. Children who suffer this hypersensitivity may develop a firm, light-brown papule, whereas most adults have only a transient wheal without formation of a persistent papule. The dermatopathologic condition of the epidermis in papular urticaria shows spongiosis with exocytosis and vesicle formation. The upper dermal layer reveals a localized perivascular infiltrate with lymphocytes, histiocytes, eosinophils, and mast cells, and a spattering of eosinophils and mast cells in the middermis.[219]

The pathophysiologic factors responsible for the itching phenomenon are complex, and there are abundant theories on the neurophysiologic basis of itch. The most traditional is that the local reaction induces production of histamine, which stimulates C nerve fibers that travel to the brain and induce the sensation of itching.[258] Histamine, however, is only one of many pruritogenic substances that stimulate a subset of specialized skin C fibers, and itching can be induced even in the absence of histamine release.[168] Other known mediators of itch include proteases, opioids, lipid peroxidation metabolites (such as leukotrienes and prostaglandins), neuropeptides (e.g., substance P), cytokines, and growth factors (e.g., nerve growth factor). Pruritus is now seen as a complex physiologic syndrome that extends into the fields of neurophysiology, neuroimmunology, neuropharmacology, protease research, internal medicine, and dermatology.

In general, mosquitoes confer disease on humans by carrying and harboring viruses from animal reservoirs. Different viruses have different transmission patterns, some with avian reservoirs and others with nonhuman primate and human reservoirs. The geographic distribution of mosquitoes and changes in their habitats affect the distribution of disease. Although mosquitoes are often thought of as living only in temperate and tropical areas, their geographic distribution extends to climatic extremes and ranges north of the Arctic Circle, where they have adapted by spending their larval stage frozen in the ice. Disease patterns differ depending on the geographic distribution of the species. Malaria, for example, is mostly found in sub-Saharan Africa, India, Bangladesh, Southeast Asia, Central and South America, and some parts of the Middle East; dengue fever is found in Southeast Asia, Central America, the Caribbean, the southwestern Pacific, and recently in the United States; and the area in which Japanese encephalitis is found ranges from the southern half of India to a northeastern direction toward Japan, covering eastern China and Southeast Asia. Geographic distributions and transmission patterns are discussed in the remainder of this chapter.

DISEASES CAUSED BY MOSQUITOES

The effects of mosquitoes on human life are far reaching. Every year, mosquitoes are responsible for transmitting a wide spectrum of diseases, such as malaria, dengue fever, yellow fever, and encephalitis, to millions of people. This chapter discusses the main diseases transmitted by mosquitoes, other than malaria (see Chapter 40). Table 39-1 summarizes the viruses discussed in this chapter.

DENGUE

Dengue was first identified in the 1940s as being caused by a virus, although it probably was present much earlier because reports of dengue fever epidemics occurred as early as 1779. Like West Nile virus (WNV), dengue viruses belong to the family Flaviviridae, genus *Flavivirus,* and have four distinct but closely related serotypes (DEN-1, DEN-2, DEN-3, and DEN-4), all of which cause infection. The incidence of dengue has increased by 30-fold over the past five decades, with the World Health Organization (WHO) identifying it as the most important mosquito-borne viral disease in the world. Although the WHO estimates that 50 to 100 million new infections occur annually in over 100 countries, the most recent research places the yearly incidence at 390 million infections, with 96 million symptomatic cases.[20,247,248]

Epidemiology and Transmission

Aedes mosquitoes are responsible for transmission of dengue viruses via a human-mosquito-human cycle: once she picks up the virus, the infected female mosquito carries it for the rest of her life and can transmit disease to many susceptible individuals. Several species of *Aedes* can transmit dengue, but the most important is *Aedes aegypti,* which is found in tropical and subtropical regions under 1000 meters and between 35 degrees north and 35 degrees south latitude globally. The virus incubation period in mosquitoes is 8 to 12 days before it is transmissible. Mosquitoes can acquire the virus from a human throughout the viremic phase, which generally lasts 4 to 5 days but can be as long as 12 days.[180]

The *Aedes* mosquito is a particularly effective vector for multiple reasons. The mosquito itself is quite susceptible to dengue virus. It feeds preferentially on human blood, inhabits highly populated areas, and breeds inside or close to houses, and the bite is often unnoticed by humans. Moreover, because the mosquitoes feed many times in a breeding cycle, numerous people living in one household can be infected by the same mosquito. *Aedes albopictus* has a larger geographic distribution than does *A. aegypti* and can also transmit the virus, but it is less often responsible for dengue transmission because these mosquitoes breed farther from households and bite humans less frequently.[38,246,248] An *A. aegypti* mosquito can be concurrently infected with two serotypes without diminishing transmissible capability.[180]

The full global burden of disease is uncertain due to underreporting and misclassification, but dengue has reemerged as a pandemic threat. Virus transmission is endemic for at least one serotype in more than 125 countries in southeast Asia, the Americas, western Pacific, Africa, and the eastern Mediterranean regions. Hyperendemic dengue occurs when there is uninterrupted circulation of numerous serotypes in one area. Epidemic dengue occurs in 3- to 5-year cycles in endemic countries and has been increasing in both severity and frequency. Human travel

TABLE 39-1 Characteristics of Mosquito-Borne Viral Diseases

Virus	Family	Geographic Distribution	Main Age Group Affected	Mortality (%)	Specific Treatment	Human Vaccine Available
Dengue fever virus	Flaviviridae	Central and South America, Africa, Asia, southeastern United States	Adults	Dengue: <1% Severe Dengue: >20	No	No
Yellow fever virus	Flaviviridae	Africa and South America	Men ages 15-45	20	No	Yes
Japanese encephalitis	Flaviviridae	Japan, China, Southeast Asia, India	Children and adults	20-30	No	Yes
West Nile virus	Flaviviridae	Africa, West Asia, Middle East, Europe, United States	Adults	3-15	No	No
St Louis encephalitis	Flaviviridae	Central, western, southern United States	Adults	5-30	No	No
Eastern equine encephalitis	Togaviridae	Eastern and Gulf coasts of United States, southern United States, South America	Children and adults	33	No	No
Murray Valley encephalitis	Flaviviridae	Australia, Papua New Guinea	Children and adults	15-30	No	No
La Crosse virus (California)	Bunyaviridae	Midatlantic and southeastern United States	Children	<1	No	No
Ross River virus	Togaviridae	Australia, Papua New Guinea, South Pacific	Children and adults	Rare	No	No
Jamestown Canyon virus	Bunyaviridae	United States (including Alaska) and Canada	Children and adults	Unknown	No	No
Chikungunya virus	Togaviridae	Africa, Asian Subcontinent, Southeast Asia, Americas	All	<1%	No	No
Zika virus	Flaviviridae	Central and South America, Africa, Southeast Asia, the Philippines	Children and adults	Unknown	No	No

between endemic countries and those that are dengue-free but contain a suitable vector has spread the disease to new regions. Autochthonous transmission recently witnessed in Europe and the United States likely originated in this manner.[103,166,247]

As shown in Figure 39-9, dengue virus has been found in all of Southeast Asia and the western Pacific islands (with hyperendemic transmission of all four serotypes present in nearly all of these countries), accounting for 75% of the globally exposed population. The hyperendemic dengue fever incidence has increased greatly and spread to all WHO regions except for Europe. Particularly significant increases have been observed in Africa, the Middle East, the Caribbean region, and South America with the broadening distribution of *A. aegypti* mosquitoes.[166,246]

Before 1970, dengue hemorrhagic fever (DHF) epidemics were found in only nine countries; over the last four decades this number has expanded more than fourfold and continues to rise (Figure 39-10). In the past, dengue fever was considered a relatively benign and nonfatal disease, localized to tropical urban centers. However, since World War II, during which time *Aedes* mosquitoes have been transported internationally in cargo with much higher frequency and transported further inland than previously, dengue fever has become more frequent, has had a wider

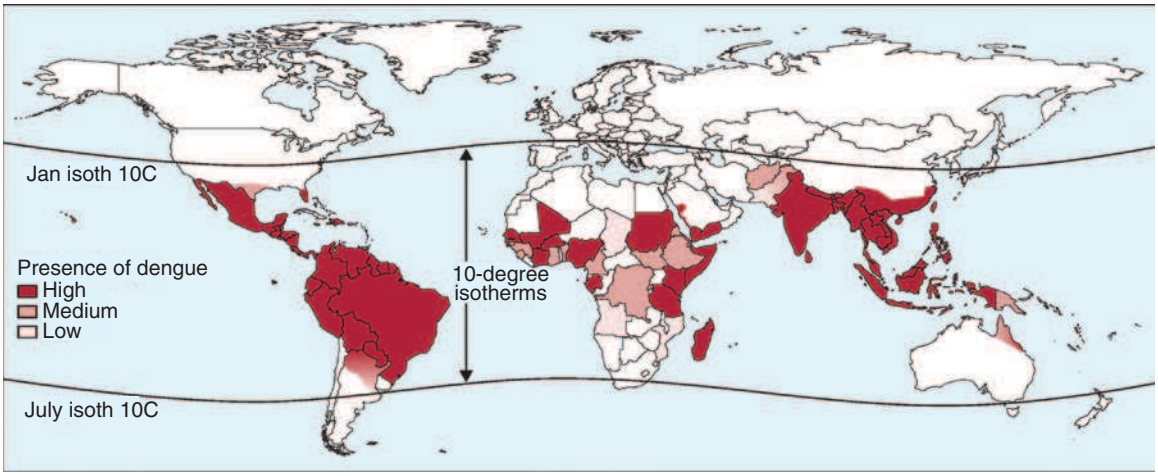


FIGURE 39-9 Distribution of dengue. *(From Guzman MG, Harris E: Dengue.* Lancet *385(9966):453-465, 2015.)*

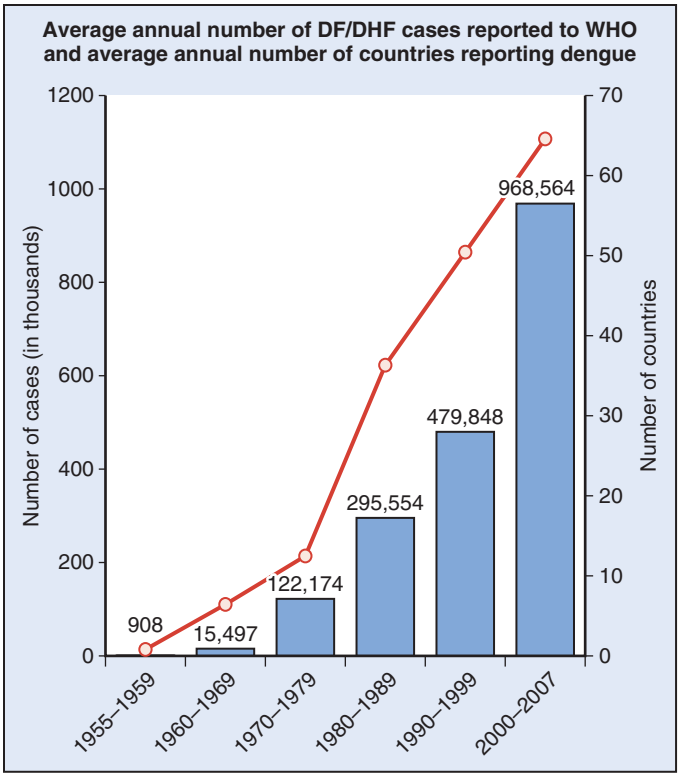


FIGURE 39-10 Growth of dengue incidence. *(From World Health Organization:* who.int/csr/disease/dengue/impact/en/; *Average Annual number of DH/DHF Graph.)*

geographic distribution, and has caused more illness and deaths. The 1980s and 1990s saw a rise in DHF in southern Asia, and in the 1980s, there was a rise in epidemic dengue fever and DHF in Taiwan and the People's Republic of China. Africa and India continue to see large and likely underestimated increases in DHF.[101,103]

Despite being effectively eliminated in the Americas in the 1960s, *A. aegypti* quickly reinfested the tropical western hemisphere after closure of a major regional eradication program.[101] After a large outbreak in Cuba in 1981, epidemics have been increasing in frequency and size throughout the region.[166] The Pan American Health Organization (PAHO) reports that 2013 was an epidemic year, with more than 2 million cases in the Americas, including approximately 37,500 severe cases and more than 1200 deaths. *A. aegypti* is now found in all of the Americas except for Canada and continental Chile. Between 2001 and 2011, autochthonous outbreaks have occurred in the states of Hawaii, Texas, and Florida.[2,166,170,248]

Demographic changes, such as population growth and increased human density, contribute to transmission and emergence of DHF. Moreover, unplanned urbanization resulting in substandard housing situations and poor water and sanitation systems leads to the same outcome. The situation is made worse by deterioration of mosquito control programs and of health systems overall in dengue-endemic countries, where the disease cannot be well controlled.[103] Climate change alters the interaction between infective mosquitoes and humans. Increased rainfall during certain seasons in tropical areas causes increased density of mosquitoes. Not only do warmer temperatures decrease the viral incubation period inside the mosquito so that the virus can be transmitted earlier, but they also allow greater mosquito population growth and raise the number of susceptible humans, who perpetuate the disease.[166]

Clinical Presentation

The clinical presentation of dengue virus can range from asymptomatic infection to self-limited mild febrile illness to life-threatening shock syndrome. Risk factors involving host genetic traits and virus strain type, along with young age, female gender, and comorbid conditions, such as obesity, asthma, hypertension, diabetes, and sickle cell anemia, influence disease severity and development of DHF or dengue shock syndrome (DSS), as opposed to simply dengue fever.[82,171,206,225,230] DHF and DSS also more commonly occur in individuals suffering sequential infections by different serotypes and in infants with a primary infection, born to dengue-immune mothers.[103]

Pathogenesis of the virus is hypothesized to be a result of indirect endothelial cell dysfunction through activation of cytokines and complement, and suppression of the reticuloendothelial system.[103,206] At autopsy, the virus is commonly found in the liver, bone marrow, thymus, lymph nodes, and lung cells.[246]

All four serotypes can cause DHF, and the four serotypes do not provide cross-protective immunity, so it is possible for one individual to sustain four separate dengue infections over a lifetime. Although previous infection provides homologous immunity to one serotype, individuals who experience secondary infection by another serotype are at higher risk for more severe forms of disease. This theory supports the observation that infants less than 1 year of age with passively acquired maternal antibodies have a higher rate of DHF/DSS. This phenomenon, known as antibody-dependent enhancement, is thought to be caused by previously existing neutralizing antibodies that, despite being unable to halt infection from a heterotopic serotype, bind Fc receptors of monocytes and cause an excessive immune response and increased infected cell mass. However, there is an incomplete understanding of dengue virus pathophysiology, because the antibody-dependent enhancement theory does not explain severe primary infections. Other mechanisms, such as activation of serotype–cross-reactive memory T cells during a secondary infection, are believed to contribute to production of proinflammatory cytokines.[103,185]

In 2009, the WHO changed the classification scheme for dengue in an effort to improve frontline triage and treatment. The previous classes of undifferentiated fever, classic dengue fever, and DHF/DSS have been replaced by dengue (with or without warning signs) and severe dengue. This new classification remains controversial, but has been shown to increase sensitivity of detecting severe infections.[116] However, the traditional dengue fever/DHF/DSS classification is still widely used.[103,246] The clinical characteristics of dengue with and without warning signs, and severe dengue, are discussed here.

Dengue is often defined by a patient who has lived in or traveled to an endemic area with a fever and at least two of the following: nausea/vomiting, rash, aches and pains, positive tourniquet test, leukopenia, or any "warning sign." The warning signs are abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleeding, lethargy or restlessness, liver enlargement of more than 2 cm, and increased hematocrit with thrombocytopenia on laboratory testing.[246]

Clinical presentations may be variable, but dengue is often characterized by a predictable three-phase course that includes an initial febrile phase, critical phase, and spontaneous recovery phase. In humans, there is a 4- to 7-day incubation period from bite to clinical infection.[180] The initial febrile phase of infection lasts from 3 to 7 days and begins with a high temperature (≥38.5°C [101.3°F]). Some or all of the previously mentioned warning signs may occur, including mild hemorrhagic manifestations. Children are generally less symptomatic during this phase despite having a high fever; this frequently creates diagnostic uncertainty. Most patients fully recover after the initial febrile phase. The critical phase occurs around defervescence and is characterized by plasma leakage that may result in severe dengue (e.g., DHF or DSS).[206] These patients can have bleeding (ranging from petechiae, ecchymoses, epistaxis, and mucosal bleeding, to more severe gastrointestinal bleeding and hematuria), thrombocytopenia (<100,000/mm^3), and, paradoxically, hemoconcentration and hepatomegaly in some settings. Symptoms include severe abdominal pain, nausea and vomiting, and restlessness or lethargy. Vascular leakage may cause pleural effusion, ascites, and hypoproteinemia, resulting in DSS with circulatory failure, hypotension, cool extremities, and altered mental status. Of note, the WHO defines severe dengue as having one of three criteria: (1) severe plasma leakage leading to shock or fluid accumulation

with respiratory distress, (2) severe bleeding, or (3) severe organ involvement.[246] The recovery phase is characterized by rapid improvement in symptoms within 72 hours, followed by significant fatigue for several weeks. Some recovering patients notice a mild maculopapular rash, likely caused by leukocytoclastic vasculitis that is self-limited.[206]

Most children infected with dengue viruses are asymptomatic or present with mild self-limited fever. Patients may also describe retroorbital pain and severe myalgias and arthralgias (hence the term *break-bone fever*). Gastrointestinal symptoms (nausea, vomiting, and diarrhea) and a confluent maculopapular rash are more common in children.[79] Serious complications can occur in all age groups. Central nervous system (CNS) involvement has been reported in dengue, manifesting as encephalitis, myelitis, Guillain-Barré syndrome, and meningitis. Although exact mechanisms are poorly understood, the virus has been detected in the cerebrospinal fluid (CSF) of affected persons.[181] Liver involvement is common and manifested by hepatomegaly or jaundice. Renal failure can occur, but is generally secondary to shock rather than a primary insult. Case reports of ocular and pancreatic involvement exist.[180]

Despite these complications, the prognosis for patients with dengue is generally good, with an acute phase of 1 week followed by several weeks of convalescence with general malaise and anorexia. Overall case fatality rates for dengue are less than 1%, but are more than 20% for untreated severe dengue.[248]

Diagnosis

Dengue is usually diagnosed clinically, because laboratory confirmation is typically only available in specialized reference laboratories. Clinical characteristics are as discussed above; however, it remains difficult to differentiate dengue from other febrile illnesses. The 2009 WHO criteria were designed to be more sensitive and allow earlier identification of potentially severe cases. A recent systematic review evaluating 12 studies published after the new guidelines found the 2009 criteria to be 59% to 98% sensitive and 41% to 99% specific for severe dengue. Improved sensitivity has been met with some concern regarding overdiagnosis of nonsevere dengue.[116] Both the old and new criteria have poor sensitivity when applied to children under 4 years of age, highlighting the need for accessible bedside testing.[102]

The tourniquet test (Figure 39-11) for capillary fragility, which describes the appearance of 20 or more petechiae over a square-inch patch on the forearm after deflation of the blood pressure cuff (held for 5 minutes between systolic and diastolic pressures) is frequently used as a screening tool. The WHO recommends use of the tourniquet test to aid in diagnosis of dengue, particularly cases with warning signs. In a large Peruvian study, the tourniquet test demonstrated 52% to 56% sensitivity and 58% to 68% specificity, with increased sensitivity in younger patients, women, and those presenting later in their disease course.[108] A comparable Brazilian study showed 19.1% sensitivity and 86.4% specificity, reinforcing the theory that although it is a useful adjunct, the tourniquet test alone is not adequate for diagnosis.[72]

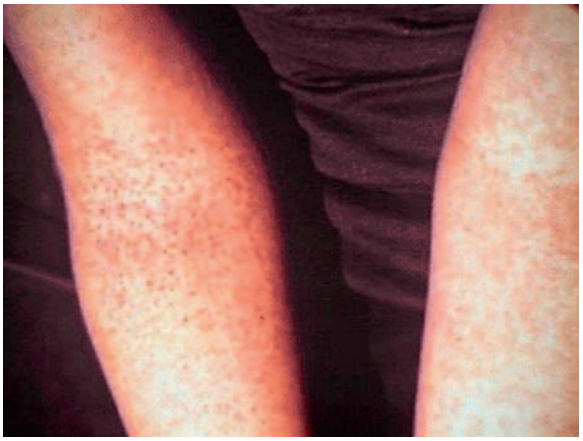


FIGURE 39-11 Positive tourniquet test.

Initial laboratory testing is important to establish a baseline hematocrit, and early findings such as leukopenia support the diagnosis of dengue. A rapid decrease in platelets coupled with a rise in hematocrit is concerning for plasma leakage and progression to the critical phase. Liver enzymes are frequently elevated, and AST or ALT over 1000 units/L indicates severe disease. Electrolyte protein abnormalities consistent with plasma leakage and dehydration can be seen on laboratory testing. A chest x-ray is useful to evaluate for pleural effusions and a urinalysis should be performed to evaluate for additional signs of renal failure.[246]

Predicting disease progression and severity is important because the risk of death dramatically increases with severe dengue. A Vietnamese study found the mortality rate in patients with DSS to be 50 times higher than the rate in those with classical dengue.[5] Some studies estimate that 30% of DSS patients suffer recurrent episodes of shock. Clinical predictors of recurrent shock that can be used to identify this subset of patients include purpura/ecchymosis, ascites/pleural effusion, thrombocytopenia, and narrow pulse pressure.[119] Utility of the "warning signs" defined in 2009 as predictors of severe dengue has been evaluated. A 2013 prospective study in Singapore found that the absence of all warning signs has a negative predictive value of 100% for severe dengue. No one warning sign alone could predict progression to severe dengue, but having any combination of two reduced the sensitivity from 100% to 46%.[142]

A definitive diagnosis of dengue can be made by detecting virus-specific antibodies or viral proteins. Immunofluorescence assay of serum or CSF with serotype-specific monoclonal antibodies (IgM enzyme-linked immunosorbent assay [ELISA]) is the test of choice to confirm the diagnosis. Although the IgM immunoassay has a sensitivity of 90% to 97%, samples collected within the first 4 to 5 days of illness may lead to false-negative results. Serologic diagnosis of dengue fever then commonly depends on demonstration of a fourfold or greater increase in IgM or IgG antibody titer between acute-phase and convalescent-phase serum samples by hemagglutination inhibition or enzyme immunoassay (and less commonly, by the complement fixation and neutralization test). ELISA detection of viral nonstructural protein 1 is useful to identify early primary infections because it has a sensitivity of 90% and can be discerned before antibodies are detectable.[103,206] The real-time reverse transcription–polymerase chain reaction (RT-PCR) is emerging as a promising diagnostic tool following validation of a Centers for Disease Control and Prevention (CDC) assay in 2013. RT-PCR is serotype specific, unlike nonstructural protein 1 detection, and allows identification within the first days of infection, before IgM or IgG antibody detection through ELISA is possible [194] Earlier attempts to develop rapid bedside tests using immunochromatographic or immunoblot technologies have been largely unsuccessful; however, a combined nonstructural protein 1–antigen and IgM/IgG antibody point-of-care diagnostic assay holds promise.[91] Virus identification can also be confirmed by inoculation of serum into mosquitoes or certain mosquito cell lines (most commonly *A. albopictus* [C6/36] and *Aedes pseudoscutellaris* [AP61]), and subsequent culture. Future testing approaches in development include microsphere-based immunoassays, biosensor technology using mass spectrometry, and laser-based microarrays.[246]

The CDC recommendation is that, for testing and reporting, both acute-phase (within 5 days of symptom onset) and convalescent-phase (6 days after symptom onset) serum samples be sent to the state health department, which will forward them to the CDC for testing. The acute-phase specimen will undergo RT-PCR and should be stored on dry ice (or unfrozen at 4° C [39.2° F] if sent within a week). The convalescent-phase specimen will undergo ELISA and should be shipped on ice (or in a rigid container without ice if next-day delivery is possible).[49]

However, despite all this, dengue infections are usually diagnosed clinically because laboratory-based diagnosis is often unavailable and has limitations. That said, dengue should be considered only after other common tropical infections such as malaria are ruled out. For the returning traveler, dengue should be considered when symptoms begin within 2 weeks after departure from an endemic country. One recent review of four prospective studies found dengue accounted for 16% of febrile

illnesses in returning travelers, with an infection incidence of 10.2 to 30 per 1000 person-months.[186] Symptoms in a traveler or an immigrant that begin 2 weeks or more after departure from an endemic area cannot be attributed to dengue, because the incubation period is less than 2 weeks.[180,206]

Treatment and Prevention

There are currently no effective antiviral agents, but substantial research is ongoing.[103] Current treatment recommendations developed by the WHO focus on supportive care and are divided across three groups stratified by risk for deterioration (Figure 39-12). Patients in group A are likely to have mild disease and can be treated at home with electrolyte oral rehydration solution, acetaminophen for fevers at 6-hour intervals, and close observation that includes daily ambulatory clinic visits.

Group B includes patients with warning signs or coexisting factors (e.g., pregnant women, infants, or elderly persons; persons who are obese or have diabetes, renal failure, or chronic hemolytic diseases) that place them at higher risk, as well as social circumstances that would make outpatient management difficult. These patients should be admitted and intravenous (IV) hydration begun with isotonic fluids. Recommended fluids include 0.9% saline, Ringer's lactate, and Hartmann's solution beginning at 5 to 7 mL/kg/hr for 1 to 2 hours, followed by 3 to 5 mL/kg/hr for 2 to 4 hours, and finally ongoing at 2 to 3 mL/kg/hr based on clinical response. A urine output of 0.5 mL/kg/hr should be maintained through the critical phase, through IV fluids switched to oral rehydration once that is possible. Any signs of decompensation, including an early rise in hematocrit and accompanying thrombocytopenia, indicate the need for more aggressive therapy.

Patients in group C have severe dengue or have failed to improve despite the aforementioned treatments. For compensated shock, aggressive fluid resuscitation is indicated at 5 to 10 mL/kg/hr repeated in doses of 10 to 20 mL/kg/hr as needed. Frequent hematocrit checks are needed, and if decreasing, blood transfusion should be considered. Hypotensive patients require isotonic fluid boluses at 20 mL/kg over 15 minutes as needed. Transitioning to colloid fluids is recommended for a patient in shock with a rising hematocrit, because this suggests rapid plasma leakage. Arterial blood pressure and urinary catheter placement for more accurate hemodynamic monitoring is indicated for patients with shock.[246]

Special considerations for patients with hemorrhagic complications include avoiding intramuscular injection and nasogastric tubes, as well as using caution with central venous access in noncompressible sites. End-organ complications of shock should be managed according to standard intensive care protocols, taking care to avoid interventions with an increased bleeding risk, such as peritoneal dialysis. Current evidence does not support prophylactic platelet transfusions or routine use of platelets and/or fresh frozen plasma for hemorrhage. There is also little evidence to support the use of steroids, IV immunoglobulins, or recombinant activated factor VII.[185,246,262]

The most common complication of treatment is fluid overload because severity can be difficult to estimate and plasma leakage frequently resolves abruptly with third-spaced fluids reentering the intravascular space. This can lead to pleural effusion, ascites, pulmonary edema, and acute respiratory distress syndrome. Thus, care should be taken to watch for such complications after administration of large fluid volumes.[246]

Recently completed vaccine trials demonstrated promising results, but there is not yet a licensed vaccine against dengue viruses. As discussed above, primary infection with one serotype induces long-term protective immunity to reinfection with the homologous serotype but not with the heterotypic serotypes. In addition, infection of any serotype can lead to severe dengue, and sequential exposure to a different serotype is positively correlated with severe dengue. Therefore, a successful vaccine would optimally induce long-lasting neutralizing antibodies to all four dengue serotypes. Two phase 3 randomized clinical trials of a recombinant, live, attenuated, tetravalent vaccine for children in the Asia-Pacific region and South America were recently completed. Although there was some serotype-specific variation in efficacy, the former showed overall efficacy of 56.5% after three injections, and 80.8% efficacy against severe dengue. The latter showed overall efficacy of 60.8%, with 95.5% against severe dengue. Both trials had safety profiles similar to placebo and were actively followed for 25 months.[34,237] At this time, it remains unclear if these studies will be used to pursue licensure, because although the findings are certainly promising, 56% to 60% efficacy is still not a dramatic solution to dengue. Other vaccine candidates are in development. The announcement of the WHO Global Strategy for Dengue Prevention and Control 2012-2020 will hopefully drive a coordinated focus on this once neglected disease, promoting surveillance, detection, vector management, evidence-based treatment, and vaccine development[247] (see Global Eradication Programs for Mosquitoes, later).

YELLOW FEVER

The first epidemic caused by the yellow fever virus is thought to have been in the Yucatan Peninsula in 1648. This single-stranded RNA flavivirus causes infection in up to 200,000 persons per year.[16,241] It was estimated that 130,000 cases and 78,000 deaths occurred from yellow fever in Africa alone in 2013.[93]

Epidemiology and Transmission

It is believed that yellow fever virus evolved approximately 3000 years ago from other arthropod viruses in Africa and was carried to the Americas by Dutch slave traders in the 17th century. During the late 17th century, epidemics and outbreaks occurred in the Yucatan Peninsula, several places on the East Coast of the United States, and the Caribbean islands. While England, Spain, and France were colonizing the Americas, yellow fever played a prominent role by decimating local populations as well as sailors and troops, especially near port cities.

Unfortunately, factors such as increased urbanization and waning yellow fever immunization programs contributed to resurgence of the disease in the 1980s.[16,188] Accurate data regarding the burden of disease remain difficult to obtain because of underreporting (especially in remote areas), lack of diagnostic facilities, and delayed recognition of outbreaks.[162] Nevertheless, of particular concern are the increasing incidence and continued outbreaks of yellow fever in Africa (which includes multiple countries suffering humanitarian crises that hinder effective immunization campaigns) and the high (>50%) case fatality rate in South America.[162] Given such concerns, the Yellow Fever Initiative was launched in 2006 as a collaborative effort toward improved yellow fever surveillance and prevention through mass vaccination campaigns.[228,257] Between 2007 and 2010, 57 million individuals across 10 African countries were vaccinated against yellow fever.[253] Some estimate these efforts have led to a reduction in the burden of disease of more than 50% in countries targeted by the initiative. Figures 39-13 and 39-14 show recent endemic areas in Africa and the Americas.[122,162]

Yellow fever in travelers to South America and Africa has been very rare, likely due to routine vaccination. Between 1970 and 2002, only 10 cases of yellow fever were reported, 9 of which occurred in unvaccinated individuals.[62]

A. aegypti was hypothesized as early as 1881 to be the vector, and is indeed one of the main mosquitoes that transmit yellow fever in urban settings. The three patterns of yellow fever transmission are urban, intermediate, and sylvatic (jungle). In urban yellow fever, no monkeys are involved in transmission, and domestic mosquitoes, such as *A. aegypti,* carry the virus from person to person. In intermediate yellow fever, mosquitoes of the genus *Haemagogus,* or other forest-canopy species, transmit this disease to both monkeys and humans; this is the most common type of transmission in recent outbreaks in Africa. Finally, in sylvatic yellow fever, nonhuman primates, such as monkeys, are the zoonotic focus, and wild mosquitoes can become infected by monkeys and pass the disease to humans.[254]

There is also vertical transmission of the virus within mosquitoes; a female mosquito can pass the virus to her offspring. Because mosquitoes serve as additional reservoirs and vectors of the virus, endemicity of the disease is ensured.[241] Peak transmission in Central and South America is during the rainy season

DENGUE CASE MANAGEMENT

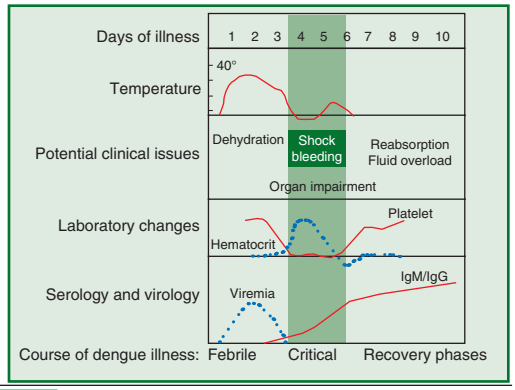
ASSESSMENT

PRESUMPTIVE DIAGNOSIS
Live in/travel to dengue-endemic area.
Fever and two of the following criteria:
- Anorexia and nausea
- Rash
- Aches and pains
- Warning signs
- Leukopenia
- Tourniquet test positive

Laboratory confirmed dengue
(important when no sign of plasma leakage)

WARNING SIGNS*
- Abdominal pain or tenderness
- Persistent vomiting
- Clinical fluid accumulation
- Mucosal bleed
- Lethargy, restlessness
- Liver enlargment >2 cm
- Laboratory: increase in HCT concurrent with rapid decrease in platelet count

*(requiring strict observation and medical intervention)



CLASSIFICATION

NEGATIVE

Coexisting conditions
Social circumstances

NEGATIVE

POSITIVE

POSITIVE

DENGUE WITHOUT WARNING SIGNS | **DENGUE WITH WARNING SIGNS** | **SEVERE DENGUE**

MANAGEMENT

Group A
(May be sent home)

Group criteria
Patients who do not have warning signs
AND
who are able:
- to tolerate adequate volumes of oral fluids
- to pass urine at least once every 6 hours

Laboratory tests
- full blood count (FBC)
- hematocrit (HCT)

Treatment
Advice for:
- adequate bed rest
- adequate fluid intake
- Paracetamol, 4 g maximum per day in adults and accordingly in children.

Patients with stable HCT can be sent home

Monitoring
Daily review for disease progression:
- decreasing white blood cell count
- defervescence
- warning signs (until out of critical period)

Advice for immediate return to hospital if development of any warning signs, and
- written advice for management (e.g., home care card for dengue).

Group B
(Referred for in-hospital care)

Group criteria
Patients with any of the following features:
- coexisting conditions such as pregnancy, infancy, old age, diabetes mellitus, renal failure
- social circumstances such as living alone, living far from hospital

Laboratory tests
- full blood count (FBC)
- hematocrit (HCT)

Treatment
- Encouragement for oral fluids
  If not tolerated, start intravenous fluid therapy 0.9% saline or Ringer's lactate at maintenance rate

Monitoring
Monitor:
- temperature pattern
- volume of fluid intake and losses
- urine output (volume and frequency)
- warning signs
- HCT, white blood cell, and platelet counts.

OR: Existing warning signs

Laboratory tests
- full blood count (FBC)
- hematocrit (HCT)

Treatment
Obtain reference HCT before fluid therapy. Give isotonic solutions such as 0.9% saline, Ringer's lactate. Start with 5–7 mL/kg/hr for 1–2 hr, then reduce to 3–5 mL/kg/hr for 2–4 hr, and then reduce to 2–3 mL/kg/hr or less according to clinical response

Reassess clinical status and repeat HCT:
- if HCT remains the same or rises only minimally -> continue with 2–3 mL/kg/hr for another 2–4 hr
- if worsening of vital signs and rapidly rising HCT -> increase rate to 5–10 mL/kg/hr for 1–2 hr

Reassess clinical status, repeat HCT, and review fluid infusion rates accordingly:
- reduce intravenous fluids gradually when the rate of plasma leakage decreases toward the end of the critical phase

This is indicated by:
- adequate urine output and/or fluid intake
- HCT deceases below the baseline value in a stable patient

Monitoring
Monitor:
- vital signs and peripheral perfusion (1–4 hourly) until patient is out of critical phase
- urine output (4–6 hourly)
- HCT (before and after fluid replacement, then 6–12 hourly)
- blood glucose
- other organ functions (renal profile, liver profile, coagulation profile, as indicated).

Group C
(Require emergency treatment)

Group criteria
Patients with any of the following features:
- severe plasma leakage with shock and/or fluid accumulation with respiratory distress
- severe bleeding
- severe organ impairment

Laboratory tests
- full blood count (FBC)
- hematocrit (HCT)
- other organ function tests as indicated

Treatment of compensated shock
Start IV fluid resuscitation with isotonic crystalloid solutions at 5–10 mL/kg/hr over 1 hour. Reassess patients' condition

If patient improves:
- IV fluids should be reduced gradually to 5–7 mL/kg/hr for 1–2 hr, then to 3–5 mL/kg/hr for 2–4 hr, then to 2–3 mL/kg/hr for 2–4 hr and then reduced further depending on haemodynamic status;
- IV fluids can be maintained for up to 24–48 hr

If patient is still unstable:
- check HCT after first bolus
- **if HCT increases**/still high (>50%), repeat a second bolus of crystalloid solution at 10–20 mL/kg/hr for 1 hr
- if there is improvement after second bolus, reduce rate to 7–10 mL/kg/hr for 1–2 hr and continue to reduce as above;
- **if HCT decreases,** this indicates bleeding and need to cross-match and transfuse blood as soon as possible

Treatment of hypotensive shock
Initiate IV fluid resuscitation with crystalloid or colloid solution at 20 mL/kg as a bolus for 15 min
If patient improves:
- give a crystalloid/colloid solution of 10 mL/kg/hr for 1 hr, then reduce gradually as above

If patient is still unstable:
- review the HCT taken before the first bolus
- **if HCT was low** (<40% in children and adult females, <45% in adult males) this indicates bleeding, the need to cross-match and transfuse (see above)
- **if HCT was high** compared to baseline value, change to IV colloids at 10–20 mL/kg as a second bolus over 30 min to 1 hr; reassess after second bolus
- **If patient is improving** reduce the rate to 7–10 mL/kg/hr for 1–2 hr, then back to IV crystalloids and reduce rates as above
- **if patient's condition is still unstable**, repeat HCT after second bolus
- **If HCT decreases**, this indicates bleeding (see above)
- **if HCT increases**/remains high (>50%), continue colloid infusion at 10–20 mL/kg as a third bolus over 1 hr, then reduce to 7–10 mL/kg/h 1–2 hr, then change back to crystalloid solution and reduce rate as above

Treatment of hemorrhagic complications
Give 5–10 mL/kg of fresh packed red cells or 10–20 mL/kg of fresh whole blood

FIGURE 39-12 Dengue treatment algorithm. *(From World Health Organization: Dengue Guidelines of Diagnosis, Treatment, Prevention, and Control. WHO 2009, pp 64-65.)*

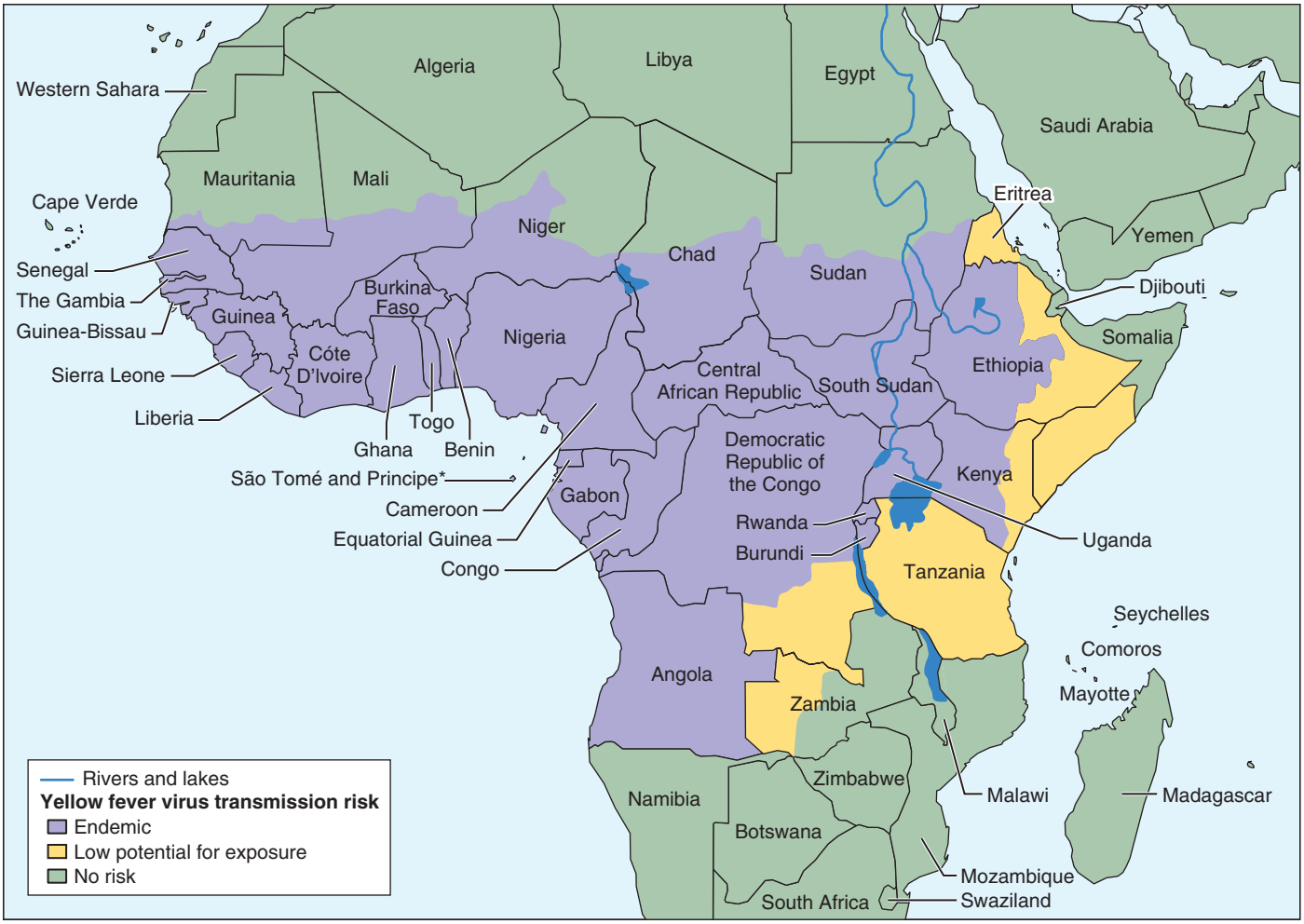


FIGURE 39-13 Yellow fever: endemic zones in Africa, 2011. *(From Centers for Disease Control and Prevention;* (cdc.gov/yellowfever/maps/africa.html.)

between January and March; in Africa, it is highest through the end of the rainy season into the early dry season (July through October).

The female mosquito inoculates about 1000 virus particles intradermally during one human feeding, and viral replication occurs at that site. It is believed that virus spreads through lymphatic channels and has a preference for replication in lymphoid cells, after which it spreads hematogenously. During this viremia, uninfected mosquitoes can become infected if they bite infected humans.

Clinical Presentation

The main risk factor for disease is exposure in endemic areas, as evidenced by the fact that a large portion of cases are in men age 15 to 45 years who have occupational exposure in mosquito-infested areas. Unvaccinated individuals (such as persons too young to have been immunized) in areas in which epidemic disease is occurring are also at higher risk, as are individuals in areas with poor health care.[241]

Although most patients infected with yellow fever suffer mild or no symptoms, there are three phases in the classic description of yellow fever: infection, remission, and intoxication. After an incubation period of 3 to 6 days, the infection stage consists of sudden onset of fever, headache, photophobia, malaise, back and epigastric pain, anorexia, and vomiting. Helpful clinical signs include Faget's sign (bradycardia occurring at the height of the fever), conjunctival injection, and a coated tongue with pink edges. The infection stage may resolve within 3 to 4 days and be followed by up to 48 hours of remission.[16,158,241]

The intoxication period occurs in an estimated 15% or more of infected individuals, manifesting with liver and renal failure (jaundice, azotemia, and oliguria), myocardial involvement, encephalopathy, and shock. Viral-induced thrombocytopenia and coagulopathy can cause severe hemorrhage, ranging from epistaxis to metrorrhagia to gastrointestinal bleeding. Spanish-speaking peoples called the disease *vomito negro,* or black vomit, before it was officially named.[30] Severe illness has a case fatality rate of approximately 20%, which may approach 50% in some outbreaks.

Diagnosis. Preliminary diagnosis is based on clinical presentation and travel history. However, given the clinical overlap with several other disease processes (e.g., leptospirosis, louse-borne relapsing fever, DHF, viral hepatitis), virus detection or serologic examination is required for definitive diagnosis. Laboratory findings may be supportive in making the diagnosis. These may include leukopenia with relative neutropenia; thrombocytopenia with reduction of all liver-produced clotting factors; elevation of liver enzymes (but usually normal alkaline phosphatase); elevated blood urea nitrogen and creatinine levels; and albuminuria.[158]

The definitive diagnosis is typically obtained by the IgM ELISA and best done with paired acute and convalescent sera. The acute sample should be drawn within several days of symptom onset, and the convalescent sample 14 days later. A neutralization test, which shows loss of infectivity through reaction of the virus with a specific antibody, can also confirm the diagnosis of yellow fever. Given the cross-reactivity between antibodies from other flaviviruses, such confirmatory tests are especially important in Africa, where multiple flaviviruses coexist. The virus can be isolated from serum specimens or liver tissue after death, via inoculation of mice, mosquitoes, or cell cultures, but these techniques are most effective in the preicteric state. Once the intoxication

FIGURE 39-14 Yellow fever: endemic zones in South America, 2011. *(From Centers for Disease Control and Prevention;* (cdc.gov/yellowfever/maps/south_america.html *Updated December 13, 2011.)*

period begins, viral RNA is usually undetectable; thus, such methods are generally not used for diagnosis. Other methods, including PCR for viral genome identification and liver biopsy for demonstration of characteristic midzonal necrosis, have been discussed but are not used for diagnosis.[14,158,241]

Treatment and Prevention

Although there is no treatment other than supportive care, there is a vaccine against yellow fever (17D-204 strain YF-VAX); 0.5 mL of reconstituted vaccine is administered subcutaneously.[161] This live-attenuated vaccine is considered very effective and safe. Seroconversion rates exceed 95%, and side effects are usually limited to injection site pain, mild headaches, myalgias, or low-grade fevers for several days.[17,90,158,161] As more travelers enter endemic areas without receiving vaccine, the number of yellow fever cases imported into the United States and Europe has increased. The CDC estimates the risk for acquiring yellow fever for an unvaccinated traveler going to endemic areas of West Africa and South America to be 50 per 100,000 and 5 per 100,000, respectively. The CDC and the Advisory Committee on Immunization Practices recommend that travelers (older than 9 months of age) to certain areas in Africa and South America be vaccinated. Some countries (not the United States) require vaccination before allowing travelers to enter from endemic areas. Vaccination guidelines (and authorized centers for vaccination) can be found on the CDC Yellow Book website at cdc.gov/yellowfever/vaccine/index.html.

International travelers must receive yellow fever vaccine approved by the WHO and administered at an approved yellow fever vaccination center, and obtain an international certificate of vaccination. Although International Health Regulations require boosters every 10 years, many studies suggest that vaccine immunity endures for more than 30 years and possibly for life. The WHO recently released a position paper suggesting that a single dose of vaccine is sufficient, and that a booster dose is not necessary.[97,252,254]

Overall, the vaccine has a high safety record, with hypersensitivity being the most common vaccine reaction.[24] Significant adverse reactions to yellow fever vaccine typically occur in first-time vaccinees and are categorized as yellow fever vaccine–associated neurotropic disease (YEL-AND) and yellow fever vaccine–associated viscerotropic disease (YEL-AVD). YEL-AND is typically due to neuroinvasion by the 17D virus and represents multiple different clinical syndromes, including Guillain-Barré syndrome and meningoencephalitis. Historically, the vaccine was associated with encephalitis in children, but vaccine standardization has decreased the incidence in the United States to 0.8 cases per 100,000 doses administered. Although the incidence is thought to be higher in older adults, the case fatality rate remains low.[17] YEL-AVD is a severe illness resembling wild-type disease, in which vaccine virus replication often leads to multisystem organ failure and death.[159] The U.S. incidence is 0.4 cases per 100,000 doses administered, with host factors such as increased age, history of thymus disease, and male gender thought to increase the risk.[146] The case fatality rate remains greater than 50%.[17] Caution is advised in administering the vaccine to infants 6 to 8 months of age (no child younger than 6 months should receive the vaccine); in individuals with a history of hypersensitivity to

vaccine products, or thymus disease; in patients with human immunodeficiency virus and CD4+ T-lymphocyte counts of 200 to 499/mm^3; and in individuals who are pregnant, nursing, immunocompromised, older than 60 years of age, or receiving other vaccines simultaneously.[17,54,201] The CDC encourages health care providers to report febrile illness thought to be caused by yellow fever vaccine to the CDC/FDA Vaccine Adverse Events Reporting System at http://vaers.hhs.gov/esub/index.

Eradication of *A. aegypti* via well-executed control campaigns in the 1970s has been successful in many Central and South American countries, with much credit owed to the PAHO. However, vigilance must be maintained, because *A. aegypti* has reestablished itself in many of these areas. Much work must be done in Africa, where the mosquito has never been eradicated.

JAPANESE ENCEPHALITIS

Japanese encephalitis (JE) virus, a member of the *Flavivirus* genus and related to the dengue, yellow fever, and West Nile viruses, is the major cause of viral encephalitis in Asia. It is estimated that approximately 68,000 cases occur and are responsible for as many as 20,400 deaths each year.[33] Between 1973 and 2011, 58 cases of JE were reported in travelers from nonendemic countries.[114] Although a vaccine for JE exists, financial and logistical barriers continue to hamper effective prevention efforts.[172]

Epidemiology and Transmission

Culex mosquitoes (usually *Culex tritaeniorhyncus*, but also *Culex vishnui* and *Culex pseudovishnui*) are the vectors for JE, and vertebrate hosts such as pigs and birds sustain the virus. Because humans do not produce levels of viremia high enough to infect new mosquitoes, they are considered dead-end hosts. However, the virus can still be maintained in an enzootic cycle even where JE immunity is high (either in endemic regions or through vaccinations) and human cases do not occur.[260] Mosquitoes breed in flooded fields associated with rice production; correspondingly, the prevalence has been shown to be higher in those areas. A higher prevalence of JE is recently being seen in urbanized areas, likely related to anthropogenic changes resulting in more breeding grounds.[239] Other environmental factors, including having large nearby pig and bird reservoir populations, also enhance the JE transmission cycle and place individuals at a higher risk of infection.[53]

Twenty-four countries are currently considered to be endemic for JE (Figure 39-15), and two main transmission patterns occur.[33] Seasonal transmission occurs in more temperate northern regions (e.g., Japan, China, Nepal, Taiwan, northern India) and can cause large epidemics. The second pattern of year-round transmission presents in tropical southern regions (e.g., southern Thailand, southern Vietnam, southern India, Indonesia, Malaysia, Philippines, Sri Lanka) and is usually more endemic or sporadic.[53,75,205,260]

The overall incidence is estimated to be 1.8 per 100,000 persons; however, this varies widely based on demographic, environmental, and social factors. For example, in children under 15 years of age, the estimated incidence is 5.4 per 100,000.[33] In South Korea, a country with an active vaccination program, the incidence has been as low as 0.01 per 100,000.[139] Several provinces in China have deployed vaccine implementation, surveillance, and education to reduce the incidence from more than 15 cases to 0.12 cases per 100,000.[92] India and China together account for more than 95% of reported cases, but presumed

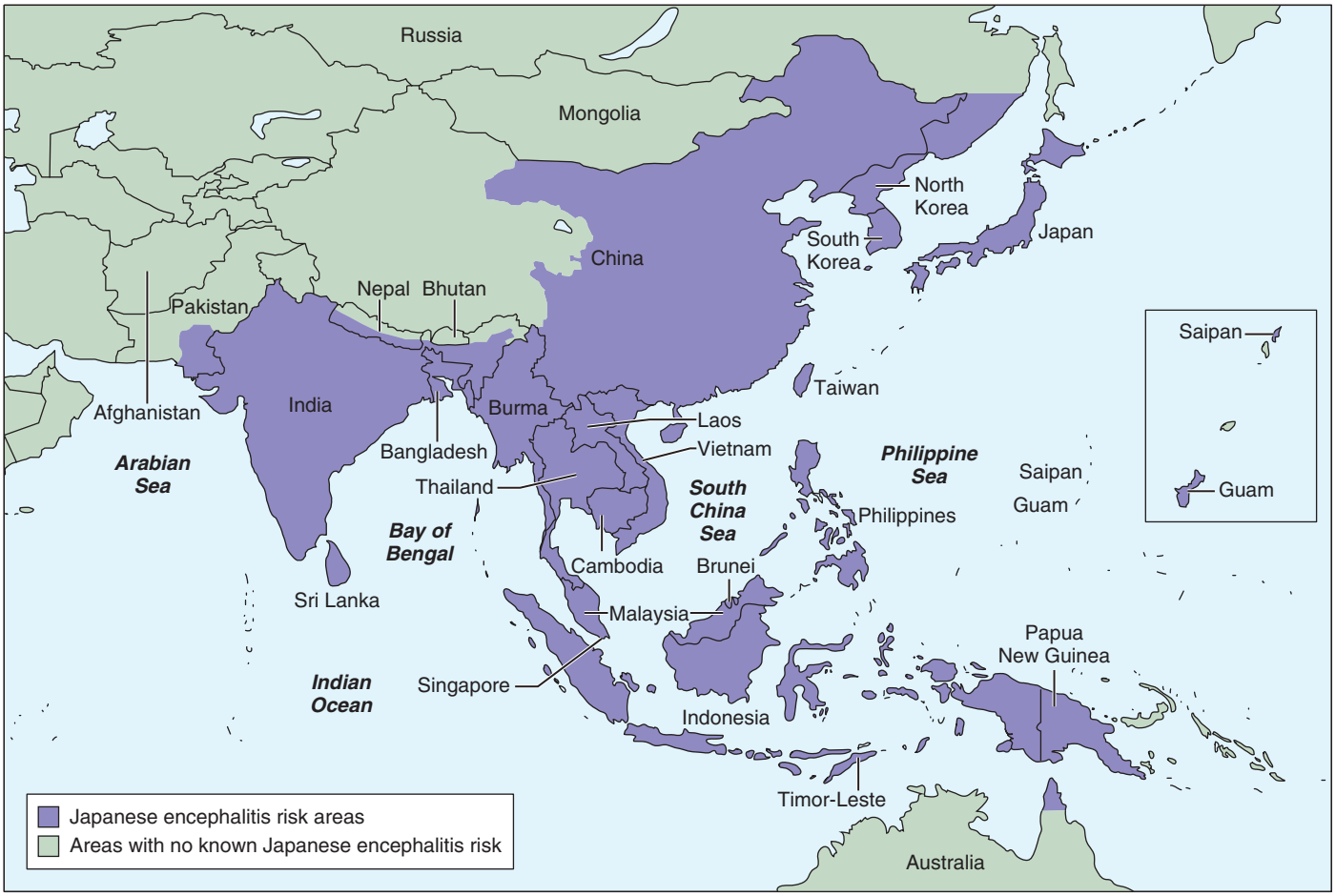


FIGURE 39-15 Geographic distribution of Japanese encephalitis. *(From Hills SL, Weber IB, Fischer M: Japanese encephalitis. In* CDC Health Information for International Travel [The Yellow Book]. nc.cdc.gov/travel/yellowbook/2014/chapter_3_infectiousdiseases_related_to_travel/japanese_encephalitis.*)*

severe underreporting in countries with either absent or less-developed surveillance systems is a recognized limitation of these data.[58]

Clinical Presentation

Persons at increased risk include individuals (residents, active duty military persons, or expatriates) living in endemic areas. Travelers have a low risk for acquiring the disease, estimated to be less than 1 in a million American travelers to endemic areas.[114] Most residents of endemic areas are infected during childhood, and seroprevalence studies have shown nearly ubiquitous infection by early adulthood in rural endemic areas.[223,251] The disease appears to affect mainly children less than 15 years of age, although there has been a secondary increase of disease in older adults.[53] Following earlier mass vaccination efforts, Taiwan and South Korea have seen a shift in incidence from primarily children to persons older than 30 years of age.[117,139]

The incubation period is 5 to 15 days.[53] The vast majority of infections with JE virus are subclinical, with less than 1% developing clinical manifestations. Of cases with encephalitis, 20% to 30% are fatal and 30% to 50% of survivors have significant neurologic sequelae.[33,53] The initial early presentation is nonspecific, with fever, diarrhea, and rigors followed by headache and vomiting. In severe disease, symptoms progress to mental status changes, focal neurologic deficits, generalized weakness, movement disorders, and seizures.[53]

The classic neurologic presentation is with parkinsonian signs such as tremor, mask-like facies, cog-wheel rigidity, and choreoathetoid movements.[18,53,195] Children in particular seem to have more convulsions than do adults infected with the virus, who tend to have more headaches and myalgias.[23,33,157,213] Of children hospitalized for JE during an epidemic in India, 98.7% presented with seizures.[136] Seizures are more often generalized tonic-clonic seizures than focal seizures.[157] An abrupt onset of a polio-like flaccid paralysis in one or more limbs can also occur.[18,215,260] In some individuals, abnormal behavior is the only clinical manifestation, so JE has been misidentified as mental illness.[212] In the Korean conflict, for example, American military personnel with JE were sometimes diagnosed with "war neurosis."[143]

Factors associated with poor outcome are recurrent witnessed seizures and abnormal breathing patterns, as well as extremes of age and elevated intracranial pressures.[149] Survivors of JE experience high rates of severe neurologic disability, including motor deficits, upper and lower motor neuron weakness, behavior changes, seizures, and cerebellar or extrapyramidal signs.[149,250] However, many experience some degree of recovery, outlining the importance of postinfection rehabilitation.[196]

Diagnosis

Laboratory analysis demonstrates that patients can have peripheral leukocytosis. Patients may have hyponatremia secondary to the syndrome of inappropriate antidiuretic hormone secretion. Fifty percent of patients have a high CSF opening pressure on lumbar puncture, and analysis of the CSF may show pleocytosis (predominantly lymphocytic) of 10 to 100 cells/mm^3, with normal glucose and slightly elevated protein. With early disease, however, there may be no CSF pleocytosis, and the leukocytes are predominantly forms of neutrophils. Thrombocytopenia and elevated liver enzymes may be seen.[23,53,114,136]

Definitive diagnosis is achieved by demonstration of IgM antibody by enzyme immunoassay antibody captured in CSF or serum; by a fourfold or greater rise in serum antibody titers against JE virus; or by isolation of virus from or demonstration of viral antigen or genomic sequence in tissue, blood, CSF, or other body fluid.[53,114] It can be difficult to isolate JE virus from blood because of a low viral burden, and unfortunately, nucleic acid amplification tests are insensitive.[53] IgG ELISA tests can be complicated by false-positive results that occur due to cross-reactivity with other flaviviruses. Anti–JE virus IgM can be detected in CSF within 1 to 4 days of illness onset, with complete sensitivity by day 7. In contrast, serum testing has low initial sensitivity that becomes far more reliable after day 9.[53,68] Point-of-care dipstick and lateral flow chromatography cassette tests are available for field use.[244]

Both noncontrast and contrast computed tomography (CT) and magnetic resonance imaging (MRI) may show lesions in the thalamus, basal ganglia, midbrain, and pons, with MRI being significantly more sensitive.[18] Although they are not sensitive for JE, thalamic lesions are very specific for the disease (23% and 100%, respectively).[78] Electroencephalography may show theta and delta coma, burst suppression, and epileptiform activity; however, this has not been found to be a good predictor of outcome.[18]

Treatment and Prevention

There is no specific treatment for JE beyond supportive care.[53] Other modalities, such as reducing intracerebral pressure with mannitol and providing seizure prophylaxis, have been suggested by some experts, but there have been no studies on whether these interventions are beneficial in JE.[232] Therapies such as corticosteroids, interferon-α, and ribavarin have all been studied in randomized, double-blind, placebo-controlled trials. JE patients do not seem to benefit from any particular treatment.[135,195,214]

With no effective treatment and the challenges of vector elimination, prevention through vaccination is widely considered the most effective approach for JE control.[260] Large campaigns have nearly eliminated the disease in parts of the world, such as China, Japan, Korea, and Taiwan; however, these countries have also witnessed a shift of the disease burden to the older unvaccinated population.[117,244]

There are four main JE vaccines: inactivated mouse brain–based vaccines, inactivated cell–based vaccines, live-attenuated vaccines, and live-chimeric vaccines. Historically, the most widely available JE vaccine has been the inactivated mouse brain–derived vaccine (JE-MB or JE-VAX), typically prepared using the Nakayama or Beijing-1 strain of JE virus. This formerly was the only vaccine routinely available to international travelers from nonendemic countries. In October 2013, China was prequalified by the WHO to produce a live-attenuated vaccine based on the strain SA14-14-2 (LA-JE), which has since become the most widely used vaccine in endemic countries.[250] This vaccine had been used in China for more than 20 years, and the WHO estimates that it was partially responsible for reducing the burden of JE from 2.5 per 100,000 in 1990 to less than 0.5 per 100,000 in 2004. Numerous large field studies and case-control studies of the SA14-14-2 vaccine have shown efficacy of more than 95% following two doses given 1 year apart.[197,211] There are also data suggesting that single-dose LA-JE is equally effective with 99.3% efficacy after 2 weeks, and 96.2% at 5 years.[222] Postmarketing surveillance of LA-JE vaccine has shown a serious adverse event rate of 1.12 per million doses, which included nine cases of meningoencephalitis and four deaths.[238]

In the United States, there is only one licensed and available vaccine, IXIARO. It is an inactivated Vero cell culture–derived vaccine (JE-VC) that was approved in March 2009 initially for individuals 17 years and older and then in May 2013 for children ages 2 months through 16 years.[58] It produces a 97% seroconversion rate after two doses administered 28 days apart; however, a booster is recommended after 1 year if further exposure will occur.[58,224] Hypersensitivity reactions and fever are the most commonly seen adverse events related to the JE-VC vaccine. Postmarketing surveillance has shown a serious adverse event rate of 1.8 per 100,000 doses, which while similar to the previously available JE-VAX vaccine, is thought to be partially artifact.[183] Prior to IXIARO, JE-VAX was the only licensed vaccine available in the United States for JE, which required three doses and had rare but serious adverse events affecting the CNS. In 2006, production of JE-VAX ceased in the United States and it is no longer used.[58,224]

The live-attenuated chimeric YF-JE vaccine (ChimeriVax-JE) is commercially available in Australia and Thailand. Studies have shown this vaccine causes 99% seroconversion with one dose; however, the need for booster doses has not yet been assessed. This and other recent advances have improved JE vaccines, but the ideal, cheap, safe, effective, and single-dose vaccine has not yet been definitively achieved.[260]

The CDC has created JE vaccine recommendations for travelers from nonendemic countries. The low rate of human disease must be balanced against the severe effects of JE infection and lack of effective treatment. Furthermore, JE infection rate in

travelers is low, and there is significant financial cost associated with the vaccine. However, recent surveillance suggests JE vaccines are now safer than previously thought. Currently, the vaccine is recommended for travelers who plan to spend a month or longer in endemic areas during transmission season, including those based in urban areas that are likely to visit high-risk rural areas. It should also be considered for short-term travelers to endemic areas if they plan to travel outside of urban areas, as well as for any travelers planning to visit an area suffering from an ongoing outbreak. Short-term travelers who will be restricted to urban areas, or those not visiting during transmission season, should not get JE vaccine.[58]

WEST NILE VIRUS

First identified in 1937 from the blood of a febrile woman in the West Nile province of Uganda, West Nile virus (WNV) is a flavivirus that prior to 1999 was found only in Africa, West Asia, and the Middle East. WNV has received significant press in North America because of its intrusion into the United States. The first report of the disease occurred in the summer of 1999 in New York,[11,169] and now WNV is considered endemic to North America.[28] The most accurate epidemiologic trend data include neuroinvasive disease (meningitis/encephalitis), because most patients with West Nile fever (WNF) are asymptomatic and do not seek care. Through February 2013, 16,196 cases of WNV neuroinvasive disease and 1549 deaths have been reported, and it is estimated that 780,000 individuals have been infected in the United States alone.[63,175] Since 1999, cases of human WNV disease have been found in all 48 continental states,[175] and WNV is now the foremost cause of domestically acquired arboviral infection in the United States.[144]

Epidemiology and Transmission

WNV is a single-stranded RNA virus, family Flaviviridae, genus *Flavivirus*. All flaviviruses have a size of approximately 40 to 60 nm (Figure 39-16), are enveloped with icosahedral nucleocapsids, and have single-stranded RNA of approximately 10,000 to 11,000 bases.[63]

Mosquitoes are the vectors for this virus, and birds are the most common reservoir. The most commonly named vector is the *Culex* mosquito species, but WNV has recently been identified in more than 64 different mosquito species in North America, which contributes to its permanent establishment and wide U.S. distribution (Figure 39-17). Different species of mosquitoes have varying host preferences and behaviors, and frequent transmission to migrating birds extends the reach of the virus.[98] Newly infected birds sustain viremia for 1 to 4 days, after which they develop lifelong immunity. During that time, mosquitoes can contract the virus. Humans and other mammals, such as horses, are considered incidental or "dead-end" hosts, because they often do not sustain viremia long enough to serve as viral reservoirs. The effects on nonhuman life can be significant; the 2002 WNV epidemic and epizootic in the United States was associated with 16,471 dead birds and 14,751 equine cases. In horses, as in humans, WNV crosses the blood-brain barrier and interferes with CNS functioning, and may result in death.[64] A recent study conservatively estimated the American crow population to have declined 45% since WNV arrival, and only two of the seven avian species documented to have been affected returned to pre-WNV levels by 2005.[137]

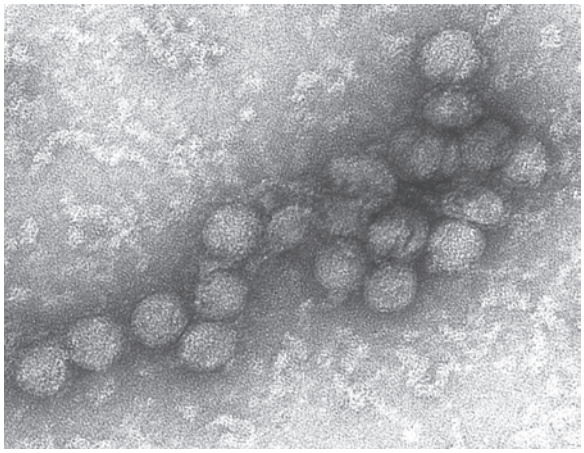


FIGURE 39-16 Electron microscopy of the West Nile virus.

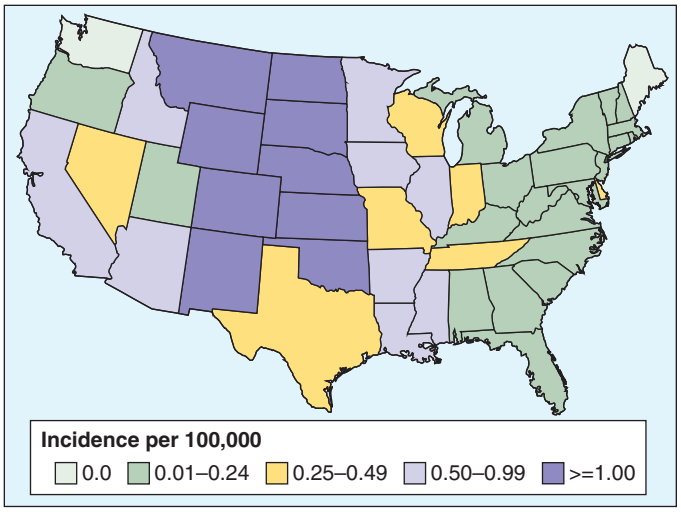


FIGURE 39-17 2013 West Nile virus neuroinvasive disease activity in the United States. *(From Centers for Disease Control and Prevention; (cdc.gov/westnile/statsMaps/finalMapsData/data/2013StateIncidenceMap.pdf).*

Other, more rare methods of transmission include organ transplantation,[46,120] blood transfusion,[44,45,174] transplacental infection,[42] and possibly human breast milk transmission.[43] Because transmission from blood transfusions reached 2.7 cases per 10,000 units during the peak of the 1999 outbreak in New York, and because there were confirmed cases of WNV transmission to organ transplant recipients, routine screening of blood donors for WNV RNA began in the summer of 2003. In 2003 and 2004, 519 donors were identified by this method, resulting in removal of more than 1000 potentially infectious units of blood products from the Red Cross supply. All donated blood continues to be screened for WNV using nucleic acid amplification tests, either on individual samples or on "minipools" of up to 16 donations.[220] A recent study of targeted nucleic acid amplification testing of individual donations in high-prevalence regions suggests that this approach may be cost-effective, because units with low levels of viremia may not be detected in minipools of blood donations.[32] Despite reduction in transfusion-related transmission with universal screening of blood, this limitation has prevented eradication and cases are still reported.[52,57]

Clinical Presentation

The virus has an incubation period of 3 to 14 days.[177] Disease usually occurs in temperate zones either in late summer or early fall, or year round in milder climates. Clinical syndromes caused by WNV include asymptomatic infection, WNF, and West Nile neuroinvasive disease (WNND). Most WNV infections in humans are asymptomatic.[263] Of the 20% of symptomatic cases, the majority develop WNF, which usually involves a mild influenza-like illness with malaise, headache, fever, anorexia, myalgias, and rash. In a case series review of 98 community-dwelling patients with laboratory evidence of WNV infection but no evidence of neuroinvasive disease, fatigue was present in 96% of patients, fever in 81%, headache in 71%, and difficulty concentrating in 53%.[240] Even in cases of WNF, the impact on quality of life can be severe. Of the 98 patients, 39% reported ongoing symptoms at 5 months of follow-up, 82% reported limitations in household activities, and there was a median of 10 days of missed school or work.[240] In a follow-up population-based cohort of 656 nonfatal cases, 91% of patients reported limitations in routine daily

activities secondary to WNV infection. Moreover, in cases of WNF alone, there was a median number of 16 school or work days missed, and 53% of this subset of patients reported symptoms of at least 30 days' duration. The impact was even more significant in patients with WNND.[173] In one longitudinal observational study of 156 Canadian patients, while recovery was slower for participants with WNND and preexisting comorbid conditions, physical and mental function generally returned to normal levels within 1 year for patients with WNV infection.[147]

WNND occurs in less than 1% of individuals infected with WNV and includes encephalitis, meningitis, meningoencephalitis, and acute flaccid paralysis/myelitis.[73] Older adults and immunocompromised patients are at increased risk for severe neurologic disease from WNV. In a retrospective medical chart review of 221 hospitalized WNV patients, 16% of those with meningitis and 32% of those with encephalitis had autoimmune disease, were immunosuppressed, or were organ transplant recipients. Male gender, age over 50 years, alcohol abuse, and diabetes have also been found to be associated with WNND.[22,39]

Although the clinical presentation of meningitis and encephalitis in WNV is nonspecific, one particular feature of WNV encephalitis is that it may manifest with parkinsonian features or other movement disorders, such as myoclonus or intention tremor. In a small prospective case series, 94% of WNV-seropositive patients experienced dyskinesias compared with 13% in the control group.[200] Another clinical syndrome associated with severe WNV disease is acute flaccid paralysis, which can rapidly progress to paralysis of one or up to all four limbs. It may also manifest as severe, asymmetric weakness, usually with sensation preserved. Affected limbs show decreased or completely absent deep tendon reflexes, most likely from anterior horn cell involvement similar to that seen in poliomyelitis.[73,98,199,200]

Other clinical findings may include ocular complications (e.g., optic neuritis, chorioretinitis, retinal hemorrhage, uveitis, conjunctivitis),[67,129,256] bladder dysfunction,[98] myocarditis, pancreatitis, and fulminant hepatitis.[177]

Diagnosis

For public health and surveillance purposes, the CDC uses specific criteria for arboviral infections and includes disease caused by California serogroup viruses, eastern and western equine encephalitis viruses, Powassan virus, St Louis encephalitis virus, and WNV. This was most recently revised in 2011 (Box 39-1).[55]

Typical findings for severe disease usually include a normal or slightly elevated leukocyte count in peripheral blood, possible hyponatremia in individuals with WNV encephalitis, pleocytosis and increased protein in the CSF, and no acute finding on brain CT scan.[63,177] Although MRI may yield abnormal results in 25% to 35% of cases, findings are nonspecific.[63,261] For definitive diagnosis, serum is ideally collected within 8 to 14 days of symptom onset, and CSF is collected within 8 days to give the highest diagnostic sensitivity. Serum or CSF should show IgM antibodies to WNV by IgM-capture ELISA (MAC-ELISA). There is, however, a chance that persistent IgM antibodies can be found in previously infected/exposed former residents of endemic areas. The diagnosis can be further confounded by the fact that these IgM ELISA tests have cross-reactivity of up to 44% with other flaviviruses during acute infection.[63,98]

The most specific test for arthropod-borne flaviviruses is the plaque-reduction neutralization test (PRNT), which is performed at reference laboratories. This test can be used both to negate false-positive results sometimes seen in MAC-ELISA or other assays, and to facilitate discrimination among flaviviruses.[63]

Efforts have been made to develop more specific and rapid serologic assays. Promising candidates include a microsphere immunoassay that discriminates between different flavivirus infections, as well as an immunofluorescence assay that has less cross-reactivity among WNV IgM antibodies and closely related flaviviruses. PCR (as used for screening blood products in the United States) or viral culture can also isolate the virus. However, the virus quickly migrates from the periphery into the CNS, leading to transient and low levels of viremia, making the sensitivity of PCR low.[63,177] One recent study showed that the combination of serologic assay and nucleic acid testing allowed for

BOX 39-1 2011 CDC Case Definition for Neuroinvasive and Nonneuroinvasive Arboviral Diseases: California Serogroup, Eastern Equine Encephalitis, St Louis Encephalitis, West Nile Virus Disease, Western Equine Encephalitis

Clinical Criteria for Diagnosis

Neuroinvasive disease
Fever and at least one of the following:
Meningitis, encephalitis, acute flaccid paralysis, or other acute sigs of central of peripheral neurologic dysfunction, as documented by a physician
AND
Absence of a more likely clinical explanation
Nonneuroinvasive disease
Fever or chills as reported by the patient or a health care provider AND
Absence of neuroinvasive disease
AND
Absence of a more likely clinical explanation

Laboratory Criteria for Diagnosis

Isolation of virus from, or demonstration of specific viral antigen or nucleic acid in, tissue, blood, CSF, or other body fluid
OR
Fourfold or greater change in virus-specific quantitative antibody titers in paired sera
OR
Virus-specific IgM antibodies in serum with confirmatory virus-specific neutralizing antibodies in the same or a later specimen
OR
Virus-specific IgM antibodies in CSF or serum

Confirmed Case

Neuroinvasive disease
Meets above clinical criteria and one or more of the following:
Fourfold or greater change in virus-specific quantitative antibody titers in paired sera
OR
Isolation of virus from, or demonstration of specific viral antigen or nucleic acid in, tissue, blood, CSF, or other body fluid
OR
Virus-specific IgM antibodies in CSF and a negative result for other IgM antibodies in CSF for arboviruses endemic to the region where exposure occurred
OR
Virus-specific IgM antibodies in serum with confirmatory virus-specific neutralizing antibodies in the same or a later specimen
Nonneuroinvasive disease
Meets above clinical criteria for nonneuroinvasive disease and one or more of the following laboratory criteria for a confirmed case:
Isolation of virus from, or demonstration of specific viral antigen or nucleic acid in, tissue, blood, or other body fluid, excluding CSF
OR
Fourfold or greater change in virus-specific quantitative antibody titers in paired sera
OR
Virus-specific IgM antibodies in serum with confirmatory virus-specific neutralizing antibodies in the same or a later specimen

Probable Case

Neuroinvasive disease
Meets above clinical criteria
AND
Virus-specific IgM antibodies in CSF or serum but with no other testing.
Nonneuroinvasive disease
Meets above clinical criteria and laboratory criteria for a probable case
Virus-specific IgM antibodies in serum but with no other testing

CDC, Centers for Disease Control and Prevention; CSF, cerebrospinal fluid.
From Centers for Disease Control and Prevention. cdc.gov/NNDSS/script/casedef.aspx?CondYrID=946&DatePub=1/1/2014.

more accurate identification of WNV cases compared with either approach alone.[231] Such studies have recommended that these measures be used as an adjunct to serologic testing.

Treatment and Prevention

There is no specific treatment for WNV; supportive care remains the mainstay of therapy.[94] Certain antivirals, antibodies, and drugs (e.g., interferon) that alter the inflammatory process have been tested, albeit largely in uncontrolled studies. In a retrospective, uncontrolled, nonblinded study of 233 human WNV cases, ribavirin was associated with poorer outcome in bivariate analysis. Although this effect was not seen in multivariate analysis, ribavirin was ineffective.[70] Similarly, there have been promising in vitro studies and human case reports evaluating the usefulness of interferon-α[6,125,165] and IV immunoglobulin,[3,19] but these treatment options remain controversial. A randomized placebo-controlled trial comparing a monoclonal antibody with saline was stopped early in 2012 due to inability to enroll (clinicaltrials.gov/ct2/show/NCT00927953). The results of a multicenter, randomized, double-blinded, placebo-controlled trial of passive immunotherapy for WNND are currently pending. Despite lack of effective therapies, many patients with neuroinvasive WNV have significant improvements.[113] For patients with neuroinvasive disease, the mortality rate has been reported at 10%. However, the rate is significantly higher for patients with encephalitis and myelitis than for those with meningitis alone.[59]

For prevention, general control measures such as blood donor screening and precautions against mosquitoes can be taken,[35,176,191] but there is no specific way to prevent WNV. Although vaccines have proved efficacious in multiple animal species, no human vaccine exists. Theoretically, there is potential for an inactivated virus to induce long-term immunity, because such a vaccine exists for JE and other flavivirus diseases. Multiple candidate vaccines against WNV are being evaluated, a couple of which have shown promise in small human studies. These include a chimeric virus (ChimeriVax-WN) based on the live, attenuated yellow fever 17D vaccine virus containing the premembrane and envelope proteins of WNV, and a single-plasmid recombinant DNA vaccine. ChimeriVax-WN02 was evaluated in a randomized, double-blinded placebo-controlled study of 45 healthy adults. The vaccine was well tolerated, and within 21 days of receiving a single inoculation dose, all study subjects developed high titers of WNV-specific neutralizing antibodies. In addition, 43 of 45 participants developed a WNV-specific T cell response.[160] A larger, follow-up, phase II trial found the vaccine to be safe and immunogenic.[21] A DNA vaccine has been evaluated in an open-label phase I trial of 15 healthy adults. The vaccine was well tolerated, and in the 12 participants that completed the three-dose vaccination schedule, all developed WNV-specific neutralizing antibodies.[152]

Surveillance and Reporting. Reporting requirements for suspected WNV infections vary across local and state health departments. However, WNV encephalitis is on the list of designated nationally notifiable conditions, and surveillance efforts are critical to achieve adequate prevention and treatment efforts.[106] The CDC may use results from commercial laboratories but may also request samples for diagnosis in its own laboratory. Information on how to send specimens can be found at cdc.gov/ncidod/dvbid/misc/arboviral_shipping.htm.

For ecologic surveillance, the CDC and other federal agencies have established specific guidelines and protocols to track avian, equine, and mosquito epizootics.

ST LOUIS ENCEPHALITIS

The St Louis encephalitis (StLE) virus is a flavivirus related to JE virus and WNV virus that is also transmitted by mosquitoes.

Epidemiology and Transmission

Culex species mosquitoes are the primary vector for StLE virus, with birds as the primary reservoir. The viremia, however, does not cause illness in birds or mosquitoes. Around the Gulf Coast and the Ohio and Mississippi River Valleys, the culprit mosquitoes are *Culex pipiens* and *Culex quinquefasciatus;* in Florida, *Culex nigripalpus;* and in the western states, *Culex tarsalis.*[52]

StLE virus is found throughout much of the Americas. In temperate parts of the United States, disease usually occurs in late summer or early fall, but it can occur year-round in the southern United States. Outbreaks can occur almost anywhere in the United States, though epidemics have occurred mainly in the Midwest and Southeast. Between 1964 and 2008, fewer than 5000 human cases of StLE were reported in the United States.[52,48] In some areas, it appears that WNV is displacing previously endemic StLE because of cross-protective avian herd immunity and differences in transmission efficiency.[187] Historically, few cases were reported from Central and South America, although there have been recent large outbreaks in Argentina and Brazil.[76,163,217]

Clinical Presentation

Less than 1% of StLE infections are symptomatic. StLE virus has an incubation period of approximately 5 to 15 days. Risk factors for infection include low socioeconomic status, outdoor occupation, and older age. Patients with symptomatic StLE infection typically present with fulminant and severe meningitis with high fever and headache. Nearly 90% of elderly persons with overt disease will develop encephalitis. Infants in particular may occasionally have convulsions and spastic paralysis. Of recognized cases, 95% are hospitalized for CNS involvement. The case fatality rate is 3% overall and up to 30% in older adults.[52]

Diagnosis

As with other arboviral diseases, clinical and epidemiologic features must be taken into account to make a presumptive diagnosis. However, StLE may be difficult to differentiate on clinical features alone. Thus, a definitive diagnosis is typically obtained by testing serum or CSF for serotype-specific monoclonal antibodies (IgM ELISA). Further confirmatory tests, such as demonstrating at least a fourfold increase in antivirus antibody titer between the acute period and the convalescent period, may be done.[52] Antigenic cross-reactivity with other flaviviruses is a known problem, encouraging some facilities to use PRNT or develop discriminatory algorithms to differentiate infections.[151] A potential additional option for diagnosis includes a newly developed rapid microsphere-based IgM assay that would shorten the test processing time to less than 5 hours.[123,124]

Treatment and Prevention

As for many viral illnesses, treatment is supportive, because there are neither specific antiviral therapies nor vaccines. One interventional pilot study of 15 patients with meningoencephalitis due to StLE showed that treatment with interferon-α2b reduced severity and length of complications. Given the small number of participants and nonrandomized nature of the study, further investigation should be conducted.[184]

EASTERN EQUINE ENCEPHALITIS

First discovered in the brain of a horse with encephalitis in 1933 in New Jersey, eastern equine encephalitis (EEE) is a serious mosquito-borne disease that appears in the eastern half of the United States and the Caribbean. It carries a high case fatality rate.[99] The virus is a member of the family Togaviridae, genus *Alphavirus,* and is related to western and Venezuelan equine encephalitis viruses.[62]

Epidemiology and Transmission

The transmission cycle involves birds and several species of mosquitoes, predominantly *Culiseta melanura* (Figure 39-18). *C. melanura* feeds almost exclusively on birds and is therefore only responsible for propagating virus within the reservoir population. Other "bridge" mosquito vectors are required for transmission to humans, and include species in the genera *Aedes* and *Coquillettidia*.[47,54] Humans and horses are considered hosts with incidental infections that can progress to severe disease.

EEE occurs mainly along the eastern and Gulf coasts of the United States, though cases have been documented in Canada as well as Central and South America.[10,37] The peak incidence of infection occurs during the late summer months.

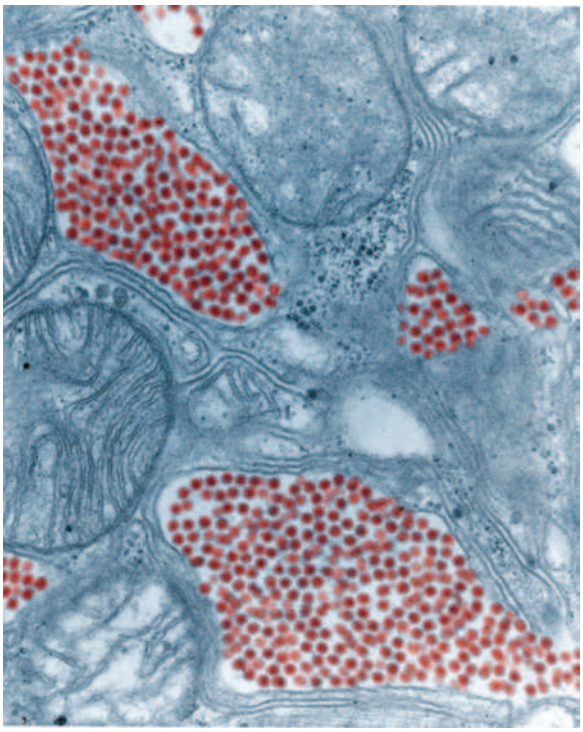


FIGURE 39-18 Micrograph of eastern equine encephalitis virus.

Between 1964 and 2010, there were approximately 270 confirmed cases in the United States, with an average of five to six cases per year. Most of the cases have been in Florida, Georgia, Massachusetts, and New Jersey, near coastal areas and freshwater swamps. The real incidence is probably higher because of underreporting and underrecognition. In 2005, 21 cases were reported to the CDC, compared with an average of 8.2 cases per year from 2000 to 2004. This included an outbreak of seven cases in New Hampshire, a state that was previously not known to harbor locally acquired EEE.[47,48] Since 2005, there has been increasing concern that EEE outbreaks are becoming more common and involving a wider geographic distribution, possibly due to changes in the ecology and epidemiology of the virus.[9]

Clinical Presentation

Individuals who live (or visit) endemic areas and those who spend significant time outdoors are at risk for developing EEE. Persons older than 50 or younger than 15 years have a greater chance of developing severe disease.

The clinical presentation is on a spectrum from mild influenza-like illness to encephalitis, coma, and death. One study of the 36 cases from 1988 to 1994 in the United States showed that clinical signs included fever (83%), headache (75%), nausea and vomiting (61%), confusion (4%), myalgias and arthralgias (36%), chills (25%), seizures (25%), focal weakness (23%), abdominal pain (22%), respiratory symptoms (11%), and cranial nerve palsies (8%).[74] The case fatality rate for EEE is 33%, making it the most severe of the arboviral encephalitides. Moreover, 50% of individuals who survive are left with mild to severe neurologic deficits.[74]

Diagnosis

Peripheral blood may show leukocytosis, and analysis of CSF may reveal elevated protein with red and white cells (predominantly lymphocytes) in the range of 600 to 2000/mm^3. Preliminary diagnosis may be completed by demonstrating IgM antibodies by capture ELISA. The definitive diagnosis lies in serologic evidence based on paired sera (acute and convalescent samples) in hemagglutinin-inhibition or neutralization assays. Acute samples should be obtained within 10 days of symptom onset, and convalescent samples approximately 2 to 3 weeks after symptom onset. It is possible to isolate the virus directly from serum in acute infection, but this method is less commonly used.[40,62]

Other helpful diagnostic modalities include MRI, which may show focal changes, particularly in the basal ganglia, thalamus, and brainstem.[74,95]

Treatment and Prevention

No specific treatment is available. There is one case report of a child being treated with corticosteroids and IV immunoglobulin,[95] but this has not been further studied. No human vaccine is available despite ongoing efforts to develop viable options.[36,243] There are equine vaccines that should be employed in endemic areas.

Surveillance and Reporting

EEE is a nationally notifiable disease that is reported to the CDC.

MURRAY VALLEY ENCEPHALITIS

Epidemiology and Transmission

Occurring mainly in Australia and New Guinea, Murray Valley encephalitis (MVE) virus (formerly known as Australian encephalitis) is from the family Flaviviridae, genus *Flavivirus,* and is transmitted via a bird–mosquito (*Culex annulirostris*)–bird cycle. Because humans do not have high levels of viremia, they are seen as dead-end hosts. Over the past century, MVE is believed to be responsible for up to six outbreaks of encephalitis in southeastern Australia, each affecting 21 to 114 people.[202] The overall burden of disease, however, remains low, with 16 cases being reported throughout Australia in 2011 after an outbreak, but only 1 case each in 2012 and 2013, and none in 2014.[12]

Clinical Presentation

Most infections are asymptomatic, and best estimates are that 1 in 150 to 1000 infections actually develop into clinical illness.[26,133] The clinical course is similar to that of JE, with prodromal headache, fever, myalgias, nausea and vomiting, and anorexia. In contrast to JE, cases seem to be largely or not at all encephalitic; that is, infections generally either remain subclinical or progress to neurologic involvement.[77,133] The neurologic involvement can involve lethargy, irritability, confusion, and/or meningismus, as well as seizures, spastic paresis, and coma. The reported case fatality rate for MVE infection is 15% to 30%, and data from the 2011 outbreak demonstrated an 18% crude case fatality rate. Epidemiologic studies on this disease have been hampered by an overall low prevalence. The prognosis is poor; more than 30% to 50% of survivors experience neurologic sequelae, and fewer than 40% fully recover.[133,202] The disease historically shows a bimodal risk for children and older adults, and a shift has been observed from aboriginal to nonaboriginal populations.[202]

Diagnosis

Due to the limited prevalence of the disease, most diagnostic methods are based on WNV and JE virus experience. Definitive diagnosis of MVE is generally accomplished by identifying IgM antibody via immunoassay of CSF or a fourfold rise in serum antibody titers. Direct viral isolation or PCR can also identify the infection in tissue, blood, or CSF. These tests can be altered by cross-reactive antibodies to other flaviviruses or previous immunization to yellow fever or JE virus. Similar to other flavivirus testing, both acute-phase and convalescent-phase samples should be sent to public health laboratories.[71,133]

Most patients have normal CT scans early in the illness, though nonspecific findings associated with encephalitis (e.g., mild hydrocephalus and cerebral edema) may be seen.[130] Typically, MRI findings will be abnormal, with cerebral peduncle and thalamic involvement. MRI signal abnormality extending beyond these areas is predictive of a worse outcome.[216]

Treatment and Prevention

There is no specific treatment or vaccine for MVE. Vaccine efforts in mice have shown mixed results, with passive IgG inoculation being potentially protective, but JE virus vaccine enhancing MVE infection.[27] Intensive supportive care is recommended, as is long-term physical therapy.[71,133] Prevention depends on adequate mosquito control and avoidance of mosquito bites.

CALIFORNIA (LA CROSSE) ENCEPHALITIS

La Crosse (LAC) virus is a California serogroup bunyavirus that can cause encephalitis (usually in children), and has historically been found in the central and eastern United States. La Crosse encephalitis constitutes 8% to 30% of all cases of encephalitis in the United States and is a major cause of arboviral illness.[193] In fact, its incidence in endemic areas (20 to 30 cases per 100,000 population per year) exceeds that of bacterial meningitis.[155]

Epidemiology and Transmission

Aedes triseriatus, the eastern tree hole mosquito, is the main vector, although *A. albopictus,* or the Asian tiger mosquito, may be emerging as another significant species. Vertebrate hosts include chipmunks, tree squirrels, and foxes. The U.S. incidence is approximately 80 to 100 cases per year; there is concern that both the incidence and geographic distribution may be increasing in southern states.[50,89,105,115] Most infections are asymptomatic and occur from late summer to early fall in the central and eastern United States.[41,50,80]

Clinical Presentation

The majority of cases are in children less than 16 years of age.[50,105,156] For 80% to 90% of infected persons, the clinical course is mild, with only headache, fever, and vomiting after an incubation period of 5 to 15 days. Approximately 10% to 20% of infected individuals develop a severe form of the disease within the first 8 to 24 hours of symptom onset. In one pediatric study of 127 hospitalized children, it was noted that 70% of patients presented with headache, fever, and vomiting. Of children, 46% had seizures (generally, focal seizures, with some progression to status epilepticus) and 20% had focal neurologic findings. Encephalitis did not always occur. Although all patients survived, more than 10% had neurologic deficits at the time of hospital discharge, and preliminary analysis suggested that patients may also suffer long-term cognitive and behavioral deficits.[154] Only one case report has mentioned California encephalitis causing infarction of the basal ganglia, leaving a child with acute hemiparesis.[138] The CDC recently described a case of possible congenital infection after identification of IgM antibodies in umbilical cord serum. The mother declined collection of infant serum to document seroconversion; fortunately, the infant remained asymptomatic and development was normal at 6-month follow-up. The CDC reports the case fatality rate to be less than 1%, although recent studies have found this to be an underestimate.[51,104,105]

Diagnosis

Laboratory findings may reveal leukocytosis with polymorphonuclear leukocyte predominance and pleocytosis in CSF (either neutrophilic or lymphocytic predominance), although studies of laboratory values for LAC and non-LAC cases show no statistically significant differences.[109] More than one-half of patients have abnormal electroencephalographic findings. A CT scan may show nonspecific cerebral edema, if there are findings at all, and MRI may reveal gadolinium enhancement in cortical areas.[154]

The definitive diagnosis is made with IgM antibody by capture immunoassay of CSF, a fourfold rise in serum antibody titers against LAC virus, or isolation of virus from or demonstration of viral antigen or genomic sequences in tissue, blood, or CSF.[40] As in almost all other viral infections discussed in this chapter, IgM antibody capture with ELISA is the most common method, with the recommendation to confirm IgG antibody with another serologic assay such as a neutralization test.

Treatment and Prevention

No specific treatment is available besides neuroprotective measures to control cerebral edema and seizures. Certain studies have looked at ribavirin, but there is no strong evidence to recommend its use.[156] No vaccine is available against this virus.

ROSS RIVER VIRUS

A mosquito-borne alphavirus in the family Togaviridae, Ross River virus (RRV) is a single-stranded, enveloped RNA virus in the same family as Chikungunya, Sindbis, and eastern and western equine encephalitis. The virus is endemic and enzootic in Australia and Papua New Guinea and causes Ross River virus disease, formerly referred to as epidemic polyarthritis.[112] RRV is the most common human arboviral disease in Australia, and although it is not fatal, it causes significant disability. It has been documented to occur in all Australian states, with the vast majority of cases reported in Queensland, the northeast region of the country; however, the largest epidemic (1979-1980), causing more than 500,000 cases, spread to Fiji, Samoa, the Cook Islands, and New Caledonia.[1,15,81,190,226] It disappeared initially from these areas upon culmination of the epidemic, but new cases have reappeared in Fiji.[131]

Epidemiology and Transmission

The disease incidence peaks in middle age, with clinically apparent infection being rare in childhood. From 2001 to 2011, the mean annual incidence rate was 54 per 100,000 persons in Queensland, Australia.[259] The main vectors are *Culex* and *Aedes* (particularly *Aedes vigilax*) mosquitoes; marsupials, such as kangaroos and wallabies, are important as vertebrate-amplifying hosts.[192] However, many other vertebrates have been proposed as reservoir hosts.[112] Tropical coastal regions with salt marsh habitats are the primary habitats for the mosquito vector species, and infections follow a seasonal pattern, with a higher incidence correlated with warmer temperatures and increased rainfall.[118,259]

Clinical Presentation

After inoculation, the virus is thought to replicate within several cell types, including monocytes and macrophages, muscle cells, and periosteal cells.[221] Although the exact pathophysiology remains unclear, RRV likely produces a local cell-mediated immune response that appears to cause arthritis.[112,221] After an incubation of 7 to 9 days (or as long as 21 days), patients can present either with acute febrile illness with arthritis and rash; with acute fever, rash, or arthritis alone; with polyarthralgia; or with arthritis.[86] The joints involved are usually symmetric and include the wrists, knees, ankles, and metacarpophalangeal and interphalangeal joints of the hands, with true arthritis present in 40% of infected individuals.[110] About 50% have fever and a sparse maculopapular rash on the limbs and trunk that may occur before or after the arthritis.[86] Whereas fever may resolve within several days, the rash may persist for several months. Joint symptoms and fatigue, on the other hand, have been reported to last years, even after fever and rash have subsided.[209] However, recent literature suggests that patients with chronic symptoms may have additional underlying comorbidities, such as rheumatic disease or depression, because patients with RRV disease alone tend to recover within 6 months.[167,221]

Diagnosis

There are no laboratory findings specific for RRV infection. Patients often have normal leukocyte counts (although mild neutrophilia or atypical lymphocytes can be found) and possibly elevation in the nonspecific erythrocyte sedimentation rate. Joint aspiration may reveal viscous fluid with predominantly mononuclear cells, and indicates viral arthritis.[86]

Serum can be screened for IgM antibody against RRV IgM, which can then be confirmed by PRNT. False-positive results secondary to cross-reactivity with Barmah Forest virus, rubella virus, Q fever agents, or rheumatoid factor can occur, and both acute and convalescent samples should be collected.[15] These tests are available at only a few reference laboratories, including the CDC.[131] Viral culture and PCR are not commonly used for diagnosis of RRV infection due to the low levels and short duration of viremia.[15,112]

Treatment and Prevention

There is no specific treatment. Management of arthralgias and myalgias is with standard analgesic and nonsteroidal antiinflammatory drugs. There does not seem to be any direct association of death with RRV. As with other arboviral diseases, prevention depends on adequate mosquito control and avoiding mosquito bites. One recent prospective case control study showed that protective measures, such as mosquito coils, repellants, and

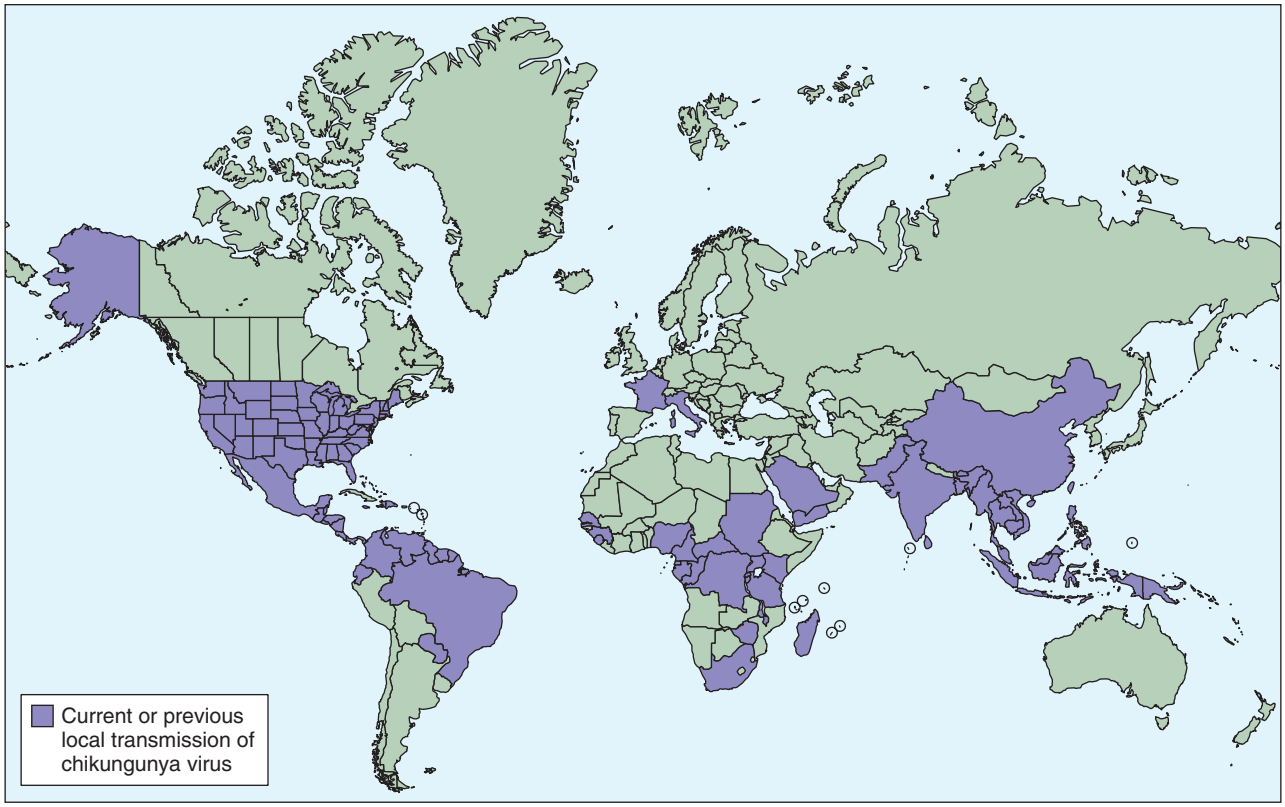


FIGURE 39-19 Geographic distribution of Chikungunya virus.

citronella candles, decreased the risk for RRV infection twofold, with a dose response for the number of protective measures used. Wearing light-colored clothing decreased the risk threefold. Camping during the 3 weeks before symptom onset increased the risk eightfold.[111]

Increasing research on the spatiotemporal patterns of RRV is helping to guide public health policy to anticipate, and hopefully prevent or mitigate, future outbreaks.[121,259] An inactivated whole-virus Vero cell culture–derived RRV vaccine has recently completed phase III trials. It was found to be safe and sufficiently immunogenic; however, efficacy was not demonstrated due to the low disease incidence. Therefore, even if the vaccine is licensed, further investigation will be needed to assess the efficacy and the need for booster immunizations.[255]

JAMESTOWN CANYON VIRUS

Jamestown Canyon virus is a California serogroup bunyavirus widely distributed throughout the United States and Canada. White-tailed deer, *Odocoileus virginianus,* are the principal vertebrate reservoirs, and boreal *Aedes* and *Ochlerotatus* mosquitoes are the primary vectors.[7,87,8] Documented human infections are scant, with only 15 reported cases in the United States between 2004 and 2011; the virus usually causes a mild febrile illness, and rarely meningitis and encephalitis.[56] The infection is difficult to distinguish from other California serogroup bunyaviruses, such as California encephalitis, snowshoe hare, Keystone, and trivittatus viruses, because of cross-reactivity in more common serologic tests and difficulty isolating the actual virus.[233] The virus has been posited as a possible emerging infectious disease,[153] but there have been few identified cases and literature on this subject is scant.

CHIKUNGUNYA VIRUS

Identified in Tanzania in 1952, Chikungunya virus is an RNA alphavirus from the family Togaviridae, spread by *Aedes aegypti* and *A. albopictus* mosquitoes. In the Bantu Makonde language, *chikungunya* means "that which bends up," likely a reference to the stooped appearance patients may develop due to debilitating joint pain caused by the virus.[189,249] Although historically a disease of Africa and Asia with only periodic outbreaks, Europe, the Caribbean, and Latin America have also been increasingly affected over the past decade.[145,164,218,249]

Epidemiology and Transmission

The virus occurs in about 40 countries worldwide, and despite relative dormancy for several decades, has more recently spread aggressively through the Indian subcontinent and southeast Asia, and into the Western Hemisphere[249] (Figure 39-19). A 2014 outbreak in Puerto Rico had a suspected case rate of 282 per 100,000 persons.[203]

Between 2010 and 2013, there were 115 laboratory-confirmed cases in the United States and more than 650,000 suspected cases throughout the Americas as a whole.[145] Although none of the 115 confirmed U.S. cases were locally acquired, autochthonous transmission was discovered in the Caribbean region in late 2013 and in Florida in 2014.[128] Between January and October of 2014, there were 272 imported cases and 11 locally acquired cases in Florida alone, with more than 1000 cases reported in the remainder of the continental United States.[128] Given the emerging threat, Chikungunya infection became a nationally notifiable condition in the United States in 2015.[61]

The majority of infected persons become symptomatic. The incubation period is 1 to 10 days; symptoms generally present 3 to 7 days after infection and always within 12 days.[60,182,229]

Clinical Presentation

Chikungunya presents similarly to dengue, with fever, malaise, and rash, so differentiating clinically between the two can be difficult.[203] Fever, arthralgias, myalgias, and headache are nearly universally present.[203] Arthralgias occur more commonly with Chikungunya infection, and myalgias are more common with dengue.[60,218,229] The rash is maculopapular, occurring on the extremities, trunk, and face; it has been reported to have an earlier onset with increased frequency in Chikungunya infection

compared with dengue. It occurs in roughly half of persons infected.[182,229]

Joint symptoms occur in up to 98% of patients, most often symmetrically and in distal joints such as the hands and ankles.[207,218] Almost half of infected persons exhibit swollen joints.[182,229] Polyarthritis is common, with involvement of more than four joints occurring more than 75% of the time.[208] Fever and other mild symptoms largely resolve within 1 to 2 weeks, but arthralgias and myalgias can persist for months to years.[182] There have been descriptions of chronic Chikungunya syndrome that is characterized by joint pain, fatigue, and neuritis. It occurs in up to 63% of infected persons. Persons older than 45 years and those with severe initial arthralgias or with rheumatologic comorbidities were at greatest risk.[150,207,208]

Severe complications of Chikungunya occur rarely. Roughly 2% of patients from the 2014 Puerto Rico outbreak suffered complications, which included jaundice, convulsions, effusions, encephalitis, and hepatomegaly.[203] In other recent epidemics, Guillain-Barré syndrome, acute flaccid paralysis, palsies, uveitis, and retinitis have been described.[218] Chikungunya carries a low mortality rate (0.4%), but infants and elderly persons often suffer increased rates of morbidity and mortality.[148] Severe presentations have been identified more commonly in recent outbreaks.[141]

Diagnosis

The clinical diagnosis may be difficult given the substantial overlap between the syndromes associated with Chikungunya and other arboviruses. Routine laboratory testing is nonspecific, but efforts have been made to identify differences between Chikungunya infection and dengue. A platelet count less than 100,000/mm^3 and any report of bleeding are predictive of dengue hemorrhagic fever.[140]

Laboratory diagnosis can be made with the use of multiple techniques, including serologic and virologic methods. Viral culture and RT-PCR can be used to isolate the virus in the acute phase of the disease, though IgM and IgG anti-Chikungunya antibodies can also be found within 5 to 8 days of symptom onset, respectively. Serum and nucleic acid amplification testing has also been shown to be highly sensitive and specific.[148]

Treatment and Prevention

There is neither a specific treatment nor a vaccine for Chikungunya virus.[31,164] Given the clinical overlap between Chikungunya and dengue, the CDC and WHO recommend that all suspected cases initially be treated as dengue while testing and observation are ongoing for warning signs of severe dengue.[203] Unlike dengue, prior exposure to the virus confers long-term immunity.[203] Because most symptoms are self-limited, supportive care is the mainstay of treatment. Acetaminophen is the first-line therapy for pain and fever reduction; NSAIDs and aspirin should be avoided if there is concern for dengue.[60] Several vaccine initiatives are under way, but none have successfully advanced past phase II testing. A virus-like particle–based vaccine was recently shown to be safe and immunogenic in phase I testing, creating a platform for future study.[69] Because humans are amplifying reservoirs, infected persons should ideally remain indoors to avoid infecting naïve mosquitoes and perpetuating an outbreak.[60]

ZIKA VIRUS

Zika virus is a single-stranded RNA flavivirus, similar to yellow fever, dengue, West Nile, and Japanese encephalitis viruses. Zika virus was first identified in rhesus monkeys in 1947 in the Zika Forest of Uganda.[76a] Rhesus monkeys and other similar primates continue to serve as the main nonhuman reservoir. Rodents in Pakistan have been shown to carry antibodies to Zika virus, suggesting that other reservoirs may exist.[72a] Human immunity was first detected in Nigeria in 1968. Since then, serologic evidence of Zika infection has been reported sporadically in Africa, Southeast Asia, and the Philippines.

The first epidemic of Zika virus infection was reported on Yap Island, Federated States of Micronesia, in 2007.[113a] Approximately 73% of Yap residents older than 3 years were infected during this epidemic; 80% of infected patients were asymptomatic.[77a] In 2013 a Zika virus epidemic accounted for approximately 19,000 cases in French Polynesia.[33a]

Thereafter, case reports traced the spread of the virus through the South Pacific to Easter Island, arriving in mainland Chile in 2014 and in Brazil by March 2015.[170a] By March 2016, Zika virus had spread to 33 countries in the Americas. The first case of Zika virus infection in the United States was reported on January 13, 2016 in a patient who had returned to Houston after traveling to Latin America.[80a] As of June 2016, there has been no local transmission in the United States.[64f]

Modes of Transmission

Zika virus is transmitted primarily by *Aedes* species of mosquitoes, particularly *Aedes africanus*, *A. aegypti*, and *A. albopictus*.[64e] Of note, these are the same vectors responsible for transmission of dengue and chikungunya viruses. Co-transmission with these viruses has been reported.[80a] Transmission from human mother to newborn during pregnancy has been confirmed, as has sexual transmission from male travelers returning from Zika-prevalent regions. Sexual transmission has occurred both while the male was symptomatic and prior to symptom development, and the virus has been detected in sperm.[176a]

Clinical Manifestations

Acute Illness. Approximately 20% of patients infected with Zika virus become symptomatic. Most patients with Zika virus infection have a mild, nonspecific, and self-limited acute illness. Manifestations include fever, maculopapular rash, arthralgias, conjunctivitis, myalgias, uveitis, and retroorbital pain. Most patients experience resolution of symptoms by 1 week. Very few require hospitalization, and death is rare.[64e] Cases of Guillain-Barré Syndrome have been reported following Zika virus infection; the exact frequency of this occurrence is unclear.[64b,64c]

Microcephaly. In November 2015 the Brazilian Ministry of Health reported an abrupt increase in the incidence of microcephaly, particularly in the northeastern state of Pernambuco. In 2014 there were 12 cases of microcephaly reported in Pernambuco. By October 2015, 268 cases had been reported that year. In all of Brazil, reported cases increased from 147 in 2014 to 399 in 2015.[156a] At the same time, the number of live births did not change significantly. This increase coincides with the arrival of Zika virus infection in Brazil (the first cases were reported in March 2015). This is an epidemiologic association and there is currently no direct proof of causality. However, Zika virus has been extracted from amniotic fluid of fetuses with diagnosed microcephaly,[169a] and from brain tissue in mice. Further, causation can be inferred on the basis of Shepard's criteria for proof of teratogenicity in humans and the Bradford Hill criteria for causation[185a] (Figure 39-20).

Testing

Zika virus infection is a nationally notifiable condition. Diagnostic tests for Zika virus are not commercially available. RT-PCR and IgM antibody assays are performed at the CDC Division of Vector-Borne Diseases Arbovirus Diagnostic Laboratory. Healthcare providers who suspect that a patient may be infected are expected to contact state health officials and the CDC.[64d] More information on how to access diagnostic services may be found at http://www.cdc.gov/zika/hc-providers/diagnostic.html.

Pregnant Mothers and Their Partners. The CDC recommends testing all pregnant women who have recently traveled to a Zika virus–endemic area if they develop two or more symptoms of acute infection (acute onset of fever, maculopapular rash, arthralgia, or conjunctivitis) during or within 2 weeks of travel. Asymptomatic pregnant women who have traveled to a Zika virus–endemic area should be offered testing within 2 to 12 weeks of return to the United States. Men who have traveled from an area with circulating Zika virus and who have a pregnant partner should abstain entirely from sexual intercourse or use condoms consistently for the remainder of the pregnancy. The virus has been found in saliva and urine, but

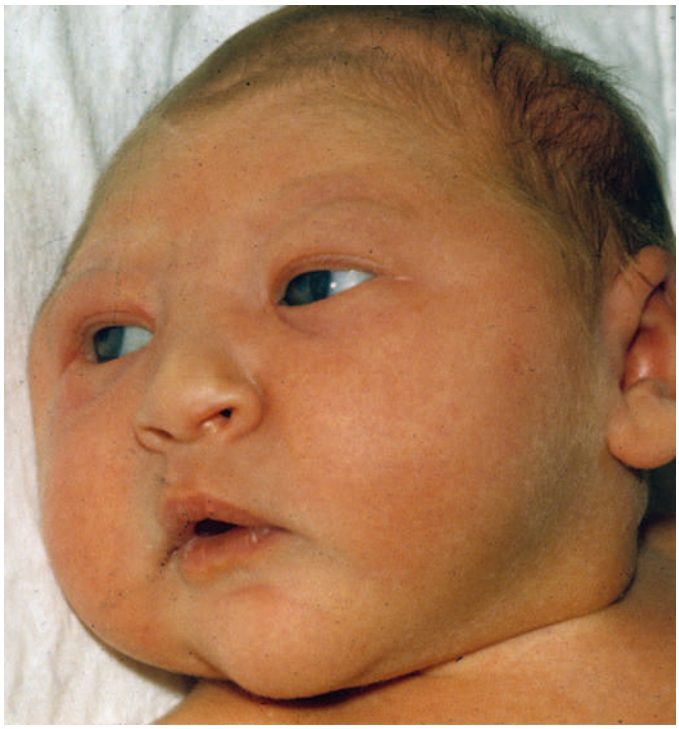


FIGURE 39-20 Microcephaly. An infant with microcephaly showing the typical normal-sized face and small neurocranium. This defect is usually associated with mental deficiency. Microcephaly has been associated in some early observations with Zika virus infection during pregnancy. *(Originally published in Moore KL, Persaud TVN, Torchia, MG. The Developing Human. Philadelphia, Elsevier, 2016, pp 79-416; Courtesy Chudley AE, MD, Section of Genetics and Metabolism, Department of Pediatrics and Child Health, Children's Hospital, University of Manitoba, Winnipeg, Manitoba, Canada.)*

the significance of this with regard to transmission has not yet been determined. All pregnant women who have ultrasound findings of fetal microcephaly or intracranial calcifications should also be tested. Testing is not indicated for women without a travel history to a Zika virus–endemic area. For pregnant women who have tested positive for Zika virus, serial ultrasounds should be performed.[64a]

Infants. The CDC currently recommends Zika virus testing for (1) infants with microcephaly or intracranial calcifications born to women who traveled to or resided in an area with Zika virus transmission while pregnant, and (2) infants born to mothers with positive or inconclusive test results for Zika virus infection.[64b]

Prevention and Treatment

No vaccine exists for Zika virus infection. Prevention centers on avoiding exposure. Travel to endemic areas should be avoided if possible, especially for pregnant women. It is highly recommended to avoid mosquito bites by wearing long sleeves and tucked pant legs, sleeping under a mosquito net, and using effective insect repellents.

There is no specific treatment for Zika virus disease. Fortunately, most acute infections are mild and self-limited. Treatment is supportive and includes hydration and antipyretics. Given the presence of dengue and chikungunya virus infections in areas where Zika virus is endemic, administration of nonsteroidal anti-inflammatory drugs should be avoided until dengue can be excluded, to avoid risk of hemorrhage.[64c]

Knowledge about all aspects of Zika virus and infection is rapidly being accumulated, so it is important for medical providers and the public to be aware of current information and recommendations.

MOSQUITO CONTROL

GENERAL GUIDELINES FOR INDIVIDUAL PROTECTION

For personal protection and prevention, individuals can take precautions, such as avoiding mosquitoes at their most active time (from dusk to dawn) and wearing loose-fitting cotton clothing covering their arms and legs (see Chapter 45). Individuals may also apply repellents to exposed areas of skin. The most effective preparations contain *N,N*-diethyl-3-methylbenzamide (DEET),[178] and concentrations need not exceed 20% to 35%.[85] DEET is safe in children older than 2 months of age and pregnant women.[63,134] However, it can rarely cause neurologic toxicity. Therefore, it should be kept away from mucous membranes and used sparingly to avoid systemic absorption. Studies have shown that a single application of a product containing 24% DEET confers an average of 5 hours (and up to 12 hours) of protection against *A. aegypti* mosquitoes. Compared with DEET, newer formulations containing the compound IR3535 fared poorly.[85] Picaridin (KBR 3023), a shorter-acting plant-derived repellent, is thought to be as effective as DEET and better tolerated.[13,126] Agents such as *p*-menthane-3,8-diol (PMD) and BioUD have not been evaluated as well but are thought to be less effective than DEET. Permethrin-containing compounds and other residual insecticides that kill rather than simply repel mosquitoes may be applied to clothing and netting. Other strategies include using mosquito coils and sprays containing pyrethroids in sleeping areas. Citronella has also been shown to be mildly effective in reducing the number of bites, but it requires frequent applications if used topically (as opposed to the candle form).[84] Current research in insect repellents involves sophisticated appreciation of the olfactory senses of mosquitoes and creation of proteins to inactivate human-specific odorants.[126,198]

GLOBAL ERADICATION PROGRAMS FOR MOSQUITOES

In general, global eradication programs for all infectious diseases, including mosquito vector surveillance and control, have declined dramatically in the past few decades. Because of the success of control programs in the 1970s and the resultant decreased public health threat, less attention has been paid to and fewer resources have been allocated to maintaining good control. One result is fewer trained personnel, because training programs are less well funded. The effect has been detrimental, with reversal of previous gains. In Central and South America, for example, dengue fever was largely eliminated with eradication of the *A. aegypti* mosquito in the 1950s and 1960s. However, because these programs were largely dismantled in the 1970s, the mosquito species has reinfested most of these tropical regions.[100]

Transmission prevention relies on a series of parallel approaches: vector control, disease surveillance, emergency preparedness, capacity building, and vector control research. Vector control has three arms: environmental management, biologic control, and chemical control.[88,132] Environmental management consists of monitoring and intervening to reduce the vector population, as well as transmission factors that sustain the human-vector-pathogen contact. For example, removing old tires, covering water storage containers with tight lids, keeping floor drains cleaned and covered, and chlorinating ornamental pools and fountains (or populating them with larvivorous fish) can help prevent mosquitoes from breeding.

Biologic control includes using organisms that naturally prey on the vector. For example, larvivorous fish and *Bacillus thuringiensis* H-14 are commonly used against larvae. Biologic control requires expense and time to raise these organisms, and may have limited success when the environment in which they are placed does not sustain their existence. A recent Cochrane review showed that in areas where a substantial proportion of larval habitats can be accessed, targeting larva can be effective at reducing transmission of mosquito-borne illness.[234]

Chemical control is the most well-known vector control. It consists of using products such as pyrethrins (e.g., deltamethrin,

TABLE 39-2 Insecticides and Cold-Spray Control of *Aedes aegypti*

Insecticide	Dosage (Grams of Active Ingredient per Hectare)
Organophosphates	
Malathion	112-693
Fenitrothion	250-300
Naled	56-280
Pirimiphos-methyl	230-330
Pyrethroids	
Deltamethrin	0.5-1
Resmethrin	2-4
Bioresmethrin	5
Permethrin	5
Cypermethrin	1-3
Lambda-cyhalothrin	1

From World Health Organization: Dengue haemorrhagic fever: diagnosis, treatment, prevention and control, ed 2, Geneva, 1997, World Health Organization.

resmethrin, permethrin) or organophosphate insecticides (e.g., fenthion, malathion, fenitrothion, temephos) (Table 39-2). These can be applied in several forms: larvicidal application, perifocal treatment, or space spraying. Larvicidal application is focal treatment to domestic water supplies that cannot be eliminated. For example, for *A. aegypti*, either 1% temephos or methoprene can be used to regulate larvicidal growth, or *Bacillus thuringiensis* H-14 can be used to safely treat drinking water. Insecticides, such as fenthion, malathion, and fenitrothion, can be used as perifocal treatment for nonpotable sources of water to eliminate larvae and adult mosquitoes. Finally, space spraying can be used against adult mosquitoes, often in emergency situations. The chemicals mentioned here can be used as aerosols or mists applied by portable machines, vehicle-mounted generators, or aircraft. Parameters for use (e.g., grams of active ingredient per hectare, wind conditions that may limit effectiveness) depend on the type of chemical, equipment, and target vector. Precautions must be taken seriously when using these products. When applying these chemicals, one must follow instructions on labels, use physical protection such as gloves and masks, and correctly dispose of chemicals.

Novel forms of vector control in development include genetic control and vulnerability mapping. Genetic control involves altering the genetic characteristics of an insect population to decrease the rate of arbovirus transmission.[4] More recently, some have advocated use of modeling tools, such as the Water Associated Disease Index, to map global dengue vulnerability. Accounting for environmental and social factors that affect disease exposure, susceptibility, and recovery ability, the Water Associated Disease Index may serve as a tool to model geographic areas that are especially vulnerable to dengue transmission. This could conceivably facilitate a more efficient, targeted approach to vector control.[88]

Integrated vector control programs that incorporate all methods, along with public education campaigns, are the most effective ways to control disease.[245] One study demonstrated success of a low-technology strategy for vector control involving community education and participation, as well as biologic control of mosquito larvae using *Mesocyclops* copepods. Although *A. aegypti* and dengue transmission were eliminated in 32 rural Vietnamese communities, it remains unclear and unlikely that such a strategy would be as effective in more urban or westernized areas.[107,127] Nevertheless, such integrated initiatives should also encourage vaccination, not only of humans but also of the animal reservoirs for which vaccines are available. This includes, for example, equine vaccinations against West Nile virus.

Recently, leading health organizations have been trying to reinstate vector and disease control, as can be seen by a short history of their efforts. In the 1950s, the WHO embarked on a mission to eradicate malaria. Despite some early success, by the mid-1970s, it was increasingly difficult to achieve the eradication goal for a number of reasons, including resistance to DDT and other insecticides. However, in 1998, the WHO, the United Nations Development Programme, the World Bank, and UNICEF established the Roll Back Malaria initiative, with a special focus on Africa. One arm of the campaign encouraged widespread use of antimalarial drugs in clinics and health centers. The other objectives were to plan and implement sustainable vector control. Experience has shown that pyrethroid-impregnated bed nets may be a better global strategy for eradicating disease, because this approach is less expensive than repeated spraying of household walls, reduces infections (and thus the human reservoir for infection in malaria), and is more effective in terms of horizontal implementation than is top-down, or vertical, programming.[25,242] Although source reduction through environmental management has been shown to be effective in some places, it is generally very difficult and may not be feasible everywhere.[204,236]

Resistance to insecticides is a problem. However, it is often a local phenomenon, so certain chemicals and insecticides should not be completely abandoned once reports of resistance are raised. For example, sampling sites only a few kilometers apart in Guatemala showed a large difference in resistance for *Anopheles albimanus* mosquitoes. Similarly, in the United States, resistance of *Culex* species to organophosphates is high in areas where vector control is well implemented, but lower in rural areas.[100]

The WHO has developed bioassays to determine resistance and keeps a database. This database, however, can be misleading because it is based on a single dataset from a single point in time that may be several years, or even decades, old and no longer relevant.[100] There are newer diagnostic methods to test resistance, including genetic linkage and physical maps, that may elucidate factors in vector competence.[29]

A further step is to detect and contain epidemics through epidemiologic surveillance and then to train personnel and build local capacity to sustain these efforts. Vector surveillance is of primary importance, not only to learn the geographic distribution and density of mosquito vectors and to evaluate control programs but also to predict and intervene to stop the advance of preventable diseases. For mosquitoes, indices have been created to study immature and adult populations (e.g., the "house index" [percentage of houses infected with larvae or pupae] and an index of adult mosquitoes' landing or biting rates per person-hour). Surveillance also includes verification of control measures, which includes periodically testing the vector's susceptibility to certain insecticides. Ongoing inspection of areas free of disease and taking measures to prevent reinfestation by vectors (e.g., removing standing water sources and environmental habitats, such as tires and cemetery vases) should be instituted. A list of references the WHO currently uses toward the goal of integrated vector management can be found at who.int/neglected_diseases/vector_ecology/ivm_concept/en/.

Many countries are committed to the idea of vector and disease surveillance (particularly aided by the work of organizations such as the PAHO, CDC, and WHO), but hundreds still fall short of pursuing these initiatives and are therefore ill prepared to effectively control disease. Concerted international efforts to collect accurate information and relay it in a timely fashion are the next herculean, but worthwhile, tasks.

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CHAPTER 40

Malaria

SHERAL S. PATEL*

Malaria is a major international health problem.[122] As global travel increases, malaria is found with greater frequency in areas where malaria is not endemic. Human malaria is transmitted by mosquitoes and caused by five species of parasitic protozoa: *Plasmodium falciparum, P. vivax, P. ovale, P. malariae,* and in parts of Southeast Asia, the agent of monkey malaria, *P. knowlesi.* Prevention of malaria infection through counseling, personal protective measures, and chemoprophylaxis can significantly reduce the risk of malaria morbidity in travelers. Because malaria infection can be life threatening, health care providers must be prepared to rapidly diagnose and manage this disease (Video 40-1).[122]

EPIDEMIOLOGY

Malaria is endemic throughout tropical areas and is usually transmitted to humans through the bite of female *Anopheles* mosquitos. Approximately 48% of the world's population (i.e., 3.2 billion people) live in malaria-endemic areas (Figure 40-1).[11,49,123] According to the World Health Organization (WHO), in 2013 there were an estimated 198 million cases (5th to 95th percentiles, 124 to 283 million cases) of malaria worldwide that resulted in an estimated 584,000 deaths (5th to 95th percentiles, 367,000 to 755,000 deaths).[123] The majority of cases (80%) occurred in Africa.[123] Most malaria-related deaths (90%) occurred in infants and children under 5 years of age in sub-Saharan Africa.[123]

P. falciparum and *P. vivax* are responsible for the majority of malaria cases and deaths.[46,45] *P. falciparum,* which predominates in Africa, is generally considered the most deadly form of malaria (Figure 40-2).[46] *P. vivax* has a wider distribution than *P. falciparum* owing to parasite characteristics that include ability to develop in *Anopheles* mosquito vectors at lower temperatures, ability to survive at higher altitudes and cooler climates, and a dormant liver stage (i.e., hypnozoite) that enables it to survive during periods (i.e., winter months) when *Anopheles* mosquitoes are not present to continue transmission (Figure 40-3).[45]

P. falciparum and *P. malariae* are found throughout malaria-endemic areas, including Latin America, sub-Saharan Africa, Asia, and the South Pacific. *P. vivax* is endemic in Latin America, Asia, and the South Pacific, but is uncommon in areas of sub-Saharan Africa. *P. falciparum* and *P. vivax* were historically endemic in temperate areas (e.g., North America and Europe) and transmission may still occur, if rarely, in these areas (Figure 40-4).[49] *P. ovale* infections occur in most malaria-endemic areas, especially in West Africa. *P. knowlesi*, the simian malaria parasite that can cause severe disease in humans, is found in Southeast Asia (Figure 40-5).[73,60]

Within endemic areas, variability in transmission is influenced by season, altitude, and type of travel. For example, the risk of acquiring malaria is lower for a business traveler to a Southeast Asian city staying in an air-conditioned hotel than for a backpacker hiking and sleeping in tents in East Africa.

Rates of malaria among U.S. civilians have been rising as travel to malaria-endemic areas increases.[29] In 2012, there were 1687 cases of malaria in the United States reported to the U.S. Centers for Disease Control and Prevention (CDC).[29] The majority were imported (1536 cases) from malaria-endemic areas of Africa (79%) and Asia (13%).[29] Of the 1399 cases with species reported, the majority identified were *P. falciparum* (70%) and *P. vivax* (20%).[29] Transmission may occur in temperate areas where *Anopheles* mosquitoes are present.[38,74,98]

Parasite resistance to antimalarials has been increasing.[11,34,84,123,124] *P. falciparum* resistance has been described to numerous antimalarials, such as mefloquine, pyrimethamine-sulfadoxine, halofantrine, and artemether.[11,123] Pyrimethamine-sulfadoxine resistance is common throughout Africa. Mefloquine resistance has been demonstrated in Burma (Myanmar), Thailand, Cambodia, Vietnam, and China.[11,123] In Southeast Asia, artemether resistance and partial resistance of *P. falciparum* to quinine and quinidine have also been reported (Figure 40-6).[123] Chloroquine-resistant *P. vivax* has been reported in Indonesia, Papua New Guinea, the Solomon Islands, Vanuatu, Myanmar, India, Brazil, and Guyana.[11,123] Chloroquine-resistant *P. malariae* has been described in Sumatra.[64]

Genetic changes that alter human red blood cells occur in populations living in areas where malaria has historically been endemic. These polymorphisms likely have arisen due to selective pressure from malaria deaths. Sickle cell disease, thalassemia, glucose-6-phosphate dehydrogenase (G6PD) deficiency, and Southeast Asian ovalocytosis (including Gerbich negativity) have all been suggested to confer protection from death due to falciparum malaria.[79,102,109,105] In sub-Saharan Africa, the risk of *P. vivax* infection, which requires Duffy antigen as a receptor for invasion, is considerably reduced by a high frequency of the Duffy negativity trait, leading to absolute protection against *P. vivax* (see Figure 40-3).[45,72]

MALARIA PARASITE

The malaria parasite is an intraerythrocytic protozoan of *Plasmodium* genus. *Plasmodium* species infect mammals, birds, and reptiles. As noted above, the five species that typically infect humans include *P. falciparum, P. vivax, P. ovale, P. malariae,* and the simian parasite *P. knowlesi.*[28]

MOSQUITO VECTOR

Female Anopheline mosquitoes are the arthropod vectors for the malaria parasite (Figure 40-7).[19] Of approximately 430 *Anopheles* species, only 30 to 40 transmit malaria.[61] These include *A. gambiae, A. funestus,* and *A. arabiensis* in Africa; the *A. punctulatus* group in Papua New Guinea; *A. culicifacies* in India; *A. darlingi* in South America; and *A. quadrimaculatus* in North America (Figures 40-8 to 40-13).[61,95] The female mosquito's proboscis pierces the skin to obtain a blood meal necessary to produce eggs. Distinguishing features of *Anopheles* mosquitoes include sensory palps that are as long as the proboscis and wings, with discrete blocks of black and white scales (Figure 40-14).[17] Unlike *Aedes* species (vectors for dengue) that rest with abdomens parallel to the surface upon which they are resting, *Anopheles* mosquitoes rest with their abdomens sticking up in the air (see Figure 40-7).[19]

LIFE CYCLE

Malaria parasite life cycles involve both vertebrate and arthropod hosts (Figure 40-15, Videos 40-2 to 40-4).[30,51,52,108] In the mosquito, the asexual haploid form of the malaria parasite is the sporozoite. Eight to twelve sporozoites may be transmitted through each bite of a nocturnal-feeding female *Anopheles* mosquito (see Figure 40-7). Sporozoites migrate through the bloodstream to the liver,

Text continued on p. 900

*This chapter reflects the views of the author and should not be construed to represent the U.S. FDA's views or policies.

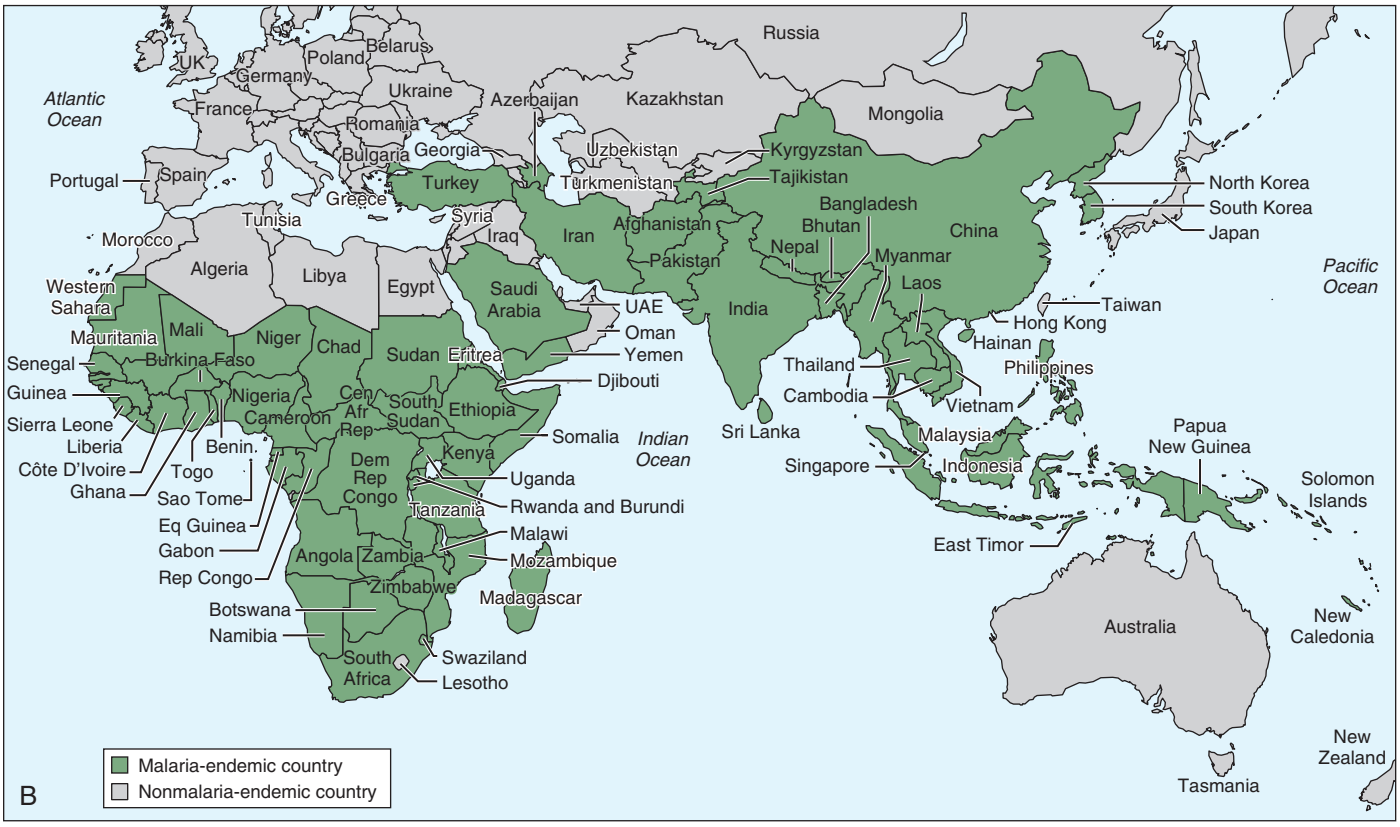


FIGURE 40-1 **A,** Malaria-endemic countries in the Western Hemisphere. **B,** Malaria-endemic countries in the Eastern Hemisphere. *(From Centers for Disease Control and Prevention:* CDC health information for international travel 2014: The yellow book, *New York, 2014, Oxford University Press.* **A** *from Map 3-09;* **B** *from Map 3-10.)*

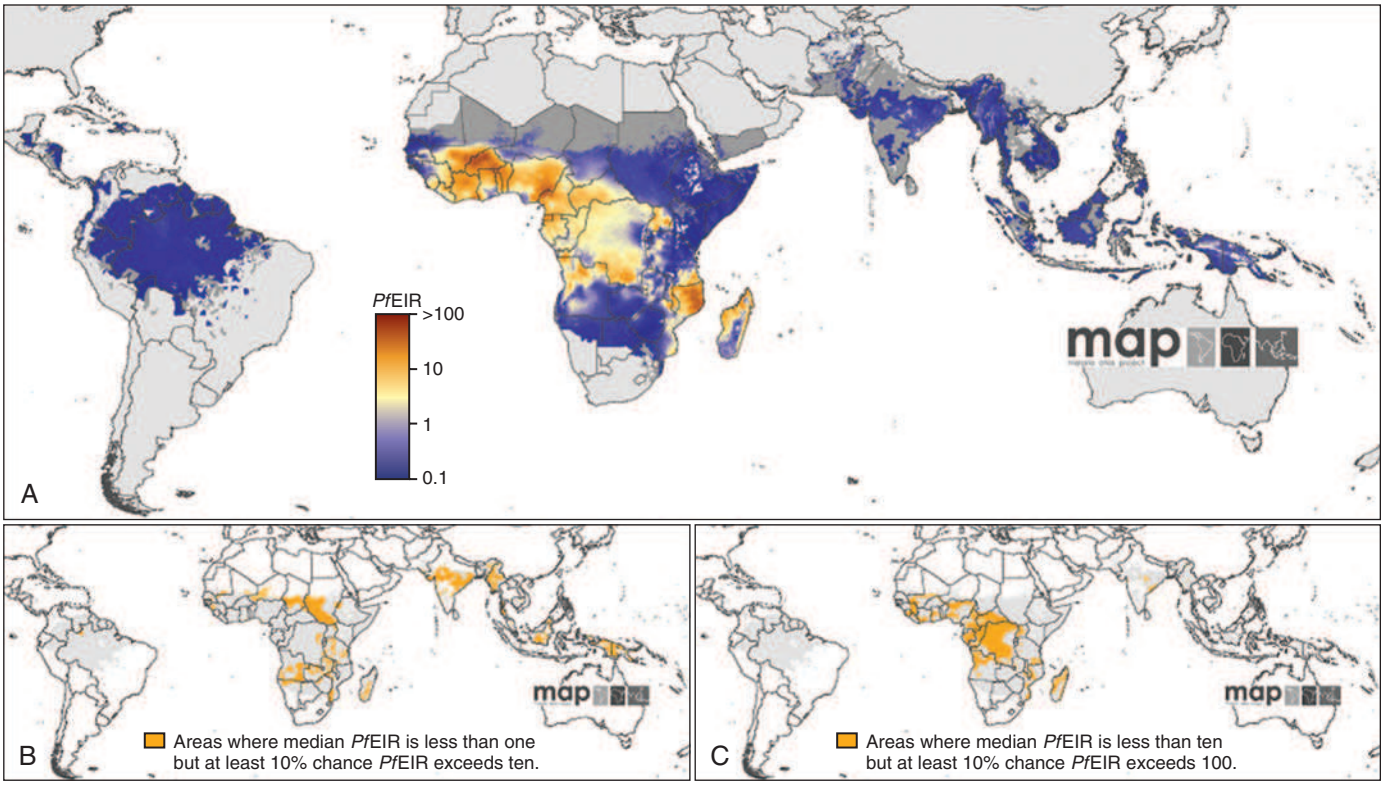


FIGURE 40-2 Spatial distribution of *Plasmodium falciparum* entomological inoculation rate (*Pf*EIR) in 2010. **A,** The point estimate (posterior median) *Pf*EIR prediction for each pixel within the stable limits of transmission in 2010. The color scale is logarithmic to allow better differentiation across heavily positively skewed distribution of values. Areas of unstable transmission (medium grey areas, where *Pf*API < 0.1 per 1000 pa) or no risk (light grey, where *Pf*API = 0 per 1000 pa) are also demarked. **B** and **C,** Two indicators of uncertainty associated with the predictions, showing areas with a median prediction less than 1 or less than 10, but where the 90th percentile is at least an order of magnitude larger. *(From Gething PW, Patil AP, Smith DL, et al:* A new world malaria map: Plasmodium falciparum endemicity in 2010. *Malar J 2011;10:378.)*

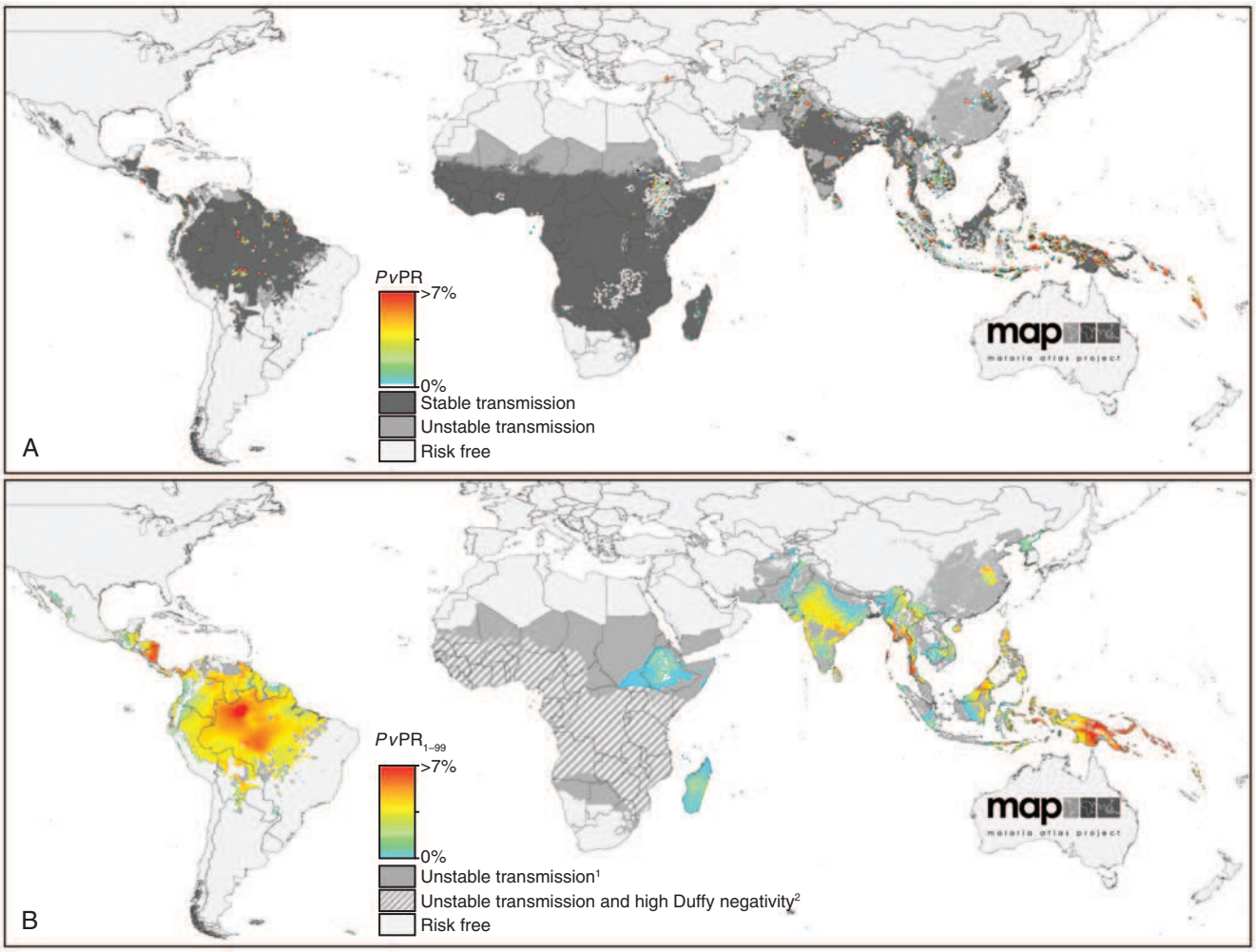


FIGURE 40-3 **A,** 2010 spatial limits of *P. vivax* malaria risk defined by *Pv*API with further medical intelligence, temperature, and aridity masks. Areas were defined as stable (*dark grey areas,* where *Pv*API ≥ 0.1 per 1000 pa), unstable (*medium grey areas,* where *Pv*API < 0.1 per 1000 pa), or no risk (*light grey areas,* where *Pv*API = 0 per 1000 pa). Community surveys of *P. vivax* prevalence conducted between January 1985 and June 2010 are plotted. Survey data are presented as a continuum of light green to red (see map legend), with zero-valued surveys shown in white. **B,** MBG point estimates of annual mean $PvPR_{1–99}$ for 2010 within spatial limits of stable *P. vivax* malaria transmission, displayed on the same color scale. Areas within stable limits in (**A**) that were predicted with high certainty (>0.9) to have a $PvPR_{1–99}$ less than 1% were classified as unstable. Areas in which Duffy negativity gene frequency is predicted to exceed 90% are shown in *hatching* for additional context. *(From Gething PW, Elyazar IR, Moyes CL, et al:* A long neglected world malaria map: Plasmodium vivax endemicity in 2010. *PLoS Negl Trop Dis 2012;6:e1814.)*

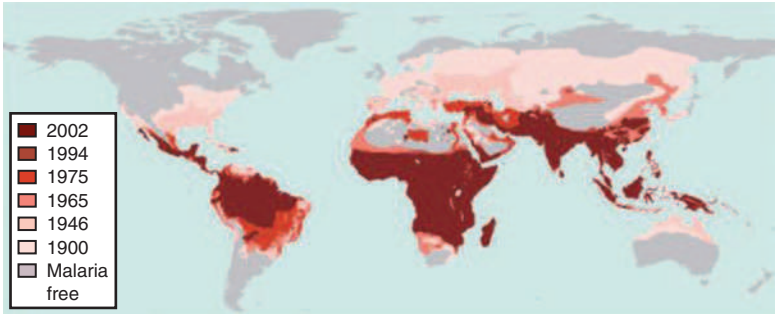


FIGURE 40-4 Global distribution of malaria since preintervention (circa 1900 to 2002). All-cause malaria distribution maps for preintervention distribution (circa 1900) and for years 1946, 1965, 1975, 1992, 1994, and 2002 were georeferenced using ERDAS Imagine 8.5 (Leica Geosystems GIS & Mapping, Atlanta, GA, USA). Maps were then digitized on-screen with MapInfo Professional 7.0 (MapInfo Corp, NY, USA). Areas of high and low risk were merged throughout to establish all-cause malaria transmission limits. The only modification of original maps was to infill areas on the 1975 map labelled as unknown in China with distribution data recorded in 1965. Each map was then overlaid to create a single global distribution map of malaria risk that illustrates range changes through time. 1992 and 1994 distributions are very similar, so 1992 distribution is excluded for clarity. *(From Hay SI, Guerra CA, Tatem AJ, et al:* The global distribution and population at risk of malaria: past, present, and future. *Lancet Infect Dis 2004;4:327-336.)*

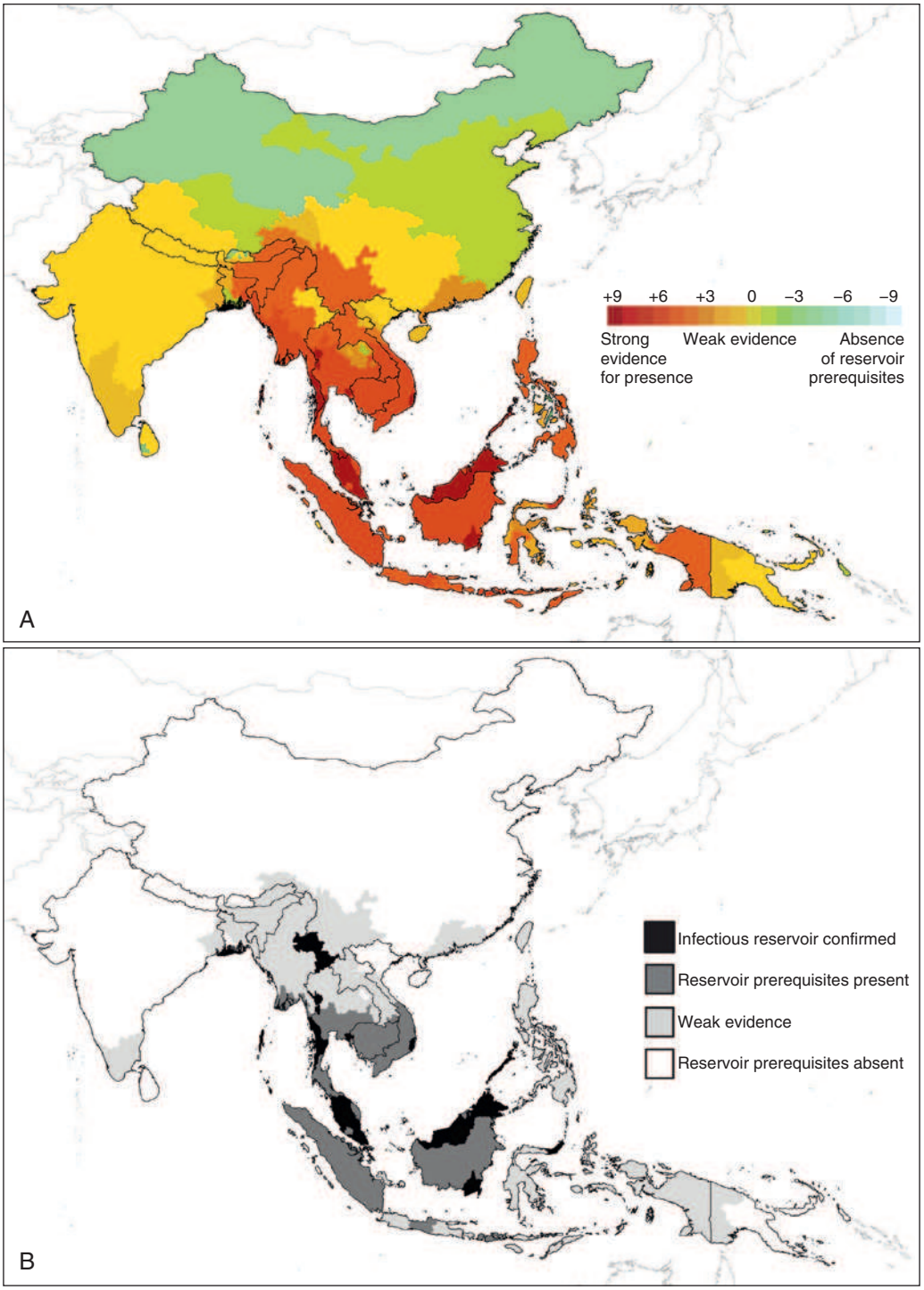
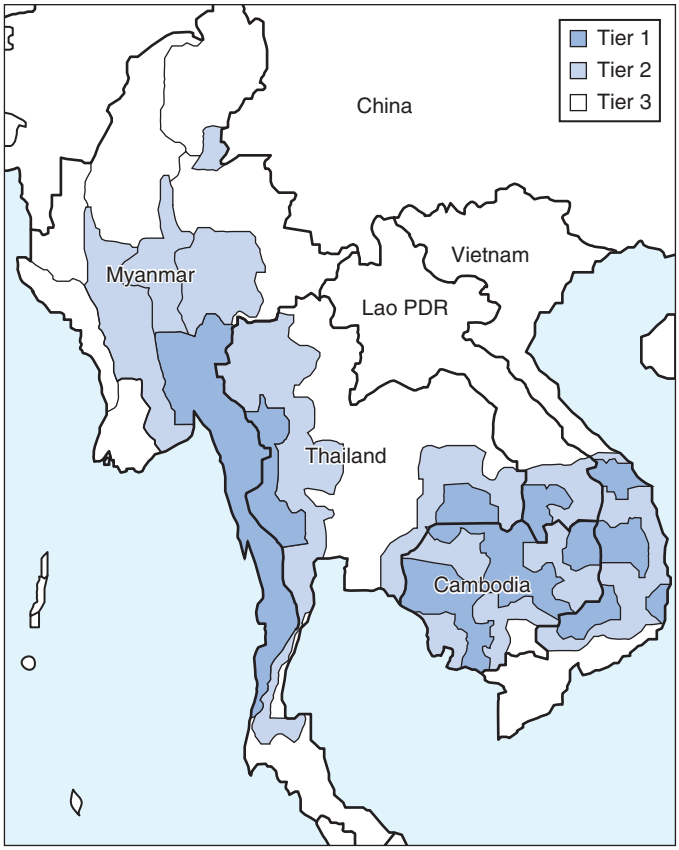


FIGURE 40-5 **A,** Evidence scores for locations that range from strong evidence for presence of a parasite reservoir infecting humans, to weak evidence, to absence of host and vector species (i.e., indicating that an infectious reservoir would not be supported). **B,** The same scores grouped into four classes. *(From Moyes CL, Henry AJ, Golding N, et al:* Defining the geographical range of the Plasmodium knowlesi reservoir. *PLoS Negl Trop Dis 2014;8:e2780.)*



Tier 1 are areas where there is credible evidence of artemisinin resistance;

Tier 2 are areas with significant inflows of people from Tier 1 areas, including those immediately bordering Tier 1;

Tier 3 are areas with no evidence of artemisinin resistance and limited contact with Tier 1 areas

PDR, People's Democratic Republic

FIGURE 40-6 Areas or tiers of differing risks of artemisinin resistance, Southeast Asia, December 2014. *(From World Health Organization: World Malaria Report 2014.)*

FIGURE 40-7 Female *Anopheles gambiae* mosquito feeding. Distinguishing features include sensory palps that are as long as the proboscis, and discrete blocks of black and white scales on wings. Both male and female *Anopheles* mosquitoes rest with their abdomens sticking up in the air. *(From the Centers for Disease Control and Prevention: Public Health Image Library. phil.cdc.gov/phil/home.asp. Left, image no. 1665; right, image no. 1664. Courtesy Dr. Jim Gathany and the Centers for Disease Control and Prevention.)*

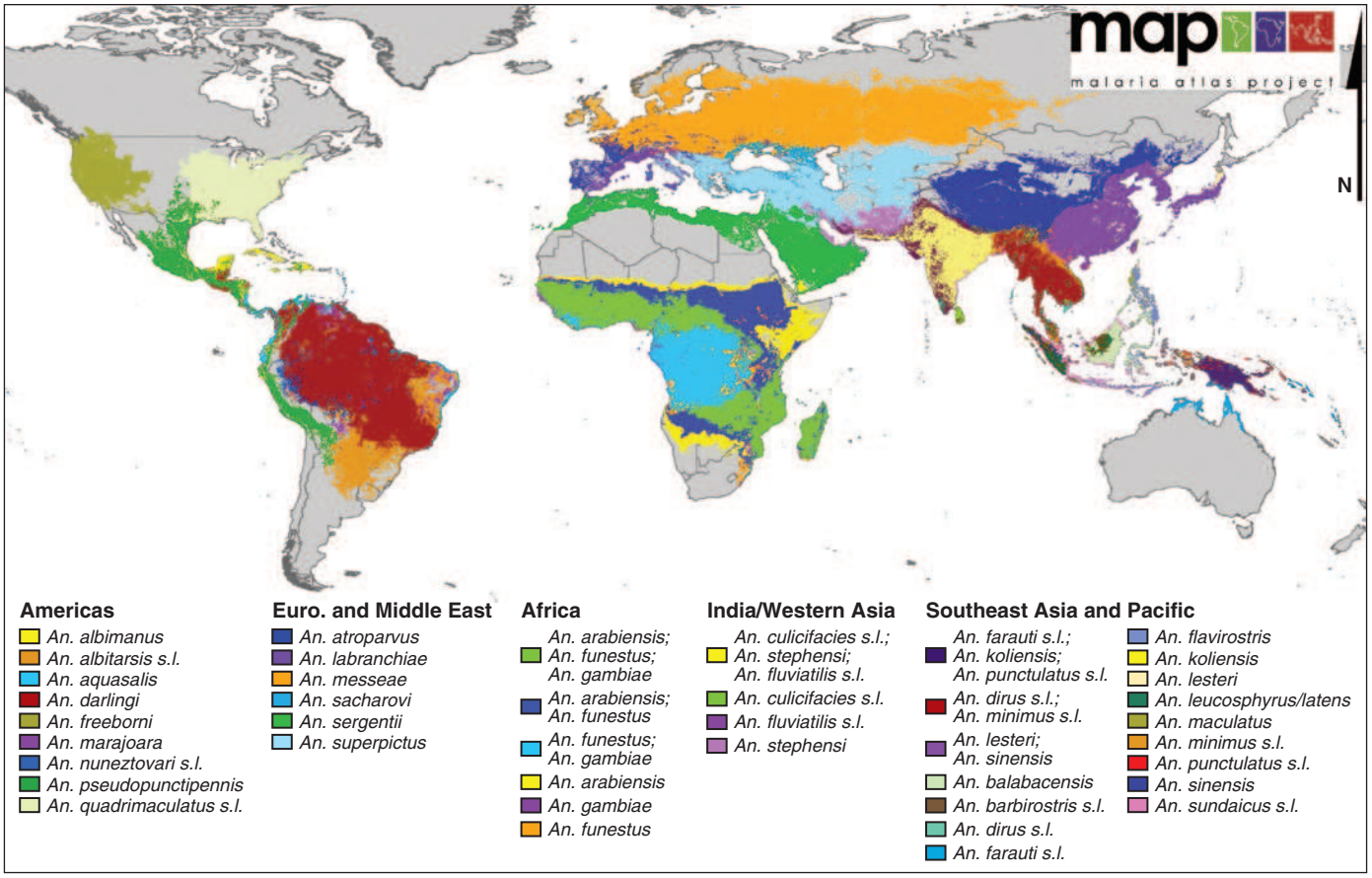


FIGURE 40-8 Global map of dominant malaria vector species. *(From Sinka ME, Bangs MJ, Manguin S, et al:* A global map of dominant malaria vectors. *Parasit Vectors 2012;5:69.)*

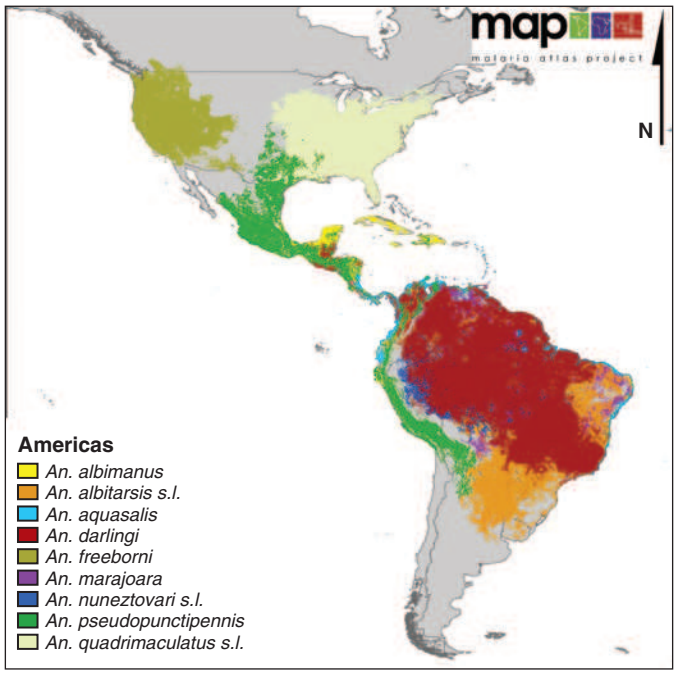


FIGURE 40-9 Regional map showing nine dominant vector species in the Americas. *(From Sinka ME, Bangs MJ, Manguin S, et al:* A global map of dominant malaria vectors. *Parasit Vectors 2012;5:69.)*

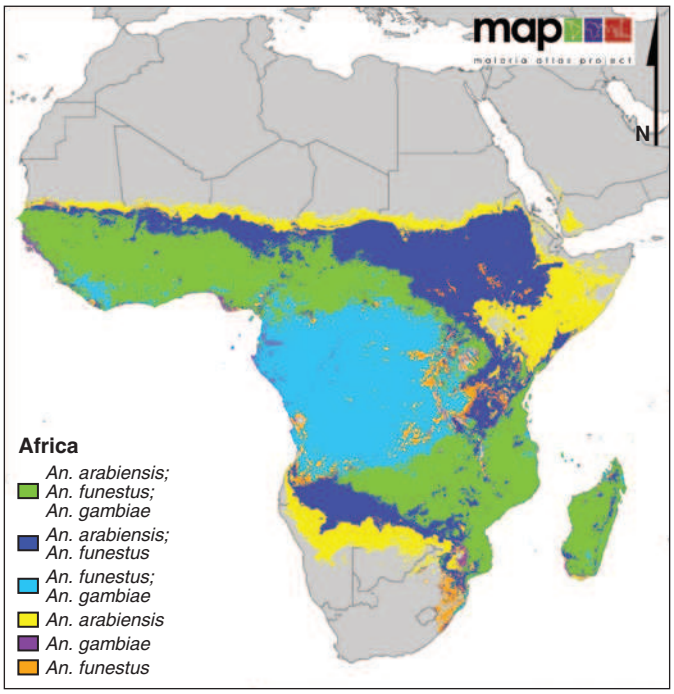


FIGURE 40-10 Regional map showing the three most dominant vector species in Africa. *(From Sinka ME, Bangs MJ, Manguin S, et al:* A global map of dominant malaria vectors. *Parasit Vectors 2012;5:69.)*

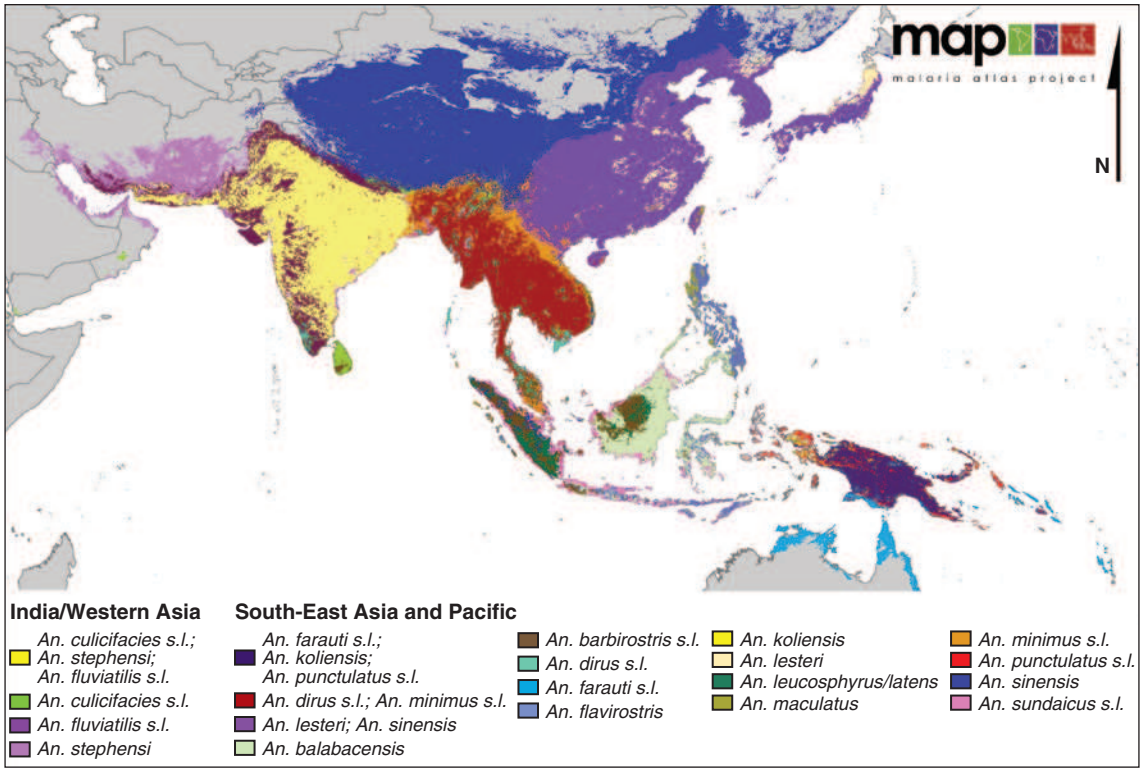


FIGURE 40-11 Regional map showing 16 dominant vector species in the Asia-Pacific region. *(From Sinka ME, Bangs MJ, Manguin S, et al:* A global map of dominant malaria vectors. *Parasit Vectors 2012;5:69.)*

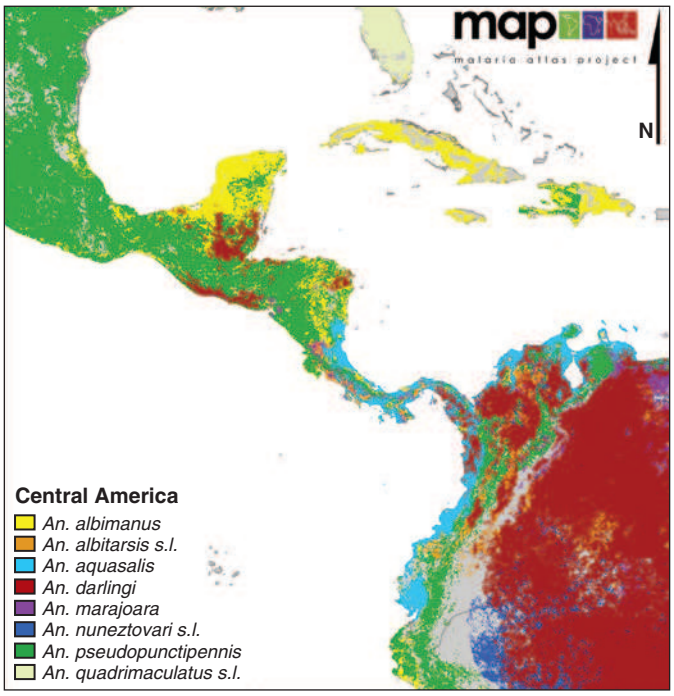


FIGURE 40-12 Closer view of the eight dominant vector species in Central America and northern regions of South America. *(From Sinka ME, Bangs MJ, Manguin S, et al:* A global map of dominant malaria vectors. *Parasit Vectors 2012;5:69.)*

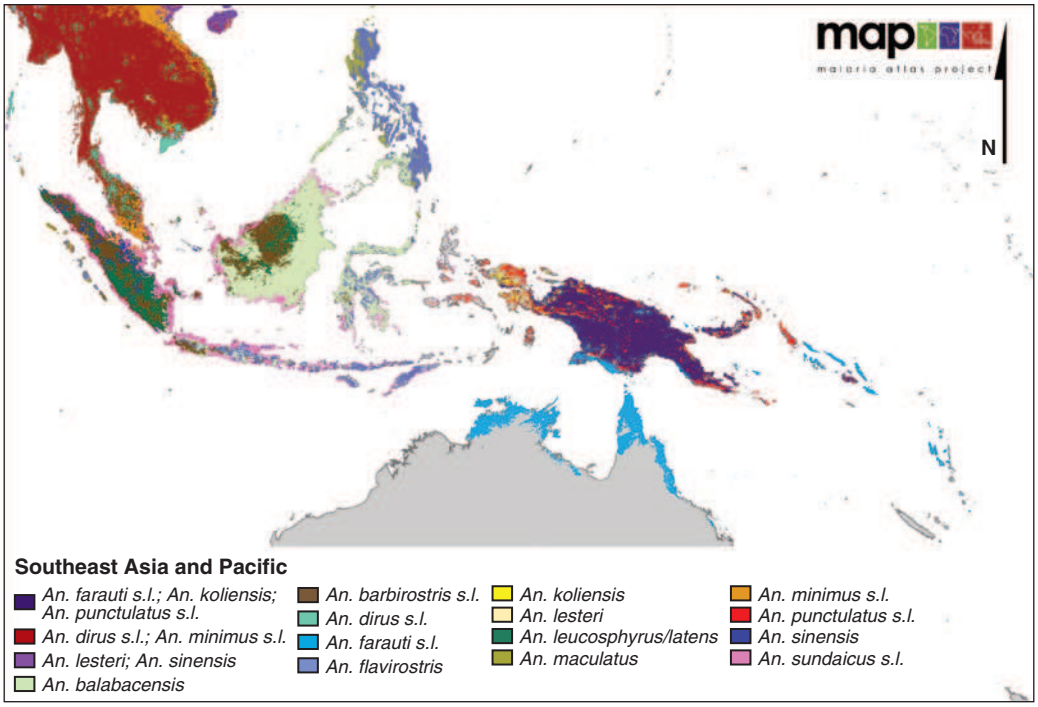


FIGURE 40-13 Closer view of complexity and diversity of dominant vector species in Southeast Asia and on Pacific Islands. *(From Sinka ME, Bangs MJ, Manguin S, et al:* A global map of dominant malaria vectors. *Parasit Vectors. 2012;5:69.)*

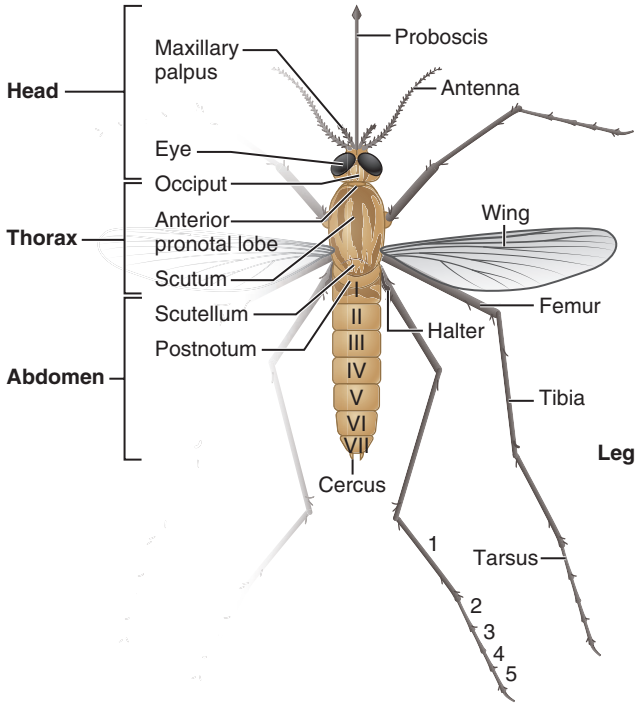


FIGURE 40-14 Diagram of female adult *Anopheles* mosquito. *(From Centers for Disease Control and Prevention. Diagram of female adult mosquito. 11-9-2012.* cdc.gov/malaria/about/biology/mosquitoes/female_diagram.html.*)*

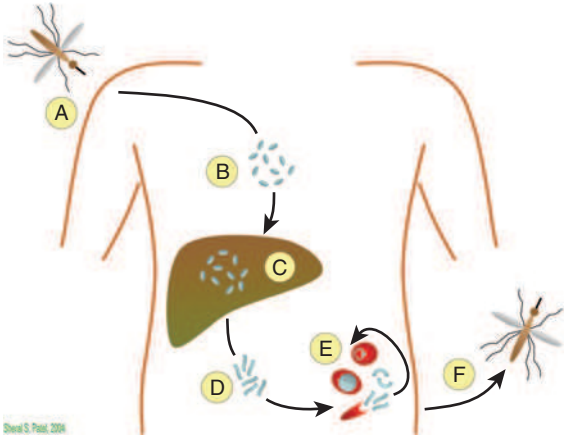


FIGURE 40-15 Malarial parasite life cycle. During the cycle, sporozoites are transmitted through the bite of a nocturnal-feeding female *Anopheles* mosquito *(A)*. Sporozoites migrate to the liver *(B)* and mature to merozoites *(C)*. A subset of *P. vivax* and *P. ovale* parasites remains dormant as hypnozoites only, to emerge months to years after initial infection to cause disease. Eight to 25 days after initial infection, 10,000 to 30,000 merozoites are released to invade erythrocytes *(D)*. Asexual parasites mature in 48 to 72 hours, each releasing 6 to 24 merozoites to invade more erythrocytes *(E)*. Some parasites develop into gametocytes (sexual stages), which may be taken up during a mosquito blood meal. Diploid zygotes form ookinetes and develop into haploid sporozoites *(F)*. Sporozoites migrate to mosquito salivary glands and continue their life cycle in humans with the next blood meal. *(Courtesy Sheral S. Patel, with permission.)*

where they mature. Each sporozoite produces 10,000 to 30,000 merozoites. Merozoites are released into the bloodstream 8 to 25 days later and invade circulating erythrocytes (see Figure 40-15).[42] Some *P. vivax* and *P. ovale* parasites may remain dormant in the liver (i.e., hypnozoites) and emerge as merozoites to establish blood-stage infection months to years after initial inoculation.[106] Merozoites enter red blood cells through specific ligand-erythrocyte receptor interactions, many of which are undefined. *P. falciparum* has several invasion pathways (e.g., glycophorins A and C); *P. vivax* depends solely on Duffy antigen for erythrocyte invasion.[65,72,79,80,126] Within red blood cells, asexual parasites consume hemoglobin and enlarge from ring forms to become trophozoites and then schizonts. As schizonts mature through multiple nuclear divisions, red blood cells burst and release 6 to 24 merozoites to invade additional circulating erythrocytes.[96] The asexual blood-stage cycle takes approximately 24 hours for *P. knowlesi*, 48 hours for *P. falciparum, P. vivax,* and *P. ovale,* and 72 hours for *P. malariae.*[108] With each cycle, the parasite population multiplies by 6 to 20 times.[92] Some parasites develop into gametocytes (which is the sexual stage). Gametocytes in the bloodstream can infect mosquitoes if ingested. After being ingested by an *Anopheles* mosquito, diploid zygotes are formed. In the mosquito midgut, zygotes mature into ookinetes.[7] Resulting oocysts expand through meiotic reduction division within 7 to 10 days and release sporozoites that localize through hemolymph to mosquito salivary glands.[7] Sporozoites may subsequently be transmitted to a human host during the next blood meal.

RECURRENT AND PERSISTENT INFECTIONS

Recurrent malaria infection can occur in several ways. Relapses from *P. vivax* or *P. ovale* can occur when dormant hypnozoites mature and release merozoites to produce blood-stage infections (Figure 40-16). Incomplete treatment or a partially effective host immune response can lead to low-concentration parasitemia and may result in recrudescence of blood-stage infections. Relapse and recrudescence are caused by the parasite clone that was responsible for the initial infection. The region where *P. vivax* infection was acquired may influence time to relapse (Figure 40-17).[106] In tropical regions, *P. vivax* relapses can occur every 3 to 4 weeks, or every 6 to 8 weeks after treatment with a slowly eliminated drug (Figure 40-18).[106] In temperate regions, *P. vivax* relapses can occur 8 to 10 months after primary infection.[106] Recrudescence can occur with any malarial species, but is most common with *P. falciparum* because of antimalarial resistance. In areas of intense transmission, simultaneous infection or reinfection with multiple parasite species or strains can occur. *P. malariae* is frequently associated with persistent infections that can remain in the bloodstream at undetectable levels for up to 20 to 30 years.

OTHER MODES OF TRANSMISSION

Natural transmission of malaria occurs through the bite of a female *Anopheles* mosquito. Blood-stage infection can also be established by transfusions of blood or blood products, organ transplantation, or sharing contaminated needles or syringes.[29,62,63,86,88,90] Congenital malaria occurs when mothers are infected during gestation.[1,47,94] When diagnosis is made in neonates 2 to 3 weeks after birth, it may be difficult to distinguish congenital malaria from natural mosquito-borne transmission.

CLINICAL MANIFESTATIONS AND PATHOGENESIS

SUSCEPTIBLE POPULATIONS

Clinically, malaria presents with variable and nonspecific signs and symptoms that may range from asymptomatic parasitemia to severe disease and death. Individuals living in areas that are heavily endemic for *P. falciparum* develop partial immunity through repeated malarial infections and rarely experience

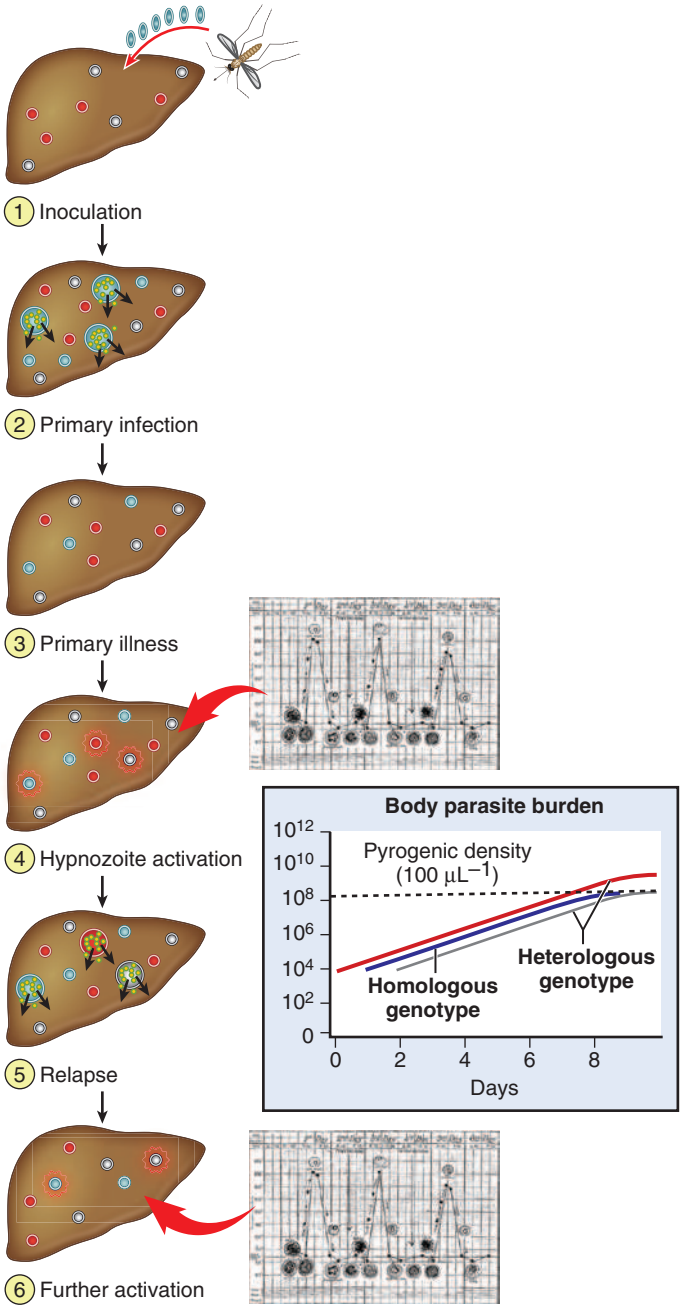


FIGURE 40-16 Proposed mechanism and sequence of *Plasmodium vivax* relapse activation in a malaria endemic area. In an illustrated example, at the time of infection (sporozoite inoculation), the individual already has hypnozoites of two different genotypes acquired from two previous inoculations that are latent in the liver. Different genotypes are denoted by different colors *(red and white)*. Half of the newly acquired infection sporozoites *(blue)* develop into preerythrocytic schizonts and half become dormant as hypnozoites (estimated proportions for tropical "strains"). Illness associated with blood stage infection activates a small fraction of hypnozoites (inset shows a "classic" *P. vivax* fever pattern in relation to asexual parasite development). In this example, there is one hypnozoite of each genotype, and each is activated by illness and each develops into a preerythrocytic schizont. By chance, progeny of one of the preexisting latent hypnozoites reach pyrogenic densities before progeny of recently inoculated hypnozoites. The inset shows logarithmic growth of three genotypically different infections. The vertical axis shows the number of parasites in the body. The consequent febrile illness then suppresses further multiplication of blood stage infection so that progeny of the other two preerythrocytic schizonts may not reach transmissible densities. The ensuing illness activates some remaining hypnozoites (the same fraction as were activated initially), and relapses continue until either the number of hypnozoites is exhausted or some fail to be activated. If some hypnozoites fail to be activated, they may be activated at a later date by a subsequent malaria infection. *(From White NJ:* Determinants of relapse periodicity in Plasmodium vivax malaria. *Malar J 2011;10:297.)*

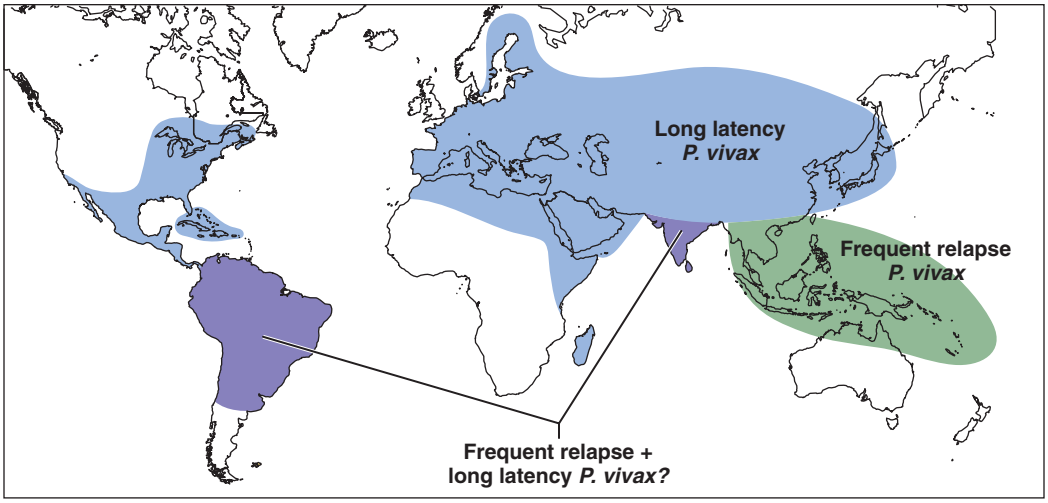


FIGURE 40-17 The areas where tropical "frequent relapse phenotypes" are prevalent are shown in *green*. The areas where both frequent relapse and long-latency phenotypes have been reported are shown in *purple,* and areas where long-latency phenotypes were prevalent are shown in *blue*. Although both South America and India are generally considered to predominantly harbor frequent relapse phenotypes, there is evidence that long-latency phenotypes are present in both areas (particularly across northern India). Without genotyping, it may be difficult or impossible to distinguish two phenotypes within an endemic area. *(From White NJ:* Determinants of relapse periodicity in Plasmodium vivax malaria. *Malar J 2011;10:297.)*

serious complications after childhood. In areas where malaria endemicity is low, malaria can affect both adults and children. Nonimmune individuals (e.g., travelers and immigrants from non-endemic areas, children from age 6 months to 5 years who are living in endemic areas, and pregnant women) are at risk for severe disease and complications, especially with *P. falciparum* infection.[91]

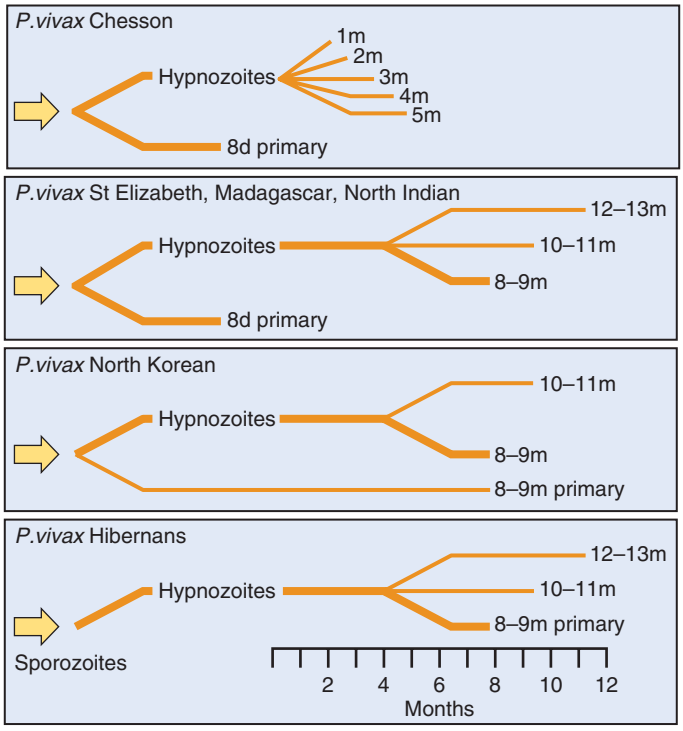


FIGURE 40-18 Schematic diagram by Hankey and colleagues of relapse patterns following Korean vivax malaria and tropical frequent relapse *P. vivax*. Note frequent relapse pattern after a long interval with Korean vivax malaria. *(From White NJ;* Determinants of relapse periodicity in Plasmodium vivax malaria. *Malar J 2011;10:297.)*

MAJOR CLINICAL FINDINGS

Clinical symptoms of malaria can develop as soon as 7 days after travel in an area endemic for malaria. Most individuals who are diagnosed in the United States experience an onset of signs and symptoms after they return to the United States.[29] Infections can develop as late as several months after exposure. Fever in a traveler who has returned from a malaria-endemic area within the previous 3 months should be evaluated urgently. Malaria, especially *P. falciparum,* is a medical emergency in a returned traveler. Rapid clinical deterioration can occur. Severe malaria can mimic other diseases (e.g., meningitis, typhoid fever, dengue, hepatitis) also common in malaria-endemic countries.[37]

The classic malarial paroxysm (i.e., high fevers, chills, rigors, sweats, and headache) results from red blood cell lysis and release of merozoites at completion of intraerythrocytic asexual reproduction (Table 40-1).[91] Paroxysms can recur in a cyclic pattern (every 48 hours with *P. vivax* and *P. ovale,* and every 72 hours with *P. malariae*). Although *P. falciparum* has a 48-hour asexual erythrocytic cycle, fever and chills typically occur without periodicity because erythrocyte lysis is not synchronized. Similarly, *P. knowlesi* has a 24-hour asexual erythrocytic cycle, but replication is typically asynchronous. Fevers occur without periodicity.[93]

Patients with malaria infection may present with nonspecific symptoms that include generalized weakness, backache, myalgias, vomiting, diarrhea, and pallor. If an appropriate travel history is not obtained, malaria infection can be mistaken for a viral syndrome or acute gastroenteritis. Partially immune individuals recently returned from endemic areas may have uncomplicated malaria characterized by few physical findings (e.g., fever, mild anemia, jaundice, or hepatosplenomegaly).[108] Children living in areas with stable malaria transmission often have recurrent malaria infections that result in chronic anemia and splenomegaly.[108] Perinatal malaria transmission is usually caused by *P. falciparum* and *P. vivax*.[47] Clinical manifestations (e.g., fever, poor appetite, irritability, and lethargy) of congenital malaria can mimic neonatal sepsis.

COMPLICATIONS OF INFECTION WITH *P. FALCIPARUM*

P. falciparum infection carries the greatest risk for complications and death. *P. falciparum* can invade erythrocytes of all developmental stages and produce overwhelming parasitemia.[71]

TABLE 40-1 Key Clinical Manifestations and Complications of Human *Plasmodium* Infection

Plasmodium Species	Manifestations and Complications
All species	Fever, chills, rigors, sweats, and headaches Weakness Myalgias Vomiting Diarrhea Hepatomegaly Splenomegaly Jaundice Anemia Thrombocytopenia
P. falciparum	Hyperparasitemia Cerebral malaria: seizures, obtundation, and coma Severe anemia Hypoglycemia Acidosis Renal failure Pulmonary edema (noncardiogenic) Vascular collapse
P. vivax and *P. ovale*	Splenic rupture Relapse months to years after primary infection because of latent hepatic stages
P. malariae	Low-grade fever and fatigue Chronic asymptomatic parasitemia Immune complex glomerulonephritis
P. knowlesi	Similar to *P. falciparum*, exception without cerebral malaria

TABLE 40-3 Severe Manifestations of *P. falciparum* Malaria in Children and Adults

Prognostic Value (+ to +++)			Frequency (+ to +++)	
Children	Adults	Clinical Manifestations	Children	Adults
+++	+++	Impaired consciousness	+++	++
+++	+++	Respiratory distress (acidotic breathing)	+++	++
+	++	Multiple convulsions	+++	+
+	+	Prostration	+++	+++
+++	+++	Shock	+	+
+++	+++	Pulmonary edema (radiologic)	+/–*	+
+++	++	Abnormal bleeding	+/–*	+
++	+	Jaundice	+	+++
		Laboratory indices		
+	+	Severe anemia	+++	+
+++	+++	Hypoglycemia	+++	++
+++	+++	Acidosis	+++	++
+++	+++	Hyperlactatemia	+++	++
++	++	Renal impairment†	+	+++
+/-	++	Hyperparasitemia	++	+

From World Health Organization: Severe malaria. Trop Med Int Health 2014;19(Suppl 1):7-131.
*Infrequent.
†Acute kidney injury.

P. falciparum–infected red blood cells adhere to endothelial cells, leading to microvascular obstruction and parasitic sequestration in vital organs, such as the brain (Figure 40-19).[71] *P. falciparum* is frequently resistant to antimalarials.[11,123,124]

Travelers from nonendemic areas, children, and pregnant women are at greatest risk for developing complications from malaria infection. A person is considered to have complicated or severe malaria when infected with *P. falciparum* and without an alternative cause; one or more of the following signs is present: impaired consciousness, acidosis, hypoglycemia, severe anemia, renal impairment, jaundice, pulmonary edema, significant bleeding, shock, or hyperparasitemia (Table 40-2).[91] Manifestations of severe *P. falciparum* malaria can differ in adults and children (Table 40-3).[91] In adults, renal impairment, jaundice, and pulmonary edema occur more frequently. In children, convulsions, severe anemia, and acidosis occur more frequently.[91] In adults and children, impaired consciousness and acidosis are associated with a poor prognosis (Figure 40-20, Video 40-5).[48,69,81,112,120]

Specific complications of *P. falciparum* infection include:

Cerebral malaria: Cerebral malaria is a syndrome of impaired consciousness or coma that often occurs accompanied by convulsions. Impaired consciousness is defined as a Glasgow Coma

TABLE 40-2 Epidemiologic and Research Definitions of Severe Falciparum Malaria*

Characteristic	Laboratory Measurement or Score
Impaired consciousness	A Glasgow Coma Scale score < 11 in adults or a Blantyre Coma Scale score < 3 in children
Acidosis	A base deficit of > 8 mEq/L or, if unavailable, a plasma bicarbonate of < 15 mmol/L or venous plasma lactate > 5 mmol/L. Severe acidosis manifests clinically as respiratory distress (rapid, deep, labored breathing)
Hypoglycemia	Blood or plasma glucose < 2.2 mmol/L (< 40 mg/dL)
Severe malarial anemia	A hemoglobin concentration < 5 g/dL or a hematocrit of < 15% in children < 12 years of age (< 7 g/dL and < 20%, respectively, in adults) together with a parasite count > 10,000/µL
Renal impairment (acute kidney injury)	Plasma or serum creatinine > 265 µmol/L (3 mg/dL) or blood urea > 20 mmol/L
Jaundice	Plasma or serum bilirubin > 50 µmol/L (3 mg/dL) together with a parasite count > 100,000/µL
Pulmonary edema	Radiologically confirmed, or oxygen saturation < 92% on room air with a respiratory rate > 30/min, often with chest indrawing and crepitations on auscultation
Significant bleeding	Including recurrent or prolonged bleeding from nose gums or venipuncture sites; hematemesis or melena
Shock	Compensated shock is defined as capillary refill ≥ 3 sec or temperature gradient on leg (mid to proximal limb), but no hypotension. Decompensated shock is defined as systolic blood pressure < 70 mm Hg in children or < 80 mm Hg in adults with evidence of impaired perfusion (cool peripheries or prolonged capillary refill)
Hyperparasitemia	*P. falciparum* parasitemia > 10%

From World Health Organization: Severe malaria. Trop Med Int Health 2014;19(Suppl 1):7-131.
*For epidemiologic and research purposes, severe malaria is defined as one or more of the characteristics in the table, occurring in the absence of an identified alternative cause, and in the presence of *P. falciparum* asexual parasitemia.

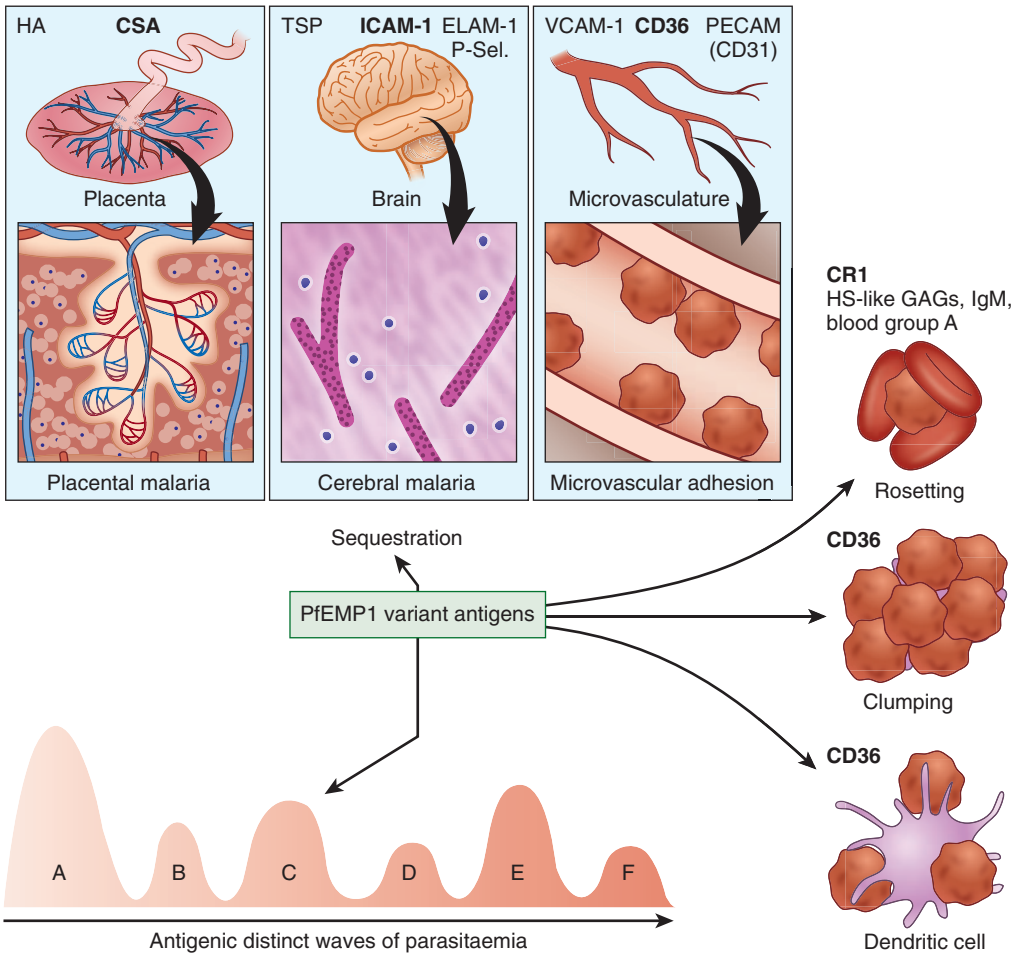


FIGURE 40-19 Host-parasite interaction and pathogenesis of *P. falciparum;* the role of PfEMP1. *(From Miller LH, Baruch DI, Marsh K, Doumbo OK:* The pathogenic basis of malaria. *Nature 2002;415:673-679.)*

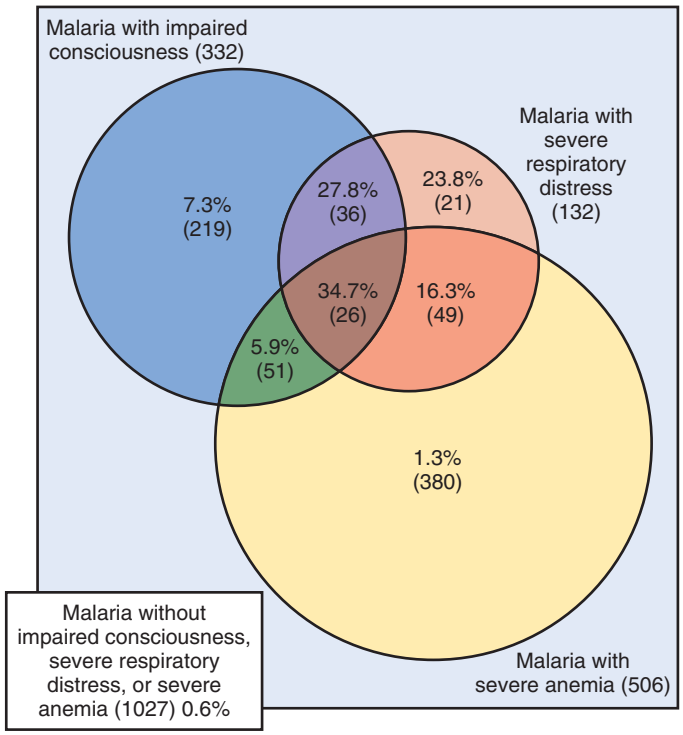


FIGURE 40-20 Prevalence, overlap, and mortality for major clinical subgroups of severe malaria in children. *(From Marsh K, Forster D, Waruiru C, et al:* Indicators of life-threatening malaria in African children. *N Engl J Med 1995;332:1399-1404.)*

Scale score of less than 11 in adults or a Blantyre Coma Scale score of less than 3 in children.[91] Convulsions can be generalized or focal, occur in children of any age, and occur at any body temperature.[91] Cerebrospinal fluid (CSF) examination is typically unremarkable, distinguishing cerebral malaria from bacterial meningitis. Retinopathy characterized by hemorrhages and retinal and vessel whitening suggests intracerebral parasite sequestration (Figure 40-21).[6,5,70,107] Most adults do not have cerebral edema on imaging. Children, especially in the agonal stages of disease, have cerebral edema.[55] Pathogenesis is due to microvascular obstruction by parasitized erythrocytes. Neurologic impairment can result from hypoglycemia, acidosis, impaired cerebral oxygenation from anemia, and pulmonary edema.[91] Mortality rates can be as high as 15% to 30% in endemic areas, and higher in nonimmune adults (e.g., travelers). Children surviving episodes of cerebral malaria often have subtle cognitive, behavioral, and motor deficits.[9,54,59] Children who survive cerebral malaria with concomitant hypoglycemia, severe anemia, repeated seizures, or coma can have severe neurologic deficits (e.g., hemiplegia, cerebral palsy, and cortical blindness).[54-56]

Severe anemia: In areas of high malaria transmission, severe anemia is the main manifestation of severe malaria in children.[8] Severe malarial anemia is defined as a hemoglobin concentration of less than 5 g/dL or hematocrit of less than 15% in children (< 7 g/dL and < 20%, respectively, in adults), together with a parasite count greater than 10,000/μL.[91] Because fingerprick blood samples may underestimate hemoglobin concentration, results should specify whether the sample was collected by vein sample or fingerprick. Anemia usually results from repeated infections, erythrocyte destruction by parasite replication, splenic removal of unparasitized erythrocytes, and ineffective erythropoiesis.[83] Chronic severe anemia can occur in areas with heavy hookworm burdens and high malaria transmission.

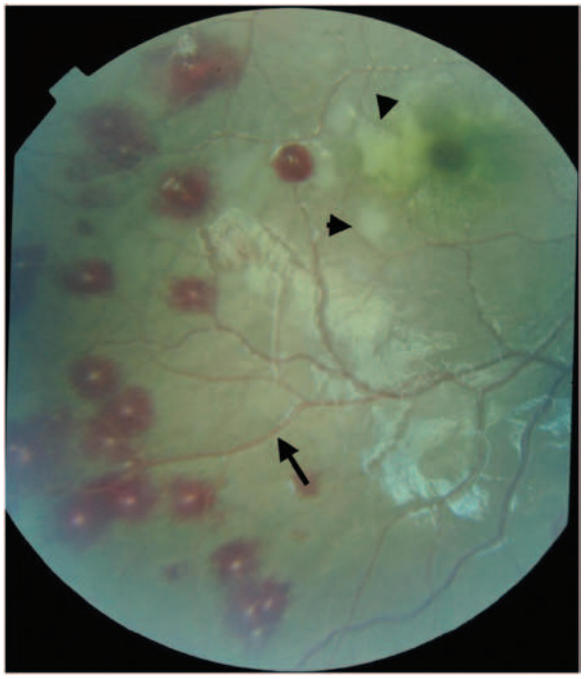


FIGURE 40-21 Retinal pathology of cerebral malaria. Fundus photograph displaying malarial retinopathy, consisting of multiple white-centered hemorrhages, macular whitening *(arrowheads),* and orange discoloration of vessels *(arrow). (From White VA, Lewallen S, Beare NA, et al:* Retinal pathology of pediatric cerebral malaria in Malawi. *PLoS One 2009;4:e4317.)*

Acidosis: Acidosis is defined as a base deficit of greater than 8 mEq/L or, if that laboratory determination is unavailable, plasma bicarbonate of less than 15 mmol/L or venous plasma lactate greater than 5 mmol/L.[91] Patients with severe acidosis can have rapid, deep, labored breathing in conjunction with a clear chest examination on auscultation.[91] Acidosis is a sign of poor prognosis and associated with death.[48,69] Lactic acid accumulation leads to acidosis and can further be complicated by ketoacidosis in children and acute renal injury in adults.[48,69] Lactic acidosis results from anaerobic glycolysis in tissues with microvascular obstruction caused by sequestered parasites, lactate production by malaria parasites, and decreased ability to clear lactate.[108]

Hypoglycemia: Children, pregnant women, and nonimmune individuals are at risk for hypoglycemia.[110] Hypoglycemia is defined as blood or plasma glucose of less 2.2 mM (< 40 mg/dL).[91] Hypoglycemia is often associated with lactic acidosis and can result from decreased oral intake, depletion of liver glycogen, parasite consumption of glucose, insulin release from the pancreas by quinine or quinidine, and inhibition of gluconeogenesis.[82]

Renal impairment: Acute renal impairment is defined as plasma or serum creatinine of more than 265 mM (3 mg/dL) or blood urea of more than 20 mM.[91] This definition assumes normal premorbid renal function. Pathogenesis of renal failure is multifactorial and includes sequestration of parasitized erythrocytes in the cortex and findings consistent with acute tubular necrosis in the medulla. Other contributing factors include hypotension, microvascular obstruction by *P. falciparum*–parasitized red blood cells, and free malarial pigment or heme.[48] Oliguric renal failure is rare among children younger than 8 years of age. In children or adults with severe malaria and blood urea of more than 20 mM, the mortality rate can be more than 30%.[33,32,57,89,91] Nonimmune individuals receiving treatment with quinine or quinidine may develop renal failure from massive hemolysis due to overwhelming parasitemia that may lead to hemoglobinuria (i.e., blackwater fever) (Figure 40-22).[103]

Jaundice: In severe falciparum malaria, jaundice is defined as plasma or serum bilirubin greater than 50 μM (3 mg/dL) in conjunction with a parasite count greater than 100,000/μL.[91] Hemolysis, hepatocyte injury, and cholestasis can lead to jaundice detected clinically by examining sclera and/or oral mucosal surfaces. Jaundice is more common in adults. Chronic hepatitis B infections may increase the risk of severe malaria.[4]

Pulmonary edema: In severe falciparum malaria, pulmonary edema is defined as radiologically confirmed edema or oxygen saturation of less than 92% on room air with a respiratory rate greater than 30/min.[91] It is often associated with crepitations on auscultation and chest indrawing.[91] Late in severe malaria, individuals can develop pulmonary edema with normal intrapulmonary and intracardiac pressures consistent with acute respiratory distress syndrome.[101] Pulmonary edema occurs more frequently in adults, especially pregnant women.

Significant bleeding: A rare complication of falciparum malaria is significant bleeding, defined as recurrent or prolonged bleeding from the nose, gums, or venipuncture sites, hematemesis, or melena.[91]

Shock: Individuals with severe malaria can develop vascular collapse and shock, often associated with adrenal insufficiency and hypothermia. In severe malaria, compensated shock is defined as prolonged capillary refill (i.e., ≥ 3 seconds) or noticeable temperature gradient on the leg (between the mid and proximal limb) in the absence of hypotension.[91] Decompensated shock is defined as systolic blood pressure lower than 70 mm Hg in children or lower than 80 mm Hg in adults with evidence of impaired perfusion (i.e., cool extremities or prolonged capillary refill).[91]

Hyperparasitemia: In the absence of local data, *P. falciparum* parasitemia greater than 10% is defined as hyperparasitemia. In areas of stable malaria transmission, parasitemia thresholds can be derived from local experience.[91]

COMPLICATIONS OF INFECTION WITH *P. VIVAX* AND *P. OVALE*

Severe vivax malaria shares the same definition (in adults and children) as severe falciparum malaria except there is no parasitemia density threshold requirement.[91] *P. vivax* invades reticulocytes, which results in lower levels of parasitemia than does *P. falciparum* infection (Table 40-4). *P. vivax* infection typically presents with fevers, chills, headaches, and myalgias. In children, severe anemia is a common severe manifestation of vivax malaria, particularly where there is intense transmission of both *P. falciparum* and *P. vivax* (e.g., in Oceania).[91,2,44,76,85] Other complications described with vivax malaria include acute lung injury and respiratory distress, acute kidney injury, shock and multiorgan dysfunction, coma and other neurologic complications, severe jaundice, and abnormal bleeding with thrombocytopenia.[2,44,76,85,91] Splenic rupture is an important complication of *P. vivax* malaria.[58,91]

Patients presenting with *P. ovale* infection are typically nontoxic in appearance. In persons chronically infected with either *P. vivax* or *P. ovale*, anemia and splenomegaly are common and splenic rupture is an important late complication (see Table 40-1).[58] Because both *P. vivax* and *P. ovale* have a hepatic hypnozoite stage, symptoms may manifest months to years after the initial infection.

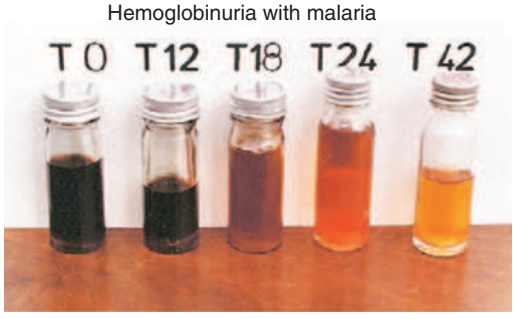


FIGURE 40-22 Hemoglobinuria with malaria. *(From Tombe M:* Images in clinical medicine: hemoglobinuria with malaria. *N Engl J Med 2008;358:1837.)*

TABLE 40-4 Key Comparison of *P. vivax* and *P. falciparum* Malaria

Life Cycle	*P. falciparum*	*P. vivax*
Minimum temperature needed for maturation in the mosquito	Lowest temperature 16°C (61°F)	For cycle to be complete lowest temperature 15°C (59°F), survival of the parasite to 10°C (50°F) for 2 days
Dormant liver stage	No	Yes
Gametocytes	Appear after asexual blood stage is established	Appear at time of asexual blood stage, often before clinical symptoms
Disease		
Severity	5% of cases develop into severe illness; responsible for majority of deaths	Risk of severe disease not firmly established
Relapse	No	Yes
Asymptomatic	Common	Very common
Diagnosis		
	Blood film, rapid tests, and PCR for blood stage	Blood film, rapid tests, and PCR for blood stage
		No test for dormant liver stage
Treatment		
Blood stage	Artemisinin combination treatment recommended	Chloroquine still efficacious in most areas
Gametocytes	Need single dose primaquine, artemesinins have some effect	Sensitive to blood stage treatment
Liver stage		14 days of primaquine

From World Health Organization: World Malaria Report 2014.
PCR, polymerase chain reaction.

Cytoadherence does not occur with *P. vivax* or *P. ovale*. All parasite stages circulate in peripheral blood. Microvascular changes associated with sequestration in deep vascular beds are not observed. As previously noted, individuals lacking expression of Duffy blood group antigen (e.g., many Africans) are protected from *P. vivax* infection because this antigen is used as a receptor for erythrocyte invasion by the *P. vivax* parasite (see Figure 40-3).[72]

COMPLICATIONS OF INFECTION WITH *P. MALARIAE*

Because *P. malariae* produces persistent low-level parasitemia, it usually manifests with mild symptoms (e.g., weakness, low-grade fever, and fatigue). Individuals can have chronic asymptomatic parasitemia for years. This can be associated with immune complex glomerulonephritis, where complement-fixing antibodies are directed against *P. malariae* antigens.[36]

COMPLICATIONS OF INFECTION WITH *P. KNOWLESI*

The simian malaria parasite *P. knowlesi* is morphologically indistinguishable on blood smear from *P. malariae*. Clinical characteristics of *P. knowlesi* infection in humans were better understood once molecular detection methods were developed to distinguish it from *P. malariae*.[91,93] Severe knowlesi malaria shares the same definitions for severe falciparum malaria (in adults and children) except for lower values of parasitemia burden and jaundice.[91] *P. knowlesi* hyperparasitemia is defined as parasite density greater than 100,000/μL. Jaundice has a parasite density cut-off of greater than 20,000/μL.[91] The risk of developing severe malaria from *P. knowlesi* infection is almost three times higher than from *P. falciparum*.[3] Patients with *P. knowlesi* parasitemia greater than 20,000/μL should be closely observed. Excepting cerebral complications, all severe manifestations of falciparum malaria have been reported with knowlesi malaria.[91,93]

DIAGNOSIS

HISTORY

Early and prompt diagnosis of malaria, particularly in nonendemic areas, requires the health care provider to take an appropriate travel history in the febrile patient and include malaria in the differential diagnosis. Most malaria cases in the United States occur among travelers who have visited malaria-endemic areas.[29] Because of the risk of complications and death, fever in returned travelers should be taken seriously. A thorough travel history must be obtained, including travel dates, destinations, and any chemoprophylaxis taken.[37,43] Because of drug resistance and potential medication noncompliance, chemoprophylaxis in a returned traveler does not exclude a diagnosis of malaria. Patients may not have typical malarial paroxysms of fever and chills. Nonspecific symptoms (e.g., fatigue, diarrhea, headache, myalgias, and sore throat) may lead the clinician to another diagnosis, such as a viral syndrome. In semiimmune individuals, fever and persistent malaise may be present. Clinicians in endemic areas must add severe malaria to the differential diagnosis of an ill-appearing child.

BLOOD SMEARS

Thin and thick blood smears are the gold standard for the clinical diagnosis of malaria (Figure 40-23).[75] Blood smears provide information on parasite species and degree of parasitemia that are important in determining treatment. Blood smears should be rapidly interpreted by skilled microscopists trained in malaria diagnosis. Because patients with malaria can quickly deteriorate without treatment, blood smears should not be sent to an offsite laboratory or batched with other tests for later processing.

Blood Smear Preparation

Thin smears are used to identify parasite species and degree of parasitemia. Place a drop of blood at one end of a slide and draw the edge of another slide across the first slide (see Figure 40-23B, Video 40-6).[10,15,20] Individuals with low parasitemia may have false-negative thin blood smears because the number of red blood cells examined in thin smears is insufficient to detect parasites. In these cases, thick smears are useful to establish a diagnosis of malaria, because the red blood cell concentration allows examiners to find parasites that may be present in small numbers. Thick smears are made by placing a drop of blood on a smear, spreading it in a circle, and allowing it to dry (see Figure 40-23*B;* Video 40-6).[10,15,20] Red blood cells are lysed by staining without methanol fixation.[27] Thus, the degree of parasitemia can be ascertained, but the size and morphology of parasitized red blood cells cannot be determined. Giemsa staining is preferred

for malaria smears because it reveals details (e.g., Schüffner dots) that are often missed with Wright staining. In areas that are not malaria endemic, Wright staining is generally more available than is Giemsa staining, and typically will reveal the presence of parasites. If the initial smear is negative and *Plasmodium* species infection remains a consideration, thin and thick blood smears should be repeated every 12 to 24 hours. Laboratory aids for blood smear preparation and staining, as well as microscopic identification of malaria parasites, are available through the CDC at cdc.gov/malaria/diagnosis.[20]

Blood Smear Examination

Oil immersion (×100) is used to examine thick and thin blood smears (Tables 40-5 and 40-6; Figures 40-24 and 40-25).[13,16,20] Begin thin smear examination at the thin edge of the smear, farthest away from where the drop of blood was placed. *P. falciparum* ring stages have a delicate cytoplasm with one or two small chromatin dots and occasional appliqué forms.[13,20] *P. falciparum* trophozoites and schizonts are rarely seen in peripheral blood. Gametocytes have a crescent or sausage shape. Red blood cells infected with more than one parasite are more common with *P. falciparum* than with the other species. *P. vivax* ring stages have a large cytoplasm with occasional pseudopods and a large chromatin dot.[13,20] Occasional Schüffner dots (morphologic alterations visible by light microscopy in Romanovsky-stained blood smears as multiple brick-red dots) are seen in red blood cells. *P. vivax* trophozoites are large, with an amoeboid cytoplasm and schizonts containing 12 to 24 merozoites. *P. vivax* gametocytes are round to oval in shape. Ring stages of *P. ovale* have a large chromatin dot. *P. ovale*–infected red blood cells occasionally have Schüffner dots and are fimbriated.[13,20] *P. ovale*

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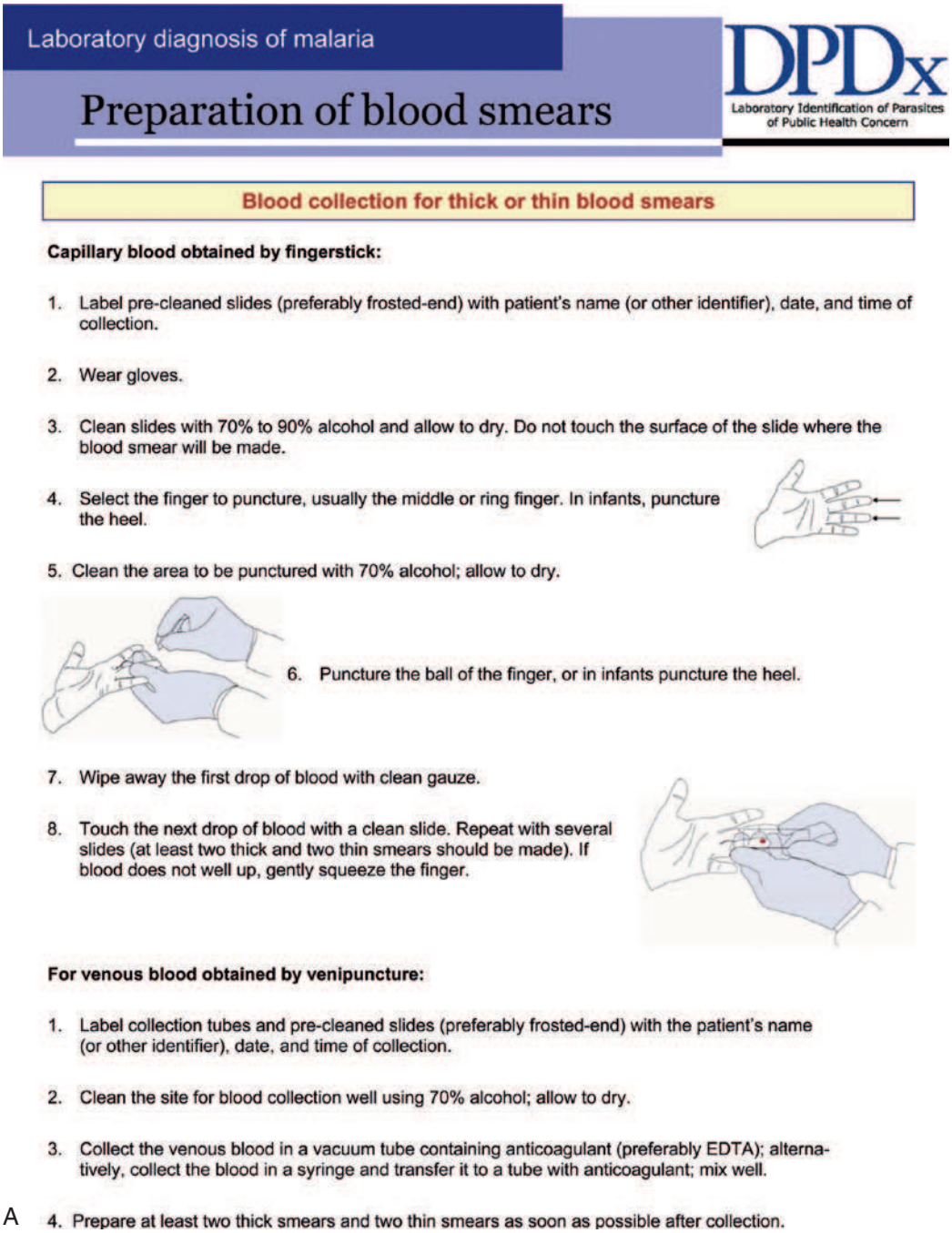
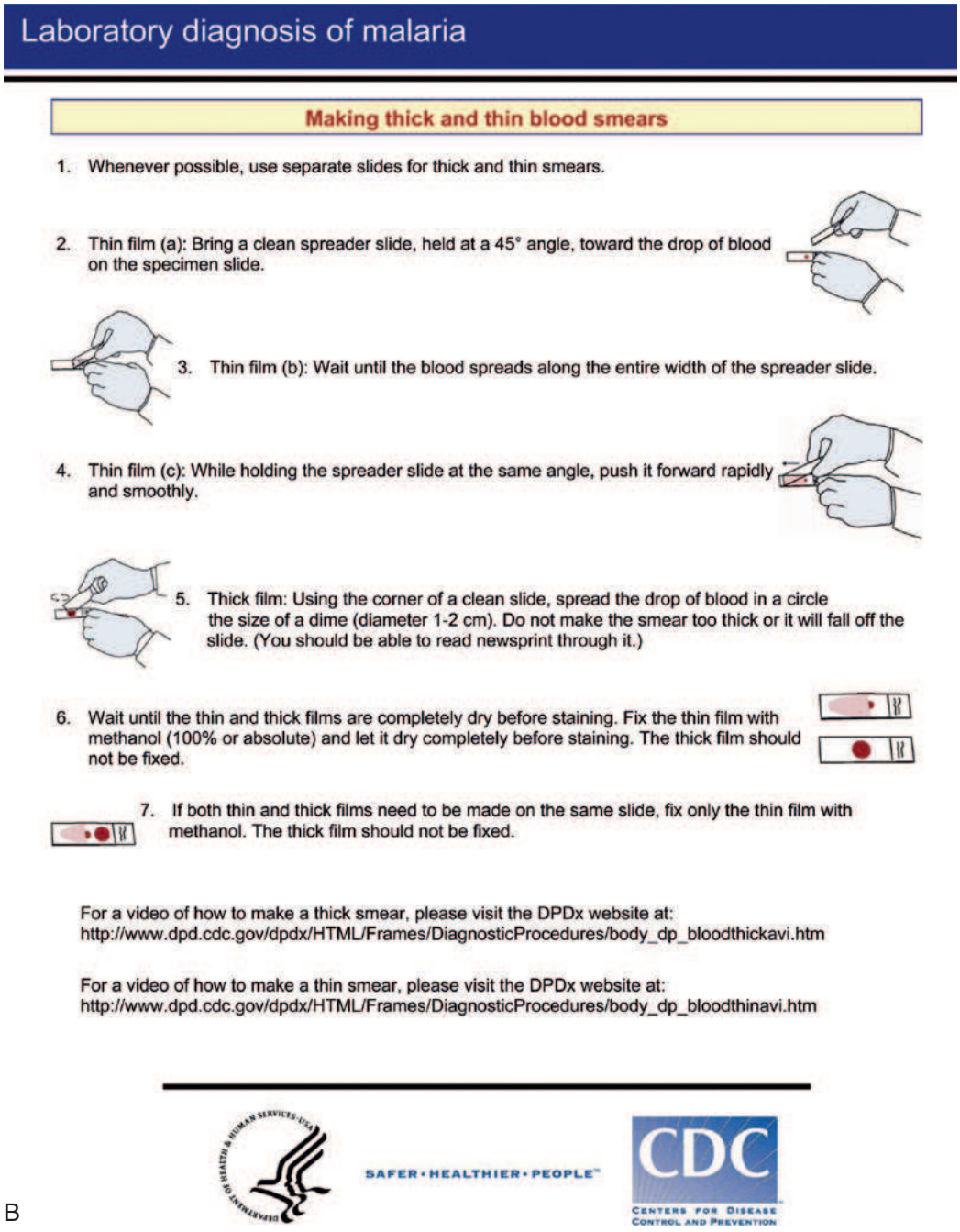


A

FIGURE 40-23 **A,** Blood collection method for blood smear preparation.



B

FIGURE 40-23, cont'd B, Preparation of thin and thick blood smears. *(From the Centers for Disease Control and Prevention:* Update: Influenza activity: United States, January 11-17, 2004, *MMWR Morb Mortal Wkly Rep 53:35, 2004.* dpd.cdc.gov/dpdx/HTML/PDF.Files/Malaria_procedures_benchaid.pdf.*)*

TABLE 40-5 Key Characteristics of *Plasmodium* Species on Human Blood Smear

	Infected Red Blood Cells				Parasites		
Plasmodium Species	**Size**	**Shape**	**Schüffner Dots**	**Rings**	**Trophozoites**	**Schizonts (Mature)**	**Gametocytes**
P. falciparum	Normal	Crescent (gametocyte)	No	Numerous delicate rings only (occasional gametocytes); multiple infected red blood cells; and numerous appliqué forms	—	8-24 (rare)	Crescent
P. vivax	Enlarged	Ameboid	Yes	Thick	Ameboid	12-24	Round
P. ovale	Enlarged	Fimbriated, elongated, and oval	Yes	Thick	Compact	6-14	Round
P. malariae	Normal	—	No	Thick	Compact, band form	6-12, rosettes	Round

TABLE 40-6 Comparison of the *Plasmodium* Species That Cause Malaria in Humans

Plasmodium Species	Stages Found in Blood	Appearance of Erythrocyte (RBC)	Appearance of Parasite
P. falciparum	Ring	Normal; multiple infection of RBC more common than in other species	Delicate cytoplasm; 1-2 small chromatin dots; occasional applique (accolé) forms
	Trophozoite	Normal; rarely, Maurer's clefts (under certain staining conditions)	Seldom seen in peripheral blood; compact cytoplasm; dark pigment
	Schizont	Normal; rarely, Maurer's clefts (under certain staining conditions)	Seldom seen in peripheral blood; mature = 8-24 small merozoites; dark pigment; clumped in one mass
	Gametocyte	Distorted by parasite	Crescent or sausage shape; chromatin in a single mass (macrogametocyte) or diffuse (microgametocyte); dark pigment mass
P. vivax	Ring	Normal to 1¼ X, round; occasionally fine Schüffner's dots; multiple infection of RBC not uncommon	Large cytoplasm with occasional pseudopods; large chromatin dot
	Trophozoite	Enlarged 1½ to 2 X; may be distorted; fine Schüffner's dots	Large ameboid cytoplasm; large chromatin; fine, yellowish-brown pigment
	Schizont	Enlarged 1½ to 2 X; may be distorted; fine Schüffner's dots	Large, may almost fill RBC; mature = 12-24 merozoites; yellowish-brown, coalesced pigment
	Gametocyte	Enlarged 1½ to 2 X; may be distorted; fine Schüffner's dots	Round to oval; compact; may almost fill RBC; chromatin compact, eccentric (microgametocyte) or diffuse (microgametocyte); scattered brown pigment
P. ovale	Ring	Normal to 1¼ X, round to oval; occasionally Schüffner's dots; occasionally fimbriated; multiple infection of RBC not uncommon	Sturdy cytoplasm; large chromatin
	Trophozoite	Normal to 1¼ X, round to oval; some fimbriated; Schüffner's dots	Compact with large chromatin; dark-brown pigment
	Schizont	Normal to 1¼ X, round to oval; some fimbriated; Schüffner's dots	Mature = 6-14 merozoites with large nuclei, clustered around mass of dark-brown pigment
	Gametocyte	Normal to 1¼ X, round to oval; some fimbriated; Schüffner's dots	Round to oval; compact; may almost fill RBC; chromatin compact, eccentric (microgametocyte) or more diffuse (microgametocyte); scattered brown pigment
P. malariae	Ring	Normal to ¾ X	Sturdy cytoplasm; large chromatin
	Trophozoite	Normal to ¾ X; rarely, Ziemann's stippling (under certain conditions)	Compact cytoplasm; large chromatin; occasional band forms; coarse, dark-brown pigment
	Schizont	Normal to ¾ X; rarely, Ziemann's stippling (under certain conditions)	Mature = 6-12 merozoites with large nuclei, clustered around mass of coarse, dark-brown pigment; occasional rosettes
	Gametocyte	Normal to ¾ X; rarely, Ziemann's stippling (under certain conditions)	Round to oval; compact; may almost fill RBC; chromatin compact, eccentric (microgametocyte) or more diffuse (microgametocyte); scattered brown pigment

From Centers for Disease Control and Prevention: Malaria. 11-29-2013. 12-19-2014.
RBC, red blood cell.

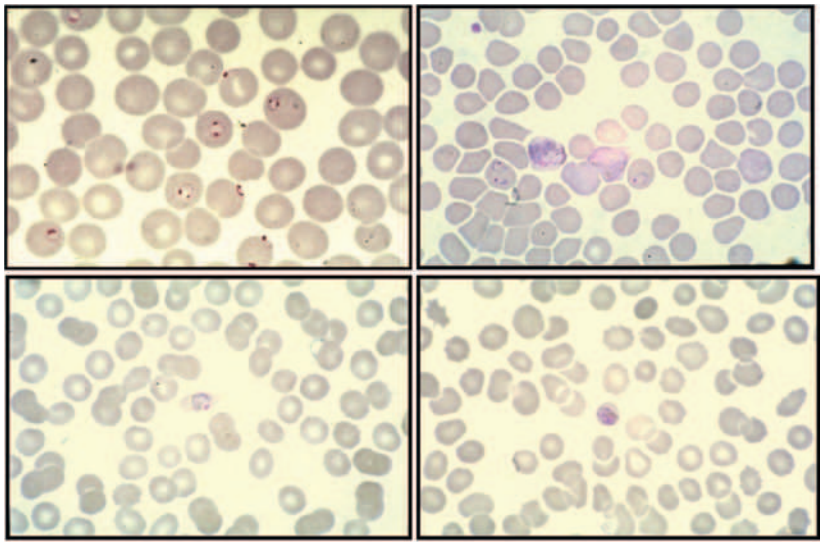


FIGURE 40-24 Representative malaria blood smears. *(Courtesy Royal Perth Hospital, Perth, Western Australia.* rph.wa.gov.au/Research/Whats-New/Online-Malaria-resources.*)*

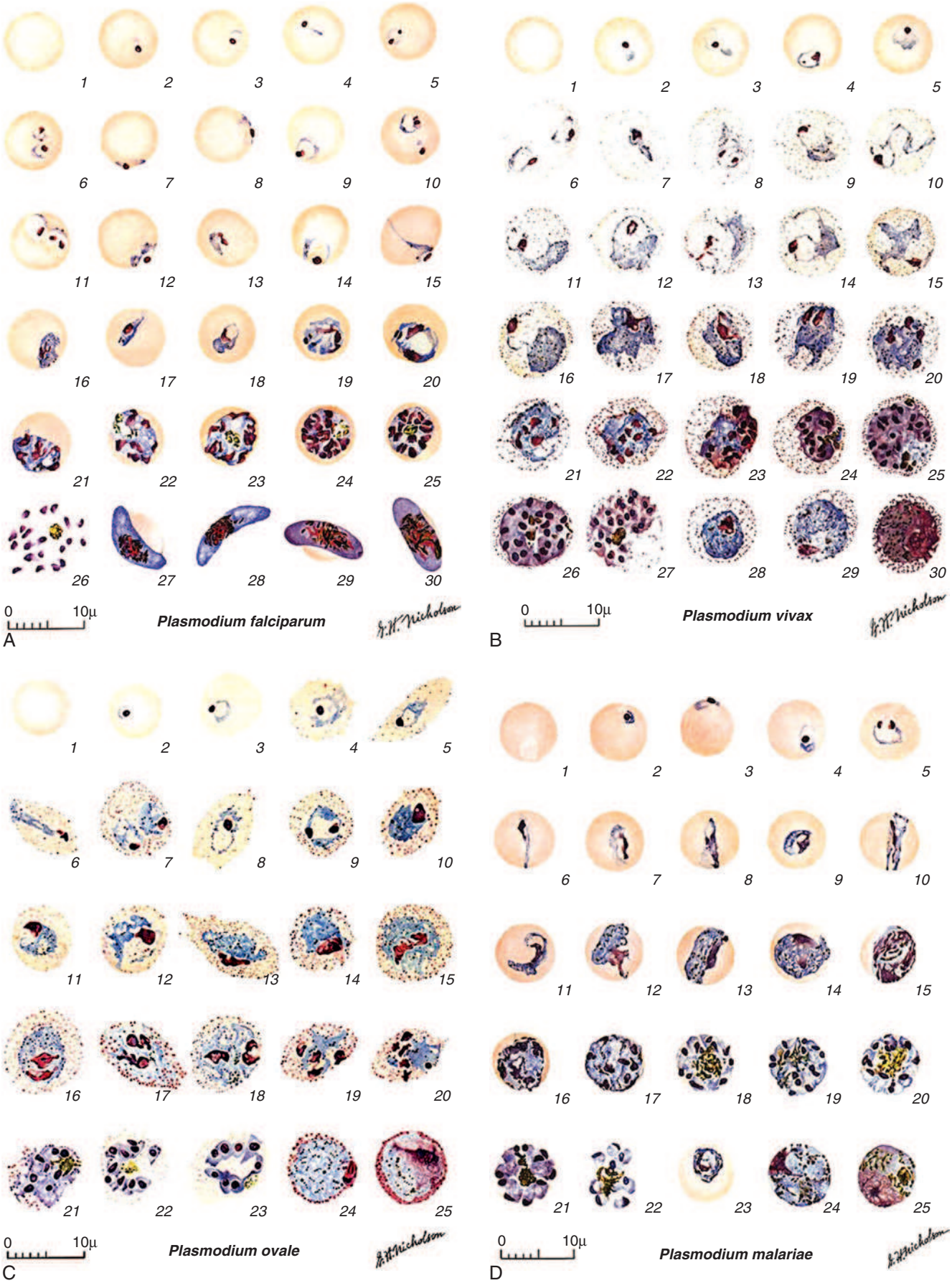
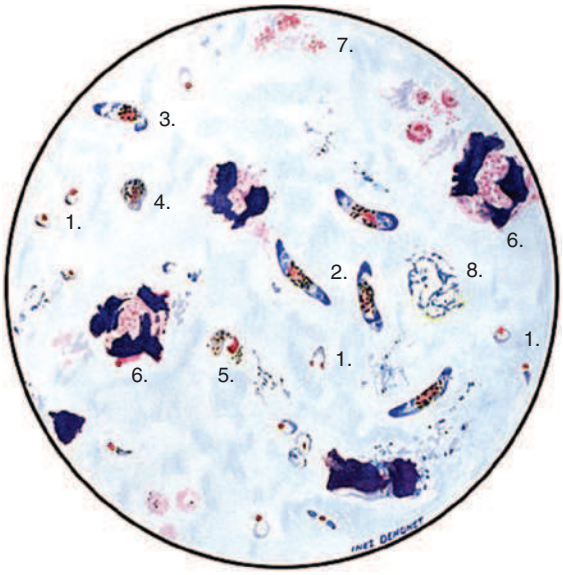


FIGURE 40-25 Thin and thick smears. **A,** Thin smears, *Plasmodium falciparum*. **B,** Thin smears, *Plasmodium vivax*. **C,** Thin smears, *Plasmodium ovale*. **D,** Thin smears, *Plasmodium malariae*.

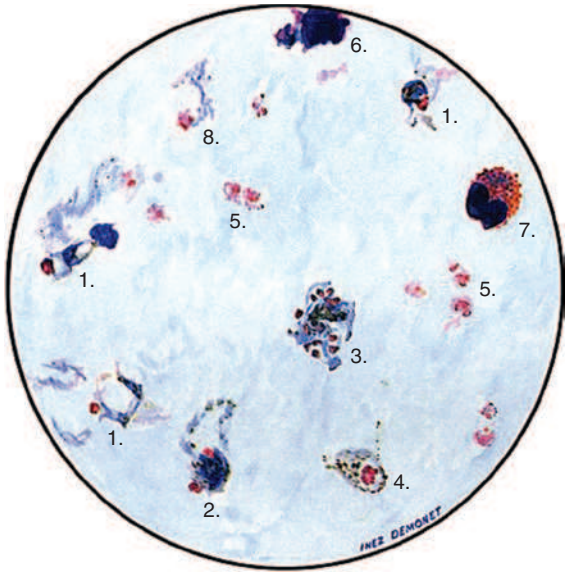
Continued



Plasmodium falciparum
Blood stage parasites, thick blood smears

1: Small trophozoites
2: Gametocytes — normal
3: Slightly distorted gametocyte
4: "Rounded-up" gametocyte
5: Disintegrated gametocyte
6: Nucleus of leukocyte
7: Blood platelets
8: Cellular remains of young erythrocyte

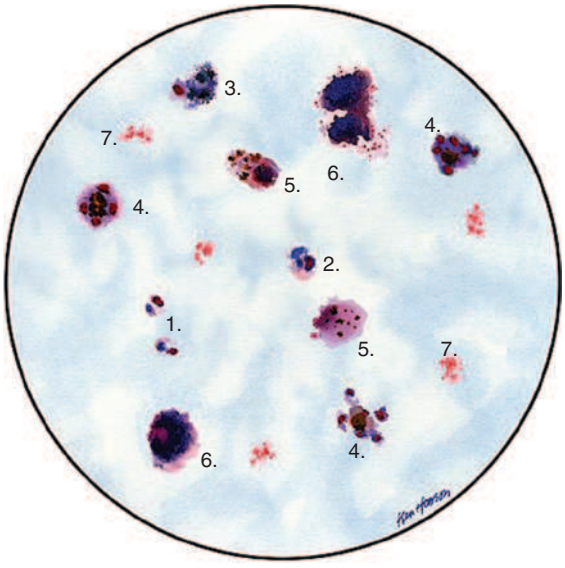
E



Plasmodium vivax
Blood stage parasites, thick blood smears

1: Ameboid trophozoites
2: Schizont — two divisions of chromatin
3: Mature schizont
4: Microgametocyte
5: Blood platelets
6: Nucleus of neutrophil
7: Eosinophil
8: Blood platelet associated with cellular remains of young erythrocytes

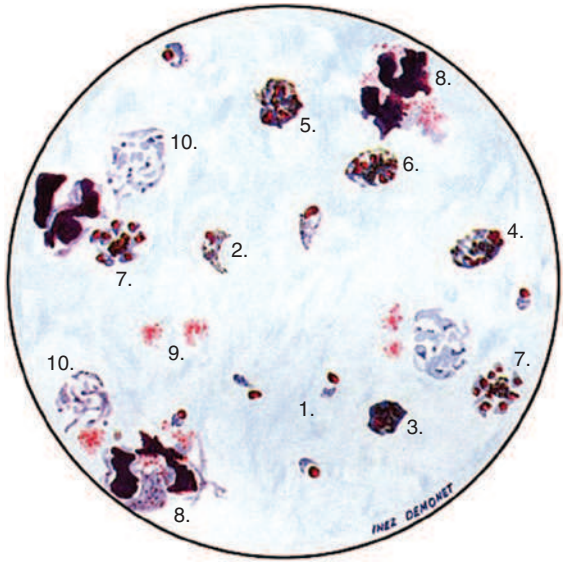
F



Plasmodium ovale
Blood stage parasites, thick blood smears

1: Small trophozoites
2: Growing trophozoites
3: Mature trophozoites
4: Schizonts
5: Gametocytes
6: Nucleus of leukocyte
7: Blood platelets

G



Plasmodium malariae
Blood stage parasites, thick blood smears

1: Small trophozoites
2: Growing trophozoites
3: Mature trophozoites
4, 5, 6: Immature schizonts with varying numbers of divisions of the chromatin
7: Mature schizonts
8: Nucleus of leukocyte
9: Blood platelets
10: Cellular remains of young erythrocytes

H

FIGURE 40-25, cont'd **E,** Thick smears, *Plasmodium falciparum*. **F,** Thick smears, *Plasmodium vivax*. **G,** Thick smears, *Plasmodium ovale*. **H,** Thick smears, *Plasmodium malariae*. (**A** *to* **D** *from Coatney GR, Collins WE, Warren M, et al:* The primate malarias, *Bethesda, Md, 1971, US Department of Health, Education, and Welfare.* **E** *to* **H** *from Wilcox A:* Manual for the microscopical diagnosis of malaria in man, *Washington, DC, 1960, US Department of Health, Education, and Welfare. All images from* cdc.gov/dpdx/malaria/dx.html.)

trophozoites are compact with large chromatin, and schizonts contain 6 to 14 merozoites with large nuclei. *P. ovale* gametocytes are round to oval in shape. *P. malariae* rings have large chromatin.[13,20] *P. malariae* trophozoites have compact cytoplasm with an occasional band form. Schizonts contain 6 to 12 merozoites with large nuclei, and gametocytes are round to oval.[13,20] *P. knowlesi* is identical to the early trophozoites of *P. falciparum* on blood smear, with double chromatin dots, multiple infections per red blood cell, and no enlargement of infected red blood cells.[93] Other *P. knowlesi* blood stages are morphologically similar to *P. malariae*, including band-form trophozoites.[93]

Parasite Density

Parasite density is typically calculated on thick smear by counting the number of parasites per 200 white blood cells (Figure 40-26).[20] The number of parasites per microliter of blood is then calculated using the white blood cell count (if available), or assuming an average of 8000 white blood cells per microliter.[15,16,27] False-positive blood smears are common when inexperienced microscopists mistake platelets or stain debris for parasites. Most false-negative blood smears result from low parasitemia (often with semiimmune state) or altered parasite morphology related to chemoprophylaxis, partial treatment, or drug-resistant parasites. If initial blood smears are negative for *Plasmodium* species but malaria is still a leading diagnosis, smears should be repeated every 12 to 24 hours during a 72-hour period.

ANTIBODY-BASED RAPID DIAGNOSTIC TESTS

The WHO recommends that rapid diagnostic tests (RDTs) and microscopy be primary diagnostic tools for confirmation and management of suspected malaria in all epidemiologic situations.[116] Antibody-based RDTs are relatively simple to perform and interpret, and do not require specialized equipment or electricity. RDTs allow a provider to exclude malaria infection in settings where reliable, experienced microscopy is unavailable.

Antibody-based RDTs detect malaria parasite antigens in blood using an immunochromatographic assay, with monoclonal antibodies directed against target parasite antigens impregnated on a test strip (Figures 40-27 to 40-29).[68,67,113] Results typically appear in 5 to 20 minutes as a colored test line.[68,113] Antibody-based RDTs detect *Pf*HRP2, malaria-specific lactate dehydrogenase, or aldolase antigens in fingerprick blood samples (see Figure 40-27). WHO's testing program and interactive guide of various products can be found online at finddiagnostics.org/programs/malaria-afs/malaria/current-projects/rdt_quality_control/interactiveguide-intro/interactive-guide/index.jsp.[117]

The U.S. Food and Drug Administration approved BinaxNOW Malaria for use by hospital and commercial laboratories in 2007 (see Figure 40-29, Video 40-7).[18,21] This test can detect *P. falciparum;* however, it cannot distinguish among *P. vivax, P. ovale,* and *P. malariae,* or determine mixed-species infections.[18,21]

All malaria RDTs should be followed by malaria microscopy. A positive malaria RDT can inform the health care worker to urgently initiate malaria treatment. A negative RDT does not exclude the diagnosis of malaria. The RDT may not be able to detect low levels of parasitemia and the species of malaria.[111,113] Furthermore, the RDT result is qualitative, so microscopy must be used to quantify infection and the response to therapy.

OTHER DIAGNOSTIC METHODS

Alternative diagnostic methods typically require microscopy to be performed in parallel to identify and quantify parasite

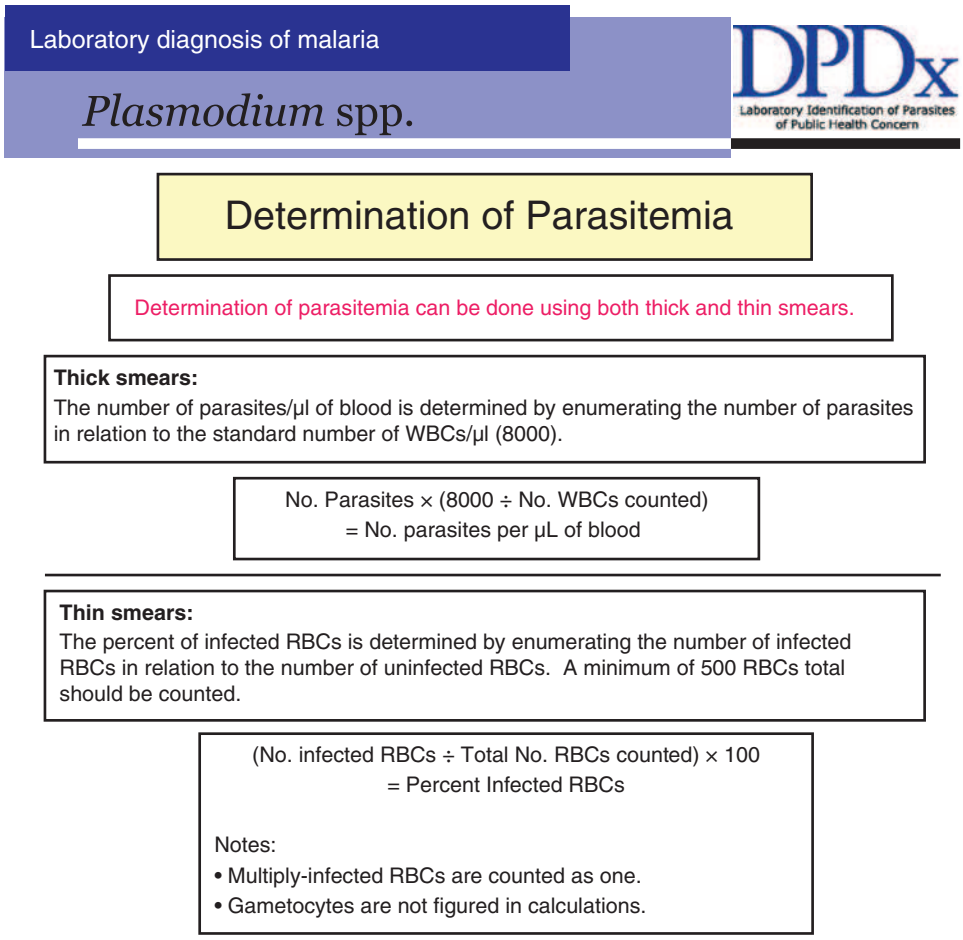


FIGURE 40-26 Determination of parasitemia. *(From Centers for Disease Control and Prevention. Malaria. 11-29-2013. 12-19-2014.)*

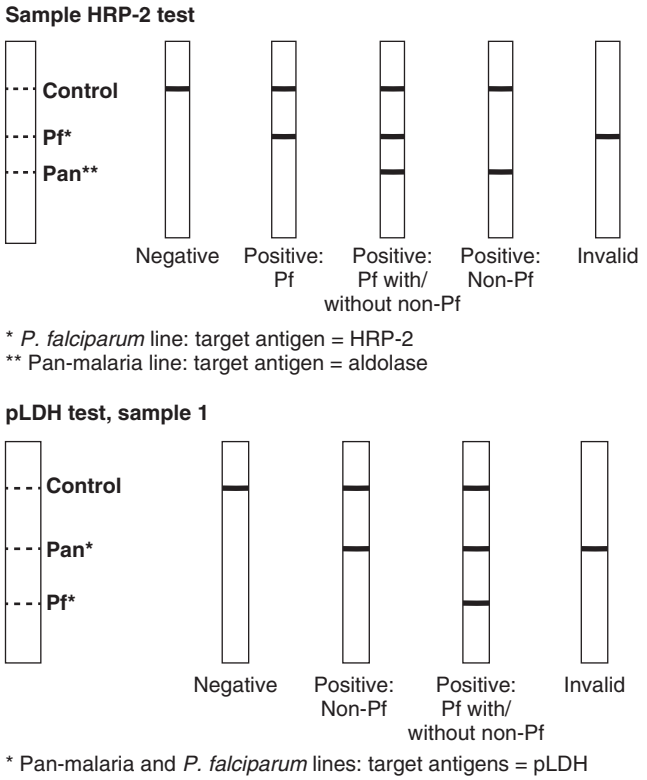


FIGURE 40-27 Sample malaria rapid diagnostic tests and results. *(From Wongsrichanalai C, Barcus MJ, Muth S, et al:* A review of malaria diagnostic tools: microscopy and rapid diagnostic test (RDT). *Am J Trop Med Hyg 2007;77:119-127.)*

species. Tests include fluorescence microscopy and nucleic acid amplification–based testing for parasite-specific sequences (Figure 40-30).[22] The WHO recommends that nucleic acid amplification–based methods should only be considered in low transmission settings where there is widespread implementation of malaria diagnostic testing and treatment, and parasite prevalence rates less than 10%.[116] The CDC offers a simian malaria species confirmation service for health care providers and laboratories to assist in diagnosing cases of malaria imported from Asia or South America.[26]

PREVENTION

Prevention of malaria infection requires appropriate counseling, personal protective measures, and chemoprophylaxis (Table 40-7).[11,53] Current recommendations for travelers can be obtained from the CDC[11,23] at cdc.gov/malaria/travelers/index.html. The CDC's Malaria Map application is an interactive map that provides global information about malaria endemicity.[12] (cdc.gov/malaria/map/index.html). Similar information can be found through the WHO International Travel and Health Interactive Map (apps.who.int/ithmap/).[115]

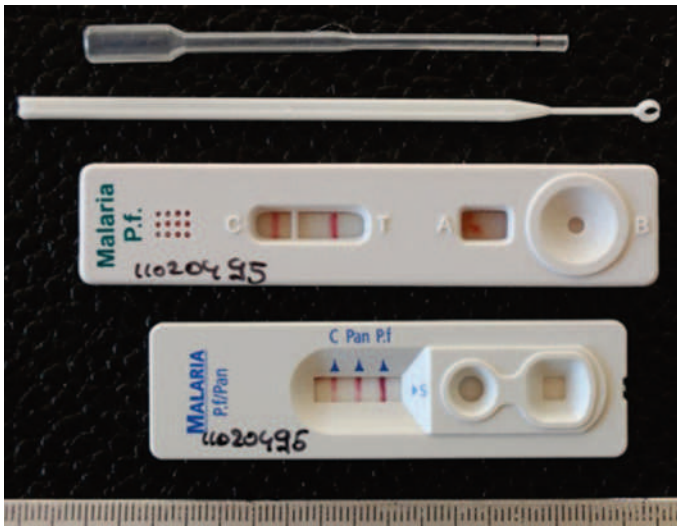


FIGURE 40-28 Two- and three-band malaria rapid diagnostic tests (MRDTs) with blood transfer devices (pipette and loop, top of photo). Two-band MRDT (middle image) displays a control line and a test line that targets *P. falciparum*–specific histidine-rich protein-2 (HRP-2) Three-band MRDT (bottom image) displays a control line and two test lines, one targeting HRP-2 and another line targeting pan-parasite lactate dehydrogenase. Control and test lines are cherry-red colored. *(From Maltha J, Jacobs J:* Clinical practice: the diagnosis of imported malaria in children. *Eur J Pediatr 2011;170:821-829.)*

COUNSELING

Risk of malaria and importance of malaria chemoprophylaxis and personal protective measures must be emphasized with each traveler.[11,53,87,125] Medication adherence should be emphasized.

FIGURE 40-29 BinaxNOW Malaria is the only brand of malaria rapid diagnostic test approved for use in the United States. *(From Howden BP et al:* Chronic falciparum malaria causing massive splenomegaly 9 years after leaving an endemic area. *Med J Aust 2005; 185:186-188.)*

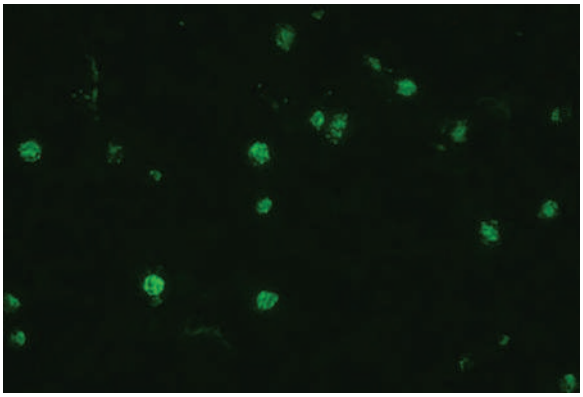


FIGURE 40-30 Indirect fluorescent antibody (IFA) test. The fluorescence indicates that patient serum being tested contains antibodies that are reacting with antigen preparation (here, *Plasmodium falciparum* parasites). *(From Centers for Disease Control and Prevention: Malaria Diagnosis (U.S.) Serology. 11-9-2012. 12-22-2014.)*

Stress the importance of taking chemoprophylactic medication on the same day each week, and preferably at the same time each day. Discuss signs and symptoms of malaria and potential side effects of any drugs prescribed for malaria prophylaxis. Treatment is most effective early during the disease. A delay in appropriate therapy can have potentially serious or fatal consequences. Travelers should know where to obtain local urgent medical care before they leave for any malaria-endemic area.

PERSONAL PROTECTIVE MEASURES

Preventing bites from infected *Anopheles* mosquitoes (see Chapter 45) is an important adjunct to chemoprophylaxis for malaria prevention in travelers (Table 40-7). Strategies to reduce mosquito contact include remaining in well-screened areas, using insecticide-treated bed nets, wearing clothes that cover the body (i.e., long-sleeved shirts, pants, and hats), and using effective insect repellent during evening and nighttime hours.[11,53] *Anopheles* mosquitoes are nocturnal feeders. Outdoor activity should be minimized from dusk to dawn, when the insects are most active. Mosquito repellent, such as N,N-diethyl-3-methylbenzamide (DEET), should be applied to exposed skin.[11,53] When used appropriately, DEET is safe and effective for adults, children, and infants older than 2 months of age. DEET formulations of 20% to 50% provide at least 4 hours of protection. Lower percentages provide a shorter duration of action.[11,53] If sunscreen is used, apply it before insect repellent.[11] Permethrin and deltamethrin are long-acting insecticides that can be applied to clothes and gear. When applied properly, permethrin-treated clothes repel mosquitoes for up to 25 launderings. A bed net treated with insecticide (i.e., permethrin) with its edges tucked underneath a mattress provides protection during peak mosquito feeding times, particularly when accommodations are not air-conditioned or enclosed by screens. Picaridin is a synthetic repellent that has been shown in clinical trials to be comparable with DEET. However, the 7% formulation available in the United States is a lower concentration than that which was tested in most studies.[53] Other agents that provide protection against mosquitoes include oil of lemon eucalyptus (or the synthetic version, para-menthane-3,8-diol [PMD]) and IR3535 (3-[*N*-butyl-*N*-acetyl]-aminopropionic acid, ethyl ester).[11] Much less reliable outdoor mosquito repellents are mosquito coils or candles.

TABLE 40-7 Checklist for Malaria Prevention in Travelers

Preventive Measure	Recommendations
Counseling	Importance of chemoprophylaxis
	Potential adverse reactions or side effects from chemoprophylaxis
	Clinical manifestations of malaria
	Plan for urgent medical care
Personal protective measures	Minimize outdoor activity at dusk and night
	Wear long sleeves, long pants, and hats at dusk and night
	Use insect repellent:
	10% to 35% N,N-diethyl-3-methylbenzamide (DEET) for exposed skin
	Permethrin for clothes, shoes, mosquito nets, tents, and other gear
	Insecticide-treated bed nets
	Mosquito coils and candles
Chemoprophylaxis	Assess malaria risk
	Determine malaria resistance patterns
	Consider the following:
	Age
	Underlying medical conditions
	Allergies
	Tolerability
	Length of stay
	Advise when to start medication and how long to continue after return
	Determine whether medication should be prescribed for presumptive self-treatment

CHEMOPROPHYLAXIS

Chemoprophylaxis is a strategy used for preventing malaria by administering medications.[11,41,53] Primary prophylaxis uses medications before, during, and after travel to prevent disease caused by initial infection by inhibiting replication of asexual parasites that have emerged from liver. Terminal prophylaxis uses medications toward the end of the exposure period to prevent relapse or delayed onset of disease caused by the *Plasmodium* liver stages, which are hypnozoites of *P. vivax* and *P. ovale*.[11] Primary chemoprophylaxis should be started before exposure to malaria parasites (often before travel) to allow antimalarial agents to reach sufficient blood concentrations. Chemoprophylaxis can be started even earlier to allow discovery of potential adverse events. Presumptive antirelapse therapy (i.e., terminal prophylaxis) is typically indicated for persons (e.g., Peace Corps volunteers, military personnel, and missionaries) who have prolonged exposure in malaria-endemic areas.[11] Routine chemoprophylaxis is not recommended for residents of malaria-endemic areas because of potential suppression of development of immunity that protects against severe disease after 3 to 5 years of age and emergence of parasite resistance. In Africa, intermittent preventive treatment (i.e., sulfadoxine-pyrimethamine) is given to pregnant women.[66]

Chemoprophylaxis should be prescribed for nonimmune individuals, including children, traveling to malaria-endemic areas.[11,31,97] In 2012, despite predeparture information on chemoprophylaxis, only 34% of U.S. civilians diagnosed with imported malaria had actually taken malaria chemoprophylaxis.[29] Eleven percent were not taking a CDC-recommended regimen.[29] Consider several factors (e.g., destination-specific malaria risk and resistance patterns, age, underlying medical conditions, concomitant medications, allergies, tolerability, and length of stay) when choosing an appropriate chemoprophylactic regimen for travelers (Table 40-8).[11] Pediatric dosages are based on weight. They should never exceed adult dosages. A summary of available medications and recommendations for malaria chemoprophylaxis can be found in Tables 40-9 and 40-10.[29]

Current information about malaria risk, resistance patterns, and recommendations for travelers is available through the CDC and WHO.[11,115] (see Resources) Most areas have chloroquine-resistant *P. falciparum,* with the exception of the Caribbean Islands, Central America west of the former Panama Canal Zone, Egypt, and some countries in the Middle East.[11] Sulfadioxine-pyrimethamine resistance is widespread in the Amazon River Basin, much of Asia,

TABLE 40-8 Considerations When Choosing a Drug for Malaria Prophylaxis

Drug	Reasons to Consider Use of This Drug	Reasons to Consider Avoiding Use of This Drug
Atovaquone-proguanil	Good for last-minute travelers because the drug is started 1-2 days before travel Some people prefer to take a daily medicine Good choice for shorter trips because you have to take the medicine for only 7 days after traveling, rather than for 4 weeks Well tolerated; side effects uncommon Pediatric tablets are available and may be more convenient	Cannot be used by women who are pregnant or breastfeeding a child that weighs < 5 kg (11.02 lb) Cannot be taken by people with severe renal impairment Tends to be more expensive than some of the other options (especially for long trips) Some people (including children) would rather not take a medicine every day
Chloroquine	Some people would rather take medicine weekly Good choice for long trips because it is taken only weekly Some people are already taking hydroxychloroquine chronically for rheumatologic conditions; such persons may not have to take an additional medicine Can be used in all trimesters of pregnancy	Cannot be used in areas with chloroquine or mefloquine resistance May exacerbate psoriasis Some people would rather not take a weekly medication For short trips, some people would rather not take medication for 4 weeks after travel Not a good choice for last-minute travelers, because drug needs to be started 1-2 weeks before travel
Doxycycline	Some people prefer to take a daily medicine Good for last-minute travelers because the drug is started 1-2 days before travel Tends to be the least expensive antimalarial People who are already taking doxycycline chronically to prevent acne do not have to take an additional medicine Doxycycline also can prevent some additional infections (such as rickettsial infections and leptospirosis), so it may be preferred by people planning to hike, camp, and swim in fresh water	Cannot be used by pregnant women and children < 8 years of age Some people would rather not take a medicine every day For short trips, some people would rather not take medication for 4 weeks after travel Women prone to getting vaginal yeast infections when taking antibiotics may prefer taking a different medicine People may want to avoid the increased risk of sun sensitivity Some people are concerned about the potential of developing gastric distress from doxycycline
Mefloquine	Some people would rather take medicine weekly Good choice for long trips because it is taken only weekly Can be used in all trimesters of pregnancy	Cannot be used in areas with mefloquine resistance Cannot be used in patients with certain psychiatric conditions Cannot be used in patients with a seizure disorder Not recommended for people with cardiac conduction abnormalities Not a good choice for last-minute travelers because the drug needs to be started ≥ 2 weeks before travel Some people would rather not take a weekly medication For short trips, some people would rather not take medication for 4 weeks after travel
Primaquine	It is the most effective medicine for preventing *P. vivax* infection, so it is a good choice for travel to places with more than 90% *P. vivax* as the cause of malaria Good choice for shorter trips because you only have to take the medicine for 7 days after traveling, rather than for 4 weeks Good for last-minute travelers because the drug is started 1-2 days before travel Some people prefer to take a daily medicine	Cannot be used in patients with G6PD deficiency Cannot be used in patients who have not been tested for G6PD deficiency There are costs and delays associated with getting a G6PD test; however, it only has to be done once; once a normal G6PD level is verified and documented, the test does not have to be repeated the next time primaquine is considered Cannot be used by pregnant women Cannot be used by women who are breastfeeding, unless the infant has also been tested for G6PD deficiency Some people (including children) would rather not take a medicine every day Some people are concerned about the potential of having gastric distress from primaquine

From Centers for Disease Control and Prevention: CDC Health Information for International Travel, 2014, Atlanta, Georgia, 2014, US Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Center for infectious Diseases, Division of Global Migration and Quarantine; nc.cdc.gov/travel/yellowbook/2014/chapter-3-infectious-diseases-related-to-travel/malaria#3938.
G6PD, glucose-6-phosphate dehydrogenase.

and large parts of Africa.[11] Mefloquine-resistant *P. falciparum* has been documented on the borders of Thailand with Myanmar (Burma) and Cambodia; in the western provinces of Cambodia and the eastern states of Myanmar; on the border between Myanmar and China, borders of Laos and Myanmar, and Thailand-Cambodia border; and in southern Vietnam.[11] Artemisinin-resistant *P. falciparum* has been described in similar areas in Southeast Asia (see Figure 40-6).[123] Chloroquine-resistant *P. vivax* has been confirmed in several parts of the world, including Papua New Guinea, Indonesia, Myanmar, Vietnam, South Korea, Turkey, Ethiopia, Madagascar, South America, and eastern India.[84]

No chemoprophylactic malaria regimen is 100% effective. Malaria should always be considered in a febrile patient returning from a malaria-endemic area.

Medications Used for Malaria Chemoprophylaxis

Medications used for malaria chemoprophylaxis are listed in alphabetical order. Unless otherwise noted, all daily medications

TABLE 40-9 Drugs Used for the Prevention of Malaria (in Alphabetical Order)*

Drug	Trade Names	Adult Dose	Pediatric Dose†	When to Start Before Travel to Malarious Area	How Long to Continue After Return	Adverse Effects	Comments
Atovaquone-proguanil	Malarone	1 adult tablet‡ orally, daily	5-8 kg (11.02-17.6 lb): ½ pediatric tablet§ daily >8-10 kg (22 lb): ¾ pediatric tablet§ daily >10-20 kg (44.1 lb): 1 pediatric tablet§ daily >20-30 kg (66.14 lb): 2 pediatric tablets§ daily >30-40 kg (66.14-88.2 lb): 3 pediatric tablets§ daily ≥40 kg (88.2 lb): 1 adult tablet§ daily	1-2 days	7 days	Headache, nausea, vomiting, abdominal pain, diarrhea, increased transaminase levels, and seizures	Take with food or milk. Contraindicated in persons with severe renal impairment (i.e., creatine clearance of <30 mL/min). Not recommended for children <5 kg (11.02 lb), pregnant women, and women breastfeeding infants <5 kg (11.02 lb). Partial-tablet doses should be prepared and dispensed by a pharmacist. For children weighing 5 to <11 kg (24.25 lb), off-label use is recommended by the CDC.
Chloroquine phosphate	Aralen, generic	300-mg base (500-mg salt) orally, once/week	5-mg/kg base (8.3-mg/kg salt) orally, once/week, up to maximum adult dose of 300-mg base	1-2 weeks	4 weeks	Pruritus, nausea, headache, skin eruptions, dizziness, blurred vision, and insomnia	Has been used extensively and safely during pregnancy. May exacerbate psoriasis.
Doxycycline	Vibramycin, Vibra-Tabs, Doryx, Periostat, and others; generic	100 mg orally, daily	≥8 years: 2.2 mg/kg up to adult dose of 100 mg/day	1-2 days	4 weeks	Gastrointestinal upset, vaginal candidiasis, photosensitivity, allergic reactions, blood dyscrasias, azotemia in renal diseases, and hepatitis	Take with food. Contraindicated in children <8 years of age and pregnant women.
Hydroxychloroquine sulfate	Plaquenil, generic	310-mg base (400-mg salt) orally, once/week	5-mg/kg base (6.5-mg/kg salt) orally, once/week, up to maximum adult dose of 310-mg base	1-2 weeks	4 weeks	Pruritus, nausea, headache, skin eruptions, dizziness, blurred vision, and insomnia	Has been used extensively and safely during pregnancy. May exacerbate psoriasis.

Continued

TABLE 40-9 Drugs Used for the Prevention of Malaria (in Alphabetical Order)*—cont'd

Drug	Trade Names	Adult Dose	Pediatric Dose†	When to Start Before Travel to Malarious Area	How Long to Continue After Return	Adverse Effects	Comments
Mefloquine	Lariam, Mephaquin, generic	228-mg base (250-mg salt) orally, once/week	≤9 kg: 4.6-mg/kg base (5-mg/kg salt) orally, once/week >9-19 kg: ¼ tablet once/week >19-30 kg: ½ tablet once/week >30-45 kg: ¾ tablet once/week ≥45 kg: 1 tablet, once/week	≥2 weeks	4 weeks	Gastrointestinal disturbances, headache, insomnia, vivid dreams, visual disturbances, depression, anxiety disorder, and dizziness	Contraindicated in persons with active depression or a recent history of depression, generalized anxiety disorder, psychosis, schizophrenia, other major psychiatric disorders, or seizures. Rare serious adverse reactions reported with treatment doses include psychoses and seizures. These reactions are seen more frequently at the higher doses used for treatment. Contraindicated in people allergic to mefloquine or related compounds (quinine, quinidine). Not recommended for persons with cardiac conduction abnormalities. Use with caution in travelers with psychiatric disturbances or a history of depression. In the United States, 250-mg tablet of mefloquine contains 228-mg mefloquine base. Outside the United States, 275-mg mefloquine tablet contains 250-mg mefloquine base. For children weighing < 5 kg, off-label use is recommended by the CDC.
Primaquine primary prophylaxis	— —	30-mg base (52.6-mg salt) orally, daily	0.5-mg/kg base (0.8-mg/kg salt) up to adult dose, orally, daily	1-2 days	7 days	Nausea, abdominal pain, and hemolytic anemia (especially in patients with G6PD deficiency)	An option for primary prophylaxis in special circumstances such as short-duration travel to areas with principally *P. vivax*. Take with food. All persons taking primaquine should have a documented normal G6PD level before beginning the medication. Contraindicated in persons with G6PD deficiency, during pregnancy, and during breastfeeding, unless the infant being breastfed has a documented normal G6PD level.
Primaquine presumptive antirelapse therapy (terminal prophylaxis)	—	30-mg base (52.6-mg salt) orally, daily	0.5-mg/kg base (0.8-mg/kg salt) up to adult dose, orally, daily	Not applicable	14 days	Nausea, abdominal pain, and hemolytic anemia (especially in patients with G6PD deficiency)	Indicated for people who have had prolonged exposure to *P. vivax*, *P. ovale*, or both. Take with food. All persons taking primaquine should have a documented normal G6PD level before beginning the medication. Contraindicated in persons with G6PD deficiency, during pregnancy, and during breastfeeding, unless the infant being breastfed has a documented normal G6PD level.

Modified from Centers for Disease Control and Prevention: CDC Health Information for International Travel, 2014, Atlanta, Georgia, 2014, U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Center for infectious Diseases, Division of Global Migration and Quarantine; nc.cdc.gov/travel/yellowbook/2014/chapter-3-infectious-diseases-related-to-travel/malaria#3939. Refer to the U.S. Centers for Disease Control and Prevention for most recent destination specific risks and chemoprophylaxis and treatment guidelines.
*Caused by *Plasmodium falciparum, P. ovale, P. vivax,* and *P. malariae*.
†Should never exceed adult dose.
‡Adult tablets contain 250 mg atovaquone and 100 mg proguanil hydrochloride.
§Pediatric tablets contain 62.5 mg atovaquone and 25 mg proguanil hydrochloride.
CDC, Centers for Disease Control and Prevention.

TABLE 40-10 Changing Medications as a Result of Side Effects During Chemoprophylaxis

Drug Being Stopped	Drug Being Started	Comments
Mefloquine	Doxycycline	Begin doxycycline, continue daily while in malaria-endemic area, and continue for 4 weeks after leaving malaria-endemic area.
	Atovaquone-proguanil	If switch occurs ≥ 3 weeks before departure from endemic area, atovaquone-proguanil should be taken daily for remainder of the stay in the endemic area and for 1 week thereafter. If switch occurs < 3 weeks before departure from endemic area, atovaquone-proguanil should be taken daily for 4 weeks after switch. If switch occurs after departure from risk area, atovaquone-proguanil should be taken daily until 4 weeks after date of departure from the endemic area.
	Chloroquine	Not recommended
	Primaquine	Not recommended
Doxycycline	Mefloquine	Not recommended
	Atovaquone-proguanil	If switch occurs ≥ 3 weeks before departure from endemic area, atovaquone-proguanil should be taken daily for remainder of stay in the endemic area and for 1 week thereafter. If switch occurs < 3 weeks before departure from endemic area, atovaquone-proguanil should be taken daily for 4 weeks after switch. If switch occurs after departure from the risk area, atovaquone-proguanil should be taken daily until 4 weeks after date of departure from endemic area.
	Chloroquine	Not recommended
	Primaquine	Not recommended
Atovaquone-proguanil	Doxycycline	Begin doxycycline, continue daily while in malaria-endemic area, and continue for 4 weeks after leaving malaria-endemic area.
	Mefloquine	Not recommended
	Chloroquine	Not recommended
	Primaquine	This switch would be unlikely because primaquine is only recommended for primary prophylaxis in areas with mainly *P. vivax* for people with normal G6PD activity. Should that be the case, begin primaquine, continue daily while in malaria-endemic area, and continue for 7 days after leaving malaria-endemic area.
Chloroquine	Doxycycline	Begin doxycycline, continue daily while in malaria-endemic area, and continue for 4 weeks after leaving malaria-endemic area.
	Atovaquone-proguanil	If switch occurs ≥ 3 weeks before departure from endemic area, atovaquone-proguanil should be taken daily for remainder of stay in the endemic area and for 1 week thereafter. If switch occurs < 3 weeks before departure from endemic area, atovaquone-proguanil should be taken daily for 4 weeks after switch. If switch occurs following departure from risk area, atovaquone-proguanil should be taken daily until 4 weeks after date of departure from endemic area.
	Mefloquine	Not recommended
	Primaquine	Not recommended
Primaquine	Doxycycline	Begin doxycycline, continue daily while in malaria-endemic area, and continue for 4 weeks after leaving malaria-endemic area.
	Atovaquone-proguanil	Begin atovaquone-proguanil, continue daily while in malaria-endemic area, and continue for 7 days after leaving malaria-endemic area.
	Chloroquine	Not recommended
	Mefloquine	Not recommended

From Centers for Disease Control and Prevention: CDC Health Information for International Travel, 2014, Atlanta, Georgia, 2014, U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Center for infectious Diseases, Division of Global Migration and Quarantine; nc.cdc.gov/travel/yellowbook/2014/chapter_3_infectious diseases_related_to_travel/malaria#3941.

should be taken at the same time each day and all weekly medications should be taken on the same day each week. Travelers to areas with limited malaria transmission should use personal protective measures only, and no chemoprophylaxis should be prescribed.[11] Detailed information on destination-specific malaria risk can be found on the CDC website (cdc.gov/malaria/travelers/index.html.[11,23]

Atovaquone-Proguanil. Atovaquone-proguanil is a fixed-dose combination drug. Primary prophylaxis should begin 1 to 2 days before travel to malaria-endemic areas, and continue once a day during travel and daily for 7 days after leaving the malaria-endemic area (see Table 40-9). Common adverse effects associated with atovaquone-proguanil prophylaxis include abdominal pain, nausea, vomiting, and headache.[11,114]Atovaquone-proguanil should not be used in pregnant or breast-feeding women, infants weighing less than 5 kg (11.02 lb), or individuals with severe renal impairment (i.e., creatinine clearance of < 30 mL/min).[11,24] Atovaquone-proguanil should be used with caution in individuals taking warfarin. A pediatric formulation of atovaquone-proguanil is available in the United States. The CDC states that atovaquone-proguanil may be used for children weighing at least 5 kg (11.02 lb); however, providers should note that prophylactic dosing for children who weigh less than 11 kg (24.25 lb) is considered off-label use in the United States.[11]

Chloroquine and Hydroxychloroquine. Chloroquine is the drug of choice for primary prophylaxis for travelers to areas with chloroquine-sensitive malaria.[11] The drug should be started 1 to 2 weeks before travel to a malaria-endemic area, continued once a week during travel, and for 4 weeks after leaving a malaria-endemic area (see Table 40-9).[11] Hydroxychloroquine

is an alternative that may be better tolerated. Side effects of chloroquine and hydroxychloroquine include gastrointestinal disturbance, headache, dizziness, blurred vision, pruritus, and insomnia.[11,114] Serious side effects (e.g., retinopathy) associated with high-dose chloroquine used for rheumatoid arthritis treatment are unlikely at lower prophylaxis dosing.[11] Chloroquine and hydroxychloroquine may exacerbate psoriasis.

Doxycycline. Doxycycline primary prophylaxis should be started 1 to 2 days before travel to endemic areas, continued once a day during travel, and continued daily for 4 weeks after the traveler leaves the endemic area (see Table 40-9).[11,99] Minocycline, often prescribed for acne treatment, has not been adequately studied for malaria chemoprophylaxis.[11] Patients on long-term minocycline should discontinue use prior to starting doxycycline chemoprophylaxis. Doxycycline can cause photosensitivity, usually manifested as an increased sunburn reaction. This can be minimized by avoiding direct sun exposure and liberally using sunscreens.[11,114] Doxycycline is associated with increased frequency of *Candida* vaginitis and may decrease effectiveness of oral contraceptives. Gastrointestinal side effects (e.g., nausea and vomiting) can be decreased if medication is taken on a full stomach. Doxycycline should not be used in children younger than 8 years of age or pregnant women because of the risk for dental staining.[11] For travelers requiring oral typhoid vaccine (i.e., Ty21a), doxycycline should be stopped at least 24 hours before that vaccine's administration.[11]

Mefloquine. Mefloquine prophylaxis should be started at least 2 weeks before traveling to an endemic area and continued once a week during travel and for 4 weeks after leaving the endemic area[11] (see Table 40-9). Rare but serious adverse reactions with prophylactic doses of mefloquine include psychoses and seizures.[11] These reactions are seen more frequently in higher doses used for treatment. Uncommon neuropsychiatric side effects include sensory and motor neuropathies (e.g., paresthesia, tremor, ataxia), agitation, mood changes, panic attacks, forgetfulness, confusion, hallucinations, aggression, paranoia, and encephalopathy.[11,114] There are reports of psychiatric symptoms and vestibular toxicity persisting after mefloquine has been stopped.[11] Other side effects include gastrointestinal disturbances, headaches, insomnia, vivid dreams, visual disturbances, depression, anxiety disorders, and dizziness.[11] Mefloquine is contraindicated in people with known hypersensitivity to mefloquine or related compounds (i.e., quinine or quinidine), seizures, active depression, recent history of depression, generalized anxiety disorder, psychosis, schizophrenia, or other major psychiatric disorders. Mefloquine is not recommended for use by people with cardiac conduction abnormalities.[11,114] Mefloquine may be used by patients taking β-adrenergic blockers without underlying arrhythmias.[11] A copy of the U.S. Food and Drug Administration Medication Guide should be provided to any traveler receiving a prescription for mefloquine: (accessdata.fda.gov/drugsatfda_docs/label/2013/076392s008lbl.pdf).

Primaquine. Primaquine can be used for primary prophylaxis in areas with primary *P. vivax* and presumptive antirelapse therapy (terminal prophylaxis).[11] Primary primaquine prophylaxis should begin 1 to 2 days before travel to an endemic area, continued once a day during travel, and daily for 7 days after the traveler leaves the endemic area (see Table 40-9). Patients receiving primaquine as primary prophylaxis do not require it for terminal prophylaxis. Primaquine should be given concurrently with the primary prophylaxis medication. When primaquine is used for presumptive antirelapse therapy, it is given for 14 days after the traveler has returned from the malarious area.[11] In situations where chloroquine, doxycycline, or mefloquine is used for primary prophylaxis, primaquine is typically given during the last 2 weeks of postexposure prophylaxis.[11] When atovaquone-proguanil is used for prophylaxis, primaquine is given for the final 7 days of atovaquone-proguanil treatment and an additional 7 days thereafter.[11] Before receiving a prescription for primaquine, the patient must have a normal G6PD level. Primaquine can cause fatal oxidant-induced hemolytic anemia and methemoglobinemia in G6PD-deficient persons. In individuals with normal G6PD levels, the most common adverse event is gastrointestinal upset, which can be minimized by taking medication with food.

Travelers to Areas with Mainly *P. vivax* Malaria

For travelers to destinations where *P. vivax* is the main malarial species, primaquine can be used as primary prophylaxis if the traveler is not G6PD deficient. In the United States, using primaquine for primary prophylaxis is considered off-label. Personal protective measures should also be used. Detailed information on destination-specific malaria risk can be found on the CDC website (cdc.gov/malaria/travelers/index.html).[11,23]

Travelers to Areas with Chloroquine-Sensitive Malaria

Travelers to areas with chloroquine-sensitive malaria can use chloroquine, atovaquone-proguanil, doxycycline, or mefloquine. In areas where *P. vivax* is the main species of malaria, primaquine can be used in non-G6PD–deficient travelers.[11] Personal protective measures should also be used. Detailed information on destination-specific malaria risk can be found on the CDC website (cdc.gov/malaria/travelers/index.html).[11,23]

Travelers to Areas with Chloroquine-Resistant Malaria

Travelers to areas with chloroquine-resistant malaria can use atovaquone-proguanil, doxycycline, and mefloquine.[11] In areas where *P. vivax* is the main species of malaria, primaquine can be used in travelers who are not G6PD deficient.[11] Personal protective measures should also be used. Detailed information on destination-specific malaria risk can be found on the CDC website (cdc.gov/malaria/travelers/index.html).[11,23]

Travelers to Areas with Mefloquine-Resistant Malaria

Travelers to areas with mefloquine-resistant *P. falciparum* should use atovaquone-proguanil or doxycycline for malaria chemoprophylaxis. Personal protective measures should also be used. Detailed information on destination-specific malaria risk can be found on the CDC website (cdc.gov/malaria/travelers/index.html).[11,23]

Prevention of Relapses with *P. vivax* and *P. ovale*

Terminal prophylaxis with primaquine decreases the risk of relapse by acting against liver stages of *P. vivax* and *P. ovale*. Individuals with prolonged exposure to malaria (e.g., missionaries, Peace Corps volunteers, military personnel) returning to nonendemic areas should be given terminal prophylaxis.[11]

CHEMOPROPHYLAXIS FOR INFANTS, CHILDREN, AND ADOLESCENTS

Infants, children, and adolescents of any age and weight are at increased risk for developing severe complications from malaria infection.[11,50,97] Drug dosages should be calculated using body weight and should never exceed adult dosages (see Table 40-9).[11] Depending on destination-specific *P. falciparum* susceptibility, chloroquine and mefloquine can be used for children of nearly all ages and weights, although the CDC-recommended dosing for younger children may be considered off-label use in the United States. Doxycycline can be used for children at least 8 years of age. Atovaquone-proguanil is available in pediatric tablets and can be used for infants and children weighing at least 5 kg (11.02 lb). Use of atovaquone-proguanil for malaria prophylaxis in children that weigh less than 11 kg (24.25 lb) constitutes off-label use in the United States.[11] Overdoses of antimalarials can be fatal. Medications should be stored in childproof containers and kept out of reach of infants and children.

Many antimalarials have a very bitter taste and are available only as tablets. This can make mediation compliance difficult. Pharmacists can pulverize tablets and place powder in gelatin capsules. Parents can open capsules and mix the contents with small amounts of sweetener (e.g., applesauce, chocolate syrup, or jelly) as needed. To ensure adequate antimalarial blood concentrations, the child should take the entire dose at one time. Minimize gastrointestinal upset and vomiting by giving each antimalarial dose on a full stomach. Personal protective measures should also be used. Detailed information on destination-specific malaria risk can be found on the CDC website (cdc.gov/malaria/).[11,23]

CHEMOPROPHYLAXIS DURING PREGNANCY

Pregnant women are at increased risk for severe malarial disease and adverse pregnancy outcomes (e.g., prematurity, abortion, and stillbirth). Women who are pregnant, or are likely to become pregnant, should be advised to avoid travel to malaria-endemic areas. If travel must occur, an effective chemoprophylactic regimen in conjunction with personal protective measures should be recommended. Malaria prophylaxis with chloroquine phosphate or hydroxychloroquine sulfate is safe and effective for pregnant women traveling to areas with chloroquine-susceptible *P. falciparum* and *P. vivax*.[11] For pregnant women traveling to areas with chloroquine-resistant *P. falciparum,* mefloquine is the drug of choice. Mefloquine is classified by the Food and Drug Administration as a category B drug (i.e., animal reproduction studies have failed to demonstrate a risk to the fetus and there are no well-controlled studies in humans).[11] There are insufficient data to recommend use of atovaquone-proguanil for prevention of malaria during pregnancy. Doxycycline is contraindicated in pregnant women because it may be associated with tooth discoloration and dysplasia, and inhibition of bone growth in the fetus.[11,99] Primaquine should not be prescribed to pregnant women. The fetus may have G6PD deficiency and develop hemolytic anemia in utero. Health care providers who require assistance with management of pregnant travelers should consult malaria experts at the CDC. Personal protective measures should also be used. Detailed information on destination-specific malaria risk can be found on the CDC website (cdc.gov/malaria/travelers/index.html).[11,23]

CHEMOPROPHYLAXIS WHILE BREASTFEEDING

The mother and breastfeeding infant should receive chemoprophylaxis. Most antimalarial drugs are not secreted in sufficient amounts in breast milk to protect the infant from malaria. Very small amounts of chloroquine and mefloquine excreted in breast milk are not harmful to the infant and are in insufficient quantities to protect the infant against malaria. Infants who require malaria chemoprophylaxis should receive recommended dosages.[11] There are limited data about the use of doxycycline in lactating women, but most experts believe the risk of adverse events in the breastfeeding infant to be remote.[11] No data are available regarding the amount of primaquine excreted in breast milk. A breastfeeding infant should be tested for G6PD deficiency before primaquine is given to the mother. It is not known whether atovaquone is excreted in human milk. Proguanil is excreted in insufficient quantities to protect the infant. Atovaquone-proguanil is not currently recommended to prevent malaria in women who are breastfeeding infants that weigh less than 5 kg (11.02 lb).[11] Atovaquone-proguanil can be used to treat malaria in a breastfeeding woman when potential benefit to the mother's life outweighs potential risk to the infant.[11]

CHANGING MEDICATIONS DURING CHEMOPROPHYLAXIS BECAUSE OF SIDE EFFECTS

Travelers should consult with a health care professional if they must change medications during chemoprophylaxis as a result of side effects. Medications recommended for prophylaxis against malaria have different modes of action that affect the parasite at different life cycle stages (Table 40-10).[11] For example, if a traveler starts with chloroquine, mefloquine, or doxycycline and then changes to atovaquone-proguanil, the standard duration of atovaquone-proguanil therapy would be insufficient. Atovaquone-proguanil would have to be continued for 4 weeks after switching or 1 week after returning from a malaria-endemic area, whichever is longer.[11] Health care providers who require assistance in management of travelers requiring a chemoprophylactic regimen switch are encouraged to consult malaria experts at the CDC.

MEDICATIONS ACQUIRED OVERSEAS

Antimalarials are widely available outside the United States. Travelers should be cautioned against purchasing medications overseas.[14,39] Medications purchased overseas may not have undergone rigorous testing and review to verify identity, potency, purity, and stability. They may be ineffective, dangerous, or contaminated (Figures 40-31 to 40-38).[77,78] Counterfeit drugs may cause unexpected side effects and allergic reactions. Information regarding counterfeit and substandard antimalarial drugs can be found at cdc.gov/malaria/travelers/counterfeit_drugs.html and fda.gov/Drugs/DrugSafety/ucm169898.htm.[14,40]

TREATMENT

Malaria treatment consists of rapid and appropriate antimalarial therapy along with supportive care. Individuals living in areas with perennial malaria transmission develop immunity against severe malarial disease. These semiimmune individuals are often asymptomatic and have a lower risk of serious complications and death. Malaria in nonimmune and at-risk populations (e.g., travelers, infants, children, pregnant women) should be considered a medical emergency, because falciparum malaria can progress rapidly and be lethal.

When initiating medical therapy, consider the likely *Plasmodium* species, clinical status of the patient, and resistance patterns.[11,24,114,119] It is important to determine *Plasmodium* species to alert clinicians to potentially rapidly progressive, severe disease (i.e., *P. falciparum* or *P. knowlesi*). *P. vivax* and *P. ovale* require treatment for hypnozoite forms that can lead to relapsing infections. The patient's clinical status is categorized as uncomplicated or severe malaria. Uncomplicated malaria can be treated with oral antimalarials. Severe falciparum malaria is a medical emergency and requires immediate treatment. Use parenteral antimalarial therapy in patients with one or more of the following clinical criteria indicating severe malaria: impaired consciousness/coma, severe anemia, renal failure, acute respiratory distress syndrome, hypotension, disseminated intravascular coagulation, spontaneous bleeding, acidosis, hemoglobinuria, jaundice, repeated generalized convulsions, and/or parasitemia of 5% or more.[11,24,114,119] Providers should determine the likely malaria parasite resistance pattern from the geographic location where the infection was acquired. In general, drugs used for malaria treatment should be different from those the patient used for malaria chemoprophylaxis. In cases where malaria is suspected but cannot be rapidly confirmed, immediately initiate antimalarial treatment against chloroquine-resistant *P. falciparum*.[24]

Health care workers requiring assistance with malaria diagnosis and treatment of malaria should consult physicians specializing in tropical medicine or infectious diseases, or the CDC. See the CDC algorithm to address malaria treatment in the United States (Figure 40-39).[24]

RELIABLE SUPPLY REGIMENS FOR PRESUMPTIVE SELF-TREATMENT

Counsel travelers with signs or symptoms of malaria to seek urgent medical evaluation. This should include thick and thin blood smears. Antimalarial medications for self-treatment may be prescribed for individuals that live in remote areas, where prompt access to medical care will be difficult (Table 40-11). A reliable treatment supply is a complete course of approved malaria treatment regimen acquired in the United States that will not interact adversely with the patient's other medicines (including malaria chemoprophylaxis) and will not deplete local resources in the destination country.[11] If a traveler develops an influenza-like illness with fever and chills and professional medical care is not available within 24 hours, presumptive self-treatment should be taken immediately. It is imperative that travelers seek medical care promptly after taking medication for presumptive malaria. Atovaquone-proguanil can be used for presumptive malaria self-treatment if it is not being used for malaria chemoprophylaxis.[11] Alternatively, artemether-lumefantrine can be used if the traveler was not taking mefloquine prophylaxis. Medical providers should consult with malaria experts or call the CDC Malaria Hotline (770-488-7788) for recommendations on reliable supply regimens for travelers who are unable to take atovaquone-proguanil or artemether-lumefantrine.

FIGURE 40-31 Map of the distribution of fake artesunate, collected by Wellcome Trust–University of Oxford SE Asian Tropical Medicine Research Programme and Collaborators, in relation to packaging type. Map drawn by Mr. Chongkham Phonekeo. *(From Newton PN, Fernandez FM, Plancon A, et al: A collaborative epidemiological investigation into the criminal fake artesunate trade in South East Asia. PLoS Med 2008;5:e32.)*

TABLE 40-11 Reliable Supply Regimens for the Treatment of Malaria †

Drug	Adult Dose	Pediatric Dose	Comments
Atovaquone-proguanil Adult tablet contains 250 mg atovaquone and 100 mg proguanil. Pediatric tablet contains 62.5 mg atovaquone and 25 mg proguanil.	4 adult tablets, orally as a single daily dose for 3 consecutive days	Daily dose to be taken for 3 consecutive days: 5-8 kg (11.02-17.6 lb): 2 pediatric tablets 9-10 kg (19.8-22.04 lb): 3 pediatric tablets 11-20 kg (24.25-44.09 lb): 1 adult tablet 21-30 kg (46.3-66.14 lb): 2 adult tablets 31-40 kg (68.34-88.14 lb): 3 adult tablets >41 kg (90.39 lb): 4 adult tablets	Contraindicated in people with severe renal impairment (creatinine clearance < 30 mL/min) Not recommended for people taking atovaquone-proguanil prophylaxis Not recommended for children weighing < 5 kg (11.02 lb), pregnant women, and women breastfeeding infants weighing < 5 kg (11.02 lb)
Artemether-lumefantrine One tablet contains 20 mg artemether and 120 mg lumefantrine.	A 3-day treatment schedule with a total of 6 oral doses is recommended for both adult and pediatric patients based on weight. Patient should receive initial dose, followed by second dose 8 hours later, then 1 dose twice per day for the following 2 days. 5 to < 15 kg (11.02 to < 33.07 lb): 1 tablet per dose 15 to < 25 kg (33.07 to < 55.12 lb): 2 tablets per dose 25 to < 35 kg (55.12 to < 77.16 lb): 3 tablets per dose ≥ 35 kg (≥ 77.16 lb): 4 tablets per dose		Not for people taking mefloquine prophylaxis. Not recommended for children weighing < 5 kg (< 11.02 lb), pregnant women, and women breastfeeding infants weighing < 5 kg (< 11.02 lb).

From Centers for Disease Control and Prevention: CDC Health Information for International Travel, 2014, Atlanta, Georgia, 2014, U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Center for infectious Diseases, Division of Global Migration and Quarantine2014.
*If used for presumptive self-treatment, medical care should be sought as soon as possible.
†Refer to the U.S. Centers for Disease Control and Prevention for most recent destination-specific risks and malaria chemoprophylaxis and treatment guidelines.

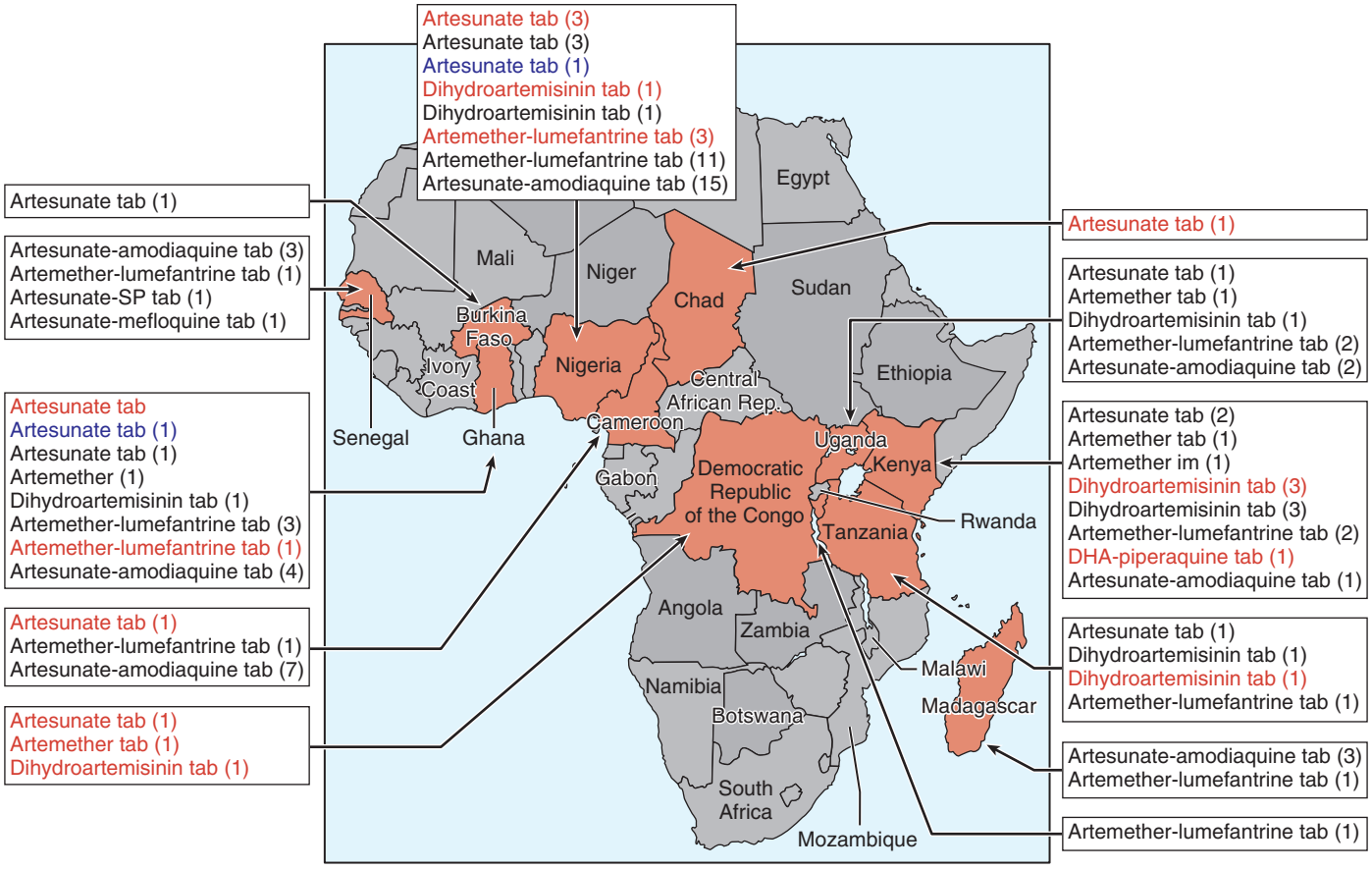


FIGURE 40-32 Map of Africa with reports of poor quality artemisinin derivatives and ACT to October 2011. Red = counterfeit, blue = substandard, black = poor quality (i.e., uncertain whether substandard or counterfeit). *(From Newton PN, Green MD, Mildenhall DC, et al:* Poor quality vital anti-malarials in Africa: an urgent neglected public health priority. *Malar J 2011;10:352.)*

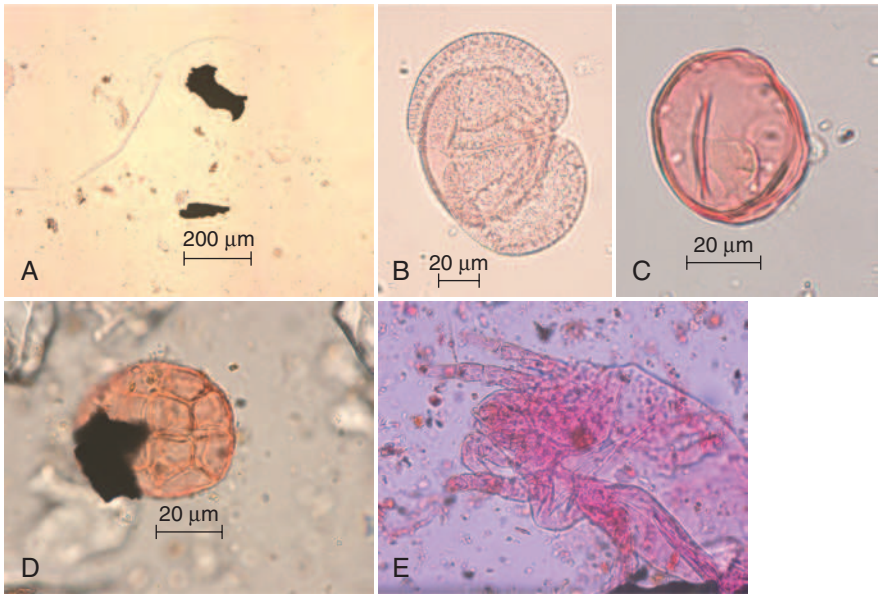


FIGURE 40-33 Photomicrographs of material found in fake artesunate tablets. **A,** Debris, including charcoal fragments. **B,** *Pinus* pollen grain. **C,** *Juglans* pollen grain. **D,** *Acacia* pollen grain with charcoal deposit. **E,** *Dermatophagoides* mite nymph. The maximum distance across the abdomen is 116 µm. Photographs by Dallas Mildenhall. *(From Newton PN, Fernandez FM, Plancon A, et al:* A collaborative epidemiological investigation into the criminal fake artesunate trade in South East Asia. *PLoS Med 2008;5:e32.)*

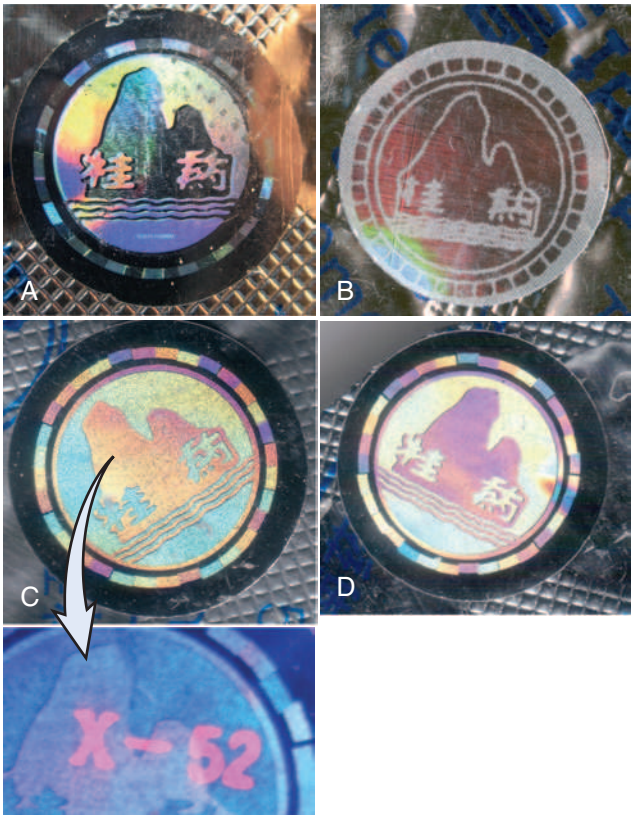


FIGURE 40-34 Examples of genuine and counterfeit holograms. **A,** Genuine Guilin Pharmaceutical artesunate blister pack hologram. **B,** Type 2 counterfeit sticker. **C,** Type 10 counterfeit hologram with the fake X-52 stamp as seen under ultraviolet light. **D,** Type 15 counterfeit hologram from seized counterfeit artesunate from the China/Myanmar border. *(From Newton PN, Fernandez FM, Plancon A, et al:* A collaborative epidemiological investigation into the criminal fake artesunate trade in South East Asia. *PLoS Med 2008;5:e32.)*

The CDC recommends presumptive treatment for *P. falciparum* malaria for refugees living in malaria-endemic areas of sub-Saharan Africa before immigration to the United States.[25] Guidelines for presumptive predeparture treatment of asymptomatic malaria, as well as directed treatment for special populations with asymptomatic malaria, are available on the CDC website.[25] Medications recommended for use in this population include artemether-lumefantrine, artesunate-amodiaquine, and oral quinine (Table 40-12).[25]

TREATMENT OF UNCOMPLICATED MALARIA

P. falciparum, or a Species Not Identified, Acquired in Areas with Chloroquine-Sensitive Malaria

Chloroquine and hydroxychloroquine are the drugs of choice for infections with chloroquine-susceptible malarial parasites (Table 40-13).[24,114] In addition, any regimen recommended for treatment of chloroquine-resistant malaria can be used for treatment of chloroquine-sensitive malaria.[24,114]

P. falciparum, or Species Not Identified, Acquired in Areas with Chloroquine-Resistant Malaria

Four treatment regimens are options for treatment of chloroquine-resistant *P. falciparum* infection (see Table 40-13).[24] These include two fixed-dose combination products (atovaquone-proguanil and artemether-lumefantrine). Quinine or quinidine, in conjunction with doxycycline, tetracycline, or clindamycin, is another option. For infections acquired in Africa and South America, 3 days of quinine treatment is needed. Infections acquired in Southeast Asia require quinine treatment for 7 days.[24] The fourth option, mefloquine, should only be used when there is no other alternative, due to rare but potentially serious severe neuropsychiatric reactions at treatment doses.[24]

Treatment options for children are the same as for adults. Weight-based dosing should not exceed recommended adult doses. If a quinine-based regimen is used in children, clindamycin (instead of doxycycline or tetracycline) should be used concomitantly. If no other treatment options are available, doxycycline or tetracycline can be used in children 8 years of age or less.

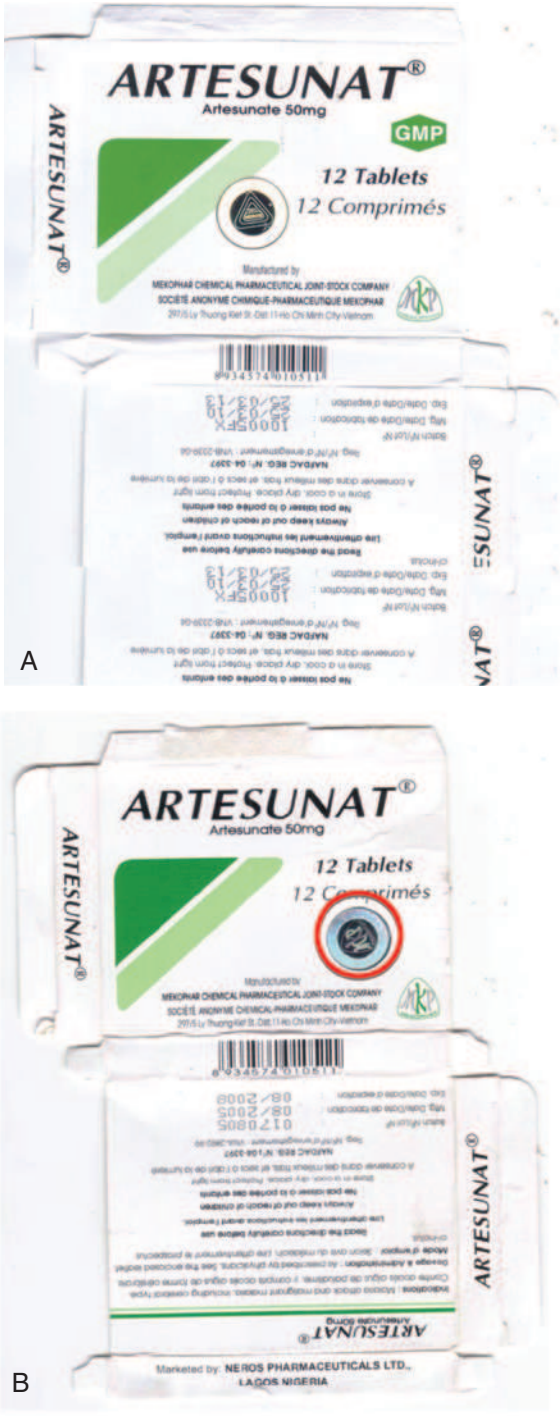


FIGURE 40-35 **A,** Genuine artesunate Mekophar Chemical Pharmaceutical Joint-Stock Company packet (Mek 10/03). **B,** Counterfeit artesunate packet labeled as made by Mekophar Chemical Pharmaceutical Joint-Stock Company (Cam S5/07). Counterfeit hologram in *red circle*. *(From Newton PN, Green MD, Mildenhall DC et al. Poor quality vital anti-malarials in Africa: an urgent neglected public health priority. Malar J 2011;10:352.)*

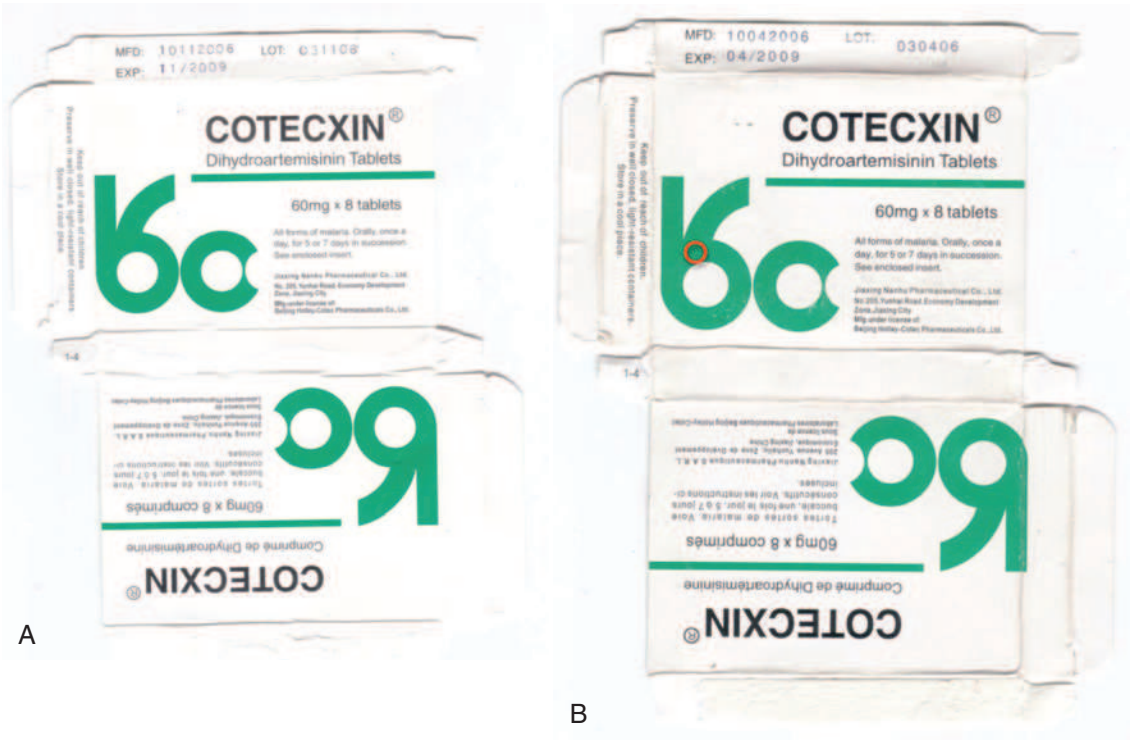


FIGURE 40-36 **A,** Genuine dihydroartemisinin (DHA) made by Jiaxing Nanhu Pharmaceutical Co. Ltd. packet (Ken 07/01). **B,** Counterfeit DHA packet labeled as made by Jiaxing Nanhu Pharmaceutical Co. Ltd. (Ken 07/02). Different shades of *green* (e.g., in *red circle*), from Ken 07/01. *(From Newton PN, Green MD, Mildenhall DC, et al:* Poor quality vital anti-malarials in Africa: an urgent neglected public health priority. *Malar.J 2011;10:352.)*

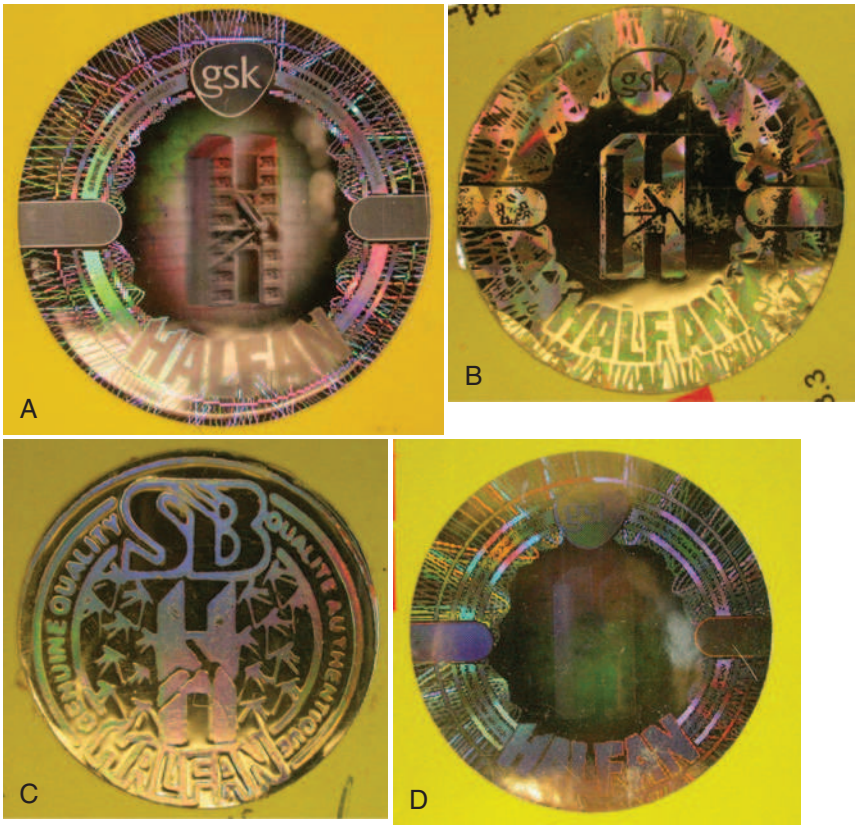


FIGURE 40-37 **A,** Genuine halofantrine Halfan GlaxoSmithKline hologram. **B,** Counterfeit Halfan hologram labeled as made by GSK (4040 and 4023). GSK = GlaxoSmithKline. **C,** Counterfeit Halfan hologram labeled as made by SB (4024). SB = SmithKline Beecham. **D,** Counterfeit Halfan hologram labeled as made by GSK (5070, 5312). GSK = GlaxoSmithKline. *(From Newton PN, Green MD, Mildenhall DC, et al:* Poor quality vital anti-malarials in Africa: an urgent neglected public health priority. *Malar J 2011;10:352.)*

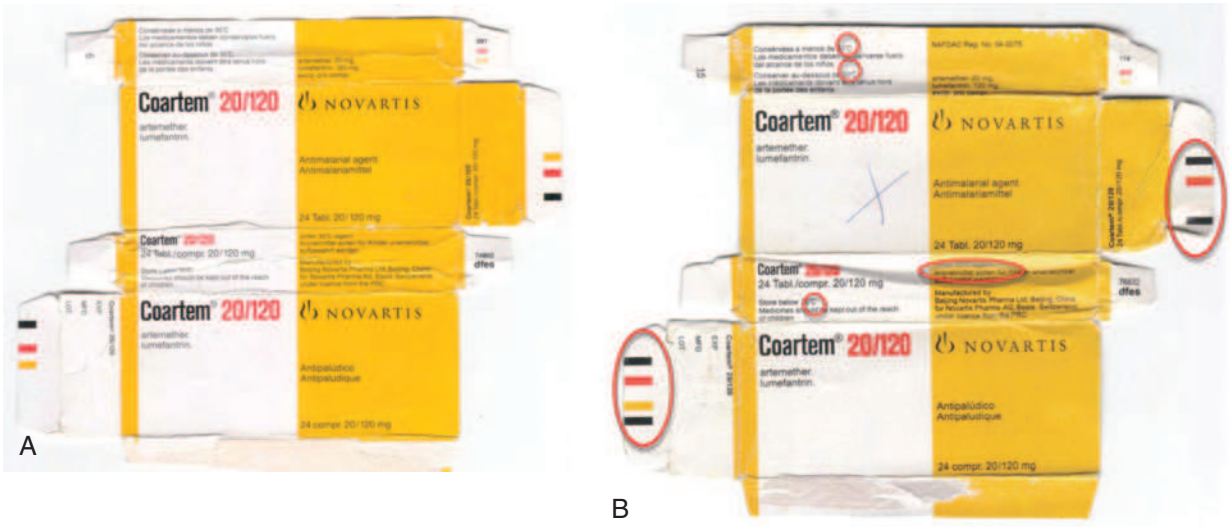


FIGURE 40-38 **A,** Genuine artemether-lumefantrine Coartem made by Beijing Novartis Pharma Ltd, Beijing, China for Novartis Pharma AG, Basle, Switzerland (Ken 06/01). **B,** Counterfeit artemether-lumefantrine. Differences from genuine sample circled. *(From Newton PN, Green MD, Mildenhall DC, et al:* Poor quality vital anti-malarials in Africa: an urgent neglected public health priority. *Malar J 2011;10:352.)*

Quinine can be given for a full 7 days, regardless of where the infection was acquired.[24]

Do not treat malaria with the same medication used for malaria prophylaxis. Mefloquine should not be used to treat malaria infection acquired in areas of reported mefloquine resistance.[24] Outside the United States, artemisinin-based combination therapy (artemether plus lumefantrine, artesunate plus amodiaquine, artesunate plus mefloquine, or artesunate plus sulfadoxine-pyrimethamine) is recommended for treatment of uncomplicated malaria.[114] For persons living in a low malaria-transmission area, the WHO recommends that a single gametocytocidal dose of primaquine (0.25 mg base per kg) be added to all artemisinin combination treatments for falciparum malaria (except in infants and pregnant women) to sterilize infection and reduce transmission of artemisinin-exposed, and potentially resistant, *P. falciparum* strains.[121]

P. malariae and *P. knowlesi*

Chloroquine and hydroxychloroquine can be used for both *P. malariae* and *P. knowlesi* infections (see Table 40-13).[24,114] In addition, any regimen recommended for treatment of chloroquine-resistant malaria can be used for treatment of *P. malariae* and *P. knowlesi*.[24,114]

Text continued on p. 930

TABLE 40-12 Overseas Refugee Health Guidelines for Malaria (Summary of Treatment and Testing)

Population	Presumptive Treatment Without Testing	Test by Blood Smear or Rapid Diagnostic Test Approved by CDC	Test Result	Treat	Medication
All children weighing more than 5 kg (except if known contraindication as listed in protocol)	Yes	No			**Option 1:** artemether-lumefantrine **Option 2** (only if option 1 is not available): amodiaquine-artesunate
All adults (except pregnant or lactating women, and persons with known contraindication as listed in protocol)	Yes	No			**Option 1:** artemether-lumefantrine **Option 2** (only if option 1 is not available): amodiaquine-artesunate
Pregnant women	No	Yes	Positive	Yes	Oral quinine, 7-day oral course
			Negative	No	None
Lactating women	No	Yes	Positive	Yes	Amodiaquine-artesunate; May also be treated with 7-day oral course, if there is a contraindication to amodiaquine-artesunate
			Negative	No	None
Children < 5 kg	No	Yes	Positive	Yes	Amodiaquine-artesunate; May also be treated with 7-day oral course of quinine if there is a contraindication to amodiaquine-artesunate
			Negative	No	None
Persons with other contraindications to recommended regimen	No	Yes	Positive	Yes	Discuss with CDC
			Negative	No	

From Centers for Disease Control and Prevention: Overseas Refugee Health Guidelines: Malaria. 3-29-2012. 12-26-2014; cdc.gov/immigrantrefugeehealth/guidelines/overseas/malaria-guidelines-overseas.html#table1.
CDC, Centers for Disease Control and Prevention.

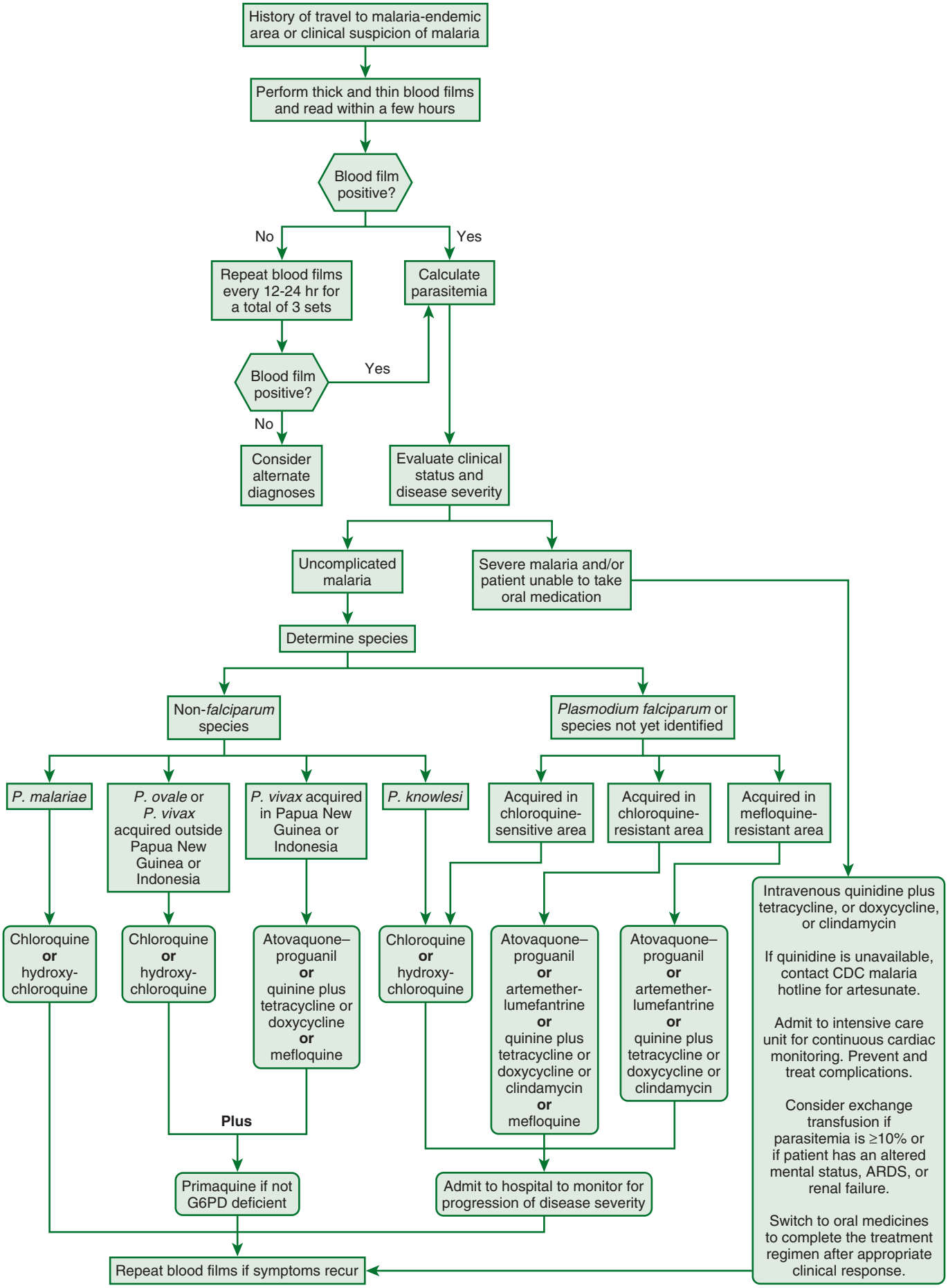


FIGURE 40-39 CDC malaria treatment algorithm for treatment of malaria in the United States. *(From the Centers for Disease Control and Prevention: Guidelines for the treatment of malaria in the United States, 2012.* cdc.gov/malaria/resources/pdf/algorithm.pdf.*)*

TABLE 40-13 Medications Used for the Treatment of Uncomplicated Malaria (Based on Drug Available in the United States)*

	Drug	Trade Names	Adult Dose	Pediatric Dose†	Adverse Effects	Comments
***P. falciparum*, or species not identified, acquired in areas with chloroquine-sensitive malaria**						
Two recommended options (A or B). If species subsequently identified as* P. vivax *or* P. ovale, *treatment with primaquine also needed.						
A.	Chloroquine phosphate‡	Aralen, generic	600-mg base (=1000-mg salt) orally immediately, followed by 300-mg base (=500-mg salt) orally at 6, 24, and 48 hours Total dose: 1500-mg base (=2500-mg salt)	10-mg base/kg (max. 600-mg base) orally immediately, followed by 5-mg base/kg orally at 6, 24, and 48 hours Total dose: 25-mg base/kg	Pruritus, nausea, headache, skin eruptions, dizziness, blurred vision, and insomnia.	Has been used extensively and safely during pregnancy. May exacerbate psoriasis.
B.	Hydroxychloroquine sulfate	Plaquenil, generic	620–mg base (=800-mg salt) orally immediately, followed by 310-mg base (=400-mg salt) orally at 6, 24, and 48 hours Total dose: 1550-mg base (=2000-mg salt)	10-mg base/kg orally immediately, followed by 5-mg base/kg orally at 6, 24, and 48 hours Total dose: 25-mg base/kg	Pruritus, nausea, headache, skin eruptions, dizziness, blurred vision, and insomnia.	Has been used extensively and safely during pregnancy. May exacerbate psoriasis.
***P. falciparum*, or species not identified, acquired in areas with chloroquine-resistant malaria or unknown resistance**						
Four recommended options (A through D). If species subsequently identified as* P. vivax *or* P. ovale, *treatment with primaquine also needed.						
A.	Atovaquone-proguanil	Malarone	4 adult tablets§ (1 g atovaquone/400 mg proguanil) orally qd × 3 days	<5 kg (<11.02 lb): not indicated 5-8 kg (11.02-17.64 lb): 2 pediatric tablets‡ orally/day × 3 days 9-10 kg (19.8-22.05 lb): 3 pediatric tablets‡ orally/day × 3 days 11-20 kg (24.25-44.1 lb): 1 adult tablet¶ orally/day × 3 days 21-30 kg (46.3-66.14 lb): 2 adult tablets¶ orally/day × 3 days 31-40 kg (68.34-88.18 lb): 3 adult tablets¶ orally/day × 3 days >40 kg (88.18 lb): 4 adult tablets¶ orally q day × 3 days	Headache, nausea, vomiting, abdominal pain, diarrhea, increased transaminase levels, and seizures.	Take with food or milk. Contraindicated for persons with severe renal impairment (i.e., creatine clearance of <30 mL/min). Not recommended for children < 5 kg (11.02 lb), pregnant women, women breastfeeding infants <5 kg (11.02 lb), and persons who received atovaquone-proguanil prophylaxis.
B.	Artemether-lumefantrine	Coartem, Riamet	1 tablet (20 mg artemether and 120 mg lumefantrine); six oral doses over 3 days (0, 8, 24, 36, 48, and 60 hours) 4 tablets/dose if ≥ to 35 kg; if < 35 kg, refer to pediatric dosing	1 tablet (20 mg artemether and 120 mg lumefantrine). Six oral doses over 3 days (0, 8, 24, 36, 48, and 60 hours) 5 to < 15 kg (11.02-< 33.07 lb): 1 tablet/dose 15 to < 25 kg (33.07-< 55.12 lb): 2 tablets/dose 25 to < 35 kg (55.12-< 77.16 lb): 3 tablets/dose ≥ 35 kg (≥ 77.16 lb): 4 tablets/dose	Headache, anorexia, dizziness, asthenia, arthralgia, and myalgia	Take with food. Contraindicated during first trimester of pregnancy. Safety during second and third trimesters of pregnancy is unknown. Contraindicated for persons taking strong CYP3A4 inducers. Warnings and precautions on the package insert include prolongation of the QT interval, concomitant use of QT-prolonging drugs and other antimalarials, drug interactions with CYP3A4, and drug interactions with CYP2D6. Should not be used in patients with cardiac arrhythmias, bradycardia, severe cardiac disease, or a prolonged QT interval. Has not been studied for efficacy and safety in patients with severe hepatic and/or renal impairment.

C.	Quinine sulfate	—	542-mg base (=650-mg salt) orally TID × 3 or 7 days	8.3-mg base/kg (=10-mg salt/kg) orally TID × 3 or 7 days	Cinchonism, hypoglycemia, sinus arrhythmias, atrioventricular block, prolonged QT interval, ventricular tachycardia, and ventricular fibrillation.	In Southeast Asia, continue treatment for 7 days because of increased relative resistance to quinine. Continue treatment for 3 days for infections acquired in Africa or South America. Contraindicated in patients with a history of blackwater fever, thrombocytopenic purpura, cardiac conduction defects and arrhythmias, myasthenia gravis or optic neuritis.
PLUS	Doxycycline	Vibramycin, Vibra-Tablets, Doryx, Periostat, and others; generic	100 mg orally BID × 7 days	>8 yr: 2.2 mg/kg orally q 12 hours × 7 days	Gastrointestinal upset, vaginal candidiasis, photosensitivity, allergic reactions, blood dyscrasias, azotemia in renal diseases, and hepatitis.	Take with food. Contraindicated in children <8 yr and pregnant women.
OR PLUS	Tetracycline	Achromycin, Sumycin, Panmycin, and others; generic	250 mg orally QID × 7 days	>8 yr: 25 mg/kg/day orally divided QID × 7 days	Gastrointestinal upset, vaginal candidiasis, photosensitivity, allergic reactions, blood dyscrasias, azotemia in renal diseases, and hepatitis.	Take with food. Contraindicated in children < 8 yr and pregnant women.
OR PLUS	Clindamycin	Cleocin and others; generic	20 mg base/kg/day orally divided TID × 7 days	20 mg base/kg/day orally divided TID × 7 days	Diarrhea, nausea, vomiting, abdominal pain, rash, pruritus, jaundice, and urticaria.	Take with food. Contraindicated in individuals with a history of antibiotic-associated colitis or ulcerative colitis. Use with caution in individuals with hepatic or renal impairment.

Continued

TABLE 40-13 Medications Used for the Treatment of Uncomplicated Malaria (Based on Drug Available in the United States)*—cont'd

	Drug	Trade Names	Adult Dose	Pediatric Dose†	Adverse Effects	Comments
D.	Mefloquine	Lariam, Mephaquin, generic	684-mg base (=750-mg salt) orally as initial dose, followed by 456-mg base (=500-mg salt) orally 6-12 hours after initial dose. Total dose: =1250-mg salt.	13.7-mg base/kg (=15-mg salt/kg) orally as initial dose, followed by 9.1-mg base/kg (=10-mg salt/kg) 6-12 hours after initial dose. Total dose: =25-mg salt/kg.	Gastrointestinal disturbances, headaches, insomnia, vivid dreams, visual disturbances, depression, anxiety disorders, and dizziness.	Contraindicated in persons with active depression or a recent history of depression, generalized anxiety disorder, psychosis, schizophrenia, other major psychiatric disorders, or seizures. Rare serious adverse reactions associated reported with treatment doses include psychoses and seizures. These reactions are seen more frequently at the higher doses used for treatment. Contraindicated in people allergic to mefloquine or related compounds (quinine, quinidine). Not recommended for persons with cardiac conduction abnormalities. Use with caution in travelers with psychiatric disturbances or a previous history of depression. In the United States, 250-mg tablet of mefloquine contains 228-mg mefloquine base. Outside the United States, 275-mg mefloquine tablet contains 250-mg mefloquine base. For children weighing <5 kg (11.02 lb), off-label use is recommended by the Centers for Disease Control and Prevention.
***P. malariae* and *P. knowlesi* acquired in all regions**						
Two recommended options (A or B)						
A.	Chloroquine phosphate	As above	As above	As above	As above	As above
B.	Hydroxychloroquine sulfate	As above	As above	As above	As above	As above
***P. vivax* and *P. ovale* acquired in areas with chloroquine-sensitive *P. vivax* malaria**						
Two recommended options (A or B).						
A.	Chloroquine phosphate	As above	As above	As above	As above	As above
PLUS	Primaquine phosphate	—	30-mg base (52.6-mg salt) orally, daily for 14 days after departure from the malarious area	0.5-mg/kg base (0.8-mg/kg salt) up to adult dose, orally, daily for 14 days after departure from the malarious area	Nausea, abdominal pain, and hemolytic anemia, especially in patients with G6PD deficiency	Use with any of the above drug regimens to prevent relapse of *P. vivax*. Take with food. All persons taking primaquine should have a documented normal G6PD level before beginning the medication. Contraindicated in persons with G6PD deficiency and during pregnancy and breastfeeding unless the infant being breastfed has a documented normal G6PD level.
OR						
B.	Hydroxychloroquine sulfate	As above	As above	As above	As above	As above
PLUS	Primaquine phosphate	As above	As above	As above	As above	As above

***P. vivax* and *P. ovale* acquired in areas with chloroquine-resistant *P. vivax* malaria**						
Three recommended options (A through C).						
A.	Quinine sulfate	As above	As above	As above	As above	As above
PLUS	Doxycycline or tetracycline	As above	As above	As above	As above	As above
PLUS	Primaquine phosphate	As above	As above	As above	As above	As above
OR						
B.	Atovaquone-proguanil	As above	As above	As above	As above	As above
PLUS	Primaquine phosphate	As above	As above	As above	As above	As above
OR						
C.	Mefloquine	As above	As above	As above	As above	As above
PLUS	Primaquine phosphate	As above	As above	As above	As above	As above
Pregnant women						
***P. falciparum*, or species not identified, acquired in areas with chloroquine-sensitive malaria**						
Two recommended options (A or B).						
If species subsequently identified as* P. vivax *or* P. ovale*, patient should be maintained on chloroquine prophylaxis for the duration of the pregnancy. After delivery, pregnant patients who do not have G6PD deficiency should receive terminal prophylaxis with primaquine.						
A.	Chloroquine phosphate‡	As above	As above	Not applicable	As above	As above
B.	Hydroxychloroquine sulfate	As above	As above	Not applicable	As above	As above
Pregnant women						
***P. falciparum*, or species not identified, acquired in areas with chloroquine-resistant malaria**						
Two recommended options (A or B).						
***If species subsequently identified as* P. vivax *or* P. ovale*, patient should be maintained on chloroquine prophylaxis for the duration of the pregnancy. After delivery, pregnant patients who do not have G6PD deficiency should receive terminal prophylaxis with primaquine*.**						
A.	Quinine sulfate plus clindamycin	As above	As above	Not applicable	As above	As above
B.	Mefloquine	As above	As above	Not applicable	As above	As above

G6PD, glucose-6-phosphate dehydrogenase.
*Caused by *Plasmodium falciparum, P. ovale, P. vivax, P. malariae*, and *P. knowlesi*.
†Should never exceed the adult dose.
‡Pediatric tablets contain 62.5 mg atovaquone and 25 mg proguanil hydrochloride.
§Adult tablets contain 250 mg atovaquone and 100 mg proguanil hydrochloride.
¶Refer to the U.S. Centers for Disease Control and Prevention for most recent destination-specific risks and malaria chemoprophylaxis and treatment guidelines.
Health care professionals requiring assistance with diagnosis and treatment of suspected or confirmed cases of malaria should refer to the CDC website cdc.gov/malaria/diagnosis_treatment/treatment.html or call the CDC Malaria Hotline (770-488-7788, or toll-free 855-856-4713, from 9:00 AM to 5:00 PM Eastern Standard Time, Monday through Friday) or the Emergency Operations Center during evenings, weekends, and holidays (770-488-7100); ask to page the person on-call for the Malaria Branch).
Modified from 1. Centers for Disease Control and Prevention: CDC Health Information for International Travel, 2014, Atlanta, Georgia, 2014, U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Center for infectious Diseases, Division of Global Migration and Quarantine; and 2. Centers for Disease Control and Prevention: Malaria Treatment (United States). 11-9-2012. 12-24-0014.

P. vivax and *P. ovale*

Chloroquine and hydroxychloroquine can be used for most *P. vivax* and *P.ovale* infections (see Table 40-13). Regimens for treatment of P. falciparum acquired from areas of chloroquine resistance can also be used.[24] In areas (e.g., Papua New Guinea or Indonesia) where chloroquine-resistant *P. vivax* exists at high prevalence, one of three treatment regimens can be used. Options include quinine sulfate plus doxycycline or tetracycline, atovaquone-proguanil, or mefloquine.[24] In areas where chloroquine-resistant *P. vivax* exists at low prevalence, it is reasonable to initially treat with chloroquine and change to a chloroquine-resistant *P. vivax* regimen if the patient does not respond. Mefloquine should only be used for treatment if the patient did not use mefloquine for malaria chemoprophylaxis. Treatment of *P. vivax* and *P. ovale* should be followed by a 14-day course of primaquine to eradicate hypnozoites that remain dormant in the liver. Screen patients for G6PD deficiency prior to initiating primaquine therapy to avoid the complication of hemolytic anemia and methemoglobinemia.

Treatment options for children are the same as for adults. Weight-based dosing should not exceed recommended adult doses. Because doxycycline and tetracycline are not indicated for use in children 8 years of age or less, quinine-based regimens that include either of these drugs should be avoided in this age group. Mefloquine is the recommended treatment option for children less than 8 years old with chloroquine-resistant *P. vivax*. Atovaquone-proguanil or artemether-lumefantrine should be used if the benefits outweigh the risks of treatment, and mefloquine is not available.[24]

PREGNANT WOMEN

Pregnant women are at high risk for developing severe malaria. Malaria infection during pregnancy is associated with perinatal morbidity (i.e., miscarriage, prematurity, low birth weight, congenital infections) as well as death.[47,94] For pregnant women with uncomplicated malaria caused by chloroquine-sensitive *P. falciparum, P. malariae, P. vivax,* and *P. ovale,* use the same treatment regimens as those recommended for nonpregnant adult patients (see Table 40-13). In pregnant patients diagnosed with chloroquine-resistant *P. falciparum* infection, use mefloquine or a combination of quinine and clindamycin for treatment.[24] Doxycycline, tetracycline, atovaquone-proguanil, and artemether-lumefantrine should not be used in pregnant patients unless no other treatment options are available and benefits outweigh the risks. Atovaquone-proguanil and artemether-lumefantrine are pregnancy class category C drugs and are generally not indicated for use in pregnant women.[24] In cases of *P. vivax* and *P. ovale,* terminal prophylaxis with primaquine should be given to pregnant patients with normal G6PD levels after delivery. Treat with chloroquine prophylaxis during pregnancy. Primaquine can be given after delivery.[24]

TREATMENT OF SEVERE MALARIA

Parenteral antimalarial therapy is recommended for patients with severe disease, regardless of the infecting malarial species.[24] Parenteral quinidine gluconate (or quinine dihydrochloride) combined with doxycycline, tetracycline, or clindamycin is recommended for treatment in the United States (Table 40-14).[24] Blood pressure, cardiac rhythms, and blood glucose levels should be monitored closely in an intensive care setting during IV administration of quinidine or quinine.[24,119] At least 24 hours of continuous infusion or three intermittent doses of parenteral quinidine therapy is recommended. Parenteral therapy should be continued until the parasite density is less than 1% and the patient can take oral treatment.[24,119] Complete the treatment course with an oral regimen of quinine, atovaquone-proguanil, or artemether-lumefantrine. If a local source for quinidine gluconate cannot be identified, contact the Eli Lily company (1-800-821-0538) or regional distributor immediately.[24] Another option for parenteral therapy is artesunate in combination with a second oral drug (atovaquone-proguanil, doxycycline, clindamycin, or mefloquine).[24] In the United States, contact the CDC for artesunate, available under an Investigational New Drug protocol.

SUPPORTIVE CARE FOR SEVERE MALARIA

Severe malaria is a medical emergency and requires aggressive supportive care. Rapid clinical assessment, confirmation of diagnosis, and initiation of parenteral therapy are associated with good clinical outcomes.[24,91,119] Nonimmune individuals diagnosed with malaria should be hospitalized until a response to treatment has been demonstrated and complications from severe disease are no longer likely (i.e., resolved fever and 24 hours since a negative blood smear).

In addition to rapid clinical assessment and initiation of antimalarial chemotherapy, correct dehydration, hypoglycemia, and acidosis. Admission to the intensive care unit is often required to manage complications (e.g., seizures, severe anemia, hypoglycemia, acidosis, renal failure, pulmonary edema, hypoxemia, and hypovolemia).[24,91,119]

Place patients receiving intravenous quinine derivatives on a cardiac monitor in the intensive care unit and perform frequent blood pressure measurements. Quinine or quinidine derivatives are typically given with a continuous infusion of 5% to 10% dextrose. Measure blood glucose levels every 4 to 6 hours. Adjust drug dosages for patients with evidence of renal failure. Patients with renal insufficiency receiving quinine derivatives should be given a standard loading dose, but if more than 48 hours of parenteral treatment is required, the maintenance doses should be decreased by 30% to 50% to prevent drug accumulation.[24,91,119] Total plasma concentrations of 8 to 15 mg/mL for quinine and 3 to 8 mg/mL for quinidine are effective for treatment of severe malaria without causing toxicity.[24,91,119] Chloroquine or artemisinin derivatives do not require dose reductions for renal failure.

Use anticonvulsants (e.g., benzodiazepines) for treatment of seizures. Empirically treat with antibiotics for bacterial meningitis until a lumbar puncture can be performed to exclude this diagnosis. Exchange transfusions have no proven benefit, as no survival advantage has been demonstrated in adequately powered randomized clinical trials.[100] Other adjunctive therapies that have no proven benefit, or are harmful, include dexamethasone for cerebral malaria, heparin for thrombocytopenia, iron chelators to reduce parasite clearance time, pentoxifylline for tumor necrosis factor synthesis inhibition, and dichloroacetate for metabolic acidosis.[119]

In children, careful attention should be paid to airway compromise, altered breathing patterns, dehydration, compensated shock, and/ or impaired consciousness. Urgently manage severe complications while the diagnosis of malaria is being confirmed. All children with severe malaria should be treated with broad-spectrum antibiotics in addition to antimalarial therapy.[91,119]

Therapeutic efficacy can be monitored by checking multiple sequential blood smears at least every 6 to 12 hours for 2 days. If high levels of parasitemia persist or clinical improvement is not evident, there may be primary drug resistance. Therapy should be changed immediately. Management of severe malaria should preferably be carried out in consultation with a tropical medicine or infectious diseases specialist, or with the assistance of the CDC. The WHO has created a practical handbook for health professionals who manage patients with severe malaria: apps.who.int/iris/bitstream/10665/79317/1/9789241548526_eng.pdf?ua=1.[119]

RESEARCH AND VACCINE DEVELOPMENT

Humans respond to malaria infection by several mechanisms. After repeated exposure to different parasite strains over years, individuals develop protection from high-level parasitemia and severe disease, but not from *Plasmodia* infection. Malarial parasite has developed multiple mechanisms to evade human immune responses. Progress toward an effective vaccine against malaria, especially *P. falciparum,* has been hindered by diversity of human populations and parasite strains.

TABLE 40-14 Medications Used for the Treatment of Severe Malaria (Based on Drugs Available in the United States)*

	Drug	Trade Names	Adult Dose	Pediatric Dose†	Adverse Effects	Comments
Severe malaria treatment: All *Plasmodium* species, all regions						
Two recommended options (A or B).* Initiate therapy immediately. *If species subsequently identified as* P. vivax *or* P. ovale *treatment with primaquine also needed (see uncomplicated malaria treatment).						
A. Quinidine gluconate plus one of the following: doxycycline, tetracycline, or clindamycin						
A.	Quinidine gluconate (IV)	—	6.25-mg base/kg (=10-mg salt/kg) loading dose IV (maximum of 600-mg salt) in normal saline slowly over 1-2 hours, followed by continuous infusion of 0.0125-mg base/kg/min (=0.02-mg salt/kg/min) for at least 24 hours. Alternative regimen: 15-mg base/kg (=24-mg salt/kg) loading dose IV infused over 4 hours, followed by 7.5-mg base/kg (=12-mg salt/kg) infused over 4 hours every 8 hours, starting 8 hours after the loading dose (see package insert). Once parasite density < 1% and able to take oral medication, complete course with oral quinine (dose as per uncomplicated malaria).	Same as adult dose	Cinchonism, tachycardia, prolonged QRS and QTc intervals, flattened T wave, ventricular arrhythmias, hypotension, and hypoglycemia	For infections acquired in Southeast Asia, continue treatment for 7 days because of increased relative resistance to quinine. Continue treatment for 3 days for infections acquired in Africa or South America. Continuous electrocardiography, blood pressure, and glucose monitoring are recommended, especially for pregnant women and children. The loading dose should be decreased or omitted for patients who have received quinine or mefloquine. For problems with quinidine availability, call the manufacturer (Eli Lilly, 800-821-0538) or the Malaria Hotline at the Centers for Disease Control and Prevention. If > 48 hr of parenteral therapy is required, the quinine or quinidine dose should be decreased by ⅓ to ½. Contraindicated in people with a history of blackwater fever, thrombocytopenic purpura, cardiac conduction defects and arrhythmias, myasthenia gravis, and optic neuritis.
PLUS	Doxycycline	Vibramycin, Vibra-Tablets, Doryx, Periostat and others; generic	100 mg BID orally × 7 days. If unable to take oral medication, give 100 mg IV every 12 hours. Switch to oral doxycycline when patient can take oral medication. Total treatment course = 7 days.	>8 yr: 2.2 mg/kg orally q 12 hours × 7 days. If unable to take oral medication, give IV. For children < 45 kg, give 2.2 mg/kg IV every 12 hours. For children ≥ 45 kg, use same dosing as for adults. Switch to oral doxycycline as soon as patient can take oral medication. Total treatment course = 7 days.	Gastrointestinal upset, vaginal candidiasis, photosensitivity, allergic reactions, blood dyscrasias, azotemia in renal diseases, and hepatitis	Take with food. Contraindicated in children <8 yr and pregnant women.
OR PLUS	Tetracycline	Achromycin, Sumycin, Panmycin, and others, generic	Dose as per uncomplicated malaria.	Dose as per uncomplicated malaria.	See uncomplicated malaria treatment.	See uncomplicated malaria treatment.

Continued

TABLE 40-14 Medications Used for the Treatment of Severe Malaria (Based on Drugs Available in the United States)*—cont'd

	Drug	Trade Names	Adult Dose	Pediatric Dose†	Adverse Effects	Comments
OR PLUS	Clindamycin	Cleocin and others, generic	20-mg base/kg/day orally divided TID × 7 days. If unable to take oral medication, give 10-mg base/ kg loading dose IV followed by 5-mg base/kg IV every 8 hours. Switch to oral clindamycin as soon as patient can take oral medication. Total treatment course = 7 days.	20-mg base/kg/day orally divided TID × 7 days. If unable to take oral medication, give 10-mg base/ kg loading dose IV followed by 5-mg base/kg IV every 8 hours. Switch to oral clindamycin as soon as patient can take oral medication. Total treatment course = 7 days.	Diarrhea, nausea, vomiting, abdominal pain, rash, pruritus, jaundice, and urticaria	Take with food. Contraindicated in individuals with a history of antibiotic-associated colitis or ulcerative colitis. Use with caution in individuals with hepatic or renal impairment.
B. Artesunate followed by one of the following: atovaquone-proguanil, doxycycline (clindamycin in pregnant women), or mefloquine						
B.	Artesunate	—	2.4 mg/kg/dose IV × 3 days at 0, 12, 24, 48, and 72 hours	2.4 mg/kg/dose IV × 3 days at 0, 12, 24, 48, and 72 hours	Gastrointestinal upset, bradycardia, rash, and fever	Available in the United States through an investigational new drug protocol from the Centers for Disease Control and Prevention (see Resources). For use in patients with severe disease who do not have timely access or who cannot tolerate or fail to respond to IV quinidine. Information regarding use in pregnant women is limited. Use with caution for individuals with renal or hepatic impairment.
Followed by	Atovaquone–proguanil	Malarone	Dose as per uncomplicated malaria.	Dose as per uncomplicated malaria.	See uncomplicated malaria treatment.	See uncomplicated malaria treatment.
OR	Doxycycline	Vibramycin, Vibra-Tablets, Doryx, Periostat and others; generic	Dose as per uncomplicated malaria.	Dose as per uncomplicated malaria.	See uncomplicated malaria treatment.	See uncomplicated malaria treatment.
OR	Clindamycin	Cleocin and others, generic	Dose as per uncomplicated malaria.	Dose as per uncomplicated malaria.	See uncomplicated malaria treatment.	See uncomplicated malaria treatment.
OR	Mefloquine	Lariam, Mephaquin; generic	Dose as per uncomplicated malaria.	Dose as per uncomplicated malaria.	See uncomplicated malaria treatment.	See uncomplicated malaria treatment.
Prevention of relapses:* P. vivax *and* P. ovale *Only						
	Primaquine phosphate	—	Dose as per uncomplicated malaria.	Dose as per uncomplicated malaria.	See uncomplicated malaria treatment.	See uncomplicated malaria treatment.

Modified from 1. Centers for Disease Control and Prevention: CDC Health Information for International Travel, 2014, Atlanta, Georgia, 2014, U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Center for infectious Diseases, Division of Global Migration and Quarantine; and 2. Centers for Disease Control and Prevention: Malaria Treatment (United States). 11-9-2012. 12-24-0014.

G6PD, glucose-6-phosphate dehydrogenase; IV, intravenous.

*Caused by *Plasmodium falciparum, P. ovale, P. vivax,* and *P. malariae* in the United States.

†Should never exceed the adult dose.

‡Pediatric tablets contain 62.5 mg atovaquone and 25 mg proguanil hydrochloride.

§Adult tablets contain 250 mg atovaquone and 100 mg proguanil hydrochloride.

¶Refer to the U.S. Centers for Disease Control and Prevention for most recent destination-specific risks and malaria chemoprophylaxis and treatment guidelines.

Health care professionals requiring assistance with diagnosis and treatment of suspected or confirmed cases of malaria should refer to the CDC website cdc.gov/malaria/diagnosis_treatment/treatment.html or call the CDC Malaria Hotline (770-488-7788, or toll-free 855-856-4713, from 9:00 AM to 5:00 PM Eastern Standard Time, Monday through Friday) or the Emergency Operations Center during evenings, weekends, and holidays (770-488-7100); ask to page the person on-call for the Malaria Branch.

More than 20 subunit vaccine constructs are being evaluated in advanced preclinical or clinical trials. No vaccine is licensed for prevention of malaria infection or disease.[118] Three strategies for vaccine development are being developed simultaneously (Figure 40-40).[104] The first strategy uses preerythrocytic vaccine to prevent infection caused by sporozoites and so prevent development of merozoites in the liver as well as asexual parasitemia responsible for clinical disease (Figure 40-41).[35] This vaccine would be ideal for travelers, because any form of clinical disease would be prevented. The second strategy of vaccine

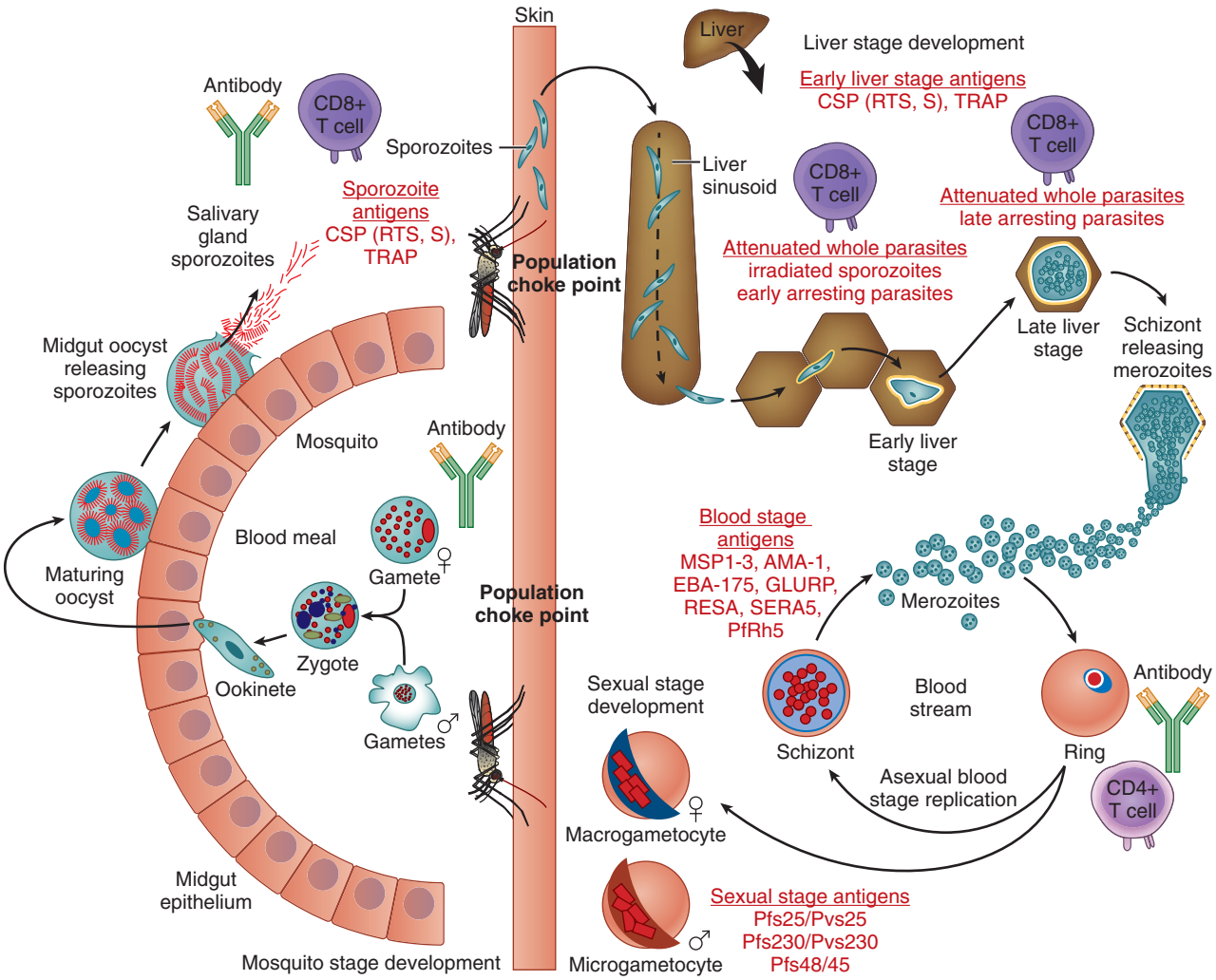


FIGURE 40-40 The malaria life cycle, parasites, and parasite targets used for vaccine development. Female Anopheline mosquitoes seeking a blood meal deposit sporozoites from their saliva under human host skin when probing for blood. Sporozoites enter the bloodstream by traversing capillary endothelia and are taken to the liver where they cross liver sinusoids and eventually infect hepatocytes. Intracellular parasites then develop over 5 to 8 days as a liver stage. On maturity, tens of thousands of exoerythrocytic merozoites enter the bloodstream within merosomes that release their merozoites in lung microvasculature. Merozoites infect erythrocytes and either cycle as asexual stages, to form 16 to 32 new merozoites over 48 hours, or terminally commit to sexual stage development as gametocytes. Gametocytes taken up during a mosquito blood meal form gametes that fuse and produce a zygote. This zygote then transforms into a motile ookinete that develops as an oocyst in the wall of the mosquito's midgut. Mature oocysts release sporozoites, which travel to the salivary gland, ready for transmission to the human host. Vaccine development focuses on favorable points of attack. These are predominantly population choke points (i.e., points in the life cycle where the number of parasites is low and thus controllable). These favorable points of attack include sporozoite/liver stage and sexual stages. Preerythrocytic whole parasite vaccines (attenuated whole parasites) leads to expansion of $CD8^+$ T cells that target malaria-infected hepatocytes early or late in the liver stage development. Preerythrocytic subunit vaccines (e.g., RTS, S) mainly target the sporozoite antigen circumsporozoite protein (CSP) but also include thrombospondin-related adhesion protein (TRAP). Vaccination needs to expand $CD8^+$ T cells that target early liver stages and create antibodies that target the sporozoite. Blood stage antigens include merozoite surface proteins 1 to 3 (MSP1 to 3), apical membrane antigen 1 (AMA-1), glutamate-rich protein (GLURP), ring-infected erythrocyte surface antigen (RESA), serine repeat antigen 5 (SERA5), erythrocyte-binding surface antigen 175 (EBA-175), and reticulocyte-binding family homolog 5 (PfRh5). Vaccination ideally results in production of antibodies that can prevent merozoite invasion. Naturally acquired immunity also gives rise to antibodies as well as to $CD4^+$ T cells that target infected erythrocytes. Sexual stage antigens (transmission blocking vaccine candidates) include *P. falciparum* Pfs25, Pfs48/45, and Pfs230, and *P. vivax* Pvs25 and Pvs230. Vaccination leads to a robust antibody response that can bind to and prevent parasite development in the mosquito midgut. *(From Vaughan AM, Kappe SH:* Malaria vaccine development: persistent challenges. *Curr. Opin. Immunol 2012;24:324-331.)*

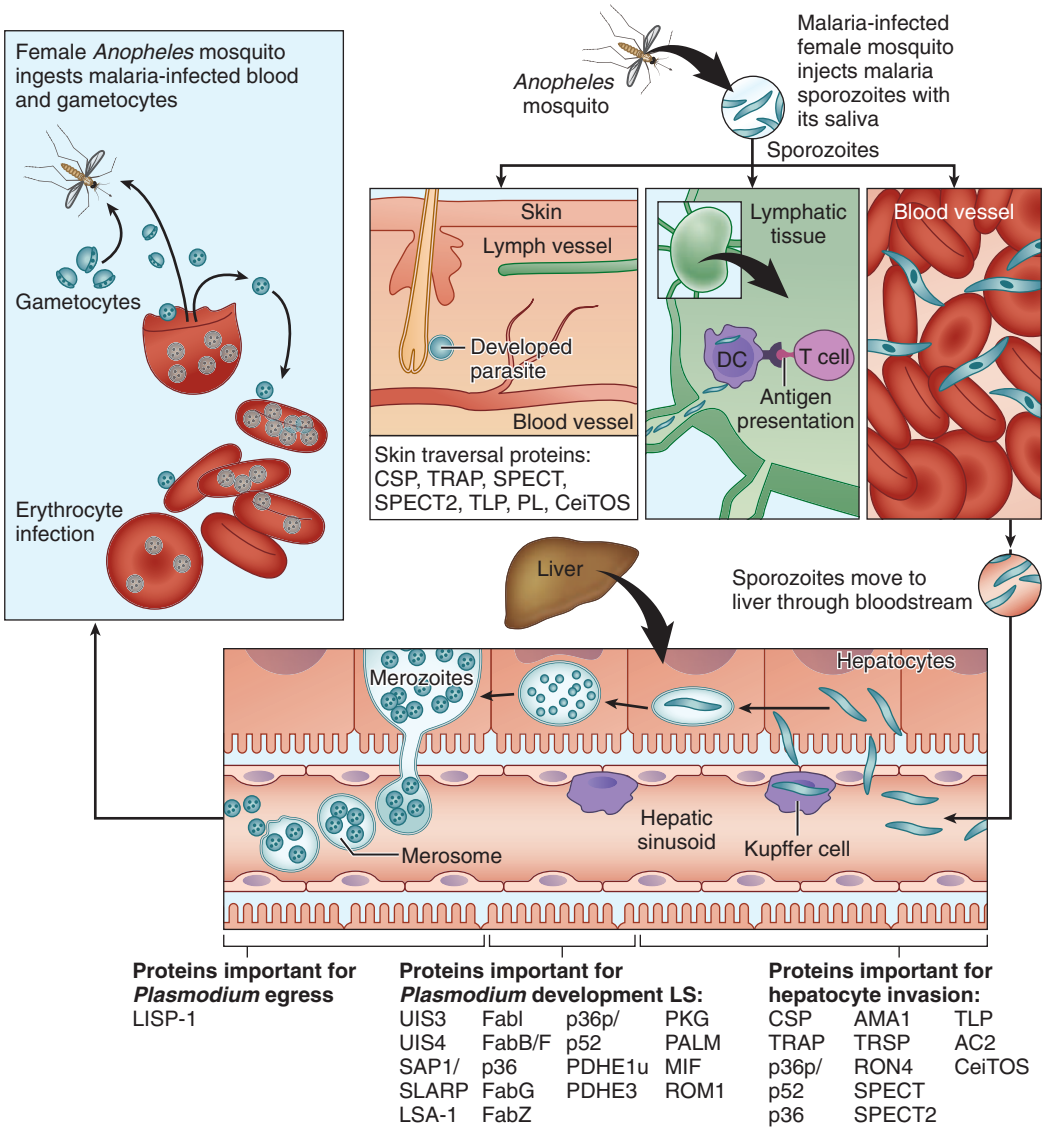


FIGURE 40-41 Preerythrocytic journey of the *Plasmodium* parasite in the mammalian host. After injection into the skin by an infected female *Anopheles* mosquito, some sporozoites may develop in skin, some migrate to draining lymph node where they can be processed and presented to T cells, and some enter the bloodstream and reach the liver for complete development. After reaching the liver, sporozoites pass through the layer of Kupffer and endothelial cells to access liver parenchymal cells. A sporozoite may pass through multiple cells before forming a parasitophorous vacuole within a final hepatocyte, within which it undergoes liver stage development and gives rise to tens of thousands of merozoites. These merozoites are then released into bloodstream as merozoite-filled packets called merosomes. DC, dendritic cell. *(Duffy PE, Sahu T, Akue A, et al:* Pre-erythrocytic malaria vaccines: identifying the targets. *Expert Rev Vaccines 2012;11:1261-1280.)*

development uses an asexual blood-stage erythrocytic vaccine that would limit parasite erythrocyte invasion and multiplication.[104] This vaccine would contribute to reduction in burden of disease in malaria-endemic countries. The third vaccine strategy uses a transmission-blocking vaccine to prevent parasite spread by inhibiting parasitic sexual development.[104] Effective vaccines may require a combination of these strategies. Because most deaths from malaria occur in children with severe malaria disease, a vaccine that can prevent severe disease is more important than one that prevents asymptomatic asexual parasitemia.

RESOURCES

Several resources are available to help health care providers with prevention, diagnosis, and treatment of malaria. Comprehensive websites include those of the CDC (cdc.gov/malaria and cdc.gov/travel), WHO (who.int/topics/malaria/en), and Malaria Foundation (malaria.org) (Table 40-15).[53]

Updated, detailed information about malaria prophylaxis can be obtained through the CDC's Traveler's Health information website: nc.cdc.gov/travel/page/yellowbook-home-2014.[11] Information about the diagnosis of malaria is available through the CDC's Laboratory Identification of Parasites of Public Health Concern diagnostic website: cdc.gov/dpdx/malaria/dx.html.[20] Health care professionals requiring assistance with diagnosis and treatment of suspected or confirmed cases of malaria should refer to the CDC website at cdc.gov/malaria/diagnosis_treatment/treatment.html or call the CDC's Malaria Hotline (770-488-7788, or toll free 855-856-4713, from 9:00 AM to 5:00 PM Eastern Standard Time, Monday through Friday), or the Emergency Operations Center during evenings, weekends, and holidays (770-488-7100; ask to page the person on-call for the Malaria Branch).[24]

TABLE 40-15 U.S. Centers for Disease Control and Prevention Sources for Malaria Prophylaxis, Diagnosis, and Treatment Recommendations

Type of Information	Source	Availability	Telephone Number, Internet Address, or Email Address
Prophylaxis	CDC's Traveler's Health Internet Site (includes online access to Health Information for International Travel)	24 hours/day	nc.cdc.gov/travel
	Health Information for International Travel (The Yellow Book)	Order from Oxford University Press, Order Fulfillment, 198 Madison Avenue, New York, NY 10016-4314	800-451-7556 or oup.com/us/
	CDC's Malaria Branch Internet Site with Malaria Information and Prophylaxis, by Country (Red Pages)	24 hours/day	cdc.gov/malaria/travelers/country_table/a.html
	CDC Malaria Map Application	24 hours/day	cdc.gov/malaria/map
Diagnosis	CDC's Division of Parasitic Diseases and Malaria diagnostic internet site (DPDx)	24 hours/day	dpd.cdc.gov/dpdx
	CDC's Division of Parasitic Diseases and Malaria diagnostic CD-ROM (DPDx)	Order by electronic mail from CDC Division of Parasitic Diseases and Malaria	dpdx@cdc.gov
Treatment	CDC Malaria Branch	9:00 AM to 5:00 PM Eastern time, Monday-Friday	770-488-7788 or toll-free 855-856-4713*
	CDC Malaria Branch	5:00 PM–9:00 AM Eastern time on weekdays and all day weekends and holidays	770-488-7100* (This number is for the CDC's Emergency Operations Center. Ask staff member to page the person on call for the Malaria Branch.) cdc.gov/malaria/diagnosis_treatment/treatment.html

From Cullen KA, Arguin PM: Malaria surveillance: United States, 2012, MMWR Surveill.Summ 2014;63(Suppl 12):1-22.
*These numbers are intended for use by health care professionals only.

Additional websites that may be useful to health care workers who are treating patients with confirmed or suspected malaria include:

CENTERS FOR DISEASE CONTROL AND PREVENTION

Treatment: Guidelines for Clinicians, including reporting, evaluation, diagnosis, and approach to treatment of severe and uncomplicated malaria can be found at cdc.gov/malaria/resources/pdf/clinicalguidance.pdf. A treatment guidelines table, with medications listed in tabular form, can be found at: cdc.gov/malaria/resources/pdf/treatmenttable.pdf.[24]

Laboratory Identification of Parasites of Public Health Concern: cdc.gov/dpdx/malaria/dx.html. This site provides free Internet-based laboratory diagnostic assistance and laboratory bench aids to laboratorians and pathologists who are investigating suspected parasitic diseases.[20]

Malaria Map Application: cdc.gov/malaria/map/index.html.[12] This interactive global map provides information about malaria endemicity. For most countries, the map displays malaria presence at national and provincial levels.

WORLD HEALTH ORGANIZATION

International Travel and Health (online edition): who.int/ith/en/. This site provides information about health risks, including malaria, for travelers.

Guidelines for the Treatment of Malaria, 2nd edition: whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf.[114] Global, evidence-based guidelines are provided for diagnosis and treatment of malaria.

Management of severe malaria: a practical handbook, 3rd edition: who.int/malaria/publications/atoz/9789241548526/en/.[38,122] This is a practical handbook for health care providers managing patients with severe malaria.

International Travel and Health Interactive Map: apps.who.int/ithmap/. This interactive tool provides information regarding malaria risk to travelers.[115]

Training Materials: who.int/malaria/publications/training/en/index.html. This link provides several free electronic resources for training, including microscopy, entomology, and prevention and control programs.

Worldwide Antimalarial Resistance Network: wwarn.org \. This site provides up-to-date information about antimalarial drug resistance.[124]

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CHAPTER 41

Arthropod Envenomation and Parasitism

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The phylum Arthropoda contains about four-fifths of the known animals of the world, and insects are the largest group of arthropods. Insects are an important part of the biota of all terrestrial and freshwater environments that support life. More species of insects exist than of any other form of multicellular life, and they may well exceed all other land animals in biomass. Insects can use most animal and plant substances as food, and their feeding plays a vital role in recycling organic compounds. They compete with other organisms for the world's food supplies but are themselves a major food source for many forms of life. They are essential for the pollination of many plants. Insect life cycles are diverse and often complex, involving developmental and sexual stages that are widely different in morphology and ways of life. Although sexual reproduction is the rule, parthenogenesis (unisexual reproduction) and pedogenesis (sexual development in the larval stage) occur. Some groups, such as ants, bees, and termites, have developed a high degree of social organization. During at least part of its life cycle, an insect's body is divided into three distinct regions, head, thorax, and abdomen, with three pairs of legs attached to the thorax. Except for a few primitive or parasitic groups, most adult insects have wings.

The greatest direct medical importance of insects is associated with their feeding on human blood and tissue fluids. In doing so, they often inject salivary secretions. This is a highly effective method of transmitting pathogenic microorganisms; moreover, the secretions are often allergenic and sometimes toxic. Other insects may carry human pathogens passively on their feet or mouthparts or in their digestive tracts.

Venoms have evolved in several insect groups, and venomous insects may attack humans, sometimes with lethal results. Skin, hair, and secretions of insects may be irritant or allergenic, producing cutaneous and respiratory syndromes. Finally, insects can be highly annoying to wilderness enthusiasts.

HYMENOPTERA (BEES, WASPS, AND ANTS)

By far the most important venomous insects are members of the order Hymenoptera, including bees, wasps, and ants (Figure 41-1). They vary in size from minute to large (up to 60 mm [2.4 inches] in body length). The abdomen and thorax are connected by a slender pedicle that may be quite long in certain wasps and ants. Bees and most wasps are winged as adults; ants are wingless, except for sexually mature adults during part of the life cycle. Mouthparts are adapted for chewing but in some species are modified for sucking. The life cycle includes egg, larval, and pupal stages before emergence of adults. Immature stages may be protected and provided with food by the adult. Both animal and plant foods are used. Many species are parasitic on other arthropods. All ants and many species of bees and wasps are social insects. Colonies range in size from a few dozen individuals to many thousands. In cold climates, most individuals die in autumn, leaving the fertilized females to winter over and found new colonies in the spring.

BEES

The honeybee *(Apis mellifera)* is one of the few domesticated insects and is maintained in hives in many countries (Figures 41-2, and 41-3). Numerous geographic races of the honeybee exist; the Italian bee *(Apis mellifera ligustica),* a common domestic strain of Europe, is also widely distributed in the United States. Feral honeybee colonies usually nest in hollow trees or crevices in rocks but may nest in the walls of occupied buildings. Since 2006, there has been concern regarding persistent loss of honeybee *(Apis mellifera)* colonies worldwide, a phenomenon referred to as colony collapse disorder. Several biologic, chemical, and environmental stressors have been linked to colony collapse disorder, including *Varroa* mites, Israel acute paralysis virus, *Nosema ceranae,* and most recently, exposure to systemic neonicotinoid insecticides, such as imidacloprid.[265]

An event of considerable health and economic significance in the Americas has been introduction of an African race of the honeybee *(Apis mellifera scutellata,* also referred to as *Apis mellifera adansonii).* This race was introduced from Africa into Brazil because it was thought to be a more efficient honey producer in the tropics. It is characterized by large populations (one queen may lay tens of thousands of eggs), frequent swarming (6 to 12 swarms a year), nonstop flights of at least 20 km (12.4 miles), and a tendency toward mass attacks on humans after minimal provocation. As a result, these Africanized honeybees, also known as "killer bees," are much more aggressive than are the typical western Hymenoptera. They attack in swarms of hundreds and chase their victims much greater distances from the hive than does any other species.[185,227,293]

The first escapes from hives occurred in the state of São Paulo in 1957, and the "Brazilian killer bees," or "Africanized bees," have spread widely. These bees are actually hybrids between *A. scutellata* and European honeybee races[426] (see Figure 41-3B). Cold climate seems to have stopped their southern spread in Argentina, but they have moved steadily northward at 322 to 482 km (200 to 300 miles) per year and in 1990 reached the southern border of the United States.[446] By mid-1991, 103 swarms had been captured in southern Texas. Populations are established in Arizona, New Mexico, Nevada, Utah, and southern California.[385] The expanded distribution of Africanized honeybees from South America to the southwest United Sates in less than 50 years is considered one of the most spectacular biologic invasions yet documented.[341,382] The resulting feral honeybee population of south Texas is now viewed as a hydrid swarm. Killer bee populations have been reported as far south and east as Louisiana, Oklahoma, Arkansas, Georgia, and Florida.[5,444] Several human deaths have occurred from multiple stings. Unless the bees acquire greater resistance to winter conditions, their range will be confined to the southern one third of the United States and may also be restricted by scarcity of suitable flowers in the arid Southwest. Recent periods of extreme climate change characterized by high temperatures and low rainfall are conducive to the greatest activity of Africanized bees and a larger number of swarms, thus giving rise to increased contact with human populations.[106] The greatest impact of Africanized bees in the United States will probably be economic, related to decreased honey production and less effective pollination of crops. The bees also present a threat to human health. Africanized bee colonies are extremely sensitive to disturbance, respond faster in greater numbers, and are up to 10 times more active in stinging than are European bees. The quantity of venom per sting is slightly less in African bees; however, there is no significant biochemical or allergenic difference between the venoms[290,306,387] Africanized

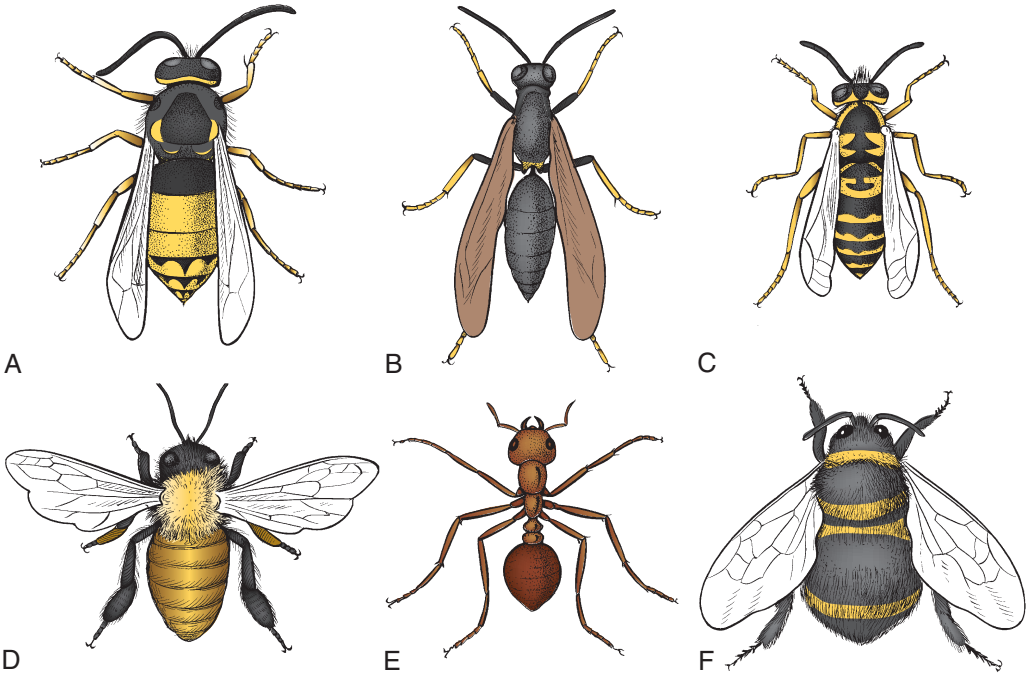

FIGURE 41-1 Representative venomous Hymenoptera. **A,** Hornet *(Vespula maculata)*. **B,** Wasp *(Chlorion ichneumerea)*. **C,** Yellowjacket *(Vespula maculiforma)*. **D,** Honeybee *(Apis mellifera)*. **E,** Fire ant *(Solenopsis invicta)*. **F,** Bumblebee (*Bombus* species).

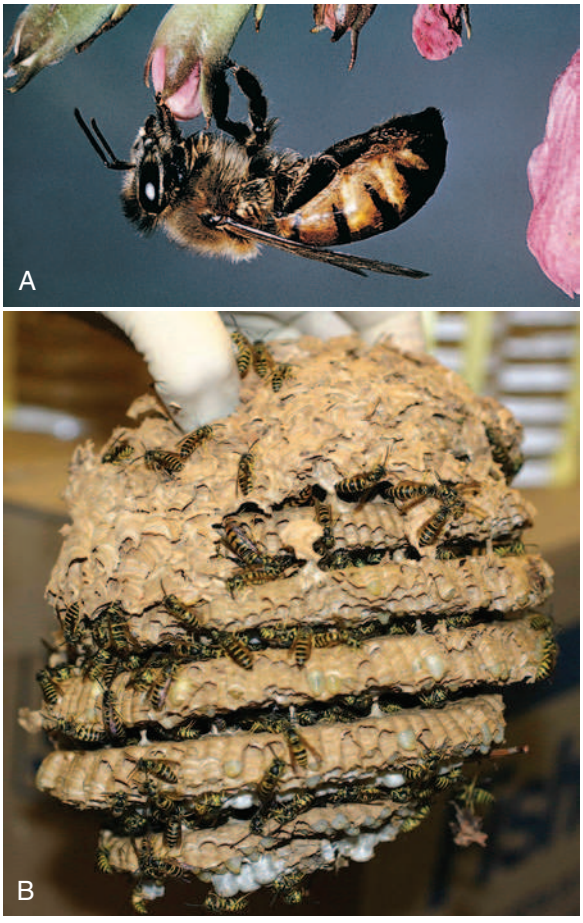

FIGURE 41-2 **A,** Worker honeybee, *Apis mellifera*. **B,** Honeybee nest.

honeybees can overwhelm and kill even healthy nonallergic victims.[40] About 50 simultaneous stings can cause systemic envenomation, and an estimated 500 are necessary to cause death induced by massive envenomation via direct toxicity.[216] As few as 30 to 50 stings have proved fatal in small children.[49]

An estimated 1000 fatal attacks have been documented worldwide. A large percentage occurred in Venezuela during 1977 and 1978. More than 300 bee attacks occurred in Mexico between 1987 and 1992, with 50 fatalities.[302] A more recent account puts future estimates at 60 deaths per year.[385] Because Mexico and the southern United States have many feral and domestic honeybee populations, researchers thought that the aggressiveness of the African bees could be dampened by hybridization. Large numbers of male European bees were released to facilitate this, and African queens were replaced by European stock when possible. However, studies indicate that European bee populations are becoming rapidly Africanized with little reciprocal gene flow, as African females take over European hives.[186,252,403,447]

Bumblebees (*Bombus* and related genera) are a largely holarctic group often found in quite cold environments. Increasing reactions to stings in Alaska may be related to the recent changing trends in climate.[105] Small colonies usually nest just under the surface of the ground, often in mammal burrows. Some species are aggressive if disturbed, although most have mild dispositions.[254]

Sweat bees (family Halictidae) are small bees of cosmopolitan distribution (Figure 41-4). They are attracted to sweaty skin and ingest perspiration. They nest in burrows, often in clay banks. Females sting if squeezed or trapped under clothing. The sting is not very painful, but anaphylactic reactions have been reported. The allergens are immunologically unrelated to those in other bee and wasp venoms.[333]

WASPS

Social wasps occur throughout most of the world but are recognized as a medical problem, chiefly in the United States and Europe. They often establish colonies close to human dwellings. Yellowjackets (*Vespula* species) may be more important than

FIGURE 41-3 **A,** Stinger of a honeybee. **B,** Africanized honey bee *(left)* and European honeybee on honeycomb.

FIGURE 41-4 Sweat bee, family Halictidae. *(From* encarta.msn.com.*)*

FIGURE 41-5 Yellowjacket, *Vespula maculiforma.*

honeybees as a cause of human stings in the northern United States[344] (Figure 41-5). They make underground nests (Figure 41-6) in rotted-out tree stumps, cavities under stones, and mammal burrows. They are strongly attracted to garbage. Paper wasps (*Polistes* species) (Figure 41-7) suspend their nests in shaded places, often in shrubbery near houses or below eaves, gutters, or window frames. Old World hornets (*Vespa* species) and white-faced hornets *(Dolichovespula maculata)* create large paper nests that may be plastered to buildings, but more typically hang from tree branches (Figures 41-8 and 41-9).

Solitary wasps are predators, feeding largely on other insects and spiders. Adults often carry the prey alive and paralyzed to the nest as food for the larvae. Some wasps excavate burrows, whereas others make mud nests that may be plastered on shaded walls of buildings or under bridges. Although many nests may be grouped together, the adult wasps have no social organization and make little effort to defend them. The cicada killers *(Sphecius speciosus)* (Figure 41-10) and tarantula hawks (*Pepsis* species) (Figure 41-11) are among the largest North American wasps. Velvet ants (family Mutillidae) are female wingless wasps that are nest parasites of other Hymenoptera (Figure 41-12). They are found in deserts and other dry and open habitats and can inflict a painful sting.

Internationally, hymenopteran insects are worldwide in distribution and often constitute a major part of a region's insect fauna. Honeybees are exploited for their honey throughout the world; even the aggressive *A. m. scutellata* is used for honey production in Africa. Honeybees in southern Asia attach huge nests to limbs of forest trees. The giant bee *Apis dorsata* of Southeast Asia has a reputation for savagery, and deaths from multiple stings have occurred. Yellowjackets and hornets are common in Europe and the Middle East, where their medical importance is similar to that in the United States. The genera *Vespula, Vespa,* and *Dolichovespula* are found all over Europe.[102] The genus *Polistes,* present throughout central Europe, is not found in the United Kingdom and represents a larger clinical problem in areas surrounding the Mediterranean Sea. Amino acid sequencing of the venom allergens of the different species of *Polistes* in Europe shows them to be very similar, but the similarities to American strains are less pronounced.[143]

Two species, *Vespula orientalis* and *Vespula vulgaris,* have recently been introduced into Australia, where they have become significant problems.[77] Paper wasps of the genus *Polistes* are plentiful in tropical America and Australia (Figure 41-13). Another Australian paper wasp, *Ropalidia revolutionalis,* constructs nests that resemble belts of bullets and hangs them from shrubs and fences. Fire wasps *(Polybia)* are found from Mexico to northern South America. The common species are black with yellow markings. They construct globular, cylindrical, or cone-shaped paper nests up to 70 cm (28 inches) long that are hung, usually from trees and sometimes under bridges. They may defend these nests with great vigor.

FIGURE 41-6 Early yellowjacket nest.

ANTS

Ants are social insects, worldwide in distribution over a wide range of habitats. Many ants sting, and others have repugnant secretions. Trap-jaw ants feature highly specialized catapult-like biting mechanisms. Their mandible closing is one of the fastest movements in the animal kingdom. The relatively large number of motor neurons that control the mandible reflects the importance of this for the behavior and survival of ants.[217] The ant species of greatest medical significance in the United States is the imported fire ant *Solenopsis invicta* (see Figure 41-1F).[222] It was apparently introduced from South America into Mobile, Alabama, in 1939 and has subsequently spread throughout the southern states from southeastern Virginia to central Texas and Oklahoma, largely eliminating another introduced fire ant

FIGURE 41-7 Paper wasp, *Polistes* species.

FIGURE 41-8 White-faced hornet, *Dolchiovespula maculata*, largest of the common social wasps in the United States.

FIGURE 41-9 Typical nest of the white-faced hornet.

FIGURE 41-10 Cicada killer wasp, *Sphecius speciosus*. *(From* ento.okstate.edu.*)*

FIGURE 41-12 Velvet ant, family Mutillidae.

FIGURE 41-13 Wasp colony. *(Courtesy Wikimedia Commons.)*

(*Solenopsis richteri*) and two native species. Mound nests are usually found in open grass settings, often in urban areas (Figure 41-14). Other states that harbor fire ants include Arizona, California, New Mexico, Oregon, and Washington, as well as Puerto Rico. As many as 600 mounds per acre have been reported. Worker colonies may reach a maximum size of 500,000 ants in 2 years and rapidly give rise to satellite colonies.[408] *S. invicta* are extremely irritable insects. They are usually easy to identify, as they do not fly away but instead grasp their victims with their mandibles and inflict multiple painful stings.[233]

Species other than imported fire ants can cause severe reactions.[232,434] Harvester ants (*Pogonomyrmex* species) of the southwestern United States and Mexico are of medical importance. Entrances to the underground nests are usually surrounded by clear zones and sometimes by rings of soil. Some species react aggressively to disturbance of the nest. The stings are painful and may be accompanied by systemic symptoms; anaphylaxis has been reported.

FIGURE 41-11 Tarantula hawk, *Pepsis* species. *(Courtesy Mary Beth Stowe, McAllen, Texas.)*

FIGURE 41-14 Fire ant mound.

There are numerous stinging species of ants in the tropics. Although native to South America, fire ants do not seem to be a major medical problem there, perhaps because of native competitors, predators, and parasites. Two fire ant species are important in areas outside the United States. *Solenopsis geminata* has been introduced into Okinawa and Guam and is widespread in Central America, Mexico, and some Caribbean islands. *Solenopsis xyloni* is common in Mexico and also occurs in California and Texas. Anaphylaxis caused by imported fire ants has also been described in Australia.[404,284] Severe human urticaria produced by the ant *Odontomachus bauri* has been reported in Venezuela.[365] Amino acid sequences of all fire ant venoms are very similar.[200] Therefore, all fire ant stings can be managed medically in the same manner.

The samsum ant, *Pachycondyla sennaarensis,* is an ecologic counterpart of the fire ant that is widely distributed in the African tropics and Arabian Peninsula. It nests in the ground but does not make a conspicuous mound. In the United Arab Emirates, it is plentiful in urban areas and may cause multiple stings.[9,116] Australian bull ants (*Myrmecia* species), such as the "jumper jack," are large insects (about 20 mm [0.8 inch] or the size of a medium cockroach) with prominent jaws (Figure 41-15).[356] They are ground dwelling and common in suburban areas in southeastern Australia. Many neotropical stinging ants live in trees. The giant black ants (16 to 22 mm [0.7 to 0.9 inch]) of the genus *Paraponera* are found from Nicaragua to the Amazon basin. Although they nest in the ground, workers forage in trees from almost ground level to high in the forest canopy. They are most active at night. The green tree ant of northeastern Australia makes a leaf nest in trees. It has no true sting but ejects formic acid into wounds made by its jaws.

HYMENOPTERA STINGING PATTERNS

Multiple stings often result from disturbance of a nest, as the first insects encountered release alarm pheromones that incite aggressive behavior in other members of the colony. With large species such as the white-faced hornet, 40 to 50 stings may create a life-threatening injury.[440] The lethal dose of honeybee venom has been estimated at 500 to 1500 stings.[395] However, most of the 40 to 50 deaths per year in North America from Hymenoptera stings are the result of anaphylaxis occurring in victims with prior stings who developed specific immunoglobulin E (IgE) antibodies.[157] In the United States and other Western nations, the incidence of serious insect stings is higher in adults than in children, and higher in males than in females. Most persons are stung while engaged in outdoor work or recreation. Apiarists, or beekeepers, are engaging in a high-risk occupation; however, many beekeepers develop considerable immunity as a result of frequent stings.[303] Other relatively high-risk occupations include farmers, house painters, carpenters, highway workers, bulldozer operators, park rangers, and emergency personnel during flooding disaster relief.[114] Wasps and bees are sometimes swept into the interior of a moving automobile, exposing the occupants to the risk of both a sting and a highway accident. Many foods, particularly meats, ripe fruit, or fruit syrups, attract yellowjackets, which often swarm around picnic areas and recycling bins. Syrups, flowers, sweat, and some perfumes attract bees. In such aggregations, the insects are not particularly aggressive but may become trapped in clothing or hair. A recent source documented that Africanized bees were more aggressive after exposure to 20% ethanol than to standard sucrose solutions placed in front of their hives.[1] In temperate zones, the incidence of hymenopteran stings is highest in late summer and early fall, when insect populations are highest.

Fire ants may invade houses during periods of heavy rain and in hot, dry weather as they seek food and water.[110] There have been increasing incidents of fire ant attacks on patients in health care facilities, such as nursing homes, where frail elderly patients are incapable of fleeing for protection.[108,168,373,417] In one report, one patient experienced a severe anaphylactic reaction and four patients died within 1 week. The presence of fire ants around immobilized, often cognitively impaired patients, such as nursing home residents, seem to be a primary risk for massive fire ant attacks.[88] Fatal anaphylaxis with indoor native fire ant stings has been described in infants.[297]

VENOM AND VENOM APPARATUS

Venom is present in many hymenopteran species and is used for both defense and subjugation of prey. The venom apparatus is located at the posterior end of the abdomen and consists of venom glands, a reservoir, and structures for piercing the integument and injecting venom. Venoms of most medically important Hymenoptera are mixtures of protein or polypeptide toxins,

FIGURE 41-15 **A,** Red bull ant. **B,** Australian jumper jack ant. *(Courtesy Wikimedia Commons.)*

enzymes, and pharmacologically active, low-molecular-weight compounds, such as histamine, serotonin, acetylcholine, and dopamine. Melittin, a strongly basic peptide, is the principal component of honeybee venom, making up 50% of the dry venom weight. It damages cell membranes through detergent-like action, with liberation of potassium and biogenic amines.[87] Peptides with similar activity occur in bumblebee venom. Histamine release by bee venom appears to be largely mediated by mast cell degranulating peptide. A third peptide, apamin, is a neurotoxin that acts principally on the spinal cord. Adolapin, a recently described bee venom peptide, has antiinflammatory activity, which may explain the effectiveness of bee venom in treating some forms of arthritis. The chief enzymes of bee venom are phospholipase A and hyaluronidase. The former is believed to be one of the major venom allergens and, with melittin, to account for much of the acute lethality. Histamine makes up about 3% of the dry weight of bee venom. The intravenous (IV) median lethal dose (LD_{50}) of honeybee venom for mice is 6 mg/kg. An average sting injects about 0.50 mL of venom containing approximately 0.05 mg of solids.

Intense pain after stings by hornets and other social wasps is largely caused by serotonin and acetylcholine, which constitute 1% to 5% of dry venom weight. Wasp kinins (peptides) contribute to pain production and have strong, brief hypotensive effects. Mastoparans are similar in action to mast cell degranulating peptide but are weaker. Phospholipase A, phospholipase B, and hyaluronidase are present in relatively large amounts. Unidentified proteins, some of which appear to be major allergens, are also present. A lethal protein in *Vespa basalis* venom releases serotonin from tissue cells and has hemolytic and phospholipase A activity.[198] The IV LD_{50} of different hornet venoms for mice ranges from 1.6 to 4.1 mg/kg.

Less is known of venoms of solitary wasps. The venom of *Sceliphron caementarium,* a mud dauber (Figure 41-16), is comparatively low in protein and contains no acetylcholine, histamine, serotonin, or kinins but does contain several unidentified low-molecular-weight compounds. Its proteins are immunologically different from those of honeybee, yellowjacket, and paper wasp venoms. Philanthotoxin (molecular weight 435) from venom of the beewolf *(Philanthus triangulum)* acts at the insect's myoneural junction and has potential value as an insecticide.

Ant venoms show great variation. In the life of the fire ant *(S. invicta),* venom plays several important roles, including prey capture, defense, and antimicrobial action. The synthesis of fire ant venom is limited to early life, and the injected venom dose appears to be carefully modulated. Older ant workers (foragers) deliver less venom per sting than do middle-age workers (reserves), and the volume from nest defenders is 50% higher than from their counterparts, particularly in the spring.[184] Venoms of more primitive ants (subfamilies Ponerinae, Myrmicinae, and Dorylinae) resemble venoms of social wasps, containing kinin-like peptides, enzymes, and unidentified proteins. In more highly evolved ants (subfamilies Dolichoderinae and Formicinae), a variety of low-molecular-weight compounds (terpenes, ketones, and organic acids) make up the bulk of the secretion, which may be sprayed rather than injected. Venoms of fire ants (*Solenopsis* species) are composed largely of piperidine alkaloids, which cause histamine release and necrosis in human skin. Proteins make up only 0.1% of the dry weight of fire ant venoms, but they are highly allergenic.[157,158] Hyaluronidase and phospholipase activities have been demonstrated.

FIGURE 41-16 Solitary mud dauber wasp.

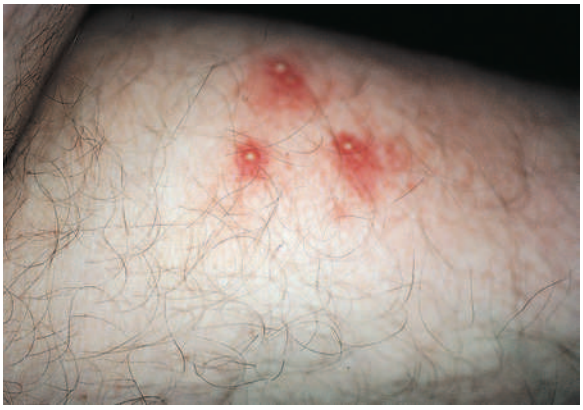

FIGURE 41-17 Fire ant lesions.

CLINICAL ASPECTS

Hymenoptera stings are most often inflicted on the head and neck, followed by the foot, leg, hand, and arm. Stings in the mouth, pharynx, and esophagus may occur when bees or yellowjackets in soft drink, iced tea, or beer containers are accidentally ingested.[311,389] A single wasp, bee, or ant sting in an unsensitized individual usually causes instant pain, followed by a wheal and flare reaction, with variable edema. Fire ants typically grasp the skin with their mouthparts and inflict multiple stings.[82] These produce vesicles that subsequently become sterile pustules (Figure 41-17). Multiple Hymenoptera stings may cause vomiting, diarrhea, generalized edema, dyspnea, hypotension, tachycardia, and collapse. Optic neuritis[458] and direct ocular stings with corneal involvement and bilateral ptosis have been described.[11,315,400,401] Widespread necrosis of skeletal muscle with hyperkalemia, rhabdomyolysis, acute tubular necrosis with renal failure, and hepatorenal syndrome with hemolysis have been reported.[7,75,229,241,257] Acute renal failure may result from toxic ischemic mechanisms, with hypovolemia or anaphylactic shock, myoglobinuria, or acute tubular necrosis.[49] Hemolytic anemia and acute renal failure requiring dialysis have also been described following massive attacks by 600 to 1500 Africanized bees, as well as following wasp stings in children.[92,93,427] Acute pancreatitis, disseminated intravascular coagulation, and multiorgan dysfunction are also well documented.[94,109,147,155,442] Myocardial infarction, atrial flutter, and atrial fibrillation in previously healthy individuals may follow multiple hymenopteran stings.[66,72,91,135,249,353,416,438] In one case, a 67-year-old man with acute ST-segment elevation myocardial infarction required fibrinolytic therapy.[263] Possible pathogenic mechanisms include severe hypotension due to hypovolemic shock, and prolonged coronary spasm with subsequent thrombosis of coronary vessels due to release of vasoactive, inflammatory, and thrombogenic substances contained in Hymenoptera venom.[66] Cerebral infarction, descending aortic thrombosis, and coagulation abnormalities are also reported.[80,264,358,420]

On the skin, large local reactions spreading more than 15 cm (6 inches) beyond the sting site and persisting for more than 24 hours are relatively common. Formation of large bullae may also occur.[257] This represents a cell-mediated (type IV) immunologic reaction, although more than one-half of these patients also have IgE antibody against venom or show a positive skin test. Later stings in these individuals usually result in another large local reaction; systemic reactions are rare.[450]

Hymenoptera stings account for more deaths in the United States than any other type of envenomation. Allergy is the most serious aspect of hymenopteran stings. Anaphylaxis and related syndromes from this source are relatively common outdoor wilderness emergencies. An estimated 0.4% of the U.S. population shows some degree of clinical allergy to insect venoms, and approximately 50 deaths are reported annually.[352] This number may be underestimated, because not all anaphylactic episodes are recognized or reported. Severe systemic reactions are related to eosinophilia, female gender, and concomitant atopic diseases.[453] Fatal anaphylaxis due to fire ant stings has also been reported.[346] Asymptomatic sensitization, as shown by a positive venom skin test, was observed in 15% of 269 randomly selected subjects with no history of an allergic sting reaction.[173] Sensitization is transient but may persist for years. These individuals are at higher risk of systemic allergic reactions than are those with negative skin tests.[174] Recent studies have reported a high prevalence of hypersensitivity symptoms after intake of wine. Wine contains many contaminants. Some of them come from Hymenoptera insects that fall into the wine when grapes are collected and pressed. Patients with allergic symptoms related to wine consumption may have been sensitized to Hymenoptera venom without previous stings.[16]

Sudden death from insect sting may not always be recognized. One-half of individuals with fatal sting reactions had no documented history of previous systemic reaction.[36] Unexplained deaths at poolsides, golf courses, or any outdoor recreational area may be caused by unrecognized Hymenoptera envenomations.[118] Of 142 sera obtained after sudden, unexpected death, 23% contained elevated levels of IgE to at least one insect venom. In contrast, 6% of sera from 92 blood donors contained comparable IgE levels. In eight fatal cases of Hymenoptera sting anaphylaxis, IgE to the putative venom source was elevated in all, although levels were not higher than those of some healthy individuals in the same population.[389] Allergy-specific IgE antibodies to imported fire ants is nearly twice as common in adults living in endemic areas, making these individuals more susceptible to severe anaphylaxis.[67] Anti–fire ant IgE and elevated serum tryptase were detected in a case of fatal fire ant sting.[303] Elevated levels of venom-specific IgE were detected in two fatal cases of wasp sting.[425] However, the level of specific IgE antibodies against venoms is not predictive of the severity of anaphylactic reaction, as documented by studies conducted to determine the reliability of postmortem specific IgE antibody testing in venom-induced anaphylactic deaths.[201]

Wasp and bee venoms contain 9 to 13 antigens, some of which are potent allergens. Available evidence indicates little cross-sensitization between honeybee and wasp venoms. About 50% cross-sensitization occurs between *Polistes* and other social wasp venoms, and nearly 100% between yellowjacket and hornet venoms. Positive radioallergosorbent test (RAST) reactions to imported fire ant venom were seen in 51% of patients allergic to bee and wasp venoms but without exposure to fire ants. The allergen appears to be identical to antigen 5 of wasp venoms.[199]

The basic tests used to diagnose allergy to Hymenoptera venom are skin tests and detection of venom-specific IgE antibodies. Specialized diagnostic tests, such as inhibition cellular tests and determination of tryptase and carboxypeptidase, can also be performed.[274,371] Examination of the sera of hypersensitive individuals for IgE and IgG antibodies against purified venom proteins indicates that phospholipase A, hyaluronidase, and acid phosphatase are important in honeybee venom, whereas phospholipase A, antigen 5, and hyaluronidase are important in wasp venoms. Antigen 5, a nontoxic protein of unknown activity, is reported to have sequence similarity to mammalian testis, human brain tumor, and certain plant leaf proteins. This may explain anaphylactic reactions to first insect stings.[230,440] Despite the small amount of protein in fire ant venoms, about 12% of persons treated for fire ant stings show systemic allergic reactions, and at least 32 anaphylactic deaths have been confirmed. Four antigens in *S. invicta* venom have been reported to be allergenic.[64]

Allergic sting reactions occur remote from the sting site and include flushing, pruritus, papular urticaria,[409] hives, and angioedema. In life-threatening reactions, marked respiratory distress with airway edema, hypotension, loss of consciousness, and cardiac arrhythmias may be seen. At least one-half of the severe reactions occur within 10 minutes after a sting, and virtually all occur within 5 hours. Most fatalities occur within 1 hour. The interval between the first known sting and the reaction-producing sting is usually less than 3 years, but may be as long as 48 years. In a group of 3236 Hymenoptera-allergic individuals, 61.5% were male and 32.3% had a history of atopy. The mean age was 30.5 years. No correlation existed between systemic reactions and the number of stings in the past or the number of stings per incident and the severity of a systemic reaction. In a series of 138 adults with a history of insect sting anaphylactic reactions, 99 had no anaphylactic reactions to later stings, 17 had more severe reactions, and 22 had mild to moderate reactions.[429] In another series of 90 adults with previous anaphylactic reactions, 60 had similar reactions when stung again, and 23 had more severe reactions.[351] In children age 10 years and younger, life-threatening reactions occur less often than in adults, and repeated sting episodes usually are not increasingly severe. However, 17% of children with a history of systemic bee or wasp sting reactions developed a systemic reaction after a sting challenge test, as did 5% of children who sustained a sting in the field.[189] Children were once thought to outgrow the allergy to insect stings, but there are no reports accurately documenting this theoretical maturation process.[171,180]

Fatalities that occur within the first hour after a sting result from airway obstruction or hypotension, or both. In 69% of fatal cases, obstruction of the respiratory tree by edema or secretions was the principal finding at autopsy; in 12%, vascular pathology was the principal finding; and 7% of the victims had primary central nervous system involvement, such as petechial hemorrhages, infarction, and cerebral edema.[28] Hemostatic defects, including reduction of all clotting factors and release of a thrombin inhibitor, may be seen with insect sting anaphylaxis. Severe fetal brain damage, presumably associated with hypoxia, has been reported. Delayed (3 to 14 days) atypical reactions after hymenopteran stings include serum sickness and Arthus reaction, which are caused by systemic and local effects of antigen-antibody complexes; nephrotic syndrome; thrombocytopenic purpura; grand mal and focal motor seizures; transient cerebral ischemic attacks; Guillain-Barré syndrome; and progressive demyelinating neurologic disease.[378] Most appear to be immunologically mediated. In one series, elevated IgE to bee or yellowjacket venom was observed in 6 of 13 such patients.[250,288]

Identification of the individual with potentially dangerous allergy to hymenopteran sting is not always possible. Skin testing with hymenopteran venoms is the most sensitive method; RAST for IgE antibody to venoms is less sensitive, but an important complementary test.[170,236] Serum tryptase and basophil responsiveness to venom allergens are also sensitive indicators and should be analyzed in patients with a history of severe sting reaction.[38,370,382] A small but significant number of individuals with no history of sting reactions have IgE antibody specific for hymenopteran venoms; prevalence of this antibody is higher in summer.[462] These methods do not identify all at risk, and antibody levels do not correlate with severity of sting reactions. In a significant number of individuals, particularly children, clinical sensitivity disappears and IgE levels fall virtually to zero 3 to 18 months after a reaction-producing sting. In about 40% of cases, sensitivity may disappear within 3 years.[247] Venom antibody (both IgE and IgG) may be found in healthy individuals (40% of beekeepers, 12% of blood donors) with no history of systemic reaction to insect stings.

No unique features distinguish Hymenoptera envenomations in other parts of the world from those in North America. Venoms of the various groups show little geographic variation. This is also true of groups at risk, with the possible exception of a few honey-gathering Asian tribes. The incidence of Hymenoptera sting allergy may be slightly higher in western Europe than in the United States, and fatal allergic reactions may be slightly more common.[79] Anaphylactic reactions to bee venom are more prevalent in the rural populations closer to the Mediterranean than in western Europe, where urban populations predominate.[294]

Paraponera ant stings are intensely painful for several hours and may be accompanied by fever and lymphadenitis. Black ant stings inflicted by *Pachycondyla sennaarensis* (Middle East) and *Pachycondyla goeldii* (Brazil) have created global health hazards.[10,88] Systemic anaphylactic reactions to stings of Australian bull or jumper jack ants, as well as samsum ants, are increasing, with reports of fatalities.[56,202,278] Anaphylaxis secondary to red fire ant *(Solenopsis geminata)* bites have been reported in India.[190] Hemolytic-uremic syndrome following *Solenopsis invicta* bites has been reported in China[251] Patients with a history of systemic reactions to samsum ant stings have IgE and positive skin test reactions to fire ant venom.[116]

TREATMENT AND PREVENTION

Treatment of anaphylaxis is conventional. Aqueous epinephrine 1:1000 should be administered intramuscularly in the prehospital setting at the first indication of serious hypersensitivity. The dose for adults is 0.3 to 0.5 mL; for children under age 12 years, it is 0.01 mL/kg, not to exceed 0.3 mL. Compared with methylprednisolone alone, early combination of epinephrine helps to further inhibit the diffusion of allergy and inflammation cytokines, and therefore reduce the severity of injury.[452] When symptoms are predominantly respiratory, epinephrine by inhalation (10 to 20 puffs for an adult; 2 to 4 puffs per 10 kg [22 lb] of body weight for a child) may provide more rapid relief.[300] In the presence of profound hypotension, the patient may be in shock and not adequately perfusing the skin. In this scenario, 2 to 5 mL of a 1:10,000 epinephrine solution may be given by slow IV push, or an infusion may be initiated by mixing 1 mg in 250 mL and infusing at a rate of 0.25 to 1 mL/min. If an IV line is delayed or cannot be established, epinephrine may be given intramuscularly, intralingually, or via an endotracheal tube.[22] Two patients with Hymenoptera-induced anaphylactic shock with profound hypotension were successfully resuscitated using 40 IU of IV vasopressin followed by a rapid fluid bolus.[226] Selective inhaled (nebulized) β_2-adrenergic agents, such as albuterol, can also be effective in relieving bronchospasm at doses of 2.5 mg/3 mL of a 0.08% solution. Aminophylline, 5 mg/kg as a loading dose followed by 0.9 mg/kg/hr as an infusion, may relieve bronchospasm not relieved by epinephrine or albuterol.

In the presence of hypotension, IV crystalloid solutions should be infused; pressor agents such as dopamine or norepinephrine may be required. Oxygen, intubation, and mechanical ventilation may be needed to correct airway obstruction. Antihistamines can alleviate symptoms of anaphylaxis but should be used only in addition to epinephrine, not as a substitute.[22] Corticosteroids are indicated by some for acute anaphylactic reactions, although the time of onset with corticosteroids is delayed and their efficacy is not definite. Propranolol is contraindicated because of the β-adrenergic blockade effect on the bronchioles. Persons taking β-adrenergic blockers may respond poorly to epinephrine. In these cases, administration of glucagon to counteract the beta blockade effect may prove beneficial.[361] Persons with insect sting anaphylaxis require close observation, preferably in the hospital, over a period of 24 hours.[300]

For mild hymenopteran stings, ice packs often provide relief. Honeybees frequently and yellowjackets occasionally leave a stinger in the wound. Although recommendations were that stingers should be scraped or brushed off with a sharp edge and not removed with forceps, which might squeeze the attached venom sac and worsen the injury, this has been refuted.[362,435] Advice to victims on the immediate treatment of bee stings now emphasizes rapid removal of the stinger by any practical method.[435] Wheal size and degree of envenomation increased as the time from stinging to stinger removal increased, even for a few seconds. The response was the same whether stings were scraped or pinched off after 2 seconds. Home remedies, such as baking soda paste or meat tenderizer applied locally to stings, are of dubious value, although the latter is often regarded as effective. Topical anesthetics in commercial "sting sticks" are also of little value. Topical aspirin paste is not effective in reducing the duration of swelling or pain in bee and wasp stings and may actually increase the duration of redness.[26] Local application of antihistamine lotions or creams, such as tripelennamine, may be helpful. An oral antihistamine, such as diphenhydramine, 25 to 50 mg for adults and 1 mg/kg for children, every 6 hours is often an effective adjunct.

All fire ant stings can be managed medically in the same manner. No therapy is effective against local effects of fire ant stings, although oral antihistamines and corticosteroids may provide some relief in severe cases. Because infection is common, topical antimicrobials (e.g., mupirocin) and prophylactic oral antibiotics are recommended. Breaking open fire ant blisters should be avoided.[86,109]

Corticosteroids, such as methylprednisolone, 24 mg/day as the initial dose tapered off over 4 to 5 days, often help resolve extensive local reactions to bee and wasp stings. This may be combined with cold packs and oral antihistamines. Chronic facial edema caused by multiple bee stings has been effectively treated with plastic surgery and liposuction.[3]

Envenomation from multiple hymenopteran stings may require more aggressive therapy. IV calcium gluconate (5 to 10 mL of 10% solution) with a parenteral antihistamine and corticosteroid may be helpful in relieving pain, swelling, nausea, and vomiting. Hypovolemic shock is managed conventionally. Plasmapheresis was used successfully to treat a person who sustained about 2000 honeybee stings.[115] Patients should be observed for 12 to 24 hours for coagulopathy and evidence of renal and neurologic damage. Urine output is monitored and urine tested for hemoglobin and myoglobin. Serum potassium, creatine kinase, and lactate dehydrogenase levels should be monitored. Oliguria with myoglobinuria, azotemia, and hyperkalemia are indications for hemodialysis.

Immunotherapy

It is suggested that at least one-half of sting fatalities in patients with a previous history of severe systemic reactions could have been avoided through the timely administration of specific immunotherapy.[37] Venom immunotherapy is 75% to 98% effective in preventing sting anaphylaxis.[170] Immunotherapy is highly effective; a 4-year series of injections reduces the incidence of subsequent sting-induced anaphylaxis to 3%.[238] Immunotherapy should be offered to patients with a history of anaphylaxis after a sting, mastocytosis, and specific IgE antibodies to the agent confirmed by positive skin testing or in vitro assays.[187,255] In addition, venom immunotherapy significantly reduces the size and duration of large local reactions.[172,392] Desensitization with purified venoms produces an excellent blocking antibody response and prevents anaphylaxis in more than 95% of patients. A protective antiidiotypic antibody to honeybee venom has been identified.[225] Venoms for desensitization generally available in the United States are honeybee, yellowjacket, wasp *(Polistes),* and mixed vespid. Systemic reactions during venom immunotherapy are significantly more frequent with honeybee venom than with vespid venom.[209] More than one venom can be given concurrently, but this requires multiple injections. Commercial preparations consisting of a mixture of yellowjacket, white-faced hornet, and yellow hornet venoms are also available.[157] A whole-body extract of fire ant containing at least three venom antigens has also been developed.[441]

Children under 16 years with only cutaneous or mild systemic allergic reactions and persons with a history of only large local reactions do not need immunotherapy.[306] Evaluation of anaphylaxis risk is recommended in children using wasp venom extract challenges.[384] As mentioned previously, children were once thought to "outgrow" their allergies to insect stings, but this has never been proved. In fact, a clinically important number of children retain their allergic reactions to Hymenoptera venom. Immunotherapy in children leads to a significantly lower risk of systemic reaction to stings, even 10 to 20 years after treatment is completed. This prolonged benefit is greater than that observed when the immunotherapy is given to adults.[171,185] Persons receiving β_2-adrenergic blockers should be shifted to other appropriate medications if possible.

Regimens for desensitization attempt to achieve tolerance to venom doses of about 100 mcg. It requires about 95 days to achieve a maintenance level of immunity. Rapid or "rush"

programs requiring 3 to 7 days for initial immunization appear to be effective in high-risk patients.[18,33,125,218,411,444] A recent study suggests that ultrarush sublingual immunotherapy may be as efficacious and better tolerated than traditional subcutaneous immunotherapy.[330] Some programs make use of both active and passive immunotherapies.[299] In a series of 1410 patients, 12% had systemic reactions during treatment, but no fatalities were reported.[261,262] A report of 26 women with 43 pregnancies does not suggest significantly increased risk from venom immunotherapy during pregnancy.[388] Maintenance doses are required at intervals after basic immunization. Standard venom immunotherapy involves administration of the maintenance dose every 4 to 6 weeks. An extended maintenance of 3 to 4 months appears to be as effective and safe and may be the best option in terms of convenience and cost-effectiveness.[398] Neither skin testing nor determination of IgG and IgE antibody levels against venom will reliably indicate success of immunization, although the majority of persons will be protected by a specific IgG antibody level of 400 RAST units/mL of serum. Actual sting challenge is the most reliable test for determining immunotherapy candidates and desensitization,[430] but this is not widely used in the United States. It must be done in the hospital with careful monitoring and consideration of economic, ethical, and safety factors.[372] If the skin test is negative after 3 years of immunotherapy, patients may be placed on immunologic surveillance. Few patients require more than 5 years of immunotherapy.[352] According to some authorities, if a sting challenge or field sting is tolerated during the period of immunotherapy, treatment can be terminated after 3 to 5 years.[347] For unknown reasons, desensitization to wasp venoms is achieved more quickly than to honeybee venom.[45] Although the low mortality and morbidity rates associated with patients who suffer subsequent stings following immunotherapy have led some to conclude that many patients are being treated unnecessarily, this conclusion is refuted by the fact that venom immunotherapy improves the quality of life and health of the vast majority of patients receiving this intervention.[47,323,322] Patients should be warned that the efficacy of venom immunotherapy might be less than optimal and they should continue to carry adrenaline autoinjectors.[249]

Like bee venom immunotherapy, purified *Myrmecia* ant venom immunotherapy has been established and shown to be highly effective for Australian bull or jumper ant and imported fire ant anaphylaxis. Serum IgE testing enhances the accuracy of diagnosis and is a prerequisite for administering species-specific Australian venom immunotherapy.[50,53,54,192,248,312]

Antivenom Therapy and Future Interventions

Development of a hyperimmune bee venom antiserum is under investigation.[386] An equine-raised F(ab)-based antivenom is a potential new treatment for victims of multiple "Africanized" bee stings. The final product contains highly specific IgG titers and is effective in neutralizing toxic effects, such as hemolysis, cytotoxicity, and myotoxicity.[405] A group in the United Kingdom has developed ovine Fab-based antivenom as a potential treatment for mass bee stings. Sera from sheep immunized against the venom of *A. m. scutellata* contained high levels of specific antibodies, as demonstrated by enzyme-linked immunosorbent assay and chromatography. Although effective experimentally in a mouse model, no human administration of the antivenom has been documented.[216]

Another approach based on genetic engineering is the use of non-IgE binding peptide fragments of the insect allergen with preserved T-cell epitopes for advanced immunotherapy. Such preparations of bee venom phospholipase A2 have been used successfully in pilot studies. Additionally, DNA vaccination with phospholipase A2 sequence plasmids has proved effective in a mouse model.[298]

Patients who experience severe anaphylaxis to venom immunotherapy can now be treated with the antiimmunoglobulin (Ig) E monoclonal antibody, omalizumab.[161,325]

Preparedness and Preventive Measures

Persons with a history of allergic reactions to insect stings (including large local reactions) should carry an emergency kit containing epinephrine autoinjectors and should wear medical identification tags.[157,238] Kits should be available in work and recreation areas where the risk of insect sting is high.[436] Two kits widely available are EpiPen and Ana-Kit (outside of the United States). EpiPen and EpiPen Jr. are autoinjectors that deliver 0.3 mg or 0.15 mg of epinephrine, respectively (Figure 41-18). They are quick and easy to use; however, patients should be cautioned against injecting the material into fingers or buttocks or directly over veins. Ana-Kit contains two doses of 0.3 mg of epinephrine in a single conventional syringe, plus chewable antihistamine tablets and a tourniquet. It is more versatile but requires more instructions for the user.

FIGURE 41-18 EpiPen preloaded delivery system for injection of aqueous epinephrine. *(Courtesy Dey, LP.)*

Frequent cleaning of garbage cans and disposal of decaying fruit makes premises less attractive to bees and wasps. Hymenopterans are highly susceptible to many insecticides, as noted with the aforementioned bee colony collapse disorder, and their control around dwellings and other inhabited buildings is rarely difficult. Spraying the nests after dark is safer because these insects are less active at night. Many hymenopterans are economically valuable as pollinators of plants or predators on other insects, so their control on a wide scale is rarely desirable. The fire ant in the southern United States has been the target of massive but marginally effective control campaigns that adversely affected local ecosystems. A new approach uses grain baits containing synthetic insect growth hormones that are carried into the nests, where they disrupt ant caste differentiation and inhibit egg production. Arrays of thousands of hormone-baited traps placed in select areas of Mexico, however, failed to stop the northward spread of Africanized bees. For controlling populations of Africanized bees, care should be taken that items such as boxes and empty oil drum containers are not left outdoors. Ceilings and walls should be sealed off as potential nesting sites for colonies and swarms.[100]

LEPIDOPTERA

VENOMOUS SPECIES AND VENOMS

Caterpillars are larval forms of moths and butterflies and belong to the order Lepidoptera.[205] Next to flies, lepidopterans are the most abundant arthropods, with more than 165,000 species worldwide, with most species posing no human threats. However, caterpillar species from approximately 12 families of moths or butterflies can inflict serious human injury.[113] Insects of the order Lepidoptera may cause human envenomation that is generally less serious than that with hymenopterans. Injury usually follows contact with caterpillars and is less frequent with the cocoon or adult stage. The larval lepidopteran (caterpillar) is usually free living, moderately active, and feeds on plants, although a few are parasites of insect nests or eat food of animal origin. The pupal stage may be free or encased in a silk cocoon. Wintering over in cold climates is usually in the pupal stage. Adults (butterflies and moths) have wings with microscopic chitinous scales. They feed primarily on nectar and other plant juices, but some eat semiliquid mammalian feces and urine. The adult provides no care or protection of immature stages. No social organization exists, although larvae and adults of some species assemble in

large aggregations. The number of monarch butterflies in North America has decreased by an estimated 90% to 35 million in the last 20 years. As a result, environmentalists and entomologists are calling for monarchs to be declared an endangered species. The dramatic reduction is largely due to glyphosate herbicide use in conjunction with increased planting of genetically modified glyphosate-tolerant crops, as well as decline of the common milkweed upon which the larvae feed.[343]

Many venomous caterpillars are broad, flat, and sluggish. Some have the dorsal surface densely covered with long hairs. Others are spiny and may have bright, conspicuous colors and markings. Some are highly camouflaged.

Venoms in Lepidoptera are purely defensive. The venom apparatus consists of spines that are simple or branched and frequently barbed. They may be scattered widely over the surface of the insect or arranged in clumps and often are intermixed with nonveniferous hairs or spines. In the most venomous caterpillars, the spines are hollow and brittle with venom glands at the bases. Muscles surrounding the glands may help in expelling venom. In other Lepidoptera, the spines are solid and function primarily as mechanical irritants or contain surface toxicants. Most caterpillar venoms are heat labile and contain proteins. Histamine and serotonin have been found in caterpillar venoms but are not common. Hairs of the brown-tailed moth *(Euproctis chrysorrhoea)* contain enzymes with esterase and phospholipase activity.

Specific syndromes caused by Lepidoptera include erucism (cutaneous reactions from contact with caterpillars, moths, or cocoons), lepidopterism (systemic involvement), ophthalmia nodosa (ocular involvement), dendrolimiasis and pararamosis (joint symptoms relating to *Lonomia* species), and seasonal ataxia (related to ingestion of *Anaphe venata*).[204]

Probably the most important venomous caterpillar in the United States is the puss caterpillar.[165,393] It is also known as the asp caterpillar[127] or woolly slug *(Megalopyge opercularis)* (Figure 41-19). This caterpillar is distributed throughout most of Texas, Louisiana, and Florida and north to Maryland and Missouri. The hairy, flat, and ovoid caterpillar reaches a length of 30 to 35 mm (1.2 to 1.4 inches) and feeds on shade trees, including elm, oak, and sycamore. Some years it may be plentiful enough to be a nuisance. In southeast Texas in 1958, 2130 persons were treated for stings, and 8 were hospitalized. A related species, the flannel moth caterpillar *(Megalopyge crispata)* (Figure 41-20), occurs in the eastern states north to New England. Its sting is less severe than that of *M. opercularis*. The large, spiny caterpillar of the io moth *(Automeris io)*[139] is pale green with red and white lateral stripes (Figure 41-21). It is widely distributed in the eastern United States, but rarely plentiful. The saddleback caterpillar[133] *(Sibine stimulea)* (Figure 41-22) and oak slug *(Euclea delphinii)* are flat and almost rectangular; both can deliver a painful injury. The gypsy moth *(Lymantria dispar)* (Figure 41-23) feeds on a variety of plants and has caused thousands of cases of dermatitis in the northeastern United States. These caterpillars have also been imported to Europe across the Atlantic Ocean on house

FIGURE 41-20 Flannel moth caterpillar, *Megalopyge crispata.*

FIGURE 41-21 Caterpillar of the io moth, *Automeris io*. Widespread in the eastern United States, this species can inflict a painful sting.

FIGURE 41-22 Saddleback caterpillar, *Acharia stimulea. (Flickr.com; uploaded to Wikimedia Commons in June 2008, by Fvlamoen.)*

FIGURE 41-19 Puss caterpillar, *Megalopyge opercularis.*

FIGURE 41-23 Gypsy moth, *Lymantria dispar. (From Wikimedia Commons.)*

FIGURE 41-24 Hickory tussock moth caterpillar, *Lophocampa caryae*. *(Courtesy EDUPIC Graphical Resource.)*

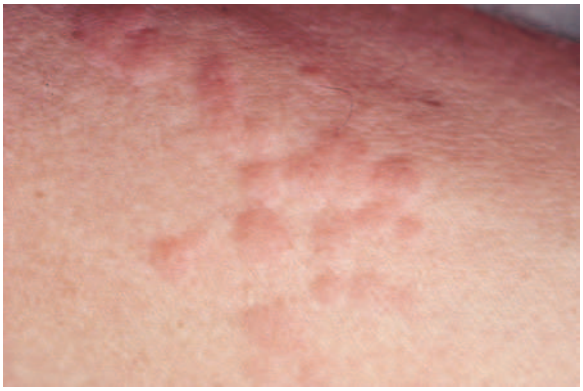

FIGURE 41-26 Nettle rash from unidentified caterpillar.

or garden plants.[85] Other common nettling caterpillars are *E. chrysorrhoea,* which also occurs in Europe, and the tussock or toothbrush caterpillar *(Hemerocampa leucostigma),* with its conspicuous red head and four tufts of bristles. Another tussock caterpillar, *Oryia pseudotsuga,* causes numerous cases of dermatitis and conjunctivitis among lumber workers and foresters in the northwestern states. The hickory tussock caterpillar *(Lophocampa caryae)* can cause skin irritation and urticaria with dermal contact, or drooling if ingested (Figure 41-24).[242,342] The eastern tent caterpillar, *Malacosoma americanum* (Figure 41-25), is native to North America. Populations fluctuate from year to year, with outbreaks occurring every several years. Defoliation of trees, building of unsightly silken nests in trees, and wandering caterpillars crawling over plants, walkways, and roads cause this insect to be considered a pest in the late spring and early summer. Eastern tent caterpillar nests are commonly found on wild cherry, apple, and crabapple trees, but may be discovered on other varieties of fruit trees.

STINGING PATTERNS

Lepidoptera are uncommonly recognized causes of localized stings, eczematous or popular dermatitis, and urticaria.[205] Caterpillar envenomation usually occurs when living insects are touched as they cling to vegetation or drop onto bare skin. Persons cutting branches, picking fruit, or climbing trees are likely to be stung. However, the largest outbreaks have been associated with spines detached from live or dead caterpillars and cocoons. These may be airborne or deposited on bedding or laundry hung outdoors. In temperate regions, caterpillar stings are most common from August to early November. Heavy caterpillar infestations seem to occur during exceptionally favorable weather and with decreases in populations of parasites and predators that serve as natural controls.

FIGURE 41-25 Eastern tent caterpillar, *Malacosoma americanum*. *(Courtesy Richard Seaman:* richard-seaman.com.*)*

CLINICAL ASPECTS

Two general syndromes are associated with lepidopteran envenomations. In the cases of caterpillars with hollow spines and basal venom glands (e.g., *Automeris, Megalopyge,* and *Dirphia*), direct contact with the live insect causes instant nettling pain, followed by redness and swelling (Figure 41-26). Puss caterpillar stings show a characteristic gridiron pattern of hemorrhagic pinpoint papules. In typical cases, no systemic manifestations occur, and symptoms usually subside within 24 hours. However, pain may be intense with central radiation, accompanied by urticaria, nausea, headache, fever, vomiting, muscle spasms, paresthesias, and lymphadenopathy. Hypotension, shock, dyspnea, abdominal tenderness, and convulsions have been reported with more severe cases of puss caterpillar stings.[139,163,165,203,393]

The second syndrome is associated with caterpillars with a less highly developed venom apparatus (e.g., *Lymantria, Euproctis, Thaumetopoea*). Contact with the living insect is not necessary; detached spines are often involved. Little or no immediate discomfort is experienced. An itching, erythematous, papular, or urticarial rash develops within a few hours to 2 days and persists for up to a week (Figure 41-27). Rarely, the lesions may be

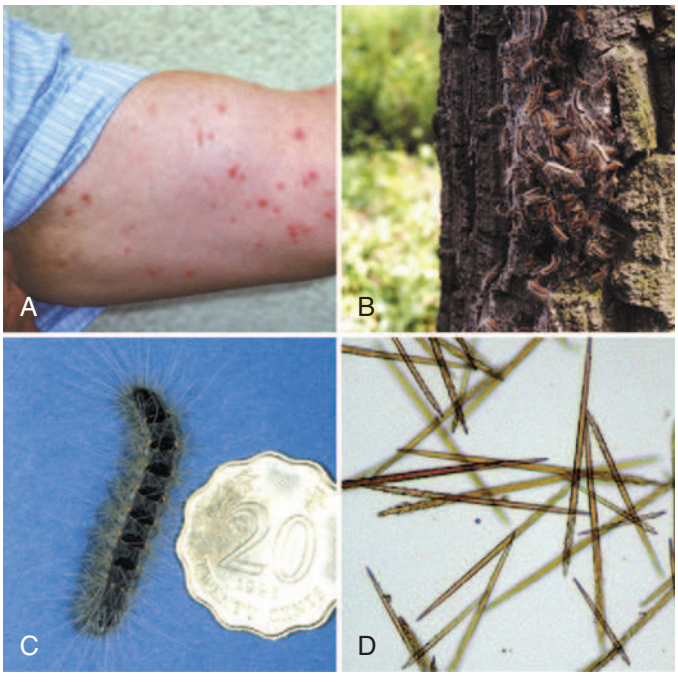

FIGURE 41-27 Lepidopterism. **A,** Toxic irritative caterpillar dermatitis. **B,** Silken nest on the trunk of an infested oak tree with living larvae. **C,** Sixth larval instar of *Thaumetopoea processionea* L. **D,** Setae (×200). *(From Spiegel W, Maier H, Maier M: A non-infectious airborne disease, Lancet 363:1438, 2004.)*

bullous. Conjunctivitis, upper respiratory tract irritation, and rare asthma-like symptoms may be seen with or without dermatitis. Ophthalmia serious enough to require enucleation may be caused by detached spines lodged in the eye. Acute anaphylactic reactions have not been reported to follow lepidopteran stings. Patch testing has demonstrated both immediate and delayed hypersensitivity. A pediatric case series reported 10 patients who ingested various caterpillar species. Adverse effects ranged from mild (drooling and refusal to drink) to diffuse urticaria. Five of the patients underwent direct laryngoscopy and endoscopy to assess for pharyngeal and esophageal injuries. None had adverse outcomes.[234]

The pine processionary caterpillar has been reported to cause a significant local reaction and airway compromise mimicking an allergic event in children with oral ingestions.[208]

TREATMENT AND PREVENTION

Treatment of lepidopteran envenomations is symptomatic. Prompt application and stripping off of adhesive tape or a commercial facial peel at the site of the sting may remove many spines and serve as a diagnostic procedure, as the spines can then be identified by microscopy (Figure 41-28). Patients with local symptoms usually obtain relief from group I corticosteroid creams, oral antihistamines, and ointments.[204] Over-the-counter preparations containing corticosteroids and antihistamines are not significantly better than simpler preparations such as calamine lotion with phenol. Oral antihistamines such as fexofenadine (60 mg twice a day) or antiinflammatory drugs such as ibuprofen (400 mg four times a day) are often effective in more severe cases. Occasionally, codeine (30 to 50 mg) or oxymorphone (1.5 mg) in combination with an antiemetic may be needed to control pain and vomiting. IV calcium gluconate has been used successfully in severe puss caterpillar envenomation to control muscle spasms.[310,339]

Trees on which caterpillars feed may be sprayed with appropriate insecticides to control species such as the puss caterpillar. Screens on windows and doors protect against moths with toxic spines.

Internationally, Lepidoptera show high diversity in the tropics with correspondingly greater medical importance, particularly in Latin America. Caterpillars of the genus *Lonomia,* native to northern South America, especially Venezuela and the southern region of Brazil, can inflict life-threatening stings[68] (Figures 41-29 and 41-30). These caterpillars are 50 to 70 mm (2 to 3 inches) long and have numerous branched dorsal spines. They live in primary tropical forests in groups of up to 50 individuals. Disturbance of their habitat has resulted in an increasing number of envenomations. Stings cause intense pain but not much local reaction. Venom of *Lonomia* is a protein that activates prothrombin and is stimulated by factor V and calcium ions.[181] Signs of coagulopathy, such as ecchymoses, bleeding gums, hematuria, and melena, may develop in a few hours or be delayed for several days. The venom-induced hemolysis or hemorrhagic syndrome results from prothrombin and factor X and promotes fibrinogenolytic activity and massive fibrinolysis.[205,206,270] Fibrinogen, factor V, factor XII, and plasminogen are decreased, fibrin degradation products are increased, and platelets usually are normal. Acute renal failure,[42,57] cerebral hemorrhage, and pulmonary hemorrhage may occur.[340] Coagulopathy may last 2 to 5 weeks. In one series of 33 cases, four were fatal.[17,57,124] Treatment with prednisone, plasma, and whole blood is ineffective. An antivenom (antilonomic serum) has been developed, and preliminary reports indicate possible clinical efficacy.[32,95,98,205,206]

Neotropical caterpillars of the genera *Dirphia, Megalopyge ("gusano-pollo"),* and *Automeris* are large, stout, spiny, and sometimes covered with hair.[19] Most are forest species but can adapt to areas of cultivation. Agricultural workers are most often stung and the incidence of stings is higher in the rainy season. Intense, centrally radiating pain with local edema, erythema, and lymphadenopathy is typical. Systemic symptoms include nausea, headache, malaise, chills, and fever. Hypotension, shock, and convulsions have been reported. An *Automeris* caterpillar bite reported from French Guyana produced syncopal pain and edematous infiltration of the thigh lasting several days.[90] Symptoms usually subside within 24 hours. Treatment is symptomatic. Oral antihistamines are often effective if given within an hour after the sting. Opioid agents are occasionally needed to control pain. A chronic granuloma known as pararama occurs on the hands of Brazilian rubber tappers after contact with *Premolis semirufa* caterpillars. Permanent extremity disability may result.[336]

FIGURE 41-29 Caterpillar of *Lonomia achelous,* which can inflict injuries characterized by potentially fatal coagulopathy.

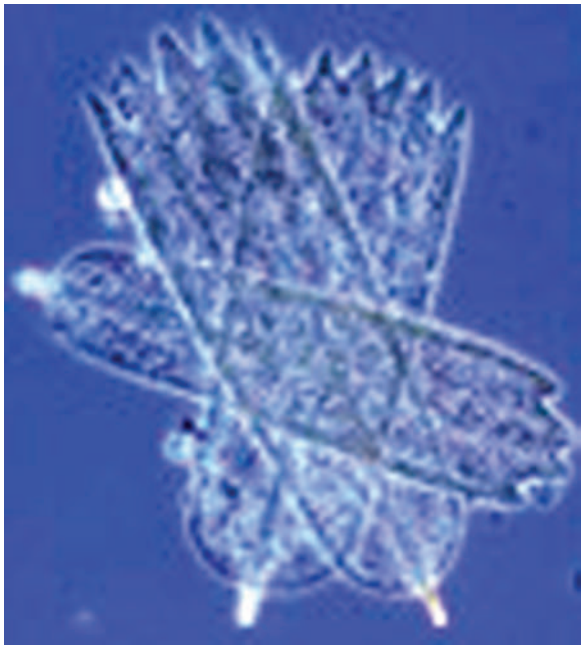

FIGURE 41-28 Microscopic view of Lepidoptera spines. *(From microscope.mbl.edu.)*

FIGURE 41-30 Moth of *Lonomia achelous,* which has no venomous spines.

FIGURE 41-31 *Euproctis* caterpillar. *(Courtesy Walwyn.)*

Moths of the genus *Hylesia* are found from southern Mexico to Argentina. The caterpillars have venomous spines, but the greatest problem is created by the moths, which have a coating of spines on their abdomen. The spines or setae are hollow and pointed, contain a toxin of unknown nature, and are freely shed into the air. The moths are attracted to lights in enormous numbers, and their airborne spines can cause great discomfort. Their activity has created serious problems at airports, shipping docks, and tourist resorts. Within a few minutes to a few hours after contact with the spines, victims develop a pruritic, erythematous rash that progresses to urticaria and excoriation. Any portion of exposed skin may be involved, but palms and soles are often spared. Irritation of eyes and mucous membranes is unusual. Symptoms subside in about a week if there is no further exposure. Topical and systemic treatments have demonstrated little benefit.[117]

In Korea, outbreaks of dermatitis, presumably caused by setae of the yellow moth *Euproctis flava,* are well known. In the summer of 1980, hundreds of U.S. soldiers were affected.[31] The caterpillars feed on hardwood trees, and great numbers of moths appear in summer and are attracted to lights. Dermatitis usually involves direct contact with moths or their cocoons or with clothing contaminated with setae. The lesions are similar to those described for *Hylesia* and are equally refractory to treatment. Other outbreaks of dermatitis ascribed to *Euproctis* moths and caterpillars have been reported in Japan and China. One outbreak in Shanghai in 1972 affected about 500,000 individuals. Outside Shanghai, where chemical insecticides would have been harmful to silkworm culture, *Euproctis* caterpillars (Figure 41-31) have been controlled by spraying with an insect virus. Cases of *Euproctis* dermatitis and ophthalmia have also been reported in Australia and Great Britain. Sensitization with elevated IgE levels may occur.[336,406]

In the Mediterranean region and the Middle East, the pine processionary caterpillars *Thaumetopoea pityocampa* and *Thaumetopoea wilkinsoni* are plentiful and make silk nests in trees. The setae from these caterpillars can cause a maculopapular rash accompanied by urticaria, bronchitis, and conjunctivitis. A non–IgE-mediated release by *Thaumetopoea* results in a type I hypersensitivity foreign-body reaction, resulting in dyspnea and bronchospasm.[407] Outbreaks typically occur when groups of tourists or military personnel camp in pine groves. The rash usually results from contact with detached setae rather than with caterpillars. The adult moth stage apparently does not have irritating spines. Systemic reactions manifesting as abdominal pain and hypertension have been reported.[155]

Moths of the genus *Calyptra,* native to Southeast Asia, have a serrate proboscis and feed on mammalian blood, including that of humans. Tropical species of several moth genera feed on human ocular secretions. Their medical importance is unknown. In Australia, five families of caterpillars (Arctiidae, Limacodidae, Anthelidae, Lymantriidae, and Spingidae) that inflict lesions resulting in local pain and urticaria have been described. All dermal reactions were responsive to ice packs and antihistamines. Ingestions resulted in no adverse side effects.[24] Contact dermatitis or erucism has been described in New Zealand from exposure to gum leaf skeletonizer *(Uraba lugens)* caterpillars in the Auckland region.[85]

CENTIPEDES AND MILLIPEDES

Centipedes are arthropods belonging to the class Chilopoda. Approximately 3000 species have been described. Centipedes are found most commonly in tropical and subtropical countries.[432] Centipedes are elongate, flattened arthropods with one pair of legs for each of the typical body segments, which may number from 15 to more than 100. The first segment bears a pair of curved hollow fangs with venom glands at the bases. The last segment bears a pair of filamentous to forceps-like caudal appendages not associated with the venom apparatus.[42] The largest species reach lengths of about 30 cm (12 inches). Most centipedes live in crevices or beneath objects on the ground. Some are burrowers and others are climbers. Many are nocturnal. *Scutigera coleoptrata,* with a body length of 25 mm (1 inch) and long thin legs, is a common house arthropod in much of the United States. *Lithobius* is a cosmopolitan ground-dwelling genus. A species common in eastern U.S. gardens is orange and 30 to 50 mm (1.2 to 2 inches) long. Envenomations by imported varieties of the Vietnamese centipede have been reported in Long Island, New York.[277] Centipedes prey chiefly on invertebrates, but larger species occasionally eat small vertebrates. Female centipedes of some species curl around their egg clusters and newly hatched young, and may actively defend them.

Centipedes use venom primarily to kill prey and only secondarily for defense. Venoms have a digestive function and a protein that causes abnormalities in lipid metabolism.[81] Enzymes, including acid and alkaline phosphatase and amino acid naphthylamidase, lipoproteins, histamine, and serotonin, are variably present.[295] Venom of *Scolopendra subspinipes* produces hypotension followed by hypertension. The major lethal toxin is an acidic protein with a molecular weight of 60,000 daltons. It produces vasoconstriction, increased capillary permeability, and cardiotoxicity.[175,176]

Like spiders, any centipede whose fangs can penetrate human skin can cause local envenomation. Centipede bites are typically pointed in shape, a feature that can help differentiate the bite of a large centipede from that of a snake.[130,258] Contrary to popular folklore, centipedes do not inject venom with their feet or caudal appendages. The jaws inject a neurotoxic venom through venom ducts. Centipede bites have been reported from numerous tropical and subtropical regions but never as a serious medical problem. Most bites have been ascribed to species of *Scolopendra,* which has a wide distribution with several species in the southern United States (Figures 41-32 and 41-33). Fatalities are almost unknown; however, a death in the United States was reported, but the locality and historical details were not documented.[246]

Burning pain, local swelling, erythema, lymphangitis, and lymphadenopathy are common manifestations of a centipede bite. Some theorize that there is a close relation between centipede allergy and bee or Hymenoptera venom allergy.[188] Swelling and tenderness may persist for as long as 3 weeks or may disappear and recur. Severe and prolonged symptoms have been described in patients with sickle cell disease.[369] Superficial necrosis may occur at the site of fang punctures. A few bites result in cellulitis, necrotizing fasciitis, and serious systemic reactions.[426] In one case ascribed to *Scolopendra heros* in the southwestern

FIGURE 41-32 Centipede, *Scolopendra heros.*

FIGURE 41-33 Centipede fangs.

FIGURE 41-35 Giant Madagascar millipede.

United States, a woman had massive edema of the leg, necrosis of the peroneal muscles, loss of motor function in the foot, myoglobinuria, and azotemia.[262] The Mexican centipede *Scolopendra viridis* contains a powerful venom, capable of inflicting immediate effects on prey.[178] An Israeli patient bitten on the neck complained of inability to turn her head, probably because of muscle spasm.[295] Other cases have been characterized by dizziness, nausea, collapse, and pyrexia.[311] An infant who ingested a centipede identified as *Scutigera morpha* developed hypotonia, vomiting, and lethargy, presumably from being bitten in the mouth or pharynx. The child recovered spontaneously after about 48 hours.[29] Centipede envenomation in a newborn inflicted by *Scolopendra gigantea* was reported in Venezuela and caused crying, irritability, and localized wound edema.[364] *Cryptops* and *Otostigmus* genera are responsible for most cases of centipede stings.[282] Acute coronary ischemia associated with myocardial infarction with electrocardiographic changes (acute ST-segment elevation) and elevated cardiac troponin has been described after envenomation from an unidentified centipede in Turkey and India.[324,455,391]

Although some centipede bites may be excruciatingly painful, they are not fatal and seldom require more than supportive care.[160] Treatment of centipede envenomation is symptomatic. Ice packs, hot water immersion, and analgesics all can improve pain from centipede envenomation.[76] Infiltration of the bitten area with lidocaine or another anesthetic promptly relieves pain. Antihistamines and corticosteroids have been suggested for more severe reactions.[432] Tetanus prophylaxis is advisable.[63,296] Hot water immersion has proved beneficial in Australia from bites of centipedes from the genera *Scolopendra, Cormocephalus,* and *Ethmostigmus*.[25]

MILLIPEDES

Millipedes differ from centipedes in having two pairs of legs per body segment and in lacking apparatus for injecting venom. Several large species of the genus *Spirobolus* are common in the southern United States (Figure 41-34). Some species are broad and short and roll into a ball when disturbed (Figure 41-35). The millipede species *Illacme plenipes* found in California comes the closest to having its namesake's mythical 1000 legs—individuals can bear up to 750 legs.[272] Millipedes are generally ground dwelling and secretive. Occasionally, they aggregate in enormous numbers. They generally feed on decaying vegetation.

FIGURE 41-34 *Spirobolus* millipede.

Millipedes are exceptionally well endowed with defensive chemical secretions that include hydrogen cyanide, organic acids, phenol, cresols, hydroquinones, and benzoquinones. Benzoquinones are strongly irritant and persistent compounds, which work well as insect repellents and are toxic to a variety of other parasites and pathogens.[101] These effectively deter most predators. Some large species can eject secretions for distances up to 80 cm (32 inches).

Human injury from millipede secretions has been reported from a number of tropical regions.[194] The most common injury is dermatitis that begins with a brown-stained area, which burns and may blister and exfoliate.[256,273,433] Millipede burns have been described in unusual sites, with pediatric cases mimicking child abuse.[97] Millipede secretion in the eye causes immediate pain, lacrimation, and blepharospasm. This may be followed by chemosis, periorbital edema, and corneal ulceration. Blindness has been reported.[187] Individuals exposed to large millipede aggregations may complain of nausea and irritation of the nose and eyes. No specific treatment is available. Prompt irrigation with water or saline should be followed by analgesics, antimicrobials, and other measures appropriate for superficial chemical burns. Ophthalmologic evaluation is mandatory for eye injuries. Infestation of the human intestines by the millipede *Nopoiulus kochi* has been described in Turkey. Antiparasitic drugs (niclosamide and albendazole) may not be effective in eradicating the problem.[136]

HEMIPTERA (SUCKING BUGS)

Hemiptera is a large order of insects characterized by sucking mouthparts, generally in the form of a beak, and a life cycle with no well-demarcated larval and pupal stages, but a gradual transition from the hatchling nymph to adult. Most hemipterans are winged as adults, with the anterior wings generally divided into chitinized and membranous sections. Most feed on plant juices, but several families are predators, and two feed on the blood of humans and other vertebrates. Hematophagous bugs are able to exploit the temperature differences observed over the skin surface to locate blood vessels. These bugs generally bite into the warmest temperature regardless of the target or background temperature.[144]

The assassin bugs (family Reduviidae) are generally recognized by their long and narrow head, a stout and three-jointed beak, long antennae, and typical hemipteran wings (Figure 41-36). Most are of a dark color; a few are brightly marked or have a checkerboard pattern along the posterior edge of the abdomen. Some species attach fragments of their prey, sand grains, or other debris to their backs. Reduviidae occur on all continents. They have a variety of habitats and are often nocturnal.

The triatomids (e.g., kissing bugs, flying bedbugs, Mexican bedbugs) are a subfamily of the Reduviidae adapted for feeding on blood. They feed on a wide range of mammals and often live in the nests or burrows of their hosts. Armadillos, dogs, opossums, and pack rats are common hosts in the southern United

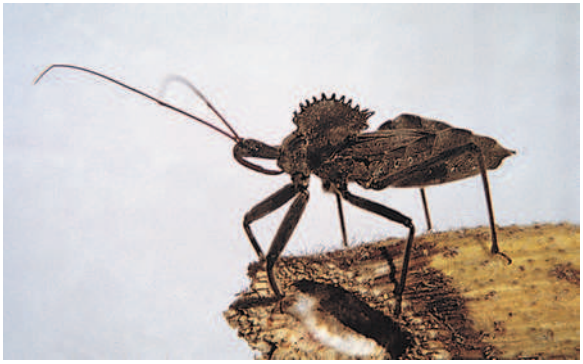

FIGURE 41-36 Wheel bug, *Arilus cristatus,* a large assassin bug common in the eastern United States.

FIGURE 41-38 Back swimmer bugs have greatly elongated hind legs. *(Courtesy Gari Weinraub.)*

States and Mexico. Some triatomids adapt readily to life in human dwellings, particularly those of adobe construction. Triatomids are primarily a neotropical group, with species ranging northward in the United States to Utah and southern Indiana. *Triatoma protracta* and *Triatoma sanguisuga* are among the better-known species. The family Cimicidae, or bedbugs, are flat, ovoid, and reddish brown insects whose wings are reduced to a pair of functionless pads. Lack of large terminal claws distinguishes them from lice.

Bedbugs are cosmopolitan in distribution and have increased dramatically in the United States, United Kingdom, and South America.[141,421] In the United States, the estimated number of emergency department visits due to their bites has increased more than sevenfold over the past decade.[245] This recent resurgence is attributed to increased travel and resistance to insecticides.[235] *Cimex lectularius* is aptly named; its genus and species are derived from the Latin words for bug and bed, respectively. Though this pest has received increased public attention and scrutiny, the bedbug is hardly a new phenomenon.[151] Two species, *Cimex lectularius* and *Cimex hemipterus,* feed primarily on humans and live in dwellings, where they hide in bedding, under wallpaper, behind baseboards, and in window frames. Homes of poorer persons and those in austere environments are more likely to be heavily infested, but the insects may be carried into well-kept residences, hospitals, hotels, and military barracks.[13] Homeless persons are more prone to exposure when residing in large shelters.[52] Other species of *Cimex,* normally parasitic on bats and swallows, occasionally attack humans.

Venomous aquatic hemipterans include the giant water bugs (family Belostomatidae) (Figure 41-37), back swimmers (family Notonectidae) (Figure 41-38), and water scorpions (family Nepidae). Water bugs are distinguished from aquatic beetles by their beak and hemipteran wings; back swimmers have greatly elongated hind legs; and water scorpions have a slender body with long, terminal breathing tubes. These insects are widely distributed in freshwater habitats.

The hemipteran venom apparatus consists of two or three pairs of glands in the thorax. Secretions are ejected through one-half of a double tube formed by the interlocking of the elongated maxillae and mandibles, which have distal tips modified for piercing. Few hemipteran venoms have been studied. Venoms of two reduviids, *Platymeris rhadamanthus* of Africa and *Holotrichus innesi* of the Middle East, contain several enzymes and nonenzymatic proteins.[128,460] Sialidase, an enzyme unusual in invertebrates, is found in *Triatoma* venom; it has anticoagulant activity.[12] Venom serves primarily for subjugation and probably digestion of prey, but the insects may defend themselves by biting. Salivary secretions of blood-sucking hemipterans also contain potent allergens.

CLINICAL ASPECTS

Triatomids usually bite at night on exposed parts of the body. Feeding may last from 3 to 30 minutes. Bites are painless. On initial exposure there is usually no reaction. Repeated bites are followed by reddish, itching papules that may persist for up to a week.[167] Bites are often grouped in a cluster or line (Figure 41-39) and may be accompanied by giant urticarial wheals, lymphadenopathy, hemorrhagic bullae, fever, and lymphocytosis. Systemic anaphylactoid reactions with respiratory or gastrointestinal manifestations may occur.[207,266] Entomologists and small children are most frequently bitten by assassin bugs, as handling induces the insect to bite. Bites of several U.S. species, such as the wheel bug *(Arilus cristatus),* black corsair *(Melanolestes picipes),* and masked bedbug hunter *(Reduvius personatus),* are described as being as painful as the sting of a hornet and accompanied by local swelling lasting several hours. Bedbug bites usually raise a pruritic wheal with a central hemorrhagic punctum, followed by a reddish papule that persists for several days.

FIGURE 41-37 Giant water bug, *Benacus griseus,* a large insect common in aquatic habitats in the eastern United States.

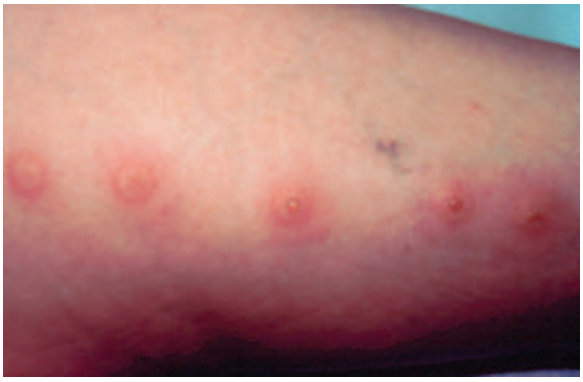

FIGURE 41-39 *Triatomid* feeding pattern.

Bullae, generalized urticaria, arthralgia, asthma, and anaphylactic shock are rare sequelae of bedbug bites.[120] Bedbug bite infestations may trigger the onset of a negative psychological state that may ultimately lead to suicide.[62] It is controversial whether the common bedbug may be a component vector of *Trypanosoma cruzi* and could pose a risk for vector-borne transmission of Chagas disease.[107,375,463] Bites by aquatic hemipterans are similar to those of assassin bugs, but few cases have been described in detail.

TREATMENT AND PREVENTION

Treatment is symptomatic and not particularly effective.[87,394] There has been an increased prevalence of resistance to chemical insecticides.[83] Various antipruritic preparations are helpful in mild cases. Topical or intralesional steroids have generally been ineffective. Immobilization, elevation, and local heat are helpful in severe limb bites. Desensitization with triatomid salivary gland extract has been used in a small series of patients with a history of life-threatening anaphylactic reactions.[366] Triatomids and bedbugs are more difficult to eradicate with insecticides than are many other household insects. A wide range of empirical treatments, including antibiotics, antihistamines, topical and oral corticosteroids, and epinephrine, have been used for bite reactions with varying results. No evidence-based interventions to eradicate bedbugs or prevent bites have been identified.[169] Benzene hexachloride has been effective against triatomids in Latin America.

BEETLES AND OTHER INSECTS

Beetles (order Coleoptera) are the largest group of insects, with at least 250,000 species. The prothorax of beetles is generally very distinct, whereas the two posterior thoracic segments are more or less fused to the abdomen (Figure 41-40). In most beetles, the anterior wings are heavily chitinized, acting as covers for the posterior membranous wings used in flight. Mouthparts are of the chewing type. The life cycle involves larval and pupal stages before emergence of the adult. Many beetles feed on plants throughout their life cycle, many are predators or scavengers, and a few are parasitic. No beetles have a bite or sting venomous to humans, but several families have toxic secretions that may be deposited on the skin. The blister beetles (family Meloidae) are a cosmopolitan group with numerous representatives in deserts and semiarid regions. A species may suddenly appear by the thousands, especially after rains, persist for a few days, and be replaced by another. The majority are of medium size (about 15 mm [0.5 inch]) and have soft, leathery forewings (elytra). Some are brilliantly colored. They are plentiful on vegetation, and some species are attracted to lights. A low-molecular-weight toxin, cantharidin, is present in the hemolymph and most of the insect's tissues. It is exuded from multiple sites if the beetle is gently pressed or otherwise disturbed. Cantharidin content of meloid blister beetles were measured at values more than 6 mg per beetle, pointing to the high risk of severe gastrointestinal and renal toxicity and even fatal poisoning when ingesting these insects.[89,281]

In the eastern United States, blister beetle dermatitis is usually caused by *Epicauta* species, which reside on many garden plants. Contact with the beetle is painless and seldom remembered by the victim. Blisters appear 2 to 5 hours after contact and may be single or multiple, usually 5 to 50 mm (0.2 to 2 inches) in diameter and thin walled. Although not naturally found in the United States, the most well-known blister beetle is the Spanish fly *(Cantharis vesicatoria catoria)* (Figure 41-41). Unless broken and rubbed, the blisters are not painful. Cantharidin dermatitis and nephritis have been reported after unusually heavy vesication but more frequently result from using a cantharidin preparation as an oral aphrodisiac. A soldier who accepted the challenge of eating a beetle *(Berbermomeloe majalis)* presented 6 hours later to an emergency department with abdominal pain, hematuria, hypotension, fever, and renal insufficiency.[89] Acute eosinophilic pneumonia has been associated with ingestion of *Ulomoides dermestoides,* or Chinese beetles.[305]

FIGURE 41-40 **A** and **B,** Beetles (order Coleoptera) represent the largest group of insects.

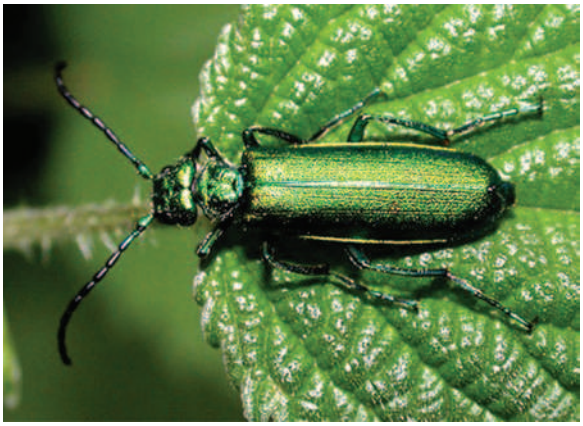

FIGURE 41-41 Spanish fly, *Cantharis vesicatoria. (Courtesy Wikimedia Commons.)*

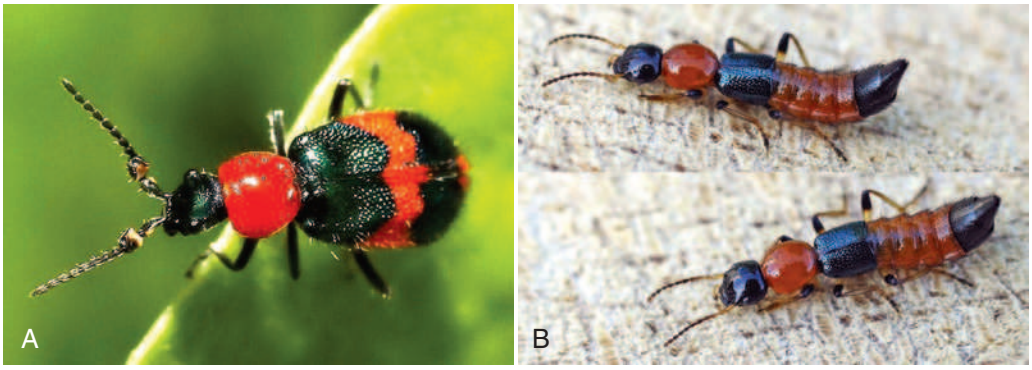

FIGURE 41-42 Rove beetles, genus *Paederus*, family Staphylinidae. (***A** courtesy Trevor Jinks, Gold Coast, Australia; **B** from Wikimedia Commons.)*

Darkling ground beetles are moderately large, dark, and heavily chitinized insects that assume a characteristic posture with head down and tail up when disturbed. They are found worldwide in arid regions, where they live under stones and other cover and crawl about at night. Most species can spray irritant secretions, mostly benzoquinones, from the tip of the abdomen to a distance of 30 to 40 cm (12 to 16 inches). These secretions are generally harmless to humans, but blistering of the skin has been reported, and eye injury is possible.[183]

No special treatment for beetle vesication is available. The injuries are best treated as superficial chemical burns. Local preparations containing corticosteroids or antihistamines are not particularly effective. An outbreak of a blistering disease was reported in a military unit training in the Arizona desert during an unusual heavy rainfall and flooding. Staphylinid (rove) beetles (genus *Paederus,* family Staphylinidae) (Figure 41-42) were collected at the site. These beetles have been responsible for vesicular dermatitis in other parts of the world but before this series were never reported in the United States.[84]

Internationally, small rove beetles of the genus *Paederus* are troublesome in many tropical and subtropical regions. The whiplash beetle or Finch Hatton bug *(Paederus australis)* caused evacuation of an entire aboriginal community in northern Australia,[303] and several cases of blistering dermatitis were reported in central Queensland.[27] A large suburban hospital in Sri Lanka had 108 cases of painful dermatitis among members of its staff on night duty.[237] More than 200 cases were reported in Turkey, resulting in lesions similar to bullous impetigo or infectious herpes zoster.[428] The furniture beetle *(Anobium punctatum)* of France can give an unusual pruritic dermatitis associated with a specific clinical finding called the "comet sign," likely secondary to the parasite *Pyemotes ventricosus* within the beetle.[103]

Pustular dermatitis epidemics from other staphylinid (rove) beetles related to the paederids have been reported in Nigeria, Egypt, and Kenya after sudden floods,[84] More recently, rove beetle dermatitis has been documented in Sierra Leone,[279] South Sudan,[211] Egypt,[20] and India,[70] and in Pakistan among deployed U.S. military personnel.[126] These beetles are slender with elongate abdomens and very short rectangular elytra. They frequent damp habitats and may be plentiful in irrigated crop fields. They usually fly after dark in hot, humid weather and are attracted to lights. Their vesicant secretion is an alkaloid present in greatest concentration in hemolymph; it is usually deposited on human skin when the beetles are pressed or crushed, but it may occasionally be spontaneously secreted. There is no immediate reaction to the secretion, but after 12 to 24 hours, painful erythematous lesions develop and soon become vesicular. The vesicles last 3 to 7 days and are followed by crusting and pigmentation.[307] Conjunctivitis results if the secretion is rubbed into the eyes. This condition is known in parts of the world as "Nairobi eye" or "Christmas eye."[84] Some persons with extensive skin involvement may show generalized symptoms. Treatment is symptomatic and not very effective. Prompt soap-and-water washing after insect contact is recommended. In an animal model, application of potassium permanganate with calamine to heal rove beetle linear dermatitis proved more effective than fluocinolone treatment.[140] Screening of sleeping and working quarters is the best prevention.

Lady beetles (ladybugs, family Coccinellidae) are widely distributed and highly beneficial as predators on aphids and scale insects. Species in the eastern United States often overwinter in houses and do no harm. However, an Australian lady beetle, *Diomus notescens,* is reported to bite, causing papules with small necrotic centers.[345] Two cases of human ear invasion by a predaceous beetle, *Crasydactylus punctatus,* or the carabid beetle, have been reported from Oman. One victim had a severe otologic injury caused by biting and chewing on the external auditory canal and tympanic membrane.[34]

Other types of insect envenomation are sporadic. Many insects that normally feed on plant juices occasionally inflict annoying bites. This behavior may be initiated by dehydration of the insect or by unknown factors. Small predatory insects, such as lacewing larvae, anthocorids, and *Sclerodermus* species, occasionally attack humans instead of their normal arthropod prey. Thrips may bite and produce itching macules.[301] A small hemipteran, *Leptodemus minutus,* caused numerous cases of dermatitis in Kuwait.[390] The stick insect, *Anisomorpha buprestoides* (Figure 41-43), a common species in Florida and adjacent states, ejects a noxious fluid from its thoracic region that deters birds and other predators. According to regional folklore, this fluid can be directed toward human eyes with painful consequences.

DIPTERA (TWO-WINGED FLIES)

Insects of the order Diptera are characterized by one pair of wings. What would have been a second pair is usually modified to form a pair of drumstick-like structures known as halteres. A typical life cycle consists of eggs, limbless larvae, pupae, and

FIGURE 41-43 Stick insect, *Anisomorpha buprestoides,* ejects a noxious fluid from its thoracic region that deters birds and other predators. *(From* penvalehouse.org.uk.*)*

TABLE 41-1 Major Groups of Biting Dipterans

Insect	Recognition Features of Adult	Larval and Pupal Stages
Mosquitoes (Culicidae, subfamily Culicinae)	Prominent proboscis; wings with scales; palps of female much shorter than proboscis; usually rests with body parallel to substrate	Aquatic in great variety of habitats; both larval and pupal stages motile
Mosquitoes (subfamily Anophelinae)	Prominent proboscis; wings with scales and often with dark mottling; palps of females about as long as proboscis; usually rests with head down and body held at an angle to substrate	Same as above
Blackflies, buffalo gnats (family Simuliidae), sand flies (family Psychodidae)	Stout; humpbacked; short antennae; wings broad, with most veins faint; body length > 2.5 mm (0.12 inch) Small (usually > 2 mm [0.1 inch] body length); hairy; wings with straight, prominent veins	Sessile in flowing water; usually attached to rocks and logs, sometimes to crustaceans In damp crevices, animal burrows, leaf litter
Biting midges, sand flies, no-see-ums (family Ceratopogonidae)	Small (> 2 mm [0.1 inch] body length); wings often mottled; most wing veins faint	In mud, wet sand, rotting vegetation; larvae very motile
Horseflies, deerflies (family Tabanidae)	Large (body length 5-25 mm [0.2-1 inch]) with large eyes; usually brilliantly colored; body stout; wings with prominent veins	In mud or shallow water
Stable flies (family Muscidae)	Similar to housefly in size and general appearance; sharp-pointed proboscis projects downward and backward	In decaying vegetable matter or urine-soaked straw
Tsetse flies (family Glossinidae)	Large (6-14 mm [0.25-0.5 inch]); proboscis projects forward; wings fold scissor-like over back	Larvae complete most of development in female; pupate in soil a few hours after birth
Snipe flies (family Rhagionidae)	Long legs; relatively slender body; large eyes; wings with prominent veins	Aquatic; in moist soil or rotten wood

winged adults, but numerous variations exist. Mouthparts are of the sucking type. Females of many species, although free-living, take blood or other tissue fluids from vertebrates, injecting salivary secretions that are not intrinsically toxic but are potent sensitizing agents for most humans. Larvae of some Diptera are human parasites. Other adult Diptera feed indiscriminately on feces and human foodstuffs. These habits make them by far the most important arthropod vectors of human disease (Table 41-1).

Most of these insects are cosmopolitan in distribution, except tsetse flies, which are restricted to Africa, and tropical and subtropical sand flies. Some species of mosquitoes and blackflies are adapted to cold temperate, sub-Arctic, and alpine environments, where their numbers may make areas uninhabitable during peak activity. Other mosquitoes and biting midges are equally abundant and annoying in some coastal areas and on islands. Two groups of biting flies and several species involved in human myiasis are largely confined to the tropics (see Table 41-1).

Tsetse flies (*Glossina* species) are of great importance as vectors of human and animal trypanosomiasis in sub-Saharan Africa (Figure 41-44). Although not closely related to deerflies and other tabanids, they are similar in appearance and habits. Their life history is peculiar in that a single large larva develops in the uterus of the female and is expelled shortly before pupation, which takes place in the soil. Tsetse fly bites produce comparatively little local reaction other than brief pain and itching. Human African trypanosomiasis, also known as sleeping sickness, continues to pose major threat to 60 million people in 36 countries in sub-Saharan Africa. Transmitted by the bite of the tsetse fly, the disease is caused by the protozoan parasites of the genus *Trypanosoma*.[8,223] Symptoms of sleeping sickness include abnormal sleep patterns, fever, body malaise, headache, and lymph node enlargement.[231] Most patients can be treated successfully with melarsoprol.[399]

FIGURE 41-44 Tsetse fly, *Glossina* species. *(Courtesy David Bowles and Mark Pomerinke, U.S. Air Force.)*

Mosquitoes (see Chapter 39) are characterized by a fringe of setae along the posterior margin of the wings and delicate scales along the wing veins. Only the females feed on blood. The prominent beak contains a kit of piercing and sucking tools. Most mosquitoes have body lengths of 3 to 4 mm (0.1 to 0.2 inch), but some large species may be about twice this size (see Table 41-1). The estimated 3000 species of mosquitoes are cosmopolitan in distribution.

Carbon dioxide, body heat, and sweat gland secretions, especially apocrine, are attractants for mosquitoes; certain skin lipids are repellent.[224] Children under 1 year of age rarely show a skin reaction to mosquito bites, but by age 5 nearly all are reactors. Both immediate and delayed types of hypersensitivity are induced. Typically, immediate pruritic wheals are followed by red, swollen, and pruritic lesions in 12 to 24 hours. These lesions are associated with both IgE and IgG antibody complexes and a lymphocyte response.[334,355]

All the classic types of immunologic injuries have been reported after mosquito bites, including injury from circulating immune complexes, asthma, and Arthus reaction.[164,196] Seasonal bullous eruptions in a coastal area of Britain were ascribed to *Aedes detritus*. Most of those affected were women with varicose veins or deep vein thromboses. Intense skin reactions accompanied by fever, lymphadenopathy, and hepatosplenomegaly have been described and are associated with infiltration of skin lesions by natural killer lymphocytes.[280] Nodular skin lesions lasting up to a month have been reported after mosquito bites in patients with acquired immunodeficiency syndrome receiving zidovudine.[119] Papulovesicular lesions with eosinophil infiltration were reported following insect (including mosquito) bites in patients with lymphocytic leukemia.[86] Among 21 Japanese patients with severe local and constitutional reactions to mosquito bites, seven

died of malignant histiocytosis before age 28. Nine others retained hypersensitivity; three lost the reaction.[196]

Treatment of mosquito bites consists of local application of antipruritic lotions or creams. Antihistamines relieve the itching of early lesions but have no effect on later ones.[354] Group I corticosteroid creams and ointments may be helpful. Desensitization with insect whole-body extract is difficult but occasionally successful.[276] Prolonged heavy exposure to mosquito bites causes some individuals to lose sensitivity, occasionally in less than 1 year. Delayed hypersensitivity is lost more readily than is immediate hypersensitivity, with decreases in both IgE and IgG.[335]

BITING MIDGES (CULICOIDES)

Biting midges are very small flies that have a bite out of proportion to their size.[240] Only females feed on blood. The wormlike aquatic larvae usually develop in water-saturated soil; mangrove swamps are a common habitat. Larvae of some species use axils of banana and similar plants. The genus is cosmopolitan but presents the greatest problem in subtropical and tropical coastal regions. Activity is often seasonal. The flies bite most intensely in still air and reduced light.

Bites are immediately painful and result in raised, red, and pruritic lesions that persist from a few hours to a week or more. Some victims develop vesicles, pustules, and superficial ulcers, particularly if bitten by the genus *Leptoconops*. Hypersensitivity is involved, although some persons seem to develop intense reactions on first exposure to the insects.

Treatment of bites is symptomatic and similar to that for mosquito bites. Artificial hyposensitization has not been successful; however, spontaneous decrease in skin reactivity may occur in some individuals.

BLACKFLIES (SIMULIIDAE)

Blackflies are small, stocky flies that have a characteristic humpbacked appearance. Adults prefer open and sunny areas and are good fliers. Not all species are anthropophilic. The sessile larvae and pupae are found in flowing water, from large rivers to small brooks. Blackflies are cosmopolitan, but their abundance and medical significance vary widely. They range well into the Arctic and constitute a major problem for both humans and domestic animals in parts of Europe, Canada, and the northern United States. In the tropics they tend to be more localized, often remaining close to streams.

Blackflies bite more commonly on the upper half of the body. They snip the skin and suck the pooled blood, leaving relatively large punctures that may bleed, a symptom rarely seen with bites of other small flies. The local pain, swelling, and redness that follow blackfly bites are unusually intense and persistent. Vesicles and weeping, crusted lesions may last for weeks.[43] Systemic symptoms, such as malaise, fever, and leukocytosis, may occur. Enlarged indurated lymphatics, particularly in the posterior cervical region, are common in Canadian children living where blackflies are abundant. Blackfly bites can infrequently cause severe hypersensitivity reactions and localized cellulitis, similar to those seen with Hymenoptera stings.[318] Hemorrhagic symptoms have been reported in Brazil. Generalized urticaria, bleeding, angioedema, cough, wheezing, toxemia, and even death may occur.[210,243,448]

No specific treatment for blackfly bites is available. Hyposensitization has been attempted with little success. Neither repellents nor ordinary clothes provide satisfactory protection against blackflies when they are present in large numbers. Avoidance of heavily infested areas during fly season is often the most practical solution. Control measures have not proved highly effective.

Onchocerciasis, also known as river blindness, is the world's second leading infectious cause of blindness. It is caused by *Onchocerca volvulus,* a nematode that can live for up to 15 years in the human body. It is transmitted to humans through the bite of a *Simulium* blackfly. The worms spread throughout the body and when they die cause intense itching and a strong immune system response that can destroy nearby tissue, such as the eye. Treatment with ivermectin is recommended.[4]

Blackfly population control in Africa has evolved over the years. In the 1960s, DDT was used. In the 1970s and 1980s, water flow manipulation was instituted for better environmental preservation. In the 1990s and currently in Africa, the organophosphate temephos and toxins produced by the bacterium *Bacillus thuringiensis* have been tested and shown to be effective.[304]

Temephos is a nonsystemic organophosphorus insecticide used to control mosquito, midge, and blackfly larvae. It is used in lakes, ponds, and wetlands. It also may be used to control fleas on dogs and cats and to control lice on humans.

HORSEFLIES AND DEERFLIES (TABANIDAE)

Horseflies and deerflies are medium to large (10 to 25 mm [0.4 to 1 inch] body length) stocky flies whose large eyes often are brightly colored. They are strong fliers and prefer open and sunny habitats. The tabanids attack a variety of large mammals, including humans. The predacious maggot-like larvae live in water-soaked soil or shallow water. Bites from these large flies, especially the deerfly (*Chrysops* species), are painful and may cause both external and subcutaneous bleeding. An itching wheal up to 1 inch in diameter develops but usually does not last long. In some victims, severe and prolonged swelling of the face or an extremity develops. About 30 cases of systemic anaphylactoid reactions have been reported. Patients with a history of systemic reactions to wasp stings had a similar reaction to a horsefly bite, commonly referred to as the wasp-horsefly syndrome.[159,193,348]

As with other fly bites, treatment is symptomatic. Hyposensitization has been attempted in a few cases, with some success.

OTHER BITING DIPTERA

Sand flies *(Lutzomyia vexator)* are very small biting flies and the vectors for *leishmaniasis*, a protozoal disease of humans and dogs in regions of Asia, Africa, and South America. Cases of visceral leishmaniasis have been reported in upstate New York with outbreaks in dog kennels.[321] Leishmaniasis has also been described in Washington County, Texas.[280] Sand flies are widely distributed in tropical and subtropical regions. They live in damp, shaded places such as mammal burrows, rock crevices, and cracks in walls of houses and other structures. Favorite habitats in Central America are gambas, which are deep clefts between the buttresses of large forest trees. Cutaneous leishmaniasis, or "Aleppo boil," has dramatically increased in Syria attributed to the negative effects of the recent war on the public health system.[191] Other endemic outbreaks have been described throughout Latin America, in Ecuador,[177] and with a high concentration in Brazil associated with human immunodeficiency virus (HIV) coinfection.[259] Larval and pupal stages are found in moist detritus in holes and crevices. The adults usually emerge at night when air is still and temperatures are above 13° C (55° F). They are poor fliers. Sand fly human biting activity is typically highest between midnight and 3 AM.[379] In addition to leishmaniasis, these flies are vectors of *Bartonella bacilliformis* in Peru and Brazilian Amazonia.[104,316] Although the cutaneous form of the disease is often self-limited, it results in significant scarring and can spread to more invasive, mucocutaneous disease.[327] Sand fly populations can be controlled with pyrethroid insecticide sprayed into the mounds and burrows. Spraying a barrier zone of 100 m (328 feet) around a campsite can reduce sand fly numbers for an extended period.[129] Other preventive measures include impregnated bed netting and clothing, specialized dog collars, and spraying of residential dwellings and animal shelters. Glucantime has been shown to be effective against Old World cutaneous leishmaniasis when used in doses recommended by the World Health Organization (20 mg/kg/day for 20 days).[146] Vaccine development for prevention of sand fly fever[96] and visceral leishmaniasis has been described. The vaccine includes a leishmania antigen and vector salivary protein that improves vaccine efficacy by targeting the parasite at its most vulnerable stage, just after transmission.[219]

Snipe flies (Rhagionidae) prey primarily on insects, but some species, such as *Symphoromyia,* feed on the blood of mammals. Their habits and life history are similar to those of tabanids.

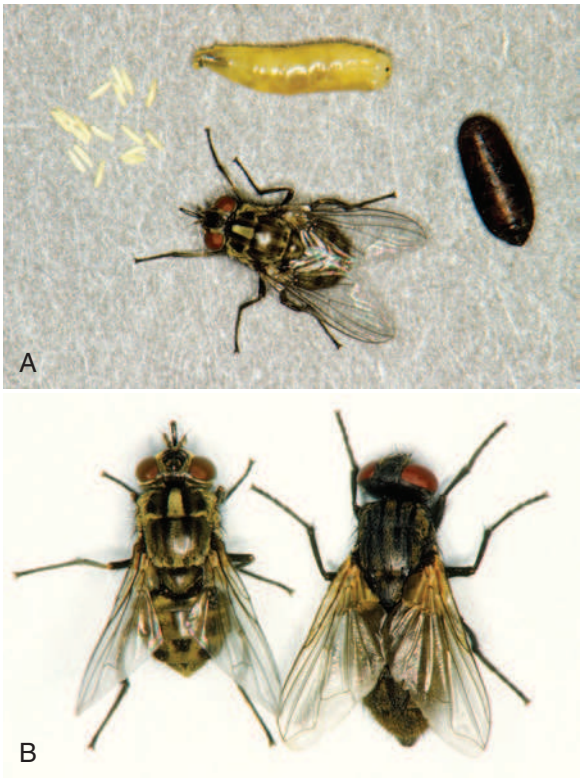

FIGURE 41-45 **A,** Stable fly life cycle. **B,** Stable house fly, *Stomoxys calcitrans*, dorsal view. *(Courtesy Jim Kalisch, University of Nebraska-Lincoln Entomology Department.)*

Reactions to snipe fly bites range from pain to anaphylaxis. A person who reacts severely may be bedridden for days.

The stable fly *(Stomoxys calcitrans)* (Figure 41-45) is related to the housefly, which it closely resembles. It is plentiful throughout most of the United States, particularly in agricultural districts. Eggs are deposited in piles of decaying vegetation, where the larvae develop. Thunderstorms seem to stimulate fly activity, which accounts for the widespread belief that houseflies bite just before a storm. Bites cause a sharp, stinging sensation, but dermal lesions are uncommon. Itching is transient.

Louse flies (Hippoboscidae) are peculiar Diptera that may lack wings entirely or have them for only part of their adult life. The wingless forms are flat, leathery insects that resemble lice or ticks. They are ectoparasites of birds and mammals. Larvae are carried in the uterus until development is almost complete; the pupal stage may be spent in the soil or on the host. The sheep ked *(Melophagus ovinus)* is a common species in the United States and sometimes bites sheep shearers and handlers. The related deer ked *(Lipoptena cervi)* is a seasonal pest in wooded sections of northern Europe, causing hundreds of cases of dermatitis annually. The pigeon fly *(Pseudolynchia canariensis)* is an avian parasite that sometimes infests buildings and bites the occupants.

Lesions from hippoboscid bites appear 1 to 24 hours after the bites as reddish itching papules that may persist for up to 3 months. Topical corticosteroids may afford symptomatic relief and hasten resolution of the lesions. Repellents are reported to be ineffective against these insects.

MYIASIS

The term *myiasis* for parasitism by fly larvae was introduced into the medical literature in 1840, although the condition has been observed since antiquity. More than one hundred species of Diptera have been reported to cause human myiasis.[292] Some are obligate parasites, for which humans are one of several hosts; some are opportunistic invaders that find parasitism an alternative to feeding on decaying tissue or its products. Nevertheless, humans are not a particularly good host for most species of fly larvae, and many infections terminate prematurely. Sensitization of host tissues to fly larvae does not occur as readily as with many other arthropod and helminth parasites.

Myiasis may be classified by clinical manifestations or etiologic agents. This chapter discusses only dermal and wound myiasis.[314] Myiases that involve primarily the gastrointestinal tract, urinary tract, eye, and nasopharynx are not covered.

Furuncular Myiasis

In furuncular myiasis, the fly larva penetrates the skin but remains sedentary, producing a boil-like lesion that usually has a central opening. Here the larva completes its development but typically emerges to pupate outside the host. As a human problem, this form of myiasis is largely confined to the tropics, although imported cases are being recognized in increasing numbers in other regions of the world,[459] particularly in North Americans who travel to more southern tropical regions.[269,359] A German travel clinic reported 13 cases in travelers returning from tropical countries during a 3-year period.[214] Tourists and divers recreating in tropical regions of Mexico, South and Central America, and Trinidad are also at risk.[26]

The classic agent of furuncular myiasis is the so-called human botfly, *Dermatobia hominis* (Figure 41-46). Humans, however, are only one of many mammals that serve as suitable hosts for the obligately parasitic larvae of this fly. It is widely distributed in the American tropics and is an important parasite of domestic cattle in many places. The adult fly resembles a bumblebee (body length, about 15 mm [0.6 inch]). It does not feed and is infrequently seen. The life cycle of this fly is unique in that the female attaches her eggs to the body of another arthropod for transfer to the host. Large mosquitoes of the genus *Psorophora* are often used (8% were found bearing *Dermatobia* eggs in one study), but about 40 other species of insects and ticks have been reported to be egg carriers. When the carrier alights on a mammal, the eggs hatch immediately, and the larvae enter the skin through the bite of the carrier or some other small trauma. Small larvae are fusiform and later become pyriform to ovoid as they reach full development at lengths of 15 to 20 mm (0.6 to 0.8 inch). They are encircled by several rings of spines. The larval stage

FIGURE 41-46 *Dermatobia hominis* larva.

lasts 6 to 7 weeks, after which the larva emerges from the skin and drops to the ground, where pupation occurs.

Infection is fairly common among rural people of Central America. Cases in returned tourists and visitors from Latin America have been diagnosed in many parts of the United States. Six cases occurred in one group of tourists visiting archaeologic sites in Guatemala.[56,206,239,326,415] Lesions may be on any part of the body exposed to insect bites and may be single or multiple. An initial pruritic papule becomes a furuncle, with a characteristic opening from which serosanguineous fluid exudes. Pain often accompanies movements of the older larvae, but the lesion is not particularly tender to palpation. Lymphadenopathy, fever, and secondary infection with systemic inflammation are less common.[431]

This form of myiasis should be suspected in patients with furuncular lesions and a history of residence or travel in endemic areas. It must be differentiated from leishmaniasis and onchocerciasis, which have a different prognosis and treatment. The sensation of movement within the lesion, accompanied by pain but little tenderness or inflammation, suggests myiasis. The tip of the larva may protrude from the central opening, or bubbles produced by its respiration may be seen. Often, simple pressure will extrude the organism, particularly if it is small.[317] Occlusion of the breathing hole may cause the larva to emerge sufficiently for it to be grasped and withdrawn.[99] An effective folk remedy is binding a piece of fat, such as bacon, over the opening.[50] This often causes the larva to leave its burrow. Another technique is injection of about 2 mL of a local anesthetic into the base of the lesion, thus extruding the larva by fluid pressure.

If these methods are unsuccessful, surgical excision under local anesthesia is indicated (Figure 41-47). Whatever method is used, care should be taken not to break or rupture the larva. This may cause a strong inflammatory reaction, often followed by secondary infection. Repeated infections tend to confer some immunity that may abort larval development. Screens, protective clothing, and use of insect repellents are helpful in preventing infestation. Vaccines against myiasis infections are being developed.[376]

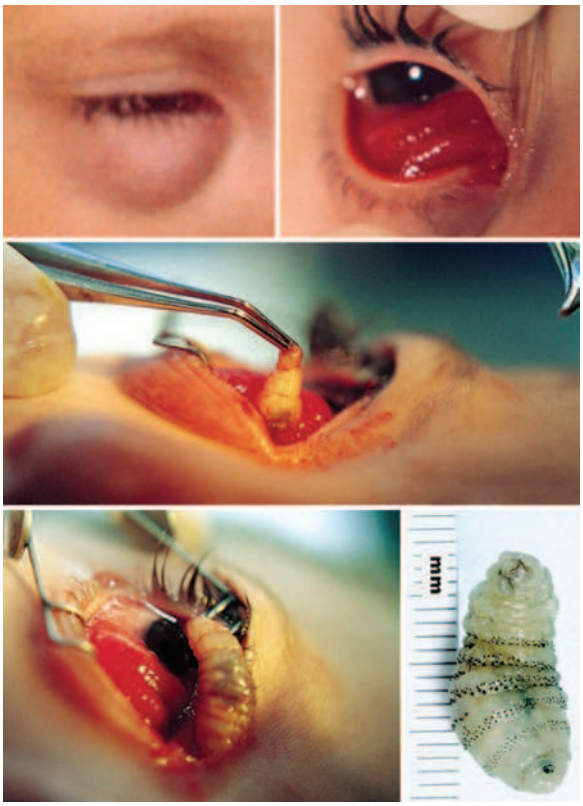

FIGURE 41-47 Multiple images of botfly larva being removed from a child's eye.

FIGURE 41-48 Furuncular myiasis. *(Courtesy Capt. Randall L. Goodman, USAF,MC: Anterior orbital myiasis caused by human botfly [Photo Essay], Arch Ophthalmol 118:1002, 2000.)*

Furuncular myiasis in tropical Africa is caused by the tumbu fly, *Cordylobia anthropophaga* (Figure 41-48). The larval stage of this fly is an obligate parasite of many mammals, but rats and dogs are the most important epidemiologically. The adult is about the size of a housefly, but stockier. It prefers shade and is most active in early morning and afternoon. Females lay eggs on dry sandy soil or on clothing. They are attracted by the odor of urine. The eggs hatch in 1 to 3 days, and hatchling larvae can survive up to 2 weeks waiting for contact with skin of a suitable host. They can penetrate unbroken skin. They become fusiform to ovoid and reach a length of 13 to 15 mm (0.5 to 0.6 inch). The larval stage is completed in 9 to 14 days.

Human infections occur in most nations of sub-Saharan Africa. Transmission increases during the rainy season. Among indigenous peoples, infection is most frequent in children, as adults evidently acquire some immunity. Infections among Americans and Europeans visiting Africa are reported regularly.[212,214,381] Lesions may be on any part of the body[267] but are more common on the legs and buttocks. The furuncles are discrete, elevated, and nontender and have a central opening. The number of lesions, up to about 50, is greater than with *Dermatobia*. Infections in children have been mistaken for chickenpox,[312] but the course of the infection is much shorter. An exceptionally heavy infection (about 150 larvae) was caused by *Cordylobia rodhaini,* normally a parasite of forest mammals. It was accompanied by lymphadenopathy, leukocytosis, and elevated IgA. Clothing left to dry on the ground was the presumed source of the parasites.[328] Principles of diagnosis and treatment are much the same as for *Dermatobia*. Avoidance of skin contact with potentially contaminated soil and ironing of clothing and bedding after open-air drying are preventive measures that often are difficult to achieve.

Hematophagous Myiasis

The sole cause of hematophagous myiasis is the Congo floor maggot, *Auchmeromyia luteola*. It is dark, distinctly segmented, ovoid, and 15 to 18 mm (0.6 to 0.7 inch) long, and it assumes the larval stage of a moderate-size yellowish fly. It is widely distributed in sub-Saharan Africa and is essentially a human parasite. It is unique among parasitic fly larvae in living apart from its host in the earthen floor of native dwellings. It seeks persons lying or sitting on the floor or on mats and feeds intermittently on blood, usually at night. The bites are trivial but may interfere with sleep. Sensitization appears to be uncommon.

Autochthonous furuncular myiasis may occur in the United States, usually in children. Most cases are caused by larvae of botflies of the genus *Cuterebra*, whose normal hosts are small rodents and rabbits. The fly eggs are attached to low vegetation and hatch on contact with skin of the host. Adult human skin seems impervious to them, but that of children may be penetrated. There is usually a history of outdoor play in weeds or grass or with a pet rabbit. In one case, eggs were apparently deposited directly on the skin.[166] Lesions typically develop on the head, neck, or chest in 1 to 2 weeks. Once recognized, the larvae can often be removed by simple pressure.[156,397] The syndrome may also be caused by larvae of *Wohlfahrtia vigil*, a large fly native to Canada and the northern United States. Its normal hosts are newborn mammals, particularly mink, dog, and fox. The fly deposits larvae on the skin, which penetrate in about an hour. Human infections are typically in infants under 9 months, and the furuncular lesions are usually on the face. Fever, irritability, and loss of appetite are common. Larvae can usually be expressed from the lesion; surgery rarely is necessary. Netting over the crib or pram when outdoors usually affords protection.

Migratory Myiasis

One type of migratory myiasis is caused by flies of the genus *Hypoderma*. Adult flies are large and hairy, resembling bumblebees. Normal hosts for the parasitic larvae are cattle, deer, and horses. The flies attach their eggs to hairs. Hatchling larvae penetrate the skin and wander extensively through the subcutaneous tissues, eventually locating under the skin of the back, where they produce furuncular lesions. The condition has veterinary importance. Humans are abnormal hosts in which the parasite is unable to complete its development. Human infections usually occur in rural areas where cattle and horses are raised and are more common in winter. Larvae migrate rapidly (as much as 1 cm/hr [0.4 inch/hr]) and erratically through subcutaneous tissues, producing intermittent, painful swellings over months. The person often senses larval movement. Larvae respond negatively to gravity, so the last lesions are usually on the head or shoulders. Eosinophilia (up to 35% eosinophils on white blood cell differential) and angioedema may be seen. Larvae may emerge spontaneously from furuncles or may die in the tissues. In rare cases, larvae were seen to have invaded the pharyngeal region, orbit, and spinal canal.

Another form of migratory myiasis is caused by larvae of *Gastrophilus*, which normally are gastrointestinal or nasal parasites of horses (Figure 41-49). In human infections, which are reported more frequently from Europe than from the United States, the young larvae burrow in the skin, producing narrow, tortuous, reddish, and linear lesions with intense itching. Lesions usually advance 1.5 cm/day (0.6 inch/day), but more rapid progress has been reported. Death of the larvae terminates the infection in 1 to 2 weeks without sequelae. This infection is clinically similar to creeping eruption, an invasion of the skin by larvae of the hookworms *Ancylostoma braziliense* and *Ancylostoma caninum*. The helminthic parasitosis occurs more often in warm, moist regions, including the southern United States, and is associated with dogs and cats. The myiasis is seen more frequently in cooler regions and is associated with horses. Definitive diagnosis can be made only by removal of the parasite from its burrow and microscopic examination.

Removal of the larvae by surgery or expression is the usual treatment for migratory myiasis, although local freezing of cutaneous burrows is sometimes successful. Ivermectin given to a patient with *Hypoderma* myiasis resulted in expulsion of the larva.[214] The most effective prevention is control of the infections in domestic animals.

FIGURE 41-49 Larvae of the botfly *Gastrophilus haemorrhoidalis* from a horse's stomach.

Wound Myiasis

About 85% to 90% of cases of wound myiasis are caused by larvae of flies of the family Calliphoridae, which includes both obligate parasites and opportunists. The most dangerous type of myiasis may be caused by larvae of the screw-worm flies—*Cochliomyia americana* (formerly *Callitroga hominivorax*) (Figure 41-50A) in the Americas and *Chrysomyia bessiana* (see Figure 41-50B) in Asia and Africa. The adults are rather stocky flies, 8 to 12 mm (0.3 to 0.5 inch) in body length, and metallic blue-green to purplish black.

The parasitic larvae are pinkish, fusiform (providing the common name), and strongly segmented. Length at maturity is 12 to 15 mm (0.5 to 0.6 inch). They are obligate parasites whose chief hosts are cattle, sheep, and goats. They are a major cause

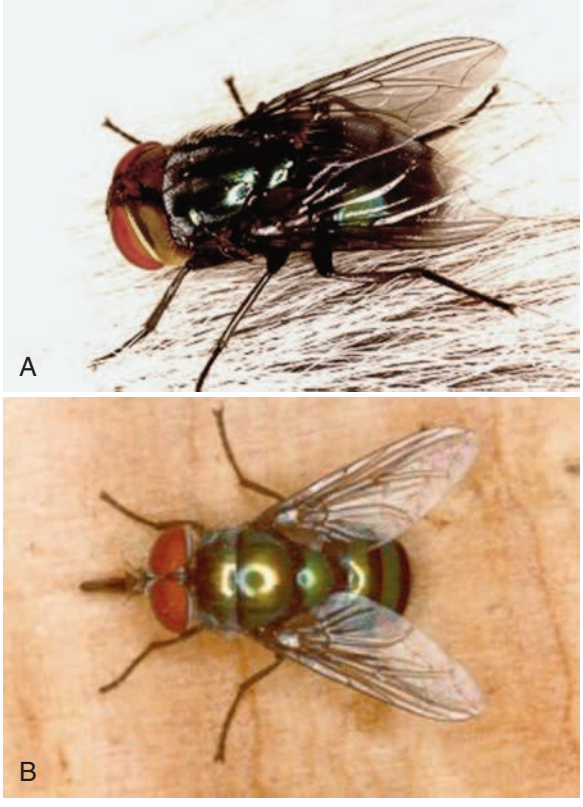

FIGURE 41-50 **A,** American (New World) screw-worm fly, *Cochliomyia*. **B,** Asian-African (Old World) screw-worm fly, *Chrysomyia*.

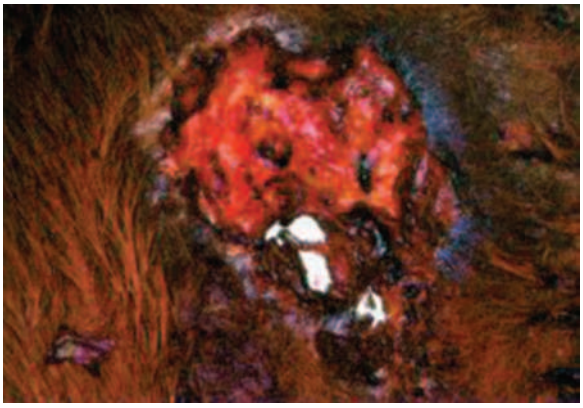

FIGURE 41-51 Scalp myiasis appearing as pediculosis capitis. *(From spc.int/rash/munual/images.)*

FIGURE 41-52 Wound myiasis. *(From icb.usp.br.)*

of economic loss among livestock. Enzootic areas are mostly in the tropics and subtropics; in the past, summer infections have occurred as far north as Colorado and Nebraska. Female flies deposit eggs near any break in the skin or around the nose, mouth, or ears if a discharge is present. Larvae invade healthy tissue, often causing considerable damage. The larval stage lasts 4 to 8 days, and the entire cycle is 15 to 20 days in enzootic areas. Screw-worm has been eradicated in the southern United States and some other areas primarily through the release of large numbers of laboratory-bred male flies sterilized by gamma irradiation. Females mate only once, so mating with a sterile male nullifies the female's reproductive effort, greatly reducing the population.

Flies may be dispersed by prevailing winds. Infection is often acquired while resting outside during the day or may result from trauma.[285] Lesions may appear on any exposed parts of the body. Lesions on the scalp may be associated with pediculosis capitis (Figure 41-51). Typical dermal lesions are ulcers or sinuses that may contain up to 200 larvae. These are surrounded by a zone of induration (Figure 41-52). Pain is variable. Secondary bacterial infection is common. Tissue destruction may be extensive and mortality is associated with nasopharyngeal invasion.

Irrigation of the wound and mechanical removal of larvae are generally sufficient for treatment. Topical application of 5% chloroform in olive oil followed by irrigation and manual removal of larvae is often adequate in dermal infections. Deeper nasopharyngeal and orbital infections require surgery. Antimicrobial therapy as dictated by culture and sensitivity tests is often necessary. The most effective prevention is elimination of the disease in domestic animals.

Opportunistic invasion of wounds by fly larvae is often seen during war and natural disasters, when injured persons are exposed to flies and medical facilities are inadequate to cope with the emergency. Wound myiasis may also be seen sporadically in nursing homes and hospitals and often is not reported for cultural and medicolegal reasons.[59] Six of 14 cases in one series were acquired in the hospital. Eleven patients were older than age 63 years, and nearly all had underlying problems, such as diabetes or peripheral vascular disease. Most of the infected lesions were on the feet or ankles.[118] In another series of 16 cases, most victims were debilitated and older than age 65. Men were affected more often than women. Seven species of flies were involved.[290] Fifty *Lucilia* larvae were removed from the nose, mouth, paranasal sinuses, and enucleated eye socket of a hospitalized patient left in a room with an open window.[96] The most common fly species involved are *Lucilia* (green-bottle flies) (Figure 41-53), *Calliphora* species (blue-bottle flies), *Phormia regina* (black blowfly), *Sarcophaga haemorrhoidalis* (flesh fly), and *Musca domestica* (housefly). The flies, whose larvae normally feed on decaying animal tissues, often deposit eggs or larvae in wounds or around body orifices if a malodorous

FIGURE 41-53 Green-bottle fly, *Lucilia*. *(From Wikimedia Commons.)*

discharge is present. The larvae feed on necrotic tissue, and damage to healthy tissues and secondary infection are uncommon. They actually may debride wounds, and "maggot therapy" with aseptically bred larvae was briefly used in the 1930s. More recently, laboratory-bred fly larvae were used to debride venous stasis ulcers and other superficial necrotic areas when antibiotic therapy and surgical debridement were unsuccessful.[396,410] Maggots serendipitously present have been used to debride lesions.[291,349] Diagnosis is usually obvious on inspection of the wound. Species identification often requires the larvae to reach maturity. If this is not feasible, examination of the spiracular plates on the last segment of the larva and the chitinized oral structures usually permits adequate identification.

LICE (ORDER ANOPLURA)

SPECIES, LIFE CYCLE, AND DISTRIBUTION

Lice are small wingless insects that are ectoparasites of mammals. They are mostly host specific, and two species are human parasites: *Pthirus pubis* (pubic louse)[162] and *Pediculus humanus*, the latter with two varieties, *Pediculus humanus capitis* (head louse) and *Pediculus humanus corporis* (body louse).[234] They are obligatory parasites, subsisting on blood from the host, and have mouthparts modified for piercing and sucking. The mouthparts are drawn into the head of the louse when not in use.

Pediculosis (capitus, corporis and pubis) has a worldwide prevalence involving millions of people annually.[121] The number of head lice infestations occurring annually in the United States is estimated at 6 to 12 million.[445] The adult head louse is about 2 to 4 mm (0.1 to 0.2 inch) long with an elongated body that is flattened dorsoventrally (Figure 41-54).[363] The head is only slightly narrower than the thorax. The three pairs of legs are about equal in length and possess delicate hooks at the distal extremities. The entire life is spent on the host's body. The eggs (nits) are deposited on hair shafts, generally one nit to a shaft (Figure 41-55). The nits hatch in about 1 week, and the freshly hatched larvae, which must feed within 24 hours of hatching or die, mature in about 15 to 16 days. The adult female lives for approximately 1 month and may deposit more than 100 eggs during her reproductive life. Body lice are slightly larger than head lice but are similar in appearance with a similar life cycle, although the nits are deposited on fibers of clothing. Head lice and body lice interbreed.

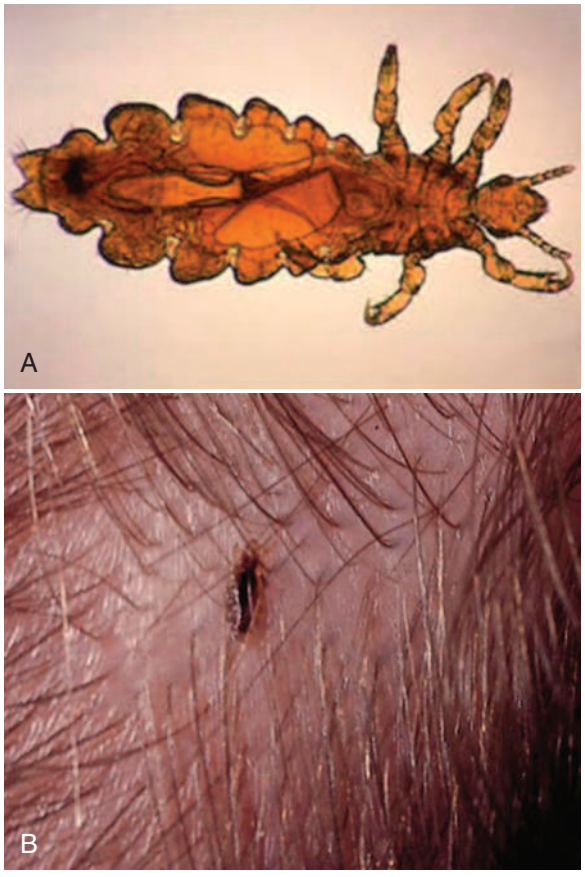

FIGURE 41-54 **A,** Full-grown human head-louse, *Pediculus humanus capitis*. **B,** Adult louse embedded in scalp skin. *(Modified from Roberts RJ: Head lice, N Engl J Med 346:1646, 2002.)*

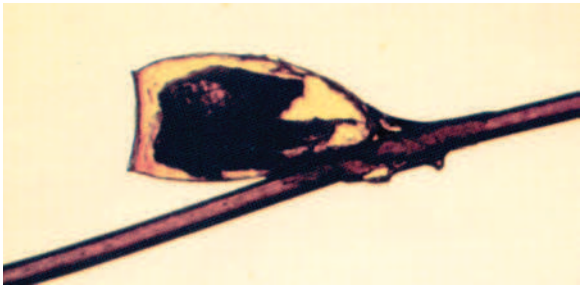

FIGURE 41-55 Unhatched nit of the head louse, *Pediculus capitis*. *(Modified from Roberts RJ: Head lice. N Engl J Med 346:1646, 2002.)*

Pubic lice maintain a worldwide parasitic population infesting 2% to 10% of human populations.[14] Adult pubic lice are about 1 to 2 mm (0.04 to 0.07 inch) long, the head is much smaller than the thorax, and the broadly oval body is flattened dorsoventrally (Figure 41-56). The anterior legs are much shorter than the second and third pairs, and the insect resembles a miniature crab. Nits are deposited on hair shafts, often several per shaft, and the egg-to-egg life cycle is approximately 1 month.

Lice are found wherever people are found. Able to exist only briefly away from the human body, lice are spread by close personal contact and by sharing of clothing and bedding. The various species not only have a particular host but often prefer a particular part of the host's body, so generalizing about transmission of the three varieties that parasitize humans is impossible. During biting and feeding, secretions from the louse cause a small red macule. Severe pruritus and marked inflammatory responses to bites are caused by the sensitization that occurs after repeated exposure to bites. Thus a victim may have lice for weeks before pruritus becomes marked. Not all people are equally attractive to lice, possibly because of differences in odor and chemical composition of sweat. Lice are medically important as vectors of systemic illnesses, as well as for dermatitis and discomfort.

CLINICAL ASPECTS

The head louse localizes on the scalp and rarely on other hairy areas of the body. Children are most frequently affected, but adults, particularly women, may also be affected. Lice are particularly common in young girls, possibly because of their long hair. Infestation is uncommon in blacks, at least in the United States, probably because the shaft of African hair has an oval

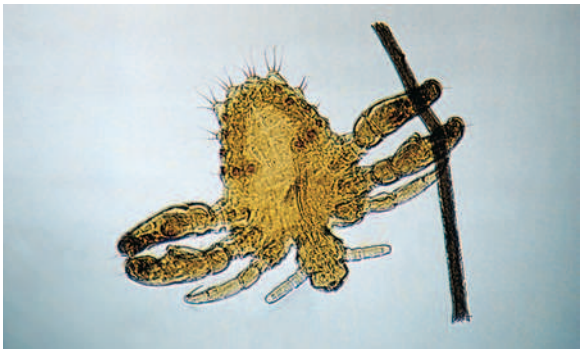

FIGURE 41-56 Pubic, or crab, louse, *Phthirus pubis*, grasping a hair.

cross section that makes it difficult for the louse to grip while depositing eggs. However, pediculosis capitis is found in Africa, where the indigenous head louse is adapted to grip the oval hair shafts. Because nits initially attach to the hair shaft close to the skin and are carried higher as the hair grows, the presence of nits near the tips indicates a longstanding infestation.

Itching is the principal symptom, and physical findings vary with duration and extent of the infestation, cleanliness, excoriations, and degree of secondary infection. Diagnosis is established by identifying nits and lice. It is not always easy to find lice, especially in early and mild cases, when they may be few in number. Lice are very active, but nits are always present and easy to identify. Nits are whitish ovals, about 0.5 mm long, and attach firmly to one side of the hair. Flakes of dandruff, which resemble nits superficially, are not attached to the hair shafts. Occipital and posterior cervical adenopathy are common and may be present even in less severe cases. A pruritic scalp accompanied by adenopathy should prompt a thorough search for lice and nits. In severe cases, oozing and crusting may be present, sometimes with matting of the hair, and lice may be numerous.

The body louse lives chiefly in the seams of clothing and is rarely seen on the skin. These lice leave clothing to feed on the skin or remain attached to the clothing while feeding, and thus are most abundant where clothing abuts the skin (e.g., at the belt line). The bite results in a small red macule with a characteristic central hemorrhagic punctum. Excoriations, crusts, eczematization, and other secondary lesions generally obscure the primary lesions by the time the victim seeks medical attention. Shoulders, trunk, and buttocks are favorite sites for bites, and parallel scratch marks on the shoulders are a common finding. The diagnosis is confirmed by identifying parasites or nits from the clothing. Bands of trousers, side seams, and underarm seams are sites of preference. Untreated cases may persist indefinitely, and massive infestations are sometimes seen in the homeless who have no ready access to frequent laundering or change of clothing or who cannot bathe regularly.

Pediculosis pubis is usually acquired during sexual activity, and it may be a marker to search for other sexually transmitted diseases.[254] It may result from unchanged bedding or nonsexual activity, either from lice that live briefly away from the human body or from egg-infested pubic hairs that are shed. The lice localize principally in the pubic hair, but are found occasionally in eyebrows, eyelashes,[268,338] and axillary hairs. Adult pubic lice are not active and hug the skin at the bases of the hair shafts, with their heads buried in the follicular orifice. They are not easy to find, but one or more can usually be found if suspicion of the diagnosis is strong enough to prompt a thorough search. A loupe is helpful. Nits are more easily found. The increased incidence of hair removal may lead to atypical patterns of pubic lice infestations or its complete eradication as the natural habitat of this parasite is destroyed.[111] Primary bite lesions are almost never seen, but intense pruritus and pubic scratching are pathognomonic. The secondary infection, crusting, oozing, excoriations, and eczematization that often accompany head and body lice are rarely seen with pubic lice. Peculiar steel-gray macules (maculae caeruleae) may appear in association with some cases of pubic lice. These lesions do not appear until the infestation has been present for several weeks and are most common on the trunk and thighs.

TREATMENT AND PREVENTION

Treatment of all types of lice strives to eradicate lice and nits and prevent reinfestation. Head lice may be treated with one application of 1% permethrin cream rinse (Nix) or 0.5% malathion lotion (Ovide).[286,445] Most studies suggest that permethrin 1% is the most cost-effective treatment.[182] Hair should be washed, rinsed, and dried, and the rinse is applied for 10 to 20 minutes before being washed off. Isopropyl myristate 50% in cyclomethicone solution (Full Marks Solution) is a new fluid treatment with a physical mode of action that uses a 10-minute contact time.[424] A fine-toothed comb may be used to remove nits after rinsing. Failure to remove all the lice is a frequent cause of treatment failure. Combing should be repeated in 1 to 2 days to confirm treatment success. A louse detection comb is a more effective method than visual screening for diagnosis.[23] If lice are found after 7 days, retreatment is indicated. Household members and those in close contact with the patient should be screened for head lice and treated simultaneously if indicated. Extensive environmental cleanup is probably not warranted, although combs and brushes should be discarded or thoroughly washed with hot water.[363] Hats and scarves should be machine-washed in a hot cycle and bed clothing dry-cleaned. Spraying or fogging a home with insecticide is not recommended.[313] Routine use of 2% piperonal spray in communities with a high prevalence of head louse infestation may provide some protection from infestation.[58] A child can return to school immediately after completion of the first proper application of an effective insecticide regardless of the presence of nits. This will avoid unnecessarily missing multiple days of school (and work days for the parents) as well as relieving public overreaction and hysteria.[163,363,380] Regular weekly detection combing is recommended for up to 7 weeks after the first cure.

Primary treatments are topical pediculicides (permethrin or malathion), but emergence of resistance against pediculicides has created the need for alternative treatments such as oral ivermectin.[121] Other pediculicides are available if the lice are resistant. Two products, RID and Triple X, contain 0.3% pyrethrins and 3.0% piperonyl butoxide. One application of either preparation usually eradicates both lice and nits. A few persons may require another application 7 days after the initial treatment.[35] Alcoholic formulations or vehicles of these products are flammable until dry. Lindane 1% (hexachlorocyclohexane, Kwell) may be used on persons who fail to respond or who are intolerant of permethrin. Kwell, which was formerly the medication most often used in the United States for treatment of louse infestations, is no longer recommended in children because of its safety profile, and it has been pulled off the shelves in many states.[149] Lindane penetrates human skin and has potential for central nervous system toxicity manifesting as seizure activity. It is contraindicated in children and must be used with strict guidelines in older patients resistant to other treatment measures.[145] Malathion (0.5% Ovide lotion) is an organophosphate and one of the only products that has retained its efficacy and safety profile over time. It is usually effective after one 20-minute application.[286,445] However, this insecticide preparation is not recommended in children younger than age 2 years.[363] Alternative treatments contain pyrethrums and piperonyl butoxide as active ingredients. Newer dry-on, suffocation-based pediculicide lotions are now being introduced that accomplish their mission without using neurotoxins, the need for nit removal, or extensive household cleaning. The results are comparable or superior with the efficacy of other pediculocides.[332] Some sources warn that treatment failures may not result from improper application, noncompliance, or reinfestation but from increasing drug resistance,[60,308] particularly in underdeveloped countries.[123,131] Extensive use of pediculicides with a neurotoxic mode of action has led to development and global spread of resistant head lice populations.[142] A recent study noted that single treatment with topical ivermectin provides significantly higher cure of infestation and faster relief of pruritus than oral ivermectin. Whether topical or oral ivermectin is used, a second dose is generally required to ensure complete eradication.[6] Ivermectin, a macrocyclic lactone antibiotic highly effective against filarial worms, *Strongyloides,* and scabies (see later), has recently been demonstrated to be effective against lice both topically and orally.[61,112]

Body lice may be treated with the same medications, but parasites and nits are not generally found on the skin. Eradication of these from the clothing is the primary objective. Treatment includes bathing, laundering all clothing, and changing to fresh clothes free of lice and nits. Dry cleaning eradicates lice and nits, as does ordinary laundering on hot settings. Malathion preparations and gamma-benzene hexachloride formulations may be used for mass delousing.

Pubic lice may be treated with the same medications used for head lice. Treatment consists of permethrin 1% cream rinse applied for 10 minutes and rinsed. Sexual partners should also be treated.[150] Crotamiton lotion rubbed into the affected area daily for several weeks to destroy hatching ova may also be used.

Eyelash infestations may be managed with physostigmine ophthalmic ointment using a cotton-tipped applicator. Machine washing and drying of sheets and clothing on hot settings will kill lice and nits.

LOUSE-BORNE RELAPSING FEVER

The differential diagnosis for tick-borne relapsing fever (TBRF) includes louse-borne relapsing fever (LBRF). LBRF is found worldwide and is caused by the spirochete *Borrelia recurrentis*. LBRF is transmitted from person to person by the body louse, *Pediculus humanus humanus,* usually in areas of human social crowding, such as wartime conditions, refugee camps, and clusters of homeless persons. It is spread by contact with clothing, where the lice live. Disease transmission occurs only when the lice go to the skin to feed.

LBRF has a very similar clinical presentation to TBRF. The two disorders are difficult to distinguish clinically, but LBRF carries a higher rate of morbidity and mortality than TBRF, because of the socioeconomic situations and lack of appropriate medical care of the endemic areas. It is often seen in travelers after they return to their home countries. An Ethiopian survey revealed that LBRF was responsible for 27% of one hospital's admissions. Central African data shows a 30% to 70% morbidity rate and 6% mortality rate.[456]

Diagnosis of LBRF is similar to that of TBRF; obtaining an appropriate travel history from the patient is crucial. For children and adults, a single oral dose of 200 mg of doxycycline or 500 mg of erythromycin is effective in LBRF.[65] Treatment is otherwise supportive.

FLEAS (ORDER SIPHONAPTERA)

SPECIES, LIFE CYCLE, AND DISTRIBUTION

Fleas are small ectoparasites of mammals and birds. The wingless body, which is covered by a hard shiny integument, is compressed laterally, enabling the fleas to scurry easily among hairs and feathers of the hosts. They are active insects with legs adapted for jumping, capable of prodigious leaps. Adult fleas subsist on blood. Some species must obtain blood from one particular host, others are less host specific, and all have mouthparts adapted for piercing and sucking. The eggs are laid on or near the host and drop to the ground as the host moves about or shakes. They hatch into small wormlike larvae that feed on droppings from adult fleas, flakes of dried blood from the host, and other organic matter. The life cycle varies among species and may vary considerably within the same species, because each developmental stage is influenced by prevailing temperature and humidity. The customary larval stage of 9 to 15 days may be prolonged for months by adverse conditions, and the pupal stage varies from a week to nearly a year. Individual adult fleas may live for years when circumstances are favorable and can live for months without feeding.

Fleas exist universally, although the distribution of various species is restricted by climate and host. They are of medical importance because of the discomfort resulting from their bites, as a cause of papular urticaria, and as vectors of disease.[213] They are more active in warm weather and cause more problems in warmer climates with a longer breeding season, such as the southwestern United States. They are a particular nuisance in California. High standards of sanitation and personal hygiene in developed countries have discouraged the human flea, *Pulex irritans,* while at the same time, the popularity of household pets has been conducive to proliferation of dog and cat fleas, *Ctenocephalides canis* and *Ctenocephalides felis*. The incidence of other species on mammals and birds remains high. Because dog, cat, and many other fleas are only partially host specific, fleas associated with many mammals and birds cause disease in humans. Most current flea-bite problems are caused by animal fleas. Hungry fleas are more often attracted to people from an area frequented by an animal than from the animal itself. If the family dog is absent, hordes of hungry fleas may persist for months. Consequently, anyone with pet cats or dogs or near domesticated animals is more likely to be bitten, but outbreaks in the absence of pets are common. One epidemic of flea bites among children in a day nursery was traced to dog fleas in a deserted fox nesting area beneath the building.[368] Another outbreak among poultry workers was caused by an infestation of hen fleas, *Ceratophyllus gallinae*.[422] Fleas from flying squirrels also have been documented as the source of bites.

Burrowing Flea

Flea infestations tend to be similar clinically and associated with the distribution of animal hosts. However, one flea, *Tunga penetrans,* is responsible for a distinctive infestation known as tungiasis (Figure 41-57).[449] The flea has a number of common names: burrowing flea, chigo, sand flea, and jigger.[195] Infestation is common in Central and South America and in Africa, where the burrowing flea is widely distributed, but the incidence in the United States is rising as increasing numbers of tourists visit international exotic destinations.[71] Vacationers who go barefoot on beaches in tropical Africa, South America, and subtropical Asia risk infestations.[309] One resident of New York City developed lesions of tungiasis on her toes after visiting several countries in East Africa, where she frequently wore sandals in rural areas.[457] In Brazil, tungiasis is endemic in some resource-poor communities where domestic and sylvatic animals act as reservoirs for this zoonosis.[337] The primary lesions of tungiasis are produced by the female flea. As soon as it is impregnated, it burrows into the skin until only the posterior end protrudes. Sucking blood, the insect becomes as large as a small pea and deposits eggs that fall to the ground. Lodged in the skin, the gestating female produces a firm itchy nodule, with the posterior end of the flea visible as a dark plug or spot in the center of the nodule. Lesions occur most often on the feet, buttocks, or perineum of persons who wear no shoes or frequently squat, because the burrowing flea is not a good jumper and abounds in the dusty soil surrounding human habitations. If the infestation is extensive, numerous papules may aggregate into plaques with a honeycomb appearance. After penetration under the nails of the feet, the ectoparasite enlarges and lesions become painful.[44] Secondary infections become painful or even crippling, and severe infections may lead to death. If the burrowing flea is not removed, the pustule ruptures, leaving an ulcer. Wearing shoes prevents most cases of tungiasis.

CLINICAL ASPECTS

The appearance of flea bites is not diagnostic, and the clinical features depend on the degree of sensitivity. A bite produces a small, central hemorrhagic punctum surrounded by erythema and urticaria. A small wheal at the bite site may be nonallergic because of primary urticariogenic substances in the flea saliva, but increasingly severe reactions are caused by sensitization to substances in the saliva. Bullae or ulcerations may result from flea bites in highly sensitive individuals. Flea bites are intensely pruritic, and scratching often results in crusting and impetiginization. Fleas have a habit of sampling several adjacent areas while feeding, and bites characteristically appear in irregular groups. Feet, ankles, and legs, as well as the hips and shoulder areas, where clothing fits snugly, are favorite targets. Although an individual lesion produced by a flea bite is not diagnostic, the typical clinical picture of grouped multiple bites is generally sufficient to establish a diagnosis, which is usually confirmed by locating and identifying fleas.

TREATMENT AND PREVENTION

Ordinary flea bites require symptomatic treatment directed at relief of pruritus and prevention of secondary infection. Corticosteroid creams or calamine lotion with phenol, systemic antihistamines, and antibiotics are helpful when indicated, but the management of flea bites consists largely of prevention. The animals that host the fleas must be treated, as well as such places as chicken coops, rat nests, sleeping sites for dogs and cats, and often dwellings where pets live. Many effective insecticides are available. Typically, *N,N*-diethyl-*meta*-toluamide (DEET; also

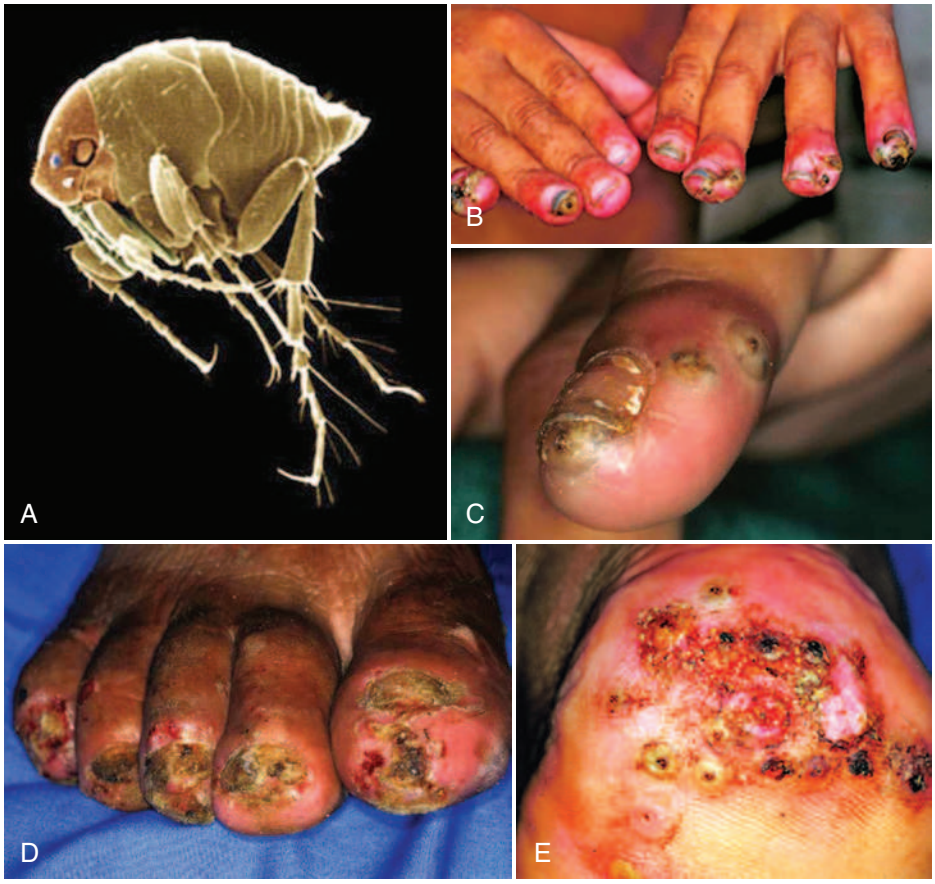

FIGURE 41-57 **A** to **E,** Tungiasis. **B** and **C,** Involvement of fingers. **D** and **E,** Toes and heel. *(Courtesy Armed Forces Pest Management Board from World Health Organization Feldmeier H, Eisele M, Sabóia-Moura RC, et al: Severe tungiasis in under-privileged communities: case series from Brazil, Emerg Infect Dis 9:949, 2003.)*

called diethyltoluamide), pyrethrins, piperonyl butoxide, and D-trans-allethrin are ingredients in sprays and foggers. An insect spray containing permethrin may be effective. Spraying or dusting must eradicate not only adult fleas but also the many larvae and pupae in grass, carpet, floorboards, furniture, and beds. Carbaryl and malathion are the active ingredients in many sprays and dusts, and the services of professional exterminators may be necessary.

Veterinary prescriptions are available for control of fleas on dogs and cats. Preparations containing 9.1% imidacloprid (Advantage) eliminate or reduce fleas on dogs when applied to the skin; 98% to 100% of fleas are killed within 12 hours of application, and reinfesting fleas are killed for 4 weeks after a single application. An oral preparation used for both dogs and cats contains lufenuron, an inhibitor of insect development. Lufenuron does not kill adult fleas, but rather controls flea populations by interrupting the life cycle at the egg stage.

Cases of burrowing fleas should be treated promptly. One method is curettage of each nodule under local anesthesia, with concomitant use of systemic antibiotics to prevent secondary infection. Ether pledgets applied to the skin will kill fleas before curettage is begun. Where burrowing fleas are endemic, eradication is important. Floors must be swept free of dust, and insecticides may be sprayed or dusted.

MITES (CLASS ARACHNIDA, ORDER ACARINA)

SPECIES, LIFE CYCLE, AND DISTRIBUTION

Mites make up the largest group in the class Arachnida. Most are small arthropods, and many are barely visible. Mites have two body regions, a small cephalothorax and a larger, unsegmented abdomen. The cephalothorax and abdomen are broadly joined, giving most mites an oblong to globular appearance. Newly hatched larvae have three pairs of legs, and larvae acquire a fourth pair after the first molt. Mites are highly diverse. Some are parasitic, with both vertebrates and invertebrates serving as hosts; some are scavengers, some feed on plants, and many are free living and predacious. Although most species are oviparous, some are ovoviviparous, and a few are viviparous. They occur worldwide and frequently in great numbers. Mites have been associated with disease transmission, allergies, and dermatologic manifestations. Of the approximately 35,000 species, about 50 are known to cause human skin lesions, and most of the cutaneous lesions are caused by mites feeding or burrowing in the skin. Because children and adults of all races are susceptible to these ubiquitous arthropods, they are responsible for considerable morbidity. The mites of medical importance are some of the sarcoptic mites, some of the trombiculid mites, a number of other acariform mites that infest organic substances such as grains and produce, and the gamasid mites that are vectors of several rickettsial and viral diseases.[213] Dermatologic manifestations of mite bites may be seasonal, as with the trombiculids; individual cases or outbreaks of varying magnitudes may be related to contact with mites that infest animals or various foods. Epidemics may occur, as is presently the case with scabies.

SCABIES

Life Cycle

Scabies infestation in humans is a complex interplay between mite, host, and host environment.[367] The human scabies mite is *Sarcoptes scabiei* var. *hominis,* an obligate human parasite that completes its entire life cycle in and on the epidermis of humans

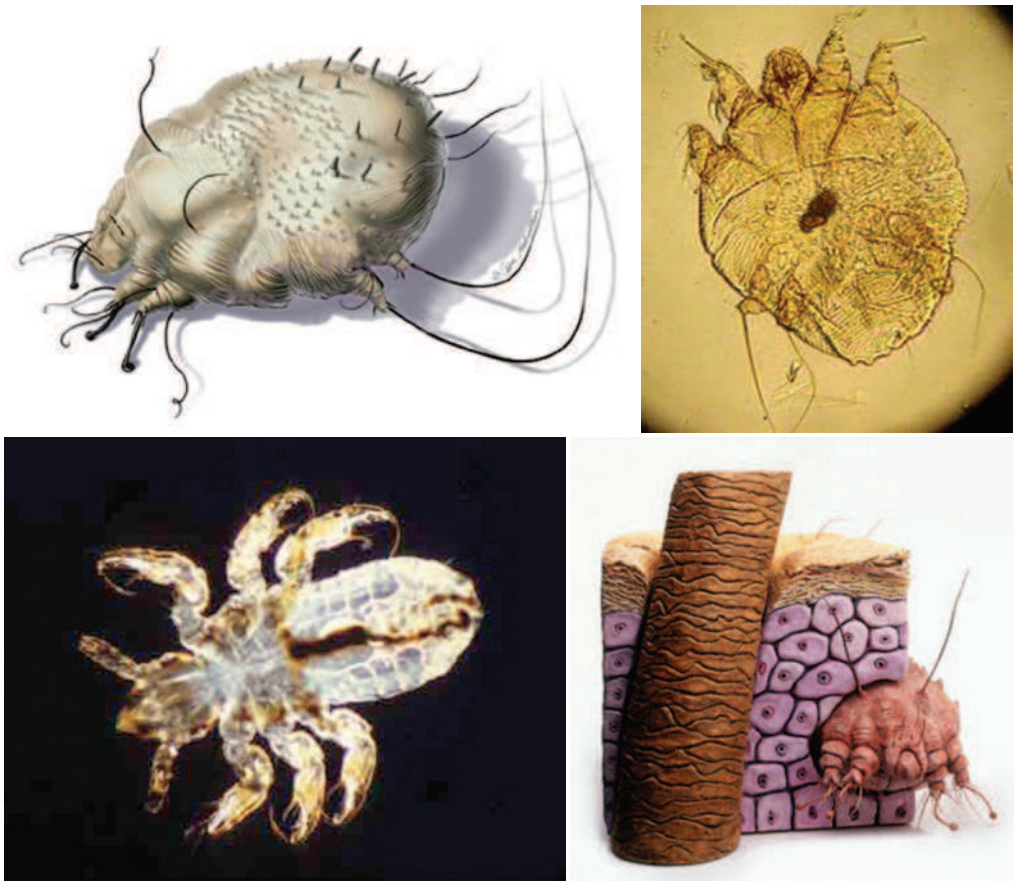

FIGURE 41-58 Scabies mite, *Sarcoptes scabiei* var. *hominis*. *(From Centers for Disease Control and Prevention Public Health Image Library; courtesy Joe Miller, Reed and Crnrick Pharmaceuticals, 1975, and Wikimedia Commons.)*

(Figure 41-58). Unless treated, scabies can persist indefinitely. The adult female is responsible for the symptoms accompanying the infestation. After impregnation, she burrows into the epidermis and remains in the burrow for a life span of about 1 month. She slowly extends the burrow, feeding during travel, during which time several eggs are deposited daily. The ovoid female mite is approximately 0.3 to 0.4 mm long. Numerous transverse corrugations and dorsal spinous processes are adaptations to prevent backward movement in the burrow. The males are much smaller than the females, spend more time on the surface, and have a brief life, dying shortly after copulation. The mite is passed in the vast majority of cases by intimate contact, but adult human scabies mites can survive off the host for 24 to 36 hours at room conditions and still remain infestive.[7] Thus, scabies can be acquired from infested bedding, furniture, and clothing. Outbreaks not related to sexual activity occur frequently among nursing home patients[413] and personnel; epidemics in schools for small children are also common.[228] Scabies became uncommon after World War II (during the war it was a common problem), but since 1964 the disease has increased to epidemic proportions worldwide.[319] Large nosocomial outbreaks with considerable morbidity among patients and health care workers have been widely described.[46,437]

Clinical Aspects

Severe nocturnal pruritus is the hallmark of scabies. Itching also may be provoked by any sudden warming of the body and generally does not involve the face. A warm bath or radiant heat may cause a paroxysm of itching. Because the pruritus is caused by sensitization, 4 to 6 weeks may elapse between infestation and the onset of severe pruritus. Reinfestation is common, because eradicating the disease from all contacts simultaneously is often difficult, and reinfestation after cure results in prompt recurrence of symptoms. Cutaneous manifestations are varied. The primary lesion is the epidermal burrow, a tiny linear or serpentine track, rarely longer than 5 to 10 mm (0.2 to 0.4 inch). The female mite may burrow anywhere on the body, but sites of predilection include the interdigital spaces, palms (Figure 41-59), flexor surfaces of the wrists, elbows, feet and ankles, belt line, anterior axillary folds, lower buttocks, and penis and scrotum. The distribution of burrows in infants may be atypical, with burrows frequently found in the scalp and on the soles (Figure 41-60). In the present epidemic, involving many people with excellent hygiene, cutaneous changes may be almost absent and burrows difficult to find. On the other hand, after the disease

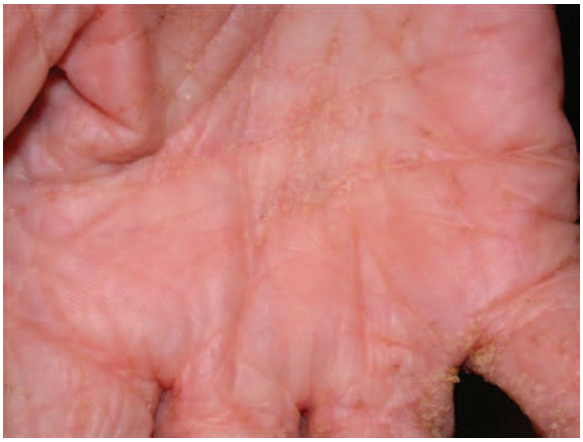

FIGURE 41-59 Scabies—palm of hand. *(From* emedicine.com.*)*

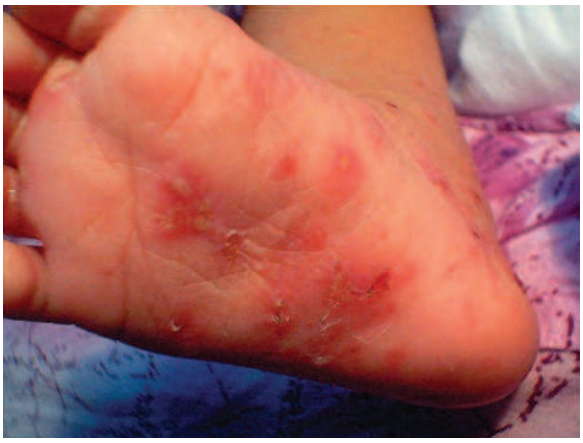

FIGURE 41-60 Scabies—sole of foot. *(From* emedicine.com*.)*

has been present for some time, eczematization, lichenification, impetiginization, myriad nonspecific papules and excoriations, and even urticaria may be present. The burrows are often the least conspicuous of various skin changes. The clinical picture varies with differences in personal hygiene, topical treatments used before diagnosis, and individual scratch threshold. Scabies can also result in secondary skin cellulitis, sepsis, and postinfective complications such as glomerulonephritis.[275,374]

Diagnosis is based on the combination of nocturnal pruritus and cutaneous findings and is confirmed by microscopic examination of burrow contents. The burrow and contents may be collected for examination by scraping with a scalpel blade or by pinching the skin to elevate it and shaving off a superficial layer. Burrows are often inflamed and no longer typical after the disease has been present for some time. The most productive sites to find burrows for examination are finger webs, sides of fingers, wrists, and elbows. Ectoparasites, ova, egg castings, feces, or pieces of mites are diagnostic.

Norwegian scabies is a term describing a particularly severe form of scabies occasionally seen in senile and mentally impaired patients, those with debilitating illnesses, immunosuppressed patients, and underserved populations (Figure 41-61).[289,414,454] Extensive crusting occurs, particularly of the hands and feet.[74] Erythema and scaling may develop, and patients are literally "crawling with mites." This form of scabies is highly contagious, resulting from the incredible number of mites on the patient and in the immediate vicinity.[69,244]

Nodular scabies is another troublesome clinical variation. Persistent pruritic nodules develop, particularly on the male genitalia or in the groin, but usually on some covered body part. Nodules may be the only finding and may persist for months after adequate antiscabetic therapy.

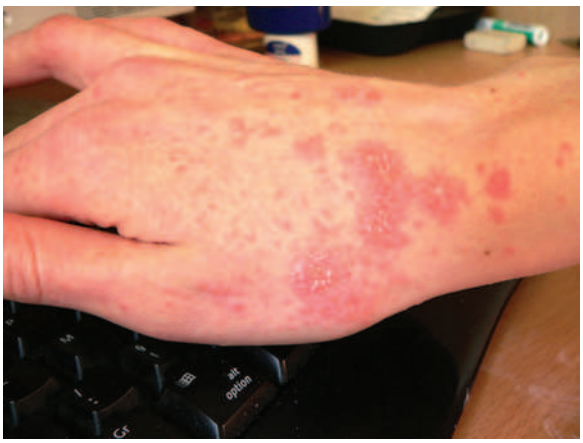

FIGURE 41-61 Case of Norwegian scabies. *(From Wikimedia Commons.)*

Treatment and Prevention

A number of topical treatments are available, including benzyl benzoate (topical), crotamiton (topical), ivermectin (oral), malathion (topical), permethrin (topical), and sulfur compounds (topical).[215] In most cases, a single overnight application of 5% permethrin cream (Elimite) is curative. Permethrin has the advantages of low mammalian toxicity and high cure rate.[418] Even after adequate therapy, symptoms may persist more than a month until the mite and mite products are shed with the epidermis. The chemical must be applied even beneath the fingernails, because ova and live mites are frequently lodged there as a result of frenzied scratching. If the itching has not abated in several weeks, the patient should be reexamined for treatment failure or reinfestation. Permethrin may be used for retreatment, or alternative scabicides may be considered. Lindane lotion is highly effective but has the potential for central nervous system toxicity, and percutaneous absorption may occur.[44] It is contraindicated in infants and pregnant women and persons known to be allergic to hexachlorocyclohexane, and it is reserved for adults with resistant strains. Sulfur in petrolatum (5% to 10%) or another suitable vehicle applied for three consecutive nights is a suitable alternative. Crotamiton 10% cream or lotion applied for two consecutive nights is also used. In the treatment of Norwegian scabies, salicylic acid ointment may be needed to soften scales and permit penetration of the scabicide. Nodular scabies can be a perplexing therapeutic problem and may necessitate intralesional injections of corticosteroids in addition to adequate antiscabetic therapy. Application of crude coal tar to the nodules has been recommended. In France, a combination of 10% benzyl benzoate and 2% sulfiram has proved useful in scabies treatment.[56]

Household contacts and health care workers should be treated simultaneously.[55] Clothing and linens should be laundered the morning after treatment to kill mites that may have strayed from the skin. When many members of a household are infested, live mites may be on the furniture; α-hexachlorobenzene sprays are available.

Control of scabies outbreaks in nursing homes and similar epidemic situations can be almost insurmountable because of the number of patients and contacts that must be treated simultaneously. An uncured case of Norwegian scabies as the focus of an epidemic may be surrounded by millions of mites. Ivermectin is a cheap and effective alternative antiscabetic when taken orally and is useful in institutional epidemics.[15,51,56,148,377] Oral ivermectin is well tolerated, nonirritating to the skin, and does not cause central nervous system side effects because it does not cross the blood brain barrier.[271] A single dose of 250 mg/kg cured 10 of 11 patients with crusted Norwegian scabies as well as all otherwise healthy persons with scabies.[179,287] This agent is also approved for use in humans for strongyloidiasis and onchocerciasis. Albendazole has been used in immunocompromised patients with HIV and crusted scabies.[122]

Zoonotic Scabies

Other burrowing mites similar to the human scabies mite infest animals, such as swine, cattle, horses, mules, sheep, dogs, and wild animals. They are relatively host specific but under conditions of close contact may cause self-limited dermatitis in humans. Because of humans' close association with dogs, the most common animal scabies is canine, caused by *Sarcoptes scabiei* var. *canis*. Studies indicate that the dog scabies mites are able to survive for at least 96 hours on human skin, even burrowing and laying eggs, but whether a perpetual life cycle can be established is not yet determined.[137] Infested dogs have reddish papules, scaling, crusting, and evidence of scratching. Humans develop itchy papules, often with some urtication, and scratching may give rise to varying degrees of secondary infection. The initial lesions are most often on areas of skin that come in contact with dogs: forearms, chest, anterior abdomen, and anterior thighs. Outbreaks are frequently traced to a kennel or litter of puppies. In one case, 15 patients developed an itchy dermatitis

FIGURE 41-62 Chigger mite, Parasitengonina, Trombiculidae, *Erythraeidae sp. (Image posted by andybadger, 2014, Wikimedia Commons.)*

from five puppies in one litter.[78] Human infestation with dog scabies mites subsides spontaneously when contact with dogs is discontinued or when the dogs are cured. The dogs must be treated with scabicides and the human victims with symptomatic therapy for pruritus. Cats, also closely associated with humans, have been known to harbor mites that can infest humans. *Notoedres cati* infestation is seen more often in Czechoslovakia and Japan than is dog sarcoptic scabies.[73]

Trombiculid Mites

Mites of the family Trombiculidae are distributed worldwide. In the United States, the most important species is *Eutrombicula alfreddugesi* (red bug, chigger [Figure 41-62], harvest mite).[132] Another species, *Eutrombicula batatas,* is also indigenous to parts of the United States. Adults are free living and predacious on small arthropods and their eggs, but the larvae are ectoparasites of vertebrates. Wild and domestic mammals, as well as reptiles, serve as hosts. The larval bite causes human dermatitis. Adult mites lay their eggs among vegetation, and newly hatched larvae crawl up on the vegetation, waiting to attach themselves to a passing host. They attach themselves to the skin with hooked mouthparts and feed on blood, falling off when full. However, humans are not good hosts, and larvae usually do not stay long. Severity of the response depends on the species of trombiculid, the irritating qualities of the mites' saliva, and the host's allergic response. The typical bite is a maddeningly pruritic, hemorrhagic punctum that usually becomes surrounded by intense erythema within 24 hours. Bites may number in the hundreds and can be associated with an allergic reaction. Hypersensitivity causes blisters and weeping of clear fluid with crusting. The surrounding area may be purplish in color, with severe swelling, particularly of the feet and ankles (Figure 41-63). The lesions regress in 1 to 2 weeks, but pruritus is persistent and often paroxysmal during this time, with secondary infection in excoriated skin. One pediatric case series reported a "summer penile syndrome," describing a seasonal hypersensitivity reaction caused by chigger bites to the penis in 94 male patients over a 4-month period from June to September.[402]

Treatment is symptomatic and consists of topical antipruritic agents, corticosteroids, systemic antihistamines, and, occasionally, pulse therapy with systemic corticosteroids. Superpotent topical corticosteroid creams and ointments, such as 0.05% clobetasol, applied sparingly to individual bites several times daily, are effective but must be used properly. Prolonged application can result in dermal atrophy, and absorption can be significant if excessive body surface is treated. Phenol (1% in calamine) often is effective. As in all self-limited conditions with no satisfactory cure, home remedies abound, such as meat tenderizer rubbed into the moistened skin. Application of clear nail polish to the individual lesions is a popular home remedy, even though no evidence suggests that this is effective.

Preventive measures consist of avoidance, and insect repellents used on skin and clothing. Clothing pretreated with permethrin has resulted in a 74.2% increase in protection compared with unprotected controls.[48] Other repellents suggested for treating clothing are ethyl hexanediol, DEET, and flowers of sulfur. Permanent residents in infested areas may develop tolerance to repeated bites.

Miscellaneous Mites

Parasitiformes. The Parasitiformes group contains gamasid mites that are parasites of birds, mammals, snakes, insects, and, rarely, humans. In addition to being vectors of disease, gamasid mites are responsible for some cases of dermatitis. The chicken mite, *Dermanyssus gallinae,* is responsible for most of the dermatitis caused by this group. This pest of poultry is widespread and is associated with both domestic and wild birds. Poultry workers are common targets, but other persons may be infested from insidious sources, such as a pet canary or a bird nest near an intake for ventilation or air conditioning. The clinical picture is nonspecific, but the diagnosis may be made by identifying the mite. Treatment consists of symptomatic therapy and eradication of the mite source.

The tropical rat mite *Ornithonyssus bacoti* has also been reported to cause dermatitis from such diverse sources as a rat nest in the attic or a colony of laboratory mice.[77,152] Snake mites have been implicated as a cause of dermatitis. Four members of one family developed a vesicobullous eruption from *Ophionyssus natricis* harbored by a pet python.[383]

Acariniformes. The Acariniformes are a huge group that includes mites that infest foods, feathers, and furs. Individual infestations and larger outbreaks are common, with increased exposure by occupation, resulting in such terms as grocer's itch, miller's itch, and copra itch. Dogs, cats, and rabbits are the primary hosts for mites of the genus *Cheyletiella,* and domestic pets are increasingly the source of mite dermatitis. Pet house cats are often involved.[360]

Mites of the genus *Dermatophagoides* are said to be the principal inhaled allergen of house dust. *Dermatophagoides scheremetewskyi* is an unusual mite that has been found in kapok and feather pillows, in a sparrow's nest, in monkey food, and on rats and other animals. This mite has been reported as the cause of feather pillow dermatitis.[21]

The most common type of dermatitis in this group is grain itch caused by *Pyemotes ventricosus.* This tiny mite parasitizes

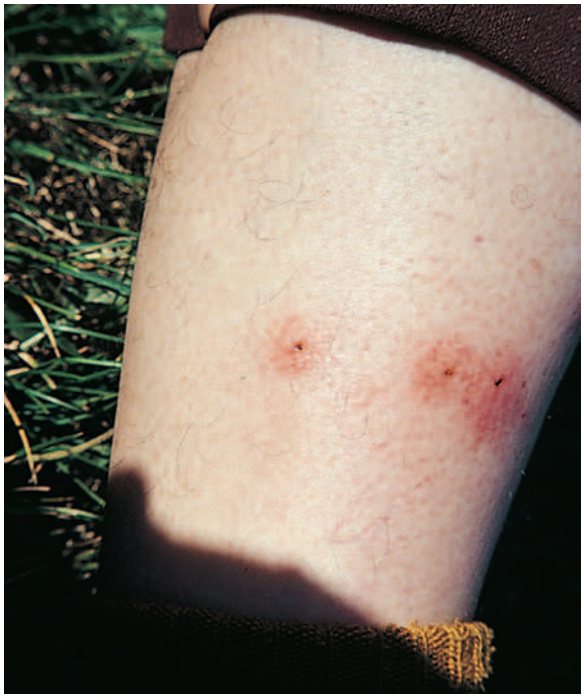

FIGURE 41-63 Chigger bites.

various insects often found in and around grain and straw. It attacks humans when a large mite population has no ready access to normal hosts. Grain itch implies an occupational bias, but outbreaks not involving farmers or rural workers have been described. During a widespread epidemic of *Pyemotes* infestation of farm workers in the midwestern United States between 1950 and 1951, straw used at the Indiana State Fair was infested. During a 2-year period, 642 visitors were treated for grain itch at a dispensary maintained on the fairgrounds, and about 1100 animal attendants and fair workers were treated over the same period at a separate facility. The reservoir of infestation by *Pyemotes* may be quite obscure. Several reported cases were associated with the common furniture beetle *Anobium punctatum* in the floor joists of a house.[145] Therapy is symptomatic. Large-scale eradication measures may require the services of professional exterminators.

GENERAL TREATMENT OF INSECT BITES

Oral antihistamines can be effective in reducing the symptoms of insect bites. Cetirizine was given prophylactically in a double-blind, placebo-controlled, 2-week crossover trial to 18 individuals who had previously experienced dramatic cutaneous reactions to mosquito bites. Subjects given the active drug had a 40% decrease in both the size of the wheal response at 15 minutes and the size of bite papule at 24 hours. The mean pruritus score, measured at 15 minutes and 1, 12, and 24 hours after being bitten, was 67% less than that of the untreated controls. In highly sensitized individuals, prophylactic treatment with nonsedating antihistamines, such as loratadine, may safely reduce the cutaneous manifestations of insect bites.[2,365]

A 3.6% ammonium solution (After Bite) relieves the type I hypersensitivity symptoms associated with mosquito bites. In a double-blind, placebo-controlled laboratory trial, 64% of mosquito-bitten subjects experienced complete relief of symptoms after a single application of the ammonium solution, and the remaining 36% had partial relief lasting 15 to 90 minutes. No subjects treated with placebo reported complete symptom relief.[461]

PROTECTION AND PREVENTION

An integrated approach to personal protection is the most effective way to prevent arthropod bites, regardless of location and species (see Chapter 45). Protection from arthropod bites is best achieved by avoiding infested habitats, wearing protective clothing, and using insect repellents.[153] Insect repellents containing DEET are the most effective products on the market, providing broad-spectrum repellency lasting several hours.[153,362] Currently available repellents that do not contain DEET do not provide protection for as long as DEET-based repellents. DEET's peak duration of action plateaus at a concentration of 50%, with no added benefit from products containing higher concentrations.[153] Additionally, liberal use of higher-concentration products with ethanol bases can lead to increased skin absorption and perhaps neurotoxicity, particularly in young children.[320,362] Topical insect repellents alone do not provide complete protection. Products containing ethyl butylacetylaminopropionate (IR3535) can provide protection for up to 3 hours and can be added to sunscreen lotions without safety concerns or potential side effects.[419,443] A piperidine derivative (Bayrepel) offers 2 to 8 hours of protection similar to DEET but is currently available only in Europe. Large doses of vitamin B_1 have not been proved effective.[153,154]

Newer agents, such as picaridin, and natural products such as oil of lemon eucalyptus are becoming increasingly popular because of their low toxicity.[221] BioUD is an arthropod repellent that contains the active ingredient 2-undecanone originally derived from wild tomato plants. In one recent study, no statistically significant difference in overall mean percentage repellency was found between BioUD and DEET.[39] Mosquitoes can find and bite any untreated skin and may even bite through thin clothing. Deerflies, biting midges, and some blackflies prefer to bite around the head and will crawl into the hair to bite unprotected areas. Wearing protective clothing, including a hat, reduces the chances of being bitten. Treating clothes and hats with permethrin, in addition to spraying DEET on the skin, offers the greatest protection by also repelling any insect that crawls or lands on the treated clothing.[153] DEET-impregnated anklets, wristbands, shoulder, and pocket strips are also available.[220] To prevent chiggers or ticks from crawling up the legs, pants should be tucked into boots or stockings.

Persons traveling to a part of the world where insect-borne disease is a potential threat should be certain to learn about indigenous insects and the diseases they might transmit. Protective clothing, mesh insect tents or bedding, insect repellent, and permethrin spray should be carried.

DELUSIONS OF PARASITOSIS

Patients with delusions of parasitosis are convinced, against all evidence to the contrary, that parasites infest their skin and often their homes and clothing.[329] Ekbom's syndrome is synonymous with delusional parasitosis or "invisible bug" infestations.[44,197,331] No single cause is known for this condition, although some cases may be associated with proved parasitic infestation. The idea may also be suggested by infestations of relatives or acquaintances. Patients older than 50 years are most often female.[412] Patients younger than age 50 years are equally male and female. Most cases of delusions of parasitosis commence with pruritus, which may be accompanied by crawling, creeping, stinging, and burning sensations. The initial reaction is to scratch, replaced soon by digging to remove the "parasites." Self-mutilation and suicidal behavior may develop. Generally, the first contact with a physician is to bring in evidence of the "infestation." Evidence typically consists of scales, lint, crusts, hairs, dust, and small pieces of skin, carefully collected in folded facial tissue or stored in a small box (defined as the "matchbox sign").[44] Medical attention is often sought not to relieve the symptoms but to eradicate the parasites. These patients tend to avoid psychiatrists and consult dermatologists, microbiologists, or general practitioners, but often lose faith in traditional medicine.[158] Patients may take the evidence to an entomologist for identification and may employ professional exterminators for repeated fumigation. Patients may be so convincing that household members or acquaintances come to share the delusion.[84,138]

Many patients with parasitophobia know that their fear is groundless but are still unable to overcome it. Other patients with delusions of parasitosis are convinced that they have an infestation and regard as incompetent the physician who makes the correct diagnosis of no infestation. A complete examination of the patient and the evidence is essential, and investigation of the home or workplace may be indicated. Other medical conditions that may produce cutaneous sensations include liver and renal disease, alcoholism and toxic states, diabetes mellitus, cardiovascular disease, lymphoma, anemia, sideropenia, vitamin B_{12} deficiency, pellagra, peripheral neuritis, dermatitis herpetiformis, drug reactions, and environmental irritants (e.g., arthropods, fiberglass).[212,423,451]

Neuroleptic medications, such as olanzapine,[283] gabapentin,[41] aripiprazole,[30] pimozide, and risperidone,[253] used to treat other monosymptomatic hypochondriacal psychoses, have been found useful in treating this condition.[46,350,357,451] In one group, 14 patients were treated with pimozide and followed for an average of 34 months. Seven had complete remissions, three had relapses that responded to treatment with pimozide, and four were treatment failures.[260] Psychiatric intervention is often unsatisfactory to both the patient and physician. Convinced that the physician is wrong, patients often seek repeated opinions and finally become despondent.

CONCLUSION

Although bites and stings from these insects may cause illness and death in humans, the venoms and secretions from arthropods

provide a promising source of natural bioactive compounds that can be employed in development of new drugs to treat diseases and cancers. The possibility of using active molecules in biotechnological processes can make these toxins a valuable and promising source of natural bioactive compounds.[134]

REFERENCES

Complete references used in this text are available online at expertconsult.inkling.com.

CHAPTER 42
Tick-Borne Diseases

GREGORY A. CUMMINS AND STEPHEN J. TRAUB

There are approximately 850 species of ticks, which rank second only to mosquitoes in importance as arthropod vectors of human disease.[208] Despite our knowledge of ticks and the diseases they carry, there is much that we do not yet know.

Tick-borne disease was first described by Hippocrates, who noted an epidemic of relapsing fever nearly 2500 years ago. In the early 18th century, European physicians described patients with signs and symptoms of Lyme disease. In 1857, David Livingstone, the British explorer of Africa, discovered that a human disease was caused by spirochetes from soft ticks. In the late 1880s, Dr. Arvid Afzelius in Europe described a ring-like lesion in association with the bite of the *Ixodes ricinus* tick. This lesion was almost assuredly Lyme disease, and a causative agent of Lyme disease in Europe, *Borrelia afzelii,* is named after him. The German physician Robert Koch confirmed the role of ticks in cases of tick-borne relapsing fever (TBRF), previously thought to be a variant of malaria, in Africa in 1904.

Ticks are the most common arthropod vectors of disease in the United States (Figure 42-1), and second worldwide, only behind mosquitoes. For those who have outdoor careers or interests in outdoor activities, ticks are unavoidable. Military personnel deployed to Afghanistan over a 3-year period showed a 3.1% seroconversion rate to various arthropod-borne illnesses.[171,323] Ticks and the diseases they transmit may also afflict persons who do not actively participate in outdoor activities, because pets may bring them into the home, where they may survive for weeks before transmitting disease. An analysis of two urban parks in Little Rock, Arkansas, yielded moderate tick populations. Of 273 ticks collected, these included *Amblyomma americanum* and *Dermacentor variabilis;* both species are active in transmitting diseases to humans. Of the *A. americanum* ticks, 98% were positive for *Rickettsia amblyommii* by polymerase chain reaction (PCR), and 7% of the *D. variabilis* ticks were positive for *Ehrlichia chaffeensis* by PCR.[40] Several tick-borne diseases are readily transmissible by blood transfusion, autologous chondrocyte transplantation, and solid-organ transplantation.[262,266,285,379]

New tick-borne infectious diseases continue to emerge, and our awareness of them continues to grow. Ticks have recently been discovered to transmit several diseases formerly unknown, not known in humans, or not formerly known to be transmitted by ticks. Ticks have recently been implicated in the transmission of West Nile virus and other bacteria and viruses, including *Pasteurella* species, *Pseudomonas aeruginosa,* and several novel viral species.[256,296,434]

The overall global warming trend has expanded both the season in which ticks are found and the window of opportunity for exposure to them.[98] The highest altitude at which tick-borne encephalitis (TBE) is found in Europe has risen over the past 30 years[492] and ticks known to transmit diseases have expanded their geographic ranges and are found at higher altitudes than they were in the past.[97,98] Changes in the global environment, combined with human social changes and encroachment on the expanding tick and disease habitats, will likely lead to increases in disease rates related to all vector-borne pathogens, as well as discovery of new diseases.

Ticks often harbor, and may transmit, multiple infectious organisms simultaneously.[8,63,206,307,456] In one region, 24% of *I. ricinus* nymphs were infected with more than one infectious organism.[342] Different genospecies of *Borrelia* have been documented in a single patient with Lyme disease,[108] and it is likely that these multiple strains came from the same tick. In addition to the classic tick-associated illnesses described in this chapter, ticks may also harbor other bacteria. *I. ricinus* ticks may carry *Pasteurella pneumotropica/haemolytica* and other gram-negative organisms, including *Pseudomonas aeruginosa.*[434]

Ticks do not respect geographic borders. Many species of ticks feed on migratory animals, such as birds, that travel great distances.[9,237] Ticks can survive unnoticed on a traveler, or in a traveler's belongings, from one continent to another. At least 29 different species of ticks have been introduced into the United States on imported reptiles.[54] Outdoor pets, especially dogs, are well-documented to carry infected ticks.[28] One study indicated that dog owners are five times more likely to get spotted fever than are non–dog owners.[316] International travel is now easier, and areas not formerly accessible are easily visited. American paleontologists working in Mongolia were tested for North Asian tick typhus, and 4 of the 13 researchers, all asymptomatic, were infected.[265]

Many tick-borne illnesses are commonly researched in biologic warfare laboratories and listed by the Centers for Disease Control and Prevention (CDC) as possible biologic agents.[41,74,226] Tularemia is listed as category A, and Q fever is listed as category B. Most other tick-borne diseases are listed as category C, meaning they are of concern but not easily grown, disseminated, or spread from person to person. Although an outbreak of any of these diseases may produce only a few fatalities, such an outbreak could seriously strain even advanced health care systems.

Most ticks are not species-selective with respect to their hosts, although some exhibit species preference. At least one, which feeds only on the Galapagos giant tortoise,[209] is completely species specific. Some ticks are more anthropophilic (readily feeding on humans) than others. Different stages of a tick species may feed on different animals, and even different orders of animals. For example, *Ixodes scapularis* larvae and nymphs feed readily on mammals, reptiles, and birds, with varying degrees of host preference,[218] whereas the adult ticks feed predominantly on large mammals.

Once the tick initiates feeding, the hypostome (feeding organ) enters the skin. The hypostome contains hundreds of barbs, pointed in reverse direction from the entry into the skin to serve

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FIGURE 42-1 Painting by Sue Oliver depicting the complex interaction among the tick vector, reservoir hosts, causative agent, and humans occurring in Lyme disease. *(Courtesy Sue Oliver.)*

as an anchor (Figure 42-2). During the attachment process, the tick secretes a mixture of salivary proteins containing anticoagulant, antiinflammatory, immunomodulating, and anesthetic properties. These salivary proteins cause a local reaction in the host at the attachment site.[259] The combination of reverse-pointing barbs and proteinaceous cement make embedded ticks difficult to remove.[85]

Ticks belong to the order Acari (which includes mites) and the class Arachnida (which includes spiders and scorpions). Taxonomists divide ticks into two major families: Ixodidae (hard ticks) and Argasidae (soft ticks).

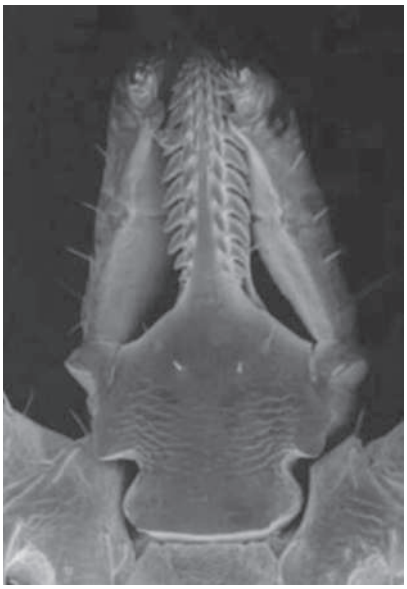

FIGURE 42-2 Electron micrograph of the hypostome of an ixodid tick.

IXODID TICKS

Ixodid ticks, which transmit a plethora of diseases (Table 42-1), possess a hard, shield-like scutum. Their mouthparts are visible from the dorsal view (Figure 42-3). The scutum covers only the anterior portion of the dorsum of the females but the entire dorsal surface of the males. The presence of the scutum limits the size of the tick during feeding. Thus, the body of the female (to a much greater extent than of the male) may expand tremendously with a blood meal, because the tick ingests up to 50 times its weight in blood and body secretions. Ixodid females generally feed and mate only once as adults, whereas males may feed and mate several times. Each female ixodid tick lays several thousand eggs in a single deposition, and then dies. These eggs hatch at approximately the same time, and if a potential host brushes by, thousands of larvae, or "seed ticks," can attach nearly simultaneously. Some species live through all three life stages (larva,

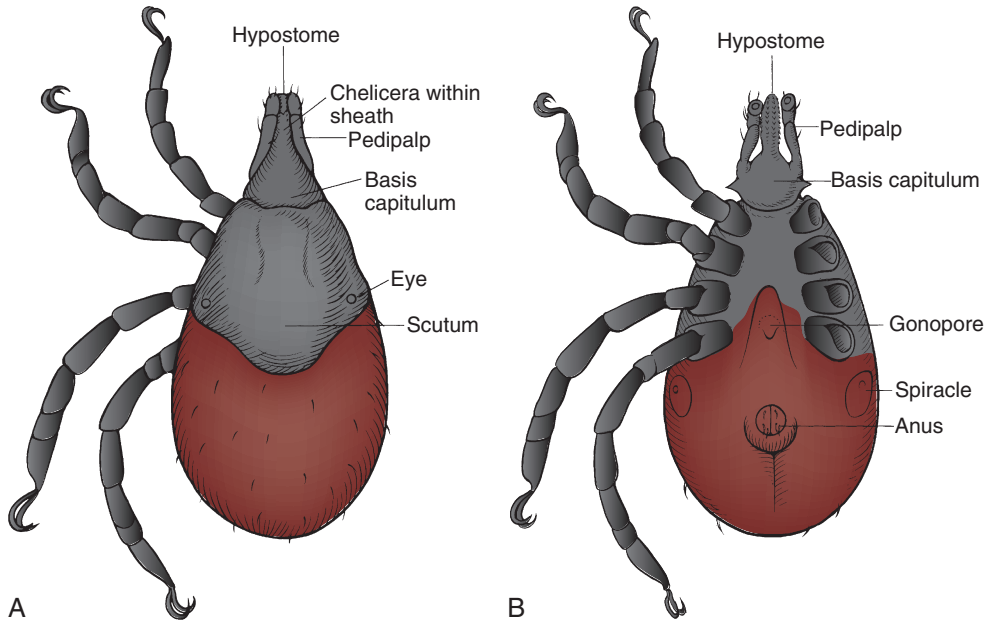

FIGURE 42-3 Tick anatomy. **A,** Dorsal aspect. **B,** Ventral surface.

TABLE 42-1 Ixodid Ticks (Ixodidae)

Tick Species	Transmitted Diseases	Geographic Distribution
Amblyomma americanum (Lone Star tick)	Ehrlichiosis, southern tick-associated rash illness, tularemia, tick bite red meat allergy, Heartland virus	Southeastern and south-central United States, Eastern Seaboard
Amblyomma cajennense (cayenne tick)	Rocky Mountain spotted fever (RMSF), ehrlichiosis	Extreme south Texas, Mexico, Central America
Amblyomma hebraeum	Boutonneuse fever	Southern half of Africa
Amblyomma maculatum (Gulf Coast tick)	Tick paralysis, RMSF, other spotted fever group rickettsial (SFGR) diseases	Coastal eastern United States, inland to Missouri and Kansas, Caribbean islands
Dermacentor andersoni (Rocky Mountain wood tick)	RMSF, Colorado tick fever (CTF), tularemia, tick paralysis, other SFGR diseases	Western half of United States, Rocky Mountain states
Dermacentor marginatum	Omsk hemorrhagic fever, Siberian tick typhus, tick-borne encephalitis (TBE), SFGR diseases	Europe, western half of Asia
Dermacentor nuttalli	Siberian tick typhus, Powassan virus infection, tularemia, SFGR diseases	Northern Asia
Dermacentor occidentalis	Tularemia, RMSF, CTF, tick paralysis, SFGR diseases	U.S. Pacific Coast, Mexico
Dermacentor silvarum	TBE, Siberian tick typhus, Powassan virus infection, SFGR diseases	Eastern Europe, northern Asia
Dermacentor variabilis (American dog tick)	RMSF, anaplasmosis, tularemia, tick paralysis, other SFGR diseases	Entire United States except Rocky Mountain states; Mexico
Haemaphysalis concinna	Siberian tick typhus, TBE	Europe and temperate Asia
Haemaphysalis leachi	Boutonneuse fever	Africa, Southeast Asia, Indonesia
Haemaphysalis spinigera	Kyasanur forest disease	Southern half of India; Indonesia
Hyalomma anatolicum	Crimean-Congo hemorrhagic fever (CCHF)	Northern half Africa, southern Europe, southern Asia
Hyalomma asiaticum	Siberian tick typhus, spotted fever group	South-central Asia
Hyalomma marginatum	CCHF	Africa, southern Europe, southern Asia
Ixodes holocyclus	Tick paralysis, spotted fever group, tick bite red meat allergy	Australia
Ixodes pacificus (western black-legged tick)	Lyme disease, anaplasmosis, babesiosis, Powassan virus disease	United States and Canada west of Rocky Mountains
Ixodes persulcatus (taiga tick)	Lyme disease, Russian spring-summer encephalitis (RSSE), Powassan virus disease	Europe, northern half of Asia
Ixodes ricinus (castor bean tick)	Lyme disease, TBE, babesiosis, tularemia, ehrlichiosis	Northern Africa, Europe, Asia
Ixodes scapularis (black-legged tick)	Lyme disease, RMSF, anaplasmosis, babesiosis, Powassan (deer tick) virus disease	Eastern third of United States
Rhipicephalus sanguineus (brown dog tick)	RMSF, other SFGR diseases, Q fever, ehrlichiosis (in China)	Worldwide

nymph, adult) on a single host (and are thus called *one-host ticks*), whereas most species feed, drop into leaf litter, molt, and seek another host for each life stage (and are called *three-host ticks*).

A typical ixodid tick life cycle is depicted in Figure 42-4. It is typically a 2-year cycle, although in warmer climes it may be 1 year.[126] The tick hatches as a six-legged larva and attaches to a host, often a rodent, bird, or reptile. After feeding for approximately 3 to 5 days, it drops off and molts to the eight-legged nymph. The nymph hibernates in nesting material, leaf litter, or soil and becomes active again in the spring. It then attaches to and feeds on a larger animal for 4 to 9 days, after which it again drops off (usually into leaf litter) and molts a second time to the adult stage. The mature tick attaches to a third host, on which feeding and mating may occur. Large mammals, such as deer, may support thousands of ticks.

Ticks do not find their hosts haphazardly. The tick's front legs are equipped with chemoreceptors to detect respiratory gases (especially carbon dioxide) and proprioceptors to detect fine vibrations. Nymphs and adults climb up grass blades and "seek" a host ("seeking" or "questing" behavior), holding up the front legs that contain small barbs that help them attach. The ticks hook onto the host's fur, feather, scale, or skin and find a place to attach, often after climbing to an area with a relatively abundant blood supply.[251] Ixodids are generally on their host for hours to a day or more before they begin to feed, and the feeding process may last from days to weeks. The duration of feeding depends more on the host than the tick; feeding on reptiles, for example, occurs more slowly than on other animals.

A blood meal and mating, which usually occurs on the host, are prerequisites to laying eggs. Females, once engorged, drop off the host, often in the night or early morning hours and typically into an animal's nest or bedding area, and lay eggs nearby in leaf litter or nest material. This provides a meal for the larval ticks upon hatching.

Ixodid ticks typically require dense vegetation and prefer areas of high animal traffic and humidity, such as leaf litter or moist soils. Questing adults are often found on animal paths or game trails.[168] They are found in temperatures from freezing to more than 38° C (100° F), although they move more slowly at cold temperatures. Ticks survive the coldest winters without difficulty.

ARGASID TICKS

Argasid ticks do not exhibit sexual dimorphism or have a hard scutum. The mouthparts are not visible from above. The body typically has a wrinkled, leathery appearance (Figure 42-5). Argasid ticks move quickly in comparison to the ixodids.

Argasid ticks usually feed completely in 10 to 30 minutes and do not cause pain when feeding. They generally feed at night, often moving unnoticed while their hosts sleep. After feeding, they drop off the host and lay dozens to a few hundred eggs and then repeat the cycle many times. The remainder of the life cycle is similar to that of the ixodids, except that nymphs have multiple stages. Argasid ticks are generally found in animal burrows, dens, and caves, and in the floors and walls of huts and cabins. They thrive in hot, dry climates.

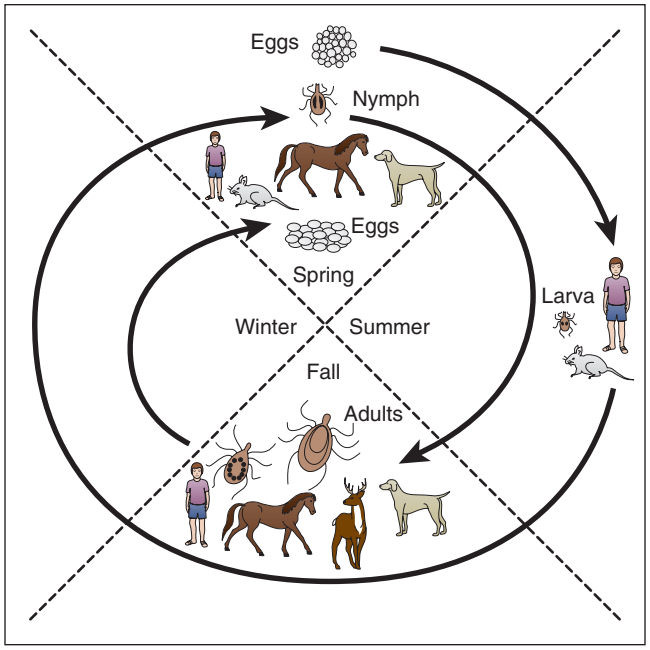

FIGURE 42-4 Life cycle of *Ixodes scapularis.* The cycle of ixodid ticks typically spans 2 years and includes three blood meals in the spring. The adult female tick releases her eggs, which hatch as six-legged larvae, during the summer. The larvae take blood meals that last approximately 2 days. Larval ticks enter a dormant phase with cooler fall weather. The ticks molt in the spring, entering the second phase of their life cycle as eight-legged nymphal ticks. In the late spring or summer, nymphal ticks take blood meals that typically last for 2 to 3 days. The nymphal ticks molt as eight-legged adults in the fall. The adults mate on white-tailed deer. After mating, the male dies, but the female takes one more blood meal before she lays her eggs and dies. *(Modified from Habicht GS, Beck G, Benach JL: Lyme disease,* Sci Am *257:78, 1987.)*

TICKS AS POISONOUS ARTHROPODS

TICK PARALYSIS

In 1912, Todd[445] recognized that an acute, ascending, flaccid motor paralysis followed the bite of certain ticks. Tick paralysis has been reported worldwide, although most human cases occur in North America and Australia.[413,476] Forty-three species of ticks have been reported to cause tick paralysis.[72] Human cases in North America are usually caused by *Dermacentor andersoni,* although *Dermacentor variabilis, Amblyomma americanum* (Figure 42-6), *Amblyomma maculatum,* and *Ixodes scapularis* have also been implicated.[476] In the United States, the Pacific Northwest and Rocky Mountain areas account for the vast majority of cases. In Australia, *Ixodes holocyclus* is primarily associated with the disease, although *Ixodes cornuatus* has been implicated.[183,186]

FIGURE 42-5 Soft ticks (family Argasidae) have a leathery integument rather than the tough scutum of hard ticks (family Ixodidae). North American argasid ticks of the genus *Antricola* have a tuberculated, or "knobby," roughened integument, as seen here from a close-up perspective. These ticks are parasites that use bats as hosts. *(Courtesy CDC, 1975.)*

FIGURE 42-6 Lone Star tick *(Amblyomma americanum),* implicated in cases of tick paralysis in North America. *(Courtesy Sherman Minton, MD.)*

Tick paralysis usually occurs during the spring and summer months (April to June),[72,113] when nymphs and mature wood ticks are feeding. Most cases occur in areas where ticks are endemic. Patients in urban areas may be affected if they have recently traveled,[179,183] and the diagnosis should not be excluded on the basis of geography alone. Children are affected more often than are adults, with most cases reported among girls less than 10 years of age. Among children, girls are affected twice as often as boys, probably because ticks on the female scalp are hidden in longer hair.[1] Among adults, men account for most cases, presumably because of increased occupational and recreational exposures to tick habitats.

A neurotoxic venom, ixobotoxin, is secreted from tick salivary glands during a blood meal and causes the paralysis. The venom inhibits membrane sodium flux, resulting in diminished acetylcholine release at the neuromuscular junction.[183,318] Electrophysiologic measurements in humans consistently demonstrate slowed motor conduction and reduction in muscle action potential amplitude.[117,311,438] The neurotoxin may also increase the stimulatory current potential necessary to elicit a response at the motor end plate.[239] The toxin appears to also have central effects.

Tick paralysis in humans typically develops 5 to 6 days after an adult female tick attaches. Initially, the victim may be restless and irritable and may complain of paresthesias in the hands and feet. Over the next 24 to 48 hours, an ascending, symmetric, flaccid paralysis develops. Deep tendon reflexes are lost. Weakness is initially greater in the lower extremities, but within 1 to 2 days, severe generalized weakness may develop, accompanied by bulbar and respiratory paralysis. Some victims develop cerebellar dysfunction with incoordination and ataxia.[1,158] Exceptions to this general pattern are reported, including facial paralysis[334,337,347] (often when the tick has attached in the auditory canal) and cranial nerve dysfunction out of proportion to muscular weakness.[102,158,181]

Case reports of Australian tick paralysis suggest that it may be more severe than its North American counterpart. Victims often appear more acutely ill. Paralysis may continue to progress for 48 hours after tick removal, and recovery may be prolonged.[19,102,336] However, one report of six cases in Australian children noted little difference in the course between Australian and North American patients.[183]

Diagnosis is made solely on clinical grounds, because specific diagnostic laboratory tests are not available. White blood cell (WBC) count and cerebrospinal fluid (CSF) analyses are normal.

If the tick is on the scalp, magnetic resonance imaging performed as part of the diagnostic workup may identify it incidentally as a small nodule that is hypointense to fat on T1 imaging, is isointense to fat on T2 imaging, and does not enhance with gadolinium.[53] Diagnosis is confirmed by resolution of paralysis after removal of the tick. If undiagnosed, tick paralysis may be fatal, at a rate as high as 12% in the older literature, prior to widespread therapeutic use of mechanical ventilation.[387]

Although a 60-year metaanalysis suggests that misdiagnosis has been more commonly reported in recent years,[113] it is not clear if this represents an actual trend or simply publication bias. The most common misdiagnosis is Guillain-Barré syndrome. The clinical features of the two diseases are strikingly similar, although ataxia has been more common in tick paralysis.[113] The results of electrophysiologic studies are often indistinguishable.[457] Although the protein level of CSF in patients with Guillain-Barré syndrome is often elevated, this finding may be absent in up to 30% of patients,[14] particularly in the early stages of the disease. For this reason, an abnormal CSF protein analysis favors a diagnosis of Guillain-Barré, but a normal analysis does not exclude it. The differential diagnosis should also include botulism, myasthenia gravis, and potassium-associated paralyses, which can all be assessed via specific testing. Misdiagnoses have included rabies, botulism, diphtheritic polyneuropathy, chronic polyneuropathy, and postinfectious polyneuritis.[113,312]

Treatment includes removal of the offending tick followed by supportive care. Severely affected patients may require ventilatory support. Tick antivenom from hyperimmunized dogs has been developed for Australian tick paralysis and may be beneficial in victims with severe disease, although treated patients have a high incidence of acute allergy and serum sickness.[186,336]

TICK BITE RED MEAT ALLERGY

In 2009, allergy researchers in Virginia became aware of patients presenting for medical care in the southeastern United States for urticaria, hives, gastrointestinal symptoms, airway difficulties, and anaphylaxis. A few years prior, allergy researchers were investigating severe anaphylactic reactions, some fatal, related to infusion of cetuximab. These reactions were much more common in the southeastern United States, at a rate approximately 35 times that in other areas of the country.[81,330] Many of these reactions occurred on first infusion. The immediacy of the reaction strongly suggested prior exposure to some component of the drug. Investigations of these two allergic phenomena led to a common link, a mammalian oligosaccharide epitope, galactose-alpha-1,3-galactose, or alpha-gal.[84,216] Alpha-gal is a sugar contained in all mammalian cells except those of old world primates (including humans). Cetuximab is a monoclonal antibody chemotherapy agent derived from a mix of mouse and human cells; use of the mouse cells is how the alpha-gal was introduced into cetuximab.

The location of the allergic reactions in the southeastern United States and reports of exposure of the patients who had these reactions to prior bites from ticks, predominantly the Lone Star tick *Amblyomma americanum,* led the allergists to the link to alph-gal.[86] The severity and timing of the reaction caused them to believe the reaction was IgE mediated. When questing ticks feed on mammals in the wild, they ingest sugars from these animals, including alpha-gal. These sugars enter the ticks' salivary proteins, which are transferred into humans when they are bitten by the ticks. Humans are naïve to an immune response to this sugar until they are bitten by a tick.

Reexposure to the sugar, either via an administered medication or ingestion of red meat, results in a reaction of varying severity. If red meat is eaten, the reaction usually occurs 4 to 8 hours after eating. This reaction can occur up to several months after a tick bite, and is more severe closer to the time of the tick bite. The severity of the reaction depends on the amount of circulating IgE and the amount of alpha-gal ingested during a meal. Patients who eat a greater quantity of meat suffer a more severe reaction.[84] The levels of IgE in blood sera are noted to increase almost immediately after a tick bite.[84] People who subsequently eat red meat may or may not suffer a reaction. The reaction is more severe in persons who are frequently exposed to ticks, because there is a larger IgE response in these individuals.[84]

Tick bite red meat allergy is also found in the eastern half of the United States and worldwide, with different tick species inciting the response in different geographic regions. *Amblyomma americanum* is the predominant cause of this reaction in the eastern portion of the United States, most notably in the southeastern United States. In Europe, *Ixodes ricinus* causes the reaction, but in Australia, it is *I. holocyclus.*[85,452] Patients in Japan and Korea have had reactions after consuming red meat after a tick bite, though the tick species is not known at this time.[471] Patients in Africa have had IgE to alpha-gal documented in their blood or sera, but there are not yet reports of related allergic reactions to red meat. Nonmammalian meats, such as poultry and fish, do not result in an IgE response, because they do not contain alpha-gal. In some cases, minimal mammalian protein, as found in gelatin in certain vitamins and milk, is sufficient to produce the symptoms.[85]

Diagnosis is by clinical presentation and history regarding tick exposure and diet. If tick bite red meat allergy is suspected, IgE levels for alpha-gal can be measured to confirm the diagnosis.

To avoid this affliction, one should avoid tick bites, mammalian cell-derived immune modulating medications in temporal proximity to a tick bite, and ingestion of red meats.

PAJAROELLO TICK BITES

In mountainous regions of coastal southern California, Mexico, and South America, the pajaroello (pajahuello) tick *Ornithodoros coriaceus* readily bites cattle, deer, and humans. The pajaroello is of a reputation such that it was depicted in ancient petroglyphs.[138] The bite may be painful and often results in a 10- to 30-mm (0.4- to 1.2-inches) erythematous papule that may become edematous and progress to ulceration or necrosis.[139] The lesion gradually resolves over 3 to 4 weeks. Treatment consists of local wound care and administration of tetanus toxoid (if needed). Secondary infection is not uncommon. Although no data strongly link the bite of *O. coriaceus* to human miscarriage, it is linked to epizootic bovine abortion, also called foothills abortion, a disease long known among cattle ranchers in endemic areas.

TICKS AS VECTORS OF INFECTIOUS DISEASES

Ticks transmit a wide variety of infectious agents, and may act either as amplifiers or as reservoirs for a given infectious agent.[208] In the *agent-tick amplifier system,* an immature tick ingests the microorganism while feeding on an infected vertebrate, and the vertebrate is the reservoir for the disease. The pathogen replicates in the tick and is passed transtadially, from larval to nymphal to adult stage. The maturing tick transmits the agent to other vertebrate hosts when it feeds. A key epidemiologic feature of this system, transtadial survival of microorganisms, is common in ticks but rare in other hematophagous insects. This important difference is primarily due to the fact that tick anatomy is relatively unchanged as the tick molts.[208]

In the *agent-tick reservoir system,* the microorganism is passed transovarially from one generation of ticks to the next. The agent replicates within the tick and depends solely on the tick population for survival. The agent may also replicate within a vertebrate host, allowing for amplification and increasing the density and prevalence of the microorganism, but it need not do so.

Table 42-2 lists the major tick-borne diseases in the United States. Lyme disease is the most common one in the United States and throughout the world.[417] Tularemia, ehrlichiosis, anaplasmosis, Rocky Mountain spotted fever, and other spotted fever group rickettsioses are observed throughout the United States and continue to produce significant rates of morbidity and mortality. TBRF and Colorado tick fever (CTF) occur in the western states and are particularly likely to affect campers, hikers, hunters, and others who frequent wilderness areas.

TABLE 42-2 Major Human Tick-Borne Diseases in the United States

Disease	Organism	Major Vectors	Geographic Distribution
Anaplasmosis	*Anaplasma phagocytophilum*	*Ixodes scapularis*	Eastern portion of United States
Babesiosis	*Babesia microti*	*Ixodes scapularis, I. Pacificus*	Coastal southern New England and mid-Atlantic states, West coast
Colorado tick fever	*Orbivirus*	*Dermacentor andersoni*	Rocky Mountain states, California, Oregon
Ehrlichiosis	*Ehrlichia* spp. (numerous)	*Amblyomma americanum,* unknown vector in California	Eastern portion of United States, California
Lyme disease	*Borrelia burgdorferi*	*Ixodes scapularis, I. pacificus, I. persulcatus, I. Ricinus*	Coastal mid-Atlantic states, northern West Coast, Wisconsin, Minnesota
Other spotted fever group rickettsial (SFGR) infections	Numerous *Rickettsia* spp.	*Dermacentor andersoni, D. variabilis, Rhipicephalus sanguineus, Amblyomma cajennense, Amblyomma americanum, Amblyomma maculatum*	South-central states, coastal southern states, Texas, Arizona, New Mexico (southern border states)
Rocky Mountain spotted fever (RMSF)	*Rickettsia rickettsii*	*Dermacentor andersoni, Dermacenter variabilis*	South-central states, coastal southern states
Tick bite red meat allergy	IgE-mediated allergic reaction	*Amblyomma americanum*	Eastern half of United States
Tick-borne relapsing fever	*Borrelia hermsii, Borrelia turicatae, Borrelia parkeri*	*Ornithodoros hermsi, O. turicata, O. parkeri*	Worldwide; most often rural and wilderness areas of western United States
Tularemia	*Francisella tularensis*	*Amblyomma americanum, Dermacentor andersoni, Dermacenter variabilis*	South-central states, Montana, South Dakota

Awareness by patients and physicians of the possibility of tick-related diseases leads to earlier recognition and initiation of appropriate antibiotics and supportive care.

TICK-BORNE BORRELIAL DISEASES

The genus *Borrelia* belongs, along with *Treponema* and *Leptospira,* to the order Spirochaetales, which are helical bacteria. Borreliae are usually 10 to 20 μm long, with 3 to 10 spirals.[145] When live cultures are viewed under dark-field microscopy (Figure 42-7), the organisms are very motile. *Borrelia* species can be stained with aniline dyes, a feature that readily distinguishes them from *Treponema* and *Leptospira* genera.[410] Borreliae can also be stained with Wright and Giemsa stains, although obtaining the organisms from blood is extremely difficult with most diseases (TBRF being an exception). Culturing *Borrelia* species is technically challenging and must be done in properly formulated media incubated under specific conditions in specially equipped laboratories. In the relapsing fever borreliae, strains cannot be differentiated on the basis of morphology but are classified according to specificity of the tick-spirochete relationship, the range of animals susceptible to infection, and cross-immunity.[21]

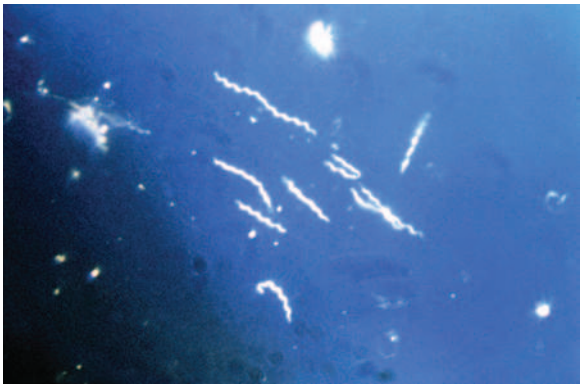

FIGURE 42-7 Lyme disease spirochete viewed under dark-field microscopy. *(Courtesy CDC Public Health Information Library.)*

The reservoir hosts, vectors, different species, and even different strains of *Borrelia* vary tremendously in different geographic areas.[52,248,267,269,451,466] The medically important diseases caused by *Borrelia* species in the United States include Lyme disease (caused by *Borrelia burgdorferi* and *B. bissettii*), and TBRF (caused by *B. recurrentis*). The Institut Pasteur currently lists more than a dozen species and nearly 200 different strains of borreliae worldwide. Other important *Borrelia* species are found regularly as more is learned about the spirochetes, hosts, and reservoirs.[383,388]

LYME DISEASE

In Europe, the rash known as erythema chronicum migrans (ECM) has been associated with the bite of *I. ricinus* for more than one hundred years.[4]

In the mid-1970s, a team from Yale University School of Medicine investigated a cluster of cases of arthritis in children near Old Lyme, Connecticut. The arthritis was initially thought to be juvenile rheumatoid arthritis. The clustering, rural setting, and some response to penicillins pointed to an infectious, most likely arthropod-borne, cause. The seasonality and frequent finding of a rash pointed to a tick vector.[417,421,427]

Epidemiologic evidence implicated the deer tick, *I. scapularis,* as the likely vector of what is now called Lyme disease. In 1982, Burgdorfer and associates[52] isolated a treponeme-like spirochete, *B. burgdorferi,* from the midgut of *I. scapularis* ticks collected from a known endemic focus of Lyme disease.[30,34] Subsequently, sera from nine patients clinically diagnosed with Lyme disease yielded high antibody titers to the spirochetes by indirect immunofluorescence.[2] Isolation of *B. burgdorferi* from the blood, CSF, and skin lesions of affected patients finally confirmed the spirochetal basis of Lyme disease.[30,422]

More than 12 species of *Borrelia* are now known to cause some variation of Lyme disease throughout the world. Most of these species cause disease in specific geographic regions and are transmitted almost exclusively by *Ixodes* ticks. In addition to numerous species of *Borrelia,* there are numerous strains of each species, and ongoing research is likely to lead to discovery of more. A retrospective analysis of 100,545 specimens collected in the United States from 2003 to 2014 revealed a new pathogenic *Borrelia burgdorferi* sensu lato genospecies (proposed name

Borrelia mayonii).[348a] This was found using polymerase chain reaction (PCR) targeting the oligopeptide- binding protein OppA1 of *B. burgdorferi*. None of the new species was found in specimens before 2012. All cases came from Minnesota, Wisconsin, and North Dakota. The spirochete counts in these cases may be up to 8000 times that of typical *B. burgdorferi*. Compared to clinical presentations seen with traditional *B. burgdorferi* infections, this new species results in atypical presentations—primarily more acute neurologic symptoms, diffuse macular rash, and nausea and vomiting. The new species results in much higher spirochete loads and symptoms, similar to those seen in borrelial relapsing fever. PCR using OppA1 is not routinely used. Traditional serologic testing and PCR may not identify this new species and can lead to false negatives. Treatment for illness related to this new species is presumed to be the same as that for illnesses generated by other *Borrelia* spp.

Borrelia burgdorferi is the primary agent in the United States, Europe, and Asia. United States isolates of *B. burgdorferi* demonstrate regional genetic heterogeneity,[290] and genetic comparison of European and North American strains indicates common ancestry.[346] *Borrelia burgdorferi, B. garinii, B. afzelii, B. lusitaniae,* and *B. valaisiana* are currently recognized causative agents of Lyme disease in Europe, and still more agents are being identified.[463] *B. burgdorferi* has been isolated in Morocco from *I. ricinus* ticks.[383] *Borrelia bissettii* (formerly *Borrelia* genomic group DN127) has been found in California, Florida, Colorado, and multiple southeastern states, as well as Europe, and is responsible for Lyme disease in those areas and most likely other areas yet to be discovered.[345,388,458] Overall, *Borrelia* species are found nearly across the globe, and new species and geographic areas are being discovered regularly.

Epidemiology

Lyme disease surveillance began in 1982 at the CDC, and Lyme disease became a nationally reportable disease in 1991. Since 2000, Lyme disease has accounted for more than 90% of all reported cases of vector-borne illness in the United States.[199]

In the United States in 2001, 17,029 cases were reported in 43 states; in 2009, there were 38,468 cases from 50 states and the District of Columbia.[77] As of December 13, 2014, CDC data show 28,416 cases reported.[77] Nineteen states reported 93.4% of the cases. New York reported the highest incidence of Lyme disease, with 3,581 cases.[77] Reasons for recent increases in prior years are multifactorial and most likely include public and physician awareness, increases of reservoir host populations, increased geographic range of the vectors, and efflux of people from urban cores to suburban areas, all of which result in more human-host-vector interfaces. Lyme disease is grossly underreported in many areas.[52,90,299] The decrease seen in 2014 is perhaps due to human host behavioral changes, such as avoiding prolonged exposure to tick-infested areas and prompt removal of attached ticks.

Patients of any age may become infected, but the incidence has two peaks: among children aged 5 to 14 years and among adults aged 50 to 59 years. Fifty-nine percent had an onset of illness in June and July, and 78% of the cases occurred in the months of May through August. Fewer than 7% of the cases began in winter months. The disease can be found year round.[62]

Lyme disease is a worldwide problem, diagnosed or found on all continents except Antarctica. However, *Borrelia burdorferi* has been detected by serology and DNA sequencing in king penguins from the French Southern and Antarctic Lands' Crozet Archipelago in the Southern Indian Ocean.[389] Sporadic cases in Australia have yet to be proved as having originated in Australia and may have been imported in patients who spent time in areas endemic for Lyme disease.[211,377] PCR analysis of approximately 12,000 field-captured ticks in Australia failed to find any evidence of *Borrelia*-like infection.[378] Other tick-borne pathogens have been isolated or found by antibody evidence in Australian ticks, humans, and animals. These include *Babesia, Bartonella, Ehrlichia, Anaplasma,* and *Rickettsia* species.[291]

The primary vectors for Lyme disease worldwide are ticks of the *I. ricinus* complex. In the eastern half of the United States, the primary vector is *I. scapularis,* known more commonly as the black-legged tick or deer tick. The primary vector in the western United States is *Ixodes pacificus,* the western black-legged tick.[328] In Europe, Asia, and Northern Africa, *I. ricinus,* the castor bean tick, is the main vector. In Japan, China, and eastern Russia, it is *Ixodes persulcatus,* the taiga tick. Transmission of the spirochetes to humans is almost exclusively by infected nymphs or adults. Larvae are usually not infected until they feed on an infected host, pick up the spirochetes from this host, and then become infective as a seeking nymph. Unlike other tick-borne diseases, there is minimal transovarial transmission of the causative spirochetes from an infected female to her eggs.[322,343]

Transmission of the disease in the United States outside of the areas in which *I. ricinus* complex ticks are found, although rare, does occur, thus implicating other vectors. Several other tick species (*Amblyomma, Dermacentor, Haemaphysalis, Rhipicephalus,* and other *Ixodes* species) have been found infected with the spirochetes, but have not been demonstrated to transmit the spirochetes to a host.[276,314] Various nontick arthropods, including some biting flies, mosquitoes, and the cat flea, have been shown to harbor spirochetes, but they do not transmit spirochetes to a host or do so very rarely.[272,277,363,442] In many of the nontick arthropod cases, disease transmission is presumed to take place by a "dirty syringe" type of mechanism, in which the vector feeds partially on a spirochete-laden host, only to momentarily later inject the spirochetes into the next host.[272,277]

Reservoir host species are numerous, and vary worldwide depending on location and climate. At least 125 species of mammals, birds, and reptiles are important hosts to *Ixodes* ticks throughout the world.[233] In the northeastern and north-central United States, the preferred host for *I. scapularis* larvae and nymphs is the white-footed mouse, *Peromyscus leucopus.* In Europe and Asia, various rodents are the primary hosts for the larvae and nymphs. Larger mammals, most often deer, usually serve as hosts for the adults. In warmer areas of the world, there is a much wider variety of hosts, including reptiles, birds, and mammals. In these climes, ticks show minimal preference as to available hosts.[218]

In the southeastern United States, the cotton mouse *(Peromyscus gossypinus),* the cotton rat *(Sigmodon hispidus),* and other mammals, reptiles, and birds serve as primary hosts for larvae and nymphs.[126,233,327] Bird species readily harbor spirochetes, whereas lizard species do not appear to do so.[92] The reptilian hosts, almost exclusively lizards, account for a large amount of the immature (larval and nymphal) tick population.[327] Lizard sera and mule deer sera appear to deactivate spirochetes via a borreliacidal protein.[250,451] A recent study showed 54% of nine species of lizards from Florida and South Carolina had positive PCR for DNA from *B. burgdorferi*.[83] The high numbers of ticks parasitizing lizards in the southeastern United States, instead of mice, and the lizards' possible ability to deactivate the spirochetes may partially account for the clinical differences in Lyme disease epidemiology due to ecologic variations between the southeastern United States and other geographic areas.[92,250]

Migration of mammalian and avian hosts is one way ticks spread into new areas, often carrying various diseases with them.[99,237] Host populations increase when appropriate predators are absent; these fluctuations can amplify tick populations tremendously. One deer can host several thousand ticks of various stages; deer population studies have shown that decreasing or eradicating deer populations leads to marked decreases in tick populations in subsequent years.[167,354]

The interaction between spirochete and host begins when the spirochete enters the salivary gland of the tick during the feeding process. Transmission to another vertebrate also occurs during the feeding process, which explains why disease transmission usually occurs only after a tick has been on a host for more than 24 hours. *B. burgdorferi* spirochetes show no transmission to mice in less than 24 hours, with maximal transmission occurring between 48 and 72 hours.[112] Another study showed that tick attachment for longer than 72 hours was more likely to transmit disease.[409]

Clinical Manifestations

Lyme disease has a myriad of constitutional, dermatologic, neurologic, cardiac, and musculoskeletal symptoms. The most

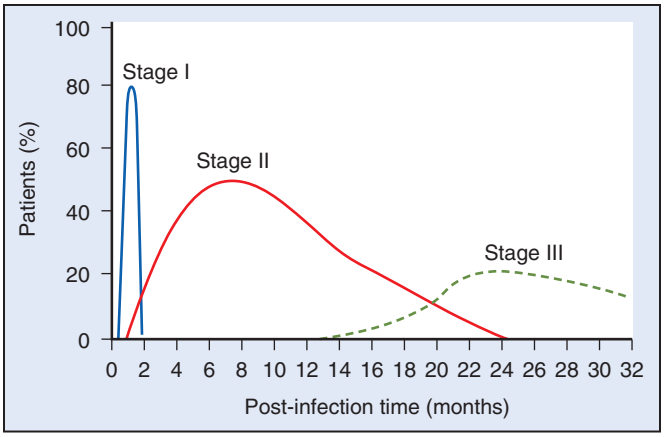

FIGURE 42-8 Time course and frequency of symptoms in Lyme disease. Approximately 50% of victims report a recent tick bite. The initial stage I symptoms occur in approximately 70% to 80% of infected individuals. Weeks after the initial tick bite, the skin, nervous system, and joints are most often affected as the spirochete spreads hematogenously. Stage II symptoms typically begin 4 to 10 weeks after the initial infection and occur in approximately 50% of untreated patients. Stage III typically starts much later, often 1.5 to 2 years and, rarely, more than 5 years after initial infection. *(Modified from Schmid GP: Epidemiology and clinical similarities of human spirochetal diseases,* Rev Infect Dis *11[Suppl 6]:S1460, 1989.)*

common are vague myalgias, headache, fatigue, neck stiffness, and arthralgias. Rarely, gastrointestinal complaints or ocular complaints, such as conjunctivitis, iritis, and keratitis, may be reported. Collectively, these symptoms are difficult to distinguish from a benign viral syndrome, which is one of the reasons Lyme disease is easily misdiagnosed by both patients and physicians.[16]

Lyme disease is multisystemic and multiphasic. The disease is classically divided into three stages based on the chronologic relationship of symptoms to the original tick bite, with different clinical manifestations at each stage (Figure 42-8). There is no clear delineation distinguishing one stage from another, however, and signs and symptoms of different stages often overlap.

The disorder usually begins as a localized infection with constitutional findings and associated symptoms (stage I) (Box 42-1).[163,319] Within days to weeks, spirochetes may disseminate through blood or lymph, and neurologic, cardiac, or joint abnormalities may develop (stage II). Finally, chronic, persistent infection of the joints, nervous system, skin, or eyes may occur months or years later (stage III).

Although the exact roles of the infecting spirochete, spirochetal antigens, and host immune responses are unclear, tissue invasion and persistence of infection probably cause many of the later manifestations of Lyme disease. This concept is supported by isolation of *B. burgdorferi* from blood, skin lesions (erythema migrans), and CSF.[30,425] The organism has also been identified in the eye,[423,424] myocardium,[280,416] and synovium.[405] Patients at all stages of disease respond to appropriate antimicrobial therapy, and early treatment generally leads to an excellent long-term prognosis.

BOX 42-1 Lyme Disease: Stage I

Incubation: 7-10 days (range, 3-32 days)
Duration: 28 days (range, 1-14 months)

Symptoms (Incidence)
Erythema migrans (60% to 89%)
Mild lymphadenopathy (23%)
Low-grade fever (19% to 39%)
Mild fatigue and malaise (54%)
Neck stiffness (35%)
Mild arthralgia and myalgia (44%)

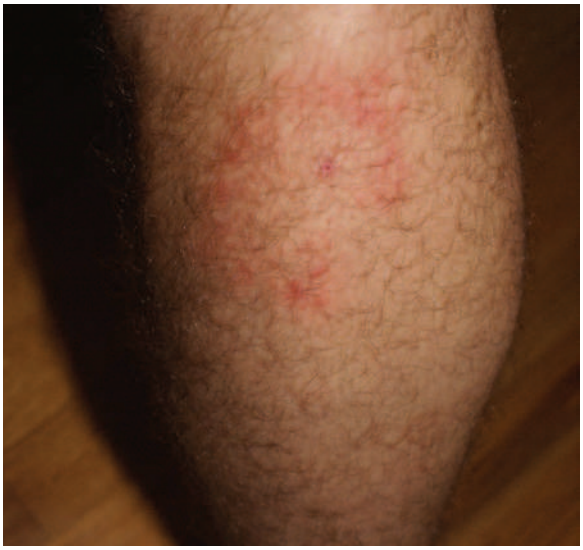

FIGURE 42-9 Author's leg with classic Lyme disease erythema migrans rash. *(Courtesy Gregory A. Cummins.)*

Early Localized Disease (Stage I). The ability of patients to remember a tick bite varies, frequently by species of tick, because some bites are more painful than others, and local immune response to the tick bite varies among individuals. Early localized disease typically begins as a localized erythema migrans rash or lesion, which occurs 7 to 10 days (range, 3 to 32 days) after a tick bite. Approximately 75% of patients with Lyme disease develop an erythema migrans lesion.[172,248,315] In one prospective study in New England, erythema migrans was reported in almost 90% of patients with Lyme disease. A large number of these patients were children, however, who often have a greater febrile and dermatologic response.[67,163,418,419] There are small regional variations in the development of erythema migrans, which may be due to infections with agents other than *B. burgdorferi,* another *Borrelia* species,[147,288,289] or the presence of other nonborrelial tick-borne disease. Erythema migrans may appear anywhere on the body but usually initially occurs at or near the site of the tick bite. In cases with a single erythema migrans lesion, the most common sites include the head and neck region (26%), extremities (25%), back (24%), abdomen (9%), axillae (8%), groin (5%), and chest (3%).[163] In Europe, up to 18% of patients present with disseminated or multilocular erythema migrans.[248]

The erythema migrans rash is variable in size, ranging from 2 cm (0.8 inch) to more than 60 cm (24 inches) in diameter, and is usually in a circular pattern. To meet the CDC case definition of Lyme disease, the lesion must be at least 5 cm (2 inches). It usually begins as a red macule or papule, with an area of central clearing that becomes more apparent as the lesion expands in size (Figure 42-9). The central region may become indurated and, rarely, necrotic. The borders, which are usually bright red, may expand as much as 1 cm/day (0.4 inch/day). The borders are usually flat, although rarely may be raised or indurated. Occasionally, there are multiple, alternating concentric rings of erythema and clearing, a rash pattern referred to as "bull's-eye." The rash is usually warm to the touch.

The lesions are sometimes difficult to differentiate from local immune reactions to the tick salivary proteins, and are sometimes confused with secondary bacterial cellulitic reactions. Local immune reactions usually occur within hours of the tick bite and are very pruritic. Secondary cellulitic reactions typically occur within a few days of the tick bite, lack central clearing, and usually lack rapid expansion.

Patients often describe the lesion as burning but may also report itching or pain. Children may develop temperatures to 40°C (104°F), but low-grade fevers are more common in adults. Constitutional symptoms, such as malaise and myalgias, may also be present. Generalized lymphadenopathy is rare, but local lymphadenopathy may occur.

Erythema migrans fades after an average of 3 to 4 weeks (range, 1 to 14 weeks) without treatment; with antibiotics, the lesion resolves after several days and seldom recurs.[426] Although the erythema migrans lesions resolve without treatment, untreated patients are at risk for developing early (stage II) or late (stage III) disseminated disease.

Early Disseminated Disease (Stage II). Untreated Lyme disease may enter the second stage, early disseminated disease, within days to weeks after the initial infection. The spirochetes spread from the skin to other organs via blood or lymphatics. Although organisms can be visualized in peripheral blood smears, they are very difficult to culture from blood. *B. burgdorferi* has a preference for certain tissues, but it can be found in nearly any organ.[449]

Dermatologic Disease. Disseminated erythema migrans is the most common manifestation of stage II disease. These secondary lesions are usually smaller, there are usually many of them, and they may lack the central clearing. They may appear anywhere on the body, with the exceptions of the palms and soles. Ten percent to 15% of patients have more than 20 such lesions; rarely, there are more than 100. Blistering and mucosal involvement do not occur—an important feature in differentiating these lesions from erythema multiforme. Other skin manifestations include a malar rash (10% to 15%) and, rarely, urticaria.[426]

Borrelial lymphocytoma, an unusual dermatoborreliosis, appears in Europe and western Asia in approximately 1% of patients. Patients typically present with a firm nodule that is red, purple, or blue and 1 cm to several centimeters in diameter. It is usually solitary, but multiple lesions occur in approximately 25% of cases. It often occurs in areas of cooler body temperature, with approximately 80% on the nipple or areola, 10% on the earlobe, and 10% on other areas (including the scrotum).[279] It is caused by *Borrelia afzelii* in approximately 90% of cases, although it has been seen with *B. bissettii* and *B. garinii*.[279] Histologically, it consists of cutaneous lymphoid hyperplasia, usually in deep portions of the dermis. It may be confused with well-differentiated nodular lymphoma.[315] There is associated pruritus, but otherwise it is benign and resolves with appropriate antibiotic therapy.

Neurologic Disease. Neurologic manifestations occur in 10% to 40% of untreated or improperly treated patients.[332] Meningitis, encephalitis, and meningoencephalitis are the major neurologic findings of early disseminated disease; lethargy, forgetfulness, disorientation, somnolence, dizziness, photophobia, and incoordination are the most common signs and symptoms. Mood disturbances may also be seen, especially in pediatric patients.[29] Nuchal rigidity is sometimes present, along with a severe headache. Lumbar puncture reveals CSF with pleocytosis (usually < 1000 cells/mm^3), typically with lymphocyte predominance and a high protein level.

Paralysis of the facial nerve (cranial nerve VII) may occur, may persist for months, and usually resolves spontaneously.[82,337] Bilateral facial nerve paresis or paralysis may occur in 25% of cases with cranial nerve VII involvement, usually evolving asymmetrically. Bilateral facial palsy is an unusual physical finding and should suggest Lyme disease, although this finding may also be caused by sarcoidosis, herpes zoster, or the human immunodeficiency virus (HIV).

Radiculoneuritis may be present in various nerves, causing burning, stabbing, or shooting pain. Large nerve bundles such as the brachial plexus are more commonly involved. Mononeuritis multiplex may be present, with peripheral motor weakness and sensory pain. Other neurologic findings are rare but include pseudotumor cerebri, chorea, and dementia, and subacute transverse myelitis.[162,217,238,365]

Gastrointestinal Disease. Ten percent of patients may develop hepatitis, hepatomegaly, and generalized abdominal pain. Hepatic involvement does not progress to hepatic failure; symptoms usually resolve in less than 1 week but may persist for several weeks. Splenomegaly may also occur.[319]

Cardiac Disease. Untreated or improperly treated Lyme disease leads to cardiac manifestations in up to 10% of cases.[420] Although cardiac involvement is usually self-limited and rarely life-threatening, temporary intervention is required in some cases.[187,231] The most common cardiac manifestation of Lyme disease is conduction delay, which may be of any degree and is found in 80% of cases with cardiac involvement.[107,329] Electrophysiologic studies indicate that the block is at the level of the atrioventricular node. The block does not respond to atropine, suggesting a direct effect on the node.[329,373] In cases of complete heart block, the presence of spirochetes can be confirmed in cardiac tissue by cardiac biopsy. Noninvasive imaging modalities such as cardiac MRI can be used to document improvement in response to antibiotics.[231]

Conduction delays usually, but not always, resolve with appropriate antibiotic therapy. Patients with first-degree atrioventricular block and a PR interval exceeding 300 msec, as well as all patients with second- and third-degree heart blocks, should be admitted for observation and antibiotic treatment. Patients with third-degree heart block require temporary transvenous pacing and may require permanent pacemaker implantation.

More diffuse cardiac involvement, such as myopericarditis, is found in about one-half of patients with cardiac involvement. The electrocardiogram in such patients usually demonstrates diffuse, nonspecific changes (Figure 42-10). Radionuclide angiography may demonstrate left ventricular dysfunction, but this is seldom clinically significant. Cardiomegaly due to Lyme disease rarely occurs in U.S. patients, although dilated cardiomyopathy is often reported in Europe.[407,416] Valvular involvement is uncommon.

At least one death has been linked to cardiac involvement,[280] but abnormalities usually resolve completely, often within 1 to 2 weeks.[421] Severe cardiac complications have been described in pediatric patients but are relatively rare.[163]

Rheumatologic Disease. Monoarticular arthritis develops in 60% of U.S. patients with erythema migrans who are not treated, usually occurring between 4 weeks and 2 years after the onset of illness.[430] Although common in North America, arthritis is rarely a finding in other areas of the world.[80,423]

In adult patients, arthritis may occur in a migratory pattern, involving many joints, usually one joint at a time. Joint involvement typically occurs for about a week (median, 8 days), but it may persist for months. Many patients have repeated episodes of arthritis, and each subsequent recurrence is less severe. Soreness often persists between episodes, never fully resolving, and persistent morning stiffness is common. The knee is most commonly affected, followed by the shoulder, elbow, temporomandibular joint, ankle, wrist, hip, metatarsals, and metacarpals.[478] Joint swelling is not common except in the knee, and the joints are typically described as more sore than painful. Chronic effusions often occur.

In pediatric patients, arthritis appears an average of 4.3 months after initial infection, with a broad range of a few days to 20 months.[163,164] Approximately 50% of pediatric patients have multiple recurrences, although complete remission between episodes is typical and chronic arthritis is uncommon. Ninety percent of children in a large study had arthritis in at least one knee.[164]

Synovial fluid of involved joints has a median WBC count of 25,000/mm^3, with polymorphonuclear leukocyte predominance.

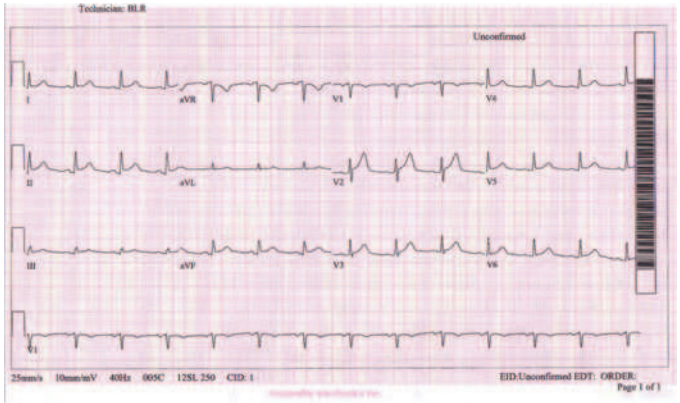

FIGURE 42-10 Electrocardiograph of a patient with acute myopericarditis. *(Courtesy Gregory A. Cummins.)*

Synovial membrane biopsy shows cellular hypertrophy, vascular proliferation, and mononuclear cell infiltrate.[424,428] PCR testing of synovial fluid is positive in 85% of cases of Lyme arthritis.[348]

The organism may also persist in synovial tissue. Four patients who completed antibiotic therapy for Lyme arthritis and who subsequently had negative PCR testing of synovial fluid had positive PCR testing of the synovial membrane.[348] This persistence may account for the reactivation of Lyme arthritis that has been described after autologous chondrocyte transplantation for degenerative joint disease or cartilage injury.[285]

Late Disease (Stage III). Late disease may occur a year or more after the initial presentation, and usually has rheumatologic, neurologic, and dermatologic manifestations. Recurrent hepatitis, eosinophilic lymphadenitis, acute respiratory distress syndrome (ARDS), and other rare manifestations may also be present.

Dermatologic Disease. Patients with late-stage dermatologic involvement present with acrodermatitis chronica atrophicans, also called diffuse idiopathic cutaneous atrophy. It is caused by *B. afzelii* and nearly strictly confined to central and southern Europe. The dermatitis, which may persist for many years, usually occurs on the distal extremities, often having begun at a previous area of erythema migrans, commonly on the extensor surfaces of extremities.[320] It begins as inflammation, hyperpigmented red or blue, and followed by skin scarring and atrophy. The atrophy causes the skin to become thin, and it later becomes hypopigmented. Hair loss and dysfunction of sweat and pilosebaceous glands also occur.[315] Other findings, such as polyneuropathy, may accompany the skin changes. *Borrelia* has been cultured from 10-year-old lesions of acrodermatitis chronica atrophicans. Histologically, fibrosis occurs early, glands become infiltrated, and the dermis reveals a patchy to band-like mononuclear infiltrate composed of lymphocytes, histiocytes, and plasma cells in greater numbers than those found in typical erythema migrans lesions.[315]

Neurologic Disease. Central nervous system (CNS) involvement may develop months to years after the initial infection. Patients most typically present with progressive encephalomyelitis, with ataxia, cognitive impairment, spastic paresis, and involvement of cranial nerves VII and VIII.[2] Rarely, strokes, seizures, and dementia may occur.[140,270] Lumbar puncture in patients with stage III CNS involvement reveals CSF with lymphocytic pleocytosis and anti—*B. burgdorferi* antibodies. Magnetic resonance imaging of the brain reveals white matter changes consistent with encephalopathy. In seropositive pediatric patients, the meningoencephalitic changes are often seen as behavioral changes, and are noted more often in boys than girls.[29,227]

Peripheral nervous system involvement may manifest as peripheral paresthesias, painful radiculopathies, and motor nerve palsies. The underlying pathophysiologic mechanism appears to be mononeuritis multiplex.[149] Such patients may present with radicular pain that is frequently asymmetric, originating in the spine and referred to the extremities. Nerve conduction and electromyographic studies show mild axonal polyneuropathy with decreased motor or sensory nerve conduction velocities, with denervation of spinal and limb muscles.[149]

Rheumatologic Disease. Arthralgias and oligoarthritis occur in approximately 50% of untreated patients.[424,428] In about 10% of patients, cartilage loss, subarticular sclerosis, osteophyte formation, cortical or marginal bone erosions, joint effusions, and other radiographic signs of degenerative arthritis may be seen.[257] The rheumatologic workup, including erythrocyte sedimentation rate, C-reactive protein, antinuclear antibodies, and rheumatoid factor, is generally negative.[428] Interestingly, late rheumatologic disease is rare in children.[485]

Posttreatment Lyme Disease Syndrome. There is considerable debate over whether a chronic form of Lyme disease exists. Some patients develop chronic persistent Lyme disease symptoms despite repeated treatment with antibiotics. Whether this is a sequela of pathogen resistance or chronic autoinflammation, autoimmunity, or a form of fibromyalgia is highly debated.[169] A collection of symptoms, lumped into a category sometimes referred to as postborreliosis syndrome or post–Lyme disease syndrome, consists of signs and symptoms such as persistent fatigue, sleep disorders, depression, cognitive defects, mood swings, and other neuropsychiatric manifestations.[271] This symptom complex fails to respond to traditional antibiotics.

A 20-year review of more than 500 British patients with Lyme disease revealed a subgroup who had suffered tick bites but had negative serologic findings for Lyme disease. These patients had persistent fatigue, neuropathy, depression, cognitive defects, and other vague neurologic symptoms. To avoid confusion with serologically positive Lyme disease, these authors and many others proposed changing "chronic Lyme disease" to "chronic arthropod-borne neuropathy"[121] or a similarly intended name. Chronic Lyme disease has been renamed posttreatment Lyme disease syndrome by the CDC.

This collection of symptoms might be an entirely separate disease, partially treated Lyme disease, or perhaps a disease variant complicated by the cystic form of borreliae. As early as the early 1900s, spirochetes were noticed to develop into cysts, also called blebs or vesicles. Today, these cysts are called spherocytes, the L-form of the spirochete, or round bodies.[45,52] These spherocytes are induced under adverse conditions, such as the presence of antibodies targeted against the spirochetes, medications, adverse pH, or adverse temperatures. Spherocytes may be able to survive conditions that would kill or deactivate the typical spirochete form.[317] When environmental conditions again become favorable for the spirochetes in vitro, the cysts or spherocytes convert back to the traditional spirochete form.[45] *B. burgdorferi* also forms biofilms or a dense collagenous matrix under adverse conditions, particularly in joints. In this setting, *B. burgdorferi* could be shielded from traditional antibiotics.[382,486] Multiple recent studies fail to show any viable *B. burgdorferi* after treatment with an appropriate antibiotic for the appropriate duration. At this time, chronic posttreatment Lyme disease symptoms should not be attributed to persistent or recurrent active infection.[326]

Further research will hopefully yield more information about the relevance of and appropriate treatment of the cystic form of the disease, such as the addition of antiprotozoal medications to the treatment regimen.[46,47] Patients afflicted with these persistent symptoms are very active in pursuing formal recognition and treatment of these disorders through political, legislative, and research means. However, at the present time, there is no evidence-based medicine to support prolonged antibiotic therapy for patients with any manifestation of Lyme disease.[488]

Lyme Disease in Pregnancy. Fetal demise may result in mothers who develop Lyme disease in pregnancy.[274,284,386,468] Transplacental transmission of Lyme disease is rare but appears to be associated with an increased risk of cardiac malformations.[477]

Lyme disease in pregnancy should be aggressively treated. A 1996 prospective study of 58 pregnant women with erythema migrans given oral or intravenous (IV) penicillin or ceftriaxone reported only seven adverse outcomes, none clearly associated with Lyme disease.[278] The American College of Obstetrics and Gynecology recommends oral penicillin or amoxicillin for 3 weeks in pregnant women with cutaneous involvement or recent tick bites in endemic areas (Table 42-3). This is the only indication for postexposure (i.e., to a tick bite) antibiotic prophylaxis against Lyme disease. For patients with severe acute disease, or disseminated or late disease, 3 weeks of parenteral penicillin is recommended. If the patient is allergic to penicillin, parenteral erythromycin is recommended.[11,132] Tetracyclines should not be used in pregnancy.

Diagnosis

The CDC has established a surveillance case definition for Lyme disease. The case definition requires exposure to ticks in an endemic county and an erythema migrans lesion of 5 cm (2 inches), diagnosed by a physician. In this definition, exposure requires outdoor activities within 30 days of the onset of the lesion. An endemic county is one in which at least two confirmed cases of Lyme disease have been acquired, or known tick vectors are established. It is important to note that Lyme disease case definitions are designed for national reporting, not individual patient diagnosis. The clinical diagnosis of Lyme disease is based on the history, clinical suspicion, and a working knowledge of the disease process and epidemiology; laboratory tests may be performed but generally serve only to confirm the presence of the disease.

TABLE 42-3 Antimicrobial Recommendations for Lyme Disease

Drug	Dose*	Duration (days)
Early Localized Disease		
Adults		
Doxycycline	100 mg PO bid	14
Tetracycline	250-500 mg PO qid	14
Amoxicillin	500 mg PO tid	14
Cefuroxime	500 mg PO tid	14
Erythromycin	1-4 g/day divided PO qid	14 (max, 4 g daily)
Children		
Amoxicillin	50 mg/kg/day PO divided tid	14
Doxycycline (>8 yr)	100 mg PO bid or <45 kg at 5 mg/kg/day divided bid	14 (max, 200 mg/day)
Erythromycin	30-50 mg/kg/day PO divided qid	14 (max 4 g daily)
Tetracycline (>8 yr)	250 mg PO qid	14
Cefuroxime axetil	30-40 mg/kg/day PO divided bid	14
Early Disseminated and Late Diseases† and Late Disseminated Neurologic Disease‡ (treatment duration based on severity of disease;14 days in nonneurologic and noncardiac cases)		
Adults		
Ceftriaxone	2 g IV/IM daily	14-28
Cefotaxime	2 g IV every 8 hours	14-28
Penicillin G	20 million IU/day IV divided every 4 hours	14-28 (max, 20 million IU/day)
Children		
Ceftriaxone	80-100 mg/kg/day IV daily	14-28 (max, 2 g/day)
Cefotaxime	90-180 mg/kg/day IV every 8 hours	14-28
Penicillin G	300,000 IU/kg/day IV divided every 4-6 hours	14-28 (max, 24 million IU/day)
Late Disseminated Arthritis		
Adults		
Amoxicillin	500 mg PO qid	14-28
Doxycycline	100 mg PO bid	14-28
Ceftriaxone	80-100 mg/kg/day IV daily	14 (max, 4 g/day)
Children		
Amoxicillin	50 mg/kg/day PO divided tid	14-28
Ceftriaxone	80-100 mg/kg/day IV/IM daily	14-28 (max 2 g/day)
Disseminated Disease and Cardiac Involvement		
Adults		
Doxycycline§	100 mg PO bid	14-28
Amoxicillin§	500 mg PO every 8 hours	14-28
Ceftriaxone¶	2 g/day IV daily	14-28
Children		
Ceftriaxone	75-100 mg/kg/day IV/IM daily	14-21 (max, 2 g/day)
Penicillin G	300,000 IU/kg/day IV divided every 4-6 hours	14-21 (max, 24 million IU/day)
Lyme Disease in Pregnancy		
Cutaneous involvement only, or tick bite in endemic area		
Amoxicillin	50 mg/kg/day PO divided tid	21
Severe acute disease or late/disseminated disease		21
Penicillin G	20 million IU/day IV divided every 4 hr	

bid, twice a day; IM, intramuscularly; IU, international units; IV, intravenously; PO, orally; qid, four times a day; tid, three times a day.
*Total daily dose shown to be divided (if necessary) as indicated.
†For multiple lesions of erythema migrans, use treatment for early localized disease for at least 21 days. For isolated facial palsy, use treatment for early localized disease for 21days.
‡Neurologic involvement limited to an isolated facial palsy should be treated as early disease.
§For mild cardiac involvement (i.e., first-degree atrioventricular block with PR interval less than 0.30 second).
¶For second- or third-degree heart block, although no evidence indicates that intravenous regimen is better than oral regimens; 28-day course recommended.
**In pregnancy, penicillin is preferred. If pregnant patient is allergic to penicillin, use erythromycin at 15-20 mg/kg/day IV divided qid.

Routine laboratory examinations may reveal nonspecific findings, such as elevated liver enzymes (alanine transaminase [ALT], aspartate transaminase [AST], and/or gamma-glutamyltransferase), decreased leukocyte count, and elevated erythrocyte sedimentation rate. Immunoglobulins A and G (IgA and IgG) are usually normal, whereas IgM is usually elevated, especially in severe disseminated disease, although it is slow to rise after infection and to fall after treatment. Culture is the gold standard for diagnosis but is often difficult to obtain. Biopsy of an erythema migrans skin lesion is positive in 60% of punch biopsies from the leading edge of the lesion, and this figure may be as high as 80% in specialty centers.[35] The production of anti–*B. burgdorferi* antibody develops slowly, and serologic assays in the first 3 to 6 weeks of illness are often negative unless severe disease is present.[305,398] In some patients, treatment with antibiotics may blunt or entirely suppress the antibody response; in others, IgG and IgM antibodies may persist for years after resolution of clinical symptoms.[142] Patients with complicated Lyme disease (with neurologic, cardiac, or joint involvement) or those in remission are more likely to have elevated specific antibody titers.[305,398] Serologic testing has the highest predictive value in patients with a pretest probability of having Lyme disease between 20% and 80%.[449] Patients from endemic areas with an 80% or higher pretest probability of having the disease benefit from empirical treatment, not testing. Patients with a pretest probability of less than 20% have a high likelihood of a false-positive test.

The indirect immunofluorescent assay (IFA), enzyme-linked immunosorbent assay (ELISA), and Western blot test are the most commonly used tools to detect antibodies to *B. burgdorferi*. For diagnostic purposes, ELISA is the most accurate, with 89% sensitivity and 72% specificity. Low levels of agreement are common between various laboratories and individual assays.[449] New tests using recombinant proteins or synthetic peptides as ELISA antigens yield detection rates for serum antibodies of 20% to 50% for early disease, 70% to 90% for early disseminated disease, and nearly 100% for late disease.[449,479] The Western blot test is a poor screening tool, but it is useful to confirm a positive ELISA result. It should never be done without a positive ELISA.

Only positive serologic assays confirmed by Western blot meet the criteria for laboratory diagnosis, according to the CDC national consensus panel. Many disease states, including other treponemal diseases, autoimmune diseases, and some viral diseases, may give false-positive ELISA results.[305] Antibodies directed toward oral flora may also cause false-positive results.[10,305]

Reverse transcriptase DNA PCR is both highly sensitive and specific for Lyme disease. With decreasing costs and increasing availability, PCR is a viable diagnostic option.[137,260,339]

Many patients present with vague nonspecific symptoms such as chronic fatigue, musculoskeletal pains, and neuropsychiatric issues, in the absence of true Lyme disease risk factors and clinical findings. Such patients usually should not undergo serologic testing for Lyme disease. Positive results in such patients are probably falsely positive, may create an inordinate amount of confusion and conflict, and may lead to inappropriate antibiotic prescribing.

The importance of appreciating the limitations of serologic testing cannot be overstated. In one study, only 23% of patients referred to the Lyme Disease Clinic at the New England Medical Center had active Lyme disease, and a majority of those without Lyme disease had been treated inappropriately with antibiotics.[429] In this study, the most common reason for lack of response to antibiotics was misdiagnosis. The limitations of laboratory testing in Lyme disease include lack of sensitivity and specificity of serologic tests and considerable interlaboratory and intralaboratory variability in test results.[392] Persistence of antibodies in patients with past or asymptomatic infection with *B. burgdorferi* also complicates serologic testing. PCR testing in these situations would likely clarify the presence of active disease.[260] If another illness develops, as occurred in 20% of patients referred to the New England Medical Center clinic, it may be incorrectly attributed to Lyme disease. This is particularly problematic in patients with nonspecific symptoms of chronic fatigue or fibromyalgia, in whom the predictive value of a positive ELISA is low.

Overdiagnosis of Lyme disease has significant health system and patient care implications. In another study of 209 individuals referred to a university-based Lyme disease clinic with a diagnosis of the disease, only 21% met the criteria for active Lyme disease, 60% had no evidence of current or previous infection, and 19% had evidence of previous but not active disease. The 79% of patients without active Lyme disease displayed significant anxiety and stress related to their diagnosis of Lyme disease, used considerable health care resources, and had frequent adverse antibiotic reactions.[364]

Treatment

Although most manifestations of Lyme disease resolve spontaneously without treatment,[381] treatment of Lyme disease with appropriate antibiotics hastens recovery in all stages of the disease. Both in vitro and in vivo studies have confirmed that *B. burgdorferi* is highly sensitive to tetracyclines, aminopenicillins, ceftriaxone, and imipenem.[197,224,225] The macrolides, oral second- and third-generation cephalosporins, and chloramphenicol all seem to have equal efficacies.[5,224] Although fluoroquinolones have traditionally not been effective against *Borrelia* species, the fourth-generation fluoroquinolone antibiotics seem to have good efficacy in vitro.[243] However, some *B. burgdorferi* strains are showing in vitro resistance to the newest fluoroquinolones.[161] Table 42-3 lists general antimicrobial therapy options and recommendations for Lyme disease.

In early localized Lyme disease (stage I), amoxicillin and doxycycline are the drugs of choice. Tetracyclines should not be used in pregnancy, lactating women, or children under age 9 years. The recommended treatment duration is 10 to 20 days. In one study, 10 days of treatment with doxycycline showed the same efficacy as 20 days, with fewer side effects. This may rarely be extended to 4 weeks if symptoms persist or recur, although no hard evidence exists for doing so.[488] Medications that will penetrate the CSF are ideal and may lead to less disease recurrence.[271] Sequestering of spirochetes in the brain may account for some apparent antibiotic failures because not all antibiotics cross the blood-brain barrier.

Within the first 24 hours of treatment with antibiotics, up to 15% of patients develop a Jarisch-Herxheimer reaction (JHR), which manifests as a rise in temperature, vasodilation, and hypotension.[320] Normal saline infusion around the time of initial dosing of antibiotics may help reduce the degree of hypotension. In rare cases, the JHR may be severe or fatal. Symptoms rarely persist beyond 24 hours.

Disseminated disease (stages II and III) should be treated according to severity. In mild disseminated disease (such as secondary erythema migrans or cranial nerve VII palsy), 3 weeks of oral doxycycline is as effective as 2 weeks of parenteral ceftriaxone.[101] In patients initially treated with oral antibiotics who are therapeutic failures or in whom disease recurs, parenteral antibiotics are indicated. Patients with severe disseminated disease (neuroborreliosis, high-degree heart block) require parenteral antibiotics for up to 4 weeks.[100,269] Ease of once-daily administration of ceftriaxone makes it a better choice for both inpatient and outpatient administration than other typically used agents requiring administration three or more times daily.[100,101]

Neurologic symptoms begin to improve with therapy within 1 week, although full resolution may take 7 to 8 weeks.[429] Prolonged oral antibiotics were previously used to treat stage III arthritis, sometimes for as long as 4 to 8 weeks.[429] A delayed clinical response in arthritis is relatively common. Nonsteroidal antiinflammatory drugs may also be used to reduce symptoms and disease recurrence by simultaneously treating inflammation.[169]

No vaccines are presently available for the prevention of Lyme disease in humans. A vaccine based on recombinant outer-surface protein A was approved in 1998 but was removed from the market by the manufacturer in 2002. The vaccine had limited efficacy, required frequent boosters, was expensive, could not be used in children, and resulted in immunogenic reactions in some vaccinated individuals.[188] Future vaccines, although still in their infancy, will most likely use polyvalent outer-surface protein C.

Treatment of asymptomatic tick bites in areas endemic for Lyme disease is controversial, although this does not stop patients from requesting care. In one survey, physicians in Maryland reported seeing 11 times as many patients seeking help after "tick bites" as they did actual cases of Lyme disease.[90] Three randomized, placebo-controlled studies have addressed antibiotic prophylaxis for tick bites.[6,89,396] Of patients in the placebo groups, 1% to 3.4% developed Lyme disease or had evidence of seroconversion, even though 15% to 30% of ticks were infected; no patients in the treatment groups developed Lyme disease. A metaanalysis of the three studies concluded that there was no significant difference between the groups, and that routine prophylaxis of tick bites is not warranted except in pregnancy, even in endemic areas.[467]

Many physicians do not adhere to this recommendation, however. Maryland physicians ordered serologic testing in two-thirds of patients with asymptomatic tick bites and treated more than one-half with prophylactic antibiotics.[153] The concern often cited for such practices is that patients with tick bites who become infected may not develop erythema migrans (when the disease is easily treated) but go on to develop the late and more serious manifestations of Lyme disease. Some of these decisions are likely driven by patient pressure, as well as defensive medicine.

The risk of serious late sequelae in untreated patients is extremely low, for three reasons. First, less than 5% of those bitten by the *I. scapularis* tick in endemic areas become infected. Second, most patients with an identified tick bite remove the tick before it has been attached for the 24 to 48 hours required to transmit an infectious inoculum of *B. burgdorferi*. Finally, 80%

to 90% of patients who become infected develop erythema migrans, which makes diagnosis and treatment straightforward. Physicians must therefore weigh a number of factors related to the likelihood of disease acquisition in deciding whether to treat asymptomatic tick bites with antibiotics. These factors include species and stage of the offending tick, duration of attachment, geographic location, and patient factors such as pregnancy. If a decision is made to treat, a 10-day course of an antibiotic appropriate for Lyme disease is reasonable.

Overtreatment of presumed Lyme disease with antibiotics has significant health care ramifications. If the patient does not have Lyme disease, treatment failure is virtually ensured. Patients being treated for Lyme disease have a significant amount of anxiety regarding the diagnosis.[364] Adverse drug reactions may occur. Overuse of antibiotics has led to resistance to multiple antibiotics by many organisms, although resistance to tetracycline is not documented for *Borrelia*.[12]

SOUTHERN TICK-ASSOCIATED RASH ILLNESS

Since the mid-1980s, erythematous rashes similar to those seen in early Lyme disease (Figure 42-11) have been found in persons from the southeastern and south-central states, a geographic area in which the presence of Lyme disease is in dispute.[364] A correlation was noted between these rashes and the bite of the Lone Star tick, *Amblyomma americanum* (see Figure 42-6). The disease has since been named southern tick-associated rash illness (STARI), but it is also known as Master's disease and southern Lyme disease.[363] It was thought to be caused by *B. lonestari,* discovered in ticks and in patients by detecting DNA from *Borrelia* in specimens and by culturing the organism.[453,454] A more recent attempt to confirm *B. lonestari* as the causative agent for STARI showed no evidence of a *Borrelia* species being involved,[324,484] and the CDC states that *B. lonestari* is not involved in cases of STARI. Subsequently, different rickettsiae, including *R. amblyommii, R. parkeri,* and others, have been implicated in STARI and many cases of Rocky Mountain spotted fever reported in some overlapping, mainly southern, states.[13,77,324,333,455] STARI-type lesions have been documented as far north as Long Island, New York, and as far south as the Caribbean islands.[143,397] *Rickettsia amblyommii* has been found in various *Amblyomma* spp. ticks in Panama, Brazil, and many other South and Central American countries.[36,106]

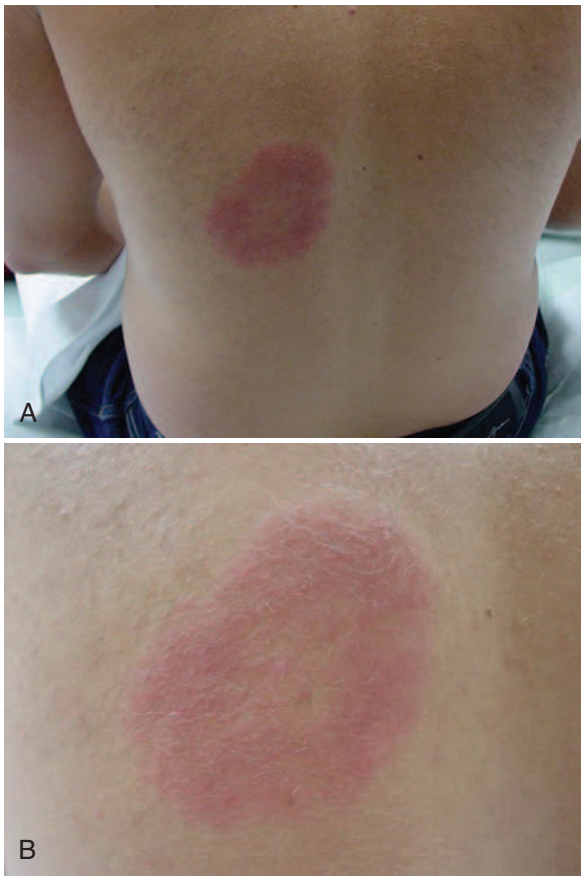

FIGURE 42-11 Presumptive southern tick-associated rash illness. **A,** Rash on patient's back. **B,** Close-up view of rash. *(Courtesy Shannon B. Snyder, MD.)*

A. americanum ticks are found throughout the southeastern and south-central United States, as well as along the eastern seaboard into Maine, and are documented in 29 states. All three stages of *A. americanum* feed aggressively on humans, and various stages are found in most of its distribution throughout the year. Of larval *A. americanum* ticks found in Mississippi, 24% tested positive by PCR for *R. amblyommii,* showing significant transovarial transmission of *R. amblyommii* in this tick species.[174] The disease importance of *A. americanum* is no longer in question.[79]

Patients present with a rash similar to erythema migrans, usually within 7 days of a bite from *A. americanum*. The lesion is usually at least 3 inches in diameter and may lack central clearing.[288,289] Skin findings may be followed by generalized fatigue, headache, myalgias, and other generalized symptoms.[39] *A. americanum* ticks have proportionately large mouthparts (see Figure 42-6) and are often very immunogenic; the rash is therefore sometimes difficult to distinguish from a local reaction. A local reaction is immunogenic and typically occurs within hours of the tick bite, whereas the STARI rash occurs several days after the bite.

Diagnosis at the present time is by clinical examination findings and tick exposure risk factors, such as geographic location. There is no specific diagnostic test. The disease is currently believed to be self-limited, although current recommendations are that it be treated with a course of doxycycline 100 mg orally twice daily for 10 days for adults, or 5 mg/kg/day divided twice daily in children or those who weigh less than 45 kg.[399] Use an alternate antibiotic for the treatment of Lyme disease if the tetracyclines are contraindicated. Research into STARI and *A. americanum* is in its infancy and will hopefully yield much more information in the future.

RELAPSING FEVERS

TICK-BORNE RELAPSING FEVER

Tick-borne relapsing fever (TBRF) is an acute borrelial disease characterized by recurrent paroxysms of fever, separated by afebrile periods.[94,182] The endemic or sporadic form occurs worldwide and is caused by a group of closely related *Borrelia* species (Table 42-4).

The *Ornithodoros* ticks that transmit TBRF act as both vectors and reservoirs for *Borrelia* organisms; wild rodents also serve as reservoir hosts.[447] Ticks ingest *Borrelia* organisms while feeding on an infected vertebrate, most often a rodent. Borreliae enter the tick hemocele and then spread to other tick tissues, including the salivary glands, coxal organs, and reproductive organs. The coxal organs in argasid ticks are specialized for excretion of excess fluids and solutes accumulated during feeding. In some *Ornithodoros* species, the coxal fluid is released near the mouthparts during feeding, allowing transmission of spirochetes to vertebrate hosts during the feeding process. Transmission occurs through saliva or regurgitated gut contents.[182] Borreliae remain infective within ticks for many months.[410]

Transovarial transmission allows all developmental stages to be potentially infective. The ticks generally feed at night and attach themselves to the host for a short time, usually less than 1 hour. The bite is usually painless and frequently goes unrecognized. The ticks are extremely resilient and may survive for years between feedings.

A high degree of specificity exists between the major strains of *Borrelia* that cause relapsing fever and their associated tick vectors. For example, the three *Borrelia* species found in the United States, *Borrelia hermsii, Borrelia turicatae,* and *Borrelia parkeri,* show complete specificity for their respective tick vectors

TABLE 42-4 Tick-Borne Relapsing Fever

Arthropod Vector	*Borrelia* Species	Geographic Distribution
Ornithodoros hermsi	*Borrelia hermsii*	Western United States and Canada
Ornithodoros turicata	*Borrelia turicatae*	Southwestern United States and Mexico
Ornithodoros parkeri	*Borrelia parkeri*	Western United States and Mexico
Ornithodoros moubata	*Borrelia duttonii*	Tropical Africa
Ornithodoros tholozani	*Borrelia persica*	Central Asia, Middle East, Greece
Ornithodoros tartakovskyi	*Borrelia latyschewii*	Iran, central Asia
Ornithodoros erraticus	*Borrelia crocidurae*	Russia, Middle East, East Africa, Turkey
Ornithodoros graingeri	*Borrelia graingeri*	Kenya
Ornithodoros talaje	*Borrelia mazzottii*	Mexico, Central America
Ornithodoros rudis	*Borrelia venezuelensis*	Central and South America
Ornithodoros asperus	*Borrelia caucasica*	Iraq, Russia
Ornithodoros marocanus	*Borrelia hispanica*	Northern Africa, southern Europe

Ornithodoros hermsi, Ornithodoros turicata, and *Ornithodoros parkeri*. This specificity is used extensively in the classification of *Borrelia* species.[103]

Epidemiology

Ornithodoros ticks generally inhabit rodent burrows and nests, and cracks and crevices in human and animal habitats, caves, and similar locations. Habits and patterns of infection vary between tick species. In parts of Africa, ticks live in the dust and cracks of earthen-floored huts, and sporadic cases are seen throughout the year. In the Middle East, Mexico, and southwestern United States, ticks live in the guano on cave floors, and human infection is often associated with visiting or camping in caves.

The majority of cases of TBRF in the United States are attributed to *B. hermsii*. Its vector, *O. hermsi,* inhabits the coniferous forest biome, where it lives in remains of dead trees and burrows inhabited by mice, rats, and chipmunks. Ticks are carried by rodents into poorly maintained cabins and huts. Lodging in such shelters by hikers and hunters is a major factor in acquiring relapsing fever.[148,210] At federally owned recreation areas in northern California, antibodies to *B. hermsii* were present in 20% of rodents, with infestation as high as 43% in some species.[159] Rodent-proofing shelters dramatically reduces the risk of acquiring TBRF.[335] Care should be taken during rodent proofing, because hantavirus and TBRF are often found concomitantly in similar habitats. Occasional cases are also caused by *O. turicata* (transmitting *B. turicatae*) in Texas and adjacent areas of the Southwest, and are associated with travel into caves; *O. parkeri* (transmitting *B. parkeri*) rarely bites humans.[208]

TBRF is found throughout most of the world, and endemic areas include 14 western states, from Colorado to California, south into Mexico, up to the Pacific Northwest,[130,148,210] and north into southern British Columbia.[127] TBRF is not a mandatory reportable disease, and is thus, like many tick-borne diseases, grossly underreported. In California, where reporting of relapsing fever is encouraged, 2 to 12 cases are reported per year, with only 25 cases per typical year nationwide.[76,130] Large outbreaks have been reported from Spokane County in Washington,[443] Colorado,[447] and the north rim area of the Grand Canyon.[70,335] Although the vast majority of cases occur in states where TBRF is endemic, a review of 450 cases of TBRF acquired in the United States from 1977 to 2000 noted that 7% of cases were diagnosed in states where it is not endemic.[127] TBRF is more common in men, presumably because of increased exposure to tick vectors, and occurs primarily during summer months. TBRF is also found throughout the plateau regions of Central and South America, central Asia, Mediterranean countries, and most of Africa. TBRF is rarely fatal in adults, but in infants younger than age 1 year, case fatality rates may be 20% or higher.[258,410]

Clinical Manifestations

Ornithodoros ticks feed for a short period (often < 1 hour) at night, so most patients have no recollection of a tick bite. After an incubation period of about a week, patients develop the characteristic clinical features of TBRF: abrupt onset of fever lasting about 3 days (range, 12 hours to 17 days), followed by an afebrile period of variable duration and then relapse with return of fever and other clinical manifestations. The initial febrile period terminates with rapid defervescence or "crisis," accompanied by drenching sweats and intense thirst. Febrile periods in TBRF are associated with spirochetemia. Resolution of fever occurs when the host develops an adequate antibody response to the spirochete. During afebrile periods, the spirochetes remain "hidden" in organ tissue and undergo antigenic conversion to a new serotype (see Antigenic Variation, later). Relapse occurs when the new serotype causes a new round of spirochetemia.

After being bitten by an infected tick, victims may develop a pruritic eschar at the site of the tick bite, but the lesion is usually absent by the time the clinical symptoms appear. Victims typically develop fever, frequently accompanied by shaking chills, severe headache, myalgias, arthralgias, upper abdominal pain, photophobia, cough, nausea, and vomiting. The temperature is usually greater than 39° C (102.2° F), and patients may present with extreme muscular weakness and lethargy. Splenomegaly develops in approximately 40% and hepatomegaly in 18% of patients with TBRF. Though less common, persons infected with *Borrelia turicatae* have 10% to 40% neurologic involvement, approaching the incidence seen in Lyme disease.[58] The most common neurologic complications are meningismus and facial nerve palsy.[58] Facial palsy, when present, typically occurs after the second febrile episode and usually resolves within 2 to 9 weeks with or without treatment. Other reported neurologic complications include neuropsychiatric disturbances, encephalitis, peripheral neuropathy, myelitis, and pathologic reflexes. Iritis or iridocyclitis occurs in up to 15% of untreated cases, typically occurring later in the fever course. Formation of adhesions between the iris and anterior lens capsule may lead to visual defects. A rash, which may consist of a macular eruption, petechiae, or erythema multiforme, develops in 25% to 30% of patients.[410]

Only rarely are clinical features severe and prolonged. Neurologic complications generally resolve spontaneously, but severe depression may persist for months. Hemorrhagic complications, pneumonia, ARDS, hepatosplenomegaly, petechiae, or myocarditis may develop rarely.[104,148,472] In 2004 within 6 months in three western states, there were three separate cases of ARDS from TBRF, all requiring mechanical ventilation.[76] In immunocompetent adults, TBRF is generally self-limited.

Relapsing fever in pregnancy results in a high incidence of spontaneous abortion, premature birth, and perinatal morbidity.[410] Fetal death is probably caused by direct placental invasion by spirochetes, which are most numerous during the febrile phase, resulting in thrombocytopenia and retroplacental hemorrhage.[489] Prior studies have linked pregnancy with a more serious maternal disease course.[301] Infection in the neonatal period usually occurs by placental transmission and appears as overwhelming sepsis with a high mortality rate.[489]

Antigenic Variation. The phenomenon of relapse in TBRF is caused by the ability of borreliae to undergo antigenic variation in an infected host. The organisms are capable of spontaneous conversion to many serotypes. Clinically, defervescence occurs when the dominant serotype is eradicated by interaction with host antibody. Spirochetemia probably persists at undetectable levels during the afebrile period and consists of mixed serotypes. Relapse occurs when a variant population reaches detectable levels. Antigenic variation is under complex genetic control and

does not appear to require contact of the organism with host antibody.[21,433]

Diagnosis

Clinical diagnosis of TBRF requires thorough knowledge of the epidemiology of the disease and a high index of suspicion. TBRF is uncommon and occurs only sporadically. A history of recent exposure to old cabins, caves, or any rodent-friendly environment should raise the specter of TBRF. Routine laboratory tests are of little value. The WBC count is usually normal but may be increased or decreased. A left shift is often present. Thrombocytopenia is common but nonspecific. The CSF is often abnormal, with lymphocytic pleocytosis (typically, 10 to 2000 cells/mm^3), usually with normal glucose and elevated protein. A false-positive serologic test for syphilis (Wassermann test) occurs in about 5% of cases.[410]

The diagnosis of relapsing fever is confirmed by demonstrating spirochetes on peripheral blood smears, and carries a higher positive predictive value when obtained early in the course of the disease, during a febrile episode. A routine peripheral blood smear (Wright-Giemsa stain) from a febrile patient is initially positive in 70% of cases.[410] The diagnostic yield can be increased by examining thick smears and by staining with acridine orange using fluorescence microscopy.[393] Inoculating laboratory animals (rats, mice) with blood and examining blood smears from the animals will also increase the diagnostic yield, though this is not practical in current medical practice. Visual yield of spirochetes in peripheral blood smears diminishes with each successive febrile sampling. *B. hermsii* can be cultured in BSK-II medium, with the yield increasing in acutely febrile patients. Serologic tests are difficult to perform and do not yet have practical usefulness.[393] TBRF was found long after delivery in a Colorado mother and newborn.[77] TBRF is underrecognized and underreported and has been misdiagnosed as Lyme disease.[127] A strong clinical suspicion coupled with a thorough history is crucial to avoid misdiagnosing patients with relapsing fevers. The differential diagnosis for TBRF includes louse-borne relapsing fever (LBRF) if the patient is in or has traveled to areas endemic for LBRF (see Chapter 41, Arthropod Envenomation and Parasitism).

Treatment

Tetracycline and erythromycin are both effective in treating relapsing fever. For TBRF, doxycycline 100 mg orally twice daily for 10 days is preferred in adults, or 5 mg/kg/day divided twice daily in children or those who weigh less than 45 kg.[399,410] In patients with a tetracycline allergy, erythromycin 500 mg orally four times a day is recommended for adults, and 30 to 50 mg/kg/day divided in four doses for children (maximum, 4000 mg/day).[399,410] The first dose is recommended to be given intravenously for moderately ill patients. Fluoroquinolones play a very limited role. The borreliae are also sensitive to penicillin and chloramphenicol, but treatment failures have been reported with these agents.[55]

In patients with CNS disease, parenteral administration of ceftriaxone for 10 to 14 days is recommended, at 1 to 2 g intravenously or intramuscularly every 12 hours in adults (maximum, 4 g/day). Children should receive 50 to 75 mg/kg divided once or twice daily.[55,399] In an Israeli study, with TBRF caused by *Borrelia persica,* soldiers who were exposed to TBRF endemic areas were prophylactically given doxycycline 200 mg orally on day 1, and then 100 mg/day for 5 days.[191,310] None of the soldiers thus treated developed TBRF, although 20% of soldiers in the same area had previously contracted the disease.[310]

The Jarisch-Herxheimer reaction (JHR) often occurs after the first dose of antibiotics when treating borreliae. In one series, 54% of patients developed the JHR.[127] It is often severe and may be fatal. The reaction begins with a rise in body temperature and exacerbation of existing signs and symptoms; vasodilation and a fall in blood pressure follow. This complex reaction is mediated in part by products of mononuclear leukocytes. The leukocytes are stimulated by increased contact with antibiotic-altered spirochetes. Neither endotoxin nor complement appears to be necessary in the pathogenesis of the JHR.[55,56] The JHR typically occurs within a few hours of initial antibiotic dosing. The JHR has been documented after administration of ciprofloxacin in a pediatric patient.[469]

TICK-BORNE VIRAL DISEASES

COLORADO TICK FEVER

Colorado tick fever (CTF) is caused by the genus *Coltivirus.* It is also called mountain tick fever, mountain fever, and American mountain fever. CTF is found in the western one-third of the United States and Canada and is primarily transmitted by *Dermacenter andersoni,* although other vectors are implicated.[253] Larval stages of *D. andersoni* ingest the virus while feeding on a viremic rodent host and pass it transtadially from larva to nymph to adult. Hibernating nymphs and adults carry the virus through the winter. Infected ticks emerge in the spring and feed on susceptible animals, renewing the cycle. Nymphal and adult ticks may also acquire the virus by feeding on viremic hosts. The virus does not appear to cause disease in its natural hosts; it cycles between the vector ticks and many reservoirs, primarily rodents.[295]

Typically, only adult ticks transmit the disease to humans, who are incidental and dead-end hosts. The attachment time required for transmission may be very brief. In human infection, viral replication occurs in bone marrow, lymph nodes, spleen, and hematopoietic erythrocyte precursor cells. The virus is thus found in mature erythrocytes, protected from the body's immune system.[230]

Disease transmission usually occurs from March through September. The incidence is 200 to 300 cases per year in the United States, usually confined to the western states, although remote cases are reported in other areas. It is not a nationally notifiable disease, though it is reported at the state level in Arizona, Colorado, Montana, Oregon, Utah, and Wyoming. CTF is primarily found in areas higher than 1219 m (4000 feet) above sea level. Blood transfusion has been documented as a means of its transmission, and the virus has been documented in blood samples up to 4 months after infection.[60]

Ninety percent of patients recall tick exposure. The incubation period is usually 3 to 6 days (range, 0 to 14 days),[178,412] after which the disease typically manifests with acute onset of fever. The fever is classically described as biphasic (like dengue fever), with fevers to 40° C (104° F) for a few days to a week, followed by a brief remission and then another bout of similar duration. This "saddle-backed" temperature pattern, however, is present in only about one-half of patients.[178,412] In some cases, further exacerbations of the fever cycle may occur. The fever may also be monophasic, presenting with persistent fever rather than defervescence and relapse. Other symptoms suggestive of a viral illness may occur in mild cases.

Severe complications can occur, particularly in children younger than age 10 years. Meningoencephalitis has been described in several children.[71,120,401,412] Two children developed a hemorrhagic diathesis and died.[178] Other unusual complications associated with CTF include pericarditis,[203] myocarditis,[133] hepatitis,[269] epididymoorchitis,[178] and pneumonitis.[178]

Information on CTF contracted during pregnancy is inconclusive, but of five cases reported, one terminated in a spontaneous abortion and in another, a live-born infant suffered multiple congenital anomalies.[308] CTF virus is known to be teratogenic in mice.[189]

Laboratory abnormalities in CTF are not specific but often parallel those of most tick-borne diseases. Leukopenia involving both granulocytes and lymphocytes is common and may be helpful diagnostically, although one-third of patients have normal WBC counts.[178] Thrombocytopenia may also develop; anemia is rare. Liver function tests may be elevated.

Diagnosis is usually made on clinical grounds. The most reliable means of laboratory diagnosis is inoculating suckling mice or cell cultures with blood or CSF from a febrile patient. PCR is used as a diagnostic tool as well, and is both highly sensitive and specific for this and many other tick-borne diseases.[339,371] Serologic testing (neutralizing antibody, complement fixation, IFA) by immunoassay is available; however, antibody titers are

slow to rise, making these tests better for following the disease course than for establishing the diagnosis.

Treatment is entirely supportive. Corticosteroids are often empirically administered for significant neurologic sequelae in viral encephalitis, such as seizures from cerebral edema, although no real benefit has been shown.[205] The specific steroid chosen and its dose and duration vary; usually, IV dexamethasone is given, 2 to 4 mg every 6 hours for approximately 5 days; use of steroids in this application is not approved by the U.S. Food and Drug Administration and thus is off label. Recovery takes several weeks, especially in persons older than 30 years,[178] and persistent malaise and weakness are common. Infection generally confers lifelong immunity.

TICK-BORNE ENCEPHALITIS

Tick-borne encephalitis viruses (TBE, or TBEV) are caused by the Flaviviridae family of viruses and found throughout Europe and northern Asia. TBE is actually a spectrum of diseases, and is known by many names, including biundulating meningoencephalitis and biphasic milk fever. They vary in severity from the mild louping ill disease in the British Isles to Russian spring-summer encephalitis (RSSE) in eastern Russia. Central European TBE often has a biphasic course, with an early viremic flu-like stage followed later by meningoencephalitis.[309] Tick-borne flaviviridae have increased both in new diseases and numbers of recognized prior diseases in the past 20 years.[257] Transmission mainly occurs by *I. ricinus* and *I. persulcatus* ticks, as well as other *Ixodes, Haemaphysalis,* and *Dermacentor* species of ticks indigenous to northern Europe and Asia.

Worldwide variants of TBE include Kyasanur Forest disease throughout India, Omsk hemorrhagic fever in Siberia, and Alkhurma virus disease in Saudi Arabia.[78] Symptoms are similar to those of the rest of the TBE complex, except that CNS symptoms are less prominent and there is usually hemorrhage of mucosal surfaces and the respiratory tract. The vector for Kyasanur Forest disease is *Haemaphysalis spinigera;* the fatality rate is 1% to 3%. Omsk hemorrhagic fever is transmitted by contact with infected animal carcasses, by drinking unpasteurized milk, and by *Dermacentor reticulatus* ticks; it has been present in Siberia since the 1940s. It initially presents in a fashion similar to other TBE cases, but rapidly progresses to pneumonia, nephrosis, and encephalitis or meningitis in one-third of patients.[255] Alkhurma virus epidemics occur in Saudi Arabia, particularly in Mecca and Jeddah during Haj (the pilgrimage to Mecca). The disease is now widespread throughout the Arabian peninsula.[302]

Symptoms range from mild viral illness to high fevers, severe headache, nausea and vomiting, delirium, coma, paralysis, and death. After an incubation period of 7 to 14 days, patients usually develop viremia (2 to 4 days of flu-like symptoms), followed by an asymptomatic period of 8 days. Patients then develop the second stage of the disease, which consists of 2 to 4 weeks of mainly CNS involvement.[309]

Treatment is purely supportive because no antiviral medication has shown benefit. A vaccine is available in Europe, Russia, China, and Canada and is recommended for persons at high risk for exposure in endemic areas, such as farmworkers, local residents, and travelers in peak incidence seasons and areas.

NORTH AMERICAN TICK-BORNE ENCEPHALITIS VIRAL DISEASES

Many viral diseases may result in encephalitis. Several newly discovered tick-borne viruses have been reported in the Unites States that cause significant rates of morbidity and mortality. Some of these flaviviruses cause diseases that parallel the course of TBE in their European and Asian counterparts.

Previously, the only TBE agent known to be endemic to North America was the Powassan (POW) virus, a Flavivirus, in Canada and the northeastern United States. Although there have been fewer than 30 confirmed cases over the past 15 years, the morbidity and mortality rates are high, often with chronic neurologic sequelae among survivors.[204] POW disease resembles mosquito-borne encephalitis and has been found when investigation for the West Nile virus is negative in clinical situations typical for West Nile virus.[75] It is often mistaken clinically for aseptic meningitis.

The vector in New England, *Ixodes cookei,* rarely bites humans.[309] Powassan virus antibodies have also been found in animals and ticks from Alaska, California, the southwestern United States, Mexico, and far eastern Russia.[222,264] The virus is transmitted by *I. scapularis* in the north-central United States, where it is regionally called the deer tick virus[128,440] and is a genotype of the POW virus.[26] Unlike most nonviral tick-borne diseases, the POW virus may be transmitted in laboratory mice as quickly as 15 minutes after attachment of nymphal *I. scapularis.* Thus, there is a very small to nonexistent "grace period" in which to remove ticks prior to disease transmission.[129] Deer tick virus cases resemble POW, with the distinguishing difference being the geographic area in which the disease is found. Reservoirs are skunks, woodchucks, hares, raccoons, and other mammals. Much is yet to be learned about these tick-borne viruses. *Dermacentor variabilis* and *D. andersoni* are also implicated in transmission of the Powassan virus. It remains to be seen if *Dermacentor* species in the United States are vectors, as they are for the TBE flaviviruses in Europe.

The usual incubation period is 7 to 14 days, after which the disease begins with sudden onset of fever to 40° C (104° F). On occasion, the incubation period can be up to 3 weeks. Along with fever, the victim suffers chills, fatigue, headache, weakness, and confusion. Nausea, vomiting, respiratory distress, and occasionally seizures may occur. Care is supportive, with antiepileptics for seizures, mechanical ventilatory support for respiratory failure, and nutritional support. As with other viral encephalitis infections, corticosteroids, usually IV dexamethasone at 2 to 4 mg every 6 hours for approximately 5 days, can be empirically administered for significant neurologic sequelae.[205] The case fatality rate for the TBE flaviviruses overall is low (1% to 5%). A notable exception is Powassan virus at approximately 10%. The morbidity rate is approximately 20% to 30% for TBEs.[204,309]

CRIMEAN-CONGO HEMORRHAGIC FEVER

Crimean-Congo hemorrhagic fever (CCHF) was first described in the 12th century in central Asia in what is now Tajikistan. Scientists in the former Union of Soviet Socialist Republics identified the disease as caused by a virus in the 1940s using "medical volunteer" subjects, and isolated the virus in 1967.[33,207] In 1967, it was also found in the Congo.[33,207] It was named Crimean-Congo hemorrhagic fever in 1973. It is also called central Asian hemorrhagic fever, or simply Congo fever, and is caused by a Nairovirus (a circular, negative-sense, single-stranded RNA virus in the Bunyaviridae family).

This virus previously affected livestock more than humans. However, human cases carry up to a 30% fatality rate. As with most tick-borne diseases, prevalence of the disease among humans has increased significantly. CCHF is endemic in more than 30 countries in southeastern Europe, Africa, Asia, and the Middle East, and has become the most geographically widespread tick-transmitted viral disease.[33,304] In Turkey from 2002 through 2011, there were more than 4400 identified cases.[195] CCHF virus is the most genetically diverse arbovirus (arthropod-borne virus). Genetically identical or similar strains are found far apart geographically, supporting the theory that the organism has spread via international livestock trade and/or migratory birds.[33] Many areas in which CCHF is found are also endemic for dengue viral disease. In these areas, it is important to distinguish between the two diseases because of the severity of CCHF and the potential for person-to-person spread of CCHF.[190,302]

The incubation period is generally 1 week if the disease is transmitted by tick bite and 7 to 10 days if it is contracted by airborne means, crushing of infected ticks, or contact during butchering and birthing of livestock. Most cases occur between June and September.

Several species of ixodid ticks are vectors; multiple species of the *Hyalomma* genus are anthropophilic and important vectors with respect to human disease. In areas endemic for CCHF, the

ticks are found in very high numbers, and often 20% to 25% of sampled questing ticks harbor CCHF.[195] Other tick genera that may transmit CCHF include *Rhipicephalus,* mainly *Rhipicephalus bursa,* and *Dermacentor* spp.[195] CCHF is also transmitted via aerosols, either from crushing ticks or from the slaughter of infected animals, or during contact with products of conception during livestock birthing. There have been multiple cases of nosocomial transmission to health care workers in Africa and Russia.[232,350] Health care personnel at a military hospital in Germany caring for U.S. military personnel from Afghanistan contracted CCHF.[87] Most nosocomial cases involve bronchoscopy and bag-mask ventilation. Airborne precautions are advised with suspected cases originating from, or in, endemic areas.

Primary symptoms are sudden onset of fever, headache, weakness, malaise, myalgias, anorexia, and mental status changes. Gastrointestinal symptoms are common, and patients present mainly with abdominal pain, hepatic enzyme elevation, and melena. Petechial rash usually occurs, sometimes leading to large areas of ecchymosis. Some cases proceed to hepatorenal syndrome, coma, and pulmonary failure within the first week. Cases with extensive multisystem organ involvement are often fatal.

CCHF is diagnosed clinically and confirmed by laboratory tests, including viral culture, PCR, and ELISA. Treatment is mostly supportive; there is some possible benefit to treatment with ribavirin.[134,475] Ribavirin has shown some benefit in postexposure prophylaxis, and should be given within 1 hour of exposure.[184] The World Health Organization recommends giving ribavirin for CCHF as a 17-mg/kg loading dose; the U.S. Department of Defense recommends a loading dose of 33 mg/kg, followed by 17 mg/kg every 6 hours for 4 days; then both protocols use 8 mg/kg every 8 hours for 6 days.[184] Little data exist for postexposure prophylaxis use of ribavirin, and it is not approved by the U.S. Food and Drug Administration for postexposure prophylaxis; therefore, this application is off label. It is best given soon after exposure, preferably within 1 hour, and may be given by IV or oral routes, with the IV route preferred if there has been a delay in initiation. The common IV regimen is 45 mg/kg as a loading dose followed by 17 mg/kg every 6 hours for 4 days, and then 30 mg/kg/day divided in three doses per day for 6 days. Oral dosing varies, from 200 mg twice daily to 4000 mg as a daily total dose for 5 to 14 days. The most common regimen is 500 mg three to four times daily for 5 to 7 days.[87] CCHF is listed by the CDC as a category C bioterrorism agent.

SEVERE FEVER AND THROMBOCYTOPENIA SYNDROME

Over the past few years, a spectrum of stereotypical cases of illness associated with tick bites have emerged in Asia and, perhaps, worldwide. These cases all demonstrate profound thrombocytopenia, leukopenia, and elevated liver transaminases, typical for many tick-borne diseases. This has been called severe fever and thrombocytopenia syndrome (SFTS).[91,351]

Cases have been reported from central and northeastern China, western Japan, and Korea since 2007, and in 2009 were found to be due to a novel Phlebovirus of the Bunyaviridae family.[91,325,351] The ixodid tick *Haemaphysalis longicornis* tested positive for the virus using PCR, although there are no vector studies to date to confirm that this tick transmits the virus.[114] One hospital in Henan province reported 538 patients with SFTS from 2011 to 2013, with encephalitis present in 19.1% of patients and an overall fatality rate of 10% to 20%; the fatality rate was as high as 44.7% in patients with encephalopathy.[91] Another hospital had 1229 cases of SFTS from 2011 to 2012 with 107 deaths. The peak incidence (69% of cases) occurred from May to July, without gender preference, and 44.2% of patients were 55 to 70 years old. The majority were farmers from rural areas.[351]

Patients presented initially with signs and symptoms of fever, fatigue, chills, myalgias, anorexia, and other vague symptoms. They later developed spontaneous bleeding and multisystem organ failure, similar to hepatorenal manifestations of hantavirus infection, CCHF, or anaplasmosis. They were found to have laboratory abnormalities similar to those associated with rickettsial diseases, including low platelet and neutrophil blood cell counts, and elevated liver transaminases.

Real-time PCR and ELISA IgM are considered the diagnostic assays of choice. There is documented person-to-person transmission.[20] Treatment is supportive.

HEARTLAND VIRAL DISEASE

A newly discovered Phlebovirus was isolated in 2009 in northwest Missouri from two farmers who presented with malaise, fever, fatigue, myalgias, and chills. They were leukopenic and thrombocytopenic. Since the initial cases, there have been eight reported cases, with one in Tennessee. Most of these required hospitalization, and the Tennessee patient, an 80-year-old male, expired. Analysis of 56,428 ticks (45,760 larvae) from the areas in Missouri from which the local cases were contracted yielded positive PCR results for a novel Phlebovirus named the Heartland virus.[296,313,384] This virus is closely related to the SFTS Phlebovirus from China, and the disease course is quite similar. No field-caught larval ticks tested positive for the Heartland virus. Only nymphal *A. americanum* ticks were positive from the above pool of ticks, evidence that the larval ticks acquire the virus from a host in the late fall or early winter, then maintain the virus through a molt, or transtadially, infecting the next host as a nymph.[384] Because questing *A. americanum* nymphs are approximately 1 mm in diameter (i.e., difficult to notice with the naked eye), education, tick awareness, and preventing the tick from attaching are crucial preventive measures.

A Kansas man presented with high fever, malaise, and fatigue and died early in the summer of 2014. The Kansas Department of Health and Environment and the CDC consider this case to be insect or tick related, given the seasonality and clinical course of the case. Known tick-borne diseases, such as those caused by *Ehrlichia, Anaplasma,* and *Rickettsia* species, as well as the new Heartland tick virus, were ruled out as causes. A novel RNA virus in the Orthomyxovirus family, of the genus *Thogotovirus,* was found to be the causative agent. It was called the Bourbon virus, named after the Kansas county in which the patient resided.[242]

TICK-BORNE RICKETTSIAL DISEASES

Species of the genus *Rickettsia* (family Rickettsiaceae) are small, fastidious intracellular parasites with gram-negative bacteria–like cell walls, a typical prokaryotic DNA arrangement, and considerable independent metabolic activity. Several major antigenic groups cause a variety of human diseases worldwide (Table 42-5). In the field of rickettsiology, there has been a plethora of new isolates of pathogens. Many of these manifest as diseases with much clinical overlap. Genetic differences between them are small, and although they may be distinguishable diagnostically, they have very similar clinical presentations.[463] Three groups are potentially transmissible to humans by ticks: spotted fever group rickettsial (SFGR) diseases, Q fever, and ehrlichial infections. Exposure to crushed ticks, or fluid from ticks, may also transmit rickettsiae.

SPOTTED FEVER GROUP RICKETTSIAL DISEASES

Rickettsiae of the spotted fever group rickettsial (SFGR) diseases share intracellular growth characteristics and a group-specific antigen. They are distributed worldwide and, with the exception of *Rickettsia akari* (rickettsial pox, transmitted by mites), are transmitted by bites of ixodid ticks (Table 42-6). Ticks serve as the natural hosts, reservoirs, and vectors for the rickettsiae.[292] The organisms replicate freely within the tick host and are passed transovarially and transtadially. Amplification of the cycle occurs when uninfected ticks feed on an infected vertebrate host or concurrently with an infected tick.

In most natural vertebrate hosts, the SFGR rickettsiae induce subclinical infection with transient rickettsemia. Human infection occurs through accidental intrusion into the natural cycle of infection or when ticks are transferred into human environments. Humans are incidental, dead-end hosts not involved in sustaining the life cycle of the organism.

TABLE 42-5 Human Rickettsial Diseases

Disease	Etiologic Agent	Arthropod Vector	Geographic Distribution
Typhus Group			
Murine typhus	*Rickettsia mooseri (typhi)*	Flea	Worldwide
Epidemic typhus	*Rickettsia prowazekii*	Body louse	Worldwide
Scrub typhus	*Rickettsia tsutsugamushi*	Chigger	Asia, Australia
Other spotted fever group	Many new *Rickettsia* spp. (see Table 42-6)	Tick	Throughout United States
Rocky Mountain spotted fever	*Rickettsia rickettsii*	Tick	Western Hemisphere
Eastern spotted fevers	*Rickettsia conorii, Rickettsia sibirica, Rickettsia australis*	Tick	Eastern Hemisphere
Rickettsial pox	*Rickettsia akari*	Mite	United States, Russia
Other			
Q fever	*Coxiella burnetii*	Tick	Worldwide
Trench fever	*Bartonella quintana*	Body louse	Africa, Mexico
Ehrlichia and *Anaplasma* infections	*Neorickettsia sennetsu, Neorickettsia risticii, Ehrlichia chaffeensis, E. ewingii, E. muris, E. ruminantium, Anaplasma* spp.	Tick	Worldwide

There have been many new rickettsial diseases found over the past several years, or found to cause human disease where they were not known to do so before this time. STARI may be caused by rickettsiae. *Rickettsia amblyommii, R. parkeri,* and novel *Rickettsia* spp. have been implicated in STARI and many cases of reputed Rocky Mountain spotted fever in some southern states.[13,68,324,333] Many previously documented RMSF cases may be due to SFGR, not specifically *R. rickettsii.*[68,333] *Amblyomma americanum* ticks in Mississippi were found to contain *Rickettsia* species, predominantly *R. amblyommii* (in 44% of questing ticks).[69] Of questing larval ticks analyzed, 24% of the larvae had *R. amblyommii,* showing a high rate of transovarial transmission.[68] SFGR diseases other than RMSF seem to have a milder disease course. However, appropriate and prompt treatment, the same as for RMSF, is generally recommended due to the significant turnaround time for diagnostic tests and the potential for severe disease caused by rickettsiae.[198]

Rocky Mountain Spotted Fever

Rocky Mountain spotted fever (RMSF) was first recognized in the Snake River Valley area of Idaho in 1896 and originally referred to as "black measles" because of the typical late appearance of the rash as dark papules. In the early 1900s, Dr. Howard Ricketts and others realized the disease was transmitted by tick vectors, and named the causative organism *Rickettsia rickettsii.* Dr. Ricketts died in 1910 from typhus, another rickettsial disease. RMSF is also known as tick typhus, Tobia fever (Colombia), São Paulo fever and fiebre maculosa (Brazil), and fiebre manchada (Mexico).

Epidemiology. RMSF is the best known of the SFGR diseases, and is found throughout the Western Hemisphere. Although the number of reported cases in the United States per year is in the thousands, the number of confirmed cases is much less. In 2014, for example, there were 3215 cases of probable RMSF reported, but only 117 were confirmed as caused by *R. rickettsii* by the CDC (from 42 states).[77] Because the 2014 data show nearly twice the number of cases as in 2010 (from 33 states), but with only 117 confirmed *R. rickettsii* cases, it is presumed that clinical overlap with some of the newly found *Rickettsia* species might be responsible for some of the cases attributed to RMSF.[36,68,333] Additionally, the 2014 cases have been found in a wider geographic distribution.

Although the disease was first discovered in the Rocky Mountains, the name is a misnomer. Most cases are found in the eastern third of the United States, with fewer than 0.2% of cases documented nationwide reported from the Rocky Mountain states. The disease has been reported in every state except Hawaii, Maine, Vermont, and Alaska, and is found in southern Canada and Central and South America. Prior to the antibiotic era and in untreated cases, the mortality rate was and is 30%.[51] With appropriate antibiotic therapy, the mortality rate has been reduced to approximately 0.5%.

Ixodid ticks of the genus *Dermacentor* are the primary vectors of RMSF in the United States: *Dermacenter andersoni,* the wood tick, in the west, and *Dermacenter variabilis,* the American dog tick, in the east. *Rhipicephalus sanguineus,* the brown dog tick, has recently been implicated in transmission of RMSF in Arizona and Mexico.[23,110] Worldwide, ticks of the *Rhipicephalus sanguineus* complex have been implicated in transmission of various spotted fevers.[165,166] In Central and South America, the main vector is *Amblyomma cajennense,* the cayenne tick. In North

TABLE 42-6 Spotted Fever Group Diseases

Disease	Etiologic Agent	Major Vector	Geographic Distribution	Primary Lesion	Usual Severity
Rocky Mountain spotted fever	*Rickettsia rickettsii*	*Dermacentor andersoni, Dermacentor variabilis*	Western Hemisphere	Disseminated vasculitic rash (only present after initial symptoms)	Moderate to severe
Other spotted fever group rickettsia (SFGR)	Numerous *Rickettsia* spp.	*Amblyomma* spp.	North America, Central and South America, Africa	Often present, varies; often isolated eschar	Mild to severe
North Asian tick typhus	*Rickettsia sibirica*	*Dermacentor* spp., *Haemaphysalis* spp.	Europe to Russian far east	Often present; eschar; may see disseminated rash	Mild
Mediterranean spotted fever	*Rickettsia conorii*	*Rhipicephalus* spp., *Ixodes* spp., *Dermacentor* spp., *Haemaphysalis* spp.	Mediterranean littoral, South Africa, Kenya, India	Often present; eschar; may see disseminated rash	Mild to moderate
Queensland tick typhus	*Rickettsia australis*	*Ixodes holocyclus*	Australia	Often present; eschar; may see disseminated rash	Mild

Carolina, *R. amblyommii* and *R. parkeri* are likely responsible for some cases of RMSF. They appear to be transmitted by *Amblyomma americanum,* the Lone Star tick, and *Amblyomma maculatum,* the Gulf Coast tick.[13,198,455] Within a vector tick species, only 1% to 5% of ticks are infected with *Rickettsia rickettsii,* although coinfection of the tick with other rickettsial species previously felt to be nonpathogenic to humans is common.[51] The duration of tick attachment required for RMSF disease transmission is as short as 6 hours. The bacterium is readily transmitted by the transovarial route, with 100% transmission in one study.[273]

Rickettsiae are well maintained in the tick population, because ticks may serve as both vectors and hosts. Large mammalian species serve as additional reservoirs. Dogs are an important host of *Dermacenter variabilis* and can develop an acute rickettsial illness consisting of rash and fever. Additionally, dogs carry infected ticks home, and many cases of RMSF have been obtained by deticking dogs, when the ticks get crushed.[28,180,316] Other tick species have recently been found to harbor rickettsiae and are responsible for newly discovered rickettsial diseases. *Amblyomma maculatum* has been found to transmit *R. parkeri* throughout the southeastern United States.[198,333,455] Many of these cases have likely previously been attributed to RMSF.[333] In 2010 in California, a *Rickettsia* species documented decades prior, called *Rickettsia* species 364D, was shown to cause fever, malaise, headache, lymphadenopathy, and the presence of a single eschar in patients. It now has a proposed name of *Rickettsia phillipi* and is transmitted by *Dermacentor occidentalis.*[253,395]

RMSF is a seasonal disease: 95% of cases in the United States occur between April and September, with a peak in May through July. Exposure to habitats for the vector ticks, such as woods and grassy areas adjacent to woods, increases the chance of acquiring the disease. There appear to be "islands" of infection, which could be partially accounted for by transovarial transmission.[287] The disease is slightly more common in males (60% of cases) and in individuals younger than age 20 years (50% of cases).[95,439,444]

Children age 5 to 9 years in the mid-Atlantic and southern states have the highest incidence.[95] The demographic groups most likely to contract the disease are more likely to participate in outdoor activities.

Pathophysiology. *Rickettsia rickettsii* are very small bacteria, 0.2 to 0.3 by 0.5 to 2.0 μm in size. They are usually introduced into the host via tick bite, although transmission via blood transfusion and aerosolization in a laboratory setting have been reported.[51,196,262] After inoculation, bacteria spread via the bloodstream and lymphatics and enter cells, specifically vascular endothelial and vascular smooth muscle cells.

Rickettsiae invade, proliferate within, and ultimately destroy capillary and precapillary endothelial cells. The organisms may also spread into larger arterioles and arteries and invade medial smooth muscle cells of vascular organs. Medial necrosis and destruction of the vascular wall may follow. At sites of endothelial cell damage, a perivascular inflammatory response ensues, and platelet and fibrin thrombi form and occlude the vessel lumen. This is the mechanism for the petechiae and eschars seen in RMSF and other SFGR cases. In severe cases, vascular thrombi lead to necrosis of peripheral body parts, including fingers, toes, external ear, and scrotum. Antibodies develop 5 to 7 days after the onset of illness but do not appear to play a significant role in the pathogenesis of the vasculitis.[482]

Clinical Manifestations and Diagnosis. The clinical appearance of RMSF ranges from very mild to fulminant, and it may be fatal within several days of onset. A history of tick exposure is present in 85% of confirmed cases.[444] The incubation period is 2 to 14 days, with a median of 7 days; fulminant disease usually has a shorter incubation period. Patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency are more likely to develop fulminant disease,[461] and RMSF is nearly always fatal in these individuals. Persons of African, Middle Eastern, or Southeast Asian descent are most likely to have G6PD deficiency. There is usually a sudden onset of fever and chills (94% of patients), with 66% reporting fever within the first 3 days, 86% reporting headache, and 85% reporting myalgias.

RMSF produces a disseminated vasculitic rash in 85% to 90% of patients. The rash, which usually occurs after onset of constitutional symptoms, usually begins on the back of the wrists, hands, ankles, and feet and spreads centripetally. It initially appears as blanching pink or red macules, 2 to 5 mm (0.1 to 0.2 inch) in diameter, that evolve into more pronounced red, papular, and nonblanching lesions. Finally, the rash becomes petechial and dark red to black; occasionally, areas of ecchymotic coalescence are noted (Figure 42-12). End-terminal vasculature areas, such as the fingertips, toes, nose, and genitalia, may become necrotic. Involvement of the scrotum or vulva is a diagnostic clue.[119] Ten percent of patients have a delayed-onset rash. Ten to 15% of patients have no rash (i.e., Rocky Mountain "spotless" fever).[192,193,196] Unfortunately, patients most likely to have no rash, mainly the immunocompromised, are also those most likely to die from the disease.[193]

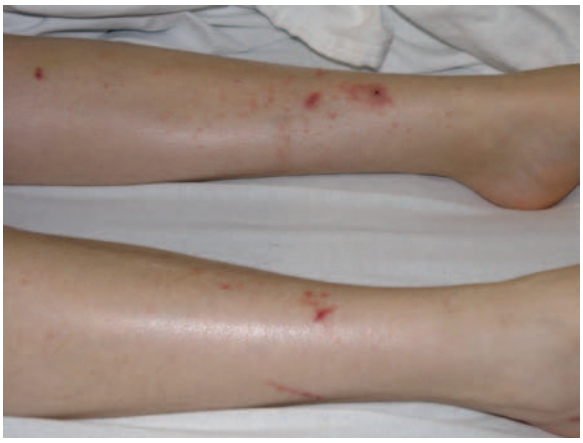

FIGURE 42-12 Typical vasculitic rash seen in Rocky Mountain spotted fever. Note erythematous, vasculitic component and early black eschar formation. *(Courtesy Gregory A. Cummins.)*

Neurologic manifestations range from minor headache to profound neurologic symptoms such as encephalopathy, seizures, ataxia, and delirium. Headache is common, occurring in approximately 90% of cases, and is of varying intensity. Lethargy and confusion are common and progress to stupor or coma in 10% of cases. Cerebral vasculitis may develop but is usually mild and transitory. CSF protein may be normal or elevated, sometimes dramatically. Mild CSF pleocytosis of lymphocytes and polymorphonuclear cells (8 to 35 cells/mm^3) may occur.

Myocarditis is frequently found at autopsy in fatal RMSF; however, the clinical significance of this cardiac involvement is unclear. Pathology studies show a patchy, interstitial, mononuclear infiltrate that appears to coincide with distribution of rickettsiae in myocardial capillaries, venules, and arterioles.[464] Abnormal left ventricular function can frequently be demonstrated echocardiographically in hospitalized patients.[146,282] Overt clinical manifestations of left ventricular dysfunction are uncommon, however. Hypotension (17% of cases) and pulmonary edema are generally attributed to noncardiogenic causes such as hypovolemia and hypoalbuminemia. Cardiac enlargement rarely may be seen on chest radiograph.[261,283] Electrocardiogram abnormalities include nonspecific ST-T changes, conduction abnormalities (primarily first-degree atrioventricular block), and arrhythmias (paroxysmal atrial tachycardia, nodal tachycardia, and atrial fibrillation).[283] Most patients have complete resolution of cardiac abnormalities with clinical improvement, but persistent echocardiographic abnormalities have been noted.[282]

Infection of the pulmonary microcirculation by *R. rickettsii* results in interstitial pneumonitis and increased pulmonary vascular permeability. Although pulmonary involvement is not usually a prominent aspect of RMSF, a significant number of patients complain of cough, chest pain, or dyspnea.[118] Patchy infiltrates are occasionally seen on chest radiographs, and noncardiogenic pulmonary edema may develop in severe cases, with potential progression to ARDS.[118,261,380]

Gastrointestinal symptoms are common in RMSF and are prominent complaints in some patients. On physical examination,

10% of patients have guaiac-positive stool. At autopsy, rickettsial vascular lesions are frequently found throughout the gastrointestinal tract and pancreas, although actual necrosis appears to be a rare event.[356] Occasionally, patients with RMSF present with an acute abdomen, suggesting appendicitis or cholecystitis.[462]

In the kidneys, focal perivascular interstitial nephritis is concentrated near the corticomedullary junction. Clinically, however, significant renal involvement is usually caused by prerenal azotemia or acute tubular necrosis after a hypotensive episode.[88] Acute renal failure has been linked to a 17-fold increase in the mortality rate.[88]

Monoarticular arthritis in the acute phase of RMSF has been reported.[437]

Major complications of RMSF result from vasculitis. In late stages of the disease, diffuse vasculitic lesions cause increased systemic capillary permeability, leading to hypovolemia and vascular collapse. Disseminated intravascular coagulation, acute renal failure, metabolic acidosis, and cardiac and respiratory dysfunction may ensue and are frequently preterminal events. Endothelial leukocyte adhesion molecules and cytokines are thought to play important roles in the pathogenesis of fulminant RMSF. The mortality rate is higher in patients with elevated serum creatinine, elevated hepatic function tests, hyponatremia, thrombocytopenia, and associated immunosuppression.[88]

Long-term sequelae among survivors of severe cases include paraparesis, hearing loss, peripheral neuropathy, bladder and bowel incontinence, language disorders, disability from limb amputation, and cerebellar, vestibular, and motor dysfunction.

Diagnosis. Early diagnosis and treatment substantially reduce the morbidity rate and virtually eliminate any possibility of death. For this reason, suspicion for RMSF is not only sufficient to begin treatment, but in the correct clinical setting, essentially mandates treatment. At the onset of illness, however, signs and symptoms may be nonspecific, leading to diagnostic confusion with viral or other infectious diseases.[229]

Serology is the best confirmatory test, but false-negative results early in the course of infection (before an appropriate antibody response) are common. A fourfold increase in titers, or a single titer over 1:64, is required for a serologic diagnosis; this is usually not achieved by the time testing is performed. Indirect IFA of *R. rickettsii* in skin biopsy specimens yields 70% to 90% sensitivity and 100% specificity and can detect rickettsiae early in the disease,[483] but this is impractical for routine use.

Routine laboratory analysis for hematology and chemistry may reveal common abnormalities that suggest RMSF. Thrombocytopenia is present in 35% to 50% of patients, and hyponatremia and anemia are common.[192,196,439]

Treatment. Antibiotics should be started empirically in patients living in or visiting an endemic area who develop any of the constitutional symptoms (myalgias, headache, fever) of RMSF. The classic triad of rash, tick bite, and fever is present in only 18% of patients within the first 3 days of illness.[196] Antibiotic treatment should not be withheld until the patient provides a classic clinical presentation. Patients started promptly on antibiotics are three times less likely to die than those started later on antibiotics.[95]

Tetracyclines are the antibiotic of choice in treating RMSF, with chloramphenicol used in rare clinical settings. For adults, doxycycline is given, 100 mg twice daily intravenously in severely ill patients or orally in mildly or moderately ill patients; or tetracycline is given, 500 mg orally four times daily. For children and adults who weigh less than 45 kg, 5 mg/kg is given in divided doses twice daily, with a maximum of 200 mg/day, generally for children 8 years or older.[399] Antibiotic treatment is generally for 5 to 7 days, or until the patient has been afebrile for at least 48 hours. Parenteral antibiotics are not necessary in nontoxic patients, but they should be used in patients who are systemically ill or unable to tolerate oral medications. Although tetracyclines are generally not used in young children because of their propensity to permanently stain developing teeth, tetracyclines are superior to other antibiotics in the treatment of RMSF, and typical courses of treatment for RMSF have been shown to have no adverse effects in the pediatric population.[59] The high mortality rate associated with improper treatment of RMSF, and the potential toxicity of chloramphenicol, warrants treatment of most young children with doxycycline, with a warning to the parents that permanent staining of teeth may occur.

Chloramphenicol should be used only if the patient is allergic to the tetracyclines or they are contraindicated; pharmaceutical levels of the drug, as well as periodic complete blood cell counts must be checked while the patient is taking chloramphenicol. Caution should be used with chloramphenicol in G6PD-deficient patients, and there are many drug interactions. The oral or IV dose for adults and children is 50 mg/kg/day divided every 6 hours, with a maximum dose of 4000 mg/day.[399] Pharmacologic consultation is recommended when using chloramphenicol.

Other antimicrobials have been used in animal studies and are as effective or nearly as effective as tetracyclines, but there are no strong data to support their use in children.[44] Even with timely and appropriate antibiotics, the mortality rate is approximately 0.5%.[193] Supportive therapy, including aggressive fluid resuscitation when indicated, is a mainstay of treatment of RMSF. Corticosteroids, usually IV dexamethasone at 2 to 4 mg every 6 hours for approximately 5 days, may be used empirically in cases of severe vasculitis or encephalitis.[293,482]

Mediterranean Spotted Fever

Mediterranean spotted fever, also called Boutonneuse fever, Carducci fever, tick typhus, Indian tick typhus, and tick bite fever, is caused by *Rickettsia conorii*. It is endemic to the Mediterranean basin, southern Asia, Africa, and India. The major vector of Mediterranean spotted fever in the Mediterranean region is the dog tick, *Rhipicephalus sanguineus*. Several tick species have been implicated as vectors in other areas; these include *Haemaphysalis leachi, Rhipicephalus simus, Dermacentor reticulatus,* and *Ixodes hexagonus*.[144] All stages of *R. sanguineus* occasionally attach to humans, and dogs may be important in transporting the ticks close to humans.[448]

Infection with *Rickettsia conorii* usually results in mild illness, although symptoms can be severe in 10% of patients, typically older adults or immunocompromised patients. Symptoms are fever, exanthems, and an eschar or necrotic plaque at the tick bite site. Fever of 39° to 40° C (102° to 104° F) and erythematous papules, primarily in the lower extremities, are nearly universal. A black eschar, appearing like a button at the site of the tick bite, is seen in 71.8% of patients (Figure 42-13). Additionally, a vasculitic rash, similar to that seen in RMSF, may occur on the palms, soles, wrists, and ankles. In some cases, the only symptom is lymphadenopathy. The incubation period is typically from 4 to 15 days but may be as long as 28 days. Although the disease is usually mild in children and young adults, a malignant form resembling severe RMSF has been described.[361,460,461] Older adults, alcoholics, and patients with G6PD deficiency appear particularly at risk.[461]

The incidence varies, from 51.6% of those reporting tick bites in Croatia, to 4.6% to 13.5% in a region of Spain, 13.3% of healthy patients in Turkey, and 16.7% in Zambia. Numerous cases have been imported, diagnosed, and confirmed in the United States and Canada from travelers to endemic regions.

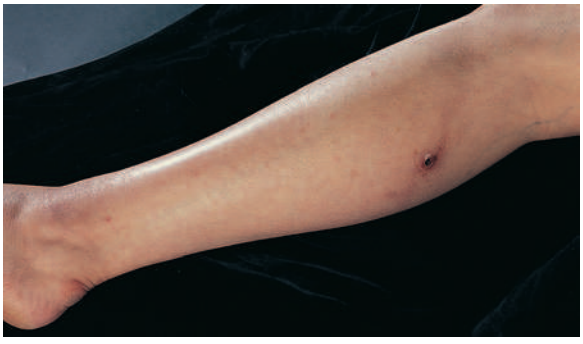

FIGURE 42-13 Tick-bite eschar associated with African tick typhus. *(From Armstrong D, Cohen J, editors:* Infectious diseases, *London, 1999, Mosby, with permission.)*

Abnormal laboratory values and other clinical symptoms share the clinical picture often seen with other tick-borne diseases. Treatment is with tetracycline, administered orally or parenterally, with typical dosing for RMSF. Chloramphenicol and the fluoroquinolones are reasonable second-line agents. Ciprofloxacin at 500 to 750 mg orally twice daily for 7 to 10 days for adults, or 20 to 30 mg/kg/day divided in two doses for children (maximum 1500 mg daily), has been used in Europe to treat Mediterranean spotted fever.[376,399]

Siberian Tick Typhus

Siberian tick typhus, or North Asian tick typhus, caused by *Rickettsia sibirica,* is found throughout northern Russia and on islands of the Sea of Japan. It is primarily transmitted by various *Dermacentor* and *Haemaphysalis* species ticks. Symptoms are very similar to RMSF, although the disease is seldom fatal. Diagnosis and treatment are the same as those for the other spotted fever group diseases.

African Tick Bite Fever

African tick bite fever is caused by *Rickettsia africae*. It is similar to Mediterranean spotted fever but typically occurs without the rash. It is transmitted by *Amblyomma hebraeum* and is endemic to sub-Saharan Africa. Although rarely reported in indigenous peoples, it is well documented in travelers to the African continent.[213,219]

Queensland Tick Typhus

Queensland tick typhus is caused by *Rickettsia australis* and is transmitted by *I. holocyclus*, which is also the primary vector of tick paralysis in Australia. It is also very similar in appearance to the other spotted fever groups, and is diagnosed and treated in the same fashion.

Q FEVER

Q fever is a worldwide zoonosis affecting both wild and domestic animals. It was first described in 1937 as an occupational disease of abattoir workers and dairy farmers in Australia.[111] The name Q fever derives from the word Query, because when the disease was discovered, the cause was unknown. Aerosol spread of *Coxiella burnetii,* the causative organism, is the usual mode of transmission to humans. Sexual transmission has been implicated but not proved.[249] Although ticks may become infected with *C. burnetii* after feeding on an infected vertebrate, tick-borne transmission to humans appears to be very rare. The incubation period is typically 2 to 4 weeks, although the incubation period should not be used as an exclusion criterion.

As of December 13, 2014, there were 138 cases of acute and chronic Q fever reported for 2014 in the United States.[77] Individuals may have asymptomatic infection. Serosurveys have shown widespread prevalence; this suggests frequent asymptomatic infection or underdiagnosis and underreporting.[185,400] Random population surveys showed 3% of people have antibodies to *C. burnetii,* with antibodies as high as 20% in high-risk (occupation) individuals.[185,297]

The most common clinical manifestation of Q fever is an influenza-like illness with fever, headache, myalgias, and pneumonitis. Abnormal liver function tests, jaundice, and hepatomegaly may be seen, and Q fever may cause acute acalculous cholecystitis.[370] Glomerulonephritis has been reported with both acute Q fever and endocarditis-associated chronic infection.[241] *C. burnetii* is not known to be teratogenic, but infection during pregnancy may cause placental insufficiency, resulting in premature delivery or even intrauterine death[360]; the risk of miscarriage is also increased.[360] Reported neurologic manifestations of Q fever include acute cerebellitis with tonsillar herniation,[385] meningitis/encephalitis/meningoencephalitis,[37] transverse myelitis,[37,465] and peripheral neuropathies.[37,406] Cardiac involvement in acute Q fever is rare but may include pericarditis,[25] endocarditis, or myocarditis.[155] In most patients, symptoms resolve spontaneously within 2 to 4 weeks of onset, with treatment hastening the resolution.

Q fever may also manifest as a chronic infection, with or without a history of an acute episode. Granulomatous hepatitis and culture-negative endocarditis are the major manifestations of the chronic forms of the disease. Endocarditis, fatal in 25% to 60% of patients, can affect native and prosthetic valves (underlying valvular disease is almost invariably present), and it has a predilection for the aortic valve.[176] Infections of aneurysms and vascular prostheses have also been described.[154] A post–Q fever syndrome involving fatigue, myalgia, arthralgia, night sweats, sleep disturbances, and mood alterations has been described and may occur in 20% to 42% of proven cases.[15,338]

Diagnosis of Q fever depends primarily on serologic testing. Two specific complement-fixing antibodies (phase 1 and phase 2) develop after infection with *C. burnetii*. In patients with acute Q fever, phase 2 antibody is usually detectable by the second week of illness; phase 1 is not detectable. The finding of phase 1 antibody indicates chronic infection. IgA subclasses (IgA1 seen in acute and chronic disease; IgA2 seen only in chronic disease) may also help differentiate between chronic and acute infection. Only patients with endocarditis were found to have IgA2 antibodies to phase 2 antigens.[61]

For the acute phase in adults, the dosage is doxycycline, 100 mg twice daily, or tetracycline, 500 mg orally four times daily. For children and adults who weigh less than 45 kg, the dosage is 5 mg/kg divided twice daily, with a maximum of 200 mg/day, generally for children 8 years or older.[399]

Treatment of chronic Q fever is not always successful. Patients probably need to be treated with tetracycline for at least 12 months, and up to 3 years if endocarditis is present.[61] Some authorities recommend adding another drug, such as lincomycin or cotrimoxazole, but efficacy of this strategy is unproved.[157,450] Patients with endocarditis typically receive treatment with tetracycline and a quinolone for at least 4 years, although new research supports shortened treatment with doxycycline and hydroxychloroquine.[359] Some recent isolates of *C. burnetii* are showing resistance to doxycycline.[371] A vaccine is used to prevent infection in high-risk abattoir workers. Preventive measures such as avoidance of potentially infectious animal tissues, especially raw milk and products of conception, should be taken. Pregnant patients should be aggressively treated with cotrimoxazole for the duration of the pregnancy, because insufficient treatment is associated with a higher rate of fetal loss.[358]

EHRLICHIOSIS AND ANAPLASMOSIS

Ehrlichiosis and anaplasmosis are febrile tick-borne diseases caused by numerous species of the genera *Ehrlichia* and *Anaplasma*. At Camp Bullis, Texas, in the 1940s, there was an epidemic of disease among World War II U.S. Army recruits. The illness was associated with bites from the Lone Star tick, *A. americanum*. The disease became known as Bullis fever.[481] In retrospect, it is very likely that Bullis fever was human ehrlichiosis.[170,173]

Ehrlichiosis was "discovered" in the mid-1980s when several individuals in rural areas of central and northern Arkansas became ill with a febrile disease that had many of the symptoms of RMSF, with which they were initially diagnosed.[152] Clusters of bacteria in intracytoplasmic inclusions were identified as an *Ehrlichia* species, similar if not identical to *Ehrlichia canis*. *E. canis* had previously been known to infect only dogs.[275] The new bacterium was later isolated and given the name *Ehrlichia chaffeensis,* after U.S. Army Fort Chaffee, Arkansas, the site of the original cultures.[415] The late 1980s and early 1990s yielded several hundred cases, including some fatalities. By the year 2000, there were more than 1000 reported cases of ehrlichiosis. As of December 13, 2014, there were more than 3440 combined reported cases of ehrlichiosis and anaplasmosis in the United States.[77] Most cases are sporadic; however, there are epidemics in some occupational and recreational groups, such as military personnel in field exercises and golfers with frequent errant shots.[171,340,414,490]

The taxonomy of the species that cause ehrlichiosis is very complicated and has undergone frequent change. This is a dynamic area of research, with new species and new vectors being found frequently worldwide.[124,125,349] The species that cause the various ehrlichioses belong to the family Anaplasmataceae

and are obligatory intracellular gram-negative bacteria. They multiply in host cell vacuoles and form large mulberry-shaped inclusion bodies called morulae. Together, *Ehrlichia* and *Anaplasma* species have become the causes of the most prevalent life-threatening tick-borne diseases in the United States.[212]

Bacteria in the family Anaplasmataceae causing human disease are divided into three genera: *Neorickettsia* (formerly *Ehrlichia sennetsu* and *E. risticii*), *Anaplasma* (formerly *Ehrlichia phagocytophilum* and *E. equi*), and other *Ehrlichia* spp. A fourth genus, *Wolbachia,* is found only in insects and noninsect invertebrates. The predominant *Ehrlichia* species causing human disease are *Ehrlichia ewingii, E. chaffeensis, E. canis, E. muris,* and *E. ruminantium*.[125] New *Ehrlichia* species affecting humans were found in California, Georgia, Minnesota, and Wisconsin and in Central and South America.[57,69,206,331,366] Dozens of different individual strains of *E. chaffeensis* have been isolated from U.S. patients in the southern states. Additional strains have been isolated from animal sources, although human involvement related to these strains is not well established.[123]

EHRLICHIOSIS

The first of the ehrlichiae identified as a cause of human disease was *E. chaffeensis,* a close relative of *E. canis,* long known to cause disease in dogs. Although reported in 46 states and worldwide, *E. chaffeensis* is found predominantly in the eastern half of the United States. It is transmitted predominately by *Amblyomma americanum,* the Lone Star tick. The newly described *E. muris*–like *Ehrlichia* (EML) in the north-central states is found in and likely transmitted by *Ixodes scapularis*.[69,349] Retrospective analysis of ticks from the 1990s in this region revealed EML present at a rate of approximately 1%. It is suspected that *I. scapularis* ticks in other areas could also transmit EML.[441] EML is unusual in that it is found in ticks and reservoir hosts that are usually involved with the anaplasmal infections; however, it causes ehrlichiosis.[349] Ehrlichiosis infects mononuclear phagocytic cells, particularly monocytes, although other cell types may also be affected. Various organs are affected, particularly those with abundant mononuclear phagocytic cells. Cross-reactivity exists between the tests for *E. chaffeensis, E. ewingii,* and *Anaplasma phagocytophilum,* so it is possible that not all cases attributed to *E. chaffeensis* are truly caused by this organism.[234] This may change as tests become more specific.

The primary vector of ehrlichiosis in the United States, *Amblyomma americanum,* has not been as extensively studied as *I. scapularis* ticks, the primary vectors for ehrlichiosis and Lyme disease. Massive amounts of research are now going into studying how much *Amblyomma americanum* is involved in tick-borne diseases in the United States. The states with the highest incidence of ehrlichiosis were Arkansas, Delaware, Kentucky, Maryland, Missouri, New Jersey, North Carolina, Oklahoma, Tennessee, Virginia, and Wisconsin.[298] As of December 13, 2014, the CDC confirmed 1384 cases of ehrlichiosis.[77]

Ehrlichiosis occurs worldwide, and was recently found in Australia.[291] Causative agents in the United States are *E. chaffeensis, E. ewingii, or E. muris*-like species. Internationally, there are multiple tick vectors, primarily ticks of the *I. ricinus* complex in Eurasia; *Amblyomma cajennense* in South America; and *Amblyomma testudinarium, Haemaphysalis yeni,* and *Rhipicephalus sanguineus* in China.[63,366,470] There are also many species of *Ehrlichia* that cause disease worldwide, with regional and geographic variants.

Nontick transmission has been suggested by the occurrence of ehrlichiosis after contact with infected animal blood.[18] *E. chaffeensis* can live in refrigerated blood for longer than 11 days, so transmission by blood transfusion is possible.[294] The ehrlichiae can also be transmitted by solid-organ transplantation, as evidenced by two renal transplant recipients who developed ehrlichiosis from a common kidney donor.[379] Both patients experienced postoperative fevers 3 weeks after transplantation, and extensive workup revealed *E. chaffeensis* as the cause. Both patients were treated and fully recovered.[379]

In the United States, ehrlichiosis is transmitted primarily in the months of March through November, with 70% of the cases occurring between May and July.[150,151,415] Cases are reported in the late fall and winter months from southern areas. Ehrlichiosis has a male-to-female ratio of greater than 2:1, and is reported more often in patients older than age 40 years.[150] Younger patients may have less symptomatic disease and thus go unreported. History of a tick bite is present in approximately 68% to 80% of patients.[136,150] The high rate of recollection of a tick bite is probably a result of the pain associated with the relatively long mouthparts of *Amblyomma americanum* and the immunogenic local reaction that can accompany the bite.

There are numerous reservoirs for the ehrlichiae. *Amblyomma americanum* is very nonselective in its feeding and is found on a variety of birds and mammals.[38,79] In the United States, the white-tailed deer is the most important host. Domestic dogs also are vital in the epizootiology of the ehrlichioses. Dogs outnumber every other large mammal in the United States and are often infected, with a Virginia study showing 38% of dogs from southeastern Virginia positive for *E. chaffeensis*.[105] Dogs also provide a large degree of interface between the wilderness areas and the domestic front, and often carry ticks into the home.[28,316] A study of coyotes in Oklahoma documented infection rates of 71%.[240] Wild turkeys also host *A. americanum,* which is so abundant on some turkeys that it is referred to as the "turkey tick" in some areas.[109]

ANAPLASMOSIS (FORMERLY HUMAN GRANULOCYTIC EHRLICHIOSIS)

In the 1990s, *Anaplasma phagocytophilum* was identified as a human pathogen. This bacteria primarily infects neutrophils. This species causes disease predominately in the north-central and northeastern United States, although like ehrlichiosis, it can be found in the eastern half of the United States. It is transmitted primarily by *I. scapularis* and *Dermacenter variabilis.* The numbers of reported cases quickly exceeded those from the original areas of *E. chaffeensis* infection. In 2014, the CDC reported 1924 confirmed cases of anaplasmosis in the United States.[77] Reservoir hosts are similar to those for ehrlichiosis, with slight geographic variances.

CLINICAL FEATURES OF EHRLICHIOSIS AND ANAPLASMOSIS

The clinical features of ehrlichiosis and anaplasmosis are very similar. Within 1 to 2 weeks of exposure to an infected tick, a prodrome of malaise, back pain, gastrointestinal symptoms, and fevers up to 39° C (102° F) develops. Symptoms usually manifest within 3 to 4 days of onset and include fever (>95%), headache (60% to 75%), myalgias (40% to 60%), nausea (40% to 50%), arthralgias (30% to 35%), and cough or dyspnea (20% to 25%).[136,150] Respiratory complications are common; cough, pulmonary infiltrates, dyspnea, and respiratory failure have been reported. Rash is noted in both ehrlichiosis and anaplasmosis, although it is more common in the former (40%) than in the latter (8%).[124] Anaplasmosis cases are generally less severe and less symptomatic than are ehrlichiosis cases.[17]

Meningoencephalitis is the most common neurologic complication. In one study of 15 patients with altered sensorium from ehrlichiosis who underwent CSF testing, 8 had abnormalities, including elevated lymphocytes (≤ 1000 cells/μL) and protein. In a review of 21 additional cases with CNS manifestations, 13 patients had abnormal CSF findings. Fourteen patients underwent brain computed tomography, revealing no radiographic abnormalities. Four of 21 patients with CNS symptoms died.[362] Fatigue, headache, weakness, and other vague neurologic symptoms may persist for weeks despite appropriate treatment.

Hematologic complications are also described. In ehrlichiosis, bone marrow and hepatic granulomas and multiorgan perivascular lymphohistiocytic infiltrates have been observed. In anaplasmosis, opportunistic fungal and viral infections are more frequent, due to rickettsial-mediated defects in host defense and immune suppression.[124,459]

Approximately half of patients require hospitalization. In severe cases, patients suffer renal failure, pancytopenia, disseminated

intravascular coagulation, ARDS, hepatic failure, profound hypotension, and death. There is an estimated 1% fatality rate, down from 5% in the mid-1990s, with the rate for ehrlichiosis slightly higher than for anaplasmosis.[298] Of patients who die, 70% are males. Death usually results from multisystem organ failure, usually with profound pulmonary, hematologic, and gastroenterologic manifestations. Generally, immunocompromised patients, individuals older than age 60 years, and those not receiving appropriate antibiotics within 5 days of the onset of symptoms are at highest risk of death.[150]

DIAGNOSIS

In patients with symptoms suggestive of ehrlichiosis or anaplasmosis, diagnosis is suggested by a history of a tick bite in an endemic area and confirmed by diagnostic testing. As in the case of RMSF, testing should never delay treatment.

Multiple abnormalities may be noted on routine blood testing. The complete blood count shows mild to moderate thrombocytopenia in 70% to 90% of patients and mild to moderate leukopenia (principally lymphocytopenia) in 60% to 70% of patients. Hepatic transaminases two to four times the normal are noted in 80% to 90% of patients at some point in their illness, often early in the course. Hyponatremia is present in up to 50% of adult patients and 70% of pediatric patients.[214] Some of these laboratory abnormalities normalize after the patient has been sick for more than 7 days.[17] Elevated creatinine, elevated fibrin degradation products, and prolonged coagulation times are indicative of more severe disease and carry a poor prognosis.

Serologic tests confirm the diagnosis, but the results are rarely, if ever, immediately available. The most widely used test is an IFA, which detects IgG and IgM, available for *Anaplasma* and *Ehrlichia* spp. A rise in titer of fourfold or greater, or a single titer of 1:256 or greater, is sufficient to confirm the diagnosis. The serologic tests use an antibody reactive to the appropriate species targeted; the degree of cross-reactivity between ehrlichiae is unclear. The gold standard is the IFA, which is 95% sensitive and 100% specific when properly performed at appropriate times. Early testing often yields false-negative results, however, because of the relatively slow human antibody response to these organisms. Suspicion of disease in the appropriate setting should therefore prompt treatment, and a negative test early in the presentation should not preclude antibiotics.

Western blot tests identify the organisms but do not play an important role in diagnosis. For *E. ewingii,* however, the Western blot test is useful for diagnosis, because there is no IFA test for this organism. ELISA tests are being developed but are not routinely used. PCR has the advantages that any tissue can be used and the disease can be detected early. Blood smear testing has very low sensitivity and specificity, is very operator dependent, and plays little role in diagnosis. In a skilled laboratory, morulae were present in the cytoplasm of WBCs at a rate of 20% to 80%, and then only if obtained in the first week of infection and when the patient was febrile, or during transient bacteremia.[17,355] In a pathology review of 14 known anaplasmosis cases, using three independent pathologists, the ideal number of granulocytes reviewed to reveal morulae was 200.[355] This makes blood smears for morulae not practical for current medical practice. Culture is feasible but is technically difficult, requires specially equipped laboratories and special media, and takes several weeks.[415]

TREATMENT

Ehrlichia and *Anaplasma* species are susceptible to tetracyclines but resistant to many antibiotics, including aminoglycosides, fluoroquinolones, penicillins, macrolides, and sulfa drugs. Tetracyclines are the antibiotics of choice in treating ehrlichiosis and anaplasmosis. For adults, doxycycline is given, 100 mg twice daily intravenously in severely ill patients or orally in mildly or moderately ill patients; or tetracycline is given, 500 mg orally four times daily. For children and adults weighing less than 45 kg, 5 mg/kg divided twice daily is given, with a maximum dosage of 200 mg/day, generally for children 8 years or older.[399] Treatment for 7 to 10 days (or for 3 days after the last febrile episode) is typically adequate. Failure to respond within 48 to 72 hours of initiation of antibiotics suggests a different diagnosis or coinfection. Other antibiotics may be considered when tetracyclines are contraindicated. Rifampin is very bactericidal in vitro, but it has not been used in large trials in vivo.[43,48] Chloramphenicol, which has been used in children with varying degrees of success,[24,263] has been shown to have weak inhibitory action, but it is not bactericidal.[236] Both rifampin and chloramphenicol are safe in children with proper administration but are rated as category C for use during pregnancy. Despite this rating, a pregnant patient with anaplasmosis was treated successfully with rifampin.[49]

BABESIOSIS

Babesia species, like malarial organisms, are pleomorphic intraerythrocytic protozoan parasites. More than 70 distinct species have been described from various vertebrate hosts.[367] Some of the most important species include *Babesia bigemina, Babesia bovis,* and *Babesia divergens* (all in cattle); *Babesia caballi* and *Babesia equi* (horses); *Babesia canis* (dogs); and *Babesia microti* (rodents). Babesiae are transmitted to vertebrates primarily through the bites of ixodid ticks.

EPIDEMIOLOGY

Babesiosis has long been recognized as an important veterinary disease, receiving biblical reference as the "divine murrain" infecting cattle of the Pharaoh, Ramses II (Exodus 9:3). Various epidemics of cattle fever have been documented throughout history.[42]

Human disease was originally reported in 1957 in a splenectomized man in Yugoslavia.[403] Five cases of human infection with bovine *Babesia* (*B. bovis*, *B. divergens*) were reported from Europe between 1957 and 1976; two cases of babesiosis of unknown species were reported from California in 1968 and 1981; a human case of *B. gibsoni* infection was reported in California in 1993; and a single *Babesia caucasia* infection was reported from Russia in 1978.[220,367,372] These cases were widely separated geographically and all occurred in splenectomized individuals.

The incidence of *B. microti* is higher than that of other *Babesia* species because of its ability to produce disease in individuals with intact spleens. Since 1970, the incidence of human babesiosis has accelerated, primarily because of *B. microti* infections in the northeastern United States. In 1969, babesiosis was recognized in a patient with an intact spleen on Nantucket Island, Massachusetts.[473] Since then, hundreds of cases have occurred in the United States.[96,300] *B. microti* is endemic to the coastal regions of southern New England, where the principal vector is the northern deer tick *I. scapularis*. Most cases are contracted on Cape Cod and the offshore islands of Massachusetts (Nantucket, Martha's Vineyard), New York (Shelter Island, Long Island), Rhode Island,[96,368] and New Jersey.[201] U.S. cases have also been reported from Wisconsin[341] and Minnesota, known foci of *I. scapularis*.[431]

Although babesiosis has historically been considered an illness predominantly of the United States and Europe, reports from Canada,[50,228] Australia,[160,394] and China[221,436] suggest that it must now be considered a worldwide disease.

Although most cases of babesiosis in the United States involve *B. microti,* infection occurs with other strains. A strain of *B. microti* termed WA-1, thought to be spread by *I. pacificus,* was isolated from an immunocompetent patient with an intact spleen in Washington State.[352] Another strain, termed MO1 and similar to (but distinct from) *B. divergens,* was isolated in Missouri.[202] *B. divergens* infection is reported in the United States but is rare.[27] *B. divergens* was found in 16% of cottontail rabbits in Nantucket, indicating an abundant reservoir in at least that area.[175] The ecology of *B. microti* parallels that of *B. burgdorferi,* the agent of Lyme disease, and coinfection may occur.[286] The major vector in both diseases is *I. scapularis*. White-footed mice *(Peromyscus leucopus)* constitute the major reservoir for *B. microti*. Larval or nymphal ticks ingest the parasite during a blood meal from an infected rodent. Babesiae replicate within the tick and are passed

transtadially. Amplification of the cycle occurs when the infected tick transmits the organism to a vertebrate host during the next blood meal. White-tailed deer *(Odocoileus virginianus)* are the principal hosts for adult ticks; larvae and nymphs feed on deer, mice, and other small mammals.[411]

Human babesiosis most often occurs when humans accidentally intrude on the natural cycle and are bitten by an infected tick. As is the case with other tick-borne diseases, the peak incidence is during the warm weather months from May to September, when ticks are actively feeding.[303]

An epidemiologic survey of 136 cases in New York State showed that the most important risk factors for severe babesiosis are advanced age, asplenia, and immunodeficiency. Babesial infection appears to be as prevalent in children as in adults, although the disease tends to be more severe in persons older than age 40 years. In one study, 23% of patients with babesiosis had concurrent Lyme disease infection.[300] Case reports have shown multiple coinfections involving borreliosis, ehrlichiosis, and babesiosis,[307] with more severe symptoms in coinfected individuals than in those infected with a single organism.[247]

Prolonged, subclinical infection creates the potential for transmission of *B. microti* through blood donation. Transfusion-associated babesiosis is well documented,[115,116,200,228,263,281,404] has reportedly transmitted new species of *Babesia,*[200] and is a growing concern.[200,228] A fatal case of transfusion-related babesiosis occurred in Delaware in 2009.[493] Seroprevalence surveys in endemic regions show donor exposure rates from 1% to 3%,[93,223,408,446,480] and a longitudinal study of exposed U.S. blood donors (defined as a 1:64 indirect fluorescent antibody titer for *B. microti*) found that 21% demonstrated active parasitemia over a 3-year period.[262]

Control of transfusion-related infection relies predominantly on identifying donors at high risk of exposure (endemic regions, history of tick bites, or seasonal exposure to tick-favorable landscapes). A pilot study found that a combination of *B. microti* IFA and PCR screening showed great promise as a mechanism to decrease transfusion-related babesiosis.[491] Although testing the entire U.S. blood supply would likely be prohibitively expensive,[93] universal antibody screening in endemic areas may prove to be a cost-effective strategy.[402]

Neonatal babesiosis may result from tick bites or transfusion (as in adults), but may also be acquired congenitally through vertical transmission.[3,155,156]

PATHOGENESIS

Babesiae are transmitted from wild and domestic animal reservoirs to humans by *Ixodes* ticks. The life cycle of *I. scapularis* (the vector for transmission of *B. microti* to humans from rodents) spans 2 years, beginning in spring of the first year with hatching of the larval form. In late spring and summer months, the larvae feed on a variety of hosts and acquire babesial infection. Typically, larvae become infected from their preferred host, the white-footed mouse *Peromyscus leucopus*. Ingested babesiae reach the gut of the feeding tick, where they reproduce asexually. The newly formed zygote eventually spreads throughout the body of the tick. After reaching the salivary glands, the babesial sporoblasts remain dormant until the next spring, when the tick larva molts to a nymph. The nymph then seeks a blood meal, infecting a new host (rodent or human). In endemic areas, as many as 60% of white-footed mice are infected by late summer. The nymph form of the tick transmits most human disease, although adult ticks may also do so.

After inoculation by a tick bite, *Babesia* sporozoites enter erythrocytes, where they differentiate into merozoites. Great pleomorphism is displayed,[246] but ring-shaped and ameboid trophozoites are the predominant forms. Multiplication occurs by asexual asynchronous budding. After the parasite multiplies, the infected erythrocyte ruptures, freeing the organisms to invade other red blood cells (RBCs). Severe hemolytic anemia may result (Figure 42-14).

Infection with *B. microti* reduces malleability of erythrocytes, leading to microvascular stasis and decreased RBC life span. Electron microscopy has shown extensive RBC wall damage,

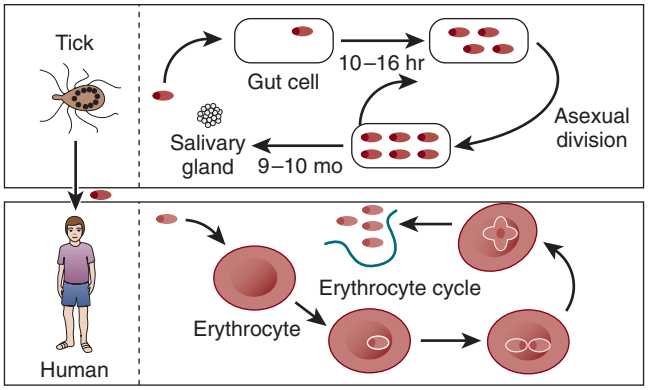

FIGURE 42-14 *Babesia* life cycle. Within a tick, babesial parasites infect gut cells, undergo asexual division, and eventually migrate to the salivary glands. The organism is introduced into a human when the infected tick takes in a blood meal. Transmission usually involves the nymphal tick, but the duration of attachment required for transmission of *Babesia* species is not known. *Babesia* species can be transmitted to humans concomitantly with *Borrelia burgdorferi. (Modified from Boustani MR, Gelfand JA: Babesiosis,* Clin Infect Dis *22:612, 1996.)*

including protrusions, perforations, and extrusions in the cell membrane. Asplenia or steroid therapy can worsen the disease and prolong parasitemia. An intact spleen preferentially destroys infected RBCs because of their decreased malleability, which plays an important role in resistance to *Babesia* organisms. Although the presence of a spleen is not protective against *B. microti,* the disease is often more severe in splenectomized patients.

Age is also an important factor in susceptibility to babesiosis. Children and young adults usually have subclinical or mild, self-limited infections, whereas older adults and those with chronic medical problems[32] are more likely to have severe, clinically apparent disease.[31,372] Prolonged parasitemia is common in babesiosis.[374] *B. microti* may persist for as long as 4 months in an otherwise healthy patient.[473] Parasitemia may remain after clinical recovery or may develop in asymptomatic individuals.

CLINICAL MANIFESTATIONS

Incubation is 1 to 4 weeks after a tick bite or 6 to 9 weeks after transmission by blood transfusion. Most victims of tick-transmitted disease do not recall a tick bite. Physical examination is usually normal, except for fever (steady or intermittent) and mild splenomegaly in some patients. Petechiae and ecchymosis rarely occur.

Acute *B. microti* infection is characterized by gradual onset of malaise, anorexia, and fatigue, followed within several days to a week by fever, sweats, and myalgias. Other, less common symptoms include headache, nausea and vomiting, depression, abdominal pain, jaundice, and dark urine. In a review of 17 patients with babesiosis, 52.9% presented with temperature greater than 38.3° C (101° F), and 4 of the 9 had morning fever spikes; 8 had relative bradycardia.[235]

The complete blood cell count usually reveals mild to moderate hemolytic anemia, a normal to slightly reduced WBC count, and (in some patients) mild to moderate thrombocytopenia. Serum lactate dehydrogenase and bilirubin levels are mildly elevated in most patients, reflecting the hemolytic anemia.[177,374] AST and ALT levels may be elevated, and urinalysis may be notable for proteinuria and hemoglobinuria. In one series, 13 of 17 patients (76.5%) had lymphopenia, and 5 (29.4%) had rouleau formation in the peripheral blood smear.[235]

A review of 139 hospitalized patients with babesiosis in New York from 1982 to 1993 attempted to identify common signs and symptoms and the prognostic factors associated with poor outcome.[474] Of the 139 patients, 9 (6.5%) died, 35 (25.2%) were admitted to the intensive care unit, and 35 (25.2%) required more than 14 days of hospitalization. Among patients with severe disease, the mean age was 62.5 years, and 62% were male. The

most common symptoms were fatigue, malaise, weakness (91%); fever (91%); shaking chills (77%); and diaphoresis (69%). Prognostic indicators for severe outcome included high alkaline phosphatase, male gender, and elevated WBC count. Only 12% of patients with severe disease had a history of splenectomy, and only 2% had received a prior blood transfusion.

Most patients with normal splenic function recover without specific therapy. Prolonged fatigue and malaise are common.[375] Spontaneous splenic rupture, although uncommon, is reported.[131] Splenectomized patients generally have more severe clinical disease, with higher levels of parasitemia and more severe hemolytic anemia.[372] Older adult patients and immunocompromised patients, such as those with HIV infection, are also at higher risk for severe infection. Pulmonary edema has been reported.[42] Typically, the level of parasitemia ranges from 1% to 10%.

In Europe, babesiosis results from infection with *B. divergens* or *B. bovis* and has been reported only in splenectomized patients. The illness is characterized by high fever, chills, headache, and severe hemolytic anemia, often resulting in hemoglobinuria, jaundice, and renal insufficiency. Major findings on physical examination include fever, hepatomegaly, jaundice, and hypotension. More than one-half of the reported cases have been fatal.[372]

DIAGNOSIS

Babesiosis should be considered in any person with an unexplained febrile illness who has lived in or traveled to an endemic region in the midsummer months, especially with a history of a tick bite or tick exposure. The diagnosis of babesiosis can be confirmed by identifying the intraerythrocytic parasites on Giemsa-stained blood smears (Box 42-2). Persons with intact spleens usually have low levels of parasitemia (<5%), and examination of repeated smears may be necessary.[177,374] The predominant forms of *B. microti* closely resemble the small rings of *Plasmodium* species. A later tetrad form (Maltese cross) may be seen and is positive morphologic evidence of babesiosis. Differentiating *Babesia* from *Plasmodium* may be difficult but is possible by noting the absence of pigment deposits in erythrocytes parasitized with the older stages of *Plasmodium* species.

When organisms cannot be detected on blood smears, the diagnosis can be made by intraperitoneal inoculation of the patient's blood into splenectomized hamsters. Serologic studies may also be helpful in confirming the diagnosis but are performed in only a few laboratories. A titer greater than 1:64 on IFA testing is considered consistent with seropositivity, and a titer greater than 1:256 is diagnostic of acute infection. No test for circulating *Babesia* antigen is available. PCR testing for *Babesia* can be as sensitive and specific as standard testing and may be reproducible enough for routine use in diagnosis of acute babesiosis.[7,246]

TREATMENT AND PREVENTION

First-line chemotherapy for patients with significant *B. microti* infection consists of 7 days of azithromycin (500 mg on day 1; 250 mg on days 2 to 7) and atovaquone (750 mg every 12 hours for 7 days). This combination has equivalent efficacy to the previously used combination of clindamycin and quinine, with less adverse drug reactions,[244] and has been used successfully in children.[3,353] Resistance to azithromycin-atovaquone therapy has been reported in severely immunocompromised individuals.[487] Usually, therapy is reserved for patients with severe disease, those with asplenia or immunosuppression, or older adults.[73] In seriously ill patients with high levels of parasitemia, exchange transfusion may also produce rapid clinical improvement.[215,435]

Patients with mild clinical disease typically recover without specific anti-*Babesia* chemotherapy, although few patients have been followed longitudinally. A recent prospective study showed that parasitemia lasted for a mean of 82 days in 24 asymptomatic subjects not treated with the standard regimen.[245]

Avoidance of ticks is the only currently effective method of preventing babesiosis. Splenectomized patients should be wary of visiting areas endemic for babesiosis.

BOX 42-2 Laboratory Diagnosis of Babesiosis

- Peripheral blood smear (Wright or Giemsa staining) showing intraerythrocytic *Babesia*
- Polymerase chain reaction
- Indirect immunofluorescent assay
- Intraperitoneal inoculation of splenectomized hamsters

TULAREMIA

Please refer to Chapter 34 for information on tularemia.

TICK-BORNE DISEASE PREVENTION AND AWARENESS

Awareness of ticks and the diseases they transmit is a necessary first step in prevention, and avoidance of ticks is crucial for all of the tick-borne diseases. Proper clothing should be light colored, because this makes ticks easier to spot. Avoiding heavily infested areas reduces exposure, as does reducing contact with leaf litter.[66,391] Reducing time in areas frequented by ticks further reduces exposure. A study of the upper surface of downed logs, as would be found and sat upon by weary hikers, yielded a large number of *I. scapularis* nymphs.[66,254] Boots provide better protection than do tennis shoes and socks.[66] Tucking pant legs into the tops of the socks reduces the ticks' ability to climb up the legs of potential hosts. A ring of masking tape or duct tape at the tops of the socks further reduces exposure.

Insecticides containing diethyltoluamide (DEET) are generally safe, work well, and may be applied directly to the skin. A light spray of a permethrin-based acaricidal spray to clothing will persist through several washings and last up to 1 month, and is highly toxic to ticks. Permethrin should not be applied to skin, because it has been associated with neurologic sequelae in mammals.[344] A light spray around bedding may deter nighttime feedings. Some outdoor gear and clothing manufacturers now produce permethrin-impregnated gear and clothing.[141] In Europe, military-issue permethrin-impregnated clothing yielded a mean rate of 95.5% protection from questing ixodid ticks.[141]

The use of the "four-poster" system in applying acaricides for wildlife or livestock has been shown to reduce tick populations significantly.[390] This system, developed by researchers in Kerrville, Texas, involves creating a feeding station for deer or cattle that has four corner posts on which are rollers soaked in a 10% permethrin solution. When livestock or wild game feed at the station, the permethrin is applied to the head and neck, an area often heavily infested with ticks. Typically, there is a 92% to 98% reduction in the tick population within 3 years.[65,390] However, ticks and other insects are showing resistance to even the most toxic of acaricidal treatments, primarily as a result of use of acaricides for livestock on a large scale.[306,357]

Frequent inspection of the body should be performed when in a tick-infested area. Although some diseases require as much as 24 to 48 hours of tick attachment, others are transmitted within an hour. The argasid ticks feed in minutes, usually while the hosts are sleeping, so avoidance or protection through habitat selection or the use of physical or chemical barriers makes sense.

Removal of attached ticks should never be done by bare or even gloved hands. A quality pair of fine-tipped forceps is necessary to safely remove embedded nymphal and adult ticks, by gently grasping the ticks as close to the skin as possible and gradually retracting outward in a straight line (Figure 42-15). Special tick-removal devices available from outdoor and camping supply companies may provide some advantage over simple forceps but generally cost more.[432] The area should then be cleaned with a local antiseptic, and the site monitored for local signs of infection or rash, with monitoring for systemic infections for up to 4 or more weeks. Other methods for tick removal, such as applying petroleum jelly to the tick, or using a lighted match or cigarette, isopropyl alcohol, or fingernail polish, do not ease

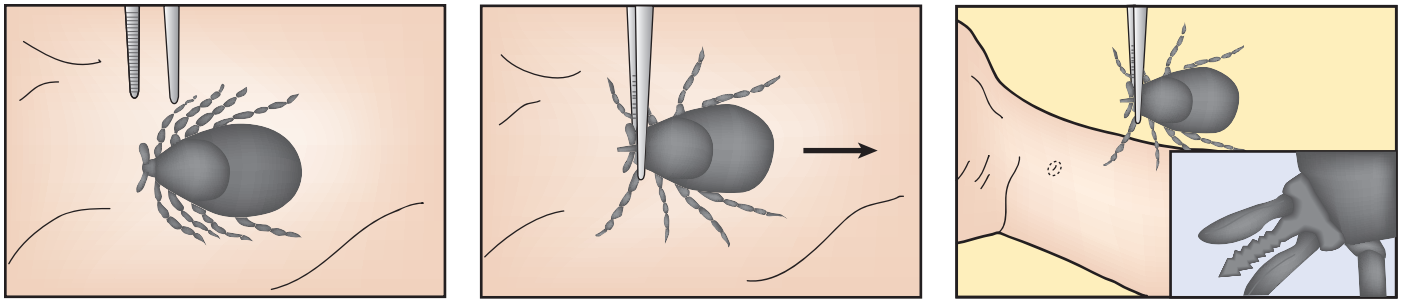

FIGURE 42-15 Ideal tick removal method. Grasp the tick near the surface of the skin and withdraw it from the skin in a steady, constant motion. Do not turn, jerk, or twist. *(From Goddard J:* Infectious diseases and arthropods, *Totowa, New Jersey, 1999, Humana Press, with permission.)*

removal. These and other "remedies" most likely increase expression of tick saliva and foregut contents, thus increasing the chance of disease transmission.[22,321] Finding attached larvae is challenging because they are less than 1 mm in size, although removal of larval ticks is easier, because their size and mouthparts are extremely tiny. A piece of tape, such as duct tape, applied to the skin or clothing and then removed, easily removes free-crawling or attached larval ticks. Lint-removing rollers also work for unattached ticks. Alternatively, the thin edge of a plastic object such as a credit card or driver's license scraped along the skin easily removes attached larvae. This method is appropriate only for larval ticks, not for nymphs or adults. Preserving removed ticks may be of benefit for identification and testing. They are ideally preserved in isopropyl alcohol, although entombing the tick between two pieces of clear tape will suffice.

Laundering clothing in hot water and drying on high heat after being in tick-infested areas generally works to kill ticks and keeps them from invading residences. However, despite exposure to hot water in the wash cycle, ticks may survive. High drying temperatures for 1 hour are generally required to kill ticks.[64] Unfortunately, expensive outdoor clothing items do not tolerate high-heat drying. Free-crawling ticks can easily be transported from the field to a vehicle during a drive home from an endemic area, and then from the vehicle to the residence. Changing clothes prior to leaving the field and placing the clothing into a large plastic bag reduces transport of ticks into the home.

For property owners and managers, proper landscaping, preferably with deer-resistant native flora, and using an appropriate barrier or buffer zone of wood chips or gravel between forested areas and formal lawn areas, has been shown to reduce the potential tick-human interaction.[122,194]

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Complete references used in this text are available online at expertconsult.inkling.com.

CHAPTER 43
Spider Bites

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SPIDERS AND THEIR VENOMS

Spiders are found in all habitats except the open sea.[39,64,219,225] There are approximately 45,500 described species. Spiders are carnivorous predators with important ecologic roles in most terrestrial ecosystems. Many are capable of wind-borne dispersal (ballooning), which has led to colonization of even the most isolated land masses. In addition to natural dispersal, spiders are common travelers in cars, planes, and ships. Spider species found and identified in international cargo arriving in North America are rarely medically significant. [316] Misidentifications often lead to costly, unnecessary, prophylactic eradication efforts, unnecessary employee training/education, unwarranted anxiety, and spoilage of perishable cargo.

As with ticks, mites, scorpions, and other arachnids, the spider's body consists of an abdomen and an unsegmented cephalothorax (prosoma) with chelicerate jaws, pedipalps, and four pairs of legs (Figure 43-1). They are distinct from other arachnids in that they have no abdominal segmentation and the male pedipalpal tarsi are modified as secondary genitalia.[271] In addition, spiders have venom that is produced in a gland in the anterior prosoma (Figure 43-2) and delivered through a cheliceral fang. On the abdomen, they have silk-producing glands and a set of spinnerets.

The overwhelming majority of spider species are carnivorous. Feeding involves a multistep process in which spiders must find, ensnare, immobilize, and digest prey externally before the liquefied meal can be consumed. The primary function of venom in spiders is to assist capture and consumption of prey. Venoms are more rarely used in defense. For their predatory function, venoms are complex mixtures of neurotoxic and proteolytic peptides, proteins, and biogenic amines.[1,15,103,194,271] A single spider's venom can have between 200 and 1000 distinct chemicals.[83] There is surging interest in spider venoms because they contain vast stores of unknown chemical compounds with potential application in research or pharmacology, or as insecticides. We direct the curious to Arachnoserver,[337] a database of sequences and structural and molecular target information of all published spider venom toxins.

Transcriptomic and proteomic analyses are beginning to reveal patterns of complexity and variation in venom composition within and among species. We focus on what is known (and

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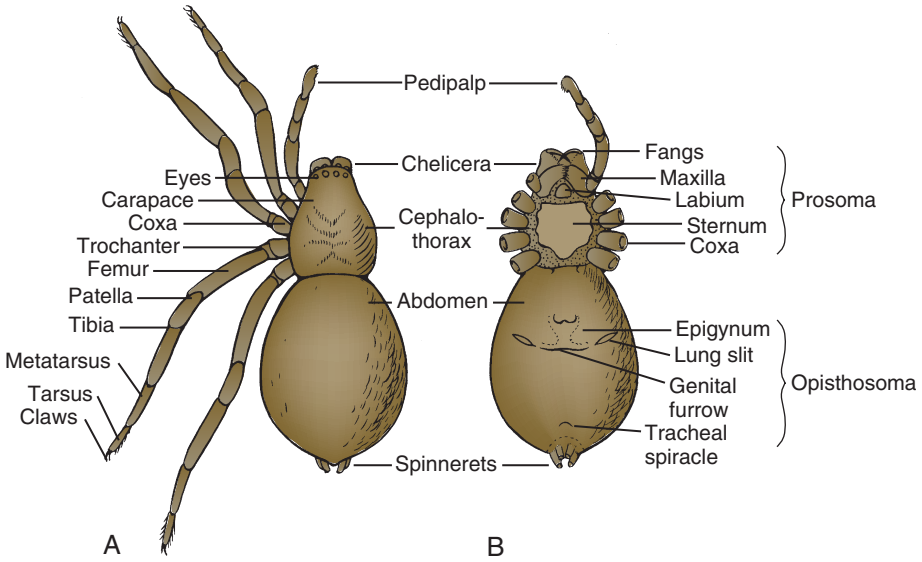

FIGURE 43-1 External anatomy of an araneomorph spider. **A,** Dorsal. **B,** Ventral (legs omitted).

unknown) about venoms and their effects on humans. Most toxins in spider venoms have target specificity, acting selectively on arthropods, vertebrates, or other groups. Some venoms have mammalian-specific activity.[1,121,216] Venom composition varies widely across spider species. Within a species, variation may exist between genders and among geographically isolated populations.[133,190] Venom potency also varies within individuals, both seasonally and developmentally. Despite this tremendous venom diversity, only a few dozen spider lineages are considered harmful to humans because most have an insufficient quantity of venom, the toxins do not affect mammals, or the fangs cannot penetrate human skin. In a few species, although laboratory evidence suggests potential mammalian toxicity, human envenomations have not been reported, perhaps because of the rarity of encounters between spiders and humans in some habitats. Table 43-1 lists an assortment of spider families, including those with species that have been reported to bite humans.

In addition to the direct action of venom toxins on humans, there are other ways that spiders are clinically relevant. Mechanical punctures of human skin by spider fangs may introduce bacteria or spider digestate into wounds. This may act to create injury not related to venom, but this suspicion has yet to be empirically substantiated. Outside of venom and bite mechanics, some theraphosids (tarantulas) produce urticating hairs that irritate skin or mucous membranes of animals or humans. Exposure to these may result from direct contact with a spider or from indirect exposure to materials, such as clothing, that may carry loose hairs.

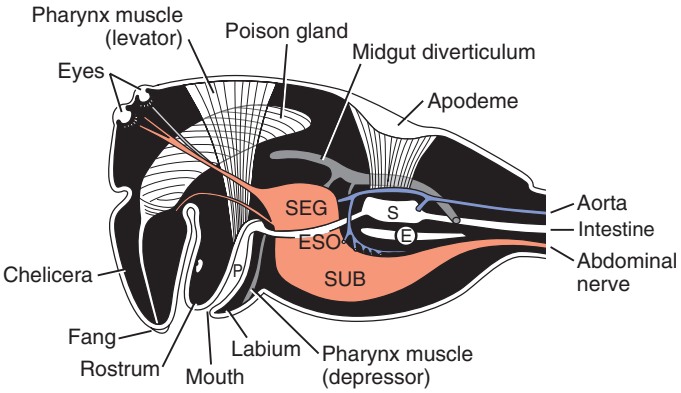

FIGURE 43-2 Longitudinal section of the prosoma. E, endosternite; ESO, esophagus; P, pharynx; S, sucking stomach; SEG, supraesophageal ganglion; SUB, subesophageal ganglion. *(Modified from Foelix RF:* Biology of Spiders, *ed 2, Oxford, UK, 1996, Oxford University Press. With permission.)*

GENERAL ASSESSMENT AND TREATMENT OF SPIDER BITES

Awareness of the differential diagnosis is crucial for management of any patient presenting for evaluation of "spider bite," because the offending creature is rarely observed and identified. Typically, it is outside of normal biologic activity for spiders to bite humans, except in defense. A defensive bite risks the spider's life and tends to occur only when its life is threatened by being crushed. This is different from what happens with parasitic and opportunistic organisms (e.g., mosquitos or bacteria) that benefit directly from association with human tissue. Because defensive situations are rare by comparison, spider bites are much less common causes of skin lesions than are insect bites or cutaneous infections.

No pathognomonic clinical signs prove the diagnosis of spider bite. The diagnosis depends on retrieval and identification of the creature that was seen biting.[249] Diagnosis of arachnidism without such direct evidence can lead to inappropriate treatment and failure to consider more severe underlying medical issues.[162,165,167,244,293] For putative spider bites, the medical history, physical examination, and laboratory evaluation must typically take into consideration alternative causes. Treatment plans should include careful follow-up and patient counseling to manage any uncertainties in the final diagnosis.

The differential diagnosis of a local lesion is broad. It may include fungal, bacterial, and viral infections, especially herpes simplex and zoster; the vesiculobullous diseases; arthropod-borne infectious diseases (e.g., Lyme disease); other bites and stings; foreign body reactions; and systemic conditions that predispose to focal skin lesions (e.g., diabetes mellitus, leukemia, lupus erythematosus). Well-intentioned but ineffective first-aid interventions may superimpose trauma, burns, or chemical irritation to mask an otherwise benign skin lesion. Systemic signs and symptoms may be due to the effects of snake or scorpion neurotoxin, pesticide toxicity, sepsis, meningitis, hemolytic anemia, or acute abdomen.

The medical history should include details of circumstances at the time of the bite to demonstrate consistency with expected spider habitat and behavior. This includes location indoors or outside, time of day or night, relationship of lesion site to clothing, and the patient's activity at the time of injury. The victim

Text continued on p. 999

TABLE 43-1 A Simplified Taxonomy of Spiders, Including Those of Medical Importance

Scientific Name* (Number of Genera and Species): Common Name	Geographic Range	Habitat	Clinical Remarks	Treatment
Phylum Arthropoda, Class Arachnida, Order Araneae (3 suborders, 114 families, 3,954 genera, ≈ 45,575 species): Spiders	Worldwide			
Suborder Mesothelae (1 family Liphistiidae, 1 genus, 91 species)	Asia (part)	Burrows in ground	None known clinically relevant	Symptomatic
Suborder Mygalomorphae (12 families): Mygales	Worldwide			
Family Theraphosidae (131 genera, 980 species): tarantulas and baboon spiders	Worldwide	Burrows in ground or tree crevices	Ophthalmic complications, minor local reaction; urticating hairs (except where noted)	Irrigation, hair removal, symptomatic and supportive care
Acanthoscurria (27)†	South America, Caribbean			
Aphonopelma (87)	New World			
Aphonopelma hentzi (previously *Dugesiella hentzi*)	New World			
Avicularia (49)	South America, Caribbean			
Euathlus (previously *Brachypelma*) (9)	New World			
Grammostola rosea: Chilean rose tarantula	South America (pet trade)			
Haplopelma minax: Thailand black tarantula	SE Asia			
Harpactirella lightfooti: baboon spider or bobbejaanspinnekop	Africa		Pain, emesis, weakness	Symptomatic and supportive
Lampropelma (2)	Asia, India			
Lasiodora (39)	South America, Caribbean			
Mygalarachne (previously *Sericopelma*) (1)				
Pamphobeteus (12)	South America			
Phormictopus (15)	South America, Caribbean			
Poecilotheria (14)	Australia, India, Sri Lanka		Local reaction and neuromuscular syndrome	Symptomatic and supportive
Pterinochilus (10)	Africa			
Selenocosmia (40)	Southeast Asia, India, Australia			
Family Hexathelidae (12 genera, 113 species): funnel-web mygalomorphs	Africa, Australia, Southeast Asia, South America	Burrows in ground or tree hollows with funnel-web	Variable, occasionally severe neurotoxicity	
Atrax (3)	Eastern Australia		Local pain; severe neurotoxicity	Antivenom, symptomatic and supportive
Atrax robustus: Sydney funnel-web spider	Eastern Australia			
Hadronyche (31)	Eastern Australia		Local pain; severe neurotoxicity	Antivenom, symptomatic and supportive
Hadronyche cerberea	New South Wales			
Hadronyche formidabilis: northern funnel-web spider	Eastern Australia			
Hadronyche infensa	Eastern Australia			
Hadronyche versutus: Australian Blue Mountains funnel-web spider	Eastern Australia			
Family Dipluridae (24 genera, 188 species): funnel-web mygalomorphs	Worldwide	Funnel webs on ground and in trees		
Trechona venosa	Brazil		Mammalian toxin; no human reports	Symptomatic and supportive
Family Idiopidae (22 genera, 322 species): front-eyed trapdoor spiders	Pantropical, India	Burrows, some with trapdoors	Minor local reaction	Symptomatic
Aganippe subtristis	Australia			
Arbanitis (3)	Australia			

Continued

TABLE 43-1 A Simplified Taxonomy of Spiders, Including Those of Medical Importance—cont'd

Scientific Name* (Number of Genera and Species): Common Name	Geographic Range	Habitat	Clinical Remarks	Treatment
Misgolas (previously *Dyarcyops, Hermeas*) (59)	Australia, New Zealand			
Family Ctenizidae (9 genera, 130 species): trapdoor spiders	Worldwide, except South America	Burrows with trapdoors	Effects unknown	Symptomatic and supportive
Bothriocyrtum (3)	North America, Taiwan			
Ummidia (27)	New World, Europe, Africa			
Family Actinopodidae (3 genera, 47 species): trapdoor spiders	Australia, Central and South America	Burrows with trapdoors		
Missulena bradleyi: mouse spider	Australia		Mammalian toxin; 1 case of systemic effects	Symptomatic and supportive
Suborder Araneomorphae (101 families): true spiders				
Family Filistatidae (18 genera, 119 species)	Worldwide		Effects unknown	Symptomatic and supportive
Filistata (20)	Worldwide	Large irregular webs		
Family Sicariidae (2 genera, 138 species): recluse, brown, or fiddle spiders	Worldwide			
Loxosceles: recluse, brown, or fiddle spiders (114)	New World, Mediterranean, Africa	Irregular webs in crevices or caves	Local necrosis; systemic syndrome	Symptomatic and supportive; antivenom where available
Loxosceles reclusa: brown recluse spider	North America (central, southeast)			
Loxosceles arizonica: Arizona brown spider	North America (southwest)			
Loxosceles rufescens	Worldwide			
Loxosceles intermedia	Brazil			
Loxosceles gaucho	Brazil			
Loxosceles boneti	Mexico			
Loxosceles spinulosa	South Africa			
Loxosceles laeta: corner spider or spider behind the pictures	South America, Australia, Finland, United States			
Loxosceles parramae	South Africa			
Sicarius: six-eyed crab spiders (25)	Neotropics, South Africa	No webs, buried in sand or soil	Local necrosis; disseminated intravascular coagulopathy	Symptomatic and supportive
Family Pholcidae (79 genera, 1455 species): cellar spiders, daddy longlegs spiders	Worldwide	Irregular webs	Minor local reaction or effects unknown	Symptomatic
Family Dysderidae (24 genera, 533 species): giant-fanged, six-eyed spiders	Worldwide	Nocturnal wandering hunters	Effects unknown	Symptomatic
Dysdera (260)	Worldwide			
Family Desidae (38 genera, 185 species): long-jawed intertidal spiders	Worldwide	Varied		
Badumna insignis: black house spider	Australia, New Guinea, New Zealand, Japan	Conspicuous messy webs	Local pain; rarely, necrosis	Symptomatic
Family Cybaeidae (10 genera, 179 species)	Worldwide	Small retreat webs in forest litter	Effects unknown	Symptomatic
Argyroneta aquatica	Europe	Under water	Local pain	
Family Gnaphosidae (122 genera, 2179 species): ground and mouse spiders	Worldwide	Wandering		
Drassodes (169)	Worldwide		Effects unknown	Symptomatic
Herpyllus ecclesiasticus: parson spider	North America		Minor local reaction; brief systemic effects	Symptomatic and supportive
Family Lamponidae (23 genera, 192 species): white-tailed spiders	Australia, Tasmania, New Zealand	Wandering		
Lampona cylindrata: white-tailed spiders	Australia, New Zealand		Minor local reaction; rarely necrotic	Symptomatic and supportive

TABLE 43-1 A Simplified Taxonomy of Spiders, Including Those of Medical Importance—cont'd

Scientific Name* (Number of Genera and Species): Common Name	Geographic Range	Habitat	Clinical Remarks	Treatment
Family Miturgidae (33 genera, 159 species): forest floor and cave spiders	Worldwide	Wandering	Effects unknown	Symptomatic
Elassoctenus harpax	Australia			
Miturga (17)	Australia, New Zealand			
Family Sparassidae (includes former Heteropodidae) (85 genera, 1147 species): giant crab, huntsman, and large, wandering crab spiders		Wandering	Minor local reaction except as noted	Symptomatic and supportive
Delena cancerides: social huntsman spider	Australia			
Heteropoda (197)	Worldwide			
Isopeda (22)	Australia, New Guinea, East Indies			
Olios (244)	Americas, Australia		Brief nausea	
*Palystes superciliosus (*formerly *natalius)*: lizard-eating spider	South Africa			
Family Oxyopidae (9 genera, 453 species): lynx spiders	Worldwide	Wandering		
Peucetia viridans: green lynx spider	North and Central America, Caribbean		Minor local reaction	Symptomatic
Family Salticidae (595 genera, 5821 species): jumping spiders	Worldwide	Diurnal wandering spiders	Minor local reaction	Symptomatic
Holoplatys (39)	Australia			
Mopsus mormon	Australia			
Ocrisiona (formerly *Breda*) *jovialis*	Australia			
Opisthoncus (32)	Australia			
Phidippus (76)	New World			
Thiodina (1)	America			
Family Thomisidae (175 genera, 2158 species): crab spiders	Worldwide	Ambush predators on plants or ground	Effects unknown	Symptomatic
Misumenoides (36)	Americas			
Family Ctenidae (41 genera, 493 species): wandering spiders	Worldwide	Wandering, no web		
Cupiennius (11)	South and Central America, Caribbean		Effects unknown	Symptomatic
Diallomus	Australia			
Phoneutria: armed spiders (8)	South America		Local pain; systemic neurotoxin	Symptomatic and supportive; antivenom when available
Phoneutria nigriventer: Brazilian armed spider	Brazil, Paraguay			
Family Lycosidae (123 genera, 2399 species): wolf spiders	Worldwide	Wandering, no web	Local pain	Symptomatic
Lycosa: wolf spiders (226)	Worldwide			
Lycosa raptoria	South America			
Lycosa tarantula: "tarantula"	Palearctic			
Lycosa godeffroyi	Australia			
Lycosa erythrognatha				
Eutichuridae (12 genera, 75 species)	Worldwide			
Cheiracanthium: sac and running spiders (209)	Worldwide	Wandering, No web	Minor local reaction; brief systemic illness	Symptomatic and supportive
Cheiracanthium mildei	Holarctic			
Cheiracanthium punctorium	Europe			
Cheiracanthium japonicum	Japan, China			
Cheiracanthium longimanum	Australia			
Cheiracanthium lawrencei	Africa			
Cheiracanthium mordax	Australia			
Cheiracanthium inclusum	America			
Family Corinnidae (67 genera, 728 species): sac spiders	Worldwide			
Nyssus coloripes (formerly *Supunna picta*)	Australia, New Zealand	Wandering	Minor local reaction	Symptomatic

Continued

TABLE 43-1 A Simplified Taxonomy of Spiders, Including Those of Medical Importance—cont'd

Scientific Name* (Number of Genera and Species): Common Name	Geographic Range	Habitat	Clinical Remarks	Treatment
Family Trachelidae (16 genera, 728 species)	Worldwide			
Trachelas (86)	Worldwide	Wandering	Minor local reaction	Symptomatic
Family Zoropsidae (25 genera, 18 species): running spiders	New World	Ground-dwelling, wandering. Some with large sheet webs	Effects unknown	Symptomatic
Liocranoides (5)	Appalachia, California			
Family Agelenidae (71 genera, 1169 species): grass and funnel-web spiders	Worldwide	Funnel webs		
Agelenopsis aperta: grass spider or funnel-web spider	Southwest U.S., Mexico		Local and systemic effects	Symptomatic and supportive
Eratigena (formerly *Tegenaria*) *agrestis*: hobo or northwestern brown spider	Europe, North America (Pacific Northwest)		Local reaction; unconfirmed systemic effects	Symptomatic and supportive
Superfamily Orbicularia				
Family Nephilidae (5 genera, 61 species)	Worldwide	Orbed webs	Effects unknown	Symptomatic
Nephila: golden-silk spiders	Pantropical			
Family Theridiidae (122 genera, 2447 species) comb-footed spiders	Worldwide	Irregular webs with sticky drops attached to substrate		
Latrodectus: widow spiders (31)	Worldwide		Pain; neurotoxicity	Symptomatic and supportive; antivenom
Latrodectus mactans: black widow spider	North America			
Latrodectus mactans hasseltii: red-backed spider	Australia			
Latrodectus hesperus: black widow spider	North America			
Latrodectus tredecimguttatus	Mediterranean			
Latrodectus pallidus	Libya to Russia			
Latrodectus indistinctus: black button spider	Africa			
Latrodectus geometricus: brown button spider	Worldwide			
Parasteatoda (formerly *Achaearanea*) *tepidariorum*	Worldwide		Trivial local reaction	Symptomatic
Steatoda (126)	Worldwide		Local pain; mild systemic effects	Symptomatic and supportive
Steatoda paykulliana: false black widow spider	Europe, Mediterranean			
Steatoda nobilis	England			
Steatoda foravae: false button spider	Southern Africa			
Family Araneidae (169 genera, 3101 species): orb-weaving spiders	Worldwide	Orbed webs	Minor local reaction	Symptomatic
Argiope: argiopes (84)	Worldwide			
Argiope argentata	Americas			
Argiope trifasciata	Worldwide			
Araneus: cross, garden, and shamrock spiders (655)	Worldwide			
Eriophora biapicata	Australia			
Neoscona: orb-weaving spiders (114)	Worldwide			
Phonognatha graeffei	Australia			

*Taxonomic information updated as of January, 2016, from the World Spider Catalog (wsc.nmbe.ch/).
†Number of species in a taxon in parentheses.

should attempt to recall the appearance of the involved arthropod. If it was believed killed through garments or bedclothes, an attempt should be made to retrieve its remains. Crushed spider parts can be examined and identified by arachnologists or entomologists at many universities and museums. Until identified, spiders may be preserved in 70% to 80% ethanol. One should note evolution of the subsequent wound and systemic symptoms along with modifiers, including home treatment and the patient's underlying health. If the local geographic area lacks species consistent with the suspected pathophysiology, consider recent travel histories of household contacts.

On physical examination, pay particular attention to the bite site as well as a general assessment for systemic effects. Local findings of importance include anatomic location (spiders are more likely to bite defensively at sites where clothing binds tightly and thin skin is more readily pierced than callous skin) and number of separate lesions (multiple bites suggest a parasitic insect bite rather than spider bite). Note central punctae, vesicles, or erosions, as well as the pattern of each lesion's margins (e.g., erythema, pallor, hemorrhage, induration, tenderness, or numbness) and local lymphatic involvement. Systemic findings, depending on the species involved, may include changes in vital signs, diaphoresis, generalized rash, facial edema, gastrointestinal distress, muscle fasciculations, spasm or tenderness, or altered mental status.

Laboratory evaluation for envenomation is usually simple, seldom requiring more than a complete blood count and urinalysis. Assessment for other elements of the differential diagnosis may be much more elaborate. As guided by the differential diagnosis, this may include viral, bacterial, or fungal culture; Lyme disease titer; radiography of the abdomen or injured part; stool test for occult blood; electrocardiogram; or skin biopsy. Under research conditions, a swab or frozen tissue may be subjected to immunoassay for venom.

General supportive measures are the mainstays of therapy for most spider bites. These include basic local hygiene, tetanus prophylaxis, analgesics, hydration, and surgical follow-up as indicated for debridement and management of extensive necrotic lesions. Corticosteroids are of unproved benefit and are generally not indicated. Antibiotics, although not of value for simple venom injury, are prescribed when bacterial cellulitis cannot be eliminated from the differential diagnosis. Specific measures that include antivenom for treatment of envenomation by particular spider species are discussed later.

Management of envenomation during pregnancy requires additional consideration of the maternal physiology, appropriate use of medications during pregnancy, and issues specific to the fetus.[41] Brown and colleagues reviewed studies of the clinical management of pregnant patients following envenomation by various creatures. Although available literature is largely limited to retrospective reviews and case series, adverse events (e.g., miscarriage, preterm birth, placental abruption, and stillbirth) appear primarily related to venom effects on the mother. Ideally, management should be venom-specific, including supportive care, antivenom if indicated, and fetal assessment.

GUIDE TO SPIDER DIVERSITY AND IDENTIFICATION

This chapter provides more information on spider diversity than do most reviews in order to inform the reader of the immense diversity of spiders that are medically insignificant and thus emphasize the rarity of spiders known to cause medical problems, emphasize the need for accurate species identification, particularly in reporting of cases for publication or teaching, and facilitate accurate identification of spiders caught in the act of biting by directing medical professionals to proper identification keys. Table 43-1 includes species worldwide that are currently known or suspected to be medically noteworthy because of the effect of their bites or their urticating hairs. Geographic range and the most recent systematic work on each group are included. Readers are directed to the World Spider Catalog, which catalogs current taxonomy on all spider lineages.[226] Box 43-1 lists spider genera of serious medical significance for each continent. For effective communication, spiders must be recognized by the same name worldwide. This chapter uses current official nomenclature.

BOX 43-1 Clinically Important Spider Genera by Geographic Distribution*

North America
Loxosceles
Latrodectus
Tegenaria

South America
Loxosceles
Latrodectus
Phoneutria

Africa
Loxosceles
Latrodectus

Europe
Loxosceles
Latrodectus

Australia
Atrax
Hadronyche (Atrax)
Latrodectus

Asia
Latrodectus

*Information from Akre RD, Myhre EA: Biology and medical importance of the aggressive house spider, *Tegenaria agrestis*, in the Pacific Northwest (Arachnida: Araneae: Agelenidae), *Melanderia* 47:1, 1991; Gross AS, Wilson DC, King LE Jr.: Persistent segmental cutaneous anesthesia after a brown recluse bite, *South Med J* 83:1321, 1990; Schenberg S, Pereira Lima FA: Venoms of Ctenidae, In Bettini S, editor: *Arthropod Venoms, Handbook of Experimental Pharmacology*, vol 48, Berlin, 1978, Springer-Verlag; and Sutherland SK, Trinca JC: Survey of 2144 cases of red-back spider bites, *Med J Aust* 2:620, 1978.

Of the three spider suborders, two contain clinically significant species: Mygalomorphae and Araneomorphae. Mygalomorphs include baboon spiders or tarantulas, trapdoor spiders, purse-web spiders, mygalomorph funnel-web spiders, and several other groups that lack common names. Most spiders are araneomorphs. These include jumping spiders, orb-weaving spiders, widow spiders, wolf spiders, and fiddleback spiders (see Table 43-1). The most conspicuous characteristics that distinguish these groups are chelicerae (jaws) orientation and number of book lungs. Spider fangs are located on the chelicerae. In Araneomorphae, fangs open perpendicular to the dorsal-ventral axis. In Mygalomorphae, fangs move in parallel to this axis, requiring spiders of this suborder to rear back to inflict a downward, snake-like strike (Figures 43-3 and 43-4). Mygalomorphae have two pairs of book lungs. Most Araneomorphae have only one pair. Lung slits, which open into the book lungs, are easily visible in a ventral view of the anterior abdomen (see Figure 43-1). Characteristics that distinguish families, genera, and species include

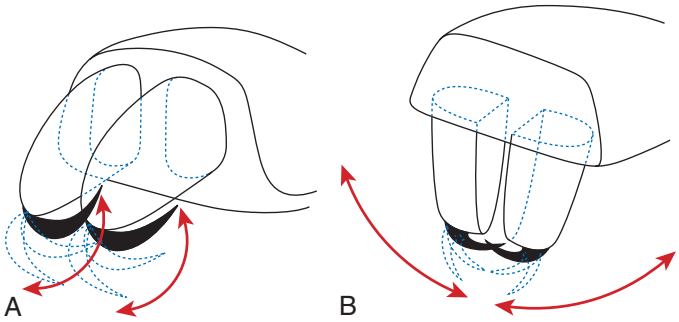

FIGURE 43-3 Movement of the chelicerae in mygalomorphs **(A)** and araneomorphs **(B).** *(Modified from Foelix RF:* Biology of Spiders, *ed 2, Oxford, UK, 1996, Oxford University Press. With permission.)*

FIGURE 43-4 Fangs of mature male tarantula (*Aphonopelma* species). *(Courtesy Michael Cardwell and Associates, 1992.)*

FIGURE 43-5 Theraphosidae. *(Courtesy Gita Bodner.)*

eye number and pattern, numbers of tarsal claws, and details of genitalia structure.

Although many spider species are geographically localized (e.g., *Atrax robustus* in Australia, *Phoneutria nigriventer* in Brazil), some, such as the widow spiders (*Latrodectus*), are found worldwide (see Table 43-1). Others, such as members of the *Loxosceles* genus, are widely distributed in more than one continent, and still others (e.g., *Tegenaria agrestis*) appear to have naturalized in specific geographic regions distant from their point of ecologic origin. Because of the resulting worldwide species diversity and overlap, the remainder of this chapter is structured according to spider taxonomy rather than isolated species or geographic location.

SUBORDER MYGALOMORPHAE

Mygalomorphs make up less than 10% of all spider species. They are found worldwide, with greatest abundance and diversity in tropical regions. Tarantulas (Theraphosidae) are the most famous mygalomorphs and include the largest spiders known, reaching up to 10 cm (4 inches) in body length. Most mygalomorphs are smaller, some less than 1 mm (0.04 inch) in adult body length. Most live for several years (some up to 20 years), and females continue to molt after reaching adulthood. They have diverse habits but typically live in silk-lined burrows or silken tubes. For the purpose of prey capture, mygalomorph silk is slightly sticky relative to araneomorph silk and is generally used to signal the presence of prey rather than to ensnare them. Once prey is detected, spiders run out of their retreat, seize the prey in their jaws, and return to their burrows to feed. Although mygalomorphs spend most of their lives in burrows or large, long-lasting webs, individuals wander when dispersing as juveniles to leave their natal nest, or as adults if their burrows or webs are damaged. Mature males also wander when searching for females during mating season.

FAMILY THERAPHOSIDAE: TARANTULAS AND BABOON SPIDERS

Theraphosidae is the largest mygalomorph family with respect to both numbers of species and sizes of the largest individuals (Figure 43-5). Approximately 990 described species are found on all continents, with the greatest abundance and diversity in tropical regions. They mature in 3 to 9 years and can live for 15 to 25 years. Individuals live in burrows, with trip-line threads extending from the entrance. Burrow entrances are sometimes located in abandoned rodent burrows or hollow trees. Theraphosids have dense tufts of specialized hairs on their tarsi (feet) that enable them to climb on smooth surfaces and may aid in prey capture. They have two tarsal claws, eight closely grouped eyes, and two pairs of spinnerets. As a group, they are found mainly in tropical and subtropical areas.

Confusingly, the word *tarantula* was first applied to *Lycosa tarantula,* a species of European spider actually belonging to the wolf spider family, or Lycosidae, which are properly classified within the suborder Araneomorphae, described later in this chapter. In the United States, the term *tarantula* usually refers only to large spiders of the family Theraphosidae, suborder Mygalomorphae.

Grammostola mollicoma is the largest tarantula known, with a body length of 7 to 10 cm (3 to 4 inches) and leg spread of 21 to 27 cm (8.3 to 10.6 inches).[43,107] *Harpactirella lightfooti,* the baboon spider or *bobbejaanspinnekop,* is a mygalomorph spider found in South Africa. The body length is 3 cm (1.2 inches). The cephalothorax is brown with a yellowish border.

Venom

Recent analyses of tarantula venom transcriptomes and proteomes of multiple species have increased our understanding.[156] In the United States, *Rheochostica henzi* and members of the genus *Aphonopelma* (Figure 43-6) have venom containing hyaluronidase, nucleotides, and polyamines.[48,57,173,258,259] Polyamines are thought to act as neurotransmitters and increase venom effectiveness, particularly to paralyze insect prey.[271] Hyaluronidase is postulated to increase venom spread, and the nucleotide adenosine triphosphate potentiates the major effects of the venom on mice. Both venoms cause rapid, irreversible necrosis of skeletal muscle when injected intraperitoneally in mice.[219] *Dugesiella (Rheochostica)* venom was found to have a necrotoxin with several similarities to sea snake venoms.[173] In comparison, the venom of *Scodra griseipes,* an African tarantula, includes higher-molecular-weight (> 25,000 Da) proteins and enzymes plus lower-weight polypeptides (4000 to 9000 Da). The second group is believed to contain polypeptide neurotoxins.[56] *S. griseipes* venom toxins have an effect on mammals, but this species is not known to be clinically relevant. Recent work suggests that venom chemotaxonomy may be a useful method of nondestructive species recognition, at least within the *Brachypelma* genus.[82]

FIGURE 43-6 Mature female *Aphonopelma iodius. (Courtesy Michael Cardwell and Associates, 1997.)*

Urticating Hairs

Several genera of tarantulas, including *Haplopelma, Lasiodora, Grammostola, Acanthoscurria,* and *Brachypelma,* possess urticating hairs that irritate skin and mucous membranes. These genera are located throughout the Western Hemisphere, with many species indigenous to the United States. When one of these spiders is threatened, it rubs its hind legs across the dorsal surface of its abdomen and flicks thousands of hairs toward the aggressor. These barbed hairs can penetrate human skin, causing edematous, pruritic papules. Itching may persist for weeks. There are four morphologic types of urticating hairs. Tarantulas within the United States possess only type I hairs, which do not penetrate the skin as deeply as do type III hairs. Type II hairs are incorporated into the silk web retreat and are not thrown off by the spider. Type III hairs can penetrate up to 2 mm (0.8 inch) into human skin. This is the type of hair most likely to cause inflammation. They are typically found on Mexican, Caribbean, and Central and South American species. Type IV hairs, which belong to the South American spider *Grammostola,* are able to cause inflammation of the respiratory tract in small mammals. Rats and mice have been reported to die of asphyxia within 2 hours after exposure to the hairs.[67,327]

Clinical Presentation

Despite the presence in venom of components toxic to rodent nerves and skeletal muscle, most tarantula bites result in only mild to moderate local symptoms in humans. A few can cause more severe pain and swelling, numbness, or lymphangitis. In a series of nine cases in Australia, by either *Selenocosmia* or *Phlogiellus* species, no major effects occurred. Local pain was the most common effect, followed by puncture marks or bleeding. Severe pain occurred in four of seven patients in which pain severity was documented. Mild systemic effects occurred in one case.[153] The species of tarantula implicated as causes of human envenomation include those in the genera *Mygalarachne* (formerly *Sericopelma*) of Panama, *Pterinochilus* (Africa), *Aphonopelma* (Mexico and the United States), *Pamphobeteus* (South America), *Euathlus* (Costa Rica), *Theraphosa* (French Guyana), *Grammostola* (Colombia), *Selenocosmia* and *Phlogiellus* (Australia), *Poecilotheria* (India), *Lampropelma* (Thailand), *Lasiodora* (Brazil), *Antrodiaetus coylei* (northwestern United States) and *Avicularia* (Central America and southwestern United States). Envenomation usually involves immediate pain at the bite site, occasionally followed by redness and swelling, typically without necrosis or serious sequelae.[43,48,57,104,192,259]

A paucity of reports in the peer-reviewed medical literature hinders proper characterization of occasional tarantula neurotoxicity, particularly in cases (e.g., *Poecilotheria*) that are reported anecdotally, including in the pet trade, to provoke severe neuromuscular symptoms. Although no fatalities have been reported, localized pain followed by emesis, weakness, and collapse have been noted after envenomation by *Harpactirella lightfooti,* the baboon spider of South Africa.[43,124,207]

Urticating hairs may cause intense inflammation with pruritus persisting for weeks. Individuals who handle tarantulas may unwittingly transfer urticating hairs from hand to eye, causing keratoconjunctivitis or ophthalmia nodosa. Keratoconjunctivitis has been described after handling a Thailand black tarantula, *Haplopelma minax.* Fine intracorneal hairs were noted on examination, and inflammation reportedly settled quickly with topical corticosteroid treatment. At 36-month follow-up, the eye was normal.[38]

More severe ophthalmic complications occurred in two cases after handling of Chilean rose tarantulas, *Grammostola cala.* In these victims, initial findings were similar, with intracorneal hairs and keratoconjunctivitis, but progressive panuveitis followed, with corneal granulomas, iritis, cataract, hyalitis, and chorioretinitis apparently related to migration of hairs through the media of the eye. Differences in outcome with exposure to the two species may result from different hair morphology. This may also explain reports of different ophthalmic injuries from tarantula or caterpillar hair exposure.[38] Similar cases of ophthalmia nodosa have been described.[24,172] Sheth reported a case of ocular inflammation after handling of a pet Chilean rose tarantula.[266] A nine-year-old boy presented with new onset of a painful red right eye, initially thought to be trauma-induced 2 weeks earlier. The left eye was unaffected and visual acuity was within normal limits. Slit-lamp examination showed right eye injection with multiple hairs at all levels of the cornea with associated opacities, and moderate anterior uveitis. In addition, hair-like vitreous lesions and peripheral full-thickness retinal infiltrates were seen. Topical therapy with corticosteroids and antibiotics was initiated and follow-up continued with long-term tapering of topical steroids. Hair removal was not attempted, because of the large number and depth of hairs. Follow-up at 18 months revealed full resolution of inflammation, normal visual acuity, and no complications (Figures 43-7 and 43-8).

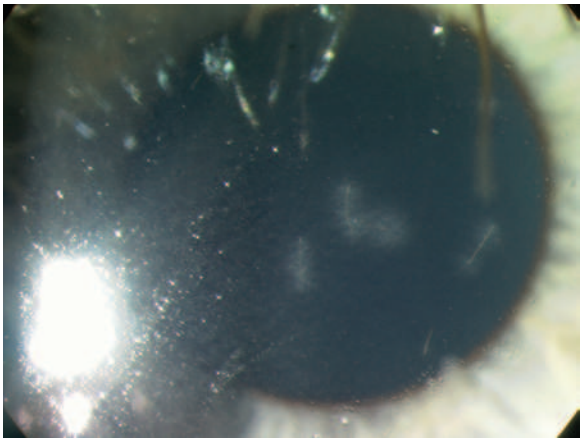

FIGURE 43-7 Cornea showing multiple tarantula hairs with associated inflammatory infiltrate and scarring. *(From Atkins JA, Wingo CW, Sodeman WA, et al: Necrotic arachnidism,* Am J Trop Med Hyg *7:165, 1958.)*

Treatment

Theraphosid bite management is symptomatic. Elevation and immobilization of the extremity and oral analgesics may help reduce pain. All bites should receive local wound care and appropriate tetanus prophylaxis. Remove urticating hairs from skin by repeated application and removal of sticky tape, followed by copious irrigation. Irrigate exposed eyes. Topical or systemic corticosteroids and oral antihistamines may also be useful for urticating hair reactions.

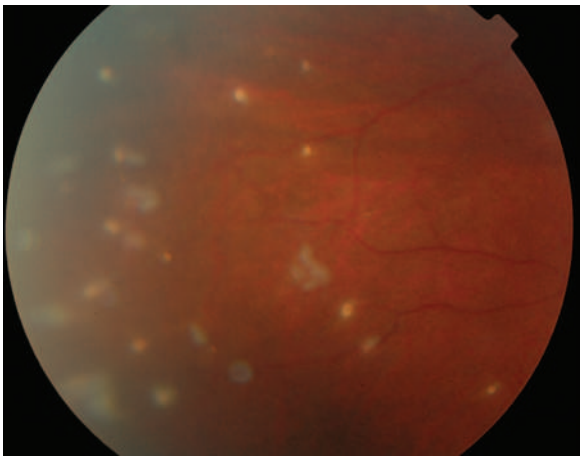

FIGURE 43-8 Retina with punched-out full-thickness inflammatory lesions associated with embedded tarantula hairs. *(From Atkins JA, Wingo CW, Sodeman WA, et al: Necrotic arachnidism,* Am J Trop Med Hyg *7:165, 1958.)*

FAMILY HEXATHELIDAE: FUNNEL-WEB MYGALOMORPHS

The family Hexathelidae includes 12 genera and approximately 113 species from the Old World, Australia, New Zealand, and Chile.[232] The funnel webs that typify members of this group are silk-lined tubular retreats that extend into a protected space (e.g., a burrow in the ground or a hole in a tree). Sheets of silk radiate from the retreat and signal the presence of prey. These webs superficially resemble webs of araneomorph spiders in the family Agelenidae. Distinguishing characteristics of the spiders include a shiny carapace; long, spiny sensory hairs on legs; and paired claws lacking claw tufts on the tips of the feet, with teeth lining the medial claw.

Clinically significant hexathelid spiders are species of *Atrax* (Figure 43-9) and *Hadronyche*. Technically, taxonomists now consider *Atrax* and *Hadronyche* species as members of only one genus.[232] To avoid confusion in the literature, species names still use either *Atrax* or *Hadronyche,* depending on their original names. We discuss these species as a cohesive taxonomic group. Among these, the species *A. robustus* is best known and most carefully studied. *Atrax* and *Hadronyche* species, all of which are believed to be dangerous, have been described in southern and southeastern Australia, Tasmania, Papua New Guinea, and the Solomon Islands. As a group, they prefer cool, moist coastal and mountainous regions.[116,118,267]

Genus Atrax/Hadronyche

Biology. Funnel-web spiders have a glossy ebony cephalothorax and velvety black abdomen. The abdominal undersurface may have brushes of red hair. The fangs reach 4 to 5 mm (0.16 to 0.19 inch) in length and are capable of penetrating a fingernail or a chicken's skull. This sometimes makes removal of the spider difficult. Females are somewhat larger than males, with a body length of 4 cm (1.57 inches). Mature males are more delicate, with a tibial spur on the second pair of legs and pointed pedipalps.[144,261]

A. robustus, the Sydney funnel-web spider, is limited to a 160-km (100-mile) range around Sydney, Australia. The spider creates a tubular or funnel-shaped, silk-lined shallow burrow under rocks, logs, fences, stumps, or thick vegetation or around foundations of houses. Colonies of up to 150 spiders have been found. Females rarely roam far from their webs. Males live a vagrant life after reaching maturity. Wandering males may enter houses or other areas of human habitation, especially during the summer months after a heavy rain. Its aggressive behavior and potent venom make the male Sydney funnel-web arachnid one of the most dangerous spiders in the world. It is responsible for all known fatal *Atrax* envenomations.[2,122,261,291]

H. formidabilis, the northern funnel-web spider, is found in the central coastal region of New South Wales and the adjacent Blue Mountains. Its tree-dwelling habit was once thought to be unique, but it is now known that other species also live in trees. The webs may be camouflaged in rough-barked trees, such as melaleuca (paper bark), banksia, and eucalyptus.[118]

FIGURE 43-9 Funnel-web spider (*Atrax* species) wearing an engagement ring. *(Courtesy Sherman Minton, MD.)*

Venom. Although many species have venom with significant in vitro toxicity, few have been implicated in human illness. The best described of these is *A. robustus*. *Atrax* venom causes widespread release of neurotransmitters.[77,118,128,274,280] This may occur by a direct action of venom on nerve membranes, producing spontaneous action potentials and consequently provoking a global outpouring of transmitters that accounts for the clinical findings of neuromotor and autonomic stimulation.

Efforts to purify active components of *Atrax* venom resulted in reports of neurotoxins of various molecular weights.[279] These were termed atraxotoxin (10,000 to 25,000 daltons, from milked venom),[118] robustoxin (4887 Da, from milked venom),[268] and atraxin (9800 Da, from ground venom glands).[119] Venoms of *A. robustus, H. cerberea, H. formidabilis, H. infensa, H. lanunstian, H. variela, H. versuta,* and an *Atrax* species preparation and *Hadronyche* species preparation have similar high- and low-molecular-weight protein electrophoretic patterns and Western blotting. This suggests that these species contain similar atraxotoxins. The relationships among these toxins are not clear, but atraxotoxin or atraxin may be a precursor to robustoxin. In addition to these components, *Atrax* venom contains various lower-molecular-weight compounds, including citric acid, lactic acid, phosphoric acid, glycerol, urea, glucose, γ-aminolevulinic acid, glycine, spermidine, spermine, tyramine, octopamine, and 5-methoxytryptamine.[76]

The best characterized of the toxins is robustoxin, a 42–amino acid protein first sequenced in 1985.[268] It is the sole lethal toxin that can be isolated by cation-exchange chromatography, and its effects in monkeys duplicate the effects of crude venom preparations. An intravenous (IV) dose of 5 mg/kg of robustoxin to monkeys causes dyspnea, blood pressure fluctuations culminating in severe hypotension, lacrimation, salivation, skeletal muscle fasciculation, and death within 3 to 4 hours of administration.[203]

Isolated human intercostal muscles were studied to determine the cause of muscle fasciculations. Muscles treated with *A. robustus* venom developed marked contractions that were abolished by *d*-tubocurarine.[51] Muscles treated with venom for more than an hour stopped contracting and could be stimulated only by increasing stimulus duration. *A. robustus* venom lacks anticholinesterase activity.[278] Venom does not directly cause muscle contractions, so acetylcholine appears to have been released from the presynaptic terminals.[95] Muscle fasciculations are apparently caused by abnormal repetitive firing of motor neurons. It is hypothesized that the venom changes the membrane's electric field and activates sodium channels without altering the transmembrane potential or damaging the neuronal membrane ultrastructurally.[77,118,274]

Initial hypertension in *Atrax* toxicity may have several causes. Morgans and Carroll[197,198] demonstrated direct α-adrenergic stimulation with vasoconstriction of isolated arterial preparations exposed to *A. robustus* venom. In rabbit atria, an initial decrease followed by an increase in cardiac inotropy and chronotropy may result from vagal acetylcholine and myocardial norepinephrine releases, respectively.[52] The combination of myocardial responses and peripheral vasoconstriction may explain the initial hypertensive response.

Animal species vary in susceptibility to *Atrax* venom. Rabbits given 15 mg of crude venom intravenously and cane toads given 12 mg of female *Atrax* venom show no effects after envenomation. Primates, including humans, are among the most susceptible species. Newborn mice, also highly susceptible, have been used as an in vivo biologic assay for venom toxicity.[118,284] Sutherland[281] found that a lethal dose of venom from a male *A. robustus* could be neutralized in newborn mice by nonimmune sera from rabbits and other nonprimate vertebrates. Sheumack and co-workers[269] later demonstrated that the active fraction of nonimmune rabbit sera contained immunoglobulins G and M (IgG, IgM).

In addition, venom potency varies with time of year, recent feeding history, maturation, and gender of the individual spider.[12] Between 1956 and 1963, Wiener[331] demonstrated significant

differences in the venoms of male and female *Atrax* spiders. Males had an average venom yield of 1.01 mg, less than the 1.84 mg average yield from females. Despite this, guinea pig lethality (75% to 90%) was much greater after a bite by a male than by a female spider (20%). Weiner concluded that significant qualitative difference exists between the venoms of males and females.

Monkeys, which have a pattern of response to envenomation similar to that in humans, provide a model in which Sutherland[284,288] has described a biphasic clinical syndrome. Phase I begins minutes after venom injection, with local piloerection and muscle fasciculation. This extends proximally, becoming generalized over the next 10 to 20 minutes. After another 5 minutes, severe hypertension, tachycardia, hyperthermia, and coma with increased intracranial pressure may occur, followed by diaphoresis, salivation, lacrimation, diarrhea, sporadic apnea, borborygmi, and grotesque muscle writhing. Death may result from asphyxia caused by laryngeal spasm, combined with copious respiratory secretions, apnea, or pulmonary edema. Laboratory evaluation reveals metabolic acidosis and elevated plasma creatine phosphokinase. Phase II begins 1 to 2 hours after envenomation as the phase I symptoms subside. The victim may return to consciousness and appear to recover. In severe cases, hypotension gradually worsens over 1 to 2 hours, with periods of apnea. Pulmonary edema and death may occur despite ventilatory support.

Clinical Presentation. Up to 90% of *Atrax* bites may not result in significant envenomation.[327] Intense pain at the bite site may result from direct trauma as well as the venom's effect, but the bite does not provoke cutaneous necrosis. Wiener[331] studied cutaneous effects of venom on himself by injecting 0.5 mg intradermally. Local pain and a wheal surrounded by erythema lasted for 30 minutes, followed by localized sweating and piloerection. No systemic effects occurred.

One case of cutaneous necrosis has been reported. Nayar and colleagues[205] described a man visiting New Zealand who was reported to have been bitten by a funnel-web spider when he reached into a bag of onions. On return to England, he was treated at a hospital with two separate incisions and drainages for suspected infection of his thumb tip. Subsequently, his thumb became necrotic, with eventual osteocutaneous necrosis extending to the midterminal phalanx. Surgical treatment consisted of a Moberg flap reconstruction. No systemic involvement was noted. He eventually returned to work.

The earliest systemic signs and symptoms may include perioral tingling, nausea and vomiting, diaphoresis, salivation, lacrimation, and dyspnea. Pulmonary edema may follow, as well as a generalized central and peripheral neurologic syndrome that includes muscle fasciculations, tremor, spasms, weakness, and impaired consciousness. Death may occur secondary to pulmonary failure, hypotension, or cardiac arrest.[280,327]

Thirteen fatalities from *A. robustus* envenomation were recorded between 1927 and 1984. Children are particularly susceptible. Those younger than 12 years of age may die within 4 hours of the bite.[91,129,285] Before the development of a specific antivenom in 1980, severe envenomations resulted in a critical period lasting for a minimum of 8 hours, followed by a 9- to 21-day hospital course.[90,285,288]

No fatalities caused by *H. formidabilis* have been recorded, although several severe envenomations have occurred.[118] Venoms of *A. robustus, A. versutus*, *A. infensus,* and *A. formidabilis* appear to have comparable vertebrate toxicity in vitro.[11]

Treatment. Immediate treatment after a bite is modeled after that for Australian snakebite and consists of four steps: (1) wrap the length of the bitten extremity with an elastic bandage, (2) splint the extremity to immobilize, (3) immobilize the victim, and (4) transport the victim to the nearest hospital with the bandage in place.[213,286] A human case report has illustrated the utility of this method, with occurrence, disappearance, recurrence, and re-resolution of symptoms coinciding with removal and replacement of the compression wrap in a man bitten by a male *A. robustus.*[113] An experimental model in *Macaca fascicularis* monkeys has supported efficacy of the pressure immobilization technique.[282,284,289]

Specific antivenom has been the mainstay of treatment for *Atrax* envenomation since 1981. Antivenom is a purified IgG product developed by Sutherland and associates[283,290] at the Commonwealth Serum Laboratories by immunizing rabbits with a combination of male *Atrax* venom and Freund's adjuvant. Antivenom was demonstrated to neutralize *Atrax* venom in vitro and to reverse symptoms in monkeys before its introduction for human use. It has been used with good effect in humans bitten by *Atrax* and *Hadronyche* species.[74,288]

If a tourniquet or bandage is in place when the victim presents for hospital care, an IV line should be initiated before the tourniquet or bandage is removed in an intensive care setting. Carefully observe for development or progression of symptoms. If systemic signs or symptoms occur, victims are usually treated with antivenom administration. Two ampules of antivenom (100 mg of purified IgG per ampule) are administered intravenously every 15 minutes until symptoms improve. Dosing is the same for children as for adults, and total doses of two to eight ampules have been reported. During a 10-year period, antivenom was given to at least 40 patients with no adverse effects or deaths reported.[288]

In addition to antivenom administration, management is symptomatic and supportive. Oxygen, mechanical ventilation, and IV fluid support may be indicated in severe cases. Atropine (0.6 mg) may be used to lessen salivation and bronchorrhea. β-Adrenergic blockers may be indicated for severe hypertension and tachycardia.

Other than antivenom, no consistently effective agent has been found to enhance survival after *Atrax* envenomation. Diazepam, atropine, and furosemide have been found to increase survival in monkeys, but this may not be the case in humans.[89,134]

Sheumack and colleagues[270] developed a toxoid from robustoxin by polymerization with glutaraldehyde. Immunization with the toxoid conferred protection against lethal effects of 50 mg/kg *Atrax* venom in monkeys for at least 26 weeks after toxoid injection.

FAMILY DIPLURIDAE: FUNNEL-WEB MYGALOMORPHS

Members of the family Dipluridae are found on all continents and are concentrated in tropical areas. Individuals build funnel webs similar to those of Hexathelidae. Diplurids are distinct from hexathelids in having posterior lateral spinnerets that are very long and widely separated. Most are 5 to 25 mm (0.2 to 1 inch) in length.

Genus *Trechona*

Biology. *Trechona venosa* is a large South American funnel-web tarantula with neurotoxic venom potentially dangerous to humans.[43,104,124] As with all *Trechona* species, *T. venosa* is sedentary, living in holes or on plants in tropical forests along the Atlantic coast. The spider may be black or gray-brown with yellow stripes on the abdomen. The mature body length may be 3 to 4.5 cm (1.2 to 1.8 inches), with legs of 6 to 7 cm (2.4 to 2.8 inches) and fangs of 3 to 4 mm (0.12 to 0.16 inch). *T. venosa* is not found in Chile, but in this region it has been confused, particularly in venom studies, with a spider in the family Nemesiidae, *Acanthogonatus subcalpeianus,* which it resembles.[232]

Venom. *T. venosa* venom is extremely toxic to rats, with an apparent action similar to that of *Phoneutria* species.[176] Little is known about the venom composition.

Clinical Presentation. No cases of human envenomation have been reported, although it is presumed that symptomatic envenomation by *T. venosa* is possible.

Treatment. Treatment is symptomatic and supportive.

FAMILY ACTINOPODIDAE

Genus *Missulena:* Mouse Spiders

Biology. *Missulena* are large spiders (10 to 35 mm [0.4 to 1.4 inches]) native to Australia. One species is found in Chile. Like all Actinopodidae, they are trapdoor spiders that burrow underground and seal the entrance with a lid that they open and

close with their fangs. Silk lines spreading from the burrow's mouth reveal the presence of prey that stumble across them. Spiders dash out, grab prey in their jaws, and retreat back into the burrow to feed. These spiders spend most of the time underground, with the exception of males searching for females in autumn. The larger females are most often encountered when their well-camouflaged burrows are accidentally dug up.

Venom. *Missulena* venoms have recently been confirmed to have a major bioactive component, δ-missulenatoxin-Mb1a,[123] which is homologous to the δ-atraxotoxins of atraxine spiders (see earlier). This toxin has strong insecticidal potency and acts by manipulation of tetrodotoxin-sensitive sodium channels. Discovery of this toxin and its homology with atraxotoxins indicate extreme conservation of this toxin family.[123] This finding also provides a mechanistic explanation for observed similarities between the toxic effects of bites of *Missulena bradleyi* and those of *Atracines* in animals.[231]

Clinical Presentation. In a series of 13 envenomations, pain was the most common complaint (severe in 10 patients), with puncture marks, bleeding, redness, and edema being the next most common complaints. Three patients exhibited neurotoxic effects; all three exhibited paresthesias, one with accompanying diaphoresis. Nonspecific systemic effects occurred in five patients. There were no cases of severe envenomation in this series. There have been a total of 40 reported *Missulena* bites, with one case of severe envenomation. This occurred in a 19-month-old child in Queensland.[150,146]

Treatment. Treatment is largely symptomatic and supportive. In the case of severe envenomation of the 19-month-old child, administration of funnel-web spider antivenom, raised against male *A. robustus* venom, produced dramatic improvement in her condition, with full recovery following a second dose.[231] Although severe envenomation is rare, it is suggested that all suspected Mygalomorphae bites be observed for 4 hours to exclude such envenomation.[150,]

SUBORDER ARANEOMORPHAE

Enormous diversity is found within the group Araneomorphae, which contains more than 85% of the approximately 45,500 described spider species.[64,224,325] Araneomorphs, or true spiders, are found throughout the world in all terrestrial (and a few aquatic) habitats. They show tremendous variability in size, appearance, and habit. No araneomorph is as large as the largest tarantulas. Characteristics that distinguish araneomorphs from mygalomorphs include spinneret features (e.g., increased diversity of silk glands and proteins) that enable them to produce various types of sticky silk. Almost all groups have only one pair of book lungs. Most have eight eyes, but eye number varies from two to eight. Prey capture tactics usually determine where a spider will be found and are generally consistent within particular groups. These tactics often provide conspicuous clues that help identify spiders (see Table 43-1).

FAMILY SICARIIDAE: RECLUSE SPIDERS

Sicariidae includes two genera, *Loxosceles* and *Sicarius,* both of which are clinically important. The family falls within a larger group of families (Scytodoids) that have only six eyes. In these two genera, the eyes are in three dyad pairs. The chelicerae are fused at the base, and the labium is fused to the sternum. Previously, *Loxosceles* was placed in its own family, Loxoscelidae, but this is now synonymized with Sicariidae.[227]

Genus *Loxosceles:* Brown or Fiddle Spiders

Biology. *Loxosceles,* commonly known as brown or fiddle spiders, build small, irregular, and sticky webs, typically in small spaces, such as under rocks, wood, or debris in human-made habitats. The genus contains 113 species, with centers of diversity in North and South America, the Caribbean Islands, and Africa.[20,75,181,251,264] These spiders are 8 to 15 mm (0.3 to 1.6 inches) in adult body length, are light to dark brown, and have a dark, violin-shaped spot centered anterodorsally, such that the neck of the fiddle extends toward the posterior end of the cephalothorax.

FIGURE 43-10 Adult female desert violin spider *(Loxosceles deserta). (Courtesy Michael Cardwell and Associates, 1994.)*

The shape and darkness of the fiddle, relative lengths of the first two pairs of legs, and characteristics of genitalia are features that help distinguish species[45,138,264] (Figure 43-10).

From the South American *Loxosceles laeta* to the South African *L. spinulosa,* these small arachnids have been associated with human pathologic conditions. Several species have been associated with necrotic arachnidism in the United States: *L. reclusa* (the true brown recluse spider, Figure 43-11), *L. rufescens, L. arizonica,* and *L. laeta.* These spiders are native to the southernmost states and Mississippi River Valley. *L. reclusa* territory extends as far north as southern Wisconsin. Species native to one region or habitat may adapt successfully to new locations after transport by humans.[210,321]

Brown spiders regularly roam in search of new web sites, and males wander in search of females. They are most active at night and emerge from rock piles, woodpiles, and rats' nests to hunt insects and other arachnids from spring through fall. South

FIGURE 43-11 Brown recluse spider. **A,** *Loxosceles reclusa.* **B,** *Loxosceles vonwredei,* a cave-dwelling species from Namibia. *(***A** *courtesy Indiana University Medical Center;* **B** *courtesy Greta J. Binford.)*

African savanna species have been observed under stones and logs, and in the tunnels of old termite nests. Spelean species are found in caves but have also appeared in homes and export warehouses.[206,209,211] Brown spiders may infest homes, generally preferring warm, undisturbed environments, such as vacant buildings and storage sheds. In Chile, the tendency to inhabit human dwellings has earned *L. laeta* the names *araña de los rincones* (corner spider) and *araña de detrás de los cuadros* (spider behind the pictures).[263] *Loxosceles* distributions are patchy, but when present can reach high densities. For example, 2055 individual *L. reclusa* were captured in a single-family home in Kansas in a 6-month period.[314] Molts, or shed exoskeletons, are good indicators of the presence of resident *Loxosceles*. Webs are made in crevices and are small, flocculent structures with a bluish tint in bright light. Egg sacs are laid flat against surfaces, typically with a layer of fluffy silk on the exposed surface. Females may live 1 to 3 years, and longer in captivity.[104,139] Naturally unaggressive toward humans, brown spiders are not prone to bite unless threatened or trapped against the skin. Bites typically follow retrieval of old bed sheets or jackets from storage. Thorough housecleaning with movement of boxes and stored items at least once per year highly reduces the likelihood of establishment of robust populations of *Loxosceles* in houses.[105]

A study by Vetter[312] showed that of 1773 spiders thought to be *L. reclusa* by medical professionals, only 324 were *Loxosceles*. In addition, true recluses were from regions historically known to be in their home range. Only one brown recluse spider was found outside the normal habitat region, and this case was explained by recent travel. Of the other 1449 submissions that were spiders, more than 38 families, 88 genera, and 158 species were identified. It was noted that more accurate identification occurred in areas with known historical populations. This study also suggests that the brown recluse has not migrated throughout the United States but remains within its home regions. With climate change, northern migration of *L. reclusa* is anticipated.[257]

Venom. Proteomic and transcriptomic analyses have identified a rich complex of components in venoms of South American *Loxosceles,*[87] and these are representative of the major components in venoms of species throughout the sicariid family. Among the most abundant components are astacin-like metalloproteinases, inhibitor cysteine knot peptides that likely act as neurotoxins on insect prey, and toxins in a gene family distinct to sicariid spiders, *SicTox*, which includes sphingomyelinase D (SMase D).[120] *SicTox* are the most clinically relevant and discussed in further detail below. Less abundantly expressed components include serine protease inhibitors, hyaluronidases, allergen factors, and translationally-controlled tumor proteins. The effects of these toxins in mammals are still under investigation. Hyaluronidase[338] probably plays a facilitating role in lesion development, by encouraging spread of other venom components. It is not itself a cytotoxin. Hydrolytic enzyme activities include esterase,[338] alkaline phosphatase,[130] lipase,[158] 5′-ribonucleotide phosphorylase,[102] and astacins.[298] None of these alone appears to explain cytotoxicity.

Enzymes in the *SicTox* protein family (32- to 35-kDa) constitute up to 18% of proteins in *Loxosceles* venom.[87] These toxins act on the cell surface by cleaving phospholipids at the D site. Sphingomyelinase D is a sufficient causative agent for formation of dermonecrotic lesions following *Loxosceles* bites.[168,295,296,299] So far, *SicTox* homologs are not known from venoms of other spiders, including *Scytodes,* that are closely related to sicariids, suggesting the toxin was evolutionarily recruited before the most recent common ancestor of this spider family. *SicTox* proteins are abundantly expressed throughout the family, including worldwide representatives of *Loxosceles* and *Sicarius*.[36,37] Recent work indicates that different proteins in the gene family differ in their substrate preferences. The better-known enzymes in the family have a binding preference for choline over ethanolamine, whereas other homologs prefer ethanolamine over choline.[170] Variation in binding preferences and differences in relative abundances in venoms among sicariid species may be important for understanding differences in clinical effects of envenomation by different species in the family. Based on current understanding of *SicTox* enzymes in venom, however, the conservative approach is to suspect all sicariids to be capable of medically relevant bites. A caveat is that many species live in habitats where they are unlikely to encounter humans, so they are of little actual threat.

Sphingomyelinase D is postulated to operate by a variety of mechanisms. Details of biochemical cascades that lead to lesion formation or systemic effects in humans are still under investigation. Activity of these enzymes induces an immune response involving the complement system.[17,264] This response involves cell membrane–binding complement activation and polymorphonuclear leukocyte neutrophil chemotaxis [100,237,272,303,304] as inferred by the inhibition of lesions in rabbits by pretreatment with nitrogen mustard to deplete polymorphonuclear leukocyte neutrophils. Histologic studies suggest similarities between venom-induced lesions and those seen with the Arthus and Schwartzmann phenomena.[272] There is much research attention focused on the role of ceramide 1 phosphates (the presumed cleavage products of sphingomyelinase D) in this cascade. [241] However, it was recently discovered that the end product of cleavage of phospholipids by *SicTox* enzymes is a cyclic phosphate. A shift in research focus that takes this crucial detail into account may facilitate a better understanding of the biochemical mechanisms underlying the complex human response to sicariid envenomation.[171]

Although the exact pathogenetic mechanism of sphingomyelinase D is unclear, much is known about physiologic responses to *Loxosceles* bites. Injected into humans, the venom is a hemolysin and cytotoxin, with enzymatic activities that may cause hemolysis and dermonecrosis. Venom toxins act as proteases against constituents of plasma and basement membranes. Because of their degenerative nature, these proteases suggest a plausible mechanism for the hemorrhage, delayed wound healing, renal failure, and associated spreading of other toxins seen in *Loxosceles* envenomations.[303]

Venom from *L. reclusa* has a direct hemolytic effect on human erythrocytes. This process depends on the presence of serum components that include C-reactive protein and calcium.[143,299] Platelet aggregation also is calcium dependent and induced in vitro by sphingomyelinase D. This process may activate the prostaglandin cascade. Platelet aggregation appears to depend on serum amyloid protein, a serum glycoprotein of previously unknown significance.[98,236,261] Lysis of erythrocytes is induced by *Loxosceles* sphingomyelinases dependent on activation of complement by the alternative pathway, caused by induction of surface glycophorin cleavage. Cleavage of glycophorins, observed after incubation of erythrocytes and *Loxosceles* toxins, results through activation of an endogenous membrane–bound metalloproteinase.[294,303]

There is striking variability in physiologic responses to *Loxosceles* bites among target species and humans. Some vertebrate species (e.g., rats and fish) are essentially unaffected by *Loxosceles* venom. Others (e.g., rabbits, mice, and dogs) are highly susceptible to its effects.[262] Some of the variability in clinical presentation among victims of *Loxosceles* envenomation may be caused by differences in the venom of males and females. Female *L. intermedia* spiders produce a greater amount and more potent venom than do males.[69] Possible roles of the full complex of components in venom, and how they vary within and among species, remain areas of current research.

Clinical Presentation. Necrotic arachnidism (loxoscelism in the case of bite by spiders of the genus *Loxosceles*) refers to the clinical syndrome that follows envenomation by a variety of spiders, for which *L. reclusa,* the brown recluse spider, is the prototype. The bites of these spiders often result in serious cutaneous injuries, with subsequent necrosis and tissue loss. Less often, severe systemic reactions may occur with hemolysis, coagulopathy, renal failure, and even death.[140,319]

Reports of a severe reaction to spider bites possibly attributable to brown spiders date back to 1872, in a report of a 45-year-old Texan woman with a febrile illness accompanying a large necrotic lesion of her thigh.[54] In 1896, death from renal failure accompanying another bite in Texas was reported.[228] A spider bite was reported as a cause of blackwater fever (massive hemoglobinuria) in Tennessee in 1940.[112] The first documented case of loxoscelism in Kansas (from *L. rufescens*) was reported in 1929.[265] *L. laeta* was identified as the cause of similar lesions in

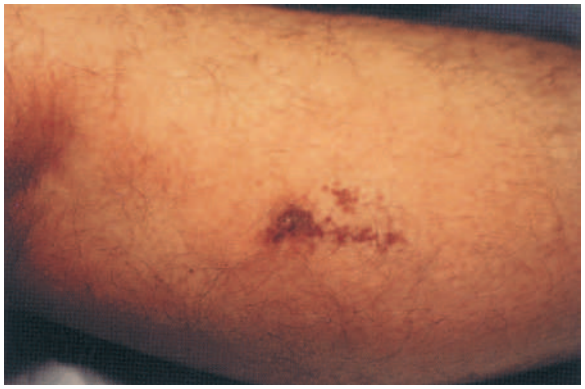

FIGURE 43-12 Brown recluse spider bite after 6 hours, with central hemorrhagic vesicle and gravitational spread of venom. *(Courtesy Paul S. Auerbach, MD, and Riley Rees, MD.)*

South America in 1937, and *L. reclusa* was the cause of necrotic arachnidism in the midwestern United States by 1958.[9,10] Since then, numerous cases of cutaneous and more severe reactions have been attributed to spiders of the genus *Loxosceles*.

The clinical spectrum of loxoscelism ranges from mild and transient skin irritation to severe local necrosis accompanied by dramatic hematologic and renal injury. Isolated cutaneous lesions are the most common presentation. Most bites resolve spontaneously without the need for medical intervention.[27,28] Many clinicians distinguish between simple local presentation and more severe systemic, or viscerocutaneous, loxoscelism.

Local symptoms usually begin at the moment of the bite. A sharp stinging sensation is possible, although a victim may be unaware of having been bitten. Frequently, the bite site corresponds to a portal of entry or a region of constricted clothing (e.g., cuff, collar, waistband, or groin area). The stinging usually subsides over 6 to 8 hours and is replaced by aching and pruritus as the lesion becomes ischemic from local vasospasm. The site then becomes edematous, with an erythematous halo surrounding an irregular violaceous center of "incipient necrosis" (actually hemorrhage and thrombosis).[46,252,299] A white ring of vasospasm and ischemia may be discernible between the central lesion and halo. Often, the erythematous margin spreads irregularly in a gravitationally influenced pattern that leaves the original center eccentrically placed near the top of the lesion (Figures 43-12 to 43-14). In more severe cases, serous or hemorrhagic bullae may arise at the center within 24 to 72 hours, and an eschar forms beneath. Pain at this stage may be severe.[221] After 2 to 5 weeks, this eschar sloughs, leaving an ulcer of varying size and depth through skin and adipose tissue, but sparing muscle.[97,132] Lesions involving adipose tissue may be extensive, perhaps from lipolytic action of the venom.[158] The ulcer may persist for many months and leave a deep scar.[193,248,323] Local sequelae depend on the anatomic location. Persistent segmental cutaneous anesthesia has been attributed to nerve injury after a recluse bite on the side of the neck.[122] Reconstructive surgery including skin grafting was necessary for necrosis following a presumed Mediterranean recluse bite.[136] (Figure 43-15). Epiglottic and periepiglottic swelling severe enough to require endotracheal intubation has been reported in a recluse bite involving a child's ear.[131]

The bite of the somewhat larger South American spider *L. laeta* is reported to cause intense pain and extensive edema, with proportionately less necrosis than that caused by *L. reclusa*. The edema is notoriously prominent with facial bites and resolves over 2 to 4 weeks.[264]

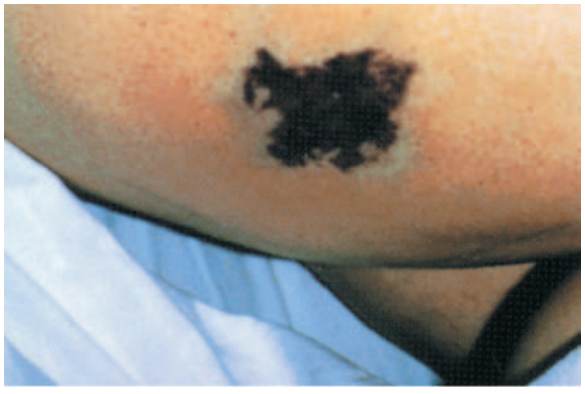

FIGURE 43-13 Brown recluse spider bite after 24 hours, with central ischemia and rapidly advancing cellulitis. *(Courtesy Paul S. Auerbach, MD.)*

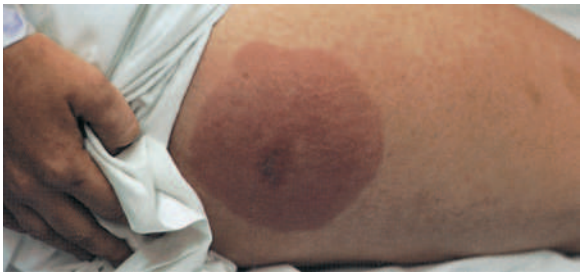

FIGURE 43-14 Brown recluse spider bite after 48 hours, with incipient central necrosis.

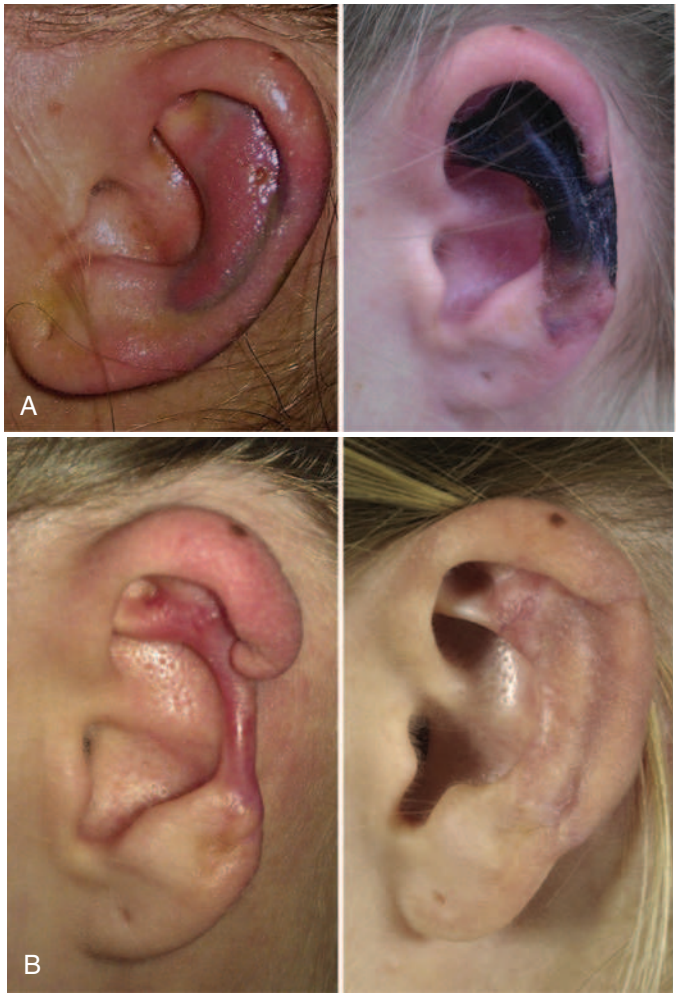

FIGURE 43-15 Partial ear necrosis due to recluse spider bite. **A,** Red, white, and blue discoloration on day 7 leading to through-and-through necrosis of middle third of the ear on day 21. **B,** Middle third defect and ear after reconstruction with costal cartilage. *(From Holtslag I, van Wijk M, Kon M: Partial ear necrosis due to recluse spider bite.* J Plast Reconstr Aesthet Surg *67(3):419-421, 2014, Figures 1 and 2.)*

Systemic involvement is less common but may occur in combination with cutaneous injury from any *Loxosceles* species. It occurs more frequently in children but may be seen in adults.[174,229,297] In a series of 26 children in the United States, Hubbard[142] reported that 85% had an inflammatory response, most (77%) with secondary cellulitis. The most prevalent systemic effects were hemolytic anemia (50%), rhabdomyolysis (27%), and acute renal failure (12%). There were no fatalities, but 65% had major morbidity, including wound complications and acute orbital compartment syndrome. A series of 35 children in Mexico included 77% with local signs only and 23% with systemic loxoscelism. Dermonecrotic ulcers occurred in 57% of cases. Among systemic cases, the authors noted leukocytosis (100% of cases), hypotension (88%), metabolic acidosis (75%), and respiratory distress (50%).[253]

Systemic reactions may develop in cases with minor-appearing local findings, making diagnosis difficult.[299] When systemic involvement occurs, hemolytic anemia with hemoglobinuria is often the prominent feature, usually beginning within 24 hours of envenomation and resolving within 1 week.[78] During this time, measured hemoglobin levels may drop markedly and be accompanied by jaundice and hemoglobinuria. Anemia is usually negative on Coombs' test, but two cases of anemia positive on Coombs' test have been reported.[319] A series of 81 patients in Brazil included two cases with massive hemolysis and renal injury, 25 with elevated serum bilirubin and LDH levels, 14.7% with anemia, and 17.6% with thrombocytopenia.[183] Fever, chills, maculopapular rash, weakness, leukocytosis, arthralgias, nausea, vomiting, thrombocytopenia, disseminated intravascular coagulation, hemoglobinuria, proteinuria, renal failure, and death have been reported.[32,39,107,204,243]

McDade and coworkers[191] reported on six adolescents treated for acute hemolytic anemia from presumed *L. reclusa* bites. The patients, all previously healthy, were treated for an acute systemic illness. Substantial anemia occurred in all six, with a median hemoglobin level of 7.1 g/dL. The direct antiglobulin test was positive for surface complement component C3 in all, and surface IgG was detected in three patients. All patients developed reticulocytosis, hyperbilirubinemia, and local dermonecrosis.

A case report by de Souza and associates[73] illustrates critical complications of *Loxosceles* envenomation resulting in skin necrosis, rhabdomyolysis, hemolysis, coagulopathy, acute kidney injury, and electrolyte disorders. A 26-year-old man in Brazil was bitten on his trunk while getting dressed. Twenty hours later, he sought treatment at a hospital and was given anti-*Loxosceles* antivenom and supportive care. The spider was brought with the patient and was positively identified as *Loxosceles*. Over several hours, he developed abdominal pain, headache, nausea and vomiting, oliguria, and respiratory distress. Forty-eight hours after the bite, he was transferred to an intensive care unit in a specialty hospital. He had generalized exanthem, jaundice, and conjunctival hyperemia. The bite site was edematous, with vesicles and ecchymosis. Renal function deteriorated, and he was begun on hemodialysis on day 2, and progressed to develop hemolysis with a hemoglobin level of 4.7 g/dL on day 7. On day 30, hemoglobin levels stabilized in the absence of transfusions, and the lesion had evolved to an eschar with areas of necrosis. Hemodialysis was discontinued on day 35, when creatinine levels began to normalize. He was discharged, and follow-up on day 61 indicated a normal creatinine level.

Diagnosis of loxoscelism is most often based on spider observation and identification, typical history, and local and systemic signs. Differential diagnosis of the local injury includes bacterial and mycobacterial infection, herpes simplex, decubitus ulcer, burn, embolism, thrombosis, direct trauma, vasculitis, Lyme disease, and pyoderma gangrenosum.[5,162,230,235,287] Although bacterial infections, particularly methicillin-resistant *Staphylococcus aureus,* have often been historically misdiagnosed as brown recluse spider bites, improved awareness has led to more accurate diagnoses.[313]

Because *Loxosceles* venom provokes an immune response in experimental animals, efforts to develop diagnostic tests are based on antigen or antibody detection in human blood. In 1973, Berger and associates[28] reported an in vitro lymphocyte transformation assay for *L. reclusa* venom, which turned positive in the lymphocytes of exposed individuals within 4 to 6 weeks of initial exposure. This test may help to document prior exposure but not to diagnose envenomation at the time of the initial bite. Barrett and coworkers[23] reported a passive hemagglutination inhibition test using rabbit antibody and human erythrocytes incubated in vitro with venom from *L. reclusa*. Barbaro and colleagues[22] demonstrated circulating IgG against *L. gaucho* venom detectable between 9 and 120 days after the bite in 4 of 20 patients. Cardoso and associates,[50] observing that efforts to detect antigen in human serum may fail because of insufficient antigenemia, have demonstrated the presence of *L. gaucho* venom in biopsy homogenate using enzyme-linked immunosorbent assay (ELISA). Venom-specific enzyme immunoassays have been used to demonstrate the presence of *Loxosceles* venom in necrotic wounds, including in a pediatric series previously described,[253] and in 46 of 56 "probable" *L. reclusa* bites.[221] A series of five proved or suspected *L. reclusa* bites to women in the second and third trimesters of pregnancy has been reported. Despite significant local injuries, rash, and microhematuria, no fetal injury was noted.[4] A woman suspected to have *L. boneti* envenomation presented at 28 weeks' gestation with a combination of severe local injury and shock, and the infant was delivered by cesarean section 4 hours after presentation, with an APGAR score of 5/7. The patient received intensive care, including mechanical ventilation, administration of specific antivenom, and surgical debridement.[255]

Treatment. Treatment of loxoscelism depends on its severity. Cutaneous loxoscelism can usually be managed on an outpatient basis. Most mild cutaneous envenomations respond to application of local cold compresses,[164] elevation of the affected extremity, and loose immobilization of the body part. Severe pain may require management with narcotics.[221] Tetanus prophylaxis should be provided as indicated. After erythema has subsided, necrotic lesions may need debridement to define the margins of the central eschar. This usually involves significant debridement 1 or 2 weeks after the bite, with close follow-up for several weeks. In severe cases, when the wound is stable, this can be followed with skin grafting or plastic surgery. Severe necrotic or infected lesions may lead to hospitalization. Although many therapies have been used for *Loxosceles* envenomation, including dapsone, glucocorticoids, hyperbaric oxygen, electric shock, antivenom, metronidazole, diphenhydramine, phentolamine, and cyproheptadine, efficacy has not been established and clinical trials have not been done. Initial studies in small mammals have been inconclusive.[79,293]

Monteiro and colleagues[196] found the anaerobic bacterium *Clostridium perfringens* in *Loxosceles* venom and fangs and suggested that it might be inoculated with the venom. In rabbits, the combination of venom and *C. perfringens* increased dermonecrotic damage. The authors suggested antibiotic therapy when treating loxoscelism in association with *C. perfringens*. Catalán and colleagues[53] isolated and characterized several species of *Clostridium,* including multiply drug-resistant *C. perfringens,* from the fangs and venom glands of *L. laeta*.

Some have advocated the use of dapsone for prevention of lesion progression in potentially necrotic wounds seen within 48 to 72 hours of a bite.[94,101] Dapsone is a leukocyte inhibitor that in theory can minimize the local inflammatory component of cutaneous loxoscelism, and may prevent or decrease subsequent skin necrosis. In 1983, King and Rees[163] reported use of dapsone for envenomation in a human bitten by *L. reclusa,* based on a successful trial of dapsone pretreatment in guinea pigs injected with recluse venom. A variety of case reports and series have supported dapsone use for treatment of potentially necrotic wounds treated in the first days after envenomation.[3,25,131,178,324] No prospective, controlled human trial has proved dapsone efficacy. Typical dosage recommendations are 50 to 100 mg orally, twice daily. Risks of dapsone therapy include hypersensitivity,[333] methemoglobinemia, and hemolysis in the presence of glucose-6-phosphate dehydrogenase (G6PD) deficiency. Because of these risks and the uncertain benefits, recent opinion has trended away from use of dapsone.[315]

Patients with systemic symptoms should be considered for admission when they have evidence of coagulopathy, hemolysis

and hemoglobinuria, or rapid progression of other systemic signs. Care is mainly supportive, usually involving wound care, fluid management, presumptive treatment for bacterial superinfection, and, occasionally, blood transfusion. Rarely, hemodialysis has been required for oliguric renal failure.[110] Discharge is appropriate when renal and hematologic status is stable.

For patients with significant local or systemic signs or symptoms, laboratory evaluation should include a peripheral blood cell count, basic coagulation screening, and urinalysis. Liver and renal function tests are indicated in severe poisonings. When use of dapsone is considered, a screening test for G6PD deficiency is indicated. Frequency of follow-up testing depends on the course and severity of envenomation. Hospitalized patients may need close follow-up of anemia and possibly altered renal function for several days.

Corticosteroids have been injected either at the wound site or systemically, but this remains of questionable benefit.[26,239] Antihistamines may help control itching but do not change the lesion. Some clinicians advocate early surgical excision of the wound site.[8,16,86,135] Others have demonstrated that outcomes are better with early medical management in human patients[71,233] as well as in experimental animals.[239] Hyperbaric oxygen treatment has been tried empirically in uncontrolled human trials, with reports of good outcome.[292] Comparison of hyperbaric oxygen treatment with no treatment in rabbits showed enhanced recovery at 24 days at the histologic level, but with no apparent clinical difference between the two groups.[276] Wong and coworkers[336] studied negative-pressure wound therapy (NPWT) using vacuum-assisted closure in pigs. The size of the wounds treated with vacuum-assisted closure on day 3 was significantly smaller than the size of control wounds.[58] Chariker reports using NPWT effectively in treating a necrotizing wound caused by a brown recluse spider bite on the ear of a boy 5 years of age.[58]

Loxosceles-specific antivenom has been tried in both North and South America. In the early 1980s, Rees and colleagues[239] reported a protective effect of treatment with antivenom in rabbits up to 12 hours after envenomation. Small-vessel occlusion, leukocyte infiltration, and necrosis were diminished in antivenom recipients. Pretreatment in a separate study abolished symptoms of systemic loxoscelism.[238] In one study, 17 patients were separated randomly into dapsone, antivenom, and combination therapy groups; all patients received erythromycin. Individual results suggested that antivenom was efficacious when given early, but the overall trial was inconclusive, indicating need for further study.[234] Gomez and colleagues[109] have studied intradermal use of anti-*Loxosceles* Fab-fragments in a rabbit model. This suggested therapeutic efficacy when the antivenom is injected up to 4 hours following envenomation. A $F(ab')_2$ antivenom developed using recombinant sphingomyelinase D[217] has been in use since 2009 in Mexico. Early experience suggests this approach may reduce the extent of dermonecrosis in local lesions.[254] Currently, no *Loxosceles* antivenom is commercially available in the United States.

In South America, an antivenom to *L. laeta* was developed in 1954 by Vellard using donkey immune serum. Furlanetto developed *L. laeta* antivenom using horse immune serum.[197] Reports of systemically administered *L. laeta* antivenom efficacy have been mixed.[264] Venom similarities throughout the genus suggest the potential to develop a globally effective antivenom to treat *Loxosceles* bites.[21] An ELISA assay, developed for detection of circulating venom antigen, has the potential to develop into a diagnostic tool for clinicians and epidemiologists.[60]

Genus *Sicarius*: Six-Eyed Crab Spiders

Biology. There are 25 described *Sicarius* species. The geographic range is limited to dry regions of South and Central America and Southern Africa. Spiders live under stones or are sand dwellers. Some hide under sand and emerge to capture passing insects. Their bodies are flattened and legs are laterigrade (i.e., the tips point anteriorly as in a crab). Adult body size ranges from 12 to 22 mm (0.5 to 0.9 inch) (Figure 43-16).

Venom. Venoms of *Sicarius* contain many of the same components as *Loxosceles* (described in detail above). Venom of the South African six-eyed sand spider *Sicarius testaceus* in a rabbit model demonstrated tissue necrosis and increased vascular permeability in the vicinity of the envenomation, as well as a dramatic decrease in platelet count. It is not clear whether this pattern is the same in humans.[302] South African *Sicarius* venoms have detectable sphingomyelinase D activity, as discussed for *Loxosceles* venoms.[36,37] South American *Sicarius* venoms have reduced detectable sphingomyelinase D activity.[36] This may result from the different substrate preferences of their venom's *SicTox* enzymes.[170] There are no records of clinically significant bites from South American *Sicarius* species.

FIGURE 43-16 *Sicarius albospinosus* male from Namibia. *(Courtesy Melissa Callahan.)*

Clinical Presentation. *Sicarius* species are occasionally implicated in human bites in South Africa. They tend to bite only when provoked and are rarely implicated in human poisonings, despite high toxicity of the venom in laboratory animals. Envenomation reportedly can cause edema, erythema, and necrosis, and is occasionally associated with disseminated intravascular coagulation.[208-210]

Treatment. Treatment of *Sicarius* envenomation is symptomatic and supportive.

FAMILY PHOLCIDAE: CELLAR SPIDERS OR DADDY LONGLEGS

Pholcid spiders are distributed worldwide and are highly diverse (1455 species). We include this section because of the widespread urban myth that "daddy longlegs spiders" are the most poisonous spiders in the world, but their fangs are too small to pierce human skin. Some pholcid spiders are capable of bites that pierce human skin (Chuck Kristensen, personal communication). Pholcid venoms are full of protein and peptide toxins,[34] but the effect of bites on humans is minimal, causing only a mild sting and, occasionally, minor erythema.

FAMILY DESIDAE: LONG-JAWED INTERTIDAL SPIDERS

About 200 species of Desidae are distributed worldwide. Their chelicerae often extend forward and have humps close to the prosomal attachment. Species range in body length from 4.5 to 12 mm (0.2 to 0.5 inch). Most spiders in this family build small, irregular webs under rocks or logs. Some desids are closely associated with marine habitats and live in the intertidal zone. These spiders feed on marine animals and at high tide retreat into empty snail shells and worm tubes and seal off the entrance with silk. Others are found only on the water surface.

Genus *Badumna*: Black House Spider

Biology. *Badumna insignis* (*Ixeuticus robustus*), or the black house spider, is a common Australian spider associated with a few human bite reports. This species is a nocturnal forager that builds tangled webs with silk retreats in and around human habitations.[327]

Venom. Venom gland extract from *B. insignis* causes increased vascular permeability, as well as dose-dependent

decreases in arterial pressure in rats, apparently from the presence of a serotonin-like substance in the venom.[154] Venom gland extract does not cause necrosis in cultured human or mouse skin.[14]

Venom of *B. insignis* contains fibrinogenolytic and gelatinolytic proteases. Sphingomyelinase activity has not been found in the venom of *B. insignis,* but has been identified in its abdominal contents.[283]

Clinical Presentation. In one report, *B. insignis* caused local pain, itching, and swelling followed by regional lymph node tenderness and discoloration of the bite area. Over 2 weeks, the lesion resolved, with some tissue necrosis and sloughing centrally.[179] In two series of *B. insignis* bites, local lesions were painful but transient and unaccompanied by necrosis.[148,328] Systemic symptoms have rarely been reported, but include nausea, vomiting, abdominal pain, pruritus, and painful knees.[327]

Treatment. Treatment of *Badumna* envenomation is symptomatic and supportive.

FAMILY ZODARIIDAE: HUNTING SPIDERS

Zodariids are a diverse group of hunting spiders.[151] The estimated 350 species are distributed worldwide but are primarily found in the tropics and subtropics. They are medium-sized (3 to 15 mm), with the anterior spinnerets usually longer than their posterior structures. They hide under stones or burrow in pebbles or sand. Very few reports of documented human envenomation exist, although *Supunna picta,* a common leaf litter–dwelling spider of Australia, reportedly caused a transient erythematous rash and slight itch in a woman bitten at home. The lesion resolved uneventfully.[40]

FAMILY GNAPHOSIDAE: GROUND SPIDERS AND MOUSE SPIDERS

Gnaphosids are common and found worldwide, with the highest densities in temperate areas. They are small- to medium-sized (2 to 14 mm) and usually dark in color (black, gray, or reddish brown). They have long, slightly flattened abdomens, and two of their spinnerets are conspicuous and cylindrical. Gnaphosids are nocturnal hunters, mostly on the ground. During the day, they retreat under stones or seek other tight quarters.

Herpyllus ecclesiasticus, the parson spider, is distributed widely throughout the United States and lives under rocks and rubbish and in houses. One case report of a bite by *H. ecclesiasticus* described pruritus, arthralgia, malaise, and nausea beginning 1 hour after the bite. There was no necrosis.[180,229]

Treatment. Treatment of bites is symptomatic and supportive.

FAMILY LAMPONIDAE: WHITE-TAILED SPIDERS

Until recently, the genus *Lampona* was placed in the family Gnaphosidae. The group was changed to family status because members do not share many of the characteristics that define Gnaphosidae.[223] Specialists believe that many undescribed genera in Australia belong to this group.

Genus Lampona

Biology. *Lampona cylindrata* is a hunting spider with a distinctive cylindric shape and white spot at the tip of the abdomen. It is often found indoors in Australia and New Zealand.[327] Individuals are wandering foragers that enter webs of other spiders and prey on them.

Venom. *L. cylindrata* venom appears to increase vascular permeability in rats, perhaps from release of endogenous bradykinin and prostaglandins.[166] Venom contains histamine and noradrenaline, both more highly concentrated in male spider venom.[230]

The venom of *L. cylindrata* contains fibrinogenolytic and gelatinolytic proteases. Sphingomyelinase activity has been identified in abdominal contents, but not venom, of *L. cylindrata.* This finding is similar to that for *Badumna insignis.*[283]

Clinical Presentation. In a series of 130 *Lampona* bites, predominantly of *L. cylindrata* and *L. murina,* pain or discomfort occurred in all and was severe in 27%. Puncture marks were present in 17% and redness or a red mark in 83% of bites. Systemic effects occurred in 9% of bites. Necrosis was not reported. There were three distinct clinical patterns: pain only (21%), pain and a red mark for less than 24 hours (36%), and a persistent painful or red lesion (44%).[149] Gray[117] reported a case of more significant illness, with nausea, lethargy, and a small zone of necrosis after a confirmed white-tailed spider bite. Although the vast majority of cases are relatively benign, significant skin necrosis may result from envenomation.[327] A recent review by White and Weinstein refutes claims of dermonecrosis made by earlier authors and confirms the relatively benign course observed in cases where an actual spider was identified.[329]

Treatment. Treatment of *Lampona* envenomation is symptomatic and supportive.

FAMILY: SPARASSIDAE: CRAB SPIDERS AND HUNTING SPIDERS

Biology

Sparassids, or "giant crab spiders," are distributed worldwide and are mostly tropical. They are large (10 to 40 mm [0.4 to 1.6 inches]) and resemble crabs, with the tips of all legs angling forward. They have flattened bodies and are capable of moving sideways. They have eight eyes in two straight rows. They are wandering hunters and typically nocturnal. In many places, they are welcome cohabitants with humans because they eat cockroaches.

Palystes natalius, the lizard-eating spider, is one of the largest true spiders in South Africa. It has a brownish-gray body and legs with bright yellow and black stripes. Females are larger than males, with body length up to 4 cm (1.6 inches).

Venom

Venom from the Australian heteropodid *Isopeda montana* has direct β-adrenoreceptor action. Venom from *Delena cancerides,* the social huntsman spider, appears to have both α- and β-adrenoreceptor activity. Although both have been shown to increase vascular permeability in rats, neither of these has been involved in recognized human envenomation.[134]

In a series of 173 spider bites, with 168 confirmed to be sparassid spiders, 95% percent of the bites were from four genera: *Isopeda* (32%), *Isopedella* (21%), *Neosparassus* (27%), and *Heteropoda* (14%). Other genera included *Delena* and *Holconia.* Most bites (95%) were on limbs; 82% occurred distally. Pain or discomfort was present in all cases, and severe in 27%. The median duration of pain was reported as 5 minutes, significantly less than with other spiders. Puncture marks (40%) or localized initial bleeding (35%) occurred in 54% of bites. Redness or a red mark occurred in 57%, swelling in 16%, and itching in 44% of bites. Systemic effects occurred in 4% and consisted of nausea and/or headache. There were no cases of necrotic ulcers or allergic reactions.[151]

Clinical Presentation

Only localized burning accompanied by slight swelling was noted after a female *P. natalius* bite to the wrist.[207,212] An *Olios calligaster* bite was followed by mild local symptoms, transient nausea, and faintness. Six bites by *Isopeda* species, predominantly *I. pessleri,* resulted in minimal local symptoms only.[328]

One case of acute conjunctival inflammation, secondary to material from a crushed *I. villosa* being accidentally rubbed into the affected eye, has been reported. This type of injury is more commonly associated with small spiders, mainly Pholcidae (daddy longlegs).[145]

Treatment

Treatment of heteropodid bites is symptomatic and supportive.

In the case of the conjunctival inflammation, treatment consisted of a topical anesthetic followed by a normal saline flush for 1 hour. Redness and swelling began to resolve approximately 2 hours after injury. The patient experienced ongoing pain and

mild photophobia and was discharged home with topical chloramphenicol ointment and an eye patch for 24 hours. Twenty-eight hours after the injury, symptoms had resolved.[145]

FAMILY OXYOPIDAE: LYNX SPIDERS

Lynx spiders are found worldwide, with the greatest abundance in the tropics. They are small- to medium-sized (4 to 18 mm [0.2 to 0.7 inch]) and have a distinctive eye pattern, with six eyes in a hexagon and two smaller eyes below. Their abdomens are pointed posteriorly. They have long leg spines (macrosetae) that help detect motion through vibrations in the air. They are diurnal hunters with good vision and actively search for prey. Most are found on vegetation, and some are arboreal.

Genus Peucetia

Biology. *Peucetia viridans,* the green lynx spider of the United States and Mexico, is a diurnal hunting spider. *P. viridans* is translucent green, with red eyes and joints[125] (Figure 43-17). This species is common in the desert Southwest of the United States, and adult individuals are large (approximately 20 mm [0.8 inch]) and conspicuous.

Venom. Whole venom of *P. viridans* causes total and reversible block of non-*N*-methyl-D-aspartate receptor-mediated transmission in the chick central nervous system.[154]

Clinical Presentation. A series of four cases in which the spider was identified as *P. viridans* reported immediate pain, burning sensation, pruritus, erythema, and induration resolving in a couple of days. Necrosis and systemic signs have not been reported.[44]

Treatment. Treatment of *Peucetia* bites is symptomatic and supportive.

FAMILY SALTICIDAE: JUMPING SPIDERS

Salticidae is the largest family of spiders, with more than 5000 described species and many more yet to be described. They are distributed worldwide, with the highest densities in the tropics. Some have called them the "butterflies of the spider world" because most are brightly colored and some have iridescent scales. Some species mimic ants, beetles, pseudoscorpions, and bird droppings. Jumping spiders have excellent eyesight, with large, posteromedian eyes. They visually search for prey and then stalk and ambush with cat-like movements. Males are often more brightly colored than are females and perform elaborate courtship dances. They are always active during the day and are small, most less than 15 mm (0.6 inch).

Bites from spiders of the genus *Phidippus* (e.g., the jumping spider *Phidippus audax* of the United States) can cause pain, erythema, pruritus, and sometimes minor ulceration. The swelling usually subsides within 2 days.[29,192,247] In Australia, local pain has been reported following the bite of spiders from the genera *Mopsus, Breda, Opisthoncus,* and *Holoplatys*. One patient bitten by a *Holoplatys* reported headache and vomiting.[327]

FIGURE 43-17 Green lynx spider *(Peucetia viridans). (Courtesy Gita Bodner.)*

FAMILY CTENIDAE: WANDERING SPIDERS

Ctenidae are abundant and conspicuous worldwide and mostly found in subtropical and tropical areas. They can be large spiders, ranging in size from 4 to 40 mm [0.2 to 1.6 inches]. They hunt nocturnally on the ground or on vegetation. They resemble and are closely related to wolf spiders, but are distinguished by their eye arrangement (three rows: two eyes, then four, then two, the last two being the largest). They sometimes travel as stowaways on bananas.

Genus *Phoneutria:* Banana Spiders (Armed Spiders)

Biology. *Phoneutria* spiders of South America are large, nocturnal creatures notorious for their aggressive behavior and painful bite. The best-known representative of the genus is *P. nigriventer*. It is known in Brazil as *aranha armadeira,* meaning "spider that assumes an armed display," because of its characteristic defensive-aggressive display.[261] *P. nigriventer* is the largest, most aggressive true spider found in South America, with an average body length of 35 mm (1.4 inches), leg length of 45 to 60 mm (1.8 to 2.4 inches), and fangs of 4 to 5 mm (0.16 to 0.19 inch) in length for females. Males are slightly smaller.[260] The body is gray to brown gray with white marks forming a longitudinal band on the dorsal abdomen. A distinguishing characteristic is the red-brown brush of hairs around the chelicerae. *P. nigriventer* is mainly found in southern Brazil, Argentina, and Uruguay. Other species have been found in Bolivia and Colombia. The spiders do not construct a web. They are nocturnal hunters, often traveling several hundred meters in search of prey. They may enter houses during this time, hiding in clothes in the light of day. According to Bucherl,[42] 600 to 800 spider bites occur each year around the city of São Paulo alone.

Venom. *Phoneutria* venom is a complex mixture of histamine, serotonin, glutamic acid, aspartic acid, lysine, hyaluronidase, and other polypeptides. Histamine, serotonin, and incompletely characterized kallikrein-kinin activating fractions contribute to local tissue swelling from increased vascular permeability that may occur with envenomation.[6,184] In addition, venom contains at least six neurotoxic polypeptides, with molecular weights between 3500 and 8500 Da.[68]

Neurotoxic components include sodium channel poisons that appear to potentiate action potentials along axons, provoking erratic or rapid uncontrolled muscle twitches in invertebrates[80] and vertebrates.[7,175] Microscopically, there is acute transient swelling of axons, particularly at the nodes of Ranvier, in a pattern similar to that caused by the venoms of the scorpions *Centruroides sculpturatus* and *Leiurus quinquestriatus*. The axons recover within a few hours of exposure, but return of nodal width to normal takes several days.[175]

Venom effects have been studied in mice, rats, guinea pigs, rabbits, pigeons, and dogs. Venom has little or no effect on frogs and snakes. It has four times greater toxicity in dogs than in mice. Rats and rabbits are very resistant to the venom's effects, but rabbit vascular smooth muscle contractions appear to be stimulated by a venom protein that acts independently of voltage-dependent sodium and calcium channels.[185] Dogs developed intense pain, manifested by yelping, followed by sneezing, lacrimation, mydriasis, hypersalivation, erection, ejaculation, and death after venom was injected subcutaneously.[261] This is well within the dose that a single spider may inject. A neurotoxin isolated from venom of *P. nigriventer* (PnTx2-6) causes prolonged erection and is under investigation for treatment of impotence.[141]

Clinical Presentation. *P. nigriventer* venom acts on both the peripheral and central nervous systems.[124] Although the majority of cases are clinically insignificant,[176] humans bitten by *P. nigriventer* may develop severe local pain that radiates up the extremity into the trunk, followed within 10 to 20 minutes by tachycardia, hypertension, hypothermia, profuse diaphoresis, salivation, vertigo, visual disturbances, nausea and vomiting, priapism, and, occasionally, death in 2 to 6 hours. Respiratory paralysis is typically the cause of death. Severe envenomation is more common among young children. Fatalities may occur in the debilitated or young, but most people recover in 24 to 48 hours. Workers who handle bananas are frequently bitten

because the spider hides in bunches of bananas. Bites have been reported in Switzerland and Argentina in produce workers inadvertently encountering these traveling spiders.[124,260,261]

Treatment. In most cases, symptomatic care is all that is necessary. Local pain control may be achieved by infiltration of local anesthetic near the bite site. This reportedly suffices for 95% of cases treated at the Hospital Vital Brasil.[176]

Development of antivenom for treatment of *Phoneutria* bites in Brazil dates to the 1920s..[177] For more severe cases, a polyvalent antivenom (Suero Antiaracidico Polivalente) and a monovalent antivenom (Belo Horizonte) active against *Phoneutria* species are available. Skin testing and antihistamine prophylaxis are recommended before their use. One to five ampules of antivenom are injected intramuscularly and/or intravenously, and clinical response is judged by relief of pain or resolution of priapism. Opiates may potentiate the venom's effects on respiration and are generally not recommended in cases of systemic envenomation.[124,260,261]

An ELISA has been developed, using anti–*P. nigriventer* antibodies, for rapid detection of venom antigens in suspected *P. nigriventer* envenomation. It has been tested in humans and shows promise as a diagnostic tool.[59]

FAMILY LYCOSIDAE: WOLF SPIDERS

Lycosidae are among the most common spiders. They are diverse, with more than 3000 species distributed worldwide. They are found from beaches to grassy fields and pastures. The Greek name lycosa (wolf) comes from the former belief that they hunted in packs.[66,335] They range in size from 3 to 25 mm (0.12 to 1 inch). Most species wander in active pursuit of prey, generally during the day. A few make deep burrows, and some even cover their burrows with doors. Most live on the ground, but some climb in vegetation. They have good vision, with conspicuously large, posteromedian eyes. Their eyes are arranged in three rows (four eyes, then two, then two). To attract mates, males wave their legs and sometimes stridulate to make sound. The female carries the egg sac attached to her spinnerets. When the young hatch, they climb on their mother's abdomen for transport. They have three claws on their tarsi.

Genus *Lycosa:* Wolf Spiders

Biology. *Lycosa* is a large and widespread genus of wolf spiders (Figure 43-18). It includes various middle-sized to large spiders with mildly cytotoxic venom capable of provoking transient inflammation in humans. The most famous wolf spider species is *Lycosa tarantula*, to which "tarantula" was first applied. Its bite was once believed to cause "tarantism," a syndrome of stupor, the desire to dance, and sometimes death, but this historic syndrome is now attributed to *Latrodectus tridecimguttatus* (neither a wolf spider nor a tarantula). Wolf spider bite is now known to cause little more than stinging pain. The South American *Lycosa raptoria* has been reputed to be more dangerous than other wolf spiders, provoking necrosis at the site of envenomation. It now appears that this was also based on a misunderstanding. Necrotic arachnidism in South America is now attributed mainly to *Loxosceles* species.

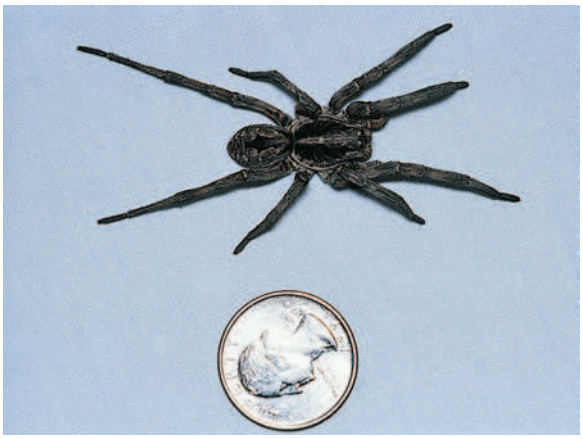

FIGURE 43-18 Wolf spider (*Lycosa* species). *(Courtesy Arizona Poison and Drug Information Center, 1996.)*

Venom. Lycosid venom is thought to be primarily cytotoxic, without hemolytic or anticoagulant activity.[335] Although scientific reports of necrosis are lacking after envenomation by the Australian wolf spider *L. godeffroyi,* media reports suggest that bites may lead to necrosis. Atkinson and Wright[13] have demonstrated that raw venom of *L. godeffroyi,* when injected into mice, causes a strong inflammatory response and cutaneous necrosis. They further hypothesized that this action may result from contamination of venom with digestive juices, in that electrically collected raw venom caused necrosis whereas venom gland extract did not.[14]

Clinical Presentation. A series of 515 cases of confirmed *Lycosa* bites in Brazil showed that most occur between the hours of 6 AM and 6 PM, at a fairly consistent rate year-round. The most common bite sites were the feet (40%) and hands (39%). The most common signs and symptoms were local and consisted of pain (83%), swelling (19%), and erythema (14%). No local necrosis was described.[240]

In a series of 45 Lycosidae bites in Australia, 73% were distal (hand or foot). Pain occurred in all bites and was uniformly reported as severe. Puncture marks or localized initial bleeding occurred in 33%, swelling in 20%, redness or a red mark in 67%, and itching in 13%. Three patients reported systemic effects, two with nausea, one with headache, and one with malaise. Necrosis or ulceration was absent in all cases.[147]

In the United States, five cases of Lycosidae bites have been documented. One resulted in skin necrosis at the bite site, probably from the combined results of envenomation and infection.[49]

Treatment. Although South American antivenom active against *Lycosa* venom was available in the past, it was used in only one case of 515 reviewed by Ribeiro and associates.[240] Since 1985, the polyvalent Butantan Institute spider antivenom has not included the antilycosid fraction.[176] Most *Lycosa* cases can be managed with tetanus immunization and ice or oral analgesics. Occasionally, local anesthetic block has been used for pain management.[240]

FAMILY EUTICHURIDAE: SAC SPIDERS

The newly erected (as of 2014) family Eutichuridae includes some species that were formerly placed in the family Miturgidae and Clubionidae. Many species are common and distributed worldwide. The highest diversity of species is in the neotropics. They are small- to medium-sized (2 to 15 mm [0.1 to 0.6 inch]) and are usually light brown to yellowish in color. They hunt nocturnally and make resting tubes in rolled leaves or under rocks or stones, where they retreat during the day.

Genus *Cheiracanthium:* Running Spiders and Sac Spiders

Biology. The genus *Cheiracanthium* as a whole has no distinctive marks or patterns.[112,335] Members may be pale yellow, brown, green, or olive. The dorsal abdomen may have a median longitudinal stripe. The body size ranges from 7 to 15 mm (0.3 to 0.6 inch), with a total diameter of 3 cm (1.2 inches), including long, slender legs.

In the United States, *Cheiracanthium inclusum* (Figure 43-19) is the only indigenous species, although several species have been introduced. *C. diversum* is widely found in the Pacific islands. It was transported into Hawaii from Australia approximately 50 years ago. *C. mildei* was introduced from Europe and is now found from New England to Alabama to Utah. It is a common biting spider in Boston. It is most abundant in autumn, when most bites occur.[275]

The South African sac spider *C. lawrencei* is a common nocturnal house spider that forages at night and may become trapped in bedding.[209] During the day, these spiders hide in the concavities of leaves, curtains, or windowsills, encased in a silk sac. They are fast moving and aggressive when threatened.[208]

FIGURE 43-19 *Cheiracanthium inclusum. (Courtesy Sherman Minton, MD.)*

Venom. Research on *Cheiracanthium* venom is limited. About 75% of guinea pigs bitten by *C. mildei* for the first time developed a wheal within 5 minutes, with 60% developing an eschar within 1 day.[275] Fractionation of dissected venom gland extracts from *C. japonicum* resulted in five fractions with lethal activity in mice. These were considered neurotoxic based on symptoms of dyspnea, flaccid paralysis, and death after intraperitoneal injection.[218]

Clinical Presentation. Spiders belonging to the genus *Cheiracanthium* have had a documented history of human envenomation since the 18th century. Species are known for their tenacious, painful bite. A pruritic, erythematous wheal appears within 30 minutes. Nausea, abdominal cramps, headache, and local necrosis have been reported.

In the United States, bites by the yellow sac spider, *C. mildei,* have been reported in association with swelling, redness, pain, sore throat, fever, and vision changes.[192] In 1901, Kobert described local swelling, erythema, pain, and fever after the author's third *C. punctorium* envenomation.[29] Maretic[187,188] described local redness, pain, and edema but no necrosis after *C. punctorium* envenomation. In another case, *C. inclusum* caused local pain that radiated from the forearm bite site up the arm, associated with nausea. No other signs developed.[29]

The Australian species *C. mordax* and *C. longimanus* caused local swelling, erythema, and pain associated with malaise, headache, dizziness, and nausea. Symptoms receded within 36 hours after treatment with antihistamines and local anesthetics.[29] Ori[218] found similar signs and symptoms after envenomation by *C. japonicum.*

In South Africa, most *C. lawrencei* bites occur at night during sleep.[207] Paired bite marks 6 mm (0.24 inch) apart are evident within the first few hours. Local edema and erythema may be slight. By the third day, the marks may become necrotic, with more edema, erythema, and pain; headache and fever may accompany this stage. The small ulcer begins to heal 7 to 10 days after the bite.[209]

Treatment. The lesion usually heals without problems, provided that secondary infections are avoided. Treatment is supportive, consisting of cool compresses, elevation, immobilization, analgesics, and tetanus prophylaxis.

FAMILY CORINNIDAE: SAC SPIDERS

Corinnids are ground-dwelling spiders primarily found in tropical regions. They were previously placed in the family Clubionidae and have similar habits. Spiders of the *Trachelas* genus are often encountered in houses in late summer and fall. *Trachelas volutus* and several other *Trachelas* species reportedly cause mild local reactions without necrosis. Bites are painful initially and may swell.[320] Vossbrinck and Krinsky[320] report a case of envenomation by *Trachelas tranquillus* (Hentz) in Connecticut in 2013. A 50-year-old woman was bitten on her leg. An erythematous macule formed at the bite site, only to disappear the next day. The spider was brought to the laboratory and identified. The authors report this to be the second confirmed case of *T. tranquillus* envenomation, and the first in Connecticut. No systemic effects have been reported.[220,300] Treatment is symptomatic and supportive.

FAMILY AGELENIDAE: HOBO, GRASS, AND FUNNEL-WEB SPIDERS

The 600 species of Agelenidae are mainly found in temperate regions of the Northern Hemisphere. They are medium-sized spiders, ranging from 8 to 15 mm (0.3 to 0.6 inch) in body length. Individuals build sheet webs that lead to a long funnel, which the spider uses as a retreat. When prey contacts the web, the spider runs out, bites it, and carries it back into the funnel. The large and conspicuous webs of these spiders often are long lasting, with spiders adding silk to make the sheet larger as the individual grows. Males may be found searching for females.

Genus *Eratigena* (Formerly *Tegenaria*): Hobo Spiders

Biology. *Eratigena agrestis* is commonly called the hobo spider or Northwestern brown spider. It is a 10- to 15-mm (0.4- to 0.6-inch), light-brown spider with a yellowish green tint and chevrons on the dorsal abdomen. Individuals typically build funnel webs in undisturbed habitats such as abandoned woodlots or along railroad tracks, with a hidden retreat beneath wood, rocks, or debris. Small amounts of silk extend beyond the cover. Spiders mature to adulthood in midsummer, then mate and lay eggs in July through September. Adult males live for 1 year, then senesce and die at the end of the mating season. Adult females live for 2 years, so adults are present throughout the year.

E. agrestis spiders are common and widespread natives of Europe and western central Asia.[127] This species was likely introduced to North America through a seaport near Seattle in the early 1900s. It was first formally identified in the 1930s.[84,85,] It has since expanded its range to British Columbia, Alaska, Oregon, Idaho, Montana, and Utah.[18,242,324] By the 1960s, individuals were often collected in and around human habitations in the Pacific Northwest.

Venom. *E. agrestis* venom has become of interest because of reports that suggest that their bites result in necrotic lesions. *E. agrestis* venom chemistry is not well characterized, and no necrotoxic component has been identified. Johnson and colleagues[157] identified potent insect-specific neurotoxic peptides and mammalian-specific peptides (5000 and 9000 Da) that were lethal to mice at high dosage.[317]

Experimental envenomation of rabbits by live male spiders results in extensive cutaneous injury and clear evidence of systemic poisoning. Local erythema appears and fades within the first day. Discolored patches are visible by day 4 and slough by day 6. Autopsy reveals petechial hemorrhages on the surfaces of the lungs, liver, and kidneys.[308]

Since the early 1980s, medically significant bites in the Pacific Northwest have been attributed to *E. agrestis*.[2,306,307,309] In Europe, no medical problems have been associated with bites from these spiders.[31,43,63] American spider venom chemistry is no different from that of English spiders, so the cause of alleged difference in medical significance is under investigation.[35] In the Pacific Northwest, male spider bites have more severe necrotic effects on mammalian tissues than do female bites.[308] Necrotic lesions attributed to this species occur throughout the year, with a trend toward increased severity in winter months.[309] None of the bites attributed to *E. agrestis* has been confirmed by catching a spider in the act of biting and having that spider professionally identified. Efforts to re-create necrotic lesions associated with *E. agrestis* bites (either by injecting venom into rabbits or by testing for transmission of bacteria by bites) have not been successful.[99]

Clinical Presentation. *E. agrestis* has been implicated in several cases of necrotic arachnidism similar to that seen in *Loxosceles* envenomation. Systemic effects reported include headache, visual disturbances, hallucinations, weakness, and lethargy. Hemorrhagic complications have been reported in experimental animals.

Direct observations of *E. agrestis* biting people who then develop necrotic lesions are scarce.[2] Vest studied 22 cases of "highly probable" *E. agrestis* envenomation and found the local

FIGURE 43-20 *Agelenopsis aperta. (Courtesy Eileen Hebets.)*

lesion followed a pattern reminiscent of loxoscelism.[308,309] The initial lesion appeared as a small reddened induration, often surrounded by a large zone of erythema. Vesicles occurred within 36 hours and then burst. Marked necrosis developed in 50% of cases. The most common symptoms included headache, weakness, and lethargy.[310] Prospective studies of verified spider bites have failed to confirm these observations. This suggests that necrotic arachnidism is not a significant issue in the parts of the Northwest United States where hobo spider bites are most feared.[192,316]

Unless a spider is positively identified in association with a lesion, we discourage attribution of necrosis to *E. agrestis* bites. Alternative diagnoses should be considered.[317]

Treatment. No studies have investigated treatment for envenomation by *Eratigena* species. As with mild cases of loxoscelism, patients should be treated supportively, with tetanus prophylaxis, careful wound debridement as needed, and observation.[317]

Genus *Agelenopsis:* Grass Spiders and Funnel-Web Spiders

Biology. *Agelenopsis aperta* is common in and restricted to the deserts of the southwestern United States, from California to East Texas (Figure 43-20). They build large, conspicuous sheet webs with retreats under rocks and logs or in tufts of grass. Adults are 13 mm (0.5 inch) in body length.

Venom. Venom of this species is among the best characterized of all spiders in terms of biochemical composition and neurophysiologic activity of the individual components. Its clinical relevance in humans has only recently been recognized.

Nineteen toxins have been characterized in *A. aperta* venom, with three distinct classes that act synergistically to rapidly subdue insect prey.[216] μ-agatoxins modify sodium channel kinetics, increasing neurotransmitter release generally, ω-agatoxins block presynaptic, voltage-sensitive calcium channels, and α-agatoxins are a family of low-molecular-weight acylpolyamines that block glutamate-sensitive receptor channels in insect muscle. Coexistence of toxins with different mechanisms of neurotoxicity appears to confer a synergistic action against insect prey. The ω-agatoxins range in target specificity from invertebrates to mammals.[305]

Clinical Presentation. Two cases of envenomation by *A. aperta* have been reported in southern California. A boy 9 years of age developed a tender but nonnecrotic bite site, followed by a 2-day systemic syndrome that included headache, nausea, disorientation, pallor, and unsteady gait. A 54-year-old male developed a painful, indurated lesion that persisted for a week. He had no systemic symptoms.[29,311] In Oregon, a series of five *Agelenopsis* bites included symptoms of local pain, swelling and redness, and back pain.[192]

Treatment. Treatment of *Agelenopsis* envenomation is symptomatic and supportive.

FAMILY THERIDIIDAE: COMB-FOOTED SPIDERS

The family Theridiidae, sometimes called cobweb or comb-footed spiders, is speciose, diverse, and distributed worldwide. The spiders are small- to medium-sized (1 to 14 mm [0.04 to 0.55 inch], usually less than 8 mm [0.3 inch]), and often have globose abdomens. They make irregular, tangly webs in which the spider hangs upside down. The silk is very sticky and easily entangles prey. Spiders ensnare prey in silk using a tiny comb at the end of the fourth leg. They then envenom prey and ingest them through a small hole in the exoskeleton. They have no cheliceral teeth for chewing.

Genus *Latrodectus:* Widow Spiders

Biology. *Latrodectus* (Latin for "robber-biter") species are among the largest theridiids. Females are 12 to 16 mm (0.47 to 0.63 inch) in body length. Males are much smaller, with longer legs relative to their body size. Individuals build typical theridiid cobwebs with very strong strands of silk. Arthropods are the most common prey, but widows also kill and consume vertebrates (e.g., small lizards and snakes). The folkloric belief that widow females kill and consume their mates is accurate, although this event does not as a rule occur, and the likelihood differs among species.

The 8- to 10- mm (0.31- to 0.39- inch) female black widow is shiny black with a characteristic red hourglass marking on the ventral abdomen. Species are distinguished based on hourglass shape and dorsal color patterns. Males are lighter in color, with white and gray markings and a faint hourglass. This feature becomes more prominent with maturity. Females spin an irregular web in sheltered corners of fields, gardens, and vineyards and under stones, logs, and vegetation. Uncommon in occupied dwellings, they may be plentiful in barns, garages, trash heaps, and outbuildings. A few *Latrodectus* species (e.g., *L. variolus*) are arboreal. The web's tattered "cobweb" appearance may belie an ongoing state of occupation, particularly during daytime when the spider is out of sight. The female seldom ventures far from the web, in which she suspends an ovoid or tear-shaped, whitish egg case.

Latrodectus spiders are distributed worldwide, most plentiful in temperate and subtropical regions, and most abundant during summer.[30] *L. mactans mactans,* the black widow, is cosmopolitan and occurs in every state except Alaska (Figure 43-21). In North America, species include *L. geometricus* (the brown widow, Figure 43-22), *L. bishopi* (the red-legged widow), *L. variolus,* and *L. hesperus* (Figure 43-23). A study by Vetter et al.[317a] suggests that *L. geometricus* (Koch), the brown widow spider, became newly established in southern California in the first decade of the 21st century. Brown widow egg sacs were collected, and data on the western black widow spider, *L. hesperus* (Chamberlin & Ivie), in abundance and distribution were compared. It is unknown if brown widows compete with black widows, but brown widows now outnumber black widows, and black widow numbers appear to be declining. Brown widow bites are generally considered to be less toxic than are black widow bites. Species known to envenom humans are endemic to Australia (*L. mactans hasseltii*, Figure 43-24) and to Europe and South America *(L. tredecimguttatus)*. Related species are found in Asia and the Middle East *(L. pallidus)* and in Africa *(L. indistinctus)*.

The species *L. tredecimguttatus* is most important in the Mediterranean region, the Middle East, and parts of Russia, where it

FIGURE 43-21 Adult female *Latrodectus mactans mactans* with fresh egg case. *(Courtesy Michael Cardwell and Associates, 1999.)*

FIGURE 43-22 Mature female brown widow spider *(Latrodectus geometricus). (Courtesy Michael Cardwell and Associates, 1999.)*

FIGURE 43-23 Mature female western black widow spider *(Latrodectus hesperus). (Courtesy Michael Cardwell and Associates, 1993.)*

is sometimes referred to as *L. lugubris.* It may have red or orange spots or may be pure black, and is known as *kara kurt* (Russian for "black wolf"). *L. indistinctus,* the black button spider of South Africa, has a narrow or broken red dorsal band, or may be black. The red-backed spider *(L. mactans hasseltii)* is medically important in Australia, New Zealand, and southern Asia. It has a dorsal red band similar to that of *L. indistinctus,* and the female also has a ventral red hourglass reminiscent of *L. mactans mactans. L. geometricus* is brown with black, red, and yellow markings and is common in southern Africa and warmer parts of the Americas.

Widow spiders tend to bite defensively when accidentally crushed. In the Mediterranean basin, southern Russia, and South Africa, bites are associated with grain harvesting and threshing and with grape picking. In the United States, most bites occur in rural and suburban areas of southern and western states, with no special age, gender, or occupational predilection. In regions where outdoor privies are in common use, human envenomation is likely to involve the buttocks or genital area.[33,106,187,334] Outbreaks of latrodectism may occur locally in epidemic fashion, lasting several years, and depend on changes in spider predator and parasite balance and on occupational variations in human-spider contact. Apparent outbreaks may also result from sudden increases in publicity and reporting.[31,160]

FIGURE 43-24 Red-backed spider *(Latrodectus mactans hasseltii). (Courtesy Sherman Minton, MD.)*

Venom. Unlike many other arthropod venoms, that of the widow spiders appears to lack locally active toxins capable of provoking inflammation. The venom contains several toxic components, including a potent mammalian neurotoxin, α-latrotoxin, that induces neurotransmitter release from nerve terminals. A thorough transcriptomic and proteomic analysis was recently published.[126]

In 1964, Frontali and Grasso[93] demonstrated three electrophoretically and toxicologically distinct fractions of *Latrodectus* venom. In 1976, Frontali and associates[92] further purified and defined these fractions, encountering one major constituent (the B5 fraction, later renamed α-latrotoxin) with significant toxicity in mice and frogs (other fractions have effects more specific to insect physiology). α-Latrotoxin, a protein mix with at least 20 distinct members within a species,[126] has an average molecular weight of 130,000 Da, and causes profound depletion of presynaptic vesicles with swelling of the presynaptic terminal at frog neuromuscular junctions. Complete blockade of neuromuscular transmission follows within 1 hour. The toxin binds irreversibly with the lipid bilayer of cell membranes and produces cation-selective channels, interfering with endocytosis of vesicle membranes.[55,88] The mechanism of action is not fully understood, but multivalent cations, including calcium, may enter the presynaptic nerve terminal through these channels and interfere with calcium-dependent intracellular processes.[114,194] These effects appear to be specific to presynaptic nerves but independent of the transmitter involved. Acetylcholine, noradrenaline, dopamine, glutamate, and enkephalin systems are all susceptible to the toxin.[245]

Grishin[121] described the venom of *L. tredecimguttatus* as including a family of seven protein toxins of high molecular weight. Recent analyses indicate that there are multiple variants of each of these seven toxins.[126] These large molecules have several functional domains responsible for ionophoric and secretogenic actions. They contain a series of ankyrin-like repeats that may provide the structural basis of the interactions between toxins and membranes.[121] They all cause massive neurotransmitter release from presynaptic endings, but differ in target animal specificity. α-Latrotoxins act selectively on vertebrate nerve endings. Five latroinsectotoxins act on insects and one toxin is specific for crustaceans. The different latrotoxins are closely related and have diversified by expansion of a gene family and evolution of functional specificity.[126] *L. indistinctus* and *L. geometricus* also contain α-latrotoxin, the former with a greater venom yield per spider.[200]

Clinical Presentation. Latrodectism, the syndrome often resulting from *Latrodectus* envenomation, is best known for widespread, sustained muscle spasm rather than for local tissue injury. Although long-term outcomes are usually excellent, victims may have significant hypertension, autonomic and central nervous system dysfunction, and abdominal pain sufficiently severe to be mistaken for an acute abdomen.

The initial bite may be sharply painful, but many bites are not recognized initially. Diagnosis is often presumptive and based on local and systemic signs. Local reaction is typically trivial, with only a tiny papule or punctum visible on examination. Surrounding skin may be slightly erythematous and indurated. In most cases, symptoms do not progress beyond this point. In one Australian series, 76% of victims presenting to a hospital for care had local symptoms only.[155]

Over a 9-year period in the United States, 23,409 *Latrodectus* bites were reported to the National Poison Data System. Of these, 33.5% reported "moderate effects," and 1.4% "major effects." No deaths were reported.[195]

Neurologic and systemic manifestations may be severe.[277] Strowd[277] reports a case of Horner's syndrome, in which a construction worker witnessed a black spider bite on his thigh and had early symptoms of chills, nausea, headache, myalgias, and localized erythema, pain, and diaphoresis. Thirty days after the

bite, neuroophthalmologic examination demonstrated a triad of partial ptosis, ipsilateral miosis, and anhidrosis.[81,96] A predominantly abdominal presentation may closely mimic an acute abdomen. Associated signs include fasciculations, weakness, ptosis, priapism, thready pulse, fever, salivation, diaphoresis, vomiting, and bronchorrhea. Compartment syndrome has rarely been described after a bite by *Latrodectus* species.[65] Pulmonary edema has been described in Europe[190] and South Africa.[169,318] Respiratory muscle weakness combined with pain may lead to respiratory arrest. Hypertension with or without seizures may complicate management in elderly or previously hypertensive individuals. Intractable crying may be the predominant feature in infants.[47] Pregnancy may be complicated by uterine contractions and premature delivery.[20,138,189,246,250] A characteristic pattern of facial swelling, known as *Latrodectus* facies, may occur hours after the bite and is sometimes mistaken for an allergy to drugs used in treatment. The usual course of an envenomation is to achieve complete recovery after a few days, although pain may last a week or more.

The clinical picture of *Latrodectus* envenomation is similar around the world. In the 1980s in California, the most common site of envenomation referred to a toxicology service was the lower extremity (48%), followed by the upper extremity (28%), trunk (18%), and head or neck (5%). The most common systemic symptom was abdominal or back pain (58%), followed by extremity pain (38%), hypertension (29%), and diaphoresis (22%).[62] In Australia, a 1961 survey showed that 37% of victims were bitten on the upper extremities, 27% on the lower extremities, 22% on the buttock or penis, 17% on the trunk, and 4% on the head or neck.[332] A 1978 report showed a decline in the incidence of genital and buttock involvement (9.7%), perhaps related to decreased use of outdoor lavatories.[291]

Australian envenomations showed a similar pattern of pain and diaphoresis, with more prominent local inflammation and lymphadenopathy and less hypertension than reported in the United States. In South Africa, envenomation by *L. geometricus* results primarily in local pain, whereas *L. indistinctus* provokes a syndrome of generalized pain, diaphoresis, and muscle rigidity similar to that seen in the United States.[199] Victims bitten by *L. tredecimguttatus* may have spasms of facial muscles, swollen eyelids, lacrimation, and photophobia that may result in *Latrodectus* facies. A rash may appear 2 to 11 days after envenomation.[186] Cardiac involvement is rarely reported. Erdur reported a case of a young man bitten by *L. tredecimguttatus* who presented with anxiety, marked hypertension, nausea and vomiting, tremor, generalized pain, diaphoresis, rhabdomyolysis, and echocardiographic evidence of anteroseptal hypokinesia and depressed left ventricular function.[81] Sari reported myocarditis in a 65-year-old man within 3 hours of the bite with chest pain and electrocardiographic changes.[256] Acute myocarditis following black widow envenomation was also reported in Turkey.[72,108,159] All patients recovered. Although the specific mechanism of myocarditis in black widow envenomation is not well known, careful observation and treatment should include cardiac evaluation. In Morocco, a case of myocarditis diagnosed by biopsy was reported in a 35-year-old patient admitted with acute cardiogenic pulmonary edema, following a spider bite.[182]

Treatment. Although the worst pain usually occurs during the first 8 to 12 hours after a bite, symptoms may remain severe for several days. All symptomatic children, pregnant women, and patients with a history of hypertension should be admitted to the hospital. Discharge is usually possible within 1 to 3 days, when hypertension and muscle spasm have subsided. A patient with a satisfactory response to antivenom may be sent home after several hours' observation.

Care of the local site includes routine cleansing, intermittent application of ice, and tetanus prophylaxis. Severe pain and muscle spasm usually respond to IV narcotics or benzodiazepines, but careful observation of respiratory status is vital when either is used. Calcium gluconate infusion, advocated in the past, has proved only minimally useful and is no longer recommended. Hypertension may be treated with nifedipine or an infusion of sodium nitroprusside, if the patient does not respond to pain control with narcotics or antivenom.

Antivenom active against *Latrodectus* venom is available in the United States from Merck and Company, in Australia from Commonwealth Serum Laboratories, in Mexico from Instituto Bioclon SA de CV, and in South Africa from the South African Institute of Medical Research. Standards for *Latrodectus* antivenom use vary around the world, as do guidelines for its administration.[62,199,288]

In the United States, *Latrodectus* antivenom, although it had never undergone clinical trials, was used for many years and believed by many clinicians to be safe and effective to reverse systemic effects and associated pain. When used properly, these products may prevent systemic sequelae that result from envenomation, and even obviate the need for hospitalization in some severe cases.[61] Priapism refractory to treatment with opiates and benzodiazepines has been reported to improve with antivenom.[137]

Concerns about a possible severe allergic reaction to antivenom have limited its use. To determine the rate of adverse effects and efficacy of antivenom,[214] Nordt and colleagues report an observational case series of the California Poison Control System electronic database. From January 1999 to December 2009, data included all cases of black widow envenomation treated with Black Widow Spider Antivenin (Merck). A total of 96 patients received antivenom. No patient required more than one vial of antivenom. One patent developed urticaria during infusion that was discontinued. One patient had generalized flushing after infusion. Two reported myalgia and paresthesias. All reported pain relief. In general, antivenom should be used in cases involving respiratory arrest, seizures, uncontrolled hypertension, or pregnancy.[251] In less severe settings, its value must be weighed against risks of acute hypersensitivity and delayed serum sickness.[215] In Australia, 0.5% to 1% of cases result in anaphylaxis. Some patients develop serum sickness.[291] Death from anaphylaxis has been reported in the United States.[6,202]

To reduce the risk of reactions against whole IgG in these patients, it has been proposed to produce a Fab fragment specific against *Latrodectus* venom or against α-latrotoxin.[61] Due to their lack of an Fc component that is present in whole IgG, Fab fragments prompt less of an immune response to the foreign protein by the recipient and so have less antigenicity.[70] Dart[70] conducted a randomized, placebo-controlled, double-blind, clinical trial that used a novel $F(ab')_2$ antivenom in patients with moderate to severe pain due to black widow envenomation. Twenty-four subjects were enrolled, 13 randomized to antivenom and 11 to placebo. Pain reduction was similar in both groups, but was reduced more rapidly in the antivenom group compared with placebo. No significant adverse reactions were noted in either group.

Efficacy of antivenom has been reported as satisfactory in Australia,[326] with anecdotal reports of efficacy even weeks to months after envenomation.[19] Effectiveness of antivenom in management of latrodectism has been contested, however, by Isbister and colleagues, who compared antivenom to saline in a randomized, multicenter trial involving 224 patients in Australia.[152] Patients all received a standardized analgesic regimen and were randomly assigned to equine $F(ab')_2$ antivenom raised against *L. hasseltii* or to placebo. No additional pain reduction was noted in the antivenom group. Whether this finding will affect medical practice is as yet unclear. Controversy is ongoing.[330]

Laboratory evaluation may include complete blood cell count, electrolyte and blood glucose levels, and urinalysis. Common findings include leukocytosis and albuminuria. In victims with severe muscle spasm, creatine phosphokinase levels may be elevated. Abdominal films and stool examination for occult blood, both of which should be normal after widow spider envenomation, may help with the differential diagnosis of abdominal pain. A pregnancy test should be done if indicated. No specific antigen or antibody detection technique is currently available for clinical diagnosis.

Genus *Steatoda:* False Widow Spiders

Biology. *Steatoda* species are found worldwide and are close relatives of *Latrodectus*. They are 3 to 8 mm (0.12 to 0.31 inch) in body length, smaller than *Lactrodectus,* and typically

dark brown, often with white abdominal markings. They build tangly cobwebs and sit in crevices under stones, in tree bark, or in cracks of buildings near the web. *S. paykulliana* of Europe, *S. foravae* of southern Africa, and *Steatoda grossa* of the United States resemble members of the *Latrodectus* genus and therefore are referred to as false widow or button spiders.

Venom. *S. foravae* venom contains a major polypeptide of the same molecular weight as α-latrotoxin and can elicit a comparable neurotransmitter release syndrome in mice. The median lethal dose, however, is significantly higher. The relative potency in mice is 10 to 20 times less than for venom of *L. indistinctus*.[201]

Clinical Presentation. In humans, *S. nobilis* of southern England has caused brief local pain and slight swelling, followed by local sweating and piloerection, facial flushing, and feverishness.[322] One report of an *S. foravae* bite in southern Africa showed a minimal local inflammatory response without systemic toxicity.[201] In one Australian report, a child 2 years of age bitten by a juvenile *Steatoda* (species unknown) developed lethargy, irritability, diaphoresis, and hypertension 22 hours after the bite. He improved gradually after administration of two ampules of red-backed spider *(Latrodectus)* antivenom.[273] In another report, 30% of *Steatoda* bites (including *S. capensis* and *S. grossa*) studied in Australia presented to an emergency department and a poison center with systemic effects and persistent pain. Local and systemic symptoms were similar to those of *Latrodectus* envenomation, but overall they were less severe.[148]

Treatment. In general, care is symptomatic and supportive. Similarities between neurotoxins in *Steatoda* and *Latrodectus* venoms, however, suggest use of *Latrodectus* antivenom in severely symptomatic cases. Several case studies from Australia using *Latrodectus* antivenom (red-backed spider antivenom, Commonwealth Serum Laboratories, Melbourne, Australia) for *Steatoda* bites have demonstrated improvement in and decreased duration of symptoms. Controlled studies have not been done.[115,148]

Genus *Parasteatoda* (Formerly *Achaearanea*): Grey House Spiders

Biology. *Parasteatoda* are common spiders worldwide. They make classic theridiid cobwebs, often in corners and windows of houses. They are excellent predators of insects in homes. Individuals are mottled brown with globose abdomens and are easily distinguished from *L. geometricus,* the brown widow, by the lack of an hourglass in the ventral abdomen.

Venom. Little information is available about *Parasteatoda* venom; however, the genome of *P. tepidariorum* has been sequenced. This will facilitate complete characterization of its venom composition.

Clinical Presentation. A series of five cases in Australia found that redness or a red mark was the only common local manifestation of *Parasteatoda* bites. In other case reports, bites to limbs produced pain that can become severe. Patients report pain that increases during the first hour and that may persist for up to 24 hours. Local or regional diaphoresis is absent, with few reports of systemic effects. In two cases, headaches were reported, one with and one without nausea. This suggests that *Parasteatoda* bites cause pain and systemic effects that are similar to, but less severe than, the effects of *Latrodectus* bites.[148]

Treatment. Treatment of *Parasteatoda* envenomation is symptomatic and supportive.

FAMILY ARANEIDAE: ORB-WEAVING SPIDERS

Members of the family Araneidae are familiar to most people because they are common and build conspicuous, mainly circular, two-dimensional orb webs in open places. This is an abundant family, with 4000 species described and distributed worldwide. Species range in adult body size from 2 to 28 mm (0.07 to 1.10 inches) and often have extreme size dimorphism, with males much smaller than females. They are extremely diverse in size, shape, web design, and prey capture tactics. They can be brightly colored, with typically ovoid abdomens and large chelicerae with several teeth. Although diverse and abundant, they are of minimal clinical concern.

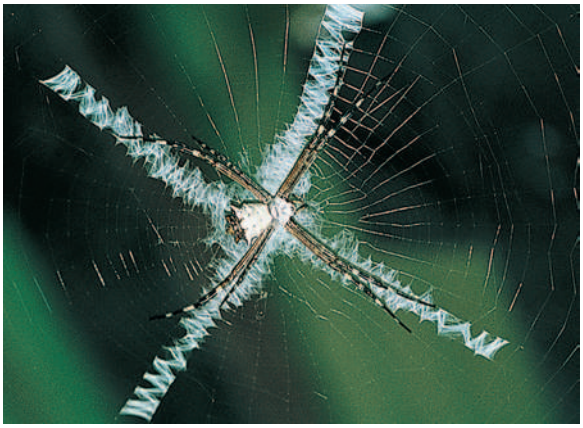

FIGURE 43-25 Orb weaver (*Argiope* species). *(Courtesy Eileen Hebets.)*

The venoms of many araneid spiders are known to have polyamine neurotoxins that postsynaptically block glutamate receptors in vertebrates.[161] These are currently known from species of *Nephila, Argiope, Araneus,* and *Neoscona.* Although these are often abundant, conspicuous, and sometimes large spiders, they are of little medical concern.

Genus *Araneus*

Biology. The large and diverse genus *Araneus* (658 species) includes many conspicuous and locally abundant orb-weaving spiders. Species are often colorful and build orbed webs in open spaces. Spiders hang head down on the center of the web, or on an attachment line of the orb, and forage on a wide range of flying insects. There is striking sexual dimorphism, with males of most species less than half the size of females.

Clinical Presentation. Bites by *Araneus diadematus* have been reported to cause redness, pain, itching, and swelling, accompanied by anxiety, nausea, headache, and muscle cramps. A single case attributed to *A. saevus,* in the same series, involved more severe pain, swelling, fever, and numbness, reportedly requiring 12 weeks to resolve.[192]

Treatment. Treatment is symptomatic and supportive.

Genus *Argiope:* Argiopes

Biology. *Argiope aurantia,* known as the black and yellow garden spider, is common in California, Oregon, and the eastern United States (Figure 43-25). Other *Argiope* species are found throughout the United States, the Orient, and Australia.[104] It is a large, brightly colored spider with a large, symmetric orb web and a leg spread of up to 7.5 cm (3 inches).

Venom. Although *Argiope* venom appears to be cytotoxic in vivo, research indicates the venom has neurotoxic effects in vitro. Venom gland extracts from *A. trifasciata* are postsynaptic blockers of neuromuscular transmission at locust glutamate receptors.[301]

Clinical Presentation. Bites may cause local pain and erythema. Bites by *A. argentata* reportedly cause local pain, erythema, and vesicle formation, which resolve within 24 hours (except for bite marks).[111,335]

Treatment. Treatment is symptomatic and supportive.

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CHAPTER 44

Scorpion Envenomation

JEFFREY R. SUCHARD

Scorpion stings occur commonly in tropical and subtropical regions around the world (Figure 44-1). Among causes of animal-related human fatalities, scorpion stings rank second only to snakebites.[203] The estimated annual number of scorpion stings worldwide is nearly 1.2 million, resulting in over 3000 deaths.[57] More than 1800 scorpion species can be found, distributed on all continents except Antarctica.[172] The stings from most scorpion species cause local pain and inflammation, similar to bites or stings from other arthropods; mild systemic symptoms may also occur, but these stings are not serious. Basic first aid and symptomatic therapy, often only with nonprescription medications, are the only interventions necessary to treat most scorpion stings.

Nevertheless, about 30 scorpion species are recognized as medically important and potentially fatal to humans. These dangerous scorpion species are distributed in both the Old World and New World, and all but one are from a single taxonomic family (Buthidae). Even among stings from dangerous scorpion species, many cases do not result in severe morbidity or death. Small children are particularly prone to developing more serious envenomation syndromes, probably because of the greater venom dose delivered per unit body weight. Stings are more common during the warmer months of the year, and in many countries they often occur in rural areas where access to health care may be more difficult. Seriously envenomed patients should certainly receive aggressive symptomatic and supportive care; however, the role of antivenom remains controversial, mostly because of the paucity of controlled clinical studies demonstrating its efficacy.

Some differences exist between the full-blown envenomation syndromes that are typically seen. Most of the dangerous scorpions, including *Tityus* species in the Caribbean region and in South America, *Androctonus* and *Buthus* species in North Africa, *Leiurus* species (particularly *L. quinquestriatus*) in the Middle East, and *Hottentotta tamulus* (formerly *Mesobuthus tamulus*) in India, cause an "autonomic storm" with prominent neurologic and cardiopulmonary effects, including hypertension, myocarditis, and pulmonary edema. A generally similar syndrome, but without the severe cardiopulmonary effects, occurs from stings of *Centruroides* species in the southwestern United States and Mexico and from *Parabuthus* species in southern Africa, which produce prominent neurologic effects associated with excess cholinergic tone. The non-Buthid scorpion *Hemiscorpius lepturus,* most commonly found in Iran, is the only dangerous species typically associated with local tissue necrosis and may also cause hemolysis and renal failure.

Identification of new scorpion species and changes in taxonomy continue to occur. Names of scorpion genera, species, and even some families have changed, such that several species' Linnean taxonomic names mentioned in the medical literature are now obsolete; these changes will be generally noted in the text discussing those scorpions.

SCORPION BIOLOGY

Scorpions are predatory arthropods of the class Arachnida. They have a lobster-like body shape with seven sets of paired appendages (Figure 44-2): the chelicerae, pedipalps (claws), four sets of legs, and pectines, a pair of comb-like structures on the ventral surface. The segmented tail curves upward dorsally, ending in a terminal bulbous segment called the telson, which contains paired venom glands and the stinger (Figure 44-3).

Scorpions feed primarily on ground-dwelling arthropods and small lizards. Scorpions grasp prey in their pedipalps and then rapidly thrust the tail overhead to sting. The chelicerae tear the food apart. The scorpion consumes only the juices and liquefied tissues of its prey, discarding the solid parts. Scorpions envenom by stinging, not biting, even though cases are occasionally misattributed to "bites" in the medical literature.[23,172] Scorpions can sting multiple times; however, it appears that the first sting depletes or nearly depletes the telson of venom. A case series of three pairs of scorpion sting victims from India found that consecutive stings by *Hottentotta tamulus* caused severe cardiovascular manifestations in the first victim but not in the second.[25] This author has anecdotally noted a similar difference in the severity of neurologic manifestations from consecutive *Centruroides sculpturatus* stings in Arizona.

A characteristic physical property of scorpions is that they fluoresce when illuminated by ultraviolet light, as from a black light or medical Wood's lamp (Figure 44-4). This property is used in collecting scorpions for breeding or venom harvesting and in providing pest control. The fluorescent pigment in the scorpion cuticle is probably riboflavin.[129]

VENOM

Scorpion venoms are complex mixtures containing mucopolysaccharides, hyaluronidase, phospholipase, acetylcholinesterase, serotonin, histamine, protease inhibitors, histamine releasers, and protein neurotoxins.[65,184] Neurotoxins are pharmacologically the most important venom constituents.[184] The neurotoxins are single-chain, basic polypeptides of 60 to 70 amino acids, reticulated by four disulfide bridges. Each of the dangerous scorpion species' venoms contains several neurotoxins, but they all share a similar structure and homologous sequences.[94,184] In neuronal membranes, these toxins cause two effects with regard to fast sodium channels involved in action potential transmission: (1) incomplete inactivation of sodium channels during depolarization, resulting in a widening of the action potential, and (2) a slowly developing, inward sodium current after repolarization, leading to membrane hyperexcitability. The net result is repetitive firing of axons, enhancing release of neurotransmitters (acetylcholine, norepinephrine, dopamine, glutamate, aspartate, γ-aminobutyric acid) at synapses and at neuromuscular junctions.[64,77,85,178,202] This is clinically demonstrated as excessive neuromuscular activity and autonomic dysfunction. Some scorpion neurotoxins also have effects on calcium-activated potassium channels,[89,176] chloride channels,[67] and L-type calcium channels.[18]

A few scorpion species have been demonstrated to produce a first droplet of "prevenom," which has a different composition (less protein) and in vitro pharmacologic properties than does the subsequent normal venom.[112] The clinical impact of prevenom, as compared with venom, is not known.

REGIONAL CONSIDERATIONS: EPIDEMIOLOGY, RISK FACTORS, AND TREATMENT

Although scorpions are found throughout the world, the bulk of the published medical literature originates from only a few countries. The absence of data about a specific country here does not exclude the possibility of scorpion envenomation occurring

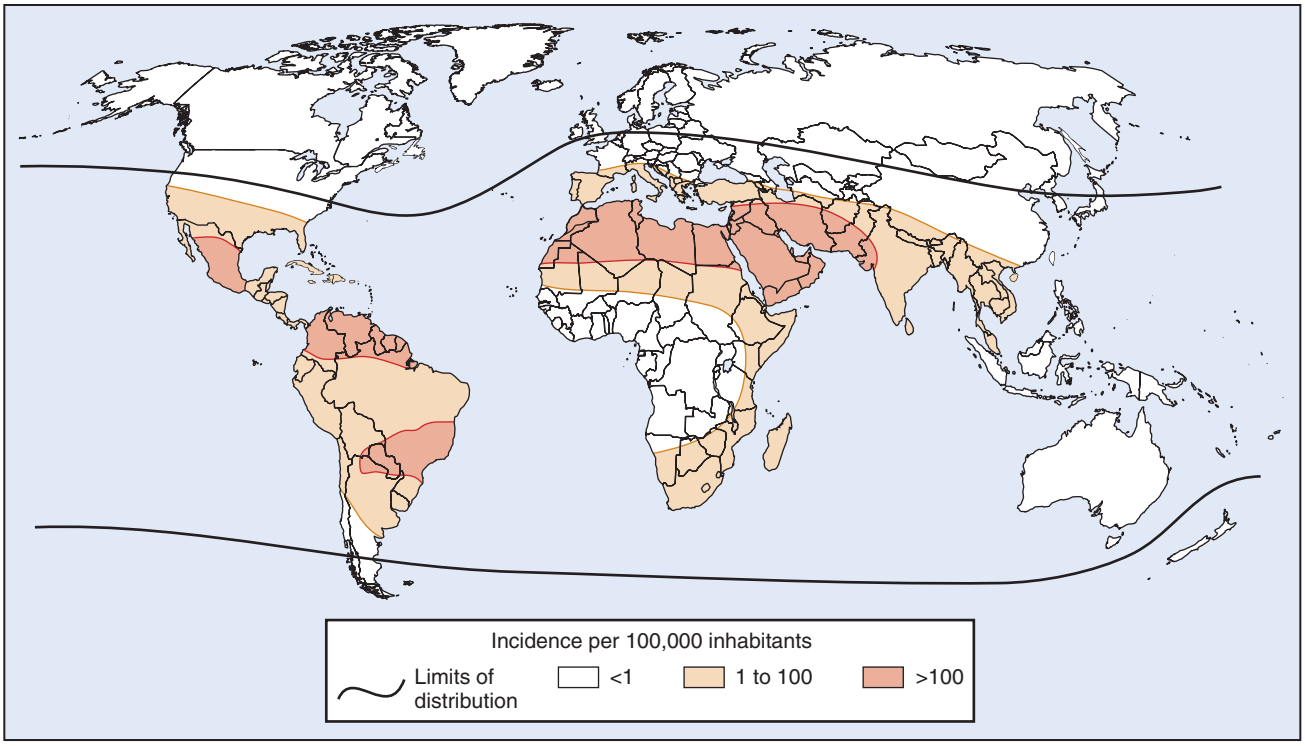

FIGURE 44-1 Scorpion sting incidence around the world. *(Modified from Chippaux JP, Goyffon M: Epidemiology of scorpionism: A global appraisal,* Acta Tropica *107:71, 2008. With permission from Elsevier.)*

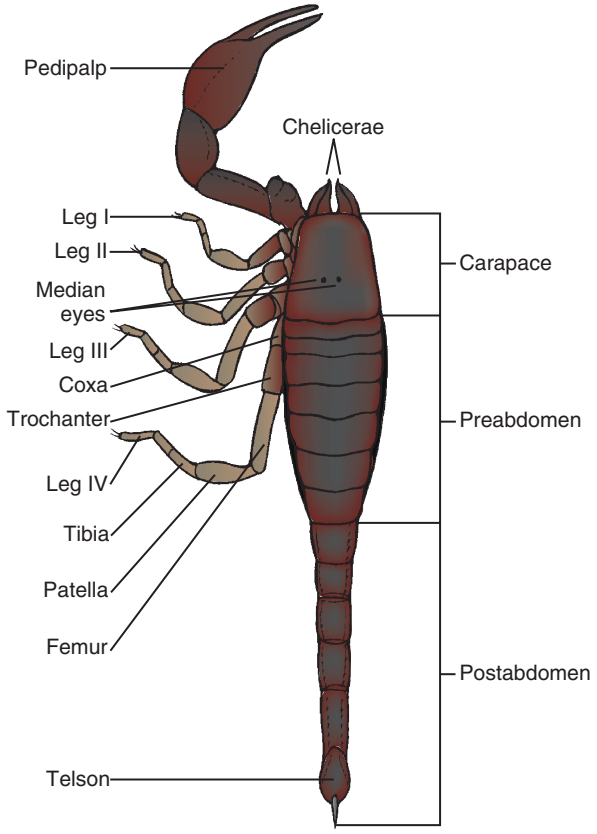

FIGURE 44-2 Anatomy of a scorpion. *(Redrawn from Keegan HL: Scorpions of medical importance. Oxford, Mississippi, 1980, University Press of Mississippi.)*

there, particularly if that country is near a known scorpion-endemic area.

NORTH AFRICA

Scorpion stings are a common problem throughout countries on Africa's Mediterranean coast, where about 100,000 stings are reported annually.[143]

Morocco

Scorpion stings are a major endemic hazard, accounting for 30% to 50% of all poisonings reported to the Moroccan Poison Control Center.[2] The annual number of stings in Morocco has been estimated at 25,000 to 40,000.[2,92] The majority of stings are caused by *Androctonus mauretanicus,* known as the "black scorpion" (Figure 44-5), and *Buthus occitanus,* the "yellow scorpion."[92] Stings are more commonly reported from Morocco's southwestern provinces of El Kalaa, El-Jadida, Agadir, and Tan-Tan. Stings occur more commonly in rural areas, in the early evening when scorpions are active seeking prey.[92] Most cases occur during the warmer summer months.[2]

Serotherapy has been advocated by some clinicians as the major therapeutic measure in Morocco since the 1970s.[92] $F(ab')_2$ fragment antivenom is made by hyperimmunizing horses with crude *A. mauretanicus* venom; this product is cross-reactive with *B. occitanus* venom. In southwestern Morocco, 49% of patients are treated with antivenom, 35% with other drugs (calcium, steroids, antihistamines), and 16% with both. Patients given higher doses of antivenom (10 mL versus 2 to 5 mL or no antivenom) showed a decrease in serum venom levels and an increase in clinical improvement.[92] However, in a 2009 series of 163 pediatric cases treated in Fez (north-central Morocco), none were treated with antivenom; the specific reason for symptomatic treatment alone was not explained, although the controversy regarding antivenom use was cited.[2] Traditional first aid often includes scarification, which consists of local incision to induce bleeding that may result in venom release. Scarification was observed in nearly 40% of children evaluated at a university hospital in Fez, but this practice is considered medically contraindicated. Ninety

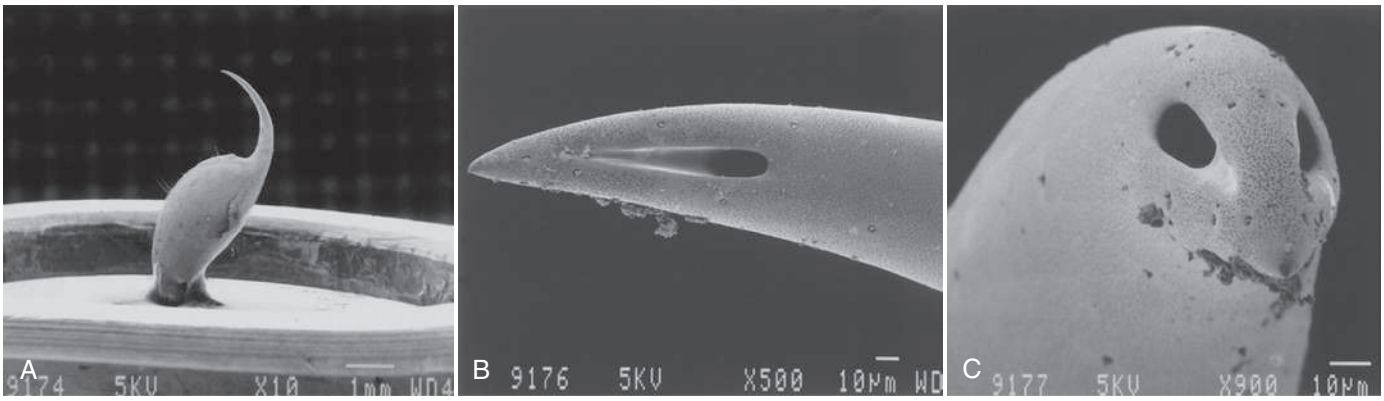

FIGURE 44-3 **A,** Electron micrograph of scorpion telson. **B** and **C,** Close-up images demonstrating stingers with paired venom pores.

percent of all fatal cases occur in children younger than 10 years old, with mortality rates ranging from 5.3% to 6.7%.[2]

Algeria

Hundreds of deaths per year are caused by scorpion stings in Algeria.[134] Most lethal scorpion stings in Algeria are caused by *Androctonus australis.* Antivenom therapy is advocated as the only indicated treatment for severe scorpion envenomation.[180]

Tunisia

Much of the published scorpion research from North Africa comes from Tunisia. Almost all stings are caused by five scorpion species: *Androctonus australis, Androctonus bicolor, Buthus tunetanus* (these first three are Buthid species), *Scorpio maurus,* and *Euscorpius sicanus.*[95] *A. australis,* locally known as the yellow scorpion (Figure 44-6), is the most common scorpion in Tunisia and accounts for most severe envenomations.[83,95] *A. aeneas* is a dangerous black scorpion found only in the southern part of Tunisia, and constitutes 1% to 2% of collected scorpion specimens. The non-Buthid scorpions are both relatively harmless and have thin tails and thick claws. The more dangerous Tunisian scorpions have long, thin claws and a thick tail (Figure 44-7).[95,128] Stings occur most often outdoors (92%) on the victim's extremities (95%) during the summer months.[128] About 80% of

FIGURE 44-4 Scorpions fluoresce in ultraviolet light.

FIGURE 44-6 *Androctonus australis,* responsible for many severe scorpion envenomations in North Africa. *(Courtesy Jan Ove Rein.)*

FIGURE 44-5 *Androctonus mauretanicus,* the "black scorpion" of North Africa. *(Courtesy Jan Ove Rein.)*

FIGURE 44-7 *Androctonus amoreuxi,* demonstrating the thin claws and thick tail characteristic of most dangerous scorpion species. *(Courtesy Jan Ove Rein.)*

all envenomations occur between June and September, with a peak in August.[50,95] Scorpion envenomation occurs more in the less-populated middle and south of the country, so severely affected patients are usually admitted to rural hospitals with limited resources.[50]

Between 30,000 and 45,000 scorpion stings are reported annually in Tunisia, correlating to an incidence of 4.5 to 20 stings per thousand inhabitants, depending on the location. About 2.5% of stings (900 to 1100 per year) result in systemic manifestations requiring hospital admission.[95] The mortality rate ranges from 0.25% to 0.4%, which is about 10% of victims with systemic envenomations, or 35 to 105 deaths per year.[7,95,128,129,130] Two-thirds of reported stings affect adults and older adolescents, but nearly all fatalities occur in younger children; the mortality rate for children is about 1%.[95,128] In a study of 951 patients admitted to the intensive care unit (ICU) between 1990 and 2002, the mortality rate was 7.5%.[50]

Scorpion antivenom is available in Tunisia and is commonly given to patients with systemic toxicity, but without good evidence of improved outcome.[50] A randomized controlled trial of 825 patients given antivenom or placebo regardless of presenting clinical severity did not show any benefit of antivenom.[5] Whether a subset of patients exists that would benefit from antivenom is not known. Horses are used as host animals to produce antivenom, although research has also been conducted with camels.[143] Corticosteroids are often administered when treating scorpion stings in Tunisia, but this treatment appears to have no benefit; in fact, it is independently associated with the need for hospitalization.[158] Dobutamine infusions are also used to treat severely affected patients with pulmonary edema.[83]

SOUTHERN AFRICA

The majority of scorpion stings in South Africa, Zimbabwe, and neighboring countries do not cause systemic effects, although fatalities occasionally occur. The more dangerous scorpion species are members of the Buthidae family, most notably *Parabuthus transvaalicus* (centered around Zimbabwe and northernmost South Africa) and *P. granulatus* (found throughout the region).[43,146] *Parabuthus* scorpions are some of the largest Buthid species in the world, ranging in size from 50 to 149 mm (2 to 6 inches).[42,146] At least 20 *Parabuthus* species are distributed throughout South Africa, Namibia, Botswana, Zimbabwe, and Mozambique, also extending northward along the eastern coast into the Sahara and Arabia.[146,153] It is recognized that *Parabuthus* scorpions have thin pincers and thick tails (Figure 44-8), whereas the relatively harmless species have thick pincers and thin tails (Figure 44-9).[43,133,146] *Parabuthus* scorpions also have stridulatory granules on the dorsal aspects of the two proximal tail segments. When alarmed, these scorpions can scrape their stingers over these granules, making a warning sound.[154] Also, several *Parabuthus* species are able to squirt their venom, an ability that has not been reported in other scorpions.[153] *Opistophthalmus glabrifrons,* a member of the Scorpionidae family widespread in southern Africa, has infrequently caused systemic symptoms in addition to local swelling, but its sting is not considered potentially fatal.[41]

FIGURE 44-8 *Parabuthus transvaalicus,* a dangerous scorpion of southern Africa. *(Courtesy Jan Ove Rein.)*

FIGURE 44-9 *Hadogenes troglodytes,* an impressive-looking yet relatively harmless scorpion of southern Africa, has large claws and a thin tail. *(Courtesy R. David Gaban.)*

Stings from the *Parabuthus* species often cause only pain, although systemic effects occur less commonly. Severe envenomations are characterized by neuromuscular hyperactivity and excessive secretions (particularly hypersalivation and diaphoresis), but without the prominent cardiopulmonary effects from a hyperadrenergic state seen from the dangerous scorpions of northern Africa, South America, the Middle East, and India.[42,43,146] This toxidrome appears identical to that seen in the American southwest from the stings of *Centruroides sculpturatus* (Video 44-1). Stings typically occur in the early evening during the warmer months of October through April, with a peak incidence in January and February.[42,43,146] Four children died in a series of 42 serious scorpion envenomations in South Africa.[146] No fatalities were noted among 244 patients (17 with severe systemic symptoms) in Zimbabwe.[43] In another study from Zimbabwe, however, five deaths occurred among 455 patients, with fatalities occurring in children less than 10 years old or adults over 55 years.[42]

Antivenom is produced in South Africa against *Parabuthus* venom, which is recommended for patients with severe systemic toxicity.[42,43,133,146,154] Injection of local anesthetics for localized pain and intracutaneous sterile water injection for regional pain have also been advocated.[43] Traditional herbal remedies are frequently used but have no apparent beneficial effect; indeed, rubbing the sting site, as is commonly practiced with such herbal remedies, more than doubles the chance of developing a severe envenomation.[42]

ASIA

Turkey

Although scorpions are present throughout the country, only a limited number of medical publications about scorpion envenomation in Turkey are available, mostly from the southeastern portions of the country. Potentially dangerous species include *Androctonus crassicauda* (Figure 44-10), *Leiurus quinquestriatus, Mesobuthus* species, and a few others.[11,49] As elsewhere, stings occur more commonly during warm months, from May through September. Studies from the early 2000s had shown pediatric lethality rates as high as 12.5%, whereas a case series of 170 patients from 2007 involved no deaths.[8] In a 2009 case series of 52 children hospitalized in southeastern Turkey, nearly one-half (46.2%) were stung by *A. crassicauda,* one (1.9%) was stung by *L. quinquestriatus,* and in the remaining cases the offending scorpion species was not known; one death was recorded. Admission from a rural area was a risk factor for severe envenomation, possibly because of increased time from envenomation to hospital presentation.[49]

Antivenom is widely used in Turkey for severe scorpion envenomation. A monovalent antivenom is produced by administering *A. crassicauda* venom to horses, then enzymatically

FIGURE 44-10 *Androctonus crassicauda,* a "black scorpion" from the Middle East that delivers a particularly painful sting. *(Courtesy Jan Ove Rein.)*

digesting and purifying the serum. Hydrocortisone and antihistamines are commonly coadministered per the national poisoning treatment procedure.[8]

Israel

Leiurus quinquestriatus, locally often called the "yellow scorpion," is the most dangerous species found in Israel (Figures 44-11 and 44-12).[47,80,110] Other native species include *Hottentotta judaicus* (formerly *Buthotus judaicus,* the "black scorpion"), *Androctonus crassicauda, A. bicolor, Nebo hierochonticus, Scorpio maurus,* and *Orthochirus innesi.*[46,47,80] More than 90% of all scorpions encountered in neighboring Jordan are either yellow or black scorpions *(L. quinquestriatus* or *B. judaicus),* with the yellow being most common.[80,110] Most scorpion stings occur during the warmer months of April through October.[39] In the Negev desert region, Bedouin children are stung about six times more frequently than are Jewish children, probably because of more time spent outdoors and lack of protective footwear. Males are affected 2.3 times more often than females; this is most likely related to differences in gender roles, such as boys herding sheep or goats.[110] The reported mortality rate in children was 18% among Palestinians living on the West Bank in 1965, 3.7% among children in the Jerusalem area in 1991,[80] and 1.2% among children in the Negev area in 1985.[110] Most scorpion stings have a mild clinical course; 13% of reported sting victims remain asymptomatic, 72% have mild illness, and 15% become moderately to

FIGURE 44-11 *Leiurus quinquestriatus,* a dangerous "yellow scorpion" of North Africa and the Middle East. *(Courtesy Jan Ove Rein.)*

FIGURE 44-12 The tail segment of *Leiurus quinquestriatus* just proximal to the telson is characteristically black on this otherwise yellow scorpion. *(Courtesy Jan Ove Rein.)*

seriously ill.[39] In a case series of 18 Israeli pediatric patients stung by *L. quinquestriatus* between 1988 and 1996, 17 had mild to moderate toxicity, and only one patient was severely affected, suggesting that routine ICU admission was not necessary.[38]

Stings from *L. quinquestriatus* initially produce intense local pain, erythema, and edema, which can be followed by an outpouring of catecholamines and acetylcholine from nerve endings. In severe cases, clinical signs of sympathetic overload predominate, with severe hypertension, tachyarrhythmias, and pulmonary edema.[3,100,101,169] Parasympathomimetic action of the venom may also cause bradyarrhythmias or atrioventricular block, usually preceding the sympathetic overload. Cardiomyopathy and myocardial damage with electrocardiographic (ECG) and serum marker (creatine kinase [CK], CK-MB, troponin) changes have been reported.[80,100,183,190] Other common findings from severe stings include agitation, convulsions, encephalopathy, hypersalivation, diaphoresis, priapism, and pancreatitis.[185,186] Treatment recommendations differ, but all emphasize aggressive symptomatic and supportive care for severely envenomed patients. However, some clinicians propose the routine use of antivenom,[80] whereas others argue that serotherapy does not significantly alter outcome based on experimental pharmacokinetic data.[100,101,103] Antivenom had no demonstrable effect in one clinical series of Israeli patients.[187]

Saudi Arabia

At least 14 species of scorpions are found in Saudi Arabia; the two species most commonly responsible for significant envenomation are *Androctonus crassicauda,* a black or dark brown scorpion, and *Leiurus quinquestriatus,* a yellow scorpion.[16,82,109,117,124,132,152] The "yellow scorpion" is usually reported to cause more stings than the "black scorpion," except in one 5-year surveillance survey from the north-central Qassim province, where the distribution was roughly equal.[123] Saudi Arabia averages 14,500 annual reported scorpion stings.[125] These account for 3% to 4% of all pediatric hospital admissions in northwestern Saudi Arabia between May and August, with few admitted in other seasons.[81,82] One author reported the incidence of "scorpion sting syndrome" as 1.3 cases per 1000 emergency department patients,[152] whereas a 15-year retrospective analysis from another hospital in the same city (Riyadh), with over 100,000 visits annually, reported only 251 cases.[10] Between 70% and 80% of cases occur between May and October, and 73% of stings occur at night between 6 PM and 6 AM.[124,152] Many victims are barefoot children playing outdoors or persons tending flocks of goats or sheep. Males are affected at least twice as often as females.[16,81,124,152] Mortality rates have decreased from 2% to 8%, as previously reported, to less than 0.05% in more recent studies.[16,81,109] Antivenom is recommended and routinely administered for scorpion envenomation in Saudi Arabia; this may be a factor in decreasing mortality rates.[16,81,82,117]

L. quinquestriatus envenomations were reviewed earlier, in the section about Israel. *A. crassicauda* stings are similar to those

of the yellow scorpion, causing hypertension and central nervous system (CNS) manifestations, but differ in other ways.[117] The pain from the *A. crassicauda* sting has been reported as particularly severe. Generalized erythema was noted in 20% to 25% of children less than 5 years of age; this is not usually seen with other scorpion stings. The cause of this erythema is not clear, especially because elevated catecholamine levels after scorpion envenomation appear to be protective against allergic reaction. Cholinergic effects are seen less often with *A. crassicauda* stings.

Of special relevance to wilderness medicine, scorpion envenomation became an issue to U.S. soldiers deployed during the Gulf War.[96] *L. quinquestriatus* and *A. crassicauda* were implicated in 57 scorpion stings over 4 months among 7000 troops of an armored cavalry division stationed in eastern Saudi Arabia. All patients with adequate data for further study recovered fully, usually with only supportive care in the field, probably reflecting that all were healthy adults. No antivenom was available. Typical signs and symptoms included local pain, tachycardia, hypertension, sweating, apprehension, headache, epigastric pain, nausea, restlessness, and local muscle cramping and paresthesias in lower extremity stings. Presumably, victims with only local pain failed to present to battalion aid stations, resulting in an apparently high incidence of systemic effects. Only two persons had serious presentations or subsequent complications. One had a clinical picture consistent with anaphylaxis and required intubation for respiratory support. The other developed a cutaneous ulcer that healed in 3 weeks with oral antibiotic therapy.[96]

Iran

More than 44 scorpion species are found in Iran, including at least 7 whose stings are considered medically important.[166] Scorpion stings are most prevalent in Khuzestan, a hot and humid province in the southwest adjacent to the Persian Gulf; about 60% of all reported stings in Iran occur in this province. In 1990, the distribution of stings by species to persons seeking medical attention in Khuzestan was 41% *Androctonus crassicauda,* 45% *Mesobuthus eupeus,* and 13% *Hemiscorpius lepturus,* the only non-Buthid scorpion generally recognized as dangerous to humans.[167] A more recent collection of 418 scorpions brought with patients evaluated at various medical centers in Khuzestan after being stung found 120 (28.7%) *A. crassicauda* specimens, 104 (24.9%) *H. lepturus,* 91 (21.7%) *M. eupeus,* 86 (20.6%) *Compsobuthus matthiesseni,* and minor contributions by three other species.[69]

Nonspecialists can rarely identify species by sight, but most can easily identify the scorpion's primary coloration. The most dangerous "black scorpions" of Iran are *A. crassicauda* and *Hottentotta schach,* whereas the dangerous "yellow scorpions" are *M. eupeus, Hottentotta saulcyi, Odontobuthus doriae,* and *Hemiscorpius lepturus*.[182] Stings occur more commonly during the warmer months of the year (90% occurring between April and October), and most occur during the night or early morning hours, reflecting times of peak scorpion activity.[166,182]

In Iran, 90% to 95% of all fatal stings are caused by *Hemiscorpius lepturus* (sometimes previously called *Hemiscorpion lepturus*), making it the most dangerous scorpion in Iran.[125,166,182] This member of the Hemiscorpiidae family causes a spectrum of disease distinctly different from that caused by the dangerous scorpions of the Buthidae family. Severe envenomation by *H. lepturus* is characterized by hemolysis, renal failure, and local tissue necrosis. Stings by *H. lepturus* are stated to not induce an acute painful response (unlike stings from other species), resulting in many patients delaying medical attention until local tissue destruction is advanced.[125,168] This last point sounds similar to many alleged brown recluse spider bites in the United States and alleged white-tailed spider bites in Australia, where dermonecrotic lesions of unknown cause (often from bacterial infection of the skin and soft tissue) are erroneously ascribed to arthropods by laypersons and health care personnel alike. However, this author is not aware of any published evidence refuting the observation that *H. lepturus* stings are not initially painful.

Envenomation by *A. crassicauda* in Iran produces pain, neuromuscular agitation, and signs of parasympathetic hyperstimulation (e.g., lacrimation, salivation, increased bronchial secretions)

FIGURE 44-13 *Hottentotta tamulus,* the dangerous "red scorpion" of India. Until recent taxonomic changes, it was most widely known as *Mesobuthus tamulus. (Courtesy Jan Ove Rein.)*

similar to other Buthid scorpions.[167] However, this report does not comment on signs and symptoms specifically related to the adrenergic/hypertensive crisis seen with many other dangerous species.

India

Nearly all of the medical literature regarding Indian scorpions relates to *Hottentotta tamulus,* sometimes called the "red scorpion," the single most dangerous native species (Figure 44-13).[147] Until recent taxonomic changes, this scorpion had been called *Mesobuthus tamulus* (and before that *Buthus tamulus* and *Buthotus tamulus*); therefore the bulk of previously published observations and research now refers to obsolete genus names. *H. tamulus* is a particular problem in southern coastal India. Stings occur predominantly in April, May, and June at night among young farmers wearing minimal clothing.[26,33] In many cases, stings occur at the tip of an extremity, with the only symptom being pain, which can be controlled with local anesthetic injections.[33,66] Systemic toxicity occurs from release of catecholamines, with major morbidity and mortality resulting from cardiopulmonary toxicity.[24,26,30,33,44,66] Fatality rates between 30% and 40% were reported in the 1960s and 1970s, but these have fallen to 2% to 3% with treatment using vasodilators and calcium channel blockers.[28,30,36] An 11.8% mortality rate, however, was found among 152 children admitted to hospitals in Calcutta from 1985 to 1989, but treatment details were not reported.[44]

H. tamulus antivenom had not been available for clinical use until quite recently. Starting in 2002, scorpion antivenom has been distributed to primary health centers (PHCs) in India free of charge; however, its use is not standard, especially because envenomation cases are commonly admitted, which does not occur at PHCs.[36] Bawaskar and Bawaskar, from Maharashtra, a state in western coastal India, are the world's foremost proponents of using antihypertensive agents (primarily oral prazosin, an α-adrenergic blocker) to treat the catecholaminergic effects of severe scorpion envenomation.[27,31-36] They cite the limited medical resources available for the majority of victims, many of whom live in rural settings and are poor, in addition to the potential risks of transporting unstable patients. Other vasodilators that have been advocated include nifedipine, IV sodium nitroprusside, and captopril.[131] Administration of *H. tamulus* antivenom did not appear to improve clinical outcome compared with treatment with oral prazosin in a nonrandomized observational study of 53 patients.[36] A potential confounder is the fact that patients treated with antivenom were all referred from PHCs to the study hospital, whereas those treated with prazosin presented directly to the hospital. Some researchers have instituted protocols relying on oral prazosin for early-presenting patients, but using dobutamine and nitroprusside for those with pulmonary edema.[45,151]

In 2010, the Bawaskars published a randomized, open-label study comparing patients treated with oral prazosin alone with

those treated with prazosin plus *H. tamulus* antivenom. This antivenom is a monospecific F(ab)2 fragment prepared from horses by Haffkine Biopharma Mumbai. Enrolled in each group were 35 patients with grade II envenomation (systemic signs and symptoms present, but without pulmonary edema or shock). The recovery time in the antivenom group was reduced (8 hours versus 17.7 hours), and there was no significant difference in the clinical deterioration rate. They noted that the total cost of treatment with antivenom "approaches a month's salary for a laborer in the region" (Rs350, $7.77), whereas prazosin costs less than one-tenth this amount.[37] Subsequent prospective studies of this scorpion antivenom with oral prazosin versus prazosin alone among pediatric patients showed improved recovery times.[163,164]

AUSTRALIA

Australia is home to more than 40 named scorpion species and is believed to harbor as many as 200 species in total. However, scorpion stings are uncommon there and do not cause major envenoming.[114,115] In a 27-month study in the early 2000s, only 192 scorpion stings were reported to Australian poison centers. The majority of stings occurred during the warmer months of the year, and they tended to occur at night and indoors. These stings generally caused severe pain (defined as greater than that from a bee sting) lasting a few hours, although 11% of the victims had systemic complaints of nausea, headache, and malaise. The majority of victims were managed without seeking additional medical attention. In 95 cases, the offending scorpion was collected and identified by an arachnologist. Most stings (72) were by small Buthid scorpions from the *Lychas* genus; however, all five stings from Tasmania were from *Cercophonius squama,* the only known species on that island.[114] *Urodacus* scorpions are larger but less commonly encountered.[115] No neurotoxins were found in *U. novaehollandiae,* the only Australian species that has had its venom studied.[192] No antivenom exists for native Australian scorpions. Supportive treatment, often with only oral analgesics, appears to be adequate. Similar to the treatment of some other envenomations, the application of hot water (e.g., immersing a stung finger) has been advocated, but this has not been studied systematically.[115,192]

SOUTH AMERICA

Colombia

A case series of 129 patients admitted after scorpion stings in Colombia has been reported.[161] The most commonly implicated species were *Tityus pachyurus, T. fuebrmanni,* and *Centruroides gracilis*. Most envenomations were mild (76%), and only children less than 6 years old were in the severe group (four patients). Commercially-available Mexican antivenom against the venom of four *Centruroides* species was used in 19 cases with systemic findings, which decreased the duration of some clinical signs and had no reported adverse effects. Thirty-two cases occurred on an Air Force base, where servicemen put on clothes or boots in which scorpions had sought shelter overnight.[161]

Venezuela

Envenomation by scorpions of medical importance in Venezuela is endemic to the densely populated northernmost sections of the country, with the northeastern states of Monagas and Sucre being particularly affected.[74,75] *Tityus discrepans* is the most common species causing stings, although 184 scorpion species were described by 2006, with 52 from the *Tityus* genus.[74,75,78] Intravenous (IV) antivenom is commonly given for severe envenomations, and there appears to be a trend toward a better outcome with earlier administration.[141,140]

Trinidad

Tityus trinitatis accounts for almost 90% of the scorpion population on Trinidad. Fatalities are rare but occur more often in children. Stings are more frequent in summer months.[22] Systemic effects of serious *T. trinitatis* envenomations include tachypnea, restlessness, vomiting, hypersalivation, cerebral edema, pulmonary edema, hypovolemic shock, seizures, and myocarditis.[65] The most striking clinical observation is the high incidence (up to 80%) of acute pancreatitis; scorpion stings are the most common cause of acute pancreatitis in Trinidad.[22,91]

Brazil

About 10,000 cases of scorpion envenomation are reported annually in Brazil, with 80% occurring in southeastern regions.[145,155] One-half of the reported stings occur in the state of Minas Gerais, although scorpions are also problematic in São Paulo and Bahia.[54,145] Most stings occur between December and February.[88] *Tityus serrulatus,* popularly known as the "yellow scorpion," is the most prevalent species in Brazil and accounts for most fatal stings, as a result of its widespread distribution in populous urban centers and high venom potency.[12,62,145] *T. serrulatus* is considered by some to be "the most dangerous scorpion in South America."[165] *T. bahiensis* is the second-most common species, although severe envenomations are much more likely from *T. serrulatus*.[52,155] Equine-derived antivenom for either *T. serrulatus* or both *T. serrulatus* and *T. bahiensis* is able to neutralize venom from all Brazilian scorpions studied.[155] Children are much more likely than adults to have severe envenomations.[87] In Minas Gerais, children less than 14 years of age accounted for 27% of scorpion envenomation admissions but for all cases of significant morbidity and mortality; 16% were treated in an ICU setting. Mortality rates with current treatment now range from 0.7% to 1.1% in children, and the rate is 0.28% overall.[87,107,145,173] A "tripartite approach" has been advocated, which employs symptomatic measures, support of vital functions, and immunotherapy.[174] Antivenom from a few manufacturers is available in Brazil and routinely used in severe envenomations.[54,87,173]

Argentina

Scorpions of medical importance in Argentina belong to the *Tityus* genus. *Tityus trivittatus* is generally recognized as the only species capable of causing severe envenomations or death, although *T. confluens* has also been implicated in a few cases.[72,73] Over a 7-year period, 511 scorpion envenomations were reported to public health authorities. Most cases occurred indoors and during the warmer months, November through April. Scorpions are hyperendemic in the provinces of Córdoba and Santiago del Estero, where 85.6% of the envenomations occurred. Local pain and inflammation were most common, whereas systemic envenomation occurred in 7% of children 10 years and younger and in 2% of older victims. Antivenom therapy was provided in 84% of cases with available treatment records; only three fatalities occurred, and none of these victims had received antivenom. Until 1996, the Argentinians used a cross-reactive Brazilian antivenom against *T. serrulatus*. Since 1997, Argentina has produced a $F(ab')_2$ fragment equine antivenom.[72]

NORTH AMERICA

Mexico

An estimated 250,000 scorpion stings occur annually in Mexico.[162] The number of resultant deaths per year has been variously reported from "about 100," to "700 to 800," to "over 1000"; regardless of the actual number, this certainly represents a serious public health concern.[59,162,171] Of at least 221 native species and subspecies, only eight members of the *Centruroides* genus (Figure 44-14) are recognized as significantly dangerous.[58,68,76,160] The *Centruroides* scorpions are relatively small and described as yellow, tan, or brown. Clavigero recognized as early as 1780 that "the venom of the small and yellow scorpions is more active than that of the big grey ones."[142] Mexican states on the Pacific Coast, particularly Colima, Durango, Guerrero, Morelos, and Nayarit, report the highest number of scorpion stings.[59,68,142,171] In 1999, Morelos had the highest incidence, with a total of 30,663 stings and 9 deaths. Nearly 2% of the population in Morelos is stung annually, and in some hyperendemic villages this figure is over 10%.[171] In urban areas of Colima, 3 stings per 1000 people occur annually; this figure rises to 18 to 30 stings per 1000 in more rural areas.[59] The peak incidence of scorpion stings occurs during the warmer months, but has been variably reported as from "March to July, coinciding with

FIGURE 44-14 *Centruroides limpidus limpidus,* one of several closely related, dangerous Mexican scorpions. *(Courtesy R. David Gaban.)*

FIGURE 44-15 *Centruroides sculpturatus,* the Arizona bark scorpion; the only species in the United States known to cause severe neurotoxic envenomations. *(Courtesy Jan Ove Rein.)*

scorpion reproduction," or between "June and October," correlating with rainfall statistics.[58,160]

The following signs and symptoms have been reported with Mexican scorpion stings, although not all effects are necessarily seen in the same victim, and no apparent sequence of effects has been observed: hyperexcitability, restlessness, hyperthermia, tachypnea, dyspnea, tachycardia or bradycardia, diaphoresis, nausea, vomiting, gastric distention, diarrhea, lacrimation, nystagmus, mydriasis, photophobia, excessive salivation, nasal secretion, dysphagia with foreign body sensation, dysphonia, cough, bronchorrhea, pulmonary edema, arterial hypertension or hypotension, heart failure, shock, convulsions, ataxia, fasciculations, and coma.[68] Unpublished verbal reports by physicians who have treated scorpion-envenomed patients in Mexico suggest that the clinical presentation is virtually identical to that caused by *C. sculpturatus* in the United States. The higher mortality rate from Mexican scorpion stings compared with American stings may be the result of differences in venom potency between species, human and scorpion population densities, ease of access to medical care (e.g., monitoring equipment, ICUs, and antivenom), and perhaps housing and protective clothing that promote human-scorpion interactions in Mexico.

Antivenom is recommended and commonly used for severe scorpion envenomation in Mexico.[58,68,76,135,160] A $F(ab')_2$ fragment antivenom is produced domestically and is commercially available. It is prepared from the venoms of four native *Centruroides* scorpions. This Mexican antivenom has also been investigated for use against *C. sculpturatus* in the United States.[53]

United States

More than 40 species of scorpions are found in the United States.[55] However, only one American species, the Arizona bark scorpion (Figure 44-15), causes a significant number of systemic reactions and is known to be potentially fatal.[40,55,64,179,193] For many years, controversy has existed regarding proper taxonomy and the medical importance of this scorpion.[201] This species has at times been called *Centruroides sculpturatus, C. exilicauda,* or *C. gertschi*. Current taxonomy holds that the Arizona bark scorpion is properly called *C. sculpturatus,* which is medically important and found in the southwestern United States (particularly Arizona), of which *C. gertschi* is a striped subspecies. *C. exilicauda* is a different species found in Baja California, Mexico; its sting is considered medically insignificant, and no fatalities have been documented.[177,201] Nevertheless, a significant proportion of the medical literature regarding scorpions refers to the medically important American species as *C. exilicauda*. Approximately 30 *Centruroides* species are found distributed throughout the New World, several of which are medically important and are mostly found in Mexico.[179]

Centruroides sculpturatus is called the "bark scorpion" because of its preference for residing in or near trees. These scorpions also often hide under wood (old stumps, lumber piles, firewood, loose bark, or fallen trees), in ground debris, or in crevices during the daytime. This is troublesome to humans, because the scorpions may hide in shoes, blankets, or clothing left on the floor during daylight hours, as well as under common ground covers and tents. *C. sculpturatus* is found statewide in Arizona and also in some areas of Texas, New Mexico, and northern Mexico; small areas of California; and near Lake Mead, Nevada.[64] The bark scorpion is relatively small, measuring up to 5 cm in length. Specimens are variously described as being uniformly yellow, brown, or tan; stripes are uncommon. The pincers (pedipalps) and tail are thin, giving the scorpion a streamlined appearance (Figure 44-16), in contrast to several of the larger but less dangerous scorpions with thick claws and tails. The presence of a subaculear tooth, a tubercle at the base of the stinger, is distinctive to *C. sculpturatus* and is helpful in differentiating this neurotoxic scorpion from other species.[64,193]

The bark scorpion presents a significant public health problem in Arizona. About 10% of all calls received by the poison control center in Phoenix are related to scorpion stings, the vast majority of which are known or highly suspected to have been caused by *C. sculpturatus*. The bark scorpion was at one time the number-one killer of humans among Arizona's venomous animals. From 1931 to 1940, more than 40 deaths were attributed to envenomation by this scorpion, mostly in young children and infants. The fatality rate fell dramatically between 1940 and 1970, probably because of improved pest control measures and advances in medical technology and supportive care. In 1972, these scorpion stings were still considered generally fatal to infants without treatment, extremely dangerous to older children, and occasionally fatal to adults with hypertension.[191] However, no deaths have been reported in the medical literature since 1968

FIGURE 44-16 Distinctive features of *Centruroides sculpturatus* include the nearly uniform yellow/tan color, thin pedipalps and tail, and subaculear tooth (*arrow*) on the telson.

FIGURE 44-17 *Centruroides vittatus,* the American common striped scorpion: male specimen. *(Courtesy Jan Ove Rein.)*

FIGURE 44-19 *Hadrurus arizonensis,* a "giant hairy scorpion" of the American Southwest. *(Courtesy R. David Gaban.)*

from scorpion envenomation in Arizona.[40] In 2001, a scorpion-related fatality was reported in Arizona, although death was ascribed to anaphylaxis rather than to direct venom toxicity, in a patient previously stung and presumably sensitized to the venom.[52] A more recent, unpublished pediatric death may have been caused by a lack of adequate airway control and/or allergic reaction to antivenom. Because death can apparently be prevented with currently available supportive care, earlier fatalities were probably caused by loss of upper airway and respiratory muscle control with the potential for aspiration, exacerbated by metabolic acidosis, hyperthermia, and rhabdomyolysis from excessive muscular activity.[64]

Centruroides vittatus, the common striped scorpion, accounts for the next most reported envenomations in the United States. *C. vittatus* has a black intraocular triangle and black stripes on the thorax (Figures 44-17 and 44-18). A review of 558 *C. vittatus* stings reported to Texas poison centers in 1997 found that 96% produced local symptoms of pain, bleeding, burning sensations, erythema, edema, hives, local paresthesias, and pruritus; systemic reactions occurred in 20% of victims.[194] The most common systemic features were paresthesias of the face, tongue, and perioral region, followed by dysgeusia, chills, sweating, dysphagia, fasciculations, nausea, and vomiting. *C. vittatus* is found primarily in the Southwest and Texas but also extends into southern Indiana and Illinois.[198]

Hadrurus species are the longest and most heavy-bodied scorpions native to North America and are known as "giant hairy scorpions" because of their size and conspicuous bristles (Figure 44-19). They are native to Arizona, California, and parts of Utah, Nevada, Idaho, and Mexico. *Vaejovis* species have a wide distribution from southern Canada, south through Wyoming, Colorado, and Texas, and west to California. Hypersalivation after *Vaejovis* envenomation has been reported. *Uroctonus* species are found in mountain habitats from southern California to Oregon.[179] *Isometrus maculatus* is the only scorpion found in Hawaii and is also found in southern Florida and California.[55,139] Envenomations cause mild systemic effects (myalgia and nausea); no fatalities have been reported.[139] *Diplocentrus* species have been found in Florida, Texas, and California.[55] The Midwest and New England are not natural scorpion habitats, although three envenomations in Michigan were caused by scorpions unintentionally transported with personal belongings or with produce—two by *Centruroides hentzi* from Florida and one by *C. sculpturatus* from Arizona.[198] The poison control center in Phoenix has also been consulted regarding stings from bark scorpion stowaways in mail to Minnesota and in personal belongings to Germany.

***Centruroides sculpturatus* Envenomation.** Stings from *C. sculpturatus* often produce significant neuromuscular effects without severe cardiopulmonary toxicity. Curry and coworkers reviewed clinical findings after *C. sculpturatus* envenomation and proposed four clinical grades of envenomation intended to direct treatment (Box 44-1).[64] Grade I envenomation is characterized by local pain and paresthesias at the sting site. Usually, no local inflammation occurs, and the puncture wound is too small to be observed. If no scorpion is seen, the diagnosis may require historic or epidemiologic clues or other physical signs. The "tap test" has been empirically recommended to confirm a bark scorpion sting, although its reliability has not been rigorously tested. With the patient looking away or otherwise distracted, gently tapping the sting site will greatly exacerbate the pain, a sign that does not occur with other envenomations.[64,193]

Victims with grade II envenomations have local symptoms plus pain and paresthesias remote from the sting site. The more distant symptoms often radiate proximally up the affected

FIGURE 44-18 Gravid female *Centruroides vittatus. (Courtesy Jan Ove Rein.)*

BOX 44-1 Grading of *Centruroides sculpturatus* Envenomation

Grade I: Local pain and/or paresthesias at site of envenomation
Grade II: Pain and/or paresthesias remote from the site of the sting, in addition to local findings
Grade III: Cranial nerve dysfunction or somatic skeletal neuromuscular dysfunction
- A. Cranial nerve dysfunction: blurred vision, wandering eye movements, hypersalivation, difficulty swallowing, tongue fasciculations, upper airway problems, slurred speech
- B. Somatic skeletal neuromuscular dysfunction: jerking of the extremity/(ies), restlessness, severe involuntary shaking and jerking that may be mistaken for a seizure

Grade IV: Cranial nerve dysfunction and somatic skeletal neuromuscular dysfunction

Modified from Curry S, Vance MV, Ryan PJ, et al: Envenomation by the scorpion *Centruroides sculpturatus, J Toxicol Clin Toxicol* 21:417, 1983-1984.

extremity but may occur in even more remote sites (e.g., contralateral limbs) or as generalized paresthesias. Victims may complain of a "thick tongue" and "trouble swallowing" in the absence of objective motor abnormalities. Children and adults frequently rub their nose, eyes, and ears, and infants may present with unexplained crying.[64]

Cranial nerve or somatic skeletal neuromuscular dysfunction is found in grade III envenomations. Cranial nerve dysfunction can be demonstrated as blurred vision, abnormal eye movements, slurred speech, tongue fasciculations, and hypersalivation. The combination of bulbar neuromuscular dysfunction and increased oral secretions may cause problems with airway maintenance. Abnormal eye movements most often are involuntary, conjugate, slow, and roving. Chaotic multidirectional conjugate saccades resembling opsoclonus and unsustained primary positional nystagmus may also be seen.[61] Many patients with abnormal eye movements prefer keeping their eyes closed. Somatic skeletal neuromuscular dysfunction can cause restlessness, fasciculations, alternating opisthotonos and emprosthotonos, and shaking and jerking of the extremities that can be mistaken for a seizure. The abnormal skeletal muscle activity appears more undulating and writhing, however, than the tonic-clonic movements of generalized seizures. Also, unlike victims with seizures, these victims often remain awake and alert the entire time.

Grade IV envenomation is characterized by both cranial nerve dysfunction and somatic skeletal neuromuscular dysfunction. On close examination, victims with skeletal muscle hyperactivity (at least grade III) usually also have cranial nerve dysfunction, meeting criteria for grade IV. In the most severe cases, stridor and wheezing occur, suggesting foreign body aspiration or reactive airways disease. Hyperthermia up to 40° C (104° F) can occur, probably resulting from excess motor activity. Respiratory failure, pulmonary edema, metabolic acidosis, sterile cerebrospinal fluid pleocytosis, rhabdomyolysis, coagulopathy, pancreatitis, and multisystem organ failure have also been reported in a few severely ill children.[41] After envenomation, symptoms may begin immediately and progress to maximum severity within 5 hours. Infants can reach grade IV in 15 to 30 minutes.[64] The symptoms abate at a rate that depends on the age of the victim and the grade of envenomation. Symptomatic improvement occurs within 9 to 30 hours without antivenom therapy.[48,60,64,193] Pain and paresthesias are exceptions and have been known to persist for days to 2 weeks.

Although adults appear to be envenomed more often, children are more likely to develop severe illness requiring intensive supportive care.[64] A review of 673 patients found that 67.8% of stings occurred in adults older than 20 years, with 14.9% in children younger than 11 years. Many more unreported envenomations probably occur in adults, placing the relative incidence for children even lower. Of the patients, 621 (92.3%) had symptoms of either grade I or II envenomations or were asymptomatic and thus required no specific therapy. Younger patients had a higher percentage of the more severe envenomations; 25.9% of children younger than 6 years of age had grade III or IV envenomations, or 34% if asymptomatic patients (most likely never stung) are excluded. Only 6.1% of adults had grade III or IV envenomations.[64]

Medically reliable descriptions of the victim's perspective of neurotoxic scorpion envenomation are rare, primarily because of the young age of those most severely affected. Box 44-2 is a personal description of *C. sculpturatus* envenomation by a critical care physician.

A notable natural experiment occurred in the United States with regard to antivenom use for scorpion envenomation. For many years, the only domestic scorpion antivenom was produced at Arizona State University in Phoenix. A goat-derived whole IgG antivenom was first produced in 1966.[90] This antivenom was produced by hyperimmunizing a small herd of goats against *C. sculpturatus* venom and then intermittently harvesting and freezing or lyophilizing their serum. Probably because of the limited geographic need, this antivenom was never approved by the Food and Drug Administration and was not available commercially; however, it was distributed free of charge on a humanitarian basis within the state by special action of the Arizona State Board of Pharmacy.[48] Nevertheless, it was not universally agreed that this antivenom should be the primary therapy for severe scorpion envenomation, and debate persisted between opposing schools of thought, with some local toxicologists preferring to use antivenom and others favoring advanced supportive care measures in an ICU setting, including IV sedatives to mitigate neuromuscular agitation.[93,138] Production of scorpion antivenom at Arizona State University ceased around the year 2000, the last batch of antivenom expired in 2004, and hospital pharmacies used up their last supplies in 2005.[53,175] By default, the only available therapy was supportive care, which resulted in increased pediatric ICU admissions in Arizona.[175] A retrospective chart review conducted from 2004 to 2006 at a children's hospital in Phoenix showed that the mean length of stay when no antivenom was available was 29 hours (range 6 to 73 hours) and that 24% of patients were intubated for airway protection.[159]

Although no manufacturer in the United States is currently (2015) producing scorpion antivenom, research has been conducted with a polyvalent antiscorpionic $F(ab')_2$ fragment antivenom produced in Mexico using a horse host and venom from four other *Centruroides* species. This product was already available in Mexico, but required proof of efficacy and safety before wider availability in the United States. Anascorp, Centruroides (Scorpion) Immune $F(ab')_2$ (Equine) Injection was subsequently approved by the Food and Drug Administration as an orphan drug on August 3, 2011, based on data collected from 1534

BOX 44-2 Personal Account of *Centruroides sculpturatus* Envenomation by a Critical Care Medicine Specialist

Arriving home in the early evening, I decided to go for a run. My running shoes were in the kitchen area, where I had left them the day before. As usual, I would wear my shoes without socks. As I put my left foot into the shoe, I felt an intense burning pain on the dorsum of my first toe. I pulled my foot out of the shoe and along with it came a 1.5- to 2-inch, clear-brown scorpion.

Having no idea what to do for a scorpion envenomation, I called the poison control center. I was informed that the systemic toxicity was usually mild for someone my age, and that if the pain was too severe, I should come in and be evaluated. As the minutes went by, I began to salivate and feel perioral paresthesias. As I walked, the paresthesias became more generalized, with a very noticeable paravertebral tingling with each step. After a few more minutes, I decided to call the poison control center to ask for advice. After dialing the number, I was unable to speak clearly because of severe dysarthria and excess salivation. The toe pain seemed to abate as other neurologic symptoms developed.

Since I was unable to talk on the phone, and no neighbors were home to drive me to the hospital, I decided to drive myself. The normal 10-minute drive took 45 minutes. I had coordination difficulties with the gas pedal, clutch, and gear shifting. It was also nighttime, and I could not process the multiple visual inputs of car lights, street lights, and road lines in a way that would allow me to drive more than 5 to 10 miles per hour. I not only had to stop frequently and close my eyes for a few seconds but also had difficulty keeping the car in my driving lane.

After arriving at the emergency department, I was ataxic, dysarthric, and drooling and had difficulty giving the admitting nurse a proper history. I'm certain that I was thought to be either mentally retarded or intoxicated. Examination by the emergency department physician revealed many abnormal cerebellar findings, continued salivation, inability to swallow liquids, continued symptomatic paresthesias, but no objective motor or sensory deficits. There were no physical signs of envenomation [at the sting site], but tapping the toe produced worsening pain. As my story became clearer to the ED physician, antivenom was ordered and administered. Within 20 minutes of finishing the infusion, all neurologic signs and symptoms were gone, except for toe pain.

Courtesy Dr. Thomas Bajo, Phoenix, Arizona.

patients in a study coordinated by investigators from the University of Arizona.[51,199,200] This antivenom is marketed to health care facilities in areas where *C. sculpturatus* is found, which includes Arizona, and portions of Clark County, Nevada, and New Mexico.[200] The cost (and related patient charges) of this antivenom can be very high. A pharmacoeconomic study used the mean cost of antivenom therapy as $10,708 for a three-vial dose, as per the package insert instructions, compared with a treatment cost of $3178 without antivenom. Although the antivenom is highly effective in reversing toxicity, it may be too costly to justify use in all but the most severe clinical situations. Even if it was deemed acceptable to spend up to $100,000 per successfully treated patient, this antivenom was only cost-effective in 13% of scenarios based on a computer model.[19]

PATHOPHYSIOLOGY AND CLINICAL EFFECTS

CARDIOVASCULAR EFFECTS

Detailed descriptions of myocardial damage and other cardiovascular manifestations from the scorpions of Israel, India, Trinidad, Tunisia, and Brazil have been reported since the 1960s.[101,106] The cardiovascular effects of scorpion envenomation are complex and varied. Stimulation of the sympathetic and parasympathetic branches of the autonomic nervous system results in different clinical presentations that may change with time. Distinct syndromes may dominate the clinical picture in severe scorpion stings. Hypertension or hypotension can occur with or without pulmonary edema, and rhythm disturbances may consist of sinus bradycardia or tachycardia, premature depolarizations, supraventricular tachycardia, atrioventricular block, and ventricular tachycardia.[86,102] Some clinicians have postulated that the cardiovascular effects follow a predictable pattern of progression from an initial hyperdynamic and hypertensive phase to a hypokinetic, hypotensive phase with left ventricular dysfunction, with or without pulmonary edema, depending on the patient's volume status.[1,126,157] Transient parasympathetic effects may occur initially, resulting in bradycardia and hypotension, and are followed by sustained adrenergic hyperactivity.[28]

Sinus tachycardia and hypertension are related to venom-induced catecholamine and angiotensin release.[28,65,104,126,132] Significant hypertension may be seen in up to 77% of patients with systemic envenomation, although a 17.5% to 30% incidence of hypertension is more common.[100] A loud protosystolic gallop, systolic parasternal lift, and transient apical murmur of papillary muscle dysfunction are associated with systemic hypertension.[28,100]

Myocarditis, with ECG changes and biochemical evidence of cardiac injury, is often reported. This myocardial damage is most likely caused by massive catecholamine discharge and sympathetic overstimulation, although direct venom cardiotoxicity has not yet been ruled out.[28,65,87,100,157,190] Many ECG changes consistent with myocardial ischemia and myocarditis, including Q waves, ST-segment elevation or depression, peaked or inverted T waves, U waves, prolonged QTc intervals, and atrioventricular and bundle branch blocks, have been found in persons stung by scorpions.[26,100,183] Most ECG abnormalities are transient, lasting only as long as the most severe clinical effects. Prolonged QTc intervals last for 48 to 72 hours, however, and T-wave inversions have persisted for 4 to 6 weeks.[22] Echocardiography has demonstrated left ventricular systolic dysfunction, which usually resolves by the next day.[132] Concurrent right ventricular dysfunction supports primary global scorpionic myocarditis rather than secondary myocardial ischemia from systemic hypertension.[157]

Elevated serum levels of CK and CK-MB have been found in about one-half of persons with systemic envenomation. Only about one-half of those with elevated CK-MB levels also have ECG changes consistent with myocardial injury.[188] Concurrent CK, CK-MB, and troponin-I elevations have also been reported in a victim with transient bradycardia and second-degree (Mobitz type I) atrioventricular block.[183] Troponin-I was found to be a more specific marker for clinical signs of myocarditis (such as heart failure, cyanosis, shock, abnormal heart sounds, and ECG changes) than were total CK, CK-MB, or LDH among scorpion-envenomed children.[144] Even in patients with severe *Tityus serrulatus* envenomation, troponin-I may be normal at admission, typically peaking within 24 to 36 hours of the sting.[63] Histologic examinations of cardiac tissue in fatal human cases have shown a mixed picture of toxic myocarditis and myocytolysis, with interstitial edema and hemorrhage, inflammatory cell infiltrates, necrotic foci, and fatty droplet deposition.[63,100]

RESPIRATORY EFFECTS

Respiratory failure after scorpion envenomation has been attributed to direct CNS depression, hypertensive encephalopathy, upper airway obstruction, bronchospasm, impaired surfactant synthesis, and pulmonary edema.[15,147,185,187] Pulmonary edema is the most severe respiratory feature in severe scorpion envenomation, occurring in 7% to 35% of victims and accounting for approximately 25% of scorpion-related deaths.[3,4,169] The etiology and pathogenesis of pulmonary edema from scorpion stings are not clear, and both cardiogenic and noncardiogenic factors have been implicated. Left ventricular systolic dysfunction may cause pulmonary edema through venom-induced myocarditis and acutely increased afterload.[4,5,98,169] Increased pulmonary capillary wedge pressures,[4] abnormal radionuclide scans,[169] and left ventricular dysfunction demonstrated by Doppler ECG studies[3] support a cardiac origin of pulmonary edema.

Noncardiogenic causes for pulmonary edema are less well documented and include shock, primary venom-induced lung injury, oxygen toxicity,[98] the presence of various inflammatory mediators (interleukins, kinins, platelet-activating factor),[5] and decreased lung liquid clearance.[61] Histologic and biochemical evidence of increased alveolocapillary membrane permeability has been demonstrated in animal studies and in a fatal human case of *Tityus serrulatus* envenomation.[13] Rabbit studies with *T. discrepans* venom found abundant intravascular microthrombi in lungs with pulmonary edema, and heparin prevented development of pulmonary edema.[78] Such findings are atypical of noncardiogenic pulmonary edema, or adult respiratory distress syndrome (ARDS), and the researchers therefore suggest that scorpion venom respiratory distress syndrome (SVRDS) be recognized as a distinct clinical entity.

NEUROLOGIC EFFECTS

Stings from dangerous *Buthid* scorpion species around the world can produce prominent neurologic effects. Scorpion venom causes repetitive and uncontrolled neuronal discharges through incomplete sodium-channel inactivation.[64] Neurologic signs are fairly common, even from scorpions categorized as cardiotoxic. Actually, all scorpions that produce systemic effects are primarily neurotoxic; however, the neurotoxic effects from some species can induce massive release of endogenous catecholamines, resulting in cardiopulmonary effects that are more prominent clinically. Neurologic signs reported with cardiotoxic scorpions include local or diffuse paresthesias, tremors, shivering, agitation, hyperirritability, apprehension, restlessness, myoclonus, oculogyric crisis (opsoclonus), convulsions, confusion, delirium, hyporeflexia, and coma.[33,54,80,101,130,187] In fatal human cases, a preterminal encephalopathic phase is typical.[123]

Intracranial pathology, such as hemorrhagic strokes thought to be related to vascular rupture from acute hypertension,[88,170] vasculitis,[23] or disseminated intravascular coagulation,[17] has been noted in several case reports of scorpion envenomation. Ischemic strokes have also been reported, probably related to cardiogenic shock.[97] Although pain and paresthesias lasting hours to a few days from the neurotoxic effects of scorpion stings are common, strokes and other persistent neurologic sequelae are rare.

Many persons with systemic scorpion envenomation exhibit anxiety and agitation, consistent with CNS excitation. Animal experiments have shown that intracerebroventricularly administered *Hottentotta tamulus* venom produces effects similar to those caused by yohimbine, a known anxiogenic agent.[43]

Although in fatal cases of *Leiurus quinquestriatus* envenomation, CNS manifestations always precede terminal hypotension and cardiac arrest, the venom crosses the blood-brain barrier poorly, if at all,[118,123,173] so any encephalopathy would be secondary to peripheral effects. Others suggest that CNS manifestations of scorpion stings are caused by hypertensive encephalopathy or excessive levels of circulating catecholamines, rather than by a direct venom effect.[186,187] Hypoxia and pain may also contribute to agitation.

GASTROINTESTINAL EFFECTS

Pancreatitis

Scorpionic pancreatitis was reported by Waterman in 1938 from *Tityus trinitatis* stings and was found in 80% of patients studied by Bartholomew in 1970.[22] Most patients had epigastric pain radiating to the back starting within 5 hours of the sting and resolving within 24 hours. Some patients with hyperamylasemia (38%) did not complain of abdominal pain, suggesting that the true incidence of pancreatitis may be significantly higher. Scorpion stings are the most common cause of acute pancreatitis in Trinidad.[22] Acute pancreatitis is the most common form of the disease, but edematous, hemorrhagic, and chronic relapsing pancreatitis may also occur.[91] Transient pancreatitis has also been reported from *Centruroides sculpturatus* envenomation in the United States and in 93% of children envenomed by *Leiurus quinquestriatus* in Israel.[39,191] Hyperamylasemia was found in 46% of patients envenomed by *T. discrepans* in Venezuela.[79] The systemic severity of the envenomation or amount of abdominal pain does not appear to correlate with the degree of elevation in the serum amylase level.[22,191] Scorpion venom is known to be a potent secretagogue, stimulating exocrine secretion of the stomach, salivary glands, and pancreas.[56,64,197] Enhanced release of proteolytic enzymes, accompanied by spasm of the sphincter of Oddi, is hypothesized to cause acute scorpionic pancreatitis.[56,91]

Other Gastrointestinal Effects

Nausea, vomiting, gastric distention, abdominal cramping, and occasional diarrhea are reported in victims with severe systemic symptoms.[68,110,132,146] Gastric distention associated with agitation and depressed level of consciousness place scorpion sting victims at increased risk for pulmonary aspiration of gastric contents. *T. serrulatus* venom increases the volume, acid output, and pepsin output of gastric juice in rats, probably mediated by release of acetylcholine and histamine. Serum gastrin levels are also elevated.[197] Pig studies with *Leiurus quinquestriatus* venom found that despite an increase in oxygen transport and consumption, oxygen utilization in the gastrointestinal tract was impaired.[185] Such impairment in oxygen utilization may occur in other tissues as well, contributing to metabolic acidosis in severe envenomations.

ENDOCRINE AND OTHER HUMORAL EFFECTS

Scorpion envenomation has long been known to cause autonomic storm with increased release of endogenous catecholamines, contributing to hypertension, tachycardia, and potentially fatal cardiopulmonary dysfunction. Envenomed patients with abnormal ECG tracings excrete elevated levels of free epinephrine, norepinephrine, and vanillylmandelic acid.[105] Elevated circulating catecholamine levels have also been reported.[13] Release of catecholamines may be caused by direct stimulation of postganglionic sympathetic neurons and the adrenal glands. Hypertension may also be caused by activation of the renin-angiotensin endocrine axis. Elevated levels of renin and aldosterone were found in victims stung by *Leiurus quinquestriatus*.[99]

Stings often induce hyperglycemia, possibly related to suppression of insulin secretion, in contrast to the enhanced secretion by the exocrine pancreas.[62,79,147] Murthy and Hase propose that this results in a syndrome of fuel-energy deficits related to inability to use existing metabolic substrates, exacerbating the cardiopulmonary insult.[147] Insulin therapy has been found to reverse ECG changes, reduce angiotensin levels and circulating free fatty acids in experimental animals, and reverse hemodynamic changes and pulmonary edema in children stung by scorpions.[147,148] *Hottentotta tamulus* venom also lowers thyroxine and triiodothyronine levels in experimental myocarditis.[149]

Kinins and other inflammatory mediators may play a role in the cardiovascular toxicity. *T. serrulatus* and *Centruroides sculpturatus* venoms potentiate the action of bradykinin by inhibiting angiotensin-converting enzyme.[136] Animal experiments show reversal, using aprotinin (a kallikrein-kinin inhibitor)[84,123] and icatibant (a bradykinin antagonist),[84] of venom-induced cardiovascular effects and augmentation with captopril, an angiotensin-converting enzyme inhibitor, of adverse effects.[20]

Serum interleukin-6 (IL-6) levels were greatly elevated in 8 of 10 Israeli children, gradually decreasing toward normal over 24 hours.[188] High levels of circulating IL-1, IL-3, IL-6, IL-10, and granulocyte-macrophage colony-stimulating factor have also been found in a severely envenomed Brazilian patient.[5] The IL-8 level appeared to correlate with envenomation severity caused by *Buthus occitanus* in Egypt.[144]

GENITOURINARY EFFECTS

Priapism is frequently reported among male patients with systemic envenomation. Priapism results from enhanced parasympathetic tone and is often associated with vomiting and profuse sweating.[23,27] The reported incidence of priapism ranges from 4% to 10%,[7,16,167] to as high as 78% to 96%.[110,189] In India, priapism, vomiting, and diaphoresis are considered premonitory diagnostic signs of severe *Hottentotta tamulus* envenomation. Priapism is reduced or absent within 6 hours of the sting even in severe cases, and the degree of priapism does not appear to correlate with the severity of envenomation.[26] In Tunisia, however, the incidence of priapism positively correlated with degree of severity.[130]

Urinary retention is found in 33% of victims with systemic envenomation in southern Africa.[41,42,146] This finding, however, is not consistent with increased cholinergic tone, which should produce increased urination, as seen in other series.[16] A dorsal nerve block with 1% lidocaine was successful in treating severe local pain from a *T. serrulatus* sting to the penis.[156]

HEMATOLOGIC EFFECTS

Scorpion stings are not generally noted to produce coagulopathies or other significant hematologic effects, although disseminated intravascular coagulation has been reported.[16,136] The occasional "defibrination syndrome" is seen more often in children, probably because of a higher relative venom dose, and can be experimentally reproduced in dogs. Platelet aggregation can be induced by catecholamines alone and may therefore be an indirect effect of scorpion venom. Increased osmotic fragility of red blood cells has been demonstrated in some experimental models.[136]

The only scorpion routinely implicated in dangerous hematologic effects is *Hemiscorpius lepturus,* which can cause severe hemolysis and consequent renal failure.[125,166,168,182] Case reports from Saudi Arabia associate severe *Nebo hierochonticus* stings with disseminated intravascular coagulation and intracranial hemorrhage.[16,17] Neither of these species is from the Buthidae family, which more characteristically causes cardiopulmonary and neurologic toxicities.

IMMUNOLOGIC EFFECTS

Scorpion toxins are antigenic and therefore capable of eliciting an immune response. Positive skin prick, intradermal skin tests, and radioallergosorbent assays have been found with the venom from *Centruroides vittatus* and *Androctonus australis hector* in previously stung patients.[69,134] Envenomation by *C. sculpturatus* has produced an anaphylactic reaction, with urticaria, wheezing, and facial angioedema but without systemic neurotoxic findings, in an otherwise healthy adult patient previously stung by a scorpion.[204] Fatalities from scorpion envenomation in the United States are extremely rare; however, a reported death in 2001

appears to have been caused by anaphylaxis to scorpion venom, rather than direct venom effect.[52]

Treatment with animal-derived antivenom puts the patient at risk for both immediate and delayed immunologic reactions. Because the treatment for hypersensitivity reactions includes epinephrine, and because many persons envenomed by cardiotoxic scorpions have elevated circulating catecholamines, such persons should be less likely to have anaphylactic reactions to antivenom. Brazilian patients stung by *T. serrulatus* were separated into groups with or without adrenergic manifestations, and both groups received antivenom.[14] The group with adrenergic toxicity developed significantly fewer (8% compared with 42.9%) signs and symptoms of early anaphylaxis.

DIFFERENTIAL DIAGNOSIS

Bites or stings from other arthropods should be considered in the differential diagnosis of scorpion envenomation. Pain at the site of *Centruroides sculpturatus* stings may be similar to latrodectism (widow spider bite; see Chapter 43). Patients with severe scorpion envenomation are often unable to lie still, whereas patients with latrodectism can maintain a position for short periods before moving again to seek a comfortable position. Widow spider envenomation may produce hypertension, tachycardia, sweating, and other signs of adrenergic excess, but it does not produce the abnormal eye movements, fasciculations, paresthesias, or positive tap test found with scorpion stings. Widow spider bites frequently produce a characteristic halo lesion at the site, whereas no lesion is usually visible after neurotoxic scorpion stings. Many other arthropods can produce a small puncture wound accompanied by local tissue inflammation; this may be difficult to differentiate clinically from a scorpion sting in the absence of cardiovascular or neurologic toxicity or without tentative visual identification of the arthropod involved.

Tachycardia, respiratory distress, excessive secretions, and occasional wheezing that occur from *C. sculpturatus* stings may be mistaken for asthma, airway obstruction with a foreign body, or poisoning with a cholinergic agent, such as an organophosphate insecticide. In the absence of the history of a scorpion sting, other disorders to be considered include CNS infection, tetanus, dystonic reaction, seizure, hysteria, and intoxication with an anticholinergic agent, sympathomimetic agent, phencyclidine, nicotine, or strychnine. Autonomic storm from a cardiotoxic scorpion sting may be confused with pheochromocytoma or a monoamine oxidase inhibitor–tyramine reaction. A victim of severe scorpion envenomation presenting late in the course may appear to have cardiac failure or sepsis.

Toxicity from illicit amphetamines is sometimes mistaken for envenomation by *C. sculpturatus*. Young children from endemic areas presenting with unusual neurologic symptoms (agitation, choreiform or repetitive motion of the trunk and extremities, abnormal eye movements) may be assumed to have been envenomed, even without the history of a scorpion sting.[150] Occasionally, caregivers are aware of this potential for misdiagnosis and claim their child was stung when they believe the child ingested methamphetamine. A series of 18 inadvertent methamphetamine poisonings among children in Arizona included 3 victims initially misdiagnosed with a scorpion sting and inappropriately treated with antivenom; one patient had an anaphylactic reaction.[127]

TREATMENT

The great majority of the medical literature regarding treatment of scorpion envenomation relates to evaluation and care rendered in a hospital setting, often within an ICU. This information, therefore, is often not directly applicable to the prehospital setting or to the provision of medical care in austere environments. For many scorpion species, stings cause only local pain and inflammation that will respond well to local care measures. On the other hand, there is little medical treatment that can be provided on-scene for the autonomic storm that can occur with envenomation by the world's dangerous scorpion species.

Ismail and colleagues summarized the current understanding of treating scorpion stings when noting,

> ***It is strange that despite the long experience with scorpion envenomation, most of the treatment protocols advocated are based on isolated clinical observations, are sometimes controversial, and not instituted on rigid or strictly controlled animal or clinical studies. … Even in serotherapy there are no quantitative studies regarding antivenom dosage, routes of administration, time-effectiveness relationship and titre of the antivenom used.***[123]

Although much controversy surrounds the proper treatment of scorpion envenomation, some consensus exists. Most victims, even those stung by potentially dangerous scorpions, demonstrate only local signs and symptoms and require only symptomatic outpatient treatment. It is prudent to observe such persons for several hours after the sting to ensure that progression to severe envenomation does not occur. Experience with *Centruroides sculpturatus* envenomation in Arizona shows that progression of envenomation grade occurs rapidly, with a mean time of 14 minutes and a median time of less than 1 minute.[137]

For localized pain, several clinicians have recommended local anesthesia with lidocaine, bupivacaine, or dehydroemetine by infiltration or nerve block, such as a digital block for fingers or toes.[33,41,42,116,156] In southern Africa, Bergman has reported successful treatment of poorly localized pain radiating up an extremity with an intracutaneous sterile water injection (ISWI), usually also with a local anesthetic infiltrated at the sting site.[41,42] ISWI is performed by injecting small amounts (about 0.1 mL) of sterile water intradermally into points of maximal pain, producing up to 10 wheals. Pain relief is said to occur within 1 to 5 minutes, but pain may return in 4 to 12 hours and can be persistent. ISWI therapy cannot be generally recommended, because it has not been tested in prospective or controlled trials or with scorpion stings elsewhere in the world.

Scorpion stings are traumatic puncture wounds, and victims should be given appropriate wound care and tetanus prophylaxis if indicated. The local trauma from neurotoxic scorpion stings, however, tends to be minimal. For instance, it is common to see no local soft tissue findings in patients with severe toxicity from *C. sculpturatus* stings.

Victims with significant systemic scorpion envenomations should receive supportive and symptomatic care in a monitored hospital setting.[81,87,101,105] Many require admission to an ICU, although treatment should begin in the emergency department or outlying facility if available. Airway control must be addressed and continuous cardiovascular and respiratory monitoring instituted. Fluid resuscitation may be indicated secondary to fluid losses from vomiting, sweating, and increased insensible losses from hyperthermia. Both hyperthermia and hypothermia have been reported from scorpion stings, and both appear to worsen toxicity.[122] Hyperthermia usually resolves with standard acetaminophen doses, and hypothermia resolves with warm blankets.

PHARMACOLOGIC THERAPY

Many drugs have been recommended for the treatment of scorpion envenomations, but few have been rigorously tested. Recommendations regarding the use of atropine vary. Many victims exhibit signs of excess cholinergic tone, such as bradycardia, vomiting, sweating, and hypersalivation. If venom induces prominent adrenergic effects, the rescuer should not administer atropine.[29,87,101] Parasympathetic venom effects are usually transient and not life threatening, although atropine may be indicated for severe bradycardia. Also, in subsequent phases with more prominent adrenergic toxicity, atropine could worsen tachycardia and hypertension. Atropine may be safe, however, for cholinergic effects from scorpion species that do not cause prominent cardiotoxicity. Published cases from southern Africa and Arizona suggest that atropine can reverse hypersalivation that interferes with airway control, which may obviate the need for intubation and decrease the risk for aspiration, although caution is still advised.[41,146,195] Scorpion envenomation in these areas is characterized by neuromuscular and dysautonomic effects but does not typically involve serious cardiopulmonary effects. Protocols for

the use of atropine and its optimal dosage have not been prospectively determined.

Treatment with corticosteroids has been regularly recommended and is still common in many countries, presumably due to the clinical similarity between many manifestations of severe scorpion envenomation and systemic allergic reactions. However, a prospective, randomized, and placebo-controlled human study of antiinflammatory corticosteroids showed no benefit.[7] In Tunisia, 600 consecutive patients received either 50 mg/kg of hydrocortisone hemisuccinate or a placebo. No differences between the two groups were found in clinical severity (baseline and 4 hours after treatment), death rates, need for artificial ventilation, or duration of hospitalization. Similarly, a retrospective case-control study 84 Tunisian adult ICU patients failed to show an improvement in outcome from steroids.[21] Glucocorticoids and antihistamines are not recommended unless administered as treatment for allergic manifestations (e.g., anaphylaxis to antivenom).[43,146]

Vasodilator therapy has received much attention. Because excessive adrenergic tone appears to cause the most significant morbidity, vasodilators should block or reverse severe cardiopulmonary effects from scorpion envenomation. Prazosin is a selective α_1-adrenergic blocker, which may lower blood pressure and help reverse other cardiopulmonary effects. Prazosin is also thought to reverse the inhibition of insulin secretion.[31,32] In India, an initial dose of 0.5 mg by mouth for adults and 0.25 mg for children is given to relieve hypertension and pulmonary edema. Repeat doses are given in 4 hours and then every 6 hours as needed for up to 24 hours. Sodium nitroprusside is used in cases of life-threatening pulmonary edema.[33] Nifedipine, 5 to 10 mg "sublingually" by puncturing and swallowing the gelatin capsule, has also been used in India, along with the initial dose of prazosin. When this protocol was compared with "conventional treatment" (with digoxin, furosemide, hydrocortisone, antihistamines, and atropine), the cohort treated with prazosin had significantly reduced morbidity and shortened recovery time.[32] In Israel, hypertension from scorpion stings unresponsive to analgesics and sedatives has been treated with IV hydralazine or sublingual nifedipine, which are believed to reverse hypertensive encephalopathy.[186] A potential benefit of vasodilators over antivenom is the rapidity of onset of therapeutic effect.[103] Captopril has also been used to treat hypertension, but theoretically this could worsen pulmonary edema.[20,33,118,126]

Insulin infusion has been used in India.[147,148] Because scorpion venoms inhibit insulin secretion, this treatment may help reverse the consequent metabolic derangements. A series of six patients treated with an insulin infusion (0.3 units of regular insulin per gram of glucose, at a rate of 0.1 g glucose per kilogram body weight per hour) showed improvement in pulmonary edema and hemodynamics, although furosemide and hydrocortisone appeared to offer little benefit.[147] Insulin therapy for scorpion envenomation is not standard in India and has not been reported from other locations.

Dobutamine infusions of 7 to 20 mcg/kg/min improved cardiac function in a series of seriously envenomed Tunisian patients.[83] A prospective, randomized trial from Turkey among patients with localized reactions but without systemic signs or symptoms showed that topical lidocaine was superior for pain control in comparison to IV acetaminophen or local application of ice.[9] Digoxin, β-adrenergic blockers, dantrolene, aminophylline, quinine, and aspirin have also been suggested as potential therapeutic adjuvants in scorpion envenomation, but these are not widely recommended.[33,108]

ANTIVENOM

Treatment recommendations diverge regarding antivenom. Most medical researchers believe that antivenom plays a crucial role in the treatment of seriously envenomed patients.[4,48,64,71,86,116,146] Proponents believe that (1) antivenom is the only specific therapy available against the primary physiologic insult and (2) it greatly improves outcome. Any previous disappointing experience with antivenom, they argue, probably results from inadequate dosing.[117,118] Researchers from Israel and India do not recommend antivenom.[27,101,189] Opponents believe that (1) morbidity and deaths are not caused by the venom but by autopharmacologic agent release, which should not be reversed by antivenom therapy, (2) pharmacokinetic data do not support a role for antivenom, (3) antivenom has not improved outcomes in Israeli studies, and (4) antivenom is often unavailable and may be prohibitively expensive for economically disadvantaged victims, so other options must be chosen. Treatment without antivenom consists of managing serious cardiopulmonary and neurologic effects with pharmacologic agents and supportive care. Even when antivenom is administered by its proponents, adjunctive therapies to treat cardiac failure, pulmonary edema, and other physiologic treatments are also used.

A major issue in the debate regarding the usefulness of antivenom relates to the pharmacokinetics of scorpion venom. Detectable circulating venom supports the use of antivenom to neutralize the toxins. *Tityus serrulatus* venom injected subcutaneously in rodents was rapidly distributed to various tissues, with peak serum levels in 30 to 60 minutes.[173,181] After 2 hours, the venom decreased rapidly, and it was no longer detectable after 8 hours. Therefore, IV serotherapy should be initiated as soon as possible, because it would become less effective when administered many hours after envenomation.[173]

Ismail and coworkers reported that scorpion venoms in animal experiments were rapidly absorbed and distributed to tissues, but had more prolonged elimination phases.[118,121] Scorpion venom has a half-life of 4.2 to 24 hours.[118] The clinicians concluded that although antivenom would theoretically be most efficacious if given immediately after envenomation, it is still indicated after a delay of several hours or more.[132,181] It is interesting to note, however, that Gueron and colleagues reviewed these data and concluded instead that serotherapy would be ineffective and recommended against it.[100,101] They suggested that the most severe cardiopulmonary effects would be present early and would not be reversed by antivenom given later. The clinical effects of scorpion envenomation are related to tissue concentrations of *Androctonus amoreuxi* venom in experimental animals, although the slower distribution of antivenom to tissues suggests that it may be less effective when given after a significant delay.[120] A series of 56 victims stung by *T. serrulatus* in Brazil correlated clinical severity to plasma venom concentrations.[70] This correlation between venom levels and clinical severity of envenomation has been seen in other studies.[79,92] IV antivenom lowers circulating levels of venom and presumably the clinical severity of envenomation; however, the effectiveness of antivenom on venom bound to other tissues has not been well defined. The role of serotherapy depends on the time to administration, becoming less effective with increasing delay.[128,141] Because scorpion venom acts indirectly through the release of autopharmacologic substances, treatment with specific blockers may be more effective than antivenom in persons with delayed presentation.[120]

In 1999, a large (825-patient), randomized, placebo-controlled Tunisian clinical trial of scorpion antivenom in humans found no significant benefit to giving antivenom in terms of progression to systemic illness.[5] However, the majority of patients in this study had mild envenomations, possibly obscuring an effect that could be seen only in more serious cases. One canine study showed that whereas simultaneous administration of antivenom and venom prevents clinical manifestations of envenomation, delayed administration of antivenom does not alter the clinical course.[6] A small series of pediatric cases from India published in 2003, after antivenom became available, is consistent with these findings. Four children with severe envenomations by *Hottentotta tamulus* who received scorpion antivenom within 1.5 hours of the sting were not observed to have any clinical improvement.[34] Another canine study found that the administration of antivenom 20 minutes after venom improves cardiac output, as does the administration of IV fluid; combination therapy worked better than either single treatment alone.[196] A treatment protocol using high doses of IV polyvalent antivenom (i.e., doses greater than the in vitro neutralizing dose) is used in Egypt and has reduced the mortality rate from 4.6% to 8% to less than 0.05%.[119]

With the recent availability of antivenom in India to treat red scorpion envenomation, investigators have reported success with

combined serotherapy and oral prazosin administration.[37,163,164] Oral prazosin is given on admission and then every 3 hours until symptoms abate (30 mcg/kg body weight; or 250 mcg for children and 500 mcg for adults) in addition to a single 30-mL dose of IV antivenom over 30 minutes (no dose adjustment for age).

The entire body of literature on scorpion antivenom appears to be a muddle, with many contradictory findings. This confusion may stem from differences between benchwork and clinical studies, differences in study design, venom and antivenom dosing, patient susceptibility, and many other factors. Scorpion-expert authors of a 2014 review article in the *New England Journal of Medicine* also recognize the heterogeneity of results and recommendations, but summarize the data as showing that antivenom administration is of some benefit.[113] Based on this author's own clinical experience with stings from *Centruroides* scorpions in the United States, the use of IV antivenom is favorable for severe scorpion envenomation.

Scorpion antivenom is generally administered intravenously. Indeed, some antivenom preparations have been approved only by their respective drug regulatory agencies for IV use. Some antivenoms (against scorpions and against other envenomations) have been administered by the intramuscular (IM) route. When compared with the IM route, administration of IV scorpion antivenom results in faster onset of action and shorter recovery times.[68] Given the small size of the patients most likely to suffer the highest-grade scorpion envenomations and the resultant neuromuscular hyperactivity, in some instances IV access may not be possible to obtain or maintain. Successful administration of scorpion antivenom in the United States by the IM and/or intraosseous routes has been reported in a few cases.[111]

A list of the major scorpion antivenoms manufactured worldwide can be found at
wikitoxin.toxicology.wikispaces.net/Scorpions.

TREATMENT IN AUSTERE ENVIRONMENTS

If travel within a scorpion-hyperendemic area is planned and evacuation to modern facilities will not be possible, consideration should be given to carrying oral prazosin in the medical kit. This treatment has been advocated in India for complications of severe scorpion envenomation (e.g., pulmonary edema) without rapid access to advanced medical care.[33,34,36] Recommended prazosin dosing is 250 mcg for children and 500 mcg for adults by mouth; it is repeated 4 hours later if needed, and then every 6 hours as long as needed (usually 24 hours).[33] More extensively prepared travelers might possibly carry antivenom against the area's dangerous scorpions, if it is available. However, out-of-hospital administration of biologic products, with its attendant risk for severe allergic reaction, should be performed only by trained medical personnel with access to appropriate resuscitation drugs and equipment. It is hard to imagine an expedition of such importance, preparation, and funding that would justify carrying scorpion antivenom, yet did not have access to urgent evacuation measures, such as by helicopter.

ANTIVENOM ADMINISTRATION RECOMMENDATIONS

Standard practices for administration of scorpion antivenom vary considerably around the world. Because antivenoms are biologic products, their use carries the risk for inducing both immediate and delayed allergic reactions (i.e., anaphylaxis and serum sickness, respectively). In general, therefore, antivenom is indicated for patients who are more seriously ill with systemic signs and symptoms, rather than for patients with local pain and paresthesias or other minor effects. Most scorpion antivenoms available worldwide are whole IgG products, which carry a higher risk for allergic reactions than do Fab fragment antivenoms.

Although in the United States the older goat-derived whole IgG antivenom is no longer available and the Fab fragment antivenom was only recently approved, considerable experience exists with administration of these products. The typical procedure previously used for administering whole IgG scorpion antivenom is shown in Box 44-3. This procedure can be considered

BOX 44-3 Previously Recommended Procedures for Administration of Goat-Derived Whole IgG *Centruroides* Scorpion Antivenom in the United States

1. Assess for contraindications—Any of the following relative contraindications (in decreasing order of importance) should suggest withholding antivenom in favor of symptomatic and supportive care only:
   a. Prior administration of antivenom derived from the same host animal species
   b. Current β-adrenergic blocker use
   c. History of asthma or atopy
   d. Current ACE inhibitor use
   e. History of allergy to the animal species from which the antivenom is derived, allergy to that animal's milk, or prior extensive exposure to the animal, especially its blood
2. Monitoring
   a. Continuous ECG monitoring
   b. Continuous pulse oximetry monitoring
   c. IV access obtained, preferably with two IV lines
3. Equipment and medications for treating anaphylaxis and respiratory arrest are made available. Medications are not given prophylactically, but are given only if an allergic reaction occurs:
   a. Epinephrine drip—Add 1 mg epinephrine to 250 mL of 5% dextrose in water (D_5W) or normal saline (NS) on a primed IV line with a pump
   b. IV methylprednisolone
   c. IV diphenhydramine
4. Antivenom Preparation
   a. If lyophilized, antivenom is reconstituted with as much sterile NS or D_5W as can fill the vial, with gentle rocking to avoid foaming
   b. Antivenom is then withdrawn from the vial and dissolved in 50 mL of crystalloid and placed on an IV pump
5. Skin Testing
   a. Up to 0.02 mL of a 1:10 dilution of reconstituted antivenom is injected intradermally with a 27- or 30-gauge needle, the site marked with a pen
   b. Patient is observed for at least 10 minutes for development of a wheal, rash, wheezing, or hemodynamic signs of anaphylaxis, any of which constitute a positive skin test, which contraindicates further antivenom therapy
   c. Any allergic reactions treated appropriately with the medications made available above
6. Antivenom Administration
   a. The antivenom is initially administered at a very slow rate (5 mL/hr), which is doubled every 2 to 3 minutes as long as the patient tolerates the infusion (i.e., develops no signs of anaphylaxis), up to 150 mL/hr
   b. Infusion of one vial by this method takes approximately 30 minutes, and most patients require only one vial of antivenom
   c. The patient is observed for at least 1 hour after the initial antivenom infusion is complete before proceeding with additional vials, because most symptoms resolve in this period. If the symptoms have resolved or regressed to a grade I or grade II envenomation and no complications (e.g., aspiration) are suspected, the patient is discharged
7. Discharge Instructions
   a. Because many patients treated with antivenom develop a delayed hypersensitivity reaction, the patient and caregivers are informed about signs and symptoms of serum sickness before discharge. An urticarial rash developing within a few days to weeks is the most common sign, although malaise, myalgias, and arthralgias also may occur; more serious problems are rare
   b. The patient may be discharged with prescriptions for antihistamines (hydroxyzine or diphenhydramine) and a tapering dose of corticosteroids to be started if serum sickness develops. Filling these prescriptions and initiating therapy immediately as prophylaxis against serum sickness are not recommended
   c. Patients treated with whole IgG antivenom should be warned that they are now likely to be allergic to serum products from the animal species used. Use of antivenom for subsequent envenomations is relatively contraindicated but can be undertaken with extreme caution if necessary

whenever giving animal-derived whole IgG antisera for scorpion envenomation. Since early 2010, a Fab fragment antivenom produced in Mexico has been frequently used in Arizona for serious *Centruroides* scorpion envenomation, initially only through an experimental protocol but now approved for wider use. Patients given Fab fragment antivenom are closely monitored with continuous electrocardiography and pulse oximetry in a setting where rapid treatment of acute allergic reaction is possible, usually in an emergency department or ICU. The product package insert recommends readiness with IV therapy with epinephrine, corticosteroids, and diphenhydramine should an allergic reaction occur, but preadministrative skin testing is not performed. Consultation with toxicologists experienced in treating *C. sculpturatus* envenomations can be obtained by calling the Banner Good Samaritan Poison and Drug Information Center in Phoenix at 602-253-3334 or the Arizona Poison and Drug Information Center in Tucson at 520-626-7899.

PREVENTION

Because on-scene treatment options for scorpion stings are quite limited, preventive measures are essential. The following guidelines are recommended when staying or traveling in scorpion-endemic areas

- Shake out your clothes and shoes before putting them on.
- Check your sleeping bag/blanket before going to sleep, especially if it is located on the ground.
- Consider clearing debris from the campsite, to decrease places where scorpions can hide.
- Be on higher alert for scorpions during the warmer months of the year, when stings are more common.

Many scorpion stings result from human practices that place persons at risk. Residences with small cracks and crevices offer many hiding places, increasing the risk for human-scorpion interactions. In several countries, playing or working outdoors with inadequate protective clothing, especially in the early evening during warm months, is associated with most scorpion stings. In scorpion-infested areas, clothing, shoes, packages, and camping gear should be shaken out and checked for scorpions. Footwear is recommended. Unnecessary ground cover and debris should be removed from around homes to reduce potential nesting places.

Certain insecticides, including organophosphates, pyrethrins, and several chlorinated hydrocarbons, are known to kill scorpions. Home spraying is often ineffective because the insecticide does not come in contact with the scorpion. Spraying insecticides around the home can work indirectly by killing other insects in the area and reducing the scorpions' food supply. A village-wide scorpion eradication program with pyrethroid insecticides in the state of Morelos, Mexico, reduced the incidence of scorpion stings by 17%.[171]

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CHAPTER 45

Protection from Blood-Feeding Arthropods

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Of all the hazards, large and small, that may befall those who work or recreate outdoors, perhaps the most vexatious come from the smallest perils—blood-feeding arthropods. Mosquitoes, flies, fleas, mites, midges, chiggers, and ticks all readily bite humans. The bites are, at best, a minor annoyance; at worst, arthropod bites transmit to humans multiple bacterial, viral, protozoan, parasitic, and rickettsial infections (Box 45-1). Vector-borne diseases account for 17% of all infectious diseases. Mosquito-transmitted diseases alone will be responsible for the deaths of 1 out of every 17 people currently alive.[161] This chapter reviews the arthropod species that bite humans, suggests ways to avoid them, and discusses various options for personal protection against these nefarious creatures.

MOSQUITOES (FAMILY CULICIDAE)

Mosquitoes are responsible for more arthropod bites than any other blood-feeding organism. They occur in all major terrestrial regions except Antarctica. These two-winged insects belong to the order Diptera, the flies. There are 170 species of mosquitoes in North America, and more than 3000 species worldwide. Anopheline, or malaria-transmitting, mosquitoes can be distinguished by their resting position on the skin; their bodies are characteristically raised high, as if they are standing on their heads. Most other species, in contrast, alight with their backs parallel to the skin surface (Figure 45-1A).

Mosquitoes are the vectors for more diseases in humans than any other blood-feeding arthropod. They transmit malaria to 200 million people each year, resulting in as many as 750,000 deaths per year.[41] In addition, about 30,000 international travelers visiting malaria-endemic countries contract the disease yearly.[70] Mosquitoes are the vectors for multiple arboviruses in humans, including several forms of encephalitis, epidemic polyarthritis, yellow fever, and dengue fever (see Chapter 39). Mosquitoes also transmit the larval form of the nematode that causes lymphatic filariasis.

Only female mosquitoes bite, requiring a blood-protein meal for egg production. Male mosquitoes feed solely on plant juices and flower nectar. Mosquitoes feed every 3 to 4 days, consuming up to their own weight in blood with each feeding. Certain species of mosquitoes prefer to feed at twilight or nighttime; others (such as the now-widespread Asian tiger mosquito, *Aedes albopictus*) bite mostly during the day. Some mosquito species are zoophilic (preferring to feed on animals, including birds, reptiles, various mammals, and amphibians), whereas others are anthropophilic (preferring human blood). Members of the genera *Anopheles, Culex,* and *Aedes* are the most common biters of humans. In some mosquitoes, seasonal switching of hosts

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BOX 45-1 Diseases Transmitted to Humans by Biting Arthropods

Mosquitoes
Zika virus
Eastern equine encephalitis*
Western equine encephalitis*
St Louis encephalitis*
La Crosse encephalitis*
Russian spring-summer encephalitis
West Nile virus infection*
Japanese encephalitis
Venezuelan equine encephalitis
Malaria
Yellow fever
Dengue fever
Lymphatic filariasis
Epidemic polyarthritis (Ross River virus)
Chikungunya fever
Rift Valley fever

Ticks
Anaplasmosis*
Lyme disease*
Borellia miyamotoi infection*
Bourbon virus infection*
Heartland virus infection*
Powassan disease*
364D rickettsiosis
Rocky Mountain spotted fever*
Colorado tick fever*
Relapsing fever*
Ehrlichiosis*
Babesiosis*
Tularemia*
Tick paralysis*
Rickettsialpox*
Southern tick–associated rash illness*
Tick typhus
Crimean-Congo hemorrhagic fever
Tick-borne encephalitis
Kyasanur Forest disease
Taiga encephalitis

Flies (Nonmosquito)
Tularemia*
Leishmaniasis*
African trypanosomiasis (sleeping sickness)
Onchocerciasis
Bartonellosis
Loiasis

Chigger Mites
Scrub typhus (tsutsugamushi fever)
Rickettsialpox*

Fleas
Plague*
Murine (endemic) typhus

Lice
Epidemic typhus
Relapsing fever

Kissing Bugs
American trypanosomiasis (Chagas' disease)

*May be found in the United States.

provides a mechanism for transmitting disease from animal to human.

Mosquitoes rely on visual, thermal, and olfactory stimuli to help them locate a blood meal.[14,16,28,34,52,54,77] For mosquitoes that feed during the daytime, host movement and dark-colored clothing may initiate orientation toward an individual. Visual stimuli appear to be important for in-flight orientation, particularly over long ranges, whereas olfactory stimuli become more important as a mosquito nears its host. Carbon dioxide and lactic acid are the best-studied attractants. Carbon dioxide serves as a long-range attractant, luring mosquitoes at distances of up to 36 m (118.1 feet).[52,53,153] At close range, skin warmth and moisture serve as attractants.[14,28] Volatile compounds, derived from sebum, eccrine and apocrine sweat, and/or the cutaneous microflora bacterial action on these secretions, may also act as chemoattractants.[61,83,103,144,170,148,171] Floral fragrances found in perfumes, lotions, soaps, and hair-care products can also lure mosquitoes.[44] One study has shown that alcohol ingestion increases the likelihood of being bitten by mosquitoes.[150] Mosquitoes are more attracted to individuals infected with transmittable malaria than to uninfected people or to treated individuals who are no longer infected.[86]

There can be significant variability in the attractiveness of different individuals to the same or different species of mosquitoes.[22,31,78] This is a point that travelers should keep in mind when visiting new areas. In some studies, men have been bitten more than women, and adults more than children.[78,113] Other studies have shown that repellents based on *N,N*-diethyl-3-methylbenzamide (DEET) (previously called *N,N*-diethyl-m-toluamide) may protect women more poorly than they do men.[56] Heavyset people are more likely to attract mosquitoes, perhaps due to their greater relative heat or carbon dioxide output.[128] Of note is that some studies have failed to confirm these findings.[22]

Mosquito bites commonly produce small local wheal reactions and associated itching. More dramatic reactions, including generalized urticaria, angioedema, and anaphylaxis, have been reported in highly sensitive individuals. The rare skeeter syndrome has been documented in five young children who developed dramatic localized redness, swelling, warmth, and induration within hours of a mosquito bite. This entity mimics cellulitis but resolves spontaneously and is associated with significantly elevated serum levels of IgE and IgG to mosquito salivary gland antigens.[152] Antihistamines may be useful when taken prophylactically to reduce the intensity of mosquito bite reactions. Compared with placebo, levocetirizine was shown to reduce the size of the 24-hour bite papules by 71% and the accompanying pruritus by 56%.[72]

During the day, many mosquito species tend to rest in cool, dark areas, such as on dense vegetation, or in hollow tree stumps, animal burrows, and caves. To complete their life cycle, mosquitoes lay eggs in standing water, which may be found in tree holes, woodland pools, marshes, drainage ditches, or puddles. To minimize the chances of being bitten by mosquitoes, campsites and other shelters should ideally be situated as far away from these sites as possible.

BLACKFLIES (FAMILY SIMULIIDAE)

At 2 to 5 mm (0.1 to 0.2 inch) in length, blackflies[19,35,55,76,104] (see Figure 45-1B) are smaller than mosquitoes. They have short antennae, stout humpbacked bodies, and broad wings. Blackflies are found globally wherever there are fast-running, clear rivers or streams, which they require for larval development. In temperate regions, adults are most prevalent in late spring and early summer and are most likely encountered near larval habitats, where they are difficult to avoid. However, unlike most mosquitoes, blackflies tend to bite during the daytime. They primarily use visual cues to locate a host. Dark moving objects are particularly attractive, but carbon dioxide and body warmth also serve as attractants. Only the female blackflies bite, taking up to 5 minutes to feed. Blackflies may be present at high densities, inflicting numerous bites on their victims.

Blackflies are particularly attracted to the eyes, nostrils, and ears of their hosts. They often crawl under clothing or into the hair to feed. The insect's mouthparts tear the skin surface, producing a pool of blood from which the fly feeds. Blood loss from the bite site often continues after the blackfly has departed. The resulting intensely pruritic, painful, and edematous papules are typically slow to heal. Rare systemic reactions, including fever, urticaria, anaphylaxis, and even death, have been reported following blackfly bites. Although these flies are not known to transmit disease to humans in North America, in the tropics, blackflies are vectors of the parasite *Onchocerca volvulus,* which causes the disease known as river blindness.

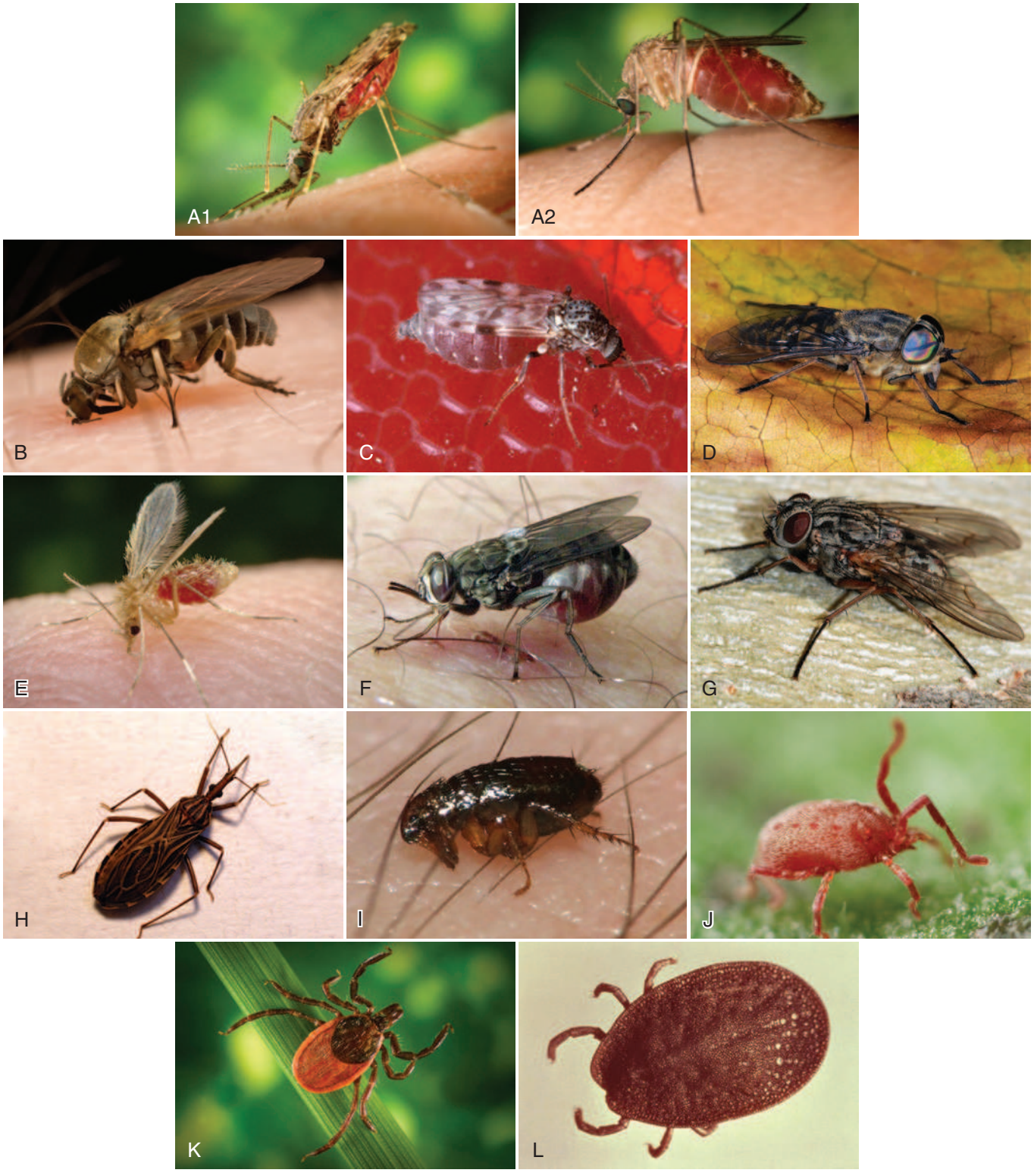

FIGURE 45-1 Biting arthropods. **A1**, *Anopheles* mosquito. **A2,** *Culex* mosquito. **B,** Blackfly. **C,** Biting midge. **D,** Tabanid fly. **E,** Phlebotamine sand fly. **F,** Tsetse fly. **G,** Stable fly. **H,** Chagas bug. **I,** Flea. **J,** Chigger mite. **K,** Hard tick. **L,** Soft tick. *(**A1, A2, D, E, G** from Wikimedia Commons; **B** from Richard Parker; **C** from US Department of Agriculture; **F** courtesy David Bygott; **H** from Wikipedia; **I** courtesy Rui Andrade; **J** courtesy Anthony Gould; **K** from Centers for Disease Control and Prevention; **L** from University of South Carolina School of Medicine.)*

BITING MIDGES (FAMILY CERATOPOGONIDAE)

Also known as no-see-ums, sand gnats, sand fleas, and sand flies, biting midges[19,35,55,104] are small, slender flies (<2 mm [0.1 inch] body length) with narrow wings (see Figure 45-1C). Their small size makes them difficult to see, and they can pass readily through common window screens. Biting midges occur from low to high latitudes worldwide. They breed most commonly in salt marshes, but larvae also develop in moist organic matter associated with freshwater wetlands and irrigated pastures. Despite their inconspicuous size, female midges are aggressive biters, frequently attacking in swarms and inflicting multiple painful and pruritic bites within minutes. Midges often crawl into the hair before biting. Depending on the species, midges may bite during the day or at nighttime. Their activity is greatest during calm weather, declining as wind speed increases. They may be avoided by moving to open areas with greater airflow or into shelters with no-see-um netting. Biting midges are not known to transmit diseases to humans in temperate regions, but they are vectors for filarial and microbial parasites in tropical regions.

TABANIDS (FAMILY TABANIDAE)

The family Tabanidae (see Figure 45-1D) includes horseflies, deerflies, greenheads, and yellow flies.[19,35,55,76,104] These insects are relatively large (10 to 20 mm [0.4 to 0.8 inch]) robust fliers, with numerous species worldwide. Tabanids breed in aquatic or semiaquatic environments, with a life cycle of more than 1 year. They are able to fly for miles and rely primarily on vision to locate a host by movement. Dark-colored clothing may increase the likelihood of being bitten. These flies are most active on warm, overcast days. Only the females bite, using scissor-like mouthparts to create within the skin a bleeding slash, which is slow to heal. Despite their size, these flies usually bite painlessly, but the resulting reaction can include intense itching, secondary infection, and, rarely, systemic reactions, such as urticaria or anaphylaxis. Because the adult fly usually has a life span of only about 1 month, and only one generation emerges per year, the potential season for being bitten is relatively short in higher latitudes and altitudes. In the United States, deerflies have been shown to be capable of transmitting tularemia to humans; in Africa, deerflies may be vectors of the filarial parasitic worm *Loa loa*.

SAND FLIES (FAMILY PSYCHODIDAE)

Sand flies[19,35,39,55,76,104] are tiny (2 to 3 mm [0.1 inch]), hairy, and long-legged flies, with multisegmented antennae and a characteristic V-shape to the wings when at rest (see Figure 45-1E). Only female sand flies are blood feeders, feeding mostly during calm, windless nights and resting during the day in animal burrows, tree holes, or caves, which should be avoided. Larvae develop in moist organic matter within such habitats. Most sand fly bites occur on the face and neck, but all exposed skin may be attacked.

In tropical and subtropical climates, sand flies have been shown to be vectors of multiple cutaneous, mucocutaneous, and systemic diseases, including bartonellosis and three forms of leishmaniasis. Visceral leishmaniasis is endemic in the tropical and subtropical regions of Central and South America, Africa, Asia, the Mediterranean, and Southern Europe. The only sand fly–transmitted disease in the United States has been cutaneous leishmaniasis, reported in Texas and Oklahoma.

TSETSE FLIES (FAMILY GLOSSINIDAE)

Tsetse flies[19,35,55,76,104] are found only in tropical Africa. They are 7 to 14 mm (0.3 to 0.6 inch) long, and yellowish-brown, with wings that fold over their backs, giving them the appearance of honeybees at rest (see Figure 45-1F). Both sexes bite, feeding in daytime on a wide variety of mammals, including humans. Light-colored, thickly-woven, loose-fitting clothing may deter biting. Tsetse flies seem to rely primarily on vision and movement to identify their hosts. Their bites are painful and may cause petechiae or pruritic wheals. Tsetse flies are vectors of African trypanosomiasis (sleeping sickness).

STABLE FLIES (FAMILY MUSCIDAE)

Stable flies[55,76] resemble common houseflies, and are most often encountered in coastal areas. Unlike a housefly, which rests with its body parallel to the surface, a stable fly rests with its head held higher than its posterior (see Figure 45-1G). Both male and female stable flies are vicious daytime biters, requiring a blood meal every 48 hours in order to survive. If disturbed, they will attempt to feed multiple times, preferring to bite the lower extremities. Horses and cattle are the preferred hosts, but hungry stable flies readily bite humans. These flies have knife-like mouthparts that they use to puncture flesh before feeding on the blood. Stable flies breed in decaying vegetation (e.g., wet hay bales, beach seaweed) and herbivore manure and are frequently found congregated on sunny walls. Moving away from these breeding habitats will reduce the likelihood of being bitten. Stable fly bites are generally self-limited. They are not known to transmit disease to humans.

KISSING BUGS (FAMILY REDUVIIDAE)

Kissing or Chagas bugs[19,35,40,55,76,104] (triatomine or assassin bugs) are large (10 to 30 mm [0.4 to 1.2 inches] adult length) insects with cone-shaped heads, overlapping wings, and an alternating pattern of dull orange and dark brown stripes on the lateral abdomen (see Figure 45-1H). Kissing bugs get their name from a tendency to bite around the human mouth, but they also bite other parts of the body. Both male and female kissing bugs bite, requiring a blood meal in order to mature through each of five nymphal growth stages. They are nocturnal feeders, attracted to their hosts by warmth, carbon dioxide, and odor. During the day, they rest in trees or indoors in crevices of house walls and ceilings. Kissing bug bites are initially painless, but frequent exposure to the bites can produce erythema, edema, and pruritus at the bite sites. Kissing bugs are the vectors for *Trypanosoma cruzi,* the causative agent of Chagas' disease, which has been reported in Central and South America, as well as in the southwestern United States. Chagas' disease symptoms are more severe with long-term repeated inoculations and are also more harmful in South America than farther north. Kissing bugs often feed on rodents that may live within thatch roofing material. Avoiding sleeping under thatch roofing in Chagas-endemic areas may reduce the probability of infection.

FLEAS (FAMILY PULICIDAE)

Adult fleas[19,35,55,76,104] are small (2 to 6 mm [0.1 to 0.2 inch]), wingless insects with powerful legs that enable adults to jump distances of up to 30 cm (11.9 inches) (see Figure 45-1I). Hungry adult fleas of both sexes feed on humans and other warm-blooded mammals and birds. Different flea species are associated with specific hosts, and they may be especially abundant around rodent and bird nests, which serve as both adult and larval habitats and should be avoided. Fleas usually move actively on the host, probing and biting several times, resulting in grouped lesions of pruritic papules. Fleas are capable of transmitting sylvatic plague and murine typhus.

CHIGGER MITES (FAMILY TROMBICULIDAE)

Trombiculid mites[19,35,55,76,104] (see Figure 45-1J) may be found worldwide. Commonly known as chiggers, redbugs, or harvest mites, these reddish-yellow insects are readily encountered in damp, grassy, and wooded areas, especially along the margins of forests, where they may number in the thousands. Only the tiny (< 0.2 mm [0.1 inch]) larval stages are parasitic, feeding on mammals, birds, reptiles, and amphibians. Chiggers are most active in the summer and early autumn. They usually infest humans by crawling up the shoes and legs, preferring to attach

to skin at areas where the clothing fits tightly, such as at the tops of socks or around the elastic edges of underwear. Chiggers do not burrow into the skin or actively suck blood. Rather, they pierce skin with their mouthparts and secrete a proteolytic salivary fluid that dissolves host tissue, which they in turn suck up. If undisturbed, chiggers may feed for several days before dropping off. In humans, this rarely occurs, because the larvae usually cause enough irritation that they are dislodged by scratching. The host response to chigger bites is brisk, often leading to intensely pruritic, bright-red 1- to 2-cm (0.4- to 0.8-inch) nodules.

Chiggers are especially abundant in warm, moist temperate climates (e.g., the southeastern United States) and tropical areas of high mammal density, including livestock pastures and natural parks and reserves, where moist grassy or understory areas can be found. These areas may seem like attractive camping areas but should be avoided. In Asia, chiggers may serve as vectors of scrub typhus. Rickettsialpox is also transmitted by a mite bite.

TICKS (FAMILIES IXODIDAE AND ARGASIDAE)

(See Chapter 42.)

Ticks,[19,35,55,76,104,156] like mites, are arachnids rather than insects. There are hard ticks (family Ixodidae) and soft ticks (family Argasidae) (see Figure 45-1K,L). Hard ticks are so named because of the presence of a sclerotized plate, or scutum, that covers part of the body. Both types of ticks may be found worldwide, but hard ticks are more commonly encountered in North America. Hard ticks are usually found in weedy or shrubby areas, along trails, and at forest boundaries, where mammalian hosts, such as deer, are plentiful. Soft ticks are more resistant to desiccation than are hard ticks. Soft ticks thrive in hot and dry climates and are commonly found in animal burrows or caves.

After hatching, both genders of ticks pass through three developmental stages—larval, nymph, and adult—all of which bloodfeed. Ticks are unable to fly or jump. Soft ticks are nocturnal and feed rapidly, in just a few minutes. Hard ticks most commonly "quest" for hosts during the day, often climbing vegetation and waiting still for hours or days, forelegs outstretched, until they detect the vibration or carbon dioxide plume of a passing host. When they encounter fur or skin, they climb onto the host and then crawl in search of an appropriate location on which to attach and feed. The attachment bite is usually painless. Hard ticks may remain and feed on a single host for days.

People in suspected tick habitats should check clothing frequently for the presence of ticks. If multiple ticks are seen on clothing, they are most easily removed by permanently trapping them on a piece of cellophane duct tape or by rolling a sticky tape–type of lint remover across them; hundreds of small ticks can be easily removed by this method. Tape can be stuck onto the inner thigh area of pants for storage between episodes of tick removal. Laundering infested garments cannot be relied on to kill nymphs, unless the clothing is subjected to the hot cycle of the dryer.[20]

Attached ticks are more difficult to remove. Tick mouthparts are barbed, and some species of tick also secrete a cement that firmly anchors the tick into the skin. Erythema, pruritus, and edema are commonly seen at the site of a tick bite. Improper partial removal of the mouthparts may initiate a long-lasting foreign body reaction, leading to secondarily infected lesions that are slow to heal, or granuloma formation that may persist for months. (For a discussion of the best method for tick removal, see Chapter 42.)

After the tick is removed, the bite site should be cleansed with soap and water, or an antiseptic, and hands should be washed. It may be prudent to save the tick, in case later identification becomes necessary. Laboratory studies of *Borrelia burgdorferi* (Lyme disease)–infected ticks show that duration of attachment is directly correlated with the risk for transmission of the spirochete.[9,123,124,126,127,155,156] Prompt removal of attached ticks will greatly reduce the likelihood of disease transmission. Although earlier published studies stated the risk of infection by Lyme borreliosis was minimal if the tick was removed within 24 to 48 hours,[125] recent studies suggest that infection can never be excluded based on a short duration of attachment.[29]

In the United States, soft ticks of the single genus *Ornithodoros* are capable of transmitting to humans the *Borrelia* spirochete that causes relapsing fever. Three genera of hard ticks transmit disease to man: *Ixodes* (which are vectors of Lyme disease, babesiosis, tick paralysis, and Russian spring-summer encephalitis), *Dermacentor* (vectors of tularemia, Rocky Mountain spotted fever, ehrlichiosis, Colorado tick fever, and tick paralysis), and *Amblyomma* (vectors of tularemia, ehrlichiosis, and tick paralysis).[107,156] Larval, nymph, and adult ticks may all transmit disease during feeding. Transovarial transmission also enables female ticks to directly infect their offspring.

PERSONAL PROTECTION

Personal protection against bites may be achieved in three ways: avoiding infested habitats, using protective clothing and/or shelters, and applying insect repellents.

HABITAT AVOIDANCE

As discussed in the sections above, awareness of biting arthropods' breeding and resting places can help reduce exposure and the chance of being bitten. Mosquitoes and other nocturnal bloodsuckers are particularly active at dusk, making this a good time to be indoors. To avoid the usual resting places of biting arthropods, campsites should ideally be situated in areas that are high, dry, and open, devoid of rodent burrows and nests, and as free as possible from vegetation. Areas with standing or stagnant water should be avoided, because these are ideal breeding grounds for mosquitoes. Attempts should be made to avoid unnecessary use of lights, which attract multiple insects.

PHYSICAL PROTECTION

Physical barriers can be extremely effective in preventing insect bites, by blocking arthropods' access to the skin. Long-sleeved shirts, socks, long pants, and a hat will protect all exposed skin except that covering the face, neck, and hands. Tucking pants into the socks or boots makes it much more difficult for ticks or chigger mites to gain access to the skin. Rubber boots are commonly worn, particularly in tropical areas, to reduce chigger and tick contact while walking and hiking. Light-colored clothing is preferable, because it makes it easier to spot ticks and is less attractive to mosquitoes and biting flies. Ticks find it more difficult to cling to smooth, closely woven fabrics (e.g., nylon).[147] Loose-fitting clothing, made out of tightly woven fabric, with a tucked-in T-shirt undergarment is particularly effective at reducing bites on the upper body. A light-colored, full-brimmed hat will protect the head and neck. Deerflies tend to land on the hat instead of the head; blackflies and biting midges are less likely to crawl to the shaded skin beneath a hat brim.

Mesh overgarments, or garments made of tightly woven material, are available to protect against insect bites. Head nets, hooded jackets, pants, and mittens are available from a number of manufacturers, in a wide range of sizes and styles (Box 45-2). Mesh garments are usually made of either polyester or nylon and, depending on the manufacturer, are available in either white or dark colors. With a mesh size of less than 0.3 mm (0.01 inch), many of these garments are woven tightly enough to exclude even biting midges and immature ticks. As with any clothing, bending or crouching may still pull the garments close enough to the skin surface to enable insects to bite through. Shannon Outdoors addresses this potential problem with a double-layered mesh that is designed to prevent mosquito penetration. Similarly, Outdoor Research manufactures head nets with a lightweight spring-steel hoop positioned to prevent the netting from collapsing against the face. Although mesh garments are effective barriers against insects, some people may find them uncomfortable during vigorous activities or in hot weather.

Lightweight insect nets and mesh shelters are available to protect travelers sleeping indoors or in the wilderness (Figure 45-2). Effectiveness of insect nets or shelters may be enhanced

BOX 45-2 Manufacturers of Protective Clothing, Protective Shelters, and Insect Nets

Protective Clothing (Includes Hooded Jackets, Pants, Head Nets, Ankle Guards, Gaiters, and Mittens)

Bug Baffler, Inc.
P.O. Box 444
Goffstown, New Hampshire 03045
800-662-8411
bugbaffler.com

The Original Bug Shirt Company
P.O. Box 127
Trout Creek, Ontario, Canada
800-998-9096
bugshirt.com

Outdoor Research
2203 1st Avenue South
Seattle, Washington 98134-1424
206-971-1496
outdoorresearch.com

Shannon Outdoors' Bug Tamer
P.O. Box 444
Louisville, Georgia 30434
800-852-8058
shannonoutdoors.com/bugtamer

Protective Shelters and Insect Nets

Long Road Travel Supplies
111 Avenida Drive
Berkeley, California 94708
800-359-6040
longroad.com

Travel Medicine, Inc.
369 Pleasant Street
Northampton, Massachusetts 01060
800-872-8633
travmed.com

Wisconsin Pharmacal Company
1 Repel Road
Jackson, Wisconsin 53037
800-558-6614
atwater-carey.com

by treating them with a permethrin-based contact insecticide (discussed below), which can provide weeks of efficacy following a single application.

REPELLENTS

For many people, applying a topical insect repellent may be the most effective and easiest way to prevent arthropod bites. The quest to develop the "perfect" insect repellent has been an ongoing scientific goal for years and has yet to be achieved. The ideal agent would repel multiple species of biting arthropods, remain effective for at least 8 hours, cause no irritation to skin or mucous membranes, possess no systemic toxicity, be resistant to abrasion and washing off, and be greaseless and odorless. No presently available insect repellent meets all of these criteria. Efforts to find such a compound have been hampered by the multiplicity of variables that affect the inherent repellency of any chemical. Repellents do not all share a single mode of action, and different species of insects may react differently to the same repellent.[22,99]

FIGURE 45-2 **A** to **C,** Protective shelters. **D,** Bed net. (**A, C,** *and* **D** *Courtesy Wisconsin Pharmacal Co.* **B** *Courtesy Long Road Travel Supplies.)*

Many chemicals that are effective repellents evaporate from or are absorbed into the skin too quickly to be of great usefulness. To be effective as an insect repellent, a chemical must be volatile enough to maintain an effective repellent vapor concentration at the skin surface but not evaporate so rapidly that it quickly loses its effectiveness. Multiple factors that play a role in effectiveness include concentration, frequency and uniformity of application, the user's activity level and overall attractiveness to blood-sucking arthropods, interaction between the individual user and repellent formulation, and the number and species of organisms trying to bite. The effectiveness of any repellent is reduced by abrasion from clothing; evaporation from and absorption from the skin surface; being washed off by sweat, rain, or water; physical activity; and a windy environment.[50,78,85,101,102,133,137] Each 10° C (18° F) increase in ambient temperature can lead to as much as 50% reduction in protection time.[85] Recent formulation developments improve the duration of effectiveness and the cosmetic properties of repellent active ingredients, such that a well-formulated mediocre active ingredient may outperform a poorly formulated stronger active ingredient. Insect repellents do not "cloak" the user in a chemical veil of protection; any untreated exposed skin can be readily bitten.[102] Individuals not wearing insect repellent may be bitten with increased frequency when standing next to someone who is wearing insect repellent.[111]

Chemical Repellents

DEET. DEET has been the gold standard of insect repellents for many decades. Only in the past 10 years have other repellents come to market that show similar broad-spectrum efficacy (discussed later). DEET has been registered for use by the general public since 1957. It is effective against many species of crawling and flying insects, including mosquitoes, biting flies, midges, chiggers, fleas, and ticks. The U.S. Environmental Protection Agency (EPA) estimates that about 30% of the U.S. population uses a DEET-based product every year; worldwide use exceeds 200 million people annually.[164,165] Decades of empirical testing of more than 20,000 other compounds has not yet led to the release of a clearly superior repellent.[33,68,81,82,129,138] The mechanism of action of DEET is only partially understood. One recent study demonstrated that DEET blocks a specific olfactory sensory neuron in mosquitoes, effectively masking odors like lactic acid that would normally attract the mosquito to a host.[36] In contrast, other studies have shown that DEET may stimulate individual olfactory neurons in mosquitoes, in a dose-dependent manner, inducing avoidance behaviors.[160] This information is encouraging further research to identify other molecules that could also stimulate these receptors, which could lead to development of new categories of safe repellents.[71,160]

DEET may be applied directly to skin, clothing, mesh insect nets or shelters, window screens, tents, or sleeping bags. Care should be taken to avoid inadvertent contact with plastics (such as watch crystals, glasses frames or lenses, other optics, equipment, and fishing line), rayon, nylon, vinyl, spandex, leather, or painted and varnished surfaces, because DEET may damage these. DEET does not damage natural fibers like wool and cotton.

In the United States, DEET is sold in concentrations from 5% to 100% in various formulations, including solutions, sprays, and impregnated wipes (Table 45-1). As a general rule, higher concentrations of DEET provide longer-lasting protection. Duration of efficacy of DEET increases only slowly above 35% concentration, and the longest-lasting (extended duration) formulations all use concentrations no higher than 35%. Higher-concentration and extended-duration DEET formulations are probably best reserved for circumstances in which the wearer will be in an environment with a very high density of insects (e.g., tundra in early summer, or salt marsh), where there is a high risk for disease transmission from insect bites, or under circumstances where there may be rapid loss of repellent from the skin surface, such as under conditions of high temperature and humidity, or rain. Under these circumstances, reapplication of the repellent will likely be necessary to maintain its effectiveness.

For most uses, however, there is no need to use the highest concentrations of DEET. Most manufacturers, responding to consumer demand, offer a large variety of low-concentration DEET products. Persons averse to applying DEET directly to their skin may get long-lasting repellency by applying DEET only to clothing that is not nylon, but they must keep in mind that exposed areas of skin will remain vulnerable to bites. DEET-treated garments, stored in a plastic bag between wearings, maintain their repellency for several weeks.[31]

Sequential application of a DEET-based repellent and a sunscreen can reduce efficacy of the sunscreen. In a study of 14 patients who applied a 33% DEET repellent, followed by a sun protection factor (SPF) 15 sunscreen, the sunscreen's SPF was decreased by a mean of 33%.[109] One study showed that efficacy of a polymer-based DEET repellent was not decreased by subsequent application of sunscreen 5 minutes later.[115] Another study, however, showed that reapplication of sunscreen 2 hours after DEET repellent was applied significantly decreased the protection time of the DEET repellent.[173] One study showed that DEET and the sunscreen oxybenzone act synergistically to enhance percutaneous absorption of the other chemical.[74] Another study, however, showed that increased dermal absorption of DEET only occurred if oxybenzone was applied over DEET on the skin; application of oxybenzone first, followed by DEET, did not enhance percutaneous absorption of DEET.[179] Combination sunscreen-DEET products are available and will deliver the SPF as stated on the label. However, these products are generally not the best choice, because it is rare that the needs for reapplication of sunscreen and repellent are exactly the same. For these reasons, in 2000 Health Canada the Canadian government decided to discontinue approval of combination sunscreen and insect repellent products, pending further safety data. Likewise, the EPA also issued a request for information regarding proper regulation of combination products, given the conflicting issues regarding proper application frequency.[166] A final ruling on this issue is due in March 2015. 3M Corporation and Sawyer Products currently manufacture extended-release formulations of DEET that make it possible to deliver long-lasting protection without relying on high concentrations of DEET. 3M's product, Ultrathon, originally developed for the U.S. military, is available to the general public. This acrylate polymer 35% DEET formulation, when tested under multiple different environmental/climatic field conditions, was as effective as 75% DEET in ethanol, providing protection of more than 95% against mosquito bites for up to 12 hours.[2,59,108,142,143,145] Sawyer Products' controlled-release 20% DEET lotion traps the chemical in a protein particle that slowly releases it to the skin surface, providing repellency equivalent to a standard 50% DEET preparation, lasting about 5 hours.[42] Sixty percent less of this encapsulated DEET is absorbed when compared with a 20% ethanol-based preparation of DEET.[43] In vitro experiments confirm that microencapsulation of DEET can reduce its cutaneous absorption.[75] Sawyer Products also markets a controlled-release 30% DEET lotion in which the chemical is slowly released from a lipid sphere (liposome). This nongreasy formulation has little odor and can provide more than 10 hours of protection. Liposomal preparations of DEET can help to retain potency of repellent on the skin surface, while minimizing percutaneous absorption.[134]

Given its use by millions of people worldwide for 50 years, DEET continues to show a remarkable safety profile. In 1980, as part of the EPA registration standard for DEET,[165] more than 30 additional animal studies were conducted to assess acute, chronic, and subchronic toxicities; mutagenicity; oncogenicity; and developmental, reproductive, and neurologic toxicities. The results of these studies neither led to any product changes to comply with current EPA safety standards nor indicated any new toxicities under normal usage. The EPA's reregistration eligibility decision,[164] released in 1998, confirmed that the agency believes that "normal use of DEET does not present a health concern to the general U.S. population."

Case reports of potential DEET toxicity have been extensively reviewed.[7,46,119,158,169] Fewer than 50 cases of significant toxicity from DEET exposure have been documented in the medical literature over the last four decades; more than three-quarters of these resolved without sequelae. Many of these cases involved long-term, excessive, or inappropriate use of DEET repellents; the details of exposure were frequently poorly documented,

TABLE 45-1 Chemical Insect Repellents

Manufacturer	Product Name	Forms	Chemical
Sawyer Products, Safety Harbor, Florida, 800-940-4664	Sawyer Controlled Release	Lotion	20% DEET
	Sawyer Ultra 30 Insect Repellent	Lotion	30% DEET
		Aerosol spray	30% DEET
	Sawyer Maxi-DEET	Pump spray	100% DEET
S.C. Johnson, Racine, Wisconsin, 800-558-5566	OFF! Family Care Insect Repellent (Tropical Fresh)	Pump Spray	5% DEET
	OFF! Family Care Unscented	Pump spray	7% DEET
	OFF! Family Care	Aerosol spray	15% DEET
	OFF! Active	Aerosol spray	15% DEET
	OFF! Deep Woods	Aerosol, pump spray, towelettes	25% DEET
	OFF! Deep Woods Sportsmen	Pump spray	25% DEET
	OFF! Deep Woods Sportsmen	Aerosol spray	30% DEET
	OFF! Deep Woods Sportsmen	Pump spray	98% DEET
Tender Corporation, Littleton, New Hampshire, 800-258-4696	Ben's Tick and Insect Repellent	Aerosol, pump spray, wipes	30% DEET
	Ben's 100 Tick and Insect Repellent	Pump spray	100% DEET
Spectrum Brands, Alpharetta, Georgia, 800-336-1372	Cutter All Family Insect Repellent	Aerosol, pump spray	7% DEET
	Cutter Skinsations Insect Repellent	Aerosol, pump spray	7% DEET
	Cutter Dry	Aerosol spray	10% DEET
	Cutter Unscented	Aerosol spray	10% DEET
	Repel Family Dry	Aerosol, pump spray	10% DEET
	Cutter Sport	Aerosol	15% DEET
	Repel Sportsmen Formula	Aerosol, stick	25% DEET
	Repel Hunter's Formula with Earth Scent	Aerosol spray	25% DEET
	Cutter Backwoods	Aerosol, pump spray	25% DEET
	Repel Sportsmen Max	Pump spray, aerosol, lotion	40% DEET
	Repel 100 Insect Repellent	Pump spray	100% DEET
Coleman Company, Jackson, Wisconsin, 800-558-6614	Coleman Insect Repellent	Aerosol spray	25% DEET
	Coleman Insect Repellent	Aerosol spray	40% DEET
	Coleman Insect Repellent	Pump Spray	100% DEET
3M, St Paul, Minnesota, 888-364-3577	Ultrathon	Pump spray	19% DEET
	Ultrathon	Aerosol	25% DEET
	Ultrathon	Lotion	35% DEET
S.C. Johnson Racine, Wisconsin, 800-558-5566	OFF! Family Care Insect Repellent II Clean Feel	Spray pump	Picaridin 5%
Avon Products, Inc., New York, 800-367-2866	Skin So Soft Bug Guard Plus Picaridin	Aerosol spray, pump spray, towelettes	Picaridin 10%
Spectrum Brands, Alpharetta, Georgia, 800-336-1372	Repel Sportsman Gear Smart Insect Repellent	Spray pump, wipes	Picaridin 15%
	Repel Tick Defense	Aerosol spray	Picaridin 15%
Tender Corporation, Littleton, New Hampshire, 800-258-4696	Natrapel 12-Hour	Pump spray, aerosol spray, wipes	Picaridin 20%

making causal relationships difficult to establish. These cases have not shown correlation between concentration of the DEET product used and risk for toxicity.

Reports of DEET toxicity that raise the greatest concern involve 18 cases of encephalopathy, 14 in children under age 8 years.[17,38,46,51,62,65,66,89,97,117,118,181] Three of these children died, one of whom had ornithine carbamoyl transferase deficiency, which might have predisposed her to DEET-induced toxicity.[65,66] The 11 surviving children recovered without sequelae. The EPA's analyses of these cases concluded that they "do not support a direct link between exposure to DEET and seizure incidence."[164] Animal studies in rats and mice show that DEET is not a selective neurotoxin.[117,136,165] Even if a link between DEET use and seizures exists, the observed risk, based on DEET use patterns, would be less than 1 per 100 million users.[164] Other studies have confirmed that children are not at greater risk for developing adverse effects from DEET when compared with older individuals.[37,84,169]

A review of adverse events reported to the DEET Registry from 1995 to 2001 concluded that individuals with underlying neurologic disorders were not predisposed to a greater risk for DEET toxicity. There was no evidence that using higher concentrations of DEET increases the risk for adverse events.[119]

Very limited studies have investigated DEET safety during pregnancy. One study followed 450 Thai women who used 20% DEET daily during the second and third trimesters of pregnancy to reduce the risk for contracting malaria.[106] Of these women, 4% had detectable levels of DEET in umbilical cord blood at the time of delivery. However, no differences in survival, growth, or neurologic development could be detected in the infants born to mothers who used DEET when compared with an equal number of mothers treated with a daily placebo cream during their pregnancies.

The EPA has issued guidelines to ensure safe use of DEET-based repellents[164] (Box 45-3). Careful product choice and common-sense application will greatly reduce the possibility of toxicity. Current recommendations of the American Academy of Pediatrics are that children over the age of 2 months can safely use up to 30% DEET.[174] When required, reapplication of

BOX 45-3 Guidelines for Safe and Effective Use of DEET Insect Repellents

When only short-term protection is needed, repellents with 10% DEET or less may provide adequate protection.

Use just enough repellent to lightly cover exposed skin; do not saturate the skin.

Repellents should be applied only to exposed skin and clothing. Do not use under clothing.

To apply to the face, dispense into palms, rub hands together, and then apply thin layer to face.

Young children should not apply repellents themselves.

Avoid contact with eyes and mouth. Do not apply to children's hands, to prevent possible subsequent contact with mucous membranes.

After applying, wipe repellent from the palmar surfaces to prevent inadvertent contact with eyes, mouth, and genitals.

Never use repellents over cuts, wounds, or inflamed, irritated, or eczematous skin.

Do not inhale aerosol formulations or get them in eyes. Do not apply when near food.

Frequent reapplication is rarely necessary, unless the repellent seems to have lost its effectiveness. Reapplication may be necessary in very hot, wet environments because of rapid loss of repellent from the skin surface.

Once inside, wash treated areas with soap and water. Washing the repellent from the skin surface is particularly important when a repellent is likely to be applied for several consecutive days.

If you suspect you are having a reaction to an insect repellent, discontinue its use, wash the treated skin, and consult a physician.

Modified from U.S. Environmental Protection Agency, Office of Pesticide Programs, Prevention, Pesticides and Toxic Substances Division: *Reregistration Eligibility Decision (RED): DEET*, (EPA-738-F-95-010), Washington, DC, 1998, EPA.

a low-strength repellent can compensate for their inherent shorter duration of protection.

Questions regarding the safety of DEET may be addressed to the EPA-sponsored National Pesticide Information Center, available every day from 8:00 AM to 12:00 PM PST at 800-858-7378 or via their website at npic.orst.edu/.

Picaridin. A piperidine derivative, picaridin (also known as KBR 3023 and icaridin), is the newest repellent active ingredient to become available in the United States. Picaridin-based repellents have been sold in Europe since 1998 under the brand names Autan and Bayrepel.

Picaridin is a synthetic repellent developed by the Bayer Corporation using molecular modeling techniques. From more than 800 screened substances, KBR 3023 showed the best repellent efficacy against a variety of arthropods,[15] along with a very favorable safety profile, low percutaneous absorption, and good aesthetic qualities.[135]

In 2005, the first picaridin-based repellent was brought to the market in the United States. It is currently available in concentrations ranging from 5% to 20% (Table 45-2). This nearly odorless, nongreasy repellent is effective against mosquitoes, biting flies, and ticks. The 7% repellent provides protection against mosquito bites for up to 4 hours. At 20% concentration, picaridin repellents offer efficacy comparable with DEET against mosquitoes, giving up to 8 or more hours of protection, depending on the species tested.[99,132] One study showed that 15% picaridin can offer DEET-like repellency against *Ixodes* ticks,[13] but documented protection times vary widely among the comparatively few studies that have been conducted.[99] The chemical is aesthetically pleasant and, unlike DEET, shows no detrimental effects on contact with plastics. The EPA found picaridin to have very low toxicity risk, and low dermal absorption. In 2005, the Centers for Disease Control and Prevention (CDC) released a statement adding picaridin to the list of approved repellents that could be used effectively to prevent mosquito-borne diseases.

IR3535 (Ethyl-butylacetylaminopropionate). IR3535 is an analog of the amino acid β-alanine and has been sold in Europe as an insect repellent for 20 years. In the United States, this compound is classified by the EPA as a biopesticide, effective against mosquitoes, ticks, and flies. IR3535 was brought to the U.S. market in 1999 and is sold by Avon Products, Inc., and Sawyer Products in concentrations from 7.5% to 20%, with and without sunscreen (see Table 45-2). Depending on the species of mosquito and testing methodology, this repellent has demonstrated widely variable effectiveness, with complete protection times ranging from 23 minutes to more than 10 hours.[5,6,21,26,47] IR3535 can provide up to 12 hours of protection against blacklegged ticks.[21] Higher concentrations give longer protection times; 20 % IR3535 is the most effective. In general, IR3535 does not match the efficacy of high-concentration DEET.[5,6,47] It is nongreasy, nearly odorless, does not dissolve plastics, and has a very good safety profile. In 2008, the CDC released a statement adding IR3535 to the list of approved repellents that could be used effectively to prevent mosquito-borne diseases.

Botanical Repellents

Thousands of plants have been tested as sources of insect repellents. Although none of the plant-derived chemicals tested to date demonstrates the broad effectiveness and duration of DEET, many show repellent activity, and some may be superior against certain important vectors such as anopheline mosquitoes. Plants with essential oils that have been reported to possess repellent activity include citronella, eucalyptus, neem, cedar, verbena, pennyroyal, geranium, catnip, lavender, pine, cajeput, cinnamon, vanilla, rosemary, basil, thyme, allspice, garlic, and

TABLE 45-2 Biopesticides

Manufacturer	Product Name	Form(s)	Active Ingredients
Avon Products, Inc., New York, 800-367-2866	Skin So Soft Bug Guard Plus IR3535 SPF 30 Cool 'N Fabulous	Lotion	IR3535 7.5%
	Skin So Soft Bug Guard Plus IR3535 Expedition	Pump spray, aerosol spray	IR3535 20%
Sawyer Products, Tampa, Florida, 800-940-4664	Sunblock Insect Repellent IR3535 (SPF 30)	Pump spray	IR3535 20%
Coleman Company (Wisconsin Pharmacal), Jackson, Wisconsin, 800-558-6614	SkinSmart	Aerosol, pump spray	IR3535 20%
Spectrum Brands, Alpharetta, Georgia, 800-336-1372	Cutter Lemon Eucalyptus	Pump spray	Oil of lemon eucalyptus 30%
	Repel Lemon Eucalyptus	Pump spray	Oil of lemon eucalyptus 30%
HOMS, LLC, Pittsboro, North Carolina, 800-270-5721	BiteBlocker BioUD	Lotion, pump spray	2-Undecanone 7.75%

TABLE 45-3 Botanical Insect Repellents (Registration Exempt)

Manufacturer	Product Name	Form(s)	Active Ingredients
TyraTech, Inc., Morrisville, North Carolina, 855-373-7210	Guardian	Pump spray	Geraniol 5%
HOMS, LLC, Pittsboro, North Carolina, 800-270-5721	BiteBlocker Xtreme Sportsman BiteBlocker Herbal	Lotion, pump spray Pump spray	Soybean oil 3%, geranium oil 6%, castor oil 8% Soybean oil 2%, geranium oil 5%
All Terrain Company, Newport, New Hampshire, 800-246-7328	Herbal Armor Kids Herbal Armor	Pump spray and lotion Pump spray	Soybean oil 11.5%, citronella oil 10%, peppermint oil 2%, cedar oil 1.5%, lemongrass oil 1%, geranium oil 0.05%, in a slow-release encapsulated formula
Quantum, Inc., Eugene, Oregon, 800-448-1448	Buzz Away Extreme	Pump spray, towelettes	Soybean oil 3%, geranium oil 6%, castor oil 8%, cedarwood oil 1.5%, citronella 1%, peppermint oil 0.5%, lemongrass oil 0.25%
Spectrum Brands, Alpharetta, Georgia, 800-336-1372	Cutter Natural Repel Natural	Pump spray Pump spray	Geraniol 5%, soybean oil 2% Geraniol 5%, soybean oil 2%

peppermint.[4,18,32,37,58,80,81,122,130,162,163] Unlike DEET-based repellents, botanical repellents have been relatively poorly studied. When tested, most of these essential oils tended to show brief protection, lasting minutes to 2 hours, after which insufficient material remained on the skin to function as a repellent. A summary of readily available plant-derived insect repellents is shown in Table 45-3.

BiteBlocker. BiteBlocker is a "natural" repellent that was released to the United States market in 1997, after being sold in Europe for several years.[10] BiteBlocker's present formulation combines derivatives of soybean oil, geranium oil, and castor oil. Studies conducted at the University of Guelph showed that this product was capable of providing over 97% protection against *Aedes* species mosquitoes under field conditions, even 3.5 hours after application. During the same time period, a 6.65% DEET-based spray afforded 86% protection, whereas Avon's Skin Soft citronella-based repellent gave only 40% protection.[93] A second study showed that BiteBlocker provided a mean of 200 ± 30 (SD) minutes of complete protection from mosquito bites.[94] A laboratory study using three different species of mosquitoes showed that BiteBlocker provided an average protection time of about 7 hours.[6] Another study showed that BiteBlocker could give about 10 hours of protection against biting black flies; in the same test, 20% DEET only protected for about 6.5 hours.[95]

BioUD (2-Undecanone). HOMS is the sole distributor in the United States of the repellent BioUD (2-Undecanone). This repellent was derived from the wild tomato plant and registered by the EPA in 2007 as a biopesticide for use against mosquitoes and ticks. In field studies against mosquitoes, 7.75% BioUD provided repellency comparable with 25% DEET.[177] BioUD repelled the American dog tick *Dermacentor variabilis* from human skin for more than 2.5 hours and was still effective 8 days after application to cotton fabric.[177] Laboratory testing demonstrated that BioUD was two to four times more effective than 98% DEET at repelling *Amblyomma americanum, D. variabilis,* and *Ixodes scapularis*.[11] BioUD was significantly better than either IR3535 or PMD (see below) at repelling *A. americanum*.[13]

Lemon Eucalyptus. A derivative (*p*-menthane-3,8-diol, or PMD) isolated from oil of the lemon eucalyptus (or pine) is an effective "natural" repellent.[32] PMD evaporates more slowly from the skin surface than do molecularly similar botanical insect repellents like citronella, and it offers longer-lasting protection. PMD has been very popular in China for years and is currently sold principally in Europe as Mosi-Guard and in the United States as Repel Lemon Eucalyptus Insect Repellent and Cutter Lemon Eucalyptus Insect Repellent. The products readily available in the United States have a strong lemony scent due to the presence of substantial lemon eucalyptus oil in addition to PMD. Tests of this repellent have shown mean complete protection times ranging from 4 to 8 hours, depending on the mosquito species and testing methodology used.[6,15,22,23,57,110,112] Several studies suggest that PMD-based repellents are superior to DEET against *Anopheles* mosquitoes that serve as vectors for malaria.[22] PMD-based repellents can cause significant ocular irritation, so care must be taken to keep them away from the eyes and ensure that they are not used in children younger than 3 years. In 2005, the CDC added this repellent to the approved list of products that can be effectively used to prevent mosquito-borne disease. It is the only botanical repellent so listed.

Citronella. Oil of citronella was initially registered as an insect repellent by the EPA in 1948. It is the most common active ingredient found in "natural" or "herbal" insect repellents marketed in the United States. Originally extracted from the grass plant *Cymbopogon nardus,* oil of citronella has a lemony scent.

Conflicting data exist on the efficacy of citronella-based products, varying greatly depending on the study methodology, location, and species of biting insect tested. Most studies show complete protection times of under 2 hours.[25,63,159]

Many citronella repellents on the market incorporate geranium oil and/or soybean oil to increase the repellent effect of the product. In general, studies show that citronella-based repellents are less effective than are DEET repellents. Citronella provides a shorter protection time, which may be partially overcome by frequent reapplication of the repellent. In 1997, after analyzing available data on the repellent effect of citronella, the EPA concluded that citronella-based insect repellents must contain the following statement on their labels: "for maximum repellent effectiveness of this product, repeat applications at one-hour intervals."[167]

Citronella candles have been promoted as an effective way to repel mosquitoes from one's local environment. One study compared the efficacy of commercially available 3% citronella candles, 5% citronella incense, and plain candles to prevent bites by *Aedes* species mosquitoes under field conditions.[92] Subjects near the citronella candles had 42% fewer bites (a statistically significant difference) than did controls who had no protection. However, burning ordinary candles reduced the number of bites by 23%. There was no statistically significant difference in efficacy between citronella incense and plain candles. The ability of plain candles to decrease biting may be due to their serving as a "decoy" source of warmth and carbon dioxide. In contrast, in a field study, candles with 5% geraniol placed 1 m (3 feet) from volunteers reduced mosquito biting pressure by an average of 56% and sand fly pressure by 62%, compared with paraffin control candles.[114] These efficacies are, unfortunately, far too low to offer useful protection from mosquito-borne diseases.

The citrosa plant (*Pelargonium citrosum* van Leenii) has been marketed as being able to repel mosquitoes through continuous release of citronella oils. Unfortunately, when tested, these plants offer no protection against bites.[27,105] In experimental hut trials in Africa, potted live plants of *Ocimum americanum, Lantana camara,* and *Lippia uckambensis* repelled an average of 40%, 32%, and 33% of mosquitoes, respectively.[149]

Efficacy of DEET Versus Botanical Repellents

Limited data are available from studies that directly compare plant-derived repellents with DEET-based products. Available data proving the efficacy of "natural" repellents are often sparse, and there is no uniformly accepted standard for testing repellent products. As a result, different studies often yield varied results, depending on how and where the tests were conducted, and which arthropod species predominates in the testing area.

Studies comparing "natural" repellents with low-strength DEET products, conducted under carefully controlled laboratory conditions with caged mosquitoes, typically demonstrate dramatic differences in effectiveness between currently marketed insect repellents.[6,47] Even low-concentration (under 7%) DEET lotions often prove to be more effective than citronella-based repellents in their ability to prevent mosquito bites and can generally be expected to provide approximately 1.5 to 2 hours of complete protection.[47,64] Reapplication of these low-concentration DEET products can compensate for their shorter durations of action. Because DEET repellents show a clear dose-response relationship, higher concentrations of DEET can be used to provide proportionately longer complete protection times—up to 6 to 8 hours after a single application. BiteBlocker and oil of eucalyptus repellents offer the best protection of the "botanical" repellents, but some consumers may object to their odor; BioUD also shows promise as an effective alternative to DEET in repelling both mosquitoes and ticks.[23,100] Citronella-based insect repellents usually provide the shortest duration of protection, often lasting only a few minutes.

Alternative Repellents

There has always been great interest in finding or creating an oral insect repellent. An oral repellent would be convenient and eliminate the need to apply topical products to the skin or put on protective clothing. Unfortunately, no effective oral repellent has been discovered. For decades, lay literature has made the claim that Vitamin B_1 (thiamine) works as a systemic mosquito repellent. When subjected to scientific scrutiny, however, thiamine has unanimously been found not to have a repellent effect on mosquitoes.[79,176] The U.S. Food and Drug Administration (FDA), prompted by misleading consumer advertising, issued the following statement in 1983: "There is a lack of adequate data to establish the effectiveness of thiamine or any other ingredient for OTC [over the counter] internal use as an insect repellent. Labeling claims for OTC orally administered insect repellent drug products are either false, misleading, or unsupported by scientific data."[168] Tests of more than 100 ingested drugs, including other vitamins, failed to reveal any that worked well against mosquitoes.[157] Ingested garlic has also never proved to be an effective insect deterrent.[151]

PERMETHRIN

Pyrethrum is a powerful, rapidly acting insecticide, originally derived from the crushed dried flowers of the daisy *Chrysanthemum cinerariifolium*.[24] Permethrin is a synthetic pyrethroid. It does not repel insects but instead works as a contact insecticide, causing nervous system toxicity that leads to death, or "knockdown," of the insect. The chemical is effective against mosquitoes, flies, ticks, fleas, lice, and chiggers. Permethrin has low mammalian toxicity, is poorly absorbed by skin, and is rapidly metabolized by skin and blood esterases.[67,180]

Permethrin should be applied directly to clothing or to other fabrics (tent walls[139] or mosquito nets[96]), not to skin. Permethrins are nonstaining, nearly odorless, resist degradation by heat or sun, and will maintain their effectiveness for at least 2 weeks, through several launderings.[140,146]

The combination of permethrin-treated clothing and skin application of a DEET-based repellent creates a formidable barrier against biting insects.[60,142,151] In an Alaskan field trial against mosquitoes, subjects wearing permethrin-treated uniforms and a polymer-based 35% DEET product had greater than 99.9% protection (one bite per hour) over 8 hours; unprotected subjects sustained an average of 1188 bites per hour.[91]

Permethrin-sprayed clothing also proved very effective against ticks.[12] One hundred percent of *Dermacentor occidentalis* ticks (which carry Rocky Mountain spotted fever) died within 3 hours of touching permethrin-treated cloth.[87] Permethrin-sprayed pants and jackets also provided 100% protection from all three life stages of *Ixodes dammini* ticks, the vectors of Lyme disease.[147] In contrast, DEET alone (applied to the skin) provided 85% repellency at the time of application; this protection deteriorated to 55% repellency at 6 hours, when tested against the lone star tick *A. americanum*.[154] *Ixodes scapularis* ticks, which may transmit Lyme disease, also seem to be less sensitive to the repellent effect of DEET.[141]

Permethrin-based insecticides available in the United States are listed in Table 45-4. To apply to clothing, spray each side of the fabric (outdoors) for 30 to 45 seconds, just enough to moisten it. Allow the clothing to dry for 2 to 4 hours before wearing it. Permethrin solution is also available for soak-treating large items, such as mesh bed nets, or for treating multiple garments simultaneously.

REDUCING LOCAL MOSQUITO POPULATIONS

Consumers may find advertisements for small ultrasonic electronic devices that are meant to be carried on the body and claim to repel mosquitoes by emitting "repellent" sounds, such as that of a dragonfly (claimed to be the "natural enemy" of the mosquito), male mosquito, or bat. Multiple studies conducted in field and laboratory settings show that these devices do not work.[8,30,45,69,90] Although most studies have shown that DEET-impregnated wristbands offered no protection against mosquito bites,[47,69] in one study, wearing impregnated anklets, wristbands, shoulder strips, and pocket strips provided up to 5 hours of complete protection.[73]

Likewise, mass-marketed backyard bug "zappers," which use ultraviolet light to lure and electrocute insects, are also

TABLE 45-4 Permethrin Insecticides

Manufacturer	Product Name	Form(s)	Active Ingredient
Sawyer Products Safety Harbor, Florida, 800-940-4464	Permethrin Clothing Gear and Tents Insect Repellent	Aerosol and pump sprays	Permethrin 0.5%
Spectrum Brands, Alpharetta, Georgia, 800-336-1372	Repel Permethrin Clothing and Gear Insect Repellent	Aerosol spray	Permethrin 0.5%
Coleman (Wisconsin Pharmacal), Jackson, Wisconsin, 800-558-6614	Coleman Gear and Clothing	Aerosol spray	Permethrin 0.5%
3M, St Paul, Minnesota, 888-364-3577	Ultrathon Clothing and Gear Insect Repellent	Pump spray	Permethrin 0.5%

ineffective; mosquitoes continue to be more attracted to humans than to the devices.[116] One backyard study showed that of the insects killed by these devices, only 0.13% were female (biting) mosquitoes.[49] An estimated 71 to 350 billion beneficial insects may be killed annually in the United States by these devices.[49] Newer technology, using more specific bait, such as a warm, moist plume of carbon dioxide, as well as other known chemical attractants (e.g., octenol), may prove to be a more successful way to lure and selectively kill biting insects. Although the manufacturers of these machines accurately claim that these machines can lure and kill thousands of mosquitoes, it remains to be proven that an individual unit can actually kill enough mosquitoes to reduce the local biting pressure. Pyrethrin-containing "yard foggers" set off before an outdoor event can temporarily reduce the number of biting arthropods in a local environment. These products should be applied before any food is brought outside and should be kept away from animals and fish ponds. Burning coils that contain natural pyrethrins or synthetic pyrethroids (such as D-allethrin or D-*trans* allethrin) can also temporarily reduce local populations of biting insects.[69,98,178] Concerns have been raised about the long-term cumulative safety of using these coils in an indoor environment.[1,121]

Wood smoke from campfires can also reduce the likelihood of being bitten by mosquitoes. The smoke's ability to repel insects may vary depending on the type of wood or vegetation burned.[120,172] Caution should be exercised when burning unfamiliar wood where toxic tree species may be present.

INTEGRATED APPROACH TO PERSONAL PROTECTION

An integrated approach to personal protection is the most effective way to prevent arthropod bites, regardless of where one is in the world and which species of insects may be attacking. Maximum protection is best achieved through avoiding infested habitats and using protective clothing, topical insect repellents, and permethrin-treated garments. When appropriate, mesh bed nets or tents should be used to prevent nocturnal insect bites.

DEET-containing insect repellents are the most effective products currently on the U.S. market, providing broad-spectrum, long-lasting repellency against multiple arthropod species. Based on strong scientific support for their efficacy and safety, the CDC has now approved picaridin, IR3535, and oil of lemon eucalyptus as alternative repellents that can be used to reduce the likelihood of contracting insect-borne disease. Insect repellents alone, however, should not be relied on to provide complete protection, especially against malaria vectors.[175] Mosquitoes, for example, can find and bite any untreated skin and may even bite through thin clothing. Deerflies, biting midges, and some blackflies prefer to bite around the head and will readily crawl into the hair to bite where there is no protection. Wearing protective clothing, including a hat, reduces the chance of being bitten. Treating one's clothes and hat with permethrin maximizes their effectiveness by causing "knockdown" of any insect that crawls or lands on the treated clothing. To prevent chiggers or ticks from crawling up the legs, tuck pants into boots or stockings; rubber boots are especially protective.

The U.S. military relies on an integrated approach to protect troops deployed in areas where arthropods constitute either a significant nuisance or medical risk. The Department of Defense's Insect Repellent System consists of DEET applied to exposed areas of skin and permethrin-treated uniforms, worn with the pant legs tucked into boots and the undershirt tucked into the waistband of the pants. This system has been proved to dramatically reduce the likelihood of being bitten by insects, although troop compliance with DEET-use mandates is poor.[50a]

Persons traveling to parts of the world where insect-borne disease is a potential threat will be best able to protect themselves if they learn about indigenous insects and the diseases they might transmit. Protective clothing, mesh insect tents or bedding, insect repellent, and permethrin spray should be carried. Travelers should check the current CDC recommendations about traveling to countries where immunizations (e.g., against yellow fever) or antibiotic prophylaxis (e.g., against malaria) should be undertaken before departure. The CDC maintains these recommendations on its website at cdc.gov/travel or by telephone at 800-CDC-INFO. An excellent summary of information on issues relating to travel health can also be found at tripprep.com. This website culls its information daily from the CDC, the journal *Morbidity and Mortality Weekly Report*, the World Health Organization, and the U.S. State Department.

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