RICKETTSIAL AND EHRLICHIAL INFECTIONS

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CHRISTOPHER D. PADDOCK, M.D., and
JAMES G. OLSON, PH.D.
National Center for Infectious Diseases, Centers for Disease Control and Prevention
Atlanta, Georgia

Rickettsiae and ehrlichiae are small, gram-negative bacteria that produce a wide spectrum of human infections, from relatively mild flulike illnesses to overwhelming, fatal diseases. These pathogens account for some of the most ancient and some of the most contemporary human infections. Effective treatment exists for all the rickettsioses and ehrlichioses; however, these infections can be exceptionally difficult to diagnose in the early stages of disease, when antimicrobial therapy is most beneficial. Most antimicrobials used as empirical therapies for bacterial infections in febrile patients (e.g., β-lactams, macrolides, aminoglycosides, and sulfa-containing drugs) are characteristically ineffective in treating rickettsial and ehrlichial diseases; appropriate treatment is almost never given unless the diagnosis is suspected. Physician awareness of these diseases and early recognition of their salient epidemiologic and clinical features form the foundation of successful patient outcomes.

Table 1 describes selected features of the endemic and imported rickettsial and ehrlichial diseases most likely to be encountered by physicians in the United States. Q fever is distinct from the other rickettsioses in its clinical and epidemiologic characteristics and requires significantly different treatment strategies; these are considered in a separate chapter. Rocky Mountain spotted fever (also described in detail in a separate chapter), rickettsialpox, flea-borne (murine or endemic) typhus, cat flea typhus, recrudescent typhus (Brill-Zinsser disease), sylvatic (flying squirrel) typhus, human granulocytic ehrlichiosis (HGE), and *Ehrlichia chaffeensis* infection (human monocytic ehrlichiosis) represent diseases endemic to the United States. Flea-borne typhus, louse-borne (epidemic) typhus, African tick bite fever, Mediterranean spotted fever (MSF), and scrub typhus are occasionally imported infections recognized in travelers returning to the United States. Other diseases not described in Table 1 that reflect the cosmopolitan, albeit geographically distinct, distribution of specific rickettsial and ehrlichial diseases include Queensland tick typhus, Japanese spotted fever, Siberian tick typhus, Israeli spotted fever, Astrakan fever, and sennetsu fever. More than half of all known rickettsial and ehrlichial diseases have been characterized only in the last decade; additional pathogens undoubtedly will be discovered in the years to come.

CLINICAL MANIFESTATIONS

Patients with rickettsial and ehrlichial infections generally present to a physician in their first week of illness. Unfortunately, early clinical signs and symptoms of these diseases are remarkably nonspecific and may mimic various other infectious and noninfectious etiologies, including measles, infectious mononucleosis, rubella, enteroviral infections, typhoid fever, meningococcemia, secondary syphilis, disseminated gonococcal infection, leptospirosis, toxic shock syndrome, thrombotic thrombocytopenic purpura, idiopathic thrombocytopenic purpura, immune complex vasculitides, and drug reactions. Patients typically present with fever, headache, myalgias, and gastrointestinal symptoms. Rash is a well-recognized manifestation of the rickettsioses but is present in only a minority of infected persons when they present for care initially. Depending on the particular disease, a rash develops in 50 to 95% of patients, generally within 3 to 8 days after the onset of constitutional symptoms. The nature and distribution of the rashes vary among illnesses and in some patients may be evanescent over the course of the disease. Rash infrequently assists in the clinical diagnosis of ehrlichiosis in adults, but it is described in as many as 60 to 70% of pediatric patients with *E. chaffeensis* infection. Here again, the rash may be highly variable in appearance and distribution. Eschars are a prominent feature of several rickettsioses, including MSF, African tick bite fever, rickettsialpox, and scrub typhus; these lesions are frequently accompanied by regional adenopathy. Pulmonary manifestations of varying severity (e.g., from cough or dyspnea to adult respiratory distress syndrome) are noted in as many as 30 to 55% of patients with ehrlichial and rickettsial infections. Hematologic and blood chemistry abnormalities, particularly thrombocytopenia, anemia, elevated hepatic transaminases (especially aspartate aminotransferase), and hyponatremia, are often identified in rickettsioses and ehrlichioses. Leukopenia, particularly absolute lymphopenia, is a common manifestation of the ehrlichioses. Although certain rickettsioses (e.g., rickettsialpox) run a self-limited, relatively mild course in otherwise healthy patients, some of these diseases may progress to multiorgan system sequelae, including myocarditis, pulmonary hemorrhage, adult respiratory distress syndrome, disseminated intravascular coagulation, meningoencephalitis, acute renal failure, and gangrene. Case-fatality ratios for patients with untreated disease may exceed 25% with some of the rickettsioses (see Table 1).

DIAGNOSIS

At present, no routinely available laboratory test provides prompt confirmatory diagnosis for acute rickettsial and ehrlichial diseases. Successful patient outcomes are guided more by the perspicacity of the evaluating health care provider than the sensitivity or specificity of a retrospective confirmatory assay. Therapeutic decisions must be based on a presumptive diagnosis developed from clinical suspicion and the epidemiologic setting. Specific signs and symptoms early in course of infection may be sparse, so a careful history must be obtained. Points to be recognized and/or elicited by physicians in this process include the following.

Exposure. A history of arthropod (e.g., tick, mite, flea, or louse) bite or exposure may be elicited by questioning patients about leisure and/or occupational outdoor activities (e.g., hunting, fishing, hiking, gardening, forestry) in the weeks preceding the illness. Exposures to arthropods may also arise from contacts with certain animals, including rats, mice, flying squirrels, opossums, deer, or dogs; these vertebrates may serve as hosts for the arthropod and as reservoirs for various rickettsial and ehrlichial pathogens.

Geography. Awareness of disease endemicities is invaluable and may sensitize physicians to subtle clues observed in patients presenting with an otherwise unknown acute febrile illness. In addition, these infections may be acquired in travel-related activities in different states and on other continents. These diseases are not restricted to rural settings; in fact, some of the rickettsioses are more

TABLE 1. Features of Selected Rickettsial and Ehrlichial Diseases

Etiologic Agent	Disease	Case-Fatality Ratio Treated (Untreated)	Ecology of Exposure	Geographic Distribution
Rickettsia prowazekii	Louse-borne (epidemic typhus)	10% (up to 60%)	Crowded, squalid conditions created by war and natural disasters that lead to body louse infestations; exacerbated by cold weather or disruption of water supply for bathing	Endemic in highlands of Africa, Asia, and the Americas
R. prowazekii	Sylvatic (flying-squirrel) typhus*	No known fatalities	Houses (e.g., attics) or other areas where flying squirrels nest; most infections occur during the winter months	Eastern United States (especially Massachusetts, Virginia, North Carolina, and Georgia)
R. prowazekii	Brill-Zinsser disease (recrudescent typhus)*	No known fatalities	Debilitation caused by stress, malnutrition, or illness in chronically infected person leads to recrudescence	Worldwide; most common in areas in which louse-borne typhus occurs or has occurred in the past
Rickettsia typhi	Flea-borne (murine, endemic) typhus*	1–2% (6%)	Urban and suburban areas in which rats (*Rattus* spp.) and their fleas are common (in the United States most common from April to August)	Worldwide, particularly in coastal areas of tropics and subtropics
Rickettsia felis	Cat flea typhus*	No known fatalities	Contact with cat fleas and opossums in suburban areas	California, Texas, and Oklahoma
Rickettsia rickettsii	Rocky Mountain spotted fever*	4% (13–41%)	Grassy areas, forest edge, roadsides, hiking trails, stream banks, unmowed areas around homes (in United States, most common from May to September)	Throughout most of the United States (most common in the southeastern states), Central America, and South America
Rickettsia conorii	Mediterranean spotted fever	2–3% (unknown)	Peridomestic areas; contact with buildings in which dogs have been housed	Southern Europe, Africa, and Asia
Rickettsia africae	African tick-bite fever	Unknown	Camping, safaris, exposure in cattle farming areas	Eastern and sub-Saharan Africa, (South Africa Zimbabwe, and Ethiopia)
Rickettsia australis	Queensland tick typhus	<1% (1%)	Outdoor activities that involve contact with vegetation harboring questing ticks	Australia
Rickettsia akari	Rickettsialpox*	No known fatalities	Contact with urban dwellings infested by house mice and their mites (occurs year-round)	Worldwide; occasionally cases occur in large metropolitan centers in the United States, especially New York City. Also reported from Croatia, Ukraine, South Africa, and Korea
Ehrlichia chaffeensis	Human monocytic ehrlichiosis (HME)*	<4% (unknown)	Grassy areas, forest edges, roadsides, hiking trails, stream banks, unmowed areas around homes (most common from May to September)	Southeastern and southcentral United States (most common in Oklahoma, Missouri, Tennessee, Arkansas, Georgia); possibly Portugal, Mali, and Italy

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TABLE 1. Features of Selected Rickettsial and Ehrlichial Diseases *Continued*

Etiologic Agent	Disease	Case-Fatality Ratio Treated (Untreated)	Ecology of Exposure	Geographic Distribution
The agent of human granulocytic ehrlichiosis (HGE) (closely related to or identical to *Ehrlichia equi*)	Human granulocytic ehrlichiosis (HGE)*	<5% (unknown)	Grassy areas, forest edges, roadsides, hiking trails, stream banks, unmowed areas around homes (most common from May to September)	Northeastern coastal and upper midwestern United States (most common in New York, Wisconsin, Minnesota, Connecticut, Massachusetts); Europe (Slovenia and possibly Germany, Sweden, Switzerland, and United Kingdom)
Orientia tsutsugamushi	Scrub typhus	<1% (<10–30%)	Areas in which regrowth of forest is occurring and contact with larval mites (chiggers) is common; plantations, clearings, building sites, river banks (most common during warmer temperatures in subtropics, and following onset of rains in tropics)	Asia (including southeastern Asia, Korea, China, far eastern Russia, Nepal, India, and Pakistan), Indonesia, northern Australia, and the Pacific islands (including Japan, Taiwan, Philippines, and Papua New Guinea)

*Diseases endemic in the United States.

frequently seen in urban or suburban habitats. Finally, distribution of these infections should be considered a dynamic process; expanding geographic boundaries of disease typically parallel changes in densities and distributions of vector and reservoir host populations.

Seasonality. The occurrence of these diseases is directly related to the life histories of their arthropod vectors; most rickettsioses and ehrlichioses encountered by health care providers in the United States occur between April and September, coincident with peak vector activity and abundance.

Serologic assays remain the primary confirmatory method for each of these infections. Depending on the patient and the particular disease, however, antibodies against these agents may not appear until 7 to 14 days after the onset of symptoms. Indirect immunofluorescence antibody assays are the most widely available tests for the rickettsioses and ehrlichioses and are offered through several commercial laboratories, state public health departments, and the Centers for Disease Control and Prevention. Availability of other techniques, including enzyme immunoassays of serum, polymerase chain reaction assays of acute phase whole blood or tissues, immunohistochemistry of biopsied tissues, and direct isolation, is generally restricted to public health reference laboratories or specialized research laboratories. The ehrlichioses are occasionally diagnosed by visualization of the distinctive intracytoplasmic aggregates of bacteria (known as morulae) in leukocytes in peripheral blood, bone marrow, or cerebrospinal fluid. However, this method lacks sensitivity, as morulae are identified in fewer than 10% and 25% of all patients with acute *E. chaffeensis* infection and HGE, respectively.

TREATMENT

Suggested treatment regimens are described in Table 2. In almost all clinical circumstances, tetracyclines are the drugs of choice. Tetracyclines are bacteriostatic against *Rickettsia* species and bactericidal against ehrlichiae. Doxycycline (e.g., Vibramycin, Doryx, Monodox) is generally preferred over other tetracyclines because of its reduced phototoxicity, safety in patients with renal insufficiency, reduced deposition in teeth and bones, and longer plasma half-life (18 hours). The most notorious side effect of the tetracyclines is their propensity to bind calcium,

TABLE 2. Antimicrobial Therapy of Rickettsial and Ehrlichial Infections

Drug	Dose	Route
Doxycycline*		
Adults and children >45 kg	200 mg/d, in 2 divided doses	PO or IV
Children <45 kg	3 mg/kg/d, in 2 divided doses	PO or IV
Tetracycline		
Adults and children >8 years	25–50 mg/kg/d, in 4 divided doses	PO
	10–20 mg/kg/d, in 4 divided doses	IV
Chloramphenicol†		
Adults	50 mg/kg/d, in 4 divided doses	PO or IV
Children	50 mg/kg/d, in 4 divided doses	PO
	50—75 mg/kg/d, in 4 divided doses	IV
Rifampin, ciprofloxacin‡		

*Doxycycline is the antimicrobial of choice for all ehrlichial and rickettsial infections in adults and children but is contraindicated in pregnancy.

†Efficacy of chloramphenicol in the treatment of ehrlichiosis is uncertain. Oral formulation is unavailable in the United States. Decreased dosages necessary in neonates.

‡Limited clinical data to suggest efficacy of these agents against specific diseases (i.e., rifampin as effective therapy in pregnant patients with ehrlichiosis, clinical success with ciprofloxacin in the treatment of Mediterranean spotted fever).

resulting in staining and hypoplasia of developing tooth enamel. For this reason, routine use of tetracyclines in children younger than 8 years of age has been discouraged. However, the benefit of tetracycline use in children with potentially life-threatening rickettsial and ehrlichial infections far exceeds the risks, and doxycycline remains the antimicrobial of choice in pediatric patients of any age. Indeed, as the degree of dental staining is dose- and duration-dependent (the threshold for cosmetically perceptible staining appears to be 6 or more multiple-day courses of therapy), the actual risk of discoloration appears minimal following a single short course of doxycycline. Doxycycline is effectively administered orally in most cases. Intravenous therapy is given to hospitalized patients with vomiting, severe multisystem disease, or obtundation. Tetracyclines are contraindicated in pregnant women because of the risk of severe maternal hepatotoxicity and pancreatitis and interference with normal development of teeth and long bones in the fetus.

Chloramphenicol (Chloromycetin) represents an alternate therapy for the rickettsioses and has been used with clinical success in pregnant patients who have severe rickettsial disease. Oral chloramphenicol is no longer manufactured in the United States. The only systemic formulation currently available is parenteral chloramphenicol sodium succinate. This drug provides broad-spectrum activity against agents of diseases that may mimic rickettsial infections (including *Neisseria meningitidis* and *Salmonella typhi*) and may be preferred in select critically ill patients when the etiology is uncertain and the differential diagnosis includes one or more of these pathogens. Chloramphenicol is neither bacteriostatic nor bactericidal against *Ehrlichia* species in vitro, and there are reports of treatment failures with this drug in some patients with ehrlichiosis. Idiosyncratic aplastic anemia, which occurs in one in 24,500 to 40,800 courses of treatment, is the most devastating adverse reaction caused by this antibiotic. There also appears to be a dose-response relationship between chloramphenicol use and some childhood leukemias (e.g., acute lymphocytic and nonlymphocytic leukemias). Chloramphenicol has a low therapeutic-to-toxic ratio, and a number of reversible, dose-related toxicities are associated with this drug, including bone marrow suppression (reticulocytopenia, granulocytopenia, and/or thrombocytopenia), cardiomyopathy, and gray baby syndrome in neonates. For this reason, serum concentrations should be monitored routinely, with the peak levels maintained between 10 and 20 μg per mL.

Rifampin (e.g., Rifadin, Rimactane) shows significant in vitro bactericidal activity against *E. chaffeensis* and the HGE agent, and anecdotal reports describe rapid clinical improvement in patients who have HGE and are treated with rifampin in the second and third trimesters of pregnancy. These data should be interpreted cautiously, however, and should not be applied uniformly to other rickettsial infections. Indeed, treatment failures have been documented in clinical trials evaluating rifampin for the treatment of MSF.

The efficacy of currently available quinolones against the ehrlichioses and rickettsioses other than MSF has not been evaluated in clinical trials. There are anecdotal reports of rapid clinical response with ciprofloxacin in the treatment of flea-borne and scrub typhus, and successful patient outcomes are well documented for MSF. Ciprofloxacin (Cipro), is not active against *Ehrlichia* species and should not be used to treat these infections. In vitro studies indicate that several newer generation quinolones possess bacteriostatic and/or bactericidal activities against spotted fever group rickettsiae (e.g., levofloxacin [Levaquin]) and ehrlichiae (e.g., trovafloxacin [Trovan]); however, these drugs have not been evaluated in patients with active disease.

Therapy with sulfa-containing antimicrobials is contraindicated, and there is evidence that these drugs may increase the severity of several rickettsial infections, including Rocky Mountain spotted fever, MSF, flea-borne typhus, and possibly ehrlichiosis.

Although no consensus exists regarding optimal duration of therapy, the best guide appears to be the clinical response: most clinicians advocate continuing antibiotic coverage for at least 2 to 3 days following defervescence, for a minimum total course of 5 days. In general, patients become afebrile within 24 to 48 hours after initiation of effective therapy, and the total duration of treatment is 5 to 10 days. Shortened (i.e., single-dose) regimens have been successfully implemented during outbreaks of louse-borne typhus, and effective single-day therapy for MSF has been reported. However, disease relapses within 2 to 8 days following termination of therapy have been described for several rickettsioses, including Rocky Mountain spotted fever, Israeli spotted fever, flea-borne typhus, and scrub typhus, particularly with abbreviated treatment regimens initiated very early in the course of infection. Relapses are more frequently associated with chloramphenicol use but have also been described with single-dose doxycycline. Longer courses of doxycycline (10 to 21 days) may be warranted in select patients with HGE if co-infection with *Borrelia burgdorferi* is suspected.

Severely ill patients may develop marked hypotension, oliguria, and shock from intravascular fluid losses. Close hemodynamic and electrolyte monitoring, coupled with careful fluid replacement and pharmacologic blood pressure support, may be warranted. Marked anemia and thrombocytopenia can develop in some patients, requiring close attention to blood counts. Standard criteria for transfusion of red blood cells and platelets should be followed. Use of high-dose corticosteroids late in the course of severe vasculotropic rickettsioses has been advocated by some clinicians, but there are no controlled trials to suggest that this therapy is efficacious.

Prophylactic therapy in non-ill patients who have had recent arthropod bites is not warranted. Administration of doxycycline before the onset of symptoms may only delay the onset of clinical disease with some rickettsial infections.