69 Tick-Borne Spotted Fever Rickettsioses

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KEY FEATURES

- Tick-borne rickettsioses are caused by obligate intracellular bacteria belonging to the spotted fever group of the genus *Rickettsia* within the family Rickettsiaceae in the order Rickettsiales.
- Ecologic characteristics of the tick vectors influence the epidemiology and clinical aspects of tick-borne diseases.
- The clinical presentation of tick-borne rickettsiosis can vary from mild to very severe, with the frequency of fatality from highly virulent rickettsiae ranging from 2% to 6%. The main clinical signs include fever, headache, rash that is maculopapular or sometimes vesicular, inoculation eschars at the site of the tick bite, and localized lymphadenopathy.
- Early empirical treatment should be started in any suspected rickettsioses before laboratory confirmation of the diagnosis. Based on in vitro susceptibility and in vivo experience, doxycycline is the currently recommended drug for treating spotted fever group rickettsioses.
- No vaccines are commercially available to prevent tick-borne rickettsioses in humans—prevention involves minimizing exposure to ticks.
- The emergence and re-emergence of these illnesses are attributed to changes in the environment and human behavior.

INTRODUCTION

Tick-borne rickettsioses are caused by gram-negative, obligate, intracellular bacteria belonging to the spotted fever group of the genus *Rickettsia*, in the family Rickettsiaceae, in the order Rickettsiales (γ-proteobacteria).[1] These zoonoses are among the oldest-known vector-borne diseases. In 1899 Edward E. Maxey reported the first clinical description of Rocky Mountain spotted fever (RMSF) in the Snake River Valley of Idaho, United States, and in 1910, Conor and Brush described the first case of Mediterranean spotted fever (MSF) in Tunis. In 1905 McCalla, an Idaho physician, demonstrated the role of the wood tick in the transmission of *Rickettsia rickettsii*, the causative agent of RMSF. With the full consent of the participants, he attached a tick obtained from the chest of a man who was very ill with spotted fever to the arm of another patient. The tick remained on the second patient for 48 hours and was then applied to the leg of a woman, where it remained for at least 10 hours. The incubation periods were 9 and 3 days, respectively. Around 1930 the role of the brown dog tick, *Rhipicephalus sanguineus*, in the transmission of *R. conorii*, the causative agent of MSF, was demonstrated using human models.[2] The history of tick-borne illnesses is one of constant renewal, with discoveries of new pathogens associated with descriptions of novel diseases concurrent with advances in molecular and cell-culture techniques.[3]

ETIOLOGY

Rickettsiae are strictly intracellular bacteria whose sizes range from 0.3 to 2.0 μm. These bacteria multiply by binary fission in the cytoplasm of eukaryotic host cells. As a consequence, they must be cultivated in tissue culture, guinea pigs, or embryonated chicken eggs. Rickettsiae are difficult to stain with ordinary bacterial stains, but are stained by the Gimenez method. To date, there are 29 formally recognized species in the genus *Rickettsia*, which can be classified into four groups: the typhus group (*R. typhi* and *R. prowazekii*); the spotted fever group (>20 species) (Table 69.1); *R. bellii;* and the *R. canadensis* group. Many other as yet uncharacterized isolates exist. Taxonomic guidelines for the identification and description of new rickettsial isolates have been proposed using sequences of the 16S rRNA (*rrs*) gene and four protein-coding genes: *gltA*, *ompA*, *ompB*, and gene D.[4]

EPIDEMIOLOGY

Tick-borne rickettsioses have a global distribution. Ticks are hematophagous arthropods that parasitize every class of vertebrates in almost every region of the world and occasionally bite humans. Each species has a particular set of optimal environmental conditions and biotopes that determine the geographic distribution of the ticks and, therefore, of the individual tick-borne rickettsioses (Fig. 69.1). The prevalence of *Rickettsiae* in different populations of ticks is variable—it ranges from usually less than 1% for *R. conorii* and *R. rickettsii* to 100% for *R. africae*. The tick vectors usually involved in transmission of tropical rickettsioses belong to the genera *Rhipicephalus*, *Ixodes*, *Amblyomma*, *Hyalomma*, *Haemaphysalis*, and *Dermacentor* (Table 69.1). Tick-borne rickettsioses may be transmitted among ticks trans-stadially (stage-to-stage) and trans-ovarially (transfer of bacteria from adult females to the subsequent generation of ticks via the eggs). As a consequence, ticks may act as reservoirs for these bacteria, such as *Amblyomma* spp. for *R. africae*, and play a role in maintaining the agent in nature. Tick-borne diseases are emerging zoonoses with a re-emergence of "old" diseases. Increasing international travel and the possibility of the ticks being carried by hosts such as birds have resulted in a number of imported cases of tick-borne rickettsioses. An analysis of the GeoSentinel database (a worldwide communications and data collection network of travel/tropical medicine clinics) showed that 3.1% of febrile travelers seeking care at specialized centers have rickettsiosis. It has also been suggested that global warming has led to a northward expansion of several tick species and to an increase in the aggressiveness of the brown dog tick, and that these have increased the incidence of *Rh. sanguineus*–transmitted pathogens, such as *R. conorii*, *R. rickettsii*, *R. massiliae*, other non-pathogenic rickettsial agents like *R. rhipicephali*, or as-yet-undescribed microorganisms.[2,5]

SPOTTED FEVER GROUP RICKETTSIOSES WITH INOCULATION ESCHAR

Mediterranean Spotted Fever

R. conorii, the causative agent of MSF, is endemic in the Mediterranean area, including northern Africa and southern Europe; cases have also been reported sporadically in central Europe and central and southern Africa. In Italy, in 2002, the national incidence rate was 1.6 cases per 100,000 persons (although in Sicily it was 10 cases per 100,000 persons); in Portugal between 1989 and 2003, the annual incidence was 8.9 cases per 100,000 inhabitants; and in Spain between 1983 and 1985, the estimated incidence was 23

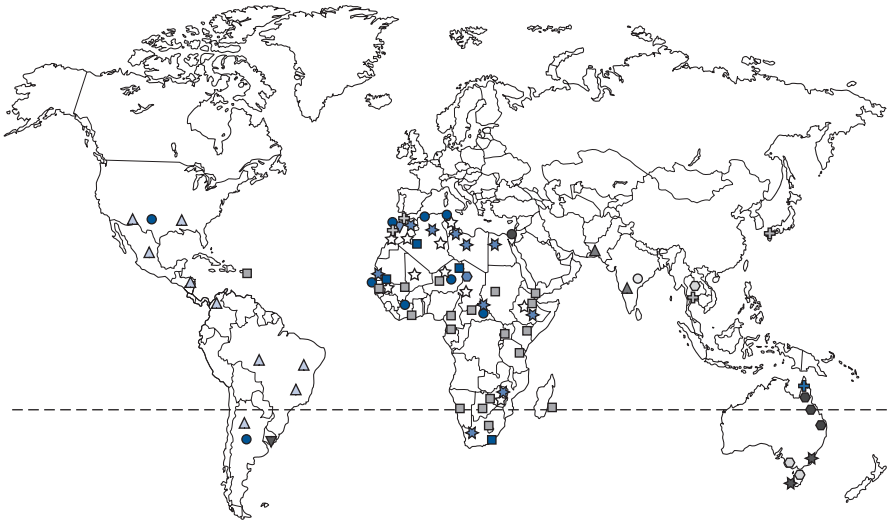

Fig. 69.1 Tick-borne rickettsiae in tropical regions.

TABLE 69.1 Tick-Borne Rickettsioses Throughout the World

	Disease	*Rickettsia*	Tick Vector	Selected Epidemiologic and Clinical Characteristics
Spotted fever group with inoculation eschar	Mediterranean spotted fever	*R. conorii conorii*	*Rhipicephalus sanguineus*	Disease occurs in urban (66%) and rural (33%) settings during summer months; cases generally sporadic. Classic single eschar and maculopapular, generalized rash (97%). Mortality: 2.5%.
	Astrakhan fever	*R. conorii caspia*	*Rh. sanguineus, Rhipicephalus pumilio*	Disease occurs mostly in rural settings. Symptoms include eschar (23%), maculopapular rash (94%), and conjunctivitis (34%). No fatal cases reported.
	Indian tick typhus	*R. conorii indica*	*Rh. sanguineus*	Rash frequently purpuric, eschar rarely found, no fatal forms.
	Israeli spotted fever	*R. conorii israelensis*	*Rh. sanguineus*	Compared with Mediterranean spotted fever, eschars are less frequent. Mild to severe illness.
	Siberian tick typhus	*R. sibirica sibirica*	*Dermacentor nuttalli, Dermacentor marginatus, Dermacentor silvarum, Haemaphysalis concinna*	Disease occurs in predominantly rural settings. Cases occur during spring and summer. Increasing reports of cases. Cases generally associated with rash (100%), eschar (77%), and lymphadenopathy.
	Lymphangitis-associated rickettsiosis	*R. sibirica mongolitimonae*	*Haemaphysalis asiaticum, Haemaphysalis truncatum, Haemaphysalis anatolicum excavatum Rhipicephalus pusillus*	Fever (100%), headache (50%), rash (83%), eschar (92%), multiple eschars (17%), adenopathy (58%), and lymphangitis (42%).
	African tick-bite fever	*R. africae*	*Aponomma variegatum, Aponomma hebraeum*	Disease occurs in predominantly rural settings. Symptoms include fever (88%), eschar (95%), multiple eschar (54%), maculopapular (49%) or vesicular (50%) eruption, and lymphadenopathy (43%). No fatal cases reported.
	Scalp eschar and neck lymphadenopathy (SENLAT)	*R. slovaca*	*D. marginatus, Dermacentor reticulatus*	Fever and rash rare. Typical scalp eschar with cervical lymphadenopathy. Alopecia and chronic fatigue. Illness mild.
	Scalp eschar and neck lymphadenopathy (SENLAT)	*R. raoultii*	*D. marginatus, D. reticulatus*	Fever, painful eschar and adenopathies, headache, asthenia. No alopecia was noted, but 50% of patients had prolonged asthenia (1–6 mo) and 25% had chronic asthenia.

TABLE 69.1 Tick-Borne Rickettsioses Throughout the World—cont'd

	Disease	*Rickettsia*	Tick Vector	Selected Epidemiologic and Clinical Characteristics
	Far-Eastern tick-borne rickettsiosis	*R. heilongjiangensis*	*D. silvarum*	Rash, eschar, and lymphadenopathy. No fatal cases reported.
	Japanese or Oriental spotted fever	*R. japonica*	*Haemaphysalis flava, Haemaphysalis longicornis, Dermacentor taiwanensis, Ixodes ovatus*	Disease occurs mainly from April to October in predominantly rural settings. Associated with agricultural activities, bamboo cutting. Fever, macular rash (100%), and eschar (91%).
	Queensland tick typhus	*R. australis*	*Ixodes holocyclus, Ixodes tasmani*	Disease occurs in rural and urban areas; cases occur from June to November. Vesicular eruption (100%), eschar (65%), lymphadenopathy (71%). Few fatal cases described.
	Flinders Island spotted fever	*R. honei*	*Aponomma hydrasauri, Aponomma cajennense, Aponomma granulatus*	Disease occurs mainly in rural areas and peaks between December and January. Symptoms include eruption (85%), eschar (25%), and lymphadenopathy (55%).
		R. honei marmionii	*Haemaphysalis novaeguineae, I. holocyclus*	Fever, headache (83%), arthralgia (50%), cough (50%), maculopapular rash (33%), pharyngitis (33%), and eschar (29%).
	Pacific coast tick fever	*R. philipii*	*Demacentor occidentalis*	Eschar (100%), fever (85%), headache (79%), lymphadenopathy (64%), rare maculopapular rash (14%).
	Spotted fever	*R. parkeri*	*Amblyomma maculatum, Amblyomma tigrinum, Amblyomma triste*	Fever, eschar, myalgia, malaise, headache. Sparse maculopapular or vesicular eruption.
	Spotted fever	*R. aeschlimannii*	*Hyalomma marginatum marginatum, Hy. marginatum rufipes, Rhipicephalus sanguineus appendiculatus*	High fever, eschar, and maculopapular generalized rash.
	Spotted fever	*R. massiliae*	*Rh. sanguineus, Rhipicephalus turanicus, Rhipicephalus muhsamae, Rhipicephalus lunulatus, Rhipicephalus sulcatus*	Two confirmed cases: eschar and maculopapular generalized rash; one case of chorioretinitis.
Spotted fever group with no inoculation eschar	Rocky Mountain spotted fever	*R. rickettsii*	*Dermacentor andersoni, Dermacentor variabilis, Rh. sanguineus, Amblyomma cajennense, Aponomma aureolatum*	Peak occurrence during spring and summer. Petechial rash including palms (60%) and soles (80%). No eschar. Fatal cases 2%–6%.
	Spotted fever	*R. helvetica*	*Ixodes ricinus, Ixodes ovatus, Ixodes persulcatus, Ixodes monospinus*	Although implicated in perimyocarditis and sarcoidosis, the validity of these associations has been debated or not accepted by rickettsiologists. Few cases documented by serology and PCR. Rash and eschar seldom occur.
	Spotted fever	*R. monacencis*	*I. ricinus*	Two confirmed cases: fever, headache, and an erythematous rash with no inoculation eschar.

to 45 cases per 100,000 persons—the same rate was also observed in Marseille during that time. This disease affects all age groups and occurs mainly in summer. Recently an increased incidence of MSF was associated with warmer weather, which increases the aggressiveness and northward expansion of *Rh. sanguineus*.[5]

The incubation period from the time of infection to onset is 6 days. Often, the patient presents with abrupt fever (100%), flulike symptoms (headache, chills, arthromyalgias), and an eschar ("tache noire") at the tick-bite site. The "tache noire," the hallmark of disease, is an inflamed red papule, the center of which becomes necrotic, black, and indolent, usually located on the trunk, legs, or arms (in infants it is often on the scalp in the retro-auricular area). Occasionally, the eschar is not found, and it is seen rarely in multiples. Unilateral or bilateral conjunctivitis may represent the eye-inoculation site of the rickettsia. A generalized maculopapular rash (97% of cases) on the extremities and then on the trunk often involves the palms, soles, and, to a lesser extent, the face (Fig. 69.2). Other common clinical manifestations are myalgias (73%), headache (69%), conjunctivitis (32%), hepatomegaly (44%), and splenomegaly (19%). Gastrointestinal symptoms may be present in about 30% of patients and are more likely to be present in children.[6] Severe disease occurs in 5% to 6% of cases and is associated with disseminated vasculitis, with renal, neurologic, and cardiovascular complications, as well as phlebitis. Recently in a prospective study conducted in Algeria, 49% of the patients were hospitalized with a severe form. The global death rate was 3.6%, but it was 54.5% in patients hospitalized with major neurologic manifestations and multi-organ involvement.

Fig. 69.2 Rash in a patient with Mediterranean spotted fever.

Astrakhan Fever

R. conorii caspia, the infectious agent of Astrakhan fever, was described primarily in patients living in rural areas in Astrakhan, a region of Russia. *Rh. sanguineus* and *Rh. pumilio* were shown to harbor this rickettsia. Clinically, the disease is similar to MSF, except for the absence of a fatal form and a lower incidence of inoculation eschar. Recently a rickettsial isolate was obtained from a patient in Chad, Africa. The patient presented with fever, dyspnea, a maculopapular rash, an inoculation eschar on the leg, and conjunctivitis of the right eye.

Indian Tick Typhus

The etiologic agent of Indian tick typhus is *R. conorii indica*, prevalent in India, which has never been isolated in human samples. Indian tick typhus differs from MSF by the presence of purpuric rash and, infrequently, an inoculation eschar at the bite site.

Israeli Spotted Fever

R. conorii israelensis is the causative agent of Israeli spotted fever (ISF). The first case was described in Israel; however, this bacterium was recently isolated from human samples and ticks in Italy and Portugal. The clinical manifestations of ISF are similar to those of other spotted fever group infections, but the eschar at the inoculation site is absent in more than 90% of cases and resembles a small, pinkish papule when visible. Several fatal cases and severe forms of ISF have been described, especially in children, as well as in travelers and those with glucose-6-phosphate dehydrogenase deficiency.

Siberian Tick Typhus

R. sibirica sibirica is the causative agent of Siberian tick typhus. The disease is described in southern and eastern Siberia, northern China, Mongolia, and Kazakhstan. The annual morbidity rates in the years 1995 to 2004 varied from 1.5 to 2.4 per 100,000 in Russia, but in the area where this disease is endemic, morbidity may reach 40 to 120 per 10,000. The peak of disease occurs in May, and the clinical course is benign. Onset is typically abrupt, with high fever, headache, myalgia, arthralgia, digestive symptoms, an inoculation eschar (62%–77%), regional adenopathy, and a cutaneous rash that appears 2 to 4 days after onset.[1,3,7]

Fig. 69.3 *Amblyomma variegatum* adult ticks (male right, female left), a vector of African tick-bite fever, the etiologic agent of *Rickettsia africae*.

Lymphangitis-Associated Rickettsiosis

Lymphangitis-associated rickettsiosis is caused by *R. sibirica mongolitimonae*. The distribution of this disease matches that of *Hyalomma* spp. ticks. Recently *R. sibirica mongolitimonae* was also detected in *Rh. pusillus* ticks in Portugal and in France. Few cases were confirmed in the literature, mostly from Europe (France, Portugal, Greece, and Spain) and less from Africa (Algeria, South Africa, and Egypt). The available clinical features for the reported cases (male to female sex ratio 1.66) include fever in all patients (range 38°C–39.5°C), chills (19%), headache (100%), myalgias (100%), arthralgia (19%), cutaneous rash (84.6%), enlarged lymph nodes (77%), lymphangitis expanding from an inoculation eschar to the draining node (46.1%), and retinal vasculitis in a pregnant woman.[3,8] Lymphangitis-associated rickettsiosis occurred primarily between March and September; a single case was reported in December in Greece.

African Tick-Bite Fever

African tick-bite fever is caused by *R. africae* and transmitted by *Amblyomma* ticks in rural sub-Saharan Africa and the West Indies (Fig. 69.3).[1,9] Some reports indicate that African tick-bite fever poses a significant problem to local populations. In Zimbabwe, the annual incidence rate of African tick-bite fever is 60 to 80 cases per 100,000 in areas where *Amblyomma* is endemic. Whereas reports on African tick-bite fever in indigenous populations are scarce, the number of reported cases has recently increased in travelers from Europe and elsewhere. Usually, grouped cases of African tick-bite fever are described, for example, several cases in the same family or in the same travel group.

The clinical course typically comprises an abrupt onset of fever (59%–100%), nausea, headache (62%–83%), and neck myalgias (81%) beginning 5 to 10 days after a tick bite. Most patients develop an inoculation eschar (53%–100%) at the site of the tick bite (Fig. 69.4), and up to 54% of patients have multiple eschars—a rather specific clinical sign. A painful regional lymphangitis (43%–100%) is common and may be seen in the absence of an inoculation eschar. A generalized cutaneous rash, sometimes vesicular and usually most visible close to the eschar, is present in 15% to 46% of patients. Less frequent clinical signs of African

Fig. 69.4 Eschar of African tick-bite fever.

tick-bite fever include aphthous stomatitis (11%) and arthralgia. Complications are rarely seen, but long-lasting fever, reactive arthritis, sub-acute cranial or peripheral neuropathy, chronic fatigue, neuropsychiatric symptoms, and myocarditis have been reported. There are no known fatal cases.[9] African tick-bite fever should be considered along with malaria and other tropical fevers in the differential diagnosis of all febrile patients returning from the tropics.

Scalp Eschar and Neck Lymphadenopathy

The tick-borne rickettsial etiologic agents of scalp eschar and neck lymphadenopathy (SENLAT) are *R. slovaca* and *R. raoultii*, which are transmitted by the ticks *Dermacentor marginatus* and *D. reticulatus*. Previous names of the disease include *tick-borne lymphadenitis (TIBOLA)* or Dermacentor-*borne necrosis erythema lymphadenopathy (DEBONEL)*. Recently the spectrum of the causative agents of SENLAT was extended, and several reports demonstrated that this syndrome can be caused by *Borrelia burgdorferi*, *Bartonella henselae*, *Coxiella burnetii*, *Candidatus R. rioja*, and *Francisella tularensis*, all transmitted by the previously cited ticks. SENLAT occurs in Europe, more frequently in women and children during the colder months. The clinical description is similar for *R. slovaca* and *R. raoultii* infection, including fever, headache, asthenia, rash, painful eschar to the scalp, painful adenopathies, and facial edema. The difference between these two infections is that alopecia lasting for several months has been recorded in 59% or more of the cases with *R. slovaca*, but not with *R. raoultii*.[10,11]

Far-Eastern Tick-Borne Rickettsiosis

The etiologic agent of this disease, also named *neglected rickettsiosis*, is *R. heilongjiangensis*. Reported cases have occurred in far-eastern territories of Russia and in northern China. Its seasonal peak runs from the end of June through July, and it mostly affects older populations; no fatal case has been reported. The clinical picture is similar to other spotted fever group rickettsioses. All reported cases had a history of tick bite, tick exposure, or having visited the endemic area. Symptoms include fever, maculopapular rash, inoculation eschar, regional lymphadenopathy, and conjunctivitis.[3]

Japanese or Oriental Spotted Fever

R. japonica, the causative agent of Japanese spotted fever, is located along the coast of southwestern and central Japan and in northeastern Thailand. The onset of the disease is 2 to 10 days after work in the fields and is abrupt, with common symptoms of headache (81%), high fever (100%), shaking chills (87%), and tick-bite eschar (94%). A macular rash (100%) appears after 2 or 3 days all over the body, including the palms and soles. It becomes petechial after 3 or 4 days and disappears in 2 weeks. In a series of 28 Japanese patients hospitalized from 1993 to 2002, 21% of Japanese spotted fever cases were classified as severe and included one fatality.[1]

Queensland Tick Typhus

R. australis, the causative agent of Queensland tick typhus, occurs only down the east coast of Australia, from the tip of the continent and Torres Strait Island to the southeastern corner (Wilson's promontory in Victoria).[12] Most cases (78%) occur between June and November. The disease is characterized by sudden onset of fever, headache, and myalgias. Within 10 days, a maculopapular or vesicular rash appears. An inoculation eschar is identified in 65% of cases and lymphadenopathy(ies) in 71% of cases.

Flinders Islands Spotted Fever

Flinders Islands spotted fever, caused by *R. honei*, occurs primarily in Australia (Tasmania, South Australia, Queensland, Torres Strait Islands), but may also occur in Thailand, Sri Lanka, and Italy.[1,12] *Aponomma hydrosauri*, the reptile tick, is suspected to be a vector of this disease. It is a relatively mild disease—no deaths have yet been recorded. The incidence of Flinders Islands spotted fever was estimated at 150 per 100,000 persons. It causes a summer febrile illness associated with a rash, being erythematous in the majority of cases, and it was purpuric in two severe cases associated with thrombocytopenia. An eschar typical for spotted fever group rickettsiosis (25%) and enlarged local nodes (55%) was observed. Recently a genetic variant of *R. honei*, the "marmionii" strain transmitted by *Haemaphysalis novaeguineae* and *Ixodes holocyclus*, was reported to cause acute disease in several patients in eastern Australia.

Pacific Coast Tick Fever

Pacific Coast tick fever (PCTF), is caused by *R. philipi*. First isolated in 1966, this species is transmitted to humans through the bite of *Dermacentor occidentalis*, the Pacific Coast tick that is predominantly found in rural areas from Oregon to northern Baja California and Mexico. As of 2016, 14 cases of PCTF have been reported in California, mostly northern California, mostly in children (mean age 15.5 years). The disease mainly occurs in late summer.[13]

Though closely related to RMSF, PCTF differs in the presence of at least one eschar (100%) and the frequent absence of a rash (14%). Multiple eschars may be observed to the head, neck, forearm, back, and shoulder. Fever (85%), headache (79%), and lymphadenopathy (64%) are common.

A spotted fever caused by *R. parkeri* has been described in the United States and South America. The first recognized case of infection in a human was reported in 2004, 65 years after the initial isolation of this rickettsia from ticks. This disease was previously confused with RMSF or with rickettsialpox. To date, more than 40 cases have been reported. This disease, transmitted by the Gulf coast tick *Amblyomma maculatum* or *A. triste* in the United States, and by *A. tigrinum* and *A. triste* in South America, is characterized by an inoculation eschar at the tick-bite site generally associated with fever, myalgias, malaise, and headache. A sparse maculopapular or vesiculopustular rash may be observed. No deaths were reported.[14]

R. aeschlimannii was detected in *Hyalomma* ticks from several African countries, southern Europe, and Kazakhstan (see Table 69.1).[7] Four clinical cases were described in the literature: one patient returning from Morocco to France, one patient returning from a hunting and fishing trip in South Africa, and two cases in

Algeria. All of these patients presented with a disease mimicking MSF: an inoculation eschar (in one case two inoculation eschars), fever, headache, and a generalized maculopapular rash.[1]
R. massiliae has been detected in several species of *Rhipicephalus* ticks in tropical African countries—the Central African Republic, Senegal, Ivory Coast, and Mali—and also in southern Europe and the United States.[1] It is an emergent pathogen with fewer than 10 cases of human infection described in Italy, France, Romania, and Argentina. These patients mostly presented with clinical signs evocative of MSF, and in one case of SENLAT. A French patient presented acute visual loss and bilateral chorioretinitis.[5]

SPOTTED FEVER GROUP RICKETTSIOSES WITH FEW OR NO INOCULATION ESCHAR

Rocky Mountain Spotted Fever

The severity of symptoms of RMSF caused by *R. rickettsii* separates this disease from other tick-borne rickettsioses. RMSF is endemic to regions of North, Central, and South America, in both rural and urban zones. The peak of disease occurs during the months of April to September. Since its initial description in the late 19th century, RMSF has been considered a lethal infection. For example, from 1904 to 1913 in Montana, 96 (63%) of 153 patients diagnosed with RMSF died from this disease. The fatality rate of RMSF was reduced to approximately 23% by advances in supportive care and the discovery of antimicrobial therapy. In the *Summary of Notifiable Diseases—United States, 2006*, a total of 3908 cases of RMSF were reported in 2002 to 2004, including 22 deaths, making the case-fatality rate 0.7%. There are a few reasons to believe that the fatal cases are more often unreported than benign cases: (1) some cases are confounded with spotted fever caused by *R. parkeri*, *R. massiliae*, *R. amblyommatis*, *R. akari*, and *R. felis;* (2) some imported cases of rickettsioses, for example, African tick-bite fever in travelers, are incorrectly reported as RMSF; and (3) in some *R. rickettsii* strains, there are variations in virulence (for example, in an early description of RMSF in the Idaho region, a 5% case-fatality rate was reported compared with 70%–80% in Montana).[15] In Brazil, where RMSF is endemic to at least five states, mortality was 40% in Minas Gerais State between 1981 and 1989. The risk factors for severity are old age, a delay between disease onset and diagnosis, wrong antibiotic choice, and no known documentation of tick bite.

Around 1 week after being bitten by an infected tick, the infected individual will develop fever, chills, myalgia, and headache. During the next few days, these symptoms continue and may be accompanied by anorexia, nausea, vomiting, abdominal pain, diarrhea, photophobia, and cough. The fever is typically high (39°C–41°C) and associated with a severe frontal headache. Rash, considered the hallmark feature of RMSF, appears on day 3 of fever as small, pink, blanching macules (typically on the wrists, ankles, and forearms) that evolve maculopapules. Within 24 hours, it spreads centrally to involve the legs, buttocks, arms, axillae, trunk, neck, and face. The entire body may be involved, including the mucous membranes of the palate and pharynx.[16] Characteristic of the rash are petechial lesions in a distribution that includes the palms and soles, which occur in 36% to 82% of patients. In some severe cases, petechiae may coalesce to form large ecchymoses. No eschar at the inoculation site is visible. Severe manifestations may include pulmonary edema and hemorrhage, cerebral edema, myocarditis, renal failure, disseminated intravascular coagulopathy, and gangrene. Three factors are independent predictors of failure by the physician to initiate therapy the first time a patient is seen: absence of a rash, presentation between August 1 and April 30, and presentation within the first 3 days of illness. In untreated patients who survive their illness, the natural course of fever terminates after 2 to 3 weeks.

R. helvetica has been detected in *Ixodes ricinus* in many European countries, northern Africa, and Asia. Among 4604 clinical rickettsial cases reported in Italy from 1998 to 2002, three cases of a mild form of rickettsiosis were serologically attributed to *R. helvetica*. The *R. helvetica* infection presented as a mild disease in the warm season and was associated with fever, headache, and myalgia and sometimes with a cutaneous rash. Additional evaluation and isolation of the bacterium from clinical samples are needed to confirm the pathogenicity of this bacterium.

R. monacensis has been detected in Europe, northern Africa, and the United States.[7] Recently four human cases have been reported: two in Spain, one case in Italy, and one case in Croatia.[2] Three cases resembled MSF, but an eschar was present in only one patient and a maculopapular rash in two. In Croatia, *R. monacensis* was identified together with *B. afzelii* from a skin biopsy of an 8-year-old patient with erythema migrans but no symptoms consistent with a rickettsial disease.

DIAGNOSIS

Standard Laboratory Features

Hematologic anomalies include anemia with thrombocytopenia, with neutropenia in the acute phase of disease and leukocytosis in the later stages. Non-specific biochemical changes include decreased levels of protein (particularly albumin), sodium, potassium, and chloride and elevated hepatic enzyme levels during the first 10 days of disease. Creatinine phosphokinase and lactic dehydrogenase are also often raised.

Diagnostic Tools

The diagnosis of tick-borne rickettsioses is based on clinical and epidemiologic findings. The diagnosis should be suspected in a febrile patient with a history of tick bite, headache, a rash, and/or a skin lesion consisting of a black necrotic area surrounded by erythema or a pseudofurunculus or crust. The classic features of tick-borne rickettsioses may only occur in 50% to 75% of patients. Confirmation of the diagnosis may be assessed by specific serology or by isolation or molecular identification of the causative organism. For serologic diagnosis, one serum sample should be collected early in the course of the disease; a second sample should be obtained 2 to 3 weeks later. If antibody titers remain negative in these two samples, a later sample must be tested (4–6 weeks). Usually, antibodies are absent in the early phase of the disease. The presence of specific IgM antibodies or a fourfold increase in titer of IgG antibodies from acute-phase illness to the convalescent phase is considered diagnostic. The interpretation of serologic data can be confounded by the cross-reactivity that occurs among spotted fever group rickettsiae. Western blot analysis will yield false-positive results because of cross-reacting antibodies that are directed mainly against lipopolysaccharides. Western blots, particularly in conjunction with sera that have been cross-adsorbed, can also be used to identify the infecting rickettsial species, but the technique is only appropriate for reference laboratories (Fig. 69.5).

To isolate rickettsial organisms from skin biopsy and, blood samples, specimens should be collected before antimicrobial therapy (preferably from the site of tick attachment in the case of skin sampling), and samples must be processed in cell culture using the shell vial technique (only in Biosafety Level [BSL] 3–specialized laboratories). Shell vial culture remains the best tool for the isolation of intracellular bacteria. Several samples can be used for the diagnosis of rickettsiosis by molecular tools, such as ethylenediaminetetraacetic acid (EDTA) blood sample, biopsy specimens of the eschar, swab of the eschar or rash lesions, paraffin-embedded tissues, and arthropods. This specimen collection should be carried out as early as possible in the course of the illness.[17,18] Biopsy material kept in formalin can be used for immunohistochemistry.

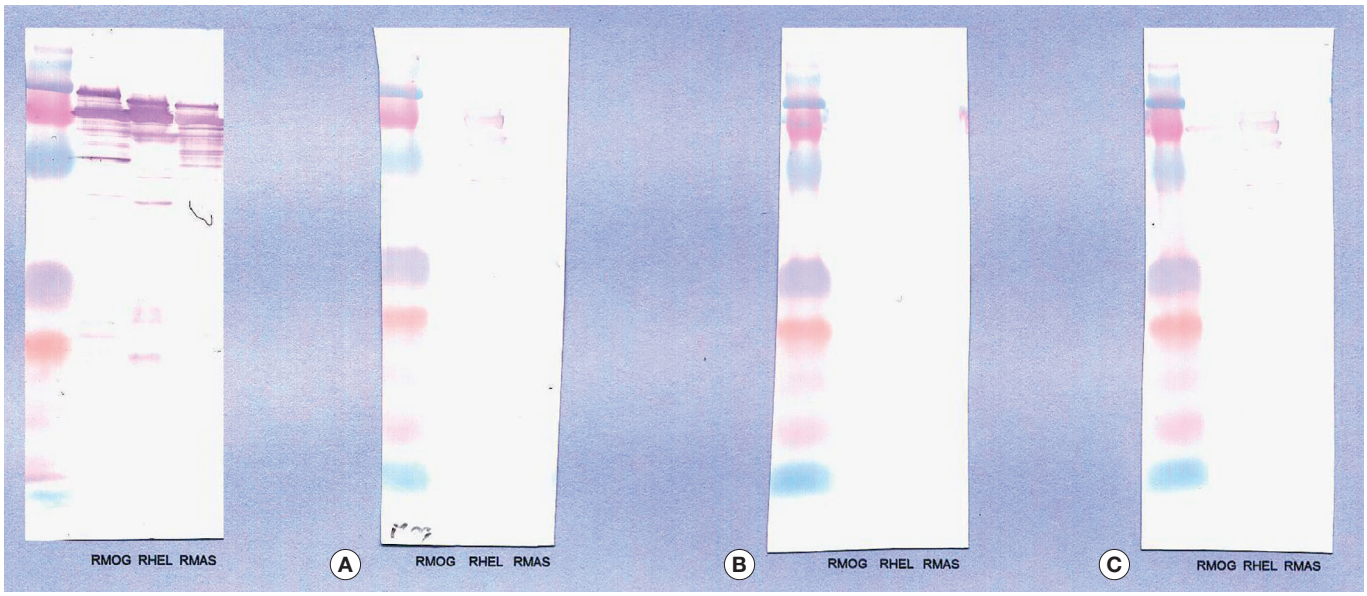

Fig. 69.5 Western blot before and after cross-adsorption with *Rickettsia sibirica mongolitimonae* (A), *R. helvetica* (B), or *R. massiliae* (C). When cross-adsorption is performed with *R. helvetica,* the specific antigen-corresponding line disappears—this implicates *R. helvetica* as the causative micro-organism.

Treatment

Early empirical treatment should be started in any suspected rickettsioses before laboratory confirmation of the diagnosis. Based on in vitro susceptibility and in vivo experience, doxycycline is currently the recommended drug for treating patients with spotted fever group rickettsioses. In adults, 200 mg of doxycycline daily for 2 to 5 days or until 24 hours after apyrexia is most commonly used, but a single 200-mg dose of doxycycline has been shown to be effective for certain spotted fever group rickettsioses.[1] In severe forms of the disease, 200 mg intravenous doxycycline per day followed by 200 mg doxycycline orally per day should be prescribed until complete recovery (10 days). In children and pregnant women, treatment with certain macrolides for 5 to 7 days has been recommended, but a single dose of doxycycline at 5 mg/kg/day is efficient and has no side effect of tooth discoloration. In those allergic to tetracyclines, ciprofloxacin (1.5 g/day orally for 5 days) or chloramphenicol (2 g day for 7–10 days) is effective against spotted fever group rickettsiae. Treatment failure was reported for chloramphenicol and rifampin. The use of corticosteroids in severe forms is controversial. Ineffective antibiotics include β-lactams, aminoglycosides, and cotrimoxazole.

Prevention and Control

Prophylaxis is based on the prevention of tick bite. Early detection (within 20 hours) and appropriate detachment of ticks is essential to avoid the transmission of tick-borne rickettsioses. The classic method of removal is to grasp the tick mouthparts as close to the skin as possible with fine forceps or tweezers and gently lever the arthropod off. To prevent further inoculation, the body should not be squeezed. Any retained fragments should not be dug out, but the site cleaned and antiseptic applied. Antibiotic prophylaxis after tick bites is not justified, even in endemic areas.

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