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The classification of the Rickettsiaceae family has undergone important changes over the past 20 years due to the generalization of the use of gene sequencing and genetic phylogeny. In this chapter, we will focus on Rickettsiae that are pathogenic for humans. Rickettsiae are intracellular alpha proteobacteria associated with eucaryotic hosts (arthropods or helminthes). Based on antigenic and genetic data, Rickettsiae are divided into three groups: (1) the spotted fever group (SFG), which accounts for most tick-borne rickettsioses; (2) the typhus group (TG), which includes *Rickettsia prowazekii*, the agent of epidemic typhus, transmitted by body louse, and *Rickettsia typhi*, the agent of murine typhus, transmitted by rat and cat fleas; and (3) *Orientia tsutsugamushi*, the agent of scrub typhus, transmitted by mites.

Until recently, the diagnosis of rickettsioses was confirmed almost exclusively by serological methods. Serology does not allow discrimination between rickettsiae belonging to the same group. As all these tests detect antibodies, they would be able to make a diagnosis only after 5–7 days of disease onset and hence play no role for initiation of therapy in a suspected case. The recognition of multiple distinct rickettsioses during the last 20 years has been greatly facilitated by the broad use of cell culture systems, molecular methods for the identification of rickettsiae, and polymerase chain reaction (PCR). As a consequence, over a dozen additional rickettsial species or subspecies have been identified as emerging rickettsioses. Another consequence is that there are multiple species of rickettsiae in each country. Several new species were identified in arthropod vectors prior to being isolated in humans. Description of the known rickettsioses could have included these new emerging rickettsioses, which can explain variable clinical descriptions of the first described rickettsioses.

Symptomatic evidence of central nervous system (CNS) involvement is a frequent feature in rickettsial infections. In a large clinical case series of patients with rickettsial disease, abnormal neurological finding (28%) was the most common complication of rickettsial diseases and included encephalopathy (15%), meningitis (5%), meningoencephalitis (5%), and encephalitis (3%). CNS involvement is a result of the systemic nature of these infections and their propensity for invasion of endothelial cells. The degree of insult to the CNS varies according to the various rickettsial infections.

**Epidemiology**

The geographic and temporal distribution of rickettsioses is mainly determined by their vectors (Table 77.1, Figure 77.1). Louse-transmitted diseases occur worldwide. Lice parasitize poor people, preferentially in cold places and during wars. Common fleas such as dog, cat, and rat fleas are reported worldwide, as are their transmitted diseases, murine typhus and flea-borne spotted fever (caused by *Rickettsia felis*). Tick species are highly dependent on their environment; very few are found worldwide, with the exception of *Rhipicephalus sanguineus*, the dog tick, vector of *Rickettsia conorii* (in the Old World). Therefore, tick-transmitted diseases are usually restricted to parts of the world where they can be fed by the local fauna.

**Table 77.1** Main clinical and epidemiological features of Rickettsiae infection.

<table>
<thead>
<tr>
<th>Group</th>
<th>Organism</th>
<th>Arthropod vector</th>
<th>Main clinical features</th>
<th>Prominent neurological features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spotted fever group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rocky Mountain spotted fever</td>
<td><em>Rickettsia rickettsii</em></td>
<td>Tick</td>
<td>No eschar. Rash often purpuric. High fever, 2–5% mortality rate.</td>
<td>Headache (&gt;80%), stupor (20%), meningitis (&gt;20%), ataxia (20%), coma (20%), seizures (10%), decreased hearing (10%), papilledema (&lt;10%)</td>
</tr>
<tr>
<td>Mediterranean spotted fever</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kenya tick typhus</td>
<td><em>Rickettsia conorii</em></td>
<td>Tick</td>
<td>Single eschar or popular rash. High fever, 2–5% mortality rate</td>
<td>Encephalitis, meningitis, meningoencephalitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Deafness, central nerve palsies, Guillain–Barre polyneuropathy</td>
</tr>
<tr>
<td>Israeli spotted fever</td>
<td><em>Rickettsia conorii</em></td>
<td>Tick</td>
<td>Eschar rare, rash, high fever</td>
<td>Encephalitis, meningitis, meningoencephalitis</td>
</tr>
<tr>
<td></td>
<td><em>Rickettsia conorii israelensis</em></td>
<td></td>
<td></td>
<td>Hearing loss (14%)</td>
</tr>
<tr>
<td>Astakhan fever</td>
<td><em>Rickettsia conorii astrakhan</em></td>
<td>Tick</td>
<td>Eschar rare, maculopapular rash (100%), high fever</td>
<td>Hearing loss (14%)</td>
</tr>
<tr>
<td>Indian tick typhus</td>
<td><em>Rickettsia conorii indica</em></td>
<td>Tick</td>
<td>Rash usually purpuric. Eschar rarely found. No lymphadenopathy.</td>
<td></td>
</tr>
<tr>
<td>Siberian tick typhus</td>
<td><em>Rickettsia sibirica</em></td>
<td>Tick</td>
<td>Rash (100%), eschar (77%), high fever</td>
<td>Encephalitis. Rare, usually mild</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Rickettsioses</th>
<th>Tick</th>
<th>Eschar (75%) may be multiple, rash (63%), lymphangitis (25%), and adenopathy. Ropelike lymphangitis between eschar and lymph node</th>
<th>Meningitis, cerebellitis (2 unreported cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japanese spotted fever</td>
<td>Rickettsia japonica</td>
<td>Eschar (91%) and rash (100%)</td>
<td>Meningoencephalitis</td>
</tr>
<tr>
<td>African tick-bite fever</td>
<td>Rickettsia africae</td>
<td>Outbreaks and clustered cases common (74%). Eschars (95%), which are often multiple (54%), maculopapular or vesicular rash (50%) and lymphadenopathy, aphous stomatitis</td>
<td>Subacute neuropathy</td>
</tr>
<tr>
<td>Queensland tick typhus</td>
<td>Rickettsia australis</td>
<td>Rash (100%) sometimes vesicular, eschar (65%), high fever, and lymphadenopathy</td>
<td>Confusion, transient visual hallucinations, seizures, rare</td>
</tr>
<tr>
<td>Flinders Island spotted fever</td>
<td>Rickettsia honei</td>
<td>Rash (85%), eschar (25%), and lymphadenopathy (55%)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Scalp eschar and neck lymphadenopathy (SENLAT), tick-borne lymphadenopathy (TBOLA)</td>
<td>Rickettsia slovaca  Rickettsia raoultii</td>
<td>Typical large eschar on the scalp with painful cervical lymphadenopathy. Fever and rash rare</td>
<td>Meningoencephalitis, very rare</td>
</tr>
<tr>
<td>Far Eastern spotted fever</td>
<td>Rickettsia helongjiangensis</td>
<td>Rash, eschar, and lymphadenopathy</td>
<td>Not reported</td>
</tr>
<tr>
<td>Rickettsial pox</td>
<td>Rickettsia akari</td>
<td>Vesicular rash, eschar, high fever</td>
<td>Headache</td>
</tr>
<tr>
<td>Flea-borne spotted fever</td>
<td>Rickettsia felis</td>
<td>Vescicular rash</td>
<td>Not reported</td>
</tr>
<tr>
<td>Rickettsia helvetica</td>
<td>Tick</td>
<td>No rash, fever, or lymphadenopathy. Sudden death</td>
<td></td>
</tr>
<tr>
<td>Rickettsia aeschlimannii</td>
<td>Tick</td>
<td>Rash, eschar, lymphadenopathy, high fever</td>
<td></td>
</tr>
<tr>
<td>American boutonneuse fever</td>
<td>Rickettsia parkeri</td>
<td>Rash, eschar, lymphadenopathy</td>
<td></td>
</tr>
<tr>
<td>Spotted fever</td>
<td>Rickettsia massiliae</td>
<td>Rash, eschar common, no lymphadenopathy</td>
<td></td>
</tr>
<tr>
<td>Rickettsia philipi</td>
<td>tick</td>
<td>No rash. Eschar, lymphadenopathy, and high fever</td>
<td></td>
</tr>
</tbody>
</table>

**Typhus**

| Epidemic typhus                                                  | Rickettsia prowazekii             | Human louse                                                                                                               | Encephalitis, frequent                          |
| Murine typhus                                                    | Rickettsia typhi                  | Flea                                                                                                                      | Encephalitis, less frequent than in epidemic typhus (<5%). Subacute meningitis or meningoencephalitis |

**Scrub typhus**

| Orientia tsutsugamushi                                          | Chigger (thrombiculide mite)     | Eschar, generalized lymphadenopathies. Rash                                                                                   | Encephalitis, meningitis, deafness, cerebellitis, papilledema |

**Figure 77.1** Geographic distribution of the spotted fever group of rickettsioses and of scrub typhus.
Tick behavior may determine the targeted human population and the seasonality. It may also influence the clinical presentation. For example, *Amblyomma* ticks are aggressive hunting ticks. They frequently attack in groups. This behavior explains clustered cases and several inoculation eschars in African tick-bite fever.

**Pathophysiology**

Rickettsiae are intracellular parasites of phagocytes that invade the CNS as part of a systemic infection. Rickettsiae can be divided into two categories according to their targets during natural infection: (1) organisms that parasitize vascular endothelial cells (*Rickettsia rickettsii, R. conorii, TG Rickettsiae*); and (2) organisms that parasitize both endothelial cells and phagocytes (*O. tsutsugamushi*). In terms of their intracellular niches, *O. tsutsugamushi* and the Rickettsiae lyse the phagosome and replicate, predominantly in the cytoplasm of host cells. The central pathophysiological event of Rickettsia infection, including CNS infection, has been identified as parasitism of vascular endothelial bacteria by blood-borne bacteria. Histological studies have confirmed rickettsial invasion of vascular endothelial cells in the brains of humans and experimentally infected mice. Rickettsiae invade and multiply at focal points in these small blood vessels, causing necrosis and proliferation of endothelial cells and development of platelet-fibrin thrombi at the site of damage, resulting in partial or even complete occlusion of the vascular lumen. These changes are associated with perivascular inflammatory response, initially consisting of polymorphonuclear and monocytes, with the subsequent appearance of lymphocytes, macrophages, and plasma cells. This is the late phase of vascular damage, in which the immune response plays a major role. The classically described “typhus nodules” in the brain show similar pathology. Vasculitis is responsible for skin rash, microvascular leakage, edema, tissue hypoperfusion, and end-organ ischemic injury.

**Clinical features**

Early diagnosis of these infections from clinical features is a difficult task due to the non-specificity of early symptoms and signs – often resembling benign viral illness – symptomatology varying from mild to severe, low index of suspicion, absence of rash in the initial 2–3 days, and rash as a clinical feature of Rickettsia being neither sensitive nor specific. Fever, rash, and headache were the initial 2–3 days, and rash as a clinical feature of Rickettsia being neither sensitive nor specific. Fever, rash, and headache were considered for years the diagnostic clues for rickettsial diseases. Indeed, this remains a major triad, but a spotless phenotype of Rocky Mountain spotted fever (RMSF) has been identified, and many of the newly described rickettsial diseases have no rash. Major findings in rickettsioses include fever in a patient with exposure to a potential vector that may be associated with rash, inoculation eschar, or localized lymphadenopathy. Table 77.1 shows major clinical symptoms with specificities for different species of Rickettsiae.

**Spotted fever group rickettsioses**

**Rocky Mountain spotted fever**

In the early phases of the disease, most patients have non-specific signs such as fever, headache, malaise, arthromyalgias, and nausea. Abdominal signs, especially in children, are often prominent, leading sometimes to erroneous diagnosis such as appendicitis. Only approximately 60% of patients recall a tick bite. The rash appears late in the course of the disease (3–5 days) and may be absent in 10% of patients. In contrast with most other SFG rickettsioses, *R. rickettsii* does not generally elicit an eschar at the tick-bite site. As a result, when only non-specific symptoms dominate the clinical presentation, misdiagnosis and treatment delay can occur.

The frequency and severity of neurological signs depend on the severity of illness. Headache is frequent (79–91%) and is one of the most consistent clinical findings in RMSF. Neurological complications are frequently the cause of death. Serious CNS complications include stupor, delirium, seizures, ataxia, papilledema, focal neurological deficits, and coma. coma is more likely to occur in fatal than in non-fatal cases. Cranial and peripheral nerve palsies can occur, of which hearing loss is the most frequent. The incidence of meningeval signs is >20% and among them about 60% are accompanied by abnormalities of the cerebrospinal fluid (CSF). The white blood cell (WBC) count in the CSF is rarely more than 100/mm³. Polymorphonuclear cells may predominate, but more commonly lymphocytes predominate. CSF glucose is decreased in 8% of patients and protein is elevated in 35% of patients. Abnormalities in neuroimaging studies are not common in patients with RMSF, and when present they are often subtle. Since RMSF may present without rash, this illness must be considered in the differential diagnosis of every patient with encephalitic manifestations in endemic countries, especially if an appropriate epidemiological history is present. In general, the CNS manifestations resolve in parallel with the fever if adequate treatment is begun early in the course of illness. However, neurological sequelae are common following RMSF. They include learning disabilities, behavioral disturbance, depression, transverse myelitis, aphasia, and deafness.

**Mediterranean spotted fever**

After an average asymptomatic incubation of 6 days (range of 1–16 days), the onset of Mediterranean spotted fever (MSF) is abrupt and typical cases present with high fever (>39 °C), flu-like symptoms (i.e., headache, chills, arthromyalgia), and a black eschar (tache noire) at the tick-bite site. Eschar is indolent and is usually localized on the trunk, the legs, and the arms. Usually the rash follows the fever within 2–3 days. It is rarely delayed until the 5th day and is almost never absent entirely (1–4% of cases). Gastrointestinal symptoms may be present in about 30% of patients and are more likely to be present in children. Headache is a common sign in MSF and is usually intense. Neurological complications occur in 10–15% of MSF cases. Hearing loss is the most frequent complication. Meningitis can occur, but is less common than in RMSF. Serious CNS complications include stupor, delirium, seizures, ataxia, focal neurological deficits, and coma and are usually associated with other organ failures representing the “malignant form” of MSF. This very severe form accounts for 5–6% of MSF cases and with a high mortality rate.

**Other spotted fever group rickettsioses**

Table 77.1 summarizes the main clinical signs of other SFG rickettsioses and identifies which of them can manifest with neurological symptoms.
Typhus group rickettsioses

Epidemic typhus
Typhus is transmitted by the human body louse, which lives in human clothing and thrives in areas of low socioeconomic status, owing largely to poor hygiene and close living quarters of multiple people and animals. Humans are the reservoirs and lice are the vectors. The organism multiplies in the gut and can survive for weeks in human feces. Patients who recover can have latent reactive infections. The majority of patients with epidemic typhus experience the abrupt onset of fever, malaise, and coughing. A severe headache is nearly invariably present in patients with typhus and has been used as a key clinical criterion for identifying suspected cases in epidemics; severe leg myalgias have also been used in this way. Infected patients may also complain of a number of other non-specific symptoms, including abdominal pain, nausea, and diarrhea.

The rash of epidemic typhus classically begins several days after the onset of symptoms, appearing as a red macular or maculopapular eruption on the trunk that later spreads centrifugally to the extremities. Rash occurs in 20–80% of people, and is rarely observed on dark skin. The majority of patients with epidemic typhus manifest one or more abnormalities in CNS function. Common neurological symptoms include confusion and drowsiness. Coma, seizures, and focal neurological signs may develop in a minority of patients. Delirium and coma have been reported in 35% and 39% of fatal cases, respectively.

Murine typhus
Murine typhus is common in hot and humid climates such as Northern Africa, Southern Europe, and Southeast Asia. Murine typhus is typically a mild illness associated with rat and opossum fleas. The onset of illness is usually abrupt, with non-specific symptoms such as fever, headache, chills, and myalgias. Gastrointestinal symptoms are particularly common in children. Rash occurs in 20–54% of patients near the end of the first week of illness. It typically begins as a maculopapular eruption on the trunk and spreads peripherally. The rash does not typically involve the face, palms of the hands, or soles of the feet. Symptoms of severe CNS disease such as seizures, stupor, and ataxia are infrequent, found in <5% of patients. However, cases of subacute aseptic meningitis or meningoencephalitis and CNS hemorrhage have been reported in patients with murine typhus without rash or other systemic findings. These cases suggest that neurological involvement in murine typhus is more common than previously described and that murine typhus should be included in the diagnosis of subacute meningoencephalitis and meningoencephalitis, especially if an appropriate epidemiological history is present.

Scrub typhus
Scrub typhus is extremely common in Asia and specifically in Southeast Asia. It is transmitted by the trombiculid mite larva. Scrub typhus may begin insidiously with headache, anorexia, and malaise, or start abruptly with chills and fever after a 10-day incubation period. Macular or maculopapular rash is infrequent. More than 50% of patients have an eschar at the inoculation site. The eschar may develop before the onset of systemic symptoms, and can occur in multiple locations. Generalized lymphadenopathy occurs in the majority of patients. Periorbital edema, edema of dorsum of hand or foot, or generalized edema, polyserositis, and hepatosplenomegaly are sometimes seen. The neurological signs are similar in many respects to other rickettsial diseases in that the headache is nearly always present. Meningismus or meningitis has been found in 5.7–13.5% of patients. However, in a series of 25 patients who underwent lumbar puncture in the absence of overt signs, 48% had reactive spinal fluid showing a mild mononuclear pleocytosis. Scrub typhus should be considered one of the causes of aseptic meningitis in areas of endemy. A small proportion of patients develop tremors, delirium, altered mental status, and coma. Acute hearing loss occurred in 6 out of 72 patients in Thailand.

Complications
Disseminated intravascular coagulation, non-cardiogenic pulmonary edema, gangrene of digits and earlobe, and hemophagocytic syndrome are some of the dreaded complications seen in rickettsial diseases (Figure 77.2).

Scoring system for diagnosis
The Rathi, Goodman, and Aghai (RGA) scoring system (Table 77.2) uses clinical, laboratory, and epidemiological features to diagnose spotted fever group rickettsias in resource-poor settings. On receiver operating characteristic (ROC) curve analysis, the cut-off score with the highest accuracy was found to be 14, with a sensitivity and specificity of 96.15% and 98.84%, and a positive predictive value (PPV) and negative predictive value (NPV) of 98.0% and 97.7%, respectively. When applied to patients presenting with fever of unknown source, a clinical score of 14 or more on the RGA scoring system has sensitivity and specificity similar to the detection of specific IgM antibody by enzyme-linked immunosorbent assay (ELISA).
SFG rickettsiae, preferably before antibiotic therapy. Molecular amplification with PCR from eschar biopsy or ethylenediamine tetraacetic acid (EDTA) blood or from ticks targets different genes (17-kd protein, citrate synthase, \textit{ompA}, \textit{ompB}, "gene D") and allows the detection and identification of the causal agent with certitude. Biopsies can also be used for immunohistochemistry. Blood sample is the best clinical sample for PCR in scrub typhus. Immunological detection using specific antibodies or monoclonal antibodies allows detection in blood and other tissues.


table 77.2 RGA scoring system to diagnose spotted fever rickettsioses (total score = 35). Source: Rathi 2011. Reproduced with permission.

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Score</th>
<th>Laboratory feature</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Living in rural area</td>
<td>1</td>
<td>Hemoglobin &lt;9 gm/dL</td>
<td>1</td>
</tr>
<tr>
<td>Pets in household</td>
<td>1</td>
<td>Platelets &lt;1,500,000/dL</td>
<td>1</td>
</tr>
<tr>
<td>Tick exposure</td>
<td>2</td>
<td>CRP ≥50 mg/dL</td>
<td>2</td>
</tr>
<tr>
<td>Tick bite</td>
<td>3</td>
<td>Serum albumin &lt;3 gm/dL</td>
<td>1</td>
</tr>
<tr>
<td>Non-exudative conjunctival congestion</td>
<td>2</td>
<td>Urine albumin &gt;2+</td>
<td>1</td>
</tr>
<tr>
<td>Maculopapular rash</td>
<td>1</td>
<td>SGPT &gt;100 U/L</td>
<td>2</td>
</tr>
<tr>
<td>Purpura</td>
<td>2</td>
<td>Serum Na &lt;130 meq/L</td>
<td>2</td>
</tr>
<tr>
<td>Palpable purpura/ ecchymosis/necrotic rash</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash appearing 48–96 hrs after fever</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pedal edema</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash on palms/soles</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>25</td>
<td>TOTAL 10</td>
<td></td>
</tr>
</tbody>
</table>

Investigations
Culturing remains extremely difficult for these organisms, and diagnosis mainly relies on serology, PCR, and immunological detection. The reference technique for serology is microimmunofluorescence (MIF). Many cross-reactions are observed, and determination of the precise infecting species may be difficult. Testing of several antigens on the same slide to compare reactivity may help in discriminating among cross-reacting agents. Western blot may be more specific in early sera and cross-absorption may help to discriminate SFG rickettsiae.

PCR is an appropriate tool for the diagnosis of rickettsioses and can be used on samples of blood, skin, and arthropods. Skin biopsy of the inoculation eschar is the best clinical sample for the SFG rickettsiae, preferably before antibiotic therapy. Molecular amplification with PCR from eschar biopsy or ethylenediamine tetraacetic acid (EDTA) blood or from ticks targets different genes (17-kd protein, citrate synthase, \textit{ompA}, \textit{ompB}, "gene D") and allows the detection and identification of the causal agent with certitude. Biopsies can also be used for immunohistochemistry. Blood sample is the best clinical sample for PCR in scrub typhus. Immunological detection using specific antibodies or monoclonal antibodies allows detection in blood and other tissues.

Treatment
Early empirical antibiotic therapy should be prescribed in any suspected rickettsioses before confirmation of the diagnosis. Early treatment may prevent many but not all cases in which CNS complications occur. Other variables such as age and G6PD deficiency may be important factors in the risk of neurological complications. The most useful treatment in children and in adults is doxycycline. The length of treatment is unknown, but it should be continued orally for at least 3 days post fever. In children, the risk of dental staining by doxycycline is negligible when a single, relatively short (5–10 days) course of treatment is administered. It can be prescribed in a shorter course (1 day) for typhus, scrub typhus, and MSF. Doxycycline should not be given to pregnant women; therefore chloramphenicol should be used. Typhus group rickettsias are also susceptible to erythromycin. Sulfonamides are contraindicated in rickettsial diseases, as they increase morbidity and mortality, either by delaying institution of appropriate antibiotics or directly stimulating the growth of organisms.

Further reading