

Typhus and the spotted fevers

Ever in the returning traveller has a wide differential diagnosis. Although the majority of patients suffer illnesses as easily acquired at home as abroad, the assessment process rightly prioritizes the exclusion of imported infections which may prove rapidly fatal or have public health implications, such as malaria and the viral haemorrhagic fevers. Given this focus and the infrequency with which many physicians assess such patients, there is potential for other imported infections to be overlooked. Rickettsial diseases are thought to be some of the most underdiagnosed infections in returning travellers (van Eekeren et al, 2018), despite being eminently treatable and potentially fatal if unrecognized. This article discusses the major *Rickettsia* species, including their epidemiology, mode of transmission and clinical and laboratory features, along with specific investigations and treatment.

What are *Rickettsia*?

Rickettsia are obligate intracellular Gram-negative bacteria, broadly subdivided into:

- The spotted fever group
- The epidemic typhus group
- *Orientia* (a closely related genus within the Rickettsiaceae family)

What diseases do they cause?

Rickettsia are responsible for a variety of different infections, with considerable overlap between the features of each disease. Important diseases and their causative organisms include:

Spotted fever group

- Rocky Mountain spotted fever (*R. rickettsii*)
- Mediterranean spotted fever (*R. conorii*)
- African tick bite fever (*R. africae*).

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Epidemic typhus group

- Endemic (murine) typhus (*R. typhi*)
- Epidemic typhus (*R. prowazekii*).

Orientia group

- Scrub typhus (*O. tsutsugamushi*).

How is infection acquired?

Rickettsia infections are vector borne, resulting from contact with one of a variety of arthropods:

Ticks and mites

The spotted fevers are spread by the bite of hard ticks (*Ixodidae* – Figure 1) with different tick species responsible for the transmission of different diseases (Eldin and Parola, 2018). *Rickettsia* infection can be passed vertically from mother to larvae, so newborn ticks can be immediately infectious. The majority of infections are caused by bites from ticks in the nymph stage of their life cycle, when they may be as small as the full stop at the end of this sentence. Given this small size it is easy to imagine how the tick could remain attached for several days without being noticed.

O. tsutsugamushi is transmitted by the bite of infected trombiculid mites (also known as chiggers) (Hendershot and Sexton, 2009) rather than ticks, with the majority of mites gaining their infection vertically rather than from an infected host.

Lice

Epidemic typhus (*R. prowazekii*) is predominantly spread by the human body louse (Bechah et al, 2008). Although lice do bite humans, the bites themselves are not infectious – instead, humans become infected either by inoculation of louse faeces through broken skin, or by inoculation of louse body fluid following the crushing of lice. A few cases in the eastern United States have been associated with exposure to the southern flying squirrel, which acts as a reservoir of infection – the exact route by which these infections are acquired remains unclear (Duma et al, 1981).



Figure 1. *Ixodidae* tick.

Fleas

Endemic (murine) typhus is spread by infected fleas, either directly through bites or indirectly by inoculation of their faeces through broken skin. The usual reservoir of infection is rodents, particularly rats, although other mammalian species can also fill this role (Peniche Lara et al, 2012).

What are the risks for infection?

As with all imported infections, a thorough exposure history is the key to narrowing down the diagnosis of *Rickettsia* infection, as is a good understanding of the geographical areas which the traveller has visited.

Exposure history

Humans are at risk of infection whenever they venture into the native habitat of the arthropod vectors. For Rocky Mountain spotted fever, African tick bite fever and scrub typhus, the exposure history is usually one of time spent in rural areas, often involving walks through long grass in regions inhabited by the mammalian species that the ticks and mites use as hosts. Mediterranean spotted fever, by contrast, is more often a disease of urban and semi-urban environments as the tick vector predominantly preys on domestic dogs (Rovero and Raoult, 2008). The risk of endemic typhus is directly related to the size of the local rodent population, thus coastal regions tend to be higher risk; buildings with rodent infestations pose a particular risk of exposure. Epidemic typhus is primarily a disease of extreme poverty, causing outbreaks in environments such as refugee and migrant camps; the risk of infection in a returning

traveller is therefore much lower than for other *Rickettsia* species, although imported cases have been reported (Raoult et al, 1998).

Geography

Different *Rickettsia* species can have quite different geographical distributions; many infections in the spotted fever group are named after the region where they are most commonly found (Figure 2, Table 1):

- Rocky Mountain spotted fever has a much wider range than its name suggests, with cases reported from almost every state within the United States of America, parts of Canada and throughout central and south America (McFee, 2018)
- Mediterranean spotted fever is found in north Africa and the countries of southern Europe, including Spain, Italy, France, Greece, Turkey and the countries encircling the Black Sea (Roverly and Raoult, 2008)

- African tick bite fever is found across much of sub-Saharan Africa, but cases have also been reported in the Caribbean (Tsai et al, 2008)
- Endemic typhus has a worldwide distribution, although it is particularly associated with port cities (Peniche Lara et al, 2012)
- Epidemic typhus tends to occur in cold conditions which cause people to wear more clothes and stay in enclosed conditions. It is therefore more common at high altitude, particularly in the horn of Africa and in central America (Bechah et al, 2008)
- Scrub typhus is found in the 'tsutsugamushi triangle' which covers much of southern and south-east Asia, stretching from Afghanistan in the west to Korea and Japan in the north east and northern Australia in the south east (Hendershot and Sexton, 2009).

What are the clinical features of *Rickettsia* infection?

One of the reasons that *Rickettsia* infections may be missed is that they often present with very non-specific symptoms, which follow an incubation period of between 5 and 10 days.

The underlying pathophysiology is of a vasculitic infection, with *Rickettsia* invading the endothelial cells of blood vessels throughout the body (Bechah et al, 2008). Fever is almost always a feature at presentation, with myalgia, arthralgia and headache also common. The textbook vasculitic rash usually follows a few days after the onset of fever, although it can be hard to determine exactly when it first appears, particularly in darker skinned individuals. In those with light skin tone it is usually obvious, presenting as a non-blanching, purpuric rash (Figure 3).

Infection of the vascular endothelium can result in pathology within any organ system

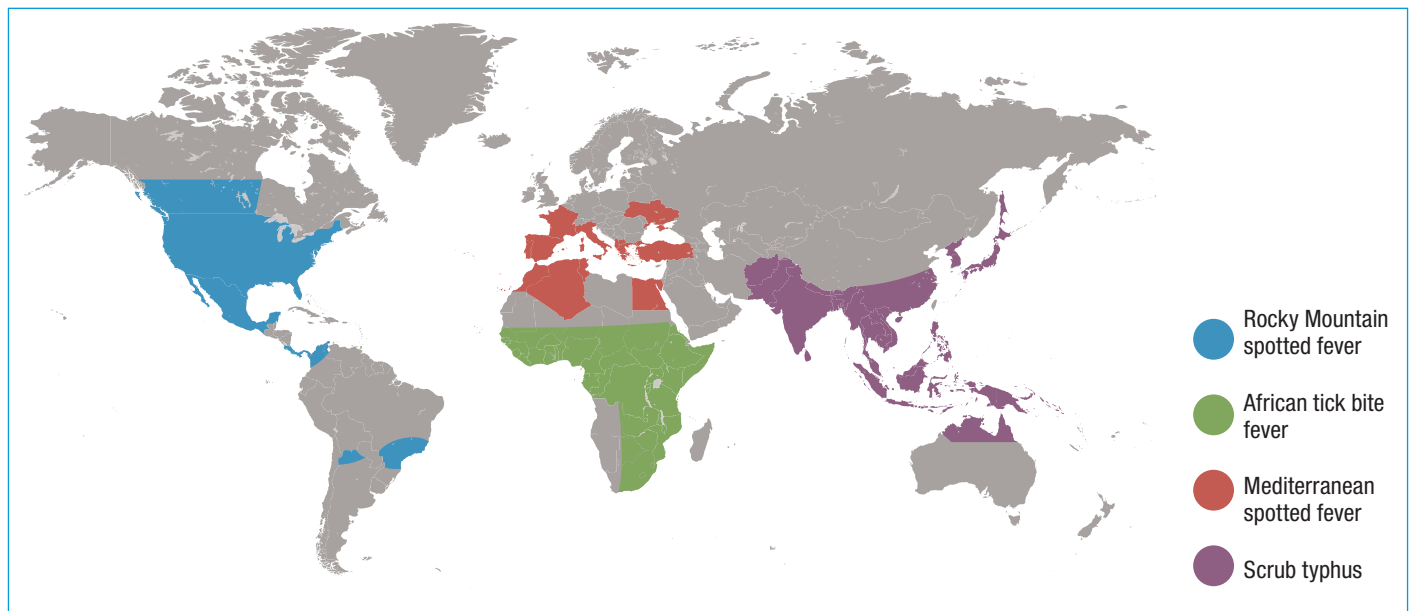


Figure 2. Endemic regions for selected *Rickettsia* species.

Table 1. Key features of selected <i>Rickettsia</i> species					
Group	Species	Disease	Vector	Geography	Eschar?
Spotted fever	<i>R. rickettsii</i>	Rocky Mountain spotted fever	Tick	Most of continental America, central and south America	Yes
	<i>R. conorii</i>	Mediterranean spotted fever		Southern Europe and north Africa	
	<i>R. africae</i>	African tick bite fever or tick typhus		Most of sub-Saharan Africa	
Epidemic typhus	<i>R. prowazekii</i>	Epidemic typhus	Louse	Mainly highland regions in south America and the horn of Africa	No
	<i>R. typhi</i>	Endemic (murine) typhus	Flea	Worldwide	No
Orientia	<i>O. tsutsugamushi</i>	Scrub typhus	Mite	'Tsutsugamushi triangle'	Yes



Figure 3. Typical rash.

with varying degrees of severity. Hepatitis is common, as is mild renal impairment, with pneumonitis a rarer complication. In severe cases ischaemia of the extremities may occur, resulting in digital necrosis and autoamputation. Neurological involvement can be severe, with manifestations such as convulsions and coma well recognized. However, in most cases the only discernible neurological feature is malaise or slowing of cognition – it was this that led the ancient Greeks to name the condition ‘typhus’, meaning ‘smoke’.

For the spotted fevers and scrub typhus, finding evidence of the inoculating bite is a very useful clue to the diagnosis. Occasionally the responsible tick or mite is found still attached, but much more commonly seen is the eschar that develops at the site of the bite (Figure 4). Eschars can be small and hidden in areas such as groin folds and the natal cleft, so a thorough examination may be required to locate them; however, they will most often be found on the lower legs. In some cases individuals may have multiple eschars – this is more common in African tick bite fever, as the species of tick that transmits this infection is particularly aggressive (Peniche Lara et al, 2012). It is important to remember that patients with epidemic or endemic typhus will not have an eschar, thus the absence of one does not exclude *Rickettsia* infection (Table 2).

While all *Rickettsia* species can cause a spectrum of disease severity, some species tend to be more virulent than others. Endemic typhus and African tick bite fever tend to cause a relatively mild illness while untreated epidemic typhus and Rocky Mountain spotted fever carry a significant mortality. Mediterranean spotted fever and

scrub typhus usually fall somewhere in between the two extremes, although fatal cases of both are well documented.

What laboratory tests should be performed?

Thrombocytopenia, raised bilirubin and transaminase levels and renal impairment are common features of all *Rickettsia* infections (Hendershot and Sexton, 2009). However, these are frequently features of other imported infections and thus can only suggest, not confirm, the diagnosis.

Rickettsia are fastidious organisms and extremely difficult to grow in culture media. As a result, alternative techniques are needed to make the diagnosis. These comprise molecular methods detecting *Rickettsia* DNA, and serological methods detecting the host immune response. In the UK these tests are processed at Public Health England’s Rare and Imported Pathogens Laboratory currently based at Porton Down; local trust laboratories can arrange for this testing to be performed if clinically indicated.

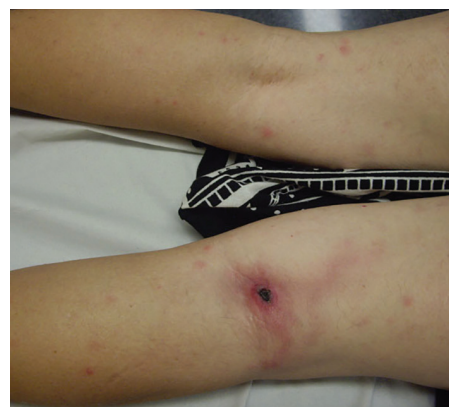


Figure 4. Tick bite eschar.

Molecular methods

Rickettsia DNA may be found in the blood of patients with an acute infection – an EDTA (ethylenediaminetetraacetic acid) sample is required for this test. However, DNA is only present in the bloodstream very briefly, usually disappearing before presentation, so this is not a reliable method of diagnosis. More likely to yield a positive result is a sample taken from the eschar, or from the cutaneous vasculitic lesions that are a feature of the disease (Fournier and Raoult, 2004). Although a swab of the eschar (in viral transport medium) may be positive, a punch biopsy of the lesion is a more reliable sample if it can be promptly obtained, although there may be logistical difficulties in achieving this. As with all tissue samples for microbiological investigation, the biopsy should be sent in sterile saline, not formalin, as the preservative interferes with the polymerase chain reaction.

Serology

Serology can be performed to look for specific antibodies to *Rickettsia* species. However, the antibody response may take several weeks to develop, thus serology cannot be used to make

Table 2. Clinical and laboratory features of *Rickettsia* infections plus empiric treatment

Clinical features	Fever Headache Malaise Arthralgia Myalgia Abdominal pain Vasculitic rash Digital ischaemia Convulsions Coma Digital ischaemia Eschar
Laboratory features	Thrombocytopenia Elevated bilirubin levels Elevated transaminase levels Renal impairment
Specific diagnostic tests	Blood – serology Blood – polymerase chain reaction Biopsy (eschar/rash) – polymerase chain reaction
Treatment	Doxycycline*
*if doxycycline is contraindicated urgently discuss therapy with an infection specialist	

an acute diagnosis of *Rickettsia* infection. Interval testing to look for seroconversion a few weeks post-infection is usually required – a four-fold rise in antibody titre is considered diagnostic. There is significant antibody cross reactivity between closely related *Rickettsia* species (La Scola and Raoult, 1997), but it is usually possible to determine at the very least which broad group of species the patient has been exposed to.

What treatment should be given?

Owing to the non-specific nature of the clinical features and initial laboratory results, plus the limitations of the molecular and serological tests, confirming a diagnosis of *Rickettsia* infection is often not possible until some time after the acute presentation. Given the potentially life-threatening nature of these infections it is essential that empiric therapy is instigated when the diagnosis is first considered, rather than waiting for confirmation. Beginning empiric therapy should occur in concert with investigation for other causes of fever in the returning traveller; malaria must always be excluded by blood films or antigen testing and blood cultures should always be performed to investigate for typhoid fever. In practice, returning travellers will often receive a combination of empiric therapies, with treatment for *Rickettsia* infection given alongside a broad spectrum antimicrobial; ceftriaxone is often favoured because of its activity against *Salmonella typhi*.

Doxycycline is the drug of choice for treating most *Rickettsia* infections and is extremely effective; indeed, failure to improve after 48 hours of treatment should prompt a reconsideration of the diagnosis (Botelho-Nevers et al, 2012). The use of doxycycline is usually discouraged in young children because of concerns about its potential side effect of teeth discolouration. However, the risk of this occurring following a short course of doxycycline is low and outweighed by the benefits of receiving the best treatment for what can be a life-threatening infection. Indeed, the United States Centers for Disease Prevention and Control currently recommends the use of doxycycline as first line treatment for children of all ages with Rocky Mountain spotted fever (Centers for Disease Control and Prevention, 2017).

When doxycycline cannot be used – in true allergy or in pregnant women – alternative agents must be considered. One

option is chloramphenicol, although it is less effective than doxycycline and comes with its own toxicity profile (Botelho-Nevers et al, 2012). Azithromycin is an effective therapy for scrub typhus (Wee et al, 2017) and can be considered for treating some other species, as can rifampicin and fluoroquinolones (Botelho-Nevers et al, 2012). The choice of agent will be influenced by the area of the world to where the patient has travelled; thus, when doxycycline is thought to be contraindicated, discussion with an infection specialist is strongly recommended.

Conclusions

Infection as a result of *Rickettsia* species may well be overlooked in returning travellers. Given the potentially severe sequelae of such infections, physicians should consider the diagnosis in patients with compatible clinical and laboratory features, instigating empiric therapy while arranging definitive diagnostic investigations. Suspected cases should be discussed with an infection specialist. **BJHM**

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KEY POINTS

- *Rickettsia* infections are an underdiagnosed cause of fever in the returning traveller.
- Although many infections are mild, more severe cases can be life threatening if untreated.
- Clinical features are non-specific but fever, headache and myalgia predominate. The characteristic rash may not always be visible and not all species are associated with eschars.
- Laboratory features that might suggest *Rickettsia* infection include thrombocytopenia and transaminitis.
- Specialist tests are required to make the diagnosis – if possible, perform a biopsy of the eschar or rash for polymerase chain reaction, as well as collecting blood samples for polymerase chain reaction and serology.
- All patients with suspected *Rickettsia* infection, including children, should be treated empirically with doxycycline – if doxycycline is contraindicated, urgently discuss the alternatives with an infection specialist.

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