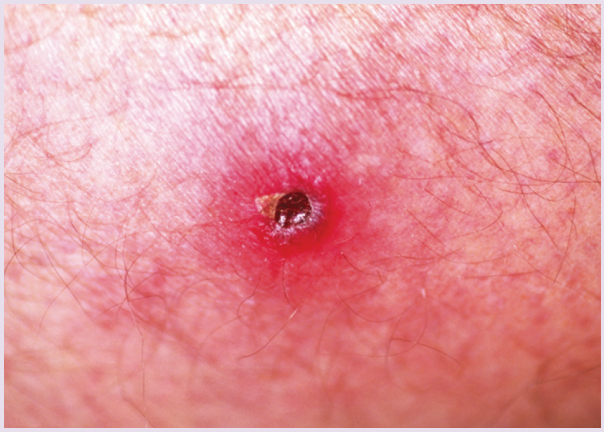
30 *Rickettsia* spp.



A university professor returned from a botanical expedition to Kenya feeling generally unwell. He was complaining of a headache. He also noticed a large, swollen, black lesion on his thigh that was painful (**Figure 30.1**). Thinking he had injured himself and that it was now infected, he went to his primary healthcare provider who gave him co-amoxiclav. Over the next few days, the lesion did not respond and he continued to feel unwell with headache and **myalgia**. He presented to a local travel clinic where the doctor identified the lesion on his thigh as a tick bite. He also noticed that the patient had regional **lymphadenopathy**. Making a provisional diagnosis of rickettsiosis the doctor took blood for **serology** and started the patient on an appropriate antibiotic.

Figure 30.1 Tick bite showing the black lesion with surrounding erythema. *From Dr P Marazzi / Science Photo Library, with permission.*

1. WHAT IS THE CAUSATIVE AGENT, HOW DOES IT ENTER THE BODY AND HOW DOES IT SPREAD A) WITHIN THE BODY AND B) FROM PERSON TO PERSON?

CAUSATIVE AGENT

The taxonomy and nomenclature of the *Rickettsiales* in the Alphaproteobacteria division has undergone a major revision based upon 16S rRNA sequences. Currently, the Rickettsiales contains the *Anaplasmataceae* and the *Rickettsiaceae*. The former contains *Anaplasma*, *Ehrlichia*, and *Wolbachia* whereas the latter contains *Rickettsia* and *Orientia* all of which cause human disease. *Coxiella burnetti* is now included in the γ-proteobacteria along with *Legionella* and *Francisella*. Other significant human pathogens in the Alphaproteobacteria are *Brucella* and *Bartonella* belonging to the *Rhizobiales*. An interesting evolutionary issue is the origin of the mitochondria in eukaryotic cells. One view puts the ancestral bacterial origin within the Rickettsiales with the closest genome sequence that of *R. prowazekii*, whereas the other opinion is the organism was a free living alphaproteobacterium that belonged to a now extinct sister group to all Alphaproteobacteria.

Frequently, *Rickettsia* are given species names relating to their original geographic location. There are many species of *Rickettsia* found in nature, only some of which have been linked to illness (**Table 30.1**) and present clinically as spotted fevers, typhus or scrub typhus. The *Rickettsia* are divided into two main groups, the arthropod-related group containing those associated with human and animal disease and a broader group that infects a wider range of hosts including protozoa, algae, moths, leeches, and beetles. Those found associated with arthropods are separated into four groups: the Ancestral Group (AG) is formed of *R. bellii* and *R. canadensis*, the Transitional Group (TRG) consisting of *R. felis* (cat-flea typhus) and *R. akari* (Rickettsial pox), the Typhus Group (TG) *R. prowazekii*, (Epidemic typhus), *R. typhi* (murine typhus) and the Spotted Fever Group (SFG) which is the largest and consists of, for example, *R. rickettsia* (Rocky Mountain Spotted Fever), *R. conori* (Mediterranean Spotted Fever or Boutonneuse Fever [RMSF]), *R. africae* (African Tick Bite Fever) and *R. sibirica* (Siberian Tick Typhus). An alternative (later) classification scheme suggests a different arrangement of groups based on a wider range of *Rickettsia*-like bacteria with four species closely related to *Rickettsia* such as *Orientia*, and *Pelagibacter* and ten groups of the *Rickettsiae* (Hydra, Torix, Rhizobius, Bellii, Adalia, Onychiurus, Canadensis, Meloidae Spotted Fever, and Transitional).

The *Rickettsia* are small bacteria (0.3–.5×0.8–2μm) that are obligate intracellular pathogens. They have a typical tri-laminar gram-negative cell wall structure and chemistry,

Table 30.1 Species of *Rickettsia* and *Orientia* causing pathogenic human infection and their arthropod vectors

Disease	Tick	Flea	Louse	Mite
Spotted fevers	*R. rickettsii* *R. conori* *R. japonica* *R. sibirica* *R. australis* *R. slovaca* *R. africae* *R. honei* *R. helvetica*	*R. felis*		*R. akari*
Typhus		*R. typhi*	*R. prowazekii*	
Scrub typhus				*O. tsutsugamushi*

although they stain poorly with the gram stain but stain well with the Giminez stain. Owing to their obligate intracellular existence there has been an evolutionary trend of genome reduction with reduced or loss of function particularly of amino-acid anabolism and cell-wall constituents, although some genetic markers have increased, particularly small RNA molecules. One of the main cell-wall components is peptidoglycan, which is a microbe-associated molecular pattern (MAMP), and the ability to synthesize this is reduced in a group of obligate intracellular bacteria (*Orientia*, *Chalmydia*, and *Wolbachia*) leading to a reduced amount of peptidoglycan, although *Rickettsia* still retain a normal peptidoglycan. The *Rickettsia* separated from *Claudobacter* about one and a half to two million years ago with a further event half a million years ago when the organism infected arthropods. The evolutionary pressure for genome reduction was discarding unwanted genomic material and presumably avoidance of stimulating an immune reaction against the organisms. The *Rickettsia* spp. have a small genome size of about 1.3 Mbp. Most of the 40 species of *Rickettsia* and all of the two species of *Orientia* have been sequenced. Comparison of the genomes indicates split genes, pseudogenes and remnants of genes, repeat palindromic sequences, genes with eukaryote motifs and selfish DNA evidencing large gene reductions due to the endosymbiotic lifestyle, horizontal transfer of genes and new gene formation. Plasmids are common in *Rickettsia* and some of them carry a large plasmid p(RF) having about 70 open reading frames many of which are closely related to genes in *R. bellii* in the AG.

Since their cytosolic habitat is rich in nutrients, amino acids, and nucleotides, they lack enzymes for sugar and amino-acid metabolism, and for lipid and nucleotide synthesis. Their genome therefore codes for several transport proteins, which enable them to utilize host cell products including ATP, although they may also synthesize ATP. They possess a **type IV secretion system** paradoxically with many component duplications, seemingly overcomplicated for its function.

ENTRY AND SPREAD WITHIN THE BODY

The bacterium is injected into the host skin by an arthropod vector (see below). It multiplies locally in the dermal tissue, primarily within the endothelial cells of the vasculature, although *R. akari* and *O. tsutsugamushi* infect monocytes. Subsequently, the organism is spread by the bloodstream to all body organs where it attaches to and reproduces in endothelial cells of the blood vessels.

PERSON-TO-PERSON SPREAD

Some *Rickettsia* spp. are only found in human hosts and are spread from one human host to the next by one of the arthropod vectors. **Table 30.2** shows the organisms found in a number of geographic locations with their reservoirs.

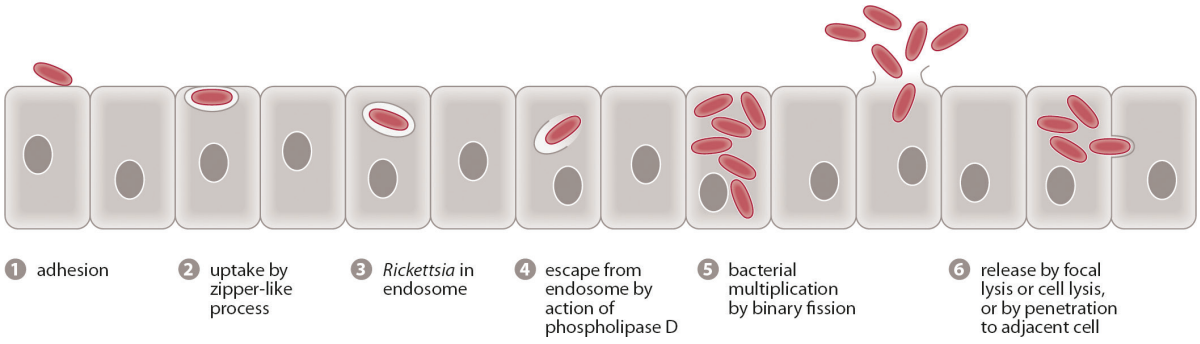


Figure 30.2 Entry, multiplication, and outcome of Rickettsia inside the endothelial cell.

Pathogenic *Rickettsiae* are spread to humans by different arthropod vectors (**Table 30.1**). Some *Rickettsia* spp. have a fairly restricted geographic location, while others can be found on all the continents. The distribution of *Rickettsia* spp. is related to that of their arthropod vectors (**Figures 30.3–30.6**), particularly since ticks, fleas, and lice are ubiquitous. The bacteria are maintained in nature by colonizing/infecting mammalian hosts (dogs, rats, ferrets, deer, etc.), which act as a reservoir for further human infection. In the case of ticks, the bacteria are transmitted **trans-stadially** and thus the vector also acts as a reservoir. Ticks transmit the organism during feeding. The tick may feed over several days and may go unnoticed. Transmission of the *Rickettsia* spp. does not occur immediately and may take a few days. It is thus important to scrutinize one's body if one has been hiking in tick-infested locations and carefully remove any ticks without crushing them.

EPIDEMIOLOGY

Horizontal transmission between ticks co-feeding on a susceptible animal maintains the rickettsia in the tick populations host. Transmission can also occur, although less commonly in immune hosts if they share the same feeding site. In the UK, there are about 20 different tick species. Thus far only one case of tick-borne disease has been acquired in the UK (babesiosis) and two cases of tick-borne encephalitis. Between 2006 and 2018, 16 tick species have been identified in returning travelers of which nine were known to be vectors for rickettsial disease in the country visited. There are many types of flea in the UK the common ones being dog, cat, bird, and human. Lice and mites are also common in the UK and can be vectors of rickettsial disease.

The prevalence of infection with *Rickettsia* spp. is probably underreported. *Rickettsia* spp. are not common in the UK and cases occur in returning travelers. Rickettsia infections in returning travelers in the UK are linked frequently with having visited game parks in sub-Saharan Africa and are usually *R. africae* or *R. conorii*. Travelers visiting Asia often acquire *R. typhi* or *O. tsutsugamushi*. However, *Rickettsia felis* has been detected in 6–12% of the cat fleas in the UK, suggesting that endemic Rickettsial disease is a possibility. Between 1990 and 2002 there were 66 imported cases. The following three species belonging to the SFG have been detected in ticks in the UK: *Rickettsia helvetica*, *R. massiliae* and *R. raoultii* but only one possible case (*R. massiliae*) may have been acquired in the UK. However, *R. helvetica* was detected in 10 of 338 *Ixodes ricinus* ticks collected between 2006 and 2009 from various locations in the UK and it has also been detected in female *Ixodes* collected from UK hedgehogs. Also, a study of 85 *Rhipicephalus sanguineus* ticks demonstrated six were positive for *Rickettsia* and monitoring at country entry points into the UK demonstrated *Rickettsia* are often carried in ticks on imported dogs, although *Rickettsia* have also been found on the ticks of migratory birds.

Figure 30.3 A tick – the vector for some rickettsial diseases. *From the Centers for Disease Control & Prevention, Atlanta, Georgia. Image is found in the Public Health Image Library #5977.*

Figure 30.4 A flea – the vector for some rickettsial diseases. *From the Centers for Disease Control & Prevention, Atlanta, Georgia. Image is found in the Public Health Image Library #5636. Additional photographic credit is given to CDC/ DVBID, BZB, Entomology and Ecology Activity, Vector Ecology & Control Laboratory, Fort Collins, CO. and was created in 2004.*

Figure 30.5 A louse – the vector for some rickettsial diseases. *From the Centers for Disease Control & Prevention, Atlanta, Georgia. Image is found in the Public Health Image Library #9217. Additional photographic credit is given to CDC/ Frank Collins, PhD and was created in 2006.*

Figure 30.6 A mite – the vector for some rickettsial diseases. *From the Centers for Disease Control & Prevention, Atlanta, Georgia. Image is found in the Public Health Image Library #5447.*

Table 30.2 The geographic distribution of *Rickettsia* and *Orientia* and their reservoirs

Organism	Location	Reservoir
R. rickettsii	North, Central, and South America	Dogs, deer, rodents, ticks
R. conori	Africa, India, Middle East, Mediterranean, Russia	Dogs, rodents, ticks
R. japonica	Japan, China	Dogs, rodents, ticks
R. sibirica	Russia, China, France, Africa	Dogs, rodents, ticks
R. australis	Australia	Dogs, rodents, ticks
R. slovaca	Europe	Dogs, rodents, ticks
R. africae	sub-Saharan Africa	Dogs, rodents, ticks
R. honei	Flinders Island Australia	Dogs, rodents, ticks
R. felis	America, Brazil, Europe	Dogs, rodents, ticks
R. akari	Eastern USA, Europe, Korea, South Africa	Mice
R. helvetica	Scandinavia	Dogs, rodents, ticks
R. typhi	Worldwide	Rat
R. prowazekii	Worldwide	Human Flying squirrels in USA
O. tsutsugamushi	Japan, Russia, Australia	Rodent, mites

In Europe, cases of *R. helvetica* have been reported from a number of countries, for example Sweden, Austria, Netherlands, Italy and Slovakia. In the Netherlands, a higher seroprevalence to SFG *Rickettsia* was noted in patients with Lyme disease compared to healthy blood donors suggesting ticks can carry more than one pathogen. Cases of *R. raoultii* have been found in France, Slovakia, and Poland. *R. massiliae* has been detected in Sicily, Spain, and France and has been detected in cats, foxes and hedgehogs.

In the US, *Rickettsial* spotted fever is a notifiable disease. RMSF, caused by the bacterium *R. rickettsii*, is the most severe and most commonly reported SFG rickettsiosis. Tick-borne SFG *Rickettsia* species in the US that are known to cause human illness is not just *R. rickettsii*, but other species have also been identified as causal agents: *R. parkeri* and a newly recognized *Rickettsia* identified as 364D with the proposed nomenclature *Rickettsia philipii*. The number of cases in 2000 was 495 and the most current data, 2017, identified 6248 cases. Incidence of cases depends on the season (when ticks are active) and the State/Country: in Arizona, cases are transmitted by *Rhipicephalus* (dog tick) with a peak April–Oct.

In Australia, a seroprevalence study showed that 5.6% of nearly 1000 individuals were positive for rickettsia, with 24% of these positive for scrub typhus. Despite its importance as a global pathogen, and indeed as an organism that could be used for bioterrorism, it has been little studied to date. **Figure 30.7** shows the global distribution of different species of the Rickettsiales.

2. WHAT IS THE HOST RESPONSE TO THE INFECTION AND WHAT IS THE DISEASE PATHOGENESIS?

The pathophysiology of *Rickettsial* infection is currently poorly understood and the details will vary according to the species of *Rickettsia*, particularly the two main groups: the SFG and the TG.

Rickettsia attach to and enter the vascular endothelium by inducing **endocytosis** using a zipper-like process whereby there is sequential interaction between ligand and an **adhesin** (**Figure 30.2**). Two cell-surface proteins appear to be involved in the adhesion process, OmpA (outer-membrane protein A) and Sca2, which are both members of an autotransporter family of proteins called surface cell antigen (Sca). Other members of this family are Sca1, Sca3, and OmpB. OmpB may also be involved in the adhesion process. A rickettsial phospholipase A2 appears to be involved in the uptake of the rickettsia into the cell. The intracellular signaling events mediating induced endocytosis involve various signaling pathways such as Cdc-42 PI 3 kinase, c-Src, and Arp2/3. Once they have entered the endothelial cell they escape the **endosome** with the aid of bacterial enzymes, for example, phospholipase D, and replicate in the cytoplasm. Like many other intracellular organisms, the rickettsia inhibit **apoptosis** of the host cell to allow their replication to proceed. They spread from an infected cell to adjacent cells by polymerizing actin monomers at one pole of the cell, thereby pushing the organism forward. RickA (a group of proteins found in the SFG of rickettsia but not in the TG) induces nucleation of actin monomers via the Arp2/3 complex, thereby mediating intracellular movement (**Figure 30.2**). Rickettsia are also released into the bloodstream using the polymerizing actin monomers.

Rickettsia affects the trans-Golgi network (but not the cis-Golgi network) by the production of ankyrin repeat protein 2 which affects protein secretion by the cell including MHC I molecules and thus inhibiting immune recognition.

Infection of vascular endothelium by *Rickettsia* leads to an increase of the membrane-bound CX3CL1 chemokine on the host cell membrane (which is involved with recruiting immune cells to the site of infection). The increased expression

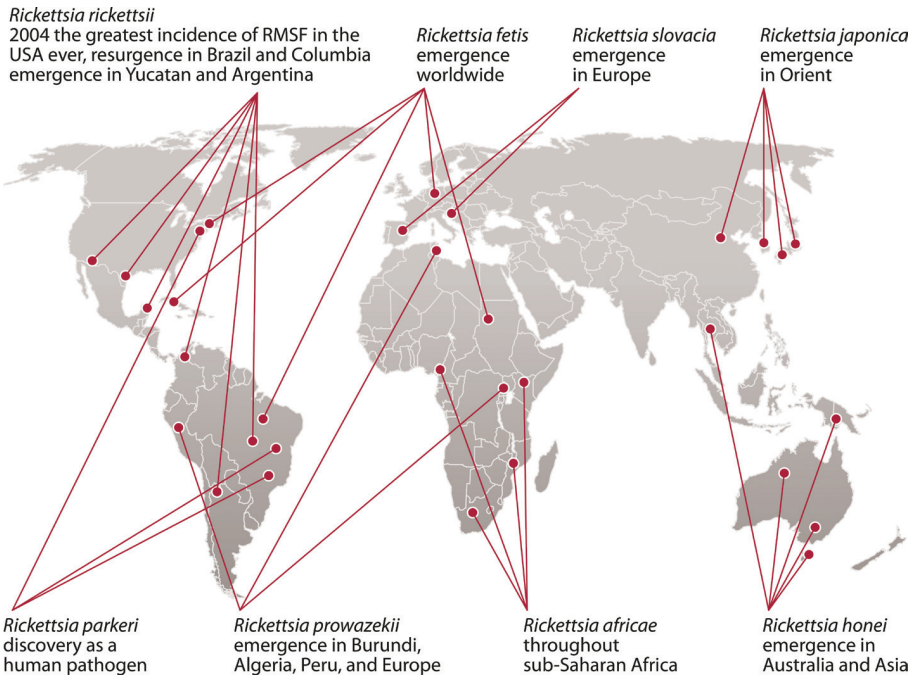


Figure 30.7 Distribution of rickettsial diseases globally, showing location of different species and detection of species from locations where they had not previously been detected. *From Walker DH Rickettsiae and Rickettsial Infection: The Current State of Knowledge. Clin Infect Dis, 45: S39–S44, 2007.*

of CX3CL1 is stimulated by miRNA-424. However, following infection by *Rickettsia*, there is a reduction in expression of miRNA-424 inhibiting the immune response to infection. During Rickettsial infection, the Lipid A moiety activates TLR4/MD2 but the clinical effect of Lipid A on outcome is unknown particularly as the structure of the Lipid A from different Rickettsial groups varies. These differences may have clinical relevance in relation to disease pathogenesis or vaccine efficiency.

Damage to the endothelial cells leads to changes in microvascular permeability. Currently, it is believed that the injury is the result of oxidative stress in the endothelial cells mediated by **reactive oxygen species**, which cause lipid peroxidative membrane damage. This is probably the direct effect on the endothelial cells by the infective organism but mostly by cells of the immune system.

Endothelial cell infection induces the production of pro-inflammatory **cytokines** such as **interleukin** (**IL**)-1α and this causes an up-regulation of E-selectin (*R. rickettsii*) allowing increased adhesion of polymorphs to the vasculature. Following infection with *R. conorii*, **E-selectin**, **ICAM-1**, and **VCAM-1** are all up-regulated, allowing adhesion of mononuclear cells including macrophages and T cells.

Endothelial damage-mediated changes in microvascular permeability result in **hypovolemia**, hypotension, and pulmonary **edema**. Membrane leakiness induced by nitric oxide, which is a host response by the endothelial cells and macrophages, can also lead to interstitial **pneumonia**, **myocarditis**, perivascular lesions in the brain and other organs, and in surface peripheral blood vessels leads to a **rash**. In skin cells from *R. conorii*-infected patients, the host responds by up-regulation of **tumor necrosis factor-α** (**TNF-α**), **interferon-γ** (**IFN-γ**), IL-10, RANTES, and inducible nitric oxide synthase (iNOS), and the levels of the cytokines correlate with severity of disease. The **vasculitis** leads to increased local consumption of platelets with a **thrombocytopenia** in a proportion of patients and a pro-coagulation state, although **disseminated intravascular coagulation** (**DIC**) and **thromboses** are rare.

IMMUNE RESPONSE

The immune response, as well as playing a role in pathogenesis, is eventually able to control the infection. Production of an enzyme **indoleamine 2,3-dioxygenase** by the endothelial cells following the effect of pro-inflammatory cytokines, limits the replication of *Rickettsia* by metabolizing tryptophan, an essential amino acid for rickettsia.

Early in infection it is thought that **natural killer** (**NK**) cells inhibit growth of *Rickettsia* in endothelial cells through release of IFN-γ. **CD4** T cells and **CD8**+ T cells are believed to produce IFN-γ and also RANTES that enhance intracellular killing of *Rickettsia* via nitric oxide production and hydrogen peroxide. CD8+ T cells are able to kill *Rickettsia*-infected endothelial cells via a **perforin**-dependent cytotoxic mechanism, which contributes significantly to recovery from infection. There is also an antibody response generated to some of the *Rickettsia* adhesion molecules, such as OmpA and OmpB, but these antibodies appear in significant amounts only after the infection has resolved. They are therefore thought to be protective against re-infection.

3. WHAT IS THE TYPICAL CLINICAL PRESENTATION AND WHAT COMPLICATIONS CAN OCCUR?

Rickettsial disease presents in one of two ways: (a) as a spotted fever or (b) as **typhus**, depending upon the infecting organism (Tables 30.1 and 30.3). The typical presentation of Rickettsial disease is abrupt onset of fever, headache, myalgia, and a rash.

SPOTTED FEVERS

The incubation period is about 7 days but may be up to 14 days. Patients present with fever, headache, myalgia, and a **maculopapular rash**.

The rash typically begins around the wrists and ankles but can also cover the trunk and may also appear on the palms and soles. In 10% of patients with RMSF or Brazilian Spotted fever caused by *R. rickettsii* the rash may be absent. Following infections with *R. slovaca* and *R. helvetica* typically there is no rash and a rash is uncommon with *R. africae*.

About 25% of patients may show signs of central nervous system (CNS) involvement with encephalitis or **seizures**. Gastrointestinal (GI) symptoms of nausea, vomiting, abdominal pain, and diarrhea may be present.

Despite the low platelets and prolonged coagulation time, bleeding and DIC are uncommon. In infections with *R. conori*, a pro-coagulation state exists and thromboses may occur in 10% of patients.

A tick bite may be visible as a black eschar (tache noire), although this is uncommon in RMSF, or as multiple eschars in infections with *R. africae*. Following infections with *R. slovaca*, the tick bite is commonly in the scalp and may lead to **alopecia**.

Complications include coma, renal failure, **adult respiratory distress syndrome** (**ARDS**), **myocarditis**, and death in about 10% of patients. Fulminant infection is more common in patients with glucose 6 phosphate dehydrogenase (G6PD) deficiency.

Laboratory investigations show a **thrombocytopenia** in about 50% of patients, **anemia**, abnormal liver function tests (LFTs), increased urea, **hyponatremia,** and **hypoalbuminemia**. Prolonged coagulation times may be observed and increased levels of creatine kinase. A chest X-ray may reveal pulmonary edema.

RICKETTSIAL POX

This presents with a fever, headache, and a rash. The rash is vesicular and starts as a **papule**, becoming vesicular, and scabs leaving a black eschar. The rash may also appear in the oral cavity as well as the palms and soles. Regional lymphadenopathy is present. The patients may also complain of profuse sweating, rigors, sore throat, and **photophobia**. Laboratory results indicate a **leukopenia** although LFTs, urea, electrolytes, and hemoglobin are usually normal.

TYPHUS

Epidemic Typhus

Epidemic typhus is associated with poor hygiene, homelessness, overcrowding, war, poverty, and natural disasters. The incubation period is about 10 days. The patient presents with fever, headache, myalgia, and a macular rash that is found on the trunk although not usually on the palms and soles. Respiratory and CNS symptoms may also be present. The case fatality rate is 15%. The disease acquired from flying squirrels is less severe.

Laboratory results indicate a leukopenia and thrombocytopenia. Elevated LFTs, creatine kinase, and blood urea are found. A chest X-ray may show interstitial shadowing.

Once infected and after apparently successful treatment, a patient may suffer a recrudescence of typhus (**Brill-Zinsser disease**) with the same signs and symptoms. This is frequently induced by stress or immune suppression.

Murine (Endemic) and Scrub Typhus

For both endemic and scrub typhus, the incubation period is 7–14 days and the patient presents with the typical symptoms of abrupt onset of fever, headache, and myalgia. A

Table 30.3 Common eponyms for some rickettsial diseases

	Species	Disease
Spotted fever	*R. rickettsii*	Rocky Mountain spotted fever (RMSF), Brazilian Spotted fever
	R. conori	Mediterranean spotted fever, Kenya tick typhus, Indian tick typhus, Boutonneuse fever
	R. sibirica	N. Asian tick typhus, Siberian tick typhus
	R. japonica	Japanese tick typhus
	R. australis	Queensland tick typhus
	R. honei	Flinders Island spotted fever
	R. africae	African tick bite fever
	R. akari	Rickettsial pox
Typhus	*R. prowazekii*	Epidemic typhus, Brill-Zinsser disease (recrudescence)
	R. typhi	Murine (or endemic) typhus
	O. tsutsugamushi	Scrub typhus

maculopapular rash on the trunk develops during the course of the illness in the majority of cases. Hepatosplenomegaly may be present in both endemic and scrub typhus. In scrub typhus, the rash is pale and transient and may be missed. GI (nausea, vomiting), respiratory (cough), and CNS symptoms (altered consciousness, seizures) may also occur. Complications similar to RMSF may occur and the case fatality rate is about 5%.

4. HOW IS THE DISEASE DIAGNOSED, AND WHAT IS THE DIFFERENTIAL DIAGNOSIS?

Diagnosis of Rickettsial disease relies on **serology** and **polymerase chain reaction** (**PCR**) because of the difficulty in culturing these organisms in a routine setting. Rapid detection using loop isothermal PCR, qPCR or unbiased WGS on a clinical sample can be used. Reference and specialist laboratories may offer a culture service where the organism is grown on cell culture using a shell-vial assay or in animals. An accurate diagnosis of the infecting species is frequently not possible using serology because of the many cross-reactions between the *Rickettsia* and other bacteria, particularly *Proteus* spp., which is the basis of the **Weil-Felix test**. Immunohistochemistry can be used on biopsy material from any rash and can help distinguish Rickettsial disease from other causes of a rash. **Immunofluorescence** or **ELISA** for serum antibodies are not useful in making a diagnosis of acute disease. The Weil-Felix agglutination test using *Proteus* OX-2 and OX-19 has a low sensitivity and specificity. More accurate diagnosis can be made using PCR combined with restriction fragment length polymorphism (RFLP) or sequencing to confirm the identity of any amplicon detected. RT-PCR and real-time PCR assays are also available. PCR is most useful using skin biopsies of the rash and is less helpful for blood samples. The primers are based on a number of different genes including those for rOmpA, rOmpB, a 17 kDa genus-specific protein (*htrA*), and citrate synthase (*gltA*).

DIFFERENTIAL DIAGNOSIS

Rickettsial disease presents with a fever and a rash and thus, in the differential diagnosis, any other infection with a similar presentation, including other Rickettsial illnesses, should be considered. Other infectious causes that should be considered are measles, rubella, varicella, arboviral infections, meningococcal and disseminated gonococcal disease, typhoid, secondary syphilis, anthrax, and leptospirosis. Of the noninfectious causes, **idiopathic thrombocytopenic purpura** and **immune complex** disease should be considered.

5. HOW IS THE DISEASE MANAGED AND PREVENTED?

MANAGEMENT

The mainstay of treatment is doxycycline. Other tetracyclines may also be used. An alternative, although less effective treatment, is chloramphenicol, which can be used during pregnancy or in cases of allergy to the tetracyclines. Azithromycin may also be an effective antibiotic in some cases. Quinolones and rifampicin have *in vitro* activity but poor clinical response. β-lactams, aminoglycosides, and sulfonamides are ineffective. In severe cases of RMSF, where IV doxycycline cannot be sourced, tigacycline can be used and is as effective as doxycycline.

Because eschars and skin necrosis can occur with both Covid-19 and Rickettsial disease, in areas where *Rickettsia* is common, it may be prudent to start doxycycline (in case the illness is a Rickettsiosis) until confirmation of the disease is obtained. Furthermore, because flea-borne Rickettsiosis (*R. typhi*, *R. felis*) present with nonspecific symptoms of myalgia, headache and fever and a rash, empirical treatment with doxycycline should be considered.

PREVENTION

Preventive measures include the use of insect repellents and protective clothing. Two vaccines have been developed, although not generally available, because of the potential threat of *Rickettsia* spp. being used as a bioweapon. Studies indicate a live attenuated vaccine is more effective than a killed vaccine.

Targeting the salivary proteins of the main tick vector of *R. prowazekii*, by developing a vaccine against them induces tick death and thus reduces vector transmission.

SUMMARY

1. WHAT IS THE CAUSATIVE AGENT, HOW DOES IT ENTER THE BODY, AND HOW DOES IT SPREAD A) WITHIN THE BODY AND B) FROM PERSON TO PERSON?

- *Rickettsia* and *Orientia* spp. are obligate intracellular gram-negative bacteria.
- They have a small genome size and restricted metabolic activity but the genome codes for several autotransporter proteins.
- The bacteria are spread by the bite of an arthropod vector: tick, flea, louse, mite.
- The bacteria are spread by the bloodstream and infect vascular endothelial cells systemically.
- Adhesins of *Rickettsia* for attachment to endothelial cells belong to an autotransporter family of proteins.
- Induced endocytosis of *Rickettsia* uses a zipperlike action.
- Intracellular signaling events depend upon Arp2/3 complex.
- *Rickettsia* escape from the endosome and replicate in the cytoplasm.
- Infection with Rickettsia up-regulates adhesion molecules on the endothelial cell, inducing adhesion of leukocytes.
- The bacteria are maintained in nature by infecting mammals such as dogs and rodents, which act as a reservoir of infection.
- Some *Rickettsia* spp. are confined to humans.
- The *Rickettsia* and *Orientia* are found on all continents although some have a more restricted geographic distribution.

2. WHAT IS THE HOST RESPONSE TO THE INFECTION AND WHAT IS THE DISEASE PATHOGENESIS?

- Damage to the endothelial cells leads to changes in microvascular permeability through oxidative stress in the endothelial cells mediated by the infection but also by cells of the immune system.
- Membrane leakiness induced by nitric oxide, which is a host response by the endothelial cells and macrophages, can also lead to interstitial pneumonia, myocarditis, or perivascular lesions in the brain.
- The vasculitis leads to increased local consumption of platelets with a thrombocytopenia in a proportion of patients.
- Cellular damage is caused by free radicals.
- Cell damage results in increased vascular permeability and edema.
- Host indoleamine 2,3-dioxygenase limits replication of rickettsia.
- CD8+ T cells are important in recovery from Rickettsial infection.

3. WHAT IS THE TYPICAL CLINICAL PRESENTATION AND WHAT COMPLICATIONS CAN OCCUR?

- Rickettsial disease presents with abrupt onset of fever, headache, myalgia, and rash.
- The incubation period is usually 7–14 days.
- The rash is maculopapular but in rickettsial pox it is vesicular.
- Gastrointestinal, respiratory, and CNS symptoms may occur.
- Evidence of an insect bite in the form of a black eschar may be found.
- Complications include renal failure, ARDS, and death in 5–15% of cases.
- Although damage occurs directly to endothelium, DIC and major vascular incidents are rare.

4. HOW IS THE DISEASE DIAGNOSED, AND WHAT IS THE DIFFERENTIAL DIAGNOSIS?

- Culture of *Rickettsia* spp. is not part of routine diagnosis but is performed in specialist or reference laboratories.
- Detection of serum antibodies is more useful as a retrospective diagnosis.
- Accurate species diagnosis by serology is difficult because of cross-reactions within the genus.
- Immunofluorescence and enzyme immunoassay are frequently used serologic assays.
- The Weil-Felix agglutination reaction has low sensitivity and specificity.
- PCR combined with RFLP or sequencing can give an accurate species identification, particularly on biopsy material from rashes.
- Differential diagnosis includes many illnesses that present with a fever and a rash.

5. HOW IS THE DISEASE MANAGED AND PREVENTED?

- The mainstay of treatment is doxycycline.
- Alternative treatments include chloramphenicol and azithromycin.
- Preventative measures include insect repellents and protective clothing.

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BMJ Best Practice, Rickettsial Diseases, 2022: https://bestpractice.bmj.com/topics/en-gb/1604

Centers for Disease Control and Prevention, Division of Viral and Rickettsial Diseases, Atlanta, GA, USA: http://www.cdc.gov/ncidod/dvrd/

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University of South Carolina, Pathology, School of Medicine Columbia, Microbiology and Immunology: http://pathmicro.med.sc.edu/mayer/ricketsia.htm

Students can test their knowledge of this case study by visiting the Instructor and Student Resources: [www.routledge.com/cw/lydyard] where several multiple choice questions can be found.