Summary

- Rickettsioses: bacterial infections of varying degrees of severity
- Transmission of typhus via lice, flies, ticks or mites
- Basic lesion is vasculitic
- Fever, rash, sometimes chancre and multi-organ involvement
- Hepatosplenomegaly, neurological signs, heart failure, renal insufficiency, bleeding
- Diagnosis clinical and often difficult; serological tests and PCR often not available
- Treatment with tetracyclines (1st choice)

General

Rickettsiae are **very small bacteria** (0.8 x 0.4 µm) that belong to the alpha-group of purple bacteria. The Rickettsiacea family contains the genera *Rickettsia* and *Orienta*. These coccobacilli are closely related to *Bartonella*, *Wolbachia*, *Cowdria* and *Anaplasma*. They multiply **intracellularly**. They have a **Gram-negative cell wall structure**, but cannot be detected by Gram staining, although they can be by Giemsa staining – with difficulty.

Rickettsia discovery

They bacterium derives its name from the American researcher, Howard Ricketts, who discovered them in 1909 in Montana, USA, as the source of a serious disease (Rocky Mountain Spotted Fever = RMSF caused by Rickettsia rickettsiae). Originally the disease was called Black Measles due to the spotted rash throughout the body of infected patients. Howard himself died from typhus in an epidemic in Mexico some years later. In 1916, Henrique da Roche Lima discovered Rickettsia prowazecki, the bacterium that causes epidemic typhus. He named it after his colleague Stanislaus van Prowazek, who had died from typhus whilst investigating the diseases in a prison hospital in Hamburg.

The historical role of Typhus in various armed conflicts

The Grande Armée of Napoleon Bonaparte lost many soldiers from epidemic typhus during the invasion of Russia in 1812. Of the invading 422,000 soldiers of the Grande Armée, only

a few ten thousand (numbers vary according to source) would return due to decimation by epidemic typhus, extreme cold, hunger and to a lesser degree battle. Several decades later during the Crimean War (1854-56) between Russia and England and France on the other, typhus took a high toll. Florence Nightingale was famous for her help to the wounded during this dreadful conflict. In the 1915 Serbian epidemic, it is estimated that nearly all the country's 400 doctors contracted epidemic typhus and more than a 100 of them died. The scale of the massive epidemics in Eastern Europe and Russia between 1918 and 1922 can hardly be imagined, with an estimated 20-30 million cases and at least 3 million deaths. Now there are occasional flare-ups of epidemic typhus, as in 1997 in Burundi with an estimated 24,000 cases in the first half of that year.

Classifications

Different classifications may be found in many textbooks and manuals, e.g. the "Spotted Fever" group (transmitted by ticks), the typhus group (transmitted by fleas and lice, no outer membrane protein OmpA) and scrub typhus. The division is based on **intracellular growth characteristics** and on **antigenic differences** between the various micro-organisms. Organisms of the spotted fever group cause rapid cell lysis and spread rapidly from cell to cell, while *R. prowazekii* – belonging to the typhus group – grows to enormous numbers intracellularly before causing the host cell to burst. Spotted fever group *Rickettsiae* are found in both the nucleus and the cytoplasm, whereas *R. prowazekii* is found in the cytoplasm only. In practical terms these divisions are not useful. They can give rise to confusion rather than clarification.

New Rickettsiae and various subtypes are still regularly being discovered. It is easier just to state that there are **various sorts of Rickettsiae and that they cause a range of diseases of varying severity**. Furthermore, not all Rickettsiae occur everywhere. Thus RMSF is not found in Asia, nor does scrub typhus exist in America.

Another way to classify rickettsioses is according to the transmitting vector, but the patient is often unaware of the ectoparasite that bit him. It is probably more useful to classify Rickettsioses according to their clinical picture's severity:

Mainly very serious course

Species	Disease	Vector	Distribution
R. prowazekii	Epidemic typhus	Louse	Worldwide
R. rickettsii	Rocky Mountain SF	Tick	America
O. tsutsugamushi	Scrub typhus	Mite	SE-Asia, Australasia

Mainly mild to moderately severe course

Species	Disease	Vector	Distribution
R. typhi (mooseri)	Endemic typhus	flea	Worldwide
R. felis	Flea typhus	flea	Europe, Americas, Africa, Thailand, New Zealand
R. conorii	Fièvre boutonneuse	tick	Mediterranean, Africa (India?)
R. africae	African Spotted Fever (SF)	tick	Africa, Caribbean
R. sharoni	Israeli SF	tick	Middle East
R. sibirica	North Asian SF	tick	Siberia, Mongolia
R. japonica	Japanese SF	tick	Japan
R. australis	Queensland SF	tick	Australia
R. honei	Flinders Island SF	tick	Australia
R. mongolotimonae	Atypical fièvre boutonneuse	tick	Asia, Europe, Africa
R. helvetica	Influenza syndrome	tick	Europe
R. slovaca	Tick-borne lymphadenopathy	tick	Europe
R. akari	Rickettsialpox	mite	USA, Africa

Transmission

With the exception of epidemic typhus, rickettsiosis are **zoonoses**. Transmission to humans occurs via **arthropods**. Ticks and mites infect humans through their bite. Lice and fleas infect humans through their faeces. Louse faeces can remain contagious for months. Ticks and mites transmit the organisms to their progeny (transovarial transmission). Mites and ticks are thus both vector and reservoir. In mites, infection with *Orientia tsutsugamushi* causes a shift in the sex-ratio in the offspring of the mites so that the female mites predominate in the following generation. This can be prevented by treating mites with tetracyclines.

Typhus transmission via lice

In 1906 Charles Nicolle demonstrated that **infection can be transmitted by body lice** (head lice and public lice are not known to transmit pathogens). Afterwards it was shown that **louse faeces** were infectious. Transmission is also possible when dry louse faeces are **inhaled** via aerosol.

Charles Nicolle

At the time Charles Nicolle was working at the Pasteur Institute in Tunis. There were numerous cases of typhus and the hospitals were over-full. In 1909 he observed that personnel in the laundry became infected when they had washed the clothing of people who had been admitted. There was however no secondary infections originating in the over-full hospital wards. Hospitalised patients were given a hot bath with soap and clean hospital clothing on their admission. Dr Nicolle suspected a pathogenic agent in the patients' dirty clothing and underwear. He injected a chimpanzee with a patient's blood. After a few days he collected some lice from the animal and introduced these insects into another, non-injected healthy chimpanzee. This second animal in turn became ill after ten days. Control experiments confirmed the results.

People who have previously survived epidemic typhus (*R. prowazekii*) often harbour the bacteria in their body for life, even though they are asymptomatic (**chronic carriers**). In the event of immunosuppression, this can result in a mild flare-up of the infection, even after

many years (**Brill-Zinsser disease**). When such a person is in the “right” circumstances, this can cause epidemic louse-borne typhus. As transmission of epidemic typhus occurs through lice, epidemics occur in conditions of poverty, overpopulation and poor hygiene (war, prisons, starvation, natural disasters, the homeless, refugee camps). The louse takes a contaminated blood meal and the bacteria proliferate in its intestinal epithelium. After 3-5 days, the infected cells burst. The intestine and faeces contain very large numbers of the bacteria. The haemolymph of the insect turns red from the passage of the intestinal contents (blood) into the body cavity. The **louse itself does not survive infection** with *R. prowazekii* and dies after 1 to 3 weeks. **It does not form a reservoir**. The American flying squirrel (*Glaucomys volans*) is a sylvatic reservoir for *R. prowazecki* with occasional transmission to humans after aerosolization of its faeces containing infected fleas and lice. Squirrel fleas (*Orchospea* howardii) will bite humans and transmit epidemic typhus to humans if their normal host, the flying squirrel, is unavailable.

Note: the body louse is also the vector of recurrent fever (see borreliosis) and trench fever.



Pediculus humanus capitis. Head louse. Copyright ITM

Typhus transmission via fleas

The reservoirs of endemic or so-called murine typhus (*R. typhi*) are rodents (mice, rats). The infection is transmitted to humans by rodent fleas such as the oriental rat flea, *Xenopsylla cheopis*. In certain circumstances, e.g. markets, grain stores,and forest fires, there is increased contact with rodents and their fleas and transmission can occur. In contrast to *R. prowazekii*, *R. typhi* does not kill the vector. A closely related organism, R. *felis* is transmitted by cat fleas (*Ctenocephalides felis*). One of the reservoirs for this bacterium is the opossum (California), but the organism has also been detected outside the USA, in Latin America, Africa, Europe, Thailand and New Zealand.



Cat flea. Ctenocephalides felis. Occasional vector of Yersinia pestis (plague) and vector of Rickettsia felis. Copyright ITM

Rickettsia transmission, via ticks


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Female hard tick. Rhipicephalus dorsal view. Notice the small dorsal shield, typical of females. Copyright ITM

Rickettsial spotted fever and **Rocky Mountain spotted fever** are transmitted by the **bite of hard ticks**. *Dermacentor variabilis* (American dog tick) is notorious in the eastern USA, while in the western USA *Dermacentor andersoni* is the principal vector (Rocky Mountain wood tick) for *Rickettsia rickettsii*. Besides those main vectors, *Rhipicephalus sanguineus*, the brown dog tick, also plays an important role in transmitting the infection to humans in the USA and Mexico. *Amblyomma cajennense* and *A. aureoloatum* play a role in Latin America and Brazil. In Africa *Rhipicephalus* species are responsible for transmission of *R. conori* and *Amblyomma* species for *R. africae*. A wide variety of **mammals constitute the reservoir**. Queensland **Spotted Fever, Japanese SF, Astrakhan SF, Israeli SF, Flinders Island SF and Siberian SF** are also transmitted by **hard ticks**. *Rickettsia slovaca* was first identified in *Dermacentor* ticks from Slovakia and has subsequently been found in *Dermacentor marginatus* and *D. reticulatus* in France, Switzerland, Portugal, Spain, Armenia and Germany. The geographical areas where certain species occur, is not well known. E.g. in 2002, the first case of infection with *R. aeschlimannii* was detected in South Africa. Transmission of this bacterium can occur via the bite of *Hyalomma* ticks and *Rhipicephalus* ticks. This bacterium must of course have existed before but was previously not identified.

Rickettsia heilongjiangensis was isolated in 2002 from *Dermacentor sylvarum* ticks in the Heilongjiang Province of China, near the Russian-Chinese border. This rickettsia is closely related to *R. japonica*.

The bacteria enter the tick as part of its blood meal and multiply. The organisms are transmitted with the saliva during the next bite. **Transovarial transmission** in ticks can be 100%, but other factors also play an important role in determining the final infectious state of the vector. In the USA <1% of Dermacentor ticks in the wild are infected with *R. rickettsii*. This may be explained by an interference phenomenon in which infection of the tick with the very commonly occurring, non-pathogenic *R. peacockii*, *R. belli*, *R. montana* or *R. rhipicephali* prevents *R. rickettsii* from becoming established in tick ovaries. Naturally occurring double infections (two species of Rickettsia in 1 tick) have yet to be observed. Vertical transmission occurs when a female tick has infected ovaries, which ensures infected tick progeny. However, it is known that *R. ricketsii* takes a substantial toll on the tick, since few larvae

emerge from infected eggs, and even fewer survive and mature into adults. Horizontal transmission depends upon transient rickettsaemia in a nonimmune host, on which uninfected ticks feed, creating newly infected ticks. Feeding adjacent (in time and space) to an infected tick allows for the acquisition of *R. rickettsii* without the presence of infection in the host (uninfected tick ingests saliva from the infected tick).

Typhus transmission via mites

Scrub typhus is caused by *Orientia tsutsugamushi* [Japanese "tsutsuga" = sick; "mushi" = insect]. The organism was classified in the past as *Rickettsia tsutsugamushi*. There are several antigenic variants (Gilliam, Karp, Kato, Shimokoshi, Kuroki, etc…). The organism is only transmitted by the **bite of mite** larvae known as "chiggers" (Leptotrombidium sp.). In nature the larvae feed on rats and other rodents while the adults feed on small invertebrate animals and insect eggs. The infection occurs **focally in Asia** where there is a specific ecological habitat of **transitional vegetation** (sides of roads, overgrown agricultural areas, disturbed rain forests, river banks, etc.). The larvae secrete an enzyme that dissolves animal tissue, after which the mite can suck up the fluid. This causes local irritation. When *Orientia tsutsugamushi* is introduced into the skin an inoculation chancre occurs in 50% of infections.

Infections with *R. akari* are not often seen in clinical practice and the condition "**Rickettsialpox**" is more of a curiosity. Transmission occurs via **mite bites**: *Liponyssoides sanguineus*. These mites parasitise mice.

Ticks that serve as vectors for Rickettsia from Eurasia, Australia and Africa.

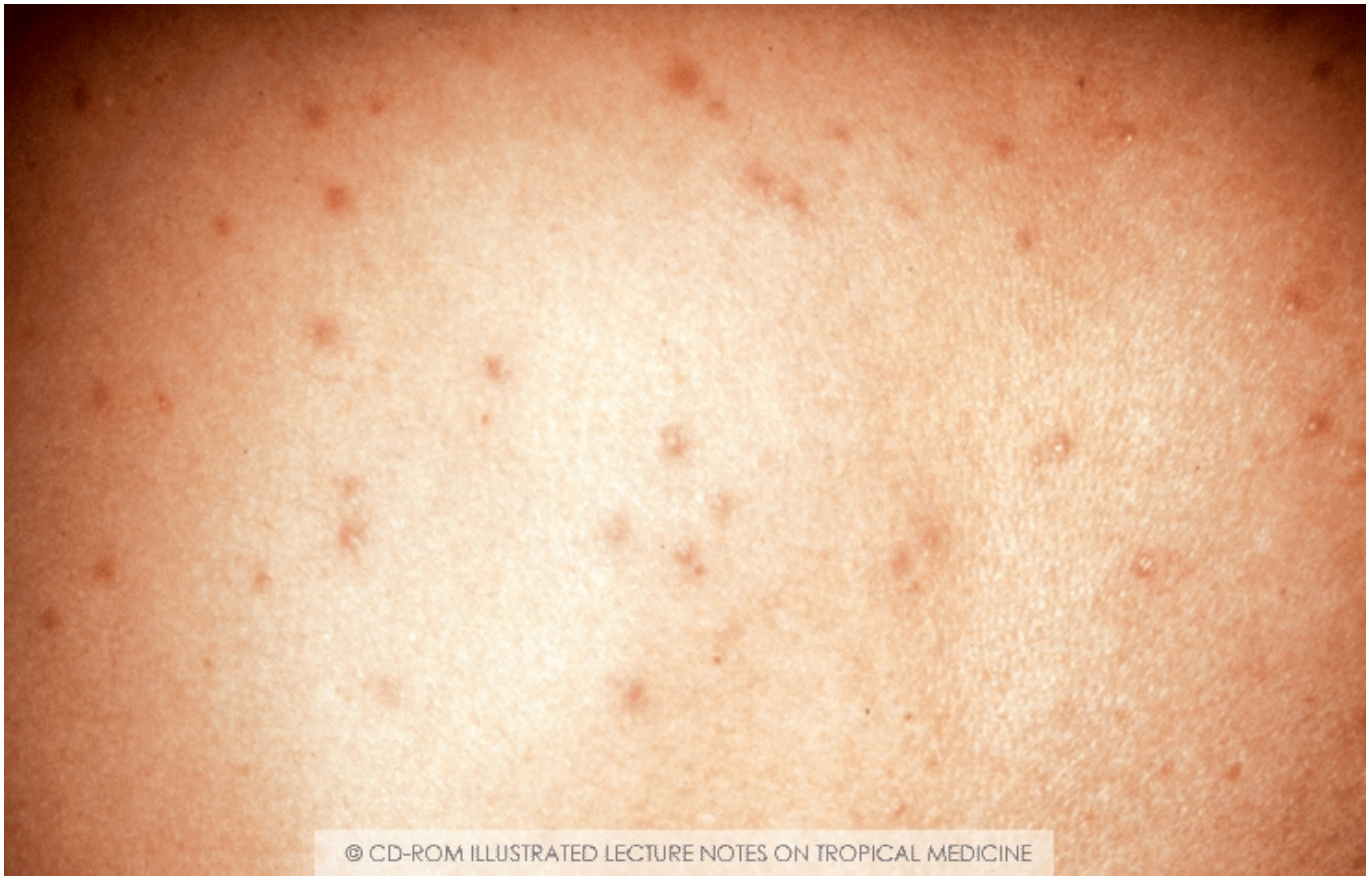
R. conorii	*Rhipicephalus sanguineus*	Mediterranean
R. sibirica	*Dermacentor* sp	Europe, former USSR, China
R. heilongjiangensis	*Dermacentor sylvarum*	China (Far East)
R. australis	*Ixodes holocyclus*	Queensland
R. japonica	*Haemaphysalis longicornis*	Japan
R. honei	Insufficient data	Flinders Island
R. africae	*Amblyomma variegatum*	Ethiopia, Southern Africa

R. mongolotimonae	*Hyalomma* sp.	France, Inner Mongolia, Africa
R. slovaca	*Dermacentor marginatus*	Europe
R. monacensis	suspected *I. ricinus*	
R. helvetica	*Ixodes ricinus*	
R. aeschlimannii	*Rhipicephalus appendiculatus,*	Africa
Hyalomma marginatum		
Astrakan fever agent	*Rhipicephalus sanguineus* and *R. pumilio*	Astrakhan region of ex-USSR

Clinical aspects

General features rickettsial disease

As there are several diseases that are caused by *Rickettsiae*, a general description is difficult. The **incubation period is 1 to 3 weeks**. After inoculation, *Rickettsiae* **proliferate intracellularly in the endothelium of small blood vessels**. Endothelial damage results in **focal occlusive endangiitis** in small venules and arterioles. Histologically this is identified in tissue sections in the form of typhus nodules (**Wolbach nodules**; not to be confused with typhoid nodules in the liver in typhoid fever!). In this way a **generalised, multifocal, multi-organ vasculitis occurs**. This can lead to thrombosis and vascular occlusion, possibly with oedema and local necrosis. As practically every organ in the body can be affected, the symptoms are extremely diverse. The various symptoms can be better understood if the localisation of the vasculitis lesions is borne in mind.



Skin rash during infection with Rickettsia conori. Copyright ITM



Inoculation chancre, Rickettsia conori, copyright ITM

The lesions appear in:

- **Skin**: At the site of the arthropod bite there is sometimes a papulovesicular lesion with local necrosis: inoculation chancre (tache noire [black spot]). The regional lymph nodes can enlarge subsequently. A chancre occurs in fièvre boutonneuse, South American RMSF ("Sao Paulo tick fever") and frequently in scrub typhus (but not necessarily). The chancre is almost always absent in North American RMSF and never present in epidemic and endemic typhus. The rash should be distinguished from severe measles, severe dengue and septicaemic purpura, e.g. due to meningococci. With a mild rash, a distinction must be made from typhoid fever (treatment differs).
- **Brain**: Meningo-encephalitis with confusion ("tuphos"), delirium and coma. Distinction from cerebral malaria is important. Often occurs with scrub typhus, epidemic typhus and RMSF. Hemiplegia can occur. In general there are features of aseptic meningitis, but in

RMSF there can also be an increase in the number of neutrophils in the cerebrospinal fluid. Deafness may persist for months in scrub typhus

- **Myocardium**: Myocarditis, heart failure, hypotension and shock. Hypovolaemia as a result of bleeding and increased vascular permeability contributes to low blood pressure.
- **Blood vessels**: Occlusion of arteries results in gangrene, possibly late onset (toes, fingers) and occurs predominantly in epidemic typhus and RMSF. Thrombophlebitis occurs as a result of vasculitis and stasis in severely ill patients.
- **Kidney**: kidney failure from vasculitis and interstitial nephritis, promoted by hypotension; albuminuria, oliguria.
- **Eyes**: Conjunctivitis, papilloedema (with cerebral involvement). Enlargement of the blind spot and scotomas occur frequently in scrub typhus.
- **Lungs**: Cough, tachypnoea, dyspnoea.

Clinical aspects of epidemic typhus, scrub typhus and RMSF

These infections usually have a **very serious course**. The incubation period is 5-10 days for scrub typhus and RMSF and ± 12 days for epidemic typhus. After a few days of generally not feeling well, a **high fever** occurs. It is associated with severe general malaise, severe headache, muscular pain, conjunctivitis, cough, hypotension, meningeal irritation, vomiting, epistaxis, confusion or coma. Hepatosplenomegaly occurs occasionally but is rare. Lymphadenopathy occurs in approximately one in four patients. **Rash appears around the 3rd to the 7th day** after the onset of fever. The absence of a rash in the first few days often makes it difficult for the diagnosis to be suspected at an early stage. The skin rash in RMSF begins on the wrists, palms and soles and spreads **centripetally** to the trunk. In epidemic typhus and scrub typhus it is the reverse: beginning on the trunk (axilla), it spreads **centrifugally** over the rest of the body, sometimes sparing the face, hands and feet. The rash may develop into purpura and can rapidly become haemorrhagic. **Gangrene** of the fingers and toes can occur. Because of diffuse intravascular coagulation (fibrinogen consumption), there may be a pronounced bleeding tendency. Rocky Mountain fever sequelae include deafness, amputations and permanent learning disabilities.

O. tsutsugamushi has several subtypes and repeated infections with scrub typhus are possible. Untreated scrub typhus fever can persist for more than 2 weeks and is often

accompanies by intense headache and diffuse myalgias. In about 50% of patients an eschar is present.

Brill-Zinsser disease is defined as the recrudescence of epidemic typhus years after the initial episode. In contrast to acute primary infection Brill-Zinsser disease is generally a mild illness.

Clinical aspects of endemic typhus

Endemic flea-borne typhus follows the **same course as epidemic typhus, but milder**. Reaching a clinical diagnosis is difficult and the disease is often missed. Rash occurs in half the cases. There is no chancre. Similar symptoms are present in infection with *R. felis*. Differential diagnosis includes typhoid fever, ehrlichiosis, dengue and other arboviroses.

Clinical aspects of tick-borne rickettsioses

Rickettsia spotted fever

This disease follows the **same clinical course as mild RMSF**. The **rash** is generalised. The inoculation **chancre is characteristic** here. During physical examination, a search for this chancre often leads to the correct diagnosis. Subcutaneous vasculitis can result in the formation of **subcutaneous nodules** (fièvre boutonneuse). *R. africae* occurs predominantly in Southern Africa. Skin rash is more confined or absent in infection with *R. africae*.

Clinical signs of infection consist of a skin lesion at the site of the tick bite and regional lymphadenopathy it is often painful. Fever and rash develop subsequently. The acute disease can be followed by fatigue and **residual alopecia** at the bite site.

Rickettsialpox

Rickettsia akari causes rickettsialpox. It is a rare infection which manifests as a self-limiting, febrile, vesicular skin rash, often **confused with varicella**. The differential diagnosis includes monkeypox, a viral pox disease which to date is endemic in Central Africa and is

known to cause epidemics in men having sex with men.

Diagnosis

Clinical

In developing countries, the diagnosis of typhus is predominantly clinical. If scrub typhus (Southeast Asia) or boutonneuse fever (Africa, Mediterranean Sea basin) is suspected, a chancre should be sought.

Eschars are may be overlooked easily when a a careful clinical exam including inspection of genitalia and skin folds under the breast is not performed.

The rash should be distinguished from, among others, dengue, rat bite fever, secondary syphilis, meningococcal septicaemia, ehrlichiosis, varicella, herpes zoster, rubella, Epstein-Barr virus infection and severe measles. Q fever does not produce a rash.

In RMSF, the cerebrospinal fluid is usually normal, although sometimes the neutrophil count is slightly raised. Scrub typhus and murine typhus can cause an increased number of lymphocytes in the cerebrospinal fluid in meningo-encephalitis so that the infections can resemble (arbo)viral infections and leptospirosis. In the blood, the white blood cell count is normal or reduced.

Diffuse intravascular coagulation often occurs which is accompanied by thrombocytopenia.

Serology

The diagnosis can be confirmed **at a late stage by serology**. A 4-fold increase in titre between acute and convalescent sera must be detected. Serologic testing is helpful for a retrospective diagnosis of rickettsiosis but will not assist in clinical decision making. IgM and IgG antibodies typically appear 7 to 10 days after the onset of the illness, the optimal time to obtain a convalescent antibody titre is at 14 to 21 days after the onset of symptoms. Treatment must be started early without waiting for laboratory confirmation.

Culture

Isolation of the organism by blood culture is usually not performed. **Culture of rickettsia is difficult**, laborious and dangerous (tissue culture or isolation on embryonated eggs). *Rickettsia* is an obligate intracellular parasite and in only a few reference labs in the world it is cultured on cell culture monolayers. Growth is confirmed using specialized stains (e.g. Gimenez) Guinea pigs can be inoculated with blood from a patient. After 4-5 days, the animals develop fever and male guinea pigs develop a swollen scrotum (Neil-Mooser reaction). There is a significant risk of laboratory infection.

PCR technology has become very important in identifying rickettsial species and strains: this is usually done on blood or skin biopsies of eschars.

Treatment

Untreated, the mortality of RMSF is 20 to 40% and of epidemic typhus ± 20%. General status (malnutrition, etc) plays a role here. Scrub typhus has a mortality rate of 6%, endemic typhus follows a milder course (mortality 2%) and fièvre boutonneuse has a low mortality (< 1%). It is not necessary to wait for confirmation of the diagnosis for treatment. If the course is fulminant, antibiotics are relatively ineffective.

Antibiotics

Tetracyclines are active against the organisms and are the first line treatment. The organisms are not 100% eliminated from the body. Recovery is determined by the patient's immunological resistance. Doxycycline is very useful in epidemics of louse-borne typhus and for scrub typhus. RMSF and endemic typhus should be treated for at least 1 week. In epidemic typhus an improvement may be expected within 24 to 72 hours.

Chloramphenicol is second choice, e.g. in pregnancy, notwithstanding the risk of "grey-baby" syndrome. **Ciprofloxacin** has some activity against Rickettsiae, but is inferior to doxycycline. Azithromycin has been used for mild forms in pregnancy. Erythromycin is not a good choice. Often the initial differential diagnosis includes bacterial meningitis caused by *Haemophilus influenza* or *Neisseria meningitidis*. Chloramphenicol is also active against these

organisms. **Penicillins, ampicillin and streptomycin are inactive against *Rickettsiae*.** Traditionally it is assumed that scrub typhus is highly susceptible to tetracyclines (this is sometimes used as a diagnostic test). In Thailand in 1996, scrub typhus infections were observed which clearly exhibited reduced susceptibility to doxycycline (both clinically and in vitro). Azithromycin or rifampicin 900 mg daily for 1 week is used as treatment in these cases.

Vector control

All patients and their clothing should be free from insects, ticks and mites. **Delousing** is of major importance in epidemics. The patient should be washed (removal of louse faeces on the skin and in the hair). Clothes and sheets should be decontaminated.

Prevention

- Epidemic typhus: Delousing (e.g. 1% permethrin or 1% malathion puffs in/on clothing, heat sterilisation of clothing), treat cases, improve general hygiene.
- Endemic typhus: Rodent control
- Scrub typhus: Preventive antibiotics, rodent control. DEET or permethrin on clothing and skin. In endemic areas vegetation must be cleared.
- RMSF and rickettsia spotted fever: Protective clothing, tick repellents in infested areas.
- Manual removal of ticks.

Weigl vaccine

The so-called Weigl vaccine was produced from 1920 to 1930. Lice were inoculated intrarectally with viable R. prowazekii. The lice fed on Dr Weigl and on the bodies of his colleagues so that the rickettsia was able to proliferate. Some of his colleagues died from typhus. Some 100 lice were necessary for one dose of vaccine. Subsequently it was decided to culture a louse strain (“Orlando”) that sucked blood from rabbits. This strain is still the reference strain for study of these insects.