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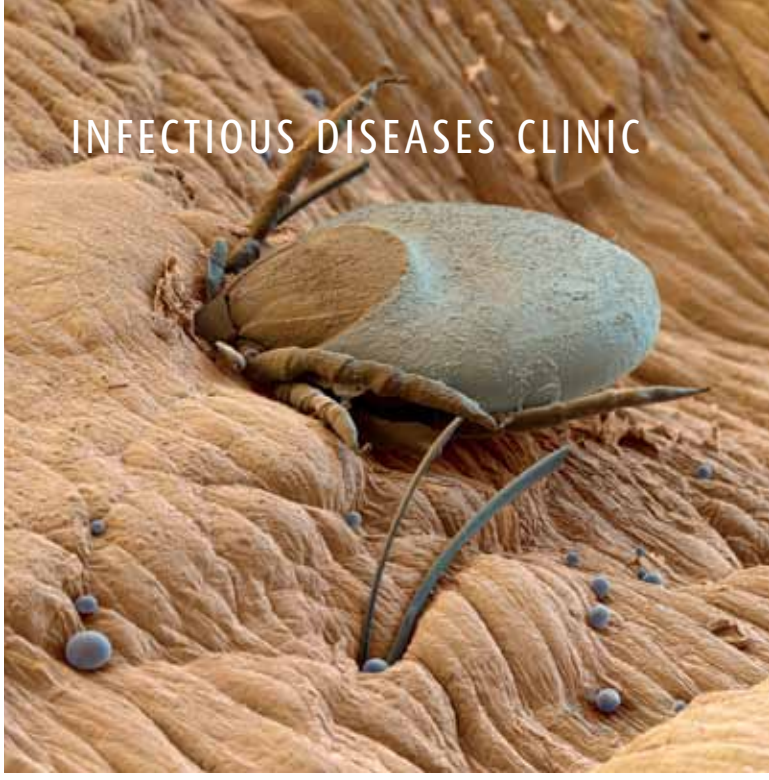

Management of rickettsial diseases and Q fever

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Australian rickettsial diseases (spotted fevers and typhus) and Q fever are readily treated with antibiotics. The greatest challenge may be to suspect the diagnosis in a patient with fever.

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What are rickettsiae? Despite their name, they have nothing to do with rickets. Rickettsiae are bacteria named after Howard Ricketts, an early investigator and victim of typhus. These bacteria have some unusual properties:

- They live inside animal (and human) cells as obligate intracellular bacteria.
- They infect the cells of both arthropod invertebrates (e.g. lice, fleas, mites and ticks) and vertebrates (e.g. rats, mice, cats and humans).
- They are transmitted from infected invertebrates to humans through a bite or the invertebrate's faeces, which may be rubbed into a bite site or inhaled into the lungs.
- They do not grow on agar plates in the microbiology laboratory.

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RICKETTSIAL DISEASES IN AUSTRALIA

Rickettsial diseases are widespread in Australia (see the Australian Rickettsial Reference Laboratory website, http://www.rickettsialab.org.au/#!about).[1,2]

Queensland tick typhus

Queensland tick typhus is transmitted by the bite of the paralysis tick *Ixodes holocyclus* and related tick species, which live naturally on bush mammals such as bandicoots and various species of native rat. This tick typhus occurs on the east coast of Australia.[3] It is caused by *Rickettsia australis,* Australia's endogenous rickettsial species, which is phylogenetically distinct from rickettsiae in other parts of the world.

Flinders Island spotted fever

Flinders Island spotted fever is transmitted by the bite of the reptile tick *Bothriocroton hydrosauri*. The disease occurs in south-eastern Australia, including Tasmania, the Bass Strait Islands (where it was first discovered on Flinders Island), Victoria and the south-eastern corner of South Australia.[4] The tick lives naturally on reptiles including the blue-tongued skink (commonly known as the blue-tongue lizard) and several species of snake (Figure 1). Contrary to popular opinion, this tick can bite humans. It transmits *Rickettsia honei.*

There is another similar disease, caused by a related rickettsia, that is still poorly understood.[5] Only seven cases have been reported to date, in Queensland, South Australia and Tasmania. The tick vector is unknown. This rickettsia (*R. honei* strain *marmionii*) has never been found in the reptile tick. The disease has been named Australian spotted fever to distinguish it from the other tick-transmitted infections in Australia.

Murine typhus

Murine typhus is transmitted by the rodent flea, via its infected

Figure 1. Reptile ticks.

faeces. It is caused by *Rickettsia typhi* and cases have been detected throughout Australia.[6-8] A common epidemiological feature is exposure to rats and hence to rat fleas and rat flea faeces. The main modes of infection are through inhalation of the flea faeces, giving rise to a community-acquired pneumonia, or transdermal, through scratching after a flea bite.

Cat flea typhus

Cat flea typhus is transmitted by infectious faeces of the cat flea. It is caused by *Rickettsia felis*, and cases have been only recently detected in Australia,[9,10] but the bacterium is likely to be widely distributed. Cats that are family pets should be kept flea-free to protect family members from this rickettsia.

Scrub typhus

Scrub typhus is a tropical disease transmitted by the bite of the larvae of a mite (*Leptotrombidium deliense*) that lives on native mammals. The causative bacterium *Orientia tsutsugamushi* is related to the rickettsiae but differs in DNA sequence, morphology, antigenicity and disease epidemiology. *O. tsutsugamushi* is highly virulent, and scrub typhus tends to be a more serious infection than the rickettsial diseases in Australia. The disease occurs in the Torres Strait Islands, north Queensland, the Top End of the Northern Territory and the Kimberley region of Western Australia.[11]

Q FEVER

Q fever, which was first reported in Australia but occurs worldwide, is not a rickettsial disease. However, many aspects of its presentation, diagnosis and treatment are similar to those of the rickettsial diseases. The causative bacterium *Coxiella burnetii*, although not closely related phylogenetically to the rickettsiae, is found in several Australia tick species and may be transmitted to humans by a tick bite.[12] Nevertheless, this mode of infection is very rare and infection is usually caused by inhalation of an infected aerosol from an infected vertebrate animal. Cattle, goats, sheep, cats, dogs and even native animals such as kangaroos and bandicoots are susceptible and can transmit the disease to humans.[13-15]

C. burnetii is excreted in large amounts in the birth products of infected female animals. The 'spore-like' bacteria collect in dust and can be spread by the wind and inhaled. Infection is more likely to occur in rural Australia.[16]

Australia is the only country with a Q fever vaccine for humans.[17] Doctors should consider vaccinating patients in rural parts of Australia, especially Queensland and NSW, where the incidence of Q fever is highest, and particularly if they have occupational contact with cattle, sheep, goats or kangaroos.[18,19] Q fever is legally notifiable to public health authorities.

RICKETTSIAL DISEASES IN RETURNED OVERSEAS TRAVELLERS

Rickettsial diseases are widespread around the world and travellers may be infected while overseas and become unwell on their return to Australia, up to three weeks after initial infection. Hence, a travel history is crucial in these patients. Patients may not mention a recent trip unless specifically asked by the doctor.

The rickettsial diseases seen most often in overseas travellers are:

- African tick typhus (*Rickettsia africae*) in travellers who have toured game parks in South Africa
- Mediterranean spotted fever (*Rickettsia conorii* subspecies *conorii*) in travellers returning from southern Europe, North Africa or the Middle East. This rickettsia is transmitted by the brown dog tick
- Indian tick typhus (*Rickettsia conorii* subspecies *indica*). This disease is seen in people who have travelled to the Indian subcontinent, particularly those who visit family as exposure to ectoparasites is more likely in domestic situations.

CLINICAL PRESENTATION

Acute rickettsial infection

Acute rickettsial infection usually presents with fever and myalgia, headache and extreme lethargy. A rash occurs several days after the onset of fever and is usually maculopapular (Figure 2), but can also be vesicular (chicken pox-like) in Queensland tick typhus.

An eschar may be present at the site of the tick, flea or mite bite (Figure 3). However, this may be difficult to find without a thorough examination as it often occurs in the flexures.

Acute Q fever

Acute Q fever has a similar presentation to acute rickettsial infection, but a rash is unusual and an eschar is extremely rare. The patient may also have pneumonia and/or hepatitis.

Chronic rickettsial infections

Some doctors and patients believe chronic rickettsial infections cause chronic fatigue.[20,21] However, the jury is still out on rickettsiae as a significant cause of chronic fatigue syndrome.

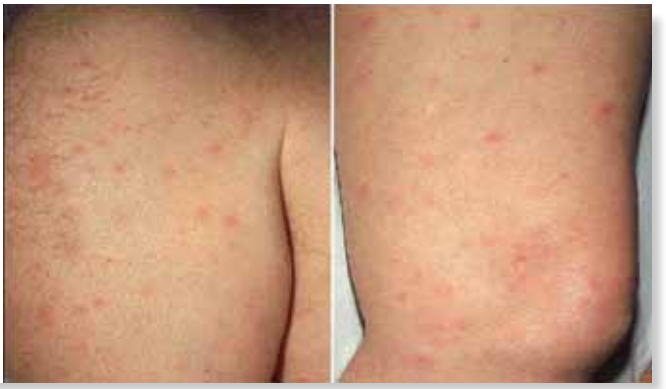

Figure 2. Maculopapular rash in Queensland tick typhus.

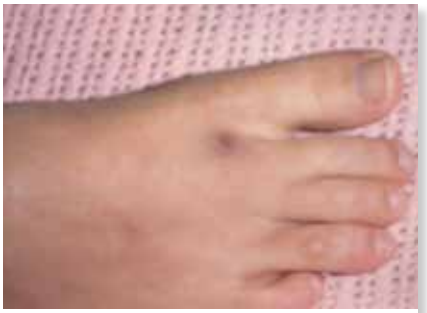

Figure 3. Eschar on foot, suggesting a tick bite in a patient with Flinders Island spotted fever.

Chronic Q fever

Chronic Q fever is a well-recognised complication of acute Q fever and occurs in about 5% of patients. It is a serious, life-threatening infection and manifests as culture-negative endocarditis, other vascular infection (including infection of an aneurysm or vascular prosthesis), osteomyelitis (especially in children) and granulomatous hepatitis.[22,23]

Another complication of acute Q fever is post-Q fever fatigue syndrome.[24,25] This is now well recognised and occurs in around 10% of patients. There is no reliable diagnostic test and no standardised treatment protocol. Fatigue may persist for months or years and have a significant impact on the patient's quality of life.

DIAGNOSIS

The most challenging part of diagnosis may be to include rickettsial diseases and Q fever among the differential diagnoses for a patient with fever, with or without a rash.

History and examination

A detailed history that includes overseas travel, exposure to the Australian bush and contact with animals can help suggest the diagnosis.

Physical examination should include a thorough examination of the patient's skin for an attached tick or eschar, including the natal cleft, under the breasts, around the scrotum and in the hair. Always explain to the patient why you are examining intimate areas when they have come with a headache and a rash.

Serological testing

Diagnosis of rickettsial diseases and Q fever is usually by serological testing. When patients present for medical care early in the illness, they may be seronegative because their immune system has not yet started to synthesise antibody. Nevertheless, it is valuable to take an acute serum sample at this stage and request that the pathology laboratory test rickettsial and Q fever serology.

If the acute serum is seronegative then a convalescent serum taken later in the illness or after recovery may be seropositive. This seroconversion is good evidence of the correct diagnosis.

If the acute serum is seropositive then the diagnosis is not necessarily confirmed as antibodies may be present because of past exposure to the pathogen. A rise in concentration of specific antibodies (titre) in the convalescent serum is good evidence of the correct diagnosis. In the case of past infection, antibody titres are the same in both acute and convalescent sera.

Australian laboratories undertake several types of serological assay, including enzyme immunoassay (EIA), complement fixation tests (CFT) and immunofluorescence (IF) tests. The most sensitive and specific assay for rickettsial diagnosis is IF testing (Figure 4). This assay may be available only at a reference laboratory, depending on the state. Nonspecific low-positive results are common, and correlation with history, known epidemiology of the rickettsial diseases and clinical symptoms is important.

Q fever IF serology tests, involving phase 2 and phase 1 *C. burnetii* antigens and different immunoglobulin classes (IgM, IgG and IgA), can often be used to diagnose the stage of the illness: recent acute infection, past infection or chronic infection. Unfortunately, Q fever serology cannot be used to diagnose post-Q fever fatigue syndrome. This is a clinical diagnosis only.

PCR tests

Nucleic acid amplification assays (e.g. by polymerase chain reaction, PCR) of EDTA-treated blood are positive for rickettsiae or *C. burnetii* early in infection. PCR tests are best performed within the first week after symptom onset; thereafter the bacteria (and their DNA) tend to disappear from blood. PCR of serum may also give positive results but is less sensitive than PCR of blood as the bacteria, being intracellular, are present in leucocytes rather than serum. PCR of a biopsy specimen from the eschar also often gives positive results.[26] In chronic Q fever, surgically removed heart valves (e.g. in Q fever endocarditis) are also often PCR-positive.

The medical microbiologist at your pathology laboratory can advise about the best diagnostic specimen to collect from your patient. Some specimens may have to be sent to a reference laboratory for processing if special laboratory techniques such as PCR are involved.

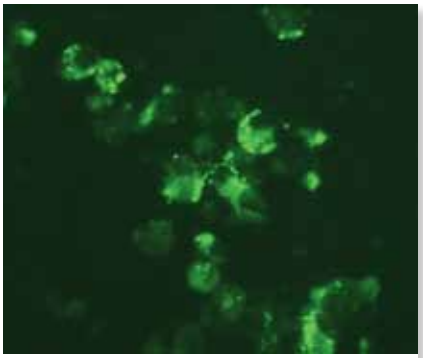

Figure 4. Positive immunofluorescence result for *Orientia tsutsugamushi* in a patient with scrub typhus.

Other laboratory tests

Other laboratory tests that can aid diagnosis include:

- a full blood count showing:
  - thrombocytopenia (very common)
  - lymphopenia and abnormal lymphocyte morphology

  Neutrophilia is uncommon despite the systemic infection, in contrast to most other bacterial infections.
- biochemical testing showing:
  - raised serum C-reactive protein level (usually more than 100 mg/L)
  - abnormal liver function with serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels raised to values in the hundreds (U/L), in contrast to the much higher levels seen in viral hepatitis.

Rickettsial diseases and Q fever are often diagnosed clinically as 'viral infection', and the above tests can help distinguish between bacterial and viral aetiologies. C-reactive protein level is particularly helpful, as it is rarely more than 100 mg/L in viral infections and nearly always more than 100 mg/L in rickettsial infections and Q fever.

TREATMENT

Rickettsial diseases

Rickettsial diseases are best treated with doxycycline (100 mg, 12-hourly for seven days) or azithromycin (500 mg, once daily for seven days). Patients usually show marked improvement by 48 hours into treatment.

Beta-lactam antibiotics should not be used as rickettsiae do not respond, because of the unusual chemical structure of their cell walls. Ineffective antibiotics in rickettsial diseases include the penicillins and cephalosporins, such as penicillin, amoxycillin, amoxycillin–clavulanate, cephalothin, cephalexin, cefazolin, ceftriaxone, piperacillin–tazobactam and ticarcillin-clavulanate.

Q fever

Acute Q fever is also best treated with doxycycline (100 mg, 12-hourly for 14 days). Treatment is recommended even if the patient's fever has spontaneously resolved, to prevent the 5% risk of chronic Q fever developing. An alternative antibiotic is sulfamethoxazole–trimethoprim (800 mg plus 160 mg, 12-hourly for two weeks), which is recommended in pregnancy.

For chronic Q fever, treatment is complex and long-term and best undertaken by an infectious diseases physician, if available.

RICKETTSIAL DISEASE AND Q FEVER: PRACTICE POINTS

- Remembering to include rickettsial diseases and Q fever among your differential diagnoses for a patient with a fever (with or without a rash) is often the most challenging part of management.
- Good history taking that includes overseas travel, exposure to the Australian bush and contact with animals can help suggest the diagnosis.
- A thorough examination of the patient's skin, including the natal cleft, under the breasts, around the scrotum and in the hair can reveal an attached tick or eschar.
- Specific rickettsial and Q fever serological testing should be requested from the pathology laboratory.
- Interpretation of rickettsial serology results should take into account the epidemiology of these infections as cross-reactions are common between different rickettsial species.
- Treatment is simple once the correct diagnosis is established: doxycycline, azithromycin or (for Q fever) sulfamethoxazole–trimethoprim. Beta-lactam antibiotics (penicillins and cephalosporins) are not effective against rickettsial infections and Q fever.
- Q fever is legally notifiable to public health authorities but rickettsial diseases are not.
- Consider Q fever vaccination for rural patients in Australia, especially those in Queensland and NSW, particularly if they have occupational contact with cattle, sheep, goats or kangaroos.

PRACTICE POINTS

Some key points for GPs regarding rickettsial diseases and Q fever are listed in the box on this page.

CONCLUSION

- Rickettsial diseases and Q fever are infections associated with animals – invertebrates (ticks, lice, fleas and mites) in the case of rickettsiae, and vertebrates (cattle, sheep, goats, dogs, cats and kangaroos) in Q fever.
- These bacterial diseases are readily treated with antibiotics (usually doxycycline), which produce a rapid response. Recognising the diagnosis is thus important to allow early treatment and rapid cure.

- Serological testing is the most common diagnostic laboratory test as these bacteria are difficult to culture in the laboratory.
- Clinically, patients have few distinguishing features, with the exception in rickettsial diseases of a possible eschar, which may be difficult to find. Nondistinguishing features include fever, myalgia, headache and, in rickettsial diseases, a maculopapular rash.
- Q fever vaccination is recommended for patients in rural parts of Australia, especially Queensland and NSW. MT

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