Review Paper:

Rickettsial Diseases: an Australian Perspective

Associate Professor Stephen Graves, Hunter Area Pathology Service, Newcastle

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RICKETTSIAL DISEASES: AN AUSTRALIAN PERSPECTIVE

Associate Professor Stephen Graves,
BSc (Hons), MBBS, PhD, FRCPA, FASM, FACTM
Director, Australian Rickettsial Reference Laboratory
Hunter Area Pathology Service
Newcastle New South Wales Australia
Director, Division of Microbiology, Hunter Area Pathology Service
New South Wales
Associate Professor, University of Melbourne and University of Newcastle Australia
Stephen.Graves@hunter.health.nsw.gov.au

What are Rickettsiae?

Rickettsiae are bacteria that have certain common features, some of which distinguish them from other bacterial groups. The main difference is the ability of rickettsiae to live in both vertebrate and invertebrate animals and to be transmitted between these two dissimilar animal groups[1,2].

The invertebrate animals involved are either insects (fleas, lice), mites or ticks (depending on the rickettsial "species") while the vertebrate animals involved consist of a large range of mammals (including humans very rarely) and reptiles (in the rare case of one Australian rickettsia).

In all these animals, the rickettsiae reside inside the eucaryotic animal cell, growing either free within the cytoplasm (or nucleus) or within a membrane-bound vesicle or a phagolysosome within the cytoplasm.

The rickettsiae are obligate intracellular bacteria and cannot be grown on normal laboratory bacteriological culture media. Cell culture is used for their propagation. Hence they are difficult to isolate from clinical specimens in the routine microbiology laboratory.

Taxonomically, rickettsiae belong to the Proteobacteria, either the α-subgroup (most rickettsiae) or the γ-subgroup (Q-fever)[3,4]. In many ways *Coxiella burnetii* (Q-fever) is not a typical rickettsia but it has been traditionally considered as such because it can be tick-transmitted and is obligately intracellular.

Metabolically, the rickettsiae have a limited range of anabolic and catabolic pathways. Like many obligate intracellular bacteria, a process of gene reduction or degenerative evolution has occurred leading to a dependence on pre-formed macromolecules provided by the intracellular milieu of the host cell[5]. This includes the high energy molecule ATP. Rickettsiae can "steal" (translocate) ATP from the host cell to the rickettsial cell, across the rickettsial cell membrane thus limiting the necessity for the rickettsia to synthesis all of its high energy molecules[6,7].

The full genome sequences of several rickettsial species have now been reported[8-10] and gene deletions are recognised. The eucaryotic cell mitrochondrion and rickettsiae seem to have a common origin[11].

Rickettsiae can be divided into six groups[12]:

1. Typhus Group rickettsiae
2. Spotted Fever Group rickettsiae
3. Scrub Typhus rickettsiae
4. Ehrlichiosis (granulocytic)
5. Ehrlichiosis (monocytic)
6. Q-fever

1. Typhus Group (TG) Rickettsiae

This group consists of two species:

- *Rickettsia prowazekii*
- *Rickettsia typhi*

Despite being very closely related genetically and antigenically, they cause quite different diseases.

R. prowazekii causes epidemic typhus, the best known of all rickettsial diseases. This is the only rickettsia where humans are the natural vertebrate host (although even this is in doubt since the discovery of an identical rickettsia associated with the flying possum in North America)[13].

R. prowazekii is transmitted by infected faeces of the human body louse which defaecates as it feeds. The rickettsiae enter the human body via the break in the skin. Uninfected lice can pick up the rickettsia by feeding on a rickettsiaemic patient**.** *R. prowazekii* is dangerous for its human host (approximately 25% mortality if untreated) and its louse host (they also die of rickettsial infection)[14].

This disease does not occur in Australia, despite having been introduced several times during the convict and 19th century immigration eras. It never became established in Australia, because people were able to wash their clothes and their bodies regularly. The disease only occurs nowadays in impoverished, cold countries, often at high altitudes.

R. typhi causes murine typhus and was first described in Australia (see later in article).

The rickettsia lives in fleas that themselves live on rodents (mainly rats and mice)[15]. This rickettsia is much less inherently virulent than the related *R. prowazekii*. It appears not to harm the flea or the rodent. However, a human who is bitten by the flea will be infected, via flea faeces. A more common mode of transmission is inhalation of dried rodent flea faeces. This can occur when a person inadvertently creates an aerosol of infected flea faeces while demolishing or cleaning a rat infested building. The disease is world wide and cases have been recently reported in Australia.

2. Spotted Fever Group (SFG) Rickettsiae

There are now over 20 species of rickettsiae belonging to the SFG rickettsiae group[16]. They are closely related to the TG and share the genus *Rickettsia* with them. There are a few genetic differences (eg: the SFG but not the TG has an omp A gene). Some genomes have been sequenced.

A spectrum of diseases occur ranging from mild (eg: Flinders Island Spotted Fever**,** *R.honei*) to severe (eg: Rocky Mountain Spotted Fever, *R. rickettsii*). SFG rickettsia are found all over the world.

The characteristic that distinguishes most members of this group are their transmission by tick-bite. Many species of hard-bodied ticks are involved. A few are transmitted by other invertebrates eg: *R.akari* transmitted via mouse mites and *R. felis* transmitted via cat fleas. When the tick takes a blood meal, the rickettsiae, which are located in the salivary glands of the tick, are inoculated into the host animal.

Many different species of host animals are known, virtually all of which are mammals. The exception is *R. honei*, which lives in a reptile tick. It is likely that ectoparasites of other animal groups will be shown to contain rickettsiae in the future.

3. Scrub Typhus (ST) Rickettsiae[17]

These microbes have significant differences from the TG and SFG rickettsiae. So much so that they have now been allocated to a separate genus, *Orientia*[18]. Despite their having considerable heterogeneity with respect to antigenicity, all ST rickettsia are considered to belong to the same species, *O.tsutsugamushi*. This rickettsia resides in a mite of the genus *Leptotrombidium* and is transmitted to humans by the bite of its larval form ('chigger'). Only this stage bites humans. The disease occurs in "the Orient" (hence its Genus name), including Eastern Asia (Russia, China, Korea, Japan), South-East Asia (Indonesia, Thailand, Papua New Guinea etc), South Asia (India etc) and parts of Oceania (Northern tropical Australia etc). The disease does not occur in Africa, Europe or the Americas.

It is usually a serious disease with a significant mortality in untreated patients. If soldiers fighting the "war in the pacific" during World War II had scrub typhus they were medically evacuated ahead of those with malaria[19].

"Hot spots" occur and are associated with dense populations of rickettsia – infected *Leptotrombidium* mites ("mite islands"), which are often very localised sites. In Australia, Lichfield National Park, just south of Darwin and Darnley Island (in the Torres Strait) are recognised "hot spots" for scrub typhus.

4. Ehrlichiosis (granulocytic)

These rickettsia grow as obligate intracellular bacteria within cytoplasmic vacuoles in leucoytes of granulocytic lineage[12]. They are tick transmitted. Only one species of human pathogen is recognised; *Anaplasma_phagocytophilum*. Recently recognised in Europe and North America, it has not yet been detected in Australia. However, a related microbe**,** *A. platys*, which infects megakaryocytes and platelets of dogs, does occur in Australia[20].

The disease is similar to other rickettsial diseases, but without the rash. A routine blood film will sometimes demonstrate the ehrlichia within polymorphonuclear neutrophils (PMNs).

5. Ehrlichiosis (monocytic)

These rickettsiae grow as obligate intracellular bacteria within leucocytes of the monocytic series. They are also tick transmitted. *Ehrlichia chaffeensis* is the main human pathogen, recently recognised as occurring in North America. It is not known to occur in Australia. Despite the serological screening of many hundreds of Australian patients' sera (sent to the Australian Rickettsial Reference Laboratory), none was positive. *E. canis* is a recognised dog disease that is a quarantinable veterinary disease in Australia. Human cases have no rash, and are clinically indistinguishable from granulocytic ehrlichiosis.

6. Q-fever[21]

Q-fever is a world wide disease (except New Zealand[22]), caused by an atypical rickettsia, *Coxiella burnetii*. This obligate, intracellular bacterium grows inside the phagolysosome, where the low pH (4.5) is optimum for the growth of the rickettsia. Its genome has been sequenced and appears to be larger than that of the other rickettsiae[10]. Many animal species are infected by *C.burnetii*, probably by tick bite, but they rarely manifest symptoms except when pregnant. The placenta of infected mammals (eg: sheep, goats) can contain extremely high concentrations of *C. burnetii*.

Humans are usually infected by an aerosol derived from dried birth products of parturient animals. A tick bite infection is theoretically possible (see case report)[23], but virtually no confirmed cases have involved ticks. Bandicoots are probably infected by tick bite in Australia however[24].

A Short History of Rickettsial Diseases in Australia

The first rickettsial diseases in Australia were those endemic to the country and present long before European colonisation. These probably include murine typhus, the spotted fever groups of illnesses (Queensland Tick Typhus, Flinders Island Spotted Fever and Australian Spotted Fever), scrub typhus and Q-fever.

However, the first one recognised by modern medicine was epidemic typhus[25]. When the convict and immigrant sailing ships arrived in Australia, after many months at sea, the passengers and crew were often louse infested ('lousy'). Consequently many had been also infected with *R. prowazekii* and either died at sea, were sick on arrival (and forced to remain in quarantine) or relapsed (Brill-Zinsser disease[26]) while living in their new communities. Such persons are rickettsiaemic and if a human body louse should take a blood meal from them during this period, it would itself become infected and could pass rickettsiae on to another person[27]. Typhus was common in prisons, hence the name "gaol fever" and many respectable citizens of the legal fraternity would sit as far away as possible from the lousy prisoner in the dock, in case the lice spread to them also!

As the colonists moved north into the tropics, they were assaulted by a number of tropical diseases, usually manifested by severe fevers. These were especially prevalent on the Queensland coast and went by the name of "Coastal Fevers"[28-30]. In retrospect they were clearly a mixture of malaria (now eradicated from Australia), leptospirosis, dengue, Ross River Fever, etc and the rickettsial diseases scrub typhus, Queensland tick typhus, murine typhus and Q-fever. But in those early days of Australian medicine it was not possible to differentiate one fever from another.

In 1916 a new laboratory test became available, the Weil-Felix test, that was positive in (epidemic) typhus[31]. Three stains of *Proteus* sp. (OX-2, OX-19,OX-K) were used as surrogate rickettsial antigens in an heterologous serological test with sera from febrile patients. Patients with typhus arriving from the old world on ships reacted with *Proteus* OX-2 and OX-19. This was a positive test for epidemic typhus.

Other patients with a typhus like illness, who were living and working in the tropics, had not recently arrived from Europe and were not infested with body lice, had serum that reacted with only the *Proteus* OX-K strain. This was clearly a different disease and later became recognised as "scrub typhus"[32] (although initially it was called 'endemic' – as distinct from 'epidemic' – typhus). It was also shown to be the same disease as occurred in Japan (tsutsugamushi disease)[33], which was associated with mites[34]. So mite transmitted scrub typhus because distinct in the medical mind from louse transmitted

Clinical Symptoms and Signs of Rickettsial Disease in Humans

Condition	Epidemic Typhus - *(Rickettsia prowazekii)*	Murine Typhus - *(Rickettsia typhi)*	Spotted Fever Group *Rickettsiae - (Rickettsia sp)*	Scrub Typhus - *(Orientia tsutsugamushi)*	Granulocytic Ehrlichiosis - *Anaplasma phagacytophilim*	Monocytic Ehrlichiosis - *(Ehrlichia chaffeensis)*	Q-fever - *(Coxiella burnetii)*
Fever	+	+	+	+	+	+	+
Eschar	-	-	+	±	-	-	-
Rash	+	+	+	+	-	-	-
Lymph-adenopathy	+	-	-	+	-	-	-
Headache	+	+	+	+	+	+	+
Myalgia	+	+	+	+	±	±	+
Pneumonia	-	+	-	+	-	-	+
Hepatitis	±	±	±	+	-	-	+
Post-Infections Fatigue	-	-	±	-	-	-	+
Encephalopathy	+	-	-	+	-	-	-

epidemic typhus. This disease is still recognised in north Queensland[35], including Torres Strait[36] and also in the Top End of the Northern Territory[37-39].

About the same time (1920s) a public health doctor in Adelaide, Dr Frank Hone, was seeing cases of "typhus" amongst lumpers (water side workers) who were loading wheat for export onto ships[40]. These men did not have body lice and their disease was mild with a low mortality rate (< 5%). Cases were also seen amongst persons living in rodent infested dwellings, especially after renovation work had been carried out. These cases were defined as typhus on the basis of a positive Weil-Felix serological reaction (OX-2 and OX-19, but not OX-K). Hone recognised that the disease was distinct from epidemic typhus and called it "endemic typhus", although today it is called "murine typhus". Hone recognised the epidemiological link with rodents. He was the first person to recognise and publish on this new rickettsial disease[41].

Over the next few decades this disease was recognised in Western Australia[42-43], especially in the port city of Fremantle, amongst lumpers loading wheat, as well as others. It was also recognised in Queensland[44], particularly amongst farmers on the Darling Downs[45] during mice plagues. Similar cases were reported in Victoria and New South Wales[46], but it was often difficult to know if they were relapses of epidemic typhus (Brill-Zinsser disease), as many cases occurred amongst soldiers who had returned from the battle fields of World War I or whether they were genuine cases of murine typhus[47]. Unfortunately, the Weil-Felix serology gives the same result in both diseases. Even today, with highly specific rickettsial serology (microimmunofluoresence) they are difficult to distinguish. Only the different titres of antibodies to *R. prowazekii* and *R. typhi* may suggest the diagnosis. Patient history is more likely to provide the correct diagnosis.

The third rickettsial disease in Australia came to light during World War II[48]. Australian soldiers training on the Atherton Tableland in Queensland, developed a characteristic illness after being bitten by a tick. From a case series of 12, a rickettsia was isolated from the blood of two patients. It was later shown to be distinct from TG rickettsiae and other SFG rickettsiae known to science at that time. It was named *Rickettsia australis* and the disease "North Queensland (later Queensland) Tick Typhus". A Queensland GP had earlier that year also reported a case of tick-transmitted typhus[49]. This rickettsia was the first of the SFG reported in Australia and one of the two isolates (PHS strain) is still in existence.

During the next 50 years this disease was recognised further and further south down the east coast of Australia. Today, many cases occur in SE Queensland and the northern suburbs of Sydney, (probably due to high human population densities in these regions and the maintenance of significant pockets of native vegetation within which the tick (*Ixodes* sp) and its natural mammalian hosts (various rat species and bandicoots) are able to survive. Cases have also been recorded on the south coast of NSW, the Gippsland region of Victoria and as far west as Wilson's Promontary in Victoria. The northern limit is uncertain but with the recognition of a case in Darnley Island, in Torres Strait[50], it is probable that the disease extends into Papua New Guinea.

R. australis is an atypical member of the SFG of rickettsiae. When various genes are sequenced and compared to other SFG "species", it always appears phylogenetically distant from the main body of SFG "species". It is probably most closely related to *R. akari* a mouse mite transmitted SFG rickettsia not known to occur in Australia. Like the fauna and flora of Australia, which are highly distinct having evolved for millenia in isolation on the Australian island land mass**,** *R. australis* is as unique to Australia as is the kangaroo and the waratah.

QTT is often reported as a mild disease, mimicking chicken-pox, with its unusual (for rickettsial diseases) vesicular rash. But the fever, headache, and systemic symptoms associated with *R. australis* growing inside endothelial cells of all end-organs, can lead to death. The few lethal cases reported[51-52] have been associated with mis-diagnosis and the exclusive use of -lactam antibiotics (to which rickettsiae are not sensitive). It probably takes several hours after attachment before *R.australis* is actually transmitted to the patient. Consequently prompt removal of a tick, by checking one's body after being in a tick infested area (eg: the Australian bush), will normally prevent rickettsial infection. Unfortunately, ticks often attach to parts of the body one normally can't see or doesn't check! eg: the natal cleft, under scrotum, in hair, etc).

Another 50 years passed before the next (4th) Australian rickettsial disease was discovered on a small island in Bass Strait. Flinders Island, with a population of about 1000, had the one doctor (Stewart). He recognised a syndrome (fever, headache, myalgia and rash) that occurred every summer[53]. Some of the patients remembered being bitten by a tick. The disease defied diagnosis, until one day a positive Weil-Felix serology result suggested that it might be rickettsial. Positive specific rickettsial serology, including cases with seroconversion, confirmed the illness as a SFG rickettsial disease[54] and it was given the name "Flinders Island Spotted Fever" (FISF). Until the isolation of the rickettsia from a rickettsiaemic patient[55] there were two school of thought; one that the disease was simply a southward extension of QTT and the other that it was a different SFG rickettsial disease.

Given that the islands of Bass Strait (and Tasmania) were part of mainland Australia only 10,000 years ago (during the last ice age) the first hypothesis was probably the most reasonable.

However, a molecular analysis of several genes of the new Flinders Island rickettsia showed that it was not *R. australis* and was a previously undescribed SFG rickettsia[56]. It was named *R. honei* in honor of Frank Hone[57], the Australian discoverer of murine typhus as discussed earlier. FISF is a relatively mild disease and no deaths have yet been reported. However, the incidence on Flinders Island is high.

Recently, cases of FISF have been detected elsewhere in SE Australia (mainland Tasmania and South Australia), and its range may overlap with *R. australis* in eastern Australia[58]. The epidemiology of the disease is unique in that it is transmitted to humans by the bite of the reptile tick (*Aponomma hydrosauri*)[59]. This tick lives on blue-tongue lizards and snakes (copper-head and tiger snakes), and a high proportion of ticks contain *R. honei*. No other rickettsia pathogenic for humans is known to live naturally in reptile ticks. All other rickettsiae pathogenic for humans live in mammalian ticks.

Within the last year or so yet another (5th) rickettsial disease has been recognised in Australia. Only six cases have been described to date. (In Queensland, including Torres Strait, Tasmania and South Australia). The illness has been called "Australian Spotted Fever" and the SFG rickettsia named *R. marmionii* (after Marmion, the developer of the Australian Q-fever vaccine – see later). At the time of writing, this work is unpublished.

R. marmionii is related to *R. honei* but has significant differences in several key genes[60].

We return to the 1930s for the last (6th) Australian rickettsial disease, Q-fever, a quasi-rickettsial disease. Derrick, in Brisbane, investigated a febrile illness amongst abattoir workers, called "Abattoir Fever"[61]. It tended to occur amongst new comers to the industry, presumably because they lacked immunity. It occurred not only amongst men involved in slaughter of animals, but others on the site also, including office staff and truck drivers. This suggested it was spread by aerosol. The affected staff did not have body lice and had not been bitten by ticks. There were no rodents associated with the premises involved. With the assistance of Burnet at the Hall Institute in Melbourne, the responsible rickettsia was isolated[62]. It was a microbe new to science and ultimately named *Coxiella burnetii***.** Independently of the Australian, Cox and co-workers in the USA had isolated the same microbe from ticks. Q-fever was so named by Derrick for "query" – as he wasn't sure of the cause of this fever amongst abattoir workers.

Q-fever is now recognised as a world wide disease (except New Zealand)[19] with many different vertebrate animals being hosts (especially sheep, goats and cows). The tick *Haemaphysalis humerosa* and the bandicoot are important reservoirs of *C. burnetii*[63-64]. Humans are infected by aerosol from infected secretions of animals (especially from the genital tract, including the placenta). *C. burnetii* has very high infectivity (1-10 bacteria can infect a human by the aerosol route) making it a candidate (in theory) for germ warfare.

However, the disease has a low mortality (untreated) and tends to incapacitate (with fever, headache, myalgia, pneumonia and hepatitis) rather than kill. The disease is important in rural Australia, especially south Queensland and northern NSW.

Marmion and co-workers developed a formalin-killed phase 1 *C. burnetii* vaccine, which is produced commercially by CSL Pty Ltd, and widely used in Australia amongst at risk groups especially abattoir workers[65-66]. It is highly effective but suffers from the practical inconvenience of having to pre-test the proposed vaccine recipient to ensure they have no antibodies (by serology) or cell medicated immunity (by skin test) to *C. burnetii* prior to immunisation.

Diagnosis of Rickettsial Diseases

Rickettsial diseases are difficult to diagnose. At a clinical level, the signs and symptoms overlap with a number of other infectious diseases. The epidemiology of the patient's illness is often not elicited by the treating doctor. Even a history of recent overseas travel may be missed unless the patient volunteers the information. As most rickettsial diseases that occur amongst Australian patients will be acquired in Australia (not overseas), an intra-Australia travel history is important, especially travel to the outback or tropical locations. Most of the time the doctor will not think of rickettsial disease, so the illness will not be diagnosed and the patient will recover, either with or without appropriate antibiotics. Death due to rickettsial disease is unusual in Australia.

The mainstay of laboratory diagnosis of rickettsial disease is serology. However during the acute illness, before antibodies have been produced by the patients' immune system, serology is not useful. At this stage, detection of the rickettsia (by culture) or its DNA (by polymerase chain reaction (PCR), is the only option. But these are highly specialised tests and available in very few (reference) laboratories (see later).

Serology

Antibodies are usually detectable by approximately five days into the illness and the antibody titre should continue to rise for several weeks.

An early serum ("acute" phase serum) is valuable because if negative, it can be used to show seroconversion with a subsequent positive serum. If positive, but with a low titre (low concentration of specific antibody), it can be used to show a rise in titre compared to a later serum, a mark of recent infection.

A stationary titre between two sera (at least a week apart) is indicative of past infection (not recent infection), although it is not possible to say how far in the past infection/exposure to the microbe occurred.

Sometimes the detection of an IgM class of antibody to the pathogen can be used as an indicator of recent infection, but this is not always reliable as some patients don't produce an IgM response. Sometimes an IgM response may last for a very long time and not be indicative of recent infection, and sometimes a positive IgM is a false-positive due to cross-reacting antibodies, the synthesis of which by the patient was in response to a completely different microbe.

The "gold-standard" serological test for rickettsial infection is the micro-immunofluoresence (MIF) assay, where the antigens used in the assay are genuine rickettsiae (usually SFG, TG & STG rickettsiae) fixed to a glass slide.

The patients' serum, at a screening dilution of 1/128, (and if positive) later at a series of doubling dilutions, is reacted directly with the fixed rickettsiae on the slide. Any antigen – antibody reaction is detected with a fluoresecein-labelled anti-human immunoglobulin antibody (produced in an animal). It may be anti-IgM, anti IgG or anti-IgA or a mixture of all three, so as to detect all of the patient's immunoglobulin classes that are reacting with the rickettsiae.

This assay, which is available commercially or via "in-house" tests, is used world wide but is expensive and time consuming as it requires skilled laboratory scientists who can read the immunofluoresence accurately, distinguish it from background "noise", make appropriate comparisons with positive and negative control sera and obtain reproducible titres when repeat assays are run using the same positive serum.

IF antibody appears to last for several years (> 5 years), but is very variable from person to person. Hence this assay cannot be used to determine a response to treatment or to estimate when the infection occurred. Eventually antibody decays and the infected person becomes sero-negative.

A more user friendly serology modality available in Australia is enzyme-immunoassay (EIA), produced commercially. This technique can be automated and operated by less skilled laboratory staff. A positive result is based on an optical density being greater than a pre-determined cut-off. Unfortunately, EIA does not produce a "titre" for the serum, simply a positive or negative result.

Often such assays have poor sensitivity (ie: they can miss genuine cases), although the specificity is usually good (ie: a positive result can be relied upon to be a genuine case).

However, for a non-specialised diagnostic laboratory the EIA is a better alternative than not offering a rickettsial serology service. However, problem sera or negative sera from probable cases should be re-tested at a reference laboratory by MIF.

The same comments apply to Q-fever serology, with the added complexity that both phase 1 (virulent) and phase 2 (avirulent) strain of *Coxiella burnetii* are used as antigen. This usually enables the differentiation of acute Q-fever (high levels of antibody to phase 2 (protein) antigens) from chronic Q-fever (high levels of antibody to phase 1 (carbohydrate) antigens), especially the IgA class to phase 1.

Detection of rickettsial DNA by PCR

During the acute illness and while the patient is still sick this is the best diagnostic test available, although it is not widely available.

Rickettsiae are present in the blood of the rickettsiaemic patient (usually within the circulating leucocytes). The DNA can be extracted and specific rickettsial genes (eg: 17kDa gene, citrate synthase gene, omp A and omp B genes, Com I gene and 16S-rDNA) can be detected by using PCR technology. The presence of a rickettsial gene is evidence of circulating rickettsiae. A real time PCR assay is most often used as it is faster and less prone to contamination.

Such assays, although becoming more widespread in diagnostic laboratories, are still restricted to reference laboratories for rickettsial diagnoses.

Culture of rickettsiae

Culture of bacteria is the traditional way of diagnosing a bacterial infection, but in the case of rickettsiae the techniques involved are more akin to traditional viral culture then bacterial culture. Because rickettsiae are obligate intracellular bacteria, they must be grown in tissue culture and because they are bacteria, the use of antibiotics in the tissue culture is not recommended. The slow growth rate of rickettsiae and the need for them to "adapt" to tissue culture, means that cultures must be incubated for long periods (eg: one month).

Consequently, rickettsial diagnosis by culture is not a viable alternative and culture is used only for research purposes, when the actual living rickettsia is required – eg: when identifying a new rickettsial disease.

Detection of rickettsiae by staining

Rash and eschar (arthropod bite site) biopsies can be stained for rickettsiae using specific anti-rickettsial antibodies or other staining methods. This is specialised histopathology and available in very few centres. It is rarely done in Australia.

In summary, serology is the main modality for diagnosing rickettsial diseases.

Treatment of rickettsial diseases

Antibiotic treatment is necessary in most rickettsial infections. The commonly used

-lactam antibiotics (penicillins and cephalosporins) do not work against rickettsiae, because of their bacterial cell wall, which is Gram-negative in chemical nature. Unfortunately, these are the antibiotics that are most commonly used by doctors to treat undiagnosed infectious diseases. A few deaths have occurred in Australia in patients with undiagnosed rickettsial disease (scrub typhus, Queensland Tick Typhus) who were being treated with -lactam antibiotics.

The drug of choice for rickettsial disease is doxycycline (orally) or an intravenous tetracycline if oral medication is not appropriate (eg: minocycline). All rickettsiae respond to doxycycline (with the possible exception of some isolates of *O. tsutsugamushi* in Thailand)[67] and it is certainly the drug of choice in Australia, even when treating children.

The (adult) dose, 100mg twice daily, orally, may be required for only 4-5 days. It is common for patients to start defervescing 24-48 hours after starting doxycycline and to be afebrile between 48-72 hours after starting this therapy.

A poor response to doxycycline should raise suspicion that the illness is not rickettsial.

Other antibiotics that have been reported as effective against rickettsiae are chloramphenicol (rarely used nowadays because of the risk of bone marrow suppression), fluoroquinolones (eg: ciprofloxacin) and macrolides (eg: azithromycin, clarithromycin).

Treatment of rickettsial infection is easy compared to the difficulty of diagnosis!

Prevention of rickettsial disease

No vaccines are available for rickettsial diseases with the exception of the Australian Q-fever vaccine. This vaccine is highly effective but is used only in Australia.

For protection against the other rickettsial diseases, methods for reducing contact with arthropod vectors are most effective eg: acaracide sprays on trousers when walking in scrub typhus endemic bush and regular checks for ticks.

For military personnel operating in rickettsia-endemic terrain prophylactic doxycycline can be used, if the risk is sufficiently high to warrant the (minimal) risk of long-term doxycycline.

Rickettsial Diseases: The Future

Rickettsiae will always be with us and so long as *Homo sapiens* remain on earth, we will suffer from rickettsial diseases. This is because the invertebrate vectors and reservoirs of rickettsiae are an integral part of the earth's micro-fauna.

New rickettsial diseases are being discovered virtually every year. Even Australia has a new rickettsial disease, Australian Spotted Fever (*R. marmionii*).

The importance of chronic rickettsial infection is likely to be studied further in the years to come and the role of chronic infection (including chronic rickettsial infection) in syndromes such as chronic fatigue (already recognised in Q-fever)[68-70] needs further study.

Doctors dealing with travel health, especially those patients returning from the tropics, need to be alert to rickettsial diseases and the difficulty of their diagnosis.

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