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REVIEW

Tick-borne rickettsioses in international travellers

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Summary *Background:* Tick-borne rickettsioses are of emerging importance in today's travel medicine but have until recently received little attention. We describe the current knowledge of tick-borne rickettsioses as they relate to international travel, their microbiological diagnosis, treatment, possible prevention, and future prospects.

Methods: Literature-based review and personal observations.

Results: During the last decade, some 400 cases of tick-borne rickettsioses have been reported in international travellers, the vast majority being African tick bite fever caused by *Rickettsia africae* and Mediterranean spotted fever caused by *Rickettsia conorii*. Only a minority of infected travellers can recall a preceding tick bite. Most patients present with a mild-to-moderately severe flu-like illness typically accompanied by a cutaneous rash and an inoculation eschar at the site of the tick bite, but potentially life-threatening disease with disseminated vaculitis is occasionally seen. Definite microbiological confirmation of tick-borne rickettsioses by isolation or antigen detection is only available at reference laboratories and diagnosis must in most cases rely on clinical and epidemiological data supported by serology. Doxycycline is the recommended treatment for tick-borne rickettsioses and prevention is based on personal protective measures against tick bites when travelling in endemic areas.

Conclusion: Tick-borne rickettsiosis should be suspected in febrile returnees from endemic areas, especially in cases with skin eruptions. Travellers to endemic areas should be encouraged to use personal protective measures against tick bites.

Introduction

Tick-borne rickettsioses are acute flu-like diseases frequently presenting with fever, severe headache, myalgia, skin rash, and inoculation eschars at the site of the tick bite. The diseases are caused by spotted fever group rickettsiae; obligate intracellular Gram-negative coccobacilli, which are maintained in nature through complex cycles involving mammal and tick reservoirs and tick vectors, with humans only as incidental hosts. Most tick-borne rickettsioses are confined to certain geographical areas limited by the presence of their tick vectors, and few are present on more than one continent.[1]

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Table 1 Current classification of tick-borne rickettsioses.

Human disease	Organism	Principal vectors	Geographic distribution	Reported in international travellers
African tick bite fever	*Rickettsia africae*	*Amblyomma* ticks	Sub-Saharan Africa, French West Indies	Yes
Mediterranean spotted fever	*Rickettsia conorii*	*Rhipicephalus* & *Haemaphysalis* ticks	Mediterranean littoral to Indian subcontinent, sub-Saharan Africa	Yes
Indian tick typhus	Indian tick typhus rickettsia	*Rhipicephalus* ticks	India	Yes
Astrakhan fever	Astrakhan fever rickettsia	*Rhipicephalus* ticks	Caspian littoral, SE Europe, Central Africa	Yes
Israeli spotted fever	Israeli tick typhus rickettsia	*Rhipicephalus* ticks	Eastern Mediterranean littoral, SW Europe	No
Rocky Mountain spotted fever	*Rickettsia rickettsii*	*Dermacentor* & *Amblyomma* ticks	North and South America	Yes
Queensland tick typhus	*Rickettsia australis*	*Ixodes* ticks	Eastern Australia	Yes
Unnamed	*Rickettsia aeschlimannii*	*Hyalomma* & *Rhipicephalus* ticks	Mediterranean area, Morocco, sub-Saharan Africa	Yes
North Asian tick typhus	*Rickettsia sibirica*	*Dermacentor* & *Haemaphysalis* ticks	Former Soviet Asia, China, European Russia	Yes
Flinder's island spotted fever	*Rickettsia honei*	Ticks of several genera	Australia, SE Asia, NW America	No
Japanese spotted fever	*Rickettsia japonica*	Ticks of several genera	SW Japan	No
Unnamed	'*Rickettsia heilongjiangii*'	*Dermacentor* ticks	NE China	No
Unnamed	*Rickettsia slovaca*	*Dermacentor* ticks	Southern and eastern Europe	No
Unnamed	*Rickettsia helvetica*	*Ixodes* ticks	Central and northern Europe	No
Unnamed	'*Rickettsia mongolotimonae*'	*Hyalomma* ticks	Mongolia, France, sub-Saharan Africa	No

Tick-borne rickettsioses have traditionally been considered rare among international travellers and until 1995 only some 80 cases had been reported in the literature.[2–9] In most published studies on imported fevers, the incidence rate of rickettsioses is very low and ranges from 0–2%.[10–12] However, due to low index of suspicion and poor availability of microbiological diagnostic tests, travel-associated tick-borne rickettsioses could be largely unrecognised and under-reported. Three recent studies support this assumption. In Switzerland, it is estimated that rickettsial infection is actually the third most frequent cause of imported acute febrile diseases, only surpassed by malaria and enteric fever.[13] In Swedish travellers to southern Africa, the estimated risk of contracting rickettsioses increased during 1997–2001 and is now four to five times higher than the risk of acquiring malaria in the same region.[14] Finally, in 530 German travellers who presented at an out-patient travel clinic with fever after a trip to southern Africa, as many as 11% had serological evidence of recent spotted fever group rickettsioses.[15]

Recently, the number of reported cases of travel-associated tick-borne rickettsioses has risen significantly world-wide. This could be explained by increased travel to endemic areas, including ecotourism, increased disease activity, or increased diagnostic awareness. Of the 15 currently-recognised tick-borne rickettsioses, eight have been reported in international travellers: African tick bite fever, Mediterranean spotted fever, Indian tick typhus, Astrakhan fever, Rocky Mountain spotted fever, Queensland tick typhus, *Rickettsia aeschlimannii* infection and North Asian tick typhus (Table 1). This review provides an outline of the current knowledge of tick-borne rickettsioses as they relate to international travel, their microbiological diagnosis, treatment, possible prevention, and future prospects.

African tick bite fever

African tick bite fever is caused by *Rickettsia africae* and is endemic in large parts of sub-Saharan Africa and the French West Indies.[16,17] The disease is transmitted by ungulate ticks of the *Amblyomma* genus, principally *Amblyomma hebraeum* and *Amblyomma variegatum*, and is typically acquired in rural areas where wild game or domestic cattle are present. The implicated tick vectors, which are active throughout the year in many areas, exhibit a notoriously aggressive behaviour and actively attack humans. An exposed individual may thus be bitten by many ticks simultaneously, and in a given group, several members may be attacked on the same occasion. For instance, during the investigation of an outbreak of African tick bite fever among Italian safari tourists to South Africa, as many as 53 tick bites, of which 34 subsequently developed into inoculation eschars, were documented in five patients.[18] Other important features of African tick bite fever include prominent neck muscle myalgia, headache, regional lymphadenitis, and, less frequently, a vesicular cutaneous rash and aphthous stomatitis.[19,20] The clinical course is frequently mild, but may be complicated by reactive arthritis and prolonged fever. To date, no fatal cases of documented African tick bite fever have been reported.

African tick bite fever was virtually unknown outside endemic areas until some ten years ago. Since then, more than 350 travel-associated cases have been reported from Europe, North America, Australia, Argentina, and Japan.[3,7,17–36] Most cases are infected in South Africa, where many popular wildlife attractions are highly endemic for *R. africae* infection[37] and where the abolition of apartheid in the early 1990s was followed by an unprecedented rise in international safari tourism. African tick bite fever has been reported in a wide spectrum of travellers, including leisure safari tourists, foreign aid workers, film crew members, game hunters, students, sports competitors, and deployed soldiers.[17] In a recent prospective cohort study of 940 short-term travellers to rural sub-equatorial Africa, the estimated incidence rates of African tick bite fever ranged from 4.0–5.3%.[19] These estimates are notable and widely exceed those reported for other travel-associated tropical fevers in temporary visitors to sub-Saharan Africa. In the same study, game hunting, travel to southern Africa (i.e. where *A. hebraeum* is the principal vector of *R. africae*), and travel during the rainy summer season (i.e. when tick populations peak in most endemic areas) were identified as independent risk factors.

Mediterranean spotted fever

Mediterranean spotted fever caused by *Rickettsia conorii* is endemic around the Mediterranean basin, the Middle East, India, and in parts of sub-Saharan Africa. The principal vectors are dog ticks of the *Rhipicephalus* and *Haemaphysalis* genera which only rarely bite humans. Nevertheless, the annual incidence rate may locally be very high, e.g. 50 cases/100,000 inhabitants in southern France, where most cases are reported from May to September.[38] Because of its close association with domestic dogs, Mediterranean spotted fever is usually confined to urban and suburban areas. Important clinical features include a single inoculation eschar (in 70% of the cases) and a generalised maculopapular rash (in >95% of the cases).[39] Complications are relatively common, and if left untreated the mortality rate may exceed 2%.

Mediterranean spotted fever is sometimes diagnosed in international travellers. Recent travel-associated cases, in most instances infected in the Mediterranean area, have been reported from the United Kingdom, Germany, Switzerland, Scandinavia, and North America.[13,40–45] A Norwegian male contracted Mediterranean spotted fever twice during visits to a village in Sicily, Italy, in 1997 and 1999, and on both occasions he had played with local dogs.[41] Travelling dogs may carry *R. conorii*-infected *Rhipicephalus sanguineus* ticks to non-endemic areas, as demonstrated in northern France and Switzerland,[46,47] and in The Netherlands, three cases of human Mediterranean spotted fever were linked to dogs that had recently returned from the Mediterranean basin.[48]

Indian tick typhus

Indian tick typhus is caused by Indian tick typhus rickettsia, a species closely related to *R. conorii*, and is transmitted by the brown dog tick *R. sanguineus*. The disease is endemic in India, where it was described as early as the beginning of the 20th century. Although the clinical presentation resembles that of Mediterranean spotted fever, the rash in Indian tick typhus is frequently purpuric, and an inoculation eschar is rarely found.[49]

A case of Indian tick typhus was reported in a French 25-year-old female who fell ill at the end of a one-month stay in India. The clinical presentation was moderately severe with a generalised maculopapular rash with petechiae but no inoculation eschar.[50]

Astrakhan fever

Astrakhan fever is caused by Astrakhan fever rickettsia, another spotted fever group rickettsia closely related to *R. conorii*. Since 1983, some 1000 cases have been reported in the Caspian basin, where the dog tick *Rhipicephalus pumilio* is the principal vector.[51] Recently, Astrakhan fever rickettsia was detected in *R. sanguineus* ticks collected from dogs and military personnel in Kosovo.[52] The clinical picture mimics that of Mediterranean spotted fever, although an inoculation eschar may be seen in only some 20% of the cases.

Astrakhan fever was diagnosed in a French 36-year-old male who fell ill a few days after a bush walk in Chad in October 2000. This case was the first outside Europe and suggests that Astrakhan fever should be considered when evaluating tick-borne rickettsioses in travellers to rural sub-Saharan Africa.[53]

Rocky Mountain spotted fever

Rocky Mountain spotted fever is caused by *Rickettsia rickettsii* and is transmitted by ticks of the *Dermacentor* and *Amblyomma* genera. The principal endemic areas in North America comprise rural areas of the Atlantic seaboard and in mid-western USA where most cases occur from April to August.[54] Some 500 cases are reported each year in the USA, predominantly in children below 16 years of age. Inoculation eschars are rarely seen in Rocky Mountain spotted fever, and a generalised exanthema, typically purpuric, may be absent in some 10% of the cases. The purpuric nature of the rash and the fact that some patients with Rocky Mountain spotted fever may develop meningitis may make this disease difficult to distinguish from meningiococcemia. Fatalities are not uncommon, but are usually associated with delay or failure in giving anti-rickettsial therapy, absence of rash, or absence of tick exposure history.[55]

Despite its significant impact on local populations, Rocky Mountain spotted fever appears to be rare in international travellers. In September 1988, a German 24-year-old male fell ill 12 days after being bitten by a tick during a camping holiday in North Carolina.[56] An American patient contracted Rocky Mountain spotted fever in the USA but developed symptoms and was diagnosed while travelling in France; this patient had an inoculation eschar on the leg (D. Raoult, unpublished data). In 1992, a Finnish 48-year-old female fell ill with probable Rocky Mountain spotted fever shortly after returning from a camping trip in mid-western USA (S. Vene, personal communication).

Queensland tick typhus

Queensland tick typhus is caused by *Rickettsia australis* and is transmitted by ticks of the *Ixodes* genus in rural areas of eastern Australia, where some 60 cases have been reported since 1946.[57] About two thirds of the patients exhibit an inoculation eschar and, as for African tick bite fever, the cutaneous rash is frequently vesicular rather than maculopapular. Fatalities are rarely reported.[58]

A 16-year-old New Zealand girl fell ill with Queensland tick typhus a few days after visiting a crocodile farm in Queensland. The clinical course was severe with renal failure, thrombocytopenia and anemia, and necessitated intensive care.[59]

Rickettsia aeschlimannii infection

Rickettsia aeschlimannii, which was first isolated in 1997, has been detected in *Hyalomma marginatum* ticks collected from cattle in Morocco, Zimbabwe, Niger, and Mali, and in a *Rhipicephalus appendiculatus* tick in South Africa. So far, only two human cases have been reported world-wide: a local hunter in South Africa with mild disease[60] and a 36-year-old male French traveller to Morocco in August 2000.[61] The latter case presented with high fever, a generalised maculopapular cutaneous rash, and a single inoculation eschar, but recovered uneventfully on doxycycline.

North Asian tick typhus

North Asian tick typhus (or Siberian tick typhus), caused by *Rickettsia sibirica*, is endemic in large parts of rural northern Asia, including the former USSR, China and Mongolia. Infections may be very common locally with seropositivity rates reported to exceed 60% in some endemic areas. Most cases occur between May and September.[62]

North Asian tick typhus appears to be very rare among international travellers, but was recently reported in a 55-year-old female volunteer in Mongolia who presented with flu-like symptoms and an eschar on the back of her head upon returning to the UK.[63] In a prospective study of 13 North American palaeontologists deployed to the Gobi desert during two consecutive summer seasons, four subjects were diagnosed with the disease. The clinical presentation included fever, headache, rash, inoculation eschars with regional lymphadenitis, and diarrhoea. Three of the four cases were given anti-rickettsial chemotherapy and all recovered uneventfully.[64]

Microbiological diagnosis

The microbiological diagnosis of rickettsioses is not straight-forward. Culture, the ultimate method, is technically cumbersome and restricted to reference centres to which samples must be shipped.[65] Also, culture requires biohazard facilities, should optimally be inoculated on the day of sampling, and is notoriously negative in cases with prior antibiotic treatment.[66] PCR detection can be performed in any laboratory equipped for molecular diagnosis, and may be applied to an array of samples, including blood, serum and tissue biopsies. The inoculation eschar, however, is the most useful biopsy sample to assay. Various genes can be used, including those encoding the citrate synthase (*glt*A),[67] the outer membranes rOmpA (*omp*A)[68] and rOmpB (*omp*B)[69] and PS120 (gene D).[70] Recently, a PCR assay with increased sensitivity, named suicide PCR, has been developed to detect DNA from blood and tissue samples.[20,52,71–73] This technique is a nested PCR using single-use primers targeting a gene never amplified previously in the laboratory.

Serology is the most commonly used microbiological method for diagnosing rickettsial infections world-wide. However, tests available in commercial laboratories, such as the archaic Weil-Felix test and immunofluorescence assay, are often unable to distinguish reliably between infections with different rickettsial species.[65] With immunoflourescence assay, the considered the serologic reference method, diagnostic antibodies are usually not detected until the second week of illness for most rickettsioses. In African tick bite fever, seroconversion may occur even later, or not at all in cases treated early with doxycycline.[74] More specific serologic methods, including Western blotting and cross-adsorption technique, are currently only available at reference centres.

Treatment

More than 50 years after their introduction, tetracyclines still remain the drugs of first choice in the treatment of tick-borne rickettsioses.[75] Doxycycline 100 mg bid should be given for five days, or until 48 hours after defervescence. In pregnant women, chloramphenicol, josamycin, or a combination of rifampin and erythromycin may be administered.[76] Early antibiotic therapy should be prescribed in any suspected tick-borne rickettsiosis. Patients with a severe course should be hospitalised and treated with doxycycline intravenously up to 24 hours after defervescence. Corticosteroids have not proven useful.

Prevention

It should be stressed that the overall risk for contracting tick-borne rickettsioses is low, or very low, for most international travellers. Many of the diseases occur only in remote areas infrequently affected by modern tourism, and most of the implicated tick vectors are highly adapted to their animal hosts and only bite humans under exceptional circumstances.[77] Nevertheless, certain travellers are at risk and should be informed about preventive measures against tick bites:

1. Travellers to the Mediterranean littoral and other areas highly endemic for Mediterranean spotted fever should avoid physical contact with local dogs, including pet dogs, which have been implicated in disease among temporary visitors.[40] Travellers who bring their own dogs should consider treating them with acaricides.
2. When hiking during the tick season in rural areas with known rickettsial activity, e.g. in eastern USA (Rocky Mountain spotted fever), in sub-Saharan Africa (African tick bite fever and other tick-borne rickettsioses), or northern Asia (North Asia tick typhus) travellers should be recommended to wear protective clothing ideally impregnated with acaricides, regularly check for and swiftly remove any ticks from clothing or skin, and use topical insect repellents on exposed skin.[77,78] Unfortunately, most commercially available skin repellents, e.g. those based on diethyl-3-methylbenzamide (DEET), piperidine compounds or citronella oil, have only short-lasting efficacy against ticks, typically for <2 hours.[79–81] Certainly, products containing >33% DEET may have more long-lasting activity,[82] but lotions containing >19.5% are not widely available outside the USA. Travellers to rural sub-Saharan Africa should be informed that the tick vectors of African tick bite fever are locally very abundant on vegetation, are very aggressive, are active the whole year in many areas, and, as opposed to mosquitoes and most other disease-transmitting insects, are active 24 hours a day.
3. If travellers returning from tick-infested areas subsequently develop flu-like symptoms, they should be sure to mention the possible exposure to their doctor.

Future prospects and conclusions

Given the significant increase in international travel (about 4% per annum),[83] and notably to remote areas in tropical and sub-tropical regions of the world, it is likely that the number of cases of travel-associated tick-borne rickettsioses will continue to rise in the years to come. Moreover, a more widespread use of culture and PCR will provide more accurate diagnoses, and, indirectly, reveal new epidemiological insights. For instance, in rural sub-Saharan Africa, where until recently African tick bite fever and Mediterranean spotted fever were the only two recognised tick-borne rickettsioses, we now know that also Astrakhan fever, *R. aeschlimannii* infection, and probably '*Rickettsia mongolotimonae*' infection,[84] may be encountered by international travellers. South-East Asia is another region with soaring tourism and where recent PCR-based studies have disclosed the presence of several rickettsial species.[85,86] Importantly, physicians evaluating febrile travellers who have visited tick-infested areas during the preceding ten days should, even in the absence of a inoculation eschar and skin rash, remember the possibility of tick-borne rickettsiosis and consider the institution of empiric anti-rickettsial therapy.

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