Manifestations and Management of Flea-Borne Rickettsioses

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Maria A Caravedo Martinez¹
Alejandro Ramírez-Hernández²
Lucas S Blanton¹

¹Department of Internal Medicine –
Division of Infectious Diseases,
University of Texas Medical Branch,
Galveston, TX, USA; ²Department of
Pathology, University of Texas Medical
Branch, Galveston, TX, USA

Abstract: Murine typhus and flea-borne spotted fever are undifferentiated febrile illnesses caused by *Rickettsia typhi* and *Rickettsia felis*, respectively. These organisms are small obligately intracellular bacteria and are transmitted to humans by fleas. Murine typhus is endemic to coastal areas of the tropics and subtropics (especially port cities), where rats are the primary mammalian host and rat fleas (*Xenopsylla cheopis*) are the vector. In the United States, a cycle of transmission involving opossums and cat fleas (*Ctenocephalides felis*) are the presumed reservoir and vector, respectively. The incidence and distribution of murine typhus appear to be increasing in endemic areas of the US. *Rickettsia felis* has also been reported throughout the world and is found within the ubiquitous cat flea. Flea-borne rickettsioses manifest as an undifferentiated febrile illness. Headache, malaise, and myalgia are frequent symptoms that accompany fever. The incidence of rash is variable, so its absence should not dissuade the clinician to consider a rickettsial illness as part of the differential diagnosis. When present, the rash is usually macular or papular. Although not a feature of murine typhus, eschar has been found in 12% of those with flea-borne spotted fever. Confirmatory laboratory diagnosis is usually obtained by serology; the indirect immunofluorescence assay is the serologic test of choice. Antibodies are seldom present during the first few days of illness. Thus, the diagnosis requires acute- and convalescent-phase specimens to document seroconversion or a four-fold increase in antibody titer. Since laboratory diagnosis is usually retrospective, when a flea-borne rickettsiosis is considered, empiric treatment should be initiated. The treatment of choice for both children and adults is doxycycline, which results in a swift and effective response. The following review is aimed to summarize the key clinical, epidemiological, ecological, diagnostic, and treatment aspects of flea-borne rickettsioses.

Keywords: *Rickettsia typhi*, murine typhus, endemic typhus, flea-borne typhus, *Rickettsia felis*, flea-borne spotted fever, rickettsiosis

Introduction

Murine typhus and flea-borne spotted fever are undifferentiated febrile illnesses caused by *Rickettsia typhi* and *Rickettsia felis*, respectively. These organisms are small gram-negative obligately intracellular coccobacilli transmitted to humans by fleas. Murine typhus is much more thoroughly characterized, and infection occurs to some degree throughout the world. Thus, the disease is also frequently referred to as endemic typhus. It is most prevalent in coastal areas of the tropics and subtropics (especially port cities), where rats are the primary mammalian host and rat fleas (*Xenopsylla cheopis*) are the vector.¹ In the United States, there is an increasing incidence and geographic distribution.² Here, a cycle of transmission involving

Correspondence: Lucas S Blanton
301 University Boulevard, Galveston, TX,
77555-0435, USA
Tel +1 (409) 747-0236
Fax +1 (409) 772-6527
Email lsblanton@utmb.edu

opossums and cat fleas (*Ctenocephalides felis*) are likely the main drivers of human disease, acting as the amplifying host and vector, respectively.¹ *Rickettsia felis* has also been reported throughout the world and is found within the ubiquitous cat flea.³ As undifferentiated febrile illnesses, these flea-borne rickettsioses often go unrecognized by physicians.⁴ Initiation of proper treatment – doxycycline – requires a high index of suspicion, so recognition is paramount. Knowledge of the clinical features and epidemiology of flea-borne rickettsioses is essential for recognizing illness, and thus, important for establishing a confirmatory diagnosis and initiating timely therapy. The intention of this review is to summarize the key clinical, epidemiological, ecological, diagnostic, and treatment aspects of flea-borne rickettsioses.

Microbiology, Pathogenesis, and Immunity

Flea-borne rickettsiae are small (~1.3 X 0.4 µm) gram-negative coccobacilli. They have evolved through tremendous genome reduction, jettisoning genes encoding for a variety of enzymes necessary for carbohydrate metabolism, nucleotide production, and lipid biosynthesis. Thus, they have a strict obligately intracellular lifestyle and depend on the host cell's cytosol to provide the nutrients to survive.^{5,6} Rickettsiae are divided into several lineages or clades (ie, the spotted fever, typhus, transitional, and ancestral groups). All but the ancestral group include human pathogens. *Rickettsia typhi* belongs to the typhus group, along with *R. prowazekii* (the agent of louse-borne epidemic typhus). *Rickettsia felis* is a member of the transitional group, which is a group of rickettsiae that share features of both the spotted fever and typhus groups.⁷ Other rickettsiae detected in fleas (*Candidatus Rickettsia senegalensis* and *R. asembonensis*) are phylogenetically similar to *R. felis* and are often referred to as *R. felis*-like organisms.^{8,9}

After the inoculation of rickettsiae into the skin, macrophages and dendritic cells target the organism, which then spread through the lymphatics to regional lymph nodes. The rickettsiae escape hematogenously and infect endothelial cells. Systemic endothelial infection and resultant inflammatory damage lead to increased vascular permeability.¹⁰ A lymphocytic vasculitis can occur within any organ, as described in clinicopathologic reports describing autopsies of fatal murine typhus.¹¹ These vasculitic lesions, when within the microcirculation of the

skin, form the characteristic macular rash of a rickettsiosis. When severe, vascular damage leads to extravasation of intravascular fluid into interstitial spaces. This results in intravascular volume depletion, hypotension, and organ hypoperfusion.¹⁰ The end effects of this process can manifest as pulmonary edema and acute respiratory distress syndrome, acute kidney injury (usually due to prerenal azotemia which can progress to acute tubular necrosis), encephalitis, and death.

Following cutaneous inoculation of rickettsiae, the local response by dendritic cells is important in the formation of an immune response. A crucial component of the innate immune response is performed by natural killer cells, which help control rickettsial infection.¹² Later, cellular responses by CD4 and CD8 T cells, as well as the formation of antibodies, help clear the organism.^{12,13} Following infection, solid long-lasting immunity is believed to occur. Host factors that are associated with severe or fatal rickettsioses include alcohol abuse, older age, and glucose-6-phosphate deficiency.^{14,15} The underlying mechanisms for these observed risk factors are unknown.

Epidemiology and Ecology of Murine Typhus

Murine typhus occurs worldwide and is most prevalent in tropical and subtropical regions, more frequently in sea-ports, where the main rodent reservoirs and flea vectors are found.^{16,17} In the US, human cases were commonly reported during the first half of the 20th century,^{17,18} and a reemergence has been evident during the last few decades in some states.^{2,14,19–22} Similarly, cases have also been reported in Mexico,^{23,24} Brazil,^{25,26} Colombia,^{27,28} and Surinam.²⁹ A similar pattern of emergence (or reemergence depending on the locality) is evident in countries across Asia,^{30,31} Europe,^{32–34} Oceania,^{35,36} and Africa.³⁷

Currently, an urban and a suburban transmission cycle are recognized for this disease, involving different vertebrate and invertebrate hosts under particular ecological conditions. The urban transmission cycle was the first described and involves synanthropic rodents and their fleas as reservoirs and vectors, respectively. Commensal rodents of the genus *Rattus*, mainly *R. norvegicus* (brown rat) and *R. rattus* (black rat), have been implicated as the primary reservoirs.¹⁷ Rats become infected in 4–7 days, do not manifest any clinical signs, and sustain a subclinical infection for long periods of time (about 3 weeks).¹⁷ Other

synanthropic rodent species, such as *Mus musculus* (house mice) and other *Mus* species have been found to be infected with *R. typhi*, as implicated by studies in Australia,³⁸ China,³⁹ and Tunis.⁴⁰ However, compared to rats, their role as reservoir hosts appear minor, as they are common in domiciles in non-endemic areas and are seldom infested with fleas.¹⁷ Fleas parasitizing rodents act as vectors in the transmission cycle. The pulicid flea, *Xenopsylla cheopis* (Oriental rat flea) is recognized as the main vectorial species (it is a common ectoparasite of rats from endemic areas), is found to be naturally infected with *R. typhi*, and successfully acquires and transmits the bacterium under experimental conditions.^{41,42} Other flea species that infest commensal rodents could have a vectorial role in specific ecological conditions and in particular locations – *Xenopsylla brasiliensis*,^{43,44} *Nosopsyllus fasciatus*,^{45,46} *Leptopsylla segnis*,^{39,47,48} and *Echidnophaga gallinacea*^{47,49,50} have been documented with natural and experimental infections.

In the suburban transmission cycle, opossums and their fleas act as reservoirs and vectors, respectively. This cycle has been recorded in the US, specifically in southern suburban areas of California^{51–53} and Texas,^{20,54–58} where murine typhus is endemic. In the southeastern US during the mid 1940s, control campaigns to capture rats and eliminate their associated fleas through the massive use of dichlorodiphenyltrichloroethane (DDT) drastically reduced the number of cases but also changed the ecological conditions for this pathogen.^{18,20,47,51,59} Opossums (*Didelphis virginiana*) are synanthropic animals, in close relation to human dwellings and activities. They are frequently infested with cat fleas (*Ctenocephalides felis*). These fleas also parasitize dogs, cats, and humans.⁶⁰ In California and Texas (depending on the location, year, and testing methods), these animals demonstrate a variable prevalence of antibodies reactive to typhus group rickettsiae.⁵⁵ Seroprevalence can reach values over 60%.^{20,58} Furthermore, low numbers of rats (or other synanthropic rodents) have been captured in these areas, and when present, they are without a serological response, which reinforces the pivotal role of opossums in the transmission cycle.^{51,54,55} As recognized by Brigham (1936), opossums are susceptible to *R. typhi* infection without manifesting fever, other clinical signs, or gross pathological lesions.⁶¹ Nonetheless, the length of time they remain rickettsemic, their ability to transmit to uninfected fleas, and the kinetics of their antibody response are still unknown. Such information would be helpful to better

understand their role as reservoirs or amplifying hosts. *Rickettsia typhi*-infected cat fleas (*C. felis*) parasitizing opossums have been found in these localities with variable infection rates (Minimum Infection Rates [MIR]) that range from 0.6 to 7.0%.^{54,55,57} Interestingly, this flea species is highly ubiquitous and is commonly found parasitizing companion animals (cats and dogs), as well as humans.⁶⁰ Recent studies have identified *R. typhi*-infected cat fleas collected from pet and feral cats.^{62,63} In spite of evidence of *R. typhi* infection and antibody response in endemic areas,^{52,58,63–67} the epidemiological role of cats is most likely as a bridge host, to act as a vehicle to bring infected fleas within close proximity to humans.^{51,62} Similarly, the role of dogs in the epidemiology and ecology of murine typhus is not clear. As similar to cats, they may act more as carriers of infected cat fleas. Several works have identified seropositive dogs in locations with human cases or in endemic areas,^{58,68–73} and others have detected rickettsial DNA from blood samples.^{68,74,75} Despite this evidence, the role of cats and dogs as true reservoirs or amplifying hosts should be further addressed through experimental infections and acquisition/transmission studies with fleas.

In addition to the aforementioned flea species, *R. typhi* has been associated with other arthropods through molecular detection, isolation, or experimental infections. Nonetheless, their vectorial competence remains unknown, and their role as vectors is controversial due to limited mobility, host range, and anthropophilic behavior.¹ Studies with ticks have amplified rickettsial DNA in species like *Rhipicephalus sanguineus*,⁷⁵ and more recently, in the Brazilian Amazon, *Amblyomma* spp. ticks are presumably involved in what authors proposed a sylvatic cycle of typhus group rickettsiae.²⁵ Additionally, lice (*Hoplopleura oenomydis*, *Pediculus humanus*, *Polyplax spinulosa*), mites (*Echinolelaps echidninus*, *Ascoschoengastia indica*, *Ornithonyssus bacoti*) and bedbugs (*Cimex lectularius*) have also been implicated as potential vectors.^{1,17}

The primary route of transmission for *R. typhi* is through the inoculation of infected flea feces on abraded skin.^{42,76} Alternatively, crushed fleas in contact with the skin⁷⁶ and aerosols produced from dry flea feces or dry flea tissues could be potential sources of exposure. As detailed by Azad (1990), infection in the flea is initiated when the rickettsiae are ingested and enter the epithelial cells of the midgut. Within the cytoplasm of the midgut cells, the rickettsiae replicate by transverse binary fission

and are released in the gut lumen to be subsequently excreted with the feces.¹

Ecology of *Rickettsia felis* and *Rickettsia felis*-Like Organisms

Since the discovery of *R. felis* infecting a cat flea colony in California in 1990,⁷⁷ it has been increasingly found within a diverse variety of vertebrate and invertebrate species throughout the world.³ Its primary recognized invertebrate host and reservoir is *C. felis*. These fleas are commonly infected with *R. felis*, and the bacterium is capable of transovarial passage to flea progeny.⁷⁸ Molecular evidence of *R. felis* has also been detected in other species of fleas (*Ctenocephalides canis*, *Pulex irritans*, *Archeopsylla erinacei*, *Xenopsylla cheopis*, *Xenopsylla brasiliensis*, *Leptopsylla segnis*, *Leptopsylla aethiopica*, *Echidnophaga gallinacea*, *Ctenophthalmus congeneroides*, *Stenoponia sidimi*, *Rhadinopsylla insolita*, *Polygenis gwyni*, *Orchopeas howardi*), ticks (*Amblyomma humerale*, *Rhipicephalus sanguineus*, *Rhipicephalus bursa*, *Amblyomma maculatum*, *Carios capensis*), lice (*Linognathus setosus*), mosquitoes (*Anopheles sinensis*, *Anopheles gambiae*, *Culex pipiens*, *Aedes albopictus*), bed bugs (*Cimex hemipterus*), and even non hematophagous insects like book lice (*Liposcelis bostrychophila*).^{3,79} For the latter, it has been proposed to play an endosymbiotic role due to its influence on parthenogenetic reproduction⁸⁰ and mycetome formation within the insect body.⁸¹ Similarly, *R. felis* has been detected, by different methods, in diverse vertebrate species including cats, racoons, rats, opossums, and dogs.^{57,82–85} A recent experimental infection in dogs reported a long period of rickettsemia (up to 100 days) and recorded *R. felis* transmission from infected dogs to uninfected cat fleas, suggesting that this species could be a natural reservoir.⁸⁴ In spite of these findings, currently, there is no definitive consensus about the vertebrate species that acts as a natural reservoir.

In addition, the other flea-borne rickettsial species, *R. asembonensis* and *Candidatus R. senegalensis*, seemingly follow a wide geographical pattern of distribution, similar to that of *R. felis*. *Rickettsia asembonensis* has been detected in different countries across Africa,^{8,86–88} America,^{79,89–95} and Asia.^{96–100} Similarly, there are reports of *Candidatus R. senegalensis* from Africa,^{9,88} America,^{55,89,94,101–103} and Asia.^{99,104,105} Both species have been associated with a variety of flea species and

other arthropods. The broad range of hosts raises questions about the type of biological relationship between these rickettsiae and its host arthropods. Another area of uncertainty is the relationship of these *R. felis*-like rickettsiae with vertebrates. In spite of nucleic acid detection from the blood and tissues of dogs,¹⁰⁶ monkeys,⁹⁶ and cats,¹⁰³ a natural reservoir is still unknown and requires investigation.

The Curious and Controversial Epidemiology of Flea-Borne Spotted Fever

Rickettsia felis infection was first reported from a patient in Texas by PCR in 1991.¹⁰⁷ In the decades following, increasing numbers of case reports implicated *R. felis* (through molecular detection or serologic means) as an etiologic cause of human disease.¹⁰⁸ In more recent years, there have been increasing reports of circulating *R. felis* DNA from febrile patients in sub-Saharan Africa^{109–111} and Asia.^{112,113} Interestingly, when control subjects have been added to similar investigations, *R. felis* DNA has also been found from non-febrile controls as well as those with fever.^{114,115} Molecular detection of the organism has been reported from skin lesions of patients as well as from swabs taken from the skin of healthy subjects.^{116,117} This brings to question the possible exogenous contamination of skin from rickettsiae-laden flea feces or infected non-hematophagous arthropods (eg, book lice).¹¹⁸ In some studies, it is unclear if other potential, and possibly more compelling, diagnoses were ruled out. Indeed, *R. felis* has been detected in the blood and CSF when other causes of disease were evident (ie, scrub typhus, malaria, and cryptococcal meningitis).¹¹⁹ The simultaneous detection of *R. felis* DNA from those with *Plasmodium* parasitemia is also curious and has led some to hypothesize the possible transmission of *R. felis* by mosquitoes.^{118,120,121} It has also been noted that in California, where flea-borne rickettsioses have been proposed to be caused by both *R. typhi* and *R. felis*, cat fleas are ubiquitously infected with *R. felis* at relatively high rates (both in endemic locations and in locations without reported cases), yet *R. typhi* is only detected in cat fleas in areas reporting rickettsial disease. It seems that if truly pathogenic, the ubiquitous presence and frequency of *R. felis*-infected cat fleas in California would lead to more widespread distribution of flea-borne rickettsiosis.¹²² These aforementioned findings have

spurred doubt in regard to the true pathogenic nature of *R. felis*.^{122–124}

Clinical Features of Murine Typhus

Murine typhus is an undifferentiated febrile illness with a vast range of severity. Although most cases are likely mild and go unrecognized under the assumption of a viral illness, disease can lead to prolonged symptoms, hospitalization, admission to the intensive care unit, and death.^{4,14,125} The incubation is 4–15 days, as estimated in those who report a distinct exposure.¹²⁶ The clinical description of murine typhus has been documented in both children and adults from a variety of geographic regions and is well summarized by Tsioutis and colleagues.¹²⁵ Fever is almost universal and is of abrupt onset.¹²⁷ Other manifestations during the early stages of illness include headache (81%), malaise (67%), myalgia (52%), and anorexia (48%). Less frequent manifestations – nausea/vomiting (27%), diarrhea (19%), and abdominal pain (18%) – can confound the clinical picture by mimicking a primary gastrointestinal illness.¹²⁵ Often considered the *sine que non* of a rickettsial illness by clinicians, the presence of rash in those with murine typhus is variable, occurring in roughly half of patients.¹²⁵ Rash is usually faint and pink in coloration. It is therefore detected in darkly pigmented individuals less often than those with light skin (81 versus 20%).¹²⁶ The rash is usually macular or papular,¹²⁶ and petechiae are occasionally observed.^{128,129} It is usually distributed on the trunk and migrates to the extremities.¹²⁶ The palms, soles, and face are usually spared.¹²⁹ Unlike many of the tick-borne spotted fever group infections (eg, Mediterranean spotted fever and African tick bite fever), an eschar or inoculation lesion is not a cutaneous feature of murine typhus and has only been described in a single case report.¹³⁰

Numerous laboratory abnormalities may be noted in those with murine typhus, but none are specific and may be noted in a variety of other infectious syndromes. Elevated hepatic transaminases, due to hepatocellular injury, are the most frequently observed abnormality and noted in 79% of patients. These elevations are usually mild, but in 27% of cases they have been reported to be over 4-times the upper limit of normal. Other abnormalities related to cellular injury include elevations in lactate dehydrogenase in 73%, alkaline phosphatase in 41%, and creatine kinase in 29% of cases.¹²⁵ Creatine kinase elevations at levels suggestive of rhabdomyolysis can occur.^{131,132} Endothelial injury contributes to

hypoalbuminemia and hyponatremia in 60% and 35% of patients, respectively. Abnormalities detected on hemogram include thrombocytopenia in 42%, anemia in 38%, leukopenia in 24%, and leukocytosis in 18% of cases. Elevation in the erythrocyte sedimentation rate is found in 60% of cases reporting this laboratory value.¹²⁵ Elevated procalcitonin, a biomarker for bacterial infection, has been reported in 71% when checked.¹³² When lumbar puncture is obtained, the cerebrospinal fluid (CSF) is usually unremarkable, but when abnormal, it resembles that of aseptic meningitis (eg, elevated protein, normal glucose, and mild lymphocytic pleocytosis).¹³³

Most patients with murine typhus recover uneventfully, but failure to treat can cause protracted symptoms. Occasionally, severe manifestations occur; a case series from Germany, which included 28 patients, found 18% had severe manifestations (eg, pneumonitis, acute kidney injury, and central nervous system involvement).¹³⁴ Pulmonary involvement, in the form of dry cough, occurs in 27% of those with murine typhus,¹²⁵ and infiltrates on chest imaging occurs in 17% of cases.¹³⁵ Progression to acute respiratory distress syndrome, albeit infrequent, has been reported.¹³⁵ Acute kidney injury is due to prerenal azotemia, but when prolonged, acute tubular necrosis may occur.¹³⁶ Severe neurologic manifestations in hospitalized patients include confusion (8%), seizures (4%), stupor (4%), and ataxia (1%).¹²⁹ The case fatality rate of murine typhus is 0.4% (a figure that holds steady in both the pre- and post-antibiotic era).^{14,137}

Clinical Features of Flea-Borne Spotted Fever

Disease attributed to *Rickettsia felis*, often referred to as flea-borne spotted fever, is not as well characterized as it is for other rickettsioses. As discussed above, there are many aspects of this organism and purported disease that need further study. Since the discovery of *R. felis*, cases have been subsequently reported throughout world. The clinical features of flea-borne spotted fever have been systematically reviewed from published case reports by Parola.¹⁰⁸ Signs and symptoms from these compiled cases include fever (94%), rash (71%), neurologic signs (15%), gastrointestinal symptoms (9%), and cough (9%). The rash is usually maculopapular, and unlike murine typhus, eschar has been noted in 12% of cases.¹⁰⁸ There are two reported deaths in patients with meningoencephalitis found to have *R. felis* detected from their CSF,¹³⁸ though the cause of

illness and death may have been attributable to an alternate diagnosis (eg, tuberculosis).

Differential Diagnosis

It is important to reiterate that flea-borne rickettsioses are undifferentiated in their presentation as a febrile illness and have a broad differential diagnosis. The differential diagnosis will vary greatly depending on the epidemiology and demographic characteristics of a patient. In general, the differential diagnosis can be as broad as that for fever of unknown origin and include common bacterial infections (eg, urinary tract infections, pneumonia, endocarditis, and meningitis) and less frequently encountered bacterial infections (eg, rat bite fever, leptospirosis, secondary syphilis, and disseminated gonorrhea). Viral diseases, including those causing mononucleosis syndromes (ie, Epstein-Bar virus, cytomegalovirus, and acute HIV) and viral encephalitides should also be considered.¹³⁹ Due to its constellation of flu-like symptoms, murine typhus has even been mistaken for Covid-19.¹⁴⁰ In the tropics, other considerations include typhoid fever and other vector-borne infections (eg, yellow fever, malaria, dengue, leishmaniasis). Noninfectious etiologies include Kawasaki disease, vasculitides, drug eruptions, immune thrombocytopenic purpura, and thrombotic thrombocytopenic purpura.¹³⁹

Diagnosis

The initial diagnosis of flea-borne rickettsioses requires a high degree of clinical suspicion based on a compatible clinical syndrome in the setting of the right epidemiologic situation. Even where the disease is endemic, it is often overlooked – in one study, the median time from onset of symptoms to a presumptive diagnosis was 9 days.⁴ When evaluating a patient with an undifferentiated febrile illness, it is important to include rickettsioses in the differential diagnosis. Historical details (eg, exposure to flea vectors, mammalian reservoirs around the home, or travel to endemic areas) may be useful when considering the pretest probability of *Rickettsia* spp. as the etiologic agent. Unfortunately, less than a quarter of patients recognize being bit by fleas.¹²⁵ A detailed physical exam should be performed to look for faint rash, or in the case of flea-borne spotted fever, an eschar. It should be noted, as discussed in the clinical features section above, that these findings are frequently absent. Abnormalities on basic hematological and biochemical laboratory testing (eg, elevated hepatic transaminases and thrombocytopenia) are

clues, but they are non-specific and found in a variety of other community acquired and vector-borne infectious diseases.

Serology is the mainstay of laboratory diagnosis for a rickettsial illness. Assays to detect anti-rickettsial antibodies are widely available to clinicians. The indirect immunofluorescence assay (IFA) for the detection of anti-typhus group antibodies is the gold standard serologic test for the diagnosis of murine typhus, but enzyme-linked immunosorbent assays (ELISA) are also commercially available. The IFA requires a fluorescent microscope and trained microscopist. It is subject to both interobserver and intraobserver variation in endpoint titer interpretation.¹⁴¹ ELISA has the advantage of being automated and offering higher throughput,¹⁴² but it does not offer an endpoint titer when performed as a standard clinical diagnostic test. Older methods, such as the Weil–Felix test, latex agglutination, and complement fixation methods have been supplanted by the aforementioned methods (ie, IFA and ELISA). The Weil–Felix test, although still used in some developing countries, is neither sensitive nor specific.¹⁴³

Serology is unable to give a species-specific diagnosis, as antibodies formed after infection with *R. prowazekii* (the agent of louse-borne epidemic typhus) will cross react with antigen derived from *R. typhi* and vice versa. Methods using cross-absorption have enabled the differentiation between infection with *R. prowazekii* and *R. typhi*, but the technique is cumbersome and only performed in the research setting.¹⁴⁴ Antibodies against *R. felis* have been shown to be more cross reactive to spotted fever group antigen than to typhus group antigen.¹⁴⁵ Thus, assays aimed to diagnose Rocky Mountain spotted fever in the US, or Mediterranean spotted fever in Europe, should be reactive following infection with *R. felis*. During the first days of illness, anti-rickettsial antibodies are seldom detected. Reactive antibodies have been detected in 15% and in 50% within a week of illness in two different studies of murine typhus.^{129,146} The serologic confirmation of diagnosis is therefore retrospective – requiring demonstration of seroconversion or 4-fold increase in antibody titer from acute- and convalescent-phase specimens. Detection of IgG is preferred over IgM. The IgM isoform exhibits more cross reactivity to non-rickettsial antigen. It is therefore less specific than IgG and is not detectable much earlier, limiting its utility to improve sensitivity during acute illness. An IgG titer of 1:64 is the usual diagnostic cutoff in the US, but in areas where the disease is highly endemic,

a demonstrable seroprevalence in the population may exist. Although a higher cutoff titer in some areas may be in order,¹⁴⁷ the regional seroprevalence to optimize these cutoffs is often unknown.¹⁴⁸

Molecular methods to detect rickettsiae from the blood have so far been disappointing. Several techniques (ie, conventional PCR, nested PCR, real-time PCR, and isothermal amplification) using a variety of gene targets have been employed, but despite the ability of nucleic acid amplification techniques to detect small quantities of DNA, there are few circulating organisms within the blood.¹⁴⁹ A systematic analysis of studies performing molecular testing for those with murine typhus reveals a median sensitivity of blood and tissue PCR of 3% and 6%, respectively.¹⁵⁰ The DNA of *R. typhi* has also been detected by next generation sequencing from the blood of 2 pregnant women during the workup for undifferentiated febrile illness.¹⁵¹ The use of isothermal amplification techniques in resource limited settings offers a cost-effective diagnostic technique for the detection of infectious pathogens. Indeed, development of such assays for the detection of rickettsiae, as recently demonstrated via recombinase polymerase amplification,¹⁵² offers a technique that rivals the analytic sensitivity of polymerase chain reaction. Interestingly, purported infection with *R. felis* has been accomplished through PCR amplification and sequencing. The seemingly frequent molecular detection of *R. felis* DNA within the blood of subjects is a departure from the paradigm known for other well-characterized rickettsioses.

The immunohistochemical detection of rickettsiae from skin biopsy specimens is an effective means to diagnose a rickettsial disease during early illness.¹³⁰ For murine typhus, the technique uses antibodies against typhus group antigen.¹¹ For Rocky Mountain spotted fever, the sensitivity of immunohistochemistry (IHC) is 70%, and the specificity is 100%.¹⁵³ The sensitivity and specificity of this technique for murine typhus are unknown. Use of IHC has not been utilized for those with reported flea-borne spotted fever. Utilization of IHC as a diagnostic modality is out of reach for most clinicians, as only a few specialized laboratories perform the technique.

Cultivation of rickettsiae is rarely undertaken and not readily available. Culture isolation requires the use of cell culture techniques using antibiotic-free medium, embryonated eggs, or infection and subsequent passage into susceptible animals (eg, guinea pigs). These techniques require technical expertise, and because of the potential for aerosolization during culture and propagation,

biosafety level 3 laboratory conditions are required.¹⁴⁹ Thus, human isolates of *R. typhi* are scarce.¹⁵⁴ To our knowledge, *R. felis* has never been cultivated from a human.

Treatment

Treatment of flea-borne rickettsioses leads to a quick and complete recovery. Although the case fatality of murine typhus is relatively low, failure to treat can lead to prolonged illness. Recognition of flea-borne rickettsiosis as a possible cause for undifferentiated febrile illness is key to the timely initiation of empiric treatment. Treatment should not await the results of diagnostic testing. As discussed above, antibodies are usually not present in early illness, and when sent to reference laboratories, there is a lag in obtaining timely results. Prompt empiric therapy with an effective drug can decrease the length of hospitalization.¹⁵⁵ Failure to recognize and treat can lead to excessive physician visits, hospitalizations, and diagnostic workup.⁴

The choice antibiotics for all rickettsioses are those in the tetracycline class, with doxycycline being the preferred agent. Tetracyclines exhibit a minimum inhibitory concentration (MIC) to typhus group organisms at concentrations of 0.06–0.25 µg/mL.¹⁵⁶ Doxycycline's MIC against *R. felis* is 0.06–0.125 µg/mL.¹⁵⁷ The effectiveness of these agents have been demonstrated by vast clinical experience over the course of many years after their introduction.¹⁵⁸ Recently, a randomized controlled trial comparing doxycycline and azithromycin for murine typhus further demonstrated its effectiveness – the median time to defervesce while on doxycycline was 36 hours.¹⁵⁹ Doxycycline is the preferred agent for the treatment of flea-borne rickettsioses. Its twice daily dosing schedule makes it more convenient than the more frequent dosing of older tetracyclines. Absorption of doxycycline, unlike older tetracyclines, is not hindered by the presence of food (the presence of food prevents or minimizes gastrointestinal upset following ingestion of these agents). Doxycycline is given to adults at 100 mg, oral or intravenous, twice daily. Doxycycline has excellent oral bioavailability, but when critical illness or severe nausea and vomiting preclude oral use, parenteral therapy should be initiated.¹⁶⁰ When illness is severe, a one-time 200 mg loading dose should be administered, followed by normal 100 mg twice daily dosing. Parenteral doxycycline is not available in some developing nations.¹⁶¹ This can prove to be problematic when treating critically ill patients. True

allergy to doxycycline is rare, but when present, desensitization protocols are available.^{162,163} Minocycline appears to be just as effective for rickettsioses. It has been used for Japanese spotted fever, a potentially serious illness.¹⁶⁴ It was used successfully for murine typhus when the price of doxycycline skyrocketed after a national shortage.²⁰ Although the older prototype tetracyclines (eg, tetracycline hydrochloride) are effective, the 4 times daily dosing and need to take on an empty stomach, thus intensifying the gastrointestinal side effects, make them undesirable.¹⁶⁰

Other antibiotics have been used as alternative agents in those with murine typhus and other rickettsioses. Chloramphenicol is recognized as an alternative. Its use is well documented in numerous reports documenting the course of murine typhus.¹⁵⁸ Chloramphenicol exhibits an MIC of 1–2 µg/mL against typhus group organisms.¹⁵⁶ Similarly, thiamphenicol (a chloramphenicol-like compound) has an MIC of 1–2 µg/mL against *R. felis*.¹⁵⁷ Although its success is documented, in a retrospective analysis the time to defervesce while on chloramphenicol was 4.0 days compared to 2.9 days in those who took doxycycline.¹⁶⁵ In Rocky mountain spotted fever there is a higher case fatality rate in those treated with chloramphenicol compared to those who had been treated with a drug in the tetracycline class (7.6% versus 1.5%).¹⁶⁶ Although *R. rickettsii*, the agent that causes Rocky Mountain spotted fever, is much more pathogenic than those causing flea-borne spotted fever, the higher case fatality in those treated with chloramphenicol is important to consider. Although the drug remains available throughout much of the world, oral chloramphenicol is no longer available in the US, and the intravenous form is difficult to obtain. The usual dose for adults is 500 mg, oral or intravenous, every 6 hours. A serious but rare side effect is aplastic anemia.

Fluoroquinolones have been used as alternative agents to treat murine typhus. Ciprofloxacin, ofloxacin, and pefloxacin have undergone in vitro testing to reveal MICs of 0.5–1 µg/mL to typhus group species.¹⁵⁶ The MIC of ofloxacin and levofloxacin to *R. felis* is also 0.5–1 µg/mL.¹⁵⁷ In those with murine typhus, fluoroquinolones do not appear to be as effective as doxycycline. The mean time to defervesce on ciprofloxacin is 4.2 days compared to the 2.9 days for those on doxycycline.¹⁶⁵ In Mediterranean spotted fever (a spotted fever group rickettsiosis cause by *R. conorii*), cases of severe illness have been associated with the use of fluoroquinolones, possibly due to the overexpression of a toxin-antitoxin system.^{167,168} This tempers the enthusiasm of fluoroquinolones as an alternative agent.

The macrolide azithromycin is an attractive choice as an alternative agent, as it has an MIC of 0.1 µg/mL to *R. typhi*.¹⁶⁹ Case reports describing its use in those with typhus group rickettsioses have been mixed. Unfortunately, in a randomized controlled trial, azithromycin was not effective when compared to doxycycline. Azithromycin was associated with a longer median time to defervesce (48 hours) than doxycycline, and it was associated with more treatment failures (4.2% versus 1.4% [$P < 0.001$]).¹⁵⁹

Many antibiotics commonly used as empiric treatment in the outpatient and inpatient settings, such as beta lactams, have no activity against flea-borne rickettsiae. Sulfonamides, such as trimethoprim-sulfamethoxazole, also have no activity.^{156,157} As recognized with other rickettsioses, their use has been associated with progression to severe disease.¹⁷⁰

Treatment in Special Populations

The preferred treatment in pregnant patients with a flea-borne rickettsiosis is doxycycline. Older tetracyclines have been implicated as having teratogenic effects on the bones and developing teeth of the fetus.^{171,172} They are also associated with the development of maternal pancreatitis and hepatotoxicity.¹⁷³ Although these adverse effects carry over as warnings for newer tetracyclines, there is little evidence that such adverse events occur in pregnant women given doxycycline.¹⁷⁴ Although there have been case reports of the successful use of azithromycin for pregnant women with murine typhus, the results of the aforementioned clinical trial, comparing azithromycin to doxycycline, are not encouraging for the efficacy of azithromycin.¹⁵⁹ Considering the lack of evidence implicating doxycycline in severe adverse events during pregnancy, the benefits of its use likely outweigh the risks.¹⁷⁵

The treatment of choice for children remains doxycycline – its use is endorsed by the Pediatric Red Book.¹⁷⁶ Doxycycline 2.2 mg/kg by mouth twice daily is the recommended dose. It should be given for 7 days. As with adults, the parenteral formulation is only necessary if nausea and vomiting are worsened by the oral version or severe enough to impede absorption. Although the potential for staining developing permanent teeth causes great hesitancy for physicians to prescribe doxycycline to children, studies have demonstrated that short and infrequent courses of doxycycline cause no appreciable differences in the shade of permanent teeth.^{177,178} Chloramphenicol (as stated above) appears to be an inferior alternative. In areas of the world where chloramphenicol is still available, the

dosing in children is 12.5 mg/kg every 6 hours. The rare but serious risk of aplastic anemia associated with chloramphenicol should be strongly considered prior to the use of this agent.¹⁶⁰ Although fluoroquinolones are not absolutely contraindicated in children, their use in the pediatric population is associated with more musculoskeletal events (eg, tendinopathy, tendon rupture, and arthropathy) when compared to other antibiotics. Considering the relatively poor performance of fluoroquinolones in adults with murine typhus, their use in children over doxycycline should be avoided. Although azithromycin is safe in children, it does not appear to be effective.¹⁵⁹

Supportive Care

As previously mentioned, most with flea-borne rickettsioses eventually recover with no sequelae, but in those hospitalized, 6% are severe enough to need stay in the intensive care unit.¹²⁵ During critical illness, supportive care is no different than that of other severe infectious diseases. Attention must be paid to the careful administration of intravenous fluids, as excessive crystalloid in the setting of endothelial injury can lead to pulmonary edema. The development of acute respiratory distress syndrome may require mechanical ventilation. Acute kidney injury, when severe or prolonged, may require renal replacement therapy. The need for renal replacement is usually temporary, as renal function typically recovers.¹⁷⁹

Prevention

The control of murine typhus following campaigns to control rat fleas by applying DDT to rat harborages after World War II is an excellent example of how vector control efforts can control an infectious disease. The decrease in flea infestation rates on rats correlated with a rapid fall in human cases. In 1944, 5,401 cases were reported in the US. Following eradication efforts, this fell to less than 100 cases by 1956.¹⁸⁰ Currently, there are no systematic integrated pest control methods to curb murine typhus in endemic areas. Interestingly, as demonstrated in one study, the use of DDT did not have a spillover effect on *C. felis* infesting opossums.¹⁸¹ Since opossums often live and forage in close proximity to human dwellings, development of methods to control fleas on opossums is an intriguing but unestablished approach. There are no studies to support the use of flea control methods around homes, but it seems reasonable that controlling fleas on domestic animals, since they may act as a bridge host to carry infected fleas in close proximity to owners, may help reduce the transmission of flea-borne

rickettsiae to humans. Many topically and orally administered flea-control products are available on the market for dogs and cats.⁶⁰ There is no available vaccine to prevent flea-borne rickettsioses, but it is believed that natural rickettsial infection confers long-lasting immunity.

Summary

Flea-borne rickettsioses are an often-unrecognized cause of febrile illness. The signs and symptoms mimic a variety of other infections. There is no rapid point of care test for the diagnosis during the acute stage of illness. Therefore, a high index of suspicion is paramount. Knowledge of the epidemiology can help the clinician ascertain important historical clues. When the diagnosis is suspected, prompt empiric therapy with doxycycline should be initiated.

Disclosure

The authors report no conflicts of interest related to this work.

References

1. Azad AF. Epidemiology of murine typhus. *Annu Rev Entomol*. 1990;35:553–569. doi:10.1146/annurev.en.35.010190.003005
2. Murray KO, Evert N, Mayes B, et al. Typhus group rickettsiosis, Texas, USA, 2003–2013. *Emerg Infect Dis*. 2017;23(4):645–648. doi:10.3201/eid2304.160958
3. Brown LD, Macaluso KR. *Rickettsia felis*, an emerging flea-borne rickettsiosis. *Curr Trop Med Rep*. 2016;3:27–39. doi:10.1007/s40475-016-0070-6
4. Vohra RF, Walker DH, Blanton LS. Analysis of health-care charges in murine typhus: need for improved clinical recognition and diagnostics for acute disease. *Am J Trop Med Hyg*. 2018;98(6):1594–1598. doi:10.4269/ajtmh.17-0411
5. McLeod MP, Qin X, Karpathy SE, et al. Complete genome sequence of *Rickettsia typhi* and comparison with sequences of other rickettsiae. *J Bacteriol*. 2004;186(17):5842–5855. doi:10.1128/JB.186.17.5842-5855.2004
6. Driscoll TP, Verhoeve VI, Guillotte ML, et al. Wholly *Rickettsia*! Reconstructed metabolic profile of the quintessential bacterial parasite of eukaryotic cells. *mBio*. 2017;8(5). doi:10.1128/mBio.00859-17
7. Gillespie JJ, Beier MS, Rahman MS, et al. Plasmids and rickettsial evolution: insight from *Rickettsia felis*. *PLoS One*. 2007;2(3):e266.
8. Maina AN, Luce-Fedrow A, Omulo S, et al. Isolation and characterization of a novel *Rickettsia* species (*Rickettsia asembonensis* sp. nov.) obtained from cat fleas (*Ctenocephalides felis*). *Int J Syst Evol Microbiol*. 2016;66(11):4512–4517. doi:10.1099/ijsem.0.001382
9. Mediannikov O, Aubadie-Ladrix M, Raoult D. *Candidatus* 'Rickettsia senegalensis' in cat fleas in Senegal. *New Microbes New Infect*. 2015;3:24–28. doi:10.1016/j.nmni.2014.10.005
10. Sahni A, Fang R, Sahni SK, Walker DH. Pathogenesis of rickettsial diseases: pathogenic and immune mechanisms of an endotheliotropic infection. *Annu Rev Pathol*. 2019;14:127–152. doi:10.1146/annurev-pathmechdis-012418-012800

11. Walker DH, Parks FM, Betz TG, Taylor JP, Muehlberger JW. Histopathology and immunohistologic demonstration of the distribution of *Rickettsia typhi* in fatal murine typhus. *Am J Clin Pathol*. 1989;91(6):720–724. doi:10.1093/ajcp/91.6.720
12. Walker DH, Ismail N. Emerging and re-emerging rickettsioses: endothelial cell infection and early disease events. *Nat Rev Microbiol*. 2008;6(5):375–386. doi:10.1038/nrmicro1866
13. Walker DH, Popov VL, Feng HM. Establishment of a novel endothelial target mouse model of a typhus group rickettsiosis: evidence for critical roles for gamma interferon and CD8 T lymphocytes. *Lab Invest*. 2000;80(9):1361–1372. doi:10.1038/labinvest.3780144
14. Pieracci EG, Evert N, Drexler NA, et al. Fatal flea-borne typhus in Texas: a retrospective case series, 1985–2015. *Am J Trop Med Hyg*. 2017;96(5):1088–1093. doi:10.4269/ajtmh.16-0465
15. Whelton A, Donadio JV, Elisberg BL. Acute renal failure complicating rickettsial infections in glucose-6-phosphate dehydrogenase-deficient individuals. *Ann Intern Med*. 1968;69(2):323–328. doi:10.7326/0003-4819-69-2-323
16. Kuo CC, Wardrop N, Chang CT, Wang HC, Atkinson PM. Significance of major international seaports in the distribution of murine typhus in Taiwan. *PLoS Negl Trop Dis*. 2017;11(3):e0005430. doi:10.1371/journal.pntd.0005430
17. Traub R, Wisseman CL, Farhang-Azad A. The ecology of murine typhus—a critical review. *Trop Dis Bull*. 1978;75(4):237–317.
18. Anstead GM. History, rats, fleas, and opossums: the ascendancy of flea-borne typhus in the United States, 1910–1944. *Trop Med Infect Dis*. 2020;5(1).
19. Ruiz K, Valcin R, Keiser P, Blanton LS. Rise in murine typhus in Galveston County, Texas, USA, 2018. *Emerg Infect Dis*. 2020;26(5):1044–1046. doi:10.3201/eid2605.191505
20. Blanton LS, Vohra RF, Bouyer DH, Walker DH. Reemergence of murine typhus in Galveston, Texas, USA, 2013. *Emerg Infect Dis*. 2015;21(3):484–486. doi:10.3201/eid2103.140716
21. Green JS, Singh J, Cheung M, Adler FC, Ashouri N. A cluster of pediatric endemic typhus cases in Orange County, California. *Pediatr Infect Dis J*. 2011;30(2):163–165. doi:10.1097/INF.0b013e3181f4cc25
22. Abramowicz KF, Rood MP, Krueger L, Eremeeva ME. Urban focus of *Rickettsia typhi* and *Rickettsia felis* in Los Angeles, California. *Vector Borne Zoonotic Dis*. 2011;11(7):979–984. doi:10.1089/vbz.2010.0117
23. Zavala-Castro JE, Dzul-Rosado KR, Peniche-Lara G, Tello-Martin R, Zavala-Velazquez JE. Isolation of *Rickettsia typhi* from human, Mexico. *Emerg Infect Dis*. 2014;20(8):1411–1412. doi:10.3201/eid2008.130095
24. Zavala-Castro JE, Zavala-Velazquez JE, Sulu Uicab JE. Murine typhus in child, Yucatan, Mexico. *Emerg Infect Dis*. 2009;15(6):972–974. doi:10.3201/eid1506.081367
25. Minervino AHH, Labruna MB, Dias SR, et al. Typhus group rickettsiosis, Brazilian Amazon. *Emerg Infect Dis*. 2020;26(9):2294–2296. doi:10.3201/eid2609.201305
26. Silva LJ, Papaioordanou PM. Murine (endemic) typhus in Brazil: case report and review. *Rev Inst Med Trop Sao Paulo*. 2004;46(5):283–285. doi:10.1590/S0036-46652004000500010
27. Hidalgo M, Salguero E, de la Ossa A, et al. Murine typhus in Caldas, Colombia. *Am J Trop Med Hyg*. 2008;78(2):321–322. doi:10.4269/ajtmh.2008.78.321
28. Hidalgo M, Montoya V, Martinez A, et al. Flea-borne rickettsioses in the north of Caldas province, Colombia. *Vector Borne Zoonotic Dis*. 2013;13(5):289–294. doi:10.1089/vbz.2012.1173
29. van Doorn HR, Lo ANSM, Ottenkamp J, Pajkrt D. Widened coronary arteries in a feverish child. *Pediatr Cardiol*. 2006;27(4):515–518. doi:10.1007/s00246-006-1324-1
30. Thompson CN, Blacksell SD, Paris DH, et al. Undifferentiated febrile illness in Kathmandu, Nepal. *Am J Trop Med Hyg*. 2015;92(4):875–878. doi:10.4269/ajtmh.14-0709
31. Aung AK, Spelman DW, Murray RJ, Graves S. Rickettsial infections in Southeast Asia: implications for local populace and febrile returned travelers. *Am J Trop Med Hyg*. 2014;91(3):451–460. doi:10.4269/ajtmh.14-0191
32. Rodriguez-Alonso B, Almeida H, Alonso-Sardon M, et al. Murine typhus. How does it affect us in the 21st century? The epidemiology of inpatients in Spain (1997–2015). *Int J Infect Dis*. 2020;96:165–171. doi:10.1016/j.ijid.2020.04.054
33. Grouteau G, Lancelot O, Bertolotti A, et al. Emergence of murine typhus in La Reunion, France, 2012–2017. *Med Mal Infect*. 2020;50(1):22–27. doi:10.1016/j.medmal.2019.06.003
34. Portillo A, Santibanez S, Garcia-Alvarez L, Palomar AM, Oteo JA. Rickettsioses in Europe. *Microbes Infect*. 2015;17(11–12):834–838. doi:10.1016/j.micinf.2015.09.009
35. Lim MY, Weinstein P, Bell A, Hambling T, Tompkins DM, Slaney D. Seroprevalence of antibodies to *Rickettsia typhi* in the Waikato region of New Zealand. *Epidemiol Infect*. 2016;144(11):2283–2289. doi:10.1017/S0950268816000698
36. Derne B, Weinstein P, Musso D, Lau C. Distribution of rickettsioses in Oceania: past patterns and implications for the future. *Acta Trop*. 2015;143:121–133. doi:10.1016/j.actatropica.2014.10.012
37. Letaief A. Epidemiology of rickettsioses in North Africa. *Ann N Y Acad Sci*. 2006;1078:34–41. doi:10.1196/annals.1374.004
38. Wheatland F. A fever resembling a mild form of typhus fever. *Med J Aust*. 1926;1:261–266. doi:10.5694/j.1326-5377.1926.tb39259.x
39. Liu W, Zia SH. Typhus Rickettsia isolated from mice and mouse-fleas during an epidemic in Peiping. *Proc Soc Exp Biol Med*. 1940;45(3):823–826. doi:10.3181/00379727-45-11849P
40. Sparrow H. Enquete sur la presence du virus typhique chez les souris de Tunis. *Arch Inst Pasteur De Tunis*. 1935;24:435–460.
41. Dyer RE, Rumreich A, Badger LF. Typhus fever: a virus of the typhus type derived from fleas collected from wild rats. *Public Health Rep*. 1931;46(7):334–338. doi:10.2307/4579944
42. Dyer RE, Ceder ET, Lillie RD, Rumreich A, Badger LF. The experimental transmission of endemic typhus fever in the United States by the rat flea *Xenopsylla cheopis*. *Public Health Rep*. 1931;46(42):2481–2499. doi:10.2307/4580215
43. Heisch RB. Urban *Rattus* as the main reservoir of murine typhus in Kenya. *J Trop Med Hyg*. 1969;72(8):195–196.
44. Leulmi H, Socolovschi C, Laidisoit A, et al. Detection of *Rickettsia felis*, *Rickettsia typhi*, *Bartonella* species and *Yersinia pestis* in fleas (Siphonaptera) from Africa. *PLoS Negl Trop Dis*. 2014;8(10):e3152. doi:10.1371/journal.pntd.0003152
45. Mooser H, Castaneda MR. The multiplication of the virus of Mexican typhus fever in fleas. *J Exp Med*. 1932;55(2):307–323. doi:10.1084/jem.55.2.307
46. Kemp HA. Endemic typhus fever: rat flea as a possible vector. *J Am Med Assoc*. 1931;97(11):775–777. doi:10.1001/jama.1931.02730110025007
47. Strandtmann RW, Eben DJ. A survey of typhus in rats and rat ectoparasites in Galveston, Texas. *Tex Rep Biol Med*. 1953;11(1):144–151.
48. Azad AF, Traub R. Transmission of murine typhus rickettsiae by *Leptopsylla segnis* (Siphonaptera: leptoptyllidae). *J Med Entomol*. 1987;24(6):689–693. doi:10.1093/jmedent/24.6.689
49. Bringham GD. Two strains of endemic typhus fever virus isolated from naturally infected chicken fleas (*Echidnophaga gallinacea*). *Public Health Rep*. 1941;32(2):1803–1804. doi:10.2307/4583855
50. Alicata JE. Experimental transmission of endemic typhus fever by the sticktight flea, *Echidnophaga gallinacea*. *J Wash Acad Sci*. 1942;32(2):57–60.
51. Adams WH, Emmons RW, Brooks JE. The changing ecology of murine (endemic) typhus in Southern California. *Am J Trop Med Hyg*. 1970;19(2):311–318. doi:10.4269/ajtmh.1970.19.311

52. Sorvillo FJ, Gondo B, Emmons R, et al. A suburban focus of endemic typhus in Los Angeles County: association with seropositive domestic cats and opossums. *Am J Trop Med Hyg.* 1993;48(2):269–273. doi:10.4269/ajtmh.1993.48.269
53. Eremeeva ME, Karpathy SE, Krueger L, et al. Two pathogens and one disease: detection and identification of flea-borne rickettsiae in areas endemic for murine typhus in California. *J Med Entomol.* 2012;49(6):1485–1494. doi:10.1603/ME11291
54. Schrieffer ME, Sacci JB, Taylor JP, Higgins JA, Azad AF. Murine typhus: updated roles of multiple urban components and a second typhuslike rickettsia. *J Med Entomol.* 1994;31(5):681–685. doi:10.1093/jmedent/31.5.681
55. Blanton LS, Idowu BM, Tatsch TN, Henderson JM, Bouyer DH, Walker DH. Opossums and cat fleas: new insights in the ecology of murine typhus in Galveston, Texas. *Am J Trop Med Hyg.* 2016;95(2):457–461. doi:10.4269/ajtmh.16-0197
56. Buttery CM, Magnuson LW, McLerran G, Villarreal T. Endemic (murine) typhus in Corpus Christi. *Tex Med.* 1984;80(8):53–54.
57. Boostrom A, Beier MS, Macaluso JA, et al. Geographic association of *Rickettsia felis*-infected opossums with human murine typhus, Texas. *Emerg Infect Dis.* 2002;8(6):549–554. doi:10.3201/eid0806.010350
58. Adjemian J, Parks S, McElroy K, et al. Murine typhus in Austin, Texas, USA, 2008. *Emerg Infect Dis.* 2010;16(3):412–417. doi:10.3201/eid1603.091028
59. Older JJ. The epidemiology of murine typhus in Texas, 1969. *JAMA.* 1970;214(11):2011–2017. doi:10.1001/jama.1970.03180110021004
60. Rust MK. The biology and ecology of cat fleas and advancements in their pest management: a review. *Insects.* 2017;8(4):118. doi:10.3390/insects8040118
61. Bringham GD. Susceptibility of the opossum (*Didelphis virginiana*) to the virus of endemic typhus fever. *Public Health Rep.* 1936;51(13):333–337.
62. Blanton LS, Vohra RF, Fistein L, Quade B, Walker DH, Bouyer DH. Rickettsiae within the fleas of feral cats in Galveston, Texas. *Vector Borne Zoonotic Dis.* 2019;19(9):647–651. doi:10.1089/vbz.2018.2402
63. Nogueras MM, Pons I, Ortuno A, et al. Molecular detection of *Rickettsia typhi* in cats and fleas. *PLoS One.* 2013;8(8):e71386. doi:10.1371/journal.pone.0071386
64. Irons JV, Bohls SW, Thurman DC, McGregor T. Probable role of the cat flea, *Ctenocephalides felis*, in transmission of murine typhus. *Am J Trop Med.* 1944;24(6):359–362. doi:10.4269/ajtmh.1944.s1-24.359
65. Raynal JH. Le chat dans l'épidémiologie du typhus exanthématique murin. *Bull Soc Pathol Exot Filiales.* 1947;40(9–10):367–375.
66. Beck MD, Van Allen A. Typhus fever in California, 1916–1945, inclusive; an epidemiologic and field laboratory study. *Am J Hyg.* 1947;45(3):335–354.
67. Lepine PP, Lorando N. Le typhus exanthématique du chat. *Bulletin De La Societe De La Pathologie Exotique Et De Ses Filiales.* 1935;28:356–360.
68. Nogueras MM, Pons I, Pla J, et al. The role of dogs in the eco-epidemiology of *Rickettsia typhi*, etiologic agent of Murine typhus. *Vet Microbiol.* 2013;163(1–2):97–102. doi:10.1016/j.vetmic.2012.11.043
69. Huxsoll DL, Shirai A, Robinson DM, Yap LF, Lim BL. Presence of antibodies to scrub typhus and murine typhus in dogs from Selangor, Peninsular, Malaysia. *Southeast Asian J Trop Med Public Health.* 1977;8(2):232–235.
70. Soliman AK, Botros BA, Ksiazek TG, Hoogstraal H, Helmy I, Morrill JC. Seroprevalence of *Rickettsia typhi* and *Rickettsia conorii* infection among rodents and dogs in Egypt. *J Trop Med Hyg.* 1989;92(5):345–349.
71. Lledo L, Gegundez MI, Serrano JL, Saz JV, Beltran M. A sero-epidemiological study of *Rickettsia typhi* infection in dogs from Soria province, central Spain. *Ann Trop Med Parasitol.* 2003;97(8):861–864. doi:10.1179/000349803225002679
72. Bacellar F, Dawson JE, Silveira CA, Filipe AR. Antibodies against rickettsiaceae in dogs of Setubal, Portugal. *Cent Eur J Public Health.* 1995;3(2):100–102.
73. Nanayakkara DM, Rajapakse RP, Wickramasinghe S, Kularatne SA. Serological evidence for exposure of dogs to *Rickettsia conorii*, *Rickettsia typhi*, and *Orientia tsutsugamushi* in Sri Lanka. *Vector Borne Zoonotic Dis.* 2013;13(8):545–549. doi:10.1089/vbz.2012.1049
74. Martinez-Ortiz D, Torres-Castro M, Koyoc-Cardena E, et al. Molecular evidence of *Rickettsia typhi* infection in dogs from a rural community in Yucatan, Mexico. *Biomedica.* 2016;36:45–50. doi:10.7705/biomedica.v36i2.2913
75. Dzúl-Rosado K, Lugo-Caballero C, Tello-Martin R, Lopez-Avila K, Zavala-Castro J. Direct evidence of *Rickettsia typhi* infection in *Rhipicephalus sanguineus* ticks and their canine hosts. *Open Vet J.* 2017;7(2):165–169. doi:10.4314/ovj.v7i2.14
76. Dyer RE, Ceder ET, Workman WG, Rumreich A, Badger LF. Typhus fever: transmission of endemic typhus by rubbing either crushed infected fleas or infected flea feces into wounds. *Public Health Rep.* 1932;47(3):131–133. doi:10.2307/4580312
77. Adams JR, Schmidtman ET, Azad AF. Infection of colonized cat fleas, *Ctenocephalides felis* (Bouche), with a rickettsia-like microorganism. *Am J Trop Med Hyg.* 1990;43(4):400–409. doi:10.4269/ajtmh.1990.43.400
78. Wedincamp J, Foil LD. Vertical transmission of *Rickettsia felis* in the cat flea (*Ctenocephalides felis* Bouche). *J Vector Ecol.* 2002;27(1):96–101.
79. Eremeeva ME, Capps D, McBride CL, et al. Detection of *Rickettsia asembonensis* in fleas (Siphonaptera: pulicidae, Ceratophyllidae) collected in five counties in Georgia, United States. *J Med Entomol.* 2020;57(4):1246–1253. doi:10.1093/jme/tjaa029
80. Behar A, McCormick LJ, Perlman SJ. *Rickettsia felis* infection in a common household insect pest, *Liposcelis bostrychophila* (Psocoptera: liposcelidae). *Appl Environ Microbiol.* 2010;76(7):2280–2285. doi:10.1128/AEM.00026-10
81. Thepparit C, Sunyakumthorn P, Guillotte ML, Popov VL, Foil LD, Macaluso KR. Isolation of a rickettsial pathogen from a non-hematophagous arthropod. *PLoS One.* 2011;6(1):e16396. doi:10.1371/journal.pone.0016396
82. Sashika M, Abe G, Matsumoto K, Inokuma H. Molecular survey of rickettsial agents in feral raccoons (*Procyon lotor*) in Hokkaido, Japan. *Jpn J Infect Dis.* 2010;63(5):353–354.
83. Tay ST, Mokhtar AS, Low KC, et al. Identification of rickettsiae from wild rats and cat fleas in Malaysia. *Med Vet Entomol.* 2014;28(Suppl 1):104–108. doi:10.1111/mve.12075
84. Ng-Nguyen D, Hii SF, Hoang MT, et al. Domestic dogs are mammalian reservoirs for the emerging zoonosis flea-borne spotted fever, caused by *Rickettsia felis*. *Sci Rep.* 2020;10(1):4151. doi:10.1038/s41598-020-61122-y
85. Hii SF, Kopp SR, Abdad MY, et al. Molecular evidence supports the role of dogs as potential reservoirs for *Rickettsia felis*. *Vector Borne Zoonotic Dis.* 2011;11(8):1007–1012. doi:10.1089/vbz.2010.0270
86. Luce-Fedrow A, Maina AN, Otiang E, et al. Isolation of *Candidatus Rickettsia asemboensis* from *Ctenocephalides* fleas. *Vector Borne Zoonotic Dis.* 2015;15(4):268–277. doi:10.1089/vbz.2014.1744
87. Jiang J, Maina AN, Knobel DL, et al. Molecular detection of *Rickettsia felis* and *Candidatus Rickettsia asemboensis* in fleas from human habitats, Asembo, Kenya. *Vector Borne Zoonotic Dis.* 2013;13(8):550–558. doi:10.1089/vbz.2012.1123

88. Bai Y, Osikowicz LM, Kosoy MY, et al. Comparison of zoonotic bacterial agents in fleas collected from small mammals or host-seeking fleas from a Ugandan region where plague is endemic. *mSphere*. 2017;2(6). doi:10.1128/mSphere.00402-17
89. Billeter SA, Diniz PPVDP, Jett LA, et al. Detection of *Rickettsia* species in fleas collected from cats in regions endemic and nonendemic for flea-borne rickettsioses in California. *Vector Borne Zoonotic Dis*. 2016;16(3):151–156. doi:10.1089/vbz.2015.1869
90. Kocher C, Morrison AC, Leguia M, et al. Rickettsial disease in the Peruvian Amazon Basin. *PLoS Negl Trop Dis*. 2016;10(7):e0004843. doi:10.1371/journal.pntd.0004843
91. Oteo JA, Portillo A, Portero F, Zavala-Castro J, Venzal JM, Labruna MB. 'Candidatus Rickettsia asemboensis' and *Wolbachia* spp. in *Ctenocephalides felis* and *Pulex irritans* fleas removed from dogs in Ecuador. *Parasit Vectors*. 2014;7:455.
92. Troyo A, Moreira-Soto RD, Calderon-Arguedas O, et al. Detection of rickettsiae in fleas and ticks from areas of Costa Rica with history of spotted fever group rickettsioses. *Ticks Tick Borne Dis*. 2016;7(6):1128–1134. doi:10.1016/j.ttbdis.2016.08.009
93. Faccini-Martinez AA, Ramirez-Hernandez A, Forero-Becerra E, et al. Molecular evidence of different *Rickettsia* species in Villeta, Colombia. *Vector Borne Zoonotic Dis*. 2016;16(2):85–87. doi:10.1089/vbz.2015.1841
94. Betancourt-Ruiz P, Martinez-Diaz HC, Gil-Mora J, et al. *Candidatus Rickettsia senegalensis* in cat fleas (Siphonaptera: pulicidae) collected from dogs and cats in Cauca, Colombia. *J Med Entomol*. 2020;57(2):382–387. doi:10.1093/jme/tjz177
95. Silva AB, Vizzoni VF, Costa AP, et al. First report of a *Rickettsia asembonensis* related infecting fleas in Brazil. *Acta Trop*. 2017;172:44–49. doi:10.1016/j.actatropica.2017.04.004
96. Tay ST, Koh FX, Kho KM, Sitam FT. Rickettsial infections in monkeys, Malaysia. *Emerg Infect Dis*. 2015;21(3):545–547. doi:10.3201/eid2103.141457
97. Sansyzbayev Y, Nurmakhanov T, Berdibekov A, et al. Survey for rickettsiae within fleas of great gerbils, Almaty Oblast, Kazakhstan. *Vector Borne Zoonotic Dis*. 2017;17(3):172–178. doi:10.1089/vbz.2016.2049
98. Low VL, Prakash BK, Tan TK, et al. Pathogens in ectoparasites from free-ranging animals: infection with *Rickettsia asembonensis* in ticks, and a potentially new species of *Dipylidium* in fleas and lice. *Vet Parasitol*. 2017;245:102–105. doi:10.1016/j.vetpar.2017.08.015
99. Nguyen VL, Colella V, Greco G, et al. Molecular detection of pathogens in ticks and fleas collected from companion dogs and cats in East and Southeast Asia. *Parasit Vectors*. 2020;13(1):420. doi:10.1186/s13071-020-04288-8
100. Nguyen HM, Theppannga W, Vongphayloth K, Douangneun B, Blacksell SD, Robinson MT. Screening of ectoparasites from domesticated dogs for bacterial pathogens in Vientiane, Lao PDR. *Zoonoses Public Health*. 2020;67(8):862–868. doi:10.1111/zph.12753
101. Cevitanes A, Di Cataldo S, Vera F, Lillo P, Millan J. Molecular detection of vector-borne pathogens in rural dogs and associated *Ctenocephalides felis* fleas (Siphonaptera: pulicidae) in Easter Island (Chile). *J Med Entomol*. 2018;55(6):1659–1663. doi:10.1093/jme/tjy141
102. Nelson K, Maina AN, Brisco A, et al. A 2015 outbreak of flea-borne rickettsiosis in San Gabriel Valley, Los Angeles County, California. *PLoS Negl Trop Dis*. 2018;12(4):e0006385. doi:10.1371/journal.pntd.0006385
103. Mullins KE, Maina AN, Krueger L, et al. Rickettsial infections among cats and cat fleas in Riverside County, California. *Am J Trop Med Hyg*. 2018;99(2):291–296. doi:10.4269/ajtmh.17-0706
104. Hornok S, Baneth G, Grima A, et al. Molecular investigations of cat fleas (*Ctenocephalides felis*) provide the first evidence of *Rickettsia felis* in Malta and *Candidatus Rickettsia senegalensis* in Israel. *New Microbes New Infect*. 2018;25:3–6. doi:10.1016/j.nmni.2018.05.001
105. Khan SA, Bora T, Chattopadhyay S, Jiang J, Richards AL, Dutta P. Seroepidemiology of rickettsial infections in Northeast India. *Trans R Soc Trop Med Hyg*. 2016;110(8):487–494. doi:10.1093/trstmh/trw052
106. Kolo AO, Sibeko-Matjila KP, Maina AN, Richards AL, Knobel DL, Matjila PT. Molecular detection of zoonotic rickettsiae and *Anaplasma* spp. in domestic dogs and their ectoparasites in Bushbuckridge, South Africa. *Vector Borne Zoonotic Dis*. 2016;16(4):245–252. doi:10.1089/vbz.2015.1849
107. Schriefer ME, Sacci JB, Dumler JS, Bullen MG, Azad AF. Identification of a novel rickettsial infection in a patient diagnosed with murine typhus. *J Clin Microbiol*. 1994;32(4):949–954. doi:10.1128/JCM.32.4.949-954.1994
108. Parola P. *Rickettsia felis*: from a rare disease in the USA to a common cause of fever in sub-Saharan Africa. *Clin Microbiol Infect*. 2011;17(7):996–1000. doi:10.1111/j.1469-0691.2011.03516.x
109. Socolovschi C, Mediannikov O, Sokhna C, et al. *Rickettsia felis*-associated unruptive fever, Senegal. *Emerg Infect Dis*. 2010;16(7):1140–1142. doi:10.3201/eid1607.100070
110. Richards AL, Jiang J, Omulo S, et al. Human infection with *Rickettsia felis*, Kenya. *Emerg Infect Dis*. 2010;16(7):1081–1086. doi:10.3201/eid1607.091885
111. Sothmann P, Keller C, Krumkamp R, et al. *Rickettsia felis* infection in febrile children, Ghana. *Am J Trop Med Hyg*. 2017;96(4):783–785. doi:10.4269/ajtmh.16-0754
112. Mongkol N, Suputtamongkol Y, Taweethavonsawat P, Foongladda S. Molecular evidence of *Rickettsia* in human and dog blood in Bangkok. *Vector Borne Zoonotic Dis*. 2018;18(6):297–302. doi:10.1089/vbz.2017.2180
113. Chowdhury NF, Paul SK, Aung MS, et al. Nationwide prevalence of *Rickettsia felis* infections in patients with febrile illness in Bangladesh. *New Microbes New Infect*. 2017;19:123–125. doi:10.1016/j.nmni.2017.07.005
114. Maina AN, Knobel DL, Jiang J, et al. *Rickettsia felis* infection in febrile patients, western Kenya, 2007–2010. *Emerg Infect Dis*. 2012;18(2):328–331. doi:10.3201/eid1802.111372
115. Mourembou G, Lekana-Douki JB, Mediannikov O, et al. Possible role of *Rickettsia felis* in acute febrile illness among children in Gabon. *Emerg Infect Dis*. 2015;21(10):1808–1815. doi:10.3201/eid2110.141825
116. Mediannikov O, Fenollar F, Bassene H, et al. Description of “yaaf”, the vesicular fever caused by acute *Rickettsia felis* infection in Senegal. *J Infect*. 2013;66(6):536–540. doi:10.1016/j.jinf.2012.10.005
117. Mediannikov O, Socolovschi C, Million M, et al. Molecular identification of pathogenic bacteria in eschars from acute febrile patients, Senegal. *Am J Trop Med Hyg*. 2014;91(5):1015–1019. doi:10.4269/ajtmh.13-0629
118. Parola P, Mediannikov O, Dieme C, Raoult D. Reply to Slesak et al.: so much about *Rickettsia felis* infection to be discovered. *Proc Natl Acad Sci U S A*. 2015;112(48):E6595–6596. doi:10.1073/pnas.1517919112
119. Dittrich S, Phommason K, Anantat T, et al. *Rickettsia felis* infections and comorbid conditions, Laos, 2003–2011. *Emerg Infect Dis*. 2014;20(8):1402–1404. doi:10.3201/eid2008.131308
120. Mediannikov O, Abat C, Sokhna C, Raoult D. Parallel decline of malaria and *Rickettsia felis* infections in Senegal. *Am J Trop Med Hyg*. 2018;99(2):360–361. doi:10.4269/ajtmh.17-0194
121. Dieme C, Bechah Y, Socolovschi C, et al. Transmission potential of *Rickettsia felis* infection by *Anopheles gambiae* mosquitoes. *Proc Natl Acad Sci U S A*. 2015;112(26):8088–8093. doi:10.1073/pnas.1413835112

122. Billeter SA, Metzger ME. Limited evidence for *Rickettsia felis* as a cause of zoonotic flea-borne rickettsiosis in Southern California. *J Med Entomol*. 2017;54(1):4–7. doi:10.1093/jme/tjw179
123. Blanton LS, Walker DH. Flea-borne rickettsioses and rickettsiae. *Am J Trop Med Hyg*. 2017;96(1):53–56. doi:10.4269/ajtmh.16-0537
124. Labruna MB, Walker DH. *Rickettsia felis* and changing paradigms about pathogenic rickettsiae. *Emerg Infect Dis*. 2014;20(10):1768–1769. doi:10.3201/eid2010.131797
125. Tsioutsis C, Zafeiri M, Avramopoulos A, Prousalis E, Miligkos M, Karageorgos SA. Clinical and laboratory characteristics, epidemiology, and outcomes of murine typhus: a systematic review. *Acta Trop*. 2017;166:16–24. doi:10.1016/j.actatropica.2016.10.018
126. Stuart BM, Pullen RL. Endemic (murine) typhus fever: clinical observations of 180 cases. *Ann Intern Med*. 1945;23:17.
127. Miller ES, Beeson PB. Murine typhus fever. *Medicine*. 1946;25:1–15. doi:10.1097/00005792-194602000-00001
128. Fergie JE, Purcell K, Wanat D. Murine typhus in South Texas children. *Pediatr Infect Dis J*. 2000;19(6):535–538. doi:10.1097/00006454-200006000-00009
129. Dumler JS, Taylor JP, Walker DH. Clinical and laboratory features of murine typhus in South Texas, 1980 through 1987. *JAMA*. 1991;266(10):1365–1370. doi:10.1001/jama.1991.03470100057033
130. Blanton LS, Lea AS, Kelly BC, Walker DH. An unusual cutaneous manifestation in a patient with murine typhus. *Am J Trop Med Hyg*. 2015;93(6):1164–1167. doi:10.4269/ajtmh.15-0380
131. Blanton LS, Berman MA, Afrouzian M. Case report: renal failure due to focal segmental glomerulosclerosis in a patient with murine typhus. *Am J Trop Med Hyg*. 2020;103(3):1017–1019. doi:10.4269/ajtmh.20-0116
132. Afzal Z, Kallumadanda S, Wang F, Hemmige V, Musher D. Acute febrile illness and complications due to murine typhus, Texas, USA 1,2. *Emerg Infect Dis*. 2017;23(8):1268–1273. doi:10.3201/eid2308.161861
133. Silpapojakul K, Ukkachoke C, Krisanapan S, Silpapojakul K. Rickettsial meningitis and encephalitis. *Arch Intern Med*. 1991;151(9):1753–1757. doi:10.1001/archinte.1991.00400090051010
134. Rauch J, Eisermann P, Noack B, et al. Typhus group rickettsiosis, Germany, 2010–2017(1). *Emerg Infect Dis*. 2018;24(7):1213–1220. doi:10.3201/eid2407.180093
135. van der Vaart TW, van Thiel PP, Juffermans NP, et al. Severe murine typhus with pulmonary system involvement. *Emerg Infect Dis*. 2014;20(8):1375–1377. doi:10.3201/eid2008.131421
136. Shaked Y, Shpilberg O, Samra Y. Involvement of the kidneys in Mediterranean spotted fever and murine typhus. *Q J Med*. 1994;87(2):103–107.
137. Doppler JF, Newton PN. A systematic review of the untreated mortality of murine typhus. *PLoS Negl Trop Dis*. 2020;14(9):e0008641. doi:10.1371/journal.pntd.0008641
138. Mawuntu AHP, Johar E, Anggraeni R, et al. *Rickettsia felis* identified in two fatal cases of acute meningoencephalitis. *PLoS Negl Trop Dis*. 2020;14(2):e0007893. doi:10.1371/journal.pntd.0007893
139. Biggs HM, Behravesh CB, Bradley KK, et al. Diagnosis and management of tickborne rickettsial diseases: rocky Mountain spotted fever and other spotted fever group rickettsioses, ehrlichioses, and anaplasmosis - United States. *MMWR Recomm Rep*. 2016;65(2):1–44. doi:10.15585/mmwr.mm6502a1
140. Patel HM. Murine typhus mistaken for COVID-19 in a young man. *BMJ Case Rep*. 2020;13:11. doi:10.1136/bcr-2020-239471
141. Phetsouvanh R, Thojakong T, Phoumin P, et al. Inter- and intra-operator variability in the reading of indirect immunofluorescence assays for the serological diagnosis of scrub typhus and murine typhus. *Am J Trop Med Hyg*. 2013;88(5):932–936. doi:10.4269/ajtmh.12-0325
142. Lokida D, Sudarmono P, Kosasih H, et al. Comparison of commercial enzyme-linked immunosorbent assay and immunofluorescence assay for diagnosis of acute *Rickettsia typhi* infections. *Vector Borne Zoonotic Dis*. 2020;20(2):93–99. doi:10.1089/vbz.2019.2451
143. Hechemy KE, Stevens RW, Sasowski S, Michaelson EE, Casper EA, Philip RN. Discrepancies in Weil-Felix and micro-immunofluorescence test results for Rocky Mountain spotted fever. *J Clin Microbiol*. 1979;9(2):292–293.
144. La Scola B, Rydkina L, Ndiokubwayo JB, Vene S, Raoult D. Serological differentiation of murine typhus and epidemic typhus using cross-adsorption and Western blotting. *Clin Diagn Lab Immunol*. 2000;7(4):612–616. doi:10.1128/CDLI.7.4.612-616.2000
145. Fang R, Raoult D. Antigenic classification of *Rickettsia felis* by using monoclonal and polyclonal antibodies. *Clin Diagn Lab Immunol*. 2003;10(2):221–228. doi:10.1128/CDLI.10.2.221-228.2003
146. Whiteford SF, Taylor JP, Dumler JS. Clinical, laboratory, and epidemiologic features of murine typhus in 97 Texas children. *Arch Pediatr Adolesc Med*. 2001;155(3):396–400. doi:10.1001/archpedi.155.3.396
147. Phakhounthong K, Mukaka M, Dittrich S, et al. The temporal dynamics of humoral immunity to *Rickettsia typhi* infection in murine typhus patients. *Clin Microbiol Infect*. 2020;26(6):781–e9. doi:10.1016/j.cmi.2019.10.022
148. Dhawan S, Robinson MT, Stenos J, et al. Selection of diagnostic cutoffs for murine typhus IgM and IgG immunofluorescence assay: a systematic review. *Am J Trop Med Hyg*. 2020;103(1):55–63. doi:10.4269/ajtmh.19-0818
149. Blanton LS, Walker DH, Bouyer DH, et al. *Rickettsia* and *Orientia*. In: Carroll KC, Pfaffler MA, Landry ML, editors. *Manual of Clinical Microbiology*. Vol. 1. 12th. Washington, DC: ASM Press; 2019:1149–1162.
150. Paris DH, Dumler JS. State of the art of diagnosis of rickettsial diseases: the use of blood specimens for diagnosis of scrub typhus, spotted fever group rickettsiosis, and murine typhus. *Curr Opin Infect Dis*. 2016;29(5):433–439. doi:10.1097/QCO.0000000000000298
151. Stafford IA, Centeno FH, Al Mohajer M, et al. Successful detection of unrecognized *Rickettsia typhi* in pregnancy using cell-free next-generation sequencing. *Case Rep Obstet Gynecol*. 2020;2020:6767351. doi:10.1155/2020/6767351
152. Kissenkotter J, Hansen S, Bohlken-Fascher S, et al. Development of a pan-rickettsial molecular diagnostic test based on recombinase polymerase amplification assay. *Anal Biochem*. 2018;544:29–33. doi:10.1016/j.ab.2017.12.018
153. Walker DH, Burday MS, Folds JD. Laboratory diagnosis of Rocky Mountain spotted fever. *South Med J*. 1980;73(11):1443–1446, 1449. doi:10.1097/00007611-198011000-00007
154. Elliott I, Batty EM, Ming D, et al. Oxford Nanopore MinION sequencing enables rapid whole genome assembly of *Rickettsia typhi* in a resource-limited setting. *Am J Trop Med Hyg*. 2020;102(2):408–414. doi:10.4269/ajtmh.19-0383
155. Howard A, Fergie J. Murine typhus in South Texas children: an 18-year review. *Pediatr Infect Dis J*. 2018;37(11):1071–1076. doi:10.1097/INF.0000000000001954
156. Rolain JM, Maurin M, Vestris G, Raoult D. In vitro susceptibilities of 27 rickettsiae to 13 antimicrobials. *Antimicrob Agents Chemother*. 1998;42(7):1537–1541. doi:10.1128/AAC.42.7.1537
157. Rolain JM, Stuhl L, Maurin M, Raoult D. Evaluation of antibiotic susceptibilities of three rickettsial species including *Rickettsia felis* by a quantitative PCR DNA assay. *Antimicrob Agents Chemother*. 2002;46(9):2747–2751. doi:10.1128/AAC.46.9.2747-2751.2002

158. Dumler JS. Clinical disease: current treatment and new challenges. In: Palmer GH, Azad AF, editors. *Intracellular Pathogens II: Rickettsiales*. Washington, DC: ASM Press; 2012:1–39.
159. Newton PN, Keoulouanghot V, Lee SJ, et al. A prospective, open-label, randomized trial of doxycycline versus azithromycin for the treatment of uncomplicated murine typhus. *Clin Infect Dis*. 2019;68(5):738–747. doi:10.1093/cid/ciy563
160. Moffa M, Brook I. Tetracyclines, glycyclines, and chloramphenicol. In: Bennett JE, Dolin R, Blaser MJ, editors. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. Vol. 1. 9th. Philadelphia: Elsevier; 2020:318–336.
161. Blanton LS, Wilson NM, Quade BR, Walker DH. Susceptibility of *Rickettsia rickettsii* to tigecycline in a cell culture assay and animal model for Rocky Mountain spotted fever. *Am J Trop Med Hyg*. 2019;101(5):1091–1095. doi:10.4269/ajtmh.19-0445
162. Fernando SL, Hudson BJ. Rapid desensitization to doxycycline. *Ann Allergy Asthma Immunol*. 2013;111(1):73–74. doi:10.1016/j.anai.2013.05.005
163. Stollings JL, Chadha SN, Paul AM, Shaver CM, Hagaman D. Doxycycline desensitization for a suspected case of ehrlichiosis. *J Allergy Clin Immunol Pract*. 2014;2(1):103–104. doi:10.1016/j.jaip.2013.08.002
164. Mahara F. Japanese spotted fever: report of 31 cases and review of the literature. *Emerg Infect Dis*. 1997;3(2):105–111. doi:10.3201/eid0302.970203
165. Gikas A, Doukakis S, Padiaditis J, Kastanakis S, Manios A, Tselentis Y. Comparison of the effectiveness of five different antibiotic regimens on infection with *Rickettsia typhi*: therapeutic data from 87 cases. *Am J Trop Med Hyg*. 2004;70(5):576–579. doi:10.4269/ajtmh.2004.70.576
166. Holman RC, Paddock CD, Curns AT, Krebs JW, McQuiston JH, Childs JE. Analysis of risk factors for fatal Rocky Mountain spotted fever: evidence for superiority of tetracyclines for therapy. *J Infect Dis*. 2001;184(11):1437–1444. doi:10.1086/324372
167. Botelho-Nevers E, Edouard S, Leroy Q, Raoult D. Deleterious effect of ciprofloxacin on *Rickettsia conorii*-infected cells is linked to toxin-antitoxin module up-regulation. *J Antimicrob Chemother*. 2012;67(7):1677–1682. doi:10.1093/jac/dks089
168. Botelho-Nevers E, Rovey C, Richet H, Raoult D. Analysis of risk factors for malignant Mediterranean spotted fever indicates that fluoroquinolone treatment has a deleterious effect. *J Antimicrob Chemother*. 2011;66(8):1821–1830. doi:10.1093/jac/dkr218
169. Keysary A, Itzhaki A, Rubinstein E, Oron C, Keren G. The in-vitro anti-rickettsial activity of macrolides. *J Antimicrob Chemother*. 1996;38(4):727–731. doi:10.1093/jac/38.4.727
170. Ruiz Beltran R, Herrero Herrero JL. Deleterious effect of trimethoprim-sulfamethoxazole in Mediterranean spotted fever. *Antimicrob Agents Chemother*. 1992;36(6):1342–1343. doi:10.1128/AAC.36.6.1342
171. Cohan SQ. Teratogenic Agents and Congenital Malformations. *J Pediatr*. 1963;63:650–659. doi:10.1016/S0022-3476(63)80375-3
172. Cohan SQ. Tetracycline staining of teeth. *Teratology*. 1977;15(1):127–129. doi:10.1002/tera.1420150117
173. Herbert WN, Seeds JW, Koontz WL, Cefalo RC. Rocky Mountain spotted fever in pregnancy: differential diagnosis and treatment. *South Med J*. 1982;75(9):1063–1066. doi:10.1097/00007611-198209000-00008
174. Cross R, Ling C, Day NP, McGready R, Paris DH. Revisiting doxycycline in pregnancy and early childhood—time to rebuild its reputation? *Expert Opin Drug Saf*. 2016;15(3):367–382. doi:10.1517/14740338.2016.1133584
175. McGready R, Prakash JA, Benjamin SJ, et al. Pregnancy outcome in relation to treatment of murine typhus and scrub typhus infection: a fever cohort and a case series analysis. *PLoS Negl Trop Dis*. 2014;8(11):e3327. doi:10.1371/journal.pntd.0003327
176. Kimberlin DW, Brady MT, Jackson MA, Long SS. demic typhus (murine typhus). In: *Red Book 2018: Report of the Committee on Infectious Diseases*. 31st ed. Elk Grove Village, IL: American Academy of Pediatrics; 2018:864–865.
177. Grossman ER, Walchek A, Freedman H. Tetracyclines and permanent teeth: the relation between dose and tooth color. *Pediatrics*. 1971;47(3):567–570.
178. Todd SR, Dahlgren FS, Traeger MS, et al. No visible dental staining in children treated with doxycycline for suspected Rocky Mountain spotted fever. *J Pediatr*. 2015;166(5):1246–1251. doi:10.1016/j.jpeds.2015.02.015
179. Hernandez Cabrera M, Angel-Moreno A, Santana E, et al. Murine typhus with renal involvement in Canary Islands, Spain. *Emerg Infect Dis*. 2004;10(4):740–743. doi:10.3201/eid1004.030532
180. Pratt HD. The changing picture of murine typhus in the United States. *Ann N Y Acad Sci*. 1958;70(3):516–527. doi:10.1111/j.1749-6632.1958.tb35408.x
181. Mohr CO, Morlan HB. The nature of parasitism of the opossum by fleas in southwestern Georgia. *J Parasitol*. 1959;45(2):233–237. doi:10.2307/3286539

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