

Manifestations and Management of Flea-Borne Rickettsioses

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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

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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 seaports, 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 bed-bugs (*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 compliment 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.

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