Murine Typhus: An Unrecognized Suburban Vectorborne Disease

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Murine typhus, an acute febrile illness caused by *Rickettsia typhi,* is distributed worldwide. Mainly transmitted by the fleas of rodents, it is associated with cities and ports where urban rats *(Rattus rattus* and *Rattus norvegicus)* are abundant. In the United States, cases are concentrated in suburban areas of Texas and California. Contrary to the classic rat-flea-rat cycle, the most important reservoirs of infection in these areas are opossums and cats. The cat flea, *Ctenocephalides felis,* has been identified as the principal vector. In Texas, murine typhus cases occur in spring and summer, whereas, in California, cases have been documented in summer and fall. Most patients present with fever, and many have rash and headache. Serologic testing with the indirect immunofluorescence assay is the preferred diagnostic method. Doxycycline is the antibiotic of choice and has been shown to shorten the course of illness.

In the past 2 decades, serious mosquito and tickborne infections, such as Lyme borreliosis and West Nile virus infection, have emerged in suburban settings throughout the United States [1, 2]. Fleaborne diseases, such as epidemic and endemic (murine) typhus, which had previously been common in high-density urban human and rodent populations, have nearly been eliminated in the United States [3–7]. However, murine typhus continues to be documented in suburban settings, where opossums, cats, and their fleas coexist [8–11]. Worldwide, murine typhus has been documented in diverse geographic areas, including the Mediterranean, Africa, Southeast Asia, and the United States [3, 4, 12–17]. In the United States, however, many clinicians do not initially suspect a diagnosis of murine typhus because of the limited geographic locations where it has been reported—primarily Texas and California—and because of its nonspecific clinical presentation. Murine typhus can mimic a long list of serious vectorborne infections (e.g., Rocky Mountain spotted fever, ehrlichiosis and anaplasmosis, West Nile virus fever, babesiosis, and dengue) and non–vector-associated infections (e.g., typhoid fever, invasive meningococcal disease, leptospirosis, viral and bacterial meningitis, measles, toxic shock syndrome, secondary syphilis, and Kawasaki syndrome) [18, 19]. Clinicians face an additional challenge in that pertinent physical and historical findings are often not revealed during clinical evaluation; patients do not present with a rash in nearly 50% of cases, and in many instances, they cannot recall a history of having received a flea bite [4, 18]. In this review, we summarize the current epidemiology and ecology of murine typhus in the United States, as well as clinical presentation, diagnostic considerations, treatments, and public health prevention strategies.

ETIOLOGY

Rickettsia typhi is the etiologic agent of murine typhus, which is often referred to as "endemic typhus" or "fleaborne typhus." The pathogenic members of *Rickettsia* species are categorized within the spotted fever group (SFG) or the typhus group (TG), of which *R. typhi* is a member. Like other rickettsiae, *R. typhi* is a small (0.4×1.3 μm), gram-negative, obligate, intracellular bacterium that depends on hematophagous arthropods (e.g., fleas and ticks) and mammals to maintain its life cycle. *R. typhi* multiplies in the epithelial cells of the flea's midgut and is shed in the feces, which are deposited while the flea is feeding [12, 20, 21]. Humans and other mammals acquire the bacteria mainly when the flea bites and feces are inoculated into the bite site [3]. The bacteria also infect the flea's reproductive organs, enabling transmission of the infection transovarially [19].

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A new rickettsial agent, *R. felis,* has been detected in cat fleas *(Ctenocephalides felis)* and opossums *(Didelphis marsupialis)* in the southern regions of California and Texas. The agent has been identified as the cause of typhus-like illness in patients from the United States (Texas), Mexico, France, and Brazil [20, 22, 23]. *R. felis* shares antigenic and genetic components of both TG and SFG rickettsiae. Although it has been placed genetically closer to species in the SFG, molecular studies have found that *R. felis* and *R. typhi* in humans are indistinguishable serologically [8, 19–22]. Differentiation between the 2 species requires analysis by PCR [8, 21].

ECOLOGY AND EPIDEMIOLOGY

Outside of the United States, human cases are concentrated in tropical and subtropical seaboard regions—and particularly in urban environments, where high populations of rats are frequently found [3, 19]. The typical cycle of *R. typhi* involves the roof and Norway rats (*Rattus rattus* and *Rattus norvegicus,* respectively) and the rat flea *(Xenopsylla cheopis).* The rat reservoir not only serves as a host for the flea vector but also makes rickettsiae available in the blood for fleas, which transmit rickettsiae back to a rat host during subsequent feeding [3]. The rat flea does not routinely bite humans but will do so in the absence of their normal hosts [20]. This rat-flea-rat cycle remains the major route of infection throughout the world, especially in the Far East and the Mediterranean [14, 20].

Field and epidemiologic surveys conducted in the Nueces County/Corpus Christi area of southern Texas and Los Angeles County in Southern California have lead to a reevaluation of the classic urban cycle. In these regions, domestic cats, opossums, and cat fleas maintain the suburban life cycle of *R. typhi* and *R. felis* [9–11, 23]. In the suburban foothills of Los Angeles County, Sorvillo et al. [11] documented a high proportion of *R. typhi*–seropositive cats (90%) and opossums (42%) in the vicinity of human murine typhus cases, whereas *R. typhi*–seropositive rats were rarely detected (2.8%), and rat fleas were not found. Furthermore, the mean number of cat fleas found on opossums was significantly higher than was found on rats (L. Krueger, personal communication) [11]. Boostrom et al. [9] provided further data on this cycle from southern Texas, where 58% of affected humans reported in 1998 resided within 0.259 km^2 of *R. typhi*–seropositive opossums.

The ubiquitous opossum and cat flea are especially effective in maintaining and transmitting murine typhus. Opossums are peridomestic animals that have little natural fear of people and are distributed in >40 states [21, 24]. If ample food supplies and sufficient harborage are available, high populations of opossum can flourish, promoting contact with domestic pets and the transfer of fleas [11, 24]. Sustained population growth is further promoted as a result of a lack of routine opossum control in most local animal and pest control programs. The cat flea is prevalent worldwide and is an indiscriminate feeder. It commonly parasitizes cats, dogs, opossums, and many animals of similar size, but it will readily switch to different hosts and will readily bite humans [9, 11, 22].

Studies of the presence of *R. felis* in the suburban cycle have found that the species infects both cat flea and opossum populations at higher proportions than does *R. typhi.* Cat fleas from opossums trapped near affected humans in southern Texas had an infection rate, as detected by PCR, of 3.8% for *R. felis* but of only 0.8% for *R. typhi* [21]. An additional seroprevalence study of opossums sampled in Corpus Christi showed that 22% were infected with *R. felis* and that 8% were infected with *R. typhi* [9]. Although both *R. typhi*– and *R. felis*–infected cat fleas have been found on opossums, cat fleas collected in the wild have never been found to be simultaneously infected [8, 9, 23]. Dual infection in opossums, on the other hand, cannot be ruled out, because antibodies against both infections were documented [9].

From the first identification in the United States in 1913 through the mid-1940s, >5000 cases of murine typhus were reported annually, mainly throughout the southeastern states and California. An aggressive campaign initiated by the US Public Health Service in 1945 to control rats and their fleas effectively reduced typhus reports to <100 cases per year by the late 1980s [3–7, 10]. Since 1980, case reports have receded to the southern regions of Texas and California where the opossum maintains the life cycle [3, 4]. Hawaii, however, experienced an outbreak of murine typhus 47 cases in 2002 across 5 islands, with Maui accounting for 74% of cases. Murine typhus remains endemic on the islands of Maui, Kauai, and Oahu [25]. Although the animal reservoir in Hawaii has not been definitively identified, the rodent-flea cycle is suspected. *R. rattus* and *R. norvegicus* rats trapped from the homes of patients in a 1998 outbreak of murine typhus on Kauai tested positive for *R. typhi.* Serologic studies of additional potential reservoirs in Hawaii have demonstrated typhus group–positive Polynesian rats *(Rattus exulans)* and house mice *(Mus musculus)* [25, 26].

Since 1950, murine typhus in California has been confined to a few southern counties, with Los Angeles County accounting for 42%–90% of cases in the state (3–21 cases annually) [6, 10, 27, 28]. Reflecting the shift in transmission cycle, typhus began to disappear from downtown Los Angeles and emerge in the adjacent foothills, a suburban area with substantial vegetation. In 2006, an outbreak of 21 cases of murine typhus was identified in areas to the west and south of Los Angeles County where typhus is not usually found. Serologic studies indicated that the suburban cycle is also propelling this new epidemic (L. Krueger, personal communication). The factors driving this eastward and southern emergence of cases are not completely understood; some public health specialists have speculated that opossum rescue societies' relocation programs and movement

of feral cat colonies could contribute (L. Krueger, personal communication). Whether this new cluster of cases represents an expansion of the area of endemicity or the emergence of a separate and distinct focus remains to be seen.

Reliable nationwide case counts are not known, because murine typhus is not nationally reportable; however, murine typhus is reportable in some states, including California, Texas, and Hawaii (J. W. Krebs, personal communication) [26, 27]. In California, 3–21 cases of murine typhus have been reported annually over the past 13 years [27, 28]. In comparison, Texas has reported 9–72 cases annually [29], and Hawaii has reported 5–6 cases annually [25]. State-to-state comparisons, however, are difficult to interpret as a result of the lack of a standard case definition.

Transmission of murine typhus correlates more closely to the population of appropriate flea vectors than it does to reservoirs. Fleas propagate most successfully in hot, dry environments. Thus, murine typhus often follows a seasonal distribution. In areas of the world affected by the classic rat-flea-rat cycle, most cases have been documented in the late summer and early fall, when *X. cheopis* fleas are most abundant [3, 6]. Hawaii, particularly Maui and Kauai, has no seasonal distribution; this is possibly due to the maintenance of infectious flea feces in dust and unique year-round food supplies [25, 26]. However, in Texas, where the suburban cycle prevails, cases are most prevalent from April through June [4, 19], whereas most cases in California are reported throughout the summer and fall [27, 28].

CLINICAL PRESENTATION AND DIAGNOSIS

The clinical presentation of murine typhus has been described in clinical series involving patients from the United States (Texas), Greece, Spain, and Thailand [4, 13, 30–34]. Although these studies originate from varied geographical locations, the use of standardized serological diagnostic testing methodologies, such as the direct immunofluorescence assay and the indirect immunofluorescence assay (IFA), allow them to globally describe the presentation of murine typhus and response to antimicrobial therapy.

Table 1 summarizes common and less common presenting signs and symptoms associated with murine typhus. After an incubation period of 7–14 days, the most common symptoms include fever, which can last 3–7 days, headache, rash, and arthralgia (table 1). Three case studies reported that fever of unknown origin was the most frequent admitting diagnosis in patients, including children, who ultimately received a diagnosis of murine typhus [4, 33, 34]. Although rash is a common hallmark of ricketsial disease diagnosis, its presence in patients with murine typhus is variable and can range from as few as 20% of patients to as many as 80% [4, 13, 31, 33, 34]. The rash associated with murine typhus is described as being non-

Table 1. Studies reporting clinical findings associated with murine typhus.

Clinical finding	Range of occurrence, %	References
Fever	98–100	[4, 13, 30–34]
Headache	41–90	[4, 13, 30–34]
Rash	20–80	[4, 13, 30–34]
Arthralgia	40–77	[4, 13, 30–34]
Hepatomegaly	24–29	[13, 30, 31, 33]
Cough	15–40	[4, 13, 30, 32–34]
Diarrhea	5–40	[4, 13, 30–34]
Splenomegaly	5–24	[13, 30, 31, 33]
Insect bite	0–39	[4, 30–34]
Nausea and/or vomiting	3–48	[4, 13, 30–34]
Abdominal pain	11–60	[4, 13, 30–32, 34]
Confusion	2–13	[4, 13, 30–34]

pruritic, macular, or maculopapular; starting on the trunk and then spreading peripherally, sparing the palms and soles; lasting 1–4 days; and occurring, on average, ~1 week after the onset of fever [4, 35]. Flea bites are occasionally found during examination and were reported in 13.6% of cases in a study from the Canary Islands, Spain [30], and in 39% of cases in a study from Texas [4].

The mortality rate for murine typhus is low with use of appropriate antibiotics (1%), and it was noted to be 4% without use of antibiotics. In most cases, it will present as an acute, self-limited illness without complications [4, 36]. The risk of clinical severity may intensify with male sex, African origin, glucose 6-phosphate dehydrogenase deficiency, older age, delayed diagnosis, hepatic and renal dysfunction, CNS abnormalities, and pulmonary compromise [4,19]. Serious complications, however, have been associated with acute infection. The diagnosis of culture-negative endocarditis due to *R. typhi* is based on the results of a physical examination, echocardiographic examination, and serial serological tests [37, 38]. Splenic rupture has been documented in both adults and children with persistent fever and abdominal pain [39–41]. Splenic rupture is diagnosed by abdominal CT or MRI [39, 40]. CNS complications have been noted to occur from 10 days to 3 weeks after the initial onset of febrile illness, with patients presenting with headache, fever, and stiff neck [42, 43]. More serious neurological signs, such as papilledema and focal neurological deficits (e.g., hemiparesis or facial nerve palsy), have also been documented [43]. The findings of analysis of CSF specimens are consistent with "aseptic meningitis," with WBC counts of 10–640 cells/mm^3 and a predominance of mononuclear cells, a normal glucose level, and normal-to-elevated total protein levels [42, 43]. Serologic studies of CSF specimens obtained from patients revealed strongly positive *R. typhi* IgM titers [42, 43].

The most frequently described laboratory abnormalities associated with murine typhus include anemia (18%–75% of cases), decreased WBC count (18%–40%), elevated WBC count (1%–29%), elevated erythrocyte sedimentation rate (59%–89%), and thrombocytopenia (19%–48%). Elevated aminotransferase levels (3–5 times the normal level) are noted in 38%–90% of cases, and hypoalbumemia has been noted in 46%–89% [4, 13, 30–34].

LABORATORY DIAGNOSIS

Although most rickettsial infections are diagnosed using serologic methods, with the IFA noted as the "gold standard," these tests are rarely diagnostic when blood specimens are collected at the onset of symptoms. A convalescent-phase specimen is usually required to confirm the diagnosis [44]. In a large series from Texas, diagnostic IFA titers were present in 50% of cases by the end of the first week of illness and in nearly all cases by 15 days after onset [4]. A ⩾4-fold increase in titer between the acute- and convalescent-phase samples is considered to be diagnostic.

The IFA contains all of the rickettsial heat-labile protein antigens and the group lipopolysaccharide antigen that provides group-reactive serologic test results. EIA uses antigens coated onto microtiter wells or immobilized on nitrocellulose. Dot EIA kits have a sensitivity of 88% and a specificity of 91% [44, 45], compared with an IFA titer of >1:64 for diagnosis of murine typhus. For many years, agglutination of the OX-19 and OX-2 strains of *Proteus vulgaris* and of the OX-K of *Proteus mirabilis*, often referred to as Weil Felix tests, were used for diagnosis of rickettsial infection. Weil Felix tests have poor specificity, compared with the IFA and EIA assays, which should be the diagnostic methods of choice [44, 45]. Other available serologic assays include the indirect immunoperoxidase assay, latex agglutination, line blot, and Western immunoblot.

Isolation of rickettsiae from blood cultures is rarely successful and is usually preformed in specialized research laboratories. If attempted, blood specimens should be collected in a sterile heparin-containing vial before the administration of antimicrobial agents active against rickettsiae (see Walker et al. [44] for details).

PCR has been used to amplify both the SFG and TG. Diagnosis has been made by PCR with use of peripheral blood, buffy coat, and plasma specimens and occasionally with fresh, frozen, or paraffin-embedded tissue specimens or with arthropod vectors acquired during ecologic surveillance (i.e., cat fleas) [44].

TREATMENT

Antimicrobial testing is not routinely performed on rickettsiae. As with other rickettsial diseases, the preferred antibiotic is a tetracycline—specifically, doxycycline for children and nonpregnant women [19, 44, 46]. Clinical series from Greece and the United States have found that doxycycline resulted in a mean duration of febrile illness of 3 days [4, 34, 47]. Chloramphenicol has also been shown to be effective and may be an alternative treatment in pregnant women who are in their first and second trimesters [19]. Quinolones, such as ciprofloxacin or ofloxacin, may also be effective alternatives. In vitro studies from Sweden and a study from Spain demonstrated that quinolones were effective therapy but that the duration of febrile illness was longer than that experienced with doxycycline treatment [47, 48]; however, in 1 case report, a traveler returning from Thailand had a poor response to ciprofloxacin [49]. The current recommendation for the treatment of suspected murine typhus in adults is doxycycline (100 mg orally or intravenously twice daily for severe infection), continued for 3 days after symptoms have resolved [19]. Doxycycline is considered to be safe for treatment of children aged <9 years who have suspected rickettsial infection, because the course is usually short (3–7 days), thus limiting the risk of dental staining [46, 50–52].

PREVENTION AND CHALLENGES

The ability of clinicians to suspect and diagnose murine typhus before receiving the results of confirmatory serologic tests will remain a challenge, because physician awareness of this infection is limited as a result of murine typhus' regional geographic setting and nonspecific clinical presentation. However, murine typhus should be considered in the differential diagnosis if a patient presents with persistent fever of 3–5 days' duration without explanation, if a history of exposure to opossum or cats (in southern California and Texas) and flea contact is likely, or if there is a history of travel to tropical or semitropical environments where large rat populations are likely to exist. Empirical treatment with doxycycline should be started while laboratory confirmation of the diagnosis is pending. All suspected cases of murine typhus should be promptly reported to the local health department because of the potential for spread.

Although murine typhus is limited to very specific areas in the United States, there is potential for cases to arise in new localities. The vector and reservoir components of both the urban and suburban maintenance cycles are ubiquitous, and *R. typhi* has been detected in a multitude of other mammals [3, 26].

The role of *R. felis* as the cause of murine typhus will need to be clarified. Both historical and current information on murine typhus is complicated by the overlapping distribution and cross-reactivity of *R. typhi* with *R. felis*. Retrospective studies of cases in Texas have demonstrated that some patients who were previously thought to be infected with *R. typhi* were, in fact, infected with *R. felis* [21]. This discovery, as well as the widespread presence of *R. felis* in wildlife (compared with *R.*

typhi) has introduced concerns about the extent of its role in human infections.

Typhus infection can be effectively prevented through flea control measures on pets, especially domesticated cats. Foliage in the yard should be trimmed so that it does not provide harborage for rodents, opossums, and stray or feral cats. Screens should be placed on windows and crawl spaces to prevent entry of animals into the house. Food sources, such as open trash cans, fallen food, and pet food that could encourage wild animals to take up residence around the home should be eliminated.

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