Murine Typhus as a Common Cause of Fever of Intermediate Duration

A 17-Year Study in the South of Spain

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Background: Fever of intermediate duration (FID), characterized by a febrile syndrome lasting from 7 to 28 days, is a frequent condition in clinical practice, but its epidemiological and etiologic features are not well described. Murine typhus (MT) is a worldwide illness; nevertheless, to our knowledge, no studies describing its epidemiological and clinical characteristics have been performed in the south of Spain. Also, its significance as a cause of FID is unknown.

Objective: To determine the epidemiological features, clinical characteristics, and prognosis of MT and, prospectively, its incidence as a cause of FID.

Design: Prospective study of cases of MT over 17 years (1979-1995) and of all cases of FID treated in a tertiary teaching hospital in Seville, Spain.

Results: One hundred and four cases of MT were included, and MT was the cause in 6.7% of 926 cases of FID. Insect bites were reported in only 3.8% of the cases of MT previous to the onset of illness. Most cases (62.5%) occurred in the summer and fall. A high frequency of rash (62.5%) was noted. Arthromyalgia (77%), headache (71%), and respiratory (25%) and gastrointestinal (23%) symptoms were also frequent. Laboratory findings were unspecific. Organ complications were uncommon (8.6%), but they were severe in 4 cases. The mean duration of fever was 12.5 days. Cure was achieved in all cases, although only 44 patients received specific treatment.

Conclusions: Murine typhus is prevalent in the south of Spain and is a significant cause of FID. Clinical signs are benign, but some patients may develop severe complications. A high degree of clinical suspicion is required for diagnosis.

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Murine typhus (MT), a zoonosis that is caused by Rickettsia typhi, occurs all over the world, with endemic areas in North and South America, Southeast Asia, Africa, Australia, and some southern European countries.1-10 The importance of this illness has been underestimated. It is more frequent than is commonly believed and represents a worldwide health problem.11 Studies on its prevalence have shown that it also occurs in Spain.12,13 Sporadic cases have been reported in Seville, Huelva, and Murcia,7-9 but, to our knowledge, no extensive studies have been performed to investigate its clinical and epidemiological characteristics. Therefore, its real incidence is not known.

Febrile syndrome without a focal condition is a common problem in outpatients who seek medical care in the community. Classically, there are 2 chronologically distinct types of febrile syndrome: fever of short duration that lasts for up to 7 days,14 and fever of unknown origin that lasts for more than 21 days.15-17 Fever that lasts from 7 to 28 days may be classified as fever of intermediate duration (FID). This condition constitutes a syndromic entity with well-defined etiologic features.18

The aim of the present study was to determine prospectively the incidence of MT in patients with FID, as well as to describe their epidemiological, clinical, serologic, and prognostic characteristics.

RESULTS

One hundred four cases of MT were included. Sixty-two cases occurred between 1983 and 1995, representing 6.7% of all patients with FID (n = 926). There was a slight predominance of males (n = 57 [54.8%]) over females (n = 47 [45.2%]). The mean age was 37.9 years (age range, 12-81 years). The monthly distribution of the cases is shown in the Figure: 62.5% of the cases occurred in the summer.
PATIENTS AND METHODS

The reference population included patients treated for FID at the Infectious Disease Unit of the University Hospital Virgen del Rocio in Seville, Spain, between 1983 and 1995. The hospital is a tertiary institution with 1474 adult beds, attending a population of 640,000 persons, most (73.75%) of whom live in urban areas. Included in the study were the patients who fulfilled the diagnostic criteria of MT during this period. Cases of MT that presented as FID between 1979 and 1982, when prospective etiologic studies were not yet performed in all cases of FID, were also included. Fever of intermediate duration was defined as a temperature higher than 38°C lasting 7 to 28 days in patients who remained without diagnosis or without findings that prompted a diagnostic procedure after anamnesis, physical examination, hemogram, serum creatinine determination, urinalysis, and radiography of the chest.

In all patients with FID, the following parameters were studied: hemoglobin level, white blood cell (WBC) count, platelet count, erythrocyte sedimentation rate, glycemia, urinary sediment, chest x-ray film, and serologic studies of Brucella (rose of bengal and immunofluorescence antibody assay [IFA]), Rickettsia conorii, R typhi, and Coxiella burnetii (IFA as well as agglutination against Proteus OX-19 and OX-2 between 1979 and 1990). In some cases, depending on the clinical features, proteinology; serologic studies for Leptospira, Legionella, Chlamydia, and Yersinia species, Toxoplasma gondii, Epstein-Barr virus, and hepatitis B virus; tuberculin testing with 2 U of purified protein derivative using trichloroacetic acid (PPD-RT23); and acid-fast staining of sputum and urine samples were performed.

The diagnostic criteria of MT were a compatible clinical picture and serological confirmation by determination of IgG antibodies by IFA. Titors of 1: 512 or higher, or a 4-fold rise between the results of 2 successive assays performed at least 14 days apart, were considered diagnostic.7 For IFA, R typhi antigen for complement fixation test fixed with acetone (Diagnostic Pasteur Laboratories, Marnes, la Coquette, France) was used as a reagent until 1986, and R typhi antigen cultivated in Vero cells (bioMérieux Laboratories, Marcy-I’Etoile, France) was used as a reagent from 1986 to 1995.

Anemia was defined as a hemoglobin level lower than 117 g/L in females and lower than 130 g/L in males, leukocytosis as a WBC count higher than 10 x 109/L, leukopenia as a WBC count lower than 5 x 109/L, and thrombocytopenia as a platelet count lower than 100 x 109/L. To evaluate possible cross-reactivity between R typhi and Legionella bozemanii, 17 serum samples from patients with high titers of IgG against R typhi (≥1:4096) were used. The IgG against L bozemanii (Wiga strain ATCC 35292) was determined by IFA.

On physical examination, the most noteworthy finding was rash, which was noted in 62.5% of the patients. The rash, which began around the fifth day after the onset of the illness (mean, 4.7 days; range, 2-12 days), was maculopapular, nonconfluent, and subtle, except in 3 cases, in which it was petechial. It was distributed over the trunk and limbs, sparing the palms and soles. The mean duration of rash was 4 days (range, 1-12 days).

Nine patients (8.6%) developed organ complications, which were severe in 4 (3.8%). The mean age of these patients was 43 years, and none had any underlying illnesses. Five of them received specific treatment. There were 6 cases of pneumonitis, with infiltrates demonstrated on the chest x-ray film; the pneumonitis was interstitial in 3 cases, alveolar in 2 cases, and interstitial with pleuropedicarditis and pulmonary thromboembolism in 1 case. One 79-year-old patient developed cerebellitis with ataxia, intention tremor, and adiadochokinesis, with diffuse cerebral involvement demonstrated on the electroencephalogram. The last 2 patients developed multiorgan failure, with hypotension and thrombopenia in both cases; pneumonitis, hepatitis, and pericarditis in the first one, and adult respiratory distress syndrome plus acute renal failure and disseminated intravascular coagulation in the second one.

Only one patient had anemia (hemoglobin, 111 g/L). The WBC count was normal in 62% of the patients; 20% of the cases were from rural settings. Only 20 patients (19%) had seen rats at home, and only 4 (3.8%) reported insect bites in the days immediately previous to the onset of fever.

The patients with MT presented with the following symptoms:

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No. (%) of Patients</th>
</tr>
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<tbody>
<tr>
<td>Fever</td>
<td>104 (100)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>63 (61)</td>
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<tr>
<td>Headache</td>
<td>74 (71.1)</td>
</tr>
<tr>
<td>Rash</td>
<td>65 (62.5)</td>
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<tr>
<td>Odynophagia</td>
<td>31 (29.8)</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>31 (29.8)</td>
</tr>
<tr>
<td>Cough/expectoration</td>
<td>26 (25)</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>23 (22)</td>
</tr>
<tr>
<td>Nausea, vomiting</td>
<td>24 (23)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 (5.7)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>5 (4.8)</td>
</tr>
<tr>
<td>Adenopathies</td>
<td>2 (1.9)</td>
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</table>

On yearly distribution of the cases is shown in Table 1. The percentage of cases from urban areas was 63.5%; the rest of the cases were from rural settings. Only 20 patients...

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of the patients had leukocytosis; and 18% of the patients had leukopenia. In 18.1% of the patients, lymphocytosis (>50% of total leukocytes) was present, and 19% had thrombopenia. The erythrocyte sedimentation rate was higher than 20 mm/h (range, 5-111 mm/h) in 59.6% of the patients. Similarly, liver enzyme levels (aspartate aminotransferase and alanine aminotransferase) were elevated in 67.3% of the patients, reaching hepatitis values (aspartate aminotransferase, >185 IU/L; alanine aminotransferase, >200 IU/L) in 25% of them. Alkaline phosphatase levels were increased in 25% of the patients.

The IFA method was used to establish the diagnosis in all cases. Seventy-six cases (73%) were diagnosed by a single titer of 1:512 or higher. The other 28 cases (27%) were diagnosed by a 4-fold increase of the initial titer. Agglutinations with Proteus OX-19 were performed in 88 cases, showing titers of 1:160 or higher in 64 (72.7%) of them.

Twenty-two patients (21.1%) met serologic criteria of boutonneuse fever (IFA IgG titer, ≥1:512 or seroconversion). In 19 cases, the titers reached against R. conori were always lower than those reached against R. typhi (14 differed in 2 or more dilutions, and 5 differed in 1 dilution). In the other 3 cases, the same titers were reached against both Rickettsia species. In these, the diagnosis of MT was established clinically (absence of tache noire and distribution of rash). In all cases, antibodies against C. burnetii were nonreactive.

Of the 17 serum samples with high antibody titers against R. typhi, 5 (29.4%) showed no antibodies against L. bozemanii, and 12 demonstrated a positive reaction against L. bozemanii. However, titers reached against R. typhi were always higher, and titers differed by fewer than 2 dilutions in only 3 cases (Table 2).

Forty-four patients (42.3%) received treatment: 40 received doxycycline hyclate, 2 received chloramphenicol, 1 received ciprofloxacin, and 1 received sulfamethoxazole-trimethoprim. The total duration of the fever was 12.5 ± 3.9 (mean ± SD) days (range, 8-27 days), with a mean duration of 9.9 days prior to the first visit and 2.6 days after the start of treatment. The total duration was 12.7 days in untreated patients and 12.4 days in treated patients. Cure was achieved in all cases.

**COMMENT**

Fever of intermediate duration is defined as a fever that lasts 7 to 28 days, in which no cause is identified after the initial evaluation, including physical examination, hemogram, plasma creatinine determination, urinalysis, and chest radiography. Chronologically, in clinical practice, this frequent syndrome is found between fever of short duration, which lasts for up to 7 days and is often of viral origin,14 and fever of unknown origin, which lasts for more than 21 days.15-17 In our environment, FID is caused by systemic infections in 69.5% of the cases (Q fever, 21%; brucellosis, 19%; MT, 8.5%; boutonneuse fever, 6.9%; and mononucleosis syndrome, 8.9%), localized infections in 7.7%, vasculitis in 1.6%, neoplasias in 0.2%, and miscellaneous diseases in 12.4%. In 18.8% of the cases, the fever disappears without a specific diagnosis having been established.18

During the prospective period of study of FID in the south of Spain (1983-1995), MT was diagnosed in 62 cases (6.7% of 926 cases of FID), which established the presence of this illness in Spain and supported previous observations over shorter periods.7,8 However, because of the benign outcome of this process and the characteristics of this study (which was hospital based), its real incidence in the community is not yet known. In Salamanca, in the north of Spain, the seroprevalence of R. typhi was 12.8% among people living in urban and rural areas.12 Data from the southwestern area of Spain are scarce. In Seville, in 1984, the seroprevalence in persons older than 10 years using Rickettsia prowazekii antigen was 0.6% to 2.0%,19 and, to our knowledge, no investigations have been carried out on rodents.

The monthly distribution of the cases in the present study is similar to that reported by other investigators,10-16 most cases occurring in the summer and fall.

### Table 1. Yearly Percentage of Murine Typhus (MT) in Patients Who Were Treated for Fever of Intermediate Duration (FID)

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</thead>
<tbody>
<tr>
<td>FID, No.</td>
<td>45</td>
<td>75</td>
<td>99</td>
<td>53</td>
<td>53</td>
<td>79</td>
<td>101</td>
<td>113</td>
<td>70</td>
<td>72</td>
<td>53</td>
<td>67</td>
<td>46</td>
<td>926</td>
</tr>
<tr>
<td>MT, No. (%)</td>
<td>8 (17.8)</td>
<td>6 (8)</td>
<td>7 (7)</td>
<td>1 (1.9)</td>
<td>5 (9.4)</td>
<td>5 (6.3)</td>
<td>7 (7)</td>
<td>5 (4.4)</td>
<td>6 (8.5)</td>
<td>2 (2.7)</td>
<td>2 (3.7)</td>
<td>4 (6)</td>
<td>4 (8.7)</td>
<td>62 (6.7)</td>
</tr>
</tbody>
</table>

### Table 2. Cross-reactivity Between Rickettsia typhi and Legionella bozemanii (Wiga Strain) Demonstrated by Immunofluorescence Antibody Assay of Serum Samples From Patients With Murine Typhus and High IgG Titers Against R. typhi

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>R typhi</th>
<th>L bozemanii (Wiga Strain)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1:1024</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1:4096</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>1:4096</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>1:16384</td>
<td>1:128</td>
</tr>
<tr>
<td>5</td>
<td>1:8192</td>
<td>1:4096</td>
</tr>
<tr>
<td>6</td>
<td>1:4096</td>
<td>1:256</td>
</tr>
<tr>
<td>7</td>
<td>1:4096</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>1:16384</td>
<td>1:1024</td>
</tr>
<tr>
<td>9</td>
<td>1:2048</td>
<td>1:512</td>
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<tr>
<td>10</td>
<td>1:16384</td>
<td>1:1024</td>
</tr>
<tr>
<td>11</td>
<td>1:4096</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>1:4096</td>
<td>1:512</td>
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<tr>
<td>13</td>
<td>1:16384</td>
<td>1:256</td>
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<tr>
<td>14</td>
<td>1:16384</td>
<td>1:8192</td>
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<td>15</td>
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<tr>
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<td>1:8192</td>
<td>1:512</td>
</tr>
<tr>
<td>17</td>
<td>1:8192</td>
<td>1:512</td>
</tr>
</tbody>
</table>
Murine typhus was also found to be predominantly urban (63.5% of the cases) in this study.

In recent years, there has been a decrease in the number of cases diagnosed. This decrease may be attributed to (1) campaigns of rat control that were carried out in Seville between 1984 and 1986; (2) a better knowledge by general physicians of the frequency of MT and other rickettsial infections in our area, illnesses that are mainly treated outside the hospital; and (3) the introduction and frequent use of fluoroquinolones in the outpatient setting. Antibiotics that have a proven activity against *Rickettsia* species.

Epidemiological data were not particularly useful for establishing diagnosis. In 81% of the cases, the source of transmission was not identified. Only 3.8% of the patients involved remembered an insect bite in the days previous to the onset of illness. Because insect bites and the presence of rodents often go unnoticed, their absence does not preclude the diagnosis. Two studies have shown that, in some areas of the United States, cat fleas (*Ctenocephalides felis*) and opossums are carriers of *R. typhi*. However, opossums are not part of the fauna in Spain. Other studies have demonstrated serologic evidence of *R. typhi* infection in cats but whether cats can serve as a reservoir for *R. typhi* is still unknown. We do not know if another reservoir or vector may be involved in the transmission of *R. typhi* in Spain.

*Rickettsia felis* (previously called ELB agent) has also been identified in *C. felis* and opossums. Using polymerase chain reaction/restriction fragment length polymorphism and partial sequencing of selected polymerase chain reaction products, it was shown that more than 50% of the cat fleas obtained from vertebrate hosts, including dogs and a bobcat, were infected with *R. felis*. The pathogenetic role of this new agent has been demonstrated in a patient with an acute febrile illness mimicking MT. In Spain, the presence of *R. felis* has never been demonstrated.

The clinical features in our study were similar to those in other studies, except that the frequency of rash was higher (62.5% of the cases), the rash was nonconfluent and subtle in all but 3 patients, and the palms and soles were not affected at all. Characteristics and frequency of rash are important data that may be clues to the diagnosis of MT. Respiratory (25%) and digestive symptoms (23%) were also frequent in our study, but occurred less often than in other studies. The analytical alterations, which were nonspecific, were the result of the infection of endothelial cells in multiple organs, leading to a diversity of clinical and laboratory findings. Both anemia, which was infrequent and mild, and thrombocytopenia, which was present in only 19% of the patients, occurred less frequently than in other studies. However, we did find a frequent increase in hepatic enzyme levels (in 67.3% of the cases).

Murine typhus is generally a benign illness, but it may result in potentially severe complications. The frequency of such complications in the present study was 3.8% (4 cases), a percentage similar to that reported by others. The patients with severe complications had no underlying illnesses; their mean age was similar to that of patients whose illness was uncomplicated; and none had received sulfonamides, factors that have been associated with a higher incidence of complications and severity in rickettsiosis.

The easiest and most specific procedure for diagnosis of MT is the detection of specific IgG antibodies by IFA. The results of *Proteus* OX-19 agglutination were positive in only 72% of the cases. This low sensitivity, along with its lower specificity, makes it a technique of poor value.

Boutonneuse fever is endemic in Spain. Cross-reactions between *R. typhi* and *R. conorii* on IFA have been described previously. In the present study, they were relatively frequent (21.1% of the patients). These cross-reactions may represent an important diagnostic problem for patients with FID in areas like ours, in which both *Rickettsia* species are present, and the problem becomes even more complicated when we consider the wide and unspecified clinical features of *R. typhi* and *R. conorii* infections. However, the rash of boutonneuse fever is also maculopapular, but the elements are bigger, more papular, and often confluent, and it affects the palms and soles. Moreover, boutonneuse fever often (75% of cases) presents with tache noire, a necrotic pustule in the site of the tick bite. We used these clinical data to support the diagnosis of MT in the 8 cases in which the antibody titers against both *Rickettsia* were the same or differed in only 1 dilution. In these cases, new techniques in development, such as latex agglutination and enzyme immunoassays, and advances in molecular biology, such as polymerase chain reaction, could represent qualitative improvements because of their high specificity and because they can lead to early diagnosis.

Immunofluorescence antibody assay has been used to demonstrate a cross-reaction between *R. typhi* and *L. bozemanii* in serum samples obtained from patients with febrile syndrome. In the present study, we found cross-reactivity in 12 of 17 serum samples with a high titer of IgG anti-*R. typhi*, but in all cases, the IgG titer against *L. bozemanii* was between 1 and 7 dilutions lower than that reached against *R. typhi*. Therefore, it did not represent a diagnostic problem.

Only 44 patients received specific treatment for MT. This small number can be explained by the frequent unspecific clinical picture of MT, the subtleness of the signs that could make the physicians suspect MT, and the common benign presentation. A high degree of suspicion and the use of knowledge-based medical decision support systems have recently led to a reduction in the number of days from initial visit to diagnosis.

The duration of fever after treatment was 2.6 days, similar to the 3 days previously reported. The total duration of fever was the same in treated and untreated patients. This lack of difference in fever duration may be explained by the relative lateness of the first visit (mean, 9.9 days) and therefore the late start of specific treatment. Another reason may be that physicians prescribed empirical treatment most frequently in patients with the most severe symptoms. Some authors have shown that early and effective treatment against *R. typhi* may con-
siderably reduce morbidity and mortality. However, because the treatment was not randomized in our study, we can draw no conclusions about the reduction of morbidity and mortality with specific and early treatment.

In summary, MT, which is prevalent in the south of Spain, is a significant cause of FID and is usually a benign illness. A high degree of clinical suspicion is necessary for diagnosis.

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REFERENCES


