RICKETTSIAL DISEASES IN BRAZIL

ABSTRACT

Rickettsiae are an important cause of human disease around the world. In Brazil, Brazilian spotted fever (BSF), the most important rickettsiosis, once considered a disease of the past, has again become a significant public health problem, mainly in Southeastern States where several cases have been reported since the 1970's. Its potential to cause serious morbidity and death, even in previously healthy young patients, underscores the importance of accurate diagnosis and prompt treatment. After a brief introduction about rickettsiosis, clinical, laboratory and epidemiologic features of BSF are described.

INTRODUCTION

The rickettsial diseases are febrile illnesses caused by rickettsiae, small bacteria transmitted to humans by arthropod vectors such as ticks, lice, mites and fleas (Table 1). Although the importance of these zoonosis is often underestimated, they occur in all countries, where they may be either sporadic or epidemic, depending upon ecological or epidemiological factors (Anstey et al. 1997; Bouyer et al. 2001; Dias & Martins 1939; Dumler 1999; Gonçalves et al. 1981; Lemos et al. 2001; Magalhães 1952; Mancini et al. 1983; Oliveira et al. 2002; Olson & Paddock 1999; Racult & Roux 1997; Raoult et al. 2001; Tiriba & Monteiro 1982; Travassos 1948; Weiss & Moulder 1984; Zoguereh et al. 2000).

The rickettsias are obligate intracellular, pleomorphic, coccobacilli microorganisms, smaller than most other bacteria. They are not visible in ordinary bacterial stains, though they may be seen
using Giemsa or Gimenez staining procedures. The organism's cell wall composition and its lipopolysaccharide are similar to those seen in gram-negative bacteria. Like other intracellular pathogens, the rickettsias must be cultivated in cell culture, embryonated eggs, or by inoculation in laboratory animals (Ormsbee 1985; Weiss & Moulder 1984).

Since 1993, after molecular analysis, several proposals to change the taxonomic classification of the Rickettsiale order have been presented (Breener et al. 1993; Cardenosa et al. 2000; Dumler et al. 2001; Tamura et al. 1995). Recently Dumler et al. proposed the reorganization of all genera in the families Rickettsiaceae and Anaplasmataceae and suggested that all members of the tribes Ehrlichiae and Wolbachiae should be transferred to the family Anaplasmataceae and the tribe structure of the family Rickettsiaceae was eliminated (Dumler et al. 2001).

The advent of molecular biological methods and the introduction of improved cell culture techniques have helped the identification of new rickettsias (Beati et al. 1993; Bouyer et al. 2001; Kordick et al. 1987, 1997; Olson & Paddock 1999; Raoult et al. 2001; Roux et al. 1997; Sekeyova et al. 1988; Uchuda et al. 1992). Thus, the number of human infection cases due to these pathogens has increased dramatically in the last 25 years. Japanese spotted fever, cat-flea typhus, African tick-bite fever and human ehrlichioses have been reported in several countries, as well as other new and rediscovered rickettsiosis (Higgins et al. 1996; Kelly et al. 1996; Parola et al. 1998; Walker 1989).

In addition to an increasing number of rickettsiosis, these zoonosis have been described in new areas in different regions of the World. Recently, cases of spotted fever have been described in Argentina (Ripoll et al. 1999) and cases of BSF have been reported in a previously unrecognized focus (Sexton et al. 1993). Cat-flea typhus, initially reported in the United States, has been documented recently in Mexico and Brazil (Oliveira et al. 2002; Zavala-Velazquez et al. 2000). African tick bite fever, previously known only in Africa, has now been described in the West Indies (Parola et al. 1998).

The increasing human intervention in previously undisturbed environments has produced rises in occupational and recreational exposures to arthropods and their usual hosts. Outbreaks of African tick bite fever among military personnel and tourists are recent examples of rickettsiosis caused by Rickettsiae africæ (Olson & Paddock 1999; Raoult et al. 2001; Raoult & Roux 1997).

The spotted fever group of rickettsiosis, epidemic typhus and scrub typhus are the most severe rickettsiosis. The overall mortality rate is high in the absence of specific treatment with chloramphenicol and tetracycline antibiotics (Olson & Paddock 1999; Ormsbee 1985; Weiss & Moulder 1984).

Rickettsiosis in Brazil

Although little is known about rickettsiosis in Brazil, BSF, Q fever, endemic typhus, Brill-Zinsser
disease and cat-flea typhus are the rickettsioses already confirmed in Brazil (Cintra & Piza 1920; Damasco et al. 1998; Dias 1938; Dias & Martins 1939; Lemos & Machado 1991; Meira et al. 1955; Oliveira et al. 2002; Ribeiro do Valle et al. 1955). Suspected cases of ehrlichiosis and rickettsialpox have also been observed (Lemos 2002, unpublished data).

Brazilian spotted fever, the only frequently reported rickettsiosis in our country, originally described in São Paulo in 1929 (Piza et al. 1932), is a febrile vasculitic illness caused by *Rickettsiae rickettsii*, a microorganism maintained in nature primarily in a cycle involving ticks and mammals (Dias 1938; Dias & Martins 1939; Lemos et al. 1997, 2001; Magalhães 1952). The most common tick vector associated with BSF is *Amblyomma cajennense*, the Cayenne tick. The larvae and nymph stages of this three-host tick are active from June through October, which corresponds to the period when most BSF cases are diagnosed (Dias 1938; Dias & Martins 1939; Lemos et al. 1997; Magalhães 1952; Monteiro 1931; Travassos 1948).

Dogs, cats, horses, sheep, goats, wild rodents, marsupials and bats, among other mammals, show seropositivity, although only small wild rodents are suspected of playing an important role in spreading the rickettsias in nature, by infected ticks which feed on them during rickettsemia (Dias 1938; Dias & Martins 1939; Lemos et al. 1996, 1996a; Travassos 1948).

A number of other species of ticks such as *Amblyomma ovale*, *Amblyomma brasiensis*, *Amblyomma cooperi*, *Rhipicephalus sanguineus*, *Boophilus microplus* are found infected with rickettsia, but only ticks of the genus *Amblyomma* are considered important in transmitting spotted fever to humans in Brazil (Dias 1938; Dias & Martins 1939; Lemos et al. 1996, 1996a, 1996b; Magalhães 1952; Rosenthal et al. 2002; Travassos & Vallejo-Freire 1944-1945).

BSF is generally acquired from the bite of an infected tick. Transmission occurs only if the tick remains attached for a minimum of four to six hours. Like Rocky Mountain spotted fever (RMSF) in the United States, the infection may also be transmitted through abrasions in the skin, accidentally by transfusion of blood, and to laboratory workers via aerosol transmission (Macdade & Newhouse 1986; Weiss & Moulder 1984).

BSF has been identified mainly in the Southeastern region of Brazil, in the states of Espírito Santo, Minas Gerais, Rio de Janeiro and São Paulo (Damasco et al. 1998; Lemos et al. 1991; Olson et al. 1993; Rosenthal et al. 2002; Sampaio et al. 1988; Souza et al. 1991). From 1929 to 1945, when BSF was an important disease, more than 850 cases were confirmed, while from 1946 to 1975, after the introduction of specific therapy, the number of clinical cases of BSF decreased to 53 confirmed cases (Tiriba & Monteiro 1982).

Since the early 1970s, several cases have been reported during the period of June to October, but only 87 cases have been confirmed (Lemos 1991, Lemos et al. 2001; Mancini et al. 1983; Tiriba & Monteiro 1982). Other suggestive cases occurred,
but diagnosis have not been confirmed due to the general non-availability of laboratory methods for the rickettsial detection, leading to an underestimation of the incidence of this illness in this period.

Since 1997, more suspected and confirmed cases of BSF have been reported (Damasco et al. 1998; Lemos 1998; Lemos et al. 2001) and recently a fatal case of BSF was confirmed in the state of the Rio de Janeiro, in a patient suspected to have dengue or leptospirosis infection (Lemos et al. 2002).

The clinical presentation of BSF closely resembles RMSF and typically presents a sudden onset with fever, malaise, myalgia, headache, chills and conjunctival injection, followed by maculopapular rash several days later. The incubation period varies from three to 12 days, with a mean of seven days. The clinical triad of fever, headache and rash should prompt the clinician to consider a rickettsial disease; however, only 3 to 18% of the patients present the classic triad in the first few days of illness (Magalhães 1952; Gonçalves et al. 1981; Helmick et al. 1984; Lemos 2001).

The early diagnosis is difficult, mainly during the first day of illness, when the clinical manifestations can also suggest leptospirosis, dengue, viral hepatitis, salmonellosis and encephalitis. With the development of rash, it may be confused with meningococcemia, measles, rubella, enteroviral infection, infectious mononucleosis, staphylococcal septicemia, gram-negative sepsis, drug eruption and systemic lupus erythematosus, among other diseases (Gonçalves et al. 1981; Helmick et al. 1984; Lemos et al. 1999, 2001, 2002).

Although rash is a major clinical component of BSF, its presence must not be considered the only condition to confirm the diagnosis. The rash often begins on the fourth day of fever with small erythematous macules at the wrists and ankles. Rash on the palms and soles is frequent and the skin lesions spread centripetally, with relative sparing of the face (Figure 1) (Gonçalves et al. 1981; Lemos et al. 2002; Sampaio et al. 1988).

Extracutaneous manifestations, particularly gastrointestinal, renal, neurological and pulmonary findings may predominate and the presence of oedema generally indicates severe disease (Damasco et al. 1998; Gonçalves et al. 1981; Lemos et al. 2001; Magalhães 1952; Tiriba & Monteiro 1982).

Laboratory abnormalities such as thrombocytopenia, anemia, hyponatremia, pre-ren al azotemia, as well as nonspecific elevations of enzymes such as alkaline phosphatase, and aspartate transaminase may suggest BSF (Damasco et al. 1998; Gonçalves et al. 1981; Lemos et al. 2001; Magalhães 1952; Mancini et al. 1983).

The diagnosis is based primarily on clinical and epidemiological findings, and it is often appropriate to treat patients with early disease solely on the basis of objective signs and a known exposure. The definitive diagnosis can be made by detection of specific antibody in serum, isolation in cell culture (Figure 2), molecular methods and by immunohistochemistry (Lemos et al. 1996b, 2002).

The diagnosis of BSF, as in other regions of the world, has most often been confirmed by serological
testing, although the specific diagnosis may be available only after 7-10 days of illness. The indirect immunofluorescence assay (IFA) is considered to be the gold standard test with high sensitivity and specificity (Newhouse et al. 1979).

Nowadays few studies on BSF have been reported. Severe complications, notably renal failure, seizures, secondary infections and coma can be attributed to misdiagnosis and delayed diagnosis and/or treatment, leading to the high mortality rate verified in our country (Gonçalves et al. 1981; Lemos et al. 1998, 2001, 2002; Sexton et al. 1996).

Brazilian spotted fever may be prevented by avoiding exposure to ticks, mainly from June to October, by inspecting the body, head and clothes after exposure and by removing the attached ticks, whenever going to wooded or grassy areas or after contact with animals.

Rickettsioses are underrecognized and underreported diseases. The establishment of a National Reference Center for Rickettsioses at Oswaldo Cruz Institute as well as the promotion of the rickettsiosis as a nationwide notifiable disease, should make it possible to confirm suspected cases, helping to reduce the high mortality rates that have been observed on reported spotted fever in Brazil. Concomitantly, more research should be done in all fields of rickettsiology, with generation of data in order to develop an active epidemiological surveillance and new diagnosis technologies which should be available in Public Health Laboratories aiming a better understanding of rickettsiosis and their agents in Brazil.

REFERENCES


8. Dias E. 1938. Depositários naturais e
transmissores da febre maculosa brasileira.  


### Table 1: Rickettsias of family Rickettsiaceae\(^1\) causing diseases in humans

<table>
<thead>
<tr>
<th>Arthropod vector</th>
<th>Species</th>
<th>Disease</th>
<th>Geographic Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ticks</strong></td>
<td><em>Rickettsia rickettsi</em></td>
<td></td>
<td>Western hemisphere</td>
</tr>
<tr>
<td></td>
<td><em>Rickettsia sibirica</em></td>
<td></td>
<td>Asia, Europe</td>
</tr>
<tr>
<td></td>
<td><em>Rickettsia conori</em></td>
<td></td>
<td>Africa, Europe, Middle East, India</td>
</tr>
<tr>
<td></td>
<td><em>Rickettsia australis</em></td>
<td></td>
<td>Australia</td>
</tr>
<tr>
<td></td>
<td><em>Rickettsia honeya</em></td>
<td>Spotted fever</td>
<td>Australia</td>
</tr>
<tr>
<td></td>
<td><em>Rickettsia israeli</em></td>
<td></td>
<td>Middle East</td>
</tr>
<tr>
<td></td>
<td><em>Rickettsia japonica</em></td>
<td></td>
<td>Japan</td>
</tr>
<tr>
<td></td>
<td><em>Rickettsia africae</em></td>
<td></td>
<td>Africa</td>
</tr>
<tr>
<td></td>
<td><em>R. mongolotimonae</em></td>
<td></td>
<td>Europe and Asia</td>
</tr>
<tr>
<td></td>
<td><em>R. slovaca</em></td>
<td></td>
<td>Europe</td>
</tr>
<tr>
<td></td>
<td><em>Ehrlichia chaffeensis</em></td>
<td></td>
<td>North America</td>
</tr>
<tr>
<td></td>
<td><em>Ehrlichia sennetsu</em></td>
<td>Ehrlichiose</td>
<td>Japan</td>
</tr>
<tr>
<td></td>
<td>Agent of the HGE(^2)</td>
<td></td>
<td>North America</td>
</tr>
<tr>
<td></td>
<td><em>Coxiella burnetii</em></td>
<td>Q fever</td>
<td>Worldwide</td>
</tr>
<tr>
<td><strong>Mites</strong></td>
<td><em>Rickettsia akari</em></td>
<td>Spotted fever</td>
<td>Western hemisphere and Asia</td>
</tr>
<tr>
<td></td>
<td><em>(rickettsialpox)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Orienta tsutsugamushi</em></td>
<td>Scrub typhus</td>
<td>Asia, Australia</td>
</tr>
<tr>
<td><strong>Lices</strong></td>
<td><em>Rickettsia prowazekii</em></td>
<td>Epidemic typhus</td>
<td>Worldwide</td>
</tr>
<tr>
<td></td>
<td><em>(Brill-Zinsser Disease)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fleas</strong></td>
<td><em>Rickettsia typhi</em></td>
<td>Endemic typhus</td>
<td>Worldwide</td>
</tr>
<tr>
<td></td>
<td><em>(murine typhus)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Rickettsia felis</em></td>
<td>Cat-flea typhus</td>
<td>Western hemisphere</td>
</tr>
</tbody>
</table>


1. Recently several changes of taxonomic classification had been observed. The family Bartonellaceae (*Bartonella quintana, B. henselae, B. claridgeiae* and *B. elizabethae*) was removed from the Order Rickettsiales. These microorganisms cause cat scratch disease, bacillary angiomatosis; parenchymal bacillary peliosis, septicemia and endocarditis.

2. Q fever is usually transmitted by inhalation of contaminated air (material from infected animals); by tick bites and ingestion of contaminated milk.

3. HGE: Human granulocytic ehrlichiose
Figure 1. Typical rash on the lower extremities in a patient with Brazilian spotted fever (Damasco et al, 1998).

Figure 2. Spotted fever group rickettsia isolation (culture of Vero cells). (Lemos et al., 1996)