

Mediterranean Spotted Fever in Israel: A Tick-Borne Disease

Kosta Y. Mumcuoglu PhD¹, Avi Keysary PhD² and Leon Gilead MD³

¹ Department of Parasitology, Hebrew University-Hadassah Medical School, Jerusalem, Israel

² Israel Center for Rickettsial Diseases, Department of Infectious Diseases, Israel Institute for Biological Research, Ness Ziona, Israel

³ Department of Dermatology, Hadassah University Hospital, Jerusalem, Israel

Key words: Mediterranean spotted fever, *Rhipicephalus sanguineus*, vector, *Rickettsia conorii*, diagnosis, treatment, prevention, control

IMAJ 2002;4:44–49

Mediterranean spotted fever is a tick-borne disease caused by *Rickettsia conorii*. The disease is widely distributed in India, Africa, Europe and the Middle East bordering the Mediterranean, sub-Saharan Africa, and around the Black and Caspian Sea. The main vector of MSF in the Mediterranean area is the brown dog tick *Rhipicephalus sanguineus* [Figure 1].

In the last few decades an increased incidence of MSF was reported for Spain, France, Italy, Portugal and Israel [1,2]. MSF was originally characterized as a benign rickettsiosis. However, there have been recent reports of severe cases in France, Spain, Israel and South Africa, manifested by cutaneous and neurologic signs, psychological disturbances, respiratory problems and acute renal failure. Fatalities have been reported in 1.4–5.6% of hospitalized patients in Israel, France and Portugal [2–5].

This review summarizes the biology and ecology of the vector ticks, as well as the clinical, therapeutic, diagnostic and prophylactic aspects of Mediterranean spotted fever.

Clinical presentation

The usual course of MSF is probably mild, uncomplicated and self-limiting. This assumption is supported by the finding of a high prevalence of MSF-positive serology (18.3%) compared to a very small proportion of clinically recognized disease [6,7].

Although the clinical presentation at the onset of disease is almost always ambiguous, early diagnosis

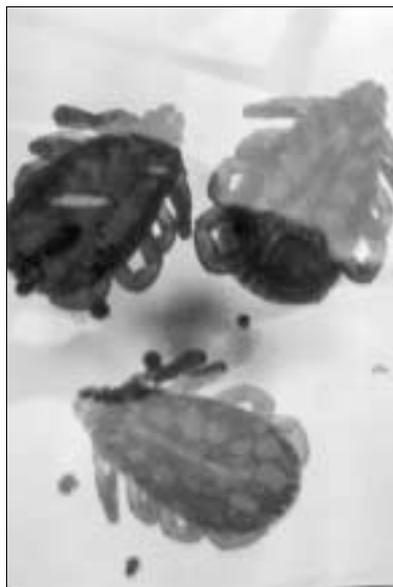


Figure 1. Three specimens of the brown dog tick, *Rhipicephalus sanguineus*.

and treatment are essential for an uncomplicated recovery. Since there are no convenient tests to diagnose the disease in its early course, the clinician has to rely on a high index of suspicion, especially if the patient is a resident of an endemic area and the relevant history includes possible contact with dogs and/or ticks.

The clinical presentation of MSF in Israel is similar to that in Europe, except for some minor differences. Patients usually present with a picture of a classical triad: fever and chills, severe headaches and/or myalgia, and a typical rash [3,7–9]. A black crusted eschar (tache noir), considered to be the site of the tick bite, is very rare in MSF patients in Israel [8,10–14].

The disease is probably more common in children, although some clinical studies have shown no significant age differences [13,15]. There is a slightly stronger tendency for infection in males than in females [3,13].

The disease starts within 6–10 days of the tick bite with fever (usually >39°C) associated with severe headache and/or

myalgia. In most patients a macular erythematous rash appears 2–4 days after the abrupt onset of fever [Figure 2]. The rash typically spares the face, but involves the palms and soles, often with minute purpura within the macules, especially on the lower limbs and on the palms and soles. In early stages the rash is often confused with a drug rash. An enanthem is not mentioned in the literature, and in our opinion was hardly ever seen. Additional physical findings are



Figure 2. A typical macular erythematous rash on the back of a patient with Mediterranean spotted fever.

MSF = Mediterranean spotted fever

Table 1. Clinical symptoms in patients with Mediterranean spotted fever in Israel

Clinical symptoms	% of patients	References
Fever	100, 100, 100, 100	10, 11, 12, 15
Skin rash	98.4, 100, 98.5, 87	10, 11, 12, 15
Myalgia	54, 23, 50	10, 11, 15
Vomiting	40	11
Headache	24, 68, 63.1	10, 11, 12
Abdominal pain	14, 55.5	10, 11
Splenomegaly	34, 46, 18, 52.4	10, 11, 12, 15
Hepatomegaly	10, 23, 16, 44.4	10, 11, 12, 15
Lymphadenitis	26.9, 23	10, 15
Thrombocytopenia	75, 8, 80, 68	10, 11, 12, 15
Leukopenia	16.7, 77, 8	10, 12, 15
"Left shift"	40, 88	10, 11
Leukocytosis	16	12
Hyponatremia	31, 62.5, 33	12, 15
Aspartate aminotransferase >40 IU/ml	58.7, 85, 58	10, 12, 15
Elevated lactate dehydrogenase levels	82	11

uncommon but may include hepatomegaly and splenomegaly and lymphadenopathy [Table 1]. Laboratory workup is usually non-contributory for the diagnosis in the acute patient, although some characteristic abnormalities include left shift in the white blood cells, relative leukopenia (sometimes leukocytosis) and thrombocytopenia, increased aspartate aminotransferase and lactate dehydrogenase levels, and hyponatremia [Table 1]. The estimated prevalence of these laboratory abnormalities varies considerably in the literature, limiting the value of these findings in establishing the diagnosis of spotted fever.

The importance of early diagnosis and treatment initiation in clinically significant cases is reinforced by the fact that severe complications may develop and the disease may unexpectedly take a rapid, fatal course. Before the era of easily available antibiotic treatment, a fatality rate of up to 30% was reported for Rocky Mountain spotted fever. The first report of what appears to be MSF, from 1949, cites a case-fatality ratio of 20% [16]. Today, with the availability of antibiotics, the fatality rate has decreased markedly, to 5–10% for RMSF and to 5% or less for MSF [3,8,10,11].

Complications

The complications reported in MSF patients are typically those of severe systemic vasculitis with its common sequelae. These complications probably develop because the rickettsiae have a special affinity for endothelial cells, and when they infect them they induce an enhanced expression of adhesion molecules on their surface [17]. This results in widespread activation of the coagulation cascade, vascular cell wall damage, and secondary

damage to the parenchyma of the liver, spleen, kidneys, lungs and brain [18]. Deterioration in liver function tests, thrombocytopenia and widespread purpura are ominous signs that should be taken seriously as predictors of further complications that could eventually be fatal.

The reported complications include acute renal failure [10–13], pneumonia [11], encephalitis [10–12], myocarditis [11,12], uveitis [11], and transient bone marrow failure with hemophagocytosis [19]. Most of the more severe complications were part of or followed disseminated intravascular coagulation, which was the major cause for multi-organ failure and death [9–13]. Serious complications such as peripheral gangrene and limb amputation were described in patients with RMSF [20], but to the best of our knowledge such symptoms were not observed in patients with MSF.

Treatment

The antibiotics of choice for treating rickettsial infections are tetracycline and chloramphenicol [21], which are rickettsiostatic. These drugs are accepted universally. The best response is achieved when treatment is initiated in the early stage of the disease. Later the response is less dramatic. Many physicians treating MSF and RMSF patients claim that the first antibiotic doses should be administered under close medical supervision in a medical facility, since an acute exacerbation requiring immediate supportive measures may develop. However, this reaction, which some physicians consider a true Jarisch-Herxheimer reaction, has never been reported in the literature associated with RMSF or MSF. It is possible that there is confusion related to Jarisch-Herxheimer reaction seen in patients with tick-borne relapsing fever transmitted by the soft tick *Ornithodoros* [22]. The use of chloramphenicol was almost completely abandoned due to its severe, idiosyncratic hematologic side effects. Doxycycline has become a common alternative for tetracycline, especially in children because of its prolonged half-life, enabling single or double daily doses, and because it is less prone to cause teeth discoloration [23].

The recommended regimen is an oral initial dose of 50 mg/kg body weight for chloramphenicol and 25–50 mg/kg body weight for tetracycline, followed by the same dose equally divided into three to four daily doses. Patients too ill to take the treatment by mouth should be given the same regimen parenterally. Initiation of treatment at least 24 hours after defervescence ensures a significant clinical improvement [21]. Several reports suggest a longer treatment period (up to 5 days past defervescence) [24], but most of these recommendations seem to be based on empiric or anecdotal evidence. A controlled prospective study [23] using doxycycline has shown that an abbreviated course (up to one day after the patient is afebrile) is as effective as the longest recommended treatment [24]. The doxycycline recommended dosage is 4.4 mg/kg body weight divided into two daily doses on the first day and 2.2 mg/kg divided into two daily doses on subsequent days [23].

Although tetracycline and chloramphenicol are considered

RMSF = Rocky Mountain spotted fever

equally effective [21], a retrospective study comparing the two antibiotics showed that there were relapses in 10 of 24 patients treated with chloramphenicol, while no relapses occurred in 108 patients treated with tetracycline [25]. Another study reported a relapse in one of two patients treated with chloramphenicol, as compared with 31 patients who were treated with tetracycline without relapses. Two cases of relapses were reported after doxycycline treatment for MSF [23].

Epidemiology of MSF in Israel

MSF was first described in Israel in 1943 [16]. Outbreaks of MSF were recorded in 1946–47 in the Haifa bay area, in 1971 in the coastal plain and the Negev, and since then throughout the country [6]. In 1981, the reported incidence of rickettsial disease in the Negev desert was 20.8 per 100,000 [15]. During the years 1972–85, between 20 and 400 (average 200) cases of MSF were reported annually to the Ministry of Health. This corresponds to an average annual incidence of 6.2 cases per 100,000 population. The incidence decreased to 0.9/100,000 persons until 1994 and increased slightly in 1995–97. During 1997–99, a total of 171 cases of MSF were reported to the Ministry of Health: 57 in 1997, 35 in 1998, and 77 in 1999. Seventy cases (41%) were reported from the Hadera district, 28 (16%) from the Beer Sheva district, and 24 (14%) from the Sharon district. However, the number of MSF cases in Israel is underestimated since many are either not recognized or not reported [15].

In 1984–86, there was an outbreak of MSF in Kibbutz Ze'elim where 4% of the population (6% of the children) acquired the disease. There was a correlation between the increase in the tick population during the hot months of the year and the appearance of MSF; most of the clinical cases in Ze'elim occurred during the summer [26].

A survey among maternity patients in a Beer Sheva hospital found that Bedouin woman had a higher incidence of anti-MSF antibodies than other population groups. This was attributed to the fact that Bedouin women live in close proximity to their domestic animals and are therefore continuously exposed to tick bites [7].

The clinical to subclinical case ratio in humans in the Negev district has been reported to be 1:2.2 [26]. In 1971, a serosurvey in Ashdod identified 7 serologically confirmed MSF cases, while 8% of the population (38 of 484) were seropositive for spotted fever group rickettsiae (Goldwasser et al., unpublished results). These findings indicate that the prevalence of the disease may be underestimated and that MSF can often occur in a subclinical form.

Biology and epidemiology of the tick vectors

R. sanguineus is a cosmopolitan species and probably the most prevalent of ixodid ticks. It is found on a large variety of domestic and wild animals, including birds and humans. In Israel this species is very abundant and has been found in all geo-climatic areas of the country [24].

The principal hosts of adult *R. sanguineus* are medium to large-size mammals such as hedgehogs, foxes, badgers, goats and dogs. Domestic animals such as dogs and goats that enter infested areas may be infested with ticks and bring them in or close to human dwellings. The hosts of the larval and nymphal stage in the wild are rodents, insectivores and lagomorphs [27].

Infested dogs lose their ticks in the vicinity of human dwellings. When engorged, females drop from the dogs; they look for suitable environmental conditions to lay their eggs from which larvae hatch after 28 days. *R. sanguineus* females lay 3,300–7,000 eggs (average 4,880) [28]. Inside and outside houses, freshly hatched larvae usually cannot find their natural hosts, therefore they infest the dog that brought the parent ticks to the house. A domestic or urban cycle of tick development starts when dozens or even hundreds of larvae, nymphs and adult ticks infest the same dog [29]. Single-family houses with a garden and dog, situated in small settlements or on the periphery of large cities, are the most prone to infestation with the domestic strains of these ticks [30]. However, any house in an urban area can be infested with ticks.

A study conducted in Kibbutz Ze'elim in the Negev desert, where several clinical cases of MSF had been reported, as well as in nearby Kibbutz Re'im, where no clinical cases of MSF were observed, showed that *R. sanguineus* and probably also *R. turanicus* are the vectors of MSF. Using flagging and CO₂-trapping techniques, approximately nine times more ticks were collected in Ze'elim than in Re'im. *R. sanguineus* constituted 99.3% of the ticks in Ze'elim, whereas in Re'im *R. turanicus* was the most abundant species. The differences in tick fauna were attributed to differences in soil temperature, ambient temperature above the soil, and soil composition in the two sites. Although ticks were present throughout the year, their numbers were highest from April through October in Ze'elim, and from April to July in Re'im. The domestic cycle of tick development was observed only in Ze'elim [27].

In the Negev desert and on the coastal plain of Israel, *R. sanguineus* was present on dogs throughout the year; however, in the hilly areas it was absent during the winter months [31]. In the colder regions of the country, only engorged nymphs and adults are able to overwinter. The time taken for a new generation of *R. sanguineus* to develop depends on the environmental conditions and can vary from 2 to 6 months. Larvae can survive without feeding for up to 3.5 months, nymphs up to 6 months and adults up to 19 months [32]. *R. turanicus* is a closely related species of *R. sanguineus* and widely distributed throughout the world. Both species are often found on the same host. Studies have shown that *R. turanicus* is a potential vector of the agent of MSF [33].

Questing ticks of both species can be found outside human dwellings on grass and other small plants up to 25 cm above the soil. They can usually be seen next to animal trails, with their head downwards and the first pair of legs in the air in an attempt to locate a potential host with their sensillae (Haller's organ) that are located on the first segment of the leg. Inside and outside human habitations the domestic strain of the tick

behaves differently, with the tendency to crawl on the walls up to 2 m where they hide in holes and crevasses, especially close to the roof [27].

Vectorial capacity of ticks

In Israel, *R. sanguineus* is the main vector of *R. conorii*. Females transmit the rickettsiae transovarially to the next generation. Nymphal stages and adult ticks remain infested with rickettsiae through trans-stadial transmission throughout their life, and therefore they also act as the main reservoir of *R. conorii*. The danger of being infected with MSF from a tick – e.g., during a hike in the country – is much less than the danger of acquiring the disease from ticks that have developed a domestic cycle close to or inside a human dwelling. Feldman-Muhsam [6] estimated that 1 of 20 cases of human infestation by the tick *R. sanguineus* results in infection with MSF.

The prevalence of spotted fever group rickettsiae was studied in questing ticks collected from Kibbutz Ze'elim and Re'im. In 1989–90, a total of 549 ticks were examined in Ze'elim and 7.3% were positive for spotted group rickettsiae, whereas in Re'im 156 *R. turanicus* were examined and 2.2% were positive for the same pathogen. In 1994, 51 of 186 ticks (27.4%) in Ze'elim and 3 of 115 ticks (2.6%) in Re'im were positive [32]. In Ze'elim, 7.1% of dog owners acquired the disease during 1984–89 compared with only 1.4% of people without dogs [27,34]. Approximately 30% of dogs randomly sampled in Israel, and 82–84% of the dogs belonging to communities where outbreaks of human spotted fever had occurred, were positive for *R. conorii* [35].

Rickettsia conorii

R. conorii belongs to the spotted fever group rickettsiae. The spotted fever group includes other agents of human diseases such as *R. rickettsii* (the agent of RMSF), *R. sibirica*, *R. australis*, *R. acari* and *R. japonica*.

R. conorii is an obligate, intracellular, gram-negative coccobacillary small bacterium, 0.8–2.0 µm long and 0.3–0.5 µm wide. Although *R. conorii* is adapted to exist within ticks, it can infect humans who are usually accidental hosts. Like other rickettsiae, it can grow in tissue cultures derived from various origins and in yolk sacs of embryonated hen eggs. *R. conorii* is a slow grower with a doubling time of approximately 8 hours. Guinea pigs and mice are usually used as experimental hosts.

Many strains of *R. conorii* were isolated in southern, eastern and northern Africa, the Indian subcontinent, southern Russia and southern Europe, as well as in Israel. Israeli strains were isolated from ticks and humans by several investigators [36]. Walker et al. [37] compared various *R. conorii* strains, including Israeli isolates, and found that all of them appeared to fall within the range of the genetic and antigenic diversity of *R. conorii* as shown by micro-immunofluorescence serotyping, Western immunoblotting, monoclonal antibody reactivity, and polymerase chain reaction amplification of the repeat domain of the outer membrane protein A (rOmpA).

Laboratory diagnosis of MSF

Diagnosis of MSF is usually based on serology. Seroconversion appears 7–10 days after the onset of the disease, therefore diagnosis during the acute phase should be based on the isolation of rickettsiae or the detection of their components in blood or in skin biopsy samples from the rash site.

Serologic tests

The Israel Center for Rickettsial Diseases uses the immunofluorescent antibody test and the enzyme-linked immunosorbent assay for detecting immunoglobulin G and M antibodies to *R. conorii* [38].

MSF can be diagnosed by direct isolation of rickettsiae from blood and biopsy samples in tissue culture, yolk sacs of hen-embryonated eggs or in guinea pigs. Rickettsiae can also be identified by immunostaining histologic sections, and detection of specific DNA sequences using the PCR technique.

According to the recommendations of the U.S. Centers of Disease Control and the National Institutes of Health, *R. conorii* is considered a bio-safety level-3 agent, therefore the isolation and growth should be conducted in appropriate laboratory and animal facilities. Blood samples or a biopsy from the rash site should be taken during the febrile stage of the disease before the patient is treated with antibiotics. The samples must be taken under sterile conditions, kept refrigerated and sent as soon as possible to the laboratory. Frozen samples should be kept at -70°C. Isolation procedures can take several days because *R. conorii* is a slow grower.

Tissue culture

The rickettsiae are isolated in a variety of tissue culture cells originating from humans, monkeys, mice and chickens. Rickettsial growth is monitored by staining culture samples using a modified Gimenez method or the IFA technique.

Chicken yolk sacs

The sample is injected into the yolk sacs of fertilized, 4 day old chicken eggs, and the viability of the embryos is monitored for 2 weeks. Smears of the yolk sacs are monitored for the presence of rickettsiae by Gimenez staining and the IFA technique.

Guinea pigs

Mature male guinea pigs are injected intraperitoneally with the sample, and rectal temperature is monitored daily. A rise to 40°C or more indicates rickettsial infection. In some animals orchitis may also be observed. The presence of rickettsiae in the spleen is detected by Gimenez staining, IFA technique, impression smears, and by seeding the spleen homogenate in tissue cells. Isolation attempts in guinea pigs are necessary when the sample is suspected of being contaminated by other bacteria.

PCR = polymerase chain reaction

IFA = immunofluorescent antibody

Immunostaining

Immunostaining is used to detect the presence of spotted fever group rickettsiae in biopsies and impression smears taken from the rash site. In fatal cases with multi-organ failure, rickettsiae can be detected in histologic sections of internal organs such as the spleen, kidney and liver. Immunostaining can be done either by immunofluorescence or by ELISA using peroxidase or alkaline phosphatase conjugates [39].

PCR

R. conorii can be detected by PCR, using specific template sequences of genes encoding 16S rRNA, 17 kDa protein, OmpA, OmpB, and citrate synthase-gltA. Acute-phase serum, skin biopsy from the rash site and paraffin-embedded tissue blocks are used for PCR. This method can also be employed to detect rickettsiae in ticks. PCR, based on sequences of the 17 kDa protein, has been used for the diagnosis of MSF during the acute phase of the disease as well as in fatal cases [40].

Isolation of rickettsiae from ticks

Rickettsia can be isolated from ticks found on host animals and humans. Ticks should be transferred to the laboratory in a small closed container. A drop of hemolymph, obtained by removing a leg of the tick, is applied onto a monolayer of cell culture.

Prevention and control

After any trip in tick-infested areas, hikers should be examined for infestation with ticks. The entire body should be inspected including all hairy parts of the body. Another person should inspect less visible areas such as the scalp and the back; a mirror can also be used for this purpose.

In order to remove a tick from the skin, the apical part of the tick should be grasped with forceps and the tick pulled out upwards. There is no need to treat the tick with toxic substances, alcoholic solvents or hot objects such as cigarettes. Removal of the tick with the fingernails is not advised, as it could be dangerous if the tick is infested with rickettsiae and squashed during the removal. Rickettsiae can enter the human body through the damaged skin from the infested hemolymph of the tick. After removal of the tick the skin should be disinfected properly.

Dogs should be inspected for ticks after each trip to forests and rural areas. The face, the area in and around the ears, the neck and the space between the toes should be carefully examined. Individual ticks should be removed with forceps as described above. Heavily infested dogs should be treated with an acaricidal shampoo or powder containing carbaryl. In cases where the ticks are adapted to living in and around human dwellings (the domestic cycle), infested areas such as the kennel, as well as the floor and exterior and interior walls of the house up to the height of 2 m, should be treated with an acaricidal spray containing 1% diazinon. A second treatment

after 3–4 weeks is recommended. A tick collar, which should be renewed approximately every 3 months, is recommended as a prophylactic measure.

Conclusion

Rickettsial diseases transmitted by ticks are a global problem posing a threat to public health. MSF is one of the most important rickettsioses in Israel and has been known as an endemic disease for over 50 years. It is a notifiable disease in this country and clinical cases should be reported to the Ministry of Health. The prospect of wide-scale development of the Negev area, which is endemic for MSF, as well as the increase in population due to mass immigration, especially from the former Soviet Union, makes a comprehensive study of the disease extremely urgent. In rural areas a very large number of people, especially children, are in permanent contact with tick-infested domestic animals and hence exposed to the tick-borne diseases. The expanding population, increase in outdoor activities and an ever-growing number of dogs kept inside or around human dwellings create the potential for an increase in MSF in the future. Since there is no vaccine against MSF, it is crucial that preventive, control and educational programs concerning tick vectors be implemented.

Knowledge of the biology and population ecology of the rhipicephalid ticks, and the study of their vectorial competence will help to assess risk factors for MSF and indicate which precautions should be taken to avoid contact with the ticks.

Israel Center for Rickettsial Diseases

The laboratory was established in 1977 in Ness Ziona by Prof. Robert A. Goldwasser and is managed today by Dr. A. Keysary. The laboratory uses IFA, isolation procedures and PCR to diagnose MSF, murine typhus, Q-fever and human ehrlichiosis. The center is located in the Israel Institute for Biological Research, 24 Reuven St., P.O. Box 19, Ness Ziona 74100. Telephone: 08-9381542/444, Fax: 08-9381574, email: keysarya@iibr.gov.il

Acknowledgment. We thank Dr. Jacqueline Miller for reviewing the manuscript.

References

1. Raoult D, Roux V. Rickettsioses as paradigms of new or emerging infectious diseases. *Clin Microbiol Rev* 1997;10:694–719.
2. Aharonowitz G, Koton S, Segal S, Anis E, Green MS. Epidemiological characteristics of spotted fever in Israel over 26 years. *Clin Infect Dis* 1999;29:1321–2.
3. Raoult D, Weiller PJ, Chagnon A, Chaudet H, Gallais H, Casanova P. Mediterranean spotted fever: clinical, laboratory and epidemiological features of 199 cases. *Am J Trop Med Hyg* 1986;35:845–50.
4. Bacellar F, Beati L, Franca A, Pocas J, Regnery R, Filipe A. Israeli spotted fever rickettsia (*Rickettsia conorii* complex) associated with human disease in Portugal. *Emerg Infect Dis* 1999;5:835–6.
5. Paddock CD, Childs JE, Sherif RZ, Berger SA. Mortality in

ELISA = enzyme-linked immunosorbent assay

- serologically unconfirmed Mediterranean spotted fever. *J Infect Dis* 2000;181:810–12.
6. Feldman-Muhsam B. Ixodid tick attacks man in Israel: medical implications *Isr J Med Sci* 1986;22:19–23.
 7. Gross EM, Goldwasser RA, Bearman JE. Rickettsial antibody prevalence in southern Israel: IgG antibodies to *Coxiella burnetii*, *Rickettsia typhus* and spotted fever group rickettsiae among urban and rural-dwelling and Bedouin women *Am J Trop Med Hyg* 1983;36:1387–91.
 8. Font-Creus B, Bella-Cueto F, Espejo-Arenas E. Mediterranean spotted fever: a cooperative study of 227 cases. *Rev Infect Dis* 1985;7:635–42.
 9. Schulchynska H, Dagan R, Schlaefer F, Keynan A. Spotted fever in the Negev. *Harefuah* 1982;102:317–19 (Hebrew).
 10. Wolach B, Franco S, Bogger-Goren S, Drucker M, Goldwasser RA, Sadan N, Bernheim J. Clinical and laboratory findings of spotted fever in Israeli children. *Pediatr Infect Dis J* 1989;8:152–5.
 11. Shaked Y, Samra M, Maeir K, Rubinstein E. Murine and spotted fever in Israel in the eighties: retrospective analysis. *Infection* 1988;16:283–7.
 12. Gutman A, Schreiber H, Taragan R. An outbreak of tick typhus in the coastal plain in Israel: 13 cases from the Sharon area. *Trans R Soc Trop Med Hyg* 1973;67:112–21.
 13. Gross EM, Yagupsky P. Israeli rickettsial spotted fever in children. *Acta Trop* 1987;44:91–6.
 14. Yagupsky P, Sarov B, Sarov I. A cluster of cases of spotted fever in a kibbutz in southern Israel. *Scand J Infect Dis* 1989;21:155–60.
 15. Gross EM, Arbeli Y, Bearman JE, Yagupsky P, Cohar K, Torok V, Goldwasser RA. Spotted fever and murine typhus in the Negev Desert region of Israel, 1981. *WHO Bull* 1984;62:301–6.
 16. Valero A. Rocky mountain spotted fever in Palestine. *Harefuah* 1949;36:99–101 (Hebrew).
 17. Silverman DJ. Adherence of platelets to human endothelial cells infected with *Rickettsia rickettsii*. *J Infect Dis* 1986;153:694–700.
 18. Martinez JA, Arboix A, Rodriguez E, Torres M. Cerebral infarction as the initial manifestation of Mediterranean spotted fever. *Med Clin Barc* 1992;24:499–516.
 19. Berner Y, Keysary A, Berrebi A. Transient histiocytic hemophagocytosis and pancytopenia in Mediterranean spotted fever. *Isr J Med Sci* 1989;25:660–1.
 20. Hove MG, Walker DH. Persistence of rickettsiae in the partially viable gangrenous margins of amputated extremities 5 to 7 weeks after onset of Rocky Mountain spotted fever. *Arch Pathol Lab Med* 1995;119:429–31.
 21. Woodward TE. Rickettsial diseases. In: Wilson JD, Braunwald E, Isselbacher KJ, Petersdorf RG, Martin JB, Fauci AS, Root RK, eds. *Harrison's Principles of Internal Medicine*. 12th edn. New York: McGraw-Hill, 1991:489–90,756.
 22. Dworkin MS, Anderson DE Jr, Schwan TG, Shoemaker PC, Banerjee SN, Kassen BO, Burgdorfer W. Tick-born relapsing fever in the northwestern United States and southwestern Canada. *Clin Infect Dis* 1998;26:122–31.
 23. Yagupsky P, Gross EM, Alkan M, Bearman J. Comparison of two dosage schedules of doxycycline in children with rickettsial spotted fever. *J Infect Dis* 1987;155:1215–19.
 24. Gold E. Rickettsial diseases. In: Behrman RE, Vaughan VDC, eds. *Nelson Textbook of Pediatrics*. 12th edn. Philadelphia: WB Saunders, 1983:819–25.
 25. Shaked Y, Samra Y, Maier MK, Rubinstein E. Relapse of rickettsial Mediterranean spotted fever and murine typhus after treatment with chloramphenicol. *J Infect* 1989;18:35–7.
 26. Sarov A, Sarov I, Galil A, Sikuler E, Yagupsky P. Detection of a high risk rural site of morbidity due to spotted fever group rickettsia (Sfgr) in southern Israel. *Virginia J Sci* 1990;41:161–2.
 27. Mumcuoglu KY, Frish K, Sarov B, Manor E, Gross E, Gat Z, Galun R. Ecological studies on the brown dog tick *Rhipicephalus sanguineus* (Acari:Ixodidae) in southern Israel and its relationship to spotted fever group rickettsiae *J Med Entomol* 1993;30:114–21.
 28. Ioffe-Uspensky I, Mumcuoglu KY, Uspensky I, Galun R. *Rhipicephalus sanguineus* and *R. turanicus* (Acari:Ixodidae): closely related species with different biological characteristics. *J Med Entomol* 1997;34:74–81.
 29. Hoogstraal H. Ticks of Sudan (with special reference to Equatorial Province and with preliminary reviews of the genera *Boophilus*, *Margaropus* and *Hyalomma*). U.S. Naval Medical Research Unit No. 3, Cairo, Egypt, 1956.
 30. Gilot B. Biologie et ecologie de *Rhipicephalus sanguineus* (Latreille, 1806) (Acariens: Ixodoidea) dans le sud-est de la France. Interet dans l'epidemiologie de la fièvre boutonneuse. *Sci Vet Med Comp* 1984;86:25–33.
 31. Mumcuoglu KY, Burgan I, Ioffe-Uspensky I, Manor O. *Rhipicephalus sanguineus*: observations on the parasitic stage on dogs in the Negev desert of Israel. *Exp Appl Acarol* 1993;17:793–8.
 32. Feldman-Muhsam B. Some observations on the hibernation of *Rhipicephalus sanguineus* in Jerusalem. Proceedings of the International Conference on Tick Biology and Control. 1981:205–7.
 33. Guberman D, Mumcuoglu KY, Keysary A, Ioffe-Uspensky I, Miller J, Galun R. Prevalence of spotted fever group rickettsiae in ticks from southern Israel. *J Med Entomol* 1996;33:979–82.
 34. Mumcuoglu KY, Frish K, Galun R, Sarov B, Manor E, Gross E. Ecological and epidemiological studies on Mediterranean spotted fever in the Negev Desert of Israel. *Virginia J Sci* 1990;41:159–60.
 35. Keysary A, Torton DN, Gross EM, Torton M. Prevalence of antibodies to *Rickettsia conorii* in dogs in Israel and its relation to outbreaks in man. *Isr J Vet Med* 1988;44:103–7.
 36. Manor E, Ighbarieh J, Sarov B, Kassir I, Regnery R. Human and tick spotted fever group rickettsia isolates from Israel: a genotypic analysis. *J Clin Microbiol* 1992;30:2653–6.
 37. Walker DH, Feng H-M, Saada JI, Crocquet-Valdes P, Radlovic S, Popov VL, Manor E. Comparative antigenic analysis of spotted fever group rickettsiae from Israel and other closely related organisms. *Am J Trop Med Hyg* 1995;52:569–76.
 38. Keysary A, Strenger C. Use of enzyme-linked immunosorbent assay techniques with cross-reacting human sera in diagnosis of murine typhus and spotted fever. *J Clin Microbiol* 1977;35:1034–5.
 39. Goldwasser RA, Shepard CC. Staining of complement and modifications of fluorescent antibody procedures. *J Immunol* 1981;80:122–31.
 40. Schattner A, Leitner M, Keysary A, Geltner D. Fatal seronegative rickettsial infection diagnosed by the polymerase chain reaction. *Am J Med Sci* 1992;303:392–4.

Correspondence: Dr. K.Y. Mumcuoglu, Dept. of Parasitology, Hebrew University-Hadassah Medical School, P.O.Box 12272, Jerusalem 91120, Israel.
 Phone: (972-2) 675-8093
 Fax: (972-2) 675-7425
 email: kostam@cc.huji.ac.il