Epidemiology, Clinical Aspects, Laboratory Diagnosis and Treatment of Rickettsial Diseases in the Mediterranean Area During COVID-19 Pandemic: A Review of the Literature

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Abstract. The purpose of the present review is to give an update regarding the classification, epidemiology, clinical manifestation, diagnoses, and treatment of the Rickettsial diseases present in the Mediterranean area.

We performed a comprehensive search, through electronic databases (Pubmed – MEDLINE) and search engines (Google Scholar), of peer-reviewed publications (articles, reviews, and books). The availability of new diagnostic tools, including Polymerase Chain Reaction and nucleotide sequencing has significantly modified the classification of intracellular bacteria, including the order Rickettsiales with more and more new Rickettsia species recognized as human pathogens. Furthermore, emerging Rickettsia species have been found in several countries and are often associated with unique clinical pictures that may challenge the physician in the early detection of the diseases.

Rickettsial infections include a wide spectrum of clinical presentations ranging from a benign to a potentially life treating disease that requires prompt recognition and proper management. Recently, due to the spread of SARS-CoV-2 infection, the differential diagnosis with COVID-19 is of crucial importance. The correct understanding of the clinical features, diagnostic tools, and proper treatment can assist clinicians in the management of Rickettsioses in the Mediterranean area.

Keywords: Rickettsiosis; Review; Epidemiology; Microbiology; Zoonosis; COVID-19.

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Introduction. Human rickettsial diseases are a variety of different clinical zoonoses caused by the genus Rickettsia and Orientia (order Rickettsiales, family Rickettsiaceae) that comprises a small (0.3–0.5 by 0.8–2.0 mm), obligately, intracellular and gram-negative bacilli, within α-proteobacteria.1–3

The development of Polymerase Chain Reaction (PCR) and nucleotide sequencing for the study of 16S rRNA has significantly modified the taxonomic classification of bacteria, in particular, intracellular bacteria. Some species sequencing for the study of 16S rRNA has demonstrated the phenotypic and genotypic differences between some microorganisms and the genus Rickettsia. For example, this is the case of Orientia tsutsugamushi that was reclassified from the genus Rickettsia into a new genus Orientia. The order Rickettsiales currently comprised the genera Anaplasma, Ehrlichia, Neorickettsia, Orientia, Rickettsia, and Wolbachia.4,5

Rickettsial infections are transmitted to human hosts mostly through arthropod bites or arthropod faeces that infect scratching lesions. The most frequent vectors responsible for the transmission are ticks, which also act as reservoirs, but some infections are associated with lice, fleas, or mites.2

Rickettsia species are split into four pathological groups or clades, based on their phenotypic characteristics, vector hosts and phylogenetic organization, that include the ancestral group, the spotted fever group (SFG), the typhus group, and the transitional group. The SFG is the largest group, and it is composed of the most common rickettsiae, such as Rickettsia aeschlimannii, Rickettsia africae, Rickettsia conorii subsp. caspia, Rickettsia conorii subsp. conorii, Rickettsia conorii subsp. indica, Rickettsia conorii subsp. israelensis, Rickettsia massiliae, Rickettsia monacensis, Rickettsia raoultii, Rickettsia rickettsii, Rickettsia rojoa, Rickettsia sibirica subsp. mongolitimonae, Rickettsia sibirica subsp. sibirica, and the Rickettsia slovaca. The typhus group is composed of Rickettsia prowazekii and Rickettsia typhi.6 The ancestral group includes Rickettsia bellii and Rickettsia canadensis.3 The transitional group includes species of clinical importance, as Rickettsia akari Rickettsia australis and the Rickettsia helvetica, phylogenetically similar to SFG species such as Rickettsia felis.7 Several authors discuss the validity of this group; in fact, these species have no relevant differences with other SFG species, except for their phylogenetic position.8

Due to their adaptation from a free-living to an obligate intracellular life in eukaryotic cells, Rickettsia species modified and reduced their genome size progressively.9,10 Unexpected property of the rickettsial genome is the presence of plasmids, the first described in obligate intracellular bacteria.11 This discovery suggests possible exchanges of genetic material by conjugation, a mechanism that was previously considered to be absent in obligate intracellular bacteria.9,11

The transmission of the infection depends on the group. SFG is transmitted by the bite of an infected tick; whereas, organisms of typhus group are transmitted through inoculation via infected louse or flea faeces (Rickettsiae prowazekii and Rickettsia typhi, respectively) through a bite, wound or mucous membranes. Once inoculated into the skin, organisms are phagocytized by dendritic cells and transported via lymphatics to local lymph nodes where they replicate. Subsequently, the bacteria spread in the bloodstream and disseminate to infect the endothelium of the microcirculation, where the Rickettsiae can infect vascular endothelial cells of the small and medium-sized blood vessels. The damage of the endothelium and the subsequent endothelial dysfunction is followed by alteration in coagulation and the cytokine network. The endpoint of this pathogenetic results in a reduction in circulating peripheral CD4 T lymphocytes and perivascular infiltration by CD4 and CD8 T lymphocytes, B cells, and macrophages, causing a vasculitis.12–14

Epidemiology. There are several pathological Rickettsia species in Europe, and in the last years, new species and subspecies have been implicated as human pathogens, and new rickettsial syndromes have been described.15

Mediterranean spotted fever (MSF) caused by Rickettsia conorii subsp. conorii is the most frequent rickettsiosis in Europe. It is endemic in southern Europe, but sporadic cases have been reported in all the continents.15,16 The first cases were first described in Tunisia in 1909 by Conor and Buch. The brown dog tick, Rhipicephalus sanguineus, is the vector and the potential reservoir of Rickettsia conorii subsp. conorii in the Mediterranean area.15,17 Most MSF cases occur in summer when climatic conditions seem to be an essential factor in increasing the aggressiveness of Rhipicephalus sanguineus ticks to bite humans.15–18

Rickettsia conorii subsp. israelensis is the agent of Israeli spotted fever (ISF), which was first reported in 1946 in the Haifa Bay area, Israel.17–20 In Europe and the Mediterranean region, the brown dog tick, Rhipicephalus sanguineus, is recognized to be the vector of Rickettsia conorii subsp. israelensis.21 The geographic distribution of the disease appears to be spread more widely in the Mediterranean countries than previously thought. Cases have been reported in Italy, Portugal, Tunisia, and Libya.22–25

Other Rickettsia conorii subspecies reported in the Mediterranean area are Rickettsia conorii subsp. caspia and Rickettsia conorii subsp. indica. The first one is the agent of Astrakhan fever, endemic in the Astrakhan region, adjacent regions of the Caspian Sea, and described in Rhipicephalus sanguineus ticks in Kosovo;

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Clinical Manifestation.

Rickettsiosis is a rare disease: the incidence is around 1 case per 100,000 people by year, but it has been increasing during the last years, probably due to better diagnostic techniques.\(^{15}\)

In Europe, the most important diseases are three: Mediterranean Spotted Fever (MSF), Lymphangitis-associated rickettsioses (LAR), and scalp eschar and neck lymphadenopathy (SENLAT).\(^{19}\) The other significant disease caused by *Rickettsia rickettsii* is the Rocky Mountain Spotted Fever (RMSF), but no cases have been reported in Europe to date.\(^{19}\)

Apart from these three pathologies, there are other minor forms caused by different pathogens.

Mediterranean spotted fever. MSF, caused by *Rickettsia conorii*, is the most common rickettsial disease in Europe, where the highest incidence is during summer.\(^{72}\) Not all people who come into contact with this bacterium develop the disease. A Spanish study, indeed, shows that 4-8% of the population carry antibodies against *Rickettsia* but without a previous clinical history of MSF.\(^{53}\)

The most common symptoms are fever (93-98%), myalgia (64-75%), headache (48-65%), and asthenia (27%). The maculopapular rash is present in 85-94% of the patients; the tache noir has been noticed in 58-64% of the patients. The classic triad, fever, maculopapular rash, and inoculation eschar, is present in 40-50% of the patients.\(^{54-56}\)

In most cases, MSF is a self-limiting disease but sometimes could be life-threatening. It was estimated that about 5-10% of MSF cases could be severe. Cases of severe respiratory distress syndrome,\(^{57}\) cardiovascular symptoms (coronary etasia,\(^ {58}\) myocarditis,\(^ {59,60}\) vasculitis\(^ {61}\)) ocular symptoms,\(^ {62-65}\) neurological symptoms\(^ {66,67}\) (sensorineural hearing loss\(^ {68,69}\), polyneuropathy\(^ {70,71}\), encephalitis\(^ {72,73}\), meningitis\(^ {74,75}\)), acute pancreatitis,\(^ {76}\) splenic rupture,\(^ {77}\) acute renal failure,\(^ {78}\) hemophagocytic syndrome\(^ {79}\), and arthritis\(^ {81,82}\) have been reported.

The most frequent hematological and biochemical modifications are thrombocytopenia, leukocyte count abnormalities, elevated hepatic enzyme levels and an increase of c-reactive protein.\(^ {54,83}\)

Mortality was around 1-3% before the antimicrobial drug era. Thus, it has been considered a benign illness. In some recent studies, MSF appears to be more severe than it has been thought. Mortality rates were 5.4% in France, 3.6% in Portugal, 3.2% in Algeria, 0.8% in Spain and 0.36% in Italy.\(^ {52,54,84-86}\)

Risk factors for severe MSF include advanced age, immunodeficiency, chronic alcoholism, G6PDH deficiency, diabetes, prior prescription of an inappropriate antimicrobial drug, or delay in treatment.\(^ {84,85}\)

Scalp eschar and neck lymphadenopathy after a tick bite. SENLAT\(^ {37}\) syndrome is also known as TIBOLA\(^ {38}\) (tick-borne lymphadenopathy) or DEBONET\(^ {44}\) (Dermacentor-borne necrotic erythema and lymphadenopathy), and it is caused by *Rickettsia slovaca* and *Rickettsia raoultii*\(^ {19}\) but also by other bacteria such as *Bartonella henselae*.\(^ {83}\) This disease is developed mostly during spring and autumn.\(^ {49}\)

The clinical description of SENLAT includes asthenia, headache, painful adenopathies (especially to the neck's lymph nodes), and a painful scalp eschar surrounded by a perilesional erythematous halo. Low fever, rash, and face edema have also been reported less frequently.\(^ {45,87,89}\) No malignant or fatal cases have been described in the literature. After the therapy, alopecia could potentially last for several months, with persistent asthenia.\(^ {89}\)

Lymphangitis-associated rickettsioses. LAR is caused...
by Rickettsia sibirica subsp. mongolitimonae. Just a few cases have been reported in Europe. In particular, until 2013, only 24 cases have been reported in the Mediterranean area.

The typical period of this disease is spring. Commons symptoms include fever, headache, an eschar (frequently more than one) on the site of inoculation, and lymphangitis, which starts from the eschar and reaches an enlarged lymph node. The difference between LAR and the other two diseases are the period of occurrence (spring), and the presence of lymphangitis and multiple eschars. 90

Until now, no deaths have been reported in patients that have been infected by Rickettsia. However, some severe cases have been reported, in particular: a retinal vasculitis,91 sepsis with disseminated intravascular coagulation, 92 myopericarditis93 and a septic shock.94,95

Mediterranean spotted fever-like. Other Rickettsiae in Europe could infect humans; most of them cause a disease very similar to MSF. For example, Rickettsia conorii subsp. caspia causes an illness called "Astrakhan fever." This disease is typical of the Caspian Sea area, but some cases have also been reported in France. 96 Astrakhan fever diverges from MSF in the percentage of patients who present with an eschar (only 20%) and because it could cause thrombocytopenia and bleed.97

Another similar disease is the Israeli spotted Fever (ISF), caused by Rickettsia conorii subsp. israelensis. In Europe, this bacterium has been found only in Portugal and in Italy. The symptoms are quite similar to MSF except for the presence of gastrointestinal symptoms in half of the patients. The main difference is the malignity; indeed, the mortality is higher (more than 25%). 4,40,46,48,98,99

Other Rickettsiae who could cause a MSF-like illness are Rickettsia monacensis, 100,101 Rickettsia massiliae, 102,103 Rickettsia aeschlimannii, 104,105 and Rickettsia helvetica which could be malignant. 51,106,107

Differential Diagnosis with other infectious diseases including COVID-19. Clinically, the patients with MSF present the classic triad, fever, tache noir, and maculopapular rash in 40-50% of cases. In the absence of this typical clinical picture, the diagnosis could be challenging.

A small percentage of patients could present only the tache noir, which is generally pathognomonic of rickettsial diseases. However, clinical cases in which the tache noir was present in other zoonoses have been reported in the literature. 108-110

The presence of fever without other signs is, probably, the most difficult challenge for clinicians because it is the expression of many diseases, both infective (bacterial, viral, fungal, and parasitic) and not infective. In these patients, a proper anamnesis, laboratory findings, and radiological features are mandatory to permit the correct diagnosis. Blood cultures should be collected at the fever peak to exclude a bacterial or fungal infection. Furthermore, in the area where SARS-CoV-2 is circulating in the population, the nasopharyngeal swab, together with acute phase serology, is recommended to rule it out. Indeed, the common symptom in patients with CoRonaVirus Disease (COVID-19) is the fever.111,112 The other symptoms that these two diseases have in common are headache, asthenia, and myalgia. The associations of dysgeusia, anosmia, and gastrointestinal symptoms could suggest the diagnosis of COVID-19.113-115

The maculopapular rash is an expression of several diseases.116 In these cases, clinicians should pay attention to the distribution, the pattern, and the relationship between the localization at the start of it and other clinical signs, especially the fever. Although respiratory symptoms are the most frequent in COVID-19, skin involvement should always be considered. Galván Casas C et al.117 described the most common cutaneous pattern, and Magro et al.118 demonstrated how SARS-CoV-2 is associated with microvascular damage and thrombosis.

Moreover, different cutaneous vasculitis-like patterns correlated with COVID-19 or SARS-CoV-2 therapy have been described.119,120

Diagnosis. Nowadays, the majority of reference laboratories in developed countries can provide quick identification of rickettsial pathogens thanks to molecular and serological assays. In many cases, the diagnosis could be made by the clinical manifestation, but the laboratory tests are necessary at the support of it.

The choice of the most appropriate diagnostic technique requires consideration of the suspected pathogen, the timing of symptoms onset, and the type of sample available for testing.121 Serological tests remain essential diagnostic tools, but Rickettsiae can be isolated from or detected in clinical specimens. The diagnostic tools available include serologic assays, molecular testing, cultures, immunochemistry, and Matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF).123

The diagnostic technique could be divided into two groups:

1) Diagnostic techniques used as routine.
2) Less common diagnostic techniques.

Diagnostic techniques used as routine (Table 1)
Serologic tests:
Indirect immunofluorescence antibody assay (IFA) is a widely accepted serologic test for the detection of rickettsial infection.124,125 It is considered the most

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sensitive and specific method among serological assays. IFA consists of rickettsial antigens fixed on a slide and detected by specific antibodies present in the patient's serum, which can be identified by a fluorescein-labeled conjugate. Serum of patients with clinical manifestation of disease must be collected on the day of the admission and 2-4 weeks after illness onset. IFA assays are highly sensitive at detecting antibodies after 2-3 weeks after illness onset, and their results are best interpreted if serum samples collected in acute and convalescent phases are tested at the same time. Most laboratories test for IgG antibodies because IgM antibodies reactive with Rickettsia rickettsii are frequently detected in patients with no other supportive evidence of a recent rickettsial infection. Therefore, the detection of IgM during the acute phase should not be considered diagnostic for an ongoing illness as there could be cross-reactivity with other species and persistence of IgM beyond acute infection.

The enzyme-linked immunosorbent assay (ELISA) detects the binding of specific antibodies to antigens in a serum sample. When secondary anti-human antibodies conjugated with an enzyme are bound to antibodies from a serum sample and subjected to a substrate, an enzymatic reaction will be measurable in a positive specimen. ELISA is sensitive, reproducible, and allows the differentiation of IgG and IgM antibodies. The results are more sensitive than IFA for the detection of low antibodies level; Absorbance of the enzyme reaction is measured with a spectrophotometer. ELISA has the advantage, compared to IFA, of eliminating the subjective evaluation since the absorbance of the enzyme reaction is measured with a spectrophotometer. The inhibition ELISA has been used only for the diagnosis of scrub typhus and seems to be more sensitive than IFA in the early phase of the disease.

Molecular diagnostic methods:

These assays are more appropriate than serology in the diagnosis of acute infection; a sample collected early at disease onset, before the development of antibodies, is more likely to produce a positive result in PCR assays. When antibody production has increased to detectable levels, bacteria are rarely found in the bloodstream or at the inoculation site. Furthermore, if antibiotic treatment has been initiated, the sensitivity of PCR assays decreases for the same reason.

The most used method is nucleic acid amplification tests (NAATs), such as PCR, which has acquired increasing importance over the past few years. The quick response allows a prompt diagnosis without the need to wait for seroconversion or cell culture's growth time, which can take from 10 to 30 days. Amplification of species-specific DNA by PCR provides a useful method for the differentiation between the several Rickettsia spp. and to gain knowledge about the genomic differences within the genus.

The conventional PCR format, due to a large number of PCR products, is more prone to contamination. For this reason, a single-use primer PCR has been introduced. Another molecular method is real-time PCR that offers the advantage of speed, reproducibility, quantitative capability, and reduced risk of contamination compared with conventional PCR assays.

Several clinical samples are suitable for PCR amplification: skin biopsy, eschar, swab, or CSF. Peripheral blood and serum could also be used, but PCR on these samples has a lower sensitivity compared to skin samples or eschar collected on the bite site.

PCR detection of Rickettsia rickettsii in the blood is possible. Still, its sensitivity is lower because of the small numbers of rickettsiae in the blood in the first stages of the disease. For this reason, during the acute phase, it is better to use the SFG tissue specimen. Doxycycline treatment decreases the sensitivity of PCR; therefore, obtaining blood before starting antibiotic therapy is recommended to minimize false-negative results.

Less common diagnostic technique (Table 2)

Shell Vial:

This method requires a large number of bacteria and specific cell lines to proliferate, such as Vero E6 cells, human embryogenic lung fibroblast, and the promyelocytic HL-60 leukemia cell line (the most widely used cell line for growing A. pompeii).
Table 2. Less common diagnostic technique.

| Type of test                                      | Methods       | Vantages                                                                 | Disadvantages                                                                 |
|--------------------------------------------------|---------------|--------------------------------------------------------------------------|------------------------------------------------------------------------------|
| Weil-Felix test                                  | Serologic     | Easy to use; low cost. It is still used in developed countries[125].      | Cross-reaction with other antigens. Low sensitivity, low sensitivity[122,168] |
| Western Blot                                     | Serologic     | Highest sensitivity to early antibody, high specificity[144].              | Expensive, technically difficult to perform, longer procedure[144].           |
| Line Blot                                        | Serologic     | High specificity and sensitivity; a large number of antigens tested[121].  | No quantitative titers available; expensive[121].                            |
| Indirect hemagglutination test                   | Serologic     | More sensitive than either the complement fixation or Weil-Felix[126]     | Rarely used, low sensitivity, long preparation[143].                         |
| Latex agglutination                              | Serologic     | High sensitivity[145]                                                    | Rarely used for the high cost[145].                                          |
| Micro immunofluorescence (MIF)                   | Serologic     | High sensitivity and specificity; tests multiple rickettsial antigens simultaneously[123] | Cross-reactivity[123]; high costs.                                           |
| Complement Fixation (CF)                         | Serologic     | Very specific; used for sero-epidemiologic studies[143]                   | Poor sensitivity, especially during the early stage of the disease[126]      |
| Indirect immunoperoxidase assay (IPA)            | Serologic     | Similar to IFA; very sensitive and specific[143]                         | Needs specific instrument and trained personal[143].                         |
| Shell Vial                                       | Culture       | Highest specific; could be used during acute disease[121,141].            | Long times[141]; low success rate; needing specific cell lines[141]; low sensitivity[124] |
| Circulating endothelial cells (CECs)             | Other         | Not influenced by previous antibiotic treatment; CECs level detected could be correlated with the severity of the disease[127] | Low sensitivity; not easy to perform[146].                                    |
| Immunohistochemistry (IHC)                       | Other         | High sensitivity[123,143]                                                 | Need biopitic sample, not easy to perform[123,143].                          |
| MALDI-TOF                                        | Spectrometry  | Early diagnoses, differentiation between species[123]                     | High costs; not always available[123]. Only used to identify infections inside the arthropods[123,147,148] |

Specimens for cell cultures should be collected before starting antibiotic treatment and should not be frozen. To identify the cultivated small intracellular Rickettsiae, the laboratories should label bacteria by fluorescent antibodies or staining with the Gimenez method.

The low success rate and the complexity of this method do not permit the routinely use of this methodic.142

Serologic methods:

The Weil-Felix test, based on the detection of immune-response to different Proteus antigens that cross respond with Rickettsia125 should not be considered a first-line testing method anymore, even if it remains an option developing countries. It allows the detection of IgM antibodies 5-10 days after clinical manifestations. Western blot assay (WBA) was demonstrated to be more sensitive than IFA for the detection of early antibodies in Rickettsia spp. Nevertheless, it is generally more expensive and technically challenging to perform than other serological methods.143 Furthermore, Rickettsia cultures are required. For these reasons, its use is limited to only a few reference laboratories.144

The line, or dot, blot immunooassay, may be particularly useful for screening the many antigens that might be considered for patients with nonspecific or atypical clinical presentation. This test can be regarded as valuable only as a first-line test for the rapid diagnosis of acute cases in areas with high prevalence.121

The microagglutination test could be divided into two different methods, which included the indirect hemagglutination test and the Latex agglutination method. The first one is specific for the detection of IgG and IgM for all Rickettsiae.143

The Latex agglutination permitted the directed detection of the R. conorii, R. prowazekii, R. rickettsia, R. typhi, and infections. This method has a high sensitivity, but it is not routinely used for the high cost.126,145

Micro immunofluorescence (MIF) assay is similar to IFA except that wells are spotted with multiple rickettsial antigens for simultaneous detection. The negative aspect of this method is cross-reactivity, and its costs.123

Complement Fixation (CF) test permitted the identification detection of antibodies specific for rickettsiae. It is peculiar, but it has shown a reduced sensitivity, especially during the early stage of the...
disease. For this reason, it is only used for seroepidemiological studies.\textsuperscript{126}

**Indirect immunoperoxidase assay (IPA).** The procedure is the same as IFA, but it used the peroxidase instead of fluorescein. It needs a specific instrument and trained personal. For this reason, it is not commonly used.\textsuperscript{143}

**Other tests:**

*Circulating endothelial cells (CECs)* method allows the detection of *R. conorii* in circulating endothelial cells isolated from whole blood by using immunomagnetic beads coated with an endothelial cell-specific monoclonal antibody.\textsuperscript{127} The sensitivity is about 50%, and it is not influenced by previous antibiotic treatment. Furthermore, the CECs level detected correlates with the severity of the infection, so it can be considered a prognostic indicator.\textsuperscript{146}

**Immunohistochemistry (IHC)** permits the Rickettsia’s detection directly from biopsy specimens, but it could only be used during the acute phase and only if there is a rash or tache noir.\textsuperscript{123,143}

The most recent diagnostic tool is the *matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF).* This technique has been using with promise application for the Tick-borne infections inside the arthropods.\textsuperscript{123} The future role of this new method could be applied to help the clinical decision. The identification of Rickettsiae inside the vector\textsuperscript{147} or in the hemolymph\textsuperscript{148} is showing great potential but remained a niche method.\textsuperscript{123}

**Biosensors** emerging technology allows the fast detection of Rickettsia-induced immune response. For example, the OmpA antigen, an outer membrane protein present in the R. rickettsia, the agent

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Figure 1. Samples that can be obtained from patients and the diagnostic techniques that could be performed on them. Green: tests commonly used; Yellow: tests used less frequently or used in the past; Grey: tests used only for research studies.
responsible for the spotted fever, allows the detection of anti-OmpA human IgG. This is possible through an amperometric immune-sensor by using a synthetic peptide, obtained from the H6PGA4 R. rickettsiia protein, homologous to OmpA.149

Treatment. Rickettsiae spp. are obligate intracellular bacteria; therefore, the standard treatment is based on tetracyclines or chloramphenicol. The gold standard therapy is indeed represented by doxycycline 100 mg per os twice daily x 7 days in adults and 2.2 mg/kg of body weight per dose twice daily, orally or intravenously.140,140 It has been demonstrated, in several studies, that doxycycline shortens the course of MSF and induces a rapid remission of symptoms. The problem is that tetracycline should be avoided in childhood, during pregnancy,151,152 in patients who are allergic to it, and in those who have a G6PDH deficiency. An alternative to doxycycline is chloramphenicol. It should be administered at a dosage of 50 mg/Kg/day in four doses for seven days.56 Since 2000, chloramphenicol was used only for patients suffering from allergy, those having adverse effects to tetracyclines or chloramphenicol. The gold standard treatment is azithromycin, josamycin, and clarithromycin vs. doxycycline.153–155

On the contrary, Munoz-Espin et al. have shown that erythromycin is less effective than doxycycline.156 Studies in vitro have tested the efficacy of fluoroquinolones against Rickettsiae spp., showing encouraging results.150,157–159 Furthermore, randomized studies have shown that there is no difference between tetracycline and fluoroquinolones.160–162 However, other studies found that fluoroquinolones are associated with increased MSF severity and the worst outcome.163 Ciprofloxacin has been shown to have a deleterious effect on Rickettsia conorii-infected cells.164 Rickettsiae spp. showed to be susceptible also to rifampicin,165 but in 1991 a small trial showed its inferiority in comparison with doxycycline.166

Even trimethoprim-sulfamethoxazole has been considered as a possible therapeutic option, but in vitro and in vivo studies have demonstrated that it is not active against Rickettsia spp.150,167

In the presence of unspecific symptoms during the spring to summer months, starting azithromycin seems reasonable given the ongoing COVID-19 epidemic in Mediterranean countries.164 References:

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