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Human Rickettsiosis: An Epidemiological and Clinical Update

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Abstract

Bacteria of the genus *Rickettsia*, *Orientia* and *Coxiella* are major causes of human illness, producing the disease known as rickettsiosis, which can manifest clinically with different clinical signs and symptoms, depending on the species involved. In this article we will present the main clinical and epidemiological elements of human infection with *Rickettsia rickettsii*, *Rickettsia prowazekii*, *Rickettsia typhi*, *Rickettsia akari*, *Orientia tsutsugamushi*, and *Coxiella burnetti*, commenting also, with less emphasis, on the clinical aspects of other species of the genus *Rickettsia*.

Keywords: Q fever; *Rickettsia*; Rickettsiosis; Rocky mountain spotted fever

Introduction

The rickettsioses are infectious diseases caused by intracellular, gram-negative, non-spore-forming bacteria, belonging to the phylum *Proteobacteria*, Rickettsiaceae family, genus *Rickettsia* [1]. Although characterized as Gram-negative bacteria, the stain technique is not as evident as in other bacteria. In contrast, it shows a very characteristic red color when stained by Giemsa and Gimenez. The Rickettsiaceae family includes the genus *Rickettsia* and *Orientia* [2], however, this article will only address the genus Rickettsia.

The rickettsioses are a zoonosis spread around various regions of the world, and the bacteria are transmitted by vectors such as mites, ticks, lice, and fleas [3]. *Rickettsia* species naturally inhabit the ovaries and salivary glands of their vectors. These two habitats are important in transovarial (when the infected eggs give rise to larvae) and horizontal transmission, when arthropods feed on the blood of infected vertebrates [4]. Therefore, the permanence of these agents in the environment is dependent upon its transmission cycle between arthropods (vectors) and their animal hosts, which may differ markedly across different geographical areas [5]. It is good to point out that transmission in humans is usually mediated by arthropods, more commonly ticks.

The main rickettsia diseases that affect humans are spotted fever, varicelliform rickettsia disease, typhus (epidemic, endemic and rural) and Q fever. These diseases are manifested, especially with fever, headache and rash; however, each one has their peculiarities. The treatment is based on the administration of antibiotics, many of them, like doxycycline, common for all rickettsia diseases. The approach of this issue is important in terms of public health and clinical practice, due to the occurrence of rickettsia diseases in different parts of the world, with extremely varied clinical manifestations. In consideration of its relevance, the aim of this manuscript is to present the main rickettsia diseases, emphasizing signs and symptoms, diagnosis and treatment.

Spotted fever

Spotted fever (in the USA, "Rocky Mountain spotted fever") is caused by *Rickettsia rickettsii*, a small intracellular organism [6]. Once the agent infects humans, it induces phagocytosis by endothelial cells, and upon binding to specific membrane proteins, can escape from the phagosome, consequently reproducing in the cytosol. Another hypothesis postulates that this mechanism is mediated by the enzyme phospholipase A2, what is not well understood [7]. Similar to other gram-negative bacteria, the cell wall of *R. rickettsii* contains a lipopolysaccharide, but does not stain as easily by Gram staining [8]. Alternatively, the Gimenez method has proved to successfully stain *R. rickettsii* [9].

In the USA, the disease most frequently affects adults aged between the ages of 40 and 64, mostly white males, and children between five and nine years of age [10]. In Brazil, from 2010 to 2014, 106 to 136 confirmed cases of Rocky Mountain spotted fever were reported. These cases were mostly concentrated in the Southeast region of the country, especially in São Paulo State [11]. In contrast, in other states the cases were sparser, and Santa Catarina may be mentioned. The incidence of this disease is directly associated with increased tick vector activity and this occurs especially during the months of June to October [according to the Information System for Notifiable Diseases (SINAN)]. The fatality rate of spotted fever in Brazil between 2010 and 2014 ranges from 25 to 39%, which is considered very high compared to that in the US, which is between 2-6%. This has been attributed to difficulties in establishing early diagnosis of the disease, due to the lack of physician awareness of the disease and the initial non-specific clinical symptoms [6].

In Brazil, the primary vector for rickettsiosis by *R. Rickettsii* is *Amblyomma cajennense*, popularly known as the star tick, horse tick or "rodoleiro", although other arthropods of the genus *Amblyomma* – or the species *Rhipicephalus sanguineus*, and *Boophilus microplus* – can also be infected with this microorganism [11]. Bacterial transmission may be transstadial, following the larva cycle - nymph and adult - and transovarial, propagating to eggs and larvae. The host is infected

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when bitten by an infected tick, which introduces the pathogen. It is estimated that about 10 micro-organisms are sufficient to elicit the disease. However, for effective transmission of the pathogen, the vector must feed on the blood of the host, on average over a couple of weeks. Following accession of the tick to the human skin, along with the vector saliva, the bacteria begins to be inoculated, in a timeframe of six to 10 hours [10]. The history of absence of bites by the vector can be attributed to painless bites of larval or immature nymph stages. Forcible removal of the tick from the skin may constitute another form of infection by contact with the animal's hemolymph. We emphasize the epidemiological importance of capybara and horses, which are regarded as two of the main reservoirs of spotted fever transmission [12].

The lesions caused by *Rickettsia* can be identified in the heart, lungs, kidneys, brain and adrenal gland, due in part to the presence of free radicals from the host response to the infection. Other changes are induced in the membranes of the host cell with inflammatory response, leading to increased vascular permeability and the formation of microvascular thrombi, which is the cause of microinfarctions and tissue edema of the endothelial cells [13]. When infected, these cells, show higher platelet consumption, followed by thrombocytopenia in approximately 32% to 52% of patients. The evolution of spotted fever depends on the host immune response. Endothelial cells are stimulated to eliminate the bacterial pathogen by CD8+ T lymphocytes and cytokine (interferon gamma and tumor necrosis factor). This action has also involvement of dendritic cells after stimulation of Toll-like receptors, quickly activating the immune response of natural killer cells [13,14].

The disease has an average incubation period of seven days, ranging from two to fourteen days [10]. The symptoms and the most common signs – which affect patients in the early days after infection – include fever, headache, myalgia, nausea, vomiting, diarrhea, malaise and anorexia. Between the fourth and fifth days of fever, rashes occur in approximately 80 to 90% of patients. These eruptions are characterized as pinkish macules initially displayed around the wrists and ankles, however, they may begin on the torso, or they may appear in a diffuse fashion from the beginning of the disease. Usually the palmar and plantar regions are affected [15]. At a later stage, these lesions may spread throughout the body but rarely affect mucous membranes. In the early stage of the disease, the macules disappear with digital pressure, however, after this period; they prove to be stationary in a reddish or purplish color, as a result of micro-hemorrhages. Inoculation eschar, though rarely observed in the spotted fever caused by *R. rickettsii*, was recently described in Bahia and Sao Paulo [6]. Skin lesions coalesce with the spread of disease in untreated patients. Edema arises after onset of systemic microcirculation, and plasma volume and colloid osmotic pressure are reduced concomitantly, which may cause prerenal azotemia. Other types of lesions include ischemic, gangrenous, and neurological manifestations, such as encephalitis (coma, ataxia and convulsion) and meningoencephalitis with high protein levels, and normal CSF glucose [16].

The liver is another organ that can be affected in about 38% of patients; the sign to be observed is the slight elevation of aminotransferases [10]. Although uncommon, jaundice and liver failure may occur. When there is ocular involvement, conjunctivitis can occur. *Flame* hemorrhages and engorgement of retinal arterial occlusion veins are observed in 30% of cases. The lack of proper treatment can cause death within weeks [10].

The variety of spotted fever clinical manifestations, especially in the early days, complicates early diagnosis. These clinical manifestations can also suggest other diseases such as leptospirosis, dengue fever, viral hepatitis, salmonella, encephalitis, malaria, viral gastroenteritis, acute surgical abdomen, *Mycoplasma pneumoniae* pneumonia, among others. With the appearance of exanthema, we could think of several differential diagnoses, such as: meningococcemia, disseminated gonococcemia, bacterial sepsis (*Staphylococcus*, *Streptococcus* and gram-negative bacteria), exanthematous viruses (enteroviruses, infectious mononucleosis, rubella, measles), other rickettsiosis, ehrlichiosis, anaplasmosis, borreliosis (Lyme disease), Brazilian purpuric fever, pharmacodermia, secondary syphilis, Kawasaki disease, systemic lupus erythematosus, thrombotic thrombocytopenic purpura, and idiopathic thrombocytopenic purpura, among others [3].

The most commonly used nonspecific tests most commonly used are blood count and biochemistry. In the first, the results that aid in diagnostic confirmation are anemia and thrombocytopenia. Generally, the white blood cell count is unaltered; however the occurrence of deviation to the left is frequent. Biochemical tests show higher values of aminotransferases (ALT and AST), the total bilirubin (BT), creatine kinase (CK) and lactate dehydrogenase (LDH). Hyponatremia is observed also in about half of infected patients [3].

The most commonly used specific tests are based on immunological methods and direct search for the pathogen (immunohistochemistry and molecular approach). Serologic testing most commonly used in the diagnosis of infection by *R. rickettsii* is the indirect immunofluorescence assay (IFA), being the method of choice for routine monitoring. The high sensitivity and specificity allows detection and quantification of specific antibodies of the immunoglobulin G (IgG) and immunoglobulin M (IgM) classes. In addition to detecting the presence of the pathogen in the infected tissues, these immunoglobulins usually are best detected from the seventh day until the tenth day of the disease. The assessment of IgM has certain limitations, especially the possibility of cross-reaction with other infectious diseases such as dengue fever and leptospirosis. IgG antibodies are more specific and therefore the most suitable for conducting the diagnostic testing [17]. The appearance of *R. rickettsii*-specific immunoglobulins in the serum of patients establishes the laboratory diagnosis by IFA. Two samples should be collected, one in the acute phase (first days of the disease process) and the other between 14 and 21 days after the first sample. The parameters for confirmation of infection are IgG titers: equal to or greater than 1:64 in a single serum sample; or greater than or equal to four times the titles of immunoglobulins in paired samples. Interpretation of results must consider the clinical and epidemiological context of the disease, which increases the importance of clinical history and physical examination. Thus, the possibility of cross-reaction with other infections caused by nonpathogenic *Rickettsia* spp should also be considered [18].

Direct analysis of *R. rickettsii* can be obtained by two different methods. The first is the immunohistochemical study, in which samples of potentially infected tissue are obtained by biopsy of skin lesions. In more severe cases, fragments of spleen, brain, heart, liver, muscle, and lung can be used. Investigation into the vasculitis lesions on the skin is considered the most sensitive method for confirming spotted fever in the early stages of the disease. The other approach used is polymerase chain reaction (PCR). This technique can be employed using different biological samples that include blood and tissue obtained through biopsy or autopsy [19]. The technique is fast; however, it has no specific pattern. Moreover, both the sensitivity and the specificity are subject to variation depending on the tissue extraction methodology. However, the molecular research enables the best and most appropriate characterization of Rickettsia groups: the spotted fever group, which include *R. rickettsii, Rickettsia parkeri, Rickettsia africae*, complex *Rickettsia conorii*, among others; and the typhus group (TG) consisting

of *Rickettsia prowazekii* and *Rickettsia typhi*. [20] Samples to be used for the examination should be obtained preferably by the fifth day of manifestations of the disease and before commencing treatment with specific antibiotics and the selection of appropriate lesion or fragment should be carefully undertaken [20]. Although the methods mentioned here are widely used and highly relevant, it is understood that pathogen isolation in culture is what provides the ideal diagnosis. The conduction of this procedure should be in biosafety level 3 conditions (NB3), available in only a few reference laboratories. The materials used for this isolation are blood (blood clot) or fragments of infected tissues such as skin and lung obtained by biopsy; or organs obtained by autopsy such as lung, spleen, and liver, and the tick removed from the patient [9].

The treatment of Rocky Mountain spotted fever is based on the use of antimicrobials. These drugs, when administered early, dramatically reduce the lethality of the disease. Tetracycline and chloramphenicol are the most effective antibiotics in treating rickettsiosis, although doxycycline has been demonstrated to have greater effectiveness compared to chloramphenicol *in vitro* [17]. In pregnant women, in order to avoid the risk of alterations in fetal enamel, chloramphenicol is considered the treatment of choice; it is however contraindicated in the last 30 days prior to delivery, because of the probability of occurrence of gray syndrome in the neonate. In these cases doxycycline is recommended, which is also the first choice for children. The recommended dose for children weighing less than 45 kg is 2.2 mg/kg doxycycline every 12 hours orally for seven days, or until the absence of fever for more than two days [20].

The treatment regimen used in adults is doxycycline 100 mg orally (PO) for 7 days at intervals of 12 hours or until the absence of fever for more than two days. Alternatively, chloramphenicol 500 mg orally may be used for the same period, at intervals of six hours or until absence of fever for more than two days [20]. The recommendation of intravenous chloramphenicol is indicated in cases of severe systemic disease in patients with nausea, vomiting or diarrhea, or even when there is no possibility of distinguishing spotted fever from meningococcal disease, at the time of the patient's admission. In this case, the drug should be administered every six hours until the recovery of the level of awareness and improvement of general condition, maintaining treatment for another seven days, orally at a dose of 500 mg every six hours. In addition to the specific antibiotic therapy, supportive treatment should be instituted as clinically indicated (dialysis, mechanical ventilation, vasoactive amines, blood transfusion, etc.). The use of glucocorticoids in such cases is controversial [21].

The best preventive measure for Rocky Mountain spotted fever is to avoid contact with the tick vector, and the rural areas known to be endemic. If not possible, the use of white or light colored clothing (for easy visualization of the ticks) that completely covers the arms and legs is advised, tucking in the shirt into the pants and the pants into the socks. When finding a tick attached to the skin, it is best to remove it with tweezers, pulling carefully and steadily until it is removed, never crushing with the fingernails in order to avoid exposure to microorganisms, which can penetrate the skin through microlesions. Currently, there is no vaccine available for prevention of spotted fever. Empiric post tick bite antibiotic therapy is not indicated even in endemic areas of the disease [22].

Spotted fever and other species of *Rickettsia*

There are different species of the genus *Rickettsia* that could also cause spotted fever, as described below.

***Ricksttsia conorii*:** *R. conorii* is the species whose transmission occurs by the *Rhipicephalus sanguineus* tick, including their larval stage [23]. Found in Europe, Africa and Southeast Asia, the name of the disease caused by *R. conorii* varies according to geographic location: Boutonneuse fever, Israel Rocky Mountain spotted fever, Astrakhan spotted fever, India typhus tick [24]. Individuals at any age can be affected by the disease, though the clinical manifestations are milder in children, and it is more common in the summer months.

The pathophysiology of the disease caused by *R. conorii* is very similar to spotted fever, with an average incubation period of six days. The most common early symptoms are nonspecific, such as fever, myalgia, chills, and headache. The tick bite site shows red inflamed papules, with a black and painless necrotic center. This is considered a sign suggestive of the disease, also called inoculation eschar. The locations are varied: torso, legs and arms in adults, or scalp and retro-auricular region in children. Subsequent to the cutaneous lesions, satellite lymph nodes are enlarged. In the fourth or fifth day of evolution, a pink colored maculopapular eruption arises in the palmar and plantar regions. Mean disease duration is 14 days, and death is uncommon. Renal, neurological, and cardiac complications suggest a more severe clinical picture. Risk factors for the more severe cases include diabetes mellitus, heart failure, alcoholism, age, and glucose 6-phosphate dehydrogenase deficiency. Tetracyclines and chloramphenicol are used in the treatment [10].

***Rickettsia japonica*:** The agent is responsible for japonica spotted fever, a disease transmitted by ticks included in the *Haemaphysalis*, *Dermacentor,* and *Ixodes* genera [25]. More frequent in rural southwestern and central Japan and Thailand, its incubation period ranges from two to 10 days. The most common symptoms are: fever, headache, inoculation eschar, and petechial rash all over the body, in severe cases, encephalitis, respiratory failure and shock can occur, and, uncommonly, death [26].

Rickettsia africae: The etiologic agent of African fever is *R. africae*, which like other pathogens of this genus are transmitted by the bite of ticks belonging to the genus *Amblyomma*. The disease often progresses with fever, nausea, headache, myalgia, and painful regional lymphangitis fistules [27]. Clinical diagnosis includes the classic triad of fever, rash, and inoculation eschar [28].

Rickettsia australis: Transmission of Queensland tick typhus occurs by ticks infected with *R. australis*. These ticks belong to the genera *Ixodes*: *Ixodes holocyclus*, and *I. tasmani*. The disease is endemic to the east coast of Australia, occurring in the summer, between the months of June to November. The characteristic symptoms are: maculopapular or vesicular rash, inoculation eschar, abrupt onset of fever, headache, and myalgia [10].

Rickettsia felis: *R. felis* was the first pathogen of the *Rickettsia* genus to be described with plasmid DNA in its genome. It is transmitted through the feces of the cat flea *Ctenocephalides felis*, reported in North and South America, Europe, Africa, Asia and Oceania [25]. Patients that contract the disease develop a fever in every case, headache, vomiting, macular rash, abdominal pain and pulmonary involvement [29].

Rickettsia sibirica sibirica: The genus *Dermacentor* ticks are the vectors that transmit *R. sibirica sibirica*. During the spring and summer, the disease caused by this bacterium usually occurs in rural areas of Russia, China, Mongolia, and Kazakhstan, causing rash, inoculation eschar, and enlarged lymph nodes [30].

Rickettsia sibirica mongolitimonae: *R. sibirica mongolitimonae* is

transmitted by ticks of the genus *Rhipicephalus* and *Haemaphysalis*. Occurring in Europe, Asia and Africa, the characteristic clinical manifestations are fever in every case, headache, rash, inoculation eschar, regional lymphadenopathy, and lymphangitis [31].

Rickettsia slovaca: *R. slovaca* is another microorganism transmitted by ticks of the genus *Dermacentor*, more specifically *Dermacentor marginatus* and *Dermacentor reticulatus* [32]. Infections in these cases, unlike other rickettsiosis, occur in winter and early spring in Europe. The most common clinical manifestations include inoculation eschar, often on the scalp, and painful cervical lymphadenopathy [32]. The occurrence of rash is rare, and fever is present in less than half of infected individuals. Prolonged duration of alopecia may occur in at least 59% of patients at the eschar site. After resolution of the clinical picture in some cases, there is persistent asthenia [33].

Rickettsia raoultii: The transmission of *R. raoultii* occurs by the same vectors as *R. slovaca* and in similar regions [34]. The majority of clinical manifestations are the same, except for the fever and the severe asthenia [35]. In the cases observed so far and reported in the literature, none of the patients presented with alopecia; however, 50% of them evolved with prolonged asthenia [36].

***Rickettsia honei*:** Ticks of the genus *Amblyomma*, *Ixodes* and *Haemaphysalis* are the vectors responsible for the transmission of *R. honei*, occurring predominantly in rural areas of Australia; however, records show their isolation in parts of Thailand, Sri Lanka, and Italy [25]. Most of the symptoms are similar to other rickettsioses, especially fever, rash, headache, arthralgia, cough, enlarged lymph nodes in more than half of cases and 25% of patients presenting with inoculation eschar [4].

Rickettsia parkeri: The agent is transmitted by *Amblyomma* ticks, occurring in the USA and South America [37]. Clinically, the symptoms are fever, myalgia, asthenia, headache, inoculation eschar, and maculopapular rash. Occasionally, the occurrence of pustular or vesicular rash is described [38]. This rickettsial disease showed no associated mortality to date.

Other spotted fevers related to other species of the genus *Rickettsia* are described in (Table 1) [10,39].

Species	Vector	Location of Occurrence	Symptoms
Rickettsia heilongjiangensis	*Dermacentor silvarum*	Eastern Russia, Thailand and China	Fever, maculopapular rash, inoculation eschar, regional lymphadenopathy and conjunctivitis.
Rickettsia aeschlimannii	*Hyalomma Rhipicephalus sanguineus appendiculatus*	Africa, Southeast Europe and Kazakhstan	High fever, inoculation eschar, headache and generalized maculopapular rash.
Rickettsia massiliae	*Rhipicephalus*	Three cases in Italy, France and Argentina	Two cases had inoculation eschar and generalized maculopapular rash, and other developed acute visual loss and acute chorioretinitis
Rickettsia helvetica	*Ixodes*	Two patients in Sweden	Acute febrile illness and other acute development of meningitis.
Rickettsia monacensis	*Ixodes ricinus*	Two cases were described in Spain	Fever, headache and rash without inoculation eschar.

Table 1: Other pathogens of spotted fever [10,39].

Diagnostic and therapeutic approach of spotted fever not caused by *R. rickettsii*

Confirmation of diseases caused by *Rickettsia* is made through laboratory tests. Among these, the most prevalent are serological tests (the most commonly used is the indirect immunofluorescence assay), PCR (blood, skin biopsy or swab of bed sores), immunohistochemistry of skin biopsy, and cell culture [17,19,40].

Treatment is currently based on the administration of antibiotics, among which the drug of choice is doxycycline 100 mg orally or intravenously [10, 41]. The intravenous route is indicated when patients present serious condition. In this case, dosing at intervals of 12 hours between seven to 10 days is the most common. However, there are alternatives widely used in infected individuals who are allergic to tetracyclines. In this context, chloramphenicol 2 g/day for 7-10 days, or ciprofloxacin, 1.5 g/day for 5 to 7 days are the most common alternatives. In milder conditions in children, depending on the etiological agent, both azithromycin as clarithromycin are administered. In severe cases, supportive care - dialysis, mechanical ventilation, vasoactive amines, blood transfusion – may be needed as medically indicated. Preventive measures for these other forms of spotted fever are similar to those adopted for traditional spotted fever [10].

Epidemic Typhus

Epidemic typhus, also known as louse-borne typhus, exanthematic typhus, historical typhus, classic typhus, sylvatic typhus, red louse disease, and jail fever [42], is caused by an obligate intracellular Gram negative coccobacillus, *Rickettsia prowazekii* [43]. Like the spotted fever, the vectors are also arthropods, the main one being body lice (*Pediculus humanus corporis*) [44].

Infection occurs by contamination of the bite site with the feces of the vector animals, which is followed by intense itching, leading to the entrance of *R. prowazekii* in the resulting microlesion [45]. Cold weather, periods of war, and natural disasters associated with poor sanitation are contributing factors to human body lice infestation [46]. Rural and suburban areas of the United States have reported cases of the disease associated with the flying squirrel, and the transmission mode to humans is still unknown. The disease is described in mountainous areas of Africa, South America and Asia. The bacterium invades the host through the blood or lymphatic pathway, it induces phagocytosis in macrophages, and when it escapes the phagosome, it is free to reproduce in the cytoplasm [47]. This is followed by infection of the endothelial cells of small blood vessels with subsequent generalized vasculitis, sometimes associated with bleeding. After an incubation period of about 16 days, symptoms arise, including abdominal pain, severe headache, myalgias, photophobia, malaise, continuous fever, anorexia, chills, arthralgia, and dry cough. During the course of the disease, there may be neurological symptoms characterized by delirium preceded by lethargy, coma, convulsions and even hearing loss [42]. The presence of erythematous macules on the torso and armpits with centrifugal spread, without spreading to the palmar and plantar regions suggests the diagnosis of this disease [48]. Another sign that can occur is the evolution of petechial rash to maculopapular lesions insensitive to finger pressure. Often both photophobia and conjunctivitis occur, and in severe situations (generally associated with malnutrition and old age) necrosis and gangrene of the extremities can be reported [22].

The recurrent form of epidemic typhus is Brill-Zinsser disease, which can occur up to 40 years after the primary infection by *R. prowazekii*, especially in immunocompromised patients or in stressful situations [44]. Of milder clinical presentation, the rashes are rare, and the infected person functions as a pathogen reservoir for several years, making it difficult to eradicate the disease. It is suggested that the diagnosis be based on clinical presentation, physical examination and detailed history. History of contact with the vector, residence where there are large concentrations of people, and inadequate housing and sanitation conditions are considered as factors that predispose to typhus. Regarding the diagnosis, the main methods of identification used are serological - indirect immunofluorescence and immunoblotting reactivity - because of the difficulty in isolating *R. prowazekii* [48]. However none of them is able to differentiate acute primary disease from Brill-Zinsser. An alternative is PCR, available in selected reference laboratories.

Similarly to spotted fever, treatment is with antibiotics, most commonly doxycycline 100 mg by oral or intravenous route, depending on disease severity. Doses should be administered from one week to 10 days every 12 hours. Eventually, in special situations such as epidemics, which might lead to reduced availability of doxycycline, a single oral dose of doxycycline 200 mg may be used. Pregnant women and patients allergic to doxycycline may be treated with oral or intravenous chloramphenicol (500mg, for five days, every six hours). Treatment with doxycycline or chloramphenicol is effective in many patients, with significant clinical improvement within 48 hours [41]. In more severe cases, supportive treatment is suggested, including dialysis, mechanical ventilation, vasoactive amines, blood transfusion, or others, according to medical indications. The best measure, however, is prevention in order to control the vector, and proper disinfection (using lindane or permethrin 1%) of the clothing used by patients. Currently, there is no available vaccine for epidemic typhus [44].

Endemic Typhus

The *Rickettsia typhi* bacterium is the causative agent of endemic or murine typhus, whose transmission to humans occurs primarily by the bite of *Xenopsylla cheopis* flea, present in rodents [49]. Rats are the main reservoir of the disease, which is related to contact with them. Transmission occurs in a manner similar to that described above for epidemic typhus. It is endemic in Mediterranean countries, Africa and Southeast Asia, being more frequent in the summer [50, 51].

Abrupt and unspecific symptoms appear after the incubation period which varies between six and 14 days: most frequently fever, myalgia, nausea, vomiting and headache [52]. Rashes are mistaken with those described in epidemic typhus. The disease is considered mild, with less than 5% lethality in untreated individuals. However, there may be some complications, such as kidney failure, respiratory failure, central nervous system abnormalities, liver failure, and cardiac dysfunction [52, 53].

Diagnosis is usually obtained through serology; however blood cultures, skin biopsy followed by specific staining, and PCR are also effective [40]. Treatment usually chosen and prevention are similar to those for epidemic typhus [44], modifying the dose for the alternative treatment (four doses of chloramphenicol 50 mg/kg/day for five days after the disappearance of fever) [48].

Rural Typhus (Tsutsugamushi fever)

Rural typhus is caused by *Orientia tsutsugamushi* transmitted by the juvenile form (chiggers) of the vector *Leptotrombidium* spp, [54]. At this stage, the larva feeds on extracellular fluids of humans and rodents, and the bite of these mites causes dermatitis in the host. The main victims of this type of typhus are living in endemic rural areas of northern Australia and central, south, and northeast Asia [55]. *O. tsutsugamushi* has tropism by mononuclear leukocytes, and studies have shown that, during the convalescent phase, there is a predominance of interferon gamma and interleukin-10 (indicative of a Th2 response) in patients affected by this rickettsial disease [56].

The incubation period is six to 18 days, and the most common symptoms are sudden onset of headache, fever (lasting up to 19 days) as well as chills. Innoculation eschar occur most frequently in the armpits and groin. The disease can also cause deafness, conjunctival suffusion and tinnitus. Meningoencephalitis, pneumonitis, myocarditis, jaundice, coagulopathy, multiple organ failure, acute renal failure and Guillain-Barré syndrome may occur due to lack of specific treatment [57].

The diagnosis of rural typhus is obtained by serology, biopsy, culture, and PCR. Indirect immunofluorescence is considered the main serological method, defined by an increase of at least four times in the titles of antibody paired samples collected 14 days apart [58]. The pathognomonic histopathological finding of the disease in the skin biopsy is *linfohistiocitic* vasculitis. Treatment of the disease is with antibiotics, usually administered orally or intravenously. Typically, the drug of choice is doxycycline 100mg every 12 hours for seven days [58]. However, there are alternatives for patients allergic to tetracyclines and for pregnant women. In the first case, the recommendation is chloramphenicol, (50-100 mg/kg/day every six hours [59], or rifampin 600 to 900 mg/day, for seven days [60] or telithromycin 800 mg/day for five days [61]. For pregnant women, recommended treatment is azithromycin 500 mg as a single dose in mild cases or a daily dose over three to five days; a loading dose of one gram may be used in more serious situations [60]. In severe cases, supportive treatment is advised, as clinically indicated: dialysis, mechanical ventilation, vasoactive amines, blood transfusion, and others [21]. Recommended prophylactic measures for rural typhus include the use of insect repellents (DEET) when visiting rural areas of endemic countries. To date, there is no vaccine available [60].

Varicelliform Rickettsial disease

Varicelliform rickettsial disease is another disease belonging to the group of rickettsioses. Caused by *Rickettsia akari*, and transmitted by *Liponyssoides sanguineus* mites, whose natural hosts are domestic rodents [62]. However, the mite can also parasitize humans. Transmission of the disease to humans occurs through the bite of mites infected by *R. akari* [63].

The average incubation period is seven days, ranging from six to 15 days. Formation of inoculation eschar at the bite site after incubation occurs in most infected patients. The first sign is a painless, non-pruritic erythematous papular lesion, up to 2.5 cm, more frequent in the extremities of the body, and often with palmar and plantar involvement. In the center of the lesion, there is a vesicle containing a transparent to opaque fluid, which when broken may form a dark, crusty ulcer [63]. Often the lesion is surrounded by a large area of erythema. The most common symptoms in addition to the cutaneous lesions are fever between 38 and 40°C, reaching peaks of 41°C, asthenia, sweating, muscle pain, back pain, and headache. Complications may occur: hepatitis, disseminated intravascular coagulation, photophobia and stiff neck. The disease usually is benign, even in patients not undergoing specific treatment. The reappearance of symptoms can occur after an interval of seven to 10 days [22].

Clinical diagnosis is essential and is confirmed by serology, detection of the causative agent in biopsy or by pathogen isolation in the blood, the latter two available in a few reference laboratories. Indirect immunofluorescence or complement fixation are the most widely used methods for the diagnosis of this rickettsial disease; PCR can also be used [64].

Tetracyclines are the drugs of choice for treatment, especially doxycycline: 100mg every 12 hours for 5 days [63]. The treatment is effective with resolution of symptoms within 48 hours. Chloramphenicol is also quite effective when used at a dose of 12.5 mg/kg for 10 days at intervals of six hours, and is considered a good alternative for patients allergic to tetracyclines. The most severe cases require supportive treatment as described above. Similarly to other rickettsiosis, no vaccine is available and the disease must be prevented, avoiding contact with rodents and their habitats [65].

Q fever

With the exception of New Zealand, Q fever is a zoonosis of worldwide distribution. The disease is caused by *Coxiella burnetti*, a pleomorphic gram-negative rod. The epidemiological importance of this pathogen was evidenced with high frequency among US military serving in Iraq and the outbreak that occurred in the Netherlands. Until then, Q fever was not considered among the critical infectious diseases. Endemic areas include countries of the Mediterranean region, such as France, Spain and Israel, where diagnosis is common both in humans and in animals. Cohorts conducted in humans in Africa showed that Q fever accounts for about 2-9% of severe cases of fever, but more accurate estimates of disease incidence on the continent are not yet available [66]. Between 2007 and 2010, the Netherlands notified more than 4,000 cases of acute Q fever, with the number of infected with *C. burnetii* estimated at more than 40,000 individuals [67]. With regard to Brazil, in Rio de Janeiro, more specifically, one study found a seroprevalence of 3.2% of *C. burnetii* antibodies in HIV-infected individuals. The understanding of the disease as a potential agent for bioterrorism is controversial, and is rejected by many experts. The microorganism has as its main host cattle, sheep, goats, poultry and some arthropods, especially ticks. Humans are considered accidental hosts, and infection occurs by direct contact with milk, urine, feces, or semen of animals containing the pathogen. Another contamination route described is the inhalation of aerosols present in the fluids of farm animals in labor. This disease is a major occupational hazard for farmers, veterinarians, animal scientists, and cattle slaughterhouses, due to close contact with bacterial habitats [68]. Due to the risks of transmission, attention should be given to the pasteurization of dairy products, to percutaneous exposure, contact with the placenta of the animals at birth, blood transfusions, and sexual relations. Another route of exposure to be considered is contaminated soils or stagnant water, which are potential sources of contagion in tropical regions [3].

Syndromic presentations of the disease range from acute to chronic forms. Incubation period lasts a median of 20 days, varying from 14 to 39 days, after which patients may develop flu-like syndrome, atypical pneumonia, endocarditis, hepatitis, osteomyelitis, neurological manifestations, and chronic fatigue syndrome [3]. Pregnant women and children are in many cases asymptomatic, and thus not associated with risks such as abortion, stillbirth, premature delivery and oligohydramnios in the former. However, in the latter group, pneumonia, fever of unknown origin, endocarditis and meningeal irritation have been reported. In patients presenting flu-like syndrome, most commonly observed are high fever, fatigue, headache and myalgia, with the disappearance of symptoms after one week. These are the same symptoms present in atypical pneumonia, plus chills, nausea, vomiting, and pleural pain, and occasionally inspiratory crackling. Some patients may also show signs of pulmonary consolidation and chest X-ray opacity in the pulmonary bases. The liver affected by Q fever, displays a dense granuloma fibrin ring, which surrounds a central greasy vacuole. Severe involvement of the central nervous system is rare, and when it occurs, symptoms include: aseptic meningoencephalitis, encephalitis, dementia, confusion, and extrapyramidal symptoms [69].

Infectious endocarditis is the most common chronic form of the disease, which is present from 0.5 to 2% of cases, affecting mainly the aortic valve or a prosthetic valve [70]. The greatest risk of endocarditis development occurs in men over the age of 40, and individuals with heart valve diseases [71]. Recently, other risk factors have been identified, such as anticardiolipin antibodies of the IgG class, due to the ability to cause acute valvular lesions and endocarditis [72]. Usually, the disease is asymptomatic, but there may be signs and symptoms such as fever, hepatosplenomegaly, and purpuric lesions. Laboratory testing may reveal hypergammaglobulinemia, elevated erythrocyte sedimentation rate, anemia and microscopic hematuria [73].

Isolation of *C. burnetii* by culturing, in some cases, can be accomplished in the blood, in bone biopsy, heart valves, and vascular tissues [74]. In culture, the isolation should be done in laboratories with NB3 biosecurity conditions, due to high infectiousness. Similarly to other rickettsioses, diagnosis of Q fever is commonly based on serology and/or PCR. Recent indirect immunofluorescence diagnosis of infection is based on the detection of titers of phase II IgG antibodies equal to or greater than 200 or exceeding 50 for IgM. A phase I IgG titer greater than 800 suggests chronic infection with persistence of high titer antibodies in anti-phase I, six months after the specific treatment. Chronic infection can also be detected by DNA presence of *C. burnetii* in blood or biopsy [75]. The Duke criteria has been revised to include diagnostic confirmation of endocarditis caused by *C. burnetii*, i.e., clinical evidence and/or microbiological and/or histological and/or echocardiography evidence. These criteria may be associated with others, such as, anti-phase I IgG titer greater than 6400 [76] and/or positron emission tomography (PET-scan) which shows the specific uptake in heart valve or the presence of mycotic aneurysm [77].

The antibiotic of choice for the symptomatic treatment of acute Q fever is doxycycline, in a dose of 100 mg orally every 12 hours for 14 days [78]. Treatment of pregnant women, given the contraindication of the most active antibiotics (doxycycline or quinolones) directed to the pathogen, is a combination of sulfamethoxazole (1600 mg/day) and trimethoprim (320 mg/day). Drugs are administered orally for at least 35 days. Combination treatment is also recommended for most patients with endocarditis. In this case the choice is doxycycline at a daily dose of 200 mg with 600 mg hydroxychloroquine in a single dose or 200 mg every eight hours [79].

The lack of effective serological response (at least fourfold reduction in phase I anti-IgG titers) justifies the increase in treatment time. In order to avoid the risk of recurrence, monitoring of antibody titers should be maintained for five years. Often, surgery for valve replacement is necessary, indicated by the hemodynamic condition of the patient. Endocarditis is admittedly prevented by antibiotic therapy in up to 100% of high-risk patients. Patients with acute illness and clinical history or echocardiogram showing valvular disease and/or cardiomyopathy should receive the combined prophylactic administration of doxycycline and hydroxychloroquine at daily doses of 200 mg and 600 mg, respectively,

for one year. Treatment options for children are more limited; however, doxycycline has been indicated in severe cases of Q fever. In acute cases, azithromycin or clarithromycin, are used, which are also alternatives for pregnant women. Supportive treatment should be added to the most serious cases, as clinically indicated [78].

In contrast to the other rickettsioses, prophylactic measures for Q fever, include of the use of a whole cell vaccine, commercially available only in Australia. In addition to the vaccine, other preventive measures may be put in place, such as the consumption of pasteurized dairy products; vector control in cattle, sheep and goats; exclusion of blood donors from endemic areas for up to four weeks of outbreaks termination; orientation and training of professionals with regard to the care of the disposal of the placenta, fetal membranes and aborted fetuses; biosafety packaging care, autoclaving and cleaning of laboratory instruments; quarantine of imported animals and isolation in situations of patients at greater risk for chronic disease development such as pregnant women and patients with valvular or vascular grafts [80].

Final Considerations

The rickettsioses, in many situations, constitute a challenge to the medical field. Clinically, the most common manifestations of the disease are nonspecific, and can be coexistent with other infections, and also with non-infectious diseases. The diagnosis is usually made by serology on account of its accessibility; however, physicians must be attentive to possible cross-reactions with other infectious diseases and non-pathogenic *Rickettsia*. In many countries, the early initiation of specific antibiotics before the results of confirmatory laboratory tests is justified, given that delay for specific treatment may result in the death of the patient between eight and 15 days from the start of symptom onset.

The use of molecular methods has the potential to provide early diagnosis of diseases, which would facilitate more specific treatment. Molecular detection of specific nucleic acid sequences by PCR is available for confirmation of bacteria of the genera *Ehrlichia* spp., *Anaplasma* spp., and *Neorickettsia* spp. However, for *Rickettsia* spp, they show low sensitivity, depending on the method. In contrast, the use of Real Time PCR has increased the sensitivity. It is expected, therefore, that in the near future, greater accuracy and agility for the specific diagnosis of rickettsiosis will become readily available, which will improve the prognosis for patients affected by these diseases.

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