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The Rickettsioses: A Practical Update

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SYNOPSIS

Rickettsia are small, obligately intracellular Gram negative bacilli. They are distributed among a variety of hematophagous arthropod vectors and cause illness throughout the world.

Rickettsioses present as an acute undifferentiated febrile illness and are often accompanied by headache, myalgias, and malaise. Cutaneous manifestations include rash and eschar, which both occur at varying incidence depending on the infecting species. Serology is the mainstay of diagnosis, and the indirect immunofluorescence assay is the test of choice. Reactive antibodies are seldom present during early illness, so testing should be performed on both acute- and convalescent-phase sera. Doxycycline is the treatment of choice.

Keywords

Spotted fever group rickettsioses; Rocky Mountain spotted fever; *Rickettsia rickettsii*; epidemic typhus; *Rickettsia prowazekii*; murine typhus; *Rickettsia typhi*; vector-borne disease

Introduction

Organisms of the genus *Rickettsia* occur throughout the world and are distributed among a variety of hematophagous arthropod vectors, which include ticks, lice, mites, and fleas.[1,2] Despite the prevalence of these organisms in nature, they are often overlooked as an important cause of illness throughout the world. This is in part due to their undifferentiated clinical manifestations, which are often indistinguishable from other acute febrile infectious diseases endemic to tropical and subtropical regions. Rickettsioses are also difficult to diagnose, as there are no rapid point of care tests available to establish the diagnosis during acute infection, and confirmation of diagnosis, when sought, is usually retrospective by use of serologic methods. Recognition of these diseases as a cause of acute febrile illness is important, as when proper treatment is administered, symptoms can be quickly alleviated.

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When highly pathogenic species are involved (e.g., *Rickettsia rickettsii*), delay in treatment is associated with poor outcomes and death.[3,4] Because clinicians often fail to recognize rickettsioses as a potential cause of illness, it is difficult to know their full societal impact, but it has been demonstrated that these illnesses can impact the productivity of those afflicted and cost a great deal to the health care system when not promptly recognized.[5,6] These pathogens also continue to emerge and reemerge as causes of illness throughout the world.[2] Even in the United States, reported tick-borne infections, such as spotted fever group (SFG) rickettsioses, have increased.[7] Additionally, as the world becomes increasingly mobile, there is risk of acquiring these diseases while traveling. Indeed, SFG rickettsioses have been increasingly recognized in travelers, especially those visiting sub-Saharan Africa, and murine typhus has been recognized in European travelers visiting Southeast Asia and the United States.[8–11] The purpose of this review is to update the reader on the epidemiology, manifestations, diagnosis, treatment, and prevention of diseases caused by organisms in the genus *Rickettsia*.

Microbiology, Taxonomy, and Pathogenesis

Rickettsia are small (0.3 to 0.5 by 0.8 to 2.0 μm), obligately intracellular Gram negative bacilli. They reside in the host cell cytosol and have active transport systems to utilize the host cell's adenosine triphosphate, amino acids, and phosphorylated sugars. These organisms have small (1.1–1.5 Mb) genomes, which have evolved through incredible genome reduction as they have found their intracellular niche.[12] The species of the genus *Rickettsia* are divided into four groups or clades: a basal ancestral group, the spotted fever group (SFG), the typhus group, and the transitional group.[13] All but the ancestral group contain pathogens capable of causing human disease. The SFG and typhus group are the classic rickettsial clades, while the transitional group consists of members with features between the SFG and typhus group. With the advent of molecular methods in the last two decades, there has been a boom in the number of species and species candidates, especially within the the SFG. Currently, the SFG is comprised of a large number of species of which at least 15 cause disease; the typhus group is composed of *R. prowazekii* and *R. typhi*, and the transitional group is composed of *R. akari*, *R. australis*, and *R. felis*.

Rickettsiae are transmitted through a person's skin. Transmission of SFG species occur during the feeding of an infected tick. Organisms of the typhus group are transmitted via inoculation of infected louse or flea feces (*R. prowazekii* and *R. typhi*, respectively) onto a bite wound or mucous membranes. *Rickettsia akari* is transmitted by *Liponyssoides sanguineus* mites. Once inoculated into the skin, organisms are phagocytized by dendritic cells and transported via lymphatics to local lymph nodes where they replicate. Organisms then enter the bloodstream and disseminate to infect the endothelium of the microcirculation. As disseminated endothelial infection occurs, damage ensues and leads to increased vascular permeability. This in turn results in manifestations such as rash, and when severe, interstitial pneumonia, meningoencephalitis, acute kidney injury, multiorgan failure, and death.[14]

Epidemiology

Spotted Fever Group Rickettsioses

The SFG rickettsiae are tick-transmitted rickettsioses (table 1). These organisms infect various tick species throughout the world and therefore have a wide geographic distribution.[1] Ticks not only serve as vectors but also serve as reservoir hosts by passing the *Rickettsia* transstadially (from one life stage to the next) and transovarially (from infected female to egg progeny). The prevalence of rickettsiae infecting ticks is variable and depends on a variety of factors that affect their ability to be passaged and/or acquired through feeding on a rickettsemic host.[15] *Rickettsia rickettsii*, considered the most pathogenic rickettsial species, is pathogenic to its tick vector, and as a result, as few as 1 in 1000 *Dermacentor* ticks are infected with the agent. Therefore, in the case of *R. rickettsii*, an amplifying mammalian host is required to maintain infection in nature.[16] In contrast, some agents (e.g., *R. africae*) are less pathogenic, undergo efficient transovarial transmission, and are therefore more prevalent within their tick host. The presence of one rickettsial species within a tick can inhibit the transovarial transmission of another species.[17] Thus, the presence of one SFG species within a tick can interfere with the ability of another SFG agent to establish itself within a population (a phenomenon known as interference).

The names of diseases associated with an agent often reflect their region of discovery but often fail to encompass their full geographic range (table 1). For example, Rocky Mountain spotted fever (RMSF), though originally described in Idaho and attributed to ticks in Montana, is a disease of the entire Americas.[18] In the United States, RMSF occurs in the southeast and south central states where is is transmitted by *Dermacentor variabilis* and in the western mountainous states were it is transmitted by *D. andersoni*.[1] An ongoing outbreak of RMSF on tribal lands of Arizona and in Sonora, Mexico is attributed to the spillover of *R. rickettsii* into *Rhipicephalus sanguineus*, which are ubiquitous amongst dogs and have the ability to cause peridomestic infestations.[3,19] In Central and South America, RMSF is transmitted by a variety of *Amblyomma* species (i.e., *A. cajennense*, *A. sculptum, A. mixtum*, *A. patinoi*, *A. tonelliae*, and *A. aureolatum*).[20] *R. parkeri* and *Candidatus* R. philippii are other causes of SFG rickettsioses transmitted throughout the Americas and along the Pacific Coast of the United States, respectively.[21–23] In the last decade, there has been a marked increase in the reporting of SFG rickettsioses in the United States,[24] but much of this increase is likely related to seroprevalence as a result of exposure to SFG species other than *R. rickettsii*. Supporting evidence includes the very low case fatality rate nationally (0.3%) compared to that in Arizona where *R. rickettsii* is the predominant pathogen (10%); the paucity of confirmed SFG cases and the predominance of cases being diagnosed with single antibody titers; and the high prevalence of other SFG rickettsiae within ticks (especially *R. amblyommatis*, which often infects the aggressive biting and highly prevalent tick, *A. americanum*).[25,26]

Mediterranean spotted fever (MSF) is caused by *R. conorii* and is transmitted by *Rh. sanguineus* in Europe, Africa, and Asia. The disease's many other names (Marseilles fever, Kenya tick typhus, Astrakhan spotted fever, Israeli tick typhus, and Indian tick typhus) attests to its broad geographic distribution.[1] Experimentally, dogs have been demonstrated to

be a competent mammalian reservoir capable of transmitting *R. conorii* to uninfected ticks.[27] Cases occur in the summer months when ticks are most active.[28] MSF has been reported to occur in those traveling to endemic areas.[29] *Rhipicephalus sanguineus* also harbors *R. massiliae*. Long thought to be nonpathogenic, the organism has since been reported to cause disease with manifestations that are similar MSF. Several cases have been reported in Europe and one in Argentina.[30] African tick bite fever, caused by *R. africae*, is transmitted by *A. hebraeum* and *A. variegatum* in sub-Saharan Africa. These ticks are highly aggressive, non-discriminant biters, and exhibit a high prevalence of infection with *R. africae*.[31] Consequently, it is a frequent cause of illness in travelers to sub-Saharan Africa.[11,29] Tick-borne lymphadenopathy (TIBOLA) is caused by *R. slovaca* and *R. raoultii* in Europe and Asia. It is transmitted by *D. marginatus*. Unlike other SFG rickettsioses which peak during warmer months, it most frequently occurs during cooler months, when these ticks are most active.[32,33]

Typhus Group Rickettsioses

Louse-borne epidemic typhus, caused by *R. prowazekii*, occurs when unhygienic conditions promote infestations of the body louse (*Pediculous humanus humanus*) (table 1). Such conditions occur when war, natural disasters, or famine promote the mass migration of people, crowding, and the inability to change and launder clothing.[34,35] The body louse lives in the clothes and they become infected when taking a blood meal from a rickettsemic patient. *Rickettsia prowazekii* infects the midgut epithelium of the louse, is shed in the louse feces, and is inoculated into louse-bitten skin by scratching or when rubbed into mucous membranes. The lice are not adapted to elevated body temperatures. When a person is infected and febrile, lice leave for a new host and spread infection. Body lice infected with *R. prowazekii* do not serve as a reservoir, as they succumb to infection. People that recover from typhus remain latently infected and may recrudesce in the setting of unknown factors that may be associated with waning immunity (e.g., malnutrition, alcoholism, and advancing age). When conditions leave louse infestations unchecked, a single case of recrudescent typhus can ignite an epidemic. Typhus epidemics in the last few decades have occured in Burundi and Rwanda.[36] The last reported outbreak occurred in a youth rehabilitation center in Rwanda were the attack rate was 10%.[37] The disease also occurs at endemic levels in the highlands of Peru. A sylvatic cycle of typhus occurs in association with flying squirrels (*Glaucomys volans*), which serve as an extrahuman reservoir of *R. prowazekii* in the eastern half of North America. The squirrels become rickettsemic without ill effect and humans become infected when in close contact with these squirrels and their ectoparasites. Infection is often sporadic but has occurred in clusters when squirrels infest the crawl spaces and walls of homes and cabins.[38]

Murine typhus, caused by *R. typhi*, is also known as endemic typhus, as it occurs at endemic levels throughout much of the world, especially in tropical and subtropical seaboard regions where *Rattus* spp. serve as the primary reservoir. The rat flea (*Xenopsylla cheopis*) acquires *R. typhi* from rickettsemic rats. Neither rats nor fleas are detrimentally affected by infection with *R. typhi*. The fleas shed the organism in their feces. Humans become infected when the *Rickettsia*-laden flea feces are scratched into a flea bite wound or into mucous membranes. Urban areas and port cities with heavy shipping traffic are often rife with rats and murine

typhus.[39] For this reason, the rat rat-flea cycle of transmision is often referred to as the urban cycle of transmision. In countries of Southeast Asia, murine typhus has been implicated as the cause of febrile illness in as few as 0.4% to as many as 7%.[40,41] Specifically in Vietnam, murine typhus has been implicated as the cause of 33% of fevers, when investigators excluded other febrile illnesses (i.e., malaria, dengue, typhoid fever, and leptospirosis).[42] In the United States the peak incidence of murine typhus was in 1944 when 5,401 cases were reported nationally. The use of dichlorodiphenyltrichloroethane (DDT) on rat harborages during the mid 1940s resulted in a dramatic decline in reported cases. By the mid 1950s, fewer then 100 cases were being reported annually.[43] Although it is unknown what the effects of DDT had on murine typhus elsewhere, the pesticide saw wide use throughout the world in the decades following World War II and may have altered the incidence elsewhere.[44] Since the 1940s, murine typhus remains endemic in southern California and in south Texas where it is likely transmitted by the cat flea (*Ctenocephalides felis*) with opossums being the amplifying host.[45,46] In Texas, the disease is being increasingly recognized in municipalities outside its recent historic range and appears to be spreading in a northward distribution.[47,48] Because it is often indistinguishable from other undifferentiated febrile illnesses in the tropics, the burden of murine typhus is likely vastly underestimated throughout the world.

Transitional Group Rickettsioses

Pathogenic rickettsial species in the transitional group include *R. akari*, *R. australis*, and *R. felis* (table 1). *Rickettsia akari*, the causative agent of rickettsialpox, has been recognized in New York City, other urban areas of the United States, Mexico, Ukraine, Croatia, and Turkey. The organism infects mice and their mites (*Liponyssoides sanguineus*).[49] The mites maintain the organism transovarially. *Rickettsia australis* is the agent responsible for the illness called Queensland tick typhus and transmitted by *Ixodes holocyclus* ticks along the eastern coast of Australia.[50] Disease attributed to *Rickettsia felis* has been termed flea-borne spotted fever. The organism was originally described within a laboratory colony of cat fleas (*Ctenocephalides felis*). These fleas are ubiquitously distributed throughout the world, and *R. felis* has since been recognized as having a worldwide distribution.[51] Interestingly, the prevalence of *R. felis* in cat fleas is often quite high and does not seem commensurate with the low burden of rickettsial disease in some areas.[52] The presence of *Rickettsia felis* DNA has been increasingly reported within the bloodstream of febrile persons in sub-Saharan Africa, yet it is also found in afebrile control subjects. It has been described from a variety of other sources including nonhemophagous arthropods (book lice), and in areas where book lice are prevalent, *R. felis* has been detected from skin swabs of control subjects. For these reasons, and the inconsistent serologic data to suggest that exposure elicits an immune response, the pathogenic potential of *R. felis* has been questioned.[43] The detection of *R. felis* DNA within various mosquito species and the experimental infection of *Anopheles gambiae* with *R. felis* is curious, but its significance is yet to be elucidated.[53]

Clinical Manifestations

Spotted Fever Group Rickettsioses

The SFG rickettsiae vary in pathogenicity and cause disease with a spectrum of severity ranging from a high case fatality rate (*R. rickettsii*)[54] to those with relatively mild manifestations (*R. slovaca*).[32] Some SFG organisms may even cause seroconversion with little or no recognized illness. For the most part, pathogenic species cause an undifferentiated febrile illness that may mimic a variety of other syndromes[55] – especially in tropical areas where mosquito-borne illness and other infectious diseases are prevalent. Because of the increasing recognition of these pathogens throughout the world, the large and growing number of recognized species, and the varying degrees of disease, having a general sense of the clinical spectrum of illness is imperative for clinicians to recognize a SFG rickettsiosis.[1] Prominent symptoms include fever, headache, and myalgia. Although not a primary gastrointestinal illness, patients may have nausea, vomiting, and abdominal pain. This has been especially noted in those with severe spotted fever group rickettsioses, such as RMSF.[56]

The presence of rash is variable. It occurs in the majority of patients with MSF and RMSF (97 and 90%, respectively), 46% in those with ATBF, and in only 2% with TIBOLA.[31,32,56–58] When present, rash is usually macular or maculopapular. In RMSF, the rash often starts on the wrists and ankles prior to appearing centrally on the trunk but may occur diffusely or start on the trunk. Although involvement of the palms and soles is often considered characteristic in RMSF, the finding is variable (36 to 82%) and often a late manifestation.[56,57] A petechial rash is frequently noted in some SFG rickettsioses, but occurs less frequently in others. In the case of ATBF and infection with *R. parkeri*, papulovesicular and papulopustular rashes have been described in addition to the more typical maculopapular rash. An important cutaneous manifestation is an inoculation eschar or tache noir. Eschars are frequently found in some SFG rickettsioses. In ATBF and MSF eschars occur in 95% and 72%, respectively.[31,58] Although eschars have been reported in RMSF, the finding is exceedingly rare or actually a manifestation of another SFG rickettsiosis (e.g., *R. parkeri* infection) occuring in an overlapping geographic location.[59] Multiple eschars are often seen in patients with ATBF, as the prevalence of *R. africae* within ticks is high and multiple tick bites often occur.[31] Lymphadenopathy is sometimes noted in those with RMSF (27%). In less severe SFG rickettsioses, regional lymphadenopathy of the nodes draining an inoculation eschar is more frequent. In the case of TIBOLA, probably the mildest spotted fever with the exception of asymptomatic seroconversion, symptoms are predominantly local. Manifestations include an eschar (usually on the head or neck), regional lymphadenopathy in up to 100%, alopecia surrounding the eschar, and asthenia. The constitutional symptoms of fever, headache, and rash occur in only 26%, 16%, and 2%, respectively.[32,33] Interestingly, cases attributed to strains of *R. raoultii* in China present with fever, rather than the local symptoms typical of TIBOLA caused *R. raoultii* in Europe.[60]

In severe SFG rickettsioses, such as RMSF, pulmonary involvement may manifest as dyspnea, cough, or respiratory failure requiring ventilatory assistance; prerenal azotemia may lead to acute tubular necrosis and the need for hemodialysis; neurologic involvement

may manifest as delirium, stupor, coma, and seizures; and gangrenous digits or extremities may complicate the course.[61] Glucose-6-phosphate dehydrogenase deficiency, alcoholism, older age, and use of sulfonamide antibiotics are risk factors for severe manifestations. In the postantibiotic era, the case fatality of RMSF is 4%[25] but is reported to be as high as 30% in Sonora, Mexico[54] and 40% in Brazil. MSF is the second most severe SFG illness with a case fatality rate of 2.5%.[28]

Typhus Group Rickettsioses

Typhus group rickettsioses (louse-borne epidemic typhus and murine typhus) are characterized by sudden onset of fever with accompanying headache and myalgias. Both diseases have a variable incidence of rash – the incidence of which is less often noted in those with darkly pigmented skin.[36,62] Although an eschar-like inoculation lesion has been described in a patient with murine typhus, eschar is otherwise not recognized as a manifestation of typhus group rickettsioses.[63] Gastrointestinal symptoms such as nausea and vomiting are noted in about half of patients.[36,62] Louse-borne typhus is more severe and is more often associated with neurologic manifestations (e.g., delirium, seizures, stupor, and coma) than murine typhus. The case fatality rate of louse-borne typhus is 13%, but it has been reported as high as 50% in the harshest of conditions.[36] In contrast, flying squirrel associated typhus and recrudescent typhus (Brill-Zinsser disease) are less severe and have never been attributed to a lethal case. Murine typhus has a case fatality rate of 0.4% overall and 4% in those severely ill enough to be hospitalized.[64,65]

Transitional Group Rickettsioses

Rickettsialpox is initially characterized by a papulovesicular lesion, which occurs within 2 days of the mite bite and progresses to an eschar with surrounding induration and edema. Constitutional symptoms such as fever, headache, and myalgias ensue 1 to 2 weeks after the initial lesion. In the days following the onset of systemic symptoms, a diffuse cutaneus eruption occurs in the form of macules which evolve to papules to papulovesicles to crusted lesions.[49] The clinical presentation of Queensland tick typhus is similar to aforementioned SFG rickettsioses with maculopapular rash in 90% and eschar in up to 65% with associated regional lymphadenopathy.[50] Although more often mild, severe and fatal cases have been documented.[66] Flea-borne spotted fever also appears to to have manifestations that are on the milder side of the clinical spectrum when compared to other SFG rickettsioses. Rash has been reported in 75% and eschar in 13%.[67]

Diagnosis

Recognition of compatible clinical symptoms and knowledge of the epidemiology is key to including a rickettsiosis in the differential diagnosis of an undifferentiated febrile illness. Historical details regarding exposure to potential vectors (i.e., ticks, fleas, lice, and mites) should be elicited, but it should be realized that many often fail to recognize bites from these arthropods – they are small in size, often feed on inconspicuous areas of the body, and in the case of ticks, are painless due to the production of antiinflammatory substances within tick saliva. Because many fail to recall bites from the aforementioned vectors, historical details regarding travel, recreational activities, and occupation may give clues to whether a person

has been in an environment to put them at risk for exposure to a potential rickettsial vector. Antibiotics should not be withheld while awaiting confirmatory laboratory testing.[68]

As with many other infectious diseases the cultivation of an isolate from a patient is irrefutable evidence of infection, but for the reasons herein discussed, techniques for the isolation of *Rickettsia* are rarely undertaken. Culture of SFG and typhus group rickettsiae may be carried out on blood or tissue biopsy specimens but requires the use of cell culture techniques using antibiotic-free medium.[69,70] Rickettsiae pose a risk to laboratory staff, as they can be aerosolized during manipulation and cause illness. Therefore, isolation techniques should be carried out in a biosafety level 3 laboratory. When compared to more typical bacteria, it may take some time for detection of these organisms in culture. Furthermore, the administration of antibiotics prior to attempts at isolation decreases the yield of successful rickettsial growth.

The immunohistochemical detection of rickettsiae within skin biopsy specimens, taken from eschars or rash lesions, is a technique with the ability to confirm infection during the acute phase. The test is performed on formalin-fixed paraffin-embedded biopsy tissue. In addition to skin biopsies, it has been used to confirm rickettsial infection from tissues collected at autopsy.[2] The technique is not available in most clinical laboratories.

Serology is the mainstay of diagnosis, and the indirect immunofluorescence assay (IFA) is the serologic method of choice.[68] IFA uses fluorescein-labeled conjugate to detect serum antibodies bound to rickettsial antigens fixed on a slide. The method is superior to older serologic techniques (i.e., complement fixation and latex agglutination) and far surpasses the Weil-Felix test, which is still used in some parts of the world despite its poor sensitivity and specificity. In the United States, IFA slides prepared with *R. rickettsii* and *R. typhi* antigen are available for the diagnosis of SFG and typhus group rickettsioses, respectively. Patients seldom have detectable antibodies during the first week of illness. The IgM isotype does not appear appreciably earlier than IgG and is less specific.[68,71] Therefore, IFA for the detection of IgG requires sera drawn during both the acute and convalescent stages of illness. Although a single reactive titer during illness may be suggestive of the diagnosis, confirmation requires seroconversion or a four-fold increase in titer from acute-and convalescent-phase sera. Group-specific antigens are cross reactive. Therefore, serology is unable to offer a species-specific diagnosis without the use of cumbersome cross absorption techniques, which are not available commercially.[72] Fortunately, this cross reactivity enables the serologic diagnosis of a rickettsiosis despite the numerous species and strains in nature.[73] When participating in the care of a traveler with a potential rickettsiosis, this cross reactivity is important, as some geographic areas have several endemic rickettsial species. Enzyme-linked immunosorbent assays are also commercially available for the diagnosis of SFG and typhus group rickettsioses but give more qualitative results (reactive versus non reactive) rather than the titer reported with IFA.[68]

Amplification of rickettsial DNA by polymerase chain reaction (PCR) has been applied to the detection of a number of rickettsial species from peripheral blood, plasma, tissues (fresh frozen or paraffin-embedded), and from swabs collected from the ulcerated base of eschars. A variety of genes have been targeted (citrate synthase, outer membrane protein A, outer

membrane protein B, and the 17-kDa lipoprotein gene), but no gene target appears more effective than another.[74,75] Conventional, nested, and quantitative real-time PCR assays have been used. When rickettsial DNA is amplified using conventional or nested PCR techniques, sequencing can offer a species-specific diagnosis. When amplification is performed using certain primer sets, restriction fragment length polymorphism analysis can help identify the etiologic agent.[76] Real-time PCR has improved analytical sensitivity over conventional and nested PCR assays – it can detect fewer than 10 copies of genomic DNA per reaction.[74] Furthermore, with the use of species-specific probes, real-time PCR assays can diagnose to the species level without sequencing.[77] Despite the ability of PCR techniques to detect very small quantities of DNA, the very limited number of circulating rickettsiae hinders the clinical sensitivity of PCR when used on whole blood or serum. A recent review analyzed data available in the literature and reports a median sensitivity of 18%.[74] In those with RMSF, PCR is more often positive and with higher copy numbers in those with fatal outcomes.[78] PCR is much more useful when applied to rash or eschar biopsy specimens, where it has a sensitivity of 48 to 92%. Swabbing the ulcerated base of an eschar with a saline dipped sterile cotton swab is an effective method to detect the nucleic acids of *Rickettsia*.[79] Since PCR requires the expense of a thermocycler, reagents, and technical expertise, more inexpensive and easy to use nucleic amplification tests are desirable. The loop-mediated isothermal amplification assay is such a method and offers the ability to detect fewer than 100 copes of DNA per reaction.[80,81] Recombinase polymerase amplification assays are also inexpensive with field applicability for use in resource-limited regions.[82] Unfortunately, these methods will likely suffer from the aforementioned clinical limitations of PCR when used on peripheral blood specimens.

There is no available sensitive rapid point of care test for the diagnosis of rickettsioses. Considering the morbidity, mortality, loss of patient productivity, and associated health care costs related to delayed recognition of rickettsial diseases, such field applicable diagnostic assays are much needed.[3,5,6]

Treatment

The most important aspect to timely and effective treatment of a rickettsial illness is clinical recognition. When a rickettsial illness is suspected or considered within reason, prompt empiric treatment with an effective antibiotic should administered.[4] It should be realized that many frequently prescribed antibiotics (e.g., penicillins, cephalosporins, and sulfonamides) have no effect on rickettsiae. In the case of sulfonamides, such as trimethoprim-sulfamethoxazole, use has been associated with poor outcomes.[83]

The drug class of choice for all SFG and typhus group rickettsioses are the tetracyclines. Although there are few prospective trials evaluating antibiotic regimens for rickettsioses, and none specifically for RMSF, decades of clinical experience support the efficacy of tetracyclines.[68,83] *In vitro*, the minimum inhibitory concentration (MIC) of these agents to *Rickettsia* spp. are 0.06 to 0.25 μg/mL.[84] With its improved tolerability and twice daily dosing, doxycycline is the preferred agent of this class (table 2).[68] Minocycline is also effective. Unlike their prototype congeners (e.g., tetracycline hydrochloride), both doxycycline and minocycline are bioavailable in the presence of food, which ameliorates the

gastrointestinal discomfort associated with the agents of this class. When critical illness or nausea and vomiting preclude oral administration, doxycycline should be given parenterally. Tetracycline has been associated with fatal hepatotoxicity and pancreatitis in pregnant women. It also deposits within the fetal skeleton and inhibits bone growth. These events appear not to occur in association with doxycycline.[85] Therefore, in the case of RMSF and other rickettsioses presenting with severe manifestations during pregnancy, the benefits of doxycycline outweigh the risks. Short and infrequent courses of tetracyclines, especially doxycycline, do not appreciably stain the developing permanent teeth of children.[86] Doxycyline is recommended for the treatment of children of all ages suspected of having RMSF or other severe rickettsiosis.[68] Although true hypersensitivity to doxycycline seems to be infrequent, desensitization protocols are available for use in closely supervised settings such as the intensive care unit.[87,88]

Chloramphenicol has long been considered an effective alternative for the treatment of rickettsioses, including RMSF. The MICs of this agent for various species of *Rickettsia* range from 0.25 – 2.0 μg/mL. Although available in much of the world, chloramphenicol is not available in the oral form in the United States, and the parenteral formulation has become exceedingly difficult for hospitals to procure. In a retrospective study of RMSF, use of chloramphenicol was associated with a higher case fatality than in patients who took tetracyclines (7.6% versus 1.5% [OR, 5.5; 95% CI, 3.9–7.7]).[89] In a retrospective study of various drug regimens for the treatment of murine typhus, those who took chloramphenicol took longer to defervesce than those who took doxycycline (4.0 versus 2.9 days).[90] Where available, the severe adverse events associated with chloramphenicol should be considered prior to choosing the agent over doxycycline.

Fluoroquinolones have in vitro activity against SFG and typhus group *Rickettsia*. The MICs of ciprofloxacin and levofloxacin on various rickettsiae range from 0.25 – 1.0 μg/mL. Agents in this class have been studied prospectively in those with milder presentations of Mediterranean spotted fever.[65] They appear to be effective in those with murine typhus, but as with chloramphenicol, their use is associated with a longer time to defervesce as compared to doxycycline (4.2 versus 2.9 days).[90] These agents can be considered an alternative for less severe SFG rickettsioses and murine typhus in the rare instances when doxycycline is contraindicated. The newer macrolides (i.e., azithromycin and clarithromycin) have activity against organisms of both the spotted fever and typhus groups. Studies in children have demonstrated that a 3-day course of azithromycin is as effective as a 5-day course of doxycycline in MSF. Clarithromycin has also been shown to be effective in MSF.[91] Otherwise, experience with these two agents is limited. Their use may be considered for mild rickettsioses during childhood or pregnancy. The successful use of rifampin has been reported in a patient with culture confirmed African tick bite fever.[92]

Prevention

There are no available vaccines for the prevention of SFG and typhus group rickettsioses. Avoidance of vectors with the use of repellents and protective clothing such as long socks to cover exposed skin is recommended. The use of permethrin-treated clothing is effective for the prevention of tick bites and lasts for at least one year on treated garments.[93] The use of

DDT on rat harborages during the mid 1940s made a significant impact on the incidence of murine typhus in the United States and demonstrates the effectiveness of vector control techniques in curtailing disease. On a smaller scale, vector control may play a role in the control of local outbreaks. During epidemics of louse-borne typhus, when conditions promote the proliferation of the body louse, washing blankets and clothing in hot water kills lice and their eggs. This is often not feasible during circumstances around a typhus epidemic. During such situations, the World Health Organization recommends mass treatment by compressed air dusting of permethrin on clothing.[94] In Arizona, Brazil, and Sonora, Mexico, where there is a relatively high incidence of RMSF, the treatment of animals and the environment with acaricides has been demonstrated to reduce the numbers of ticks and shows promise in reducing the burden of local disease.[19,95,96]

Summary

Rickettsial diseases occur throughout the world and are associated with a variety of hematophagous arthropod vectors. They continue to emerge and remerge as important causes of febrile illness. Their clinical manifestations are largely undifferentiated and may range from a relatively mild illness to one that is quite severe. Recognition of compatible signs and symptoms in the setting of the right epidemiology is key to the timely administration of empiric treatment and initiation of appropriate medical workup.

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KEY POINTS

- Organisms in the genus *Rickettsia* are small, obligately intracellular Gram negative bacilli that are transmitted to humans via hematophagous arthropod vectors (i.e. ticks, lice, mites, and fleas).
- Pathogenic *Rickettsia* are found throughout the world and continue to emerge and reemerge as important causes of febrile illness.
- Rickettsioses present clinically as an undifferentiated febrile illness, and they are often accompanied by rash and an eschar.
- Serology is the mainstay of laboratory diagnosis, but serum should be tested during both the acute and convalescent phase, as antibodies are rarely present during early illness.
- Doxycycline is the treatment of choice for all rickettsioses – it should be initiated empirically when a rickettsial illness is suspected.

Table 1.

Epidemiologic features of rickettsial diseases

Disease	Organism	Group	Distribution	Vector	Severity
Rocky Mountain spotted fever	*R. rickettsii*	Spotted fever	Americas	Tick	+++++
Mediterranean spotted fever	*R. conorii*	Spotted fever	Europe, Africa, Asia	Tick	+++
Siberian tick typhus	*R. sibirica*	Spotted fever	Eurasia, Africa	Tick	++
Japanese spotted fever	*R. japonica*	Spotted fever	Japan, eastern Asia	Tick	++
Flinders Island spotted fever	*R. honei*	Spotted fever	Australia, Asia	Tick	++
Far Eastern spotted fever	*R. heilongjiangensis*	Spotted fever	Eastern Asia	Tick	++
African tick bite fever	*R. africae*	Spotted fever	Sub-Saharan Africa, Caribbean islands	Tick	++
Maculatum disease	*R. parkeri*	Spotted fever	Americas	Tick	++
Tick-borne lymphadenopathy	*R. slovaca*	Spotted fever	Europe, Asia	Tick	+
Tick-borne lymphadenopathy	*R. raoultii*	Spotted fever	Europe, Asia	Tick	+
Unnamed	*R. massiliae*	Spotted fever	South America, Europe	Tick	+*
Pacific Coast tick fever	*Candidatus* R. philippii	Spotted fever	United States	Tick	+*
Unnamed	*R. aeschlimannii*	Spotted fever	Europe, Africa	Tick	+*
Unnamed	*R. monacensis*	Spotted fever	Europe	Tick	+*
Unnamed	*R. helvetica*	Spotted fever	Europe	Tick	+*†
Asymptomatic or mild illness with seroconversion	*R. amblyommatis*	Spotted fever	Americas	Tick	+/−†
Typhus	*R. prowazekii*	Typhus	South America, Africa, Eurasia	Body louse, Ectoparasites of flying squirrels	++++
Murine typhus	*R. typhi*	Typhus	Worldwide	Flea	+++
Rickettsialpox	*R. akari*	Transitional	North America, Eurasia	Mouse mite	++
Queensland tick typhus	*R. australis*	Transitional	Eastern Australia	Tick	++
Flea borne spotted fever	*R. felis*	Transitional	Worldwide	Flea	+

*Clinical data based on a limited number of patients reported in the literature.

†Implicated as a cause of subclinical infection with subsequent seroconversion.

Table 2.

Treatment of rickettsial diseases.

	Medication	Adult dose	Pediatric dose	Duration
First choice for RMSF and all other rickettsioses	Doxycycline oral or intravenous	100 mg twice daily	2.2 mg/kg (max 100 mg) twice daily	≥3 days after defervescence (minimum 5 – 7 day course)
Alternative for RMSF and all other rickettsioses *	Chloramphenicol oral or intravenous	500 mg every 6 hours	12.5 mg/kg every 6 hours	≥3 days after defervescence (minimum 5 – 7 day course)
Alternative for MSF and other less severe SFG rickettsioses	Oral fluoroquinolones: • Ciprofloxacin • Levofloxacin Oral macrolides: • Clarithromycin • Azithromycin	• 500 mg twice daily • 500 mg daily • 500 mg twice daily • 500 mg daily	• Not recommended • Not recommended • 7.5 mg/kg twice daily • 10 mg/kg daily	5 – 7 days • 7 days • 3 days
		• 500 mg X 1 then 250 mg daily	• 10 mg/kg X 1 then 5 mg/kg daily	• 5 days
Alternative for epidemic louse-borne typhus †	• Short course oral doxycycline	• 200 mg once		
Alternative for murine typhus	Oral fluoroquinolones: • Ciprofloxacin Levofloxacin	• 500 mg twice daily • 500 mg daily	• Not recommended • Not recommended	5 – 7 days

* Chloramphenicol is inferior to doxycycline for RMSF. Its oral form is not available in the U.S., and the parenteral form is difficult to procure.

† Only recommended if needed for mass treatment during an outbreak (relapses have been documented).

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