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Travel Medicine (O Vielemeyer, Section Editor)

Treatment of Tropical and Travel Related Rickettsioses

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Opinion statement

Infections with organisms of the genera *Rickettsia* and *Orientia* are undifferentiated in regard to their manifesting signs and symptoms. Hence, a high degree of suspicion is required when a patient has a compatible illness coupled with exposure to potential vectors. Confirmatory diagnosis is usually retrospective, as it is obtained through serologic methods to determine seroconversion or a fourfold increase in antibody titers from acute to convalescent phase sera. Since many of these infections are associated with considerable morbidity and mortality, empiric treatment is imperative when illness is suspected. Antibiotics in the tetracycline class are highly active in vitro and have an excellent track record in the treatment of these diseases. Of the antibiotics in this class, doxycycline is the drug of choice, as it has excellent bioavailability, ease of twice daily dosing, and more favorable gastrointestinal tolerability. The usual duration of treatment is 7 days. In the most severe rickettsiosis, Rocky Mountain spotted fever, use of the usual alternative, chloramphenicol, is associated with a higher case fatality rate. Therefore, doxycycline is recommended in children <8 years of age—short courses do not cause appreciable staining of developing permanent teeth. Chloramphenicol is not available in its oral form in the USA, and the parenteral formulation is becoming difficult to acquire. In countries where available, it should be used with careful consideration of the risk-benefit ratio when weighed against the pathogenicity of the suspected agent. For infection with less pathogenic spotted fever group and typhus group rickettsiae (e.g., *R. conorii* and *R. typhi*),

fluoroquinolones are an alternative. The agent that causes scrub typhus, *Orientia tsutsugamushi*, is intrinsically resistant to fluoroquinolones. Azithromycin can be used for scrub typhus in areas where there is reported failure of doxycycline or when a safer agent is required (i.e., pregnancy).

Introduction

Organisms belonging to the family Rickettsiaceae are a diverse group of small, obligately intracellular, Gram-negative coccobacilli that cause human disease across the globe. The family contains two genera (*Rickettsia* and *Orientia*). These organisms are transmitted to humans by hemophagous arthropod vectors (i.e., ticks, lice, fleas, and mites). Disease is largely characterized by an acute undifferentiated febrile illness that may be accompanied by a localized inoculation eschar and/or rash [1•]. With their worldwide distribution, nonspecific signs and symptoms of disease, and difficulty in establishing a laboratory diagnosis, many cases go undiagnosed and are mistaken for diseases such as malaria or dengue fever. Despite this, rickettsioses are becoming recognized as important causes of febrile illnesses in the tropics and returning traveler [2••, 3•, 4•, 5].

Epidemiology

The species of the genus *Rickettsia* are divided into one of three biogroups—the spotted fever group (SFG), typhus group (TG), and transitional group [6–8]. The SFG, composed of over 20 named species and species candidates, are transmitted via the bite of infected ticks (Table 1) [9]. The most pathogenic rickettsial species, *R. rickettsii*, causes Rocky Mountain spotted fever (RMSF) [10••] which is distributed throughout the Americas (in Brazil, it is known as Brazilian spotted fever) [11]. Another species, *R. conorii*, is the agent responsible for Mediterranean spotted fever (MSF)—an important rickettsiosis in Europe, North Africa, and Asia. Its wide distribution is attributed to the ubiquitous nature of its tick vector, *Rhipicephalus sanguineus*, which feeds on dogs [9]. Although RMSF and MSF can be severe, life-threatening diseases with recent case fatality rates reported as high as 40 % [12] and 13 % [9], respectively, others are much less severe. For example, no case of fatal *R. africae* infection has been reported [2••].

The typhus group is made up of two species, *R. prowazekii* and *R. typhi* (Table 1). *Rickettsia prowazekii* is the agent responsible for typhus, which is transmitted by inoculating or scratching the rickettsiae-laden feces of the body louse (*Pediculus humanus corporis*) into bite wounds or onto mucous membranes. Typhus, also called epidemic typhus or louse-borne typhus, occurs in outbreaks during times of war, mass migration, or after natural disasters when cold, overcrowding, and impoverished conditions favor infestations of body lice. The southern flying squirrel, *Glaucomys volans*, is also a reservoir for *R. prowazekii*. Close contact with these squirrels, and resultant exposure to their *R. prowazekii*-infected ectoparasites, causes sporadic disease in humans in North America [7, 13]. *Rickettsia typhi*, the bacterium responsible for murine or endemic typhus, has a worldwide distribution, especially along tropical and subtropical coastal areas. It is transmitted by the inoculation of *R. typhi*-infected flea feces into flea bite sites or onto mucous membranes. In most of the world, rats are the primary reservoirs, and the rat flea (*Xenopsylla cheopis*) is the primary vector. In the remaining endemic areas of the USA (Texas and southern California), opossums and their fleas (*Ctenocephalides felis*) play a role in the epidemiologic cycle of infection [6].

The genus *Orientia* contains only two named species, *Orientia tsutsugamushi* (there are over 70 named strains) [14•], and the recently discovered *O. chuto* [15••]. While little is known regarding the clinicoepidemiology of the latter organism, *O. tsutsugamushi* is known to be endemic to a large region comprised of the area within lines drawn from northern Australia, to Far East Russia, and to Afghanistan (Table 1). It is estimated that one million cases occur annually in the ecdemic region. The bacterium is transmitted by the bite of infected larval trombiculid mites (chigger) [4•, 14•].

Table 1. Epidemiology of important rickettsial infections

Agent	Disease	Vector	Distribution
Rickettsia rickettsii	Rocky Mountain spotted fever	Tick	Americas
Rickettsia conorii	Mediterranean spotted fever	Tick	Europe, Africa, Asia
Rickettsia sibirica	North Asian tick typhus	Tick	Eurasia, Africa
Rickettsia heilongjiangensis	Far Eastern spotted fever	Tick	Eastern Russia, Asia
Rickettsia japonica	Japanese spotted fever	Tick	Japan, eastern Asia
Rickettsia honei	Flinders Island spotted fever	Tick	Australia, Nepal
Rickettsia parkeri	Maculatum disease	Tick	Americas
Rickettsia africae	African tick bite fever	Tick	Sub-Saharan Africa
Rickettsia slovaca	Tick-borne lymphadenopathy	Tick	Europe
Rickettsia australis	Queensland tick typhus	Tick	Eastern Australia
Rickettsia akari	Rickettsialpox	Mouse mite	North America, Eurasia
Rickettsia felis	Flea-borne spotted fever	Flea	Worldwide
Rickettsia typhi	Murine (endemic) typhus	Flea	Worldwide
Rickettsia prowazekii	Louse-borne (epidemic) typhus	Body louse	South America, Africa, Eurasia
Orientia tsutsugamushi	Scrub typhus	Mite (chigger)	Southern and eastern Asia, northern Australia

Pathogenesis

After inoculation into the skin, the organisms are presumably spread in mononuclear phagocytes through the lymphatics with subsequent hematogenous dissemination. The organisms infect endothelial cells, which lead to the hallmark pathophysiologic mechanism of rickettsial illness—endothelial injury. When severe, this injury results in vasodilation and increased vascular permeability, which may lead to hypotension, azotemia, pneumonitis, respiratory failure, encephalitis, and death [16, 17]. Although infection with a SFG or TG organism is thought to induce lifelong immunity, infection with *O. tsutsugamushi* does not stimulate lasting protection from reinfection with heterologous or even homologous strains [14•].

Diagnosis

Rickettsioses are difficult to distinguish clinically from other infectious diseases acquired in the tropics, but the presence of an eschar and/or maculopapular rash are important clues for an examining clinician. Currently, there is no rapid test to aid in the diagnosis during acute illness. Although serology is the mainstay of diagnosis, confirmation is generally retrospective—patients rarely have detectable antibodies in the first few days of illness. Serologic diagnosis therefore requires seroconversion during convalescence or a fourfold rise in antibody titer from sera obtained during the acute and convalescent phase [18]. Polymerase chain reaction (PCR) of the blood is relatively insensitive [19•], but it can be quite valuable when performed from a biopsy of an eschar or petechial lesion [20••]. Immunohistochemical analysis of a skin biopsy is a useful technique, but this is not widely available [21]. Culture of these organisms is problematic, as it requires technical expertise and should be performed in biosafety level 3 laboratory conditions.

Management

Since diagnosis is difficult in the early stages of illness, knowledge and awareness is key to the proper management of those afflicted with a rickettsial infection. Early recognition and timely administration of effective antibiotic therapy based upon clinical suspicion is paramount to prevent morbidity and mortality related to severe rickettsial infections. Treatment should not be delayed while awaiting laboratory confirmation. Tetracyclines, such as doxycycline, are the preferred antimicrobial agents [22].

Treatment

Pharmacologic treatment

Tetracyclines

- Antibiotics in the tetracycline class are the treatment of choice for all the aforementioned rickettsioses (Fig. 1). Tetracycline hydrochloride has a relatively short half-life, which necessitates frequent dosing (four times daily). The drug is not as bioavailable in the presence of food, and as consequence of taking on an empty stomach, gastrointestinal side effects occur at greater frequency than its congeners, doxycycline and minocycline [23]. The twice-daily dosing interval of doxycycline, its bioavailability in the presence of food, and its low cost make doxycycline the drug of choice among the other agents in this drug class.

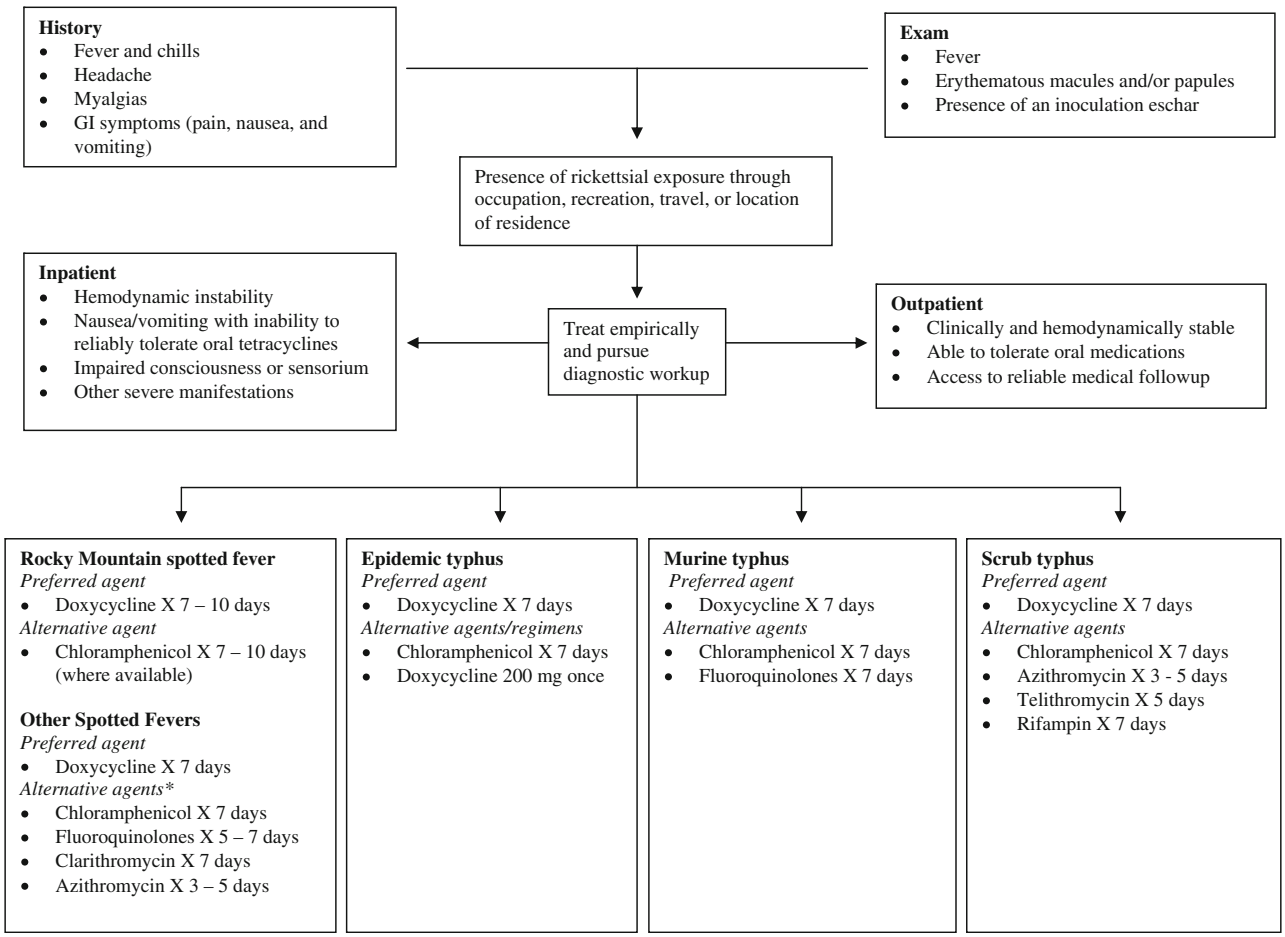

Fig. 1. Evaluation and treatment for suspected spotted fever group rickettsioses, typhus group rickettsioses, and scrub typhus.

- As determined by various methods, the in vitro susceptibility of tetracyclines to organisms in the genera *Rickettsia* and *Orientia* is superior to all other drug classes [24–26]. The MICs of the TG and major SFG rickettsiae are 0.06–0.25 μg/ml [25]. It should however be noted that the methods to obtain in vitro susceptibility data for these organisms are not standardized as they are for other bacteria.
- Although most recommend doxycycline as first line treatment for these diseases, minocycline is also effective and has documented success in Japanese spotted fever cases. A recent shortage of oral doxycycline in the USA has elevated prices and decreased availability. Patients treated with minocycline for murine typhus during this doxycycline shortage had excellent clinical outcomes [27].
- There are no randomized clinical trials regarding use of tetracyclines for RMSF, but there is overwhelming experience and retrospective evidence to support its efficacy. In cases of confirmed or probable RMSF analyzed by the Centers for Disease Control, the case fatality rate was greater in patients treated with chloramphenicol compared to those treated with tetracyclines (7.6 versus 1.5 % with an odds ratio of 5.5) [28].
- The usual course of treatment for RMSF is to continue treatment for 3 days following resolution of fever, which often results in a 7-day course. For those treated with doxycycline, the dose is 100 mg twice daily (orally or intravenously). In severe illness, a loading dose of 200 mg can be given. In children weighing less than 45 kg, 2.2 mg/kg/day should be given in two divided doses.
- RMSF in someone with a known severe allergy to doxycycline is a diffcult situation. In light of the severity of RMSF, the current inavailability of chloramphenicol in the USA (see below), and the uncertainty of the efficacy of other agents, allergy consultation for possible desensitization should be saught.
- Abbreviated courses of therapy have been studied in cases of MSF [29]. In adults treated with either 1 day of doxycycline (two 200 mg doses separated by 12 h) or 10 days of tetracycline (500 mg every 6 h), outcomes were similar [30]. A trial in children with MSF showed that doxycycline treatment continuing for 24 h after patients become afebrile had similar outcomes compared to children receiving a full week of doxycycline. One child in the short-course group, however, did experience a relapse [31]. Although they appear effective in those with MSF, short courses of tetracycline therapy should not be used in RMSF cases.
- The usual treatment for epidemic or louse-borne typhus is doxycycline 100 mg orally twice daily for 5 days [13]. During large outbreaks, a single 200 mg dose of doxycycline may be useful to treat large numbers of people and curtail an epidemic [32, 33], but relapses have been documented [34].
- Tetracyclines are a well-documented successful treatment of murine typhus. As in the case of RMSF, no prospective head to head

comparison studies comparing tetracyclines to other antibiotics have been performed. A careful analysis of 886 murine typhus cases collected from 26 case reports and 23 case series published in a monograph, demonstrates the effectiveness of tetracyclines in patients with murine typhus [22].

- The MICs of tetracyclines to tested strains of *Orientia tsutsugamushi* range between 0.15 and 0.31 μg/ml [24].
- Short courses of doxycycline have been studied in those with scrub typhus. In Malaysia, a single 200 mg dose of doxycycline was as effective as a 7-day course of tetracycline (500 mg every 6 h) to resolve symptoms (i.e., fever, headache, cough, and malaise) [35]. In a multicenter study in Korea, patients receiving 3 days of doxycycline (100 mg twice daily) had similar outcomes to those treated with 7 days of tetracycline (500 mg every 6 h) [36]. Because of a few reported relapses with short courses of therapy, courses with durations similar to those used for RMSF should be considered if all possible.

Chloramphenicol

- Chloramphenicol is active against SFG and TG rickettsiae in vitro with MICs of 0.25–2.0 μg/ml [24, 25]. The drug is also active in rickettsial infections of embryonated eggs, mice, and guinea pigs for *R. rickettsii*, *R. akari*, *R. prowazekii*, and *R. typhi* [37, 38]. The MIC of chloramphenicol against *O. tsutsugamushi* is between 1.25 and 2.5 μg/ml [24].
- It had long been considered an acceptable alternative to tetracyclines, but with evidence of higher case fatality rates in those with RMSF treated with chloramphenicol (discussed above), it is considered an inferior agent [28]. Furthermore, its potential for rare but serious toxicity (i.e., aplastic anemia) has to be considered when used for less severe rickettsial infections, where the risk to benefit ratio does not favor its use. Its effectiveness has been demonstrated in scrub typhus, but its use is associated with longer durations of fever and an increased chance of relapse when compared to those treated with tetracycline [39].
- The drug is available in much of the world, but is no longer manufactured or available in its oral form in the USA. There are currently severe shortages of the parenteral form in the USA, making it all but impossible to obtain the drug.
- Where chloramphenicol is available, and when tetracyclines are contraindicated, chloramphenicol can be given to adults at doses of 500 mg every 6 h orally or intravenously. The pediatric dose is 12.5 mg/kg every 6 h intravenously.

Fluoroquinolones

- Fluoroquinolones have in vitro activity against SFG and TG rickettsiae. The MIC of ciprofloxacin, sparfloxacin, ofloxacin, and levofloxacin

range from 0.25 to 1.0 μg/ml to the major pathogenic SFG and TG rickettsiae tested [25, 40–43].

- There are no human data to support fluoroquinolones to treat suspected RMSF but their use has been documented for less severe rickettsioses as outlined below.
- In one report, five patients with MSF were treated with 8 days of ciprofloxacin, four became afebrile within 3 days. The fifth, a man with acquired immunodeficiency syndrome and malignant MSF, survived but did not become afebrile until day 7. The regimen consisted of parental infusions of 200 mg every 12 h during the first 2 days, with transition to 750 mg oral twice daily thereafter [44].
- A study comparing oral ciprofloxacin 750 mg twice daily to oral doxycycline 100 mg twice daily, each for 7 days, in the treatment of MSF showed no statistical difference in the time to defervescence after initiation of therapy—50.1 versus 55.2 h in the ciprofloxacin and doxycycline groups, respectively. The patients receiving ciprofloxacin had fewer gastrointestinal side effects than those taking doxycycline. Of note, the authors state that none of the patients had a serious form of MSF [45].
- Subsequent observations raise concerns regarding the use of fluoroquinolones in the treatment of MSF. In a retrospective study to assess risk factors associated with severe MSF, early doxycycline use appeared to protect patients from the development of severe forms of disease (relative risk 0.248, 95 % confidence interval 0.08–0.76), whereas the use of fluoroquinolones was associated with increased severity (relative risk 2.53, 95 % confidence interval 1.40–4.55) [46]. It is hypothesized that fluoroquinolones are linked to the overexpression of a toxin-antitoxin system as demonstrated experimentally within *R. conorii*-infected cells [47].
- Fluoroquinolones have been reported with both success and failure in case reports describing patients with murine typhus [48]. A retrospective series analyzing the clinical data of 87 patients suggests good outcomes with ciprofloxacin but longer times to defervesce than with doxycycline (2.89 days for doxycycline, 4.23 days for ciprofloxacin, and 4.00 days for chloramphenicol) [49].
- Since fluoroquinolones appear effective for the treatment of MSF and murine typhus, they are likely acceptable alternatives for use in other mild to moderate rickettsioses. They should not be used in those with severe forms of disease or in those with suspected or confirmed RMSF.
- High concentrations of ciprofloxacin appeared effective against *O. tsutsugamushi* in vitro [50] and in infected mice [51], but clinical failures in humans receiving fluoroquinolones have prompted further investigation into their appropriateness during *O. tsutsugamushi* infection. Sequencing of a key section of *gyrA*, the target gene of fluoroquinolones, has revealed a mutation conferring intrinsic resistance [52, 53•]. Therefore, fluoroquinolones should not be used in those with suspected scrub typhus.

Macrolides and ketolides

- Erythromycin has an MIC to TG rickettsiae of 0.06–0.125 μg/ml and an MIC to the most clinically relevant SFG rickettsiae of 4–8 μg/ml [25, 54]. In a trial comparing erythromycin versus tetracycline in children with MSF, those on erythromycin had a mean time to defervescence that was longer than those receiving tetracycline (3.5 versus 2.2 days; $p < 0.0005$). Although all the children recovered, the authors concluded that erythromycin should not be used in those with severe illness [55].
- Josamycin, which is not available in the USA, has MICs of 0.5–1 μg/ml to organisms in the TG and most rickettsiae in the SFG [25, 56]. A trial comparing 1 day of doxycycline to 5 days of josamycin showed no significant difference in the length of time to defervesce after initiation of therapy. The authors conclude that josamycin is an alternative for MSF in pregnancy or in those with allergy to tetracyclines [56].
- Clarithromycin and azithromycin are newer macrolides available in the USA. They are attractive for the use in SFG and TG rickettsioses, as they have excellent bioavailability, attractive pharmacokinetic properties, high levels in effector cells and tissues, and are safe in pregnancy. Azithromycin is superior in these aforementioned qualities, has less drug-drug interactions, and has a better side effect profile than clarithromycin.
- The in vitro analysis of various SFG and TG rickettsiae in the presence of clarithromycin and azithromycin shows a wide range of MIC values—*R. rickettsii* (2–8 μg/ml), *R. conorii* (1.0–16 μg/ml), *R. akari* (0.25–2 μg/ml), *R. prowazekii* (0.125–0.25 μg/ml), and *R. typhi* (0.1 μg/ml) [57–59]. This variation is likely related to differences in technique.
- A study of RMSF infection in dogs revealed a longer period of time to defervescence and increased retinal vascular lesions in dogs treated with azithromycin compared to doxycycline [60]. There are no data regarding the use of azithromycin in humans with RMSF.
- In children with MSF, newer generation macrolides look promising as alternative agents. In one study, children treated with 7 days of clarithromycin defervesced faster than children receiving chloramphenicol [61]. In another study, the course of illness in those treated with 3 days of azithromycin was no different than those receiving 5 days of doxycycline [62].
- Azithromycin has been studied as an alternative treatment in those with scrub typhus, as there have been reports of poor response to those receiving doxycycline in northern Thailand [63]. Additionally, there is a need for safer treatments during pregnancy [64]. Azithromycin is effective in cell culture assay systems and in mice infected with strains from northern Thailand [64, 65].
- A single 500 mg dose of azithromycin has been shown to be as effective as a 1-week course of doxycycline in a prospective, open

labeled, randomized trial in South Korea [66]. A 3-day dosing schedule of azithromycin has been studied in Thailand and was found to be non-inferior to a 1-week course of doxycycline [67]. In the latter study, azithromycin was better tolerated but noted to be more expensive. Based on these studies, azithromycin appears to be an effective alternative for the treatment of mild to moderate scrub typhus [68, 69].

- Telithromycin is a ketolide antibiotic with a favorable pharmacokinetic profile, which facilitates once daily dosing. It has good in vitro activity against *R. conorii*, *R. rickettsii*, *R. africae*, *R. typhi*, and *R. prowazekii* (0.5–1 μg/ml) [70]. There have been no in vivo studies to guide its clinical use in those with SFG or TG rickettsioses. Furthermore, reports of severe liver injury have prompted relabeling with emphasis on hepatotoxicity. Reports of exacerbation of symptoms in myasthenia gravis have prompted a "black box warning" to indicate contraindication of telithromycin in patients with this syndrome. These severe adverse events have dampened enthusiasm for telithromycin's widespread use.
- Telithromycin has been shown to be as effective as doxycycline (each a 5-day course) for mild to moderate scrub typhus infection in South Korea [71].

Rifamycins

- Rifampin has in vitro effectiveness to many species of the SFG (*R. rickettsii*, *R. conorii*, *R. sibirica*, *R. japonica*, *R. honei*, *R. africae*, *R. parkeri*, and *R. slovaca*), transitional group (*R. akari* and *R. australis*), and TG (*R. typhi* and *R. prowazekii*) [25]. The MICs of these susceptible rickettsiae range from 0.06 to 1.0 μg/ml [25].
- Despite rifampin's in vitro effectiveness, there is little clinical data to support its clinical efficacy. It has been reported with success in combination treatment with erythromycin during a pregnancy complicated by MSF [72]. In a prospective study of patients with MSF, rifampin administered for 5 days was inferior to 1 day of doxycycline—defervescence occurred 36 h later in those receiving rifampin. Furthermore, 4 of the 15 patients in the rifampin group were deemed treatment failures [73].
- Based on the aforementioned study in those with MSF, we believe that rifampin is not a reliable medication for the treatment of SFG and TG rickettsioses.
- In susceptibility testing, rifampicin appears highly efficacious against *O. tsutsugamushi*. In a trial comparing doxycycline versus standard and high dose rifampicin, both rifampicin regimens had significantly shorter times to defervescence after initiation of therapy [74]. Furthermore, the widespread use of rifamycins in an area where tuberculosis is highly endemic raises the issue of inducing rifampicin-resistant *Mycobacterium tuberculosis*.

Pediatric considerations

- The American Academy of Pediatrics endorses the use of doxycycline for the use in children of any age with suspected RMSF [75]. Teeth staining through doxycycline use is not likely to occur in young children with even a few short courses of doxycycline. This has been demonstrated using various methods to evaluate tooth shade [76•, 77].
- In children over 40 kg, doxycycline can be given as it is to adults—100 mg twice daily. In smaller children, it should be given in two equally divided doses totalling 4.4 mg/kg body weight per day.
- Among surveyed physicians, only 35–39 % recognize doxycycline as being the treatment of choice for RMSF in children younger than 8 years of age. The higher case-fatality rate in children makes this an important issue for physician education [78, 79].

Considerations in pregnancy

- Tetracyclines may deposit in the fetal skeleton and result in temporary inhibition of bone growth [80]. They can also cause staining of deciduous teeth in children when mothers received the antibiotic during pregnancy [81]. In addition to their effects on the fetus, tetracycline use during pregnancy has also been associated with maternal pancreatitis and hepatotoxicity [82]. In pregnant women with RMSF, chloramphenicol has generally been considered the preferred antibiotic, however, not without risk. Chloramphenicol is associated with gray baby syndrome (abdominal distention, pallor, cyanosis, and vasomotor collapse) when given to neonates, and the transplacental concentration of the drug can reach 30–50 % of that in the maternal blood stream [83]. When chloramphenicol cannot be quickly obtained, or for treatment of women in their last trimester of pregnancy when there is risk of gray baby syndrome, doxycycline should be used.
- Fluoroquinolones are contraindicated in pregnancy, but azithromycin is safe and can be used to treat other rickettsioses (MSF, murine typhus, scrub typhus) presenting with non-life-threatening manifestations.

Prevention

- There are no studies regarding antimicrobial prophylaxis for the prevention of SFG or TG infections in travelers. There are limited data regarding antibiotic prophylaxis in the setting of a tick bite [84], but considering the relative infrequency of highly pathogenic SFG rickettsiae infecting ticks (~0.001 % in North America for *R. rickettsii*), prophylaxis after tick bite is not recommended.

- For those traveling or deployed to endemic areas, scrub typhus can be prevented with the oral administration of doxycycline at 200 mg per week [85, 86], but strict adherence to this regimen is essential to ensure the efficacy of prophylaxis.
- Use of protective clothing (e.g., long sleeves, pants, and high socks) may help prevent contact with vectors such as ticks or mites. Clothing treated with permethrin has proven effective in reducing tick bites in both in the laboratory and the field [87–89].
- Prompt tick removal will help prevent rickettsial transmission. A study in guinea pigs showed that unfed ticks infected with *R. rickettsii* need up to 10 h for bacterial transmission. In contrast, partially fed *R. rickettsii*-infected ticks can transmit the pathogen in as few as 10 min [90].
- In the case of rickettsioses transmitted by the brown dog tick, such as infection with *R. rickettsii* and *R. conorii*, control of ticks on dogs may be useful to decrease infestations of infected ticks in peridomestic areas. A study comparing two communities of eastern Arizona showed that the application of anti-tick dog collars and use of liquid acaricide on yards, reduced infestations of ticks on dogs (<1 % infested in the intervention community compared to 64 % infested in the control community) [91•]. It has yet to be determined if these interventions will reduce rates of RMSF in communities undergoing these control measures.
- The spread of typhus within susceptible populations can be curbed with attention to hygiene as a means of controlling the body louse. The application of heat to blankets or garments with hot water or dry air is an effective method to kill lice and their eggs [92]. The use of hot air (i.e., tumble dryers) may not be practical on a large scale, but use of boiling water has been effective in field conditions [93]. During large outbreaks, when the aforementioned methods are not possible, treatment of clothed individuals with permethrin (30–50 g per adult and approximately half that for children) can be employed. Application in this manner will simultaneously treat the clothing and skin [94, 95].
- The incidence of murine typhus was greatly lowered in the USA when the broad use of dichlorodiphenyltrichloroethane (DDT) decreased the rat-flea burden [96, 97]. Although the indiscriminate use of pesticides for vector control (as in the case of DDT) is not applicable to an individual and may carry untoward environmental consequences, targeted use of safe agents to control ectoparasites may be beneficial as a public health measure during times of high disease burden.
- To date, there are no available vaccines for the prevention of infection with bacteria in the family Rickettsiaceae.

Conclusion

In order to not miss infection caused by *Rickettsia* sp. or *Orientia tsutsugamushi*, a high degree of clinical suspicion is required as there are no rapid point-of-care tests available to aide in its diagnosis. Doxycycline is the drug of choice for all of these infections. When a SFG (other than *R. rickettsii*) or TG rickettsiosis is

suspected, alternative agents such as chloramphenicol (where available), fluoroquinolones, and azithromycin can be considered. Fortunately, severe *bona fide* allergies to doxycycline are rare. Fluoroquinolones are not active against *O. tsutsugamushi*, but azithromycin is an effective alternative.

Compliance with Ethical Standards

Conflict of Interest
Dr. Lucas Blanton declares that he has no conflict of interest.
Dr. David Walker declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by the authors.

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- •• Of major importance

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