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184 Genital Mycoplasmas: *Mycoplasma genitalium*, *Mycoplasma hominis*, and *Ureaplasma* Species

David H. Martin

SHORT VIEW SUMMARY

Microbiology and Taxonomy

- The genital mycoplasmas include *Mycoplasma hominis, Mycoplasma genitalium, Ureaplasma urealyticum,* and *Ureaplasma parvum.* The two *Ureaplasma* spp. were assigned to separate species only more recently.
- The genital mycoplasmas lack cell walls and have the smallest genomes of known free-living microorganisms.

Epidemiology

- All of these organisms are primarily sexually transmitted but also may be transmitted to infants at birth. There is evidence that they may persist in children into adulthood.
- The epidemiology of infection with *M. genitalium* closely parallels that of *Chlamydia trachomatis* and *Neisseria gonorrhoeae.*

Clinical Manifestations

- *U. urealyticum* causes urethritis, whereas *U. parvum* appears to be a colonizer. Only relatively sexually inexperienced men are susceptible to *U. urealyticum* disease, which is likely due to the development of immunity after multiple exposures to this common urethral organism.
- Although the pathogenesis is unclear, the ureaplasmas are strongly associated with bronchopulmonary dysplasia in very-low-birth-weight infants.
- Both *Ureaplasma* spp. may cause hyperammonemia syndrome in immunocompromised patients, especially patients receiving lung transplants.
- *M. hominis* plays a minor role in genital tract disease but is implicated in postpartum fever, bacteremia, and postoperative mediastinal and wound infections.
- *M. genitalium* is a cause of urethritis in men and endocervicitis in women. It also is associated with pelvic inflammatory disease, infertility, ectopic pregnancy, and preterm birth.

Diagnosis

- Most clinical laboratories are not equipped to diagnose infections caused by these organisms. Only *M. hominis* is detectable using methods routinely employed in clinical laboratories, but sensitivity is poor. The ureaplasmas require special media for growth, and *M. genitalium* cannot be cultured at all outside research laboratories. Nucleic acid amplification assays for this organism are increasingly becoming available for clinical use.

Therapy

- Tetracyclines are active against most ureaplasmas and *M. hominis* but not *M. genitalium.* Macrolides are effective for the ureaplasmas but not for *M. hominis* and are only partially effective for *M. genitalium.* Quinolones, especially moxifloxacin, are active against all of the genital mycoplasmas.

TAXONOMY AND MICROBIOLOGY

The clinically important genital mycoplasmas—*Mycoplasma hominis, Mycoplasma genitalium, Ureaplasma urealyticum,* and *Ureaplasma parvum*—belong to the Mollicutes class and Mycoplasmataceae family of bacteria. *Mycoplasma* spp. and *Ureaplasma* spp. are the only two genera in this family. In this chapter the trivial term *genital mycoplasmas* is used to refer to these genera collectively. *Ureaplasma* spp. are most prominently distinguished from *Mycoplasma* spp. by virtue of their ability to hydrolyze urea for energy production. The two *Ureaplasma* spp. differ phenotypically and genotypically and were officially designated as separate species in 2002.[1] Originally they were believed to be biovariants of a single species and were first known as T-mycoplasmas and later renamed *Ureaplasma urealyticum.* This background information is important because textbooks and research papers published before 2002 did not distinguish the two species. The trivial term *ureaplasmas* is used in this chapter in reference to published research that did not differentiate the two species or in reference to conditions that are associated with both species.

Mollicutes in general have the distinction within the bacterial kingdom for having the smallest genomes of any known self-replicating organisms. The smallest of these is the genome of *M. genitalium,* which is only 580,000 base pairs in length and therefore is believed to be close to the minimal set of genes necessary for independent life. For this reason, its genome was among the first to be completely sequenced as well as the first to be completely reconstructed in vitro.[2,3] Mollicutes evolved from *Clostridia*-like gram-positive bacteria by virtue of extensive gene deletion. *M. genitalium* is very closely related genetically to *Mycoplasma pneumoniae,* having evolved away from this organism by additional gene deletions.[4] As with all members of the Mollicutes class of bacteria, the genital mycoplasmas lack a cell wall and thus are osmotically fragile. Reflective of their small genomes, they have limited biosynthetic capacity, which is why complex growth media containing sterols are required for their cultivation in vitro.

The natural habitat of the genital mycoplasmas is the human genitourinary tract, where they adhere to mucosal surface epithelial lining cells, although *M. genitalium* also can be found intracellularly.[5,6] They are found outside this environment less frequently, and, when they are, it is often in the setting of immune deficiency such as that found in very-low-birth-weight premature infants. Although the mechanisms differ among species, the genital mycoplasmas all have the ability to vary immunogenic proteins on their cell surface.[7] This appears to be the major mechanism by which they avoid the host immune response and is the reason they are able to persist for months to years in the same host.[7,8] *Mycoplasma fermentans* and *Mycoplasma penetrans* are two other mycoplasmas that have been identified in the human genitourinary tract, but they have not been consistently associated with human disease.[9] These are not discussed further in this chapter.

EPIDEMIOLOGY

All of the genital mycoplasmas are sexually transmitted, although their roles in genital tract disease vary significantly, as discussed in detail in "Clinical Manifestations."[10–13] The ureaplasmas are more commonly found in both the male and female genital tracts than either of the two *Mycoplasma* spp. In a study of healthy college men, ureaplasmas were present in the urethras of 29%, whereas *M. hominis* was present in 7%. For both organisms, prevalence correlated strongly with the number of sex partners.[14] Among sexually active female nursing students, the same group of investigators found that the prevalence of ureaplasmas varied from 38% to 75% and the prevalence of *M. hominis* varied from 9% to 17%, depending on the number of lifetime sex partners.[11] In a nationally representative sample of young adults in the United States, the prevalence of *M. genitalium* was 1.0%, whereas in the same population

the prevalence of *Chlamydia trachomatis* was 4.2%.[15] In this and another survey study,[16] prevalence of *M. genitalium* was related to the number of reported sex partners. Evidence for sexual transmission of *M. genitalium* was further strengthened by studies demonstrating high rates of genotype concordance within couples.[17,18] The epidemiology of *M. genitalium* closely parallels that of *C. trachomatis* and *Neisseria gonorrhoeae.* All are found more frequently in younger sexually active men and women and are more common in African Americans than in other racial groups.[15,19] Young age is also a risk factor for infection by the ureaplasmas and *M. hominis,* but racial associations have been less well studied.[14,20]

Neonates born vaginally are frequently colonized in both the genital and the respiratory tracts by ureaplasmas and less frequently by *M. hominis*.[21,22] Colonization after cesarean section occurs less commonly, supporting the hypothesis that exposure to vaginal secretions at birth is the primary risk factor for acquisition in neonates. Boys in general are less likely to be colonized than girls.[22,23] Colonization of the genital tract in girls persists in some cases and is likely to be a reservoir for infection of boys when sexual intercourse is first initiated.[24,25] Much less is known about transmission of *M. genitalium* to neonates at delivery. However, it was reported that 9% of 319 children undergoing bronchoscopy for medical indications at a mean age of 8 years had *M. genitalium* detected in lavage fluid by polymerase chain reaction (PCR) assay. This was compared with positivity rates of 10% for *M. pneumoniae,* 5% for *M. hominis,* and 9% for *U. parvum*.[26] If these data can be confirmed, it may be that all the genital mycoplasmas have the ability to colonize the respiratory tract and possibly may be present for long periods of time.

CLINICAL MANIFESTATIONS

See Table 184.1.

Ureaplasmas

The role of ureaplasmas in nongonococcal urethritis (NGU) has long been controversial in that numerous earlier studies failed to show that the organisms were more common in men with disease compared with control subjects without disease.[27] The best evidence for a pathogenic role for ureaplasmas in NGU comes from studies of men who are relatively inexperienced sexually and are having their first episodes of urethritis. In these men, the rate of isolation and the concentration of ureaplasmas in first-voided urine specimens are significantly greater in those with *C. trachomatis*–negative NGU than in those with *C. trachomatis*–positive NGU and in men without urethritis.[28] Data compiled from three Seattle studies showed that ureaplasmas were isolated significantly more often from men with a first episode of urethritis than from those who had had previous episodes or from men without urethritis.[28–30] The results of studies of selective antibiotic eradication of ureaplasmas also support their role in NGU.[28,30,31] Further evidence that the ureaplasmas cause NGU comes from self-inoculation studies performed by two investigators, both of whom developed evidence for urethral inflammation that responded to treatment.[32] Studies over the 15 years subsequent to differentiation of the two *Ureaplasma* spp. have further enhanced understanding of the role of these organisms in NGU. The evidence indicates that *U. urealyticum* is a urethral pathogen, whereas *U. parvum* does not appear to induce inflammation at this site.[33,34,35] The study by Wetmore and coworkers[35] reproduced the results of the previous studies by Bowie and colleagues[28,29,30] in that the strongest association of *U. urealyticum* with NGU was among men with the fewest lifetime sex partners. *U. parvum* was not associated with NGU at all in this study.[35] Thus, although it is reasonably clear now that *U. urealyticum* is a cause of symptomatic urethritis in men, this occurs in a subpopulation of men with relatively little sexual experience, so overall the proportion of NGU cases caused by this organism is small.

Ureaplasmas are present in the amniotic fluid of some women experiencing preterm labor and delivery and in cases of preterm premature rupture of membranes, leading to the hypothesis that the organism causes these conditions.[36] Supporting this hypothesis is a study of amniotic fluid obtained from normal pregnant women between 15 and 17 weeks of gestation, which showed that 11% were positive by PCR assay for ureaplasmas and that these women were significantly more likely to have preterm labor and delivery than women who were uninfected.[37] Additionally, the presence of ureaplasmas in the placenta at the time of delivery is strongly associated with chorioamnionitis.[38] However, a placebo-controlled treatment trial in pregnant women vaginally colonized with ureaplasmas did not show any benefit of erythromycin treatment.[39] These seemingly disparate outcomes may be explained by a molecular analysis of amniotic fluid from women in preterm labor with intact membranes. In addition to ureaplasmas, a number of fastidious bacteria were found that would have been missed by older culture-based studies, suggesting the possibility that the effect previously attributed to ureaplasmas could have been caused by other organisms.[40]

TABLE 184.1 Relationship Between *M. genitalium* and Disease Compared With *M. hominis* and *Ureaplasma* Species

	M. GENITALIUM		*M. HOMINIS*		*UREAPLASMA* SPP.	
CONDITION	**A**	**C**	**A**	**C**	**A**	**C**
Nongonococcal urethritis						
Acute	++++	++++	–		+++[b]	+++
Persistent	++++	++++	–		++	++
Balanoposthitis	++	+	–		–	
Chronic prostatitis	+	+	–		–	
Epididymitis	+	+	+	–	++	++
Bacterial vaginosis	++	–	++++	–	++	–
Cervicitis	+++	+++	–		–	
Infertility	+++	++	–		+	–
Ectopic pregnancy	+	?	+	–	+	–
Pelvic inflammatory disease	+++	+++	++	++	+	–
Postpartum fever	NS		+++	+++	+	–
Preterm delivery	+++	+++	+	–	+++	+
Neonatal lung disease	NS		+	?	+++	+

[a]Shown are the relative probabilities of the indicated mycoplasma being associated with (A) or causing (C) the conditions shown in the first column. ++++, very high; +++, high; ++, moderate; +, low; –, zero; ?, not certain; NS, not studied.
[b]The values shown for the nongonococcal urethritis categories are based on studies of *U. urealyticum.*
Modified from Taylor-Robinson D, Jensen J. Mycoplasma genitalium: *from chrysalis to multicolored butterfly.* Clin Microbiol Rev. *2011;24:498–514.*

As noted earlier in "Epidemiology," ureaplasmas are frequently transmitted to neonates at the time of delivery. Especially among very-low-birth-weight infants, ureaplasmas are associated with bronchopulmonary dysplasia.[7,36,41] However, antibiotic treatment trials in colonized preterm infants have not clearly demonstrated efficacy for the prevention of bronchopulmonary dysplasia.[42] Ureaplasmas may be isolated from the cerebrospinal fluid of preterm infants, but the significance is unknown.[43] In a prospective study, cerebrospinal fluid white blood cell counts and protein and glucose levels did not differ between *Ureaplasma* PCR-positive samples and culture-negative samples. Moreover, the infections appeared to resolve without therapy.[44] Similarly, cord blood and venous blood specimens are positive in 15% to 20% of very-low-birth-weight infants, but the clinical significance is unclear.[7,36] There appears to be no difference between the two *Ureaplasma* spp. in their potential to cause neonatal disease, but further studies are required.

Ureaplasmas can cause systemic infections in adults. Postpartum fever occasionally is a consequence of *Ureaplasma* bacteremia or endometritis.[45] The ureaplasmas are urease positive and have been implicated rarely as a cause of urinary infection stones.[46] There is evidence from two studies using suprapubic urine aspirations that ureaplasmas cause some cases of cystitis and urethral syndrome in women,[47,48] although there is no evidence that they are a cause of pyelonephritis.[49] Pericarditis and mediastinitis following open heart surgical procedures have been reported, especially in heart and lung transplant cases.[50] Postoperative sternal wound infections rarely occur in immunocompetent patients.[51] Hypogammaglobulinemic individuals appear to be at higher risk for systemic ureaplasma infections, especially septic arthritis.[52,53] Single cases of ambulatory peritoneal dialysis–associated peritonitis, meningitis, and brain abscess have been reported.[53–55] Because appropriate culture methods for ureaplasmas are not available in most clinical microbiology laboratories, the reported cases may represent the "tip of the iceberg." Ureaplasmas should be considered in culture-negative cases of any of these conditions.

Hyperammonemia is an uncommon but usually fatal syndrome in immunocompromised patients, particularly among recipients of lung transplants. A recent study has shown that this syndrome is caused by ureaplasmas, which is a major advance in that these infections readily respond to appropriate antibiotics.[56] Both *Ureaplasma* spp. have been implicated.

Mycoplasma hominis

Although a common inhabitant of the male genital tract, *M. hominis* is not a cause of NGU. Numerous studies have shown no difference in the prevalence of this organism in urethral specimens of symptomatic and asymptomatic men.[49] *M. hominis* has been implicated in a few cases of pyelonephritis.[57] *M. hominis* is frequently present in vaginal fluid, and in this setting it is strongly associated with bacterial vaginosis.[58] Moreover, quantitative PCR studies have demonstrated that significantly higher concentrations of the organism are present in women with bacterial vaginosis than in women whose microbiota is dominated by *Lactobacillus* spp.[59,60] Thus, although *M. hominis* has been associated with genitourinary tract syndromes such as vaginal discharge and pelvic inflammatory disease, it is not clear whether it is a true pathogen or is simply one of the many organisms comprising the bacterial communities associated with bacterial vaginosis, itself a well-documented risk factor for multiple genitourinary tract morbidities in women.[61] However, Sha and associates[59] reported that after controlling for bacterial vaginosis as defined by the Nugent score, high levels of *M. hominis* correlated strongly with shedding of human immunodeficiency virus (HIV) in the vagina. Interestingly, *M. hominis* has a symbiotic relationship with certain strains of *Trichomonas vaginalis*. In fact, the organism can survive intracellularly in the parasite.[62] There appears to be a subset of women with trichomoniasis with high levels of *M. hominis* in vaginal fluid in the absence of bacterial vaginosis who have clinical evidence of marked cervical and vaginal inflammation compared with other women with trichomoniasis.[61] Taken together, these data suggest that high levels of *M. hominis,* perhaps as the result of *T. vaginalis* coinfection, may be a risk factor for HIV transmission independent of bacterial vaginosis.[63]

M. hominis colonizes neonates and has been isolated from the chorioamnion of premature infants along with the ureaplasmas.[64] However, several recent studies using molecular methods for bacterial detection in amniotic fluid and placentas obtained from women delivering premature infants only rarely found *M. hominis* even in the presence of chorioamnionitis.[38,40,65]

These data argue against a significant causative role for *M. hominis* in prematurity. Moreover, the organism does not appear to be associated with chronic lung disease in very-low-birth-weight infants, in contrast to the ureaplasmas.[7] However, *M. hominis* has been isolated from blood in 13% of women with postpartum fever,[49,66] as it has from women with postabortion fever.[67]

Among the genital mycoplasmas, *M. hominis* is most commonly reported to play a role in systemic infections. At least in part, this may be because *M. hominis* is the only one that can be cultivated, albeit with some difficulty, using the standard media used by clinical laboratories (see "Laboratory Diagnosis"). Particularly well documented are postoperative wound infections, especially after open heart procedures. These include sternal wound infections, mediastinitis, and pericarditis.[68] In 1997, Garcia-Porrúa and associates[69] reviewed 17 cases of septic arthritis caused by *M. hominis*. The organism has been reported uncommonly as the cause of pneumonia in immunocompromised patients, patients in intensive care, and healthy people.[70,71] Often these infections are manifested by the sepsis syndrome.[72] Occasional cases of endocarditis have been documented,[73] and the organism is capable of forming abscesses, although this is relatively rare.[74–76] The key clinical point to remember is that *M. hominis* should be considered in all well-documented systemic or local infections in which properly collected samples do not reveal an etiologic agent in the absence of prior antibiotic treatment.

Mycoplasma genitalium

Of all the genital mycoplasmas, the evidence for *M. genitalium* as a genitourinary tract pathogen is strongest. Its role in systemic infections has not been investigated because it is the most difficult of all of the genital mycoplasmas to cultivate in vitro. *M. genitalium* is the second most common cause of urethritis in men after *C. trachomatis*.[77] The clinical manifestations are very similar to those associated with *C. trachomatis,* and both include milder symptoms and signs of inflammation than observed with gonococcal urethritis. Because *M. genitalium* is relatively resistant to the antibiotics recommended for NGU treatment, it is the most common cause of persistent or recurrent symptomatic NGU.[77] The role of *M. genitalium* in epididymitis has not been studied, but given the similarity between diseases caused by this organism and *C. trachomatis,* a well-documented cause of epididymitis, it seems likely that at least a few cases are caused by this organism.

Endocervicitis, evidenced by mucopurulent discharge, cervical friability, and erythema, is associated with *M. genitalium,* although the relationship does not appear to be as strong as it is with *C. trachomatis*.[78] Several studies of clinically diagnosed pelvic inflammatory disease have found an association with *M. genitalium*.[78] Meta-analyses indicate that the organism also is associated with abnormal pregnancy outcomes including spontaneous abortion and preterm delivery.[78] The evidence suggesting that *M. genitalium* also is associated with infertility is less strong than for the above-mentioned complications, but this issue needs further study.[78] Despite evidence that *M. genitalium* infection is associated with morbid events in women, the case cannot yet be made for a national prevention program for this relatively common sexually transmitted infection. Clear evidence is lacking that a population-based *M. genitalium* screening and treatment program can prevent outcomes such as infertility, PID, HIV infection, or abnormal pregnancy outcomes and that doing this is not harmful and is cost-effective.[79]

LABORATORY DIAGNOSIS

Most clinical microbiology laboratories do not routinely test for the genital mycoplasmas. Optimal in vitro growth of both *M. hominis* and the ureaplasmas requires specialized liquid and solid media containing amino acids, nucleic acid precursors, and horse or fetal calf serum. Additionally, urea is required by the ureaplasmas and arginine is required by *M. hominis* as sources of energy.[7,80] Cultures for these organisms from clinical specimens can be done at selected reference laboratories. Only *M. hominis* is sometimes detectable using methods routinely employed in clinical laboratories, although sensitivity is poor. Growth

of *M. hominis* in the commonly used blood culture systems is inhibited by the anticoagulant polyanethole sulfonate. This can be neutralized by the addition of gelatin to a 1% concentration in the blood culture medium, but this is not done routinely.[81] Automated blood culture systems rely on production of gas, primarily carbon dioxide, for the detection of growing bacteria including *M. hominis* followed by Gram stain of a sample of the culture medium to preliminarily identify the organism. A clue to the presence of *M. hominis* is the fact that the Gram stain of the medium is negative. Acridine orange DNA staining will reveal the organism, but subculture on blood agar is required to confirm the diagnosis. *M. hominis* grows slowly on blood agar, producing tiny translucent nonhemolytic colonies after 2 to 7 days of incubation.[72] *M. hominis* will grow directly on blood agar from specimens obtained from abscesses and wound infections if not overgrown by other organisms and if incubated long enough. Nucleic acid amplification assays are becoming the standard for diagnosing infections caused by *M. hominis* and the ureaplasmas. These tests are increasingly becoming available from reference laboratories. Antibiotic susceptibility determination is dependent on cultured isolates and is rarely available outside of research laboratories.

In vitro growth of *M. genitalium* requires cocultivation with mammalian cell cultures. Vero cells are used most commonly, but these systems are available only in a few research laboratories. Moreover, the organism grows very slowly and may not be detectable for weeks. Even Vero cell cocultivation cultures are negative in many cases of documented infection.[82] A number of different nucleic acid amplification tests have been developed for *M. genitalium* detection.[82,83] In the United States, most of these tests are available only for research, although a growing number of reference laboratories are providing Clinical Laboratory Improvement Act–approved *M. genitalium* tests. In some cases these tests include detection of the common gene mutations associated with macrolide resistance.[83]

THERAPY

A number of in vitro antibiotic susceptibility studies have been done with *M. hominis* and the ureaplasmas, but there have been no comparative clinical trials to establish optimal therapeutic approaches. The opposite is true of *M. genitalium*. Because of the difficulty in culturing the organism, only a few in vitro studies have been done, whereas there have been several well-designed clinical treatment trials using nucleic acid amplification testing to assess clinical efficacy. The mycoplasmas do not have cell walls and therefore are not susceptible to β-lactam and glycopeptide antibiotics. In addition, mycoplasmas do not synthesize folic acid, and thus sulfonamides are not active against them. Of ureaplasma strains, 85% to 90% are susceptible in vitro to tetracyclines.[84] Tetracycline resistance is due to the *tetM* determinant, and it appears that this has become more common in recent years.[85] Men with NGU who fail treatment with a tetracycline class drug may be infected with one of these strains and should be re-treated with a 1-g dose of azithromycin in addition to metronidazole, which is recommended in this circumstance for the possibility of a *Trichomonas* infection.[88] Ureaplasmas are generally susceptible to the macrolide and quinolone classes of antibiotics, although resistance to the latter may occur. For patients with systemic ureaplasma infection, azithromycin should be the antibiotic of choice. A recent in vitro study of 250 ureaplasma clinical isolates in the United States showed that 95% of strains were susceptible to levofloxacin, whereas ciprofloxacin was less active,[86] so levofloxacin is an alternative drug for infections caused by these organisms. Use of both azithromycin and levofloxacin for patients with the life-threatening hyperammonemia syndrome is advisable at least initially.[56] *M. hominis* is uniformly resistant to the macrolide drugs but is generally susceptible to tetracyclines, although the *tetM* determinant also has been found occasionally in this organism. Levofloxacin also has good activity against *M. hominis*.[82,85]

Clinical studies of *M. genitalium* infections have shown that doxycycline has relatively little activity against the organism because microbiologic treatment failure rates are 55% to 70%.[87–89] Azithromycin is more active but results in microbiologic treatment failure rates of 13% to 32% in most studies,[87,88,90] although in one study it was 60%.[89] Thus it is now clear why *M. genitalium* is a major cause of recurrent and persistent NGU in men. Molecular studies have shown that organisms in patients failing azithromycin treatment have mutations in the V region of the 23S rRNA gene.[91] An azithromycin 1.5-g dosage given over 5 days only modestly improves the cure rate and does not decrease the rate of resistance emergence significantly.[92] Thus in the United States the 1-g single dose of azithromycin is still recommended for initial treatment of NGU.[77] Moxifloxacin 400 mg daily for 7 days is very effective in curing men with NGU who have clinically failed azithromycin treatment. For such patients this drug in combination with a single 2-g dose of metronidazole for possible *Trichomonas* is the most reasonable approach.[77] The problem is that moxifloxacin is relatively expensive and is not provided by public health departments, so some men will be unable to access treatment. Further complicating the cost issue is the fact that sexual partners should be treated similarly as their male partners. Quinolone resistance genes are increasingly being reported in many parts of the world, and so even this class of drug may be effective for only a limited time.[92] Investigations into new drugs for treating *M. genitalium* are underway, so there is hope that new options for *M. genitalium* infections will become available in the future.[92]

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The complete reference list is available online at Expert Consult.

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E Rickettsioses, Ehrlichioses, and Anaplasmoses

185 Introduction to Rickettsioses, Ehrlichioses, and Anaplasmoses

Didier Raoult

BACTERIOLOGY

Originally, all small gram-negative bacteria, associated (or not) with arthropods and strictly or facultatively intracellular, were considered Rickettsiaceae. The advent of 16S ribosomal RNA gene sequencing and phylogeny has deeply challenged this classification. The controversy has centered on how much difference between strains should constitute a subspecies.[1–5] Among the agreed-upon changes, *Orientia* was created from an independent branch of its phylum. The *Ehrlichia* group has been reclassified[6] into four genera, with *Ehrlichia* and *Anaplasma* being associated with ticks, *Neorickettsia* with helminths, and *Wolbachia* with both arthropods and helminths. This chapter is limited to the Rickettsiales. All are intracellular Alphaproteobacteria associated with eukaryotic hosts (arthropods or helminths). Based on antigenic and genetic data, pathogenic rickettsiae are traditionally divided into three groups—the spotted fever group, the typhus group, and the scrub typhus group (Table 185.1). The spotted fever group accounts for most tick-borne rickettsioses. The typhus group comprises *Rickettsia prowazekii,* the agent of epidemic typhus that is transmitted by the human body louse, and *Rickettsia typhi,* causing murine typhus, which is transmitted by rat and cat fleas. The scrub typhus group comprises *Orientia tsutsugamushi* only, which is transmitted by chiggers (Trombiculidae).

HISTORY AND EMERGING DISEASES

The development of polymerase chain reaction (PCR) and DNA sequencing, as well as the use of cell culture assays, has allowed the description of many new rickettsioses and ehrlichioses during the past 30 years (Table 185.2).[7] Seven ehrlichioses and 14 rickettsioses have been described since 1980. Three major conditions determined the description and separation of these species. Some were discovered after clinical description in countries where spotted fever had been unknown (*Rickettsia japonica* in Japan, *Rickettsia honei* on Flinder's Island, and Astrakhan fever in Russia). Some were recognized by bacterial identification based on culture and PCR in places where the new pathogen was confounded with another known rickettsial pathogen (*Rickettsia africae* with *Rickettsia conorii, Rickettsia heilongjiangensis* with *Rickettsia sibirica, R. sibirica* subsp. *mongolitimonae* and *Rickettsia aeschlimannii* with *R. conorii, Rickettsia felis* with *R. typhi,* and *Anaplasma phagocytophilum* and *Ehrlichia ewingii* with *Ehrlichia chaffeensis*). Some were identified through association by physicians and microbiologists when an atypical unknown disease (*E. chaffeensis, Rickettsia slovaca, Rickettsia raoultii,* and *Rickettsia helvetica*) was being explored.[7]

In addition to the description of new species, old rickettsioses, such as epidemic typhus or scrub typhus, reemerged apparently because of lack of social control or ecologic changes. These diseases, which were the more deadly rickettsioses for the human species, remain a threat. Studies in Asia identified rickettsioses such as murine typhus and scrub typhus among the most common causes of fever.[8]

Wolbachia, an essential symbiont of human filarial worms, has been shown to play a major role in the pathology and clinical manifestations of filariasis. It introduces a completely new concept in infectious diseases.[9] It appears that inflammatory reactions of patients during the disease and during the treatment of filariasis are caused by the release of lipopolysaccharide-like molecules from the symbiotic *Wolbachia.*

Many rickettsiae were found in their vectors long before a particular disease could be associated with them. However, the denomination *nonpathogenic rickettsiae,* which is used for bacteria found only in ticks, is misleading.[7] Among famous pathogens first classified as nonpathogenic rickettsiae are *Legionella pneumophila; Coxiella burnetii,* the agent of Q fever; *Rickettsia parkeri*[10]; and *R. africae.* Several rickettsiae have been found in ticks throughout the world, the pathogenic potential of which remains unknown. A rarely recognized febrile disease caused by *Neorickettsia sennetsu,* acquired by eating raw infected fish, has been described in Laos and may be present throughout Southeast Asia.[11]

PATHOPHYSIOLOGY

Rickettsia, Ehrlichia, and *Anaplasma* species are host-associated pathogens. These pathogens depend on their environment for the supply of many nutriments. *Rickettsia* species escape rapidly from the phagosome to multiply within the cytoplasm. Spotted fever rickettsiae, which are motile in the cytoplasm through actin polymerization,[12] invade neighboring cells. *Rickettsia prowazekii* is devoid of such motility and is released only by destruction of the host cell. Phospholipase D may play a key role in cellular invasion.[13]

The target cell of *Rickettsia* is the vascular endothelial cell, except for *Rickettsia akari* and *O. tsutsugamushi,* which multiply in monocytic cells. *Ehrlichia chaffeensis* and *Ehrlichia muris* subsp. *eauclairensis* multiply in monocytic cells; *A. phagocytophilum* and *E. ewingii* multiply in polymorphonuclear cells. Some animal ehrlichiae multiply in blood platelets.

GENETICS

The complete genome sequences of most *Rickettsia, Orientia, Ehrlichia, Anaplasma, Neorickettsia,* and *Wolbachia* species have been published. These bacteria have small genomes (0.7–2.1 Mb) with or without plasmids and are undergoing genomic reduction through progressive gene degradation and loss.[14] This phenomenon has been suggested to be associated with increasing virulence.[15]

EPIDEMIOLOGY

The geographic and temporal distribution of rickettsioses and ehrlichioses is mainly determined by their vectors (see Table 185.1). Louse-transmitted diseases occur worldwide, and the human louse is distributed worldwide. Lice often parasitize poor people, preferentially in cold places and during wars. Common fleas, such as cat and dog fleas (*Ctenocephalides felis*

TABLE 185.1 Rickettsioses, Ehrlichioses, and Anaplasmoses of Humans and Their Vectors

	TICK-BORNE	FLEA-BORNE	LOUSE-BORNE	MITE-BORNE	OTHER
Rickettsiae					
Spotted fever group	*R. rickettsii* *R. conorii* *R. japonica* *R. sibirica* *R. australis* *R. slovaca* *R. africae* *R. honei* *R. aeschlimanii* *R. helvetica* *R. parkeri* *R. heilongjiangensis* *R. raoultii* *R. massiliae* *R. monacensis* *R. philipii* strain 364D	*R. felis*		*R. akari*	
Typhus group		*R. typhi*	*R. prowazekii*		
Scrub typhus group *(Orientia)*				*O. tsutsugamushi*	
Anaplasma	*A. phagocytophilum* *A. capra*				
Ehrlichia	*E. chaffeensis* *E. ewingii* *E. muris* subsp. *eauclairensis*				
Candidatus Neoehrlichia	*Candidatus* N. mikurensis				
Neorickettsia sennetsu					Raw fish
Wolbachia					Helminths

TABLE 185.2 Historical Data on Diseases Caused by *Rickettsia* Species (First and Senior Authors)

YEAR	DISCOVERY	AUTHORS
1760	Description of exanthematic typhus	Boissier de Sauvage
1879	First report of scrub typhus	Nagayo
1899	Description of Rocky Mountain spotted fever	Maxcy
1906	Isolation of *Rickettsia rickettsii*	Ricketts
1909	Role of body lice in typhus	Nicolle [Nobel Prize]
1909	Description of Mediterranean spotted fever	Conor et al.
1910	Serology test based on *Proteus*	Wilson
1911	Isolation of *Rickettsia prowazekii*	Nicolle
1914	Tick role in Mediterranean spotted fever	Wilson
1916	Weil-Felix test	Weil and Felix
1921	Identification of *Rickettsia typhi*	Mooser
1925	Description of the tâche noire in Mediterranean spotted fever	Pieri
1930	First isolation of *Orientia tsutsugamushi* (*Rickettsia orientalis*)	Nagayo
1930	Role of chiggers in scrub typhus	Kawarimura
1930	Role of fleas in murine typhus	Dyer
1932	Isolation of *Rickettsia conorii*	Brumpt
1935	Description of Siberian tick typhus	Shmatikov et al.
1938	Isolation of *Rickettsia sibirica*	Krontovuka et al.
1940	*Rickettsia phagocytophila*	Gordon
1946	Description of rickettsialpox	Huebner
1946	Isolation of *Rickettsia akari*	Huebner
1946	Isolation of *Rickettsia australis*	Plotz and Smadel
1946	Queensland tick typhus	Plotz and Smadel
1956	*Ehrlichia sennetsu*	Kobayashi
1968	Isolation of *Rickettsia slovaca*	Brezina et al.
1974	Culture of *R. conorii*	Goldwasser

Continued

TABLE 185.2 Historical Data on Diseases Caused by *Rickettsia* Species (First and Senior Authors)—cont'd

YEAR	DISCOVERY	AUTHORS
1979	Isolation of *Rickettsia helvetica*	Burgdorfer and Peter
1981	*Ehrlichia chaffeensis*	Anderson
1984	Japanese spotted fever	Mahara
1985	Culture of *Rickettsia heilongjiangensis*	Udida and Walker
1987	First case of human ehrlichiosis in United States	Maeda and McDade
1989	Culture of *Rickettsia japonica*	Lov
1990	First human cases of granulocytic ehrlichiosis	Bakken
1990	Isolation of *Rickettsia africae*	Kelly
1991	Flinder's Island spotted fever	Stewart
1992	Molecular identification of *Ehrlichia ewingii*	Anderson
1992	First case of infection by *R. africae*	Kelly and Raoult
1992	Culture and identification of *R. conorii*	Tarasevitch and Raoult
1992	Culture of *Rickettsia honei*	Baird et al.
1993	Culture and identification of *R. sibirica* subsp. *mongolitimonae*	Yu and Raoult
1994	First case of flea-borne spotted fever	Schriefer and Azad
1996	Infection by *R. sibirica* subsp. *mongolitimonae*	Raoult et al.
1997	First infection by *R. slovaca*	Raoult et al.
1997	Culture of *Rickettsia aeschlimanii*	Beati and Raoult
1999	Description of Astrakhan fever	Tarasevitch and Raoult
1999	First human cases of infection with *E. ewingii*	Buller
2000	Role of *Wolbachia* in filariasis	Taylor
2000	First case of acute infection by *R. helvetica*	Fournier and Raoult
2000	Culture of *Rickettsia felis*	Raoult et al.
2002	First case of infection by *R. aeschlimanii*	Raoult et al.
2004	First case of infection by *Rickettsia parkeri*	Paddock et al.
2006	Description of infection by *R. heilongjiangensis* (Far Eastern spotted fever)	Mediannikov et al.[35]
2007	First case of *Rickettsia monacensis* infection	Jado et al.[36]
2008	First case of *Rickettsia massiliae* infection	Parola et al.[37]
2008	First case of infection with *Rickettsia raoultii*	Parola et al.[38]
2009	First infection with *Ehrlichia muris* subsp. *eauclairensis*	Pritt et al.[39]
2010	First case of infection with *Rickettsia philipii* strain 364D	Shapiro et al.[40]
2010	First infection with *Candidatus* Neoehrlichia mikurensis	Welinder-Olsson et al.[41]
2015	First case of *Anaplasma capra* infection	Li et al.[42]

Data from Raoult D, Roux V. Rickettsioses as paradigms of new or emerging infectious diseases. Clin Microbiol Rev. *1997;10(4):694–719; and Shapiro MR, Fritz CL, Tait K, et al. Rickettsia 364D: a newly recognized cause of eschar-associated illness in California.* Clin Infect Dis. *2010;50:541–548.*

and *Ctenocephalides canis,* respectively) and rat fleas (*Xenopsylla cheopis* and *Pulex irritans*) are also present worldwide, as are their transmitted diseases—murine typhus *(R. typhi)* and flea-borne spotted fever (caused by *R. felis*). Lice, fleas, or exposure to ectoparasite excreta may account for the continued appearance of clusters of flying squirrel *(Glaucomys volans)*–associated sylvatic typhus.[16] Tick species are highly dependent on their environment; very few are found worldwide, with the exception of *Rhipicephalus sanguineus*—the brown dog tick, vector of *R. conorii* in the Old World and *R. rickettsii* in the United States and of *Rickettsia massiliae* and *Ehrlichia canis* worldwide. Tick-transmitted diseases are usually restricted to areas of the world where they can be transmitted by the local fauna. Among rickettsioses and ehrlichioses transmitted by ticks, only *A. phagocytophilum* is currently found worldwide.

Tick behavior may determine the targeted human population and the seasonality. It may also influence the clinical presentation. For example, *Amblyomma* ticks are aggressive hunting ticks. They frequently attack in groups, a behavior that explains grouped cases and several inoculation eschars per patient. *Dermacentor* species wait for their host in an ambush strategy, falling onto a hairy host from a height of 1 m.[17] Therefore they bite frequently in the hair, and children are a primary target. As a consequence, *Dermacentor*-transmitted rickettsioses, such as Rocky Mountain spotted fever (RMSF), and infections by *R. slovaca* more frequently involve children than do other rickettsial diseases.[18] Wide variations in the annual incidence of tick-transmitted diseases, such as RMSF and Mediterranean spotted fever, have been observed. The incidence from 2008 to 2012 in the United States has been reported and suggests significant differences in the risk of death among different ethnic groups (relative risk, 5.2 for American Indians/Alaska Natives compared with white race and 5.7 for Asians/Pacific Islanders) and children (case-fatality rate, 1.6%).[19]

Finally, rickettsialpox, caused by *R. akari* and transmitted to humans by *Liponyssoides sanguineus* (the mouse mite), is diagnosed in the United States, Europe, Ukraine, Korea, and South Africa (see Chapter 187).

TABLE 185.3 Clinical Findings and Target Cells for Rickettsioses, Ehrlichioses, and Anaplasmoses

DISEASE	RASH	RASH SPECIFICITY	ESCHAR	ENLARGED LYMPH NODES
Rocky Mountain spotted fever *(Rickettsia rickettsii)*	90%	45% purpuric	No	No
Mediterranean spotted fever *(Rickettsia conorii)*	97%	10% purpuric	72%	Rare
Siberian tick typhus *(Rickettsia sibirica* subsp. *sibirica)*	100%	Macular	77%	Yes
Queensland tick typhus *(Rickettsia australis)*	100%	Vesicular	65%	Yes
Israeli spotted fever *(R. conorii* subsp. *israelensis)*	100%	Macular	Rare	No
Flinder's Island spotted fever *(Rickettsia honei)*	85%	8% purpuric	28%	Yes
Astrakhan fever *(R. conorii* subsp. *caspiensis)*	100%	Macular	23%	No
African tick-bite fever *(Rickettsia africae)*	30%	Vesicular	100% multiple	Yes
Japanese spotted fever *(Rickettsia japonica)*	100%	Macular	90%	No
Lymphangitis-associated rickettsiosis *(R. sibirica* subsp. *mongolitimonae)*	Yes	Macular	Yes (could be multiple)	Yes
Tick-borne lymphadenopathy *(Rickettsia slovaca, Rickettsia raoultii)*	No	Macular	Yes	Yes
Rickettsia helvetica	No	No	No	No
Far Eastern spotted fever *(Rickettsia heilongjiangensis)*	Yes	Macular	Yes	Yes
Rickettsia aeschlimanii	Yes	Macular	Yes	No
Rickettsia parkeri	Yes	Macular	No	Yes
Pacific coast tick fever (*Rickettsia philipii* strain 364D)	Yes	Yes	Yes	No
Rickettsia monacensis	50%	Macular	30%	No
Flea-borne spotted fever *(Rickettsia felis)*	Yes	Macular	Yes	?
Rickettsialpox *(Rickettsia akari)*	100%	Vesicular	100%	Yes
Epidemic typhus *(Rickettsia prowazekii)*	50%	Macular	No	No
Murine typhus *(Rickettsia typhus)*	50%	Macular	No	No
Scrub typhus *(Orientia tsutsugamushi)*	30%	Macular	50% (could be multiple)	Yes
Ehrlichiosis *(Ehrlichia chaffeensis)*	36%	Macular	No	25%
Anaplasmosis *(Anaplasma phagocytophilum)*	<10%	Macular	No	No
Infection by *Anaplasma capra*	36%	Macular	Yes	29%
Infection by *Ehrlichia ewingii*	No	No	No	No
Infection by *Ehrlichia muris* subsp. *eauclairensis*	No	No	No	No
Neorickettsia sennetsu	No	No	No	Yes
Infection by *Candidatus* Neoehrlichia mikurensis	No	No	No	No
Filariasis *(Wolbachia)*	No	No	No	No

CLINICAL FINDINGS

Fever, rash, and headache were considered for years the diagnostic clue for rickettsial diseases. Indeed, this remains a major triad, but spotless RMSF has been reported, and many of the newly described rickettsial diseases have no rash.[20] Major findings in rickettsioses and ehrlichioses include fever in a patient with exposure to a potential vector that may be associated with rash, inoculation eschar, and/or localized lymphadenopathy (Table 185.3). Biologically, neutropenia, thrombocytopenia, and moderate increases in transaminases are common. This may prompt a diagnostic test and eventually treatment with doxycycline.

The severity of these diseases varies with the causative agent and the host. Some *Rickettsia* species, such as *R. rickettsii* and *R. prowazekii,* and *O. tsutsugamushi* are often more severe. Some variations in the same disease are seen between regions for scrub typhus and RMSF. Currently, the RMSF fatality rate reported by the Centers for Disease Control and Prevention is very low, possibly suggesting misdiagnosis.[5] Host factors also play a role in severity. Old age, alcoholism, and deficit in glucose-6-phosphate dehydrogenase have been associated with more severe disease.[21] In such patients, a multiple-organ dysfunction syndrome that usually leads to a fatal outcome can be observed. Purpuric rash and gangrene of the extremities can also be observed in severe cases. The year-round occurrence in Arizona in the United States, in combination with a lack of specificity of clinical and laboratory abnormalities, has highlighted the need for broad awareness by treating physicians in that context, with a low threshold for early treatment with doxycycline.[22,23]

DIAGNOSIS

Culture remains extremely difficult for these organisms and is usually restricted to laboratories equipped for cell culture, and diagnosis mainly relies on serology and PCR. Swabbing vesicular or escharotic lesions has been proven very efficient for molecular detection. The reference technique for serology is immunofluorescence. Many cross-reactions among species are observed, and precise determination of the infecting agent may be difficult. Testing of several antigens on the same slide, to compare reactivity, may help in discriminating among cross-reacting agents. Western blotting may be more specific in early sera. Cross-absorption, coupled with immunofluorescence or Western blot, may help to resolve these problems, but it is technically demanding and expensive.[7]

PCR has been effectively used for the diagnosis of ehrlichiosis and anaplasmosis from blood samples. Observation of morulae in monocytes or neutrophils in blood smears has also been helpful in the diagnosis of those infections. With rickettsiosis, biopsies of skin lesions are preferable

because biopsies can also be used for immunohistochemistry.[24,25] PCR from early sera and swabs of eschars may also be of value for patients with rickettsial disease.[26]

TREATMENT

The most useful drug in children and adults for the treatment of rickettsiosis, ehrlichiosis, and anaplasmosis is doxycycline. It can be prescribed in short courses or even single doses (for typhus, scrub typhus, and Mediterranean spotted fever). Dental problems should not be a problem for children if fewer than three courses of several days of doxycycline are prescribed during childhood. Chloramphenicol should not be prescribed as first-line therapy because it is not active for ehrlichiosis[27] and it is less active than doxycycline for RMSF. However, it remains widely used in Asia, where rickettsiosis and typhoid are common. Quinolones, which have been disappointingly inactive in cases of typhus and scrub typhus despite good in vitro efficacy (see Chapters 189 and 191), are not effective for ehrlichiosis.

REMAINING QUESTIONS AND PERSPECTIVES

In the United States in recent years, increased reporting of cases of RMSF with a low fatality rate is evidenced by the fact that several rickettsial diseases prevalent in the United States were circulating under this name,[5] including those associated with the serologically indistinguishable *R. parkeri,*[10] *Rickettsia amblyommatis*, *R. massiliae*, and *Rickettsia philipii* strain 364D.[28,29] Changes in the range of the tick host are also consistent with a broader distribution of less pathogenic species and stability of *R. rickettsii* incidence.[30]

The high incidence of *R. felis* in febrile patients in sub-Saharan Africa,[31,32] paralleling that of malaria, has questioned the possibility that this rickettsia might be transmitted by mosquitoes.[33] DNA of *R. felis* has been detected in *Aedes* and *Anopheles* mosquitoes, the vectors of malaria,[31,34] and it was recently demonstrated that *Anopheles gambiae* has the potential to be a vector of *R. felis* infection.

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186 *Rickettsia rickettsii* and Other Spotted Fever Group Rickettsiae (Rocky Mountain Spotted Fever and Other Spotted Fevers)

Lucas S. Blanton and David H. Walker

SHORT VIEW SUMMARY

Etiology
- Spotted fever group (SFG) rickettsiae are small, gram-negative, obligately intracellular bacteria that cause tick-, mite-, and flea-borne human infections.
- In humans, rickettsiae infect endothelial cells and exert their pathophysiologic effects through endothelial injury, with a resultant increase in vascular permeability.

Epidemiology
- *Rickettsia rickettsii* is the agent that causes Rocky Mountain spotted fever (RMSF). *Dermacentor variabilis, Dermacentor andersoni,* and *Rhipicephalus sanguineus* ticks transmit the infection in the eastern two-thirds, western, and southwestern United States, respectively. RMSF also occurs in Central and South America.
- In the United States, RMSF is most prevalent in the South Atlantic and South Central regions. Infections usually occur during the late spring and summer, when ticks are most active.
- Other tick-borne SFG rickettsiae with a broad range of distribution include *Rickettsia conorii* (Europe, Africa, and South Asia), *Rickettsia sibirica* (eastern Russia and Asia), *Rickettsia africae* (sub-Saharan Africa and West Indies), *Rickettsia parkeri* (North and South America), and *Rickettsia slovaca* (Europe).

Clinical Manifestations
- RMSF typically manifests with fever early in the course. Other manifestations include headache, myalgias, nausea, vomiting, and abdominal pain.
- Rash is common but may not occur in the first few days of illness. Rash typically starts on the wrists and ankles before spreading proximally. Involvement of the palms and soles occurs in 36% to 82% of cases but is often a late sign.
- Skin necrosis, gangrenous digits, neurologic complications, azotemia, pulmonary edema, and acute respiratory distress syndrome are manifestations of severe infection.
- The case-fatality rate of RMSF is 23% without appropriate antimicrobial treatment and up to 4% despite appropriate antimicrobials.
- Other SFG rickettsioses manifest with a wide spectrum of disease severity but are generally less severe than RMSF and often have an associated eschar at the tick bite site.

Diagnosis
- The indirect immunofluorescence assay is the serologic method of choice. A fourfold rise in immunoglobulin G (IgG) titer from acute illness to convalescence retrospectively confirms the diagnosis.
- Immunohistochemical detection of SFG rickettsiae in skin biopsy specimens can establish the diagnosis during acute illness.
- Polymerase chain reaction amplification of rickettsial nucleic acids in blood, skin or eschar biopsy specimen, or eschar swab is a useful tool for diagnosis and species identification.
- Treatment should not be withheld pending laboratory confirmation.

Treatment and Prevention
- Doxycycline, 100 mg twice daily for 7 to 10 days, is the treatment of choice for RMSF and other SFG rickettsioses.
- Where available, chloramphenicol is an alternative, but its use is associated with a higher case-fatality rate in those with RMSF.
- Azithromycin and clarithromycin are alternatives for less severe SFG rickettsioses.
- Prevention is aimed toward the avoidance of contact with vectors through repellents and protective clothing.

The spotted fevers comprise a large group of tick-, mite-, and flea-borne zoonotic infections that are caused by closely related rickettsiae. These include Rocky Mountain spotted fever (RMSF), boutonneuse fever, African tick bite fever, North Asian tick typhus, lymphangitis-associated rickettsiosis, Queensland tick typhus, Flinders Island spotted fever, Japanese spotted fever, tick-borne lymphadenopathy, Far Eastern spotted fever, flea-borne spotted fever, and rickettsialpox. Rickettsiae are emerging or reemerging pathogens in many parts of the world.[1–29] Associated diseases have a broad spectrum of severity; the most virulent, RMSF (historically in Montana), exhibited a case-fatality rate of 66%.[30] Even young and previously healthy people may die of RMSF. In recent years, the wide distribution and potential severity of the other spotted fevers have been recognized, especially in Europe, Africa, Australia, Asia, and Japan. Early diagnosis remains deceptively difficult.

ROCKY MOUNTAIN SPOTTED FEVER

The Pathogen

RMSF was first described in Idaho in the late 19th century.[31] Ricketts established the infectious nature of the illness and demonstrated the role of ticks as the vector in western Montana in 1906.[31,32] Wolbach, in 1919, clearly identified the causative rickettsiae in endothelial cells.[33,34] The causative agent was designated *Rickettsia rickettsii.* Geographic origin, clinicoepidemiologic observations, and serotyping were the historical basis for species designation of subsequent rickettsial isolates. Phylogenetic analyses have more accurately revealed the evolutionary relationships among the rapidly increasing number of clinical and environmental isolates. It is likely that virulence was a relatively late mechanism of evolutionary survival for *Rickettsia*, which arose as vertically transmitted symbiotes of insects, arachnids, leeches, and amebas,[35] with gain of virulence associated with genome reduction.[36,37] Contemporary phylogenomics based on whole-genome sequences has defined the ancestral, typhus, transitional, and spotted fever groups.[38] *Rickettsia australis, Rickettsia felis*, and *Rickettsia akari* are members of the transitional group. Criteria for species designation of *Rickettsia* based on historically named species, an approach considered inappropriate by some respected taxonomists,[39] have been proposed to be determined by the divergence of 16S ribosomal RNA (rRNA), citrate synthase, outer membrane proteins A and B, and Sca4 of the most closely related, previously named species.[40] These criteria have resulted in proposals for species designation of rickettsial strains that are much more closely

related than other bacterial species. For example, a proposed criterion of 0.2% divergence of the 16S rRNA gene has created many more species names than the usual 1% to 1.3% divergence of other bacterial taxa.[41,42] An attractive approach, concatenated phylogeny based on multilocus sequence typing using eight loci of *Rickettsia* genes has revealed that species designation of *Rickettsia sibirica, Rickettsia africae*, and *Rickettsia parkeri* should be subject to further discussion.[43] The spotted fever group (SFG) rickettsial strains that have been strongly or weakly associated with human infections (*R. rickettsii, R. conorii, R. africae, R. sibirica* [including the *mongolitimonae* strain], *R. honei, R. japonica, R. slovaca, R. parkeri, R. massiliae, R. monacensis, R. aeschlimannii, R. heilongjiangensis, R. amblyommatis*, and *R. helvetica*) definitely merit identification that is useful for clinical and epidemiologic purposes. It is controversial whether they and a rapidly growing number of candidates merit separate designations as different at the species level. An excellent guide for diagnosis and management of spotted fever rickettsioses has been published by the Centers for Disease Control and Prevention (CDC).[44]

Virulence Factors

SFG rickettsiae are obligately intracellular bacteria that reside in the cytosol and less often in the nuclei of host cells. These rickettsiae are small, measuring approximately 0.3 by 1.0 µm. They have one of the smallest bacterial genomes, ranging between 1.1 and 1.6 Mb. The cell wall, which has the ultrastructural appearance of a gram-negative bacterium, contains peptidoglycan and lipopolysaccharide (LPS). Rickettsiae are difficult to stain with ordinary bacterial stains but are conveniently stained with the Gimenez method or with acridine orange. They have not been cultivated in cell-free medium. Growth requires living host cells, such as the yolk sac of embryonated eggs, experimental animals, or cell culture (e.g., Vero, HEL, and L-929 cells). Rickettsiae have undergone remarkable genome reduction with exploitation of their cytosolic environment by being highly adapted for intracellular survival with effective transport systems for adenosine triphosphate, amino acids, and phosphorylated sugars, in addition to their own independent metabolic enzymes. Rickettsiae exhibit a large family of surface proteins, (autotransporters) that are a major source of antigenic differences.[45] Among these, OmpA (190 kDa) and OmpB (135 kDa) contain conformational epitopes that are targets of humoral immunity and were the antigenic basis for serotyping; other antigens are also shared among the SFG.[46,47] The LPS of SFG rickettsiae contains highly immunogenic antigens that are strongly cross-reactive among all members of the group. However, antibodies to LPS do not provide protection against infection.[48]

Epidemiology

The role of a tick bite in the transmission of RMSF was demonstrated by McCalla and Brereton and reported in 1908[33]; a tick obtained from a patient with RMSF transmitted the disease to two volunteers. The seasonal distribution of RMSF parallels tick activity. The tick is both the vector and the main reservoir.[49] *Dermacentor variabilis,* the American dog tick, is the prevalent vector in the eastern two-thirds of the United States and the Far West; *Dermacentor andersoni,* the Rocky Mountain wood tick, in the western states; *Rhipicephalus sanguineus,* in Mexico and Arizona[50]; and *Amblyomma cajennense, Amblyomma sculptum, Amblyomma mixtum, Amblyomma patinoi, Amblyomma tonelliae,* and *Amblyomma aureolatum* in Central and South America.[51-55] *Amblyomma tenellum* is a potential vector for *R. rickettsii* in Mexico and is likely involved in its maintenance in nature.[56] Causes for the variation in infection rates among populations of ticks are not clear, although in *Dermacentor* only a small portion of ticks (generally 4%) carry any rickettsiae, and fewer than 1 in 1000 ticks carry virulent *R. rickettsii.* One limiting factor is the deleterious effect that *R. rickettsii* has on ticks; another is the inhibition of establishment of transovarial transmission of *R. rickettsii* by the presence of another *Rickettsia* species in the tick.[57–60] Humidity, climatic variations, human activities altering the vegetation and fauna, and the use of insecticides have been suspected to play a role in the fluctuation of tick populations and the prevalence of human rickettsiosis.

R. rickettsii is transmitted transstadially (stage to stage) and transovarially in ticks, thus maintaining the agent in nature. Horizontal transmission through vertebrate hosts would also appear to occur to a small degree and to be a necessary factor for the maintenance of *R. rickettsii* in nature.[49] In most mammals, rickettsemia is of very short duration and low titer, allowing infection of only a small proportion of feeding ticks. Of the three tick stages—larva, nymph, and adult—only adult *Dermacentor* ticks feed on humans. The prevalence of pathogenic rickettsiae in various populations of ticks, their efficiency at transstadial and transovarial transmission, and their ability to infect uninfected ticks while cofeeding on the same host are variable.[61–63] Many rickettsiae of unknown pathogenicity have been isolated and characterized in the United States, including *Rickettsia bellii, Rickettsia montanensis, Rickettsia rhipicephali*, and *Rickettsia peacockii.*[58,64]

The tick transmits the disease to humans during a prolonged period of feeding that may last for 1 to 2 weeks. The blood meal and host temperature associated with tick feeding modulate the expression of genes that may upregulate virulence factors of rickettsiae.[65] Furthermore, salivary products of the tick may enhance establishment of rickettsial infection.[66] The bite is painless and frequently goes unnoticed. After the attached tick has fed for 6 to 10 hours, rickettsiae begin to be injected from the salivary glands. An even longer period may be required for reactivation of rickettsial virulence in unfed ticks. Humans can also be infected by exposure to infective tick hemolymph during the removal of ticks from persons or domestic animals, especially when the tick is crushed between the fingers.

The mean infectious dose of *R. rickettsii* is 23 organisms, but as few as one bacillus can cause infection.[67] Laboratory-acquired infection[68] transmitted by infectious aerosols or parenteral inoculation of *R. rickettsii* may be prevented with careful technique and the use of biohazard containment hoods, masks, and gloves.[69]

From the 1870s until 1931, RMSF was recognized as existing only in the western United States. At present, the prevalence of the disease is higher in the South Atlantic states and in the South Central regions than in the Rocky Mountain states (Fig. 186.1).[70–73] Local prevalence in highly endemic areas, such as North Carolina, has been as great as 14.59 per 100,000.[71] The incidence reported among American Indians is as high as 16.8 per 100,000 according to passive national surveillance data and 94.6 per 100,000 with use of International Classification of Diseases, Ninth Revision (ICD-9) codes from Indian Health Service records.[74,75] Tribal lands in Arizona have been found to be highly endemic areas for RMSF. These populations are affected economically through medical costs, loss of productivity, and loss of life related to the disease.[76] Indeed, the 10% case-fatality rate in Arizona is currently higher than in other areas of the United States.[77] The report of a focus in the South Bronx emphasizes that the ecologic conditions that permit the establishment of RMSF are widely distributed.[78] Most cases are diagnosed during late spring and summer. However, especially in the southern states, a few cases occur during the winter.

In the southern states, incidence is highest in children, adults 60 to 69 years old, and patients who are known to be exposed more often to ticks than are matched controls.[73,79] In the western mountainous states, because of transmission by the wood tick *D. andersoni,* a higher proportion of men contract the disease because of occupational exposure. On tribal lands of Arizona, incidence is highest in children younger than 10 years, and cases are associated with exposure to ticks and contact with dogs.[80] The case-fatality rates reported from 1999 to 2012 are highest for children younger than 10 years old and those older than 70.[77,81]

Consistent with unexplained 30- to 40-year cycles of waxing and waning incidence of RMSF, the number of cases reported to the CDC has skyrocketed (13,561 cases from 2008 to 2012); Fig. 186.2).[77] Problematic issues are the low proportion of laboratory-confirmed cases (15%, with only 5% with specific evidence for *R. rickettsii*); a significant population of healthy persons with serum antibodies reactive with *R. rickettsii,* which shares antigens with other SFG rickettsiae; discovery that *R. parkeri* transmitted by *Amblyomma maculatum* causes human infections; evidence that highly prevalent *R. amblyommatis* carried by *Amblyomma americanum* ticks causes mild or subclinical infections; and a reported RMSF case-fatality rate of 0.4% compared with 23% in the preantibiotic era and 5% in recent years.[82–88,89,90,91–93] It is likely that many of these patients had human monocytotropic ehrlichiosis and were misdiagnosed based on the presence of antibodies stimulated at

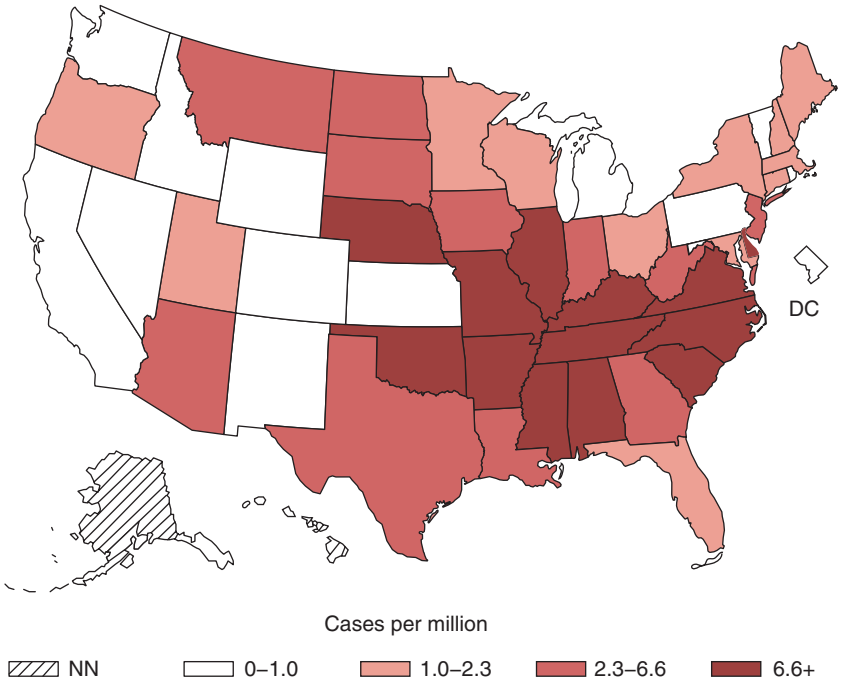

FIG. 186.1 US incidence of Rocky Mountain spotted fever, 2014. *NN,* Not notifiable.

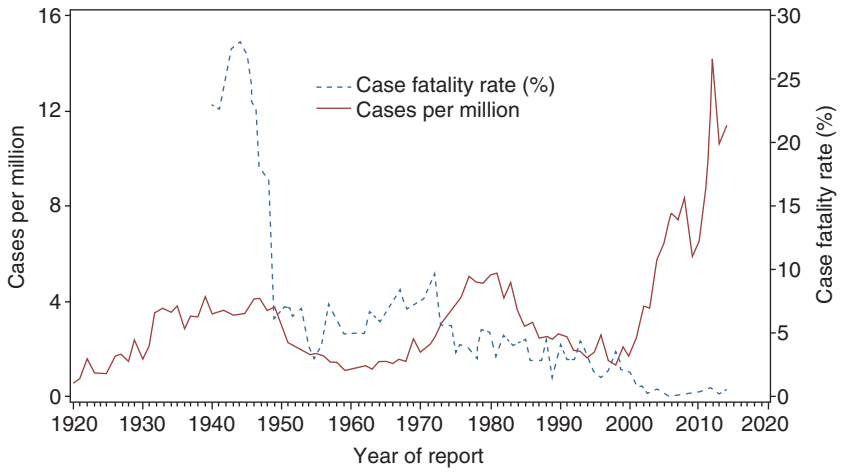

FIG. 186.2 Reported Rocky Mountain spotted fever (RMSF) incidence and case-fatality rate in the United States, 1920 to 2014.

a previous time by *R. amblyommatis*. Some of them likely were infected with *R. parkeri*.[2]

Phylogenetic analysis of isolates of *R. rickettsii* has demonstrated that the organism exists in several clades, likely originated in North America, and subsequently drifted into Central and South America,[94,95] where it is currently emerging in Argentina and reemerging in Brazil, Colombia, Panama, Costa Rica, and Mexico, largely unrecognized, and misdiagnosed as dengue or other febrile exanthems.[10,11,15,16] *R. rickettsii* infections appear to be more severe in these regions, with case-fatality rates of up to 40% in Brazil and Mexico.[96,97,98] The alarming situation in northern Mexico has prompted the Mexican Ministry of Health to declare an epidemiologic emergency.[98,99] Cases originating from northern Mexico have spilled over into the United States with fatal outcomes due to delay in early treatment.[100] Cases have also occurred with community and familial clustering likely associated with large populations of *R. sanguineus*.[101,102]

Pathogenesis

Rickettsiae introduced into the skin apparently spread via lymphatics and small blood vessels to the systemic and pulmonary circulation where, by means of OmpA, OmpB, Sca1, Sca2, and fibroblast growth factor receptor-1, they attach to and induce phagocytosis by their target cells—the vascular endothelium—to establish numerous disseminated foci of infection.[103–113,114] Comparison of the genomes of highly passaged isolates of *R. rickettsii* originating from the western and eastern United States, three virulent and one attenuated, has revealed numerous deletions and amino-acid substitutions between western and eastern isolates.[115,116] A notable mutation in the avirulent stain was disruption of the *ompA* gene leading to absence of its expression. Targeted knockout of *ompA* in the virulent Sheila Smith strain failed to attenuate disease in an animal model, indicating alternative mechanisms contributing to pathogenesis.[117] Other mutations in the eastern isolates include four amino-acid substitutions in OmpB,[116] which in the case of the attenuated Iowa strain does not undergo normal posttranslational processing.[118] After entry, the rickettsiae escape rapidly from the phagosome into the cytosol in association with expression of membranolytic phospholipase D and hemolysin C,[119] and less frequently invade the nucleus. Rickettsiae proliferate intracellularly by means of binary fission. The movement of spotted fever rickettsiae within the cytoplasm, into projections invaginating into the nucleus and into cell projections from which they are released

extracellularly or spread into the adjacent cell, is caused in part by propulsion by the host cell's actin filaments.[120] SFG rickettsial protein Sca2 is associated with activation of Arp2/3 and polymerization of actin at one pole of the rickettsiae, and RickA also plays a role during the early stage of infection in actin-based mobility.[121–125,126] Evolutionary and experimental disruption of actin-based motility seems to attenuate SFG rickettsial virulence.[127,128]

The consequence of cell-to-cell spread in the body is a focal network of hundreds of contiguous infected endothelial cells corresponding to the lesions (e.g., maculopapular rash). The presence of greater quantities of rickettsiae in damaged cells supports the concept of direct cell injury.[121] No convincing data support endotoxin or exotoxin as a pathogenic mechanism. Rickettsial injury to the host cell is caused, at least in part, by free radical–induced damage to host cell membranes and rickettsial phospholipase and protease activities.[129–134] More pathogenic rickettsiae are associated with increased endothelial injury and cell death.[135] The major pathophysiologic effect of endothelial cell injury is increased vascular permeability, which in turn results in edema, hypovolemia, hypotension, and hypoalbuminemia.[136] Endothelial cell induction of heme oxidase and cyclooxygenase, production of prostaglandins, and phosphorylation-induced destabilization of vascular endothelial cadherin may contribute to vasodilatation and increased vascular permeability.[127–141] Hyponatremia is the result of secretion of antidiuretic hormone as an appropriate response to hypovolemia.[142] High quantities of rickettsiae infecting the pulmonary microcirculation are associated with increased vascular permeability and cause noncardiogenic pulmonary edema.[143,144] Vascular injury and the subsequent host lymphohistiocytic response correspond to the distribution of rickettsiae and include interstitial pneumonia, interstitial myocarditis, encephalitis, and similar vascular lesions in the rash, gastrointestinal tract, pancreas, liver, skeletal muscles, and kidneys. However, even severe vascular injury rarely leads to clinically significant hemorrhage. Platelets are consumed locally in numerous foci of infection; consequently, thrombocytopenia is observed in 32% to 52% of patients.[145,146] A procoagulant state ensues, including endothelial injury, release of procoagulant components, activation of the coagulation cascade with thrombin generation, platelet activation, increased antifibrinolytic factors, consumption of natural anticoagulants, activation of the kallikrein-kinin system, and secretion of coagulation-promoting cytokines.[147–150,151–154] These observations are supported by numerous studies of endothelial cells in culture, such as the demonstration that tissue factor is secreted by *Rickettsia*-infected endothelial cells,[155–157] but true disseminated intravascular coagulation occurs only rarely, and occlusive vascular thrombosis is not the basic pathophysiologic event.[150,158]

The host immune and inflammatory responses are critical for clearance of infection, but cytokines may contribute also to increased vascular permeability, and T-regulatory cells may contribute to suppression of immunity in overwhelming fatal illness.[159,160,161] T lymphocytes (particularly CD8 cells) are important effectors of immune clearance of rickettsiae, and interferon-γ (IFN-γ) and tumor necrosis factor-α activate infected endothelial cells to kill intracellular rickettsiae.[103,162–165,166] Dendritic cells stimulated via Toll-like receptor 4 activate natural killer cells in the early innate immune response and secrete IFN-γ, which dampens the rickettsial burden.[159,167–169] The adaptor molecule MyD88 is a key component of Toll-like receptor–mediated recognition of *Rickettsia*.[170] In macrophages, activation of the inflammasome contributes to host control of the bacterium.[171] The ability to invade and proliferate in macrophage-like cells has been noted in pathogenic but not in nonpathogenic rickettsiae.[172] Cytotoxic T lymphocytes are crucial to the clearance of rickettsial infection.[173] OmpA and OmpB cell wall proteins are important immunogens.[174–179]

Clinical Manifestations

The incubation period of RMSF ranges from 2 to 14 days, with a median of 7 days. Variation in incubation time may be related in part to inoculum size. The disease usually begins with fever, myalgia, and headache, most likely the effects of proinflammatory cytokines (Table 186.1). The temperature is higher than 102°F (38.9°C) in 63% of patients during the first 3 days and in 90% later.[145] The variable incidences of reported headache and myalgia in different series are likely related to the proportion of young children who may not articulate the concept of pain.

TABLE 186.1 Features of Rocky Mountain Spotted Fever (RMSF), Boutonneuse Fever (BF), and African Tick Bite Fever (ATBF)

FEATURE	RMSF (%)	BF (%)	ATBF (%)
Fever	99–100	100	81–88
Headache	79–91	56	83
Rash	88–90	97	26–46
Vesicular rash			16–45
Tache noire	<1	72	32–95
Multiple eschars	0	0	21–54
Myalgia	72–83	36	63–87
Nausea, vomiting	56–60		
Abdominal pain	35–52		
Petechial rash	45–49	10	
Conjunctivitis	30	9	
Lymphadenopathy	27		43–49
Stupor	21–26	10	
Diarrhea	19–20		
Edema	18–20		
Ataxia	5–18		
Meningismus	18	11	
Splenomegaly	14–16	6	
Hepatomegaly	12–15	13	
Jaundice	8–9	2	
Pneumonitis	12–17		
Cough	33	10	
Dyspnea		21	
Coma	9–10		
Seizures	8		
Shock, hypotension	7–17		
Decreased hearing	7		
Arrhythmia	7–16		
Myocarditis	5–26	11	
Death	4–8	2.5	
Increased aspartate transaminase level	36–62	39	
Thrombocytopenia	32–52	35	
Anemia	5–24		
Hyponatremia	19–56	25	
Azotemia	12–14	6	

Other signs and symptoms are frequently prominent early in the course before the onset of rash, at which time gastrointestinal involvement with nausea, vomiting, abdominal pain, diarrhea, and abdominal tenderness occurs in substantial numbers of patients; this may suggest gastroenteritis or an acute abdominal condition requiring surgery.

The rash, the major diagnostic sign, appears in a small fraction of patients on the first day of the disease and in only 49% during the first 3 days, usually appearing 3 to 5 days after the onset of fever and occurring in 88% to 90% of patients overall. Rocky Mountain "spotless" fever occurs more often in older patients and in black patients.[145,180] A delay in diagnosis is occasionally associated with the absence or late onset of rash. The rash typically begins around the wrists and ankles but may start on the trunk or be diffuse at the onset. Involvement of the palms and soles is considered characteristic, but it occurs in only 36% to 82%

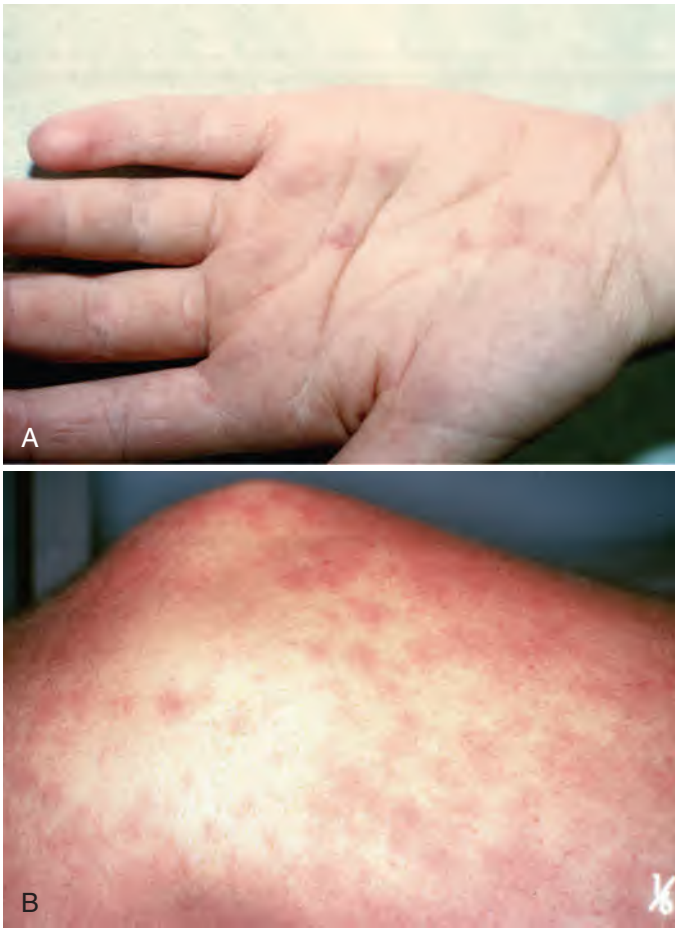

FIG. 186.3 Rocky Mountain spotted fever rash. (A) The wrist and palm manifest the rash of Rocky Mountain spotted fever with central petechiae in some of the maculopapules. (B) Early petechial rash on arm.

FIG. 186.4 Late acute stage of Rocky Mountain spotted fever. The lower portion of the arm shows a florid petechial rash.

of patients who have a rash; it often appears late in the course (Figs. 186.3 and 186.4). Skin necrosis or gangrene develops in only 4% of cases as a result of rickettsial damage to the microcirculation.[146] Gangrene involves the digits or limbs and occasionally necessitates amputation. Careful examination seldom reveals an eschar at the site of the tick bite in RMSF.[181,182] Headache is usually quite severe. Focal neurologic deficits, transient deafness, meningismus, and photophobia may suggest meningitis or meningoencephalitis. The cerebrospinal fluid (CSF) contains increased leukocytes in one-third of patients, with either lymphocytic or polymorphonuclear predominance[146]; CSF protein concentration is increased in one-third of patients. However, glucose concentration is low in the CSF of only 8% of patients.

The electroencephalogram may show diffuse cortical dysfunction. In general, neurologic involvement portends a bad prognosis. Among 37 patients followed for 1 to 8 years after acute RMSF, including some in the preantibiotic era, 21 had residual neurologic abnormalities.[183] These sequelae were headache and other subjective findings, but 12 cases involved electroencephalographic abnormalities. In a more recent series of cases of children with RMSF, 15% of survivors had neurologic deficits at discharge, including global encephalopathy, ataxia, and blindness.[184] Sequelae occur less often in patients with early antibiotic treatment. On funduscopic examination, retinal vein engorgement, arterial occlusion, flame hemorrhage, and papilledema without increased CSF pressure have been noted. These changes may reflect retinal vasculitis with increased permeability and focal thrombosis. Renal failure is an important problem in severe RMSF.[185] Prerenal azotemia related to hypovolemia responds to intravenous hydration; however, in patients with acute tubular necrosis, hemodialysis may be required. Pulmonary involvement is suggested by cough and radiologic changes, such as alveolar infiltrates, interstitial pneumonia, and pleural effusion.[186] Patients with pulmonary edema with impairment of pulmonary function or acute respiratory distress syndrome may require oxygen therapy and ventilatory assistance. Echocardiographic studies reveal minimal myocardial dysfunction,[187] and normal pulmonary capillary wedge pressure measurements document the noncardiogenic nature of the pulmonary edema.

In classic RMSF, death occurs 7 to 15 days after the onset of symptoms when appropriate therapy is not given in a timely manner. In fulminant RMSF, death occurs within the first 5 days. Several features account for the extreme difficulty associated with the diagnosis of fulminant RMSF—the course is rapid, the rash develops shortly before death if at all, antibodies to *R. rickettsii* do not have time to develop, and the pathologic lesions even appear different, containing more thrombi and lacking the characteristic lymphohistiocytic component.[188] Fulminant RMSF is more often observed in black males with glucose-6-phosphate dehydrogenase (G6PD) deficiency, apparently because of an unidentified secondary effect of the usually moderate degree of hemolysis. After hemolysis has depleted the older red blood cells (RBCs) with low G6PD content, evaluation of hemolysis through plasma haptoglobin may be more revealing than assay of G6PD activity in the remaining RBCs. Hemolysis may be the pathogenic factor, rather than the reduced G6PD enzyme activity itself. Other risk factors for a lethal outcome in classic RMSF include older age and possibly alcoholism.

Characteristic laboratory data may support the clinical diagnosis of classic RMSF but are relatively nonspecific.[145,146] The white blood cell count is generally normal, but increased quantities of immature myeloid cells occur frequently. Anemia is observed in 5% to 30% of cases. Thrombocytopenia occurs in more severe cases but also in some patients with mild disease. Coagulopathy with prolonged coagulation times and decreased concentrations of fibrinogen and other clotting factors occurs infrequently because the hemostatic system usually functions effectively to prevent severe bleeding from vascular lesions and generally does not contribute significantly to the pathologic state.[150] Disseminated intravascular coagulation is rarely documented. Hyponatremia is observed in half of patients with RMSF. Increased concentrations of serum lactate dehydrogenase, creatine kinase, and other enzymes are related to diffuse tissue injury, such as multifocal rhabdomyonecrosis.

The prognosis in RMSF is largely related to the timeliness of initiation of appropriate therapy.[189,190] The intervals between onset of disease and appearance of the rash, clinical diagnosis, and effective antibiotic treatment are significantly longer in patients who die than in those who survive.[30,145,189] Patients with fatal cases more frequently have hepatomegaly, jaundice, stupor, and renal insufficiency and report a history of tick exposure less often.[191] Patients who survive RMSF have solid immunity to *R. rickettsii.* Long-term sequelae are mainly neurologic or result from amputation of gangrenous limbs.[192,193]

Diagnosis

The diagnosis of RMSF before the onset of rash is clinical and epidemiologic. Early clinical diagnosis remains essential for this life-threatening disease. The differential diagnosis at the first consultation includes typhoid fever, measles, rubella, respiratory tract infection, gastroenteritis, acute abdominal condition requiring surgery, enteroviral infection, meningococcemia, disseminated gonococcal infection, secondary syphilis, leptospirosis, immune complex vasculitis, immune thrombocytopenic purpura, thrombotic thrombocytopenic purpura, infectious mononucleosis, drug reaction, ehrlichiosis, anaplasmosis, and other rickettsial diseases. Laboratory diagnosis of RMSF may be achieved through isolation of *R. rickettsii* from the blood. Because *R. rickettsii* is a Biosafety Level 3 organism, few laboratories undertake its isolation, which can be performed by means of inoculation of guinea pigs, embryonated hen's eggs, or cell culture. A centrifugation-enhanced cell culture system—the shell vial assay—has been successfully applied to rickettsial isolation[194] and has been successfully modified to be carried out on a 24-well plate.[195]

Some hospitals and public health laboratories can demonstrate *R. rickettsii* in cutaneous biopsy specimens with immunohistochemistry, a timely diagnostic method used during the acute phase for patients with a rash.[196–198] Serology, the usual method for confirmation of the diagnosis, is retrospective; serum antibodies usually become detectable during convalescence. Therefore, serologic confirmation of diagnosis requires seroconversion or demonstration of a fourfold rise in titers from acute- and convalescent-phase sera.[44] Serology does not allow discrimination of the particular causative SFG *Rickettsia* species unless Western immunoblotting and cross-absorption with appropriately selected antigens are performed.[199] The Weil-Felix test, using *Proteus* OX-19 and OX-2 agglutination, is not to be relied on. This method lacks sensitivity and specificity. Antibodies to rickettsial antigens are detected with indirect immunofluorescence and enzyme immunoassay. The indirect immunofluorescence assay for immunoglobulin G (IgG) reactive against SFG antigens is the most sensitive and specific test. Immunoglobulin M (IgM) lacks specificity and, compared with IgG, does not appear much earlier in illness to make it of great usefulness.[44,200] Indirect immunofluorescence and dot enzyme immunoassay have commercially available reagents.

Polymerase chain reaction (PCR) amplification of the 17-kDa protein, citrate synthase, and *ompA* and *ompB* genes has been employed to identify rickettsiae from a variety of specimens.[201] Unfortunately, amplification of *R. rickettsii* DNA has not proved to be a sensitive diagnostic method for blood samples, except late in the course, particularly for fatal cases.[202–204] Although real-time PCR offers improved analytic sensitivity, the few circulating organisms within the blood limit its clinical sensitivity.[205] When used on banked clinical specimens, real-time PCR revealed rickettsiae in 18% compared with 16% for nested PCR.[206,207] PCR has been successfully applied to other SFG rickettsioses, such as specimens from biopsies of cutaneous rash and eschars during Mediterranean spotted fever (MSF) and other SFG rickettsioses.[199] A multiplexed real-time PCR assay, used by the CDC on formalin-fixed, paraffin-embedded skin biopsy specimens, has the ability to differentiate RMSF from other SFG rickettsioses of concern in the United States.[208] Although not necessary for clinical care, nor available in clinical laboratories, sequencing of PCR products or use of restriction fragment length polymorphism analysis can confirm *R. rickettsii* as the etiologic agent when a species-specific diagnosis is sought.[209] Loop-mediated isothermal amplification assays for the detection of rickettsiae have been developed.[210] Although this platform offers a simple and potentially field-applicable platform, it will likely have the same limitations as PCR when used on blood in the clinical setting.

Treatment

Doxycycline is the treatment of choice. Since the introduction of chloramphenicol and the tetracyclines, including doxycycline, the lethality of the disease has decreased dramatically but remains significant at 3%.[70] In vitro and in ovo, *R. rickettsii* is susceptible not only to chloramphenicol and tetracycline but also to rifampin, some quinolone compounds, including ciprofloxacin and levofloxacin, and the macrolides clarithromycin and azithromycin. Clinical experience with these agents has been insufficient to enable recommendation of their use for RMSF.[211,212] The organism is resistant to β-lactam antibiotics, aminoglycosides, erythromycin, and trimethoprim-sulfamethoxazole.

Tetracyclines are the drug class of choice to treat RMSF, and doxycycline 100 mg every 12 hours is the preferred agent. Doxycycline is effective when given orally but should be given intravenously to patients with nausea and vomiting and to those who are seriously ill. Treatment is usually administered for 7 days or is continued for 3 days after the patient has become afebrile. Single-day treatment with 200 mg of doxycycline has proved to be safe and efficient in adults and children with MSF but has not been tested and is not recommended for RMSF. Tetracyclines have been avoided in young children because of concerns for staining the teeth, but it is recommended that doxycycline be used for suspected RMSF in children of all ages because of the life-threatening nature of RMSF and the demonstration that a single course of doxycycline does not stain the teeth.[213–215] Although the issue of doxycycline in children with RMSF is addressed in clinical guidelines, health care workers are often unaware of this important recommendation.[216–218]

Chloramphenicol, 50 to 75 mg/kg/day given in four divided doses, is also effective for the treatment of RMSF, but it is no longer available in the United States. It is also associated with a higher case-fatality rate when compared with those receiving tetracyclines such as doxycycline.[219] The effects of tetracycline on fetal bones and teeth and fatal hepatotoxicity during pregnancy are rarely seen with doxycycline.[220] When not treated appropriately, RMSF during pregnancy can have devastating consequences for both the mother and the fetus.[221] In addition, chloramphenicol is also not effective for ehrlichiosis, an infection that closely resembles RMSF. For these reasons, doxycycline should be used during pregnancy. Hypersensitivity to doxycycline is a rare event, but desensitization protocols are available when this scenario arises.[222,223]

Avoidance of therapeutic delay is critical for a favorable prognosis.[30,189,190] Severely ill patients require intensive supportive care. Fluid management is critical for maintenance of organ perfusion. Because of increased vascular permeability and risk of extravasation of fluid into pulmonary alveoli, a Swan-Ganz catheter may be needed to monitor hemodynamics in some patients. Glucocorticoids are sometimes given to severely ill patients, but there is no documentation of efficacy and they are not recommended.

Prevention

Although no vaccine is available currently, immunodominant surface proteins have been identified, and the major surface protein antigens (OmpA and OmpB) of *R. rickettsii* and *R. conorii* are candidate vaccine antigens. Immunization of guinea pigs with OmpA provided protective immunity against a virulent challenge, and protective fragments of OmpB have been identified.[174–177] The presence of antibodies to OmpA or OmpB is associated with protection.[48] The surface exposed protein YbgF is also protective.[224,225] A vaccine may be developed that would protect against all SFG rickettsiae, or even typhus group and SFG rickettsiae, but currently no vaccine is available for any of the SFG rickettsiae.[226–228]

Currently, the best means of prevention remains the avoidance of contact with ticks through the use of repellents and protective clothing. Permethrin-treated clothing is effective at reducing the number of tick bites[229] and is effective through at least a year of regular wear.[230] In experimental conditions, infected unfed ticks may take up to 12 hours to transmit *R. rickettsii,* but partially fed ticks may transmit the bacterium in as few as 10 minutes.[231] Therefore, frequent checks of the body, including scalp, pubic, and axillary hair, should be performed to allow removal of ticks before rickettsial transmission. To remove an attached tick, one should use forceps to detach the intact tick without leaving mouth parts in the skin. The tick bite wound should be cleansed. In foci with high rates of RMSF, methods to treat the environment or infested animals with acaricides have been shown to reduce tick populations,[232,233] but such efforts are expensive and laborious.[98]

OTHER SPOTTED FEVER GROUP RICKETTSIOSES

Other SFG rickettsioses have been given a variety of names, including geographic names, that often do not indicate their full distribution (e.g.,

Flinders Island spotted fever, which also occurs in mainland Australia and Southeast and South Asia),[12,234,235] and clinically descriptive names (e.g., tick-borne lymphadenopathy).[3] Aside from the latter highly distinctive disease, the other SFG rickettsioses form a spectrum of similar clinical illnesses with indistinguishable symptoms at onset and subsequent courses with overlapping clinical manifestations, such as varying in severity from occasionally life-threatening to nonfatal; in incidence of the rash from almost all to only half; in characteristics of the rash (usually maculopapular; in some illnesses, occasionally vesicular-pustular, frequently petechial to never petechial); in incidence of eschars; in incidence of regional lymphadenopathy that may be painful (from frequently to never); and in incidence of lymphangitis (from almost half to never). The severity of illness is associated with both the particular *Rickettsia* species or strain and host factors. Among the 15 other SFG *Rickettsia* species reported with evidence to have caused infection of humans (*R. conorii, R. sibirica, R. japonica, R. australis, R. honei, R. africae, R. parkeri, R. slovaca, R. aeschlimannii, R. massiliae, Candidatus* R. philipii*, R. heilongjiangensis, R. helvetica, R. felis,* and *R. akari*), the first 13 are transmitted by tick bite. SFG cross-reactive protein and LPS antigens are detected serologically, and cross-protection is shared among SFG rickettsiae.[226,236] *R. conorii,* a typical SFG rickettsia with high genetic homology with *R. rickettsii,* appears to have greater intraspecies antigenic and genetic diversity than *R. rickettsii* and consists of four strains.[237,238] *R. sibirica* has two distinct strains.[239] The proposal to designate the strains as subspecies is controversial because several already named species are so closely related that some taxonomists would combine them into one. This situation could create the rationale to convert some former species names into subspecies.

Boutonneuse Fever (Mediterranean Spotted Fever)

The most severe SFG rickettsiosis other than RMSF is boutonneuse fever, caused by *R. conorii.* Infection has been designated by many geographic names: Marseilles fever, MSF, Kenya tick typhus, Israeli tick typhus, Astrakhan spotted fever, and Indian tick typhus. Historically, boutonneuse fever was first described by Conor and Bruch in 1909 in Tunisia, although the *tache noire* (black spot)—that is, the eschar at the site of the tick bite—was not described until 1923 by Pieri in Marseilles.[241] *R. conorii* has been identified in India, Pakistan, Israel, Russia, Georgia, Bulgaria, Turkey, Ukraine, Ethiopia, Kenya, South Africa, Morocco, and southern Europe.[241–243] The epidemiology of boutonneuse fever and ecology of *R. conorii* are closely related to *R. sanguineus* ticks. *R. conorii* is maintained transovarially in ticks and is transmitted to humans by tick bite. Dogs have been experimentally shown to be a competent reservoir for *R. conorii,* serving as a reservoir for acquisition and transmission of the agent to *R. sanguineus* ticks.[244,245] Experiments in immune dogs have also demonstrated horizontal transmission through cofeeding (acquisition of *Rickettsia* by naïve ticks during simultaneous feeding adjacent to *Rickettsia*-infected ticks).[246] The frequent absence of a history of tick bite is likely because of transmission by immature larvae and nymphs, which are often not noticed. Cases occur mainly in the warm months, with peak incidences in July, August, and September in many Mediterranean locations. Imported cases occur in travelers returning to the United States and northern Europe from southern Europe. Necropsies of fatal cases of boutonneuse fever reveal disseminated vascular infection and injury by *R. conorii,* including meningoencephalitis and vascular lesions in kidneys, lungs, gastrointestinal tract, liver, pancreas, heart, spleen, and skin.[247,248] Hepatic biopsy specimens reveal multifocal hepatocellular necrosis and granuloma-like lesions.[249] In a large series of well-documented cases, patients infected with the *R. conorii* Israeli spotted fever (ISF) strain were more severely ill than those infected with the Malish strain. Although eschars were present in many patients with both strains, tick bite inoculation lesions occurred more often with Malish strain. Severity and fatality were manifested by more frequent petechial rash, gastrointestinal symptoms, obtundation, dehydration, tachypnea, hepatomegaly, leukocytosis, coagulopathy, acute renal failure, hyperbilirubinemia, and elevated serum transaminase and creatine kinase levels.[250] Host factors that are risks for severity include diabetes mellitus, cardiac insufficiency, alcoholism, old age, and G6PD deficiency.[250,251,252] The disease is milder in children. In France, Israel, and Spain, the death rate among hospitalized patients ranges from 1.4% to 5.6%, similar to that of RMSF.[252] In contrast, SFG rickettsiosis in northeastern Spain documented with cross-reactive serology is a milder illness, suggesting that another strain might be the actual agent.[253] Other rickettsiae that share antigens and cause similar disease in Europe include *R. massiliae, R. monacensis, R. sibirica mongolitimonae* strain, and *R. akari.*[18,20,23,254,255] Boutonneuse fever is associated with a procoagulant state,[148–150,151,256] and 9.6% of cases are complicated by deep venous thrombosis late in the course.[257] Plasma levels of tumor necrosis factor rise during infection.[154] After a mean incubation period of 7 days, fever, myalgias, and headache characterize the onset (see Table 186.1). Careful clinical examination may reveal an eschar, which facilitates the clinical diagnosis.

Spotted Fevers: Moderate Severity

R. sibirica was discovered in the 1930s in eastern Russia and subsequently in China, Mongolia, and Pakistan. A genomic variant considered a strain or a subspecies, named *mongolitimonae,* has been found in Europe, Asia, and Africa.[20,258–260] *R. sibirica* causes North Asian or Siberian tick typhus, which closely resembles RMSF. Nearly half of patients infected with the *R. sibirica mongolitimonae* strain manifest a very unusual ropelike lymphangitis between an inoculation eschar and the draining lymph node.[20,261] This clinical feature led to the term *lymphangitis-associated rickettsiosis* and sometimes also is present in infections with other rickettsial species. Severe complications, including retinal vasculitis and septic shock, have been reported.[262,263] *R. australis* is limited to eastern Australia, and *R. honei*, the causative agent of Flinders Island spotted fever, also causes human infections on mainland Australia and in Asia.[12,24,234,235]

Although Japanese spotted fever has been described as a typically moderate SFG rickettsial illness (fever 100%, rash 100%, and eschar 90%), more severe illness, including meningoencephalitis, respiratory failure, shock, and even death associated with elevated proinflammatory cytokines, does occur.[264–268] *R. heilongjiangensis*, the agent of Far Eastern spotted fever, is present in eastern Russia, Thailand, and China.[25] It causes typical non–life-threatening SFG rickettsiosis, with some patients exhibiting ropelike lymphangitis.

R. africae is prevalent throughout sub-Saharan Africa, where the vector ticks—*Amblyomma hebraeum* and *Amblyomma variegatum*—are present.[24] The identification of *R. africae* infections in the West Indies apparently conforms to the distribution of *A. variegatum.*[26] African tick bite fever is the only tick-transmitted rickettsiosis in which several inoculation eschars are observed in a high proportion of cases.[26] *R. africae,* the most frequently imported rickettsiosis, is often observed in patients who have hunted or traveled in the bush in southern Africa.[26,269,270–273] The attack rate in an exposed group can be rather high. In a cohort of 940 Norwegian travelers to South Africa, a 4% attack rate was observed in all travelers and in 25% of those traveling to hunt game.[274] Patients with African tick bite fever typically have headache, fever, and myalgia, and acute-stage elevations of serum tumor necrosis factor-α, interleukin (IL)-6, IL-8, IL-13, IFN-γ, RANTES (*r*egulated on *a*ctivation, *n*ormal *T*-cell *e*xpressed and *s*ecreted), and MIP-1α (macrophage inflammatory protein-1α).[275] Rash may be vesicular, maculopapular, sparse, or even absent in more than half of patients. Distinctive features include frequent regional lymphadenitis that drains the region of the eschars. The infection is common among native Africans, in whom it is frequently suspected to be malaria or typhoid fever.[21] Local seroprevalence rates are highest in habitats that favor abundant tick populations.[276]

R. parkeri infection has been documented in about 40 patients in the United States,[277] transmitted largely by the Gulf Coast tick *(A. maculatum).* The agent has been detected in 20% to 40% of *A. maculatum* ticks collected in several states.[278–280] *R. parkeri* is also associated with human infections in Uruguay, Brazil, Colombia, and Argentina,[2,13,14,85,281–283] where it is apparently transmitted by *Amblyomma triste, Amblyomma tigrinum,* and *Amblyomma ovale.*[284–288] Transmission by *A. triste* was also documented in Arizona.[289] It causes a spotted fever very similar to African tick bite fever, the agent to which *R. parkeri* is closely related. It is likely one of the causes of cases reported as RMSF based on serology, although *R. parkeri* infection is less severe than RMSF. As another

possible difference from RMSF, more than 90% of patients develop an eschar, which provides useful tissue for PCR diagnosis.[277,281,282,289,290] Other eschar-associated infections in North and South America have been described. In California, the agent designated *Candidatus* R. philipii strain 364D, likely transmitted by *Dermacentor occidentalis,* causes an eschar-associated spotted fever rickettsiosis.[291,292] Cases of eschar-related disease in Brazil have been reported and attributed to a strain of *R. parkeri.*[293,294]

Spotted Fevers: Mild Severity

In Europe, human infections with *R. slovaca*, *Rickettsia raoultii,* and sometimes other species (e.g., *Candidatus* Rickettsia rioja and *R. massiliae*) are called TIBOLA (*ti*ck-*b*orne *l*ymph*a*denopathy) or SENLAT (*s*calp *e*schar and *n*eck *l*ymphadenopathy *a*fter *t*ick bite).[3,19,27,295–301] *R. slovaca* is transmitted to humans most often by the bite of adult *Dermacentor marginatus* ticks during winter and early spring. The illness is characterized by an eschar, typically on the scalp, and enlarged, often tender, draining cervical lymph nodes. Fewer than half of patients manifest a fever, and rash occurs rarely. The eschar site may have prolonged alopecia. There is persistent asthenia in a small fraction of patients, despite response to antirickettsial treatment. It should be noted that other bacteria have been documented in those with clinical presentations as similar to the aforementioned syndrome (i.e., *Francisella tularensis*, *Bartonella henselae*, *Borrelia burgdorferi*, and *Coxiella burnetii*).[299] *R. raoultii* has been found to cause illness in China, but, unlike in Europe, fever is a more prominent finding, and eschar and lymphadenopathy are less frequently reported.[302,303] The isolation of an *R. slovaca*–like agent from *D. variabilis* originating from the southeastern United States raises the possibility of another pathogenic rickettsial species in the United States.[304]

The possibility of chronic symptoms following an SFG rickettsial infection has also been suggested in patients in Australia.[305] The fact that SFG rickettsiae can cause an eschar or papule with surrounding erythema—the mildest manifestation of illness, short of asymptomatic seroconversion—and did so in two otherwise healthy persons[306,307] was demonstrated for *R aeschlimannii.*[4] Another case of *R. aeschlimannii* infection manifesting as typical SFG rickettsiosis has also been reported.[17] *R. massiliae* infects *R. sanguineus* ticks in the United States and worldwide.[308,309] It has been isolated from a patient in Sicily[23]; identified molecularly in patients from France, Argentina, Tunisa, and Sicily[310–313]; and implicated through serologic cross-absorption techniques in Romania.[301] A patient with acute febrile illness in Sweden was reported with molecular and serologic evidence of *R. helvetica* infection.[28] Another patient from Sweden with mild meningeal symptoms accompanying fever had *R. helvetica* isolated from CSF.[314] In addition, numerous distinct SFG rickettsiae (e.g., *R. amblyommatis, R. montanensis, R. peacockii, R. rhipicephali,* and *R. andeanae*) have been identified only in ticks.[1,240,315] Some of these may prove to be pathogenic for humans, even if they cause only a short, nonexanthematous, febrile illness or asymptomatic seroconversion.[87]

Flea-borne Spotted Fever

R. felis, the agent of flea-borne spotted fever, is maintained transovarially in fleas, largely cat fleas, and is presumably transmitted by them.[6] It was the first *Rickettsia* shown to contain a plasmid.[316] The cat flea host, *Ctenocephalides felis,* is ubiquitously distributed throughout the world, and infections have been documented molecularly or serologically in North and South America, Europe, Africa, Asia, Australia, and Oceania. A review of 34 documented cases in the literature describe the following: fever (32 cases), rash (usually maculopapular; 24 cases), eschar (4 cases), gastrointestinal symptoms (3 cases), and pulmonary involvement (4 cases).[317] Although infections tend to be mild, severe manifestations (e.g., hepatitis, meningitis, and a splenic infarct) have been reported.[318–320] *R. felis* DNA has been detected from febrile persons in Africa but has also been detected in afebrile control subjects,[321,322] from skin swabs of ulcerative skin lesions and from the skin of healthy volunteers,[323] and from a variety of hematophagous and nonhematophagous arthropods.[324] These findings have brought scrutiny to the significance of *R. felis* as a pathogen.[325,326]

Diagnosis

The diagnosis of SFG rickettsiosis may be established by immunohistologic demonstration of organisms in skin biopsy; PCR assay has been used with blood, skin biopsy, or swabs of eschar bases for *R. conorii, R. africae, R. slovaca, R. felis*, *R. japonica, R. sibirica, R. australis, R. honei, R. monacensis,* and *R. massiliae.*[a] Pitfalls associated with ascribing an illness to a causative agent by PCR are emphasized in the dubious association of *R. helvetica* with sarcoidosis and chronic myopericarditis.[334–337] A novel approach that can be used to diagnose boutonneuse fever before the onset of rash is immunofluorescent detection of *R. conorii* in circulating endothelial cells captured by immunomagnetic beads coated with a monoclonal antibody to the human endothelial cell surface.[196,202,338] Timely diagnosis can also be established by isolating SFG rickettsiae in a shell vial cell culture system.[194,339] As with other infectious agents, the sensitivity of isolation is decreased with prior effective antimicrobial therapy.[340] Serology is the mainstay of diagnosis, but reactive antibodies are usually absent during early illness. Thus, convalescent-phase serum demonstrating seroconversion or a fourfold rise in titer is often necessary to establish a diagnosis. Production of antibodies to SFG rickettsiae can be demonstrated with the use of microimmunofluorescence, latex agglutination, enzyme immunoassay, Western blot, or complement fixation. Commercially available multiplexed slides with the ability to use automated techniques have been developed.[341] Antibodies to *R. africae* appear late in convalescence in African tick bite fever.[342] The detection of rickettsial nucleic acid from ticks removed from humans has been proposed as a tool to assess the risk of infection.[343]

Treatment

Tetracyclines such as doxycycline and minocycline are the drugs of choice for SFG rickettsioses. Unlike RMSF, wherein recommendations for tetracyclines are based on extensive clinical experience, there have been prospective studies of tetracyclines and various other drugs for the treatment of MSF.[344] For MSF and other SFG rickettsioses, successful treatment is achieved with doxycycline, 100 mg twice daily for 7 days. Shorter regimens have been studied. In adults with MSF, a single day of doxycycline (taken in two 100-mg doses) was as effective as a 10-day course of tetracycline hydrochloride.[345] Effectiveness was demonstrated with ciprofloxacin, 750 mg twice daily for 7 days, in those with mild-to-moderate MSF,[346,347] but the findings of a subsequent study suggest that fluoroquinolone use may be associated with severe courses.[348,349] The newer macrolides clarithromycin and azithromycin have been shown to be effective in those with mild disease[350,351,352] and can be considered during pregnancy. Chloramphenicol has long been considered an effective antibiotic, but with effective and safe alternatives, the potential for serious adverse events should raise caution regarding its use.

[a]References 5, 6, 199, **241**, 247, 254, 327–333.

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187 *Rickettsia akari* (Rickettsialpox)

Pierre-Edouard Fournier and Didier Raoult

SHORT VIEW SUMMARY

Definition
- Vesicular fever with eschar caused by mite bites; may be confused with anthrax.

Epidemiology
- Found worldwide but is particularly common in New York City.

Microbiology
- Infection caused by the intracellular bacterium *Rickettsia akari.*

Diagnosis
- Based on serology and polymerase chain reaction assay of swab from a vesicle or eschar.

Therapy
- Doxycycline, 100 mg twice daily for 7 days.

Prevention
- Mouse eradication from buildings will prevent transmission to humans.

Rickettsialpox is a worldwide mite-borne rickettsiosis presenting as a febrile and vesicular eruption. It is caused by *Rickettsia akari,* associated with mice, and transmitted by its ectoparasite, the mite *Liponyssoides sanguineus.*

ETIOLOGY

Rickettsia akari is classified among spotted fever group rickettsiae based on antigenic and genetic data. Its genome has a size (1.23 Mb) similar to those of other *Rickettsia* species but its plasmid content varies, possibly according to the strain and/or culture passage, as described for other closely related species such as *Rickettsia felis.*[1,2]

It differs from other *Rickettsia* species in that its target cell in humans is the macrophage and not the endothelial cell,[3] and it is transmitted by the bite of *Liponyssoides sanguineus,* the mouse mite.

EPIDEMIOLOGY

The epidemiology of rickettsialpox is linked to house mice. Another vector (perhaps the tick or flea) is suspected in that the seroprevalence of *R. akari* is high in New York City dogs.[4] In Korea, a sylvatic cycle of *R. akari* in voles is suspected.[5] Rickettsialpox was initially described in New York City in 1946[6] and has since been reported in Europe, Ukraine, Korea, and South Africa.[7,8] The 2001 bioterrorist attack with anthrax directed the attention of physicians to skin eschars and rash and allowed the identification of 34 cases of rickettsialpox in New York City[7] from February 2001 to August 2002. The patients were suspected of suffering cutaneous anthrax or smallpox. The usual yearly incidence in New York City is 5 cases. A surprisingly high seroprevalence of *R. akari* has been reported in intravenous drug users from Baltimore[9] and in patients using a free clinic in Los Angeles County.[10] Because this disease is not actively tracked, its overall prevalence is completely unknown.

CLINICAL MANIFESTATIONS

The typical triad of the disease, which includes fever, vesicular rash, and eschar,[11] was found in 92% of patients investigated in New York City (Table 187.1). Indeed, the disease is recognized by only a few physicians; in the New York City cases, half of patients were identified by a single physician and 75% by three. The incubation period is approximately 7 to 14 days. Eschar is the clinical hallmark of the disease.[12] It starts as a primary papule; a vesicle then appears in the center and, when it dries, it leaves a brown or dark eschar (Fig. 187.1). Palpable regional lymph nodes draining this eschar are common and are usually tender.[11] The rash usually appears on the third or fourth day. It is papular at the beginning and becomes vesicular in many patients. The vesicles dry, and each leaves a black crust. Patients typically have 20 to 40 skin lesions. In contrast with other spotted fever group rickettsioses, palms and soles are not involved. The disease is benign, and patients usually recover. A transient leukopenia can be documented, as can thrombocytopenia and elevated aminotransferases.[13] A case was described of a human immunodeficiency virus–positive patient who recovered.[14]

DIAGNOSIS

Serology has been the easiest tool that can be used for diagnosis. Cross-reactions have been noted between *R. akari* and *Rickettsia rickettsii.* Assay of homologous antigens is more sensitive and is preferable. Immunoglobulin M and immunoglobulin G are detected 7 to 15 days after onset. Immunohistochemistry is of value with skin biopsies and was considered the most efficient tool in the New York City series. A polymerase chain reaction (PCR) assay targeting DNA sequences coding for a 17-kDa antigen was used on fresh tissues.[7] Recently, it was found that swabbing eschar or vesicles of patients with rickettsioses allows DNA detection by PCR[15,16] and should be the preferred sample. Isolation from skin biopsy may be performed on Vero cells in specialized laboratories. Consideration of *R. akari* in the differential diagnosis is critical in that its eschar can be misdiagnosed as inoculation anthrax. Moreover, it is one of the few infections that causes vesicular rashes, along with smallpox, varicella, herpes zoster, herpes simplex, and some other rickettsioses (e.g., Queensland tick typhus and African tick-bite fever).

THERAPY

Treatment[17] for rickettsialpox is doxycycline, 200 mg per day, given as 100 mg twice daily, for 7 days. The alternative treatment is chloramphenicol. Although clinical efficacy is unknown, *R. akari* is susceptible to many antibiotics, including azithromycin.

FIG. 187.1 Patient with eschar of rickettsialpox in 2002. *(Courtesy C. Paddock.)*

TABLE 187.1 Clinical and Epidemiologic Findings in Rickettsialpox

SERIES	PADDOCK ET AL.[7]	GREENBERG ET AL.[6]	KASS ET AL.[11]
Number of cases	34	144	13
Year of study	2003	1947	1994
Fever	97%	100%	100%
Mice at residence or work	67%	—	—
Eschars	90%	99.8%	100%
Any rash	100%	100%	100%
Vesicular rash	—	—	92%
Fever plus eschars plus rash	92%	—	100%
Hospitalization	32%	—	—
Headache	NA	90%	100%

NA, Not available.

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188 *Coxiella burnetii* (Q Fever)

Joshua D. Hartzell, Thomas J. Marrie, and Didier Raoult

SHORT VIEW SUMMARY

Definition
- Q fever manifests as a self-limited febrile illness, pneumonia, endocarditis, or hepatitis. There are many less common manifestations such as meningitis, encephalitis, and osteomyelitis. Infections are divided into acute and chronic (persistent) focalized forms.

Epidemiology
- Q fever is a zoonosis that is acquired by inhalation or, much less commonly, by ingesting unpasteurized milk.
- Cattle, sheep, and goats are the most common reservoirs.
- Infected parturient cats are important in the spread of *Coxiella* in some areas.
- There is an extensive wildlife reservoir.
- The environment is contaminated at the time of parturition by an infected animal.
- Windborne spread from the contaminated environment can occur over a distance of at least 10 km.
- Distribution is worldwide except for New Zealand, Polynesia, Antarctica, and the Arctic.

Microbiology
- *Coxiella burnetii* is a pleomorphic gram-negative (structurally—does not stain with Gram stain) coccobacillus.
- *C. burnetii* is an intracellular pathogen.
- The organism has a spore stage.
- *C. burnetii* undergoes phase variation.
  - Acute infection leads to antibody predominantly against phase II antigens, whereas persistent infections such as endocarditis are characterized by immunoglobulin G (IgG) antibody predominantly against phase I antigens.

Diagnosis
- Indirect immunofluorescent serologic tests are most commonly used.
- A fourfold rise in titer between acute and convalescent samples or presence of IgM or positive polymerase chain reaction (PCR) is diagnostic of acute disease.
- Persistent focalized infection is diagnosed on the basis of evidence of a lesion (e.g., endocarditis, osteomyelitis, vascular infection) in conjunction with an IgG phase I titer at least 1:800, positive PCR of the blood, or biopsy.
- In persistent Q fever, the IgG phase I titer is usually much higher than the phase II IgG titer, but rare cases occur in which the phase II titer is higher.
- Isolation of *C. burnetii* by a shell vial technique can be done.
- PCR assay can be used to amplify *C. burnetii* DNA from a variety of clinical specimens such as blood, heart valves, and joint fluid. Fluorescent in situ hybridization can identify organisms in tissue, although standard histopathologic stains are negative.

Therapy
- Acute Q fever: 14 days of doxycycline or minocycline
- Q fever endocarditis: doxycycline plus hydroxychloroquine for 1½ years for patients with native valve endocarditis and 2 years for patients with prosthetic valve infections

Prevention
- Good animal husbandry practices should be in place.
- Seronegative sheep or goats should be used in research facilities.
- Vaccination should be offered to high-risk groups where available.
- Pregnant women and patients with valve lesions or prosthetic valves should avoid contact with reservoir.

Q fever remains an intriguing disease despite being studied for more than 80 years. Molecular diagnostics and genomic analysis are adding to our understanding of the disease. The large outbreak in the Netherlands,[1] other outbreaks, and longitudinal studies from France are changing diagnostic and treatment approaches.[2] Although progress has been made, the name *Q fever* ("Q" for query) remains appropriate, as many questions remain unanswered.

Q fever is an acute febrile illness that occurs worldwide.[3] The most common animal reservoirs for this zoonosis are cattle, sheep, and goats, but a large wildlife reservoir exists, and soft ticks may be infected. Domestic ungulates, when infected, shed the desiccation-resistant organisms in urine, feces, milk, and especially birth products. The placenta of an infected sheep contains up to 10^9 organisms/g of tissue. Humans are infected by inhalation of contaminated aerosols and after an incubation period of 20 days (range, 1–39 days) become ill with severe headache, fever, chills, fatigue, and myalgia. There is a dose-response effect on the incubation period, with incubation periods of only 2 days occurring on occasion. Other signs and symptoms depend on the organs involved.

PATHOGEN

Coxiella burnetii is the causative agent of Q fever. *C. burnetii* is a highly pleomorphic coccobacillus with a gram-negative cell wall. It measures 0.3 to 0.7 µm long[4] and enters the cell by a passive mechanism. It survives within the phagolysosome of host cells; the low pH of this environment is necessary for the metabolic functioning. Large and small variants exist, and a spore stage has been described, which explains the ability of *C. burnetii* to withstand harsh environmental conditions.[5,6] It survives for 7 to 10 months on wool at 15°C to 20°C, for more than 1 month on fresh meat in cold storage, and for more than 40 months in skim milk at room temperature.[7] Although it is destroyed by 2% formaldehyde, the organism has been isolated from infected tissues stored in formaldehyde for 4 to 5 months. It has also been isolated from fixed paraffinized tissues. Either 1% Lysol or 5% hydrogen peroxide kills *C. burnetii*.

C. burnetii undergoes phase variation.[7] In nature and in laboratory animals, it exists in the phase I state, to which the immunoglobulin G (IgG) response, but not the IgM response, is delayed compared with phase II. Repeated passage of phase I virulent organisms in embryonated chicken eggs leads to gradual conversion to phase II avirulent forms by chromosomal deletions.[8] There is no morphologic difference between the two phases, although they differ in the sugar composition of their lipopolysaccharides,[9] in their buoyant density in cesium chloride, and in their affinity for hematoxylin and basic fuchsin dyes. *C. burnetii* lipopolysaccharide is nontoxic to chicken embryos at doses greater than 80 mg/embryo, in contrast to *Salmonella typhimurium* smooth-type and rough-type lipopolysaccharide, which is toxic in nanogram amounts.[10] Plasmids have been found in both phase I and phase II cells.[11] Some

strains are without plasmids. There are variations in virulence depending on the strain.[3]

The *C. burnetii* genome contains genes with potential roles in adhesion, invasion, intracellular trafficking, and host cell modulation.[12] A difference from other intracellular bacteria is the observation that the genome of *C. burnetii* contains 32 insertion sequences dispersed in the chromosome.[12] The genomes of many[13] strains of *C. burnetii* have been sequenced.[14] The ability to grow *C. burnetii* in an axenic medium will enhance studies of the molecular biology of this microorganism.[15]

Epidemiology

History

In 1935, Derrick, a medical officer in Queensland, Australia, investigated a febrile illness that affected 20 of 800 employees of a Brisbane meatworks.[16] He coined the term *Q* (or *query*) *fever* for this illness, for which he had no diagnosis but suspected was a new disease. Burnet and Freeman[17] showed that the microorganism isolated from the blood and urine of Derrick's patients was a rickettsia. At about the same time, Davis and Cox[18] isolated a microorganism from ticks *(Dermacentor andersoni)* collected near Nine Mile Creek, Montana. Later, Dyer[19,20] showed that *Rickettsia burnetii* (Burnet and Freeman's organism) was the same as *Rickettsia diaporica* (Cox's organism); it is now known as *Coxiella burnetii.*

Zoonotic Sources

C. burnetii has been identified in arthropods (specifically soft ticks), fish, birds, rodents, marsupials, and livestock.[4] The most common animal reservoirs are cattle, sheep, and goats, although a variety of animals (horses, dogs, swine, camels, water buffalo, pigeons, ducks, geese, turkeys, several species of wild birds, squirrels, deer mice, harvest mice, rats, cats, and rabbits) may be infected.[21] Collared doves have been suspected of carrying *C. burnetii* from Western Europe to Ireland. In Nova Scotia, exposure to infected parturient cats resulted in several outbreaks of Q fever.[22,23] A recent outbreak in Guyana was linked to three-toed sloths.[3,24] Animal reservoirs are key to infection, as they lead to high levels of environmental contamination. One study in the United States reported 24% of 1600 samples including nonagricultural sites being positive via quantitative polymerase chain reaction (PCR).[25]

Q fever has a worldwide distribution except for French Polynesia, New Zealand, the Arctic, and Antarctic.[26,27,28] Growing evidence suggests that Q fever is underreported in areas of Africa.[29] It is usually an occupational disease affecting people with direct contact with infected animals such as farmers, veterinarians, and abattoir workers, although indirect contact with infected animals has resulted in outbreaks of Q fever, as in Switzerland, where more than 350 people who lived along a road over which sheep traveled from mountain pastures developed Q fever.[30] Exposure to contaminated straw, manure, or dust from farm vehicles resulted in Q fever in British residents who lived along a road traveled by these vehicles.[31] Exposure may be even more indirect, as in the case of laundry workers who developed Q fever after handling contaminated laundry.[32] Ingestion of contaminated raw milk,[33,34] exposure to infected parturient cats,[22] and skinning of infected wild rabbits are also ways in which Q fever may be acquired. *C. burnetii* has also been isolated from human milk[35] and human placentas.[36] *C. burnetii* is known to undergo reactivation during pregnancy in animals other than humans. It is likely that this happens in humans as well, and Q fever complicating human pregnancy is probably underdiagnosed.[37] Laboratory exposure to *C. burnetii*[38] and transport of infected sheep through hospitals to research laboratories have resulted in large outbreaks of Q fever.[39,40] Nearly 250 travel-acquired cases of acute Q fever have been reported.[41] Q fever is associated with military operations with more than 150 cases occurring in US soldiers deployed to Iraq.[42] Live-cell therapy, an injection of processed fetal cells from animals, was associated with Q fever in travelers to Germany from the United States and Canada, where the procedure is not approved. Patients presented with symptoms compatible with Q fever and seroconversion to *C. burnetii*.[43]

Transmission Between Humans

Q fever has been transmitted by blood transfusion,[44] during autopsies,[45–47] and rarely during clinical care. It appears that delivery of pregnant women infected with Q fever or procedures leading to potential aerosolization present the highest risk. An obstetrician developed Q fever after delivery of a woman infected with *C. burnetii*.[48] A female patient who shared a room and toilet with another patient with acute Q fever who had delivered during their time in the same room together subsequently developed Q fever.[49] Following removal of an infected breast implant, three health care providers (one of three had taken prophylactic doxycycline) seroconverted without clinical disease.[50] There was apparent human-to-human transmission among members of a household.[51] *C. burnetii* may also be transmitted sexually.[49,52]

Incidence

Q fever became a notifiable disease in the United States in 1999 because of its potential as a biological warfare agent.[53,54] From 2000 to 2012, 1366 cases were reported.[55] The male-to-female ratio was 3:1. There were no reported cases of Q fever among pregnant women during this time period in the United States. Despite agriculture being listed as the most common occupation (36%), 61% of patients denied direct contact with livestock. Among patients, 8.4% reported drinking unpasteurized milk, which is double the national prevalence of this practice.[55]

Karakousis and colleagues[56] reviewed the published cases of Q fever endocarditis from the United States. They found seven such cases, likely a gross underestimate, from 1976 to 2004. From 2008 to 2012, 110 cases were reported, which again suggests the disease is underreported.[55] This suggestion is supported by a study by Dahlgren and coworkers,[57] who compared two different reporting systems within the United States. They compared case report forms submitted to the US Centers for Disease Control and Prevention (CDC) and National Death Certificate data and estimated that Q fever endocarditis was underreported by a factor of 14 for case report forms and a factor of 5 for death certificates.

Seroprevalence data in the United States show that 3.1% of Americans test positive for *C. burnetii*.[58] Seropositivity was more common in males (3.8% vs. 2.5%), in Mexican Americans (7%), in older individuals, in foreign-born individuals, and in individuals living in poverty. Data suggest that Q fever remains underrecognized and underreported in the United States.

Outbreaks

Q fever has historically been a disease that causes intermittent outbreaks, which often provide important learning about the disease. A superspreading infected ewe at a farmer's market resulted in hundreds of cases of Q fever in Germany.[59] Urbanization of sheep farming is a major factor in the spread of Q fever in Germany; in one outbreak, people who lived within 50 m of a sheep meadow had an attack rate of 11.8%.[60]

One of the most remarkable events in the history of Q fever has been the outbreak in the Netherlands from 2007 to 2010 resulting in more than 4000 cases[1] from multiple genotypes from likely one strain previously found in Germany and France.[61] Although high-density goat farming in proximity to urban populations was the source and explanation for ongoing transmission of infection, environmental factors also played a role.[62] Farms without transmission had higher vegetation densities and shallower ground water conditions than farms where transmission did occur.[63] The ability to detect organisms in ambient air in the year following the outbreak revealed an association between the intensity of detection and goat kidding as well as the distance to and size of the farm.[64]

PATHOGENESIS

In the most likely sequence of events in the cycle of transmission of *C. burnetii* to humans, the organism is maintained in ticks or other arthropods. These ectoparasites infect domestic and other animals including a variety of small mammals by bite or through contamination of the skin by infected feces. Infected domestic ungulates are usually asymptomatic, although abortion or stillbirth may result. The placenta contaminates the environment at the time of parturition. Air samples are positive for up to 2 weeks after parturition, and viable organisms are present in the soil for up to 150 days.[65–67] Humans are infected by the inhalation of contaminated aerosols. Clinical severity of infection depends on the strain—the QPH_1 plasmid-containing strain being more

virulent than the QPRS-containing plasmid both in humans and experimental models. The microorganisms proliferate in the lungs, and bloodstream invasion follows. This invasion results in the onset of systemic symptoms and a variety of clinical manifestations depending on the dose of the microorganism inhaled and probably on the characteristics of the infecting strain.[68] Depending on the host, primary infection may be symptomatic (acute Q fever) or asymptomatic. Children and women are less likely to be symptomatic, which may partly be dependent on steroid hormones.[69] Pregnant women are even more commonly asymptomatic after primary infection.[70] The evolution to endocarditis does not appear to be related to specific strains[71] but mainly to host factors, and it can follow symptomatic or asymptomatic primary infection. Multiplication of *C. burnetii* is controlled by macrophages, and granulomas are formed. In some people, the macrophages cannot kill *C. burnetii,* seemingly because of the secretion of interleukin-10 (IL-10).[72] Patients with endocarditis have increased levels of IL-10 secreted by stimulated blood monocytes. Patients with cancer, valve lesions, or arterial aneurysms or who are pregnant are at increased risk for endocarditis if infected with *C. burnetii.*[73] High levels of IgG antibodies to cardiolipin have been reported to be associated with development of acute or chronic endocarditis.[74] The early role of antiphospholipid (aPL) antibodies in the generation of aseptic vegetations is suspected and is associated with increased risk of thrombosis.[74]

CLINICAL MANIFESTATIONS

Humans are the only animals known to develop illness regularly as a result of *C. burnetii* infection.[75] In one large series of 207 patients, the mortality rate was 2.4%, which is consistent with US fatality data (2%).[55,76] There are several clinical syndromes, as follows:

1. Self-limited febrile illness (2–14 days)
2. Pneumonia
3. Endocarditis and vascular infections
4. Hepatitis
5. Osteomyelitis
6. Q fever in the immunocompromised host
7. Q fever in infancy
8. Neurologic manifestations: encephalitis, aseptic meningitis, extrapyramidal disease
9. Q fever in pregnancy
10. Post–Q fever fatigue syndrome

SELF-LIMITED FEBRILE ILLNESS

Self-limited febrile illness is probably the most common form of Q fever. In many areas, 11% to 12% of individuals have antibodies to *C. burnetii;* most do not recall pneumonia or other severe illness.[77] The age at which infection occurs, the sex, and the dose of the agent likely determine clinical severity.[78–80]

PNEUMONIA

Pneumonia is the most common presentation of Q fever and occurs as rapidly progressive pneumonia, atypical pneumonia, or pneumonia as an incidental finding in a febrile patient.[81,82] The rapid form mimics legionnaires' disease and the pneumonic form of tularemia.[83] Cough is present in only 28% of patients with radiographically confirmed Q fever pneumonia. Fever occurs in all patients. Severe headache is present in about 75% of patients and is a useful clue to the diagnosis. Other symptoms and the frequency with which they occur are fatigue (98%), chills (88%), sweats (84%), myalgia (68%), nausea (49%), vomiting (25%), pleuritic chest pain (28%), and diarrhea (including as presenting symptom; 21%).[84]

Physical examination of the chest is often unremarkable. The most common physical finding is inspiratory crackles.[81]

Radiologic Findings

The radiographic picture of Q fever pneumonia is variable. Nonsegmental and segmental pleural-based opacities are common, and atelectasis and hilar adenopathy may occur.[85,86] Multiple rounded opacities are very suggestive of Q fever that follows exposure to infected parturient cats.[85] Pleural effusion has been found and is usually small.[86] The resolution time ranged from 10 to 70 days.[86]

Outcome

C. burnetii pneumonia is rarely fatal, and in such instances there is usually a coexisting condition.[87] Information regarding the histology of this form of pneumonia in humans is limited. Pierce and coworkers[88] found small coccobacilli in alveolar macrophages on a transbronchial biopsy specimen in a patient with Q fever. A fatal case of pneumonia in a 43-year-old man was characterized by severe intraalveolar hemorrhagic and focal necrotizing pneumonia, with associated necrotizing bronchitis. Histiocytes, lymphocytes, and plasma cells were in the alveoli. This was thought to be Q fever pneumonia on the basis of organisms seen with a modified Giemsa stain.[89] A resolving, *C. burnetii* pneumonia lesion was characterized by an inflammatory pseudotumor (subsequently described in additional patients),[90] a lung mass composed of mixtures of macrophages, giant cells, plasma cells, and lymphocytes. The bronchiolar epithelium was focally absent, regenerated, or hyperplastic.[91] The changes that result from the inoculation of the lungs of rhesus monkeys resemble changes reported in humans. The resulting consolidation is peribronchial or peribronchiolar.[92] The interstitial infiltrate had more lymphocytes than monocytes (Fig. 188.1).

Laboratory Findings

The white blood cell count is usually normal, but one-third of patients have an increased count. Moderate thrombocytopenia is very common, but thrombocytosis (platelet counts >1 million/mm^3) may occur. Elevation (two to three times normal) of the hepatic transaminase level occurs in many patients. The serum bilirubin level is usually normal; however, jaundice may occur.[82] Rarely, the syndrome of inappropriate secretion of antidiuretic hormone occurs.[93]

Diagnosis of Acute Q Fever

The initial diagnosis of acute Q fever cannot be made on clinical grounds but may be suspected, and treatment should not be delayed while awaiting results of diagnostic testing.[94] The diagnosis of Q fever pneumonia is confirmed serologically or by PCR. *C. burnetii* is highly infectious, and tissues from patients with Q fever should be processed under Biosafety Level 3 conditions. PCR assays are an option if available but are most useful early in illness.[94,95–97]

Microagglutination,[98] complement fixation,[99] and immunofluorescent tests[100,101] as well as enzyme-linked immunosorbent assay[102] have been used in the serologic diagnosis of this illness. The indirect immunofluorescent test is best for the diagnosis of acute and chronic Q fever. Cutoff titers for a positive test may vary by population and laboratory methods.[103,104] The source of antigen can also influence the results. When treating patients with endocarditis, it is critical that laboratories store serum samples so that the previous sample can be tested concurrently with the current sample. This is the only way that a change in titer can be definitively determined.

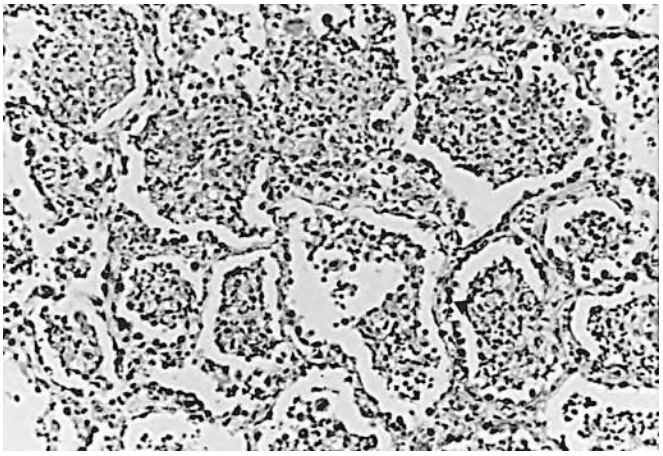

FIG. 188.1 Photomicrograph of an open lung biopsy specimen from a patient with Q fever pneumonia. The alveolar spaces are filled with an inflammatory exudate consisting of lymphocytes and macrophages. Note the hyperplasia of the alveolar lining cells. (Hematoxylin and eosin stain, ×500.)

A fourfold rise in titer between acute and convalescent samples is diagnostic of Q fever. Most patients seroconvert within 2 weeks (90% by week 3).[94] Cross-reactions have been reported between antibodies to *Bartonella* and *Legionella micdadei* and antibodies to *C. burnetii*.[3] Some authors have advocated using the indirect immunofluorescent test to detect antibodies to IgM so that a single serum specimen may be used for the diagnosis of acute Q fever.[73] A titer of 1:50 or higher has a high positive predictive value.[105] However, IgM antibodies may persist for 678 days[106]; in one study,[107] 3% of 162 patients still had a significant IgM antibody level 1 year after the infection. The CDC considers a phase II IgG ≥1:128 consistent with probable infection.[94]

Treatment of Acute Q Fever

The treatment of choice for acute infection with *C. burnetii* including pneumonia is doxycycline, 100 mg twice a day for 14 days.[94] Sobradillo and colleagues[108] performed a prospective, randomized, double-blind study of doxycycline and erythromycin in the treatment of pneumonia presumed to be caused by Q fever. Of 48 patients with Q fever proven by serologic studies, 23 received doxycycline, 100 mg twice daily, and 25 received erythromycin, 500 mg four times daily for 10 days. Fever resolution was faster in the doxycycline-treated group (3 ± 1.6 days vs. 4.3 ± 2 days for erythromycin-treated patients; $P = .05$). The authors concluded that doxycycline is more effective than erythromycin but recognized the self-limiting nature of most cases of Q fever pneumonia.

A retrospective review of 113 patients with acute Q fever pneumonia requiring hospitalization treated between 1989 and 1996 was performed by Gikas and coworkers.[109] This was a retrospective study with patients divided into three treatment groups: doxycycline, macrolide, and β-lactam. Patients treated with doxycycline had a quicker resolution of fever (2.39 days) than patients treated with macrolides (clarithromycin [3.3 days], roxithromycin [3.89 days], and erythromycin [3.93 days]) or β-lactams (6.4 days).

Morovic[110] reported on the effectiveness of doxycycline, clarithromycin, and moxifloxacin for treatment of 77 patients with Q fever pneumonia. Time to defervescence was similar: 2.4 days for doxycycline ($n = 20$), 1.9 days for clarithromycin ($n = 32$), and 2.2 days for moxifloxacin ($n = 25$). The regimens were well tolerated, and there were no documented relapses. The outbreak in the Netherlands provided the largest cohort to date looking at antibiotic regimens for acute Q fever. Dijkstra and colleagues[111] reported on 438 patients with acute Q fever. Patients treated with doxycycline and moxifloxacin had lower risk of hospitalization compared with azithromycin and β-lactams. Doxycycline was the most efficacious. Doxycycline is usually effective as outlined, but rarely a strain may be resistant, or a patient may be intolerant of doxycycline. In such situations, trimethoprim-sulfamethoxazole (TMP-SMZ), chloramphenicol, and rifampin are efficacious.

Monitoring Patients With Acute Q Fever

There is debate about the best way to follow patients with a diagnosis of acute Q fever, although there is agreement that patients should be monitored for development of cardiovascular infection.[26,42,94,112–114] This debate as well as evolving evidence has led one of the authors (D.R.) to propose that the term *chronic Q fever* be abandoned and replaced with *persistent focalized infection,* as chronic infection without focalization does not exist.[26,115] The hope is that this change in nomenclature and the evolving evidence will help provide clarity in the approach to persistent infection. This is necessary to clarify that patients with high antibody titers (phase 1 IgG >1:800) but no lesions or fever do not have "chronic" Q fever.

Monitoring serology every 3 months for up to 2 years after an episode of acute Q fever has been advocated for early detection of endocarditis.[26,94] This is based on the observation of endocarditis or other forms of persistent infection following acute Q fever, especially in patients with unrecognized or mild valvular heart lesions.[116] The risk of endocarditis in patients with acute Q fever and valvular heart disease was 39% in one study.[117] This increased risk in patients with underlying valvulopathies has led some to the recommendation that all patients with acute Q fever undergo screening transthoracic echocardiography (TTE).[26,117] TTE may be performed as soon as possible to detect acute endocarditis.[118] This is important because studies in France and the Netherlands found that prolonged treatment of acute Q fever with doxycycline and hydroxychloroquine prevented development of endocarditis in patients with preexisting valve lesions (bicuspid aortic valve or other significant valvulopathy).[119] We recommend that these patients be treated with hydroxychloroquine and doxycycline for 1 year and followed closely.

If the initial TTE is negative, patients should continue serologic follow-up. For patients who have rising serologic titers (phase I IgG >1:6400 [France] and phase I IgG >1:1024 [United States and Netherlands]) following treatment of acute infection, additional evaluation is warranted to ensure there is not a persistent infection (e.g., endocarditis, vascular infection, osteomyelitis). Evaluative approaches vary based on clinical guidelines.[26,94,120] If there are concerns for infection based on clinical status and not serology alone, repeat TTE or transesophageal echocardiography or both can be pursued. PCR of the blood can be done looking for *Coxiella*. Positron emission tomography (PET) has demonstrated promise when looking for evidence of persistent infection and resulted in adjustments to treatment in 20% of patients in one study.[121] PET is particularly efficient in detecting mycotic aneurysm and osteoarticular infection.[122]

Risk factors to consider during follow-up are rapid rise in antibody to phase I antigen, age older than 50 years, male sex, and appearance of aPL antibody. A newly described syndrome in France associates aPL antibodies with valvular vegetations in patients without prior valvular heart disease. The intensity of the aPL antibody (>100 IgG phospholipid units) and immunosuppression were independently associated with acute Q fever endocarditis, which was present in 1.2% of Q fever cases followed at the National Reference Center from 2007 to 2014.[118] A more recent study demonstrated that aPL antibody levels were significantly higher among patients proven to have endocarditis offering a potential marker of infection.[123]

ENDOCARDITIS

It is now recognized that chronic Q fever has a variety of persistent manifestations including endocarditis, infection of a vascular prosthesis, infection of aneurysms, osteomyelitis, hepatitis, interstitial pulmonary fibrosis, and pseudotumor of the lung.[124] Endocarditis is the prime manifestation of chronic Q fever.[125–147,148] The incidence of Q fever endocarditis is increasing, but this may reflect increased recognition of this entity.[2,112,125,138,146,149] This is supported by the decrease of endocarditis in France following prophylaxis.[114] Usually, abnormal native or prosthetic cardiac valves are affected[147]; however, any part of the vascular tree may become infected,[145] including clot in a left ventricular aneurysm. Such patients have a defective cell-mediated immune response to *C. burnetii*. Q fever endocarditis is rare in children.[143,150]

Clinical Manifestations of Endocarditis

The clinical presentation is consistent with culture-negative endocarditis, and the presence of fever is variable. Marked clubbing of the fingers, hypergammaglobulinemia, splenomegaly, and hepatomegaly may occur depending on diagnostic delay. A purpuric rash related to leukocytoclastic vasculitis may occur in about 20%. The erythrocyte sedimentation rate is usually increased; anemia and microscopic hematuria are also found. Arterial emboli complicate the course of some patients.

The vegetations in chronic Q fever may be absent in half of cases. The gross (Fig. 188.2) and microscopic appearance differ from vegetations seen in pyogenic bacterial endocarditis. Microscopically, there is a subacute and chronic inflammatory infiltrate. Many large foamy macrophages are present. Characteristic microorganisms are seen within these cells on electron microscopy.

Diagnosis of Endocarditis

Confirmation of the diagnosis in most cases is serologic (Table 188.1). A complement fixation titer of 1:200 or higher to phase I antigen has been said to be diagnostic of chronic Q fever, although not all patients in the series of Turck and coworkers[125] had this titer. In acute Q fever, complement fixation antibody titers to phase I antigen do not typically reach this level but can be observed in convalescent sera.

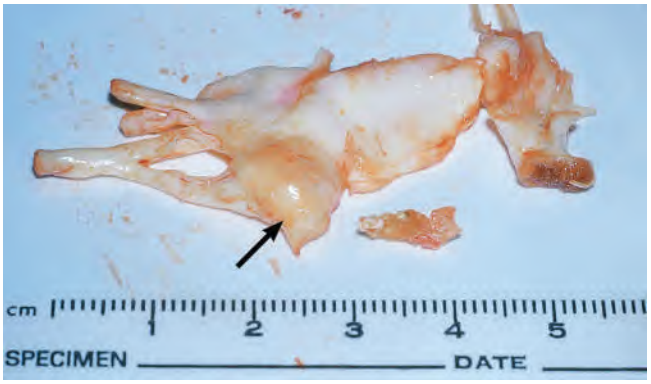

FIG. 188.2 Mitral valve of a patient with Q fever endocarditis. The nodule *(arrow)* was full of *Coxiella burnetii* organisms within foamy macrophages. *(From Raoult D, Raza A, Marrie TJ. Q fever endocarditis and other forms of chronic Q fever. In: Marrie TJ, ed.* Q Fever: The Disease. *Boca Raton, FL: CRC Press; 1990:179–199.)*

TABLE 188.1 Definition of Q Fever Endocarditis

A. Definite
Positive culture, PCR, or immunochemistry for *Coxiella burnetii* of a cardiac valve
B. Major Criteria
Microbiology
Positive culture or PCR of blood or an embolus for *C. burnetii* or serology with IgG phase I antibodies ≥1 : 6400
Evidence of Endocardial Involvement
Echocardiogram positive for IE: oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of alternative anatomic explanation; or abscess; or new partial dehiscence of prosthetic valve; or new valvular regurgitation (worsening or changing of preexisting murmur not sufficient)
PET scan showing a specific valve fixation and mycotic aneurysm
C. Minor Criteria
Predisposing heart condition (known or found on echography)
Fever, temperature >38°C
Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm (see at PET scan), intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions
Immunologic phenomena: glomerulonephritis, Osler nodes, Roth spots, or rheumatoid factor
Serologic evidence: IgG phase I antibodies ≥ 1 : 800 < 1 : 6400
Diagnosis Definite
1 A criterion 2 B criteria 1 B and 3 C criteria (including microbiologic evidence and cardiac predisposition)
Diagnosis Possible
1 B criterion, 2 C criteria (including 1 microbiologic evidence and cardiac predisposition) 3 C criteria (including positive serology and cardiac predisposition)

IE, Infective endocarditis; *IgG,* immunoglobulin G; *PCR,* polymerase chain reaction; *PET,* positron emission tomography.
Modified from Raoult D. Chronic Q fever: expert opinion versus literature analysis and consensus. J Infect. *2012;65:102–108.*

TABLE 188.2 Criteria for Diagnosis of Q Fever Vascular Infection

A. Definite
Positive culture, PCR or immunochemistry for *Coxiella burnetii* of arterial samples (prosthesis or aneurysm) or periarterial abscess or spondylodiskitis linked to aorta
B. Major Criteria
Microbiology
Positive culture, PCR of blood or embolic material for *C. burnetii,* or serology with IgG phase I antibodies ≥6400
Evidence of Vascular Involvement
CT scan: aneurysm or vascular prosthesis plus periarterial abscess, fistula, or spondylodiskitis
PET scan: specific localization to aneurysm or vascular prosthesis
C. Minor Criteria
Serologic IgG phase I antibodies ≥ 1 : 800 < 1 : 6400
Fever, temperature ≥38°C
Emboli
Underlying vascular predisposition (aneurysm or vascular prosthesis)
Diagnosis Definite
1 A criterion 2 B criteria 1 B criterion and 2 C criteria (including microbiologic evidence and vascular predisposition)
Diagnosis Possible
Vascular predisposition, serologic evidence, and fever or emboli

CT, Computed tomography; *IgG,* immunoglobulin G; *PCR,* polymerase chain reaction; *PET,* positron emission tomography.
Modified from Raoult D. Chronic Q fever: expert opinion versus literature analysis and consensus J Infect. *2012;65:102–108.*

Studies have reported high titers of IgA antibodies to phase I antigen in endocarditis and granulomatous hepatitis,[106,151] whereas another study found that patients with acute Q fever also produced IgA antibodies to phase I antigen, albeit in low titer.[106] Fournier and colleagues[152] used a phase I IgG antibody titer of 1 : 800 or greater by immunofluorescence as diagnostic of Q fever endocarditis, which was added as a major criterion to the Modified Duke Criteria for diagnosis of endocarditis.[153] Updated criteria for the diagnosis of Q fever endocarditis were proposed by Raoult in 2012 (Table 188.2).[26,114] Reliance on serology only to make the diagnosis of Q fever endocarditis is to be discouraged.[94] Instead, clinical judgment and using all the information available, as listed in Table 188.1, is recommended. Wegdam-Blans and associates[113] reviewed the literature on chronic Q fever and found 607 reports; after applying a number of criteria, they were left with 17 articles that they analyzed. Eight reports dealt with echocardiographic criteria, 6 of which described valvular vegetations that were present in 21% to 50% of cases; abscesses were described in 4 reports and were present in 7% to 20% of patients (Fig. 188.3).[149] PET can be useful in the diagnosis of Q fever endocarditis, osteomyelitis, and endovascular infection.[133]

Treatment of Q Fever Endocarditis

There is a growing body of evidence guiding the treatment of Q fever endocarditis and other persistent forms of Q fever.[2,26] An algorithmic approach used by one of the authors (DR) has demonstrated good clinical outcomes and is available online for use by health care providers.[153a] For cases that do not fit into these algorithms, health care providers should contact an expert.[120]

The preferred treatment regimen for Q fever endocarditis is doxycycline, 100 mg twice daily, plus hydroxychloroquine, 200 mg three times per day, for 1½ years for patients with Q fever native valve endocarditis and 2 years for patients with prosthetic valve infection.[3,94,154] Maurin and colleagues[155,156] reported that the bactericidal effect of doxycycline is enhanced when the phagolysosome is alkalinized with chloroquine or amantadine. Some experts have recommended hydroxychloroquine and doxycycline serum levels be monitored, as they may vary among patients, and adjusted to maintain a serum concentration between 0.8 µg/mL and 1.2 µg/mL for hydroxychloroquine and >5 µg/mL for doxycycline, whereas others have recommended checking levels if a patient fails to respond clinically and serologically.[94,157–159] Resistance to doxycycline appears to be rare, but in one patient who died, the minimal inhibitory concentration of his *C. burnetii* to doxycycline was 8 µg/mL.[158]

The combination of hydroxychloroquine plus doxycycline has been compared with other regimens, and there are options if they are not

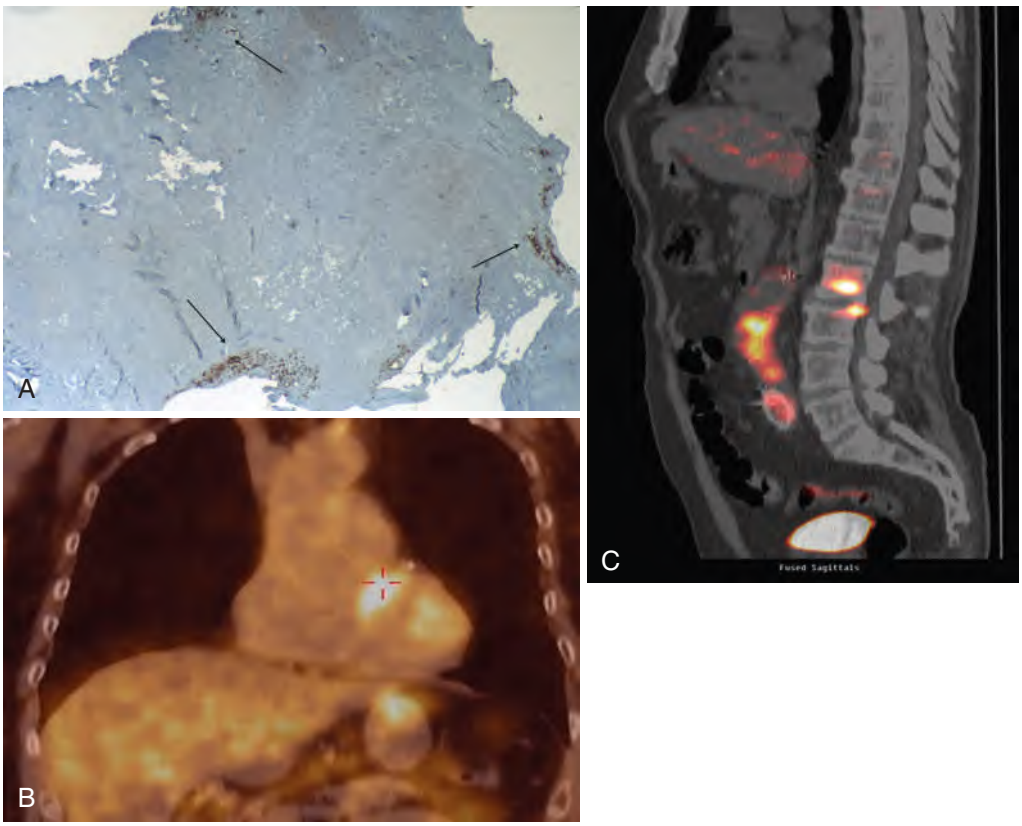

FIG. 188.3 (A) Analysis of an excised cardiac valve from a patient with Q fever endocarditis. Focal and small inflammatory infiltrates with infected macrophages *(arrows)* show that Q fever endocarditis is an insidious latent infection that can evolve over years without any symptoms. (B) ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) scan showing hypermetabolism of the aortic valve in an asymptomatic patient 3 months after febrile hepatitis was diagnosed as acute Q fever. Although the patient was asymptomatic, PET scan led to a diagnosis of Q fever endocarditis, together with serology (phase I immunoglobulin G [IgG] was 52,000). Transthoracic echocardiography was negative, but vegetation was later demonstrated by transesophageal echocardiography. After 5 months of treatment with doxycycline and hydroxychloroquine and surgery of an infected abdominal aortic aneurysm, hypermetabolism completely disappeared. A good outcome was confirmed by serology (phase I IgG was 12,800 at 1 year). (C) ^{18}F-FDG-PET scan led to identification of a Q fever vascular infection with contiguous spondylodiskitis.

tolerated or unable to be used. Hydroxychloroquine is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency, but the evidence of the risk of hemolysis is weak. Preexisting retinal or visual field deficits is a contraindication according to some authors,[94] although the French group does not exclude these patients.[159a] A Dutch group led by van Roeden[160] compared tetracyclines plus hydroxychloroquine versus tetracyclines plus quinolones and found no difference in outcomes, but a longer follow-up may be necessary to identify relapses.[2] The study by van Roeden and associates[160] showed high rates of clinical failure if monotherapy was used, which supports previous findings. A prior study using doxycycline in combination with ciprofloxacin or rifampin for 2 years had lower success rates.[154] Patients with aneurysms or vascular prosthetic infection have poor outcomes and high mortality (24% in Dutch outbreak).[161] Treatment requires prolonged doxycycline and hydroxychloroquine, and surgery has been found to be critical for the cure of infected prostheses.[162]

Follow-Up

Patients being treated with doxycycline and hydroxychloroquine need to be monitored for clinical and serologic response monthly as well as for side effects of these medications. Hydroxychloroquine can cause retinal toxicity, so a baseline ophthalmic examination as well as examinations every 6 months should be conducted to monitor for visual deficits. Recommendations for serologic monitoring during treatment vary from monthly[94] to every 3 to 6 months during therapy and every 3 months for the first 2 years after the cessation of therapy. Successful therapy is accompanied by a declining erythrocyte sedimentation rate, correction of anemia, and resolution of hyperglobulinemia. Valve replacement is frequently necessary but should be dictated by the patient's clinical status. Empirically, in France, we recommend a duration of 2 years for prosthetic valve infection and 1½ years for native valve and stop the treatment if IgG antibody levels have decreased by fourfold.[163]

HEPATITIS

Hepatitis or elevation of the aminotransferases is the most common manifestation of acute Q fever infection in France.[76,164,165] In the United States, hepatic involvement is present in most cases of Q fever. Hepatitis is more frequent in sheep-breeding and goat-breeding areas.

There are three presentations of Q fever hepatitis, as follows:[166–171]

1. An infectious hepatitis–like picture
2. Fever of unknown origin with increased transaminases
3. An incidental finding in a patient with acute Q fever pneumonia

In patients with fever of unknown origin related to Q fever, the typical doughnut granuloma is seen on liver biopsy, but liver biopsy is rarely performed now.[167,168] This granuloma with a dense fibrin ring surrounded by a central lipid vacuole is suggestive of Q fever but may be seen in other diseases (Hodgkin disease and infectious mononucleosis). *C. burnetii* has been isolated from the liver of patients with Q fever hepatitis, but the organism has not been visualized within the hepatic parenchyma.[125] Antibiotic treatment for 2 weeks is probably sufficient. The rare cases of Q fever hepatitis with high antibodies should be investigated, as isolated chronic hepatitis is mainly a consequence of endocarditis. These patients should be observed with serial antibody titers until the liver enzymes are normal and the titers decrease.

Some patients with hepatitis continue to have fever despite appropriate antibiotic therapy. These patients frequently exhibit anti–smooth muscle and aPL antibodies,[126] and a rapid defervescence of fever occurs with short-term corticosteroid therapy.[127,128] The autoimmune antibodies that are seen in Q fever hepatitis have prompted some authors to suggest that this infection may trigger autoimmune liver disease such as primary

biliary cirrhosis.[129] Our recommendation at the present time is to treat these patients with hydroxychloroquine until the fever resolves. Rarely, cholestatic jaundice and acalculous cholecystitis may complicate acute Q fever.[82,125]

NEUROLOGIC MANIFESTATIONS

Severe headache (often resulting in lumbar puncture) is the most common manifestation and probably represents central nervous system infection, although there is little evidence of serious brain involvement in Q fever.[172,173,174,175] Aseptic meningitis, encephalitis, or both complicate 0.2% to 1.3% of cases of Q fever.[173] A review of 16 cases of Q fever meningoencephalitis revealed that 8 patients had an elevated cerebrospinal fluid white blood cell level (predominantly mononuclear cells), ranging from 18 to 1392 cells/mm^3.[176] The protein level was usually increased, and the glucose level was normal.[176] The electroencephalogram was abnormal in 5 of 6 patients.

In a study from Plymouth, England, Reilly and coworkers[177] reported an astoundingly high 22% incidence of neurologic complications in 103 patients, of whom 46 had acute Q fever, 5 had chronic Q fever, and 52 had past infections. Of the 45 patients with acute Q fever, 6 had residual neurologic impairment including weakness, recurrent meningismus, blurred vision, residual paresthesias, and sensory loss involving the left leg. The meningoencephalitis of Q fever may be accompanied by seizures and coma.[178] Behavioral disturbance, cerebellar symptoms and signs, cranial nerve palsies, extrapyramidal disease, and the Miller-Fisher variant of Guillain-Barré syndrome (areflexia and ophthalmoparesis) have been reported to complicate acute Q fever. Demyelinating polyradiculoneuritis developed in a 71-year-old man 10 weeks after the onset of *C. burnetii* pneumonia.[179]

Q FEVER IN THE IMMUNOCOMPROMISED HOST

Q fever has been reported infrequently in the immunocompromised host[180–184]; however, this may reflect a lack of consideration. When Raoult and colleagues[184] examined serum samples from 500 human immunodeficiency virus (HIV)–positive individuals, they found that 10.4% of the 500 individuals had IgG antibodies to *C. burnetii* at a titer of 1:25 or greater compared with 4.1% of 925 apparently healthy blood donors ($P < .001$). They also found that from 1987 to 1989, 5 of 68 patients (7.3%) hospitalized with Q fever were positive for HIV. They estimated that in HIV-positive individuals, the number of cases of Q fever was 13 times higher, and these patients were symptomatic more frequently than the general population.

In a review of all cases of chronic Q fever in France from 1982 to 1990, the investigators noted that 20% of 84 patients were immunocompromised (cancer, chronic myeloid leukemia, acquired immunodeficiency syndrome, renal transplantation, corticosteroid therapy, renal dialysis, postpartum state, and chronic alcoholism).[124] *C. burnetii* infection resulted in a fatal interstitial pneumonia in an 11-year-old boy with chronic granulomatous disease.[185] In several cases, we have observed the concurrence of lymphoma and Q fever endocarditis. In a review from the French National Referral Center for Q fever, an association with non-Hodgkin lymphoma has been described. An excess risk of follicular lymphoma and diffuse large B-cell lymphoma was detected in patients with Q fever from 2004 to 2014. Although not a causative association, the complex and multifactorial risk for lymphoma may now include Q fever with other infectious diseases in some settings.[186] Patients with history of Q fever and adenopathy should be followed and evaluated for lymphoma.

OTHER MANIFESTATIONS OF Q FEVER

Osteomyelitis is an uncommon manifestation of *C. burnetii* infection, although there are increased reports in recent years possibly related to improved diagnostics including PET.[187–189] Q fever may also occur in infancy; it has caused pneumonia, febrile seizures, pyrexia of unknown origin, malaise, and meningeal irritation in infants.[190] Hematologic manifestations include bone marrow necrosis,[191] histiocytic hemophagocytosis,[192] and hemolytic anemia[193]; occasionally this disease may have simulated lymphoma.[194] Other hematologic manifestations include transient hypoplastic anemia[195] and splenic rupture.[196] Optic neuritis[197] and erythema nodosum[198] have also rarely been reported.

Q Fever in Pregnancy

C. burnetii replicates within trophoblasts.[199] In a trophoblast cell culture, by day 3 there is a 90-fold increase in the inoculum, and by day 9, 2.6×10^6 colony-forming units. Most data suggest that Q fever infection during pregnancy leads to worse fetal outcomes including abortion if infection occurs during the first trimester.[37,200,201,202,203,204] A study from Spain showed that women who had spontaneous abortions were more frequently seropositive than women who gave birth.[203] The study also found that phase II IgG antibody titers ≥1:160 were present in 9.6% of the abortion case group versus 3.1% of the group that delivered, and overall Q fever accounted for 12% of the spontaneous abortions.[203]

Data suggest that outcomes in pregnancy may vary depending on geographic region.[201,205,206] During the outbreak in the Netherlands, pregnancy outcomes were no different for seropositive women compared with seronegative women, although there was a small association with infants being small for gestational age.[201,205,206] However, these patients did not have acute Q fever, and there may be strain differences possibly related to specific plasmids (QpVD) between isolates from France and the Netherlands.[201] The combined data leave it unclear whether or not to screen pregnant women for *C. burnetii* infection during an outbreak.

Q fever during pregnancy should be treated with TMP-SMZ for the duration of the pregnancy.[94,204] In one retrospective study, this approach reduced obstetric complications from 81% to 44%. There were no intrauterine fetal deaths in the TMP-SMZ–treated group.[207] Patients with a chronic Q fever serologic profile should be treated with doxycycline and hydroxychloroquine for 1 year after delivery.

Post–Q Fever Fatigue Syndrome

The term *Q fever fatigue syndrome* (QFFS) is used to describe the protracted state of fatigue that can develop in up to 20% of patients who develop acute infection with *C. burnetii.*[208,209] This syndrome consists of a constellation of symptoms including fatigue, headaches, sweats, arthralgia, myalgias, blurred vision, muscle fasciculations, and enlarged and painful lymph nodes.[75] In a case-control study performed 5 years after a large outbreak of Q fever in individuals in a community in the West Midlands, England, Ayres and coworkers[210] found that participants in whom acute Q fever was diagnosed during the initial outbreak had more complaints of fatigue, sweats, blurring of vision, and dyspnea than age-matched, sex-matched, and geographically matched control subjects and that 42.3% of the infected individuals fulfilled the CDC criteria for chronic fatigue state.[211,212] In a study conducted in Newfoundland, in which 49 patients with goat-related Q fever were followed and the Short Form–36 health survey was used to assess quality of life, 38% (19 of 49) who had acute Q fever during the outbreak had persistent symptoms 3 months later and had significantly lower scores on all components of the Short Form–36 health survey than patients who did not have persistent symptoms.[213] During the outbreak in the Netherlands approximately half of infected patients had fatigue and reduced quality of life up to 4 years following the outbreak,[214] and one study suggested symptoms may last 7 years.[215]

Hickie and coworkers[216] enrolled 253 patients with Epstein-Barr virus infection ($n = 68$), Q fever ($n = 43$), Ross River virus infection ($n = 60$), and an unconfirmed group ($n = 82$) in a prospective longitudinal study to determine the frequency of chronic fatigue after each of these acute infections and the factors that predict the fatigue state. There was no difference in incidence among the infecting agents, and the authors concluded that aspects of the host response were the likely determinants of the postinfective fatigue syndrome. Other evidence suggests "cytokine dysregulation and immunomodulation from persistence of *C. burnetii*" in the host may be responsible for QFFS.[211,212]

Few studies have examined the effects of treatment for QFFS. A small study compared 4 patients with postinfective fatigue treated with 3 months of doxycycline with control subjects and demonstrated a decrease in headaches and mean body temperature.[217] Another study of 20 patients with QFFS reported similar decreases in fatigue and

headaches.[218] A randomized controlled trial in patients with QFFS comparing doxycycline, cognitive-behavioral therapy, and placebo showed a decrease in fatigue-related symptoms when comparing cognitive-behavioral therapy with placebo. The doxycycline arm showed no difference compared with placebo.[219] Consequently, patients with QFFS should not be given doxycycline. Additionally, some patients with QFFS have high levels of antibodies without evidence of ongoing infection, which prompted the new classification of Q fever to avoid treating patients with fatigue and high antibody titers by antibiotics.[220]

PREVENTION

Vaccination

Vaccination of people at risk for infection (e.g., abattoir workers, veterinarians) is an effective strategy to prevent infection.[221,222] At the present time, the vaccine, Q-VAX (Commonwealth Serum Laboratories, Victoria, Australia), is licensed and available only in Australia. It is a formalin-killed, whole-cell vaccine and has an estimated effectiveness for preventing clinical disease of 92% to 98%.[223,224] Skin testing is required before vaccination because individuals with prior exposure are at risk for adverse site reactions. Vaccination has also been used in animals as a potential means of reducing human exposure.[225]

Risk Reduction

The CDC has outlined steps to prevent infection in research facilities and hospitals.[94] Because of the lack of person-to-person spread, there is no need to isolate patients hospitalized with Q fever, unless the patient is undergoing a procedure that causes aerosolization or has recently given birth.[94] Simple measures such as the consumption of only pasteurized milk serve to eliminate cases of Q fever transmitted in this manner. In Cyprus, the incidence of *C. burnetii* infection among sheep and goats was reduced by a program in which aborted material was destroyed, affected dams were isolated, and the premises were disinfected.[226] Control of ectoparasites on cattle, sheep, and goats is also important in the control of Q fever. It seems prudent not to accept blood donors from a region undergoing an outbreak of Q fever, both during the outbreak and for up to 4 weeks after cessation of the outbreak. Ensuring veterinarians engage in practices that could prevent zoonotic transmission is important and may be overlooked.[227]

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The complete reference list is available online at Expert Consult.

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189 *Rickettsia prowazekii* (Epidemic or Louse-Borne Typhus)

Lucas S. Blanton and David H. Walker

SHORT VIEW SUMMARY

Microbiology
- *Rickettsia prowazekii* is a small, obligately intracellular gram-negative coccobacillus.
- Its 1.1-Mb genome has undergone evolutionary reduction, resulting in the reliance on the host cell cytosol for many biosynthetic functions.
- An extracellular dormant form remains infectious in louse feces for months or longer.

Epidemiology
- The agent is transmitted between patients by the human body louse *(Pediculus humanus corporis).*
- Lice become infected while feeding on rickettsemic patients. The organism is inoculated into a new host by scratching of rickettsiae-laden louse feces into louse-bitten skin or by being rubbed into mucous membranes.
- Recovered patients remain latently infected, are susceptible to reactivation with rickettsemia, and can serve as a source for an epidemic. Brill-Zinsser disease is recurrence of typhus, often in milder form, even decades after the initial infection.
- Epidemics are associated with conditions that promote louse infestations through poor hygiene—poverty, cold climate, jails, and displacement of populations by war and other calamities.
- In eastern North America, an extrahuman reservoir of *R. prowazekii* exists in flying squirrels *(Glaucomys volans),* with infections transmitted to humans through mucous membrane or inhalational exposure to the squirrel's flea or louse feces.

Clinical Manifestations
- Frequent symptoms include fever, headache, chills, myalgia, and rash (see Table 189.1).
- Untreated illness may progress to cause pulmonary edema, encephalitis, and death.
- Recrudescent typhus and flying squirrel–associated typhus manifest similarly but are less severe.

Diagnosis
- The indirect immunofluorescence assay is the mainstay of serologic diagnosis. A fourfold rise in immunoglobulin G (IgG) titer from acute illness to convalescence confirms the diagnosis.
- Polymerase chain reaction assay and immunohistochemical detection of *R. prowazekii* in blood or tissue, respectively, can establish the diagnosis during acute illness.
- Treatment should not be withheld while one awaits laboratory confirmation.

Treatment and Prevention
- Doxycycline, 100 mg twice daily for 7 days, is the treatment of choice.
- Control of body lice by changing and washing garments in hot water is essential for prevention and outbreak control.

Rickettsia prowazekii is the only rickettsial species that can cause devastating, naturally occurring epidemics capable of killing a substantial proportion of human populations infested with body lice. Epidemics are associated with conditions that prevent bathing and washing of clothes in hot water, such as war and poverty, natural disasters such as earthquakes and floods, displacement of populations, jails, and lack of hygiene. Historical accounts of typhus epidemics in Mexico, associated with times of extreme poverty and hunger, have been correlated with drought through the study of tree-ring data to infer annual precipitation.[1] A continued problem in impoverished, louse-infested populations, epidemic typhus threatens to reemerge as it did during the Civil War in Burundi, where an estimated 100,000 persons developed typhus in 1997.[2]

Based on his observations of an Italian epidemic in 1528, epidemic typhus was described vividly by Hieronymus Fracastorius as a previously unknown, life-threatening disease in which a petechial rash appeared 4 to 7 days after the onset of fever and was accompanied by stupor and delirium. The word *typhus* is derived from the Greek *typhos,* meaning "smoky" or "hazy," which describes the state of confusion accompanied by stupor. Luis de Toro described the same course and signs of an illness that occurred in soldiers on the Iberian Peninsula in 1557, also noting winter seasonality and association with contact with clothing of the ill. The term *exanthematic typhus* was proposed by Boissier de Sauvages in 1760 and differentiated the disease from typhoid.[3] During an epidemic of typhoid fever in Philadelphia in 1836, Gerhard distinguished these diseases by the presence of intestinal lesions in typhoid patients. In 1909, Charles Nicolle experimentally established the fact that typhus was a transmissible infection with the human body louse as its vector. Investigations from 1910 to 1922 by Ricketts, von Prowazek, da Rocha-Lima, and Wolbach used microscopy, xenodiagnosis in lice, and histochemistry to establish that the agent was a bacterium that proliferated in human endothelial cells and louse gut epithelium but could not be cultured axenically.[4]

In 1896 and 1910, Nathan Brill described a series of patients in New York with a febrile illness that was shown by Hans Zinsser in 1934 to be a rickettsial infection.[5,6] Zinsser hypothesized correctly that the illness is a recrudescence of long-latent *R. prowazekii,* now called Brill-Zinsser disease. The distinction of *Rickettsia typhi* as a separate agent that causes an endemic, clinically similar disease transmitted to humans by fleas from a zoonotic cycle involving rats was established by the work of Neill (1917),[7] Mooser (1928),[8] Maxcy (1929),[9] and Dyer (1931).[10] The feared specter of epidemic louse-borne typhus receded with the following: (1) the success of a killed *Rickettsia* vaccine in preventing the deaths of allied soldiers during World War II; (2) the effectiveness of insecticides in curtailing epidemics by louse control; and (3) the effective treatment of illness with tetracyclines and chloramphenicol. Currently, epidemics of typhus are increasingly recognized, lice resistant to various insecticides have been detected, antibiotic-resistant rickettsiae have been developed, and aerosol-transmitted, weaponized *R. prowazekii* has emerged as a biothreat. Lack of direct human-to-human transmission is a limitation of use as a bioterror weapon. *R. prowazekii* has been isolated from *Amblyomma* and *Hyalomma* ticks in Ethiopia and in *Amblyomma tenellum* ticks in Mexico.[11,12] The presence of *R. prowazekii* DNA has also been found within *Ixodes ricinus* ticks in the Netherlands.[13] Moreover, in 1975, *R. prowazekii* was identified in a highly prevalent zoonotic cycle in flying squirrels in the eastern United States.[14]

MICROBIOLOGY

The causative agent of louse-borne typhus, *R. prowazekii*, is an obligately intracellular, small (1 × 0.3 µm) coccobacillus. Its 1.1-Mb genome has undergone considerable reduction, contains a subset of the genes of

Rickettsia conorii,[15] and exhibits little variation among isolates.[16] *R. prowazekii's* conserved structure necessitates its ability to manipulate host cell processes, as demonstrated for small GTPases.[17] Many biosynthetic functions are provided by the organism's milieu in the resource-rich host cell cytosol, to which it has adapted by means of evolutionary selection for transport mechanisms for adenosine triphosphate (ATP), amino acids, phosphorylated sugars, and triose phosphate.[15,18] Its gram-negative cell wall contains an abundant 135-kDa, immunodominant, tetragonally arranged, S-layer surface protein; lipopolysaccharide; and peptidoglycan.[19] Differential expression of genes occurs with its infection of mammalian or arthropod host cells.[20] It possesses an extracellular dormant form that remains infectious in louse feces for months or more. Technical barriers to the genetic manipulation of *R. prowazekii* have limited extensive study of its virulence mechanisms, but development of insertional mutants,[21,22] site-directed knockouts,[23] and maintenance of inserted plasmids offer tools for more extensive study.[24] To date, only phospholipase D and phospholipase A have been identified as virulence factors of *R. prowazekii.*[23,25]

EPIDEMIOLOGY

Louse-Borne Epidemic Typhus

Typhus affected the outcomes of wars from the 1500s until the end of the 19th century.[26] During the Russian campaign of 1812, typhus was responsible for the deaths of many of the 700,000 troops of Napoleon.[27] During World War I, the Bolshevik revolution, and its aftermath, an estimated 30 million cases of typhus occurred in the Soviet Union alone, with 3 million deaths.[28] During World War II, epidemics of typhus occurred in eastern Europe, North Africa, concentration camps, and southern Italy, where dichlorodiphenyltrichloroethane (DDT) was used against lice to abort an epidemic in Naples in 1944.

R. prowazekii is transmitted between patients by the human body louse *(Pediculus humanus corporis)*, which is strictly adapted to humans, lives in the clothes, and takes a blood meal five times daily.[29] Lice become infected while feeding on the blood of rickettsemic patients. *R. prowazekii* enters the louse gut epithelial cells and replicates by means of binary fission until the massively infected cells burst[30] and are released into the louse feces 5 to 7 days after ingestion. Lice are not adapted to an elevated body temperature and leave febrile patients for a new host. *Rickettsia*-laden louse feces are deposited on the skin and clothes and are introduced into the new host by being scratched into the louse-bitten skin or being rubbed into mucous membranes such as the conjunctiva; they are also transmitted through inhalation.

Persons who recover from typhus fever remain latently infected and are susceptible to reactivation of the infection and rickettsemia, which can infect body lice and ignite an epidemic under circumstances of crowding, extreme poverty, cold climate, and poor hygiene, which can lead to a high prevalence of louse infestation (Fig. 189.1). The louse population can expand rapidly (11% daily).[30,31] Lice are currently prevalent in poor countries and found on homeless persons in developed countries. In France, 35% of members of the homeless population have lice. Risk factors for reactivation of latent infection in humans have not been determined, but waning immunity, poor nutrition, alcoholism, and stress have been hypothesized as potentially important.

Typhus is endemic in the Peruvian Andes, Burundi, and Rwanda. The most recently documented outbreak occurred in a youth rehabilitation center, where the recorded attack and case-fatality rates were 10% and 3.5%, respectively.[32] Cases have been diagnosed in Russia, in patients from Morocco, Algeria, and Senegal, and in a homeless person in France.[2,33–37] Given the geographic distribution of latent typhus infection from known historic epidemics, the neglect with which this disease has been handled, and the limited availability of laboratory diagnostic methods, the current epidemiology of louse-borne typhus, particularly in marginal populations of mountainous areas in Asia, South and Central America, and Africa, is unknown.

Sylvatic Typhus

An extrahuman reservoir of *R. prowazekii* exists in a large portion of southern flying squirrels *(Glaucomys volans),* which are distributed from Florida to Maine and westward to Minnesota and eastern Texas.[14] In stark contrast with the louse-human cycle, in which 15% of humans

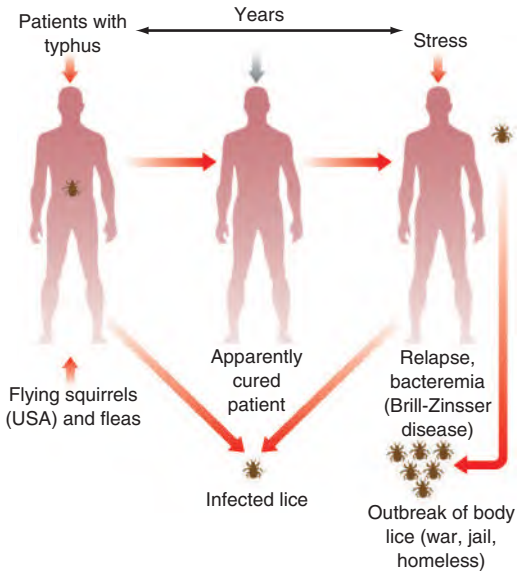

FIG. 189.1 Transmission of typhus.

die and 100% of lice develop rickettsial destruction of the intestine with extravasation of the red blood meal into the hemocele and death, *R. prowazekii* causes subclinical rickettsemia in flying squirrels and no ill effects on the squirrel's own species of lice and fleas.[38] Infections are apparently transmitted to humans by flying squirrel fleas or mucous membrane or inhalation exposure to the feces of the flea or louse. These illnesses occur mainly during winter, when flying squirrels enter buildings.[39] Clusters of cases have occurred in association with flying squirrel–infested attics and walls of dwellings.[40,41] A case of recrudescent typhus has been described in a patient 11 years after *R. prowazekii* infection related to close contact with flying squirrels.[42] The role of ticks in transmitting *R. prowazekii* is currently unknown, although this source would appear to be a potential explanation for a case of *R. prowazekii* originating in southern Texas.[43]

PATHOGENESIS

After inoculation into the skin, *R. prowazekii* spreads throughout the body via the bloodstream. Rickettsiae enter mainly endothelial cells and, to a lesser extent, macrophages by induced phagocytosis; they escape from the phagosome into the cytosol, where they proliferate until the cell bursts.[44] Phospholipase D has been found to play a significant role in pathogenesis, with evidence for mediating rickettsial phagosomal escape in concert with rickettsial hemolysin C.[45,46] The posttranslational methylation of *R. prowazekii* outer membrane protein B appears to play a role in virulence.[47] Point mutation–derived inactivation of a methyltransferase is responsible for the attenuation of the Madrid E strain (the historical vaccine strain).[48] *R. prowazekii* lacks actin-based mobility that mediates the cell-to-cell spread of spotted fever group rickettsiae. Rickettsial phospholipase A_2 activity has been hypothesized to play a role in lysis of infected cells. A gene for a patatin-like protein has been identified in *Rickettsia,* with sequence similarity to phospholipase A.[49,50] The *R. prowazekii* genome encodes two of these proteins.[51] One is similar in sequence to the *Pseudomonas aeruginosa* cytotoxin ExoU phospholipase A and similarly exhibits superoxide dismutase–dependent activation without experimental evidence for pathologic effect.[25] The principal pathophysiologic effects of rickettsial infection include increased vascular permeability and petechial hemorrhage. Thrombosis occurs in only a tiny minority of foci of vascular infection and injury, and ischemic necrosis is a rare consequence.[4] The most important vital target organs are the brain and the lung. The petechial maculopapular rash is a manifestation of cutaneous vascular infection by *R. prowazekii.* Classic pathologic lesions are composed of swollen, infected endothelial cells in the microcirculation, with adjacent perivascular infiltration by lymphocytes and macrophages, which represents the host effector cellular immune response.[4,52] The primary animal model for epidemic

typhus is guinea pigs infected intraperitoneally with *R. prowazekii.* Lesions typical of typhus encephalitis are produced.[53] Balb/C mice have been reported to become infected by a narrow dose range of *R. prowazekii,* develop illness associated with growth of *R. prowazekii,* mount an effective immune response, and develop recrudescence after immunosuppression with corticosteroids.[54,55] Nonhuman primate models have been described that reproduce the pathologic lesions of human typhus.[56,57]

CLINICAL MANIFESTATIONS

Louse-Borne Epidemic Typhus

Experiments in human volunteers during the preantibiotic era demonstrated that after an incubation period of 8 to 16 days (mean, 11.1 days) and a prodrome of 2 days, rash developed in 79% of subjects an average of 4 days after onset of illness, and the fever lasted for 12 days. In an epidemic in Poland after World War I, a prodrome of 1 day or longer occurred in 88%, followed by fever (100%), headache (89%), chills (74%), myalgias (54%), rash (an entry criterion of the study), conjunctival injection (87%), and rales (74%).[4] Erythematous 2- to 6-mm macules appeared most often on the trunk on day 5 and later on the extremities. Without the availability of antibiotics, the course was characterized by marked delirium (48%), severe cough (38%), hemorrhagic rash (34%), gangrene (4%), coma (6%), death (13%) at a median of 12.5 days after onset, or defervescence at a median of 14 days after onset. Studies from Ethiopia and Burundi have demonstrated a lower incidence of visible rash in darkly pigmented skin, marked myalgia, variable incidence of stupor, cough, and conjunctivitis (Table 189.1), and a lower case-fatality rate resulting from effective antimicrobial treatment in many patients.[2,58]

Onset is usually abrupt, with rigors, malaise, and severe headache. The tongue is dry and the patient is constipated. The rash progresses through macules that disappear on pressure to maculopapules with petechiae. The face, palms, and soles are usually spared. In darkly pigmented patients, cutaneous lesions are more easily visible in the axilla. Chest radiographs frequently reveal interstitial pneumonia. Cases have not occurred in settings in which clinical laboratory abnormalities have been studied extensively, except for the Ethiopian series, which demonstrated values characteristic of disseminated rickettsial vascular injury and increased vascular permeability (Table 189.2).[58]

TABLE 189.1 Clinical Manifestations of Epidemic Typhus

	PLACE	
MANIFESTATION	**BURUNDI**	**ETHIOPIA**
Number of cases	102	60
Fever >39°C	100%	100%
Headaches	100%	100%
Any rash	25%	38%
Purpuric rash	11%	33%
Stupor	81%	35%
Coma	4%	—
Cough	70%	38%
Nausea, vomiting	57%	43%
Conjunctivitis	15%	53%
Diarrhea	13%	—
Splenomegaly	8%	13%
Photophobia	—	33%
Myalgias	100%	70%

Data for Burundi from Fournier PE, Ndihokubwayo JB, Guidran J, et al. Human pathogens in body and head lice. Emerg Infect Dis. *2002;8:1515–1518; data for Ethiopia from Perine PL, Chandler BP, Krause DK, et al. A clinico-epidemiological study of epidemic typhus in Africa.* Clin Infect Dis. *1992;14:1149–1158.*

Sylvatic Typhus

Flying squirrel–associated typhus cases have generally been less severe, with no fatalities recorded. Patients have developed fever (100%), headache (81%), maculopapular rash (66%), confusion (44%), and myalgia (42%).[39,59–61]

Recrudescent Typhus

In 1910, Brill's clinical description of recrudescent typhus was that of an illness resembling nonfatal typhus, with onset characterized by chills, intense headache, fever, myalgias, nausea, and sometimes vomiting. Patients are prostrate with apathy, dulled sensorium, and persistent headache as an overriding symptom. Between the fifth and seventh days of illness, a maculopapular rash appears on the back and abdomen and spreads rapidly. Congested conjunctivae and constipation are prominent features in many cases. The untreated illness lasts about 2 weeks. Brill stated, "In the case of an epidemic of typhus fever, in my opinion, it would be simply impossible to say that these cases which I have described were not mild typhus fever."[5] Twenty-four years later, Hans Zinsser isolated rickettsiae from the blood of similar patients—louse-free immigrants from typhus-endemic regions of Europe. Thus, the eponymous designation, Brill-Zinsser disease, is used to refer to recrudescent typhus.[6]

DIAGNOSIS

In the midst of a recognized epidemic, the patient with a late-stage florid rash or even one with fever, severe headache, and myalgia without a rash would likely be diagnosed with louse-borne typhus. The diagnosis of louse-borne typhus early in an outbreak, when only a few cases have been reported, is more challenging. The most important differential diagnoses are typhoid fever and malaria in tropical countries.[33] The prominent cough and crackles often suggest a diagnosis of pneumonia. Neurologic signs and cerebrospinal fluid pleocytosis may lead to consideration of viral or bacterial meningoencephalitis. Nausea, vomiting, and abdominal tenderness raise the diagnostic possibilities of viral or bacterial enterocolitis or even an acute abdominal condition requiring surgery. Jaundice and elevated hepatic enzyme levels suggest viral hepatitis. The hemorrhagic rash may lead to diagnostic consideration of arenaviral and filoviral hemorrhagic fevers.[62] Other differential diagnoses include leptospirosis, arboviral and enteroviral infections, meningococcemia, trench fever, relapsing fever, and other rickettsioses.

Other circumstances under which *R. prowazekii* infection should be considered involve immigrants from regions where epidemic typhus has been prevalent, persons who have been exposed to flying squirrels, and homeless persons.[34,39,59] It is unlikely that cases of aerosol-transmitted typhus in a bioterrorist attack would be diagnosed clinically before the onset of rash, if even then.[63]

The laboratory diagnosis of louse-borne typhus generally relies on the detection of antibodies with a fourfold rise in titer in convalescence.

TABLE 189.2 Clinical Laboratory Findings in Patients With Epidemic Typhus

FINDING	**INCIDENCE (%)**
White blood cell count	Low, 3; elevated, 14
Thrombocytopenia	43
Increased serum AST	63
Increased serum ALT	35
Increased serum LDH	82
Increased serum CPK	31
Increased BUN	31
Decreased serum protein	38

ALT, Alanine aminotransferase; *AST,* aspartate aminotransferase; *BUN,* blood urea nitrogen; *CPK,* creatine phosphokinase; *LDH,* lactate dehydrogenase.
Modified from Perine PL, Chandler BP, Krause DK, et al. A clinico-epidemiological study of epidemic typhus in Africa. Clin Infect Dis. *1992;14:1149–1158.*

Usually, a diagnostic titer is detected during the second week of illness. The standard serologic method is indirect immunofluorescence assay, and an immunoglobulin G (IgG) titer of 1:128 or an IgM titer of 1:32 confirms the diagnosis. Enzyme immunoassays that yield reliable results have also been developed. Although the *Proteus vulgaris* OX-19 agglutination (Weil-Felix reaction) has been demonstrated to be poorly sensitive and nonspecific, it may be useful when it is the only method available in a developing country. Antibodies stimulated by *R. prowazekii* react with shared antigens of *R. typhi,* allowing diagnostic detection of cross-reactive antibodies. A fourfold higher titer against *R. prowazekii* than *R. typhi* distinguishes epidemic typhus from murine typhus in fewer than half of cases.[64] The predominance of IgG antibodies and the absence of IgM and Weil-Felix antibodies in recrudescent typhus is controversial.[65]

Although serodiagnosis is retrospective, methods that can establish a diagnosis during the acute stage of infection—namely, the polymerase chain reaction (PCR) assay and immunohistochemical detection of *R. prowazekii* in blood or tissue, respectively—are seldom available in regions where typhus epidemics occur.[66–68] Although loop-mediated isothermal amplification offers a relatively rapid and field-applicable molecular diagnostic tool,[69] the presence of few circulating rickettsial organisms within the bloodstream limits the utility of even the most analytically sensitive molecular assays for clinical use.[70] Feasibility has been demonstrated for serodiagnosis on blood spotted onto filter paper and for rickettsial isolation or PCR detection in lice removed from the patient, either of which can be sent to a referral laboratory by mail.[71,72] Strain typing with PCR to amplify a minimal gene set may be useful to study the origin of strains during an epidemic or to identify strains used in bioterrorism.[73] Rickettsiae may also be isolated most effectively from blood, buffy coat, plasma, or tissue in shell vial cell culture.[74]

TREATMENT

The treatment of choice for all patients who are not allergic to tetracyclines and who are not pregnant is doxycycline, 100 mg twice daily for 7 days.[75] Under chaotic epidemic conditions and in other situations in which doxycycline availability is limited, a single dose of 200 mg of doxycycline is effective, although in a small portion of patients relapse may occur.[76] Where available, chloramphenicol, 60 to 75 mg/kg/day in four divided doses (not to exceed 4 g total), and tetracycline, 25 to 50 mg/kg/day in four divided doses, are also effective. Other antibiotics, including β-lactams, aminoglycosides, and sulfonamides, are ineffective. Although fluoroquinolones, rifampin, and some of the newer macrolides show inhibition of growth of *R. prowazekii* in cell culture, none has proven to be efficacious clinically.

PREVENTION

Control of body lice is the mainstay in the prevention of epidemic typhus. When an outbreak of lice appears, the first step is to change all garments and wash them in hot water. Introducing regular washing of clothes will stop outbreaks. Only when this is impossible is delousing with insecticides, such as Lindane in powder form, useful. Application of 30 to 50 g of 1% permethrin dusting powder per adult both inside and outside of clothing and on bedding may be repeated every 6 weeks to kill lice.[77] Mass treatment of clothed individuals with permethrin can be achieved by use of a compressed air duster.[78]

No vaccine is currently available for the prevention of typhus. However, the identification of the attenuating point mutation of a previously successful live vaccine (E strain) that was prone to reversion offers the opportunity to develop a permanently attenuated protective vaccine against *R. prowazekii.*[48,79,80] The discovery of protective T-cell antigens via the in silico analysis of 834 *R. prowazekii* proteins shows promise for further vaccine development.[81]

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190 *Rickettsia typhi* (Murine Typhus)

Lucas S. Blanton, J. Stephen Dumler, and David H. Walker

SHORT VIEW SUMMARY

Microbiology
- Murine typhus is caused by *Rickettsia typhi,* an obligately intracellular gram-negative bacterium.
- The organism infects endothelial cells in mammalian hosts and midgut epithelial cells in flea hosts.

Epidemiology
- Murine typhus is distributed worldwide and is prevalent in tropical and subtropical seaboard regions where rats (*Rattus* spp.) and their fleas (*Xenopsylla cheopis*) serve as reservoirs and vectors, respectively.
- In the United States, most cases are reported in southern Texas and southern California where the cat flea (*Ctenocephalides felis*) is the predominant vector and opossums are the suspected reservoir.
- The disease is transmitted by the inoculation of infected flea feces into a flea bite wound. The incubation period is 1 to 2 weeks.

Clinical Manifestations
- Frequent symptoms in early illness include fever, headache, nausea, and vomiting.
- Rash occurs in about one-half of patients. It is usually described as macular or maculopapular, and is most often observed on the trunk.
- The clinical course is usually uncomplicated, but occasionally central nervous system abnormalities, renal insufficiency, respiratory failure, and death occur.
- Elevations in serum hepatic aminotransferase levels are frequent laboratory findings. Vascular injury often leads to hypoproteinemia, hypoalbuminemia, and electrolyte abnormalities (e.g., hyponatremia and hypocalcemia).

Diagnosis
- Early diagnosis of murine typhus is based on clinical suspicion and epidemiology.
- Immunofluorescence assay is the mainstay of serologic diagnosis, which is generally retrospective. A fourfold rise in immunoglobulin G titer from acute illness to convalescence confirms the diagnosis.
- Immunohistochemical detection of *R. typhi* in a skin biopsy specimen can establish the diagnosis during acute infection. Polymerase chain reaction assay amplification of rickettsial nucleic acids in blood or skin biopsy samples can also establish the diagnosis, but sensitivity is poor on blood.
- To avoid prolonged illness and severe or potentially fatal infection, treatment should not be withheld while awaiting laboratory confirmation.

Treatment and Prevention
- Doxycycline, 100 mg twice daily for 7 to 10 days, is the treatment of choice.
- Prevention is directed toward the control of flea vectors and potential flea hosts.

In 1922, Hone first described human infections "closely resembling typhus fever."[1] Since 1926, when Maxcy successfully identified murine typhus as a distinct clinical and epidemiologic entity, and 1931, when Dyer isolated a new typhus group named *Rickettsia* from rats and fleas, murine typhus has been recognized as a worldwide zoonotic problem.[2] Often underrecognized and believed to be clinically mild, murine typhus may occur in epidemics or with high prevalence in certain geographic regions.[3–9] Illness may be severe, particularly in the elderly, with death occurring in a small proportion of individuals.[10,11] The association with both rat and cat fleas is now well established.[12,13]

MICROBIOLOGY

Rickettsia typhi, the causative agent of murine typhus, is an obligately intracellular bacterium that infects endothelial cells in mammalian hosts and midgut epithelial cells in the flea hosts.[12] A new rickettsial agent, *Rickettsia felis,* has been recognized as sharing some antigenic and genetic components with *R. typhi* but is best phylogenomically characterized as a transitional group bacterium between typhus and spotted fever group rickettsiae.[14,15] As typical for the genus *Rickettsia, R. typhi* contains rickettsial outer membrane protein B (OmpB) and the autotransporter Sca4, but its lack of rickettsial outer membrane protein A (OmpA), a characteristic of spotted fever group rickettsiae, resembles the typhus group.[16] In addition to *ompB,* three other autotransporters—*sca1, sca2,* and *sca3*—are expressed.[17] OmpB mediates adhesion and entry events for other *Rickettsia* spp., and Sca2 also functions as an adhesin in spotted fever rickettsiae.[16,18] In addition, the *R. typhi* genome encodes genes for several potentially membranolytic proteins (*tlyA, tlyC, pldA,* and two phospholipase A2 genes) and RalF, a type IV secretion system effector that could facilitate cell invasion or endosomal escape.[15,19–22] These organisms are well adapted for intracellular life because they lack enzymes for carbohydrate metabolism, lipid biosynthesis, nucleotide synthesis, and amino acid metabolism and a complete tricarboxylic acid cycle but possess several ATP-ADP translocase genes that likely mediate host energy parasitism.[15] The genome encodes Sec, TolC, and type IV secretion system components.[15,23–25] As in the case of TolC-dependent secretion of an ankyrin repeat–containing protein, Rickettsia ankyrin repeat protein 1 (RARP-1), these secretion system components suggest delivery of effector proteins into the host cell to influence cell function and fate.[25] Unlike the situation for spotted fever group rickettsiae, *R. typhi* lacks *rickA,* which encodes a protein promoting intracellular motility via actin polymerization.[16]

EPIDEMIOLOGY

Murine typhus is found worldwide and is especially prevalent in tropical and subtropical seaboard regions, where the most important rat reservoirs (*Rattus* spp.) and flea vectors (*Xenopsylla cheopis*) are found (Fig. 190.1).[2,12,26] Urban ports, often rife with rats, have been associated with a higher prevalence of murine typhus.[27] An important vector in some areas (southern Texas and southern California) is the cat flea (*Ctenocephalides felis*), and opossums have been implicated as a potential reservoir in these areas.[8,12,26,28–30] Thus residents and visitors to these urban and suburban regions are at risk when flea-bearing animals bring infected fleas into close proximity to humans. The demonstrable seroprevalence to typhus group antibodies in areas where the disease is endemic, and in areas where the disease is not well recognized, indicates that murine typhus is likely vastly overlooked.[31–34]

Murine typhus was once more prevalent in the United States, especially in the warm humid South. In 1944, at the peak of reporting, there were 5401 cases.[35] Efforts to control rat populations, and more likely the strategic use of DDT on rat runs and harborages, made dramatic strides

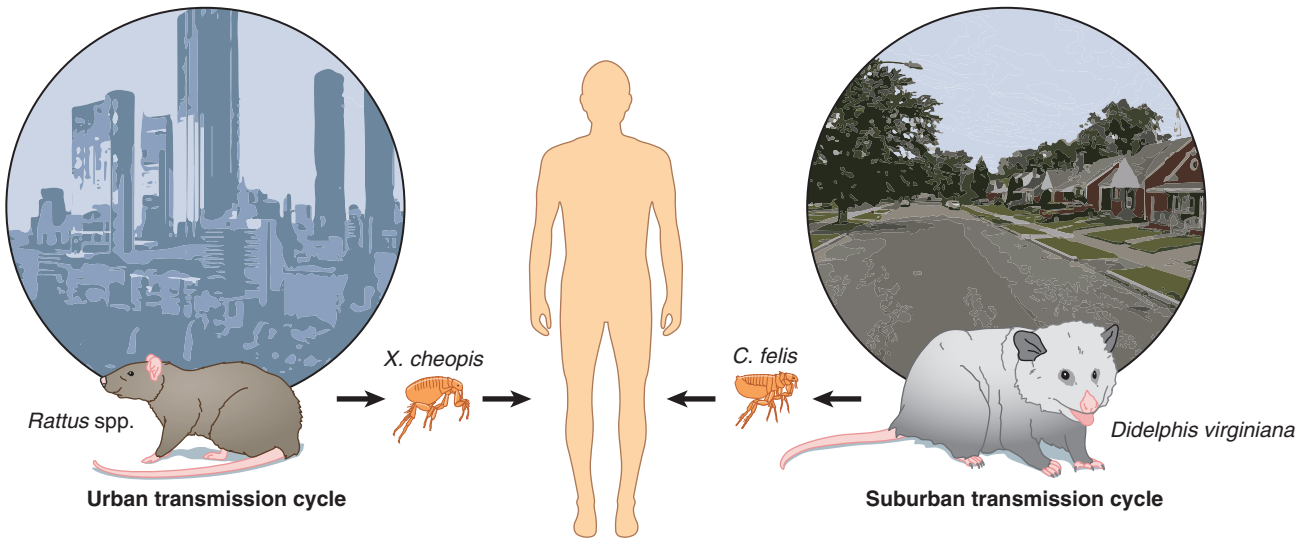

FIG. 190.1 Transmission of murine typhus. In the urban transmission cycle, rats (*Rattus* spp.) serve as reservoirs and their fleas (*Xenopsylla cheopis*) serve as vectors. In the suburban transmission cycle, the cat flea (*Ctenocephalides felis*) is the predominant vector and opossums (*Didelphis virginiana*) are the suspected reservoir.

to break the rat-flea transmission cycle and decrease the prevalence of murine typhus.[36,37] By 1956 fewer than 100 cases were reported in the United States.[35] In the decades following this dramatic decline of murine typhus, there persists a low but increasing level of reported infections, with most cases seen in south Texas and southern California.[29] In Texas, the last several decades have witnessed the majority of cases occurring in the southernmost counties along the Mexican border, but in the last 10 years there have been increasing reports of murine typhus occurring in more northern municipalities.[38,39] Outbreaks in an urban area of central Texas, the northern Texas coast, and in Orange County, California, have been associated with opossums and *R. typhi*–infected *Ct. felis.*[30,32,40,41] Epidemiologic observations have led to the hypothesis that cats, hosts for *Ct. felis,* play a role in the transmission of murine typhus.[28,42] In addition, *R. typhi* has been isolated from *Rhipicephalus sanguineus* ticks collected from dogs.[43] More studies are needed to elucidate the role domestic animals play in the transmission and maintenance of *R. typhi.*

Outbreaks throughout the world occur when there is inadequate vector and reservoir control.[2,44–48] Among displaced Khmers at the Thailand-Cambodia border with unexplained fever, 70% were cases of murine typhus, with an attack rate of 172 per 100,000 adults.[9] Murine typhus has been implicated in as many as 4% to 26% of cases of undifferentiated febrile illness in Nepal,[49–52] 0.4% to 7% in countries of Southeast Asia,[53–55] and as few as 0.5% in northern Tanzania.[56] In northern Vietnam, when malaria, dengue, typhoid fever, and leptospirosis are excluded, *R. typhi* has been attributed to 33% of undifferentiated febrile illness.[57] Most patients are adults, although persons of all ages may become ill.[58] Cases are recognized year-round, with peak prevalence from April through June in Texas[8] and during the warm months of summer and early fall elsewhere.[2,46,59]

Murine typhus has been increasingly recognized as a febrile illness in travelers returning from endemic regions throughout the world. In an analysis of 3655 travelers considered to have acute and potentially life-threatening illnesses, murine typhus was the seventh most prevalent cause (identified in 16), and when excluding the diagnosis of *Plasmodium falciparum* malaria, occurred in 1.9% of febrile patients.[60] Africa, Southeast Asia, South Asia, and the Americas have been reported as sites of disease acquisition in returning travelers.[60–62]

The disease is transmitted after the inoculation of infected flea feces into a flea bite wound. The incubation period is 1 to 2 weeks, commonly 12 days. Because predominantly gut epithelial cells are infected in the flea vector, a reservoir of infected fleas is maintained mostly by horizontal transmission from flea to vertebrate host to uninfected flea.[63] Once infected, the flea maintains the rickettsial infection for the duration of its life. *Rickettsia typhi* may also infect the flea reproductive organs, which explains the low levels of transovarial (vertical) transmission.[64] The longevity of fleas is unaffected by gut epithelial cell or disseminated *R. typhi* infection.[12]

PATHOLOGY AND PATHOGENESIS

Few accurate descriptions of the histopathology of murine typhus are available, despite the fact that the case-fatality rate ranges between 1% and 4%.[8] Pathologic findings indicate systemic endothelial infection similar to epidemic typhus and Rocky Mountain spotted fever.[65,66] Lymphohistiocytic vasculitis may affect any organ, and in fatal cases interstitial pneumonitis, interstitial nephritis, interstitial myocarditis, meningoencephalitis, and portal triaditis may be present. Rickettsiae may be demonstrated in many organs and are especially numerous in foci of vasculitis.[65] This underlying vasculitic lesion and the rickettsia-induced vascular injury account for most of the clinicopathologic abnormalities. Evaluation of serum markers reveals endothelial damage and activation of the coagulation and fibrinolytic pathways.[67] As vascular injury accumulates, a substantial loss of intravascular volume, albumin, and electrolytes occurs, and platelets are consumed at foci of infection. With multifocal heavy infection and attendant inflammation, vascular and parenchymal injury may yield localized symptoms, signs, or laboratory findings related to the sites of infection and injury. The induction of hypovolemia insufficiently corrected by normal homeostatic mechanisms further exacerbates tissue perfusion compromise and may lead to renal insufficiency. Mild-to-moderate hepatic injury is a frequent finding in murine typhus and probably results from multifocal infection of hepatic sinusoidal and portal endothelium, with bystander hepatocyte damage.[8,68] Ocular manifestations, which are often subclinical, are detected by careful ophthalmologic examination, and reflect retinal choroidal vascular injury.[69] With extensive rickettsial vascular injury and hypoperfusion secondary to volume loss, the result may be renal failure, respiratory failure, central nervous system abnormalities, or multiorgan failure.[8,65]

Immunity to *R. typhi* is mediated mainly by early interactions with and maturation of dendritic cells, and early control is provided by natural killer cells. This is followed by adaptive responses via CD4 and CD8 T lymphocytes, their cytokine products interferon-γ and tumor necrosis factor-α, and antibody, which likely plays an adjunctive role.[70–75]

CLINICAL MANIFESTATIONS

Signs and Symptoms

Only a small proportion of patients (median, 4%) with murine typhus recall a flea bite or exposure, and an incubation period of 1 to 2 weeks may transpire before abrupt onset of illness occurs. The presentation

FIG. 190.2 Truncal rash of murine typhus.

FIG. 190.3 Petechial rash of murine typhus.

is often nonspecific, and fever (93%–100%), headache (10%–91%), myalgia (10%–78%), and nausea or vomiting (14%–59%) are the most frequently reported early clinical manifestations.[8,46,76–80] Rash is noted in up to 18% of patients at presentation, but over the course of illness as few as 3% and as many as 80% will develop this sign, which is more often detected in lightly pigmented than darkly pigmented skin (Fig. 190.2).[81] As the illness progresses, most patients continue with fever and can have gastrointestinal (nausea, 48%; vomiting, 40%; and anorexia, 35%) or respiratory tract (cough in 14%–44%) involvement. Some studies record the presence of hepatomegaly and splenomegaly in up to 22% and 17% of patients, respectively.[82–85] Severe neurologic complications occur in as many as 17% of patients, usually manifesting as photophobia, confusion, stupor, seizures, or localized findings such as ataxia.[86,87]

The absence of rash or lack of petechiae should not dissuade one from a diagnosis of murine typhus. In fact, when rash is identified, it is described as macular or maculopapular in 75% to 80% of cases and petechiae are noted in less than 13% (Fig. 190.3).[8,58,81,83] The rash is most often distributed on the trunk (88% of cases), but involvement of the extremities is not infrequent (>45%). The initial rash distribution is equally frequent on the extremities and on the trunk and is present on the palms and soles in less than 3% of patients.[46]

The clinical course of murine typhus is usually uncomplicated, and childhood murine typhus is often mild,[45,83,88] with one series reporting only nighttime fever with normal daytime activities.[77] The case-fatality rate in the postantibiotic era is 0.4%.[10] However, occasional patients develop central nervous system abnormalities,[69,89–94] renal insufficiency,[78] or respiratory failure requiring intubation.[95] Patients are ill enough that 10% require admission to an intensive care unit, and up to 4% of hospitalized adult patients die of the infection.[8]

Once the diagnosis has been considered and appropriate therapy begun, most patients defervesce rapidly (median, 3 days). Findings associated with severe illness include leukocytosis, elevated blood urea nitrogen or creatinine levels, and a high blood urea nitrogen–to-creatinine ratio. Advanced age and a prolonged interval before the administration of specific antirickettsial therapy are also significantly correlated with severity.[8,11] One report has suggested a link between hemolytic disorders such as glucose-6-phosphate dehydrogenase deficiency, hemoglobinopathy, and thalassemia and more severe illness, including jaundice.[68] A trend toward more severe infection is also noted in patients treated with trimethoprim-sulfamethoxazole.

Laboratory Features

Early mild leukopenia (which coincides with thrombocytopenia) is present in 25% to 50% of patients during the first 7 days of illness. Subsequently, leukocytosis develops in less than one-third. Prothrombin times are occasionally prolonged, but true disseminated intravascular coagulation with hypofibrinogenemia is infrequently documented. The most frequent laboratory abnormality in murine typhus, a mild-to-moderate elevation in serum aspartate aminotransferase levels, is present in most patients (67%–92%), and related indices of hepatic and cellular injury (alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase levels) are often elevated in parallel.* Rickettsia-induced vascular damage frequently leads to hypoproteinemia (45%) and hypoalbuminemia (89%) and is probably responsible in large part for multiple serum electrolyte abnormalities, especially hyponatremia (60%) and hypocalcemia (79%). Even in the presence of symptomatic central nervous system abnormalities, cerebrospinal fluid examination can be normal or reveal findings resembling viral or leptospiral meningoencephalitis. The fluid is usually clear with a normal glucose concentration; abnormalities include pleocytosis, usually lymphocytic, with an increased protein concentration.[90,96]

DIAGNOSIS

Early diagnosis of murine typhus is still based mostly on clinical suspicion. Because timely specific antirickettsial therapy is indicated to avoid severe or potentially fatal infection, treatment should not be withheld while laboratory confirmation is awaited.[8,58] When early suspicion is followed by prompt empirical treatment, length of hospitalization is decreased.[97] Although it affords a definitive diagnosis, culture is rarely attempted because of a reputation of biohazard and difficulty, reducing the use of this potentially valuable adjunct to diagnosis. The shell vial culture technique—or a modification using a 24-well plate—has been successfully used to obtain isolates.[32,98,99]

*References 8, 29, 38, 52, 65, 67.

The predominant method of laboratory confirmation is serologic. Because antibodies are infrequently detected during acute illness, serologic diagnosis is retrospective.[83] Obsolete Weil-Felix agglutination reactions have proved insensitive, are intrinsically nonspecific, and, as such, should not be used to establish a definitive diagnosis.[100] Instead, sensitive serologic tests that use specific *R. typhi* antigens, such as indirect fluorescent antibody (IFA) assay, are preferable. With the use of a sensitive and specific test such as the IFA assay, diagnostic titers are present in approximately 50% of murine typhus patients within 1 week and in almost all patients within 15 days after the onset of illness.[8,83] Although a single reactive immunoglobulin G titer during a clinically compatible illness is suggestive of the diagnosis, confirmation generally requires seroconversion or a fourfold rise in immunoglobulin G titer between acute- and convalescent-phase sera. Even in areas where the disease is recognized to be endemic, confirmatory testing is often not performed or reported.[101,102] The accuracy of IFA end point titers are subject to microscopist experience and often exhibit interobserver variability.[103] Sera from blood-spotted filter paper may be an inexpensive yet effective method for sample collection and storage prior to serologic testing.[104] Because typhus group rickettsiae share antigens, routine serologic evaluation does not distinguish between epidemic and murine typhus.[105] In occasional sera, reactions against both typhus and spotted fever groups are observed, creating further diagnostic difficulties.

Other methods for laboratory confirmation of rickettsiosis include the immunohistologic demonstration of *R. typhi* in tissues, but the sensitivity, specificity, and predictive value are unknown.[65,106,107] Polymerase chain reaction (PCR) assay amplification of rickettsial nucleic acids in peripheral blood or skin biopsy samples has been achieved. Unfortunately, despite the ability of quantitative real-time PCR to detect very low copy numbers of target genes, the low numbers of circulating rickettsiae within the bloodstream limits its clinical sensitivity. A meta-analysis reveals that PCR for the detection of typhus group rickettsiae has a median clinical sensitivity of 3% and 6% from blood and tissue specimens, respectively.[108] Considering this limitation, it is doubtful that development of more field-applicable, rapid turnaround assays (e.g., loop-mediated isothermal amplification and recombinase polymerase amplification) will have much clinical utility in their current forms.[109,110] Neither immunohistochemistry nor PCR is generally available in clinical laboratories.

Most patients are initially investigated for fever of undetermined origin, and less often patients are investigated for upper or lower respiratory tract infection, urinary tract infection, cerebrovascular accident, gastroenteritis, or neoplasm, among other diagnoses.[8,111] Initial diagnostic workup may be extensive and costly prior to the consideration of murine typhus.[112] Despite the occasional presence of findings that suggest alternative diagnoses because of attention to isolated organ system involvement, an early clue toward the successful diagnosis of murine typhus is recognition of the systemic manifestations associated with fever. Other rickettsioses may cause considerable difficulty in the differential diagnosis. In the Western Hemisphere, Rocky Mountain spotted fever is the most frequent, whereas in Europe, Africa, and Asia, other spotted fever rickettsioses or scrub typhus should be considered. Murine typhus and spotted fever rickettsiosis may be distinguished on the basis of the history, clinical presentation, and fourfold differences in titers in specific serologic tests.[113] Many patients with murine typhus are exposed to animals or flea vectors in urban or suburban regions,[3,13,59,114] and a small proportion (1%–40%) report a flea bite or exposure, whereas patients with Rocky Mountain spotted fever often acquire illness after outdoors exposure or documented tick bites and more often develop rash and petechiae. An inoculation lesion or eschar is exceedingly rare in both murine typhus and Rocky Mountain spotted fever but is more often present in other spotted fever group rickettsioses and scrub typhus.[107] In areas where both murine typhus and scrub typhus are common, those living in more densely populated areas, such as urban centers, are more likely to be exposed to the vectors of *R. typhi* than those of *Orientia tsutsugamushi*.[115] The distribution of rash is of little help in individual cases.[8,58,59,78] The likelihood of monocytic ehrlichiosis or human granulocytic anaplasmosis is diminished if leukopenia and thrombocytopenia are minimal or absent, although serum hepatic aminotransferase levels may be elevated in both murine typhus and ehrlichiosis. Murine typhus, spotted fever rickettsiosis, and ehrlichiosis or anaplasmosis occur during warm seasons, when the arthropod vectors are most active. In contrast, the louse vector of epidemic typhus is most active and likely to spread *Rickettsia prowazekii* in cool seasons when layers of clothing are worn, persons are crowded indoors, and personal hygiene of extremely poor persons diminishes. Differentiation of sporadic cases of sylvatic typhus caused by *R. prowazekii* from murine typhus may be difficult, but the former illness is suggested when exposure to the flying squirrel reservoir is elicited.

There are many differential diagnoses of murine typhus because of its usually nonspecific presentation. Aside from the rickettsioses and ehrlichiosis, alternative diagnoses include meningococcemia, measles, typhoid fever, bacterial and viral meningitis, secondary syphilis, leptospirosis, toxic shock syndrome, and Kawasaki disease.

TREATMENT AND PREVENTION

The preferred drug for treatment of *R. typhi* infection is a tetracycline, such as doxycycline. In vitro, doxycycline, rifampin, chloramphenicol, and the fluoroquinolones (e.g., ciprofloxacin and levofloxacin), as well as azithromycin, inhibit rickettsial growth and have ratios of maximal serum concentration to minimal inhibitory concentration achievable in human therapy.[116–118] No prospective clinical trials have been conducted regarding treatment of murine typhus; thus all current recommendations are based on retrospectively analyzed series and cases. The current recommendation is for administration of twice-daily doxycycline, 100 mg orally or, in severely ill patients, intravenously. The use of doxycycline and tetracycline is supported by extensive experience as detailed in a monograph that analyzed over 600 patients from numerous case series and reports.[119] Although chloramphenicol, 50 to 75 mg/kg/day in four divided doses, has been long advocated as the best alternative treatment for murine typhus, the evidence for its use is derived from case series comprising treatment in only 97 patients. Oral chloramphenicol is not currently available in the United States, and the parenteral formulation is exceedingly difficult to procure. Clinical trials of fluoroquinolones for treatment of spotted fever rickettsioses have shown their effectiveness as alternatives to tetracyclines, and for murine typhus, reports of successful treatment[92,120–125] with ciprofloxacin outnumber reports of poor responses,[126] although these data only involved treatment of 37 patients. Corticosteroids are occasionally used for severe central nervous system disease, but no controlled study to evaluate their efficacy has been performed. Infected pregnant patients must be evaluated individually, and when possible, doxycycline is preferred. Although tetracycline has been associated with serious adverse events in pregnant women (hepatotoxicity) and in the developing fetus (teratogenicity and tooth discoloration), these tetracycline class effects appear less prevalent with doxycycline.[127] Poor outcomes associated with a third of neonates in a cohort of pregnant women with suboptimal treatment for murine typhus must be considered when weighing the risks and benefits of doxycycline in this population.[128] Alternately, and where available, chloramphenicol can be used (early trimester). Case reports touting good outcomes with azithromycin during pregnancy[129] are tempered by the lack of benefit in neonatal outcomes in the aforementioned cohort.[128] Antimicrobial therapy should be continued until 3 days after defervescence. After initiation of therapy, patients become afebrile at a median interval of 3 days. Single-dose doxycycline therapy was effective in almost 80% of patients in one study[82] but is not routinely advocated because relapse may occur.

Prevention is directed primarily toward the control of flea vectors and potential flea hosts.[12] Success of this approach is exemplified by the control efforts using dichlorodiphenyltrichloroethane (DDT) in the United States during the 1940s.[35,36] Because of the potential for epidemic spread associated with foci of infected flea infestations, all suspected cases of murine typhus should be reported promptly to local public health authorities. Although it is usually considered a mild illness, murine typhus may be fatal or severe if misdiagnosed or inadequately treated. Unfortunately, no vaccine of proven effectiveness exists for murine typhus. Recovery from natural infection confers solid, long-lasting immunity to reinfection.