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rifampin. Although antimicrobial susceptibility testing is not rou tinely performed and resistance to doxycycline does not appear to be a common problem in clinical practice, doxycycline-resistant isolates do exist.

Treatment of acute Q fever with doxycycline (100 mg twice daily for 14 days) is usually successful. Quinolones also are effective. When Q fever is diagnosed during pregnancy, treatment with TMPSMX is recommended for the duration of the pregnancy. Treatment with doxycycline and hydroxychloroquine for 6−12 months following acute infection should be considered in patients with valve abnormalities, a prosthetic heart valve, an aneurysm, or vascular prosthesis. This appeared to be effective in preventing progression to chronic Q fever in patients with valvulopathy. The exact indications and duration of prophylaxis should be based on a careful consideration of possible benefits and side effects. Decisions on treatment of chronic Q fever are challenging, so consultation with an infectious diseases expert is recommended. There is no indication for antibiotic therapy in those with possible chronic Q fever (only elevated phase I IgG without symptoms or an infectious focus). Addition of hydroxychloroquine (to alkalinize the phagolysosome) renders doxycycline bactericidal against C. burnetii in vitro, and the combination of doxycycline 100 mg twice daily with 200 mg hydroxychloroquine three times daily is the favored regi men. It is advised to determine serum levels of doxycycline aiming for concentrations between 5 and 10 mg/L, often requiring higher doses than 200 mg per day. Patients treated with this regimen must be advised about photosensitivity, but side effects should not lead to cessation of doxycycline too easily since it appears to be the most effective approach for this serious infection that has a high mortality despite treatment. Patients treated with hydroxychloroquine are at risk for developing retinopathy, so they should be evaluated by an ophthalmologist before starting treatment and every 6−12 months during the course of therapy. If doxycycline-hydroxychloroquine cannot be used, the regimen chosen should include at least two anti biotics active against C. burnetii. In a study including 322 patients with chronic Q fever, treatment with doxycycline combined with a quinolone appeared to be a safe alternative. PART 5 Infectious Diseases Minimum treatment duration is 18 months after PCR on blood had become negative (if positive before) and adequate doxycycline levels have been reached for native valve endocarditis and other manifestations without prosthetic material and 24 months for patients with prosthetic valve endocarditis or infected vascular prostheses. Many patients with vascular infection need prolonged treatment before the infection resolves, and surgical intervention is often necessary to remove an infected graft if the patient does not respond to antibiotic therapy. Abscesses need drainage for

antibiotic therapy to be successful. Defining cure of chronic Q fever after the minimum treatment duration should be based on a combination of imaging (if abnormal at diagnosis), decline of serologic titers, nega tivity of PCR on blood or serum, and improvement of symptoms. FOLLOW-UP After acute Q fever, patients without risk factors for developing chronic Q fever should be evaluated clinically and serologically after 6 months. When IgG phase I is <1024 and clinical symptoms do not suggest chronic infection, follow-up can be stopped. For patients with a very high risk of developing chronic Q fever who have received antibiotics for 6−12 months, patients with immu nosuppression or other risk factors not treated with antibiotics for a prolonged period of time, or patients with possible chronic Q fever (only phase I IgG ≥1024), follow-up with serology and PCR every 3−6 months for 2 years is recommended. During treatment of chronic Q fever, patients should be followed every 3 months to evaluate symptoms, side effects, serology, and PCR. When new complications are suspected, imaging should be repeated. After the end of treatment, relapse has been described up to 5 years later. It is therefore recommended to continue monitoring with serology and PCR until a minimum of 5 years after end of treatment.

Prevention A whole-cell vaccine (Q-Vax) licensed in Australia effectively prevents Q fever in abattoir workers. Vaccine is given only to people without a history of Q fever and negative results in both serologic and skin testing that is performed with intradermal diluted

C. burnetii vaccine to prevent side effects. Cases among abattoir work ers in Australia declined dramatically as a result of a vaccination pro gram, but the vaccine has not been approved outside Australia. Good animal-husbandry practices are important in preventing widespread contamination of the environment by C. burnetii. These practices include isolating aborting animals for up to 14 days, raising feed bunks to prevent contamination of feed by excreta, destroying aborted materials (by burning and burying fetal membranes and still born animals), and wearing masks and gloves when handling aborted materials. Vaccination of sheep and goats and a culling program were effective in the Dutch outbreak. During an outbreak of Q fever and for 4 weeks after it ceases, blood donations should not be accepted from individuals who live in the affected area. Acknowledgment The authors thank Thomas Marrie, MD, for his significant contributions to this chapter in the previous editions. ■ ■FURTHER READING Biggs HM et al: Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever and other spotted fever group rickettsioses, ehrlichioses, and anaplasmosis—United States. MMWR 65:1, 2016. Buijs SB et al: Still new chronic Q fever cases diagnosed 8 years after a large Q fever outbreak. Clin Infect Dis 73:1476, 2021. Gillespie J, Salje J: Orientia and Rickettsia: Different flowers from the same garden. Curr Opin Microbiol 74:102318, 2023. Ismail N, Mcbride JW: Tick-borne emerging infections: Ehrlichiosis and anaplasmosis. Clin Lab Med 37:317, 2017. Varghese GM et al: Intravenous doxycycline, azithromycin, or both for severe scrub typhus. N Engl J Med 388:792, 2023. R. Doug Hardy

Infections Due to

Mycoplasmas Mycoplasmas are prokaryotes of the class Mollicutes. Their size (150–350 nm) is closer to that of viruses than to that of typical bacteria. Unlike viruses, however, mycoplasmas grow in cell-free culture media; in fact, they are the smallest organisms capable of independent replication. The entire genomes of many Mycoplasma species have been sequenced and have been found to be among the smallest of all prokaryotic genomes. Sequencing information for these

genomes has helped define the minimal set of genes necessary for cellular life. The absence of genes related to the synthesis of amino acids, fatty acid metabolism, and cholesterol dictates the mycoplasmas' parasitic or saprophytic dependence on a host for exogenous nutrients and neces sitates the use of complex fastidious media to culture these organisms. Mycoplasmas lack a cell wall and are bound only by a cell membrane. The absence of a cell wall explains the inactivity of β-lactam antibiotics (penicillins and cephalosporins) against infections caused by these organisms. At least 13 Mycoplasma species, 2 Acholeplasma species, and 2 Urea plasma species have been isolated from humans. Most of these species are thought to be normal inhabitants of oral and urogenital mucous

membranes. M. pneumoniae, M. hominis, M. genitalium, U. urealyti cum, and U. parvum have been shown conclusively to be pathogenic in immunocompetent humans. M. pneumoniae primarily infects the respiratory tract, while M. hominis, M. genitalium, U. urealyticum, and U. parvum are associated with a variety of genitourinary tract disorders and neonatal infections. Other mycoplasmas may cause disease in immunocompromised persons. MYCOPLASMA PNEUMONIAE ■ ■PATHOGENESIS M. pneumoniae is generally thought to act as an extracellular pathogen. Although the organism has been shown to exist and replicate within human cells, it is not known whether these intracellular events contrib ute to the pathogenesis of disease. M. pneumoniae attaches to ciliated respiratory epithelial cells by means of a complex terminal organelle at the tip of one end of the organism. Cytoadherence is mediated by interactive adhesins and accessory proteins clustered on this organelle. After extracellular attachment, M. pneumoniae causes injury to host respiratory tissue. The mechanism of injury is thought to be mediated by the production of hydrogen peroxide and of an ADP-ribosylating and vacuolating cytotoxin of M. pneumoniae that has many similarities to pertussis toxin. Because mycoplasmas lack a cell wall, they also lack cell wall–derived stimulators of the innate immune system, such as lipopolysaccharide, lipoteichoic acid, and murein (peptidoglycan) frag ments. However, lipoproteins from the mycoplasmal cell membrane appear to have inflammatory properties, probably acting through Toll-like receptors (primarily TLR2) on macrophages and other cells. Lung biopsy specimens from patients with M. pneumoniae respiratory tract infection reveal an inflammatory process involving the trachea, bronchioles, and peribronchial tissue, with a monocytic infiltrate that coincides with a luminal exudate of polymorphonuclear leukocytes. Experimental evidence indicates that innate immunity provides most of the host's defense against mycoplasmal infection in the lungs, whereas cellular immunity may actually play an immunopathogenic role, exacer bating mycoplasmal lung disease. Humoral immunity appears to provide protection against dissemination of M. pneumoniae infection; patients with humoral immunodeficiencies do not have more severe lung disease than do immunocompetent patients in the early stages of infection but more often develop disseminated infection resulting in syndromes such as arthritis, meningitis, and osteomyelitis. The immunity that follows severe M. pneumoniae infections is more protective and longer-lasting than that following mild infections. Genuine second attacks of M. pneu moniae pneumonia have been reported infrequently. ■ ■EPIDEMIOLOGY M. pneumoniae infection occurs worldwide. It is likely that the inci dence of upper respiratory illness due to M. pneumoniae is up to 20 times that of pneumonia caused by this organism. Infection is spread from one person to another by respiratory droplets expectorated dur ing coughing and results in clinically apparent disease in an estimated 80% of cases. The incubation period for M. pneumoniae is 2–4 weeks; therefore, the time-course of infection in a specific population may be several weeks long. Intrafamilial attack rates are as high as 84% among children and 41% among adults. Outbreaks of M. pneumoniae illness often occur in

institutional settings such as military bases, boarding schools, and summer camps. Infections tend to be endemic, with spo radic epidemics every 4–7 years. Most significantly, M. pneumoniae is a major cause of communityacquired respiratory illness in both children and adults and is often grouped with Chlamydia pneumoniae and Legionella species as one of the most important bacterial causes of “atypical” community-acquired pneumonia. For community-acquired pneumonia in adults, M. pneu moniae is the most frequently detected “atypical” organism. Analysis of 13 studies of community-acquired pneumonia published between 1996 and 2001 (which included 6207 ambulatory and hospitalized adults) showed that the overall prevalence of M. pneumoniae was 22.7%; by comparison, the prevalence of C. pneumoniae was 11.7%, and that of Legionella species was 4.6%. The summation of 26 more recent

investigations of “atypical” organisms in community-acquired pneu monia in adults published between 2002 and 2015 found the overall prevalence of M. pneumoniae was 7.2%; by comparison, the prevalence of C. pneumoniae was 4.3%, and that of Legionella species was 2.8%.

M. pneumoniae pneumonia is also referred to as Eaton agent pneumo nia (the organism having first been isolated in the early 1940s by Mon roe Eaton), primary atypical pneumonia, and “walking” pneumonia.

■ ■CLINICAL MANIFESTATIONS Upper Respiratory Tract Infections and Pneumonia Acute

M. pneumoniae infections generally manifest as pharyngitis, tracheo bronchitis, reactive airway disease/wheezing, or a nonspecific upper respiratory syndrome. Little evidence supports the commonly held belief that this organism is an important cause of otitis media, with or without bullous myringitis. Pneumonia develops in 3–13% of infected individu als; its onset is usually gradual, occurring over several days, but may be more abrupt. Although Mycoplasma pneumonia may begin with a sore throat, the most common presenting symptom is cough. The cough is typically nonproductive, but some patients produce sputum. Headache, malaise, chills, and fever are noted in the majority of patients. On physical examination, wheezes or rales are detected in ~80% of patients with M. pneumoniae pneumonia. In many patients, however, pneumonia can be diagnosed only by chest radiography. The most common radiographic pattern is that of peribronchial pneumonia with thickened bronchial markings, streaks of interstitial infiltration, and areas of subsegmental atelectasis. Segmental or lobar consolidation is not uncommon. While clinically evident pleural effusions are infre quent, lateral decubitus views reveal that up to 20% of patients have pleural effusions. CHAPTER 193 Overall, the clinical presentation of pneumonia in an individual patient is not useful for differentiating M. pneumoniae pneumonia from other types of community-acquired pneumonia. The possibility of M. pneumoniae infection deserves particular consideration when community-acquired pneumonia fails to respond to treatment with a penicillin or a cephalosporin—antibiotics that are ineffective against mycoplasmas. Symptoms usually resolve within 2–3 weeks after the onset of illness. Although M. pneumoniae pneumonia is generally selflimited, appropriate antimicrobial therapy significantly shortens the duration of clinical illness. Infection uncommonly results in critical illness and only rarely in death. In some patients, long-term recur rent wheezing or reactive airway disease may follow the resolution of acute pneumonia. The significance of chronic infection, especially as it relates to asthma, is an area of active investigation. Infections Due to Mycoplasmas Extrapulmonary Manifestations An array of extrapulmonary manifestations may develop during M. pneumoniae infection. The most significant

are neurologic, dermatologic, cardiac, rheumatologic, and hematologic in nature. Extrapulmonary manifestations can be a result of disseminated infection, especially in patients with humoral immunode ficiencies (e.g., septic arthritis); postinfectious autoimmune phenomena (e.g., Guillain-Barré syndrome); or possibly ADP-ribosylating toxin. Overall, these manifestations are uncommon, given the frequency of

M. pneumoniae infection. Notably, many patients with extrapulmonary M. pneumoniae disease do not have respiratory disease. Skin eruptions described with M. pneumoniae infection include erythematous (macular or maculopapular), vesicular, bullous, petechial, and urticarial rashes. In some reports, 17% of patients with M. pneu moniae pneumonia have had an exanthem. Erythema multiforme major (Stevens-Johnson syndrome) is the most clinically significant skin erup tion associated with M. pneumoniae infection; it appears to occur more commonly with M. pneumoniae than with other infectious agents. A wide spectrum of neurologic manifestations has been reported with M. pneumoniae infection. The most common are meningoen cephalitis, encephalitis, Guillain-Barré syndrome, and aseptic menin gitis. M. pneumoniae has been implicated as a likely etiologic agent in 5–7% of cases of encephalitis. Other neurologic manifestations may include cranial neuropathy, acute psychosis, cerebellar ataxia, acute demyelinating encephalomyelitis, cerebrovascular thromboembolic events, and transverse myelitis.

TABLE 193-1 Diagnostic Tests for Respiratory Mycoplasma pneumoniae Infectiona TEST SENSITIVITY, % SPECIFICITY, % Respiratory culture ≤60

Respiratory PCR 65–90 90–100 Serologic studiesb 55–100 55–100 aA combination of PCR and serology is suggested for routine diagnosis. If macrolide resistance is suspected, resistance testing by culture and/or PCR is available. bAcute- and convalescent-phase serum samples are recommended. Abbreviation: PCR, polymerase chain reaction. aAntimicrobial resistance has been reported in mycoplasmas, as described in the text. Hematologic manifestations of M. pneumoniae infection include hemolytic anemia, aplastic anemia, cold agglutinins, disseminated intravascular coagulation, and hypercoagulopathy. When anemia does occur, it generally develops in the second or third week of illness. In addition, hepatitis, glomerulonephritis, pancreatitis, myocarditis, pericarditis, rhabdomyolysis, and arthritis (septic and reactive) have been convincingly ascribed to M. pneumoniae infection. Septic arthritis has been described most commonly in hypogammaglobulinemic patients. ■ ■DIAGNOSIS Clinical findings, nonmicrobiologic laboratory tests, and chest radi ography are not useful for differentiating M. pneumoniae pneumonia from other types of community-acquired pneumonia. In addition, since M. pneumoniae lacks a cell wall, it is not visible on Gram stain. Although of historical interest, the measurement of cold agglutinin titers is no longer recommended for the diagnosis of M. pneumoniae infection because the findings are nonspecific and assays specific for M. pneumoniae are now available. PART 5 Infectious Diseases Acute M. pneumoniae infection can be diagnosed by polymerase chain reaction (PCR) detection of the organism in respiratory tract secretions or by isolation of the organism in culture (Table 193-1). Oropharyngeal, nasopharyngeal, and pulmonary specimens are all acceptable for diag nosing M. pneumoniae pneumonia. Other bodily fluids, such as cerebro spinal fluid, are acceptable for extrapulmonary infection. M. pneumoniae culture (which requires special media) is not recommended for routine diagnosis because the organism may take weeks to grow and is often dif ficult to isolate from clinical specimens. In contrast, PCR allows rapid, specific diagnosis earlier in the course of clinical illness. The diagnosis can also be established by serologic tests for IgM and

IgG antibodies to M. pneumoniae in paired (acute- and conva lescent-phase) serum samples; enzyme-linked immunoassay is the recommended serologic method. An acute-phase sample alone is not adequate for diagnosis, as antibodies to M. pneumoniae may not develop until 2 weeks into the illness; therefore, it is important to test paired samples. In addition, IgM antibody to M. pneumoniae can persist for up to 1 year after acute infection. Thus, its presence may indicate recent rather than acute infection. The combination of PCR of respiratory tract secretions and sero logic testing constitutes the most sensitive and rapid approach to the diagnosis of M. pneumoniae infection. TREATMENT Mycoplasma pneumoniae Infections Although in the majority of untreated cases symptoms resolve within 2–3 weeks without significant associated morbidity,

M. pneumoniae pneumonia can be a serious illness that responds to appropriate antimicrobial therapy (Table 193-2). Randomized, double-blind, placebo-controlled trials in adults have demonstrated that antimicrobial treatment significantly decreases the duration of fever, cough, malaise, hospitalization, and radiologic abnor malities in M. pneumoniae pneumonia. Treatment options for acute

M. pneumoniae infection include macrolides (e.g., oral azithromy cin, 500 mg on day 1, then 250 mg/d on days 2–5), tetracyclines (e.g., oral doxycycline, 100 mg twice daily for 7–14 days), and respiratory fluoroquinolones. However, ciprofloxacin and ofloxacin are not rec ommended because of their high minimal inhibitory concentrations

TABLE 193-2 Antimicrobial Agents of Choice for Mycoplasma Infectionsa ORGANISM(S) DRUGS Mycoplasma pneumoniae Azithromycin, clarithromycin, erythromycin, doxycycline, levofloxacin, moxifloxacin, gemifloxacin (not ciprofloxacin or ofloxacin) Ureaplasma urealyticum, Ureaplasma parvum Azithromycin, clarithromycin, erythromycin, doxycycline Mycoplasma hominis Doxycycline, clindamycin Mycoplasma genitalium Azithromycin, moxifloxacin, doxycycline against M. pneumoniae isolates and their poor performance in experimental studies. A 7- to 14-day course of quinolone therapy appears adequate. Even though appropriate antibiotic therapy signif icantly reduces the duration of respiratory illness, it does not appear to shorten the duration of detection of M. pneumoniae by culture or PCR; therefore, a test of cure for eradication is not suggested. In Asian countries, a high prevalence (range 34–76%) of

M. pneumoniae resistant to macrolides has been reported. In Europe and in the United States, macrolide-resistant M. pneu moniae is less common. In the United States, national surveillance from 2018 found that 10.2% of isolates demonstrated macrolide resistance. Furthermore, national surveillance from 2015–2018 found macrolide resistance of 15.2–21.7% in the eastern United States and 1.9–2.8% in the western United States. Clinical studies have demonstrated that, when treated with macrolides, patients with community-acquired pneumonia due to macrolide-resistant

M. pneumoniae experience a significantly longer duration of symp toms than do patients infected with macrolide-sensitive organisms; thus, macrolide resistance in M. pneumoniae does appear to have clinical significance. In addition, clinical investigations have indi cated that for macrolide-refractory M. pneumoniae pneumonia, tetracycline class therapy results in shorter duration of fever and hospital length of stay compared with macrolide therapy. If macro lide resistance is prominent in a particular geographic locale or is suspected, then a nonmacrolide antibiotic should be considered for treatment; in addition, in these instances, a respiratory sample may be sent to a

Mycoplasma reference laboratory for the detection of macrolide resistance by culture or PCR. While the 2019 Infectious Diseases Society of America and American Thoracic Society guidelines do not recommend routinely using corticosteroids in community-acquired pneumonia, growing clinical literature suggests that the addition of glucocorticoids to an antibiotic regimen may be of value for the treatment of severe or refractory M. pneumoniae pneumonia. A 2019 meta-analysis of 24 randomized controlled trials in children found that use of corticosteroids in macrolide-refractory M. pneumoniae pneumonia significantly reduced hospital days and duration of fever. Clinical literature in adults also shows benefit, but these data are limited and more observational in nature. The roles of antimicrobial drugs, glucocorticoids, and IV immunoglobulin in the treatment of neurologic disease due to

M. pneumoniae remain unknown. UROGENITAL MYCOPLASMAS ■ ■EPIDEMIOLOGY M. hominis, M. genitalium, U. urealyticum, and U. parvum can cause urogenital tract disease. The significance of isolation of these organ isms in a variety of other syndromes is unknown and in some cases is being investigated. M. fermentans has not been shown convincingly to cause human disease. While urogenital mycoplasmas may be transmitted to a fetus during passage through a colonized birth canal, sexual contact is the major mode of transmission, and the risk of colonization increases dra matically with increasing numbers of sexual partners. In asymptom atic women, these mycoplasmas may be found throughout the lower

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