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164 Legionella Infections

have been reported. Shewanella species also cause chronic ulcers of the lower extremities, bacteremia, osteomyelitis, biliary tract infections, pneumonia, sepsis, and potentially chronic otitis media. A fulminant course is associated with cirrhosis, hemochromatosis, diabetes mellitus, malignancy, or other severe underlying conditions. These organisms are often susceptible to fluoroquinolones, third- and fourth-generation cephalosporins, β-lactam/β-lactamase inhibitors, carbapenems, and aminoglycosides (Table 163-2), but multidrug resistance is increasing. Chromobacterium violaceum is a facultative anaerobic organism found in soil and water in tropical or subtropical regions. After expo sure, it can cause rare but serious—often fatal—skin and soft tissue infections of limbs, although several recent reports suggest a more benign course with lower mortality. Life-threatening infections with severe sepsis and metastatic abscesses occur most often in patients with underlying illness, particularly in children with defective neutrophil function (e.g., those with chronic granulomatous disease). C. violaceum is frequently resistant to multiple drugs; carbapenems are most often used empirically. Fluoroquinolones and trimethoprim-sulfamethoxazole also can be active (Table 163-2). Organisms that can cause nosocomial infections of medical devices in compromised hosts, such as central venous catheters, include Ochrobac trum anthropi, Pseudomonas (formerly Flavimonas) oryzihabitans, and Sphingobacterium. Alcaligenes faecalis has been associated with hospitalacquired infections, such as bloodstream infections, due to contaminated hemodialysis and IV fluids or respirators. Sphingomonas koreensis was associated with a small cluster of nosocomial cases at one hospital and was traced to a reservoir in the plumbing system. Ralstonia species also can contaminate water supplies, including hospital water systems. Cases of bacteremia, osteomyelitis, pneumonia, and meningitis have been described. Pandoraea commovens primarily infects patients with cystic fibrosis. However, an outbreak described in Germany resulted in critical illness. Patients were more likely to be receiving mechanical ventilation and have had prior surgery or antimicrobial exposure. Sphingomonas paucimobilis, a rare cause of infection in both healthy and immunocom promised patients, can cause bloodstream infections, respiratory distress, and sepsis. It has a predilection for bone and soft tissue infection, osteo myelitis, and septic arthritis. Other organisms can cause rare human infections such as Weeksella species; Bergeyella species; various Centers for Disease Control and Prevention (CDC) groups; and Oligella urethra lis. The reader is advised to consult subspecialty texts and references for further guidance on these and other organisms. ■

■FURTHER READING Bläckberg A et al: Infective endocarditis caused by HACEK group bacteria—a registry-based comparative study. Eur J Clin Microbiol 40:1919, 2021. Dernoncourt A et al:

Prognostic factors of Pasteurella infections: A single-center retrospective cohort study over a 14-year period (2005–2018). Int J Infect Dis 116:197, 2022. Spencer HK et al: An overview of the treatment of less common non-lactose-fermenting gram-negative bacteria. Pharmacotherapy 40:936, 2020. Steven A. Pergam, Thomas R. Hawn

Legionella Infections Bacteria of Legionella species cause two primary human diseases: Legionella pneumonia (often referred to as Legionnaires' disease) and Pontiac fever; collectively, these diseases are referred to as legionellosis. Legionnaires' disease was first described in 1976 in an outbreak among members of the American Legion participating in a conference at a hotel in Philadelphia, Pennsylvania. Since their original description,

Legionella-related infections have increased in frequency throughout the world as techniques to diagnose them have improved, clinical awareness has increased, cities have grown, and water systems have both aged and become more complex. Most cases of legionellosis are linked to waterborne exposures. These infections can be either spo radic or due to common-source community or nosocomial exposures. Outbreaks of legionellosis are well described. After exposure, legionel losis occurs primarily among persons with risk factors for disease, including older adults and those with primary organ dysfunction, immunocompromise, or other chronic illnesses. Clinical awareness is important, as the similarity of signs and symptoms of legionellosis to those of other respiratory illnesses can lead to delayed treatment. Despite appropriate therapy, Legionella pneumonia is associated with significant morbidity and mortality.

■ ■PATHOGEN AND PATHOGENICITY Legionellae are aerobic gram-negative bacteria that are ubiquitous in aquatic environments, damp soil, and compost. Of the more than 60 Legionella species, approximately half have been documented to lead to clinical disease, but most clinical disease is driven by Legionella pneumophila, primarily serotype 1. The primary habitats for growth and replication of Legionella are amoebae and other free-living proto zoa, in which these bacterial species can thrive intracellularly; humans are accidental hosts. Legionellae are reliant on host-derived amino acids and nutrients for intracellular replication. The organisms have a biphasic life cycle: a replicative phase in nutrient-rich conditions (e.g., in their protozoal hosts) and a noninfective transmissive phase under scarcity of resources. Therefore, they can persist in complex biofilms in both natural and engineered water systems (e.g., premise plumbing—a building's hot and cold water piping systems) and are phagocytized by waterborne protozoa. In premise plumbing systems, where tempera ture and nutrients support the protozoal hosts of legionellae, the bacte ria can replicate to concentrations sufficient to cause human infection. CHAPTER 164 After exposure to Legionella through inhalation or aspiration of small aerosol particles, the organisms attach to immune cells and are phagocytized. After phagocytosis, they can evade intracellular defenses and replicate in human alveolar macrophages and monocytes. Patho genic Legionella species have numerous virulence systems that they use to evade the human immune system, including the development of Legionella-containing vacuoles within immune cells, downregula tion of cytokine receptors, inhibition of host protein synthesis, and avoidance of lysosomal degradation. Despite their ability to replicate and persist in an intracellular environment, innate immune compo nents that target intracellular pathogens—specifically, pattern recogni tion receptors, including Toll-like receptors and nucleotide-binding oligomerization domain–like receptors—activate immune responses. Adaptive CD4 and CD8 cytotoxic T-cell involvement and these innate immune responses eventually lead to the production of interferon γ and tumor necrosis factor, the

promotion of neutrophil recruitment into the lung, and other proinflammatory responses. This cascade can be beneficial and result in clearance of the pathogen. However, these inflammatory responses can also cause immunopathology and adverse outcomes. L. pneumophila is more cytopathogenic than most nonpneumophila Legionella species, a characteristic that may be partially responsible for its association with severe disease. Legionella Infections ■ ■EPIDEMIOLOGY Legionella species are responsible for >50% of all waterborne outbreaks and >10% of disease related to drinking water in the United States. A National Academies of Sciences, Engineering, and Medicine report estimates that 50,000–70,000 Americans develop Legionnaires' disease per year. Incidence rates of legionellosis in the United States are report edly 2–3 cases per 100,000 persons, but higher rates have been reported in other parts of the world. Numerous global epidemiologic studies assessing legionellosis have shown an increasing prevalence over the past few decades; this increase has been hypothesized to be due to a variety of causes, including an aging population, improved diagnostics, global temperature changes, and an aging water infrastructure. Legio nellosis is associated with substantial health care costs.

Legionella species are found throughout the world, but most epi demiologic data focus on legionellosis in large metropolitan areas in Australia/New Zealand, Europe, and North America. Rates of infection in other parts of the world are unknown, as surveillance systems and laboratory testing are less readily available in large portions of Africa and Asia. More than 80% of cases of Legionnaires' disease are linked to L. pneumophila—in particular to serotype 1, which is the most frequently isolated Legionella pathogen. Although L. pneumophila pre dominates as a cause of disease, species predilection varies regionally. In Australia and New Zealand, for example, the rate of disease due to Legionella longbeachae approaches or exceeds that for L. pneumophila.

As previously mentioned, most reported cases are due to L. pneumophila serotype 1—a reflection of its pathogenicity. However, this predomi nance is also due to the frequency and ease of use of urinary antigen testing that targets this pathogen and allows more effective diagnosis in the community. It is unclear how large a role non-pneumophila spe cies and non–serotype 1 L. pneumophila play in disease. However, in studies in Europe, where respiratory cultures are more frequently col lected, nearly 10% of Legionnaires' disease patients were infected with species other than L. pneumophila. In the United States, nearly 10% of culture-confirmed cases are due to non–serogroup 1 L. pneumophila. Immunosuppressed patients, such as cancer patients and transplant recipients, may be more likely to develop pneumonia caused by nonpneumophila species such as Legionella micdadei, Legionella bozemanii, and L. longbeachae. Despite increases in cases in the United States (Fig. 164-1) and throughout the world, incident cases are still thought to be underre ported. Many cohort studies of community-acquired pneumonia do not require routine testing for Legionella or assess only for L. pneumophila serotype 1 (by urinary antigen testing) and therefore may underestimate true prevalence. For example, a large administrative database of studies shows that, of patients with clinically proven community-acquired pneu monia, only 26% underwent Legionella-specific testing; even patients with documented risk factors for legionellosis are not always tested for Legionella. In studies that routinely assess for legionellosis, the prevalence of Legionella pneumonia ranges between 2 and 10% of all communityacquired pneumonia cases. In addition, extrapulmonary presentations and Pontiac fever are less likely to be identified or to result in presenta tion for health care, and this trend leads to further underestimation of the true burden of legionellosis. PART 5 Infectious Diseases Seasonality and Climate Geoclimatic changes, storms, and sea sonality are thought to be important components of

Legionella’s epide miology. The incidence of Legionella disease increases in the summer and fall—specifically, in warmer weather and with increased rain and humidity. Studies that screen all respiratory samples for Legionella find that legionellosis is indeed diagnosed most frequently in the United States during warmer summer/fall months and periods of greater 3.50 Incidence (cases per 100,000 population) 3.00 2.50 2.00 1.50 1.00 0.50 0.00

Year FIGURE 164-1 Increasing Legionella disease incidence in the United States over the past two decades (2000–2019). (From https://www.cdc.gov/legionella/about/history.html.)

humidity. Furthermore, seasonal storms, which may disrupt water pipes or cause increased flooding, can result in contamination of water systems with soil and lead to Legionella exposures. There is concern that, with ongoing climate shifts and rising global temperatures, cases of legionellosis may continue to increase. Community and Health Care–Associated Outbreaks Small and large clusters and point-source outbreaks of Legionella cases lead to public health investigations, but these situations account for only ~5–10% of all Legionella cases yearly. Outbreaks occur when two or more people become ill after shared exposures in a community. In health care systems, a single proven case should trigger a Legionella investigation. The Centers for Disease Control and Prevention (CDC) recommends an outbreak investigation if a single patient with Legio nella is identified who did not leave the facility/campus for the 10 days prior to illness onset. Additionally, an outbreak investigation within a health care system is warranted if there are at least two possible Legio nella patients who spent any time in the hospital/long-term care facility within 12 months of each other (see “Clinical Presentations” below). Most common outbreaks are linked to water sources dispersing aerosol droplets that increase the area of particle spread (e.g., cooling towers or fountains) or to large building structural water systems that cause multiple prolonged exposures (e.g., those in hospitals, hotels, or apartments). The most commonly reported sources include not only cooling towers and fountains but also water misters; centralized heat ing, ventilation, and air-conditioning systems; hot tubs/spas; pools; ice machines; and showerheads and sinks in large premise plumbing struc tures (Fig. 164-2). When used as primary sources of water, ground water and wells have also been associated with Legionella exposures. The majority of exposures are related to engineered hot-water systems, which are often maintained at temperatures that limit scalding but are ideally suited for Legionella’s growth. Legionella can also be found in cold water, particularly in warmer summer months, as a consequence of the warming water temperature; engineering issues (e.g., heating lamps in fountains); or unexpected breaks in plumbing systems (e.g., malfunctioning thermostatic mixing valves), which can lead to hotwater contamination of cold-water systems. Buildings with inconsistent use patterns, such as hotels in seasonal travel destinations, can be linked to outbreaks of legionellosis, as water stagnation leads to low chlorine/disinfectant levels and organism proliferation can reach high enough levels to cause disease. Outbreaks have also been linked to cruise ships and boats. Following stay-athome orders during the SARS-CoV-2 pandemic, when buildings (e.g., hotels) were reopened, limited water movement and stagnation led to increases in cases of legionellosis. Modern buildings with water-saving devices, which aim to limit water and energy use, may increase the risk of legionellosis, as they can decrease water temperatures and limit water flow. Outbreaks in health care and long-term care facilities are identified more frequently than outbreaks in other facilities, as they often bring together at-risk patients, prolonged water expo sures, accessible testing, elevated awareness, and regulations that help ensure that cases are more easily linked to common sources. The outbreak examples listed in Table 164-1 demonstrate the wide variety of common sources and

the number of cases associated with such factors. As previously mentioned, most large outbreaks involve cooling towers, which can spread aero sol droplets over a wide area. The largest out break reported to date involved a cooling tower in Spain that was linked to 449 documented cases of Legionnaires' disease. Outbreaks are increasingly discussed in the media, such as outbreaks linked to cooling towers in the Bronx neighborhood of New York City, a large hotel outbreak in Atlanta, and the outbreaks associ ated with the Flint, Michigan, water crisis that

FIGURE 164-2 Sources of waterborne Legionella exposures and spectrum of presentation. The spectrum of sporadic to common-source outbreaks is a continuum. For example, premise plumbing in a large office building can lead to a large outbreak, and travel exposures can be related to large outbreaks. Most sporadic cases have no documented source of exposure, while outbreaks often involve mechanisms that spread water aerosol droplets over long distances (e.g., cooling towers), with a consequent ability to infect more individuals. (Reproduced with permission from Kyoko Kurosawa.) led to numerous deaths. It is not uncommon for lawsuits to be initiated when deaths are linked to outbreaks. Sporadic Cases The vast majority of cases of Legionnaires' disease occur sporadically in the community, manifesting as communityacquired pneumonia. Identification of the transmission source is more difficult in community-acquired cases than in nosocomial cases, despite reporting and review by local public health jurisdictions. In nearly 90% of all cases of legionellosis, a source of exposure is never identified. Since the spectrum of water exposures in the community is so broad and incubation periods can be long, identifying indi vidual exposures often is not possible. Transient exposures to common sources, travel-related exposures, and exposures to less commonly linked sources (e.g., potting soil and compost) may also be hard to identify. Furthermore, studies of domestic hot water have demon strated that 5–30% of households may have Legionella species detected, but the role that households play in clinical legionellosis is hard to determine, as home water testing is infrequently a part of usual contact TABLE 164-1 Examples of Legionella Common Source Outbreaks, Indicating the Wide Variety of Sources and Casesa SITE YEAR ORGANISMa REPORTED SOURCE(S) CASES Hotelb

L. pneumophila serotype 1 Potable water, fountain, spa 85 (29 suspect) Hospitalc

L. pneumophila Potable water 22 cases Communityd

L. pneumophila serotype 1 Cooling tower 334 cases Hospital/communitye 2014-15 L. pneumophila Potable water, household, cooling towers Long-term care facilityf

L. pneumophila Potable water 74 cases Communityg

L. pneumophila Hotel cooling towers 128 cases Hospitalh

L. pneumophila serotype 1 Potable water, showers 13 cases Hoteli

L. pneumophila Fountain 13 LP (66 suspect) Communityj

L. pnuemophilak Hot-tub display 141 cases Communityl

L. pneumophila serotype 1 Cooling tower 17 cases aLarge community outbreaks most commonly linked to cooling towers. Cases not noted to be a specific serotype, were not reported. bSmith SS et

al: Open Forum Infect Dis 2:ofv164, 2015. cDepartment of Veteran’s Affairs Inspector General. https://www.va.gov/oig/pubs/VAOIG-13-00994-180.pdf. dShivaji T et al: Eurosuveillance 19:20991, 2014. eSmith AF et al: Environ Health Perspect 127:127001, 2019. fState of Illinois, Auditor General. https://auditor.illinois.gov/Audit-Reports/Performance-Special-Multi/ Performance-Audits/2019_Releases/19-Quincy-Legionnaires-Disease-Perf-Digest.pdf. gNew York City Department of Health and Mental Hygiene. https://www1.nyc.gov/assets/doh/downloads/pdf/han/alert/legionella-in-bronx-source-identified.pdf. hKessler MA et al: Am J Infect Control. 49:1014, 2021. iBrown E: New York Times. 2019. https://www.nytimes.com/2019/08/16/us/legionnaires-disease-atlanta-hotel-reopen.html. jNorth Carolina Department of Health. https://epi.dph.ncdhhs.gov/cd/legionellosis/MSFOutbreakReport_FINAL.pdf. kNon–serotype 1. lGrossman NV et al: Morbid Mortal Wkly Rep 72:1315, 2023. https://www.cdc.gov/mmwr/volumes/72/wr/mm7249a1.htm.

investigations. Because of underdiagno sis, it is likely that diagnosed sporadic community-acquired cases represent only patients who are ill enough to present to health care for evaluation. Risk Factors A number of epidemio logic and demographic risk factors are associated with legionellosis. Older age is a risk factor; most studies suggest that risk begins to increase at an age of ~40 years. Furthermore, elderly patients are at the highest risk for major complica tions. Males are at approximately three times greater risk for Legionella disease than are females in most large epide miologic studies. Children are thought to be less likely to develop severe infec tions. However, since routine testing is less common among children, cases may be underreported.

Sporadic Premise plumbing Aspiration Travel Cooling towers Water features Common source/outbreak Smoking has been strongly linked to legionellosis. Inhalation of smoke leads to anatomic changes in the airway epithe lium, impairs neutrophil and monocyte phagocytosis, and has negative effects on airway ciliary clearance—all of which can increase the risk of pneumonia. Studies have shown that cigarette smoking is a dose-dependent risk factor. Smoking cannabis has also been associated with increased risk. Risk and severity of illness are further associated with smoking-related pulmonary diseases such as chronic obstructive pulmonary disease or emphysema, which in turn lead to increased risk for complications. Patients with other organ dysfunction/failure, such as those with renal disease (including those on dialysis), hepatic disease, nonsmoking pulmonary disease, and cardiac disease, are at increased risk for legionellosis, although it is unclear whether these factors are related to disease severity or to greater awareness and con sequent recognition by health care providers. CHAPTER 164 Legionella Infections Immunosuppressed patients are at increased risk for legionellosis and Legionella-related complications. Patients undergoing treatment for cancer (including recipients of hematopoietic cell transplantation) and solid organ transplant recipients are at high risk for legionellosis due to immunosuppression as well as disease- and treatment-related comorbidities. Use of prednisone and other glucocorticoids is strongly associated with legionellosis; however, in light of the heterogeneity of immunosuppressive agents and their use, it remains unclear whether 86 cases

most other single agents are as strongly associated with the disease. Combination immunosuppressive regimens increase risk. Patients treated with these regimens are more likely to develop non-pneumophila legionellosis and non–serotype 1 L. pneumophila infections that may be missed by routine urinary antigen testing. Patients with autoim mune diseases receiving tumor necrosis factor inhibitors, either with or without concomitant glucocorticoid use, are also at

increased risk for legionellosis. Furthermore, studies suggest a possible association of legionellosis with genetic polymorphisms in components of the innate immune system that are important in recognizing and responding to intracellular pathogens (e.g., Toll-like receptors and interferon genes). There has also been transmission to lung transplant recipients from donor lungs.

Transmission The Legionella species involved in human disease are usually waterborne pathogens. However, disease development requires sufficient levels of the organism at the exposure site, the formation of small particles that can be inhaled or aspirated into pulmonary alveoli, and an at-risk host. Legionella-containing aerosol particles must be <10 μm in diameter for deposition into the alveoli. The infective dose during exposures is unknown but likely depends on the host: disease development in at-risk individuals may require a more limited expo sure. Strain virulence is also thought to be important in disease devel opment: L. pneumophila serotype 1 is more apt to lead to outbreaks and disease than, for example, Legionella anisa, which has only rarely been associated with disease in high-risk patients. Because of the necessity for these various factors, estimated attack rates during an exposure are only ~5% for pneumonic presentations. Attack rates for Pontiac fever (see below) are thought to be higher—up to 90% among those exposed. Most exposures occur through the inhalation of contaminated aerosols from mists, sprays, or other mechanisms that produce small water droplets that can be inhaled into the distal alveoli. In homes, the most common sites of exposure are showerheads and sinks, which are especially apt to produce particles small enough for inhalation. The role played by aspiration or microaspiration in exposures is more con troversial but is hypothesized to be a secondary route for developing pneumonia. Although human-to-human transmission is not a common pathway, a single presumptive case has been reported. After exposure, L. pneumophila has an incubation period of ~2–10 days; this period has been reported to be longer in immunosuppressed hosts. In contrast, symptoms of Pontiac fever occur within 24–48 h after exposure. PART 5 Infectious Diseases ■ ■CLINICAL PRESENTATIONS Legionella Pneumonia Legionella pneumonia is the most common manifestation of legionellosis. In clinical practice, Legionella pneumo nia is often referred to by clinicians as an “atypical pneumonia” (i.e., pneumonia that lacks the classic signs and symptoms of bronchopneu monia). Other bacterial pathogens, such as Chlamydia pneumoniae and Mycoplasma pneumoniae, are also considered as etiologic agents of atypical pneumonia. Initial symptoms of Legionella pneumonia are nonspecific and include fever, myalgias, headache, shortness of breath, and either a dry or a productive cough (Table 164-2). Patients with pneumonia who present with neurologic or gastrointestinal symptoms such as anorexia, nausea, or vomiting may be more likely than others to have legionellosis. Immunosuppressed patients may present without typical symptoms such as fever. Patients who have recently traveled, who present during a known or possible Legionella outbreak, or who develop pneumonia while hospitalized should undergo testing for legionellosis. Patients with severe pneumonia presentations, including acute respiratory failure, and those with pneumonia and sepsis-like presentations should undergo testing for Legionella as per current community-acquired pneumonia guidelines. Patients with Legionella pneumonia classically present with rales, rhonchi, and—when consolidation is present—egophony and dull ness to percussion. Not all patients, particularly immunosuppressed patients, present with pulmonary findings on clinical examination. Ini tial laboratory findings in patients with Legionella pneumonia include leukocytosis or leukopenia, thrombocytopenia, and elevated liver enzyme levels; hyponatremia and/or renal dysfunction are frequent.

TABLE 164-2 Clinical and Epidemiologic Features of Legionella Pneumonia (Legionnaires' Disease) and Pontiac Fever LEGIONELLA PNEUMONIA PONTIAC FEVER FEATURE Incubation period 2–10 daysa 24–72 h Pathogenesis Legionella infection Legionella infection or exposure Common symptoms Abdominal or chest pain Anorexia Cough, sputum production Confusionb Cough Diarrhea Fatigue Fever/chills Headache Myalgias Nausea/vomiting Vertigo Diarrheab Fatigue Fever/chills Headache Myalgias Nausea/vomitingb Shortness of breath Risk factors Age >40 years Male Smoker Immunosuppressed host Neurologic disease Chronic lung disease Organ dysfunction/ chronic illness Factors associated with increased exposure Attack rate among exposed individuals ~5%c ~90% Hospitalization rate

> 90% <1% ICU admission rate 30–50% Extremely low Treatment Antibiotics (macrolide or fluoroquinolone) Supportive care Case-fatality rated 10% Extremely low aIncubation period in immunosuppressed hosts may be longer than 14 days. bThis symptom is strongly associated with Legionella pneumonia. cAttack rates are highly dependent on method of exposure, level of the pathogen in source water, and host's level of risk. dCase-fatality rates are much higher among immunosuppressed patients and those with severe underlying lung disease, ranging from 30 to 50%. Abbreviation: ICU, intensive care unit. Source: Modified from https://www.cdc.gov/legionella/clinicians/clinical-features. html. Levels of nonspecific laboratory markers of inflammation, such as C-reactive protein, can also be elevated; however, procalcitonin levels may not be as useful as a diagnostic tool. Although clinical symptoms and laboratory findings tend to be nonspecific, a number of clinical prediction tools, such as the Winthrop-University Hospital Criteria and the Legionella Score, have been developed to assist with the diag nosis of Legionella pneumonia. These scoring systems may be more useful for their negative than for their positive predictive value. An important subset of Legionella pneumonia cases are those that are linked to health care systems—i.e., nosocomial cases. Although cases of hospital-acquired legionellosis are rare, their identification is necessary as they may be harbingers of contamination of water systems, devices, and/or potable water sources. Because of the rarity of nosocomial cases, outbreaks have sometimes occurred over years before the source is identified within the health care system. In this regard, the CDC offers the following definitions: (1) A presumptive health care–associated case of Legionnaires' disease is one developing in a patient with Legionella pneumonia after ≥10 days of continuous stay at a health care facility during the 14 days before onset of symp toms. (2) A possible case is one that develops in a patient with Legionella pneumonia who has spent a portion of the 14 days before symptom onset in one or more health care facilities but not enough time to meet the criteria for a presumptive case. To ensure that singular cases lead to

more system-wide evaluations, the CDC also recommends an investi gation if a health care system detects one or more cases of presumptive health care–associated Legionnaires' disease at any time or two or more possible cases within 12 months of one another. ■ ■PONTIAC FEVER Pontiac

fever is an influenza-like illness whose primary symptoms are fever, headache, myalgias, chills, vertigo, nausea, vomiting, and diar rhea (Table 164-2). Compared with Legionella pneumonia, Pontiac fever is a milder, self-limited illness that is defined by the absence of pneumonia. Although studies have shown that Pontiac fever is associ ated with exposure to higher counts of colony-forming units in water sources, the role of the pathogen in the disease is not clear. Symptoms usually develop 24–48 h after exposure and can last for 2–5 days. Since many other illnesses resemble Pontiac fever, the diagnosis usually relies on the recognition of typical clinical features during an outbreak situation; therefore, sporadic cases are likely to be missed even when patients present for health care. Studies documenting specific Legionella species as the cause of Pontiac fever clusters find that most are due to L. pneumophila exposure; however, non-pneumophila species such as L. anisa have also been associated with this presentation. Extrapulmonary Disease A number of rare presentations for legionellosis have been described. Skin and soft tissue infections that resemble cellulitis, including cases due to tap water contamination of postsurgical wounds, have been reported. Endocarditis, primarily culture-negative prosthetic valve endocarditis, and myocarditis and pericarditis have also been reported. Rarely, Legionella species have been associated with septic arthritis and sinusitis. ■ ■DIAGNOSIS The diagnosis of legionellosis on the basis of clinical findings alone is difficult. Additional workup is needed to make a definitive diagnosis, even when cases are potentially linked to a possible outbreak. To make a diagnosis, laboratory confirmation is needed, and invasive proce dures may be required—e.g., bronchoscopy, particularly for patients whose results on urinary antigen testing are negative and who cannot produce sufficient sputum for testing or for patients with severe disease requiring intensive care unit (ICU) admission. As current treatment guidelines for community-acquired pneumonia recommend empiri cal coverage that includes antibiotics active against Legionella species, diagnostic testing is not routine even among persons who meet the criteria for Legionella-specific testing. Furthermore, not all currently available diagnostic laboratory assays, including urinary antigen test ing, are accessible or rapidly available in primary care clinics, urgent care facilities, and emergency rooms where patients may present with their initial symptoms. Radiologic Findings On chest radiography, Legionella pneumo nia presents as focal infiltrates or consolidations, most frequently in the lower lobes, that are indistinguishable from those due to other causes of pneumonia (Fig. 164-3). On computed tomography (CT), air-space disease in one or more lobes is often with associated ground-glass opacities (Fig. 164-4); pleural effusions and lymphadenopathy are less frequently seen. In immunocompromised patients, Legionella can pres ent with similar lower-lobe consolidations or atypically as pulmonary nodules—with or without cavitation—that mimic fungal infections (Fig. 164-5) or even as lung abscesses. Progression during early therapy is not uncommon in immunosuppressed patients. Laboratory Diagnostics • CULTURE Cultures—of sputum, bronchoalveolar lavage fluid, lung tissue, or extrapulmonary sites—are the gold standard for diagnosis of Legionella pneumonia because they are critical for epidemiologic investigations. Legionella species require special nutrients, such as cysteine, for growth and therefore require specialized media, such as buffered charcoal yeast extract (BCYE) agar. Legionellae grow slowly, usually over 3–5 days, with non-pneumophila species often requiring longer incubation times. Once growth is seen, Legionella can be stained with standard Gram stain, and colonies often fluoresce blue or white under ultraviolet light. L. micdadei is the only

FIGURE 164-3 Chest x-ray of a patient with Legionella pneumonia and rightlower-lobe consolidation. A 64-year-old woman presented with fever, dry cough, and shortness of breath 7 days after returning from international travel. Legionella urinary antigen testing was positive for L.

pneumophila serotype 1. CHAPTER 164 Legionella species that is also modified-acid-fast positive. Sensitivity varies with the sample but is highest among lower respiratory tract samples. At some referral centers, lower-tract samples from high-risk immunosuppressed patient populations are routinely sent for culture. Unfortunately, because of current community-acquired pneumonia guidelines, patients are often treated empirically, and many either never have samples sent for Legionella-specific cultures or have such samples collected only after antibiotic administration, which decreases sensitivity. Respiratory cultures from patients with legionellosis are crucial during outbreak investigations, as clinical and environmental cultures can be compared molecularly to help identify common-source outbreaks; cultures are also used for serotyping of L. pneumophila. Legionella Infections URINARY ANTIGEN TESTING Legionella urinary antigen tests are widely available at many hospitals and commercial laboratories and are char acterized by ease of use, simple specimen collection, rapid turnaround time, high sensitivity, and the ability to detect the most prevalent Legionella species associated with clinical disease—L. pneumophila sero type 1. Urinary antigen testing has limitations, however: it detects only L. pneumophila serotype 1 and gives false-negative results in most cases caused by clinically important non–serotype 1 L. pneumophila and nonpneumophila species. Sensitivity for L. pneumophila serotype 1 is ~70% for most assays, but specificity is very high. The urinary antigen test can be negative very early in the disease and can remain positive for months after an infection, particularly in immunosuppressed patient popula tions; it cannot be used for patients who are anuric. Urinary antigen testing is not recommended for routine use in screening for exposures among asymptomatic patients in outbreak investigations. SEROLOGY Acute- and convalescent-phase titers of antibody to Legionella have limited sensitivity in diagnosing acute Legionnaires' disease but can be useful during outbreak investigations. A case is confirmed by documenting a fourfold or greater rise in titer of specific serum antibody to L. pneumophila serogroup 1. A case is suspected in tests using pooled antigens by (1) a fourfold or greater rise in antibody titer to specific species (e.g., L. longbeachae) or non–serogroup 1 L. pneumophila or (2) a fourfold or greater rise in antibody titer to mul tiple species of Legionella. Some experts think that a single antibody level of ≥1:256 may be an adequate basis for diagnosing a presumptive case, but most prefer paired serology for confirmation. Serology is an imperfect tool; data suggest that as many as 20–30% of patients with

 A B FIGURE 164-4 Right-upper-lobe infiltrate in a patient with L. pneumophila pneumonia on chest x-ray and computed tomography (CT). An immunosuppressed patient from a long-term care facility presented with cough, sputum production, fever, and chills. New renal insufficiency and hyponatremia were documented. A chest x-ray (A) was consistent with a small right-upper-lobe infiltrate (white arrow), which was confirmed by CT (B). Urinary antigen testing for L. pneumophila serotype 1 was negative, but polymerase chain reaction on bronchoalveolar lavage fluid was positive for L. pneumophila. A B FIGURE 164-5 Nodular disease presentation on computed tomography (CT) in an immunosuppressed patient infected with L. micdadei. A. CT scan in a hematopoietic cell transplant recipient presenting with fever and cough. A pulmonary nodule was noted in the right upper lobe. Bronchoscopy was performed; cultures were positive on day 5 for small white colonies on buffered charcoal yeast extract plates, and these colonies were eventually identified as L. micdadei. B. Repeat CT scan at day 12 demonstrated an enlarging nodule, diffuse infiltrates, and possible cavitation. The patient required intensive care unit admission and intubation despite appropriate targeted antibiotic therapy. proven legionellosis may not mount an antibody response that is suf ficient for diagnosis, and the sensitivity and specificity of seroconver sion with regard to non-pneumophila Legionella species are unclear

among patients with altered immunity. Serology can provide important information for epidemiologic investigations, helping to identify addi tional cases missed by other diagnostic methods. In addition, the use of serologic testing during outbreak studies allows the investigation of patients without severe disease (e.g., those with Pontiac fever). DIRECT FLUORESCENT ANTIBODY TESTING The sensitivity of direct fluorescent antibody (DFA) testing of sputum is lower than that of other testing modalities, ranging from 20 to 70% depend ing on the assay used. Most available assays target specific species (e.g., L. pneumophila) or serotypes. DFA testing may have a higher positive predictive value in patients with severe pneumonia or symptoms consistent with Legionnaires' disease, but it is not recom mended for screening of low-risk patients because of the frequency of false-positive results. MOLECULAR TESTING Polymerase chain reaction (PCR), loop-mediated isothermal amplification (LAMP), and other nucleic acid amplifica tion tests are highly sensitive for lower respiratory tract specimens

(e.g., sputum) and are becoming more widely available. Molecular methods can detect Legionella from multiple sources but are most com monly used for respiratory specimens such as sputum and bronchoal veolar lavage fluid. PCR is more sensitive than culture; in some studies, up to two to four times as many cases of lower tract disease were detected only by molecular methods. Molecular techniques also are useful in diagnosing infection in patients during antibiotic therapy. However, PCR methods are not used to determine L. pneumophila serotypes—information that is needed for epidemiologic investigations—and most commercially available assays target only L. pneumophila. Multiplex PCR tests for pneumonia and other respiratory pathogens are increasingly available and may include L. pneumophila. TREATMENT Legionella Pneumonia Treatment of Legionella pneumonia involves antibiotics that target intracellular pathogens, whereas patients with Pontiac fever do not require antibiotic therapy. Macrolides and fluoroquinolones are the first-line agents for Legionella pneumonia according to guidelines in the United States and Europe (Table 164-3). Macrolides disrupt protein production critical for survival of the organism. Although erythromycin and clarithromycin are both effective, azithromycin is the preferred agent, as it is easier to tolerate and has fewer drugdrug interactions. Azithromycin and clarithromycin also reach higher intracellular concentrations than erythromycin. Fluoroquinolones are potent agents against Legionella species. Data from both in vitro and in vivo models of infection suggest that fluoroquinolones may be more effective than macrolides, but no randomized clinical trials have yet compared the two drug classes for treatment of legionellosis. In nonrandomized observational studies, fluoroquinolones have been shown to be more effective than macrolides (erythromycin and clarithromycin) in terms of fever resolution and decreased duration of hospitalization; other such studies have shown no difference in outcome. Both macrolides and fluoroquinolones are available as IV and oral formulations. Most experts prefer IV therapy during the first TABLE 164-3 Legionella Treatment Options DISEASE SEVERITY DISEASE MILD MODERATE/SEVEREa,b Pontiac fever None N/A Legionella pneumonia A) Fluoroquinolone: Levofloxacin, 750 mg PO once daily or Ciprofloxacin, 500 mg PO twice daily or Moxifloxacin, 400 mg PO once daily A) Fluoroquinolone:c Levofloxacin, 750 mg IV once daily or Ciprofloxacin, 500 mg IV twice daily or Moxifloxacin, 400 mg PO twice daily or B) Macrolide: Azithromycin, 500 mg PO once daily (day 1), followed by 250 mg PO once daily (for minimum of 4 days) or B) Macrolide:c Azithromycin, 500 mg IV daily or Clarithromycin, 400 mg IV twice daily or Clarithromycin, 400 mg PO daily Note: Agents in bold type are considered first-line treatment. aAll immunosuppressed patients should be considered to have moderate or severe disease and started on IV therapy if possible. bAll patients requiring inpatient care should receive IV therapy until improving, when they can be switched to an oral agent. cConsider dual therapy,

either with dual fluoroquinolone and macrolide therapy, or either agent with another secondary agent (e.g., rifampin). Secondary agents include doxycycline, minocycline, rifampin, and trimethoprimsulfamethoxazole, all with varying efficacy for treatment. Abbreviations: IV, intravenous; N/A, not applicable; PO, oral.

few days of treatment for patients with severe Legionella pneumo nia. Secondary agents, such as rifampin, doxycycline, minocycline, and, less frequently, trimethoprim-sulfamethoxazole, have also been used, with mixed responses. Tigecycline, a third-generation glycylcycline related to tetracyclines, has been used for treatment of patients with significant antibiotic allergies. The novel aminometh ylcycline antibiotic omadacycline appears to be efficacious in vitro, but its clinical efficacy has not been studied to date, and it is not currently recommended for routine use. Although data are limited, combination therapy does not appear to improve outcomes.

The optimal duration of treatment for Legionnaire's disease is unknown. For community-acquired pneumonia, guidelines rec ommend treatment until the patient achieves clinical stability and for a minimum of 5 days. In the absence of data, a similar duration of treatment for Legionella is a reasonable approach. For immunosuppressed patients and patients with severe disease, a more protracted course of therapy is recommended. The duration of therapy for extrapulmonary manifestations of Legionella infec tion is unknown and depends on the site involved and clinical improvement. Resistance to macrolides and fluoroquinolones has been reported only rarely. Susceptibility testing is not routinely performed but is available in specialized laboratories and public health departments. ■ ■OUTCOMES Legionella infections are associated with significant morbidity and mortality, leading to hospitalization and ICU admission of most patients who develop pneumonia. Case-fatality rates of Legionella pneumonia are reported to be ~10%, with death more likely among patients who are admitted to the ICU or have major comorbidities. Among patients in whom antibiotic treatment is delayed, mortality rates are approximately three times higher than among those treated earlier. Patients who develop nosocomial pneumonia attributable to health care–associated exposures, particularly those due to L. pneu mophila, have case-fatality rates of ~25%. Death is a much more com mon outcome among immunocompromised hosts, whose mortality rates can reach ~30–50%. Assessment of long-term follow-up among patients who recover from severe Legionella pneumonia demonstrates that more than one-quarter have ongoing complications after recovery, including recurrent hospitalizations, acute renal failure, respiratory complications, and recurrent pneumonias. In contrast, recovery from Pontiac fever usually takes place within 3–5 days, as the disease is selflimiting; hospitalization, complications, and death related to Pontiac fever are extremely rare. CHAPTER 164 Legionella Infections ■ ■PREVENTION Prevention of legionellosis starts with addressing water systems. Large municipal water systems provide water throughout the globe, but the quality of these systems varies regionally; many areas have limited access to potable water. Only limited regions have the resources to address Legionella water contamination; most water-monitoring agen cies focus on control of enteric pathogens, such as Escherichia coli and other coliform bacteria, and do not have an adequate infrastructure to address Legionella. Even in countries and cities with more complex water systems, there is wide variation in how waterborne pathogens are addressed, and rules and regulations are often country dependent. In the Netherlands, for example, chlorination is not routine, whereas the United Kingdom and most countries in the European Union use chlorine routinely as the primary mode of disinfection for public water systems. Although regulated by the Environmental Protection Agency, management and treatment strategies in the United States vary by state and, in some instances, by city. Prevention in the United States focuses on health care organizations and hospitals, where

water-based exposures are more often linked to case fatalities. Federal requirements to reduce Legionella risk in the United States were first established in June 2017, when the Centers for Medicare and Medicaid Services required that all health care organi zations develop and adhere to water management plans. These plans require the development of multidisciplinary teams, an understanding

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Revision #1
Created 2026-01-06 16:33:08 UTC by Omar Ayman
Updated 2026-01-06 16:33:08 UTC by Omar Ayman