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legionnaires’ disease Diego Viasus and Jordi Carratalà ESSENTIALS Legionellaceae are Gram-negative bacilli, of which Legionella pneumophila is the principal cause of human infections. Their natural habitats are freshwater streams, lakes, thermal springs, moist soil, and mud, but the principal source for large outbreaks of legionellosis is cooling systems used for air conditioning and other cooling equip- ment. Legionella spp. are principally transmitted to humans through contaminated water aerosols. Middle-aged men, smokers, regular al- cohol drinkers, and those with comorbidity are most at risk. Clinical features and diagnosis—(1) Legionnaires’ disease (pneu-

monia)—typically presents with high fever, shivers, headache, and muscle pains; respiratory symptoms are sometimes minimal; confusion and diarrhoea may dominate the clinical picture. The radiographic and nonspecific laboratory findings overlap with typical and atypical pulmonary pathogens. (2) 'Pontiac fever'—an acute nonpneumonic form that presents as a self-limiting, influenza-like illness. Detection of urinary antigen has become the mainstay for diagnosis. Treatment, prognosis, and prevention—aside from supportive care, the first-choice antibiotics are macrolides (mainly azithromycin) and/ or fluoroquinolones (especially levofloxacin). Case fatality is 5–15% in previously well adults, but much higher in those who are immuno- compromised or develop respiratory failure. Prognosis is improved by early administration of effective anti-legionella antibiotic therapy. Prevention is by the correct design, maintenance, and monitoring of water systems. Notification of a case allows a public health investiga- tion into the likely source and the detection, prompt treatment, and/ or prevention of additional cases. Introduction and historical perspective Legionella spp. was first recognized as a pathogen in 1977, when L. pneumophila was identified as the agent responsible for an out- break of severe pneumonia among delegates to the 1976 American Legion Convention at a Philadelphia hotel. Several new serogroups of L. pneumophila and other Legionella spp. have since been discovered. Legionellosis refers to the two main clinical syndromes caused by bacteria of the genus Legionella. Pontiac fever is an acute, self- limited, nonpneumonic, influenza-like condition caused typically by L. pneumophila serogroup 1; legionnaires' disease is an acute pneumonia syndrome caused by Legionella spp. Aetiology The family Legionellaceae consists of the single genus Legionella. Legionella are aerobic, nonsporing, Gram-negative bacteria. The genus Legionella consists of 58 species encompassing at least 70 serogroups (Table 8.6.39.1). The bacterium displays dramatic pleo- morphism, presenting coccoid, bacillary, and/or long filamentous Table 8.6.39.1 Some Legionella species L. adelaidensis L. longbeachae L. anisa L. lytica L. bozemanii L. micdadei L. brunensis L. moravica L. cherril L. nautarum L. dumoffi L. parisiensis L. fairfieldensis L. pneumophila L. feeleii L. quateirensis L. gormanii L. rubrilucens L. gratiana L. santicrusis L. hackeliae L. spiritensis L. israeliensis L. taurinensis L. jordanis L. waltersii L. lansingensis L. yabuuchiae

 forms depending on the temperature, available nutrients, and type of medium. They grow on various solid-selective and nonselective media. Iron, L-cysteine, α-ketoglutarate, and charcoal-containing yeast extract agar buffered with an organic buffer (BCYE) is the preferred growth medium for clinical isolation. The identifica- tion of legionella at the species level requires more sophisticated testing: growth requirements, agglutination and fluorescent anti- body technique, fatty acid, carbohydrate or ubiquinone analysis, protein profiling, and various molecular techniques. Legionella species are found worldwide. Legionella bacteria have been isolated from aqueous environments such as rivers, ponds, lakes, and thermal pools. The organisms are able to survive in moist environments for long periods of time and can withstand temperat- ures of 0–68ºC. Legionella is primarily adapted for survival and repli- cates within numerous protozoan genera, including Acanthamoeba, Naegleria, Hartmanella, and Tetrahymena, and secondarily as a free- living or biofilm-associated aquatic bacterium. This relationship increases the resistance of L. pneumophila to biocides, antibiotics, acids, and osmotic and thermal stress. L. pneumophila is the principal cause of human infection. Serogroups 1, 4, and 6 of L. pneumophila are the most frequently isolated. Seventeen other species have been implicated in human infections, including L. micdadei, L. bozemanii, L. dumoffi and L. longbeachae (30–55% of legionnaires' disease cases in Australia and New Zealand). Epidemiology The exact incidence of legionnaires' disease worldwide is difficult to establish, mainly because countries differ

in terms of levels of awareness, diagnostic methods, and reporting. In any case, legion- naires' disease is substantially underdiagnosed and underreported. Population-based incidence data suggest that more than 10 000 cases of legionnaires' disease occur annually among adults in the United States. A significant increase in the incidence of legionellosis in the United States has been documented in recent years. According to the European Working Group for Legionella Infections, the overall incidence for Europe was 8.2 cases per million population, with wide variations between countries (range 0–21.4 per million). Legionellosis incidence also shows marked seasonality, with most cases being reported in summer or fall. Legionella spp. are increasingly recognized as a cause of both spor- adic and epidemic community-acquired pneumonia requiring hos- pitalization, being responsible for between 2% and 16% of all cases. The disease is rare in children, and most cases occur in those older than 50 years. Infection is more common in men. Hospital-acquired legionellosis is uncommon but can occur when hospital water supplies are contaminated with the organism. Nosocomial infection mainly af- fects highly susceptible or immunosuppressed patient populations. Although Legionella spp. have been detected in virtually all sources of fresh water supplies, natural water supplies are rarely identified as sources of human infection. Aerosols from artificial reservoirs of water are most often implicated in community-acquired outbreaks, and cooling towers continue to be the most frequently suspected sources. Other well recognized sources include whirlpool spas or warm-water baths, decorative fountains, automatic car washes, and potting compost (L. longbeachae in Australia). Legionnaires' disease may be associated with a history of recent travel. The most common source of infection is contaminated water in hotel fountains and showers, but travel-associated legionnaires' disease has also been linked to cruise ships. Pathogenesis Legionella spp. are principally transmitted to humans through in- halation. Aspiration and instillation of contaminated water are also possible routes of transmission, but there is no evidence of person- to-person transmission. Legionnaires' disease due to L. longbeachae is thought to have a different route of transmission—exposure to potting compost or soil, or gardening activities. Although many people are exposed to Legionella spp., very few develop legionnaires' disease. Susceptibility to disease is associated with older age, smoking, chronic cardiovascular or respiratory dis- ease, alcoholism, diabetes, and immunosuppression. L. pneumophila possesses many of the traditional bacterial de- terminants that are important for pathogenicity in other bacteria, including lipopolysaccharide (LPS), flagella, pili, a type II secretion system (T2SS) termed Lsp, and outer membrane proteins. The mip gene was the first L. pneumophila virulence-associated gene de- tected. It is required for efficient host cell infection and is conserved throughout the genus. In addition, L. pneumophila has a type IV secretion system (Dot/Icm T4SS) that translocates several effector proteins, including many proteins with eukaryotic similarity that act on diverse host cell pathways, such as the establishment of the L. pneumophila-containing vacuoles, bacterial entry, inhibition of host cell apoptosis and the egress of the bacteria from the host cell. In human macrophages, L. pneumophila multiplies intracellularly by avoiding phagosome-lysosome fusion. Legionella spp. inhibit the bactericidal activity of the phagocyte, permitting prolonged intra- cellular survival within the phagosome. Additional virulence factors include cytotoxins, compounds associated with iron uptake, and β-lactamases. Clinical features and differential diagnosis Legionnaires' disease does not have specific, defining clinical features because it presents as a range of clinical symptoms and signs (Table 8.6.39.2). Legionnaires' disease most commonly presents acutely and resembles pneumococcal or other bacterial pneumonias. The incubation period is between two and 14 days. Table 8.6.39.2 Clinical features and laboratory findings associated with legionnaires' disease Incubation period 2–14 days Prodromal illness Headache, myalgia, asthenia, and anorexia Physical examination Fever, relative

bradycardia, cough, purulent sputum, shortness of breath, rales, altered mental status Radiographic findings Progressive asymmetrical patchy infiltrates, cavitation, or abscess formation is rare, pleural effusion Laboratory findings Increased serum transaminase levels, microscopic haematuria, leucocytosis with relative lymphopenia, hypophosphatemia, increased serum ferritin and creatine phosphokinase levels, hyponatraemia Others Loose stools or watery diarrhoea

section 8 Infectious diseases 1228 A prodromal illness can occur, with symptoms such as headache, myalgia, asthenia, and anorexia. Physical manifestations of Legionella pneumonia are not specific: fever (often up to 39oC); cough with purulent sputum in around 50% of patients; shortness of breath; and rales, sometimes accompanied by pleural effusion. Relative bradycardia has been associated with Legionella pneu- monia and is often documented in elderly patients with advanced infection. The radiographic and nonspecific laboratory findings in le- gionnaires' disease overlap with typical and atypical pulmonary pathogens. Chest radiographic findings in legionnaires' disease are nonspecific. Although practically all radiological manifestations have been described, the most characteristic findings are rapidly progressive asymmetrical patchy infiltrates. The progression of in- filtrates on chest radiograph is common, despite appropriate anti- biotic therapy within the first week. Cavitation or abscess formation is rare and most commonly reported in immunosuppressed patients receiving corticosteroids. Pleural effusion is present in up to a third of patients, but empyema is rare. Like other atypical pulmonary infections, legionnaires' disease is associated with extrapulmonary manifestations. Legionella most frequently presents with pneumonia and encephalopathy, mainly mental confusion. The hepatic manifestations of legionnaires' dis- ease are mildly and transiently increased serum transaminase levels. Other extrapulmonary manifestations include loose stools or watery diarrhoea and microscopic haematuria. Characteristic laboratory findings are leucocytosis with relative lymphopenia, hyponatraemia, hypophosphatemia, increased serum ferritin, and raised creatine phosphokinase levels. Although some presenting clinical features suggest legionella pneumonia, it is difficult to express them in a reliable scoring system. Combining positive and negative signs, symptoms, and laboratory features is the basis of a syndromic diagnosis using a weighted point system. However, the scores available do not differentiate reliably between Legionella pneumonia and pneumo- coccal pneumonia. As with any pneumonia, the most important complication is re- spiratory failure. Up to 20% of cases might require mechanical ven- tilation. Acute kidney injury can also occur but is usually reversible. Rarely, pericarditis and myocarditis have been described, as has meningitis. Pontiac fever Pontiac fever is the benign, acute nonpneumonic form of legionella infection which presents as a self-limited influenza-like illness. The incubation period is from 1 to 3 days. There are no specific clinical findings or laboratory tests for its diagnosis and no agreed clinical case definition. Antimicrobial treatment is usually not needed, and symptoms usually subside within 4 to 5 days. Laboratory diagnosis Laboratory-confirmed cases of legionellosis are based on culture of the organism from respiratory specimens, a fourfold rise in serum antibody level against L. pneumophila serogroup 1, or detection of L. pneumophila serogroup 1 antigen in urine (Table 8.6.39.3). Culture and isolation remain the gold standard for detection of legionella and diagnosis of legionnaires' disease. Enriched and permissive agar such as BCYE is needed for Legionellae cul- ture. Legionellae can be isolated from a variety of sample types, although lower respiratory tract secretions are the samples of choice. The cultures usually take 3–5 days to become positive. The major limitation of the sputum culture is that fewer than half of patients with legionnaires' disease produce sputum. However, a positive isolate implies disease as colonization is thought not to occur. Isolation of Legionella allows microbiological identification and subtyping by DNA studies to determine the

environmental source of infection. The Legionella urinary antigen test is a rapid, relatively low cost, uncomplicated procedure that detects antigens of L. pneu mophila serogroup 1 in urine and has become the mainstay of diagnosis at many centres. Legionella antigenuria can be de- tected as early as one day after onset of symptoms and usually disappears within two months. The rapidity of diagnosis is an important advantage of the urinary antigen test, since it means that cases can be detected early and therapeutic decisions taken promptly. The test's major disadvantage is its inability to detect organisms other than L. pneumophila serogroup 1 reliably; a negative urine antigen test does not necessarily exclude legion- ella infection. Serologic comparison of acute and convalescent serum specimens demonstrating a fourfold rise in titre (≥1:128) of the immunoglobulin G antibody is highly specific when the L. pneumophila serogroup 1 antigen is used but less specific for other Legionella antigens. In any case, the clinical utility of serologic diagnosis is limited because four to eight weeks are required to mount a full antibody response. Furthermore, underlying medical conditions or immunosuppres- sion may occasionally prevent or delay increases in titre. Serological assays face further challenges such as cross-reactivity, which may complicate the interpretation of results. In practice, serology is not used for clinical diagnosis but might sometimes be useful as an epi- demiological tool: a single high titre is suggestive but not confirma- tory of infection. Direct fluorescent antibody staining can identify Legionella antigens in respiratory specimens and tissues and might be useful for bronchoalveolar lavage (BAL) specimens. This technique has the advantage of providing a result within two to four hours but it is technically demanding and must be performed by skilled laboratory staff. A positive direct fluorescent antibody result in the absence of other supporting evidence is currently not accepted as sufficient for diagnosis of Legionella infection. Table 8.6.39.3 Laboratory diagnosis Test Comments Culture Detects most species, including fastidious organisms, variable sensitivity, usually takes 3–5 days to become positive Direct fluorescent assay Variable sensitivity, result within 2–4 hours, technically demanding, not accepted as sufficient for diagnosis Urinary antigen test Low cost, uncomplicated procedure; easy to collect samples; only detects antigens of L. pneumophila serogroup 1, sensitivity nearly 70% Serology testing Around 4–8 weeks are required for antibody response, cross-reactivity, useful as an epidemiological tool Nucleic acid-based detection Requires trained personal and sophisticated machines, detects all species, sensitivity nearly 90%

8.6.39 Legionellosis and legionnaires' disease 1229 Nucleic acid-based tests for Legionella detection, diagnosis, and typing are becoming more widespread. Both retrospective and prospective clinical and epidemiological studies have valid- ated detection of the mip gene particularly in a variety of speci- mens, including water from cooling towers, rivers, and hot tubs as well as sputum, serum, and urine. Legionella nucleic acid-based detection offers significant advantages over serology and culture in terms of sensitivity, and is the only approach currently suitable for diagnosis of legionnaires' disease due to non-pneumophila Legionella species in a time frame that could positively influence patient management. In addition, these techniques establish a direct link between environmental and clinical isolates by means of subtyping. One inherent complication with all nucleic acid amp- lification methods is the difficulty in assessing bacterial viability. In addition, this technology still requires specially trained staff and sophisticated machines. Treatment Delay in the initiation of appropriate antibiotic therapy for Legionella pneumonia significantly increases mortality. Therefore, it is recom- mended that anti-legionella agents be included early in the empiric therapy of severe community-acquired pneumonia and in those who are immunocompromised. Although there have been no pro- spective randomized trials addressing the subject, most authorities have recommended therapy with fluoroquinolones or macrolides, mainly levofloxacin (500 mg/ 24 hours) or azithromycin (500 mg/ 24 hours).

Doxycycline can also be considered. In this regard, studies of animal models of Legionella pneumophila have demon- strated the superiority of most fluoroquinolones and azithromycin over erythromycin. Similarly, observational prospective studies comparing levofloxacin versus older macrolides (erythromycin or clarithromycin) in the treatment of legionnaires' disease have shown that the use of levofloxacin is associated with a shorter time to reach clinical stability, shorter hospital stay, and fewer complications. One of the key factors is the ability of the antibiotics to reach therapeutic concentrations within alveolar macrophages where the legionella bacterium multiplies. Combined therapy, adding rifampicin to macrolides or quin- olones, has been used in severe or life-threatening legionella pneu- monia. Nevertheless, there is no convincing evidence of any added benefit. In addition, the use of combinations increases the risk of toxicity and drug interactions. Clinicians should be alert to the risk of prolongation of the QT interval on the electrocardiogram (ECG). The total duration of quinolone treatment should be 10–14 days, al- though a 21-day course has been recommended for immunosup- pressed patients. The recommended duration of treatment with azithromycin is 3–5 days for mild cases, and 5–10 days for immuno- suppressed patients. In severe cases or in the immunocompromised, therapy should continue until the fever subsides and clinical signs improve. Prognosis Because legionnaires' disease occurs primarily in older adults, prognosis depends largely on the host comorbidities. Prognosis is also directly related to the early administration of effective anti- legionella therapy. Although legionnaires' disease has an overall mortality rate of 5–15%, it is lower when early diagnosis allows prompt treatment, but higher in immunosuppressed individuals (up to 70%) and in those requiring intensive care unit admission. Long-term sequelae might occur, such as tiredness or poor concen- tration, but these are not well characterized. Prevention As person-to-person spread does not occur, the main aspect of le- gionella control involves good environmental health measures, such as water testing and environmental surveillance, coupled to ensuring safe water supplies. There are World Health Organization (WHO) guidelines for the latter. Prompt diagnosis of severe pneu- monias and investigation of clusters of cases can pinpoint sources of infection and appropriate interventions. Areas of uncertainly and future developments More research is currently needed to estimate the incidence of legionnaires' disease and to quantify the new risk factors, the as- sociated morbidity and mortality (especially long-term survival or sequelae) and the economic burden. Prospective random- ized controlled trials should be conducted to assess the merits of different classes of antibiotics and determine whether mono or combination therapy is preferable. Such trials could, poten- tially, be done in the setting of an outbreak. Further research is needed to improve the diagnostic accuracy of tests. The valid- ation of molecular assays might help to achieve the diagnostic accuracy and rapidity required to guide disease management, the study of environmental distributions of strains and their relation to infection, and the exploration of genotypic factors in disease causation. FURTHER READING Bartram J, et al. (2007). Legionella and the prevention of legionellosis. World Health Organization Press, Geneva. Cunha BA (2010). Legionnaires' disease: clinical differentiation from typical and other atypical pneumonias. Infect Dis Clin N Am, 24, 73–105. Cunha BA, Burillo A, Bouza E (2016). Legionnaires' disease. Lancet, 387, 376–85. Fernández-Sabe N, et al. (2003). Clinical diagnosis of Legionella pneumonia revisited: evaluation of the Community-Based Pneumonia Incidence Study Group scoring system. Clin Infect Dis, 37, 483–9. Guyard C, Low DE (2011). Legionella infections and travel associated legionellosis. Travel Med Infect Dis, 9, 176–86. Mercante JW, Winchell JM (2015). Current and emerging Legionella diagnostics for laboratory and outbreak investigations. Clin Microbiol Rev, 28, 95–133. Newton HJ, et al. (2010) Molecular pathogenesis of infections caused by Legionella pneumophila. Clin Microbiol Rev, 23, 274–98. Pedro-Botet L, Yu VL. (2006). Legionella: macrolides or quinolones?. Clin Microbiol Infect, 12 Suppl 3, 25–30. Phin N, et al. (2014). Epidemiology and clinical

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