37.1 Epidemiology

37.1.1 Prevalence and Incidence in the Community and Hospital Setting

The incidence of legionnaires’ disease (LD) seems to increase with age, particularly in males [36]. It was considered an infrequent cause of pneumonia in the past, but it currently ranks second to pneumococcus in the list of etiologic agents of severe community-acquired pneumonia (CAP) of bacterial origin [2, 24, 60, 89]. Considering less severe cases, in a series of 145 pneumonias in which BCYE culture, serology and the Legionella urinary antigen (LUA) test were systematically applied, Vergis et al. [91] reported a prevalence of LD of 13.7%. In another series of 392 adult patients with CAP treated in a university hospital, Sopena et al. found a prevalence of 12.5%, and LD was the second cause of pneumonia [83].

The incidence of LD is most likely underestimated. The number of Legionella spp. progressively identified as a cause of severe pneumonia is increasing and most of these species are not detected by routine laboratory tests. Legionella waltersii is the last Legionella species associated with severe pneumonia [43]. Although LD tends to occur more frequently during summertime, it seems that wet, humid weather is significantly associated with the acute appearance of this disease [27]. Although the expected rate of legionellosis in the USA ranges from 8,000 to 18,000 cases yearly [53], the mean number of cases reported to the Center for Diseases Control (CDC) from 1980 to 1998 was 360 per year [5]. According to the European Working Group for Legionella Infections (EWGLI), the number of cases in the European dataset provided by more than 30 countries increased from 1,255 in 1995 (annual incidence rate of 3.7 per million population) to 4,588 in 2004 (annual incidence rate of 10.1 per million population) [69]. However, in some eastern European countries, this incidence continued to be below 1 case per one million inhabitants [40]. Reporting Legionella infection is not mandatory in many European countries and in some geographic areas, especially those with a more depressed economy, LUA is not usually ordered in most cases of CAP.

Legionella infection has also been considered a rare cause of hospital-acquired pneumonia (HAP). However, the majority of published studies have been conducted in the ICU setting or only in mechanically ventilated patients. ICUs are usually well delimited areas with a relatively small number of patients who are not usually exposed to aerosols (showers, hot tap water). That is why LD has rarely been detected in ICUs with the only exception of those cases associated with the use of contaminated water in nasogastric tubes or mechanical ventilation equipment [11].

Legionella infection has been increasingly recognized as a cause of HAP, especially in non-ICU areas. Environmental studies have demonstrated that colonization of the potable water distribution is a common feature in many hospitals [76]. When the water supply of a hospital is known to be colonized by Legionella, the index of suspicion of infection by Legionella rises and appropriate testing is then systematically ordered. Consequently, sporadic cases of LD and nosocomial outbreaks are then more frequently reported and even historical cases, previously unrecognized, are retrospectively identified. [44, 47]. Everts et al. reported a series of HAP in which Legionella was the most frequent cause of nosocomial pneumonia [22]. In a multicenter study performed in 12 Spanish University hospitals, with active surveillance of HAP in non-ventilated patients and systematic use of LUA test, L. pneumophila was diagnosed in seven patients in five different hospitals not in an outbreak setting [78]. In one hospital, it was the first case of nosocomial legionellosis diagnosed in that center [85]. Diagnosis of Legionella should be considered in any case of HAP in a hospital with water distribution known to be colonized by these microorganisms [77].

37.1.2 Sources of Infection

Cooling towers and health spas continue to be the most frequently reported sources of infection in community outbreaks of LD [6, 18, 30, 31]. Potable water has been
the environmental source of almost all reported hospital outbreaks [77]. However, potable water should not be neglected as a potential source of infection both in sporadic cases and small clusters detected in the community [62]. Moreover, cases of LD in newborns, most likely caused by aspiration of bath water, have also been reported [80].

### 37.1.3 Mode of Transmission

The most commonly accepted mechanism of transmission of *Legionella* in humans is inhalation of contaminated aerosols. However, aspiration of contaminated water could also be a major mode of transmission, especially in hospital-acquired legionellosis [77]. In a prospective study of patients with head and neck cancer undergoing tumor resection with postoperative sequelae of aspiration, 30% of postoperative pneumonias were due to *L. pneumophila* [39]. Surprisingly, several studies have failed to show a link between showering and risk of infection [23, 26, 44, 81]. Others have even reported that showering could be protective for legionnaires’ disease [7]. The presumed reason for this paradoxical finding is that patients who are able to take showers are ambulatory and less likely to aspirate [77]. Nasogastric tubes [52, 90] have been linked to hospital-acquired legionellosis in several studies; the authors presumed that microaspiration of contaminated water was the cause of infection.

### 37.1.4 Risk Factors

In most cases of CAP caused by *Legionella*, classical risk factors such as travel or hotel accommodation are not identified. Smoking habit is, by far, the most consistently reported risk factor in most series. Underlying diseases are a major risk factor for the acquisition of *Legionella* pneumonia, especially in the hospital setting. Since aspiration is increasingly recognized as a mode of transmission, patients with swallowing disorders or those who undergo surgery requiring general anesthesia are at greater risk. The single most important factor is organ transplant. Among organ receptors heart transplants show the highest incidence and bone marrow transplants the lowest one [54, 68]. Steroid administration is an independent risk factor [44, 47]. Other forms of immunocompromise may also predispose to LD [48]. Paradoxically, AIDS patients do not appear to be at increased risk for hospital-acquired legionnaires’ disease [63].

### 37.2 Clinical Features

The non-specific clinical data of LD cannot usually be distinguished from those found in typical bacterial pneumonia caused by other aerobic microorganisms. Initial retrospective series suggested that clinical findings such as diarrhea or central nervous system symptoms were so frequent in legionellosis that they could be considered as highly suggestive of LD [41]. Later studies have already emphasized the lack of usefulness of those allegedly distinctive clinical data [25, 70]. Prospective, randomized, comparative studies between CAP and HAP caused by *Legionella* and those caused by other bacterial etiologies have shown that there is a marked overlap between clinical, radiological and analytical signs [35, 51, 70, 92, 93]. Serum levels of inflammatory markers, such as C-reactive protein, procalcitonin and neopterin, are often high in LD [1, 28, 65]. However, the clinical or therapeutic implications of this analytical finding remain obscure. The uncertainty in clinical differential diagnosis of CAP and HAP, as well as the potential severity of LD, supports the choice of an antibiotic that is also effective against *Legionella* in the initial therapeutic approach of most instances of hospitalized CAP and at least in suspicious epidemiological situations in the case of HAP.

In some cases of Pontiac fever, usually a flu-like benign illness, shortness of breath and an abnormal oxygen saturation have been reported [13]. In the population with advanced emphysema or severe immunocompromise that present with fever of unknown origin, a normal chest X-ray does not completely rule out pneumonia [12, 66], including that caused by *Legionella* spp. (personal observation). In this group of patients, computed tomography of the chest is recommended since an early diagnosis and therapy of radiologically unsuspected pneumonia are favorable prognostic factors.

### 37.3 Diagnosis

Definitive diagnosis of LD is established by recovery of the microorganism from respiratory secretions on BCYE. The selective medium recommended is BCYE-alpha supplemented with polymyxin B, anisomycin, vancomycin and dyes (PAV). To optimize the recovery of *Legionella* some authors recommend the use of two more media: BCYE media, PAV and BCYE supplemented with polymyxin, anisomycin, cefamandole and dyes (PAC) [87]. The addition of dyes facilitates the visualization of the colonies, making identification of *L. micdadei* and *L. maceachernii* easier. Pretreatment of sputum with acid is necessary to reduce the overgrowth of other bacteria. Vancomycin containing medium is pre-
ferred when *L. micdadei* is an issue since cefamandole inhibits this species [57]. The quality of sputum does not necessarily correlate with recovery of *Legionella*. This microorganism has been recovered from so-called inadequate specimens for culture (few polymorphonuclear leukocytes and numerous epithelial cells). Culture of respiratory samples continues to be the most valid diagnostic method and should be mandatory in all centers. The isolation of *Legionella* allows its microbiologic classification and subtyping by DNA studies. Molecular typing is crucial to establish an epidemiological link between environmental and clinical isolates.

Direct fluorescent antibody (DFA) is a rapid test for diagnosing LD, with results available within a few hours. DFA allows direct visualization of *Legionella*. Monoclonal antibodies against *L. pneumophila* are used in the DFA test. The sensitivity of this test is low (30–70%) due to the large respiratory inocula required. Thus, in severe pneumonia with large infiltrates, DFA is often positive. The test should always be performed by an experienced technician.

Diagnosis by serology requires a fourfold rise in antibody titers from 1 to 128 in acute and convalescent sera. A single titer of 1:256 is not, at present, considered specific enough for diagnosing LD [64]. It should not be used as criteria of definitive diagnosis of LD. Convalescent sera should be obtained at 4–6 weeks after presentation of the disease. It should be taken into account that antibody response may be delayed as long as 3 months after onset of the illness. A lack of antibody response has been observed by some authors [15]. Serology is a useful tool for epidemiological studies but it is clearly unhelpful in the acute setting.

The detection of the *Legionella* urinary antigen is a very useful technique to diagnose LD. The urinary antigen is detected very early during the course of the disease and usually disappears within 2 months, although its excretion may be longer, particularly in patients receiving immunosuppressive or steroid treatment [84].

The main limitation of the urinary antigen is that it only detects the soluble antigen of *L. pneumophila* serogroup 1. However, its usefulness is reinforced by the fact that this serogroup causes at least 80% of cases of LD [94]. Several kits are currently available for determining *Legionella* urinary antigen: Binax (*Legionella Urinary Antigen, Binax, Portland, USA*), Biotest (*Biotest AG, Dreieich, Germany*) and Bartels (*Bartels EIA Legionella Urinary Antigen, Intracel, Issaquah, Washington USA*). Some authors have observed an increase in the sensitivity of the test, without any decrease in specificity, if urine is concentrated [17].

A rapid immunochromatographic assay has been developed by Binax (*Binax Now Legionella Urinary Antigen, Portland USA*) to detect *L. pneumophila* serogroup 1 antigen in urine. This test has shown to be useful as a method of rapid screening in both sporadic cases and outbreaks. The sensitivity and specificity of this test are similar to those reported with ELISA. This test considerably reduces the time required for detecting *Legionella* urinary antigen with ELISA assays. It is particularly useful for small laboratories without the specialized equipment required to use ELISA or when the number of samples to be tested is small.

Some authors have suggested that, in the outbreak setting, the sensitivity of urinary antigen test is related to the degree of severity on clinical presentation [8]. However, the reported low mortality of this series (<4%) raises some concern about the actual clinical relevance of this study.

DNA amplification by polymerase chain reaction (PCR) of *Legionella* has been tested in several specimens from patients with pneumonia [58]. A rapid real-time PCR assay for *L. pneumophila* is now commercially available (BD Probe-Tec, BD Diagnostics, Sparks, Maryland, USA) [67]. However, clinical experience with the use of PCR techniques is still very limited. Although the number of cases of LD that are diagnosed exclusively on the basis of PCR testing is increasing, controlled studies are needed to establish the clinical usefulness of this technique [32, 42, 55].

### 37.4 Treatment

In vitro susceptibility studies do not correlate with clinical efficacy since *Legionella* is an intracellular pathogen. Treatment guidelines are supported by data obtained from in vitro studies, experimental studies with the animal model, and observational studies, some of which come from prospective clinical studies in CAP. Optimal therapy against *Legionella* infection is based on agents with high intrinsic activity, an appropriate pharmacokinetic and pharmacodynamic profile, including the ability to penetrate phagocytic cells, a low incidence of adverse reactions and an advantageous cost-efficacy relationship.

Retrospective information from the first studies of LD provided very useful clues of which antibiotics were really clinically effective [16]. It became evident that erythromycin treated patients showed the lowest mortality rate (6%), while those cases that were treated with aminoglycosides, beta-lactamic antibiotics or chloramphenicol showed a 30–40% fatality rate.

Since then, a number of clinical studies have proven that erythromycin is highly effective against *Legionella*, and until some years ago it was considered the treatment of choice. In fact, a series published in 2003 confirms that it continues to be an effective agent [37]. Route, dose and length of administration of erythromycin are critical factors in obtaining a maximum effectiveness. The recommended optimal dosing of 1 g IV
Table 37.1. Recommended therapy in legionnaires' disease

| Antimicrobial agents | Dosage | Route |
|----------------------|--------|-------|
| **Macra-azalides**<sup>b</sup> | Azithromycin<sup>d</sup> 500 mg every 24 h IV, p.o. | |
|                      | Clarithromycin 500 mg every 12 h IV, p.o. | |
|                      | Erythromycin<sup>c</sup> 1 g every 6–8 h IV, p.o. | |
| **Tetracyclines**    | Doxycycline 100 mg every 12–24 h IV, p.o. | |
| **Fluoroquinolones** | Levofoxacin<sup>e</sup> 500–750 mg every 24 h IV, p.o. | |
|                      | Moxifloxacin<sup>e</sup> 400 mg every 24 h IV, p.o. | |
|                      | Gemifloxacin<sup>e</sup> 320 mg every 24 h p.o. | |
|                      | Gatifloxacin<sup>e</sup> 400 mg every 8–12 h IV | |
|                      | Ciprofloxacin 500–750 mg every 12 h p.o. | |
|                      | Ofloxacin 400–800 mg (total daily dose) IV, p.o. | |
| **Ketolides**        | Telithromycin<sup>e</sup> 800 mg every 24 h p.o. | |

<sup>a</sup> Oral therapy is recommended only in those mild cases that do not require hospitalization. Some antibiotics are only commercially available in selected countries

<sup>b</sup> In mild cases other oral macrolides are also effective: josamycin (1 g every 12 h), roxithromycin (150 mg every 12 h), dirithromycin (300 mg every 24 h)

<sup>c</sup> Less active than other macrolides; risk of fluid overload, phlebitis and transitory deafness with IV administration

<sup>d</sup> Recommended in the more severe cases, particularly in the immunocompromised

<sup>e</sup> Because of short accumulated clinical experience their use is recommended only in mild to moderate cases

every 6 h is associated with some side effects [72], such as risk of fluid overload and transitory deafness.

Other more recent macrolides share with erythromycin the ability to penetrate phagocytic cells with the advantage of showing an overall better intrinsic activity against *Legionella*. Besides this superior in vitro activity against *Legionella*, they offer pharmacokinetic and pharmacodynamic advantages. Relatively minor differences in the in vitro activity among the new macrolides have also been found in different comparative studies [3]. Consequently, the treatment of choice has changed from erythromycin to the newer macrolides and fluoroquinolones (Table 37.1). Recent studies [9, 59, 79], which unfortunately show many limitations because of methodological drawbacks [46], suggest that in terms of mortality and complications both macrolides and fluoroquinolones are equivalent for most cases of LD that require hospitalization. At least in experimental studies, monotherapy with rifampicin has been associated with a rapid development of resistance.

Duration of therapy has to be decided on an individualized basis.

Combined therapy is recommended for severe episodes by some international guidelines, but there is no evidence supporting this suggestion. For most patients monotherapy with a macrolide or a selected fluoroquinolone usually leads to a more cost-effective outcome [20, 21, 73, 74].

Recent data from a Spanish multi-center severe CAP study [10] suggest that in the subset of patients with most severe legionnaires’ disease [74], the majority of them under mechanical ventilation, combined therapy is most likely associated with a better outcome when compared to monotherapy. The most frequently used combined therapy in this study was clarithromycin associated with rifampicin. It is not clear which combined antibiotic approach is preferable although rifampicin is the most commonly used agent in combination therapy. Given that the risk of transient liver toxicity (hyperbilirubinemia) related to rifampicin therapy seems to increase with the length of treatment, we recommend using it for just a few days [38].

Additional toxicities of combining more than one antibiotic should be taken into account, particularly in the intensive care unit setting.

Rifampicin appears to add little to the activity of the more active drugs in cell models of infection but, at least in guinea pigs, it seems to be beneficial in combination with erythromycin, and probably clarithromycin. The combination of erythromycin and rifampicin has been reported to be more active against *L. pneumophila* than other options such as combining erythromycin and ciprofloxacin or rifampicin and ciprofloxacin [56]. In guinea pigs the addition of rifampicin causes a higher rate of bacterial killing, a decrease in the extent of pneumonia, and a lower mortality rate [19, 33].

Respiratory failure, particularly when adult respiratory distress syndrome (ARDS) is present, is a major cause of fatality [4, 29, 73]. In patients that require mechanical ventilation, the goal is to improve gas interchange and avoid causing ventilatory-induced lung injury, maintaining plateau pressures under 25. A strategy of ventilation using low tidal volumes (<7 ml/kg) is recommended to protect the lung in acute lung injury. Patients with LD and ARDS may most likely benefit from this approach. FiO₂ should be minimized to target an acceptable SaO₂ up to 90%. Recruitment maneuvers may prevent alveolar collapse and improve oxygena-
tion. Ventilating patients in the prone position may be used as rescue therapy for the most severe episodes. Preliminary studies in the animal model have raised some concern about the risk of hyperoxia in severe legionellosis. Extra-corporeal membrane oxygenation (ECMO) has been anecdotally reported as a successful therapeutic option in treating severe Legionella-associated ARDS. Since many patients may recover, even without sequelae, after many days of mechanical ventilation, an aggressive approach is mandatory whenever respiratory failure appears.

Shock and acute renal failure are both associated with a high risk of death [29, 72, 73]. Hemodynamic

Table 37.2. Extrapulmonary manifestations of legionnaires’ disease

| Category          | Manifestations                                                                 |
|-------------------|-------------------------------------------------------------------------------|
| Cardiovascular    | Pericarditis, myocarditis, aortic graft involvement                           |
| Neurological      | Encephalitis that may mimic that caused by herpes, brain abscess, cerebellar ataxia, corpus callosum involvement |
| Digestive         | Colon involvement that may mimic ulcerative colitis, pancreatitis, digestive tract abscess, liver involvement, spleen rupture, severe diarrheaa |
| Renal             | Kidney abscess, acute renal failure, interstitial nephritis                    |
| Blood             | Thrombopenia, disseminated intravascular coagulation (DIC)                    |
| Joint and bone    | Arthritis, osteomyelitis                                                      |
| Miscellaneous     | Wound infection, cellulitis, rhabdomyolysis, post-traumatic stress disorder   |

Some of these manifestations are just reactive and they do not mean real local infection. A short course of steroid therapy may then be useful

Table 37.3. Polymicrobial infection in legionellosis

| Category          | Infections                                                                 |
|-------------------|----------------------------------------------------------------------------|
| Other Legionella  | Dual infections by different species of Legionella and different serotypes of L. pneumophila |
| spp.              |                                                                             |
| Other bacteria    | Streptococcus pneumoniae, Proteinus mirabilis, Staphylococcus aureus, Escherichia coli, Prevotella intermedia, Enterococcus faecium, Enterobacter cloacae, Klebsiella pneumoniae, Haemophilus influenzae, Streptococcus mitis, Listeria monocytogenes, Nocardia asteroides, Neisseria meningitides |
| Mycobacteria      | Mycobacterium tuberculosis                                                  |
| Virus             | Herpesvirus, influenza, cytomegalovirus                                      |
| Fungus            | Aspergillus, Cryptococcus                                                   |
| Parasites         | Pneumocystis jiuroveci, Leishmania                                           |

Mixed infections in legionellosis should be kept in mind in the immunocompromised population since there are many reports of death when clinicians failed to identify and treat the dual component of infection [72, 73]. A list of these mixed infections is enumerated in Table 37.3.

A proposed algorithmic approach to severe legionellosis with poor clinical resolution is suggested in Fig. 37.1. In patients with delayed resolution, superinfection by Pseudomonas aeruginosa should be suspected early. In patients with persisting or relapsing Legionella infections development of antibiotic resistance has never been reported [72, 73].

37.5 Prognostic Factors

An early, appropriate treatment usually implies a better outcome and a lower mortality rate, particularly in those cases with severe clinical presentation that require admission to the intensive care unit [29]. Severe disease itself, acute renal failure, smoking habit, and immunocompromise are the most consistently identified prognostic factors of death in LD [72, 73].

In our experience (data from the CAPUCI study presented at the 6th International Conference on Legionella, Chicago, 2005), we identify the following variables as being significantly associated with death: immunocompromise, shock, acute renal failure and APACHE II score > 15. Diabetes mellitus was another variable associated with a trend to lower survival. On univariate logistic regression analysis the following variables were
also found to be associated with death: diabetes mellitus, APACHE score and Acute Physiologic Score. The only variable that remained statistically significant on multivariate logistic regression analysis was APACHE score (OR 1.86) at UCI admission.

37.6 Prevention

The ubiquity of Legionella makes it very difficult to control LD, especially in the community setting, where the potential sources of infection are diverse. A correct design of the installations at risk and a strict observance of the maintenance schedules are crucial issues in preventing LD outbreaks. However, sporadic cases of LD in the community are difficult to prevent. Despite our increased knowledge about the sources, transmission and predisposing factors to acquiring Legionella infection, many aspects of LD prevention are still controversial. The exact role of the cooling towers in sporadic cases is insufficiently known. On the other hand, some cases of community-acquired LD may be associated with contamination of domestic water supply. Aspiration, especially in the elderly with swallowing disorders, could then play an important role in the pathogenesis of this disease.

Hot water distribution systems constitute the main reservoir for Legionella in hospitals. In fact, this colonization is a challenge for traditional disinfection methods. Legionella colonization of cold water systems is usually much lower. Disinfection with chlorine is a useful and cost-effective measure in the latter setting. A strict control of the key points of water distribution supply and adequate maintenance of chlorination levels [77] is strongly recommended.

When distal sites from a hospital water distribution system are positive for Legionella, strategies to minimize the problem are needed, particularly if cases of HAP by Legionella have been eventually detected. Thus, review of hydromechanical systems, temperature control of hot water and chlorine levels, as well as maintenance procedures are mandatory. It is generally agreed that the most effective control is to keep the water temperature above 50°C. This approach does not guarantee the elimination of Legionella from the water supply but at least minimizes the inoculum and could be effective in preventing cases of HAP by Legionella. However, if cases of LD continue to appear, complementary measures of disinfection are then required. Superheat and flush methods have been used for shock disinfection in cases of heavy contamination of water or in the setting of hospital outbreaks. However, the efficacy of disinfection measures may be only transitory.
and recolonization of *Legionella* followed by new cases of HAP by *Legionella* has been reported [49].

The most commonly used methods for continuous hot water disinfection are copper/silver ionization [34, 50, 88]. Some experiences using chlorine dioxide have also been successful in some hospitals [86]. It has been suggested that monochloramines could be more effective than chlorine in decreasing *Legionella* colonization of potable water distribution systems of large buildings [45].

Local measures, such as filters, have been used to decrease the risk of *Legionella* infection among severely immunocompromised patients [82]. Whenever the water supply of a health care center has become colonized by *Legionella*, some relatively common hospital practices such as using tap water for oral toilet, nasogastric tubes, enteral nutrition, pureed diet, medication and respiratory devices should be prohibited because of the high risk of aspiration of inpatients [14].

## References

1. Almirall J, Bolibar I, Toran P, Pera G, Boquet X, Balanzo X, et al. (2004) Contribution of C-reactive protein to the diagnosis and assessment of severity of community-acquired pneumonia. Chest 125:1335–42
2. Álvarez-Sánchez B, Álvarez-Lerma B, Jordá R, Serra J, López Cambra MJ, Sandar MD (1998) Prognostic factors and etiology in patients with severe community-acquired pneumonia. Study Group on Severe Community-Acquired Pneumonia in Spain. Med Clin (Basc) 111:650–4
3. Amsden GW (2005) Anti-inflammatory effects of macrolides – an underappreciated benefit in the treatment of community-acquired respiratory tract infections and chronic inflammatory pulmonary conditions? J Antimicrob Chemother 55:10–21
4. Benhamou D, Chidiac C, Étienne J, Léophonte P, Marty N, et al. (2005) *Legionnaires’ disease*: definition, diagnosis and treatment. Med Mal Infect 35:1–5
5. Benin AL, Benson RF, Besser RE (2002) *Legionnaires’ disease*, 1980–1998: declining mortality and new patterns of diagnosis. Clin Infect Dis 35:1039–46
6. Benkel DH, McClure EM, Woolard D, Rullan JV, Miller GB Jr, Jenkins SR, et al. (2000) Outbreak of *Legionnaires’ disease* associated with a display whirlpool spa. 29:1092–8
7. Blatt SP, Parkinson MD, Pace E, Hoffman P, Dolan D, Lauderdale P, Zajac RA, Melcher GP (1993) Nosocomial *Legionnaires’ disease*: aspirations as a primary mode of disease acquisition. Am J Med 95:16–22
8. Blázquez RM, Espinosa FJ, Alemany L, Ramos RM, Sánchez-Nieto JM, Segovia M, et al. (2005) Antimicrobial chemotherapy for *Legionnaires’ disease*: Levofloxacin versus macrolides. Clin Infect Dis 40:800–6
9. Blázquez RM, Espinosa FJ, Martínez-Toldos CM, Alemany L, García-Orenes MC, Segovia M (2005) Sensitivity of urinary antigen test in relation to clinical severity in a large outbreak of *Legionella* pneumonia in Spain. Eur J Clin Microbiol Infect Dis 24:488–91
10. Bodi M, Rodríguez A, Solé-Violan J, Gilavert MC, Garnacho J, Blanquer J, et al. (2005) Antibiotic prescription for community-acquired pneumonia in the Intensive Care Unit. Impact of adherence to IDSA guidelines and outcome. Clin Infect Dis 41:1709–16
11. Borau J, Ceap RT, Strellecker RA, Venezia RA (2000) Long-term control of *Legionella* species in potable water after a nosocomial legionellosis outbreak in an intensive care unit. Infect Control Hosp Epidemiol 21:602–3
12. Brown MJ, Miller RR, Müller NL (1994) Acute lung disease in immunocompetent patients: diagnostic accuracy of high-resolution CT. Radiology 190:247–254
13. Castor ML, Wagstrom EA, Danila RN, Smith KE, Naimi TS, Besser JM, et al. (2005) An outbreak of Pontiac fever with respiratory distress among workers performing high-pressure cleaning at a sugar-beet processing plant. J Infect Dis 191:1530–7
14. Crnich CJ, Safdar N, Makki DG (2005) The role of the Intensive Care Unit environment in the pathogenesis and prevention of ventilator-associated pneumonia. Respiratory Care 50:813–838
15. Darell J, Lofgren S, Malmvall BE, Olinder-Nielsen MA, Briheim G, Hallander H (2003) *Legionella pneumophila* serogroup 1 antibody kinetics in patients with *Legionnaires’ disease*: implications for serological diagnosis. Scand J Infect Dis 35:15–20
16. Davis GS, Winn WC Jr, Beaty HN (1981) *Legionnaires’ disease*. Infections caused by *Legionella pneumophila* and *Legionella*-like organisms. Clin Chest Med 2:145–66
17. Dominguez JA, Manterola JM, Blavia R, Sopena N, Belda FJ, Padilla E, et al. (1996) Detection of *Legionella pneumophila* serogroup 1 antigen in nonconcentrated urine and urine concentrated by selective ultrafiltration. J Clin Microbiol 34:2334–2336
18. Dondero TJ, Jr, Rendtorff RC, Mallison GF, Weeks RM, Levy JS, Wong EW, et al. (1980) An outbreak of *Legionnaires’ disease* associated with a contaminated air-conditioning cooling tower. N Engl J Med 302:365–370
19. Edelstein PH, Calarco K, Yau VK (1984) Antimicrobial therapy of experimentally induced *Legionnaires’ disease* in guinea pigs. Am Rev Respir Dis 130:849–56
20. Edelstein PH (1998) Antimicrobial chemotherapy for *Legionnaires’ disease*: time for a change. Ann Intern Med 129:328–330
21. Edelstein PH (2002) Chemotherapy of *Legionnaires’ disease* with macrolide or quinolone antimicrobial agents. In: Marre R (ed) *Legionella*. ASM Press, Washington DC, pp 183 –88
22. Everts RJ, Murdoch DR, Chambers ST, Town GI, Withington SG, Martin IR, et al. (2000) Nosocomial pneumonia in adult general medical and surgical patients at Christchurch Hospital. N Z Med J 113:221–4
23. Ezzedine H, VanOssel C, Delmee M, Wauters G (1989) *Legionella* spp. in a hospital hot water system: effect of control measures. J Hosp Infect 13:121–131
24. Falco V, Fernández de Sevilla T, Alegre J, Ferrer A, Martínez Vázquez JM (1991) *Legionella pneumophila*. A cause of severe community-acquired pneumonia. Chest 100:1007–1011
25. Fang GD, Stout JE, Yu VL, Goetz A, Rihs JD, Vickers RM (1990) Community-acquired pneumonia caused by *Legionella damoiffii* in a patient with hairy cell leukemia. Infection 18(6):383–5
26. Farr BM, Gratz J, Tartaglino J, Getchell-White SI, Groschel DH (1988) Evaluation of ultraviolet light for disinfection of hospital water contaminated with *Legionella*. Lancet 2:659 –672
27. Fisman DN, Lim S, Wellenius GA, Johnson C, Britz P, Gaskins M, et al. (2005) It’s not the heat, it’s the humidity: wet weather increases legionellosis risk in the greater Philadelphia metropolitan area. J Infect Dis 192:2066–73
28. Franzin L, Cabodi D (2005) *Legionella* pneumonia and serum procalcitonin. Curr Microbiol 50:43–6
29. Gacouin A, Le Tulzo Y, Lavoue S, Camus C, Hoff J, Bassen R, Arvyiaux C, Heurtin C, Thomas R (2002) Severe pneumonia due to Legionella pneumophila: prognostic factors, impact of delayed appropriate antimicrobial therapy. Intensive Care Med 28:686–691

30. Garbe PL, Davis BJ, Weisfeld JS, Markowitz L, Miner P, Garrity F, et al. (1985) Nosocomial Legionnaires' disease – epidemiologic demonstration of cooling towers as a source. JAMA 254:521–524

31. Garcia-Fulgueiras A, Navarro C, Fennol D, Garcia J, Gonzalez-Diego P, Jimenez-Bunuales T, et al. (2003) Legionnaires' disease outbreak in Murcia, Spain. Emerg Infect Dis 9:915–921

32. Ginevra C, Barranger C, Ros A, Mory O, Stephan JL, Freymuth F, et al. (2005) Development and evaluation of Chlamydia, a new commercial test allowing simultaneous detection and identification of Legionella, Chlamydophila pneumoniae, and Mycoplasma pneumoniae in clinical respiratory specimens by multiplex PCR. J Clin Microbiol 43:3247–34

33. Gibson DH, Fitzgeorge RB, Baskerville A (1983) Antibiotic therapy of experimental airborne Legionnaires' disease. J Infect 7:210–27

34. Goetz A, Yu VL (1997) Copper-silver ionization: Cautious optimism for Legionella disinfection and implications for environmental culturing. Am J Infect Control 25:449–51

35. Granados A, Podzamczer D, Gudiol F, Manresa F (1989) Pneumonia due to Legionella pneumophila and pneumococcal pneumonia: similarities and differences on presentation. Eur Respir J 2(2):130–4

36. Gutierrez F, Masia M, Mirete C, Soldan B, Rodriguez CJ, Padilla S, et al. (2006) The influence of age and gender on the population-based incidence of community-acquired pneumonia caused by different microbial pathogens in a population-based prospective cohort study. J Infect 53(3):166–74

37. Howden BP, Stuart RL, Tallis G, Bailey M, Johnson PD (2003) Treatment and outcome of 104 hospitalized patients with Legionnaires' disease. Intern Med J 33:484–8

38. Hubbard RB, Mathur RM, MacFarlane JT (1993) Severe community acquired Legionella pneumonia: treatment, complications and outcome. Q J Med 86:327–32

39. Johnson JT, Yu VL, Best M, Vickers RM, Goetz A, Wagner R, et al. (1985) Nosocomial legionellosis uncovered in surgical patients with head and neck cancer: Implications for epidemiologic reservoir and mode of transmission. Lancet 2:298–300

40. Joseph C (2005) Legionnaires disease in Europe – A ten year epidemiological review 1995–2004. 6th International Conference on Legionella. Abstracts, p 44. Chicago, IL: October 16–20, 2005

41. Kirby BD, Snyder KM, Meyer RD, Finegold SM (1980) Legionnaires' disease: report of sixty-five nosocomially acquired cases of review of the literature. Medicine (Baltimore) 59:188–205

42. Khanna M, Fan J, Pehler-Harrington K, Waters C, Douglass P, Stalock J, et al. (2005) The Pneumoplex assays, a multiplex PCR-enzyme hybridization assay that allows simultaneous detection of five organisms, Mycoplasma pneumoniae, Chlamydia (Chlamydophila) pneumoniae, Legionella pneumophila, Legionella micdadei, and Bordetella pertussis and its real-time counterpart. J Clin Microbiol 43:565–71

43. Konig C, Hebestreit H, Valenza G, Abele-Horn M, Speer CP (2005) Legionella waltersii – a novel cause of pneumonia? Acta Pediatr 94(10):1505–7

44. Kool JL, Fiore AE, Kioski CM, Brown EW, Benson RF, Pruckler JM, et al. (1998) More than ten years of unrecognizing nosocomial transmission of Legionnaires' disease among transplant patients. Infect Contr Hosp Epidemiol 19:898–904

45. Kool JL, Carpenter JC, Fields BS (1999) Effect of mono-chloramine disinfection of municipal drinking water on risk of nosocomial Legionnaires' disease. Lancet 353:272–277

46. Kraus CN, Zalkikar J, Powers JH (2005) Levofloxacin and macrolides for treatment of Legionnaires' disease. Multiple comparisons give few answers. Clin Infect Dis 41:416

47. Lepine LA, Jernigan DB, Butler JC, Pruckler JM, Benson RL, Kim F, et al. (1998) A recurrent outbreak of nosocomial Legionnaires' disease detected by urinary antigen testing: evidence for long-term colonization of a hospital plumbing system. Infect Contr Hosp Epidemiol 19:905–910

48. Li Gobbi, Benucci M, Del Rosso A (2005) Pneumonitis caused by Legionella pneumophila in a patient with rheumatoid arthritis treated with anti-TNF-alpha therapy (infliximab). J Clin Rheumatol 11:119–20

49. Lin YS, Stout JE, Yu VL, Vodic RD (1998) Disinfection of water distribution systems for Legionella. Semin Res Infect Dis 13:147–159

50. Liu Z, Stout JE, Tedesco L, Boldin M, Hwang C, Diven WF (1994) Controlled evaluation of copper-silver ionization in eradicating Legionella pneumophila from a hospital water distribution system. J Infect Dis 169:919–922

51. Macfarlane JT, Miller AC, Roderick Smith WH, Morris AH, Rose DH (1984) Comparative radiographic features of community acquired Legionnaires’ disease, pneumococcal pneumonia, mycoplasma pneumonia, and psittacosis. Thorax 39(1):28–33

52. Marrie TJ, Bezans G, Haldane DJM, Burbridge S (1992) Colonization of the respiratory tract with Legionella pneumophila for 63 days before onset of pneumonia. J Infect 24:81–86

53. Marston BJ, Plouffe JF, File TM Jr, Hackman BA, Salstrom SJ, Lipman HB, et al. (1997) Incidence of community-acquired pneumonia requiring hospitalization. Results of a population-based active surveillance study in Ohio. The Community-Based Pneumonia Incidence Study Group. Arch Intern Med 157:1709–1718

54. Mathys W, Der JD, Meyer J, Junge-Mathys F (1999) Fatal nosocomial Legionnaires' disease after heart transplantation: clinical course, epidemiology, and prevention strategies for the highly immunocompromised host. J Hosp Infect 43:242–246

55. McDonough EA, Barrozo CP, Russell KL, Metzgar D (2005) A multiplex PCR for detection of Mycoplasma pneumoniae, Chlamydophila pneumoniae, Legionella pneumophila, and Bordetella pertussis in clinical specimens. Mol Cell Probes 19:314–22

56. Moffie BG, Mouton RP (1988) Sensitivity and resistance of Legionella pneumophila to some antibiotics and combinations of antibiotics. J Antimicrob Chemother 22:457–62

57. Muder RR, Stout JE, Yu VL (2000) Nosocomial Legionella pneumophila infection in transplant patients: fortune favors the prepared mind. Am J Med 108:346–348

58. Murdoch DR, Walford EJ, Jennings LC, Light GJ, Schousboe MI, Chershsky AY, et al. (1996) Use of the polymerase chain reaction to detect Legionella DNA in urine and serum samples from patients with pneumonia. Clin Infect Dis 23:475–480

59. Mykietiuk A, Carrassal J, Fernández-Sabe N, Dorca J, Verdaguer R, Manresa F, et al. (2005) Clinical outcomes for hospitalized patients with Legionella pneumonia in the antigenuria era: the influence of levofloxacin therapy. Clin Infect Dis 40:794–9

60. Pachón J, Prados MD, Capote F, Cuello JA, Garnacho J, Ver-
37 Legionnaires' Disease

ano A (1990) Severe community-acquired pneumonia. Etiology, prognosis, and treatment. Am Rev Respir Dis 142:569–73

61. Patel MC, Levi MH, Mahadevi P, Nana M, Merav AD, Robbins N. (2005) L. micdadei PVE successfully treated with levofloxacin/valve replacement: case report and review of literature. J Infect 51:265–8

62. Pedro-Botet ML, Stout JE, Yu VL (2002) Legionnaires' disease contracted from patients' homes: the coming of the third plague. Eur J Clin Microbiol Infect Dis 21:699–705

63. Pedro-Botet ML, Sabria M, Sopena N, García-Núñez M, Domínguez Mej, Reynaga E, et al. (2003) Legionnaires' disease and HIV infection. Chest 124:543–7

64. Plouffe JE, File TM, Breiman RF, Hackman BA, Salstrom SJ, Marston BJ, et al. (1995) Reevaluation of the definition of Legionnaires' disease: use of the urinary antigen assay. Community Based Pneumonia Incidence Study Group. Clin Infect Dis 20:1286–91

65. Prat G, Domínguez J, Andreo F, Blanco S, Pallares A, Cu-chillo F, et al. (2006) Procalcitonin and neopterin correlation with aetiology of and severity of pneumonia. J Infect 52(3):169–77

66. Ramila E, Sureda A, Martino R, Santamaría A, Franquet T, Pazo C, et al. (2000) Bronchoscopy guided by high resolution computed tomography for the diagnosis of pulmonary infections in patients with hematologic malignancies and normal plain chest X-rays. Hematología 85:961–966

67. Rantakokko-Jalava K, Jalaba J (2001) Development of conventional and real-time PCR assays for detection of Legionella DNA in respiratory specimens. J Clin Microbiol 39:2904–2910

68. Redd SC, Schuster DM, Quan J, PILkayatis BD, Spika JS, Co-hen ML (1988) Legionellosis cardiac transplant recipients: results of a nationwide survey. J Infect Dis 158:651–653

69. Ricketts K, Joseph C (2005) Legionnaires' disease in Eu-rope 2003–2004. Euro Surveill 10:12

70. Roig J, Aguilar X, Ruiz J, Domíngo C, Mesalles E, Manterola J, et al. (1991) Comparative study of Legionella pneumo-phila and other nosocomial-acquired pneumonias. Chest 99:344–50

71. Roig J, Carreras E, Domíngo C (1993) Treatment of Legionnaires' disease. Drugs 46:63–79

72. Roig J, Sabria M, Pedro-Botet ML (2003) Legionella spp.: community-acquired and nosocomial infections. Curr Opin Infect Dis 16:145–151

73. Roig J, Rello J (2003) Legionnaires' disease: a rational approach to therapy. JAC 51:1119–1129

74. Roig J, Rello J (2006) Treatment of Legionnaires' disease. In: Cianciotto NP (ed) Legionella. ASM Press, Washington DC (in press)

75. Roig J, Casal J, Gisbert P, Gea E (2006) Antibiotic therapy of community-acquired pneumonia caused by atypical agents. Med Mal Infect (in press)

76. Sabria M, García-Núñez M, Pedro-Botet ML, Sopena N, Gimeno JM, Reynaga E, et al. (2001) Presence and chromosomal subtyping of Legionella species in potable water systems in 20 hospitals of Catalonia, Spain. Infect Control Hosp Epidemiol 21:845–8

77. Sabria M, Yu VL (2002) Hospital-acquired legionellosis: solutions for a preventable infection. Lancet Infect Dis 2:368–73

78. Sabria M, Modol JM, García-Núñez M, Reynaga E, Pedro-Botet ML, Sopena ML, et al. (2004) Environmental cultures and hospital-acquired Legionnaires' disease: a 5 year prospective study in 20 hospitals in Catalonia, Spain. Infect Control Hosp Epidemiol 25:1072–6

79. Sabria M, Pedro-Botet ML, Gómez J, Roig J, Vilaseca B, Sopena N, et al. (2005) Fluoroquinolones versus macrolides in the treatment of Legionnaires' disease. Chest 128:1401–5

80. Skogberg K, Nuorti JP, Saxon H, Kusnetsov J, Mentula S, Fellman V, et al. (2002) A newborn with domestically acquired legionnaires' disease confirmed by molecular typing. Clin Infect Dis 35:82–5

81. Shands K, Ho J, Meyer R, Gorman GW, Edelstein PH, Mal-lison GF, et al. (1985) Potable water as a source of Legion-naires' disease. JAMA 253:1412–1416

82. Shaffer PJ, Stout JE, Wagener MM, Muder RR (2005) Efi-cacy of new point-of-use water filter for preventing expo-sure to Legionella and waterborne bacteria. Am J Infect Control 33(Suppl 1):S20–25

83. Sopena N, Sabria M, Pedro-Botet ML, Manterola JM, Matas L, Domínguez J, et al. (1999) Prospective study of commu-nity-acquired pneumonias of bacterial etiology in adults. Eur J Clin Microbiol Infect Dis 18:852–8

84. Sopena N, Sabria M, Pedro-Botet ML, Reynaga E, García-Núñez M, Domínguez J, et al. (2002) Factors related to per-sistence of Legionella urinary antigen excretion in patients with Legionnaires' disease. Eur J Clin Microbiol Infect Dis 21:845–8

85. Sopena N, Sabria M (2005) Multicenter study of hospital-acquired pneumonias in non-ICU patients. Chest 127:213–9

86. Srinivasan A, Bova G, Ross T, Mackie K, Paquette N, Merz W, et al. (2003) A 17-month evaluation of a chlorine diox-ide water treatment system to control Legionella species in a hospital water supply. Infect Control Hosp Epidemiol 24:575–9

87. Stout JE, Yu VL (1997) Legionellosis. N Engl J Med 337:682–7

88. Stout JE, Yu VL (2003) Experiences of the first 16 hospitals using copper-silver ionization for Legionella control: im-plications for the evaluation of other disinfection modal-ities. Infect Control Hosp Epidemiol 24:563–8

89. Torres A, Serra-Batllés J, Ferrer A, Jimenez P, Celis R, Cobo E, et al. (1991) Severe community-acquired pneumonia. Epidemiology and prognostic factors. Am Rev Respir Dis 144:312–318

90. Venezia RA, Agresta MD, Hanley E, Urquhart K, Schoonmaker D (1994) Nosocomial legionellosis associated with aspiration of nasogastric feedings diluted in tap water. In-fect Control Hosp Epidemiol 15:529–533

91. Vergis E (2000) Azithromycin vs cefuroxime plus erythro-myacin for empirical treatment of community-acquired pneumonia in hospitalized patients: a prospective, ran-domized, multicenter trial. Arch Intern Med 160:1294–1300

92. Woodhead MA, Macfarlane JT (1987) Comparative clinical and laboratory features of legionella with pneumococcal and mycoplasma pneumonias. Br J Dis Chest 81(2):139–9

93. Yu VL, Kroboth FJ, Shonnard J, Brown A, McDearman S, Magnusen M (1982) Legionnaires' disease: new clinical perspective from a prospective pneumonia study. Am J Med 73(3):357–61

94. Yu VL, Plouffe JE, Pastoris MC, Stout JE, Schousboe M, Widmer A, et al. (2002) Distribution of Legionella species and serogroups isolated by culture in patients with sporadic community-acquired legionellosis: an international collaborative survey. J Infect Dis 186:127–8