37 Legionnaires' Disease

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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 sevre 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 studied 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[a]

Antimicrobial agents		Dosage	Route
Macro-azalides[b]	Azithromycin[d]	500 mg every 24 h	IV, p.o.
	Clarithromycin	500 mg every 12 h	IV, p.o.
	Erythromycin[c]	1 g every 6 – 8 h	IV, p.o.
Tetracyclines	Doxycycline	100 mg every 12 – 24 h	IV, p.o.
Fluoroquinolones	Levofloxacin[d]	500 – 750 mg every 24 h	IV, p.o.
	Moxifloxacin[d]	400 mg every 24 h	IV, p.o.
	Gemifloxacin[e]	320 mg every 24 h	p.o.
	Gatifloxacin[e]	200 – 400 mg every 24 h	IV, p.o.
	Ciprofloxacin	400 mg every 8 – 12 h	IV
		500 – 750 mg every 12 h	p.o.
	Ofloxacin	400 – 800 mg (total daily dose)	IV, p.o.
Ketolides	Telithromycin[e]	800 mg every 24 h	p.o.

[a] Oral therapy is recommended only in those mild cases that do not require hospitalization. Some antibiotics are only commercially available in selected countries
[b] In mild cases other oral macrolides are also effective: josamycin (1 g every 12 h), roxithromycin (150 mg every 12 h), dirithromycin (500 mg every 24 h)
[c] Less active than other macrolides; risk of fluid overload, phlebitis and transitory deafness with IV administration
[d] Recommended in the more severe cases, particularly in the immunocompromised
[e] 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. FiO_2 should be minimized to target an acceptable SaO_2 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 control is the cornerstone of therapy in those patients with hemodynamic instability. If deterioration of renal function occurs, appropriate therapeutic measures including diligent administration of substitutive treatment are mandatory until complete recovery of the renal function is achieved.

Table 37.2. Extrapulmonary manifestations of legionnaires' disease

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

[a] 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[a] in legionellosis

Other *Legionella* spp.	Dual infections by different species of *Legionella* and different serotypes of *L. pneumophila*
Other bacteria	*Streptococcus pneumoniae, Proteus mirabilis, Staphylococcus aureus, Escherichia coli, Prevotella intermedia, Enterococcus facium, 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 jiroveci, Leishmania*

[a] Alleged mixed infections with *Mycoplasma pneumoniae, Chlamydia pneumoniae and Coxiella burnettii* have been reported on the basis of serology, which raises much concern about specificity

Extrapulmonary manifestations of legionellosis are uncommon and tend to occur in patients with immunocompromise (Table 37.2). Suppurated focus of infection should be drained by catheter insertion or performing a surgical procedure [61, 72].

It is possible that some selected, non-immunocompromised patients with severe LD may potentially benefit from a short course of steroid therapy, as has been suggested in other types of SCAP. However, there is no good evidence to recommend this approach routinely. Steroids may also be useful in the proliferative phase of diffuse alveolar damage (in patients with ARDS), in some reactive extrapulmonary manifestations (arthritis, myocarditis, renal, neurological or hematological features), and when an inflammatory pattern is identified in representative samples of lung tissue in patients with a protracted course [73, 75].

Mixed infections in legionellosis should be kept in mind in the inmunocompromised 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

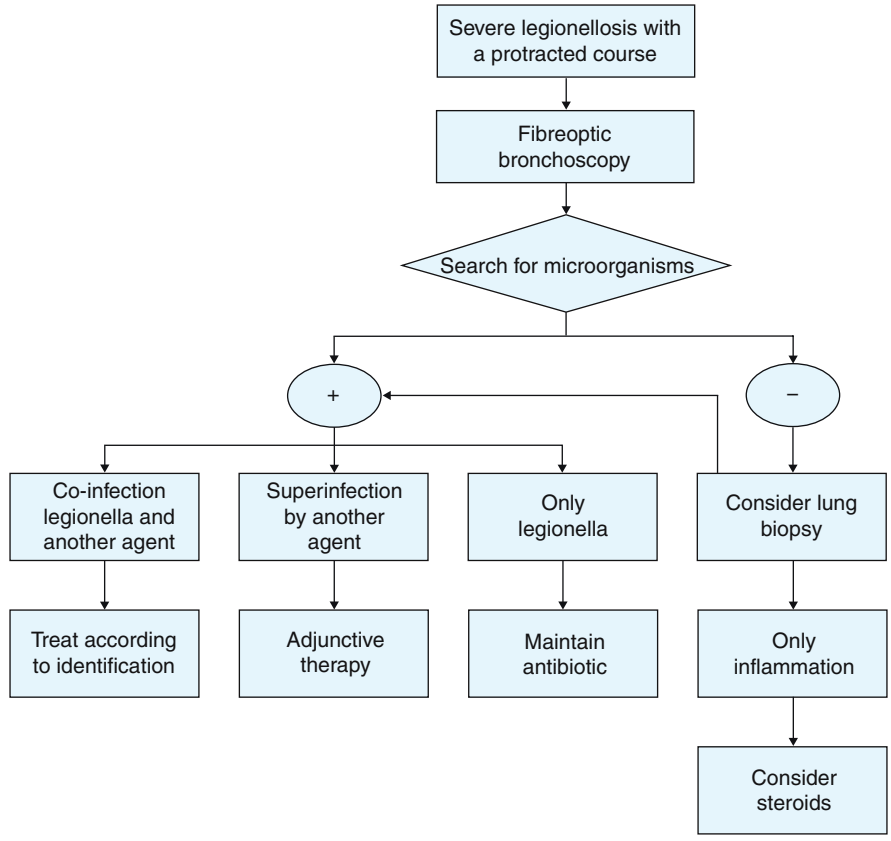

Fig. 37.1. Proposed algorithmic approach to management of intubated patients with non-resolving legionellosis. (From Roig and Rello, JAC 2003; 51:1119 – 1129; with permission of The British Society for Antimicrobial Therapy)

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].

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