Drugs 2005; 65 (5): 605-614
0012-6667/05/0005-0605/$39.95/0

Treatment of Legionnaires' Disease

Guy W. Amsden

Department of Adult and Pediatric Medicine, Section of Clinical Pharmacology and The Clinical Pharmacology Research Center, Bassett Healthcare, Cooperstown, New York, USA

Contents

Abstract

Legionnaires' disease is pneumonia, usually caused by *Legionella pneumophila*, which can range in severity from mild to quite severe. While it is commonly acquired in the community, it can just as easily be acquired nosocomially from water sources that have not been appropriately decontaminated. While historically initial treatment was always with erythromycin, current case series and treatment recommendations suggest that outpatients receive immediate treatment with one of the following antibacterials: azithromycin, erythromycin, clarithromycin, telithromycin, doxycycline or an extended-spectrum fluoroquinolone. If the symptoms are severe enough to warrant hospitalisation then the patient should receive treatment with parenteral azithromycin or extended-spectrum fluoroquinolones followed by step-down to oral formulations to complete the regimens. While a shorter course of 7–10 days for more severe infections may be possible for intravenous/oral azithromycin, other antibacterials should be administered for a total of 10–21 days and started as soon as possible upon presentation to optimise outcomes.

The world's first known outbreak of Legionnaires' disease occurred in the US in 1976 when several members of the Pennsylvania chapter of the American Legion staying in a Philadelphia hotel developed sudden and severe pneumonia within the first few days of their convention. Investigation by the Centers for Disease Control and Prevention identified the cause of the pneumonia as a previously undescribed bacterium that was subsequently classified as *Legionella pneumophila*.[1] Additional research using stored sera revealed that, although finally identified in 1976, *L. pneumophila* was the most likely cause of at least three additional epidemics dating as far back as 1957.[2,3] Since then, not only do reports of local epidemics appear in the medical literature and/or the lay press but it is also considered a relatively common cause of community-acquired pneumonia (CAP), depending on severi-

ty of its presentation. Whereas *L. pneumophila* appears to be an uncommon cause of CAP not requiring hospitalisation, its incidence is second only to bacteraemic pneumococcal pneumonia as a cause of severe CAP that requires intensive care treatment.[4-7]

1. Epidemiology

Although *L. pneumophila* is the most common species associated with *Legionella* infection there are actually over 40 species within the Legionellaceae family, which in turn consists of 64 serogroups.[8] Despite Legionnaires' disease being classically associated solely with *L. pneumophila*, more recent definitions have sometimes allowed patients with pneumonia who have any *Legionella* spp. isolated to be termed as having Legionnaires' disease. Regardless of this, *L. pneumophila* is the species that is responsible for >80% of the infections caused by members of the Legionellaceae family. Other *Legionella* spp. (i.e. *L. micdadei*, *L. bozemanii*, *L. dumoffii* and *L. longbeachae* [this isolate is a frequent cause of *Legionella* pneumonia in Australia[9]]) typically may occur in patients who have immunosuppression secondary to corticosteroid therapy, organ transplantation anti-rejection agents or treatment of malignancy.[10,11] Although *L. pneumophila* contains 15 serogroups, only three of them, serogroups 1, 4 and 6, account for the majority of strains identified as being associated with human infection. Whereas nosocomial isolates may be any species or serogroup of the Legionellaceae family, community-acquired infections are usually caused by *L. pneumophila* serogroup 1.

Legionella spp. are an aerobic, non-encapsulated, Gram-negative bacilli found in water distribution systems and transmitted to humans via aerosolisation, aspiration or even instillation. These systems are likely to be associated with a hot water tank, with *L. pneumophila* being found in the bottom of the tank on the surface of accumulating sediment. Growth of large colonies of *L. pneumophila* occurs secondary to the sediment, stimulating growth of commensal bacteria and the latter stimulating that of *L. pneumophila*. The pathogen can then infect anyone using the water system, such as has happened in nosocomial outbreaks of Legionnaires' disease in hospitals.[8,12]

2. Laboratory Diagnosis

When presented with a case that is suspicious for infection or co-infection with *Legionella* spp. a number of different laboratory tests using various biological samples can be performed to confirm or rule out the diagnosis, including culture, serological testing, direct fluorescent antibody (DFA) staining of respiratory secretions, urinary antigen assay and polymerase chain reaction (PCR) assays. However, before deciding on the test to be performed it is important to know not only whether the biological sample comes from a patient with CAP or nosocomial pneumonia, but also the sensitivity and specificity of the test so that precious time and resources are not wasted in the process.[8,13,14]

PCR assays of sputum, serum, urine or water system samples have relatively good sensitivity (33–70%) and excellent specificity (98–100%), and can be completed in a short amount of time (2–4 hours); however, they are not practical because of the great expense involved and the lack of approved reagents.[8] DFA staining of sputum is also a rapid turnaround test (2–4 hours), and has a sensitivity and specificity similar to that of PCR analysis. However, interpretation of results takes significant expertise and positive results require the presence of a large pathogen load that will most likely only be present in those with multilobar pneumonia. Unless a baseline IgG and/or an IgM titre is ≥1 : 128 in a patient with pneumonia, serology is not very useful for the clinician as the 4-fold rise between acute and convalescent titres may take several weeks to be detected/documented. Sputum culture utilising specialised media is the gold standard documentation method with both high sensitivity (≈80%) and specificity (100%).[8] The only drawback to this method is the length of time it can take to produce positive results, which ranges from 2 to 7 days. The urinary antigen test is an ideal test for CAP patients who are immunocompetent as it has excellent sensitivity and specificity (90–100% each) and has a turnaround time of

a few minutes to a couple of hours depending on the type of test used.[8] Since the majority of *Legionella* infections are with *L. pneumophila* serogroup 1, the fact that the urinary antigen test is only able to detect this one species and serogroup may not be a significant disadvantage.[8,13,14] Evidence of this is available in the latest CAP treatment guidelines from the Infectious Diseases Society of America, which recommends a combination approach to testing for Legionnaires' disease via urinary antigen test with sputum culture conducted for confirmation.[14]

3. Pathogenesis

To understand the best way to actively treat *Legionella* infections it is necessary to first understand their pathogenesis, be it something simple such as Pontiac fever or the more severe Legionnaires' disease. Since colonisation of the oropharynx has yet to be demonstrated in the literature, aspiration or inhalation of contaminated water into the oropharynx is the most likely initialising exposure. From here, whether a person actually gets ill or not depends on their defence array. If the person smokes, has chronic pulmonary disease or is a chronic alcoholic and has chronically damaged mucociliary clearance mechanisms they can be at increased risk of developing Legionnaires' disease. Even if a patient does not have these risk factors, *Legionella* spp. are able to form pili and hook onto pulmonary epithelial cells, thereby gaining a threshold into the lungs.[8] Once within the trachea, *Legionella* invade the epithelial lining cells and replicate, spreading down the airways towards the alveoli. After the bacteria reach the alveoli, the true clinical outcome lies within the virulence of the organism as well as the competence of the host's immune system in terms of resisting infection.

Legionella are phagocytosed by alveolar macrophages within the alveoli; however, the bacteria block the fusion of phagosomes with lysosomes preventing their digestion by the highly toxic contents of lysosomes, and proceed to replicate to a point where the cells rupture, thereby releasing their progeny which further infect other alveolar macrophages and start the process all over again.[8] In addition to these local, specialised cells, the cells that respond to the infection acutely from the blood stream via chemotaxis also have atypical responses to the invading pathogens. While monocytes that have migrated from the blood are as susceptible to the same reproductive host fate as the larger differentiated alveolar macrophages, polymorphonuclear leucocytes (PMNs) [neutrophils] do not become an incubator for the pathogen or its progeny; however, they are uncharacteristically not overly effective phagocytes either. Despite the fact that *Legionella* spp. are susceptible to oxygen-dependent microbicidal systems, they are immune to the effects of the PMNs unless they are in the presence of specific antibodies or complement. It is only at this time that *Legionella* can be effectively ingested and cleared by PMNs.[8] Although this may seem like a one-sided battle, it remains so only temporarily unless the patient is deficient in cell-mediated immunity (i.e. transplant patients on anti-rejection drugs), as local macrophages will start to produce interferon-γ and peripheral lymphocytes and the macrophages will start to produce tumour necrosis factor-α. These cytokines not only allow the macrophages/monocytes to better resist becoming infected with the *Legionella* organisms and prevent any further intraphagocytic replication, but also allow these macrophages/monocytes and the PMNs to become phagocytic once again against them.[15]

4. Treatment

Treatment of *Legionella* infections includes active and preventive treatment. Preventive treatment has been discussed in other reviews and refers to decontamination of reservoirs of the bacteria once they have been identified.[8,16]

The choice of appropriate antibacterial to assist the patient's immune system to overcome *Legionella* infections can be difficult for those not familiar with their pathogenesis, or the pharmacokinetic properties of the various classes of antibacterials and the different ways to test their actions against the pathogen. First, the efficacy of antibacterials can be tested *in vitro* in buffered yeast extract and buffered charcoal-yeast extract, both supplemented with α-

ketoglutarate in which *Legionella* spp. grows well. Several classes of antibacterials, including β-lactams, would be highly active *in vitro*.[17] However, since *Legionella* is an intracellular pathogen and β-lactams do not penetrate mammalian cells, *in vitro* results would not be reflective of clinical outcomes. Although there were some isolated reports of clavulanic acid being added to amoxicillin resulting in *in vitro* and animal model successes,[18-21] these results have never been replicated clinically in humans.

A second method to identify clinically effective antibacterials is to have *in vitro* cell lines that have *Legionella* spp. intracellularly. Cell lines that have been used include guinea pig alveolar macrophages, human monocytes and macrophages, HeLa and HL-60 cells. With the exception of gentamicin, which is active against *Legionella* grown in cell lines but not in animal or human disease, the correlation between activity of an antibacterial against intracellular *Legionella* and actual clinical outcome is good.[17]

A third method utilises either a respiratory/severe pneumonia or an intra-peritoneal infection guinea pig model to test antibacterial activity. Although the latter method can be useful, the antibacterial outcome in the pneumonia model correlates clinically with human outcomes.[17]

The final method that can be used to investigate various pharmacological classes of antibacterials, and respective members thereof, to identify the most active option(s) and potential primary/secondary therapies of *Legionella* infections is actual human comparative clinical trials. The aforementioned testing aside, the true test of any treatment is a comparative trial done in a proper, non-biased manner (i.e. randomised [equal randomisation], double-blind [with blinding not broken until analysis is over and with intention-to-treat analysis]). There should be more than one of such trials performed, each using the latest technology and appropriate comparators, and involving large numbers of patients so that the recommendations once they are put forward should not be questioned. While this sounds entirely appropriate and is something that we expect and can get for CAP in general or even for pneumococcal pneumonia,[14] it is something that will probably never exist for Legionnaires' disease. This is because of the infrequency with which it is prospectively diagnosed, even with the rapid urine screen and despite the incidence that it is quoted to occur, especially in severe cases of CAP. As a result, it is virtually impossible to prospectively enroll the numbers of patients necessary in a phase III trial that will meet the inclusion/exclusion criteria and have consistent disease severity to be able to effectively compare two antibacterials, let alone to repeat it for any additional comparisons.

The pharmacokinetics of a number of classes of antibacterials, and/or members of these classes, make them potential treatment candidates as a result of their ability to penetrate macrophages/monocytes. These classes, and/or their members, include macrolides, fluoroquinolones, trimethoprim/sulfamethoxazole, tetracyclines and rifamycins. However, to date, the macrolides and the fluoroquinolones have the most consistent clinical successes in the literature. Despite the relatively recent focus on the use of pharmacokinetic/pharmacodynamic dosage optimisation strategies to try to better assure positive clinical and microbiological outcomes, these concepts have yet to be applied to the treatment of intracellular bacterial pathogens.[22]

Although erythromycin was the original macrolide used after the first outbreak of Legionnaires' disease, the introduction of the newer macrolides (azithromycin, clarithromycin, roxithromycin and telithromycin) have made it a much less attractive option. This is due to its significant adverse effect and drug interaction profiles, lack of patient compliance and high fluid load with the intravenous formulation. Not only does erythromycin have these disadvantages but, whereas azithromycin produces bactericidal effects in the guinea pig alveolar macrophage model and up to a 5-day post-antibacterial effect (PAE) when it is removed from the system, erythromycin produces only bacteriostatic effects and no PAE.[17] Evidence of the clinical impact of these differences is presented in table I and table II, where in multiple reports patients were unable to be effectively treated with erythromycin monotherapy and sometimes even with ery-

Table I. Summary of Legionnaires' disease (LD) studies

Study	Study type	Pts (n)	Pts characteristics	Drug and regimen	Results	Comments
Hamedani et al.[28]	op, nc	46	Moderate-to-severe chest infection/ pneumonia[a]	CLA 500–1000mg bid for mean 27d; 500mg bid in 43/46 pts	98% (43/44 pts) clinically cured	9/43 withdrew early due to feeling better; cures on CLA when failed ERY
Kuzman et al.[29]	rs, nc	16	Hospitalised, serogroup 1 positive[b]	AZI 500 mg/d × 3d or 500 mg/d on d1, 250 mg/d on d2–5	Mean hospitalisation 20.5d (range 11–52d); none admitted to ICU; 15 afebrile in 48h – last pt afebrile in 96h	1 pt with transient eosinophilia; 2 pts with transient serum transaminase increase
Plouffe et al.[30]	pr, op, mc	25	Hospitalised, serogroup 1 positive	IV AZI 500 mg/d × 2–7d followed by PO AZI 1.5g over 3–5d	Mean therapy 7.9d; 95% and 96% of clinically evaluable pts were clinically cured after 10–14d and 4–6wk treatment, respectively; 9 pts had 11 mild-to-moderate AEs	AZI IV to PO step-down monotherapy well tolerated/efficacious for hospitalised LD pts
Carbon and Nusrat[31]	mc[c]	16	Pts (intention-to-treat) with mild-to-moderate CAP, age ≥13y[d]	PO TEL 800mg od × 5–10d	14/16 pts (87.5%) clinically cured at 17–24d post-treatment visit	Of the two pts who were not cured one stopped treatment after one dose because of dizziness and hypotension, the other had insufficient improvement after 7d of TEL
Santos et al.[32]	pr, r, mc[e]	28	Pts from CAP trial with LD[f]	PO GEM 320 mg/d × 7d vs PO TRV 200 mg/d × 7d	14 pts had mixed *Legionella* infections; 1 GEM pt discontinued due to rash; 1 TRV pt needed treatment for 14d; 1 TRV pt did not respond after initial improvement for 7d treatment then had early recurrence; 25 pts (89.5%) cured at 14–21d post-treatment visit	TRV now restricted to hospital use only because of hepatic AEs; rash to GEM more common in pts aged ≥40y, especially women – more common in post-menopausal women on hormone replacement therapy – generally occurs 8–10d after start of GEM
Dournon et al.[24]	rs	196	ICU LD pts[g]	Three treatment groups: IV PEF (mean 0.8 g/d) ± ERY ± RIF (n = 20); IV ERY (mean 2–6 g/d, n = 20); IV ERY ± RIF (mean 1.2–2.4 g/d) [n = 20]	PEF group was more immunocompromised than ERY/RIF group; LD deaths in all groups (15–35%, highest in the ERY-only group, lowest in the PEF group); pts on PEF alone (n = 7) had no deaths	18/20 pts in each group immunocompromised ± on mechanical ventilation; >5 pts in each group had very poor prognosis prior to onset of LD because of comorbidities; 8 pts not originally on PEF received it as add-on-therapy and 4 survived

a 15 pts were previously treated with anti-*Legionella* regimens that failed and included ERY, OFL, TET and RIF.

b 11 pts were smokers, patients had no other cardiac/pulmonary disease or immunodeficiencies.

c Pooled results from 8 trials.

d Pts with severe or nosocomial pneumonia excluded.

e Subanalysis of LD pts from phase III CAP study.

f 13 pts with definite LD by seroconversion (only two urine tests positive); the other 15 pts had possible *Legionella* infection by single elevated IgG titre (≥1 **:** 512).

g Three groups matched for age within 5y, duration of LD before treatment within 2d, need for mechanical ventilation before or within 72h of active treatment and immune status.

AEs = adverse events; **AZI** = azithromycin; **bid** = twice daily; **CAP** = community-acquired pneumonia; **CLA** = clarithromycin; **ERY** = erythromycin; **GEM** = gemifloxacin; **ICU** = intensive care unit; **IV** = intravenous; **mc** = multicentre; **nc** = noncomparative; **od** = once daily; **OFL** = ofloxacin; **op** = open-label; **PEF** = pefloxacin; **PO** = oral; **pr** = prospective; **pt(s)** = patient(s); **r** = randomised; **RIF** = rifampicin; **rs** = retrospective study; **TEL** = telithromycin; **TET** = tetracycline; **TRV** = trovafloxacin.

Table II. Summary of Legionnaires' disease case reports

Study	Patient history	Treatment history	Results	Comments
Dorrell et al.[33]	38yo male with 5-d history of headache, abdominal pain and foul-smelling urine; treated with TMP/SMX, got worse with dry cough, dyspnoea, fever; admitted to hospital with bilateral lung consolidation	IV AMX/CLV for pneumonia and pyelonephritis; got worse, intubated; changed to IV ERY/CFT for positive urine *Legionella*; worsened; IV RIF added; worsened – sepsis, renal failure; IV AZI bid added	With AZI addition clinical/x-ray improvement in 48h, ERY/RIF stopped after 24h; pt discharged 5wk later with normal renal function and clear chest x-ray	Serology positive for *Legionella* serogroups 1 and 6; ERY/RIF treatment not useful
Matute et al.[34]	60yo woman hospitalised with a 2-d history of fever/neutropenia; chest x-ray positive for right pleural effusion/left superior lobe infiltrate; PaO_2 60mm Hg; urine positive for *Legionella* serogroup 1	IV CEF/ERY started but ERY changed to PO AZI × 5d within 24h; CEF stopped after 5d; pt returned 10d after last AZI dose with recurrence of fever/dyspnoea but normal WBC; given PO CLA 500mg bid × 14d	Pt afebrile 72h after start of CLA; no recurrence within 6mo	Proof that longer AZI course necessary in immunocompromised pts

AMX/CLV = amoxicillin/clavulanic acid; **AZI** = azithromycin; **bid** = twice daily; **CEF** = ceftriaxone; **CFT** = cefotaxime; **CLA** = clarithromycin; **ERY** = erythromycin; **IV** = intravenous; **PaO_2** = arterial oxygen pressure; **PO** = oral; **pt** = patient; **RIF** = rifampicin; **TMP/SMX** = trimethoprim/sulfamethoxazole; **WBC** = white blood cell count; **yo** = year-old.

thromycin-based combination therapy, whereas they consistently improved with treatment with one of the newer macrolides as monotherapy, most commonly azithromycin. As a result of these data the oral forms of any of the newer macrolides would be expected to have high cure rates in immunocompetent patients with mild-to-moderate Legionnaires' disease. In contrast, treatment in those with severe disease or who are immunocompromised is usually limited to intravenous azithromycin monotherapy or possibly combination therapy with intravenous erythromycin and rifampicin (rifampin) as they are the only ones with parenteral forms available commonly. Although intravenous clarithromycin is available in certain countries, its availability in general is limited and its utility is further limited as a result of phlebitis with a subsequent incidence of treatment discontinuations that exceeds that associated with parenteral erythromycin (50% vs 8%).[23] Although historically there has been an emphasis on dual therapy for patients with severe infections including pneumonia,[14] the use of dual therapy (typically erythromycin and rifampicin) as compared with monotherapy for *Legionella* infections (see table I and table II) has had no clear impetus one way or the other.[17,24,25] Rather than using combination anti-*Legionella* agents, combination therapies, especially in patients with severe CAP, that consist of an effective anti-*Legionella* agent as well as a second agent that would be active against potential co-pathogens such as *Pseudomonas aeruginosa* or *Streptococcus pneumoniae* may be more desirable.[26,27]

Although the systemic fluoroquinolones have been available for a similar length of time as the newer macrolides, aside from the small percentage of cases in comparative CAP trials they appear to have marginally less available data specific to *Legionella* pneumonia. Although there is no shortage of *in vitro* and animal model data[35-37] with fluoroquinolones, specific patient data are sparse (see table I). Regardless, the data that do exist appear to be supportive of using the systemic fluoroquinolones as monotherapy even when treating patients with severe Legionnaires' disease.

5. Timing is Key to Efficacy

As noted in the most recent treatment recommendations, empirical antibacterial therapy for patients hospitalised with CAP should be started within 4 hours (down from 8 hours in previous recommendations) to better assure positive outcomes and shorter lengths of stay.[14] Although more variable in terms of the threshold time window, the treatment of Legionnaires' disease also appears to be influenced by whether treatment starts within the limit of the threshold window or not. As an example, a retrospective study examined a hospital's 10 years' in-

tensive care unit (ICU) admissions for *Legionella* pneumonia and the presence or absence of prognostic factors associated with the outcome of therapy.[38] Forty-three consecutive patients with no previous treatment with macrolide or fluoroquinolone with an average symptom duration of 5 days were identified. Approximately 35 patients had at least one comorbidity and 18 were immunocompromised as a result of corticosteroid administration. Thirty-six patients were treated with a fluoroquinolone (ofloxacin, pefloxacin or ciprofloxacin) in combination with a macrolide (erythromycin or spiramycin), whereas two patients received erythromycin with rifampicin, two received erythromycin alone and three received ofloxacin monotherapy. The mean time to administration of macrolides from time of admission to the ICU ranged from 4 to 11 hours and that for fluoroquinolones was approximately 7 hours. The mean simplified acute physiology score (SAPS II) was 47 at admission (range 16–107). The results demonstrated a mortality rate of 33% with all of the deaths secondary to the progression of their underlying Legionnaires' pneumonia. By univariate analysis the factors that were associated with a higher incidence of mortality included a SAPS II score >46 ($p = 0.006$) and intubation requirement ($p = 0.012$). Those factors that were associated with a higher incidence of survival included receiving a fluoroquinolone ($p = 0.011$) or erythromycin ($p = 0.044$) within 8 hours of admission to the ICU. When the factors were re-analysed using logistical regression analysis, a SAPS II score >46 (odds ratio [OR] 8.7; 95% CI 1.15, 66.7) and symptoms prior to ICU admission for >5 days (OR 7.4; 95% CI 1.17, 47.6) were both independent risk factors for death. This was in contrast to the administration of fluoroquinolones within 8 hours of ICU admission, which was associated with lower mortality (OR 0.8; 95% CI 0.03, 0.97). Although the initiation of a macrolide therapy within 8 hours of ICU admission did not correlate with lower mortality by logistical regression analysis, the investigators did not group the macrolides as a whole, instead analysing them separately despite analysing the three fluoroquinolones together. Whether this would have changed the outcomes regarding whether the macrolides correlated with a positive outcome or not is unknown, but the investigators should have remained consistent in their methodology throughout. Regardless of this anomaly, the investigators concluded that patients with severe Legionnaires' disease will have a better potential for a positive outcome if effective antibacterial therapy is begun within 8 hours of presentation.[38]

In a separate report of a large Legionnaires' disease outbreak following a flower show in The Netherlands, the opportunity was taken to look at what constituted prognostic factors that would not only decrease mortality but also keep the patient out of the ICU.[39] Of the 77 061 people that visited the flower show in 1999, 188 developed confirmed or probable Legionnaires' disease. 161 patients provided consent to have their patient information collected but 20 patients were excluded as they were not ill enough to be admitted to the hospital and had incomplete data collections. Of the remaining 141 patients in the study (120 confirmed/21 probable) 42 patients (40 confirmed cases) [30%] were admitted to the ICU with severe Legionnaires' disease. Results demonstrated that the incubation times for patients with severe and non-severe disease were similar (mean 6.8 vs 7.8 days, respectively; $p = 0.13$). This was also true when results for patients admitted to the ICU were compared with those not admitted (mean 7.0 vs 7.7 days; $p = 0.26$). In contrast, mortality rates for ICU and non-ICU patients contrasted sharply (36% vs 13%). Upon univariate analysis of demographic and medical history data it was discovered that the following issues lead to a greater incidence of ICU admission or death: smoking, dyspnoea, fever >38.5°C, plasma creatinine level of at least 100 mmol/L or a chest radiograph positive for bilateral infiltrates or pleural effusions. When reperformed using multivariate analysis it was discovered that smoking, fever >38.5°C and having bilateral infiltrates on chest radiograph were independent risk factors for ICU admission or death. When the impact of initiating effective antibacterials (defined as a macrolide or fluoroquinolone) within 24 hours of admission on the ICU-free survival rate was studied, a significantly higher survival rate was

Table III. Antibacterial therapy for *Legionella* infection[8,14,40]

Antibacterial	Route of administration	Dosage regimen	Total treatment days	
			immunocompetent/ outpatient	hospitalised or immunocompromised
Azithromycin	PO	500mg q24h	3–5	
	IV[a]	500mg q24h[a]		7–10
Clarithromycin	PO	500mg q12h	14–21	
	IV[a]	500mg q12h[a]		14–21
Roxithromycin	PO	150–300mg q12h	14–21	
Erythromycin	PO	500mg q6h[b]	14–21	
	IV[a]	1000mg q6h[a]		14–21
Telithromycin	PO	800mg q24h	7–10	
Ciprofloxacin	PO	750mg q12h	7–10	
	IV[a]	400mg q8–12h[a]		14
Levofloxacin	PO	500–750mg q24h	7–10	
	IV[a]	500–750mg q24h[a]		10–14
Gatifloxacin	PO	400mg q24h	7–10	
	IV[a]	400mg q24h[a]		14
Moxifloxacin	PO	400mg q24h	7–10	
	IV[a]	400mg q24h[a]		14
Doxycycline	PO	200mg load then 100mg q12h	14–21	
	IV[a]	200mg load then 100mg q12h[a]		14–21
Rifampicin (rifampin)[c]	PO	300–600mg q12h		5
	IV[d]	300–600mg q12h[d]		5
Trimethoprim/sulfamethoxazole	PO	160/800mg q12h	14–21	
	IV[a]	160/800mg q8–12h[a]		14–21

a Any patient started on IV therapy should be changed to the PO formulation to finish the total number of days of therapy once patient demonstrates a clinical response including defervescence.[8]

b Milligram dose will depend on salt formulation prescribed.

c Should only be used in combination with some other antibacterial for the first 5 days of therapy.

d Should be changed to oral form as soon as possible.

IV = intravenous; **PO** = oral; **q*x*h** = every *x* hours.

demonstrated when this occurred (78% vs 54%; p = 0.005).[39] Since the highest mortality rate was within the ICU (36% vs 13% overall) and the previous study[38] demonstrated lower mortality when a patient received a fluoroquinolone within 8 hours of ICU admission, it is possible that the ICU-free survival rate could have improved further if the definition of effective antibacterial timing was less broad (i.e. within 8–12 hours instead of 24 hours).

6. Choosing the Right Regimen

The most current CAP treatment guidelines recommend that for patients who have or are suspected of having Legionnaires' disease and can be treated as outpatients (see table III for specific regimens), treatment should be started as soon as possible with one of the following oral medications: erythromycin, doxycycline, azithromycin, clarithromycin or an extended-spectrum fluoroquinolone (levofloxacin, gatifloxacin, moxifloxacin).[8,40] For patients who require hospitalisation or are immunocompromised, intravenous treatment should be started as rapidly as possible with azithromycin or an extended-spectrum fluoroquinolone.[8,40] Although some of these agents (i.e. levofloxacin, telithromycin) have recently received new indications for short-course (5–7 days) treatment of CAP, none of the Legionnaires' disease data support treating the disease on a regular basis with any of them. In fact, the opposite is true as most experts continue to recommend that

immunocompetent Legionnaires' outpatients should receive at least 7–10 days of treatment and that those with significant co-morbidities, any degree of immunocompromise or who require hospitalisation should receive up to 21 days of treatment. Because of the stubborn nature of the pathogen, the same experts often wait a little longer (anywhere from 3 to 5 days) to see if a patient is responding to therapy before they decide whether to continue on this therapy, step-down to oral therapy or if they need to switch to a different treatment because of a lack of response.[8,14]

However, on the basis of the literature discussed in this review, there appears to be one exception to this length of therapy rule – azithromycin because of its unique pharmacokinetics. On the basis of the *in vitro* and clinical literature to date, the prolonged half-life and tissue retention of azithromycin and the most recent treatment recommendations, it is the one drug that can be administered as a 3- to 5-day oral regimen of 500 mg/day in outpatients without significant comorbidities. However, once a patient becomes more severely ill and requires hospitalisation, or is immunocompromised, it is probably naive to believe that azithromycin administration can be continued as if nothing has changed, as was suggested in one letter to the editor.[34] Rather, these patients would benefit from intravenous to oral step-down regimens with relatively limited oral follow-on, even for severely ill patients, as was recently published.[30]

7. Conclusion

Although a lot has been learnt since that fateful week in Philadelphia in the 1970s, we still know little about *Legionella* spp. compared with many other pathogens that are dealt with on a regular basis as causes of CAP. While we have a number of antibacterials that have demonstrated efficacy against *Legionella* infections, initiating antibacterial therapy as soon as possible is just as important as choosing the appropriate therapy. Despite the advances made in the detection and therapy of Legionnaires' disease there is still a plethora of topics that need answers if we are to continue to improve the outcomes to this mysterious illness.

Acknowledgements

Dr Amsden is a consultant, speaker and researcher for Pfizer, Inc. and Pliva dd, is a current researcher for Abbott and has conducted antibacterial research for Bayer, Bristol-Myers Squibb and GlaxoSmithKline. No funding was received for the writing of this invited manuscript.

References

1. Fraser DW, Tsai TR, Ovenstein W, et al. The field investigation team. Legionnaires' disease: description of an epidemic of pneumonia. N Engl J Med 1977; 297: 1189-97
2. Terranova W, Cohen ML, Fraser DW. Outbreak of Legionnaires' disease diagnosed in 1977. Lancet 1978; 2: 122-4
3. Osterholm MT, Chin TD, Osborne DO, et al. A 1957 outbreak of Legionnaires' disease associated with a meat packing plant. Am J Epidemiol 1983; 117: 60-7
4. Marrie TJ, Peeling RW, Fine MJ, et al. Ambulatory patients with community-acquired pneumonia: The frequency of atypical agents and clinical course. Am J Med 1996; 101: 508-15
5. Stout JE, Yu VL. Current Concepts: Legionellosis. N Engl J Med 1997; 337: 682-7
6. Fang GD, Fine M, Orloff J, et al. New and emerging etiologies for community-acquired pneumonia with implications for therapy: a prospective multicenter study of 359 cases. Medicine (Baltimore) 1990; 69: 307-16
7. Torres A, Sera-Batilles J, Ferrer A, et al. Severe community-acquired pneumonia: epidemiology and prognostic factors. Am Rev Respir Dis 1991; 144: 312-8
8. Yu VL. Legionella pneumophila (Legionnaires' disease). In: Mandell GL, Bennett JE, Dolin R, editors. Principles and practice of infectious diseases. 5th ed. Philadelphia (PA): Churchill Livingstone, 2000: 2424-35
9. Camerson S, Walker C, Roden D, et al. Epidemiological characteristics of Legionella infection in South Australia: implications for disease control. Aust N Z Med 1991; 21: 65-70
10. Muder RR. Other Legionella species. In: Mandell GL, Bennett JE, Dolin R, editors. Principles and practice of infectious diseases. 5th ed. Philadelphia (PA): Churchill Livingstone, 2000: 2435-41
11. Fang GD, Yu VL, Vickers RM. Disease due to Legionellaceae (other than Legionella pneumophila): historical, microbiological, clinical and epidemiological review. Medicine (Baltimore) 1989; 68: 116-39
12. Best M, Yu VL, Stout J, et al. Legionellaceae in the hospital water supply: epidemiological link with disease and evaluation of a method of control of nosocomial legionnaires' disease and Pittsburgh pneumonia. Lancet 1983; 2: 307-10
13. Roig J Rello J. Legionnaires' disease: a rational approach to therapy. J Antimicrob Chemother 2003; 51: 1119-29
14. Mandell LA, Bartlett JG, Dowell SF, et al. Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. Clin Infect Dis 2003; 37: 405-33
15. Friedman H, Yamamoto Y, Klein TW. Legionella pneumophila pathogenesis and immunity. Sem Pediatr Infect Dis 2002; 13: 273-9

16. Stout JE, Lin YSE, Goetz AM, et al. Controlling Legionella in hospital water systems: experience with the superheat-and-flush method and copper-silver ionization. Infect Control Hosp Epidemiol 1998; 19: 911-4

17. Dedicoat M, Venkatesan P. The treatment of Legionnaires' disease. J Antimicrob Chemother 1999; 43: 747-52

18. Smith GM Sutherland. Activity of amoxycillin-clavulanic acid against Legionella pneumophila in vitro and in an experimental respiratory infection model. J Hosp Infect 1992; 22 Suppl. A: 61-7

19. Smith GM, Abbott KH, Sutherland R. Bactericidal effects of co-amoxiclav (amoxycillin clavulanic acid) against a Legionella pneumophila pneumonia in the immunocompromised weanling rat. J Antimicrob Chemother 1992; 30: 525-34

20. Stokes DH, Wilkinson MJ, Tyler J, et al. Bactericidal effects of amoxycillin/clavulanic acid against intracellular Legionella pneumophila in tissue culture studies. J Antimicrob Chemother 1989; 23: 547-56

21. Smith GM, Abbott KH, Wilkinson MJ, et al. Bactericidal effects of amoxycillin/clavulanic acid against a Legionella pneumophila pneumonia in the weanling rat. J Antimicrob Chemother 1991; 27: 127-36

22. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis 1998; 26: 1-10

23. Zimmerman T, Riedel KD, Laufen H, et al. Intravenous toleration of azithromycin in comparison to clarithromycin and erythromycin [abstract no. A82]. In: Abstracts of the 36th Interscience Conference on Antimicrobial Agents and Chemotherapy. New Orleans (LA): American Society for Microbiology, 1996: 16

24. Dournon E, Mayaud C, Wolff M, et al. Comparison of the activity of three antibiotic regimens in severe Legionnaire's disease. J Antimicrob Chemother 1990; 26 Suppl. B: 129-39

25. Hubbard RB, Mathur RM, MacFarlane JT. Severe community acquired legionella pneumonia: treatment, complications and outcome. Quart J Med 1993; 86: 327-32

26. Rello J, Bodi M, Mariscal D, et al. Microbiological testing and outcome of patients with severe community-acquired pneumonia. Chest 2003; 123: 174-80

27. Tan MJ, Tan JS, File Jr TM. Legionnaires disease with bacteremic coinfection. Clin Infect Dis 2002; 35: 533-9

28. Hamedani P, Ali J, Hafeez S, et al. The safety and efficacy of clarithromycin in patients with legionella pneumonia. Chest 1991; 100: 1503-6

29. Kuzman I, Soldo I, Schönwald S, et al. Azithromycin for treatment of community acquired pneumonia caused by Legionella pneumophila: a retrospective study. Scand J Infect Dis 1995; 27: 503-5

30. Plouffe JF, Breiman RF, Fields BS, et al. Azithromycin in the treatment of Legionella pneumonia requiring hospitalization. Clin Infect Dis 2003; 37: 1475-80

31. Carbon C, Nusrat R. Efficacy of telithromycin in community-acquired pneumonia caused by Legionella pneumophila. Eur J Clin Microbiol Infect Dis 2004; 23: 650-2

32. Santos J, Aguilar L, García-Méndez E, et al. Clinical characteristics and response to newer quinolones in Legionella pneumonia: a report of 28 cases. J Chemother 2003; 15: 461-5

33. Dorrell L, Fulton B, Ong ELC. Intravenous azithromycin as salvage therapy in a patient with Legionnaire's disease. Thorax 1994; 49: 620-1

34. Matute AJ, Schurink CAM, Hoepelman IM. Is a 5 day course of azithromycin enough for infections caused by Legionella pneumophila? J Antimicrob Chemother 2000; 45: 919-31

35. Edelstein PH, Shinzato T, Doyle E, et al. In vitro activity of gemifloxacin (SB-265805, LB20304a) against Legionella pneumophila and its pharmacokinetics in guinea pigs with L. pneumophila pneumonia. Antimicrob Agents Chemother. 2001; 45: 2204-9

36. Edelstein PH, Edelstein MAC, Ren J, et al. Activity of trovafloxacin (CP-99,219) against Legionella isolates: in vitro activity, intracellular accumulation and killing in macrophages, and pharmacokinetics and treatment of guinea pigs with L. pneumophila pneumonia. Antimicrob Agents Chemother 1996; 40: 314-9

37. Dubois J, St-Pierre C. In vitro activity of gatifloxacin compared with ciprofloxacin, clarithromycin, erythromycin, and rifampin, against Legionella species. Diagn Microbiol Infect Dis 1999; 33: 261-5

38. Gacouin A, Le Tulzo Y, Lavoue S, et al. Severe pneumonia due to Legionella pneumophila: prognostic factors, impact of delayed appropriate antibiotic therapy. Intensive Care Med 2002; 28: 686-91

39. Lettinga KD, Verbon A, Weverling G-J, et al. Legionnaires' disease at a Dutch flower show: prognostic factors and impact of therapy. Emerg Infect Dis 2002; 8: 1448-54

40. Edelstein PH, Cianciotto NP. Legionella. In: Mandell GL, Bennett JE, Dolin R, editors. Principles and practice of infectious diseases. 6th ed. Philadelphia (PA): Churchill Livingstone, 2004: 2711-24

Correspondence and offprints: Dr *Guy W. Amsden*, Clinical Pharmacology Research Center, Bassett Healthcare, Cooperstown, One Atwell Road, NY 13326, USA.
E-mail: guy.amsden@bassett.org