1. Introduction

In 1977, the US Centers for Disease Control (CDC) described the first outbreak of Legionnaires' disease. Patients treated with erythromycin or tetracycline seemed to fare better than those treated with β-lactam agents or aminoglycosides [1]. This impression was later confirmed in an animal model [2].

The discovery of the intracellular location of this pathogen was considered relevant to the efficacy of the antibiotic [3]. Antibiotics capable of achieving intracellular concentrations higher than the minimum inhibitory concentration (MIC) were more clinically effective than antibiotics with poor intracellular penetration. Tetracyclines, macrolides, rifampin and quinolones have good intracellular penetration and were more likely to be efficacious.

Comparative controlled trials of antibiotics for the treatment of Legionnaires' disease have never been conducted because of the relative rarity of confirmed Legionella infections, due to underdiagnosis. As laboratory methodologies were developed, the lack of a rapid diagnostic test rendered enrollment of patients with confirmed Legionnaires' disease logistically difficult. Moreover, when hospital-acquired outbreaks occurred, disinfection of the drinking water source was performed, such that subsequent cases were unlikely to occur.

2. In vitro and in vivo susceptibility testing studies

The susceptibility of Legionella species to antimicrobial drugs has been based on intracellular models in vitro and animal models of Legionella infection. Results based on in vitro dilution and disc diffusion tests proved unreliable because growth of Legionella on standard microbiology media is erratic and the charcoal

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**Keywords:** animal model, azithromycin, clarithromycin, community-acquired pneumonia, erythromycin, hospital-acquired pneumonia, Legionella, Legionella pneumophila, Legionnaires' disease, levofloxacin, macrolides, quinolones, rifampin, tetracyclines.
used for BCYE, the media used for *Legionella*, is inhibitory to the action of antibiotics.

### 2.1 Intracellular models in vitro

Several *in vitro* intracellular models have been developed [4]. Antimicrobial agents are added to the *Legionella*-infected cells and the degree of inhibition of intracellular bacterial growth is determined by quantifying bacterial concentration. Subsequent removal of the antimicrobial agent and recording the time required for regrowth of the bacteria in the tissue or cell culture gives a measure of the intracellular activity of the antimicrobial agent. Antimicrobial agents have been classified as not inhibitory (growth of intracellular *L. pneumophila* occurs despite presence of antimicrobial agent), reversibly inhibitory (slow regrowth of *L. pneumophila* occurs after antimicrobial agent removal from the culture), or cidal or causing prolonged inhibition of growth after the antimicrobial agent is removed [5].

### 2.2 Animal models of *legionella*

Models of respiratory tract infections and peritonitis have been developed. Pneumonia produced in animals is pathophysiologically more appealing than experimental *Legionella* infection induced by intraperitoneal inoculation. *Legionella* peritonitis results in localized infection without histopathologic evidence of disseminated (pulmonary, splenic, hepatic) disease [2]. Antimicrobial agents presumed to be clinically effective (erythromycin, tetracycline) have been effective in the animal models, while those considered clinically ineffective (gentamicin, cefoxitin) were also inactive in animal models. Disadvantages of animal models include the differing pharmacokinetics in animals as compared to humans, as well as the expense and logistics involved.

### 2.3 Tetracyclines

The tetracyclines are the least active of the anti-*Legionella* antibiotics when assessed by *in vitro* dilution methods [4]. Doxycycline was less active than rifampin and erythromycin in inhibiting growth of *L. pneumophila* within monocytes [6]. In a guinea-pig model of *Legionella* pneumonia, doxycycline was more active than rifampin but was less active than pefloxacin and erythromycin [7]. For the non-*pneumophila* species, except *L. micdadei*, doxycycline was less active than rifampin, macrolides and quinolones using *in vitro* dilution methods and a guinea-pig model of *Legionella* pneumonia [8,9]. Tigecycline is active *in vitro* and in animal models [10]. It has proven efficacious in a few patients with Legionnaires’ disease [11].

### 2.4 Macrolides

#### 2.4.1 Erythromycin

The original anecdotal success of erythromycin was confirmed by *in vitro* dilution methods [4]. Growth of *L. pneumophila*, *L. micdadei* and *L. bozemanii* within different cell tissues has been inhibited by erythromycin [12]. Studies in experimental animals have shown its superiority over other antibiotics including penicillin, tetracycline, chloramphenicol, and gentamicin [13].

#### 2.4.2 Azithromycin

Azithromycin appears to be the most active macrolide in intracellular models and within HL-60 cells [12]. In several animal models, azithromycin resulted in 100% survival, and this rate was always higher than that of erythromycin [14-16]. Similar data have been published for non-*pneumophila* species [17]. In an immunosuppressed A/J mice model of pneumonia, survival with administration of azithromycin was 92% [18].

#### 2.4.3 Clarithromycin

In a guinea-pig model of *Legionella* pneumonia, clarithromycin resulted in 100% survival, whereas no treatment resulted in 0% survival [15]. Despite good extracellular and intracellular activity, its effect was bacteriostatic against *Legionella* in experimental studies [19,20]. Dubois and colleagues found that clarithromycin did not prevent regrowth and did not kill *L. pneumophila* after removal of extracellular antibiotic in human monocytes [19]. Similarly, Edelstein and co-workers found that clarithromycin reduced bacterial counts of two *L. pneumophila* strains grown in guinea-pig alveolar macrophages by 0.5 – 1 log 10, but that regrowth occurred over a 2-day period [20]. Clarithromycin was more active than erythromycin [12] and azithromycin and roxithromycin in inhibiting the growth of *L. micdadei* and *L. bozemanii* [17] within HL-60 cells.

### 2.5 Rifampin

Rifampin was more active in inhibiting the growth of *L. pneumophila* than erythromycin and quinolones within guinea-pig peritoneal macrophages [21] and monocytes [6]. In a guinea-pig model of *Legionella* pneumonia, rifampin was more active than macrolides and quinolones, resulting in 100% survival compared with 0 – 90% for the other agents [22]. The development of resistance to rifampin has sporadically been reported as an *in vitro* phenomenon associated with mutations of the RPO B gene [23].

### 2.6 Quinolones

Quinolone agents are more active than any of the macrolides in all *in vitro* and *in vivo* methods (Table 1). The quinolones were more active than erythromycin in irreversibly inhibiting the growth of *L. pneumophila* within various intracellular models [12,24-29]. Levofloxacin showed greater activity than erythromycin or rifampin in the growth of *L. pneumophila* in the human monocyte intracellular model [30,31]. Levofloxacin was also more active than erythromycin and clarithromycin in the guinea-pig alveolar macrophage model [20]. Ciprofloxacin showed greater activity than azithromycin in the HL-60 intracellular model [32]. Experimental animal models have shown the superiority of
quinolone agents compared with erythromycin or no therapy [22,33,34]. Furthermore, ofloxacin resulted in a 92% survival in an immunocompromised mice model of Legionella pneumonia [18]. Similar results were obtained for the non-pneumophila Legionella species.

3. Clinical studies

Erythromycin, the first well-established antibiotic for Legionnaires’ disease, was clinically effective, but other problems arose: adverse effects (especially phlebitis and gastrointestinal intolerance) and drug interactions, especially with immunosuppressive medications for transplant recipients. Reversible ototoxicity was found with the use of higher doses recommended at that time for Legionnaires’ disease.

Azithromycin was approved for community-acquired pneumonia in 1991. This new azalide had desirable pharmacokinetic properties, including a longer elimination half-life and higher lung tissue concentrations. It was also better tolerated and was associated with fewer adverse effects (e.g., lower frequency of gastrointestinal intolerance, ototoxicity and phlebitis). Azithromycin was effective for Legionnaires’ disease in non-comparative studies [35-39]. In a prospective, randomized trial, intravenous azithromycin followed by oral administration resulted in 92% cure, while the comparative regimen of cefuroxime plus erythromycin resulted in 88% cure [40]. Although in vitro and in vivo studies [12,28] have demonstrated that the efficacy of azithromycin is comparable to that of quinolones, no comparative clinical studies have ever been performed. The intravenous formulation of azithromycin is not available in most European countries where many of the antibiotic studies have been conducted.

A number of studies have addressed the issue of the comparative efficacy of quinolones versus macrolides [41-45]. Blazquez-Garrido and colleagues conducted an observational, prospective study of 292 patients with Legionella pneumonia during the Murcia, Spain outbreak [41]. Patients were stratified according to the severity of pneumonia in order to compare those who received clarithromycin (n = 65) with those who received levofloxacin (with and without rifampin) (n = 143). There was no significant difference in clinical outcomes for mild-to-moderate pneumonia, although patients treated with levofloxacin had a shorter mean hospital stay (4.4 vs 7.2 days). In the subset of 40 patients with severe pneumonia, levofloxacin appeared superior; levofloxacin was associated with fewer complications (4.4 vs 27.2%) and a shorter mean hospital stay (5.5 vs 11.2 days). The addition of rifampin showed no additional benefit.

Mykietiuk and co-workers conducted a prospective, observational series of 1934 consecutive cases of community-acquired pneumonia in non-immunocompromised adults [42]. A total of 139 cases of Legionnaires’ disease were diagnosed; those treated with levofloxacin (n = 40) were compared with those receiving macrolides (erythromycin or clarithromycin; n = 80). Treatment with levofloxacin produced a more rapid time to defervescence (2 vs 4.5 days) and clinical stability (3 vs 5 days) and a shorter hospital stay (8 vs 10 days).

Sabià and colleagues conducted a retrospective, observational, multicenter study of Legionnaires’ disease including 76 patients who received macrolides (erythromycin or clarithromycin)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Antimicrobial agents</th>
<th>Legionella</th>
<th>Animal/Model</th>
<th>Outcome survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saito et al., 1986 [34]</td>
<td>Ery vs Cipro</td>
<td>Lp</td>
<td>Guinea-pig</td>
<td>60%</td>
</tr>
<tr>
<td>Saito et al., 1985 [22]</td>
<td>Ery, Josa vs Oflox</td>
<td>Lp</td>
<td>Guinea-pig</td>
<td>100%</td>
</tr>
<tr>
<td>García de Lomas et al., 1998 [109]</td>
<td>Ery vs Trova</td>
<td>Lp</td>
<td>Guinea-pig</td>
<td>100%</td>
</tr>
<tr>
<td>Dournon et al., 1986 [110]</td>
<td>Ery vs Peflo</td>
<td>Lp</td>
<td>Guinea-pig</td>
<td>Mortality was significantly lower for quinolones</td>
</tr>
<tr>
<td>Edelstein et al., 1990 [26]</td>
<td>Ery vs Spar</td>
<td>Lp</td>
<td>Guinea-pig</td>
<td>No differences in mortality, but lung cultures from survivors were significantly more frequently positive for Lp in the Ery-treated animals</td>
</tr>
<tr>
<td>Tzianabos &amp; Rodgers, 1989 [111]</td>
<td>Ery vs Cipro</td>
<td>Lp, serogroup 1</td>
<td>Hen’s eggs</td>
<td>Quinolones were more effective in reducing the incidence of lesions and for prolonging embryo viability</td>
</tr>
</tbody>
</table>

Adapted from [112].

Azithro: Azithromycin; Cipro: Ciprofloxacin; Ery: Erythromycin; Gemi: Gemifloxacin; Josa: Josamycin; Levo: Levofloxacin; Oflox: Ofloxacin; Peflo: Pefloxacin; Spar: Sparfloxacin; Trova: Trovafloxacin.
and 54 patients who received quinolones (levofloxacin or ofloxacin) [43]. The main differences from previous studies were that the authors included patients with hospital-acquired Legionella pneumonia, and 20% of the patients were transplant recipients or had cancer. There were no significant differences in clinical complications (17 vs 24% with a macrolide) or mortality (5.5 vs 7.8% with a macrolide). However, treatment with a quinolone was associated with a significantly more rapid time to defervescence (48 vs 77 h with a macrolide), an earlier switch from intravenous to oral therapy (5.3 vs 9.9 days with a macrolide) and, consequently, a trend towards a shorter hospital stay (7.6 vs 9.9 days). It is important to point out that the starting doses of quinolones were double (500 mg twice daily) those of standard doses or doses recommended by the manufacturer (Sanofi-Aventis, Paris, France) for cases of pneumonia (500 mg/24 h).

Falcó and co-workers conducted a prospective observational study of 113 patients with Legionnaires’ disease and analyzed the clinical efficacy of clarithromycin (n = 52), azithromycin (n = 43) and levofloxacin (n = 18) [44]. The underlying diseases, the initial severity, and the number of patients who required intensive care unit admission were similar in all patients. There were no significant differences in fever duration, length of hospital stay or mortality among the three groups of patients. It should be noted that the patients treated with azithromycin were from an outbreak and were promptly diagnosed and appropriately treated. Only 18 patients from the series were treated with levofloxacin versus 52 with clarithromycin.

Finally, Haranaga and colleagues compared the course of Legionella pneumonia treated with ciprofloxacin (n = 9) with those treated with erythromycin (n = 18) [45]. No significant differences were observed between the two groups with regard to age, gender, underlying diseases or disease severity. In addition, the period of time from the onset of the disease until appropriate therapy did not differ significantly between the two groups. Although there were no significant differences, the time to defervescence, normalization of leukocytosis and a 50% decrease in C-reactive protein occurred within a shorter timeframe for ciprofloxacin than for erythromycin group (3.5 vs 4 days, 4 vs 5.2 days, and 2.9 vs 10.3 days, respectively). Furthermore, the duration of antibiotic treatment in the ciprofloxacin group was significantly shorter than in the erythromycin group.

In summary, the results of these five observational studies totalling 598 patients suggest that quinolones (levofloxacin, ofloxacin and ciprofloxacin) were more effective than macrolides (erythromycin and clarithromycin) based on time to defervescence and length of hospital stay. It must be noted that the mortality was similar for both class of antibiotics (Table 2). The studies by Blazquez-Garrido and colleagues [41] and Mykietiuk and co-workers [42] recorded the incidence of treatment-related adverse events; when the results of both studies were combined, the rate was 23.4% for patients receiving macrolides (clarithromycin and erythromycin) and 12.5% for patients receiving levofloxacin. Phlebitis was the most frequent adverse effect observed with intravenous erythromycin.

The initial doses of levofloxacin are probably important for optimal outcome. Quinolones are concentration-dependent drugs, and the dynamic variable most clearly linked to killing rate and outcome is the relation between the AUC and the MIC [46]. The practical impact of the pharmacokinetics is reinforced by the experimental data from a human monocyte model showing a statistically significant decrease in colony-forming units per milliliter of L. pneumophila with increasing concentrations of levofloxacin [39]. Reports of treatment failure have been described using low doses of ofloxacin [47] or ciprofloxacin [48,49] in Legionnaires’ disease. Dosing 500 mg twice daily should produce levofloxacin concentrations that exceed the MIC for a longer period with an increase in improving the AUC/MIC ratio [43]. Yu and colleagues found a surprising 0% mortality in 75 patients with Legionnaires’ disease receiving levofloxacin (500 – 750 mg daily) who were enrolled in six clinical trials performed for FDA approval [50].

The duration of therapy is based on consensus [51]; controlled comparative studies addressing duration have never been performed (Table 3). When only erythromycin was available for the treatment of Legionella infection, longer treatment schedules were thought to be necessary; recurrence in immunocompromised patients in one of the hospitals with documented hospital-acquired Legionnaires’ disease led to the recommendation that duration be extended to 3 weeks [52]. It now seems possible that some of these patients with hospital-acquired pneumonia may have been reinfected by drinking water contamination rather than actual recurrence. Azithromycin and fluoroquinolones have more favorable pharmacokinetic and pharmacodynamic profiles such that duration of therapy has been shortened. A 7- to 10-day course of therapy is usually sufficient. However, therapy duration may be extended for patients with lung abscesses, empyema, endocarditis, and extrapulmonary infection. In immunosuppressed patients with prolonged illness, prolonging the length of treatment to 21 days is reasonable, but probably unnecessary for patients who respond rapidly to antibiotics.

4. Monotherapy versus combination therapy

Despite the advances in the diagnosis and treatment of Legionnaires’ disease, the mortality rate continues to be in the range of 20 – 30% in some subgroups of patients. Patients with solid or hematologic neoplasms undergoing immunosuppressive treatment and HIV-infected patients have increased morbidity/mortality. Likewise, patients presenting late in the course of disease with bilateral infiltrates usually do poorly. Thus, combinations have often been used in these patients, the most frequent being macrolides–rifampin or macrolides–quinolones.
Table 2. Clinical response of macrolides compared with quinolones in five observational studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients, n</th>
<th>Time to defervescence (h)</th>
<th>Hospital stay (days)</th>
<th>Complications</th>
<th>Mortality</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>Q</td>
<td>M</td>
<td>Q</td>
<td>M</td>
<td>Q</td>
</tr>
<tr>
<td>Sabrià et al., 2005 [43]</td>
<td>76</td>
<td>54</td>
<td>77.1</td>
<td>48</td>
<td>9.9</td>
<td>7.6</td>
</tr>
<tr>
<td>Mykietiuk et al., 2005 [42]</td>
<td>80</td>
<td>40</td>
<td>108</td>
<td>48</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Blázquez-Garrido et al., 2005 [41]</td>
<td>65</td>
<td>143</td>
<td>108</td>
<td>104</td>
<td>7.2</td>
<td>4.4</td>
</tr>
<tr>
<td>Falcó et al., 2006 [44]</td>
<td>95</td>
<td>18</td>
<td>60</td>
<td>60</td>
<td>8.5</td>
<td>10.9</td>
</tr>
<tr>
<td>Haranaga et al., 2007 [45]</td>
<td>18</td>
<td>9</td>
<td>96</td>
<td>84</td>
<td>20</td>
<td>16.7</td>
</tr>
<tr>
<td>Total or mean</td>
<td>334</td>
<td>264</td>
<td>89.8</td>
<td>68.8</td>
<td>11.2</td>
<td>9.5</td>
</tr>
</tbody>
</table>

M: Macrolides; NA: Not available; Q: Quinolones. Means have been computed for time to defervescence and hospital stay.
Table 3. Antibiotic doses for Legionella infection.

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>Dosage*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetracyclines</td>
<td></td>
</tr>
<tr>
<td>Doxycycline</td>
<td>100 mg orally or i.v. every 12 h</td>
</tr>
<tr>
<td>Tigecycline**</td>
<td>100 mg initially, i.v., 50 mg every 12 h</td>
</tr>
<tr>
<td>Macrolides</td>
<td></td>
</tr>
<tr>
<td>Erythromycin</td>
<td>500 mg orally or i.v. every 6 h</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>500 mg orally or i.v. every 12 h†</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>500 mg orally or i.v. every 24 h§ **</td>
</tr>
<tr>
<td>Rifampin†</td>
<td>600 mg orally or i.v. every 24 h</td>
</tr>
<tr>
<td>Quinolones</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>400 mg i.v. every 8 h initially, 400 mg i.v. every 12 h</td>
</tr>
<tr>
<td></td>
<td>750 mg orally every 12 h</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>400 mg i.v. or orally every 12 h</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>500 mg or i.v. every 24 h</td>
</tr>
<tr>
<td>Moxifloxacin†‡</td>
<td>400 mg every 24 h orally or i.v.</td>
</tr>
</tbody>
</table>

*The dosages are based on clinical experience, not on controlled trials.
†Intravenous formulation not available in the United States.
‡Intravenous formulation not available in most European countries.
§In combination with another antibiotic.
#If weight > 50 kg, 450 mg if weight < 50 kg.
**We recommend doubling the first dose.
††Clinical experience is minimal.

4.2 Macrolides–quinolones

4.2.1 In vitro and in vivo studies

To date, six laboratory studies on the efficacy of the combination of macrolides and quinolones against Legionella have been published (Table 4) [30,54,61-64]: four using the in vitro dilution test [54,61-63] and two intracellular model studies [30,64]. Although the combination of ciprofloxacin plus erythromycin seemed to enhance the activity of erythromycin by time-kill curve analysis in the study by Barker and colleagues [61], the combination of levofloxacin plus erythromycin in the Smith and co-workers [64] study did not improve the reduction of regrowth of Legionella in human mononuclear phagocytes as compared to levofloxacin alone. In the study by Martin and colleagues [62], synergy or partial synergy was present in most of the L. pneumophila isolates tested by the agar dilution method with the combinations of clarithromycin–levofloxacin and azithromycin–levofloxacin. Furthermore, with the non-pneumophila Legionella species, the combination of levofloxacin with any of the macrolides appeared to have more activity than ciprofloxacin alone in this study.

4.3 Quinolones–rifampin

4.3.1 In vitro and in vivo studies

The combination of ciprofloxacin and rifampin was synergistic against one isolate of L. pneumophila [61] but did not improve killing of L. pneumophila in another study by the time-kill method [65]. This combination was indifferent against 80% (16/20) L. pneumophila strains in a checkerboard method and did not eradicate the rifampin-resistant subpopulation of L. pneumophila [54]. Combinations of levofloxacin + rifampin and ofloxacin + rifampin were synergistic (time-kill curve) [53]. In a human monocyte model of Legionella infection, the addition of erythromycin or rifampin did not affect the antibacterial activity of levofloxacin [30]. The rate and degree of regrowth of L. pneumophila pretreated with a combination of levofloxacin and rifampin was similar to that seen with single drugs [64]. The combination of pefloxacin with rifampin

care unit admission and compared clarithromycin treatment with combined clarithromycin–rifampin therapy. In four patients, rifampin was added owing to radiological and clinical progression of the disease while on monotherapy with clarithromycin. Combination therapy of clarithromycin and rifampin had no additional benefit compared with clarithromycin monotherapy and m have prolonged the length of stay owing to possible negative drug interactions. Patients who received rifampin had a 50% longer length of stay and trend towards higher bilirubin levels. Length of stay was directly correlated with the duration of rifampin treatment. This antibiotic was withdrawn in two patients because of alterations in liver function tests. The authors suggested that the negative effect of rifampin may have led to a reduction in the efficacy of clarithromycin. Rifampin induces the CYP3A4 isoyme, the main isoyme in clarithromycin metabolism, thereby reducing clarithromycin serum levels [58-60].
Table 4. *In vitro* and *in vivo* studies on macrolide–quinolones combination therapy for *Legionella*.

<table>
<thead>
<tr>
<th>Author</th>
<th>Species</th>
<th>Drugs</th>
<th>Type of study</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baltch et al.,</td>
<td><em>Legionella pneumophila</em></td>
<td>Erythro + Levo</td>
<td>Intracellular model</td>
<td>The addition of Erythro did not affect the antibacterial activity of Levo</td>
</tr>
<tr>
<td>Barker &amp; Farrell,</td>
<td><em>Legionella pneumophila</em></td>
<td>Cipro + Erythro</td>
<td>Time-kill curve</td>
<td>Combination enhanced the bactericidal activity of Erythro</td>
</tr>
<tr>
<td>1990 [61]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Martin et al.,</td>
<td><em>Legionella spp.</em></td>
<td>Erythro, Clarithro, Azithro</td>
<td><em>In vitro</em> agar dilution</td>
<td>Clarithro + Levo &gt; Azithro + Levo &gt; Erythro + Levo &gt; Azithro + Clarithro</td>
</tr>
<tr>
<td>1996 [62]</td>
<td></td>
<td>each in combination with Cipro</td>
<td>method (FIC index)</td>
<td>Clarithro &gt; Erythro + Clarithro &gt; Clarithro + Cipro</td>
</tr>
<tr>
<td></td>
<td></td>
<td>or Levo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Martin et al.,</td>
<td><em>Legionella spp.</em></td>
<td>Clarithro + Cipro ± 14-OH-clarithromycin</td>
<td><em>In vitro</em> agar dilution</td>
<td>The 14-OH metabolite of Clarithro significantly increased the activity of both fluoroquinolone + Clarithro combinations</td>
</tr>
<tr>
<td>1997 [63]</td>
<td></td>
<td>and Clarithro + Levo ± 14-OH-clarithromycin</td>
<td>method (FIC index)</td>
<td></td>
</tr>
<tr>
<td>Moffie &amp; Mouton,</td>
<td><em>Legionella pneumophila</em></td>
<td>Ciprofloxacin + Erythromycin</td>
<td><em>In vitro</em> agar dilution</td>
<td>The combination showed indifference (FIC &gt; 1 – 4)</td>
</tr>
<tr>
<td>1988 [54]</td>
<td></td>
<td></td>
<td>method (FIC index)</td>
<td></td>
</tr>
<tr>
<td>Smith et al.,</td>
<td><em>Legionella pneumophila</em></td>
<td>Erythromycin + Levofloxacin</td>
<td>Intracellular model</td>
<td>The combination did not improve the reduction of regrowth observed with Levo alone</td>
</tr>
<tr>
<td>1997 [64]</td>
<td>sg 1</td>
<td></td>
<td>(human mononuclear phagocytes)</td>
<td></td>
</tr>
</tbody>
</table>

Azithro: Azithromycin; Cipro: Ciprofloxacin; Clarithro: Clarithromycin; Ery: Erythromycin; Levo: Levofloxacin; FIC: Fractional inhibitory concentration.
showed an additive effect and no antagonism on the multiplication of *L. pneumophila* within human monocyte-derived macrophages [6]. Addition of rifampin to fleroxacin provided neither synergy nor antagonism inhibiting *L. pneumophila* multiplication within human macrophages [66].

Ciprofloxacin was as effective as rifampin in the treatment of experimentally induced *Legionella* pneumonia; the combination had no advantages over single-agent therapy [67].

### 4.4 Clinical studies

We have often added rifampin for several days’ duration in addition to a quinolone in severely ill patients. Hyperbilirubinemia is common, but it does not indicate hepatotoxicity. It is reversible when the rifampin is discontinued. Nevertheless, the efficacy of combination therapy of rifampin with a quinolone is unproven. No improvements in outcome were seen for 45 case patients treated with levofloxacin plus rifampin as compared to 45 control pairs who were treated with levofloxacin alone [41]. Dournon and colleagues conducted a retrospective study of severe cases of Legionnaires’ disease treated with pefloxacin alone or in combination with erythromycin and/or rifampin, and suggested that pefloxacin alone was as active as combination therapy [55].

To our knowledge, at least six anecdotal cases have been reported suggesting the efficacy of combination therapy in patients with severe *Legionella* pneumonia (Table 5) [68-73]. One of the six cases was a child, and three were immunocompromised. In three cases, combination therapy was the initial treatment. In two patients, the quinolone was added because of clinical progression of infection; both survived. Azithromycin was added to levofloxacin in a 47-year-old HIV patient because of clinical and radiological progression; the patient improved following addition of azithromycin and ultimately survived [73]. The anti-inflammatory activity of the macrolides and the bactericidal action of the fluoroquinolones may be relevant in selected patients who are severely ill and have not responded to monotherapy. Two uncontrolled series of patients with Legionnaires’ disease suggest that combination therapy may be superior to monotherapy [74-75].

<table>
<thead>
<tr>
<th>Author</th>
<th>Species</th>
<th>Characteristics of patients</th>
<th>Drugs</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ishii et al., 2005 [70]</td>
<td><em>L. pneumophila</em></td>
<td>Male, 75-year-old</td>
<td>Pazu + Clarithro</td>
<td>Alive</td>
</tr>
<tr>
<td>Ogunna et al., 2004 [71]</td>
<td><em>L. pneumophila</em></td>
<td>Male, 64-year-old</td>
<td>Cipro + Ery</td>
<td>Alive</td>
</tr>
<tr>
<td>Trubel et al., 2002 [68]</td>
<td><em>L. pneumophila</em></td>
<td>Immunocompromised child</td>
<td>Cipro + Clarithro</td>
<td>Alive</td>
</tr>
<tr>
<td>Pedro-Botet et al., 2006 [73]</td>
<td><em>L. pneumophila</em></td>
<td>Immunocompromised 47-year-old HIV-infected female</td>
<td>Levo + Azithro</td>
<td>Alive</td>
</tr>
</tbody>
</table>

5. **Antibiotic selection**

5.1 **Prognostic factors**

With the advent of improved diagnostic methods leading to earlier diagnosis of Legionnaires’ disease, mortality has been reduced to < 10%, especially in outbreak cases [76,77]. Reports from the 1980s showed a mortality as high as 80% [78]. Hospital acquisition [79], strain virulence [80-82], initial severity of the pneumonia [83] or delay in the initiation of appropriate treatment [84,85] have been associated with a worse prognosis. The immunosuppressive status of the patient also affects mortality and recurrence [86]. Mortality in the transplant recipients was in the range of 8 – 70% [87]. Likewise, the mortality among AIDS patients has been reported to be 20% [88].

5.2 **Legionella infection in non-severely ill patients**

For the purposes of this review, we define ‘non-severely ill’ patients as those having a low severity of illness score (PSI I, II, III) [89], CURB-65 [90], or Pitt Bacteremia Score [91]. Either quinolones or macrolides could be used; the physician should choose the antibiotic based on individual circumstances and personal preferences.

5.3 **Legionella infection in severely ill patients**

These patients have high severity-of-illness scores using PSI (IV,V), CURB-65 [4,5] and Pitt Bacteremia Score criteria, and are often in the ICU. In some studies, quinolones have demonstrated a shorter time to defervescence and, perhaps, a more rapid restoration of feelings of well-being when compared to erythromycin and clarithromycin. Moreover, comparative *in vitro* studies show that quinolones are more active than any of the macrolides. Therefore, in patients who are severely ill, we favor the use of quinolones over macrolides, although definitive evidence of their superiority over azithromycin is lacking. Other factors that may influence preference of a quinolone over a macrolide might be delayed administration of active antibiotic therapy and compromised immune status of the host.
5.4 Non-antibiotic drug therapy
Success has been reported in some anecdotal cases of severe Legionella pneumonia in which intravenous pulses of methylprednisolone seemed beneficial [92-94]. One case of Legionella pneumonia with acute respiratory distress syndrome, myocarditis, and septic shock was successfully treated with activated drotrecogin alpha [95]. Sivelestat sodium hydrate was effective in combination with methylprednisolone and antibiotics in two cases of Legionella pneumonia complicated by adult respiratory distress syndrome [71,96].

6. Expert opinion
The incidence of legionellosis is increasing due to a combination of increased use of laboratory diagnostic testing and possibly changes in environmental ecology [97,98].

It is well established that clinical manifestations are unreliable in diagnosing Legionnaires’ disease [99]. Thus, diagnostic laboratory tests for Legionella should be routinely applied to all patients with community-acquired pneumonia, including ambulatory patients [100-102]. Attention has also been called to undiagnosed occurrence of Legionnaires’ disease in children [97,103], so hospitalized children with pneumonia should also undergo Legionella testing (especially if the hospital water supply is colonized with Legionella) [97,103]. The urinary antigen is a rapid diagnostic test that we recommend for all patients with community-acquired pneumonia, including ambulatory patients [104]. Culture for Legionella using selective media should be more widely available since its sensitivity is notably higher than the urinary antigen.

We recommend the use of azithromycin or levofloxacin (or other quinolones) as drugs of choice for Legionella pneumonia. Clarithromycin is an alternative choice in countries in which azithromycin is not readily available. Dosage of quinolones should be maximal. Combination therapy of quinolone plus azithromycin can be considered for patients who are severely ill or have extrapulmonary manifestations.

Most patients will have a clinical response (usually defervesence) within 72 h. The duration of therapy is 7 – 10 days for those who respond expeditiously; a longer duration of therapy can be individualized for those experiencing a stormy course or for severely immunosuppressed patients. The prognosis is generally excellent, although one study with a follow-up of 17 months showed residual nonspecific complaints, especially fatigue, in many patients [105].

Once a case of Legionnaires’ disease is confirmed, most countries require notification to the health department. If the case is hospital-acquired, culturing of the hospital drinking water is mandatory [106-108].

Declaration of interest
Dr Yu has received grant funding from Orhto McNeil Pharmaceuticals and Pfizer Laboratories.

Bibliography
Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.
6. Microbial agent activity against intracellular L. pneumophila was classified into three major groups: those agents allowing significant growth, those allowing no significant growth but static in nature, and those that significantly reduced the bacterial concentration (bactericidal).
• The rank order of intracellular activity from high to low against L. pneumophila serogroup 1 wasquinolones > ketolides > macrolides.
Drusano G, Lebro MT, Cars O, et al. •• Monotherapy with levofloxacin was a safe and effective treatment for Legionnaires’ disease, including in patients with severe disease. In these patients, levofloxacin appeared to be more effective than clarithromycin.


**Monotherapy with levofloxacin was a safe and effective treatment for Legionnaires’ disease, including in patients with severe disease. In these patients, levofloxacin appeared to be more effective than clarithromycin.**


In an observational study, combination therapy of clarithromycin and rifampin had no additional benefit compared with clarithromycin monotherapy. The length of stay might have been prolonged owing to possible negative drug interactions. We note that liver function test abnormalities, especially hyperbilirubinemia, are common and reversible. In our opinion, short courses of rifampin may still be useful.


Pohlol D, Saravolatz LD, Somerville MM. Inhibition of Legionella pneumophila multiplication within human macrophages...
Treatment strategies for *Legionella* infection


• This study showed a trend between complications and basal immunosuppression with patients on immunosuppressive therapy having the highest mortality.


• *Legionnaires’* disease had a more severe clinical presentation and worse evolution in patients with HIV.


• The US Centers for Disease Control and Prevention have noticed a substantial increase of reported legionellosis cases in recent years, particularly in the eastern United States and among middle-aged adults. They recommend that *Legionella* infection be considered in the differential diagnosis of any patient with pneumonia.
98. Health Protection Agency, United Kingdom. National increase in Legionnaires’ disease. 03 Aug 2007

** Classic clinical manifestations of Legionnaires’ disease may be nonspecific, such that milder cases are overlooked.


** The German multicenter study of the Competence Network for Community-Acquired Pneumonia (CAPNETZ) confirmed that clinical manifestations are not useful in predicting the likelihood of Legionella pneumonia and that a rapid laboratory test for determining the etiology of the pneumonia should be performed for CAP patients. Legionella was a common cause of community-acquired pneumonia. Ten per cent of community-acquired cases were caused by other species or serogroups not detectable by the urinary antigen test. There was an unacceptably high rate of inadequate initial antimicrobial treatment.


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** Awareness of Legionella as a potential cause of pediatric pneumonia is particularly important because antimicrobial therapy, often used for empirical therapy in children, is not effective against Legionella.


** A 20-hospital prospective study in Catalonia, Spain, showed that routine environmental cultures of the hospital drinking water led to the discovery of hospital-acquired Legionnaires’ disease.


** A 20-hospital prospective study in the United States showed that routine environmental cultures of hospital drinking water led to the discovery of hospital-acquired Legionnaires’ disease. None of the hospitals had experienced known cases of Legionnaires’ disease prior to the study.


** Dosage of quinolones should be maximal. Macrolides and quinolones are the drugs of choice. In four observational studies totalling 458 patients, mortality was similar for both macrolides (erythromycin and clarithromycin, but not azithromycin) and quinolones (levofloxacin, ofloxacin, ciprofloxacin). Clinical response was more rapid for quinolones.

Affiliation
M Luisa Pedro-Botet MD & Victor L Yu MD
1Author for correspondence
2Professor of Medicine
Universitat Autònoma de Barcelona, Badalona, Spain
3Special Pathogens Laboratory, 1401 Forbes Avenue, Suite 207, Pittsburgh, PA 15219, USA
Tel: +1 412 434 8488; Fax: +1 412 281 7445; E-mail: vly@pitt.edu

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