Expert Opinion

Treatment strategies for *Legionella* infection

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Given the nonspecific clinical manifestations of Legionnaires' disease and the high mortality of untreated Legionnaires' disease, we recommend routine use of *Legionella* testing, especially the *Legionella* urinary antigen test, for all patients with community-acquired pneumonia. This includes patients with ambulatory pneumonia and hospitalized children. Legionella cultures should be more widely available, especially in hospitals where the drinking water is colonized with *Legionella*. Azithromycin or levofloxacin can be considered as first-line therapy. Other antibiotics including tetracyclines, tigecycline, other fluoroquinolones and other macrolides (especially clarithromycin) are also effective. The clinical response of quinolones may be somewhat more favorable compared to macrolides, but the outcome is similar. If the Legionnaires' disease is hospital-acquired, culturing of the hospital drinking water for *Legionella* is indicated.

Keywords: animal model, azithromycin, clarithromycin, community-acquired pneumonia, erythromycin, hospital-acquired pneumonia, *Legionella*, *Legionella pneumophila*, Legionnaires' disease, levofloxacin, macrolides, quinolones, rifampin, tetracyclines.

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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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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

Table 1. Activity of macrolides compared with quinolones in animal models.

Reference	Antimicrobial agents	*Legionella*	Animal/Model	Outcome survival	
				Macrolide	Quinolone
Saito *et al*., 1986 [34]	Ery vs Cipro	Lp	Guinea-pig	60%	80%
Saito *et al*., 1985 [22]	Ery, Josa vs Oflox	Lp	Guinea-pig	Ery 60% Josa 0%	80%
Edelstein *et al*., 2001 [28]	Azithro vs Gemi, Levo	Lp	Guinea-pig	100%	Gemi 100% Levo 100%
García de Lomas *et al*., 1998 [109]	Ery vs Trova	Lp	Guinea-pig	90%	100%
Dournon *et al*., 1986 [110]	Ery vs Peflo	Lp	Guinea-pig	Mortality was significantly lower for quinolones	
Edelstein *et al*., 1990 [26]	Ery vs Spar	Lp	Guinea-pig	No differences in mortality, but lung cultures from survivors were significantly more frequently positive for Lp in the Ery-treated animals	
Tzianabos & Rodgers, 1989 [111]	Ery vs Cipro	Lp, serogroup 1	Hen's eggs	Quinolones were more effective in reducing the incidence of lesions and for prolonging embryo viability	

Adapted from [112].
Azithro: Azithromycin; Cipro: Ciprofloxacin; Ery: Erythromycin; Gemi: Gemifloxacin; Josa: Josamycin; Levo: Levofloxacin; Oflox: Ofloxacin; Peflo: Pefloxacin; Spar: Sparfloxacin; Trova: Trovafloxacin.

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).

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

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 [30]. 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.

Study	Patients, n		Time to defervescence (h)		Hospital stay (days)		Complications		Mortality		Adverse effects	
	M	Q	M	Q	M	Q	M	Q	M	Q	M	Q
Sabrià *et al.*, 2005 [43]	76	54	77.1	48	9.9	7.6	23.6% (18/76)	16.6% (9/54)	7.8% (6/76)	5.5% (3/54)	NA	NA
Mykietiuk *et al.*, 2005 [42]	80	40	108	48	10	8	25% (20/80)	25% (10/40)	5% (4/80)	2.5% (1/40)	30% (24/80)	20% (8/40)
Blázquez-Garrido *et al.*, 2005 [41]	65	143	108	104	7.2	4.4	4.6% (3/65)	0.6% (1/143)	0% (0/65)	0.6% (1/143)	15.3% (10/65)	10.4% (15/143)
Falcó *et al.*, 2006 [44]	95	18	60	60	8.5	10.9	NA	NA	5.2 % (5/95)	5.6% (1/18)	NA	NA
Haranaga *et al.*, 2007 [45]	18	9	96	84	20	16.7	NA	NA	11.1% (2/18)	0	NA	NA
Total or mean	334	264	89.8	68.8	11.2	9.5	18.5% (41/221)	8.4% (20/237)	5% (17/334)	2.2% (6/264)	23.4% (34/145)	12.5% (23/183)

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.

Antimicrobial agent	Dosage*
Tetracyclines	
Doxycycline	100 mg orally or i.v. every 12 h
Tigecycline‡‡	100 mg initially, i.v., 50 mg every 12 h
Macrolides	
Erythromycin	500 mg orally or i.v. every 6 h
Clarithromycin	500 mg orally or i.v. every 12 h‡
Azithromycin	500 mg orally or i.v. every 24 h § **
Rifampin¶	600 mg orally or i.v. every 24 h
Quinolones	
Ciprofloxacin	400 mg i.v. every 8 h initially, 400 mg i.v. every 12 h 750 mg orally every 12 h
Ofloxacin	400 mg i.v. or orally every 12 h
Levofloxacin	500 mg# orally or i.v. every 24 h
Moxifloxacin‡‡	400 mg every 24 h orally or i.v.

*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.

4.1 Macrolides–rifampin

The combination of erythromycin–rifampin was the first used in patients with severe disease or immunosuppressed clinically deteriorating on monotherapy, based on its synergistic effect in the experimental model [3,30,53,54]. Dournon and colleagues [55] retrospectively compared the efficacy of three antibiotic regimens in 60 patients with severe *Legionella* pneumonia, including nosocomial cases. The highest mortality rate (50%; 10/20) was reported with erythromycin, the lowest rate (28.6%; 2/7) being reported with pefloxacin. The combination of erythromycin plus rifampin also presented a high mortality rate (40%; 8/20). However, crude mortality rates did not differ among groups.

Hubbard and co-workers [56] retrospectively analyzed 30 cases of severe *Legionella* community-acquired pneumonia. The mortality rates were 25% (3/12) in erythromycin-treated patients and 33.3% (5/15) in patients treated with erythromycin plus rifampin. Patients receiving rifampin presented a total bilirubin peak level higher than those who did not receive it, and also had more jaundice. Rifampin was discontinued in 6 out of 15 patients (40%). The authors concluded that the addition of rifampin had no advantage. In both studies, the addition of rifampin to erythromycin showed no advantage on the mortality rate compared with the other treatments tested.

Grau and colleagues [57] conducted an observational study of 32 patients from an outbreak who did not require intensive 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 isozyme, the main isozyme in clarithromycin metabolism, thereby reducing clarithromycin serum levels [58-60].

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. pneum*ophila [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

Table 4. *In vitro* and *in vivo* studies on macrolide–quinolones combination therapy for *Legionella*.

Author	Species	Drugs	Type of study	Effect
Baltch *et al.*, 1998 [30]	*Legionella pneumophila* sg 1	Erythro + Levo	Intracellular model (human monocytes)	The addition of Erythro did not affect the antibacterial activity of Levo
Barker & Farrell, 1990 [61]	*Legionella pneumophila*	Cipro + Erythro	Time-kill curve	Combination enhanced the bactericidal activity of Erythro
Martin *et al.*, 1996 [62]	*Legionella* spp.	Erythro, Clarithro, Azithro each in combination with Cipro or Levo	*In vitro* agar dilution method	Clarithro + Levo > Azithro + Levo > Erythro + Levo > Azithro + Clarithro > Erythro + Clarithro > Clarithro + Cipro
Martin *et al.*, 1997 [63]	*Legionella* spp.	Clarithro + Cipro ± 14-OH-clarithromycin and Clarithro + Levo ± 14-OH-clarithromycin	*In vitro* agar dilution method (FIC index)	The 14-OH metabolite of Clarithro significantly increased the activity of both fluoroquinolone + Clarithro combinations
Moffie & Mouton, 1988 [54]	*Legionella pneumophila*	Ciprofloxacin + Erythromycin	*In vitro* agar dilution method (FIC index)	The combination showed indifference (FIC > 1 – 4)
Smith *et al.*, 1997 [64]	*Legionella pneumophila* sg 1	Erythromycin + Levofloxacin	Intracellular model (human mononuclear phagocytes)	The combination did not improve the reduction of regrowth observed with Levo alone

Azithro: Azithromycin; Cipro: Ciprofloxacin; Clarithro: Clarithromycin; Ery: Erythromycin; Levo: Levofloxacin; FIC: Fractional inhibitory concentration.

Table 5. Clinical cases of *Legionella* pneumonia treated with combined therapy reported in the literature.

Author	Species	Characteristics of patients	Drugs	Outcome
Ishii *et al*., 2005 [70]	*L. pneumophila*	Male, 75-year-old	Pazu + Clarithro	Alive
Oguma *et al*., 2004 [71]	*L. pneumophila*	Male, 64-year-old	Cipro + Ery	Alive
Okano *et al*., 2001 [72]	*Legionella* spp.	Male, 54-year-old	Cipro + Ery	Alive
Stroup *et al*., 2004 [69]	*Legionella* spp.	Male, 30-year-old, HIV^+	Moxi + Azithro + Rif	Alive
Trubel *et al*., 2002 [68]	*L. pneumophila*	Immunocompromised child	Cipro + Clarithro	Alive
Pedro-Botet *et al*., 2006 [73]	*L. pneumophila*	Immunocompromised 47-year-old HIV-infected female	Levo + Azithro	Alive

Azithro: Azithromycin; Cipro: Ciprofloxacin; Clarithro: Clarithromycin; Ery: Erythromycin; Levo: Levofloxacin; Moxi: Moxifloxacin; Pazu: Pazufloxacin; Rif: Rifampin.

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].

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 defervescence) 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

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