Chapter

Advances in Treatment and Outcomes of Patients with *Legionella* Infection

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Abstract

Manifestations of *Legionella* infections range from benign, mild disease to a more severe form with increased morbidity and mortality, especially in untreated patients. Despite diagnostic advances, clinical diagnosis remains elusive. Macrolides and respiratory fluoroquinolones remain the antibiotics of choice for treatment of *Legionella*; however, several new antibiotics are currently under development or in clinical trials. The recommended duration of antibiotics is 5–7 days; although, some critically ill or immunosuppressed patients may require longer treatment. In vivo resistance to these antibiotics is rare, and there is no evidence that combination therapy is more beneficial than monotherapy. Early suspicion, diagnosis, and treatment are paramount for improving outcomes.

Keywords: *Legionella*, treatment, pneumonia, outcomes, antibiotics

1. Introduction

Initial recognition of Legionnaires' disease dates back to 1976 during an outbreak of respiratory illness in Philadelphia, PA at an American Legion convention [1]. The *Legionellaceae* family is extensive and contains more than 40 species, but less than half produce disease in humans, with *Legionella pneumophila* being the most common [2]. *Legionella* infections usually manifest in two forms. The most benign presentation is Pontiac fever, which typically presents as an acute, febrile, upper respiratory tract infection (non-pneumonic) that is often unrecognized and resolves spontaneously [3]. The most severe presentation is Legionnaires' disease, caused by *Legionella pneumophila*. It is an atypical pneumonia, generally affecting the lungs and gastrointestinal tract [4]. The disease affects people of all ages and causes significant morbidity and mortality, especially in patients with certain comorbid conditions. An estimated 10,000–18,000 people worldwide are infected with *Legionella* each year [5].

In a recent review, most *Legionella* pneumonia cases were reported in the Northern hemisphere. Common workplaces associated with this infection were industrial settings, office buildings, and healthcare facilities [6]. *Legionella* pneumonia was associated with mortality in 4.1% of all cases.

The clinical and radiological manifestations of *Legionella* are nonspecific. As a result, if suspected, empiric antibiotics treatment is recommended to improve

morbidity and mortality associated with the disease [7, 8]. The goal of this review is to provide a concise discussion regarding indications for treatment of *Legionella*, update the information about antibiotic management, and discuss outcomes of the disease.

2. Pathogenesis

Legionella are aerobic, Gram-negative, facultative, intracellular bacilli found widely in the environment; they have been isolated from many water sources and often colonize manufactured water systems. Humans are infected by exposure to water contaminated with *Legionella*. Person-to-person transmission has been demonstrated in only one case thus far and is not considered to be a primary means of transmission. Thus, the human body may be considered a "dead-end" for *Legionella*. *Legionella* can cause sporadic and potentially life-threatening infections in immunocompromised individuals, especially the young and elderly.

Infection begins when humans inhale *Legionella*, which travels to the lower respiratory tract where the organism binds to alveolar macrophages and engulfed into the phagosomal vacuoles (also known as phagosomes). *Legionella* then blocks fusion of the phagosome with lysosomes, preventing the release of lysosomal enzymes that destroy bacterial cells. Consequently, the bacteria can freely divide in the phagosome. Eventually, the cell ruptures, releasing bacteria that can infect other cells, resulting in inflammation and sepsis. Given the lifecycle of *Legionella*, an effective antibiotic requires both anti-*Legionella* activity and a high intracellular minimum inhibitory concentration in alveolar macrophages [9]. Antibiotics that have demonstrated clinical effectiveness in Legionnaires' disease include macrolides, fluoroquinolones, tetracyclines, trimethoprim-sulfamethoxazole (TMP-SMX), and rifampin [9]. We describe the details of each of these antibiotics below.

3. Treatment

3.1 Macrolides

Bacterial ribosomes have two subunits (30S and 50S) that function in protein synthesis. In contrast, the ribosomes in animal cells have 40S and 60S subunits, and this difference ensures that different classes of antibiotics are active against bacteria and not human cells. Macrolides are bacteriostatic agents that bind reversibly to the 50S ribosomal subunit and inhibit protein synthesis [10]. They are active against a wide range of bacteria, including intracellular pathogens such as *Legionella*. Macrolides, especially azithromycin, reach peak concentration in 2–3 hours and are rapidly absorbed and distributed throughout body tissues and with good cell distribution [10]. In the past, macrolides, especially erythromycin, have been the drug of choice for treatment of Legionnaires' disease. A newer derivative, azithromycin, recently surpassed erythromycin, because azithromycin has fewer side effects and fewer interactions with other drugs than erythromycin or its counterpart, clarithromycin.

Despite macrolides' effectiveness, bacteria have developed multiple resistance mechanisms to these drugs. One mechanism is an active efflux pump to pump the drug out of the cell. Another resistance mechanism involves changing the ribosomal subunit, either by inducing genes to produce a methylase enzyme (*ermA*,

ermB, and *ermC*) that modifies the ribosome target or by causing chromosomal mutation of the 50S ribosomal subunit. Changes in the ribosomal subunit structure decrease drug binding to the ribosome and result in decreased efficacy of the drug [10].

Common side effects of macrolides include gastrointestinal disturbances like dyspepsia, anorexia, flatulence, and arthralgias, and disturbance in taste and smell. Rarely, hepatitis, hepatic failure, thrombocytopenia, interstitial nephritis, photosensitivity, and renal failure are observed [10]. A prolonged QTc is more common with older macrolides, such as erythromycin and clarithromycin. Azithromycin, even is taken with antacids, appears to be free of drug interactions." Caution is advised, nevertheless, when using azithromycin in conjunction with drugs known to interact with erythromycin [10].

3.2 Fluoroquinolones

Along with macrolides, fluoroquinolones (levofloxacin, moxifloxacin, and ciprofloxacin) have increasingly become a drug of choice against *Legionella*. These drugs have broad-spectrum activity against Gram-positive and Gram-negative organisms, such as *Legionella* [11]. Fluoroquinolones inhibit DNA gyrase subunit A, a bacterial enzyme that relieves the tension produced when DNA unwinds during replication. Binding to DNA gyrase inhibits the transcription of bacterial DNA, resulting in bacterial cell death. Levofloxacin has an advantage in treating pneumonia, as this drug has two to five times higher concentrations in lung tissue than in serum. Bioavailability for levofloxacin is 99% for oral and intravenous (IV) medications [11]. Fluoroquinolones exhibit concentration-dependent antimicrobial activity [12].

Bacterial resistance to quinolones mostly occurs by chromosomal mutations to the DNA gyrase gene, resulting in reduced affinity of the drug to the enzyme. Also, similar to macrolides, alterations in drug efflux or cell membrane porin channels can occur, decreasing the intracellular concentration of drug [11].

Side effects of fluoroquinolones include benign rash, headaches, nausea, vomiting, diarrhea, prolonged QTc, and arrhythmia. Tendonitis and tendon rupture have been reported in young and elderly patients. Fluoroquinolones can also cause liver dysfunction. Many over-the-counter (e.g., iron, calcium, zinc, and non-steroidal anti-inflammatory drugs) and prescription medications (e.g., warfarin) can interact with levofloxacin [13].

3.3 Tetracyclines

Tetracyclines are a class of antibiotics that include doxycycline, minocycline, tetracycline, and tigecycline. These drugs are reversible competitive inhibitors and inhibit protein synthesis at the level of the ribosome via inhibition of the codon-anticodon interaction between tRNA and mRNA. These antibiotics block binding of tRNA to the 30S ribosomal subunit, thus preventing the addition of new amino acids for protein building. Because this process is reversible, these drugs are bacteriostatic [14].

Resistance to tetracyclines is acquired via bacterial conjugation, where plasmids or transposons containing resistance genes are transferred to the previously sensitive bacteria. The resistance genes produce modified bacterial porins, preventing uptake of the tetracyclines into the bacterial cell. Other mechanisms of resistance include increased drug efflux, decreased ribosomal binding, and enzymatic inactivation [14].

Tetracyclines can cause many adverse effects, including several that are life-threatening. Tetracyclines concentrate in growing teeth and bones and thus should be avoided by children and pregnant patients [14]. Additionally, tetracyclines can cause nephrotoxicity and hepatotoxicity due to fatty degeneration. Pregnant women are at increased risk of hepatotoxicity, and tetracyclines can potentiate the nephrotoxic effects of aminoglycosides and other nephrotoxic drugs. Furthermore, tetracyclines can induce photosensitivity in persons exposed to the sun during treatment [14].

3.4 Trimethoprim-sulfamethoxazole

TMP-SMX is one of the most widely used antibiotics in the world. Sulfonamides such as SMX are competitive inhibitors of para-aminobenzoic acid, and TMP inhibits dihydrofolate reductase to block the formation of tetrahydrofolate, a key cofactor in the construction of purine, thymidine, DNA, and amino acids [15]. Bacterial dihydrofolate reductase is inhibited 50–60,000 times more than mammalian enzymes; thus, this antibiotic has minimal effect on human cells [15]. Both sulfonamides and TMP act synergistically and have maximal activity when the concentration of SMX is 20 times greater than that of TMP.

Although well tolerated, TMP-SMX can cause many gastrointestinal side effects, including nausea, vomiting, and anorexia as well as rash. Sulfonamides can cause skin rashes, including hypersensitivity reactions that can progress from a mild reaction to erythema multiforme as Stevens-Johnson syndrome. Rarely, TMP-SMX can cause aplastic anemia, agranulocytosis, and fulminant hepatic necrosis [15]. Sulfonamides can cause hemolytic anemia in patients with glucose-6-phosphate dehydrogenase deficiency.

3.5 Rifampin

Rifampin is also effective against *Legionella*, as this drug inhibits bacterial and mycobacterial RNA synthesis by binding to the beta subunit of DNA-dependent RNA polymerase to prevent RNA transcription [16]. Rifampin is absorbed readily and has good penetration into the lungs and pleural fluid. Depending on concentrations reached in the infected cell and the susceptibility of the organism, rifampin can exert either bactericidal or bacteriostatic effects [16]. Most bacteria develop resistance to rifampin as the result of a gene mutation in the beta subunit of DNA-dependent RNA polymerase. Rifampin therapy is recommended only for patients with severe disease or significant comorbid conditions (e.g., poorly controlled diabetes, tobacco use, or obstructive lung disease) including immunocompromised hosts and those refractory to conventional monotherapy regimens. Significant adverse drug events and drug-drug interactions should be considered with the use of rifampin.

Rifampin should not be used as monotherapy but rather can provide a significant synergistic effect when used in combination with other antibiotics such as macrolides or quinolones [17].

Oral and IV dosing is equivalent. Rifampin induces many hepatic CYP450 isoenzymes and can enhance the metabolism of endogenous substrates, including adrenal hormones, thyroid hormones, and vitamin D. Other side effects include maculopapular rash, fever, nausea, and vomiting. Furthermore, this antibiotic can cause *Clostridium difficile* colitis, hepatitis, and liver toxicity and can result in yellow, red, or orange discoloration of bodily fluids. Soft contact lenses may be permanently stained. Rifampin can also cause postnatal hemorrhages in the mother and infant [16] (**Table 1**).

3.6 Drug dosing and duration

A summary of the most common antibiotics used with doses and duration can be seen below in **Table 1**.

Antibiotic	Administration	Dose	Frequency	Duration (days)
Ciprofloxacin	IV	200–400 mg	Every 12 hours	10
		or		
	Oral	500 mg	Every 12 hours	10
Levofloxacin	IV or oral	500 mg	Daily	7–14
Moxifloxacin	IV or oral	400 mg	Daily	14
Azithromycin	IV or oral	500 mg	Daily	7–10
Erythromycin	IV	1 g	Every 6 hours	10–14
Doxycycline*	IV or oral	200 mg	Twice a day	3
	IV or oral	100 mg	Twice a day	11

**Doxycycline administered 200 mg 2×/day for 3 days followed by 100 mg 2×/day for 11 days.*

Table 1.
Recommended drug dosing and duration for antibiotics effective against Legionella.

3.7 Macrolides compared with fluoroquinolones

Previous studies have shown that patients treated with older macrolides have a higher recurrence of disease after antibiotics are withdrawn. Levofloxacin and azithromycin appear to be the ideal drugs against *Legionella* because re-growth is not observed. In fact, numerous societies, including Infectious Diseases Society of America, British Thoracic Society, and the Dutch Association of Chest Physicians, recommend fluoroquinolones or azithromycin as the preferred antimicrobial therapy for *Legionella* [18]. Comparison of levofloxacin with azithromycin in the treatment of *Legionella* has shown no difference between the two antibiotics regarding time to defervescence, time to achieve clinical stability, length of IV therapy, or length of hospital stay [12].

Other antibiotics potentially effective for *Legionella* include tigecycline. A small study in eight patients with *Legionella* suggest tigecycline as potential second-line agent for treatment of patients with severe Legionnaire's responding poorly to conventional first line agents such as levofloxacin and azithromycin [19].

4. Outcomes

A majority of patients with *Legionella* pneumonia have favorable outcomes. Mortality ranges from 1.8 to 10%. Mortality is higher in patients with sporadic infections compared to outbreak-related cases [20, 21]. Mortality is also higher in patients with hospital-acquired legionellosis, transplant recipients with unusual presentations, and missed diagnosis with negative urinary antigen [22, 23]. ICU admissions vary based on severity and underlying conditions, especially immunocompromised status.

Clinical features of *Legionella* infection in immunocompromised patients include infection (most commonly presenting as pneumonia), cavity, and empyema. Extrapulmonary disease can be present, and the urine antigen test is less

sensitive [24]. There are no differences in mortality rates, length of hospital stay, development of *C. difficile* infection, or hospital costs based on chosen therapy (fluoroquinolones versus azithromycin) [25].

4.1 *Legionella* pneumonia and extracorporeal membrane oxygenation (ECMO)

Patients with *Legionella* pneumonia with severe acute respiratory distress syndrome can be treated with ECMO. Several case reports describe the outcomes of patients with *Legionella* pneumonia requiring ECMO [26–28]. With respect to outcomes for refractory respiratory failure in patients with *Legionella* pneumonia, Roncon et al. reported that 14 of 112 patients treated with ECMO had *Legionella* pneumonia [29]. *Legionella* pneumonia was associated with earlier ECMO initiation, higher static compliance and a non significant trend towards hospital survival.

4.2 HIV infection and *Legionella* pneumonia

Legionella pneumonia in HIV-infected patients is uncommon; however, some studies suggest that it occurs 40 times more frequently in patients with AIDS than in the general population [30–32]. There are also conflicting reports on the severity and outcomes of HIV infection and *Legionella* pneumonia [33]. A recent review reported that the incidence of *Legionella* pneumonia occurs in 6% of bacterial pneumonias in HIV infected patients [34]. .Some reasons for a lower incidence in AIDS patients include a possible protective role of *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis with TMP-SMX or the failure to isolate or diagnose *Legionella* as a coinfection. A recent study revealed that *Legionella* could be found in the bronchoalveolar fluid in AIDS patients presenting with tuberculosis and PJP [35]. This study also revealed that species-specific coinfection could occur, associating *L. pneumophila* with *M. tuberculosis* and other *Legionella* species with *P. jirovecii*.

Although most of the data on *Legionella* pneumonia in HIV patients are from case reports, a recent case-matched, case-control study reported that HIV patients presenting with community-acquired *Legionella* pneumonia have similar outcomes compared to non-HIV patients. HIV infection is not associated with higher ICU admission or increased length of hospital stay in these patients [36], and the duration of therapy is similar to non-HIV patients.

4.3 Pregnancy and *Legionella* pneumonia

The estimated prevalence of antepartum pneumonia is similar to that for the non-pregnant population at 0.78–2.7 per 1000 [37]. Although *Streptococcus pneumoniae* is the most common responsible pathogen, *Legionella* has also been reported [38, 39]. *Legionella* was implicated as a causative agent in 1.2% of pneumonias in pregnancy [40]. Treatment is similar to that of non-pregnant women. Worse outcomes have not been described, and fetal demise rarely occurs [38, 39, 41]. Factors associated with favorable outcomes include a high index of suspicion, the institution of appropriate early therapy, and presentation in the late third trimester [38].

5. Conclusions

Appropriate and timely administration of antibiotics in patients suspected with *Legionella* infection is highly recommended. Macrolides and fluoroquinolones are considered the drugs of choice for treatment. In critically ill patients or those patients not responding appropriately, combination therapy should be considered

with careful evaluation of side effects and drug interactions. As for other infections, outcomes are not only related to the choice of antibiotics but also specific host factors and aggressive supportive measures. Furthermore, it is important to review antibiotic resistance patterns not only in clinical patients but also in environmental strains that are a potential source of the clinical infections [18].

Conflict of interest

The authors have no conflict of interest to declare.

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