Antimicrobial Therapy for Legionnaire's Disease

Antibiotic Stewardship Implications

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KEYWORDS

• Legionnaire's disease • Antimicrobial therapy • Community-acquired pneumonia
• Antimicrobial stewardship • Doxycycline

KEY POINTS

- Effective antibiotic therapy for legionnaire's disease is based on anti-*Legionella* activity and high antibiotic concentrations in alveolar macrophages.
- Antibiotics used for legionnaire's disease include doxycycline, quinolones, and azithromycin. Alternately, tigecycline, trimethoprim-sulfamethoxazole, and rifamycin are also effective in legionnaire's disease.
- Legionnaire's disease outcomes depend not only on effective anti-*Legionella* therapy but also, importantly, on host factors (ie, cardiopulmonary function, degree or duration of impaired cell-mediated immunity, and immunomodulatory or immunosuppressive drugs).
- When the pathogen is unknown, empiric therapy for community-acquired pneumonia has been with a ß-lactam plus an anti-*Legionella* antibiotic.
- If legionnaire's disease is likely, based on characteristic extrapulmonary findings, monotherapy with an anti-*Legionella* antibiotic provides effective therapy.

BACKGROUND

Effective antibiotic therapy against legionnaire's disease depends on the antibiotic's degree of anti-*Legionella* activity and ability to concentrate in alveolar macrophages (AMs), the primary site of infection in the lung in legionnaire's disease.[1–10] Antibiotics with anti-*Legionella* activity that do not penetrate into AMs are clinically ineffective.[7,11,12] The anti-*Legionella* antibiotic concentrations in AMs range from 10 to 30 times greater than serum concentrations.[3,4,6] Differences in serum concentration or relative minimum inhibitory concentrations are clinically irrelevant considering the supratherapeutic serum concentrations in AMs.[2,10] (**Table 1**). Effectiveness of

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Table 1
Pharmacokinetic determinants of antibiotic penetration into alveolar macrophages in legionnaire's disease

Antibiotic-Penetration Pharmacokinetic Factors into AMs		Clinically Useful Anti-*Legionella* Antibiotics with High AM Levels
Optimal AM Penetration (eg, Doxycycline, Quinolones) Major Factors • Lipid solubility = high V_d (>0.4 L/kg) • Low protein binding • Active intracellular antibiotic transport • Concentrated to AM levels (10–30 × simultaneous serum levels) Minor Factors • Molecular size • pKa • Degree of inflammation	Poor AM Penetration (eg, ß-lactams) • Low lipid solubility = low V_d (~0.2 L/kg) • Relatively high protein binding • Low intracellular AM levels (<10% of simultaneous serum levels)	Preferred Therapy • Doxycycline • Macrolides • Quinolones Alternate Therapy • Tigecycline • TMP-SMX • Rifampin

Abbreviations: pKa, ionization potential; V_d, volume of distribution.
[a] Imipenem has anti-*Legionella* activity in vitro but does not concentrate in AM and is not effective in Legionnaire's disease. Some other antibiotics (eg, clindamycin and chloramphenicol) concentrate in AM but have no anti-*Legionella* activity.

antibiotic therapy for legionnaire's disease also depends on host factors (ie, preexisting cardiopulmonary status, intactness of cell-mediated immunity [CMI], and early initiation of therapy).[13–15] The commonly used antibiotics with demonstrated clinical effectiveness in legionnaire's disease are doxycycline, trimethoprim-sulfamethoxazole (TMP-SMX), rifampin, quinolones, macrolides, and tigecycline.[14–20] These antibiotics have been used in treating legionnaire's disease alone or in combination.[21–25] With effective early therapy, there is slow clinical improvement over 5 to 7 days. Duration of therapy is important to assure cure as well as preventing relapse, not uncommon with less than 2 weeks of therapy.[26,27] Legionnaire's disease severity relates to inoculum size and host factors (ie, degree of decreased T-lymphocyte function or CMI).[27] Decreased CMI may be due to age and concurrent immunomodulating infections; for example, cytomegalovirus or disorders associated with impaired CMI (eg, human immunodeficiency virus, cancer chemotherapy, steroids, and immunomodulatory or immunosuppressive agents such as anti-TNF-α).[28–32] Clearly, early therapy is associated with better outcomes than late therapy and suboptimal therapy results in worse outcomes than optimal antibiotic therapy.[33] Careful analysis is needed in interpreting effectiveness of antibiotic therapy in legionnaire's disease because many nonsevere cases of community-acquired pneumonia (CAP) due to legionnaire's disease will improve or resolve with no therapy or suboptimal therapy (eg, imipenem).[11,12,32]

PHARMACOKINETIC CONSIDERATIONS

Historically, optimal monotherapy for legionnaire's disease has been with doxycycline, a quinolone, or azithromycin.[16,19,20,22,32] Therapeutic failures have been related to host factors.[34,35] Particularly in severe cases, rifampin or TMP-SMX have been used

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