

Levofloxacin for the Treatment of Respiratory Tract Infections Based on Treatment Guidelines



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Due to the persistent and continuous increase of antimicrobial resistance, therapeutic strategies should be aimed at decreasing the emergence of resistant strains and ensuring clinical efficacy. Treatment of respiratory tract infections (RTIs) is, for the most part empirical, therefore any antibiotic treatment should cover both typical and atypical pathogens.

Most guidelines recommend levofloxacin for the treatment of outpatients with community-acquired pneumonia (CAP), who have comorbidities or recent antibiotic exposure. Evidence from clinical trials of levofloxacin indicates that fluoroquinolone monotherapy provides clinical efficacy for hospitalized CAP patients and supports the use of high-dose levofloxacin (750 mg) for nosocomial pneumonia. Because of its excellent penetration, favorable pharmacodynamic profile and, unlike aminoglycosides, lower nephrotoxicity, current American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) guidelines for the treatment of hospital-acquired pneumonia (HAP) recommend levofloxacin for early- and late-onset HAP. The Canadian Thoracic Society and Canadian Infectious Disease Society guidelines recommend fluoroquinolones as potential first-line therapy for patients with acute exacerbations of chronic bronchitis (AECB) and other risk factors. Levofloxacin is also the preferred oral agent for the treatment of drug-resistant tuberculosis or when first-line agents cannot be used because of intolerance.

Levofloxacin is beneficial because it has low resistance, good activity and high respiratory penetration, and is well tolerated. It can be easily switched from intravenous to oral therapy, and it can be used as short-course, high-dose therapy to help decrease the emergence of resistant strains. Levofloxacin is therefore a promising agent for the first-line treatment of RTIs.

Introduction

Respiratory tract infections (RTIs) are a frequent cause of morbidity and mortality worldwide. Pneumonia is the sixth-leading cause of death in the USA, and in Taiwan it was responsible for 24.44 deaths per 100,000 population in 2004. The burden of cost of treatment of RTIs is also very high throughout the world, therefore, determining the best way to treat RTIs is a very important issue. In this article, we attempt to focus on the review of levofloxacin for the treatment of RTIs. Levofloxacin has been available for a long time and currently remains very active against the majority of common bacterial respiratory tract pathogens.

The characteristics of levofloxacin

Levofloxacin has low resistance, good activity levels and high respiratory penetration, and it is well tolerated with good adherence (1–6). In addition, levofloxacin is particularly well suited for shorter courses of therapy at higher doses (7).

Short-course, high-dose therapy may reduce the emergence of resistant strains, decrease the impact on endogenous flora, and offer high cure rates. Additionally, short-course, high-dose therapy results in less total drug exposure, avoidance of adverse effects, enhanced patient and healthcare convenience, and greater adherence. High-dose, short-course levofloxacin (750 mg for 5 days) therapy has been found effective in eradicating *Streptococcus pneumoniae* and reducing relapse.

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In a multicenter, randomized, double-blind investigation of 530 patients with mild-to-severe community-acquired pneumonia (CAP), levofloxacin 750 mg daily for 5 days was compared with levofloxacin 500 mg daily for 10 days. Clinical success rates were comparable in both groups, at 92.4% for the 750-mg group and 91.1% for the 500-mg group. At day three, 67.4% of patients in the 750-mg group reported resolution of fever, compared with 54.6% of patients in the 500-mg group. The 750-mg dose increased the area under the curve (AUC) /minimum inhibitory concentration (MIC) and peak concentration (C_{max})/MIC by increasing peak antibiotic concentration, which may reduce the risk of resistant organisms (7). This higher dose and shorter course regimen was well tolerated, reduced total antimicrobial exposure by 25%, resolved fever significantly faster, and may reduce cost.

There is a great deal of evidence suggesting that monotherapy with levofloxacin is as effective and safe as combination therapy. A randomized, multicenter, phase 4 comparative trial ($n = 269$) demonstrated that levofloxacin monotherapy is as efficacious as combination of β -lactam and macrolide (ceftriaxone/erythromycin) therapy in the treatment of serious CAP. The clinical success rate was 89.5% in the levofloxacin group compared with 83.1% in the comparator group (8). Another study compared levofloxacin monotherapy with combination therapy of azithromycin/ceftriaxone in the treatment of moderate-to-severe CAP. The clinical success rate was 94.1% in the levofloxacin-treated group compared with 92.3% in the azithromycin/ceftriaxone-treated group (9). In addition, levofloxacin provides more pathogen coverage than either ceftriaxone or azithromycin alone. It is indicated by the US Food and Drug Administration (FDA) for penicillin-resistant *S. pneumoniae* (PRSP); neither ceftriaxone nor azithromycin is indicated for PRSP.

A prospective observational study of hospitalized CAP patients ($n = 459$) compared levofloxacin monotherapy (500 mg daily) with combination therapy (ceftriaxone 2 g daily plus clarithromycin 500 mg every 12 hours). The percentage of patients who developed acute respiratory failure due to the extension of pneumonia after admission was significantly lower in the levofloxacin group (6.0%) than in the ceftriaxone/clarithromycin group (12.4%). In all, 12% of patients in the ceftriaxone/clarithromycin group died, while only 6% of patients in the levofloxacin-treated group died (10).

Because the frequency of both penicillin resistance and multidrug resistance is increasing among *S. pneumoniae* isolates, levofloxacin or

moxifloxacin are preferred over ciprofloxacin in the treatment of pneumonia (11,12). Levofloxacin can be used to treat RTIs in which the major pathogens are Gram-negative bacteria, as evidenced by several *in vitro* studies that demonstrate the broad spectrum of Gram-negative antimicrobial activity. A comparison of *in vitro* susceptibility of levofloxacin, ciprofloxacin, and moxifloxacin against several Gram-negative clinical isolates demonstrated that susceptibility rates for ciprofloxacin and levofloxacin were > 85% for *Escherichia coli*, *Enterobacter cloacae*, *Enterobacter aerogenes*, and *Klebsiella pneumoniae*, and 80% for *Serratia* spp. and *Acinetobacter* spp. (13).

Ratios of AUC values for free drug to modal MICs for ciprofloxacin and levofloxacin were similar (> 125; target ratio for *Pseudomonas aeruginosa*), whereas the ratios for gatifloxacin and moxifloxacin were significantly lower. Levofloxacin and ciprofloxacin are considered to have comparable antipseudomonal activity on the basis of *in vitro* activity and therefore either may be used as an antipseudomonal fluoroquinolone (11,14). A recent study showed that levofloxacin monotherapy is a safe and effective treatment for Legionnaires disease, including severe disease, and that it appears to be more effective than clarithromycin (15).

Levofloxacin is effective against intracellular atypical pathogens. Bioavailability data for levofloxacin shows that blood levels are similar with either intravenous (IV) or oral (PO) administration. This makes levofloxacin ideal for switch therapy (16).

Evidence from clinical trials of levofloxacin for the treatment of hospitalized CAP patients showed it is clinically efficacious, and supports the use of high-dose levofloxacin (750 mg) for nosocomial pneumonia. Current American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) guidelines for the treatment of hospital-acquired pneumonia (HAP) recommend levofloxacin, moxifloxacin, or ciprofloxacin for early-onset HAP and levofloxacin or ciprofloxacin for late-onset HAP (17). Therefore, levofloxacin and ciprofloxacin are the only fluoroquinolones recommended for patients with or without risk factors for multidrug-resistant (MDR) pathogens, and for both early- and late-onset HAP. Of the two drugs, levofloxacin is preferred to ciprofloxacin for patients with early-onset HAP because of the coverage on drug-resistant *S. pneumoniae*.

Resistant stains

The latest data from global surveillance studies indicates that high-level resistance to penicillin (MIC ≥ 2 mg/L) among isolates of *S. pneumoniae*

varies widely by geographic location. Rates exceed 20% in the USA, Mexico, Japan, Saudi Arabia, Israel, Spain, France, Greece, Hungary, and the Slovak Republic, while in South Africa, Hong Kong, Taiwan, and South Korea rates exceed 50%.

Resistance to the macrolide (erythromycin) in *S. pneumoniae* isolates is high in Taiwan (> 90%), France (60.6%), Greece (48.6%), and Italy (35.6%), while rates are less than 15% in the Netherlands, Portugal, Austria, the Czech Republic, and Poland (5). Previous studies showed increasing trends of penicillin nonsusceptibility and erythromycin resistance among clinical isolates of *S. pneumoniae*.

The prevalence of fluoroquinolone resistance and nonsusceptibility in *S. pneumoniae* isolates increased two-fold between 1999–2000 and 2001–2002. Ciprofloxacin resistance more than doubled, rising from 1.2% to 2.7%, while levofloxacin nonsusceptibility increased from 0.6% to 1.3%. Although resistance to these two fluoroquinolones has doubled, it is still considered low (18).

β -lactamase production was found in 50–60% of *Haemophilus influenzae* isolates and more than 95% of *Moraxella catarrhalis* isolates. Nonsusceptibility to trimethoprim–sulfamethoxazole (TMP–SMX) and clarithromycin was found in 52% and 34% of *H. influenzae* isolates, respectively (4).

Treating CAP

Assessment of the likely causative pathogens and risks of infection with an antimicrobial-resistant strain are necessary to determine the most appropriate antimicrobial therapy. In the USA, the etiology of CAP was *S. pneumoniae* (20–60%), *H. influenzae* (3–10%), *Staphylococcus aureus* (3–5%), Gram-negative bacilli (3–10%), miscellaneous (including *M. catarrhalis*, group A *Streptococcus*, and *Neisseria meningitidis*; 3–5%), *Legionella* spp. (2–8%), *Mycoplasma pneumoniae* (1–6%), *Chlamydia pneumoniae* (4–6%), viruses (2–15%), and aspiration (3–6%). *S. pneumoniae* is the leading cause of bacterial CAP, followed by *H. influenzae* and atypical pathogens (17).

The treatment of CAP has evolved during the past few decades because of the increase in antimicrobial-resistant pathogens, e.g. PRSP and macrolide-resistant *S. pneumoniae* (MRSP), and the increase in prevalence of infection with atypical pathogens. Emerging resistance of *S. pneumoniae* to antimicrobial agents has affected empirical treatment of CAP, thus the need for fluoroquinolones to overcome pneumococcal resistance is clear.

Severity of infection and risk factors for drug resistance

The Pneumonia Patient Outcomes Research Team

(PORT) formulated a prediction rule to stratify patients into five classes with respect to the risk of death and adverse outcomes. This rule suggests that patients in classes I and II could possibly be treated as outpatients, patients in class III could be treated as outpatients or inpatients, and those patients in classes IV and V could be considered for hospitalization. However, the use of this approach has several limitations, especially when applied to those with social needs or the very young or very old (19).

Drug resistance, especially penicillin resistance, is a worldwide problem, and recognition of risk factors for infection with resistant pathogens can aid in the selection of an appropriate antimicrobial agent. The Alexander Project is a multinational, longitudinal surveillance program that has monitored the susceptibility of respiratory tract pathogens to antimicrobials since 1992. It has revealed growing resistance among *S. pneumoniae* isolates to penicillin and macrolides (5).

The ATS guidelines identify risk factors for penicillin-resistant pneumococci as age > 65 years, β -lactam use within the previous three months, alcoholism, immunosuppressive diseases, corticosteroid use, medical comorbidities, and exposure to a child who attends daycare. The ATS guidelines also recognize risk factors for infection with enteric Gram-negative organisms and *P. aeruginosa*. Patients who reside in a nursing home, have underlying cardiopulmonary disease or multiple comorbidities, or who have received recent antimicrobial therapy are more prone to infection with enteric Gram-negative organisms. Risk factors for *P. aeruginosa* include structural lung disease (bronchiectasis), corticosteroid use (prednisone > 10 mg/day), recent broad-spectrum antimicrobial use (> 7 days within the past month), and malnutrition (17).

Fluoroquinolones in CAP guidelines

Empiric antimicrobial treatment should be initiated based on the most likely pathogen and the antimicrobial susceptibility of the pathogen, as well as the patient's age, comorbidities, concomitant medications, severity of illness (17), and any medication allergies the patient may have. A recent analysis of US Medicare hospitalization rates showed improved outcomes with initiation of antimicrobial therapy within 4 hours of arrival at the hospital (20,21).

The 2001 ATS guidelines (Table 1, 2, 3) recommend fluoroquinolone monotherapy for outpatients with cardiopulmonary disease and/or a modifying factor, and inpatients not in the intensive care unit (ICU). For those patients in the ICU, fluoroquinolones combined with other

Table 1. Outpatients with cardiopulmonary disease and/or other modifying factors^{a,b}

Organisms	Therapy ^c
<i>Streptococcus pneumoniae</i> (including DRSP)	β-lactam (oral cefpodoxime, cefuroxime, high-dose amoxicillin, amoxicillin–clavulanate; or parenteral ceftriaxone followed by oral cefpodoxime)
<i>Mycoplasma pneumoniae</i>	
<i>Chlamydia pneumoniae</i>	
Mixed infection (bacteria plus atypical pathogen or virus)	<i>plus</i>
<i>Haemophilus influenzae</i>	Macrolide or doxycycline ^d
Enteric Gram-negatives	
Respiratory viruses	<i>or</i>
Miscellaneous	
<i>Moraxella catarrhalis</i> , <i>Legionella</i> spp., <i>Mycobacterium tuberculosis</i> , aspiration (anaerobes), endemic fungi	Antipneumococcal fluoroquinolone (used alone)

^a Excludes patients at risk for HIV.

^b In roughly 50–90% of the cases, no etiology was identified.

^c In no particular order.

^d High-dose amoxicillin is 1 g every 8 hours; if a macrolide is used, erythromycin does not provide coverage of *H. influenzae*, and thus when amoxicillin is used, the addition of doxycycline or of an advanced-generation macrolide is required to provide adequate coverage of *H. influenzae*.

Abbreviations: DRSP = drug-resistant *Streptococcus pneumoniae*, spp. = species.

Adapted from reference (17).

antibiotics is one choice (17).

In the 2003 IDSA guidelines, fluoroquinolone monotherapy is recommended for outpatients that have recently received antimicrobials or have comorbidities, or with influenza and bacterial super infection, or in nursing home patients. Fluoroquinolone monotherapy is also a choice for inpatients not in the ICU. Patients admitted to the ICU for whom pseudomonal infection is not a concern can be treated with a β-lactam combined with azithromycin, clarithromycin, or a fluoroquinolone (21).

The 2000 Canadian guidelines for the initial management of CAP recommend respiratory fluoroquinolone monotherapy for outpatients with modifying factors and nursing home residents. Respiratory fluoroquinolone monotherapy is also a choice for inpatients not in the ICU, while fluoroquinolones combined with other antibiotics are recommended for patients in the ICU (22).

Consensus recommendations sponsored by the Texas Academy of Family Physicians and the Primary Care Education Group, suggest that fluoroquinolone monotherapy or combination therapy is appropriate for patients with comorbid medical conditions, those who had antibiotic therapy within the previous three months, and for penicillin-resistant pneumococci and Gram-negative pathogens (23).

Treating HAP, VAP, and HCAP

The 2005 ATS/IDSA guidelines (Table 4, 5) indicate that antibiotic selection for the treatment of HAP, ventilator-associated pneumonia (VAP),

and healthcare-associated pneumonia (HCAP) should be based on the risk factors for MDR pathogens and the time of onset. If there is early onset (< 5 days) and no risk factors for MDR, limited-spectrum antibiotic monotherapy (fluoroquinolone or ceftriaxone or ampicillin–sulbactam or ertapenem) is recommended. In patients with late onset (≥ 5 days) or risk factors for MDR pathogens, broad-spectrum antibiotic combination therapy for MDR pathogens (antipseudomonal cephalosporin or antipseudomonal carbapenem or β-lactam/β-lactamase inhibitor plus antipseudomonal fluoroquinolone or aminoglycoside plus linezolid or vanomycin) is recommended (11).

Acute exacerbations of chronic bronchitis

Infection of the lower respiratory tract has been suggested to account for up to 80% of acute exacerbations of chronic bronchitis (AECB) episodes. There are three classes of pathogens commonly implicated in exacerbation: respiratory viruses, atypical bacteria, aerobic Gram-positive and Gram-negative bacteria.

Respiratory viruses with or without a superimposed bacterial infection are associated with 30% of cases. Significant viral pathogens include influenza, parainfluenza, and rhinovirus. Atypical bacteria, mostly *C. pneumoniae*, are implicated in < 10% of cases. Aerobic Gram-positive and Gram-negative bacteria occur in approximately 40–60% of all cases. New sampling techniques, including protected specimen sampling, have found *P. aeruginosa* and other Gram-negative bacilli in a high percentage of patients (28% in one study) (24).

Table 2. Inpatients not in ICU^{a,b}

A. Cardiopulmonary disease and/or modifying factors (including being from a nursing home)	
Organisms	Therapy ^c
<i>Streptococcus pneumoniae</i> (including DRSP)	Intravenous β -lactam ^d (cefotaxime, ceftriaxone, ampicillin–sulbactam, high-dose ampicillin)
<i>Haemophilus influenzae</i>	
<i>Mycoplasma pneumoniae</i>	
<i>Chlamydia pneumoniae</i>	plus
Mixed infection (bacteria plus atypical pathogen)	Intravenous or oral macrolide or doxycycline ^e
Enteric Gram-negatives	or
Aspiration (anaerobes)	
Viruses	Intravenous antipneumococcal fluoroquinolone (used alone)
<i>Legionella</i> spp.	
Miscellaneous	
<i>Mycobacterium tuberculosis</i> ,	
<i>Pneumocystis carinii</i> , endemic fungi	
B. No cardiopulmonary disease, no modifying factors	
Organisms	Therapy ^c
<i>S. pneumoniae</i>	Intravenous azithromycin alone
<i>H. influenzae</i>	
<i>M. pneumoniae</i>	If macrolide allergic or intolerant: Doxycycline and a β -lactam
<i>C. pneumoniae</i>	
Mixed infection (bacteria plus atypical pathogen)	or
Viruses	Monotherapy with an antipneumococcal fluoroquinolone
<i>Legionella</i> spp.	
Miscellaneous	
<i>M. tuberculosis</i> ,	
<i>P. carinii</i> , endemic fungi	

^a Excludes patients at risk for HIV.

^b In roughly one-third to one-half of the cases, no etiology was identified.

^c In no particular order.

^d Antipseudomonal agents such as cefepime, piperacillin–tazobactam, imipenem, and meropenem are generally active against DRSP, but not recommended for routine use in this population that does not have risk factors for *P. aeruginosa*.

^e Use of doxycycline or an advanced generation macrolide (azithromycin or clarithromycin) will provide adequate coverage if the selected β -lactam is susceptible to bacterial β -lactamase.

Abbreviations: ICU = intensive care unit, DRSP = drug-resistant *Streptococcus pneumoniae*, spp. = species.

Adapted from reference (17).

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines 2004 strongly recommend the use of antibiotics to manage exacerbations of chronic obstructive pulmonary disease (COPD). Because there is no rapid, reliable way to identify the pathogens responsible, physicians must rely on clinical judgment and epidemiologic factors to predict the most likely cause.

The ATS/European Respiratory Society (ERS) 2004 guidelines recommend that antimicrobial choice for the treatment of COPD for outpatients should be based on local bacterial resistance patterns. Amoxicillin/ampicillin, cephalosporins, doxycycline, or macrolides are suggested. If the patient has previously failed on antibiotic therapy, treatment should be changed to amoxicillin–clavulanate or a respiratory fluoroquinolone. Hospitalized patients should also receive amoxicil-

lin–clavulanate or a respiratory fluoroquinolone, while combination therapy should be considered if *Pseudomonas* spp. and/or other *Enterobacteriaceae* spp. are suspected (25).

The current guidelines of the Canadian Thoracic Society and Canadian Infectious Disease Society recommend macrolides as first-line treatment for AECB patients without risk factors. Risk factors include forced expiratory volume in one second (FEV₁) < 50% of predicted, > 4 exacerbations per year, and comorbid conditions. Fluoroquinolones are recommended as potential first-line therapy for patients with AECB who have risk factors (26).

Levofloxacin for pulmonary tuberculosis

The 2003 ATS guidelines, recommend levofloxacin as the preferred oral treatment for drug-resis-

Table 3. ICU-admitted patients^{a,b}

A. No risk for <i>Pseudomonas aeruginosa</i>	
Organisms	Therapy ^{c,d}
<i>Streptococcus pneumoniae</i> (including DRSP)	Intravenous β -lactam (cefotaxime, ceftriaxone) ^d
<i>Legionella</i> spp.	<i>plus either</i>
<i>Haemophilus influenzae</i>	
Enteric Gram-negative bacilli	Intravenous macrolide (azithromycin)
<i>Staphylococcus aureus</i>	<i>or</i>
<i>Mycoplasma pneumoniae</i>	
Respiratory viruses	Intravenous fluoroquinolone
Miscellaneous	
<i>Chlamydia pneumoniae</i> , <i>Mycobacterium tuberculosis</i> , endemic fungi	
B. Risk for <i>Pseudomonas aeruginosa</i> ^e	
Organisms	Therapy ^{c,d}
All of the above pathogens	Selected intravenous antipseudomonal β -lactam (cefepime, imipenem, meropenem, piperacillin–tazobactam) ^f
<i>plus</i>	<i>plus</i>
<i>P. aeruginosa</i>	Intravenous antipseudomonal quinolone (ciprofloxacin)
	<i>or</i>
	Selected intravenous antipseudomonal β -lactam (cefepime, imipenem, meropenem, piperacillin–tazobactam) ^f
	<i>plus</i>
	Intravenous aminoglycoside
	<i>plus either</i>
	Intravenous macrolide (azithromycin)
	<i>or</i>
	Intravenous antipseudomonal fluoroquinolone

^a Excludes patients at risk for HIV.

^b In roughly one-third to one-half of the cases, no etiology was identified.

^c In no particular order.

^d Antipseudomonal agents such as cefepime, piperacillin–tazobactam, imipenem, and meropenem are generally active against DRSP and other likely pathogens in this population, but not recommended for routine use unless the patient has risk factors for *P. aeruginosa*.

^e Combination therapy required.

^f If β -lactam allergic, replace the listed β -lactam with aztreonam and combine with an aminoglycoside and an antipneumococcal fluoroquinolone as listed.

Abbreviations: ICU = intensive care unit, DRSP = drug-resistant *Streptococcus pneumoniae*, spp. = species.

Adapted from reference (17).

tant tuberculosis caused by organisms known or presumed to be sensitive to this antimicrobial or when first-line agents cannot be used because of intolerance. This is based on the cumulative experience that suggests a good safety profile with long-term use of levofloxacin. The concentration in cerebrospinal fluid (CSF) after administration of a standard dose of levofloxacin is 16–20%. Drug levels are not affected by hepatic disease and levofloxacin is presumed safe for use in patients with

severe liver disease. However, as with all drugs, it should be used with caution (27).

Conclusion

Levofloxacin is broad spectrum antimicrobial that has low resistance, good activity and high respiratory penetration. It is well tolerated and can easily be switched from IV to PO therapy. Levofloxacin is also beneficial because it can be used as short-course, high-dose therapy, which may decrease the

Table 4. Initial empiric antibiotic therapy for HAP or VAP in patients with no known risk factors for multidrug-resistant pathogens, early-onset, and any disease severity

Potential pathogen	Recommended antibiotic
<i>Streptococcus pneumoniae</i> ^a	Ceftriaxone
<i>Haemophilus influenzae</i>	<i>or</i>
Methicillin-sensitive <i>Staphylococcus aureus</i>	
Antibiotic-sensitive enteric Gram-negative bacilli	Levofloxacin, moxifloxacin or ciprofloxacin
<i>Escherichia coli</i>	<i>or</i>
<i>Klebsiella pneumoniae</i>	
<i>Enterobacter</i> spp.	Ampicillin–sulbactam
<i>Proteus</i> spp.	<i>or</i>
<i>Serratia marcescens</i>	Ertapenem

^a The frequency of penicillin-resistant *S. pneumoniae* and multidrug-resistant *S. pneumoniae* is increasing; levofloxacin or moxifloxacin are preferred to ciprofloxacin and the role of other new quinolones, such as gatifloxacin, has not been established. Abbreviations: HAP = hospital-acquired pneumonia, VAP = ventilator-associated pneumonia, spp. = species. Adapted from reference (11)

Table 5. Initial empiric therapy for HAP, VAP, and HCAP in patients with late-onset disease or risk factors for multidrug-resistant pathogens and all disease severity

Potential pathogen	Combination antibiotic therapy ^a
<i>Streptococcus pneumoniae</i>	Antipseudomonal cephalosporin (cefepime, ceftazidime)
<i>Haemophilus influenzae</i>	<i>or</i>
Methicillin-sensitive <i>Staphylococcus aureus</i>	
Antibiotic-sensitive enteric Gram-negative bacilli	Antipseudomonal carbapenem (imipenem or meropenem)
<i>Escherichia coli</i>	<i>or</i>
<i>Klebsiella pneumoniae</i>	
<i>Enterobacter</i> spp.	β-lactam/β-lactamase inhibitor (piperacillin–tazobactam)
<i>Proteus</i> spp.	<i>plus</i>
<i>Serratia marcescens</i>	
MDR pathogens	Antipseudomonal fluoroquinolone ^b (ciprofloxacin or levofloxacin)
<i>Pseudomonas aeruginosa</i>	
<i>Klebsiella pneumoniae</i> (ESBL+) ^b	<i>or</i>
<i>Acinetobacter</i> spp. ^b	
Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)	Aminoglycoside (amikacin, gentamicin, or tobramycin)
<i>Legionella pneumophila</i> ^b	<i>plus</i>
	Linezolid or vancomycin ^c

^a Initial antibiotic therapy should be adjusted or streamlined on the basis of microbiologic data and clinical response to therapy.

^b If an ESBL+ strain, such as *K. pneumoniae*, or an *Acinetobacter* spp. is suspected, a carbapenem is a reliable choice. If *L. pneumophila* is suspected, the combination antibiotic regimen should include a macrolide (e.g., azithromycin) or a fluoroquinolone (e.g., ciprofloxacin or levofloxacin) should be used rather than an aminoglycoside.

^c If MRSA risk factors are present or there is a high incidence locally.

Abbreviations: HAP = hospital-acquired pneumonia, VAP = ventilator-associated pneumonia, HCAP = healthcare-associated pneumonia, spp. = species, MDR = multidrug-resistant, ESBL+ = extended-spectrum β-lactamases positive.

Adapted from reference (11).

emergence of resistant strains. The persistent and continuous increase of resistance means that therapeutic strategies should be aimed at decreasing the emergence of resistant strains and ensuring clinical efficacy. Because the treatment of RTIs is

primarily empirical, antibiotic treatment should cover both typical and atypical pathogens. Levofloxacin is therefore a promising agent of first-line treatment of RTIs.

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