The American Journal of Medicine (2005) Vol 118 (7A), 29S–38S

ELSEVIER

THE AMERICAN JOURNAL of MEDICINE®

Antimicrobial treatment of lower respiratory tract infections in the hospital setting

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KEYWORDS:
Antibiotics;
Community-associated pneumonia;
Healthcare-associated;
Hospital-acquired;
Quinolones;
Ventilator-associated

Respiratory tract infections (RTIs) that may require hospitalization include acute exacerbations of chronic bronchitis (AECB), community-acquired pneumonia (CAP), and hospital-acquired pneumonia (HAP), which includes ventilator-associated pneumonia (VAP). Healthcare-associated pneumonia (HCAP) is treated similar to HAP and may be considered with HAP. For CAP requiring hospitalization, the current guidelines for the treatments of RTIs generally recommend either a β-lactam and macrolide combination or a fluoroquinolone. The respiratory fluoroquinolones (levofloxacin, gatifloxacin, moxifloxacin, and gemifloxacin) are excellent antibiotics due to high levels of susceptibility among gram-negative, gram-positive, and atypical pathogens. The fluoroquinolones are active against >98% of *Streptococcus pneumoniae*, including penicillin-resistant strains. Fluoroquinolones are also recommended for AECB requiring hospitalization. Evidence from clinical trials suggests that levofloxacin monotherapy is as efficacious as combination ceftriaxone-erythromycin therapy in the treatment of patients hospitalized with CAP. For early-onset HAP, VAP, and HCAP without the risk of multidrug resistance, ceftriaxone, ampicillin-sulbactam, ertapenem, or one of the fluoroquinolones is recommended. High-dose, short-course therapy regimens may offer improved treatment due to higher drug concentrations, more rapid killing, increased adherence, and the potential to reduce development of resistance. Recent studies have shown that short-course therapy with levofloxacin, azithromycin, or telithromycin in patients with CAP was effective, safe, and tolerable and may control the rate of resistance.

Lower respiratory tract infections (RTIs) are the main cause of death due to infectious disease in the United States.[1] RTIs treated in the hospital include severe cases of acute exacerbations of chronic bronchitis (AECB) and community-acquired pneumonia (CAP) as well as hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP) and healthcare-associated pneumonia (HCAP). Pneumonia alone is the sixth most common cause of death, with 2 to 3 million cases of CAP and 45,000 deaths occurring each year.[1] About 300,000 cases of HAP occur annually, and HAP has an attributable mortality rate of approximately 33% to 50%.[2] Chronic obstructive pulmonary disease (COPD), which is characterized by AECB, results in approximately 119,000 deaths per year in the United States.[3]

Direct costs of RTIs such as AECB are estimated to cost US$1.2 billion for patients aged ≥65 years and $419 million for patients <65 years.[4] The cost of care for CAP is estimated between $8.4 billion and $9.7 billion dollars annually.[5] Finally, HAP results in $2 billion of direct costs annually.[2] In total, these add up to over $12 billion annually. In 1997 the cost to US employers of patients with respira-

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0002-9343/$ -see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.amjmed.2005.05.011

tory infections was $112 billion, including direct costs of medical treatment and indirect costs of time lost from work.[6]

The decision to admit a patient with either CAP or AECB to the hospital is based on the severity of symptoms. For patients with CAP, the American Thoracic Society (ATS) and the Texas Academy of Family Physicians recommend using the Patient Outcomes Research Team (PORT) Severity Index (PSI) as a guideline to stratify patients.[7,8] The index uses demographic factors, coexisting conditions, and physician and laboratory findings to divide patients into 5 risk classes. It is recommended that patients in the fourth and fifth classes (i.e., those with the most severe illness) be hospitalized.[7] ATS guidelines note that the PSI should be used in conjunction with good clinical judgment, taking into consideration risk factors for a complicated course as well as potential nonmedical reasons for admission.[8] However, the PORT approach may oversimplify the process of risk stratification of individual patients even when their severity of illness is profoundly different.[8] Additionally, it gives heavy emphasis on age as a variable, requiring physicians to collect more data for younger patients to categorize them in a risk group. Finally, PORT scores do not include rare clinical conditions such as severe neuromuscular disease as factors in the prediction rules, thus affecting final scores.[8] PORT scores also are cumbersome to obtain and difficult to use.

The validity of the PSI system to determine treatment in outpatient care versus hospitalization was confirmed in a low-risk subset of CAP patients.[9] For selected patients, outpatient care was as safe and effective as hospitalization. Further support for the use of PSI in guiding the admission decision for low risk CAP patients was seen in separate studies in hospitals in Canada and the United States, which resulted in admission of fewer low-risk patients without compromising the effectiveness of treatment or well-being of the outpatients.[10,11]

The decision to admit a patient with COPD who is experiencing an AECB is based on the number of symptoms and risk factors. Symptoms include shortness of breath, increased sputum production, and increased sputum purulence. Risk factors for hospitalization include percentage of predicted forced expiratory volume in 1 minute (FEV_1), ischemic heart disease, and mucous hypersecretion.[7]

Inappropriate antibiotic therapy, or overuse and/or misuse of antibiotics, is a common occurrence that may increase a patient's duration of stay in the hospital, and may predispose patients to increased resistance to a class of antibiotics.[12,13] A study in the United States on excessive antibiotic use in acute respiratory infections involving the upper and lower respiratory tract showed that 55% of the total prescriptions in 1998 were prescribed in excess.[12] Additionally, inappropriate initial antibiotic therapy may increase hospital mortality rates for patients in hospital intensive care units (ICUs). For example, a retrospective study in France for the outcomes of VAP patients between 1992 and1997 found initial antibiotic therapy was appropriate in 49.5% of patients (N = 111). The study concluded that, in comparison with appropriate initial antibiotic treatment, inappropriate initial antibiotic treatment could increase the duration of stay and the crude hospital mortality in VAP patients for patients with equal severity of illness at the time of VAP diagnosis.[13]

As described below, major recommendations set forth by various healthcare groups aim at avoiding unnecessary and inappropriate therapy, particularly when selecting initial antibiotic treatment options for a patient admitted with an RTI.

The Council for Appropriate and Rational Antibiotic Therapy Criteria

A number of health organizations, including the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC), are currently spearheading efforts to reduce the incidence of antibiotic resistance.[14–16] The WHO emphasizes the importance of choosing the correct drug at the correct dose for the correct duration of treatment to control resistance. In today's environment, many treatment options are available. The Council for Appropriate and Rational Antibiotic Therapy (CARAT) has defined the following 5 core criteria to assist clinicians in determining the right drug, right dose, and right duration of treatment to improve outcomes and decrease the risk of future resistance: (1) evidence-based results; (2) therapeutic benefits; (3) safety; (4) optimal drug for optimal duration; and (5) cost-effectiveness. This article discusses the application of these criteria to the management of CAP and AECB due to bacteria, or acute bacterial exacerbations of chronic bronchitis (ABECB), in the hospital setting.

Evidence-based results

Management of CAP in the hospital setting

The importance of appropriate treatment is underlined by the data: each year in the United States there are 45,000 deaths, 10 million physician visits, and 500,000 hospitalizations due to CAP. Among hospitalized patients with CAP, the average mortality is approximately 14%.[1,17] However, better management may help to improve patient care.

Despite efforts to control antibiotic resistance, which is believed to be caused mainly by the overuse and misuse of antibiotics, patients with RTIs are frequently treated with antibiotics that are incorrect, suboptimal, or unwarranted.[18] The CARAT guidelines recommend determining a need for antimicrobial treatment before prescribing antibiotics.

A number of established guidelines provide evidence-based recommendations for treatment (**Table 1**).[1,8,19,20] The ATS, the British Thoracic Society (BTS), and the Infectious Diseases Society of America (IDSA) all recom-

Table 1 Community-acquired pneumonia treatment guidelines for inpatients

Treatment	IDSA	ATS	BTS
Early treatment	Prompt treatment; 8-hr delay associated with increased mortality	First dose within 8 hr of admission	Within 2 hr; immediate treatment if life-threatening or if admission is delayed
Non-ICU	FQ preferred, or a cephalosporin-macrolide	IV macrolide if no risk of DRSP, gram negative, or aspiration; if risk exists, β-lactam–macrolide or FQ alone	β-Lactam–macrolide; FQ in patients intolerant of penicillin or macrolides; levofloxacin combined with another agent active against *Streptococcus pneumoniae*
ICU	If *Pseudomonas* not an issue, β-lactam–macrolide or FQ; if *Pseudomonas* an issue, antipseudomonal agent + ciprofloxacin, or an aminoglycoside + FQ or macrolide	β-Lactam–macrolide or quinolone + 2 antipseudomonals in at-risk patients	β-Lactam–macrolide or cefuroxime, cefotaxime, or ceftriaxone, plus erythromycin or clarithromycin; alternatively, FQ with enhanced antipneumococcal agent, e.g., benzylpenicillin (all IV)

ATS = American Thoracic Society; BTS = British Thoracic Society; DRSP = drug-resistant S *pneumoniae*; FQ = fluoroquinolone; ICU = intensive care unit; IDSA = Infectious Diseases Society of America; IV = intravenous.

Adapted from Clin Infect Dis,[1,20] *Am J Respir Crit Care Med*,[8] and *Thorax*.[19]

mend that inpatients with CAP receive prompt antibiotic treatment.[1,18–20] The 2003 IDSA guidelines for CAP note that initial therapy of patients within 4 hours after arrival at the hospital was associated with improved outcomes and reduced mortality in the hospital.[20,21]

Guidelines delineate a role for fluoroquinolones for both non-ICU and ICU patients (see Table 1), either as first-line monotherapy or as part of combination therapy.[1,8,19,20] The ATS recommends respiratory fluoroquinolones, such as levofloxacin, gatifloxacin, moxifloxacin, and gemifloxacin, for their ability to cover gram-negative, gram-positive, and atypical pathogens, generally with once-daily therapy.[8] These newer fluoroquinolones show greater in vitro activity against respiratory pathogens, particularly *Streptococcus pneumoniae*, regardless of susceptibility to penicillin.[19] Despite >20 years of clinical use, fluoroquinolones are active against >98% of *S pneumoniae* strains in the United States, including penicillin-resistant strains.[20] This may give respiratory fluoroquinolones a more prominent role in the future if bacterial resistance to penicillin and macrolides continues to increase.[19] The respiratory fluoroquinolones are also active against *Haemophilus influenzae*, atypical pathogens and *Legionella* species.[19]

ATS guidelines also recommend starting patients on intravenous (IV) therapy but switching to oral therapy when possible. Switch therapy may be either sequential or step-down. When an agent attains the same serum levels when given by IV or orally, as with doxycycline, linezolid, and some quinolones, the switch is considered sequential therapy. When decreased serum levels are achieved with oral dosing, such as with β-lactams and macrolides, the switch is considered step-down therapy. Although good clinical results have been documented with either approach, agents with similar serum levels when dosed either by IV or orally may allow for some moderately severe patients to be treated outside of the hospital and may also allow for a more rapid IV-to-oral switch and subsequent discharge.[8]

Treatment with a β-lactam and macrolide combination is often recommended for CAP requiring hospitalization. Generally, combination therapy requires more complicated dosing regimens, which may decrease patient compliance. Additionally, combination therapy is associated with the adverse event profiles of the individual agents, such that there is increased risk of adverse events as well as greater chances of drug–drug interactions. A meta-analysis of all prospective randomized trials compared β-lactam with β-lactam and aminoglycoside in patients with sepsis, 1200 of whom were infected with either HAP or CAP. The study found a significantly higher rate of nephrotoxicity with β-lactam and aminoglycoside combination therapy than with β-lactam monotherapy.[22]

In addition, there is a great deal of evidence suggesting monotherapy with a fluoroquinolone 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 β-lactam and macrolide (ceftriaxone-erythromycin) therapy in the treatment of serious CAP. The results are shown in **Table 2**.[23] In the clinically evaluable population, 89.5% of patients achieved clinical success in the levofloxacin group compared with 83.1% of patients in the comparator group (95% confidence interval [CI], −16.8 to 4.2).[23]

Another study that compared levofloxacin monotherapy with combination therapy was a phase 4, multicenter, open-label, randomized trial that compared levofloxacin monotherapy with azithromycin-ceftriaxone in the treatment of moderate-to-severe CAP. In the clinically evaluable population, the clinical success rate (including both cured and

improved patients) was 94.1% in the levofloxacin-treated group compared with 92.3% in the azithromycin-ceftriaxone–treated group. Microbiologic eradication rates were 89.5% in the levofloxacin-treated group and 92.3% in the azithromycin-ceftriaxone–treated group.[24] In addition to clinical data, levofloxacin provides more pathogen coverage than either ceftriaxone or azithromycin alone, and is also indicated by the US Food and Drug Administration (FDA) for penicillin-resistant *S pneumoniae* (PRSP); neither ceftriaxone nor azithromycin has received this indication.[25–27]

A prospective, observational study of hospitalized CAP patients (N = 459) compared monotherapy with levofloxacin (500 mg every 24 hours) with combination therapy (ceftriaxone 2 g every 24 hours plus clarithromycin 500 mg every 12 hours). The percentage of patients who developed acute respiratory failure due to extension of pneumonia after admission was significantly lower in the levofloxacin group than in the ceftriaxone-clarithromycin group (6.0% vs. 12.4%, respectively; $P = 0.02$). Decompensation of baseline disease was seen more frequently in the ceftriaxone-clarithromycin group than in the levofloxacin group (combination therapy vs levofloxacin, 4.8% vs 3.2%; $P = 0.038$). Median total treatment duration was 10 days in the levofloxacin group and 12 days in the ceftriaxone-clarithromycin group ($P = 0.06$). No significant differences were identified in rate of pleural effusion, acute respiratory failure, heart failure, severe sepsis, or renal failure. In all, 12% of patients in the ceftriaxone-clarithromycin group died compared with 6% of patients in the levofloxacin-treated group ($P = 0.024$). The authors did not discuss cause of death, however, so differences in mortality cannot be attributed to drug treatment.[28]

Comparisons among fluoroquinolones have also been made. Levofloxacin 500 mg qd monotherapy was compared with moxifloxacin 400 mg qd monotherapy in 2 studies. In a recent CAP study in elderly patients (≥65 years), the clinical cure rates of those treated with levofloxacin compared with patients who received moxifloxacin were equivalent (88% vs 93%, respectively; 95% CI, −1.9% to 11.9%).[29] Another CAP study not restricted to elderly patients reported similar results, with 86% clinical success in the levofloxacin group and 74% in the moxifloxacin group.[30]

Guidelines vary in recommending an optimal duration of treatment for CAP.[31] ATS guidelines state that traditional treatment has been for 7 to 14 days, but recognize the lack of existing data on treatment duration, as well as new data indicating that shorter treatment can be as effective as longer treatment.[8] In addition, the WHO has recognized the potential benefits of shorter courses of therapy, including decreasing the disruption of the normal flora, decreasing selection pressure (which favors the development of drug-resistant organisms), and encouraging patient adherence to treatment.[32]

Several recent studies have shown that short-course therapy in patients with CAP of varying severity, including severe CAP, can be effective, safe, and tolerable, and may help control the rate of resistance. For example, in hospitalized patients, a short course of azithromycin (5 days) was found to be as effective as a longer course of erythromycin (10 days) in the treatment of nonpneumococcal CAP.[33] In addition, a short course of telithromycin (5 or 7 days) was shown as effective as a longer course of clarithromycin (10 days) in a group that included both outpatients and inpatients.[34]

In the treatment of mild-to-severe CAP in a population that included both hospitalized and nonhospitalized patients, 750 mg/day of levofloxacin for 5 days was as effective as 500 mg/day for 10 days in patients in PSI classes I to IV.[14] Too few patients in PSI class V were included to generalize the results of this study to that population. The 750-mg dose increases the area under the curve (AUC)/minimum inhibitory concentration (MIC) and peak concentration (C_{max})/MIC by increasing peak antibiotic concentrations, which may reduce the risk of selection of resistant organisms.[14] The incidence of adverse events was similar for the 2 groups, indicating that the higher-dosage, shorter-duration therapy is as safe and tolerable as the lower-dosage, longer-duration therapy.[14] Both regimens are well tolerated.[35] The shorter course reduced total antimicrobial exposure by 25%, resolved fever significantly faster, and may reduce costs.[10,35,36]

Table 2 Clinical success rates by treatment group

Population, Clinical Outcome	N (%) Levofloxacin Group	N (%) Ceftriaxone Group	95% CI
Intent to treat			
Success	96 (72.7)	88 (64.2)	−19.9 to 2.9
Failure	14 (10.6)	19 (13.9)	—
Unable to evaluate	22 (16.7)	30 (21.9)	—
Total	132 (100)	137 (100)	—
Clinically evaluable			
Success	85 (89.5)	74 (83.1)	−16.8 to 4.2
Failure	10 (10.5)	15 (16.9)	—
Total	95 (100)	89 (100)	—

CI = confidence interval.
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Treatment of HAP, VAP, and HCAP

Appropriate therapy for treatment of HAP, VAP, and HCAP should follow the guidelines from the ATS as well as the principles of the CARAT criteria for the accurate use of antibiotics. Compared with patients with CAP, those with HAP are often at greater risk for colonization and infection with a wider variety of multidrug-resistant (MDR) bacterial pathogens.[22] The major clinical strategies for HAP, VAP, and HCAP include initial management of the disease on the basis of time of onset and risk for MDR pathogens, adequate

Table 3 American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) treatment guidelines for initial empiric treatment of hospital-acquired pneumonia

Early-Onset with No Known Risk Factors for MDR Pathogens	Late-Onset or Risk Factors for MDR Pathogens Present
• Third-generation cephalosporin —Ceftriaxone • Extended-spectrum fluoroquinolone —Levofloxacin, moxifloxacin, ciprofloxacin* • Amino-penicillin —Ampicillin-sulbactam • Narrow-spectrum carbapenem —Ertapenem	• Antipseudomonal cephalosporin —Cefepime, ceftazidime • Antipseudomonal carbapenem —Imipenem, meropenem • Antipseudomonal penicillin —Piperacillin-tazobactam • Antipseudomonal fluoroquinolone —Ciprofloxacin or levofloxacin • Aminoglycoside —Amikacin, gentamicin, tobramycin

MDR = multidrug resistant.
Adapted from *Am J Respir Crit Care Med*.[22]
*The frequency of penicillin-resistant *Streptococcus pneumoniae* is increasing; levofloxacin or moxifloxacin are preferred to ciprofloxacin.

Table 4 American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) treatment guidelines for initial empiric treatment of hospital-acquired pneumonia

Antibiotic	Dosage*
Antipseudomonal cephalosporin	
Cefepime	1–2 g every 8–12 hr
Ceftazidime	2 g every 8 hr
Carbapenems	
Imipenem	500 mg every 6 hr or 1 g every 8 hr
Meropenem	1 g every 8 hr
β-Lactam/β-lactamase inhibitor	
Piperacillin-tazobactam	4.5 g every 6 hr
Aminoglycosides	
Gentamicin	7 mg/kg per day†
Tobramycin	7 mg/kg per day†
Amikacin	20 mg/kg per day†
Antipseudomonal quinolones	
Levofloxacin	750 mg every day
Ciprofloxacin	400 mg every 8 hr
Vancomycin	15 mg/kg every 12 hr‡
Linezolid	600 mg every 12 hr

Reprinted with permission from *Am J. Respir Crit Care Med*.[22]
*Dosages are based on normal renal and hepatic function.
†Trough levels for gentamicin and tobramycin should be <1 μg/mL; for amikacin they should be <4–5 μg/mL.
‡Trough levels for vancomycin should be 15–20 μg/mL.

dosing during empiric therapy for MDR pathogens, and broad-spectrum initial antibiotic therapy followed by appropriate antibiotic de-escalation to limit development of resistance.[22] These approaches are consistent with the CARAT criteria, which support initial broad-spectrum therapy with optimal antibiotic dosage to achieve appropriate pharmacodynamic parameters. Once the pathogen is identified, therapy can be streamlined to limit collateral damage from antibiotic therapy.

Choosing the initial, appropriate IV antibiotic regimen has become more difficult due to the rapid emergence of different types of MDR pathogens such as *Pseudomonas aeruginosa, Klebsiella pneumoniae, Acinetobacter* species, and methicillin-resistant *Staphylococcus aureus*. Joint guidelines from ATS and IDSA for the treatment of HAP, VAP, and HCAP have been published recently.[22] Recommendations for initial empiric treatment are summarized in **Table 3**, and dosing recommendations for HAP are listed in **Table 4**.[22] These recommendations are consistent with the CARAT principles and should provide safe and well-tolerated regimens, prevent unnecessary prescribing of antibiotics, decrease treatment costs, and increase adherence. It is recommended that patients without MDR risk factors and early-onset HAP or VAP initially be treated with ceftriaxone, ampicillin-sulbactam, ertapenem, or one of the fluoroquinolones (moxifloxacin, ciprofloxacin, or levofloxacin), with the exception of gatifloxacin. Because the frequency of both penicillin resistance and MDR is increasing among *S pneumoniae*, levofloxacin or moxifloxacin are preferred compared with ciprofloxacin.[22] levofloxacin may be used to treat several RTIs in which the major pathogens are gram-negative bacteria, as evidenced by several in vitro studies that demonstrate the large 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 *K pneumoniae*, and 80% for *Serratia* and *Acinetobacter* species.[37]

Patients with late-onset HAP, VAP, or HCAP or those with known risk factors for MDR pathogens should be treated with an antipseudomonal cephalosporin (cefepime or ceftazidime), an antipseudomonal carbapenem (imipenem or meropenem), or piperacillin-tazobactam. An antipseudomonal fluoroquinolone or an aminoglycoside should also be given. Linezolid or vancomycin should be given if there are risk factors for methicillin-resistant *S aureus* (MRSA) present, including a high local incidence of MRSA.[22] 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.[22]

The efficacy of the fluoroquinolones for the treatment of nosocomial pneumonia is comparable to antibiotics that have been more commonly used. In a clinical trial including 438 adult patients with nosocomial pneumonia, 220 patients were treated with levofloxacin 750 mg qd IV and then orally for 7 to 15 days, and 218 were treated with imipenem-cilastatin 500 to 1,000 mg IV every 6 to 8 hours, followed by oral ciprofloxacin 750 mg every 12 hours for 7 to 15 days. Patients with documented or suspected *P aeruginosa* or MRSA also received adjunctive therapy as required by the study protocol. Clinical success was comparable in patients evaluable for microbiologic efficacy (58.1% vs. 60.6%), as was eradication (66.7% vs. 60.6%).[38] In the subgroup of patients with VAP, 111 of whom were treated with levofloxacin and 111 with imipenem-cilastatin, the clinical success rates were 58.6% and 63.1%, respectively. Microbiologic success and 28-day mortality rates were also comparable.[39] Together, these studies indicate that levofloxacin is as effective and well tolerated as imipenem-cilastatin in patients with HAP.

It should be noted that nosocomial pneumonia therapy in the ICU often involves excessive antibiotic use, mainly due to the associated high mortality.[40] An operational approach to reducing the amount and duration of antibiotic use in the ICU is reevaluation of patients after initiation of therapy, using an operational criterion such as the clinical pulmonary infection score (CPIS). Reevaluation with the CPIS has been shown to successfully identify patients for whom short-course therapy would be appropriate. This resulted in shorter durations of antibiotic treatment and significantly reduced costs of treatment.[40]

Management of severe ABECB associated with COPD in the hospital setting

Severe exacerbations of COPD generally require hospitalization. Risk factors for hospitalization include ischemic heart disease, other cardiopulmonary disease, >3 COPD admissions in the past year, and poor underlying lung function (indicated by FEV_1 percent predicted).[41] In addition, patients with significant compromise of lung function may develop respiratory failure as a consequence of an acute exacerbation, and up to 60% of these patients will require mechanical ventilation.[42] Hospital mortality rates from severe AECB range from 10% to 30% for patients with significant compromise of lung function.[42]

In those patients most likely to be hospitalized, current guidelines recommend treatment with medications such as fluoroquinolones to provide coverage for resistant organisms.[41] In patients with FEV_1 <35% of predicted, treatment should be targeted to the identified pathogen. *P aeruginosa* and *Enterobacteriaceae* species are common, so the agent chosen should have activity against these pathogens.[41]

Therapeutic benefits

Susceptibility patterns can be used as guidelines to minimize the chances of clinical failure. In vitro resistance of the pathogen has been shown to correlate with clinical failure.[43] Therefore, if a substantial percentage of patients in a particular geographic area demonstrate resistance to a particular class of antibiotics, a different class of drug should be considered in that area.[18]

Therapeutic benefits in the treatment of CAP

In hospitalized patients, *S pneumoniae* is the most common pathogen responsible for CAP, occurring in up to 60% of episodes of culture-positive pneumonias.[8] Other likely pathogens are *Haemophilus influenzae, S aureus*, enteric gram-negatives, *Legionella* species, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and viruses.[8] *P aeruginosa* has been recovered in some patients with severe CAP.[8] In 20% to 70% of cases, however, no etiologic agent is identified.[8]

A goal of the CARAT criteria is to encourage use of the optimal drug for the optimal duration in order to improve patient outcomes and reduce the incidence of resistance. Antimicrobial resistance is a global problem resulting in high hospitalization rates, mortality, and costs.[44] According to data gathered by the Tracking Resistance in the US Today (TRUST) program, a comprehensive surveillance of the resistance patterns of *S pneumoniae, H influenzae*, and *M catarrhalis*, resistance of *S pneumoniae* to penicillin and macrolides is high in the United States.[45] In other parts of the world, such as in France, Spain, and several Asian countries, the resistance among clinical *S pneumoniae* isolates is even higher.[46] The Asian Network for Surveillance of Resistent Pathogens (ANSORP) study found very high erythromycin resistance among *S pneumoniae* isolates in France and Spain (58% and 57%, respectively), whereas in many Asian countries >70% of isolates were erythromycin resistant.[46] Fluoroquinolones, however, have the lowest resistance rates of all commonly used respiratory antibiotics.[44] A study of resistance in *S pneumoniae* found that 99% of isolates remain susceptible to fluoroquinolones, whereas resistance is >20% for macrolides and >10% for all other agents tested except vancomycin and ceftriaxone.[47]

In an investigation of RTI isolates of *S pneumoniae*, penicillin-intermediate and penicillin-resistant rates were 15% and 6%, respectively.[48] Nonsusceptibility rates were 11% for tetracycline, 8% to 9% for macrolides, and only 0.3% for fluoroquinolones.[48]

These data emphasize regional differences in antimicrobial resistance. Local resistance patterns should be used as guidelines to minimize the chances of clinical failure, as clinical failure is a major risk factor for increases in resistance.

Table 5 Proposed classification of patients with acute bacterial exacerbations of chronic bronchitis (ABECB)

Classification of ABECB	Clinical Status	Pathogens
Mild to moderate	Simple chronic bronchitis	*Haemophilus influenzae* *Moraxella catarrhalis* *Streptococcus pneumoniae* (possible β-lactam resistance)
Moderate	Complicated chronic bronchitis	*Haemophilus influenzae* *Moraxella catarrhalis* *Streptococcus pneumoniae* (resistance to β-lactam common)
Severe	Chronic bronchial infection	*Pseudomonas aeruginosa* Enterobacteriaceae *Haemophilus influenzae* *Moraxella catarrhalis* *Streptococcus pneumoniae*

Adapted with permission from *Chest*.[42,50]

Therapeutic benefits in the treatment of ABECB

Antimicrobial therapy should be directed against the most likely pathogens.[49] In patients hospitalized with ABECB, the bacterial etiology correlates closely with the severity of accompanying lung disease.[50] In patients with mild disease, *S pneumoniae* is the most common. In patients with moderate disease, *H influenzae* and *M catarrhalis* are commonly found.[50] In patients with severe COPD, gram-negative *Enterobacteriaceae* and *Pseudomonas* species are the dominant bacteria occurring during infective exacerbations. Common pathogens are listed in **Table 5**.[42,50]

Gatifloxacin, levofloxacin, and ciprofloxacin are active against all *M catarrhalis* and *H influenzae*, and gatifloxacin and levofloxacin are active against >99% of *S pneumoniae*.[51] The fluoroquinolones are consistently more active than the macrolides, amoxicillin-clavulanate, cefuroxime axetil, and tetracycline against these pathogens.[51] In addition, levofloxacin and ciprofloxacin remain effective against both *P aeruginosa* and *E cloacae*.[45]

Safety and tolerability of therapies

Safety and tolerability vary among agents. Gatifloxacin and moxifloxacin, for example, have been linked to problems with glucose hemostasis in patients with diabetes.[52,53] Several fluoroquinolones are associated with prolongation of the QT_c interval to varying degrees. Moxifloxacin and gatifloxacin have been associated with prolongation of the QT_c interval and should be avoided in patients receiving class IA or class III antiarrhythmic agents.[52–54] The package insert for gatifloxacin warns that it should also be avoided in patients with uncorrected hypokalemia.[52] Gemifloxacin may also prolong the QT_c interval in some patients and should be avoided in individuals with uncorrected electrolyte disorders and those receiving class IA or class III antiarrhythmic agents.[55] Finally, telithromycin, similar to the macrolides from which it is derived, also has been shown to cause prolonged QT_c intervals in some patients.[56]

The safety of newer agents is an unknown. In fact, 8% of all newly approved drugs received ≥1 black-box warnings, a marker of serious adverse reactions, from 1975 to 2000.[57] In the same period, another 3% were removed from the market.[57] It is known that telithromycin, for example, can cause visual disturbances, severe in some cases, and interacts with certain statins, including simvastatin, lovastatin, and atorvastatin. Therapy with these statins should be stopped during the course of treatment with telithromycin.[56,58] Gemifloxacin has been associated with a rash that is most common in female patients aged <40 years old.[53,54] The true presence or incidence of other adverse events, especially those that are rare, will not be known until these agents have been on the market for some time.

In recent years, some agents with a long history of use have shown severe drug–drug interactions. Erythromycin and the coadministration of strong inhibitors of CYP3A enzyme such as nitroimidazole antifungal agents, diltiazem, verapamil, or troleandomycin increase the risk of sudden death from cardiac causes and therefore should be avoided in concurrent use in clinical practice.[59] Case studies with clarithromycin also deserve attention and should be judged critically for select patient groups. In patients with type 2 diabetes taking sulfonylurea medications, clarithromycin coadministration may lead to severe hypoglycemia.[60] Additionally, clarithromycin should be used with caution in patients stabilized on digoxin therapy because of a significant risk of bradycardia resulting from digoxin toxicity.[61,62]

These safety issues are important when determining the potential of an antimicrobial for higher-dose, short-course therapy. For example, gatifloxacin should probably not be used for higher-dose therapy due to its concentration-dependent effects on glucose homeostasis, and high-dose therapy with moxifloxacin is also not recommended due to its dose-dependent effects on the QT_c interval.[53] Levofloxacin and ciprofloxacin, however, have comparable safety profiles at higher and lower doses and are therefore good candidates for higher-dose, short-course therapy.[53]

The optimal drug for the optimal duration

Clinical evidence increasingly supports the idea that optimal antibiotic therapy may consist of higher doses for shorter durations of treatment. When the initial antibiotic therapy is appropriate, there is evidence to support the contention that clinical effectiveness of short-term antibacterial therapy is comparable to a longer-term therapy and may provide the advantage of reduction in emergence of bacterial resistance. The optimal duration of treatment for ICU patients with VAP was examined in a large randomized double-blind trial comparing 8-day and 15-day antibiotic therapy. ATS guidelines were followed, with initial empirical combination therapy consisting of an aminoglycoside or a fluoroquinolone and a broad-spectrum β-lactam, followed by narrow-spectrum therapy based on laboratory results.[63] Patients in the 8-day group consumed less antibiotic compared with the 15-day group, but did not exhibit higher mortality than the 15-day group (18.8% vs. 17.2%, respectively [1.6% difference]; 90% CI, −3.7% to 6.9%). Further, no increases in pulmonary infection-recurrence were found in the 8-day group, demonstrating no added benefit of prolonged 15-day treatment as well as noninferiority of 8-day treatment.[63]

Clinical evidence also supports the idea that the optimal duration of therapy is one that is short term at high doses.[31,64–66] These regimens may reduce the risk of resistance by providing faster, more complete bacterial killing while providing the added benefits of improving tolerability and patient adherence.[31,35,66] Conversely, long-term, low-dose antibiotic treatment may increase resistance.[67]

The pharmacodynamic and pharmacokinetic properties of fluoroquinolones support high-dose, short-course therapy regimens.[66,68–71] Fluoroquinolones exhibit concentration-dependent killing; therefore, higher concentrations in key tissue spaces should enhance efficacy. Higher C_{max} and AUC/MIC values with higher doses lead to increased bactericidal activity, and eradication of difficult pathogens.[66] A full discussion is presented elsewhere in this supplement by Poole and colleagues[72] and Martinez and associates.[73]

Cost-effective choices for treating community-acquired pneumonia

Cost-effectiveness is the final CARAT criterion in choosing optimal therapy. Some factors that affect cost-effectiveness are treatment failures, patient adherence, efficacy, duration of therapy, hospital versus outpatient treatment, and, for patients treated in the hospital, length of stay. Acquisition costs for antibiotics constitute almost 6% of the total cost of treatment per patient.[74]

The largest treatment cost is treatment failure, which incurs both the cost of the failed treatment and the cost of retreatment. Agents that maximize the success of first-line therapy reduce costs by decreasing the high costs of treatment failure, illustrating the need to ensure that the first treatment is effective.[49]

In the hospital, the timing of step-down therapy from intravenous to oral treatment is often dependent on clinical signs and symptoms, and a faster switch can facilitate the change to outpatient treatment.[75] Therapy with higher-doses can result in faster symptom resolution. For example, in the treatment of mild to severe CAP, administration of 750-mg levofloxacin (once daily for 5 days IV or orally) resulted in resolution of fever on day 3 in 67.4% of patients compared with 54.6%, in patients treated with 500-mg levofloxacin (once daily for 10 days IV or orally) ($P = 0.006$ by 2-sample McNemar test).[76] Therefore, in patients admitted with severe CAP, faster symptom resolution may allow for early discharge and shortened hospital stay.[8,75]

Antimicrobial agents with both intravenous and oral formulations can also facilitate step-down therapy.[75] Agents with high bioavailability that achieve similar serum levels with intravenous or oral therapy, including levofloxacin, moxifloxacin, and gatifloxacin, may allow some patients who are normally hospitalized to be treated on an outpatient basis, and also may allow earlier discharge of hospitalized patients due to a faster switch from IV to oral treatment.[8,36]

Implementing a critical pathway that provides specific criteria for admission, as well as the implementation of step-down therapy, has been associated with more low-risk patients being appropriately treated on an outpatient basis, as well as a reduction in length of stay for hospitalized patients. Both of these outcomes would be expected to produce significant cost savings.[10] Another method of reducing the cost of treating hospitalized patients may be for hospital formularies to choose a single fluoroquinolone. At the University of Kentucky Hospital, levofloxacin was chosen over ciprofloxacin and gatifloxacin as the sole fluoroquinolone for the drug formulary. The change saved the hospital $100,000 in the first 12 months.[77]

Summary

Higher-dose, short-course regimens provide additional benefits, including faster symptom resolution with no compromise of safety. Short-course, higher-dose therapy allows antimicrobial agents to achieve higher C_{max} levels, leading to more rapid and complete bacterial killing. Furthermore, patients are exposed to less total antibiotic, which, in combination with more rapid and complete killing, can potentially prevent increases in resistance. Finally, shorter courses are likely to result in better patient adherence, reducing treatment failures. Short-course, higher-dose therapy fulfills WHO recommendations and is in accordance with the CARAT criteria.

Evidence from clinical trials of levofloxacin indicates that fluoroquinolone monotherapy provides clinical efficacy for hospitalized CAP, and supports the use of high-dose levofloxacin (750 mg) for nosocomial pneumonia. Current ATS/IDSA guidelines for the treatment of HAP recommend levofloxacin, moxifloxacin, or ciprofloxacin for early-onset

HAP and levofloxacin or ciprofloxacin for late-onset HAP. Therefore, levofloxacin and ciprofloxacin are the only fluoroquinolones recommended for patients with or without risk factors for MDR pathogens, and for both early- and late-onset HAP. Of the 2 drugs, levofloxacin is preferred to ciprofloxacin for patients with early-onset HAP.

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