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Principles of antibiotic treatment of community-acquired pneumonia in the outpatient setting

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Community-acquired pneumonia (CAP) is a common illness with high rates of morbidity and mortality. Nearly 80% of the treatment for this condition is provided in the outpatient setting. Among the etiologic agents associated with bacterial CAP, the predominant pathogen is *Streptococcus pneumoniae*. Treatment of CAP for the most part is empirical; therefore, any antibiotic treatment should cover both typical and atypical pathogens. The β-lactams have historically been considered standard therapy for the treatment of CAP. However, the impact of rising resistance rates is now a primary concern facing physicians. For patients with comorbidities or recent antibiotic therapy, current guidelines recommend either combination therapy with a β-lactam and a macrolide or an antipneumococcal fluoroquinolone alone. Fluoroquinolones are broad-spectrum antibiotics that exhibit high levels of penetration into the lungs and low levels of resistance. Evidence from clinical trials indicates clinical success rates of >90% for moxifloxacin, gatifloxacin, and levofloxacin in the treatment of CAP due to *S pneumoniae*. Data from comparative clinical trials suggest fluoroquinolone monotherapy is as efficacious as β-lactam–macrolide combination therapy in the treatment of CAP patients. The respiratory fluoroquinolone levofloxacin has also been shown to be effective in CAP patients for the treatment of macrolide-resistant *S pneumoniae*. The use of azithromycin, telithromycin, and fluoroquinolones in short-course regimens has been shown to be efficacious, safe, and tolerable in patients with CAP. Based on clinical evidence, high-dose, short-course therapies may represent a significant advance in the management of CAP.

Each year, there are 2 to 3 million cases of community-acquired pneumonia (CAP) in the United States, resulting in approximately 10 million physician visits.[1] Up to 80% of treatment for the condition is provided in the outpatient setting.[2] Although CAP is the leading cause of death from infection and the sixth-leading cause of death overall in the United States, mortality from CAP among outpatients is estimated at <1%.[1,3]

Etiology of community-acquired pneumonia

The etiology of CAP among outpatients has not been well studied.[2] Furthermore, no etiologic agent is found in as many as 50% of cases, even when extensive diagnostic testing is performed.[3] In those cases in which an etiologic agent is identified, *Streptococcus pneumoniae* accounts for approxi-

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mately 66% of all cases of bacterial pneumonia.[1] Other implicated bacterial pathogens are *Haemophilus influenzae, Mycoplasma pneumoniae, Chlamydia pneumoniae, Staphylococcus aureus, Streptococcus pyogenes, Moraxella catarrhalis, Klebsiella pneumoniae,* and other gram-negative rods.[1] *M pneumoniae* is more common among ambulatory patients than among those admitted to the hospital.[2] For individuals treated on an outpatient basis, *M pneumoniae* is the etiologic pathogen in up to 37% of patients.[2]

Antimicrobial management of community-acquired pneumonia

A diagnosis of CAP is often made based on clinical signs and symptoms as well as laboratory and radiographic tests.[2] Signs and symptoms that are indicative of CAP include fever, new cough, purulent tracheobronchial secretions, and focal respiratory abnormalities (i.e., decreased/altered breath sounds and/or crackles).[2] Other tests include chest radiograph, sputum Gram stain and culture, and blood cultures.[2] Using signs, symptoms, and tests is well accepted in the diagnosis of CAP; however, little evidence exists to determine the utility of these criteria individually.[2]

Physicians generally treat outpatient CAP empirically.[2] Empiric treatment requires the consideration of many patient and clinical variables.[1] Therefore, a set of treatment criteria would be useful in helping clinicians choose an effective initial treatment that would prevent the need for retreatment for a wide range of possible pathogens. The Council for Appropriate and Rational Antibiotic Therapy (CARAT) emphasizes evidence-based results, therapeutic benefits, safety and tolerability, optimal drug for optimal duration, and cost-effectiveness as criteria for evaluating treatment options.

Evidence-based results

The CARAT criteria recommend prescribing an antibiotic based on established guidelines and clinical evidence. Guidelines published by the Infectious Diseases Society of America (IDSA) and recommendations published by the Texas Academy of Family Physicians recommend a macrolide or doxycycline to treat infections caused by pneumococcal and atypical pathogens only for patients who have not had recent antibiotic therapy and who do not have comorbidities such as chronic obstructive pulmonary disease (COPD), diabetes mellitus, renal failure, congestive heart failure, or malignancy. Fluoroquinolones or combination therapy are recommended for patients with any of these comorbid medical conditions and for penicillin-resistant pneumococci and gram-negative pathogens.[4,5] These recommendations are outlined in **Table 1**.[5]

Similarly, joint guidelines from the Canadian Infectious Disease Society (CIDS) and the Canadian Thoracic Society (CTS) recommend respiratory fluoroquinolones as a first choice for outpatients who have had antibiotics within 3 months or corticosteroid treatment, as well as those who have modifying factors such as COPD or *H influenzae* or in whom enteric gram-negative rods are implicated.[2] American Thoracic Society (ATS) guidelines recommend either a β-lactam–macrolide combination or monotherapy with an antipneumococcal fluoroquinolone for more complex outpatients with modifying factors such as cardiopulmonary disease.[3]

Although guidelines are an excellent resource for evidence-based recommendations, clinical evidence should also be taken into account. For the treatment of CAP, the effectiveness of the fluoroquinolone moxifloxacin (400 mg once daily) was compared with that of standard therapy with amoxicillin (1 g given 3 times daily) or clarithromycin (500 mg twice daily) alone or in combination in a randomized, double-blind, controlled trial (N = 564). Clinical success rates were similar for moxifloxacin and standard therapy (93.5% vs. 93.9%, respectively).[6] Recent trials also support the use of gatifloxacin to treat CAP, particularly when it is caused by *S pneumoniae*. In an open-label, noncomparative trial (N = 136) of oral gatifloxacin (400 mg daily for 7 to 14 days), clinical benefit was achieved in 95.3% of evaluable patients.[7] The same dosage regimen of gatifloxacin was evaluated in a prospective, single-arm, open-label, noncomparative study of patients with confirmed or suspected CAP (N = 1,488). Clinical benefit occurred in 91%, 94%, and 92% of patients diagnosed with *S pneumoniae, H influenzae,* and *M catarrhalis,* respectively.[8]

For CAP, there is significant evidence to support the use of monotherapy with a fluoroquinolone rather than combination therapies (e.g., with a β-lactam and a macrolide). Intravenous or oral levofloxacin monotherapy (500 mg) was compared with combination therapy with parenteral ceftriaxone (1 to 2 g once or twice daily) and/or oral cefuroxime axetil (500 mg twice daily), with erythromycin or doxycycline added at the investigator's discretion in a prospective, multicenter, randomized trial (N = 456). Clinical success rates were significantly higher in the levofloxacin-treated group (levofloxacin vs. comparator, 96% vs. 90%; 95% confidence interval [CI], −10.7 to −1.3).[9] Two other randomized, multicenter trials comparing monotherapy with combination therapy in hospitalized CAP patients found comparable results[10,11] and are described in the article by Grossman and colleagues in this supplement.[12]

Accumulating data support the use of shorter courses of antibiotics at higher doses to increase efficacy and decrease the chance for inducing further resistance.[13] Azithromycin, given in 3- or 5-day courses, for the treatment of nonsevere pneumonia in children was assessed in a randomized, double-blind, placebo-controlled trial (N = 2,188). Cure rates were equivalent between the groups (89.5% vs. 89.9%, P = not reported).[14] Short-course, high-dose amoxicillin therapy has also been shown to prevent increases in carriage of penicillin-nonsusceptible *S pneumoniae* (PNSP) in children

Table 1 Treatment guidelines for initial empiric therapy for outpatients with community-acquired pneumonia

Patient type	No recent antibiotic therapy	Antibiotic therapy within 3 months
Previously healthy	• Azithromycin, clarithromycin, or erythromycin *or* • Doxycycline	• Gatifloxacin, gemifloxacin, levofloxacin, or moxifloxacin *or* • Azithromycin or clarithromycin + amoxicillin 1 g tid or amoxicillin-clavulanate 2 g bid
Comorbidities (COPD, diabetes mellitus, renal failure, congestive heart failure, malignancy)	• Azithromycin or clarithromycin *or* • Gatifloxacin, gemifloxacin, levofloxacin, or moxifloxacin	• Gatifloxacin, gemifloxacin, levofloxacin, or moxifloxacin *or* • Azithromycin or clarithromycin + amoxicillin 1 g tid or amoxicillin-clavulanate 2 g bid, cefpodoxime, cefprozil, or cefuroxime
Suspected aspiration with infection	• Amoxicillin-clavulanate or clindamycin	
Influenza with bacterial superinfection	• Amoxicillin 1 g tid daily, amoxicillin-clavulanate 2 g bid, cefpodoxime, cefprozil, or cefuroxime *or* • Gatifloxacin, gemifloxacin, levofloxacin, or moxifloxacin	

COPD = chronic obstructive pulmonary disease.
Reprinted with permission from *Consensus Recommendations: Community-Acquired Respiratory Tract Infections.*[5]

with respiratory tract infections.[15] In an open-label, randomized study of 40 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 (79% vs. 76%, P = NS).[16] Finally, a short course of telithromycin (800 mg daily for 5 or 7 days) was compared with a longer course of clarithromycin (500 mg daily for 10 days) in a study of 575 patients with CAP. Clinical cure rates were statistically equivalent in all 3 (telithromycin 5-day, telithromycin 7-day, and clarithromycin 10-day) groups (89.3%, 88.8%, and 91.8%, respectively).[17]

Although *S pneumoniae* is the most common cause of CAP, atypical pathogens account for a significant proportion of the pathogens isolated from patients with this disease.[18,19] Furthermore, it has been found in patients with pneumonia requiring hospitalization that using treatment regimens covering both typical and atypical pathogens results in lower mortality rates. These regimens include a nonpseudomonal third-generation cephalosporin plus a macrolide, a second-generation cephalosporin plus a macrolide, or a fluoroquinolone alone.[20] Therefore, when choosing a treatment for CAP empirically, initial antibiotic therapy should cover both typical and atypical pathogens.[19] Dunbar and coworkers[21] reported a subgroup analysis of a randomized controlled trial of levofloxacin at doses of 500 mg or 750 mg for patients with CAP. This subgroup included 149 patients diagnosed with *Legionella pneumophila, C pneumoniae,* or *M pneumoniae,* and found that levofloxacin was highly effective against atypical pathogens, with clinical success rates of 95.5% for the 750-mg group and 96.5% for the 500-mg group. In addition, a significantly greater proportion of patients treated with 750 mg of levofloxacin experienced resolution of fever by day 3 of treatment (P = 0.031).[21] Other agents effective against atypical pathogens are the advanced-generation macrolides such as azithromycin and clarithromycin; therefore, the ATS guidelines also recommend these drugs for outpatient treatment of CAP patients without cardiopulmonary disease. Doxycycline therapy is recommended in patients who are intolerant of macrolides.[3]

Therapeutic benefits

Local resistance patterns should be taken into account when evaluating the potential efficacy of antimicrobial therapy. Clinicians, however, tend to consider resistance a national issue, rather than one that affects their own practices and institutions.[22] Although 70% of pathogens in US hospitals have developed resistance to ≥1 antimicrobial, many clinicians do not perceive the extent of the problem in their practices.[23,24] Physicians must therefore become more knowledgeable about resistance patterns in their own communities in order to help control the rise in microbial resistance.

National resistance trends vary among the common CAP pathogens. According to the 2002–2003 Tracking Resistance in the US Today (TRUST) 7 Study, *S pneumoniae* susceptibility was 96.1% for ceftriaxone, 93.4% for amoxicillin-clavulanate, 72.2% for azithromycin, and 99.1% for levofloxacin.[25] In the 2003–2004 TRUST 8 data, susceptibilities were similar to these values. Susceptibilities of *S pneumoniae* were 96.7% for ceftriaxone, 91.7% for amoxi-

Table 2 Comparison of antimicrobial resistance in *Streptococcus pneumoniae*

	Resistance (%)		
Antimicrobial agent	TRUST 6 (2002)	TRUST 7 (2003)	TRUST 8 (2004)
Penicillin	18.4	17.4	19.0
Azithromycin	27.6	27.6	25.4
TMP-SMX	26.0	24.1	21.5
Ceftriaxone	1.6*	1.5*	1.4*
Levofloxacin	0.9	0.9	1.1
No. of institutions	260	226	220
No. of isolates	7,671	4,452	4,233

TMP-SMX = trimethoprim/sulfamethoxazole; TRUST = Tracking Resistance in the US Today.
Data presented at the TRUST 8 Investigators meeting.[26]
*Ceftriaxone (nonmeningitis) National Committee for Clinical Laboratory Standards breakpoints: susceptible, $\leq$ 1 μg/mL; intermediate, 2 μg/mL; resistant, $\geq$4 μg/mL.[27]

Table 3 Comparison of antimicrobial resistance in *Haemophilus influenzae*

	% Resistant (β-Lactamase–positive)		
	TRUST 6 (2002)	TRUST 7 (2003)	TRUST 8 (2004)
Ampicillin	27.0	29.2	28.8
TMP-SMX	17.9	18.2	15.2
Amoxicillin-clavulanate	0.1	0.1	0.2
Ceftriaxone	0	0	0
Cefuroxime	0	0.1	0.1
Azithromycin*	0.7	0.2	0.1
Clarithromycin	3.3	NT	NT
Levofloxacin*	0.1	0	0.3

NT = not tested; TMP-SMX = trimethoprim-sulfamethoxazole; TRUST = Tracking Resistance in the US Today.
Data presented at the TRUST 8 Investigators meeting.[26]
*Shown as percent nonsusceptible.

cillin-clavulanate, 73.8% for azithromycin, and 98.7% for levofloxacin.[26] Antimicrobial resistance in *S pneumoniae* has been sustained over the last 2 years for some agents; azithromycin resistance, for example, was 27.6% in 2002, 27.6% in 2003, and 25.4% in 2004 (**Table 2**).[26,27] In the Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin United States (PROTEKT US) Study, the emergence and spread of antimicrobial resistance among isolates of *S pneumoniae, S pyogenes*, and *H influenzae* were tracked across the country. This study found that 1% of the *S pneumoniae* were resistant to levofloxacin. The *H influenzae* isolates were 99.7% susceptible to the respiratory fluoroquinolones levofloxacin, moxifloxacin, and gatifloxacin compared with 96.3% for telithromycin.[28]

Resistance varies considerably among geographic regions of the United States. In TRUST 7, regional *S pneumoniae* azithromycin resistance rates ranged from 15.2% to 40.6%; the highest regional resistance rates for levofloxacin were 1.7%.[25] TRUST 8 data show a continuation in regional variation.[26]

According to TRUST 8 data, resistance to β-lactams and first-generation cephalosporins is high for *H influenzae and M catarrhalis* (**Tables 3 and 4**).[26] Fluoroquinolone resistance for these microbes is low, however.[26] Short-course, higher-dose therapies can help to address the growing concern of microbial resistance by reducing selection pressure on pathogens and increasing adherence.[29]

These national resistance levels, as well as local resistance patterns, should be taken into account when choosing antibiotic treatment for CAP. When high levels of resistance are present, the appropriate treatment choice is the one that is effective in patients who have resistant pathogens or in those at risk for resistant pathogens. Levofloxacin was shown to be effective in the treatment of patients with CAP who were infected with macrolide-resistant *S pneumoniae* in an analysis of data from 7 phase 3 and 4 clinical trials.[30] The percentage of patients who achieved a clinical cure or improvement was 96.9% in patients with macrolide-resistant *S pneumoniae* compared with 95.1% of the general population of patients. Results for microbiologic eradication were similar (96.9% eradication for patients with macrolide-resistant *S pneumoniae* and 93.5% eradication for all patients). These data indicate that levofloxacin is an appropriate choice in the treatment of CAP when macrolide-resistant *S pneumoniae* is present in the community.[30]

Table 4 Comparison of antimicrobial resistance in *Moraxella catarrhalis*

	MIC_{90}, μg/mL (β-Lactamase–positive)		
	TRUST 6 (2002)	TRUST 7 (2003)	TRUST 8 (2004)
Ampicillin	8	8	8
Cefuroxime	2	2	4
Ceftriaxone	1	1	1
Amoxicillin-clavulanate	0.25	0.25	0.25
Azithromycin	0.03	0.03	0.03
Clarithromycin	0.25	NT	NT
TMP-SMX	0.25	0.25	0.25
Levofloxacin	0.06	0.06	0.06

NT = not tested; TMP-SMX = trimethoprim-sulfamethoxazole; TRUST = Tracking Resistance in the US Today.
Data presented at the TRUST 8 Investigators meeting.[26]

Increases in resistance are a major concern for healthcare providers. The prevalence of fluoroquinolone resistance and nonsusceptibility in *S pneumoniae* increased 2-fold between 1999–2000 and 2001–2002 for ciprofloxacin resistance (from 1.2% to 2.7%) as well as for levofloxacin nonsusceptibility (from 0.6% to 1.3%).[31] Although resistance to these agents has doubled, it is still extremely low. In addition, the introduction and use of more potent respiratory fluoroquinolones with high pneumococcal activity has been speculated to minimize the emergence of fluoroquinolone resistance.[32]

Three major antibiotic-resistant pathogens include extended-spectrum β-lactamase (ESBL)—producing gram-negative bacteria, vancomycin-resistant enterococci (VRE) such as *Enterococcus faecalis,* and methicillin-resistant *S aureus* (MRSA). The third-generation extended-spectrum cephalosporin ceftazidime has been associated with increased ESBL production in *Klebsiella* and *Enterobacter* species.[32] Ciprofloxacin may also increase the prevalence of highly resistant VRE, and ciprofloxacin or ceftazidime use has been associated with increases in MRSA. This evidence emphasizes that use of any antibiotic may be associated with potential selection for resistance, although it has been argued that not all antibiotics select for resistance.[33]

Identifying those patients who are more likely to have resistant pathogens can also help achieve treatment goals and reduce resistance pressure. Patient groups with increased risk for developing resistant pneumococcal infections include those with recent antibiotic treatment, malignancies, human immunodeficiency virus infection, and sickle-cell disease, or other significant comorbidities.[3,34]

Safety and tolerability

The prominent antibiotic therapies for CAP are the advanced macrolides and respiratory fluoroquinolones.[5] The safety profiles of available agents vary, however. Fluoroquinolones have demonstrated landmark safety profiles while their concentration-dependent adverse effects differ, which may limit the clinical use of higher doses and longer duration of therapy with some drugs in this class.[35]

The most common adverse effects with fluoroquinolones involve the gastrointestinal tract and the central nervous system, and they are usually transient and mild to moderate in severity. Exceptions include trovafloxacin, which can cause serious hepatic toxicity that has led to restrictive use in the United States, and temafloxacin and grepafloxacin, which have been withdrawn from markets worldwide.[35]

Additionally, although short-course, higher-dose therapy for CAP has benefits, only antibiotics that are safe at standard doses and have been shown to possess favorable safety profiles at higher doses should be considered appropriate for higher-dose therapy. Levofloxacin is generally well tolerated, and common adverse effects are usually mild, with nausea and diarrhea being the most frequent side effects.[36] Furthermore, levofloxacin exhibits comparable rates of drug-related adverse effects regardless of whether patients with CAP are treated with once-daily dosing regimens of either levofloxacin 500 mg for 10 days or 750 mg for 5 days (**Table 5**).[35]

Third-generation cephalosporins are relatively nontoxic, with the most common side effects—skin rash and drug

Table 5 Safety data for 2 levofloxacin regimens for treatment of community-acquired pneumonia (CAP)

	Levofloxacin	
Outcome (%)	500 mg × 10 days	750 mg × 5 days
≥1 Treatment-emergent AE	59.6	57.8
≥1 Drug-related AE*	5.7	7.0
≥1 Serious AE†	14.0	9.8
Discontinuation of therapy	8.3	7.0
Death	3.4	1.9

AE = adverse event.
Reprinted with permission from *Clin Cornerstone.*[35]
*The most common drug-related AEs for the 500-mg group were rash, insomnia, and diarrhea; and for the 750-mg group they were nausea, rash, and aggravation of CAP symptoms.
†Worsening of CAP was the most frequently reported serious AE (3.4% for 500-mg group and 3.5% for 750-mg group).

fever—occurring with similar frequency among the agents.[37] Incidence of *C difficile*–associated diarrhea (CDAD) is particularly correlated with use of cefotaxime, ceftriaxone, and ceftazidime.[38] In a district general hospital in the United Kingdom, ceftriaxone as a first-line therapy was associated with increased CDAD, whereas switching to levofloxacin was associated with a reduced incidence of CDAD.[39] In addition to third-generation cephalosporins, use of gatifloxacin has also been associated with CDAD. A study in a long-term care facility showed CDAD rates associated with gatifloxacin were higher than for levofloxacin (34% vs. 17%, respectively).[40] This is attributed to the broader anaerobic activity of gatifloxacin. Further information concerning safety and tolerability of antibiotic therapies is given by Grossman and colleagues.[12]

Optimal drug for optimal duration

The CARAT criteria, as well as the World Health Organization (WHO) recommendations, emphasize the importance of choosing the optimal drug for the optimal duration to prevent the further emergence of resistant bacterial strains.[41] Both scientific principles and recent clinical data indicate that the optimal dose to achieve the highest potential for efficacy is a higher-dose regimen. Data also suggest that with appropriate antibiotic selection, based on appropriate spectrum, potency, and pharmacokinetic/pharmacodynamic profile, lower respiratory tract infections in outpatients can be successfully treated in <7 days rather than the 7 to 14 days currently recommended.[29]

A shorter course of therapy may reduce the selection pressure for the treated pathogen and may also decrease the impact on endogenous flora.[29] Additionally, high cure rates may be achieved when a short-course, higher-dose therapy with a potent, rapidly acting agent is used.[42] Other potential benefits of a short-course, higher-dose therapy include less total drug exposure, avoidance of adverse effects, enhanced patient and healthcare worker convenience and adherence, and improved cost-effectiveness.[42]

Short-course, higher-dose regimens therefore have the potential to reduce the emergence of antibacterial resistance in the pathogen as well as other commensal flora, in both the patient being treated and the wider population.[42] Some studies have found reduced carriage of, or infection with, resistant organisms in patients treated with either short-course, or short-course, higher-dose regimens.[15,43] Although it is not yet clear that short-course, higher-dose therapy can reduce resistance, there is ample evidence that low-dose, long-duration therapy promotes resistance. Studies indicate that a low daily dose and a long duration of treatment with an oral β-lactam contribute to selective pressure in promoting penicillin-resistant *S pneumoniae* (PRSP).[44] Additionally, use of β-lactams, sulfonamides, and macrolides is associated with PRSP. Both short-term and long-term β-lactam use significantly increases the risk of penicillin-resistant infection.[45]

A reduced exposure to total drug amount may also increase patient tolerability and adherence.[29,42] In one study, adherence was better among children who received a 3-day regimen of amoxicillin compared with those who received a 5-day regimen.[29] Additionally, a review of 76 studies determined that adherence is significantly improved with once-daily dosing as compared with 3 or 4 daily doses.[29] Overall, short-course therapy for CAP is more convenient for the patient, improves adherence, decreases adverse effects, and may significantly help to slow the emergence of antimicrobial resistance.[29] A complete discussion of the pharmacokinetic principles behind high-dose, short-course antimicrobial treatment can be found in the accompanying article by Poole and Portugal.[46]

A number of studies have demonstrated the comparable or superior effectiveness of short-course, high-dose regimens.[42] Higher-dose, short courses of levofloxacin (750 mg for 5 days) have been found effective in eradicating *S pneumoniae* and inducing remission.[13] Increasing the dose of levofloxacin from 500 mg to 750 mg increases peak drug concentration and allows for a shorter course of treatment without diminishing therapeutic benefit. In a multicenter, randomized, double-blind investigation of 530 patients with mild-to-severe CAP, levofloxacin 750 mg daily for 5 days was compared with levofloxacin 500 mg daily for 10 days.[13] In the clinically evaluable population, the clinical success rates were comparable in both groups, at 92.4% for the 750-mg group and 91.1% for the 500-mg group (95% CI, -7.0 to 4.4). At the posttherapy visit, eradication rates for common pathogens were similar for both groups. In addition, at day 3, 67.4% of patients in the 750-mg group reported resolution of fever, compared with 54.6% of patients in the 500-mg group ($P = 0.006$).[13]

The 750-mg course of levofloxacin also offers an effective tool for the management of CAP caused by atypical pathogens.[21] Levofloxacin is effective against intracellular atypical agents, such as *L pneumophila* and *C pneumoniae*, whereas penicillin and cephalosporins are not. In addition, *M pneumoniae* is not susceptible to β-lactams.[20] For atypical pneumonia, macrolides, doxycycline, and fluoroquinolones are recommended.[21]

Cost-effectiveness

Antibiotic efficacy is a prime factor in cost-effectiveness and in preventing the high costs of retreatment, particularly hospitalization. Decreased patient adherence increases costs as well, and simpler, less-frequent dosing regimens result in better compliance. For several therapeutic classes, patient adherence has been shown to decrease proportionally as the number of daily doses increases. For medications in general, adherence is significantly higher for once-daily versus 3- or 4-times daily dosing.[47]

Clinical success and patient adherence factors also drive the increase in microbial resistance. Initial treatment of CAP with a therapy that is well tolerated, active against the

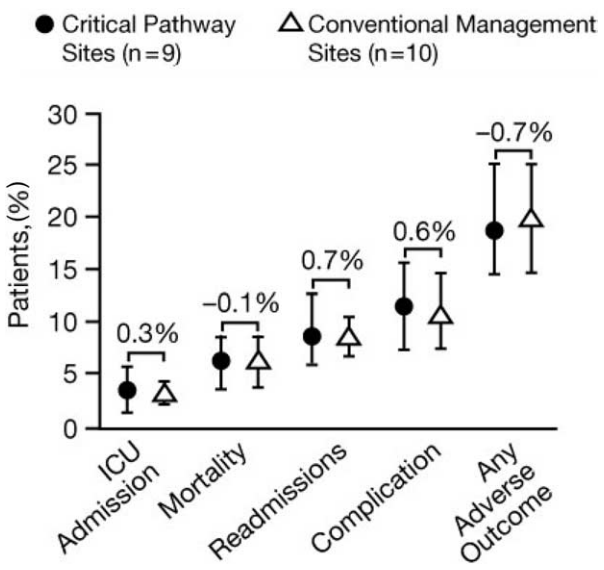

Figure 1 Percentage of patients experiencing the specified clinically relevant outcomes by treatment group. All estimates are based on institutional data displaying the mean (2-sided 95% confidence interval). Any adverse outcome is a composite of intensive care unit (ICU) admission, mortality, readmission, or occurrence of a complication. The absolute difference in rates between the experimental groups (critical pathway minus conventional management) is shown above the brackets. The upper limit of the 1-sided 95% confidence limit of this value (for ICU admission, 2.0%; mortality, 2.5%; readmissions, 3.6%; complications, 4.6%; and any adverse outcome, 4.6%) gives an estimate of the outermost deleterious effect of the critical pathway compared with conventional management. (Reprinted with permission from *JAMA*.[51])

predominant pathogens, low in resistance, and taken once daily may result in better patient adherence, faster symptom resolution, and reduced costs of care. Fluoroquinolones have demonstrated low resistance and high effectiveness, and some of these agents meet the criteria of once-a-day dosing (levofloxacin, gatifloxacin, moxifloxacin, and gemifloxacin).[36,48–50]

In addition to increasing patient adherence, evidence from clinical trials supports the use of critical pathways to improve patient outcomes and decrease costs in the treatment of CAP. The Community-Acquired Pneumonia Intervention Trial Assessing Levofloxacin (CAPITAL) study found that using critical pathways can reduce the use of institutional resources and cost without an increase in adverse outcomes. A significantly greater percentage of low-risk patients presenting to hospitals that used critical pathways were treated as outpatients without an increase in adverse clinical outcomes (**Figure 1**),[51] indicating that critical pathways can be used to identify patients who can be safely treated on an outpatient basis. In addition, the levofloxacin-treated patients were more likely to receive treatment with a single class of antibiotic compared with patients treated with conventional management (64% and 27%, respectively; $P < 0.001$).[51]

Summary

When choosing an antimicrobial, effective treatment depends on proper patient evaluation and the identification of numerous factors, such as recent antibiotic exposure, diabetes, or COPD. Although patients without these conditions may be treated effectively with a macrolide, for example, for patients who have these conditions and have used antibiotics or oral steroids within the past 3 months, a fluoroquinolone is recommended.

Fluoroquinolones meet the recommendations outlined in the CARAT criteria and in general offer the optimal drug at the optimal dosage for antibiotic treatment of patients with CAP. Higher-dose, short-course fluoroquinolone treatment may represent a significant advance in the management of CAP. Short courses of a fluoroquinolone may also decrease the emergence of resistant strains, as well as minimizing therapeutic failures and the need for retreatment.

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