Challenges in the Management of Community-Acquired Pneumonia: The Role of Quinolones and Moxifloxacin

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Current strategies and guidelines for the treatment of community-acquired pneumonia are directed toward making care cost effective, by treating patients on an outpatient basis whenever possible. The use of the new fluoroquinolones could help to achieve these goals. These agents are highly bioavailable and can facilitate the oral treatment of certain patients who otherwise might be admitted to the hospital, as outpatients. The good absorption and bioavailability of these agents can allow moderately ill patients to rapidly achieve effective serum levels of the drug after oral administration and can also facilitate early discontinuation of intravenous therapy and early discharge for responding inpatients. For inpatients or outpatients with clinical risk factors for acquiring drug-resistant pneumococci, quinolones represent a reliable monotherapy option and an effective alternative to a β-lactam/macrolide combination. Although the in vitro differences among the various quinolones remain of unclear clinical relevance, preliminary data suggest that agents with enhanced in vitro activity against pneumococci, such as moxifloxacin, may have greater clinical efficacy and may lead to more-rapid resolution of fever and, potentially, less selection of future pneumococcal resistance to quinolones than that associated with agents with less intrinsic activity.

Community-acquired pneumonia (CAP) remains a common illness in the United States, with 5.6 million cases occurring annually, the majority of which are managed on an outpatient basis. A total of 4.5 million episodes of CAP occur in outpatients, yet, of the $8.4 billion spent on the care of this illness, most ($8.0 billion) is spent on the care of the 1.1 million inpatients [1]. Pneumonia is the number one cause of death due to infectious diseases in the United States, and our management of CAP continues to evolve. At present, we are trying to achieve more cost-effective management of CAP, a goal that can be accomplished through the use of accurate empirical therapy and the application of management approaches that help us shift care to the outpatient setting whenever possible. Shifting care to the outpatient setting can be facilitated by the use of quinolones, a highly bioavailable class of antibacterials that achieve the same serum levels with oral (po) administration as with intravenous (iv) administration. This feature, combined with the excellent antimicrobial spectrum of quinolones, may allow us to treat sicker, “borderline” patients with CAP with po therapy on an outpatient basis. In addition, for patients who are admitted to the hospital, we may be able to rapidly transition from iv to po therapy by switching therapy to a po quinolone as soon as the patient has a good clinical response to initial iv therapy.

BACTERIOLOGIC FINDINGS FOR CAP

Patients with CAP generally fall into 3 groups: those treated on an outpatient basis, those admitted to the hospital but not the intensive care unit (ICU), and those with severe CAP who are admitted to the ICU [2, 3]. For all 3 groups, the predominant etiologic pathogen of CAP is Streptococcus pneumoniae, an organism that not only remains common but is increasingly becoming
resistant to a wide range of antibiotics. In all patients with CAP, infection with an atypical pathogen is also common, with these organisms either causing the pneumonia or perhaps serving as coinfecting pathogens along with bacterial organisms [4]. The common atypical pathogens causing CAP are *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella* species. *Haemophilus influenzae* is also a common organism among outpatients with CAP, especially cigarette smokers. Other etiologic pathogens of pneumonia in outpatients include the respiratory viruses, such as influenza virus, adenovirus, and respiratory syncytial virus (which, among adults, is most common in institutionalized elderly patients). Enteric gram-negative bacteria rarely cause CAP in outpatients, except in those who have underlying cardiopulmonary disease or certain other “modifying” factors that also put them at risk for infection with drug-resistant *S. pneumoniae* (DRSP), enteric gram-negative bacteria, or even *Pseudomonas aeruginosa* [2].

When a patient with CAP is admitted to the hospital, the spectrum of etiologic pathogens is similar. However, outside the ICU, it is relatively uncommon to see enteric gram-negative bacteria as etiologic pathogens, unless the patient has entered the hospital from a nursing home, has a serious underlying comorbidity, or recently was exposed to antibiotic therapy. One classic example of a relationship between comorbid illness and CAP due to enteric gram-negative bacteria is the finding of *Klebsiella pneumoniae* in alcoholics. In both patients in the ICU and hospitalized patients not admitted to the ICU, infection with DRSP becomes more likely, especially if the patient has certain modifying factors present [2]. When a patient with CAP is admitted to the ICU, pneumococcus remains the dominant pathogen, but *Legionella* species may also be important. Recent studies have confirmed that atypical pathogens are commonly associated with severe CAP, but the identity of the etiologic pathogen may vary over time [5]. In some calendar years, *Legionella* species may predominate, whereas, in other time periods, *M. pneumoniae* and *C. pneumoniae* become more predominant. Other organisms leading to severe CAP include *H. influenzae* and the enteric gram-negative bacteria. *P. aeruginosa* is an etiologic pathogen that may occur in up to 10%–20% of patients with CAP admitted to the ICU [3, 6]. *Staphylococcus aureus* may also cause severe CAP, and infection with this species is an important consideration for any patient who develops pneumonia after influenza infection. Some recent reports of methicillin-resistant *S. aureus* have appeared, but the occurrence is sporadic and, fortunately, not common [7].

The likely etiologic pathogens in patients with CAP change when certain clinical features and historical data are present. Modifying factors that place patients at risk for infection with DRSP include age >65 years, receipt of β-lactam therapy within the past 3 months, alcoholism, immune suppression (which includes receipt of corticosteroid therapy), multiple medical comorbidities, and exposure to a child in day care. Risk factors for infection with gram-negative bacteria include residence in a nursing home, underlying cardiopulmonary disease, multiple medical comorbidities, and any recent antibiotic therapy. Infection with *P. aeruginosa* specifically becomes a consideration when patients have bronchiectasis, exposure to >10 mg of prednisone daily, receipt of broad-spectrum antibiotics for >1 week during the past month, and malnutrition [2]. There has been some debate about whether gram-negative bacteria actually cause CAP. One recent publication evaluated 559 consecutive patients with CAP, using reliable sampling methods, such as blood cultures, pleural fluid samples, transthoracic needle aspiration, and bronchoscopy. The investigators determined that ~10% of all cases of CAP were caused by enteric gram-negative bacteria, and two-thirds of these organisms were *P. aeruginosa* [6]. In that study, the risk factors for pneumonia due to gram-negative bacteria included probable aspiration, prior hospitalization, prior receipt of antibiotic therapy, and pulmonary comorbidity. The risk factors that are specific for infection with *P. aeruginosa* were pulmonary comorbidity and prior hospitalization.

**GUIDELINES FOR THE MANAGEMENT OF CAP IN AN ERA OF PNEUMOCOCCAL RESISTANCE**

Since 1993, a variety of organizations have developed guidelines for the management of CAP. Starting with the 1998 guidelines of the Infectious Diseases Society of America, these management recommendations have discussed how therapy should be altered when there are concerns about DRSP. Currently, published guidelines from the Canadian Thoracic Society, the Canadian Infectious Disease Society, the American Thoracic Society, and the Infectious Diseases Society of America all deal with the management of CAP and how to specifically modify therapy when infection with DRSP or certain unusual pathogens are a possibility [2, 3, 8].

In the 2001 American Thoracic Society CAP guidelines, quinolones assumed an important role and were recommended for the treatment of many categories of patients, with the exception of outpatients and patients without risk factors for DRSP or unusual pathogens, who can receive monotherapy with a macrolide (such as azithromycin or clarithromycin or azithromycin iv). These patients specifically have no history of cardiopulmonary disease and no modifying factors, which means that there is no substantial risk of infection with DRSP, enteric gram-negative bacteria, or *P. aeruginosa* [2]. Outpatients who have risk factors for these pathogens or a history of cardiopulmonary disease, inpatients not admitted to the ICU, and all patients admitted to the ICU are potential candidates for quinolone therapy, but different agents may be required for different groups of patients. Patients treated on an outpatient basis and those inpatients who are not admitted to the ICU can be ef-
fectively treated with one of the new antipneumococcal quinolones (e.g., gatifloxacin, gemifloxacin, levofloxacin, and moxifloxacin) as monotherapy. For patients admitted to the ICU, all of the current guidelines agree that quinolone monotherapy should not be used, but these agents could be part of a combination therapy regimen. The reasons for not using quinolone monotherapy for severely ill patients include a lack of strong data showing the efficacy, safety, or proper dosing of quinolones for this population and concern that quinolone monotherapy might not be adequate for patients with severe pneumococcal pneumonia complicated by unsuspected meningitis.

Empirical therapy for CAP is determined by predicting the most likely etiologic pathogen for each population of patients, but most current guidelines recommend modifications of therapy when infection with DRSP is a consideration, and all current guidelines also recommend therapy that provides coverage for atypical pathogens, which may commonly cause coinfection. The rationale for modifying therapy when infection with DRSP is a concern is based on 2 considerations. First, the selected therapy should assure clinical efficacy against organisms that harbor in vitro resistance. In general, current levels of pneumococcal resistance do not affect outcome until organisms reach a penicillin MIC of at least 4 mg/L, a level that, fortunately, is uncommon [9]. Thus, the use of a wide range of antibiotics still leads to a good clinical response in patients with CAP due to DRSP. Although outcomes are generally not affected by in vitro penicillin resistance, a much more important rationale for using highly active pneumococcal therapy for patients with risk factors for infection with DRSP is to manage the problem of future resistance. Although this is a theoretical concern, as discussed below, recent case series have shown the emergence of resistance during therapy with certain less-active antipneumococcal quinolones; thus, it probably is important to assure rapid and complete eradication of even temporarily resistant organisms. This approach could minimize the chance that, when patients recover, they will still be colonized by a potentially drug-resistant organism, which could spread to others in the community.

A number of recent studies have suggested that atypical pathogens are common in CAP, and that outcomes are improved if empirical therapy provides coverage for these organisms [10–12]. These studies have shown that up to 60% of all patients with CAP have serologic evidence of a recent infection with an atypical pathogen and that as many as 40% of all patients have a mixed infection involving atypical pathogens along with bacterial pathogens [4]. Although, traditionally, we have thought of atypical pathogens as predominating in young, otherwise healthy, individuals, a population study from Ohio demonstrated that M. pneumoniae, Legionella species, and C. pneumoniae were nearly as common as pneumococci in patients of all age groups but were more common in patients >65 years old than in patients 18–34 years old [13]. When coinfection with an atypical pathogen occurs, some data suggest that these organisms potentiate the severity of pneumococcal infection [14]. Thus, recent studies have demonstrated atypical pathogens to be more common than we previously thought, occurring in patients of all ages, often as part of a mixed infection; when a mixed infection is present, it may enhance the severity of the coexisting bacterial infection. Although none of these data directly show that atypical pathogens should be treated in patients with CAP, a number of outcome studies involving inpatient elderly individuals, as well as younger individuals, have documented that, when empirical therapy accounts for atypical pathogens, mortality is reduced [10–12]. These data have shown that mortality is reduced when a macrolide is added to a β-lactam or when a quinolone is used as monotherapy. The explanation for these data may be coinfection with an atypical pathogen, because, in at least one study, the benefit of providing coverage for atypical pathogens varied over the course of time, when 3 different calendar years were examined [11]. In some years, coverage of atypical pathogens led to better outcomes than in other years, implying that there may be temporal or geographic variability in the frequency of coinfection with atypical pathogens.

THERAPY CHOICES FOR CAP WHEN DRSP IS A CONCERN: THE ROLE OF QUINOLONES

For all patients with risk factors for infection with DRSP, treatment should involve either the combination of a selected β-lactam with a macrolide or tetracycline or, alternatively, an antipneumococcal quinolone given as monotherapy [2, 3, 8]. For the treatment of outpatients, the acceptable po β-lactams include cefpodoxime, cefuroxime, amoxicillin-clavulanate, and high-dose amoxicillin (3 g/day). For patients admitted to the hospital, the acceptable β-lactam therapies include cefotaxime, ceftriaxone, ertapenem, and ampicillin-sulbactam. Agents such as cefepime, piperacillin-tazobactam, imipenem, and meropenem may also be effective, but these latter 4 drugs are also antipseudomonal and should be reserved for patients who have specific risk factors for pseudomonal infection (table 1) [2]. The American Thoracic Society guidelines did not include ceftazidime among the acceptable therapeutic choices for these patients, because its pneumococcal activity was not as effective as that of the other antipseudomonal agents listed.

Although outcome studies have not definitively shown that the combination of a β-lactam and a macrolide leads to a different outcome than does quinolone monotherapy, the use of the newer antipneumococcal quinolones represents a very effective therapy for patients who are at risk of infection with DRSP. The currently available antipneumococcal quinolones include gatifloxacin, levofloxacin, and moxifloxacin (which are all available both iv and po) and gemifloxacin (which is only...
Table 1. Acceptable intravenous antibiotic therapy options for patients at risk of acquiring community-acquired pneumonia (CAP) due to drug-resistant Streptococcus pneumoniae.

<table>
<thead>
<tr>
<th>Therapy options</th>
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<tr>
<td>Selected β-lactam (plus a macrolide)</td>
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<tr>
<td>Ampicillin-sulbactam</td>
</tr>
<tr>
<td>Cefotaxime</td>
</tr>
<tr>
<td>Ceftriaxone</td>
</tr>
<tr>
<td>If patient also has pseudomonal risk factors, use one</td>
</tr>
<tr>
<td>of the following antipseudomonal β-lactams</td>
</tr>
<tr>
<td>Cefepime</td>
</tr>
<tr>
<td>Imipenem</td>
</tr>
<tr>
<td>Meropenem</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
</tr>
<tr>
<td>Antipneumococcal quinolones (use as monotherapy</td>
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<tr>
<td>unless severe CAP)</td>
</tr>
<tr>
<td>Gatifloxacin</td>
</tr>
<tr>
<td>Levofloxacin</td>
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<tr>
<td>Moxifloxacin</td>
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**NOTE.** Data are derived from Niederman et al. [2].

available orally). As discussed below, these agents have different activity against pneumococci on an in vitro basis. The choice among these quinolones should be based on a number of considerations, including safety, efficacy, and tolerability, but, from an efficacy standpoint, the in vitro differences among these drugs may also have clinical relevance. A variety of other agents may also be considered when patients have risk factors for infection with DRSP. Although vancomycin is effective, it should be used very selectively; linezolid (an oxazolidinone) is generally reserved for gram-positive resistance in patients with nosocomial infection, even though it is effective against DRSP. A new class of agents, the ketolides, may also play a role in the management of CAP, because they provide good activity against DRSP; however, their exact role is unclear, and they do not have activity against enteric gram-negative bacteria.

When a patient with CAP is admitted to the ICU, therapy is based on whether there are risk factors for *P. aeruginosa* infection, but all patients in the ICU also require empirical therapy for DRSP infection. If a patient with severe pneumonia has no risk factors for pseudomonal infection, recommended therapy includes a selected β-lactam, such as cefotaxime, ceftriaxone or ertapenem, combined with an iv macrolide or an iv quinolone. If risk factors for pseudomonal infection are present, recommended therapy includes an antipseudomonal β-lactam, such as cefepime, piperacillin-tazobactam, imipenem, or meropenem; these agents should be combined with ciprofloxacin. Alternatively, a 3-drug approach could be applied, by use of one of the same β-lactam agents plus an aminoglycoside and either an iv macrolide or an iv antipneumococcal quinolone.

In therapy for CAP, quinolones offer the advantage of a good spectrum of activity against pneumococci (both penicillin-susceptible and -resistant organisms), enteric gram-negative bacteria, and atypical pathogens. In addition to this excellent spectrum of activity, quinolones are highly bioavailable and achieve the same serum levels with po therapy as with iv therapy [15]. One other potential use for quinolones is in the treatment of moderately ill outpatients who are going to be sent to the hospital for admission. Recent studies have documented that, for these moderately ill patients, rapid administration of antibiotics can reduce mortality [16]. In fact, when a patient comes to the emergency department, new data have shown that, in a population of patients covered by Medicare, administration of antibiotics within 4 h of arrival to the hospital is associated with a significant reduction in mortality, compared with administration of antibiotics at later time points [16]. With this consideration in mind, it may be possible for moderately ill outpatients to achieve immediate serum levels of an effective antibacterial by ingesting a po quinolone in the doctor’s office. This approach will certainly assure rapid attainment of good serum levels and an avoidance of a delay in the administration of effective antibacterial therapy. The benefit of rapid therapy, however, should be balanced against the likelihood that this therapy could negate the value of diagnostic testing, particularly that of blood cultures. Recent information has clearly demonstrated that the use of antibiotics prior to the collection of blood cultures makes it very likely that the blood culture results will be negative or misleading [17].

**THE NEED FOR 2 DIFFERENT QUINOLONES TO TREAT CAP**

With the wide array of quinolones that are currently available and the broad range of pathogens that cause CAP, it may be necessary to treat different patients with agents that have a different spectrum of antimicrobial activity. For the majority of patients with CAP, an agent should be chosen that is highly active against pneumococci, including drug-resistant pathogens. With this consideration in mind, the antipneumococcal quinolone that is chosen should be highly active against pneumococci, based on in vitro MIC values, to assure efficacy and avoid the selection of future quinolone-resistant pneumococci. However, there is a group of patients with CAP who are at risk for infection with *P. aeruginosa*, and an antipseudomonal quinolone may be necessary for this population.

In selecting quinolone therapy for CAP, assurance of efficacy is an especially important consideration for patients who have clinical conditions associated with an increased risk of resistance to penicillin. Although DRSP are common in the United States, their effect on outcome remains uncertain. In one large study of nearly 6000 patients with bacteremic pneumococcal pneumonia, in vitro resistance had very little effect on mortality, but the study did not examine the effect of specific antibacterial therapies on outcome [9]. However, there was a small subset...
of patients in whom in vitro resistance was associated with an increased mortality rate. This association between in vitro resistance and an increased mortality rate specifically occurred in patients who did not die during the first 4 days of therapy and whose infecting pathogens also had a penicillin MIC of at least 4 mg/L. This degree of resistance is relatively uncommon, and, in fact, the number of patients whose infecting pathogens had this degree of clinically relevant resistance was only 19 of nearly 6000 patients. These findings may explain the general observation that, in patients with CAP, in vitro resistance is not associated with increased mortality, because the number of patients who harbor a pathogen with a clinically relevant degree of resistance is, fortunately, quite small.

Resistance develops not only to penicillin but, also, to other classes as well, thus leading to the emergence of “multidrug-resistant pneumococci.” Resistance to macrolides has been increasing through the 1990s, and, at present, rates of pneumococcal resistance to macrolides are approaching 35%-40%. However, it is important to recognize that there are 2 types of macrolide resistance [18]. In the United States, the majority of macrolide resistance in pneumococci occurs via an efflux mechanism, and this is a relatively low level of resistance, which may not be clinically relevant. On the other hand, some pneumococci are resistant to macrolides through a ribosomal mechanism, and this represents a very high level of resistance, which may lead to clinical failure. Throughout the 1990s, as the rates of resistance to macrolides have increased, most of this increase has been in the efflux mechanism, and it appears that it is this increase in efflux-mediated resistance that has been driven by the widespread use of macrolides [18]. There are not yet data to show that the widespread use of macrolides has led to a corresponding increase in the ribosomal mechanism of resistance.

For patients with CAP, clinical failures can occur with many different classes of antibiotics. Clinical failures can occur whether patients are infected with susceptible or resistant organisms, but the issue of breakthrough bacteremia is an important one, and this phenomenon has been documented to occur in association with β-lactams, macrolides, and selected quinolones. Breakthrough bacteremia has been documented to occur with macrolide therapy, but the exact frequency is very difficult to estimate, and, in the report in which this has occurred [19], it is also difficult to determine whether patients complied with the therapy and whether they were appropriate candidates for macrolide monotherapy. Because treatment failures have occurred with all classes of antibiotics for decades, the exact relationship between in vitro resistance and breakthrough bacteremia remains uncertain.

Quinolones have been considered to be a therapeutic option that may have great value, especially when in vitro resistance is suspected. However, the MIC values for the currently available antipneumococcal quinolones vary widely. Levofoxacin has an MIC of 1.0–2.0 mg/L, gatifloxacin has an MIC of 0.25–0.5 mg/L, moxifloxacin has an MIC of 0.25 mg/L, and gemifloxacin has an MIC of 0.12 mg/L [15]. Although most clinical trials have not shown differences among these agents, there is concern that, when the less active agents in this class, such as levofloxacin, are used, there is a greater chance of intermittent clinical failures and of selection of quinolone-resistant pneumococci [20–22].

Quinolones are antibiotics that are known to kill bacteria in a concentration-dependent fashion. Therefore, the higher the concentration of the antibacterial relative to the MIC against the target organism, the more rapidly and completely the bacteria are killed [15, 23]. This concentration-dependent killing can be expressed as the ratio of the maximum serum concentration divided by the MIC against the target organism, or as the ratio of the area under the concentration-time curve (AUC) to the MIC against the target organism. When the AUC:MIC has been examined, the target value for pneumococci has been a ratio of at least 30. When the available quinolones are used in currently approved doses, this target value cannot always be achieved. At a 500-mg dose, levofloxacin achieves an AUC value of 47.5 and, therefore, would fall below the target AUC:MIC of 30, if an organism had an MIC of 2 mg/L. This problem can be avoided by using a higher dose, such as 750 mg once daily [24]. On the other hand, an agent like moxifloxacin achieves an AUC of 30 and, when this value is divided by an MIC of 0.25 mg/L, it leads to an AUC:MIC well above 120, which is certainly beyond the target value needed to both ensure efficacy and rapid eradication of bacteria.

Although these pharmacokinetic parameters are only theoretical considerations, they may explain recent clinical observations of increasing rates of levofloxacin-resistant pneumococci and occasional treatment failures [20–22, 25]. For example, one case series described 4 patients with pneumococcal pneumonia for whom po levofloxacin therapy failed; 1 of the patients died [20]. For 2 of these 4 patients, the infecting pathogens acquired resistance during therapy, an event likely related to the borderline activity of levofloxacin against pneumococci. In addition, there were 2 patients who initially had resistant organisms as a consequence of recent exposure to quinolones; the authors of that report suggested that, if patients have a history of recent quinolone use, quinolones should not be used again in the treatment of CAP.

Although it remains unclear whether there are truly clinical differences among the available quinolones, there are now a number of studies that have documented the efficacy of moxifloxacin in the therapy of CAP [26–33]. For example, po moxifloxacin has been studied alone and in comparison to other agents as po therapy. In one report, Patel et al. [32] evaluated 254 patients (most of them outpatients) in an uncontrolled, nonblinded fashion. These patients were treated with 400 mg
of po moxifloxacin for 10 days, and clinical resolution occurred for 94% of patients by the end of therapy. Ninety-two of these patients also were treated effectively for documented infection with an atypical pathogen. In another study, Hoeffken et al. [31] conducted a prospective, randomized, double-blinded trial of outpatients. In that study, 229 patients were treated with 200 mg of moxifloxacin daily for 10 days, 224 patients were treated with 400 mg of moxifloxacin daily for 10 days, and 222 patients were treated with 500 mg of clarithromycin twice daily for 10 days. All groups had excellent clinical success rates (>90%), thus documenting the efficacy of all of these regimens. Other studies of po therapy have involved sicker populations of patients. Petitprez et al. [30] conducted a multinational, randomized, double-blind trial of 400 mg of po moxifloxacin for 10 days, compared with 1000 mg of amoxicillin 3 times daily for 10 days. In that trial, 79% of patients were hospitalized, and clinical success rates were 91.5% for moxifloxacin, compared with 89.7% for high-dose amoxicillin. Torres et al. [29] conducted a randomized double-blind study of 278 patients treated with 400 mg of moxifloxacin daily for up to 14 days, compared with 285 patients who received standard therapy, which included either amoxicillin or clarithromycin for up to 14 days. In that study, 62% of all patients were hospitalized, and clinical success rates were >90% in the per-protocol population for both treatment groups.

Not only is efficacy important in the therapy of CAP, but the safety of quinolones has been a great concern. Recently, Faich et al. [26] reported the experience of >18,000 outpatients treated with po moxifloxacin in physicians' offices; >1300 of the patients received 400 mg of moxifloxacin daily for at least 10 days as therapy for CAP. The success rate in this population was >90%, and adverse events were relatively uncommon. A total of 13% of patients had drug-related adverse events, which included headaches, nausea, diarrhea, vomiting, and occasional dizziness. In that study, there were no reports of ventricular arrhythmias, and there were 6 deaths, which were not considered to be related to arrhythmias. The limitation of these data is that the number of patients studied with electrocardiogram (EKG) monitoring was not specified. However, recently, a comparative study of moxifloxacin and levofloxacin for the therapy of elderly patients with CAP was completed [34]; in that study, all 195 patients treated with moxifloxacin and 199 patients treated with levofloxacin underwent a baseline EKG test, 72 h of Holter monitoring, and then a second EKG test. All the patients were >65 years old, 75% had cardiac disease, and only 1 patient (treated with levofloxacin) had torsade de pointes; 1 patient with moxifloxacin had nonlethal sustained ventricular tachycardia (duration, >30 s).

Moxifloxacin has also been used as an iv therapy for hospitalized patients with CAP. Finch et al. [27] conducted a multinational, randomized, open-label study of 400 mg of iv moxifloxacin for at least 3 days, followed by po therapy, for a total of 7–14 days. In that trial, the comparator was amoxicillin-clavulanate given iv, with optional clarithromycin. In both arms of the study, iv therapy was administered for a minimum of 3 days, followed by po therapy. Overall, there were 258 clinically valid (per protocol) patients treated with moxifloxacin and 280 valid patients treated with the comparator agent. There were a statistically significant better rates of clinical cure and bacteriologic success associated with moxifloxacin (93% and 94%, respectively), compared with the control agent (85% and 82%, respectively), but, importantly, there was a difference in the rate at which patients became afebrile. With moxifloxacin, 60% of patients became afebrile on day 2 of therapy, compared with <50% of patients treated with the comparator agent. This translated into 50% of all moxifloxacin-treated patients being transitioned to po therapy by day 3, compared with <20% of comparator-treated patients being transitioned to po therapy. In the economic analysis of these same data, by use of both a German and French health care–system approach, the more rapid treatment response achieved with moxifloxacin correlated with more cost-effective management of CAP [33].

The other study of iv moxifloxacin was reported recently by Lode et al. [28]. This report included pooled data from 2 prospective randomized trials, focusing only on patients with severe CAP. Patients randomly received either iv/po moxifloxacin or iv/po amoxicillin-clavulanate, with or without clarithromycin, in one study and iv/po moxifloxacin or iv/po trovafloxacin-levofoxacin in the second study. The clinical success rate for patients with severe pneumonia was 88% for the moxifloxacin-treated patients, compared with 85% for comparator-treated patients. These differences were not statistically significant. On the other hand, a more rapid switch to po therapy was associated with moxifloxacin, compared with the comparator regimen, occurring in 73% of severely ill patients by day 5 with moxifloxacin but in only 60% of patients treated with the comparator.

Recently, there has been interest in using high doses of highly active antipneumococcal quinolones to reduce the duration of therapy for CAP. Dunbar et al. [24] reported a comparison of 500 mg of levofloxacin daily for 10 days and 750 mg of levofloxacin daily for 5 days. Clinical success rates for both regimens were identical, but, by day 3, significantly more patients became afebrile with the high-dose regimen than with the low-dose regimen, leading to the conclusion that 5 days of high-dose therapy with levofloxacin was effective for treatment of CAP. When these data are compared with those of the Finch study [27], it appears that the use of 400 mg of moxifloxacin daily, which represents a greater degree of in vitro pneumococcal activity, is associated with an even more rapid rate of patients becoming afebrile (figure 1). Treatment with 500 mg of levofloxacin once daily led to 40% of the patients becoming afebrile by day 3 of therapy, treatment with 750 mg of levo-
Figure 1. Percentage of patients treated for community-acquired pneumonia (CAP) who became afebrile at day 3 of treatment with either 500 or 750 mg of levofloxacin (L) [24]. Significantly more patients were afebrile at this time point with the higher dose, which represented more antipneumococcal activity, on the basis of area under the concentration-curve: MIC values. In a separate study [27], by day 2, even more patients were afebrile after treatment with 400 mg of moxifloxacin (M) than after treatment with either dose of levofloxacin.

Table 2. Potential role of quinolones in the therapy of community-acquired pneumonia.

<table>
<thead>
<tr>
<th>Role of quinolones</th>
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<tbody>
<tr>
<td>Help avoid hospitalization for some patients who are “borderline” for admission</td>
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<tr>
<td>High bioavailability: same serum levels with po as iv therapy</td>
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<tr>
<td>Allows rapid initiation of therapy for moderately ill patients: as a po agent</td>
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<tr>
<td>Rapid attainment of good serum levels</td>
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<tr>
<td>Documented efficacy of po therapy for sicker patients, even some with bacteremia</td>
</tr>
<tr>
<td>Reliable monotherapy for patients with clinical risks for PRSP: inpatient and outpatient</td>
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<tr>
<td>Monotherapy alternative to a β-lactam/macrolide combination for admitted non-ICU inpatients</td>
</tr>
<tr>
<td>Allows for “heterogeneity” of antibiotic choice, especially if patient received recent antibiotic therapy with a β-lactam or macrolide</td>
</tr>
<tr>
<td>Facilitates rapid switch from iv to po therapy for admitted patients</td>
</tr>
<tr>
<td>High bioavailability allows reliable switch to po therapy, maintaining same serum levels</td>
</tr>
<tr>
<td>Rapid resolution of fever when good pneumococcal activity is present can shorten the time needed for iv therapy. Documented to occur when pneumococcal activity is optimized.</td>
</tr>
</tbody>
</table>

NOTE. ICU, intensive care unit; iv, intravenous; po, oral; PRSP, penicillin-resistant Streptococcus pneumoniae.
of an optimally active in vitro agent could minimize the emergence of quinolone-resistant pneumococci.

When a large body of data is examined, it is quite clear that recent therapy with a variety of antibiotics increases the likelihood of pneumococcal resistance to multiple classes of agents. For example, recent therapy with β-lactams, macrolides, or quinolones predicts pneumococcal resistance to that same class of agents [20, 35, 36]. One recent study suggested that the use of β-lactams or macrolides within the past 6 months increases the likelihood of pneumococcal resistance to penicillin, whereas recent use of quinolones does not increase the risk of penicillin-resistant pneumococci [35]. Nonetheless, it seems that, because recent antibiotic therapy can predispose to pneumococcal resistance to the same class of antibacterial that was used, it may be important in the therapy of CAP to obtain a history of recent antibiotic use. With this information, an effort should be made to treat patients with an agent to which they have not been recently exposed. Therefore, for all patients with CAP, it is important to introduce antibiotic heterogeneity and not have all patients receive the same therapy repeatedly, in an effort to avoid failures related to usage-driven resistance.

One other consideration is the potential for “collateral damage” that comes from the use of quinolones for treatment of CAP. Quinolones are being used widely now for a variety of appropriate and, occasionally, inappropriate indications; if an agent such as levofloxacin is used, it may have effects not only on pneumococcal resistance but, also, on the other end of the spectrum (i.e., pseudomonal resistance) [37, 38]. Neuhauser et al. [37] observed that, as quinolone use increased through the 1990s (most of this increase involved the use of levofloxacin), there was an increase in ciprofloxacin-resistant P. aeruginosa. Thus, even though ciprofloxacin was not being used widely, the use of an agent like levofloxacin promoted pseudomonal resistance to ciprofloxacin. The presumed mechanism for this observation is the limited activity of levofloxacin against P. aeruginosa, which did not eradicate the organism but, rather, selected for more quinolone-resistant P. aeruginosa.

**SUMMARY**

Quinolones clearly have a variety of important roles in the management of CAP (table 2). Because of their high bioavailability, quinolones can help avoid hospitalization for some patients who are otherwise borderline for hospital admission. As po agents, quinolones allow for the rapid initiation of therapy for moderately ill patients and achieve serum levels that are highly effective. For patients who have clinical risk factors for infection with DRSP, either inpatients or outpatients, quinolones are a reliable monotherapy and serve as an effective alternative to combination therapy with a β-lactam and a macrolide. Finally, quinolones may facilitate the switch from iv to po therapy for hospitalized patients and may enable such patients to be discharged from the hospital rapidly. Although the in vitro differences among the various quinolones remain of unclear clinical relevance, preliminary data suggest that these differences may correlate with greater efficacy, more-rapid resolution of fever, more-rapid transition from iv to po therapy, and potentially less selection for future quinolone resistance among pneumococci.

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