Widespread Use of Fluoroquinolones Versus Emerging Resistance in Pneumococci

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During the past decade, respiratory-tract pathogens have shown an increase in resistance to all classes of antimicrobial agents. Although the increasing prevalence of penicillin-resistant Streptococcus pneumoniae has resulted in an increased reliance on newer classes of agents, such as the fluoroquinolones, the broad use of these agents has contributed to increasing prevalence of strains with in vitro fluoroquinolone resistance, which are associated with treatment failures, nosocomial outbreaks, and patient fatalities. Strategies to limit this emerging dilemma and preserve the clinical utility of these agents are needed.

In 1998, there were ∼84 million primary care office visits for upper respiratory tract infections, which resulted in 45 million antibiotic prescriptions [1]. Streptococcus pneumoniae is the most significant bacterial cause of such infections [2]. Historically, the management of patients with community-acquired pneumococcal infection was relatively straightforward; cure typically was achieved following a 7–10 day course of β-lactam or macrolide therapy. However, the broad use of antimicrobial agents has directly contributed to the emergence and increasing prevalence of resistant strains [3–6]; currently, 35%–40% of pneumococcal isolates are resistant to penicillin, of which ∼60% express high-level resistance (defined as an MIC of penicillin ≥2 μg/mL) [2]. The increasing prevalence of penicillin resistance also appears to be a marker for resistance to other non-β-lactam antimicrobial agents, such as erythromycin, clindamycin, tetracycline, chloramphenicol, and trimethoprim-sulfamethoxazole [2, 3, 7–13]. This “cross-resistance” is not the result of a common mechanism of resistance or of genotypic linkage but is possibly the result of the clonal spread of a few β-lactam–resistant isolates that have developed resistance mediated by other mechanisms [14–17]. Unfortunately, the presence of endemic multidrug-resistant phenotypes is associated with increasing rates of resistance to other, seemingly unrelated, classes of agents.

The increasing prevalence of penicillin resistance has resulted in reliance on newer classes of agents, such as the fluoroquinolones. The broad use of these agents contributes to the increasing prevalence of fluoroquinolone-resistant microorganisms, which may compromise their long-term clinical utility. In 1998, Dr. S. Levy, then President of the American Society for Microbiology, noted 5 principles of antimicrobial resistance [18], which are as follows: (1) given enough time and drug use, the development of resistance is inevitable; (2) resistance is progressive; (3) an organism that becomes resistant to one drug will likely become resistant to other agents; (4) once resistance occurs, it usually will not diminish; and (5) use of an antibiotic in one individual will ultimately affect others. The present article attempts to consider these espoused principles with respect to the relationship between fluoroquinolone use and the epidemiological emergence of resistant isolates.

SURVEILLANCE STUDIES: FLUOROQUINOLONE RESISTANCE PARALLELS FLUOROQUINOLONE USE

Increasing β-lactam resistance among pneumococci has resulted in the recommendation that fluoroquinolones be used for the empirical treatment of respiratory-tract infections in adults. As occurred with the use of β-lactam agents [19], selective pressure associated with this increased use has resulted in a near-linear pattern of increasing fluoroquinolone resistance.

To date, 2 surveillance studies [3, 11] have examined the parallel between fluoroquinolone use and the emergence of bacterial resistance. Chen et al. [3] reported that, in Canada, the rapid increase in the
annual number of fluoroquinolone prescriptions (from 0.8 to 5.5 prescriptions per 100 persons per year between 1988 and 1997) was tied to an equally abrupt increase in the prevalence of pneumococci with reduced fluoroquinolone susceptibility. They noted that the percentage of pneumococci with reduced susceptibility to fluoroquinolones (defined as an MIC of ciprofloxacin of $\geq 4 \mu g/mL$) increased from 0% of isolates in 1993 to 1.7% of isolates in 1997 and 1998 ($P = .01$). The prevalence of resistant pneumococci was highest among patients aged $\geq 65$ years (2.6% of isolates), but the greatest increase in prevalence was observed among patients aged 15–64 years (from 0.5% of isolates in 1993 to 2% of isolates in 1997 and 1998). Because fluoroquinolones are relatively contraindicated for pediatric patients, it was not surprising that the investigators did not find this pattern among pneumococcal isolates from pediatric patients.

The Centers for Disease Control and Prevention (CDC) analyzed fluoroquinolone prescription data from the National Hospital Ambulatory Medical Care Survey for 1993–1998 and correlated it with surveillance data on invasive pneumococcal disease from the Active Bacterial Core Surveillance program for 1995–1999 [11]. During 1993–1998, fluoroquinolone prescriptions in the United States increased from 3.1 to 4.6 prescriptions per 100 persons per year, whereas the overall number of antimicrobial prescriptions decreased from 53.5 to 51.5 prescriptions per 100 persons per year. The frequency of fluoroquinolone prescriptions was highest for persons aged $\geq 65$ years; it increased from 8.2 to 12.4 prescriptions per 100 persons per year (figure 1) [11]. Susceptibility testing of 8763 isolates obtained from 1995 through 1997 showed that the prevalence of ofloxacin-nonsusceptible isolates (defined as an MIC of ofloxacin of $\geq 4 \mu g/mL$) increased significantly, from 2.6% isolates in 1995 to 3.8% of isolates in 1997 ($P = .02$); such isolates were more common among individuals aged $\geq 18$ years than among individuals aged $<18$ years (3.6% vs. 2.6%). Among adults, the prevalence of ofloxacin-resistant isolates increased from 3.1% of isolates in 1995 to 4.5% of isolates in 1997 ($P = .02$).

On the basis of a 2-year longitudinal study (1997–1998 and 1998–1999) of 96 US medical centers, Sahm et al. [20] noted the need for annual surveillance of resistance among $S. \text{pneumoniae}$ isolates. They showed that risk factors for infection with a resistant strain included coselection due to antibiotic use (including use in animals), and spread of a clone that resulted in nosocomial infections. The prevalence of resistance to $\geq 3$ antimicrobial agents increased from 5.9% to 11% of isolates. The level of penicillin and levofloxacin resistance increased “significantly” ($P < .05$), although the absolute level of fluoroquinolone resistance remained relatively low (0.1%–0.6% of isolates). However, 2 phenotypes with fluoroquinolone resistance that were not found in 1997–1998 were encountered in 1998–1999.

Levofloxacin susceptibility testing performed on 6529 isolates noted that, in 1998 and 1999, among isolates from adults, the prevalence of levofloxacin nonsusceptibility (defined as a levofloxacin
MIC of ≥4 µg/mL was 0.2% [11]. A disproportionate proportion of the levofloxacin-resistant isolates (8 of 15 isolates) were from connecticut residents. Pulsed-field electrophoresis revealed 8 unrelated patterns for these 8 isolates, which suggests that the resistance did not result from the spread of a single clone. However, isolates from connecticut were found to have a 0.9% rate of levofloxacin resistance, compared with 0.2% for isolates from all other areas monitored. Thirteen of the 15 levofloxacin-resistant isolates identified in this study were also resistant to trovafloxacin, suggesting that increased use of fluoroquinolones contributes to the emergence of fluoroquinolone resistance. Although not confirmed by the data presented by the CDC, this suggests that resistance may spread horizontally in a geographic region.

These surveillance studies indicate that selective pressure associated with the increased use of antimicrobial agents is the most important predictor of resistance [3, 19]. If a pathogen, such as S. pneumoniae, is easily transmissible between individuals, it may quickly spread horizontally, and a resistant strain is not readily lost [7].

MECHANISMS OF FLUOROQUINOLONE ACTIVITY AND OF RESISTANCE

The potency of each fluoroquinolone is defined by its activity against 2 bacterial enzymes, DNA gyrase and topoisomerase IV. In general, DNA gyrase is the primary drug target in gram-negative bacteria, and topoisomerase IV is the primary target in gram-positive bacteria [21]. Spontaneous mutations arise in enzyme subunits of DNA gyrase (gyrA and/or gyrB) and/or topoisomerase IV (parC and/or parE), and can exist in small numbers of cells (ranging from 1 per 10^6 to 1 per 10^9 bacteria) in large populations of bacteria [21, 22].

In S. pneumoniae, resistance to ciprofloxacin, levofloxacin, norfloxacin, and trovafloxacin is conferred by a parC alteration in topoisomerase IV, whereas resistance to gatifloxacin and sparfloxacin is conferred by gyrA alterations in DNA gyrase [23]. Pfaller et al. [22] noted the occurrence of phenotypically cryptic parC mutations in S. pneumoniae. Higher levels of resistance may occur by a second mutational step(s), in which the amino acid alterations are selected in the secondary target enzyme subunit [21, 24–27]. Table 1 summarizes the proposed mechanisms of fluoroquinolone resistance in selected pathogens [25, 26].

The pattern of alternating, stepwise mutations in target enzymes implies that both the high intrinsic potency of a drug against the primary target and the similarity of a drug’s potency against both targets will affect the likelihood of selection of a strain with a first-step resistance mutation. The greater the extent to which a fluoroquinolone has similar (and ultimately equal) potency against both enzyme targets, the lower the incremental increases in the MIC of the fluoroquinolone that occur in a bacterium with a first-step drug-target mutation.

It was recently reported that fluoroquinolone-resistant S. pneumoniae were isolated from 2 patients treated for pneumonia with levofloxacin [12]. Nucleotide-sequence analysis of bacterial DNA showed that the isolates contained mutations in both parC and gyrA. For the resistant isolates, MICs of ciprofloxacin, gatifloxacin, sparfloxacin, levofloxacin, and trovafloxacin were greater than the maximum drug concentrations (C maks) in serum reported for standard dosage regimens of

<table>
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<tr>
<th>Primary target enzyme</th>
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<td>Class of organism, organism</td>
<td>Drug-target mutations in DNA gyrase or topoisomerase IV</td>
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<td>Altered enzyme subunit</td>
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<td>Gram-positive</td>
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<td>Streptococcus pneumoniae</td>
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<td>Helicobacter pylori</td>
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<td>Mycobacteria</td>
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NOTE. Adapted from [25] and [26]. Cpfx, ciprofloxacin; Gtfx, gatifloxacin; Lvfx, levofloxacin; Nrfx, norfloxacin; Spfx, sparfloxacin; Tvfx, trovafloxacin.
^a Antimicrobials to which the amino acid alterations in the enzyme confer resistance. For many bacteria, the basic resistance mechanism applies for all quinolone agents. However, in some bacteria, such as S. pneumoniae, the resistance mechanism will vary depending on the type of quinolone, as indicated here for Cpfx and Spfx.
^b Several different types of active efflux mechanisms exist; this data indicates only whether an active efflux mechanism of resistance has been found in a bacterial organism.
^c No or unknown.
those agents. However, the MICs of gemifloxacin and moxifloxacin were below the Cmax in serum. The investigators suggested ifloxacin and moxifloxacin were below the MICs of gemifloxacin and moxifloxacin would decrease the potential for replication of mutants; however, additional resistant mutants were readily obtained by plating mutant bacteria on gemifloxacin- or moxifloxacin-containing agar. Therefore, the “more potent” fluoroquinolones may not halt further accumulation of resistance mutations among S. pneumoniae, once mutant enrichment has been initiated [21].

PHARMACOKINETIC AND PHARMACODYNAMIC MARKERS OF ANTIMICROBIAL EFFICACY AND RESISTANCE

As fluoroquinolones exhibit concentration-dependent killing, it appears that maximal bactericidal activity, with use of the Cmax:MIC ratio and the area under the curve (AUC):MIC ratio as the major pharmacokinetic/pharmacodynamic markers, correlates with clinical efficacy. Several studies have found that clinical efficacy correlates slightly better with the AUC:MIC ratio than with the Cmax:MIC ratio [28–30]. The issue of whether the percentage of free unbound drug or the percentage of total drug has the most impact on antibacterial activity has been much debated. It has been speculated that the percentage of free unbound drug is more germane than total drug to the determination of antibacterial activity.

The importance of the Cmax:MIC ratio is illustrated by the observation that in vitro regrowth of bacteria was inhibited within 24 h after exposure to a fluoroquinolone at a Cmax:MIC ratio of ≥8 [31]. In contrast, regrowth was observed when bacteria were exposed to fluoroquinolone at Cmax:MIC ratios of <8 [31]. With use of this paradigm, a review of the Cmax versus time profiles achieved with selected older and newer fluoroquinolones suggests that, at standard doses and dosing regimens, many of these agents may fail to attain the target concentration for the majority of the dosing interval [32–35].

Ciprofloxacin at a dosage of 500 mg twice daily achieves a mean Cmax of 2.5 μg/mL and does not demonstrate bactericidal activity against S. pneumoniae because the drug concentration remains well below 8 times the MIC90 [32].

Levofloxacin at a dosage of 500 mg once daily achieves a mean Cmax of 5.1 μg/mL and thereby, relative to an MIC90 of 1.0 μg/mL, achieves a peak concentration that is 5 times the MIC90 [33]. Application of the concept of concentration-dependent killing indicates that higher doses than currently recommended are needed to reduce the risk of mutant selection and the emergence of resistance [31]. In contrast, trovafloxacin at a dosage of 200 mg/day produces a Cmax:MIC ratio of 8 (2.0/0.25 μg/mL) [35].

In vitro modeling studies suggest that AUC:MIC ratios on the order of 30–60 may be sufficient to produce gram-positive bacterial eradication [36, 37]. With use of this in vitro paradigm (but not in vivo findings), the standard dosing regimens for ciprofloxacin (750 mg twice daily), levofloxacin (500 mg per day), and trovafloxacin (200 mg per day), which have AUC values of 72, 40, and 34 mg/h/L, respectively, and MIC90 values of 2.0, 1.0, and 0.5 mg/mL, respectively, have AUC:MIC ratios of borderline acceptability for S. pneumoniae (AUC:MIC ratios, 36, 40, and 69, respectively) [38]. Gatifloxacin appears to have an acceptable AUC:MIC ratio, on the basis of the assumption of an AUC of 51 mg/h/L and an MIC90 of 0.5 mg/mL [36]. In contrast, moxifloxacin, which has an AUC of 48 and MIC90 of 0.12, achieves an AUC:MIC ratio of 400. It appears the treatment of gram-negative bacterial infections requires higher MIC:AUC ratios than does the treatment of gram-positive bacterial infections [30, 39].

Ambrose and Grasela [40] used Monte Carlo simulations to estimate the probability of attaining AUC:MIC ratios of 30, 50, 70, and 100; they used AUC values for patients who were treated with either gatifloxacin or levofloxacin and data on these agents’ microbiological activity against S. pneumoniae from the 1997 SENTRY Antimicrobial Surveillance Program. The investigators plotted the probability curves for 5000 patient simulations and found that treatment with gatifloxacin consistently had a higher probability of attaining predefined AUC:MIC ratio targets than did levofloxacin treatment (figure 2) [40]. The probabilities of attaining AUC:MIC ratios of 30, 50, 70, and 100 were 94%, 86%, 78%, and 62%, respectively, for gatifloxacin, and were 80%,
51%, 31%, and 17%, respectively, for levofloxacin [40]. The median AUC:MIC ratio for gatifloxacin was 120 and that for levofloxacin was 50.5.

The mutant prevention concentration (MPC) is the theoretical threshold above which the selection and proliferation of antimicrobial-resistant mutants rarely occurs. In general, MPC values for fluoroquinolones range from 4 to 10 times the MIC. Several groups of investigators have recently reported on the MPC thresholds of individual fluoroquinolone agents and noted increased potency (i.e., reduced potential to select resistant mutants) among those agents with a methyl group or a methoxy group at position 8 or ring structures at position 7 (e.g., gatifloxacin, moxifloxacin, and trovafloxacin) [41–43]. Blandeau et al. [43] ranked the fluoroquinolones according to their potential MPCs for S. pneumoniae, in descending order, as follows: moxifloxacin > trovafloxacin > gatifloxacin > levofloxacin. It must be stressed that the concept of MPC is theoretical and has not been correlated with clinical findings.

**TESTING FOR FLUROQUINOLONE RESISTANCE**

Richardson et al. [44] found that, among S. pneumoniae isolates, only those with both parC and gyrA mutations or with no recognized resistance mechanisms were reliably identified using broth microdilution, disk diffusion, and E-test susceptibility testing procedures. Virtually all resistance can be tracked to the antibacterial treatment paradigm that applies to the particular set of circumstances—that is, if fluoroquinolones are used extensively in the treatment of respiratory tract infections, then resistance will likely appear among the gram-positive pathogens most frequently associated with these infections, such as S. pneumoniae.

Strategies to monitor resistance trends as well as to improve patient care include testing the susceptibility of isolates against fluoroquinolones that are included in the formulary and against other, alternative classes of antimicrobials. Microbiologists should also use established MIC breakpoints for determining resistance levels [45], and resistance patterns for S. pneumoniae need to be reviewed on an annual basis [20]. Some clinicians have found that, in patients with severe bacteremic pneumococcal pneumonia, even monotherapy with an active agent may be suboptimal [46]. In a retrospective study of 225 patients, those receiving monotherapy were 6.4 times more likely to die of their illness than were patients receiving “dual effective therapy” (P = .02; OR, 3.0; 95% CI, 1.2–7.6). In that study, “most patients in the double antibiotic therapy group received either a macrolide-cephalosporin or quinolone-cephalosporin combination” [46, p. 1840]. The investigators offer several explanations, in addition to resistance, for why double therapy might have been more effective than monotherapy: antimicrobial synergy or, at least, an additive antibacterial effect; immunomodulatory effects of antimicrobials; cytokine release; and the presence of multiple but uncultured pathogens, against which dual therapy might have been more effective. Consequently, conventional practices and conventional wisdom seem to be challenged and in need of further analysis. Unfortunately, readily available clinical laboratory tests to determine the degree of drug resistance, such as gene probes for the identification of parC, parE, gyrB, and other mutations, have not yet been developed.

**WHAT CAN BE DONE CLINICALLY?**

Clinicians are greatly concerned about the possibility of increased resistance in pneumococci. The average clinician wants to be able to select a drug for empirical therapy that will be effective in almost all cases. In many instances, sputum specimens are not obtainable, and, even when they are, the unreliability of sputum culture results for diagnosis of pneumococcal pneumonia poses a dilemma [47]. The tendency is to rely increasingly on active agents, perhaps at increasing doses, until resistance to those agents develops as well. In the 1970s, procaine penicillin at a dosage of 600,000 U given im twice daily was adequate to treat hospitalized patients with pneumococcal pneumonia. Today, much higher dosages of intravenous penicillin are recommended, and its efficacy against infections with intermediate-resistant pneumococci (excluding infections of the CNS) remains to be determined.

What has been seen among pneumococcal isolates from various geographical locations is fluoroquinolone “MIC creep” that may be a harbinger of full resistance. There has been discussion about the use of higher dosages of fluoroquinolones, such as a dosage of 750 mg/day of levofloxacin for hospitalized patients suspected of having pneumococcal pneumonia, to improve the C_{max}:MIC ratio. The increased use of pneumococcal vaccine has also been advocated. As the US population ages, there is concern that pneumococcal fluoroquinolone resistance seems to be more likely to develop in patients aged >65 years [11]. As a consequence, no single agent should be routinely used as the “decerebrate” agent of choice. Rather, several alternative agents should be available, and clinicians should be encouraged to consider using possible appropriate agents to treat specific individuals and at specific locations.

Clearly, the problem of antimicrobial resistance among community-acquired pathogens in the United States, as well as worldwide, continues to grow, and no class of agents is immune to the problem. Among S. pneumoniae, resistance to the fluoroquinolones, although currently at a low level, is emerging and may herald a significant future threat to the long-term utility of these agents. Several reports of fluoroquinolone treatment failure, nosocomial outbreaks of resistant S. pneumoniae infection, and fatal infection have surfaced [48].

Rather than looking for the next new antimicrobial agent on the horizon to
solve this potential dilemma, management of patients should entail a constellation of microbiological testing, reporting, and treatment strategies to curb the emergence of resistance. Microbiological strategies that increase the rate of the identification of resistant isolates and limit their development are urgently needed. A recent report by the CDC [11] encourages clinicians to report episodes of infection with fluoroquinolone-resistant pneumococcal isolates recovered from blood or CSF to the state or local health department. Recently, Musher et al. [49] recommended that clinical laboratories reexamine their current methods of reporting data on susceptibility and resistance and to consider reporting pathogen-related information by distinguishing the site of infection and by relating MICs to antimicrobial dosages. Clinicians should change a patient’s empiric treatment regimen to specific therapy once the pathogen is isolated and susceptibility information is available.

Repeated exposure to antimicrobial therapy predisposes patients to colonization with more-resistant stains; therefore, administration of unnecessary therapy and the use of inappropriate (especially subtherapeutic) dosing regimens should be avoided. A number of organizations have issued guidelines for the treatment of patients with community-acquired pneumonia [50–53]. The Drug-Resistant S. pneumoniae Therapeutic Working Group suggested alternative agents, such as the macrolides, doxycycline (for patients aged ≥8 years), or oral β-lactam agents with good activity against pneumococcus, as appropriate choices for empiric treatment [50]. This report also recommends that, to limit the emergence of fluoroquinolone-resistant strains, use of the new fluoroquinolones should be limited to those adults (1) for whom another regimen has failed, (2) who are allergic to alternative agents, or (3) who have a documented infection with highly drug-resistant pneumococci [50]. Studies indicate that respiratory fluoroquinolones do have a role in the treatment of certain patients.

CONCLUSIONS

The fluoroquinolones currently remain useful to treat patients with respiratory-tract infections. Knowledge of local epidemiological data, susceptibility testing of individual isolates, annual monitoring of resistance trends, and reporting of treatment strategies are essential for appropriate antimicrobial selection. However, changes in our approach to judicious antimicrobial selection, such as the use of alternative antimicrobial agents for treatment of appropriate patients with upper respiratory tract infections, may help delay the resistance-induced obsolescence of the fluoroquinolones.

References


