Susceptibility Trends in Respiratory Pathogens:
The Role of the Newer Fluoroquinolones

ABSTRACT: Resistance to the various classes of antimicrobials continues to increase in virtually all clinically significant gram-negative and gram-positive bacteria. In particular, rates of resistance to β-lactam and macrolide antimicrobial agents are on the rise among the most common bacterial pathogens, including Streptococcus pneumoniae and Haemophilus influenzae. In the bacterial cell, the fluoroquinolones inhibit, to varying degrees, the enzymes DNA gyrase (topoisomerase II) and topoisomerase IV. The newer fluoroquinolones (such as gatifloxacin, gemifloxacin, and moxifloxacin) inhibit these enzymes more than the older agents in this class (ciprofloxacin and levofloxacin); gemifloxacin has a greater affinity for these 2 vital target enzymes. When both enzymes are strongly inhibited, any genetic mutation in a microorganism leads to a smaller increase in minimum inhibitory concentration (MIC) than would occur with a quinolone that targets only 1 enzyme. Gemifloxacin exhibits extremely low MIC results against the clinically significant respiratory pathogens—lowest among clinically available fluoroquinolones.

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Bacterial resistance to antimicrobials is a significant problem in the United States and throughout the world. For many years, there have been 2 schools of thought on the problem of resistance. One school holds that as resistant organisms evolve, newer antimicrobial agents will be developed to which these strains of bacteria will be susceptible. However, this approach is fraught with danger, because, as one prominent infectious disease clinician stated several years ago, “the bugs always win.” The second school of thought strives to reduce the likelihood of antimicrobial resistance through a program of education, research, and surveillance. Surveillance is the stepping-off point, because if we do not know which microbes are developing resistance to which drugs, we can neither educate clinicians on appropriate prescribing nor direct research.

In this article, I review trends of resistance of both non–respiratory tract pathogens and respiratory tract pathogens to many antimicrobial agents and the overall problem of resistance in both the outpatient and the inpatient clinical settings. I also review the unique characteristics of the newer fluoroquinolones that are important in counteracting antimicrobial resistance during treatment of respiratory tract infections. Of the newer fluoroquinolones, gemifloxacin has been a benchmark agent because of its high potency and because data gathered during the past 3 years show its continued usefulness.

SURVEILLANCE DATA

Many surveillance programs are nationally based and sponsored by various governmental or other agencies, in both the United States and Europe. In addition, several programs monitor veterinary pathogens because of the controversy about the use of antimicrobial growth promoters in animals. One surveillance network, known as the SENTRY Antimicrobial Surveillance Program, was established in 1997 to gather data on antimicrobial resistance patterns of nosocomial and community-acquired infections from multiple locations in the United States (30 sites), Canada (8 sites), South America (10 sites), Europe (24 sites), and the Asia-Pacific region (17 sites).¹

¹ The antimicrobial resistances of greatest clinical concern are those exhibited by specific
gram-positive microorganisms (staphylococci, certain enterococci, and multidrug-resistant streptococci) and gram-negative microorganisms (Enterobacteriaceae and multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter* species).

Common resistance mechanisms among gram-negative bacilli include:
- Inactivating enzymes, such as extended-spectrum β-lactamases and metallo-β-lactamases.
- Alteration of antimicrobial targets, such as fluoroquinolone action sites on DNA gyrase and topoisomerase IV.
- Activation of efflux pumps that can carry several classes of antimicrobial “out of its bacterial cell.”
- Deletions of membrane transport proteins.

Common resistance mechanisms among *Streptococcus pneumoniae* include the following:
- Efflux pumps and target methylation genes directed against macrolide-, lincosamine-, and streptogramin B–resistant agents (macrolides and clindamycin).
- Altered protein-binding protein targets directed against β-lactam drugs.
- DNA gyrase and topoisomerase gene mutations and efflux pumps affecting quinolone activity.

**RESISTANCE PATTERNS**

Even in 1981, when the third-generation cephalosporins were introduced in the United States, some species of *Enterobacter* were already resistant to these agents. Certain microorganisms were able to produce a group of enzymes known collectively as the β-lactamases that destroy the extended-spectrum third-generation cephalosporins. The β-lactamases inactivate penicillin and cephalosporin antimicrobial agents by splitting the amide bond of the β-lactam ring, thereby rendering it inactive. In particular, one class of β-lactamases—the metalloenzymes—represents a very serious problem because their synthesis would also render carbapenems inactive and are encoded by transmissible genetic elements. Therefore, high levels of resistance to certain β-lactams could reach epidemic proportions in the future.

In some areas of the world, the frequency of resistance among certain organisms appears to
be increasing. For instance, among 12,000 isolates of *Klebsiella* that were examined by the SENTRY Program from 1997 through 2002, the annual frequencies of extended-spectrum β-lactamase phenotypes tended to show an increase in both Europe and Latin America but were relatively stable at 5% to 7% in the United States (Figure 1). On the other hand, in North America, the rate of resistance of *Enterobacter* to the third-generation cephalosporin ceftazidime is closer to the rates of resistance in Latin America and Europe (Figure 2). In all 3 survey regions, the rate of resistance of *Enterobacter* appears to be stable or even decreasing slightly. Apparently, clinicians may be using the third-generation cephalosporins less frequently. Instead, in the hospital setting, the trend appears to be the use of combinations of penicillin with β-lactamase inhibitors, carbapenems, and fourth-generation cephalosporins.

**Gram-negative organisms.** Except for *Acinetobacter* species and, to a lesser extent, *P aeruginosa*, resistance of the gram-negative pathogens to the fluoroquinolone ciprofloxacin has generally not been a significant problem in North America.
In North America, more than 90% of isolates of *P aeruginosa* are susceptible to the aminoglycosides, and more than 80% of strains remain susceptible to certain β-lactams (Table 1). The fluoroquinolones were initially effective against *P aeruginosa* but now show reduced effectiveness. The susceptibility rate of *P aeruginosa* to ciprofloxacin has decreased year by year and now approaches only 70%, possibly because of increased use of less active anti-*Pseudomonas* fluoroquinolones or a total selective pressure by the entire class. In this regard, ciprofloxacin is becoming very similar to other members of this class of drugs in anti-pseudomonal spectrum, such as gatifloxacin, moxifloxacin, and levofloxacin.

**Gram-positive organisms.** Among the various gram-positive microorganisms, methicillin-resistant *Staphylococcus aureus* (MRSA) continues to be a problem. In all 3 regions (Europe, Latin America, and North America) surveyed by the SENTRY Program, the rates of MRSA among isolates of *S aureus* have increased each year and now exceed 40%. Throughout the world, the percentage of isolates of hospital-acquired *S aureus* that are methicillin-resistant has in-
creased each year (Figure 3). As if this situation were not bad enough, isolates from community-acquired infections indicate that MRSA rates are now as high as 7% to 10%.

Resistance of MRSA to vancomycin also has emerged, although there are only a limited number of case reports. Similarly, MRSA that is resistant to linezolid—the only member of the class of antimicrobials known as the oxazolidinones that is available at this time—has been re-

**Table 1 – In vitro activity of 7 selected antimicrobials against Pseudomonas aeruginosa (SENTRY Program, North America 2001; 815 isolates)**

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt; (µg/mL)</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; (µg/mL)</th>
<th>Susceptible (%)</th>
<th>Resistant (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>4</td>
<td>8</td>
<td>96.7</td>
<td>2.7</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>0.5</td>
<td>2</td>
<td>91.7</td>
<td>7.7</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>0.25</td>
<td>&gt; 2</td>
<td>75.7</td>
<td>18.9</td>
</tr>
<tr>
<td>Cefepime</td>
<td>4</td>
<td>16</td>
<td>84.9</td>
<td>6.3</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>2</td>
<td>&gt;16</td>
<td>83.4</td>
<td>13.4</td>
</tr>
<tr>
<td>Imipenem</td>
<td>1</td>
<td>8</td>
<td>86.6</td>
<td>8.5</td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>8</td>
<td>&gt; 64</td>
<td>88.6</td>
<td>11.4</td>
</tr>
</tbody>
</table>

MIC<sub>50</sub>, minimum inhibitory concentration against 50% of isolates; MIC<sub>90</sub>, minimum inhibitory concentration against 90% of isolates.

From Jones RN. *Semin Respir Crit Care Med.* 2003.
ported in several instances; this resistance is usually related to long courses of linezolid therapy exposure.\textsuperscript{6}

The group D streptococci—the enterococci—also have begun to display resistance to vancomycin; to teicoplanin; and to quinupristin/dalfopristin, a streptogramin combination agent. For the treatment of vancomycin-resistant \textit{Enterococcus faecium} infection, linezolid is not as useful as it was previously, nor is quinupristin/dalfopristin.\textsuperscript{6} In 1991, the percentage of hospital- and community-acquired enterococci that were resistant to vancomycin was between 1\% and 2\%. By the end of 2002, that combined percentage was 17\%, but almost 60\% of the hospital-acquired enterococci isolates were resistant to vancomycin.\textsuperscript{4}

\textbf{Respiratory pathogens.} The clinically important respiratory pathogens include \textit{S pneumoniae}, \textit{Haemophilus influenzae}, \textit{Moraxella catarrhalis}, \textit{Mycoplasma pneumoniae}, \textit{Chlamydia pneumoniae}, and \textit{Legionella pneumophila}. Of these respiratory pathogens, \textit{S pneumoniae} and \textit{H influenzae} are of greater practical clinical importance than the others.
For many years, virtually all isolates of *S. pneumoniae* were susceptible to penicillin and other β-lactams and to several other classes of antimicrobial agents—such as the macrolides and the fluoroquinolones. However, this pattern has been slowly changing. Recently, isolates of the pneumococcus have been found to be resistant to ciprofloxacin. The minimum inhibitory concentration (MIC) of ciprofloxacin for these strains of pneumococcus is ≥4 µg/mL, whereas susceptibility is defined as an MIC ≤1 µg/mL and intermediate susceptibili-

**Table 2 – Trends in the susceptibility of *Streptococcus pneumoniae* isolates to 4 quinolones in the SENTRY Program from community-acquired respiratory tract infections for 1999 through 2001**

<table>
<thead>
<tr>
<th>Quinolone tested</th>
<th>% of isolates with MIC of ≥4 µg/mL*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1999</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1.5</td>
</tr>
<tr>
<td>Garenoxacin</td>
<td>0.0</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>0.9</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>0.9</td>
</tr>
</tbody>
</table>

MIC, minimum inhibitory concentration.


ty is defined as 2 µg/mL.\(^8\) This pattern of increasing resistance to ciprofloxacin first appeared about a decade ago when the MIC of ciprofloxacin for these strains was noted to be between 1 and 2 µg/mL. Since then, the number of pneumococcal strains with elevated resistance to ciprofloxacin has increased at least 3-fold, indicating an evolving resistance to the fluoroquinolones (Table 2). Therefore, ciprofloxacin is a marker of this resistance trend for all the fluoroquinolones.\(^3,8\)

**Anti-pneumococcal effects of other fluoroquinolones.** Given the trend toward increasing pneumococcal resistance to levofloxacin, gatifloxacin, moxifloxacin, gemifloxacin, and ciprofloxacin, the question arises about the newer respiratory fluoroquinolones. Indeed, there appears to be a trend toward increasing numbers of isolates exhibiting resistance to the various fluoroquinolones. Surveillance of 7551 isolates of *S. pneumoniae* in Canada found that of 75 isolates for which the MIC of ciprofloxacin was ≥ 4 µg/mL, many also exhibited increasing resistance to the other fluoroquinolones.\(^8\)

However, the MIC of gemifloxacin for these ciprofloxacin-resistant strains of pneumococcus remained exceedingly low.\(^8\) Against 32% of these 75 resistant isolates, gemifloxacin exhibited an MIC of ≤ 0.03 µg/mL and against 61% of the ciprofloxacin-resistant isolates, the MIC of gemifloxacin was ≤ 0.06 µg/mL. With such low MICs, gemifloxacin is an unusual fluoroquinolone and is at least 32 times more potent than levofloxacin. Even with moxifloxacin, a trend toward increasing resistance by ciprofloxacin resistant pneumococci is apparent. The reason that gemifloxacin is so potent is its dual-targeting action, which is discussed below.\(^9\)

**CO-RESISTANCE AND CROSS-RESISTANCE**

Is resistance to one type or class of antimicrobial agent associated with resistance in another type or class of antimicrobial agent? In the case of pneumococci, resistance to penicillin is not readily or commonly associated with resistance to the fluoroquinolones, but it is associated with resistance to cephalosporins, macro-
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Table 3 – MIC$_{90}$ of various antibiotics against ciprofloxacin-susceptible pneumococcal strains with susceptibility patterns to penicillin

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Penicillin-susceptible (n = 64)</th>
<th>Penicillin-intermediate (n = 68)</th>
<th>Penicillin-resistant (n = 75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemifloxacin</td>
<td>0.03</td>
<td>0.06</td>
<td>0.06</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>0.06</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>0.25</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>0.5</td>
<td>&gt; 128</td>
<td>&gt; 128</td>
</tr>
</tbody>
</table>

MIC$_{90}$, minimum inhibitory concentration against 90% of isolates.
Adapted from Davies TA et al. Antimicrob Agents Chemother. 2000.10

Lides, tetracycline, and trimethoprim-sulfamethoxazole. Table 3 shows the MICs of a group of pneumococcal strains susceptible to ciprofloxacin that have varying susceptibilities to penicillin. The MIC$_{90}$ of gemifloxacin, ciprofloxacin, and levofloxacin were not influenced by the degree of resistance of the pneumococcal strains to penicillin. In contrast, amox-
icillin, the macrolides, and the cephalosporins (represented by cefuroxime) have increasing MIC\textsuperscript{90}.\textsuperscript{10} Yet, illogically perhaps, when a penicillin-resistant strain of pneumococcus is encountered in clinical practice, the agent that is often selected empirically is either one of the semisynthetic penicillins or a cephalosporin. The MIC\textsuperscript{90} of azithromycin (which is representative of the macrolides) for the penicillin-resistant and the penicillin-intermediate groups of pneumococci is even greater (> 128 µg/mL).

Even though resistance to a β-lactam antibi-

Table 4 – Activity of various fluoroquinolones against 28 ciprofloxacin-resistant pneumococcal strains

<table>
<thead>
<tr>
<th>Fluoroquinolone</th>
<th>Range of MIC (µg/mL)</th>
<th>MIC\textsuperscript{50} (µg/mL)</th>
<th>MIC\textsuperscript{90} (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemifloxacin</td>
<td>0.03 to 1</td>
<td>0.25</td>
<td>0.5</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>8 to 32</td>
<td>16</td>
<td>&gt; 32</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>4 to &gt; 32</td>
<td>16</td>
<td>&gt; 32</td>
</tr>
<tr>
<td>Sparfloxacin</td>
<td>0.25 to 32</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Grepafloxacin</td>
<td>0.5 to 16</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Trovaflaxacin</td>
<td>0.25</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

MIC, minimum inhibitory concentration; MIC\textsuperscript{50}, MIC against 50% of isolates; MIC\textsuperscript{90}, MIC against 90% of isolates.

From Davies TA et al. Antimicrob Agents Chemother. 2000.\textsuperscript{10}
otic or to a macrolide does not translate into resistance to the fluoroquinolones, a class effect does exist within the fluoroquinolone group. Thus, if a strain of pneumococcus is resistant to ciprofloxacin, there is a tendency for increasing MICs and resistance to other fluoroquinolones (Table 4). However, a slight increase in the MIC\textsubscript{90} of gemifloxacin for penicillin-resistant pneumococci is probably not significant because this fluoroquinolone has such a low MIC\textsubscript{90} to begin with. Nevertheless, a tendency toward resistance of penicillin-resistant pneumococci to some of the other fluoroquinolones has emerged after several years of exposure of the pneumococci to this class.

Clonal spread of organisms that exhibit multidrug resistance to some of the fluoroquinolones has also gradually increased since 1995. For instance, in isolates from Hong Kong, resistance of pneumococci to levofloxacin has increased from \(< 0.5\%\) in 1995 to 13.3\% in 2000. This also conferred increased resistance to gatifloxacin and moxifloxacin. All strains that were resistant to fluoroquinolones were also resistant to penicillin, cefotaxime, and erythromycin.

In North America, the situation is much better. More than 99\% of strains of \textit{S pneumoniae} are susceptible to the newer quinolones and 94.7\% of strains were susceptible to amoxicillin/clavulanate, but fewer than 77\% of strains were inhibited by cefuroxime or erythromycin at susceptible breakpoint concentrations. On the other hand, more than 92\% of strains of pneumococci were susceptible to clindamycin.

**FLUOROQUINOLONE MECHANISMS**

To understand how resistance to the fluoroquinolones may develop, it is first necessary to understand how these antimicrobial agents exert their bactericidal effect.

**Mechanisms of action.** The fluoroquinolones exert their bactericidal effect by interfering with the replication of bacterial DNA. Within the bacterial cell, both chromosomal and plasmid DNA are configured in a circular shape. Before DNA can replicate and transcript the bacterial genes, it must be transformed from this circular shape into a negative superhelical configuration. The enzyme DNA gyrase (also
known as topoisomerase II) and other enzymes of the topoisomerase class regulate the induction of negative superhelicity of the parent DNA and the breaking off of both strands of the daughter (duplicated) DNA from the parent DNA. Topoisomerase IV promotes partitioning of the cell after DNA has been replicated. These enzymes also reseal the break in the DNA that occurs during replication.

Fluoroquinolones inhibit the enzymatic activities of bacterial DNA gyrase, and by interfering with DNA synthesis, these drugs cause rapid death of the bacterial cells. The fluoroquinolones bind to the gyrase-DNA complex rather than to gyrase alone, forming a temporary quinolone-gyrase-DNA complex. Some of the fluoroquinolones also bind to topoisomerase IV instead of to DNA gyrase (Table 5).14

DNA gyrase is a tetramer of 4 subunits: 2 A subunits and 2 B subunits, each encoded by gyra and gyrB genes, respectively. Topoisomerase IV is also a tetramer with 2 C subunits and 2 E subunits. The genes encoding these subunits are parC and parE, respectively.15

Mechanisms of resistance. Single amino acid changes are simple mutations within the genes encoding for either of the subunits of DNA gyrase or topoisomerase IV that can prevent various quinolones from binding to the enzyme-DNA complex. Thus, a substitution of phenylalanine at position 81 for serine (Ser81-Phe), for example, in gyrA has been found to be associated with an increase in the MIC value of gemifloxacin for S pneumoniae to ≥ 0.25 µg/mL, compared with a usual MIC of gemifloxacin against pneumococci that have no mutations in either gyrA or parC in the order of 0.015 to 0.03

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levofoxacin</td>
<td>Topoisomerase IV</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>DNA gyrase*</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>DNA gyrase*</td>
</tr>
<tr>
<td>Gemifloxacin</td>
<td>Topoisomerase IV, DNA gyrase</td>
</tr>
</tbody>
</table>

* Said to be “dual action” agent.
µg/mL.¹⁰

For pneumococci that are susceptible to the fluoroquinolones, the MIC₉₀ is in the order of 0.015 µg/mL for gemifloxacin, 0.12 µg/mL for moxifloxacin, and 0.05 to 1 µg/mL for levofloxacin. However, if there is a mutation in parC, the MIC₉₀ of gemifloxacin increases to between 0.03 and 0.12 µg/mL, that of moxifloxacin increases to between 0.12 and 0.5 µg/mL, and that of levofloxacin increases to between 1 and 2 µg/mL. If the first mutation is in gyrA, the MIC increases to about the same level as with a mutation in parC. However, if there is a mutation in both genes, there is a significant increase in the MIC₉₀ of both moxifloxacin and levofloxacin, but not of gemifloxacin."¹⁶

A dual mode of action. As noted, the MIC of most fluoroquinolones for a microorganism will be increased if a mutation develops in any one of the genes that controls the synthesis of the target enzyme. However, when both enzymes—DNA gyrase and topoisomerase IV—are simultaneously inhibited by a drug, a genetic mutation will lead to a smaller increase in the MIC than would occur if only one enzyme was the target of the antibiotic. Although both moxifloxacin and gatifloxacin have inhibitory effects on DNA gyrase and topoisomerase IV, the extent of this dual action is not as great as that of gemifloxacin. For instance, based on its ability to convert substrate DNA to the linear form in the presence of either gyrase or topoisomerase, gemifloxacin was found to be 16 times more potent than ciprofloxacin in inhibiting DNA gyrase and 25 times more potent than ciprofloxacin in inhibiting topoisomerase IV in a strain of S pneum-
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*Haemophilus influenzae* that was susceptible to the fluoroquinolones.\(^\text{14}\)

**Figure 4** shows the comparative potencies of some of the newer fluoroquinolones against *S. pneumoniae*. These data support the FDA approval of gemifloxacin as dually active at thera-

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* Data on file. GlaxoSmithKline. 2000.\(^\text{22}\)
* Waites KB et al. American Society for Microbiology. 2001.\(^\text{23}\)
* Roblin PM et al. Antimicrob Agents Chemother. 1999.\(^\text{24}\)
* Yu VL. Interscience Conference on Antimicrobial Agents and Chemotherapy. 2000.\(^\text{25}\)
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peutic levels of the drug.

The MIC$_{90}$ of gemifloxacin for the penicillin-resistant strains was $0.03 \mu g/mL$, considerably less (32-fold) than the MIC$_{90}$ of levofloxacin for the penicillin-resistant strains ($1 \mu g/mL$). In marked contrast, the MIC$_{90}$ of clarithromycin for the penicillin-resistant strains of pneumococci was $>16 \mu g/mL$ and that of azithromycin was $>64 \mu g/mL$. \(^{17,18}\)

Against the other frequently encountered respiratory pathogens, including the atypical organisms, *M pneumoniae, C pneumoniae, and L pneumophila*, gemifloxacin has very low MICs (Figure 5). This drug is very potent against the 3 respiratory pathogens most frequently encountered—*S pneumoniae, H influenzae, and M catarrhalis*.

**The post-antibiotic effect (PAE).** This is an important phenomenon that also contributes to the greater efficacy of the fluoroquinolones against respiratory pathogens. The concept of PAE arose from the observation made several years ago that a combination of intermittent dosing of antimicrobials and prolonged intervals between doses was often more effective than continuous infusion of the drug.\(^{19}\) One explanation for this effect is that even after the concentration of antimicrobial at the site of the infection has fallen below the MIC, regrowth of the microorganisms may be delayed.

PAE is but one of the many factors that contribute to the overall pharmacodynamic profile of an antimicrobial agent that includes the MIC, the bactericidal rate, and the effect of sub-inhibitory concentrations of the antimicrobial on bacteria that were previously exposed to supra-inhibitory dosages. The last factor is known as the post-antibiotic sub-MIC effect.\(^{19}\)

The PAE depends on several factors. In addition to the type or class of antimicrobial and the concentration of drug to which the bacteria are exposed, the PAE is a function of the time during which the bacteria were exposed to the antimicrobial, the bacterial species, and even the particular strain of bacterium being studied. Thus, in gram-positive cocci, all antimicrobials are associated with a PAE, but in gram-negative bacilli, most $\beta$-lactam agents induce no PAE or a very short PAE.\(^{19}\)

On the other hand, the fluoroquinolones
generally have a very long PAE against both gram-positive and gram-negative bacteria. When various bacteria were exposed to gemifloxacin in a concentration that was 4 times the MIC, the PAE of gemifloxacin on *H influenzae* was greater than 6 hours, whereas the PAE of ciprofloxacin was only 2.4 hours using the same test conditions. Similarly, the PAE of gemifloxacin was greater than 6 hours against *P aeruginosa* and *Proteus vulgaris*. Generally speaking, the PAEs of gemifloxacin against most bacteria—the exceptions being *Escherichia coli*, *Staphylococcus saprophyticus*, and *S aureus*—were equal to or greater than those of ciprofloxacin.

**OTHER MECHANISMS OF BACTERIAL RESISTANCE: THE EFFLUX PUMP**

Bacterial resistance is not entirely explained by the production of antimicrobial-inactivating enzymes, as with the β-lactam agents, or by genetic modifications, as with the fluoroquinolones. Antimicrobials must penetrate the bacterial cell membrane to produce their effect within the cell, and this penetration may involve simple diffusion or an active transport system.

To protect cells from toxic substances, active transporters, known as efflux pumps, have evolved to remove potentially harmful compounds from within the cell. Such efflux pumps play an important role in eliminating antimicrobials from within the bacterial cell. The efflux pumps are transport proteins; about 20 such proteins that transport antimicrobials have been identified to date. Depending on the type of microorganism, the efflux pump may be a large protein with several domains that span the thickness of the cell membrane (the situation in gram-positive bacteria). Alternatively, it may be a multicomponent system with an inner component linked to an outer component through a fusion protein (the situation in gram-negative bacteria).

One reason for bacterial resistance to the macrolides in the United States is the presence of efflux pumps. About 70% of all bacterial species, especially *S pneumoniae*, that exhibit increased resistance to the macrolides (erythromycin, clarithromycin, and azithromycin) have efflux pumps. For instance, in 75% of re-
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Resistant strains of pneumococci, the reason for resistance to macrolides is an efflux pump, and in 25% of strains, the reason for resistance is ribosomal methylation encoded by \textit{erm}.

As with all proteins, the synthesis of the efflux pump proteins is controlled by specific genes. One such gene is responsible for the efflux pump that causes resistance to the macrolides—the so-called M-phenotype of pneumococcal resistance.

KEY POINTS

The fluoroquinolones are broad-spectrum antimicrobial agents that are active against the gram-negative bacilli and the respiratory tract pathogens. Although resistance to ciprofloxacin is emerging among some strains of \textit{S pneumoniae}, the same level of resistance has not emerged with many of the newer fluoroquinolones. In particular—apparently because of its dual action against both DNA gyrase and topoisomerase IV and potency—gemifloxacin continues to exhibit extremely low MIC values against the 3 most clinically significant respiratory pathogens—\textit{S pneumoniae}, \textit{H influenzae}, and \textit{M catarrhalis}—as well as against the atypical respiratory pathogens—\textit{M pneumoniae}, \textit{C pneumoniae}, and \textit{L pneumophila}. This agent is approved for multidrug-resistant \textit{S pneumoniae} infections based on high intrinsic in vitro activity also demonstrating in vivo favorable outcomes.

REFERENCES:

6. Mutnick AH, Enne V, Jones RN. Linezolid resistance since 2001:

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