INTRODUCTION

Most decisions with regard to the selection of appropriate antimicrobial therapy were based on whether a drug would safely attain the necessary concentration in serum in order to inhibit or kill the infecting organism, and the following factors were usually considered: activity against the likely pathogen, resistance patterns, adverse effects and allergies, ease of dosing, cost, pharmacokinetics and pharmacodynamics.\(^1\)\(^2\)

This static parameter, referred to as the “minimum inhibitory concentration (MIC)” was the final arbiter of potential treatment success or failure.\(^1\) However, this in vitro measurement cannot provide information on either the rate of eradication of the organism or whether alterations in dosage or delivery of the drug would result in improved eradication, decreased emergence of resistance, or, ultimately, increased survival.\(^2\)
This review will summarize the pharmacokinetics and pharmacodynamic principles of antimicrobial therapy and apply these principles to the currently available fluoroquinolone class of antimicrobials.

**FLUOROQUINOLONES**

Quinolones are unusual among antimicrobials in that they were not isolated from living organisms, but rather synthesized by chemists. The first quinolone, nalidixic acid, was derived from the antimalarial drug chloroquine. Subsequent agents were derived through side chain and nuclear manipulation. The development of the fluoroquinolone class may be described in generational terms, with each generation sharing similar features or antimicrobial spectra. First-generation agents possess activity against aerobic gram-negative bacteria, but little activity against aerobic gram-positive bacteria or anaerobes. Second-generation agents are the original fluoroquinolones, named for the addition of a fluorine atom at position C-6 (Fig. 1). These agents offer improved coverage against gram-negative bacteria and moderately improved gram-positive coverage. Third-generation agents achieve greater potency against gram-positive bacteria, particularly pneumococci, in combination with good activity against anaerobes. Fourth-generation fluoroquinolones have superior coverage against pneumococci and anaerobes.

**1. Structure-Activity Relationships**

Decades of fluoroquinolone development provide considerable insight into the effects of structural modification upon the antimicrobial activity and pharmacologic properties of these agents. Fig. 1 depicts the core quinolone nucleus. Position 1 affects drug potency, pharmacokinetics, and the potential for interaction with theophylline. Positions 2, 3, and 4 determine antibacterial activity by influencing the affinity for bacterial enzymes. Additionally, positions 3 and 4 are involved in metal chelation and the resulting interaction with di- and trivalent cations. The presence of a methoxy side chain at position 5 enhances gram-positive activity and phototoxicity. The addition of a fluorine atom to position 6 transforms a quinolone into a fluoroquinolone, enhancing drug penetration into the bacterial cell and activity against gram-negative bacteria. Position 7, like position 1, is instrumental in drug potency, pharmacokinetics, and the interaction with theophylline. This position is also implicated in the central nervous system toxicity of some fluoroquinolones owing to their proclivity to bind to gammaaminobutyric acid. The addition of a piperazine moiety at position 7 augments activity against *Pseudomonas aeruginosa*, whereas a pyrrolidine group improves gram-positive activity. The presence of any halogen at position 8 can increase a drug’s half-life, absorption, and anti-anaerobic activity; however, the resulting phototoxicity of di-halogenated compounds renders them unacceptable for clinical use. In contrast, superior pneumococcal activity is achieved by the addition of a methoxy group at position 8 without attendant phototoxicity.

**PHARMACOKINETICS**

Fluoroquinolones have favorable pharmacokinetic properties that have encouraged their widespread use. They are well absorbed and have good tissue penetration, which facilitates their use for many clinical syndromes.

**1. Absorption**

Fluoroquinolone antimicrobials normally exhibit rapid dissolution in the gastrointestinal tract and are absorbed in the duodenum and jejunum. Peak serum concentrations are usually attained 1-2 hours after dosing in healthy persons. The third-generation quinolones also exhibit maximal serum concentration (Cmax) in 1-2 hours, with the exception of sparfloxacin. Sparfloxacin is more slowly absorbed, and its Cmax is observed in 4-5 hours. This finding is most likely the result of the lower solubility of sparflaxacin in aqueous solution. Coingestion with food usually increases the time to peak serum concentration by 1 hour for these fluoroquinolones, but other pharmacokinetic values are unaltered.

The Cmax varies significantly among these compounds.
Following a 200-mg dose, peak levels in the range of 0.7 μg/ml (sparfloxacin) to 2.9 μg/ml (trovafloxacin) are attained. In dose-ranging studies it has been observed that an increase in dose will result in a linear increase in the Cmax for these fluoroquinolones.8,10,12,15 The area under the serum concentration-time curve (AUC) for these agents also increases linearly in proportion to dose. In contrast to its low Cmax, sparfloxacin has a large AUC due to its long elimination half-life (Table 1).

2. Distribution

The distribution volumes of the third-generation fluoroquinolones are large and may exceed those of second-generation compounds. For instance, the distribution volumes of grepafloxacin and sparfloxacin have been estimated to be 3.5 L/kg and 4.5 L/kg, respectively.14 These compounds, like their predecessors, exhibit low protein binding. Displacement of highly protein-bound drugs is unlikely with these fluoroquinolones, including trovafloxacin.13 The penetration of third-generation quinolones into several different tissues and body fluids in humans has been demonstrated. Levofloxacin has been most extensively studied and has characteristics similar to those of ofloxacin.9 Levofloxacin concentrations in most tissues or fluids are generally higher or similar to those observed in plasma.15 Inflammatory fluid penetration of several of the newer fluoroquinolones has been studied.14,16 In healthy volunteers, peak concentrations in chemically induced blisters ranged from 41-81% of those found in serum (Table 2).

High concentrations of these antimicrobials have also been observed in kidney parenchyma, gallbladder tissue and bile, and genital tract tissues.9,17,18 In a study of six surgical patients, mean grepafloxacin concentrations of 0.9 μg/ml, 5.6 mg/kg, and 51 μg/ml were attained in serum, gallbladder tissue, and bile, respectively, at 2-5 hours after oral administration of 300 mg.17

3. Elimination

The fluoroquinolones are removed from the body by both renal and nonrenal routes of elimination.7 High concentrations of unchanged drug can be found in the urine, bile, and feces. When analyzing the urinary excretion of the third-generation quinolones, one finds that these compounds fall into two distinct groups. Greater than 60% of unchanged drug can be recovered in urine following administration of levofloxacin and clinafloxacin.9,12 In contrast, lower than 10% of unchanged drug is found in the urine after doses of grepafloxacin, sparfloxacin, and trovafloxacin.8,13,14

### Table 1. Pharmacokinetic properties of fluoroquinolones

| Fluoroquinolone | Oral dose (mg) | tmax (h) | Cmax (μg/ml) | t1/2β (h) | AUC ([mg·h]/L) |
|-----------------|--------------|---------|--------------|----------|----------------|
| Sparfloxacin    | 200          | 4.0     | 0.7          | 21.0     | 19.0           |
| Levofloxacin    | 200          | 1.5     | 2.0          | 6.0      | 20.0           |
| Grepafloxacin   | 200          | 2.1     | 0.7          | 11.0     | 8.8            |
| Trovafloxacin   | 200          | 0.7     | 2.9          | 7.8      | 24.0           |
| Clinafloxacin   | 200          | 1.5     | 1.6          | 6.3      | 11.0           |

tmax: time after dosing for maximal concentration to be reached, Cmax: maximal serum concentration, t1/2β: elimination half-life, AUC: area under the serum concentration curve.

### Table 2. Inflammatory fluid penetration of fluoroquinolones

| Parameter                  | Grepafloxacin (400 mg) | Levofloxacin (300 mg) | Sparfloxacin (400 mg) | Trovafloxacin (200 mg) |
|----------------------------|------------------------|-----------------------|-----------------------|-----------------------|
| Serum                      |                        |                       |                       |                       |
| tmax (h)                   | 2.0                    | 1.2                   | 2.7                   | 0.75                  |
| Cmax (μg/ml)               | 1.5                    | 6.6                   | 1.6                   | 2.9                   |
| t1/2β (h)                  | 5.2                    | 8.0                   | 18                    | 7.8                   |
| AUC ([mg·h]/L)             | 12                     | 53                    | 32                    | 24                    |
| Blister fluid              |                        |                       |                       |                       |
| tmax (h)                   | 4.8                    | 3.7                   | 5.0                   | 4.0                   |
| Cmax (μg/ml)               | 1.1                    | 4.3                   | 1.3                   | 1.2                   |
| t1/2β (h)                  | 13                     | 8.0                   | 20                    | 7.1                   |
| AUC ([mg·h]/L)             | 22                     | 54                    | 37                    | 15                    |
| Percentage penetration     |                        |                       |                       |                       |
| Cmax                       | 73                     | 65                    | 81                    | 41                    |
| AUC                        | 180                    | 100                   | 117                   | 63                    |

tmax: time after dosing for maximal concentration to be reached, Cmax: maximal serum concentration, t1/2β: elimination half-life, AUC: area under the serum concentration curve.
Changes in renal function can have a significant impact on the elimination of these drugs, including those that have low urinary recovery. For instance, the serum elimination half-life of sparfloxacin in patients with moderate or severe renal impairment (glomerular filtration rates of 22 ml/min and 7.7 ml/min, respectively) was found to be approximately two times higher than observed in healthy volunteers. The effect of renal impairment on the pharmacokinetics of levofloxacin has also been studied. The mean elimination half-lives in patients with creatinine clearances of 40-70 ml/min, 20-40 ml/min, and <20 ml/min were 6.4, 11, and 28 hours, respectively. The serum elimination half-life of the third-generation quinolones ranges from 4.6 to 21 hours in healthy adults (Table 1).

**PHARMACODYNAMICS**

Almost 30 years ago, several investigators proposed that antibacterials can be divided into 2 major categories on the basis of their major mechanism of bacterial killing: time-dependent or concentration-dependent activity (Table 3).25

### 1. Time-Dependent Antibacterials

The first group of antibacterials includes agents whose effect depends on the length of time that the drug is in contact with the bacteria at concentrations exceeding the MIC. Maximum killing is achieved at concentrations approaching 4-5 times the MIC, but any further increases in concentrations provide little to no additional benefits. Therefore, the length of time that the drug concentration is above the MIC (T>MIC) has been determined to be the most important parameter for determining clinical and microbiological success.

For β-lactam antibacterials, when the T>MIC exceeds 40% to 50% of the dosing interval, clinical and bacteriological efficacy theoretically approaches >90% (Table 4). However, a few qualifying statements need to be made. Additionally, maximizing the T>MIC may improve outcomes for hospitalized patients infected with relatively

| Parameter         | Class of antimicrobial                                      |
|-------------------|-------------------------------------------------------------|
| T > MIC           | Penicillin                                                  |
|                   | Cephalosporins                                              |
|                   | Carbapenems                                                 |
|                   | Macrolides                                                  |
| Cmax/MIC          | Aminoglycosides                                             |
|                   | Fluoroquinolones                                            |
| AUC24/MIC         | Fluoroquinolones                                            |
|                   | Azalides                                                    |
|                   | Ketolides                                                   |

MIC: minimum inhibitory concentration, T>MIC: time that the drug concentration is above the MIC, Cmax: maximal serum concentration, AUC: area under the serum concentration curve.
resistant pathogens. Increasing the dosing frequency, total dose, or duration of infusion may maximize the \( T_{\geq} > MIC \) in select circumstances, thereby improving the outcome.\(^{26,27}\) Further studies will be necessary before standard recommendations can be made.

### 2. Concentration-Dependent Antibacterials

The second group of antibacterials includes agents whose effects depend on increasing concentrations of the antibiotic (Table 4). The parameters that most closely correlate with the success of these agents include the ratio of Cmax to the MIC (Cmax/MIC) and the ratio of the 24-h area under the plasma concentration curve (AUC\(_{24}\)) to the MIC (AUC\(_{24}\)/MIC).\(^2\) Most authors agree that only the concentration of free drug is important in making these calculations or for allowing accurate comparisons between drugs of the same class with different degrees of protein binding.\(^{26}\) Throughout the remaining discussion, “AUC:MIC” refers to free AUC/MIC, unless otherwise noted. Fluoroquinolones, aminoglycosides, and ketolides have been classified primarily as concentration-dependent antibiotics (Table 4). Many recently published studies in this field have focused on dissecting these parameters with regard to the fluoroquinolones. Overall, the AUC/MIC has had the greatest correlation with outcome in either in vitro or animal models of infection,\(^{28}\) but the greatest debate has focused on the magnitude of the AUC/MIC that is necessary to maximize outcome or prevent emergence of resistance. The correlation of drug concentration and pharmacodynamics of an antibiotic class is based on the integration of microbiological activity and pharmacokinetics.\(^{29}\) The fluoroquinolones exert concentration-dependent killing, and both the AUC/MIC and Cmax/MIC ratios have been shown to be pharmacodynamic correlates of efficacy.\(^{30}\) In vitro models suggest that Cmax/MIC ratios of \( >8 \) and AUC\(_{24}\)/MIC ratios of \( >125 \) are necessary for rapid bacterial eradication and prevention of regrowth with resistant subpopulations of certain bacteria.\(^{29,30}\)

Animal and patient studies have confirmed these findings. In a neutropenic rat model of *Pseudomonas aeruginosa* sepsis, the serum peak/MIC ratio was linked to survivorship, particularly when high ratios (20:1) were obtained.\(^{31}\) In a study of acutely ill patients treated with ciprofloxacin, an AUC\(_{24}\)/MIC ratio of \( >125 \) was highly predictive of a microbiological and clinical cure.\(^{30}\) These findings suggest that the clinical utility of this fluoroquinolone will depend on whether it can attain high Cmax/MIC (10:1) or AUC\(_{24}\)/MIC (125:1) ratios against clinically important pathogens.

### CONCLUSIONS

Fluoroquinolones have gained widespread use owing to their favorable pharmacokinetics, pharmacodynamics, and broad antimicrobial spectra. These quinolones are concentration-dependent killers, however, a new high dose and short course approach, while keeping pharmacodynamic principles in mind, may work faster, encourage better patient compliance, have similar toxicity, decrease cost, and prevent resistance development.

### CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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