

# Pharmacodynamic Approach to Antimicrobial Treatment for Respiratory Infections

*Michael R. Jacobs, MD, PhD*

Department of Pathology, Case Western Reserve University,  
Cleveland, Ohio USA

## ABSTRACT

To understand the relationship between drug dose to efficacy, pharmacokinetic with pharmacodynamic characteristics need to be integrated. Patterns of antimicrobial activity fall into one of two patterns: time-dependent killing and concentration-dependent killing. The first pattern, time-dependent killing, characteristic of many antibiotic classes ( $\beta$ -lactams, macrolides), seeks to optimize the duration of exposure of a pathogen to an antimicrobial. The major pharmacokinetic/pharmacodynamic parameter correlating with efficacy of time-dependent antimicrobials is the serum concentration present for 40-50% of the dosing interval. This enables development of pharmacokinetic breakpoints, which are the serum concentrations maintained for at least 40-50% of a dosing interval by particular dosing regimens of antimicrobial agents. Therefore, the  $MIC_{90}$  of an antimicrobial against a pathogen needs to be less than or equal to the pharmacokinetic breakpoint for the agent to be useful empirically. The second pattern, concentration-dependent killing, seeks to maximize antimicrobial concentration and is seen with aminoglycosides, quinolones and azalides. The major pharmacokinetic/pharmacodynamic parameter correlating with the efficacy of concentration-dependent antimicrobials is the 24-hour area under the curve to MIC ratio, which should be  $\geq 25$ . Pharmacokinetic breakpoints for such agents can therefore be calculated from the formula  $AUC \div 25$ . In designing regimens, one needs to consider the ability of an antimicrobial dosing regimen to meet these pharmacokinetic/pharmacodynamic parameters for efficacy against pathogens. This is particularly important for oral dosing regimens for treating emerging resistant respiratory tract pathogens.

## **INTRODUCTION**

Do drug pharmacokinetics have any relation to patient care? They do, and the relationships between pharmacokinetics and pharmacodynamics, learned during the previous 20 to 30 years, apply to designing rational and optimal therapeutic regimens. Pharmacokinetic and pharmacodynamic characteristics both influence drug doses. For 2 decades, the focus has been on pharmacokinetic characteristics--what the body does to the drug and the overall disposition of the drug in the body. This is reflected most often by the serum concentration profile over time. Of particular interest as well is the penetration of drug into sites of infection.

Medications are administered, however, for their pharmacodynamic characteristics--what the drug does in the body. Susceptibility of the pathogen to the drug, determined by measuring the minimum inhibitory concentration (MIC), and is a reflection of the potency of a drug. But to be able to understand the application or the relevance of drug dose to efficacy, we have to integrate pharmacokinetic characteristics with pharmacodynamic characteristics.

The increasing occurrence of antibiotic-resistant pathogens complicates the integration of pharmacokinetics and pharmacodynamics, and has an impact on treatment approaches to respiratory tract infections. Clearly, as pathogens become more resistant to antimicrobial agents, the efficacy of standard dosing regimens may be reduced. This stimulates the need for newer regimens and newer antimicrobials. In this review I will focus on looking at how integration of pharmacokinetics and pharmacodynamics offers newer ways to evaluate susceptibility data and dosing regimens.

## **PATTERNS OF ANTIMICROBIAL ACTIVITY**

The lack of clear pharmacokinetic/pharmacodynamic endpoints has been a challenge in antimicrobial therapy. Although serum concentrations have been measured for years, the clinical significance of these have often been unclear. More recently, many pharmacokinetic/pharmacodynamic studies of antimicrobials showed that the magnitude of the pharmacokinetic/pharmacodynamic parameter required for efficacy is similar in various animal species and in humans. Thus, results from animal studies could predict antimicrobial activity in humans. This would be useful for dosing regimen design in situations in which it is difficult to collect sufficient clinical data, such in instances of newly emerging resistance.

Despite the large number of classes of antimicrobial agents, patterns of antimicrobial activity fall into one of two major patterns: time-dependent activity and concentration-dependent activity.

## 1. TIME-DEPENDENT KILLING

Time-dependent killing refers to the time it takes for a pathogen to be killed by exposure to an antimicrobial. The goal of time-dependent killing is to optimize the duration of exposure. With time-dependent killing, post-antibiotic effects (persistence of antimicrobial action after the antimicrobial is removed) are minimal. Time-dependent killing is characteristic of  $\beta$ -lactam antibiotics (penicillins, cephalosporins, monobactams, and carbapenems), macrolides, and clindamycin. The major pharmacokinetic/pharmacodynamic parameter that correlates with clinical and bacteriologic efficacy of these drugs is the time the serum concentration exceeds the MIC of the pathogen.  $\beta$ -Lactam antibiotics are the most commonly used antimicrobials in clinical practice, especially in treating infections of the upper and lower respiratory tract. In animal models of human infection, different classes of  $\beta$ -lactams require different times above the MIC for net and maximum bactericidal activity. As would be expected, the required time above the MIC varies, depending on the pathogen, infection site, and drug, but is generally 40-50% of the dosing interval. Similar times above the MIC are required to achieve 80% or greater rates of bacteriologic cure in otitis media and in sinusitis caused by *Haemophilus influenzae* and *Streptococcus pneumoniae* and with  $\beta$ -lactam antibiotics (figure 1). Using mortality after 4 days of therapy as an endpoint, the relationship between time above the MIC and efficacy of penicillins and cephalosporins in animal models shows similar findings (figure 2). These correlations serve as the foundation for defining the pharmacodynamic correlates between time above the MIC and bacteriologic and clinical outcome.

The next step is to find out if dosing regimens are likely to achieve sufficiently high serum antibiotic concentrations to exceed the MICs of pathogens for 40-50% of the dosing interval. Tables 1 and 2 show conservative adult and pediatric dosing regimens for common parenteral and oral antimicrobials. Using this information, and knowing the antibiotic half-life, we can predict if a dosing regimen will be successful. Tables 1 and 2 also show the pharmacokinetic breakpoints for these agents and dosing regimens, reflecting the serum concentrations present for 40-50% of the dosing interval. As an example, figure 1 shows the serum concentration of amoxicillin when 500 mg of this agent is administered at 8-hour intervals during a 24-hour period. Amoxicillin has a half-life of 30 to 45 minutes. With this dosing regimen, amoxicillin achieves a concentration of 2  $\mu\text{g/ml}$  for 3.3 hours of each 8-hour dosing interval, (or 9.9 hours of a 24-hour day), which is 41% of the dosing interval. Therefore, this regimen achieves an amoxicillin concentration of 2  $\mu\text{g/ml}$  for over 40% of the time, and should therefore be active against organisms with MICs of  $\leq 2 \mu\text{g/ml}$ . If 875 mg is administered at 12-hour intervals, the amoxicillin concentration exceeds 2  $\mu\text{g/ml}$  for 4.5 hours of each dosing interval (9 hours of a 24-hour day). Therefore, this regimen achieves an amoxicillin concentration that exceeds 2  $\mu\text{g/ml}$  for approximately 40% of the dosing interval. Thus both dosing regimens achieves serum concentrations above the 2  $\mu\text{g/ml}$  for about 40% of the dosing interval. The pharmacodynamic breakpoint of amoxicillin can therefore be determined to be 2  $\mu\text{g/ml}$  for both these dosing regimens.

How can these observations contribute to clinical decision-making? Taking into

account the dosing regimens and accepting the defined pharmacodynamic correlate of the concentration present for 40-50% of the dosing interval, pharmacokinetic breakpoints can be determined for defined dosing regimens of various  $\beta$ -lactams (tables 1 and 2). These pharmacokinetic breakpoints can then be compared to MICs of individual pathogens or to collections of strains, and noting if the the MIC of a strain or the MIC<sub>90</sub> of a group of strains is at or below this breakpoint (i.e., susceptible) or above the breakpoint (i.e., resistant). For some parenteral  $\beta$ -lactams such as penicillin G, the MIC<sub>90</sub> for *S. pneumoniae* is below the pharmacokinetic breakpoint, predicting clinical and bacteriologic success. For others, the MIC<sub>90</sub> is above the breakpoint, predicting clinical failure for the most resistant strains.

How do these breakpoint apply to common pathogens? Table 3 shows the percentage of dosing intervals that serum concentrations of oral  $\beta$ -lactams are above the MIC<sub>90</sub>s against common respiratory pathogens. The calculations are based on the dosing regimens shown. Amoxicillin/clavulanate is the only oral  $\beta$ -lactam to exceed the MIC<sub>90</sub>s of all three pathogens for  $\geq 40\%$  of the dosing interval. Although the cephalosporins maintain good activity against penicillin-susceptible *S. pneumoniae*, they are inactive or inadequately active against penicillin-intermediate and -resistant strains. Some of these antibiotics are also inadequate against *H. influenzae* or *Moraxella catarrhalis*.

Time above the MIC is also the important parameter for determining efficacy of the macrolides (but not azalides such as azithromycin). Macrolides provide unbound drug concentrations that are greater than the MIC<sub>90</sub>s against macrolide-susceptible strains of *S. pneumoniae* for at least 50% of the dosing interval (table 4). However, unbound serum drug concentrations do not exceed MICs of *H. influenzae* or macrolide-resistant *S. pneumoniae*. This might reflect many of the problems that have been noted in the use of macrolides against *H. influenzae* infections.

## **2. CONCENTRATION-DEPENDENT KILLING WITH POST-ANTIBIOTIC EFFECTS**

The goal of concentration-dependent killing is to maximize concentration and attain the highest possible antimicrobial concentration at the site of infection. With concentration-dependent killing, prolonged post-antibiotic activity, persisting even when concentrations are below MICs, is also often present. Concentration-dependent killing is characteristic of aminoglycosides, quinolones, azalides (azithromycin), ketolides, and vancomycin. The major pharmacodynamic parameters that correlate with clinical and bacteriologic efficacy of these drugs are the 24-hour area under unbound serum drug concentration curve (AUC) to MIC ratio, or the peak drug concentration to MIC ratio. So, again the MIC remains a primary correlate of pharmacodynamic potency when correlated with the appropriate parameter. The parameters that correlate with clinical and bacteriological efficacy are 24-h AUC:MIC ratios of  $\geq 25$  in immunocompetent patients,  $\geq 125$  in immunocompromized patients, and peak:MIC ratios of  $\geq 10$ . Pharmacodynamic breakpoints can therefore be determined by the formula  $AUC \div 25$  or  $AUC \div 125$ . For azithromycin, with a 24-h AUC of 3

mg.L/h, pharmacodynamic breakpoint for immunocompetent patients is therefore 0.12 µg/ml (3÷25), which results this agent being clinically effective against macrolide-susceptible *S. pneumoniae* (MIC<sub>90</sub> of 0.12 µg/ml), but not *H. influenzae* (MIC<sub>90</sub> of 1-2 µg/ml) or macrolide-resistant *S. pneumoniae* (MIC<sub>90</sub> of >8 µg/ml). For the quinolones, AUC:MIC ratios of 25 have also been used to determine breakpoints (Tables 5 and 6). MICs of *H. influenzae* are considerably below these breakpoints for all quinolones. However, MIC<sub>90</sub>s of *S. pneumoniae* are above these breakpoints for older agents such as ciprofloxacin and ofloxacin, while MIC<sub>90</sub>s for newer agents are below these breakpoints.

## CONCLUSIONS

Pharmacokinetic and pharmacodynamic characteristics are major determinants of efficacy of antimicrobial therapy and susceptibility breakpoints. Previously, values such as MICs, concentrations at peak or trough, and half-life were not integrated. It is now clear that pharmacokinetic and pharmacodynamic characteristics have to be considered to enable the use of optimal dosing regimens for antimicrobials and in determining clinically-relevant susceptibility breakpoints. The ability of an antimicrobial dosing regimen to meet the pharmacokinetic/pharmacokinetic parameter required for efficacy against emerging resistant bacteria needs to be considered in designing antimicrobial regimens and in selecting empiric therapy. Basing susceptibility breakpoints on pharmacokinetic/pharmacodynamic parameters requires changing many of the breakpoints in current use.

## REFERENCES

1. Anzueto A, Niederman MS, Tillotson GS : Etiology, susceptibility, and treatment of acute bacterial exacerbations of complicated chronic bronchitis in the primary care setting: ciprofloxacin 750 mg b.i.d. versus clarithromycin 500 mg b.i.d. *Clin Ther* 1998; 20: 885–900
2. Bartlett JG, Breiman RF, Mandell LA, File TM : Community-acquired pneumonia in adults: guidelines for management. *Clin Infect Dis* 1998; 26:811–838
3. Brook I : Microbiology and management of sinusitis. *J. Otolaryngol* 1996; 25:249–256
4. Campbell DG : Overview of community acquired pneumonia. Prognosis and clinical features. *Med Clin North Am* 1994; 78: 1035–1048
5. Chodosh S, Schreurs A, Siami G, Barkman Jr HW, Anzueto A, Shan M, Moesker H, Stack T, Kowalsky S : Efficacy of oral ciprofloxacin vs. clarithromycin for treatment of acute bacterial exacerbations of chronic bronchitis. The Bronchitis Study Group. *Clin Infect Dis* 1998; 27: 730–738
6. Craig WA : Interrelationship between pharmacokinetics and pharmacodynamics in determining dosage regimens for broad-spectrum cephalosporins. *Diagn Microbiol Infect Dis* 1995; 22: 89–96
7. Craig WA : Antimicrobial resistance issues of the future. *Diagn Microbiol Infect Dis* 1996; 25:213–217
8. Craig WA : Postantibiotic effects and dosing of macrolides, azalides, and streptogramins, p. 27–38. In S. H. Zinner, L. S. Young, J. F. Acar, and H. C. Neu (eds), *Expanding indications for the new macrolides, azalides and streptogramins*. Marcel Dekker, 1997 New York, N.Y.
9. Craig WA : Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. *Clin Infect Dis* 1998; 26: 1–10
10. Craig WA, Dalhoff A : Pharmacodynamics and pharmacokinetics of fluoroquinolones in experimental animals.. In J. Kuhlman, A. Dalhoff, H. J. Zeiler (eds), *Handbook of experimental pharmacology V127: quinolone antibacterials*.
11. Dagan R : Can the choice of antibiotics for therapy of acute otitis media be logical? *Eur J Clin Microbiol Infect Dis* 1998; 17: 1–5
12. Dagan R, Abramson O, Leibovitz E, Lang R, Goshen S, Greenberg D, Yagupsky P, Leiberman A, Fliss DM : Impaired bacteriologic response to oral cephalosporins in acute otitis media caused by pneumococci with intermediate resistance to penicillin. *Pediatr Infect Dis J* 1996; 15: 980–985
13. Dagan R, Leibovitz E, Greenberg D, Yagupsky P, Fliss DM, Leiberman E : Early eradication of pathogens from middle ear fluid during antibiotic treatment of acute

- otitis media is associated with improved clinical outcome. *Pediatr Infect Dis J* 1998; 17:776–782
14. Dagan R, Leibovitz E, Jacobs M, Fliss D, Leiberman A, Yagupsky P : Bacteriologic response to acute otitis media caused by *Haemophilus influenzae* treated with azithromycin, abstr. K-102. In Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy 1997. American Society for Microbiology, Washington, D.C.
  15. Dagan R, Piglansky L, Fliss DM, Leiberman A, Leibovitz E : Bacteriologic response in acute otitis media: comparison between azithromycin, cefaclor and amoxicillin, abstr. K-103. In Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy 1997. American Society for Microbiology, Washington, D.C.
  16. De Abate CA., Henry D, Bensch G, Jubran A, Chodosh S, Harper L, Tipping D, Talbot GH : Sparfloxacin vs ofloxacin in the treatment of acute bacterial exacerbations of chronic bronchitis: a multicenter, double-blind, randomized, comparative study. Sparfloxacin Multicenter ABECB Study Group. *Chest* 1998; 114: 120–130
  17. Dowell SF, Butler JC, Geibink GS, Jacobs MR, Jernigen D, Musher DM, Rakowsky A, Schwartz B and the Drug-resistant *Streptococcus pneumoniae* Therapeutic Working Group. 1999. Acute otitis media: management and surveillance in an era of pneumococcal resistance – a report from the Drug-resistant *Streptococcus pneumoniae* Therapeutic Working Group. *Pediatr Infect Dis* 1999; 18: 1–9
  18. Drusano GL, Craig WA : Relevance of pharmacokinetics and pharmacodynamics in the selection of antibiotics for respiratory tract infections. *J Chemother* 1997; 9(Suppl. 3) : 38–44
  19. Fine MJ, Smith MA, Carson CA, Mutha SS, Sankey SS, Weissfeld LA, Kapoor WN : Prognosis and outcomes of patients with community-acquired pneumonia. *JAMA* 1996; 275: 134–141
  20. Forrest AD, Nix E, Ballow CH, Goss TF, Birmingham MC, Schentag JJ : Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. *Antimicrob Agents Chemother* 1993; 37: 1073–1081
  21. Goldstein FW : 1997. Choice of an oral beta-lactam antibiotic for infections due to penicillin-resistant *Streptococcus pneumoniae*. *Scand J Infect Dis* 1997; 29: 255–257
  22. Goldstein F, Bryskier A, Appelbaum PC, Bauernfeind A, Jacobs M, Schito GC, Wise R. The etiology of respiratory tract infections and the antibacterial activity of fluoroquinolones and other oral antibacterial agents against respiratory pathogens. *Clin Microbiol Infect* 1998; 4(Suppl 2): 2S8–2S18
  23. Grossman RF : How do we achieve cost-effective options in lower respiratory tract infection therapy? *Chest* 1998; 113(Suppl. 3): 205–210
  24. Grüneberg RN, Felmingham D and the Alexander Project Group : Results of the Alexander Project: a continuing, multicenter study of the antimicrobial susceptibility of community-acquired lower respiratory tract bacterial pathogens. *Diagn Microbiol*

Infect Dis 1996; 25:169–181

25. Hoberman A, Paradise JL, Block S, Burch DJ, Jacobs MR, Balanescu MI : Efficacy of amoxicillin/clavulanate for acute otitis media: relation to Streptococcus pneumoniae susceptibility. *Pediatr Infect Dis J* 1996; 15: 955–962
26. Jacobs MR, Bajaksouzian S, Zilles A, Lin G, Pankuch GA, Applebaum PC : Susceptibility of Streptococcus pneumoniae and Haemophilus influenzae to 10 oral antimicrobial agents based on pharmacodynamic parameters: 1997 U.S. surveillance study. *Antimicrob Agents Chemother* 1999(in press)
27. Marchant CD, Carlin SA, Johnson CE, Shurin PA : Measuring the comparative efficacy of antibacterial agents for acute otitis media: the ‘Polyanna phenomenon’. *J Pediatr* 1992; 120: 72–77
28. Preston SL, Drusano GL, Berman AL, Fowler CL, Chow AT, Dornseif B, Reichl V, Natarajan J, Corrado M : Prospective development of pharmacodynamic relationships between measures of levofloxacin exposure and measures of patient outcome. *JAMA* 1998; 279: 125–129

**Table 1. PK/PD breakpoints – serum concentration of oral **b**-lactams present for >40% of dosing interval**

| Drug        | Dosing regimen |              | <i>S. pneumoniae</i>      | PK/PD      |
|-------------|----------------|--------------|---------------------------|------------|
|             | Adult          | Pediatric    | MIC <sub>90</sub> (ug/ml) | breakpoint |
| Amox ± clav | 500 mg TID     | 13 mg/kg TID | 2                         | 2          |
|             | 875 mg BID     | 23 mg/kg BID | 2                         | 2          |
| Cefaclor    | 500 mg TID     | 13 mg/kg TID | >64                       | 0.5        |
| Cefuroxime  | 500 mg BID     | 15 mg/kg BID | 8                         | 1          |
| Cefprozil   | 500 mg BID     | 15 mg/kg BID | 16                        | 1          |
| Loracarbef  | 400 mg BID     | 15 mg/kg BID | >64                       | 0.5        |
| Cefixime    | 400 mg QD      | 8 mg/kg QD   | 32                        | 0.5        |

**Table 2. PK/PD breakpoints - serum concentrations of parenteral beta-lactams present for >40% of dosing interval**

| <b>Drug</b>  | <b>Dosing regimen</b>   | <b><i>S. pneumoniae</i><br/>MIC<sub>90</sub> (ug/ml)</b> | <b>PK/PD breakpoint<br/>(ug/ml)</b> |
|--------------|-------------------------|--|-------------------------------------|
| Penicillin G | 2X10 <sup>6</sup> u QID | 4  | 4                                   |
| Ampicillin   | 1g QID                  | 4  | 2                                   |
| Cefuroxime   | 0.75 g TID              | 8  | 4                                   |
| Cefotaxime   | 1 g TID                 | 2  | 2                                   |
| Ceftriaxone* | 1 g QD                  | 2  | 2                                   |
| Cefepime     | 1 g BID                 | 4  | 4                                   |
| Ceftazidime  | 1 g TID                 | 32   | 8                                   |
| Meropenem    | 0.5 g TID               | 2  | 1                                   |

\*based on free serum level

**Table 3. Percentage of dosage interval serum levels of oral  $\beta$ -lactams are above MIC<sub>90</sub>s of pathogens**

|                   | <i>Strep. pneumoniae</i> |       |       | <i>Haem. influenzae</i> | <i>Moraxella catarrhalis</i> |
|-------------------|--------------------------|-------|-------|-------------------------|------------------------------|
|                   | Pen-S                    | Pen-I | Pen-R |                         |                              |
| Amoxicillin       | 100                      | 59    | 46    | 0                       | 0                            |
| Amoxicillin-clav. | 100                      | 59    | 46    | 41                      | 70                           |
| Cefpodoxime       | 83                       | 21    | 0     | 82                      | 37                           |
| Cefuroxime        | 75                       | 35    | 0     | 33                      | 33                           |
| Cefprozil         | 75                       | 32    | 0     | 21                      | 41                           |
| Cefixime          | 59                       | 0     | 0     | 88                      | 48                           |
| Cefaclor          | 60                       | 0     | 0     | 0                       | 35                           |
| Loracarbef        | 50                       | 0     | 0     | 9                       | 26                           |

**Table 4. PK/PD breakpoints for macrolides**

| <b>Drug</b>    | <b>Regimen</b> | <b>Breakpoints (ug/ml)</b> |                      |                      |
|----------------|----------------|----------------------------|----------------------|----------------------|
|                |                | <b>PK/PD</b>               | <b>NCCLS</b>         |                      |
|                |                |                            | <i>S. pneumoniae</i> | <i>H. influenzae</i> |
| Erythromycin   | 500 mg qid     | 0.25                       | 0.25                 | -                    |
| Clarithromycin | 250 mg bid     | 0.25                       | 0.25                 | 8                    |
| Azithromycin   | 500 mg od      | 0.12                       | 0.5                  | 4                    |

**Table 5. PK/PD breakpoints for various fluoroquinolones against *S. pneumoniae***

| Drug          | Dose (mg) | <i>S. pneumoniae</i> MIC <sub>90</sub> (g/ml) | MIC breakpoint |       |
|---------------|-----------|---|----------------|-------|
|               |           |   | PK/PD          | NCCLS |
| Enoxacin      | 400 BID   | 8   | 1              | -     |
| Lomefloxacin  | 400 QD    | 8   | 1              | -     |
| Ciprofloxacin | 750 BID   | 2   | 1              | -     |
| Ofloxacin     | 400 BID   | 2   | 2              | 2     |
| Levofloxacin  | 500 QD    | 1   | 2              | 2     |
| Sparfloxacin  | 400 QD    | 0.25  | 0.5            | 0.5   |
| Grepafloxacin | 600 QD    | 0.25  | 0.5            | 0.5   |
| Trovafloxacin | 200 QD    | 0.25  | 1              | 1     |
|               | 300 QD    | 0.25  | 1              | 1     |

**Table 6. AUC/MIC ratios for selected quinolones**

| <b>Drug</b>   | <b>Dose<br/>(mg)</b> | <b>24-h AUC<br/>(mg.h/L)</b> | <b><i>S. pneumoniae</i> MIC<sub>90</sub><br/>(ug/ml)</b> | <b>24-h AUC/MIC</b> |
|---------------|----------------------|------------------------------|--|---------------------|
| Enoxacin      | 400 BID              | 32                           | 8  | 4                   |
| Lomefloxacin  | 400 QD               | 30                           | 8  | 4                   |
| Ciprofloxacin | 750 BID              | 34                           | 2  | 17                  |
| Ofloxacin     | 400 BID              | 70                           | 2  | 35                  |
| Levofloxacin  | 500 QD               | 50                           | 1  | 50                  |
| Sparfloxacin  | 400 QD               | 20                           | 0.25   | 80                  |
| Grepafloxacin | 600 QD               | 23                           | 0.25   | 92                  |
| Trovafloxacin | 200 QD               | 27                           | 0.25   | 108                 |
|               | 300 QD               | 40                           | 0.25   | 160                 |