Clinical efficacy and antimicrobial pharmacodynamics

Richard Wise

Changes in the susceptibility of bacterial pathogens and the availability of new antimicrobial drugs mean that physicians need to understand the underlying pharmacodynamics of each antimicrobial therapy. Antimicrobial pharmacodynamics determine clinical efficacy and should therefore be carefully considered when selecting appropriate antibiotic agents in the therapeutic setting.

In the last two decades significant antibiotic resistance has emerged throughout the world, especially among those commonly used to treat respiratory tract infections (RTIs), including β-lactams, cephalosporins and macrolides (Doern, 1996; Rikitomi et al, 1996; Doern et al, 1998). As a consequence of these changes in susceptibility, physicians have been prompted to consider alternative treatment options. The newer systemic fluoroquinolones may offer an alternative therapeutic option in the management of RTIs.

RTIs are a common source of mortality and morbidity, with pneumonia being the number one cause of death from infectious diseases in the USA. There are about 261 000 cases of community-acquired pneumonia (CAP) annually in the UK, and 32% of cases are treated in hospital (Guest and Morris, 1997). Although the overall mortality rate associated with pneumonia is relatively low in the community (1–5%), it can result in death in up to 25% of patients with CAP who required hospitalization (Marrie et al, 1989; Ortqvist et al, 1985; Pachon et al, 1990; Torres et al, 1991).

Chronic obstructive pulmonary disease is the leading cause of mortality and morbidity throughout the world (Whittemore et al, 1995). The prevalence of chronic bronchitis in developed countries is 3–17%, rising to 13–27% in less developed countries (Ball and Make, 1998). In the UK, chronic bronchitis causes 5% of deaths per year and is responsible for 28 million lost working days (Turner-Warwick et al, 1990). RTIs thus pose a therapeutic challenge and are associated with significant health-care costs in hospitalized patients.

Susceptibility tests do not always accurately predict clinical outcome (Wise, 1999). Observational studies report that in general infections 81% of patients improved if the isolate from the bloodstream was reported as sensitive, although 9% of patients died. However, it is important to note if the bloodstream isolate was resistant, mortality rose to 17% ($P \leq 0.05$) (Phillips et al, 1990; Phillips, 1991). Clinicians need to consider the dynamics and kinetics of agents as well as in-vitro laboratory reports.

Treatment of RTIs continues to place a significant burden on clinical budgets. Newer antimicrobials when carefully chosen may offer an important, cost effective, alternative in the light of increasing resistance to traditional therapy because of their bactericidal spectrum and pharmacodynamic profile. In RTIs where *Streptococcus pneumoniae*, β-lactamase-producing pathogens or an atypical infection could be responsible, it is important that initial empirical therapy has a broad spectrum of action and is promptly administered.

AETIOLOGY OF RTIS

Community-acquired RTIs may be caused by Gram-positive organisms (predominantly *S. pneumoniae*), Gram-negative organisms (*Haemophilus influenzae* and *Moraxella catarrhalis*) and 'atypicals' (for example, *Chlamydia pneumoniae*, *Legionella pneumophila* and *Mycoplasma pneumoniae*). In CAP, hospital-acquired pneumonia (HAP) and acute exacerbations of chronic bronchitis (AECB) mixed infections are common (Finch, 1995). Penicillin resistance has emerged among pneumococci, while β-lactamase production among *H. influenzae*, *M. catarrhalis* and many Gram-negative bacilli has led to alterations in first-line therapy options. Physicians in hospital and community practice therefore need to consider the

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specific spectrum of each antimicrobial, how antimicrobial pharmacodynamics affect therapeutic outcome and local antimicrobial sensitivity patterns of individual bacterial species.

In-vivo efficacy cannot be solely predicted by in-vitro minimum inhibitory concentration (MIC) data alone. Some antimicrobials, notably the β-lactams, require serum concentrations to be maintained above the MIC for an organism for the majority of the dosing interval. However, for other antimicrobials, such as aminoglycosides and fluoroquinolones, the absolute serum concentration and the area under the concentration time curve (AUC) correlate more closely with clinical outcome (Craig et al, 1991; Craig and Ebert, 1992; Wise, 1999) (see below).

RISING RESISTANCE

Rising antimicrobial resistance among respiratory pathogens is a major problem. As this problem continues to increase, the newer extended spectrum oral antimicrobials will assume an increasingly important role for the future management of respiratory infections. The three primary pathogens responsible for lower RTIs use multiple mechanisms to effect resistance against different antimicrobials (*Table 1*).

Streptococci

Streptococcus pneumoniae is the most important respiratory pathogen, being responsible for 1–36% of cases of CAP and 7–76% of cases of HAP (Blinkhorn Jr, 1998; Finch and Woodhead, 1998). Penicillin-resistant pneumococci were first observed in the USA in 1964, and the first clinically significant isolates were recognized in New Guinea 3 years later (Appelbaum, 1992). The incidence of penicillin-resistant *S. pneumoniae* is nearly 40% in some parts of the USA (Jacobs, 1999), and more than 50% of *S. pneumoniae* strains are resistant to penicillin in Spain and Hungary.

The incidence of penicillin resistance among streptococci has generally been low (about 3.5%) in the UK (Felmingham et al, 1998), however, there are nationwide reports suggesting that there is a significant increase in the level of resistance (Goldsmith et al, 1997). There is wide variation, as shown in a survey of 30 hospitals within the UK (Wise et al, 1998). Hospitals in some cities (Leicester and Sheffield) had no proven penicillin resistance among *S. pneumoniae* isolates, whereas the combined rate of intermediate and high level resistance was 46.2% in a Belfast hospital (but only 10% in another Belfast hospital) and 22.5% in a Birmingham hospital. In the latter, resistance was mainly high-level, whereas in hospitals in Dudley and Southampton it was intermediate resistance that predominated. Clearly, hospitals should undertake regular monitoring of local rates of antibiotic resistance, rather than relying on national data, and formulate policy on antibiotic choice and administration accordingly.

About 10–15% of *S. pneumoniae* strains are resistant to macrolides, such as erythromycin, clarithromycin and azithromycin (Bartlett, 1997), making these antimicrobials a less than ideal choice for treating RTIs. The mechanism of *S. pneumoniae* resistance to penicillin is by alterations in the targets of penicillin activity — specifically penicillin-binding proteins. These penicillin-binding proteins are also important in manifesting the effect of other β-lactam antimicrobials, e.g. cephalosporins. As a result of clonal spread β-lactam antibiotics in general have diminished activity against penicillin-resistant strains of *S. pneumoniae*.

Haemophilus

H. influenzae is the most common pathogen (23–60%) isolated from cases of AECB (Ball and Make, 1998; DeAbate et al, 1998). It is often isolated as lung function deteriorates and is implicated in the cycle of repeated infection and inflammation (Wilson, 1994). Among clinical isolates of *H. influenzae* resistance has been observed against ampicillin, amoxicillin/clavulanic acid and trimethoprim (Doern, 1996). The percentage of strains producing β-lactamase varies from country to country: 13% in Sweden (Henning et al, 1997) but 31–8% from 1994–99 in the USA (Derecola et al, 1999).

Amoxicillin and penicillin resistance among the common respiratory pathogens has increased over the period 1992–6 (Felmingham and Gruneberg, 1996; Felmingham et al, 1998) (*Table 2*). This rise in β-lactam resistance is a

TABLE 1.
Resistance mechanisms of common respiratory tract bacteria

Pathogen	Resistance mechanism	Agent affected
Haemophilus influenzae	β-lactamase production	Amoxicillin
	Penicillin-binding protein	Amoxicillin
	Ribosomal alterations	Macrolides
	Efflux mechanisms	Tetracyclines
Moraxella catarrhalis	β-lactamase production	Amoxicillin
	Ribosomal alterations	Macrolides
Streptococcus pneumoniae	Penicillin-binding protein	Penicillin
	Ribosomal alterations	Macrolides
	Efflux mechanisms	Tetracyclines

From Niederman (1996)

TABLE 2.
Amoxicillin and penicillin resistance among common respiratory pathogens

	Resistance to amoxicillin and penicillin (% of isolates)	
	1992	1996
Streptococcus pneumoniae	0.6	1.2–4.5
Haemophilus influenzae	3.1	13.8
Moraxella catarrhalis	66.4	96.7

From Felmingham and Gruneberg (1996), Felmingham et al (1998)

cause for concern as it is often associated with concurrent resistance to other classes of antibiotics, especially the macrolides (Jones et al, 1997, 1998). Resistance is a common cause of treatment failure.

The fluoroquinolones are unaffected by the principal mechanisms of resistance encountered in the common respiratory pathogens. The newer fluoroquinolones have a number of advantages in the treatment of RTIs. They have broad-spectrum activity against both Gram-positive and Gram-negative pathogens and they are rapidly bactericidal, which helps to prevent selection of antimicrobial-resistant strains of bacteria. They also have a post-antibiotic effect (PAE), which is a continued inhibition of bacterial growth after short exposure to an antimicrobial, an effect that continues in the absence of the antimicrobial agent. The more pronounced the PAE, the less likely that bacteria will resume growing during periods of sub-inhibitory antimicrobial concentrations in the tissue or serum. The PAE may also contribute towards preventing the emergence of antimicrobial resistance.

Inappropriate use of any antimicrobials can, of course, lead to an increase in antibiotic-resistant pathogens by selective pressure. Overuse of fluoroquinolones has also been accompanied by increasing resistance. The likelihood of resistance development can be reduced, and the lack of therapeutic effect overcome, by restricting antimicrobial use to genuine infections, by careful appraisal of prophylactic usage, and by choosing the most appropriate antimicrobial for the type of infection (Blondeau, 1999). In this respect, rapid bactericidal activity and pharmacokinetic characteristics that achieve a high concentration in tissue that is above the MIC for an organism(s) are very important.

TISSUE PENETRATION AND THERAPEUTIC OUTCOME

The concentration of an antibiotic in plasma may not reflect the antibiotic concentration at the site of infection. Tissue penetration is important in determining antimicrobial activity and therapeutic outcome (Wise et al, 1991). *Table 3* compares the tissue concentrations of antimicrobials that are commonly used to treat RTIs. Fluoroquinolones and macrolides accumulate within the tissues such that tissue concentrations exceed those in plasma.

TABLE 3.
Comparison of plasma and lung tissue concentrations of antibiotics that are commonly used to treat respiratory tract infections

				Lung concentrations (mg/kg* or mg/l†)			MIC_{90} (mg/l)		
Antibiotic	Oral dose (mg)		Plasma concentration (mg/l)	Bronchial mucosa*	Alveolar macrophage†	Epithelial lining fluid†	*Streptococcus pneumoniae*	*Haemophilus influenzae*	*Moraxella catarrhalis*
Co-amoxiclav	500/250	Peak	6.3–6.9	3.0	0	0.9	0.062	1–16	0.25
		Trough	4.3–5.3	1.7	0.8	1.0			
Cefuroxime	500	Peak	3.4–4.6	3.8			0.062–0.25	1–8	0.25
		Trough							
Azithromycin	500	Peak	0.5–0.6	8.1	23.0	2.2	0.12–0.25	0.06–1.0	≤0.015
		Trough	0.01						
Clarithromycin	500	Peak	4.0	16.8	372.7	20.5	0.02–16	8–32	0.06
		Trough	0.7–1.0						
Levofloxacin	500	Peak	6.6	8.3	41.9	10.9	1–2	0.015–0.031	0.06–0.125
		Trough	1.2	ND	13.9	ND			
Moxifloxacin	400	Peak	2.5–5.0	5.5	113.6	24.4	0.125–0.5	0.031–0.063	0.125
		Trough	0.5	1.0	38.6	3.5			
Trovafloxacin	200	Peak	1.4–2.2	1.5	19.1	4.8	0.12–0.25	0.01–0.05	0.03
		Trough	0.4	ND	10.2	0.9			

From Wise (1999). MIC = minimum inhibitory concentration; ND = not detectable.

Fluoroquinolones accumulate in tissues to the extent that local concentrations usually exceed serum concentrations by a ratio of greater than 2:1–3:1 in the bronchial mucosa, 8:1 in epithelial lining fluid and >25:1 in alveolar macrophages (Wise, 1999). Free antibiotic concentration, and not the protein bound fraction, is probably the most relevant parameter for pharmacokinetic/pharmacodynamic correlations. Moxifloxacin concentrations in bronchial mucosa and epithelial lining fluid are considerably higher than the MIC of 90% of the strains (MIC_{90}) of the common respiratory pathogens. Azithromycin and levofloxacin also achieve levels sufficient to inhibit the most common respiratory pathogens. Cefuroxime, clarithromycin and co-amoxiclav may not achieve concentrations sufficient to inhibit *H. influenzae*.

In the management of RTIs, tissue concentration above the MIC_{90}s of the common respiratory pathogens has been associated with good clinical outcome.

PHARMACOKINETIC INDICES AND THERAPEUTIC OUTCOME

The MIC of an antimicrobial for a micro-organism is one of the factors to be considered when treating RTIs. However, the pharmacokinetic behaviour of an antimicrobial also needs to be borne in mind. For example, an antimicrobial may be eliminated at a rate that causes the serum concentration of the drug to be below the MIC for a pathogen for much of the dose period, leading one to predict a poor clinical outcome (Hyatt et al, 1995).

There are two classes of antimicrobial effects, concentration-dependent or concentration-independent (Craig, 1998; Stahlmann and Lode, 1998):

1. Antimicrobials that cause concentration-dependent killing and a significant PAE, e.g. aminoglycosides and fluoroquinolones
2. Those that cause time-dependent killing with a minimal or moderate PAE, e.g. β-lactams and macrolides.

For the first category, peak serum concentration of the drug, i.e. C_{max} and AUC, are important parameters for assessing clinical response, whereas the time that serum concentrations remain above the MIC is the most important parameter for the latter. There are three pharmacokinetic and pharmacodynamic relationships that have been used to try to predict the clinical outcome of treating bacterial infections with antimicrobials (Hyatt et al, 1995; Wise, 1999):

C_{max}:MIC

One therapeutic indicator used to assess the likely outcome of treatment is C_{max} relative to the antimicrobial MIC for a particular organism or organisms. A number of studies have shown that the serum concentrations of antimicrobials (such as fluoroquinolones and aminoglycosides) related to the MIC correlate strongly with clinical response. In vitro studies have shown that a C_{max}:MIC ratio of >10 prevented the emergence of antimicrobial-resistant micro-organisms (Blaser et al, 1987; Marchbanks et al, 1993; Michea-Hamzehpour et al, 1987). The most recent clinical trial data on levofloxacin suggest that a ratio of at least 12.2 correlates with favourable clinical and microbiological outcome (Preston et al, 1998).

AUIC

In addition to the predictive value of the C_{max}:MIC ratio for clinical response and propensity for resistance development, pharmacokinetic information and data on in vitro inhibition of micro-organisms by an antimicrobial can be integrated as the ratio of the AUC over 24 hours above the MIC_{90}, i.e. the area under the inhibition curve (AUIC). This is shown diagrammatically in *Figure 1*. AUIC has become an extremely important predictor of clinical and microbiological success (Schentag et al, 1996).

- AUIC values above 125 and C_{max}:MIC ratios of 8–10 have been associated with optimal antibacterial activity
- Lower values may relate to less rapid bactericidal activity and the selection of resistant bacteria
- A target AUIC may be achieved with either a single agent or it can be the sum of AUIC values of two or more antimicrobials.

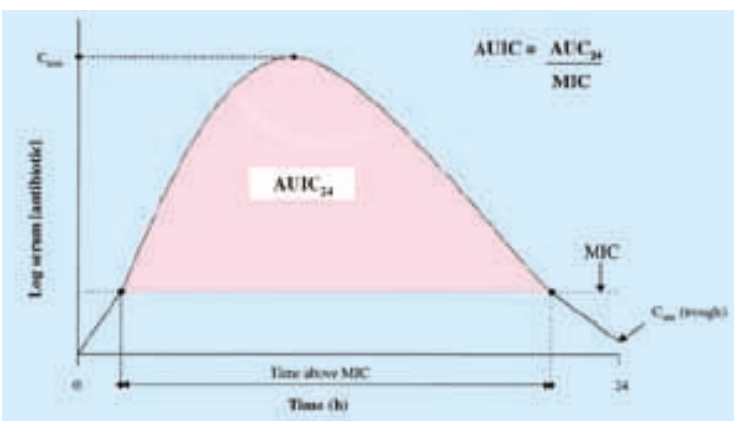

Figure 1. Calculation of the area under the inhibition curve (AUIC). C_{max} = peak serum concentration; C_{min} = trough serum concentration; MIC = minimum inhibitory concentration.

Beta-lactams, even when dosed to an AUIC of 250, often require longer treatment duration to eliminate the bacterial pathogen, because the in vivo bacterial killing rate of β-lactams is slower than that of fluoroquinolones. This remains true even at AUIC values of 250 for both compounds, although this is theoretically identical dosing (Schentag et al, 1996, 1997).

Time that serum concentration exceeds the MIC

A third predictor of clinical efficacy for some antimicrobials is the time that plasma concentrations of the drug remain above the MIC for a particular organism (*Figure 1*). This parameter is particularly important for the bactericidal activity of β-lactam antibiotics and it has been suggested, although not established, that T>MIC is also an important parameter related to efficacy of the glycopeptides, such as vancomycin and teicoplanin (Wise, 1999).

Generally, antimicrobials have a spectrum of activity that is bimodal in terms of an organism's susceptibility or resistance (*Figure 2*). This susceptibility is determined in vitro in the laboratory and reported to the physician. Marginal organisms (i.e. MIC at the breakpoint) are the first organisms to express resistance. Emergence by selective pressure occurs when dosing is lowered below the MIC (*Figure 3*). Thomas et al (1998) found that an AUIC of <100 was associated with a significant increase ($P<0.001$) in the development of resistance in 107 acutely ill patients with nosocomial lower RTIs. Among patients in whom an AUIC of >100 was achieved, only 8% of organisms developed resistance by 20 days after initiation of therapy.

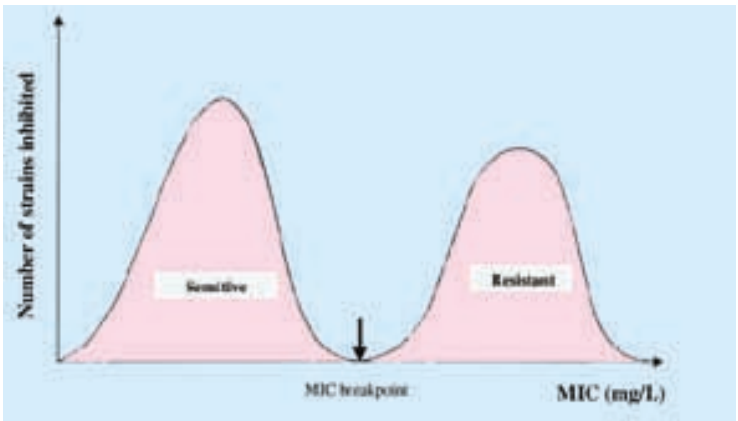

Figure 2. Identifying breakpoints: bimodal minimum inhibitory concentration (MIC) distribution.

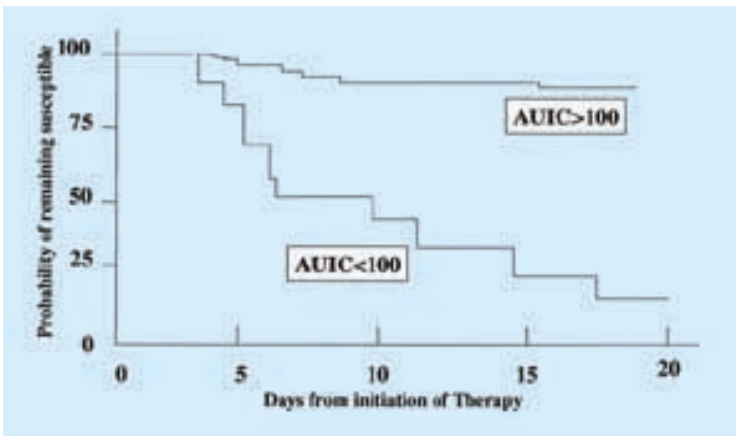

Figure 3. Area under inhibitory curve (AUIC) vs bacterial resistance development (Thomas et al, 1998).

THERAPEUTIC OPTIONS

Clinical efficacy is affected by a complex series of factors, both pharmacokinetic and antimicrobial. Therapeutic properties that should be sought in the effective treatment of RTIs are shown in *Table 4*. These features are particularly important in the treatment of CAP which is associated with significant mortality (Fine et al, 1996).

Antimicrobials selected for the treatment of RTIs should possess activity against the common and atypical pathogens and have optimal pharmacokinetic and pharmacodynamic parameters that facilitate a convenient dosage schedule and good tissue penetration. The newer fluoroquinolones, such as moxifloxacin, would appear to fulfil these criteria.

FLUOROQUINOLONES IN THE TREATMENT OF RTIS

Although the quinolone class of drugs has been in existence since 1962, only since the fluorination of the molecule in 1983 has the class been considered a major antibacterial force. The classic fluoroquinolones such as ciprofloxacin, levofloxacin, norfloxacin, ofloxacin and sparfloxacin have had strong activity against Gram-negative bacteria, but the effectiveness of

TABLE 4.
Suggested features of an antibiotic for the treatment of respiratory tract infections

Activity against common causative pathogens
Resistance to degradation by β-lactamase
Good penetration into sputum and bronchial tissue
High sputum concentration/minimum inhibitory concentration ratio against target organisms
Bactericidal activity
Likelihood of compliance

these compounds has been debated where Gram-positive bacteria have been isolated (Thys et al, 1989, 1991; Vogel, 1995).

The fluoroquinolones developed during the 1990s, notably clinafloxacin, grepafloxacin and moxifloxacin have demonstrated enhanced activity against a range of bacteria compared with earlier agents (Klugman and Capper, 1997; Souli et al, 1998). The broader spectrum and favourable pharmacodynamics of the newer fluoroquinolones therefore makes these drugs an attractive therapeutic alternative to traditional agents for common respiratory infections.

The fluoroquinolones are bactericidal against both growing and non-growing Gram-negative bacteria, unlike the β-lactams and aminoglycosides which kill only actively growing bacteria. Newer fluoroquinolones have enhanced activity against Gram-positive and atypical organisms while maintaining activity against Gram-negative bacteria. Clinically relevant resistance to these drugs is uncommon among the common respiratory tract pathogens. Indeed, penetration of these fluoroquinolones into bronchial tissue in concentrations that substantially exceed the MIC_{90} values for respiratory tract pathogens make these agents an excellent therapeutic choice for the treatment of RTIs.

CONCLUSIONS

Recent changes in the sensitivity of the key pathogenic organisms associated with RTIs mean that today's physician needs up-to-date knowledge of local susceptibility patterns, particularly when initiating empirical therapy. However, it is essential that in vitro sensitivity is considered alongside the specific pharmacokinetic and pharmacodynamic properties of the antibiotic chosen for therapy. In this context, the newer fluoroquinolone agents may offer an important therapeutic alternative to traditional agents, and their place in the treatment of RTIs will be established by clinical trials. HM

Conflict of interest: Professor Wise acts as a consultant to a number of pharmaceutical companies including Bayer.

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KEY POINTS

- In the last two decades significant resistance has emerged worldwide against antimicrobials commonly used to treat respiratory tract infections (RTIs), including β-lactams, cephalosporins and macrolides. In vivo efficacy cannot be predicted by in-vitro minimum inhibitory concentration (MIC) data alone.
- Antimicrobial pharmacodynamics predict clinical efficacy.
- Tissue penetration is an important determinant of antimicrobial activity and therapeutic outcome.
- In the management of RTIs tissue concentrations above the MIC_{90s} of the common respiratory pathogens has been associated with good clinical outcome.
- Area under the inhibitory curve (AUIC) values above 125 and C_{max}:MIC ratios of 8–10 have been associated with optimal antibacterial activity.
- Antimicrobials selected for the treatment of RTIs should possess activity against the common and 'atypical' pathogens and have optimal pharmacokinetic and pharmacodynamic parameters that facilitate a convenient dosage schedule and good tissue penetration.
- The newer fluoroquinolones may offer an important therapeutic alternative to traditional agents.

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