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Application of Pharmacokinetics and Pharmacodynamics to Antimicrobial Therapy of Community-Acquired Respiratory Tract Infections

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Pharmacokinetics · Pharmacodynamics · Fluoroquinolones · Macrolides · Beta-lactams · Respiratory infections

Abstract
To achieve bacteriologic and clinical success, sufficient concentrations of antimicrobial at the site of infection must be maintained for an adequate period of time. These dynamics are determined by combining drug pharmacokinetic and pharmacodynamic (PK/PD) data with minimum inhibitory concentrations. Bacteriologically confirmed failures have been reported in otitis media and, with a lesser degree of evidence, in pneumococcal pneumonia with a variety of agents that include β-lactams, macrolides and fluoroquinolones. These failures have been shown to be due to infection by resistant pathogens or suboptimal therapy. However, no clinical failure has been reported during therapy for bacteremic pneumococcal pneumonia with adequate doses of β-lactams. The failures reported with macrolides or fluoroquinolones have been due to either preexisting resistance to these agents that cannot be overcome by increasing the dose of the antimicrobial or, more rarely, the emergence of resistance during therapy. In this review, we offer an overview of the most important attributes of the main antimicrobials that are currently used in the treatment of community-acquired respiratory tract infections from a PK/PD perspective.

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Introduction

Community-acquired respiratory tract infections (community-acquired RTIs) are the commonest cause of morbidity in the western world. Viruses are, by far, the most frequent etiologic agents followed at a considerable distance by bacteria with special tropism for the airways. Unfortunately, neither the clinical features nor the diagnostic tools available are sensitive enough as to allow the practicing physician to make a diagnosis of a bacterial infection with accuracy. This is the main reason for unnecessary antibiotic prescribing and its negative consequences of development of resistance, increased toxicity and increased costs.

The three most frequently identified bacterial pathogens in RTIs are *Streptococcus pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis*. All three patho-

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gens now exhibit resistance to commonly prescribed antimicrobials, although resistance prevalences vary considerably [1]. Empirical antibiotic therapy of community-acquired RTIs should always include adequate coverage for *S. pneumoniae* because this organism is the most common cause of bacterial respiratory infection at all levels of the airways, from the middle ear down to the alveolar space; moreover, it is the major cause of morbidity and mortality in RTIs, and is the organism that has accumulated most resistance determinants over time [2]. Thus, the increasing prevalence of resistance to penicillin and other drugs among pneumococci has considerably complicated the empirical treatment of respiratory tract infections. Worryingly, many resistant isolates are also resistant to multiple classes of antimicrobials [3], which seriously impact many first-line antimicrobial therapies. In some areas of the USA, Europe and East Asia, a prevalence of macrolide resistance as high as 35% [4] or more has been reported. Fluoroquinolone resistance is currently low but on the increase in some areas of the world.

Suboptimal prescribing is a major cause of concern as it increases the risk of clinical failure. Also, it is an avoidable risk factor for the development and spread of bacterial resistance [4]. Until recently, antimicrobial choice was based on in vitro susceptibility data and clinical efficacy from trials powered only to show equivalence between agents [5].

During the last decade, important progress has been made in the application of pharmacokinetic (PK) and pharmacodynamic (PD) principles in the rational choice of antibiotic therapy and its appropriate dosing; advances in our understanding of PK/PD from animal models [6] now enable us to predict antimicrobial bacteriologic efficacy in RTI. It is now understood that to achieve bacteriologic and clinical success, sufficient concentrations of antimicrobial at the site of infection must be maintained for an adequate period of time. These dynamics are determined by combining drug PK and PD (PK/PD) data with minimum inhibitory concentrations (MIC). PK/PD parameters are predictive of bacteriological and clinical outcomes, and can be used to optimize antibacterial dosing regimens and have become essential for making a rational choice and calculating dosage. Finally, PK/PD principles can be used to set performance standards for both the optimization of currently available compounds and the development of new agents.

Traditionally, β-lactams have been the drugs of choice for the treatment of community-acquired RTIs. Allergy and increasing resistance to many agents of this class have favored the use of alternative drugs for this indication. Over the last 50 years, tetracyclines, chloramphenicol, macrolides, trimethoprim/sulfamethoxazole and, more recently, fluoroquinolones, have been widely used. The initial susceptibility of *S. pneumoniae* to all these agents made possible their continued use for many years, with apparent success. Toxicity and progressive resistance to many of them have severely reduced our current armamentarium against pneumococcal infections, particularly in the case of meningitis. The three main classes of antimicrobials used today for the treatment of extrameningeal pneumococcal infections include selected β-lactams, macrolides and their derivatives (ketolides), and modern fluoroquinolones with enhanced activity against gram-positive cocci.

Antibiotic therapy is an essential part of the management of pneumonia, but is not the only therapeutic intervention to consider. In severe pneumonia, the importance of inflammation is increasingly recognized and other important coadjuvants to control the inflammatory reaction are called to play a major role in this setting. This aspect goes beyond the scope of this article. An excellent review of the therapeutic targets in pneumonia has recently been been published [7]. In this article, and from a PK/PD perspective, we offer an overview of the most important attributes of the main agents of these three classes of antimocrobials that are currently used in the treatment of community-acquired RTI.

Pharmacodynamics and Pharmacokinetics

PK characteristics describe the absorption, distribution and elimination of the antimicrobial. Combined with the dosage regimen, these factors determine the time course of drug concentration in serum, which in turn determines the time course of drug concentrations in tissues and body fluids.

For modeling purposes, PK parameters can be calculated either as one- or two-compartment models. In a one-compartment model, it is assumed that the drug is distributed equally and simultaneously to all body tissues. In a two-compartment model, drugs are considered to be distributed in the body in two phases: an initial equilibrating distribution phase into the blood and tissues with high blood flow and a second, slower, equilibrating phase [8].

PD is the relationship between concentration and the antimicrobial effect. Susceptibility of the pathogen to the drug, determined by measuring the MIC, is a reflection of the potency of a drug.

MICs and minimum bacteriostatic concentrations (MBCs) have been the major parameters used to quan-

tify the activity of an antibacterial drug against the infecting pathogen. Although these parameters are good predictors of the potency of the drug-organism interaction, they do not provide any information on the time course of antimicrobial activity.

Some parameters such as postantibiotic effect (PAE), the postantibiotic sub-MIC effect (PAE-SME) and postantibiotic leukocyte enhancement (PALE) more accurately describe the drug-bacteria interaction over time.

PAE refers to the persistent suppression of bacterial growth following exposure to an antimicrobial. A long PAE prevents regrowth after antimicrobial concentrations fall below the MIC. Prolonged in vivo PAEs are observed for all antimicrobials with staphylococci and for imipenem and inhibitors of protein and nucleic acid synthesis with streptococci and gram-negative bacilli. Thus, β-lactams that exhibit time-dependent killing usually have minimal or short PAEs [9]. Antimicrobials exhibiting PAEs may be administered less frequently than would be predicted based on elimination half-life. Thus PAEs have a major impact on dosing.

Sub-MIC concentrations of antibiotics are known to slow growth and produce morphological changes such as filaments. A long period of growth suppression may be obtained when a low concentration ($\leq 0.3 \times$ MIC) is added to bacteria previously exposed to a supra-inhibitory concentration. This phenomenon has been named the postantibiotic sub-MIC effect (PAE-SME). Since a period with sub-inhibitory concentrations will often exist between the doses when intermittent dosing of antibiotics is used, the PAE-SME probably reflects the in vivo situation more closely than the PAE [10].

PALE operates through increased susceptibility of antibiotic-damaged bacteria to the intracellular killing mechanisms of leukocytes as some studies on the rates of phagocytosis and intracellular killing have shown. Exposure of *Escherichia coli* and *Staphylococcus aureus* to high levels of certain antibiotics for brief periods of time increased the susceptibility of the organisms to the antimicrobial action of normal human leukocytes [11].

Mutant prevention concentration (MPC) has been proposed as a means by which selection of resistant mutant strains can be restricted [12]. Therapeutic concentrations of antimicrobials that are active against the majority of susceptible pathogens are often those at which the resistant mutant population of the bacterial colonies can become selectively enriched. The MPC is defined as the lowest concentration of antimicrobial that prevents bacterial colony formation from a culture containing more than 10^{10} bacteria. The mutant selection window is defined as the concentration range in which the resistant mutants are selectively enriched during antimicrobial therapy [13].

Antibacterials can be divided into 2 major categories on the basis of their major mechanism of bacterial killing: time-dependent or concentration-dependent activity.

Time-Dependent-Killing Antibiotics

Time above the MIC has consistently been the only PK/PD parameter that correlates with the therapeutic efficacy of the so-called time-dependent-killing antibiotics, namely, β-lactams, macrolides, clindamycin and oxazolidinones. The goal of a dosing regimen for these drugs would be to optimize the duration of exposure [14]. Maximum killing is achieved at concentrations approaching 4–5 times the MIC [15], but any further increases in concentrations provide little to no additional benefit. Therefore, the length of time that the drug concentration is above the MIC has been shown to be the most important parameter for determining clinical and microbiological success.

The required time above the MIC varies, depending on the pathogen, infection site and drug, but is generally 40–50% of the dosing interval [16]. There is some evidence that for the carbapenems, a shorter time above the MIC is necessary for efficacy (20–30%) than for β-lactams [17]. The degree of antibacterial protein binding can alter the T > MIC. Ceftriaxone with a higher protein binding than cefotaxime requires a larger T > MIC when calculations are based on the total drug concentration, supporting the concept that free drug is the biologically relevant parameter [18]. (The percentage of protein binding depends to some extent on the dosis administered; it ranges from 60 to 96% for ceftriaxone, and 20–50% for cefotaxime.)

With the time-dependent-killing antimicrobials, PAEs are minimal. However, azithromycin, tetracyclines, glycopeptides and oxazolidinones also exhibit time-dependent killing and produce prolonged persistent effects. The dosing frequency is usually not a major factor in the efficacy of these drugs. The 24-hour AUC/MIC is the primary parameter to correlate with in vivo efficacy [19].

Therefore, in this class of antimicrobials, it is critical to assess whether standard doses are likely to achieve sufficiently high serum antibiotic concentrations to exceed the MICs for 40–50% of the dosing interval, which depends not only on the MIC of respiratory tract pathogens but also on the pharmacokinetic characteristics of the antibiotic.

Concentration-Dependent-Killing Antibiotics

For antimicrobials that exhibit concentration-dependent killing, the ratios of serum C_{max}/MIC and the ratio of the 24-hour area under the plasma concentration curve (AUC_{24}) to the MIC (AUC_{24}/MIC) are the parameters that correlate best with bactericidal efficacy [20, 21]. Most authors agree that only 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. The goal of a dosing regimen for these drugs would be to maximize their concentrations as increasing the dose of a drug with concentration-dependent effects is associated with increased bacterial killing. The aminoglycosides and fluoroquinolones are drugs that exhibit concentration-dependent killing and produce prolonged persistent effects [22]. Because higher doses will result in better killing, once-daily dosing of these agents that maximize the peak/MIC ratio could enhance their antimicrobial activity [23].

β-Lactams

Since the introduction of penicillin, the β-lactam agents have been the mainstay of RTI therapy [24]. Despite the emergence and spread of resistance to penicillin and other antibacterial agents, penicillin G remains among the therapies of choice for uncomplicated community-acquired pneumonia (CAP) caused by penicillin-susceptible *S. pneumoniae*. The β-lactams, as a class, are still effective even for penicillin-resistant *S. pneumoniae* (PRSP) when dosed appropriately [25].

The prevalence of PRSP varies from less than 10 to 80% [26, 27]. The mechanism of resistance to penicillin and other β-lactam is due to alterations of penicillin-binding proteins (PBPs) leading to decreased binding affinity. The loss of affinity for the PBPs affects all β-lactams although this may vary substantially depending on the drug.

The effect of increased antibiotic resistance is noted first in infections at sites of restricted drug penetration. The reason for this is that much higher levels of antibiotic are achieved in the blood and the alveoli compared with the CSF and the middle ear. In fact, treatment failures were first described in association with decreased penicillin susceptibility in children with otitis media receiving oral β-lactams and in both adults and children with meningitis on intravenous penicillin or third-generation cephalosporins [28–30].

As already pointed out, time above the MIC is the PK/PD parameter that correlates with the therapeutic efficacy of the various β-lactam antibiotics. Studies in animal infections as well as clinical studies in acute otitis media, where routine repeated tympanocenteses of middle ear fluid were done, demonstrate that in general a time above the MIC of >40% is required to achieve an 85–100% bacteriologic cure and that greater amounts of antibiotic do not increase bactericidal capacity [31, 32].

With respect to pneumonia, the correlation between pneumococcal susceptibility and outcome is not as clear. Some studies have revealed that resistance does not negatively impact outcome with respect to mortality rate [33–37] whereas others suggest a trend toward a higher 30-day mortality rate or other complications [38–40]. Nevertheless, no documented failure, defined by the persistence of positive blood cultures while on oral or intravenous penicillins or third-generation cephalosporins (cefotaxime, ceftriaxone) at adequate dosage for MICs, has been reported so far in patients with bacteremic pneumococcal pneumonia caused by strains with penicillin MICs as high as 4 μg/ml. This lack of clinical failures in CAP due to PRSP treated with adequate doses of β-lactam can be easily explained based on the aforementioned PK/PD data. Most parenteral β-lactams provide serum levels that exceed the MIC_{90} of resistant strains for >40% of the dosing interval. Thus, it is not surprising that treatment with these drugs did not result in any difference in outcome for patients infected with penicillin-resistant strains. Some investigators [41] consider that β-lactams cannot be used in the treatment of pneumococcal pneumonia due to strains with penicillin MIC >4 mg/l. The low prevalence of these strains and the rarity of severe infections caused by these strains minimize their importance and suggest a possible inverse relationship between virulence and high level penicillin resistance [42].

Variability exists among different β-lactams to achieve the PK/PD target of T >40% MIC for drug-resistant pneumococcal strains. Among the oral agents, aminopenicillins and cephalosporins are able to attain these levels for fully susceptible strains. As the penicillin MIC increase, fewer oral agents will be suitable for the treatment of penicillin-resistant isolates and only amoxicillin at high doses will achieve T >40% for pneumococcal extrameningeal infections caused by resistant pneumococci [43]. Thus, amoxicillin at an adequate dose remains the most active oral β-lactam (table 1). Although recently some cases of breakthrough bacteremia in patients receiving coamoxiclav have been described, the underdosing regi-

men (500/125 twice daily) administered was the most probable cause of the breakthrough bacteremia [44]. It is noteworthy that infections caused by *S. pneumoniae* strains with MICs of 4–8 μg/ml to amoxicillin have responded to a new oral formulation of amoxicillin at a dose of 2,000 mg twice daily in a similar way to infections caused by strains with an amoxicillin MIC of <0.06 μg/ml (table 2). Its pharmacokinetics explains its success: Time > MIC is achieved in 35–49% of the dosing interval (table 1). Among oral cephalosporins, cefditoren and cefpodoxime are the most active. Nevertheless, although cefpodoxime in a mouse thigh model was able to cover strains with and MIC of ≥ 1 μg/ml for >30% of the dosing interval by increasing doses, the doses necessary to reach this level of coverage would not be achievable in humans [45]. Among parenteral agents, carbapenems are the most active β-lactams available against PRSP.

Among parenteral cephalosporins, those with good activity are cefotaxime, ceftriaxone, cefepime and cefpirome. It is important to note that other parenteral third-generation cephalosporins are considerably less active – e.g., ceftizoxime and ceftazidime. The latter has been linked to a poor clinical response in neutropenic patients with pneumococcal disease due to penicillin-resistant strains [46]. Finally, intravenous cefuroxime (750 mg/q8h) has been associated with a higher mortality rate in patients with bacteremic pneumococcal pneumonia infected with cefuroxime nonsusceptible strains [37], a good example of the predictive value of modern PK/PD in humans with respiratory tract infection.

Table 1. T > MIC for amoxicillin/clavulanate against isolates of *S. pneumoniae*

AMOX/CLAV formulation	Dosing regimen	Mean time above MIC for amoxicillin, % of dosing interval			
Percentage of isolates 1998–1999 [76]		MIC = 1 (11%)	MIC = 2 (13%)	MIC = 4 (4.4%)	MIC = 8 (4.2%)
500/125	b.i.d.	36	–	–	–
500/125	t.i.d.	55	43	–	–
875	b.i.d.	42	28	–	–
875/125	t.i.d.	63	43	34	–
1,000/125	t.i.d.	>65	55	41	–
2,000/125	b.i.d.	>70	60	49	35

MIC = Minimum inhibitory concentration in μg/ml; AMOX/CLAV = amoxicillin/clavulanate.

Table 2. Success rates for amoxicillin/clavulanate (AMOX/CLAV) 2000/125 b.i.d. against isolates of *S. pneumoniae* in the bacteriology per protocol population [77]

AMOX/CLAV MIC μg/ml	Isolates (n = 550)[a]	Success	
		n	%
<0.01–0.25	482	456	94.6
0.5	7	6	85.7
1	15	13	86.7
2	31	31	100
4	7	6	85.7
8	8	7	87.5

[a] Two patients each had one *S. pneumoniae* pathogen for which the amoxicillin MIC was unknown.

Macrolides

Macrolides have been widely used as initial empirical antibacterial therapy for a variety of community-acquired RTIs as a classical alternative to β-lactams in the case of allergy, and in response to the evolution of β-lactam-resistant *S. pneumoniae*. Macrolides also provide coverage for the so-called atypical bacterial pathogens *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae* and *Legionella pneumophila*, making them particularly well placed for the treatment of community-acquired pneumonia. Erythromycin-resistant strains are predictably resistant to clarithromycin, azithromycin and roxithromycin and are usually resistant to penicillin and several other antibiotics.

Macrolide resistance in *S. pneumoniae* occurs by two main mechanisms: target site modification or efflux of the drug out of the cell. In the most common form of target site modifications, a specific adenine residue on the 23S rRNA (A2058) is dimethylated by an rRNA methylase. The predominant methylase responsible for macrolide resistance in SP is encoded by *erm*(B) [47]. This methylation is thought to lead to conformational changes in the ribosome, resulting in decreased binding of all macrolide, lincosamide and streptogramine antibacterials (the so-called MLS_B phenotype). Pneumococci harboring the *erm*(B) gene exhibit high to very high levels of resistance to all macrolides, with MIC_{90} of both clarythromycin and azythromycin of 256 μg/ml or more. Macrolide efflux is mediated by the product of the *mef*(A) gene, which usually causes MICs lower than the *erm*(B)

isolates (MICs of 1–32 μg/ml) and retain susceptibility to clindamycin and other 16 membered macrolides (the so-called M-phenotype) [48]. The acquisition of both a methylase and an efflux mechanism in the same strain has been described as well. An increasing number of erythromycin-resistant isolates, either obtained in vitro after serial passages in macrolide-containing media or found in clinical isolates that lack *mef*(A) or *erm*(B) genes are being recognized. Mutations at different positions in domains V and II of 23S rRNA and in genes that encode the ribosomal proteins L4 and L22 have been identified in such strains [49, 50]. The prevalence of the main two resistance mechanisms is different depending on the local epidemiology [51]. The *erm*(B) genotype predominates in the majority of European countries, whereas in the US, the most commonly identified mechanism has been the presence of *mef*(A) [52]. A small percentage of strains carries both genes. Other mechanisms of macrolide resistance are rare, accounting for less than 1.5% of all isolates.

Since the initial descriptions in the early 1990s of failures of macrolides in patients with pneumococcal pneumonia, an increasing number of cases that failed therapy with macrolides have been reported in recent years. Breakthrough bacteremia during macrolide or azalide therapy has been described among patients infected with erythromycin-resistant pneumococci, with erythromycin MICs as low as 4 mg/ml [53].

In animal models it is possible to increase the dose of macrolides and azalides to meet the PK/PD target for eradication of *S. pneumoniae* strains with MICs in the range conferred by *mef*(A) resistance and in most strains of *H. influenzae*. In humans, however, limitations in PK added to safety issues that arise with increased dosages make optimization difficult [54].

Although studies suggest that the magnitude of the time above MIC required for efficacy of macrolides against *S. pneumoniae* is also 40–50% of the dosing interval, studies on bacteriologic cure have been limited to macrolide-susceptible strains. For these organisms, erythromycin and clarithromycin provide prolonged time above MIC (90–100%) of the dosing interval, and produce high rates of bacteriologic cure [55]. The AUC/MIC is the PK/PD parameter correlating best with the efficacy of azithromycin. In a murine thigh infection model, a value of approximately 25–30, which is equivalent to averaging 1 times the MIC during 24 h, is required for efficacy [56]. This value is easily obtained with standard dosing for azithromycin-susceptible strains of *S. pneumoniae*; however, the 24 h AUC/MIC for azithromycin-resistant strains due to the MLS_B mechanism is <0.1, and bacteriologic failure has been observed [56].

Clinical studies allow PK/PD breakpoints to be calculated that predict the MIC cut-offs for maximal bacterial eradication. These breakpoints are based on the dosing regimen used and the site of infection, and apply to approved the oral dosing regimen and to infections other than meningitis, where the site concentration profiles differ substantially from the serum concentration profiles. On the basis of these studies in patients or in animal models, the susceptibility breakpoint for macrolides has been determined as ≤0.5 mg/ml. Application of the aforementioned macrolide MIC breakpoint results in 20–35% of *S. pneumoniae* strains and 95% of *H. influenzae* strains being classified as macrolide resistant [57]. These interpretations are in agreement with numerous animal models of infections due to these pathogens as well as with bacteriologic outcome and studies of acute otitis media and sinusitis. As an example, in a study in acute otitis media treated with azithromycin at 10 mg/kg where tympanocentesis was performed on entry into the study and 3–4 days after initiation of treatment, a clear correlation was found between the persistence of *S. pneumoniae* with increased MICs of azithromycin [58]. However, as bacteriological failures occurred in patients infected with *H. influenzae* independently of the MIC values, the clinical breakpoint for azithromycin must be somewhere below the current NCCLS MICs for *H. influenzae,* and above the MICs for macrolide-susceptible *S. pneumoniae*. Therefore, in acute otitis media the clinically derived breakpoint for azithromycin should be around 0.25 mg/l [59]. Nevertheless, taking into account that azithromycin median levels measured in middle-ear fluid were 2.32 mg/ml, the role of macrolides and azalides in the treatment of acute otitis media, especially when caused by *H. influenzae* must be revised.

Ketolides have a concentration-dependent activity although the PK/PD relationships of these agents are still under investigation [60]. For the first member of this family, telithromycin, the AUC/MIC ratio that correlates with efficacy for *S. pneumoniae* may be much higher (between 50 and >200) than for other agents in this class [61]. In fact, AUC/MIC ratios of telithromycin when compared to azithromycin for *S. pneumoniae* and *H. influenzae*, have values of 208 vs. 19.9 h, and of 10.4 vs. 2.1 h, respectively, clearly more favorable in the case of telithromycin.

Table 3. Pharmacodynamics of major fluoroquinolones against *S. pneumoniae* [73]

Antimicrobial	Dosage	Free drug, %	Antibacterial activity MIC_{90}	Pharmaco-dynamics AUC_{24} (free drug)	Potency	
					AUC_{24}/MIC (free drug)	relative potency
Ciprofloxacin	750 mg p.o. b.i.d.	70	1	28.9	28.9	1×
Levofloxacin	500 mg p.o. q.d.	70	1	33.3	33.3	1×
Gatifloxacin	400 mg p.o. q.d.	80	0.25	26.8	107	3×
Moxifloxacin	400 mg p.o. q.d.	50	0.12	24.0	192	6×

Fluoroquinolones

Modern fluoroquinolones (levofloxacin, gatifloxacin and moxifloxacin) are highly active against *S. pneumoniae* and have been used as empirical therapy both in ambulatory CAP [62] and in severe CAP requiring ICU [63].

Currently, there is little resistance to fluoroquinolones among pneumococcal isolates, although this is increasing in some regions of the world [4]. Maintaining this low prevalence of quinolone resistance is important because once a strain becomes resistant, the activity of most, if not all, of the quinolones is compromised.

Quinolones act by binding to complexes that form between DNA and gyrase or topoisomerase IV. DNA gyrase and topoisomerase IV control the topology of the chromosomal DNA to facilitate replication, recombination and expression. DNA gyrase is a tetramer of two subunits encoded by the *gyr*A and *gyr*B genes. Topoisomerase IV is a homologue of DNA gyrase, comprising four subunits, two of C and two of E, encoded by the *par*C and *par*E genes, respectively.

Resistance to quinolones occurs in a stepwise fashion with mutations being observed first in either *par*C or *gyr*A, leading to decreased fluoroquinolone susceptibility. Strains usually become fully resistant with the addition of a mutation in the other target gene (either *gyr*A or *par*C) [64]. Mutations in *par*E and *gyr*B and efflux pump are less important mechanisms of resistance.

Fluoroquinolones have concentration-dependent bactericidal effects. The free-drug area under the concentration-time curve at 24 h related to the MIC_{90} against SP (AUC_{24}/MIC_{90}) is the PD parameter with the strongest correlation with outcome in vitro, in animal models and in human infections [22]. In a recent study, a free-drug AUC/MIC_{90} ratio of >33.7 was associated with 100% microbiological response [65]. In general, optimal bactericidal activity of all the fluoroquinolones against gram-positive pathogens occurs at an AUC/MIC ratio of at least 25–30 [66]. In contrast, according to studies on lower RTIs caused by gram-negative pathogens, AUC/MIC ratios for the quinolones should be at least 100 or 125 for optimal bactericidal efficacy [67]. Values of >250 are associated with a very rapid elimination of gram-negative bacilli from respiratory secretions of patients with nosocomial pneumonia [20]. A comparison of PD parameters for quinolones against *S. pneumoniae* is shown in table 3.

Older fluoroquinolones have only moderate in vitro activity against pneumococci and complications during ciprofloxacin therapy such as pneumococcal bacteremia, sinusitis, meningitis and arthritis have been described [68–70]. That could be explained because the estimated 24-hour AUC/MIC ratios for ciprofloxacin are around 10–20 with doses of 400 mg given intravenously every 12 h [56].

The newer fluoroquinolones have increased activity against gram-positive cocci, specifically *S. pneumoniae*; however, resistance and also clinical failure are issues of major concern. Several cases of levofloxacin failure in treating a variety of pneumococcal RTIs have been reported. All these cases were due to levofloxacin-resistant strains (MIC >4 to >32 mg/l) where the 24-hour AUC/MIC ratio would be <10 [56]. Clinical failures have also been related to the appearance of resistance in previously susceptible strains.

Emergence of resistance during the course of antimicrobial therapy is most likely to develop from strains that already carry one mutation since they require only one additional mutation in one of the other target genes to become resistant. To meet PK/PD targets for resistant strains, the total daily dose would need to be increased, which is best achieved by increasing the single daily dose rather than increasing the frequency of dosing. The fluoroquinolones, however, have a relatively narrow safety window, limiting the options for increasing the dosage and frequency, and most currently available agents would

Table 4. Effect of *gyr*A and *par*C resistance mutations on fluoroquinolone activity (adapted from Li et al. [78])

S. pneumoniae strain	MIC_{99}		MPC		Survival[1] at wild-type MPC	
	MOX	LEVO	MOX	LEVO	MOX	LEVO
ATCC49619 (wild type)	0.15	0.7	0.5	2.3	0.004	0.008
KD2139 *gyrA*	0.56	0.9	6	30	2.2	80
KD2138 *parC*	0.29	1.7	10	50	1.7	170

MIC = Minimum inhibitory concentration; MPC = mutant prevention concentration; MOX = moxifloxacin; LEVO = levofloxacin.

[1] Survival was determined relative to that of cells present immediately before addition of fluoroquinolone. Survival >100% indicates cell growth.

not be able to overcome quinolone resistance in *S. pneumoniae* while still maintaining acceptable safety/tolerability profiles [57].

As mentioned above, MPC reflects the concentration that prevents the growth of first-step mutants. Based on their potential for restricting the selection of resistant mutants, not all fluoroquinolones are alike and they can be classified according to their MPC in descending order as moxifloxacin, trovafloxacin, gatifloxacin, grepafloxacin and levofloxacin [71]. Adding to the complexity, intrinsic differences between drugs of the fluoroquinolone class with regard to resistance selection may exist even at the same attained AUC/MIC [72] (table 4). In in vitro PK models [73], it has been demonstrated that with high inocula, therapeutic concentrations mimicking levels of levofloxacin in humans led to isolation of mutants in a quinolone-susceptible *S. pneumoniae* and in strains with preexisting mutations. In contrast, therapeutic concentrations of moxifloxacin did not select for resistance in susceptible strains or in the strain with preexisting *par*C mutation, it occurred however, when a *gyr*A mutation was present. Of note, normalization of AUM:MPC did not completely eliminate the difference in resistance selectivity, suggesting that intrinsic differences in resistance selection do exist and that they favor the quinolones possessing the C8-methoxy group (i.e., gatifloxacin and moxifloxacin) [74, 75].

Conclusions

Suboptimal prescribing in community-acquired RTIs is a major cause of concern as it increases the risk of clinical failure and is a major risk factor for the development and spread of bacterial resistance. Until recently, in vitro susceptibility data and clinical studies designed to show noninferiority were the most important parameters on which to base a rational choice of antimicrobial treatment. Advances in our understanding of PK/PD now enable us to predict antimicrobial bacteriologic efficacy; the choice of the antimicrobial and its administration at the right dose optimize antibacterial therapy, the risk of failure is minimized and the high eradication rates should decrease the risk of emergence of resistance and its subsequent spread.

Empirical therapy of community-acquired RTI should always be active against *S. pneumoniae*, which is the most prevalent pathogen and the most difficult to treat because of the increasing number of resistance determinants it has been able to accumulate over time. Bacteriologically confirmed failures have been reported in otitis media and, with a lesser degree of evidence, in pneumococcal pneumonia with a variety of agents that include β-lactams, macrolides and fluoroquinolones. These failures have been shown to be due to infection by resistant pathogens or suboptimal therapy. However, no clinical failure has been reported during therapy for bacteremic pneumococcal pneumonia with adequate doses of β-lactams, including benzyl or aminopenicillins and the 3rd-generation cephalosporins, ceftriaxone and cefotaxime, confirming the predictive value of the modern concepts of PK/PD applied to the treatment of community-acquired RTI. The failures reported with macrolides or fluoroquinolones have been due to either preexisting resistance to these agents that cannot be overcome by increasing the dose of the antimicrobial or, more rarely, to the emergence of resistance during therapy. The latter event is related to mutations at the ribosome in the case of the macrolides or in *par*C and/or *gyr*A in the case of the fluoroquinolones.

We have learned that not all β-lactams are alike and that the combination of intrinsic potency and PK of each one of these agents determines its in vivo activity. Likewise, not all fluoroquinolones are equal and some are not only more potent but have lesser ability to select for resistant mutants. These properties should be used to prioritize the use of those that have more eradicating power and select less resistant mutants. Thus, a proper selection of the antimicrobial coupled with the right dosing according to the PK/PD parameters mentioned above in the empirical therapy of community-acquired RTI should lead to the optimization of dosage regimen to improve the outcome and reduce the selection of resistant mutants.

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