

Review

Judicious use of antibiotics to minimize emerging resistance: the macrolide clarithromycin as a case study



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Practice Points

- Macrolides are useful for treating respiratory tract infections.
- Pneumococcal resistance to macrolides has increased but low-level resistance may still be successfully treated with conventional doses.
- Tissue concentrations of macrolides exceed serum concentrations.
- Macrolides have an established safety profile.
- Once-daily dosing improves compliance.
- Macrolides are recommended therapies in numerous treatment guidelines.
- Longer drug half-lives may increase the risk for resistance selection.

SUMMARY Infections remain a major cause of death worldwide and antimicrobial resistance is increasing. With fewer new antimicrobial agents in development it is imperative for available antibiotics to last by observing key points: judicious use, appropriate doses and optimizing regimen compliance in order to reduce the risk of increasing resistance. This review discusses these issues, using treatment of the respiratory tract pathogen *Streptococcus pneumoniae* with the macrolide clarithromycin as a case study. Clarithromycin is active against common respiratory pathogens achieving high tissue, fluid and serum levels, and has a relatively short half-life. These characteristics influence the risk of developing resistance when compared with erythromycin or azithromycin. High local drug concentrations further reduce the risk of therapeutic failure. Long half-lives associated with a long tail in the curve of minimum inhibitory concentration (MIC) over time may increase the risk of emerging resistant strains. Azithromycin has the longest biological half-life among macrolides and

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was found to be statistically more likely than clarithromycin or erythromycin to select for organisms with higher MIC values. Poor adherence to antibiotic regimens may accelerate the development of resistance. Compliance is enhanced by convenient dosing regimens, for example with extended-release formulations. The ideal antibiotic regimen should achieve maximal-eradication MIC while minimizing the total time with sub-MICs present in the treated population, and have mutant prevention concentration values within clinically achievable and sustainable drug concentrations.

Despite the continuing development of new antibiotics during the 20th century, which fed the belief that infectious disease had been conquered, infections remain the primary cause of >80% of all deaths worldwide [20]. Today, the problems of increasing antimicrobial resistance and there being too few new antibiotic compounds in the pipeline of pharmaceutical companies are acute and frequently highlighted in specialist as well as general media. The number of approved antibacterial agents has been dropping since the early 1990s [1,2]. In addition, supply of some antibiotics that have become generic over the last two decades has been unreliable, for example, frequent shortages of doxycycline and amoxicillin/clavunate. Although the development of new antibiotics remains an active field, the commercial risk remains large and many promising compounds never make it to clinical use.

Paradoxically, this is due in part to the availability of large numbers of generic antibiotics from successful drug classes, which can lead to the perception that all drugs within a class are more or less equivalent. Such perceptions in turn reduce the willingness to pay for new and potentially superior entrants within a class. A recent example is the ketolide cethromycin ABT-773 a highly promising agent with excellent activity against *Streptococcus pneumoniae* and penicillin-resistant pneumococci [3–5]. After years of promising results mixed with regulatory tribulations, the owner of the patent announced in May 2011 that operations were to be suspended due to economic constraints that precluded meeting all regulatory requirements for clinical data on the compound [6].

In light of such difficulties, and considering that it will take an average of 8 years (and ~US\$800 million) to bring any currently evaluated lead compound from Phase I clinical testing to product launch [7], it is essential that current agents be maximized [8]. This means the careful

consideration of several factors: judicious use, appropriate doses to provide adequate serum and tissue drug concentration and, last but not least, optimizing compliance with treatment regimens in order to reduce the risk of target organisms developing resistance.

The typical *in vitro* measurement of an organism susceptibility or resistance to an antimicrobial agent is the minimum inhibitory concentration (MIC). MIC measurements are based on the testing of 10^5 cfu/ml – a bacterial density that may be lower than bacterial densities present in acute infection [9–11]. As such, the MIC measurement may over estimate the organism susceptibility, especially when higher bacterial densities are encountered. The mutant prevention concentration (MPC) was described by Dong *et al.* as the lowest drug concentration blocking the growth of the least susceptible bacterial cell present in high density bacterial populations (i.e., $\geq 10^9$ cfu) [12].

This review will look into these issues, using the macrolide clarithromycin as a case study.

Clarithromycin & other macrolides

Macrolides are a broad class of antibiotics derived from the naturally occurring molecule erythromycin, which is produced by *Saccharopolyspora erythraea*. Macrolides are recommended in the clinical practice guidelines for the treatment of upper and lower respiratory tract infections [13–17]. Clarithromycin is a macrolide with greater *in vitro* activity than erythromycin against many common respiratory pathogens (Table 1) [18]. The MIC of clarithromycin against *S. pneumoniae* is typically half that of erythromycin [19,20]. Metzler *et al.* recently reported on the MIC values of 191 clinical isolates of *S. pneumoniae* that were macrolide susceptible [21]. The MIC_{range} and MIC₉₀ values, respectively, were as follows: azithromycin: 0.031–0.5 µg/ml and 0.25 µg/ml; clarithromycin: ≤0.016–0.25 µg/ml and 0.063 µg/ml; erythromycin: ≤0.016–0.25 µg/ml and 0.125 µg/ml. In

the same study, MPC values were also reported, and the MPC_{range} and MPC₉₀ values, respectively, were as follows: azithromycin: 0.12 to ≥8 µg/ml and 4 µg/ml; clarithromycin: 0.063 to ≥8 µg/ml and 0.5 µg/ml; erythromycin: 0.063 to ≥8 µg/ml and 2 µg/ml. By MPC measurements, the clarithromycin MPC₉₀ value was eightfold lower than for azithromycin and fourfold lower than for erythromycin and, as such, requires lower drug concentrations to restrict growth of resistant subpopulations. Generic clarithromycin has been available in Canada since 2007.

Structurally, macrolides share a common 14-membered lactone ring with ten asymmetric centers and two sugars (L-cladinose and D-desosamine) and differ in the side chains attached to the structure. In clarithromycin, one hydroxyl group is replaced by a methoxy group (Figure 1), which results in improved oral bioavailability and upper GI tract toxicity profile compared with erythromycin [22]. Another common macrolide, azithromycin, has the 14-membered ring modified by the insertion of a nitrogen atom (Figure 1) and, as a result, has a long half-life of 76 h. It should be noted that all macrolides are associated with very low toxicity. Allergic reactions are rare. The most common adverse effects are gastrointestinal reactions, which are usually mild in intensity [18].

Macrolides block protein synthesis in susceptible bacteria by binding to the 50S ribosomal subunit, preventing the elongation of newly synthesized peptide chains and, secondarily, by preventing the assembly of ribosomes. Resistance in Canada is primarily due to the acquisition of an efflux pump (*mef(A)*) [23]. The second most common mechanism of resistance is due to target-site modification. This is due to the acquisition of an *erm(A/B/C/TR)* gene, resulting in methylation of the target and reduced binding [24].

There has been a significant increase in macrolide resistance among clinical isolates of *S. pneumoniae* reported both in Canada and globally by investigators over the last 20 years (Table 2) [25]. Data collected through the Canadian Bacterial Surveillance Network (1993–2009) has shown a steady increase in macrolide-resistant pneumococci from ~2–3% in 1993 to ~14% by 2002 and 24% by 2009 [202]. Although clinical failure in patients treated with macrolides is reported less frequently than expected, considerable published clinical evidence suggests that macrolide resistance, in particular high-level *erm(B)* resistance,

Table 1. Comparative *in vitro* activity of macrolides against selected pathogens.

Pathogen	Macrolides		
	Azithromycin, MIC ₉₀ (mg/ml)	Clarithromycin, MIC ₉₀ (mg/ml)	Erythromycin, MIC ₉₀ (mg/ml)
<i>Haemophilus influenzae</i>			
β-lactam positive	1–4	8–16	4–16
β-lactam negative	1–4	8–16	4–16
<i>Moraxella catarrhalis</i>			
β-lactam positive	2	0.19	0.25
β-lactam negative	0.094–2	0.125	0.25
<i>Streptococcus pneumoniae</i>			
Pen S	0.12–4	0.06	0.06–4
Pen I	16 to >32	16 to >32	8 to >32
Pen R	16 to >32	8 to >32	8 to >32
<i>S. pneumoniae</i> (MPC) [†]	4	0.5	2
<i>Klebsiella pneumoniae</i>	16–64	0	0 to >64
<i>Staphylococcus aureus</i>			
Methicillin S	1–8	0.05 to >8.7	1 to >10
Methicillin R	>27.3–128	64	64 to >100
<i>Streptococcus pyogenes</i>	0.12–0.5	0.015–0.16	0.03–0.18
<i>Legionella pneumophila</i>	0.5–1.2	0.06–0.22	0.46–0.5
<i>Chlamydophila pneumoniae</i>	0.25–0.33	0.11–0.25	0.19–0.5
<i>Chlamydia trachomatis</i>	<0.125–0.25	0.008–0.125	0.06–2
<i>Mycoplasma pneumoniae</i>	0.00024 to <0.01	0.008–0.5	0.011

[†]Based on 191 clinical macrolides of *Streptococcus pneumoniae* [21].
I: Intermediate; MPC: Mutant prevention concentration; Pen: Penicillin; R: Resistance; S: Sensitive.
Adapted with permission from [89].

is clinically relevant and can result in therapeutic failure in patients [25].

■ **The importance of doses & half-life**

The goals of antibiotic therapy are to eradicate the causative pathogen, promote resolution of clinical symptoms and prevent emergence of resistant organisms [26]. Judicious use of antibiotics requires administration of the most appropriate dose, while avoiding the exposure of pathogens to subtherapeutic drug levels for a long period of time [27]. Thus, a good antimicrobial agent must show adequate tissue penetration and be capable of reaching efficacious concentrations at the site of infection for a sufficient length of time [28,29], but must be rapidly removed from the system once the organism has been cleared. Macrolides are lipophilic and extensively distributed in tissues and body fluids. For azithromycin, mean tissue concentrations exceed serum concentrations by 10–100-fold as compared with 2–20-fold for clarithromycin [30–32].

In terms of MIC, clarithromycin is more active than erythromycin or azithromycin as seen by lower MIC values. The modal MIC values

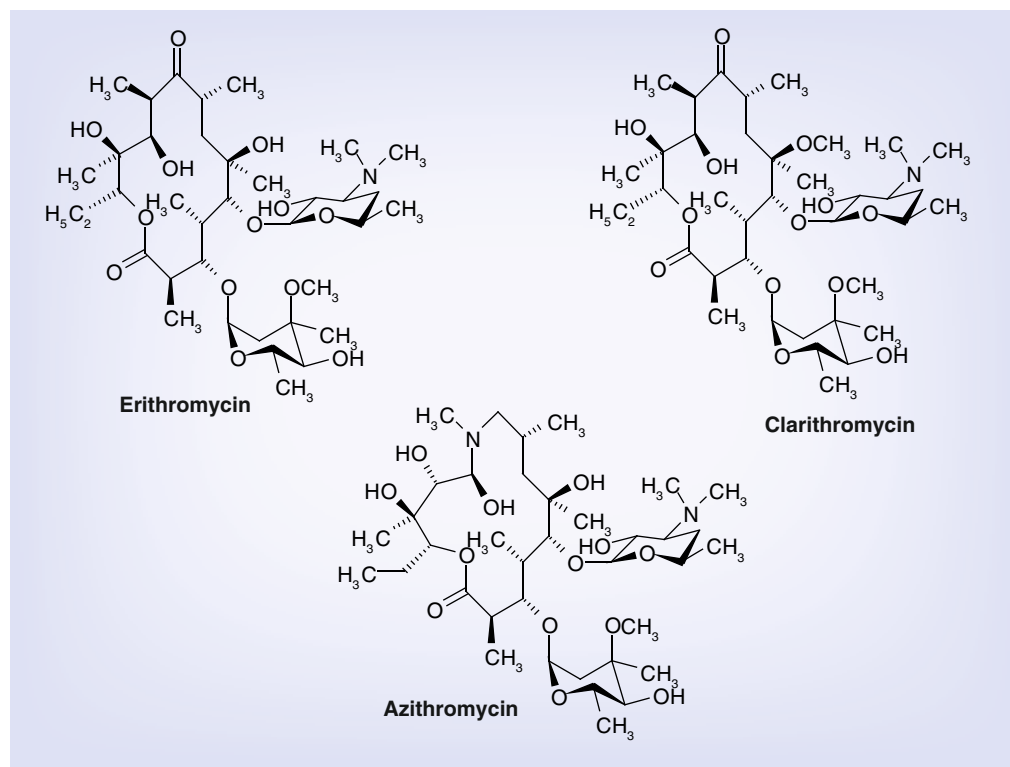


Figure 1. Erythromycin, azithromycin and clarithromycin, currently the three most important macrolides.

for macrolide-susceptible strains of *S. pneumoniae* are 0.03–0.06 mg/ml for clarithromycin, 0.06 mg/ml for erythromycin and 0.12 mg/ml for azithromycin [33]. More importantly, local drug concentrations seem to be significantly higher with clarithromycin than with azithromycin. Serum levels of clarithromycin (based on twice-daily [b.i.d.] dosing) are reported to be almost 40-times higher than levels of azithromycin [34]. The same study also reported 4.4-times higher clarithromycin than azithromycin levels in alveolar macrophages. This favorable pharmacokinetic profile, together with the higher *in vitro* activity, leads to a 20–30-times greater potency than azithromycin [35]. High concentrations reduce the risk of therapeutic failure as only organisms with high MICs are likely to fail [36,37]. The lower MPC values for clarithromycin versus azithromycin and erythromycin further reduce the likelihood for resistance selection from susceptible populations. **Table 3** summarizes pharmacological parameters for azithromycin, clarithromycin and erythromycin.

However, the dynamics of pathogen elimination are complex and comparison of MICs does not provide the whole picture. In addition to the

acute killing by antimicrobial agents, there are also postantibiotic effects that may be prolonged, intermediate or absent. Depending on which of these is associated with an antibiotic, the pharmacodynamic index predictive of successful response will vary. When postantibiotic effects are prolonged, maximum concentration/MIC is most important; for intermediate effects it is the area under the curve/MIC; and for those drugs where there are no postantibiotic effects but only time-dependent killing (such as β -lactams) the time at which antibiotic concentration exceeds the MIC will give the best indicator of treatment effects [38,39]. For a compound with a long half-life, such as azithromycin, the area under the curve:MIC ratio seems to be the best predictor of successful elimination of pathogens from the host, but there are few clinical studies available that demonstrate exposure–response relationships [25,40].

Half-lives need to be adequate to achieve a reasonable MIC or MPC to eradicate the pathogen but, from the perspective of emerging antibiotic resistance, longer-acting drugs may not necessarily be better. Paradoxically, they may actually be worse [41]. Studies on

azithromycin have indicated that half-lives of more than 3 days are associated with a long tail in the curve of MIC or MPC over time. Such situations may facilitate the emergence of drug-resistant strains, as has been demonstrated for erythromycin [42]. Because clearance of a drug or decrease in concentration to below the MIC takes between five and seven half-lives, a drug may persist at subinhibitory concentrations for extended periods of time before dipping below the minimal antibiotic concentration. Minimal antibiotic concentration is the lowest concentration that produces a tenfold decrease in the number of organisms per ml compared with a no-drug environment. Azithromycin might persist *in vivo* for at least 3–4 weeks after cessation of treatment [43]. The selective time window for azithromycin has been found to be wider than that for clarithromycin (half-life: 6 h) [44]. It also appears that azithromycin selects quantitatively more resistant organisms in the early post-therapy phases (i.e., after drug stopped) than does clarithromycin [45]. Similarly, the mutant selection window (MSW) defines the antimicrobial drug concentration range between the MIC and MPC drug concentration. It has been argued that therapeutic drug concentrations that fall and remain within the MSW for extended duration over the dose have an increased probability for the selective amplification of resistant subpopulations. The wider the window the greater the risk. Clarithromycin has a narrower MSW than either azithromycin and erythromycin, based on recently published data [21].

A direct comparison between clarithromycin and azithromycin in children treated for upper respiratory tract infection found significantly higher proportions of children with resistant strains when treated with azithromycin 10 mg/kg once daily over 3 days than with a 7-day regimen

Table 2. Selected studies reporting on macrolide resistance of *Streptococcus pneumoniae*.

Country/region	Year	Resistance (%)	Ref.
Canada	2007–2009	19	[90]
China	2001–2003	50–74	[91,92]
France	2005	41	[93,203]
Hong Kong	2000–2001	77	[94]
India	1996–2001	1–5	[92,94]
Italy	2005	27	[93,203]
Japan	1999–2002	77–80	[92]
Korea	1999–2001	69–81	[94,95]
Portugal	2005	19	[93,203]
Spain	2005	23	[93,203]
Taiwan	2000–2006	86–91	[94,96]
Thailand	2000–2001	37	[94]
USA	2005–2006	35	[97]

of clarithromycin 7.5 mg/kg b.i.d. [27]. Although the proportions of children with resistant strains in the first week after starting therapy were similar in both groups (70%), at 6 weeks the proportion with resistant strains diminished to 10% in the clarithromycin group but rose to 90% in the azithromycin group [27,46]. In addition, 11.7% of the patients receiving azithromycin therapy became reinfected versus only 1.6% of the clarithromycin patients.

This potential is confirmed in a study by Davidson *et al.* [47], and commented on by Blondeau [48], on the prevalence of macrolide-resistant *S. pneumoniae* and the use of clarithromycin, erythromycin and azithromycin in Canadian provinces. The authors found a strong correlation between the use of azithromycin and resistance rates, which was not evident for the other two macrolides investigated. A linear regression model indicated that every percentage point increase in azithromycin use was associated with a 0.42 percentage point increase in macrolide resistance ($p = 0.03$). No

Table 3. Pharmacokinetic and pharmacodynamic values for azalide/macrolide agents.

Compound	Dosage	C_{max}	AUC_{24}	C_{max}/MIC_{90}	C_{max}/MPC_{90}	AUC_{24}/MIC_{90}	AUC_{24}/MPC_{90}	T > MIC ₉₀	T > MPC ₉₀	T _{MSW}	Ref.
Azithromycin [†]	500 mg	0.4	3.4	1.6	0.1	13.6	0.85	>24	0	24	[30]
Clarithromycin XL	2 × 500 mg	3.77	48.09	59.8	7.5	763.3	96.2	24	24	0	[204]
Erythromycin base [†]	500 mg	0.9	8	7.2	0.45	64	4	~14 [‡]	~1 [‡]	13 [‡]	[30]
Erythromycin estolate	500 mg	3.1	20.39	12.4	6.2	163.12	10.2	~18	~5	13	[98]

All concentrations are in mg/l.

[†]Mean values based on a single 500-mg oral dose.

[‡]Data taken from [98].

AUC_{24} : Area under curve over a 24-h time period; C_{max} : Serum maximum concentration; MPC: Mutant prevention concentration; T: Time; T_{MSW}: Time inside the mutant selection window (h).

Adapted with permission from [21].

such correlation was found with a change in either clarithromycin ($p = 0.206$) or erythromycin ($p = 0.286$) use. Other reports support these conclusions. A study looking at the correlation between prescription rates and macrolide resistance in *S. pneumoniae* across Canada found the decrease in erythromycin prescriptions to be the main driver of resistance and that the strongest effect on increased resistance comparing azithromycin and clarithromycin was from azithromycin ($p = 0.0005$) [49]. A number of population studies in other regions have reported that use of macrolides with a long half-life (mostly azithromycin) is associated with a greater prevalence of macrolide resistance among clinical isolates of pneumococci or group A streptococci [50–52].

The downside of macrolides with short half-lives is a variation in steady-state drug levels between drug administrations. The benefits of high peak concentrations may be negatively compensated by repeated periods of sub-MICs offering a window for the development of resistance. Extended-release formulations surmount this problem. Even if the peak concentrations achieved with extended-release regimens may be somewhat lower than those reached with shorter-acting b.i.d. formulations, the longer plateau phase reduces the risk of resistance while maintaining effective MICs (and MPCs) between dosing [53].

The question of what regimens and half-lives are best suitable for eradication is particularly complex with macrolides, as the two different mechanisms of resistance confer different degrees of resistance to the pathogens. The resistance bestowed by the efflux mechanism (MICs: 1–4 $\mu\text{g/ml}$, for some strains as high as 32 $\mu\text{g/ml}$) is several-fold lower than that conferred by target methylation (MICs >64 $\mu\text{g/ml}$). This can be seen, for example, if MIC frequency distributions are plotted for a large number of resistant isolates of *S. pneumoniae*. In such plots the resistant bacteria typically fall into two groups: one larger efflux-resistance group with low-to-intermediate MIC elevations (1–32 $\mu\text{g/ml}$); and one smaller (~30% of strains) high-level resistance group (MICs ≥ 64 $\mu\text{g/ml}$) [35]. This implies that, at sufficiently high doses, macrolides will be able to eradicate susceptible strains as well as low-level resistant strains [36]. By selecting a macrolide with the optimal profile and using maximal dosing, the likelihood of successful treatment, even in light of low-level resistance, is increased. This, coupled with judicious use, might result in

a stabilization of macrolide resistance and potentially a decrease in resistance.

One of the authors (J Blondeau) previously questioned whether there was a differential impact of various macrolide compounds on the selection of macrolide resistant *S. pneumoniae* [48]. Published literature suggested higher macrolide resistance rates following azithromycin use [47,52]. As previously mentioned, standardized measurements of *in vitro* susceptibility/resistance by MIC utilizes 10^5 cfu/ml of test organism exposed to various drug concentrations in a controlled environment. Dong *et al.* [12] suggested that at higher bacterial densities such as those seen during infection [9,54,55], less susceptible or resistant subpopulations may be present. Such subpopulations would not be detected by routine MIC testing as an insufficient number of cells are tested. MPC is a novel *in vitro* measurement to determine the drug concentration necessary to block the growth of the least susceptible cells within high density ($\geq 10^7$ cfu) population [56]. Blondeau *et al.* tested 170 clinical isolates of *S. pneumoniae* by MPC against azithromycin, clarithromycin and erythromycin, and found that azithromycin was statistically more likely to select for organisms with an inhibitory concentration of 1 $\mu\text{g/ml}$ (nonsusceptible) than clarithromycin ($p < 0.0001$) and erythromycin ($p < 0.0001$) [57]. Such observations are worthy of consideration when one compares either serum or epithelium lining fluid drug concentrations for azithromycin and clarithromycin where MPC values are exceeded by conventional dosing of clarithromycin. Alveolar macrophage drug concentration also exceeds serum drug concentrations and MPC values; such observations are likely important for intracellular organisms versus those in the intracellular space.

■ Adherence & the impact of treatment regimen complexity

It was noted by Haynes *et al.* a decade ago, that “increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatments” [58]. In saying this, Haynes was actually rephrasing Hippocrates’ dictum from 2500 years ago that physicians should not be content with doing what is right themselves, but also ensure that patients co-operate [59]. This remains one of the biggest issues in medicine.

Adherence is a substantial problem, not only in chronic diseases where approximately half

of patients do not follow prescribed courses of medication [60], but also in infectious disease. Poor adherence to antibiotic regimens may accelerate the development of resistance among bacteria. It has been reported that as many as 37.8% of patients fail to complete all prescribed antibiotic doses [61]. Most studies on adherence have focused on chronic disease, with less data available on antibiotic regimens. However, most available studies from a variety of settings agree that complex treatment regimens and greater number of daily doses are associated with decreased adherence [62–65]. The data suggest that a 10% decrease in adherence will occur with each additional daily dose [66]. These considerations support the use of extended-release formulations of antibiotics, facilitating once-daily dosing regimens. Indeed, early observational studies on antibiotic treatment examining the processes and outcomes of consultations of randomly selected primary care physicians reported that a greater percentage of patients complied with once-daily dosage compared with b.i.d. regimens (95.2 vs 76.2%) [67].

Recently, a targeted analysis of compliance specifically with clarithromycin was carried out by Kardas *et al.*, who compared compliance rates with a once-daily clarithromycin extended-release formulation to those with a b.i.d. regimen in patients with community-acquired acute respiratory tract infection [68]. The treatment period was 7 days. Although compliance rates were >80% with both formulations, all studied parameters indicated significantly better compliance with the once-daily than with the b.i.d. formulation. Overall compliance rates were 93.7 vs 81.3% ($p < 0.001$) and the correct number of doses were taken on 80.3% of days with the extended-release formulation versus 68.6% with the b.i.d. regimen ($p < 0.0001$).

The study made use of ‘medication event monitoring systems’ equipped with microprocessors in the bottle caps that registered the date and time of each opening of the medication bottle. This enabled the collection of dose timing data in addition to compliance. With the once-daily dose, 74.4% of interdose intervals were correct, compared with 56.4%, of interdose intervals with the b.i.d. formulation ($p < 0.001$). The mean interdose intervals were 95.6 and 106.3% of the expected values, respectively ($p < 0.001$). Thus, not only do patients appear to be taking their drugs with greater diligence when on

a once-daily regimen, they also maintain more regular intervals between their medications. This interpretation is supported by repeated observations with different medications. Morning doses of b.i.d. regimens are taken more regularly than the evening doses [69,70].

In addition to complexity, compliance may be affected by tolerability, in particular the rate of premature discontinuations from a therapeutic regimen. Side effects will vary between drugs, but even within a class, different formulations may influence the tolerability profile. Extended-release formulations, by effecting a slower rise in drug concentrations than shorter-acting formulations, appear to be associated with fewer and milder adverse events [53,71]. This has been shown to translate into reduced discontinuation rates [71,72] and thus, less associated risks for development of resistant strains from prematurely interrupted treatment regimens. A summary of reported side effects and discontinuation rates is shown in **Table 4**.

A third factor influencing compliance is the duration of therapeutic regimens. This is a particular problem with chronic diseases but the phenomenon is observable even within the limited timespan applicable to many antibiotic treatments. Combining short-course and once-daily regimens can have a dramatic effect on compliance. In a study comparing short, 3-day therapy regimens with once-daily azithromycin and a 10-day standard treatment with three-times daily penicillin V in the treatment of acute group A streptococcal tonsillopharyngitis, 94–95% compliance was observed with azithromycin versus 62% with penicillin V [73].

The study on clarithromycin by Kardas found that the shape of the curves of compliance over time were remarkably similar for once-daily and b.i.d. dosing regimens [61]. Both curves showed

Table 4. Incidence of macrolide-related adverse events.

Event	Azithromycin (%)	Clarithromycin [†] (%)
Nausea	2.6–5	3–3.8
Diarrhea	3.6–6	2.7–3
Taste perversion	–	<1
Headache/nervous system	1.3	2
Gastrointestinal	12.6	7.5
Discontinuations	<1	3.2
Abdominal pain	2.5–4	1–6

[†]Gastrointestinal adverse events with extended-release formulation tended to be less severe and resulted in fewer discontinuations. Data taken from [30,99,100].

compliance rates peaking at approximately the third day of therapy. However, both the increase in compliance from day 1 to day 3 and the decline in compliance after day 4 were dramatically steeper with the b.i.d. regimen (Figure 2). The impact of the patient 'feeling better' also needs consideration. This indicates that the ideal antibiotic regimen should be of short duration and use formulations that allow for once-daily dosing in order to achieve maximal eradication MIC (and MPC) in as many patients as possible, while minimizing the total time where sub-MICs (and MPCs) are present in the treated population.

The argument for shorter therapeutic regimens is supported by *in vitro* time–kill analyses. In such assays, macrolides typically reduce the number of viable bacteria by $>10^3$ over 24 h at two- to four-times the MIC [39,74–76]. Clarithromycin studies comparing longer and shorter regimens have also found similar effectiveness of a shorter, 5-day regimen with extended-release formulation as that of a standard, 7-day b.i.d. dosing regimen in patients with acute bacterial exacerbations of chronic bronchitis [77].

When evaluating the benefits from once-daily dosing over b.i.d. regimens, the half-life of the compound again becomes relevant. Comparisons have frequently used daily and b.i.d. regimens as a proxy for longer- and shorter-acting compounds, when arguing to support claims

that longer-acting agents may increase the prospects of emerging resistance [27,78,79]. However, this reasoning is not applicable when extended-release formulations are available. Indeed a longer half-life has the advantage of maintaining high serum concentrations without the need for frequent dosing. However, a combination of moderate half-life and extended-release formulations with once-daily dosing combines improved compliance with rapid clearance from the system at the end of therapy without the agent's persisting at subtherapeutic levels for extended periods of time.

■ Cost considerations

Among the US population there are approximately 160 million antibiotic prescriptions for a total of 23 million kg of antibiotics per year [80]. Not only do the costs of these drugs need to be considered, but also the consequences of antibiotic resistance from overprescription or inadequate treatment regimens and compliance. Furthermore, by reducing the number of physician visits and premature treatment discontinuations, drugs with improved tolerability profiles may generate savings over those that cause adverse events [81]. Song *et al.* commented on the clinical and economic burden of community-acquired pneumonia (CAP) in elderly patients in the Asia–Pacific region [82]. In 2003, a New Zealand study estimated the annual economic burden of CAP to exceed US\$36 million with ~US\$16.8 million associated with direct medical costs and ~US\$19.2 million with lost productivity. The cost per episode was US\$636 [83]. CAP in Taiwan in elderly patients was estimated to cost ~US\$3221 and in Singapore a 4–6-day stay cost US\$1294 versus US\$3456 for a 10-day stay. Yu reviewed the clinical and economic burden for CAP (patients ≥ 18 years) in the Medicare fee-for-service population (2007–2008) and reported the average cost of CAP was US\$8606 and ranged from US\$18,670 for inpatients versus US\$2394 for outpatients [84]. The total economic burden was established to be US\$13 billion in this population.

An example of the staggering costs associated with managing patients harboring antimicrobial-resistant pathogens stems from a study examining healthcare issues in patients with methicillin-resistant *S. aureus* [85]. The authors calculated an additional total

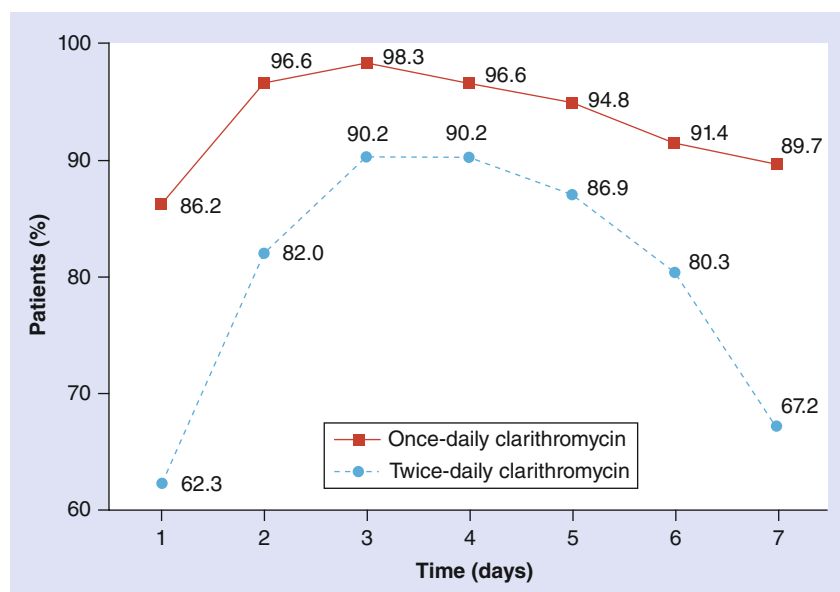


Figure 2. Compliance rates with once-daily and twice-daily clarithromycin regimens.

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US\$14,360 per patient attributable to the treatment of methicillin-resistant *S. aureus*. In the USA, the annual cost of treating antibiotic-resistant infections has been calculated at more than US\$4 billion [80]. Maragakis *et al.* indicated that patients with infection due to antimicrobial resistant organisms have higher costs (US\$6000–30,000) than patients with infections caused by drug-susceptible pathogens [86]. Other consequences of resistance include the long-term effects on patients with resistant infections, increased time off work, convalescence costs and the emotional costs to patients infected with these organisms [87]. Quite simply, infections are expensive and drug-resistant organisms increase costs.

■ Outlook

The WHO policy package to combat antimicrobial resistance recognizes the importance of the rational use of antimicrobials [88]. However, the choice of appropriate antibiotic regimens is less clear-cut than may be supposed. Whether the decision is driven by economic considerations or acute needs of patients, intuitive conclusions may not be the correct ones. Once-daily, extended-release formulations may reduce the risk of developing resistance and in doing so reduce overall costs compared with generic antibiotics. In order to ‘extend the shelf life’ of available drugs as long as possible in the hope that new agents will emerge from the pipeline in the future, a critical look at how we use today’s agents may be repaid in the long-term health of our patients. Clinical outcome and reducing the likelihood for resistance selection should be the goal of antimicrobial resistance.

The 2007 guidelines for empiric treatment of community-acquired pneumonia in adults suggested the following: “Because overall efficacy

remains good for many classes of agents, the more potent drugs are given preference because of their benefit in decreasing the risk of selection for antibiotic resistance” [14]. The recently reported MPC values for azithromycin, clarithromycin and erythromycin against clinical isolates of *S. pneumoniae* indicate that clarithromycin is the least likely to select for resistance with this important respiratory pathogen. Such data should inform our thinking.

Future perspective

Macrolides continue to be important drugs for the treatment of patients with infectious diseases. Continuing to monitor trends in antimicrobial resistance (specifically macrolides) will inform our thinking regarding the ongoing clinical utility of these drugs. Similarly, documentation of clinical success or failure in patients treated with macrolides and infected with low-level resistant *S. pneumoniae* would also be of value. Updated treatment algorithms (guidelines) highlighting recommendations for macrolide use will be valuable to clinicians.

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