Update on the use of the macrolides for community-acquired respiratory tract infections

Joseph M Blondeau
Department of Clinical Microbiology, Royal University Hospital & Saskatoon Health Region and Departments of Microbiology & Immunology & Pathology, University of Saskatchewan, 103 Hospital Drive, Saskatoon, Saskatchewan, S7N 0W8, Canada
Tel.: +1 306 655 6943
Fax: +1 306 655 6947
joseph.blondeau@saskatoonhealthregion.ca

The use of macrolides dates back more than 50 years, when erythromycin was the first of this class to be introduced into clinical practice. In the early 1990s, the so-called 'newer' or extended-spectrum macrolides were approved for clinical use in patients with a variety of infectious diseases. While clinically efficacious, the pharmacokinetic (frequent daily dosing) and adverse-events profile (specifically gastrointestinal) of erythromycin initially limited its use as an alternative agent for patients with allergy to β-lactam agents. Erythromycin could be characterized as being active against Gram-positive and atypical pathogens but has limited *in vitro* activity against Gram-negative organisms (particularly *Haemophilus influenzae*). The newer macrolide compounds, azithromycin and clarithromycin, were characterized has having *in vitro* antibacterial activity that was similar to that of erythromycin but with enhanced *in vitro* activity against Gram-negative respiratory tract pathogens, most notably, *H. influenzae*. These 'newer' macrolides also offered better pharmacokinetic/pharacodynamic properties with less frequent daily dosing and reduced gastrointestinal side effects. The role of atypical and/or new pathogens combined with the global escalation of acquired antimicrobial resistance continues to redefine and impact on the selection of empiric versus organism-directed therapy for respiratory infectious diseases. Macrolide compounds continue to be a valuable class of antimicrobial compounds, as evidenced by their continued prominent place in various guidelines. The key to the long-term viability of the macrolide class appears to be centered around understanding the factors that lead to the selection of macrolide resistance and the role that different macrolide compounds may have in this process.

Initial milestones in anti-infective therapy include the discovery of penicillin and the subsequent discovery and clinical use of the macrolide antibiotics. Early in the anti-infective era, the macrolides were a new class of agents at a time when there were few antimicrobial options available and, as such, were a major development in anti-infective therapy. Erythromycin was derived from *Streptomyces erythreus* and, as the first macrolide antibiotic, was originally marketed in 1952 and was seen as an alternative therapy to β-lactam antibiotics (e.g., penicillin) – especially in penicillin-allergic patients – for treating infections caused by Gram-positive cocci, such as *Staphylococcus* and *Streptococcus* species, including *Streptococcus pneumoniae*. The *in vitro* activity of erythromycin against the atypical pathogens (*Mycoplasma* and *Chlamydia* species) as well as against *Legionella* species and pathogens associated with infection outside of the respiratory tract, provided a broader spectrum of clinical use of these compounds for treating human infections.

Despite the many years that erythromycin has been used, and continues to be used, to treat infection, it is far from a perfect compound. From data summarized by others, some limiting characteristics of erythromycin include [1–4]:

- Poor oral bioavailability
- Inactivation in acidic environment necessitating enteric coating formulation
- Gastrointestinal (GI) side effects, such as nausea, cramping and diarrhea
- Short half-life – multiple daily dosing
- Poor activity against *Haemophilus influenzae*

Regardless of these less desirable features, erythromycin has been a mainstay of anti-infective therapy and remains widely used in clinical practice.

Compared with other classes of antimicrobial compounds, most notably the β-lactams, advances in macrolide development were slow. Clarithromycin (twice-daily formulation) and azithromycin were approved for clinical use in 1992 (40 years after erythromycin) and 1994, respectively. The once-daily formulation of clarithromycin was

Keywords: azithromycin, erythromycin, clarithromycin, macrolides

Future Drugs Ltd

approved for clinical use in 2003. Several other macrolide compounds have been developed; however, none have been approved or used extensively in North America. Some of the major characteristics of newer macrolide compounds, including azithromycin and clarithromycin, that were improvements over erythromycin include [1–4]:

- Expanded spectrums of activity to include fastitidious Gram-negative bacilli, such as *H. influenzae* and *Neisseria* species, as well as other Gram-negative bacilli (**Table 1**)
- Improved pharmacokinetics allowing for once- or twice-daily dosing
- Marked reduction in GI side effects

Infectious diseases are an ever-evolving field with advances that improve the clinical and laboratory diagnosis of infection and the understanding of disease transmission and pathogenesis. Such advances ultimately impact on study design and refine our knowledge of the association of various pathogens with an infectious process. Some advances over the past 20–30 years have involved the recognition or appreciation of a greater prevalence of atypical pathogens (*Mycoplasma* spp., *Chlamydia* spp.) associated with community-acquired pneumonia (CAP) and, more recently, with acute bacterial exacerbations of chronic bronchitis [5]. Have we witnessed a true increase in the prevalence of atypical pathogens in respiratory tract infections (RTIs), or merely defined what has always been by advances in diagnostic technology? Perhaps it is a little of both but, from a practical point of view, it doesn't really matter since this information results in better patient management by selecting a more appropriate antimicrobial compound – that is, β-lactam compounds are not active against *Mycoplasma* spp. and *Chlamydia* spp., whereas macrolides and fluoroquinolone compounds are. While redefining organism prevalence in patient populations is important for clinical management, it has also become increasingly important to continue to define the prevalence of increasing antimicrobial resistance and its clinical impact. Antimicrobial resistance has been recognized for decades – since the initial release of penicillin in the 1940s and the subsequent discovery of penicillinase-producing strains of *S. aureus* within a few years; however, the dramatic increase in drug resistant pathogens over the past 15–20 years has been astounding. Antimicrobial drug resistance has now been described for virtually every bug–drug combination, with few exceptions.

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

Macrolides	MIC_{90} (mg/ml)		
	Azithromycin	***Clarithromycin***	***Erythromycin***
Haemophilus influenzae	0.5–4.0	8–16	4–16
β-lactam positive	1–4	8–16	4–16
β-lactam negative	1–4	8–16	4–18
Moraxella catarrhalis	0.06	0.25	0.25
β-lactam positive	2	0.19	0.25
β-lactam negative	0.094–2.0	0.125	0.25
Streptococcus pneumoniae	0.12–4.0	0.015–16.0	0.25
Penicillin susceptible	0.12–4.0	0.06	0.06–4.0
Penicillin intermediate	16–>32.0	16–>32	8–>32.0
Penicillin resistant	16–>32.0	8–>32	8–>32.0
Klebsiella pneumoniae	16–64	0	0–>64.0
Staphylococcus aureus			
Methicillin susceptible	1–8	0.05–>8.7	1–>10
Methicillin resistant	>27.3–128	>59.9	?64–>100
Streptococcus pyogenes	0.12–0.5	0.015–0.16	0.03–0.18
Legionella pneumophilia	0.5–1.2	0.06–0.22	0.46–0.5
Chlamydia pneumoniae	0.25–0.33	0.11–0.25	0.19–0.5
Chlamydia trachomatis	<0.125–0.25	0.008–0.125	0.06–2.0
Mycoplasma pneumoniae	0.00024–<0.01	0.008–0.5	0.011

MIC_{90}: Minimum inhibitory concentration at which 90% of strains are inhibited.

How do we interpret antimicrobial resistance and the clinical impact? Is the level of *in vitro* resistance paralleled by similar levels of clinical failures? This is doubtful given that serum drug concentrations, upon which susceptibility breakpoints are established, are substantially lower than pulmonary or urinary drug concentrations, an observation likely to be important for respiratory or urinary tract infections, respectively.

Macrolides have been used successfully for the treatment of infections involving the upper and lower respiratory tract, as well as infections at other anatomical locations and against pathogens for which the compounds have appropriate *in vitro* activity. This review will only focus on RTIs and highlight the microbiological, pharmacological, clinical and safety data associated with the macrolides, with a greater emphasis on azithromycin and clarithromycin. A discussion on the position of the macrolides in the pneumonia and bronchitis guidelines will also be presented. Readers are referred to other reviews for data on macrolide use outside of the respiratory tract and against uncommon or unconventional pathogens [6,7].

Macrolide development

Structurally, erythromycin and clarithromycin are 14-membered macrolide antibiotics, whereas azithromycin has a nitrogen addition to the 14-membered ring, resulting in a 15-membered compound that is more accurately referred to as an azalide antimicrobial agent. Specifically, the basic macrolide structure has a methyl-substituted nitrogen in place of the carbonyl at the 9a position of the glycone ring. This modification is thought to enhance the Gram-negative activity when compared with erythromycin [8–10]. Azithromycin is protected against acid degradation, has higher tissue penetration (compared with erythromycin) and a longer elimination half-life as a result of its structural modifications [10–12]. Clarithromycin has a methylated hydroxyl group at position 6, resulting in protection from acid degradation and improved bioavailability, as well as reduced GI side effects [1,13]. Azithromycin has a longer half-life than clarithromycin (68 vs 6 h for the twice-daily formulation, respectively). The once-daily formulation of clarithromycin has a half-life slightly longer than the twice-daily formulation; however, the modified formulation results in both immediate and delayed release of the drug over the dosing interval of 24 h. The chemical structures of azithromycin, clarithromycin and erythromycin are shown in **Figure 1**.

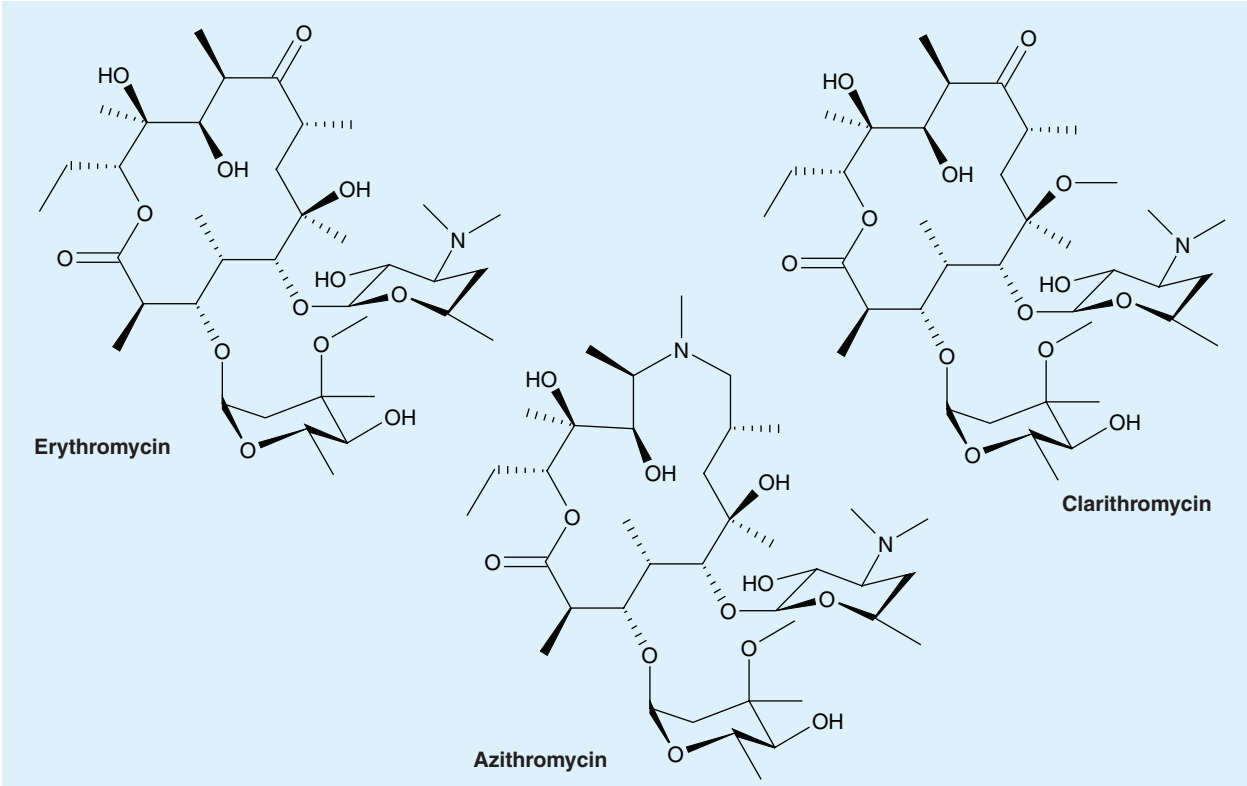
Mechanism of action

Macrolides and azalides have the same mechanism of action: they reversibly bind to the 50*S* ribosomal subunit of susceptible organisms and inhibit the mRNA-directed protein synthesis – a bacteriostatic effect. However, bactericidal activity may occur under certain conditions or against specific micro-organisms [13,14]. The clinical significance or benefit of a bactericidal versus bacteriostatic effect in patients with mild-to-moderate RTI remains unclear [15]. Recently, Blondeau and colleagues demonstrated a bactericidal effect for azithromycin and clarithromycin when high-density bacterial inocula of *S. pneumoniae* were exposed to each agent and killing was increased *in vitro* [194]. Erythromycin stimulates the dissociation of peptidyl–tRNA during translocation, thus suppressing RNA-dependent protein synthesis and inhibiting bacterial growth [16–19].

In vitro activity

The *in vitro* activities of azithromycin, clarithromycin and erythromycin are shown in **Table 1**. In general terms, macrolides are more active *in vitro* against Gram-positive and atypical agents than against Gram-negative pathogens, and have little or no intrinsic activity against enteric Gram-negative bacilli or *Pseudomonas aeruginosa* and other afermentative Gram-negative bacilli. For clarithromycin, MIC_{90} values are based on the testing of the parent compound and not that of the 14-OH metabolite that has been previously shown to have antimicrobial activity. Macrolide susceptibility testing is influenced by a number of factors, such as pH, the addition of serum and/or incubation in a CO_2 environment, and these variables may either increase or decrease the *in vitro* susceptibility measurements [20]. As with other classes of compounds, the *in vitro* activity of the macrolides is not uniform against all respiratory pathogens. For example, the MIC_{90} values for clarithromycin against Gram-positive organisms are lower than those for azithromycin and erythromycin, suggesting better *in vitro* activity for clarithromycin against these Gram-positive organisms. Despite the higher MICs for azithromycin against Gram-positive organisms, they are still within clinically achievable therapeutic levels. Methicillin-resistant *staphylococci* and *Enterococcus* species are not within the spectrum of the macrolides. Unfortunately, macrolide resistance appears to be a class effect and, as such, Gram-positive organisms resistant to erythromycin are also cross-resistant to azithromycin and clarithromycin. However, recent data suggest differences in drug-specific resistance

Figure 1. Chemical structures of erythromycin, clarithromycin and azithromycin.



within the macrolide class, indicating a different propensity of various compounds to select for resistance. The unfortunate consequences of this phenomenon is that a resistant organism selected by one macrolide is generally resistant to other compounds in the class. As such, a compound that selects for resistance more frequently than others may compromise the entire class. Macrolides are generally active against clinical isolates of *S. pneumoniae* that are susceptible to penicillin; however, significant co- or cross-resistance occurs for strains that are highly resistant to penicillin (i.e., penicillin MICs > 2 µg/ml).

Azithromycin and clarithromycin are more active *in vitro* against *H. influenzae* than erythromycin and azithromycin tends to have lower MIC values. However, susceptibility testing with clarithromycin must take into account the 14-OH metabolite to fully appreciate the true level of susceptibility for this pathogen. Clarithromycin demonstrates lower MIC values against *Legionella pneumophila* and *Chlamdyia pneumoniae* than azithromycin and erythromycin. However, MIC values tend to be lower for azithromycin than for the other two agents against *Moraxella catarrhalis* and *Mycoplasma pneumoniae*.

A summary of MIC_{90} values for azithromycin, clarithromycin and erythromycin against respiratory pathogens are listed in **Table 1**.

Antimicrobial resistance

Two mechanisms of resistance to macrolides are altered target binding site and efflux. Macrolide, lincosamide and streptogramin B resistance occurs as a result of the synthesis of ribosomal RNA methylases that cause methylation of an adenine residue in the 23*S* ribosomal RNA of the 50*S* subunit [21]. This is encoded by the erythromycin ribosomal methylase (*erm) B* gene (also referred to as *ermAB*) and pneumococcal strains possessing this gene usually express high-level macrolide resistance ($MIC_{90} \geq 64$ µg/ml) [22]. Genes encoding for macrolide resistance may be plasmid based or chromosomally located, inducable or expressed constitutively, and induced by both older and newer macrolides [19,23,24].

Efflux (the ability of organisms to pump antimicrobial agents out of the bacterial cells) is an important mechanism of macrolide resistance that is encoded by the *mefE* gene [22,25]. Efflux results in an insufficient concentration of drug within the cell to inhibit protein synthesis and, as such, the

organism is resistant. Pneumococcal strains possessing the *mefA* gene usually express low-level resistance ($MIC_{90} \geq 4$ µg/ml) to the macrolides; however, cross-resistance to lincosamides and streptogramin B does not usually occur [26].

Epidemiological surveys of resistance

It has been previously suggested by Carbon and Poole that the prevalence of resistance to macrolides is related closely to the extent to which these agents were used, most notable for *S. pneumoniae* and *S. pyogenes* [188]. Macrolide resistance in *M. catarrhalis*, *M. pneumoniae*, *C. pneumoniae* and *L. pneumophila* has not yet developed.

A substantial number of investigators have documented the prevalence of drug-resistant respiratory pathogens globally [26–33]. Amongst the respiratory pathogens, multidrug-resistant *S. pneumoniae* is a concern, especially the observation that prevalence rates have risen dramatically throughout the 1990s, and continue to this day. From data summarized from the Alexander Project, mean prevalence rates of macrolide-resistant pneumococcus was 22%, varying from 78% in Hong Kong to 2% in the Czech Republic, and macrolide resistance was found to be higher against penicillin-resistant strains. Resistance was also problematic with penicillin-susceptible strains, such that macrolide-resistance rates were higher than penicillin-resistance rates for 11 out of the 18 countries participating in the Alexander Project in 1997 [34].

Several recent reports have documented the prevalence of macrolide susceptibility of respiratory pathogens in North America (Canada and the USA). Doern and colleagues reported that approximately 25.2–25.7% of 1531 clinical isolates of *S. pneumoniae* collected and tested in the USA were macrolide nonsusceptible and, for isolates highly resistant to penicillin, cross-resistance to the macrolides was 77–78% [35]. More recently, Doern and colleagues reported on the *in vitro* susceptibility of 1817 *S. pneumoniae* isolates from 44 US medical centers and reported that approximately 27–28% of strains were macrolide resistant [36]. Doern also noted that, while the prevalence of macrolide resistance has increased since 1999–2000, the rate of increasing resistance has slowed since this time, suggestive perhaps of a plateau period. Doern also noted that clarithromycin MICs were consistently twofold lower that those for erythromycin which, in turn, were twofold lower than the MIC values for azithromycin.

Hoban and colleagues recently reported on macrolide-resistant *S. pneumoniae* in Canada and found that 215 out of 2688 (8%) strains were resistant [26]. These 215 macrolide-resistant strains were characterized and 48.8% were PCR-positive for *mefA* (efflux) and 46.5% were PCR-positive for *ermB* (target site), suggesting that both mechanisms of resistance are prevalent in Canada.

Shortridge and colleagues studied 60 clinical pneumococcal isolates from four New York City (NY, USA) medical centers [37]. The isolates demonstrated varying degrees of penicillin resistance. The *ermB* gene was present in 22% of isolates with intermediate resistance to penicillin compared with 38% for isolates with high-level penicillin resistance. By contrast, efflux was present in 8, 11 and 19% of the pneumococcal isolates that were sensitive, intermediate- or high-level penicillin resistant, respectively. Marchese and colleagues studied pneumococcal isolates from central and northern Italy and reported that 82.6% of the macrolide-resistant strains possessed the *ermB* gene, while the remaining isolates were macrolide-resistant due to efflux [38]. Tonoli and colleagues examined 117 penicillin-susceptible macrolide-resistant *S. pneumoniae* isolates and found that 88% expressed the *ermB* gene and 12% were resistant due to efflux [39].

Studies characterizing the prevalence rates of antimicrobial-resistant organisms are necessary for the appropriate use of antimicrobial agents in any one geographical area. Similarly, documenting the prevalence of the different mechanisms of macrolide resistance (*ermB* and *mefA*) in *S. pneumoniae* is also essential given the different levels of resistance (higher and lower MICs) and the potential impact on appropriate clinical use.

Such observations might suggest that the mere use of a macrolide would be problematic from a resistance perspective; however, more recent data suggest a differential or drug-specific impact of the various macrolide compounds on the selection of macrolide-resistant *S. pneumoniae*. Macrolide resistance does not always translate into clinical failure [22]. Surveillance studies documenting the prevalence of resistance are necessary; however, studies specifically investigating the clinical activity of macrolides against organisms demonstrating various levels of resistance to these drugs have not been performed.

Drug half-lives

It has long been suggested that macrolide use precedes macrolide resistance and the use of long-acting macrolides are more likely to correlate with

resistance development, whereas short-acting compounds were not [40]. When compared with erythromycin with a relatively short half-life (2 h), both azithromycin and clarithromycin would be considered longer-acting agents due to the prolonged half-life. However, for azithromycin, the half-life is ten-times longer than that of clarithromycin (60–70 vs 6 h). Is there any evidence to suggest that, despite the relatively extended half-lives of both compounds, the likelihood of selecting macrolide resistant organisms is greater with azithromycin than it is with clarithromycin? The answer to this question appears to be yes! Several recent lines of evidence suggest that there may be a differential impact on macrolide resistance when organisms are exposed to azithromycin and clarithromycin, with the former being more likely to be associated with resistance [41].

Minimum inhibitory & mutant-prevention concentration testing

Blondeau and colleagues applied MIC and mutant-prevention concentration (MPC) testing to more than 170 randomly collected unique clinical isolates of *S. pneumoniae* and found that 14–16% of strains had MICs of greater than 1 µg/ml to azithromycin, clarithromycin and erythromycin – a finding consistent with current levels of macrolide nonsusceptibility in Canada [42–45]. When tested by MPC, the percentage of strains with MPCs greater than 1 µg/ml increased to 73% in the presence of azithromycin, 23% in the presence of clarithromycin ($p > 0.0001$ compared with azithromycin) and 33% in the presence of erythromycin ($p > 0.0001$ compared with azithromycin; $p = 0.03$ compared with clarithromycin). The MPC approach tests more than 10^9 colony-forming units (cfu) of bacteria on agar plates containing drug – an inoculum most likely to contain resistant subpopulations, if present, and also a bacterial burden present during various human infectious diseases [46–49]. For MIC testing, 10^5 cfu/ml are tested as recommended by the Clinical and Laboratory Standards Institute (CLSI, formerly the National Committee for Clinical Laboratory Standards [NCCLS]).

In a more recent report, Blondeau and colleagues tested 191 clinical isolates of *S. pneumoniae* by MPC testing against azithromycin, clarithromycin and erythromycin [50]. For all but two strains, MICs were less than 0.25 µg/ml to all compounds and a substantial number of strains had MICs to all three drugs less than 0.12 µg/ml. By MPC testing, azithromycin was statistically more likely to select for bacterial subpopulations with MPCs greater than 1, 2, 4 and 8 µg/ml than clarithromycin ($p > 0.004$–<0.0001 for 1, 2 and 4 µg/ml). Erythromycin was more likely to select for macrolide resistance than clarithromycin ($p = 0.044$–<0.001 for all comparers). Challenging antimicrobial compounds against higher-density bacterial inocula is relevant and is more likely to provide a better understanding of the dynamics of heterogeneous bacterial populations containing mutants present during infection and when exposed to drug. While pulmonary drug concentrations for macrolides are higher than serum concentrations, the propensity for azithromycin to select for resistant subpopulations at a frequency statistically higher than either clarithromycin or erythromycin suggest, in this model, a differential or drug-specific impact within the macrolide class on resistance. Could a possible explanation of this observation relate to the substantially longer drug half-life of azithromycin that may serve to prolong the time that drug concentrations remain with the mutant selection window (MSW)? The MSW is the drug concentration between the measured MIC and MPC values. Does prolonged exposure of bacteria to subinhibitory drug concentrations of bacteriostatic versus bactericidal agent contribute to the resistance selection process?

Resistance & clinical impact

Recently, Vanderkooi and colleagues reported on predicting antimicrobial resistance in invasive pneumococcal infections [51]. As the prevalence of multiantimicrobial resistance increases worldwide among clinical strains of *S. pneumoniae*, the recognition of risk factors that would identify those likely to have an antibiotic-resistant pathogen might assist in selecting the most appropriate empirical therapy. This prospective study was carried out in Toronto, Canada, and involved analysis of more than 3300 patients with invasive pneumococcal infection from 1995 to 2002. Following multivariate modelling, risk factors for infection with penicillin-resistant as opposed to penicillin-susceptible pneumococci were:

- Year of infection (odds ratio [OR]: 1.28; $p < 0.001$)
- Absence of chronic organ system disease (OR: 1.72; $p < 0.03$)
- Previous use of penicillin (OR: 2.47; $p < 0.006$)
- Previous use of trimethoprim/sulfamethoxazole (TMP/SMX; OR: 5.97; $p < 0.001$)
- Previous use of azithromycin (OR: 2.78; $p < 0.05$)

Risk factors for infection with TMP/SMX-resistant *S. pneumoniae* were:

- Absence of chronic organ system disease (OR: 1.64; $p < 0.001$)
- Previous use of penicillin (OR: 1.71; $p < 0.03$)
- Previous use of TMP/SMX (OR: 4.73; $p < 0.001$)
- Previous use of azithromycin (OR: 3.49; $p < 0.001$)

Risk factors for infection with macrolide-resistant *S. pneumoniae* were:

- Previous use of penicillin (OR: 1.77; $p < 0.03$)
- Previous use of TMP/SMX (OR: 2.07; $p < 0.04$)
- Previous use of clarithromycin (OR: 3.93; $p < 0.001$)
- Previous use of azithromycin (OR: 9.93; $p < 0.001$)

Risk factors for infection with fluoroquinolone-resistant *S. pneumoniae* were:

- Previous use of fluoroquinolones (OR: 12.1; $p < 0.001$)
- Current residence in a nursing home (OR: 12.9; $p < 0.001$)
- Nosocomial acquisition of pneumococcal infection (OR: 9.94; $p < 0.003$)

In this study, some 24 patients had received erythromycin therapy compared with 67 that received clarithromycin and 37 that received azithromycin. According to the authors, azithromycin was associated consistently with an increased risk of resistance to agents from all classes except the fluoroquinolones. As such, they concluded that macrolides were not homogeneous with respect to their association with antimicrobial resistance. For example, erythromycin use was not associated with infecting organisms that were resistant to any antimicrobial class. Clarithromycin use was associated with an increased likelihood of erythromycin resistance. Azithromycin use was associated with an increased risk of resistance to macrolides, penicillin and TMP/SMX in infecting strains. Indeed, greater than 50% of isolates recovered from patients with invasive pneumococcal strains who had received azithromycin during the 3-month period prior to infection were resistant to erythromycin. As some data have suggested that this association may be related to a long half-life leading to sub-MIC blood and pulmonary drug levels (especially in the epithelial lining fluid), the selective pressure for resistance may be reduced if shorter-acting macrolides are used preferentially or those that attain higher drug concentrations [52–55].

Kastner and Guggenbichler studied the impact that various macrolides had on the promotion of resistance in the oral flora of children [56]. Children were randomly assigned to receive azithromycin, clarithromycin, erythromycin, roxithromycin and josamycin for RTI. Throat swabs were collected for culture prior to treatment and weekly thereafter, for 6 weeks. At 1 week post-treatment, 90% of children harbored macrolide-resistant strains in their oral flora. With the exception of azithromycin, the percentage of patients colonized by resistant organisms decreased to 17% for clarithromycin, erythromycin and josamycin and to 33% for roxithromycin-treated patients after 6 weeks. For the azithromycin group, 85% of patients remained colonized by macrolide-resistant organisms after 6 weeks and 11.6% suffered from reinfection. The authors argued that the long elimination half-life of azithromycin allows for subinhibitory serum and epithelial lining fluid drug concentrations over a period of several weeks post-treatment, and this may impact on the emergence of resistance. From the study, they concluded that azithromycin therapy appears to put selective pressure on the infective and native flora of children, thereby, promoting the carriage of macrolide-resistant strains.

Macrolide resistance/consumption

Davidson and colleagues reported on macrolide-resistant *S. pneumoniae* in Canada and correlated the findings (by province) with azithromycin, clarithromycin and erythromycin use [57]. The study was conducted by collecting pneumococcal isolates from across Canada, and following standardized susceptibility testing, macrolide-resistant strains were genetically characterized to detect the presence of the *erm* or *mef* genes. Susceptibility data was correlated with macrolide usage that was normalized for population.

According to the data summarized, the incidence of macrolide resistance with *S. pneumoniae* varied considerably throughout Canada in 2002, however, despite this, three distinct trends were recognized:

- Coastal provinces had macrolide resistance rates approximating 5%
- Prairie provinces and Ontario had macrolide-resistance rates between 9 and 14%
- Quebec and the Maritime provinces had macrolide-resistance rates exceeding 20%

The following points regarding azithromycin consumption were summarized:

- Azithromycin consumption in the coastal provinces remained low at less than 20% of prescribed macrolides
- Azithromycin accounted for greater than 44% of all macrolide use in the three provinces with the highest macrolide-resistance rates
- Azithromycin accounted for 25–32% of macrolide use in the prairie provinces

There was no statistically significant correlation identified between total macrolide consumption and the regional differences in macrolide resistance. According to the data of Davidson and colleagues, regions with the lowest rates of macrolide resistance used significantly less azithromycin compared with other macrolides [58]. The provinces with the highest macrolide resistance rates used more azithromycin compared with other macrolide compounds. Davidson and colleagues concluded that their data suggested azithromycin may have a greater propensity to select for macrolide-resistant *S. pneumoniae* compared with clarithromycin and erythromycin.

Doern commented on antimicrobial use and the emergence of antimicrobial resistance with *S. pneumoniae* in the USA [59]. One point in his arguments was that "the more potent an antimicrobial agent, the less likely it is to select for resistance...Within each class, potencies differ." Regarding macrolides, Doern indicated that azithromycin is consistently three- to fourfold less active than clarithromycin for the pneumococcus, based on *in vitro* MIC measurements. Additionally, peak serum drug levels of azithromycin following administration of standard dosages are approximately a tenth of those achieved with clarithromycin. Doern argued that serum levels are appropriate for pharmacodynamic analysis and, as such, azithromycin was inferior to clarithromycin in terms of *in vitro* activity and pharmacokinetics. To support his position, Doern cited studies by Diekema and colleagues [60] and Leach and colleagues [61] indicating that azithromycin use was more likely to select for macrolide resistance than clarithromycin. In 2002, Edelstein responded to the arguments of Doern by indicating that the studies cited do not contain any data regarding the relative emergence rates for azithromycin and clarithromycin and that serum drug levels may not be the correct parameter to assess the pharmacodynamic behavior of azithromycin (in pneumonia) as it ignores good evidence regarding the delivery of azithromycin to the infection site by drug-containing neutrophils [62].

In a subsequent rebuttal to the points raised by Edelstein, Doern [63] cited studies by Ghaffar and colleagues [64] and Gray and colleagues [65] showing the emergence of macrolide resistance in *S. pneumoniae* isolates following exposure of infected persons to azithromycin. However, as these studies were noncomparative, there was no attempt to assess the affect of clarithromycin exposure on the emergence of macrolide-resistant *S. pneumonia*. From studies published by Hyde and colleagues and Garcia-Rey and colleagues, associations were made between macrolide use and macrolide-resistant *S. pneumoniae* [66,67]. Doern indicated that these two studies suggest the higher probability of macrolide resistance following azithromycin therapy since, in the USA, the vast majority of macrolide use in pediatric patients is azithromycin and, for the study conducted in Spain, the once-daily administered macrolide was presumably azithromycin. In the Spanish study, the once-daily administered macrolide had a 1.5-times greater statistical association with the emergence of macrolide-resistant *S. pneumoniae* than macrolides that were administered two- to three-times each day.

Doern suggested that the relative potency of azithromycin compared with clarithromycin against *S. pneumoniae* may be related to the differential impact observed between azithromycin and clarithromycin on the selection of *S. pneumoniae* resistance to macrolides [63]. Edelstein argued that alveolar lining fluid drug concentrations may not be the correct parameter to assess azithromycin pharmacodynamics owing to high drug concentrations delivered by drug-containing neutrophils. To this point, Doern argued that, for extracellular pathogens, such as the pneumococcus, epithelial lining fluid drug concentrations are likely more relevant than intracellular drug concentrations. Comparing clarithromycin with that of azithromycin suggests that epithelial cell lining fluid levels of clarithromycin are approximately 30-fold higher than those of azithromycin [68–71]. Thus, one can imagine that if drug concentrations within an infected compartment do not achieve or exceed the minimum amounts required to inhibit the growth of the infecting pathogen, antimicrobial resistance could ensue if subinhibitory drug concentrations (perhaps within the MSW) promoted the selection and amplification of resistant bacterial subpopulations – particularly those likely to exist in high-density populations. Such a point has previously been argued from our laboratory based on the MPC approach and the suggestion that the drug

concentration shown to be therapeutic may, in fact, be the same drug concentrations that allow the selective amplification of resistant subpopulations when the concentration is insufficient to inhibit the growth of resistant cells [44].

Subsequently, Gordon and Blumer argued in favor of single-dose, shorter-course therapy with azithromycin. Their arguments in support of this strategy were based on the observations that azithromycin has a long elimination half-life (>50 h), is concentrated within phagocytic cells and tissues and the drug achieves targeted delivery by the cells to the site of infection (Trojan horse phenomenon) – data supported by *in vitro* and *in vivo* models according to the authors [72]. Clearly, this debate remains unresolved.

What does the data summarized above suggest and how should it be used? From *in vitro*, clinical and drug-usage data, it suggests that there appears to be a differential impact of various macrolides for their propensity to select for macrolide resistance. Each study identifies azithromycin as being more frequently associated with macrolide resistance. In its simplest terms, macrolide resistance would refer to any organism requiring more drug than the susceptibility breakpoint for inhibition. Despite these observations, the subcellular mechanism(s) of this differential impact remain undefined. Also, the arguments above are for *S. pneumoniae* only and it may be that, for different pathogens where azithromycin activity is greater than for other macrolides, that resistance would be selected less often for particular pathogen. However, as mentioned previously, resistance has been slower to develop to macrolides for other respiratory pathogens and, therefore, emphasis on the differential impact of the various macrolides on *S. pneumoniae* resistance is necessary, appropriate and justified.

Pharmacological properties

Pharmacokinetics & pharmacology of azithromycin

The following characteristics are associated with azithromycin and its 15-member macrolide ring structure (**Table 2**): increased acid stability, a longer elimination half-life and an increased tissue penetration compared with erythromycin [10–12]. Azithromycin is also well absorbed and has a low serum concentration in the presence of protracted serum and tissue half-lives [68,73,74], and food decreases the bioavailability of azithromycin by up to 50%. Each dose of azithromycin should be taken at least 1 h before or 2 h after meals.

The mean peak plasma or serum concentration of azithromycin is approximately 0.45 mg/l and is attained approximately 2.5 h after administration [68,75] of a 500 mg single oral dose and, following administration of the 500 mg intravenous dose, higher serum concentrations (3.6 ± 1.60 µg/ml with 2-h trough levels of approximately 0.20 ± 0.15 µg/ml) have been observed [76]. Another characteristic of azithromycin relates to the high affinity for cells and tissues. Drug levels in leukocytes, macrophages, fibroblasts and various tissues are ten- to 100-times higher than serum drug concentrations [77]. Excretion of azithromycin is primarily in feces and bile, and only 6 and 12% (approximately) of the oral and intravenous dose of azithromycin, respectively, is recovered from urine [9,68,75,78]. Dosage adjustments do not appear necessary in patients with hepatic and/or renal dysfunction. A unique observation with azithromycin is the unusually long half-life of approximately 68 h [73].

Several animal and human studies have demonstrated the high affinity of azithromycin for cells and tissues and have shown that the uptake into cell types is rapid and dependent on extracellular

Table 2. Properties of macrolides [188].

Agent	Dosage, extent of dosing (mg)	C_{max} (µg/ml)	$t_{½}$* (h)	Urinary recovery (%)	Bronchial mucosa (mg/kg body weight)	Epithelial lining fluid (µg/ml)	Alveolar macrophages (µg/ml)
Azithromycin	500‡	0.62	~48 h	4.5–12.2			
Clarithromycin	250§	1.1	6.8			26.1 ± 7.0	222 ± 816#
Erythromycin	250¶	2.9 ± 0.8	1.5–3.0				

**Values represent the mean and are generally for administration of a single dose of the oral agent.*

‡500 mg (2 × 250 mg) day 1, then 250 mg daily for 5 days.

§250 mg twice daily for 7 days.

¶250 mg 6-hourly for 5 days.

#8 h after last dose.

C_{max}: Maximum drug concentration; $t_{½}$: Half-life.

drug concentration, pH, viability of the cell and concomitant administration of cytokines [77,79]. Intracellular drug concentrations for azithromycin in human and mouse polymorphonuclear (PMN) leukocytes, human fibroblasts, murine peritoneal macrophages and mouse and rat alveolar macrophages may be up to 226-times the extracellular concentrations [77,80]. The intracellular accumulation of azithromycin within human PMN leukocytes is prolonged and may last up to 24 h compared with 30 min with erythromycin [80]. Finally, after 72-h incubation, human fibroblasts accumulated 21-fold more azithromycin than erythromycin [77] and it has been suggested that azithromycin-loaded fibroblasts may serve as a drug reservoir, allowing the slow release of the drug into the circulation [77].

Pharmacokinetics & pharmacology of clarithromycin

The methylation at position 6 of clarithromycin allows for the improved bioavailability, protection from acid degradation, excellent tissue penetration, high intracellular drug concentrations and fewer GI side effects compared with erythromycin [1,8,13,81].

Clarithromycin has a higher bioavailability than azithromycin (37 vs 55%, respectively) and food increases the rate of absorption of clarithromycin but does not affect overall bioavailability. Clarithromycin can be taken with or without meals [68,82]. Following oral dosages of 250 and 500 mg twice daily, the mean peak steady-state serum concentrations are 1 and 2–3 µg/ml, respectively [83]. The serum half-life of clarithromycin is 3–4 h following a 250-mg dose and 5–7 h following a 500-mg dose, and the extended half-life permits twice-daily dosing with steady-state serum concentrations usually achieved following five doses [81,84,85].

Clarithromycin has been formulated for once- and twice-daily dosing. Pharmacokinetics of the once-daily formulation, at dosages of 500 mg and 2 × 500 mg, were evaluated and compared with those of the twice-daily formulation, at equal dosages of 250 and 500 mg. Absorption, as assessed by the steady state area under the curve (AUC_{SS}), was equivalent between the two formulations and comparative between dosages. Relative bioavailability for the 500-mg total daily dose was 96.3 and 95.3% for the parent compound and the 14-OH metabolite, respectively, and comparable results were observed at the 1000-mg total daily dosage: relative bioavailability of 97.4 and 111.7% for the parent compound and 14-OH metabolite, respectively. The relative increase in the formation of the active 14-OH metabolite with the once-daily formulation appears to be related to the longer T_{max} and may be important for coverage of *H. influenzae*. The kinetics for clarithromycin were similar for both formulations, as observed in their serum half-lives of approximately 5–6 h at time points beyond the C_{max} [86].

The 14-OH-clarithromycin active metabolite is somewhat unique and offers the following characteristics: it is formed within 3 h of administration and has a half-life of up to 7 h [81]; is as active as clarithromycin against a variety of Gram-positive and -negative bacteria; and is more active *in vitro* and *in vivo* than clarithromycin against *H. influenzae*, *M. catarrhalis*, *Legionella* species and some streptococci and staphylococci [87]. Up to 40% of clarithromycin is recovered in urine. Patients with creatinine clearance of less than 30 ml/min may require dosage adjustments [88]; however, dosage adjustments are not usually necessary in patients with normal renal function but moderate to severe hepatic dysfunction [89].

Clarithromycin, as with azithromycin, is extensively distributed in cells and body tissues, achieving drug concentrations that are two- to sixfold higher than in serum. In comparative distribution studies in animals, clarithromycin was shown to achieve higher concentrations in organs and tissues than erythromycin, especially in the lungs [90–93]. Patel and colleagues provided evidence suggesting that the levels of clarithromycin achieved in the epithelial lining fluid and alveolar macrophages are higher than those of azithromycin [69]. This observation may have important consequences for the selection of antimicrobial resistance during drug therapy (as discussed above). From their study in 41 healthy volunteers administered clarithromycin (500 mg twice-daily for nine doses) or azithromycin (500 mg initial dose and 250 mg once-daily for the remaining four doses), Patel and colleagues reported the absolute clarithromycin concentrations in epithelial lining fluid and alveolar macrophages were higher than those of azithromycin for up to 8 and 12 h, respectively, following the last dose [69].

Drug interaction & drug safety

Theophylline, carbamazepine and terfenadine drug interactions are seen with erythromycin and clarithromycin, but not with azithromycin [3,94].

In a study by Guay investigating adult patients treated with azithromycin, approximately 45% of adult patients that received the drug reported no significant interactions with warfarin, theophylline, carbamazepine, methylprednisolone, oral contraceptives, terfenadine or zidovudine [95]. Similarly, no major drug interactions have been associated with erythromycin use in combination with numerous other agents [96].

The safety and tolerability of azithromycin was studied in over 6600 patients (42% female, 58% male; 61% aged ≥ 16 years) [97]. For 15.4% of adult patients treated with azithromycin, the following side effects were reported: GI in 12.6% of cases; 1.4% or less for effects on CNS and PNS, cardiovascular, skin and liver. In total, investigators felt that 43% of the adverse events were related to azithromycin therapy compared with 52% for comparator agents. There was no difference in tolerability of azithromycin by elderly and young patients. The severity of side effects was classified as 64% mild, 30% moderate and 6% severe, whereas the severity profile for comparative agents was classified as 52% mild, 36% moderate and 12% severe. Laboratory abnormalities were not detected consistently in adults or children treated with azithromycin that resulted in their withdrawal from therapy; 2.3% or less of liver enzymes, white blood cells, hemoglobin, platelets, creatinine, blood urea nitrogen, potassium or calcium were found to be abnormal from 1900–3800 assessments and most had abnormal percentages of 0.7% or lower (**Table 3**).

Clarithromycin use may include side effects such as nausea, diarrhea, abdominal pain, metallic taste and headache. Similar to azithromycin, clarithromycin is generally considered to be a nontoxic drug (**Table 3**) [98] and demonstrated fewer side effects than erythromycin when the compounds were used in comparative studies [99]. High-dose clarithromycin (1000 mg twice daily) administered to elderly patients with atypical mycobacterial lung infections was associated with more severe adverse reactions, including nausea, vomiting, metallic taste, abnormal results of liver function tests and CNS toxicity [100]. Dosages of 500 mg twice daily was better tolerated by patients and mild and transient and/or isolated side effects associated with clarithromycin use have included leukopenia, abnormal liver enzyme values, pancreatitis, myasthenic syndrome, cholestatic hepatitis and fulminant hepatic failure (**Table 3**) [101–104].

Erythromycin is associated with drug interactions since it interacts with the cytochrome P450 system. Drug interactions include coadministration of clarithromycin with carbamazepine, theophylline, caffeine, digoxin, triazolin, ergotamine, cyclosporine, warfarin, astemizole, terfenadine, valproate, disopyramide, midazolam and nicotine [20,105–116]. Clarithromycin may also interact with zidovudine and other antiretroviral agents [117–121].

Clinical indications

The macrolides are indicated for a wide range of clinical infections, with some differences between the agents with respect to specific indications. For this review, only the RTI indications will be summarized. Readers are referred to other comprehensive reviews for other potential indications for the various macrolide compounds [6,41]. Review of the clinical efficacy of the macrolides in RTIs are summarized in the following sections (**Tables 4–11**) and include clinical and bacteriological outcome results. As previously summarized by Blondeau, several points regarding the summary of the clinical trials data must be emphasized and include [7]:

- The number of patients is based on those evaluated for clinical efficacy;
- The number of patients evaluated for bacteriological outcome tends to be lower than those evaluated for clinical efficacy;

Table 3. Incidence of macrolide-related adverse events.

Event	Azithromycin (%)	Clarithromycin (%)
Nausea	2.6–5.0	3–3.4
Diarrhea	3.6–6.0	2.7–3.0
Taste perversion		<1
Headache/nervous system	1.3	2
Gastrointestinal	12.6	7.5
Discontinuations	<1	3.2
Abdominal pain	2.5–4.0	1–6

Data from [1,97].

- Not all trials had microbiological evaluations;
- Not all trials had follow-up data for either clinical efficacy, bacteriological efficacy or both;
- While drug dosages are summarized, readers should refer to the specific studies for clarification if the summarized data is unclear;
- Readers should make note of the number of patients in the studies summarized and recognize that the calculation of percentage is profoundly affected by low patient number values;

Table 4. Summary of selected antimicrobial comparator trials in adults with community-acquired pneumonia.

Treatment	Dosage	Duration (days)	No. patients	End of Treatment		Ref.
				Clinical outcome	Bacteriological outcome	
Azithromycin						
Azithromycin	500 mg day 1 and 250 mg daily on days 2–5	5	48	92	91	[140]
Amoxicillin/clavulanate	500 mg three times a day	10	56	87	89	
Azithromycin	500 mg day 1 and 250 mg daily for 2–5 days	5	191	96	88	[141]
Cefaclor	500 mg three times a day	10	81	95	88	
Azithromycin	500 mg day 1 and 250 mg daily on days 2–5	5		100		[142]
Erythromycin	500 mg daily	10		100		
Azithromycin	500 mg day 1 and 250 mg daily on days 2–5	5	32	94	80	[143]
Cefaclor	500 mg three times a day	10	39	100	93	
Azithromycin	500 mg daily		54	81	81	[144]
Benzylpenicillin	1 mu daily		50	70	70	
Azithromycin	250 mg daily		53	94	94	[143]
Cefaclor	500 mg three times a day		66	100	100	
Azithromycin	2.0-g microsphere	Single dose	213	89.7	90.7	[153]
Levofloxacin	500 mg OD	7	214	93.7	92.3	
Clarithromycin						
Clarithromycin	500 mg twice daily	10	162	88.9		[145]
Sparfloxacin	400 mg loading; 200 mg daily	10	150	89.3		
Clarithromycin	250 mg twice daily		175	89	89	[145]
Sparfloxacin	200 mg daily		167	89	89	
Clarithromycin	500 mg twice daily		188	95	95	[146]
Moxifloxacin	400 mg daily		194	95	95	
Clarithromycin	250 mg twice daily	10	208	88.5		[147]
Grepafloxacin	600 mg daily	10	211	82.9		
Clarithromycin	500 mg twice daily	7–10	156	94.2		[148]
Trovafloxacin	200 mg daily	7–10	144	95.8		
Clarithromycin	250 mg twice daily	7–14	92	97	89	[149]
Erythromycin	500 mg daily	7–14	81	96	100	
Clarithromycin	500 mg twice daily	7–14	103	86	91	[150]
Cefixime	400 mg daily	7–14	110	88	90	
Azithromycin vs clarithromycin						
Clarithromycin	250 mg twice daily	10	101	95	95	[151]
Azithromycin	500 mg daily	3	102	94	94	
Azithromycin	2.0-g microsphere	Single dose	202	92.6	91.8	[155]
Clarithromycin	1.0 g once daily	7	209	94.7	90.5	

- Readers should always refer to the original study publication in order to fully appreciate the study designs, data evaluations and/or any specific modification factors that may have influenced the data but may be beyond the scope for inclusion in this review article;
- Clinical trials are designed to show equivalency and, as such, statistical differences relating to clinical efficacy are unlikely. Also, many studies may exclude patients with a pathogen that is resistant to either study drug;
- For some of the studies summarized in this review, statistical differences were observed between some compounds for bacterial eradication. Additionally, some differences were organism specific. Such specific data was not included in the tables in this report in an attempt to keep the tables simple. Readers should refer to specific studies in order to fully appreciate how the study was conducted, sample size, statistical methods and any other variables that may influence the interpretation of the results.

Clinical use in children

Pharyngitis and tonsillitis in children aged between 5 and 15 years is usually caused by *Streptococcus pyogenes* (group A *Streptococci*). Penicillin remains the drug of choice owing to its proven efficacy and lack of clinically significant resistance. The macrolides have been

Table 5. Empirical antimicrobial selection for adult patients with community-acquired pneumonia: Canadian guidelines.

Type of patient factor(s) involved	Treatment regimen	
	First choice	**Second choice**
Outpatient without modifying factors		
	Erythromycin, azithromycin or clarithromycin	Doxycycline
Outpatient with modifying factor		
COLD (no recent antibiotics or oral steroids within prior 3 months)	Azithromycin or clarithromycin	Doxycycline
COLD (recent antibiotics or oral steroids within prior 3 months; *Haemophilus influenzae* and enteric Gram-negative rods implicated)	Levofloxacin, gatifloxacin or moxifloxacin	Erythromycin, azithromycin or clarithromycin plus amoxicillin/clavulanate or second-generation cephalosporin
Suspected macroaspiration oral anerobes	Amoxicillin/clavulanate macrolide	Levofloxacin, gatifloxacin or moxifloxacin plus clindamycin or metronidazole
Nursing home resident		
Streptococcus pneumoniae, enteric Gram-negative rods; *H. influenzae* implicated	Erythromycin, azithromycin or clarithromycin plus amoxicillin/clavulanate or levofloxacin, gatifloxacin or moxifloxacin monotherapy	Erythromycin, azithromycin or clarithromycin plus second-generation cephalosporin
Hospitalized	Treatment identical to other hospitalized patients (see below)	
Hospitalized patient or medical ward		
S. pneumoniae, *Legionella pneumophila*, or *Chlamydia pneumoniae* implicated	Levofloxacin, gatifloxacin or moxifloxacin monotherapy	Erythromycin, azithromycin, or clarithromycin plus second-, third- or fourth-generation cephalosporin
Hospitalized patient in ICU		
P. aeruginosa not suspected; *S. pneumoniae*, *L. pneumophila*, *C. pneumoniae*, or enteric Gram-negative rods implicated	Levofloxacin, gatifloxacin or moxifloxacin (i.v.) plus cefotaxime, ceftriaxone or β-lactam/β-lactamase compound	Erythomycin or azithromycin (i.v.) plus cefotaxime, ceftriaxone or β-lactam/β-lactamase compound
P. aeruginosa suspected	Ciprofloxacin or another antipseudomonal fluoroquinolone plus an antipseudomonal β-lactam agent or an aminoglycoside	Triple therapy with antispeudomonal β-lactam (e.g., ceftazidime, piperacillin, tazobactam, imipenem or meropenem) plus an aminoglycoside and erythromycin, azithromycin or clarithromycin

COLD: Chronic obstructive lung disease; i.v.: Intravenous. Reproduced with permission from [138].

shown to be effacious in the treatment of group A *Streptococci* pharyngitis and remain a suitable alternative in patients with penicillin allergy.

Several different bacterial pathogens have been associated with acute and chronic otitis media (OM) and include *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *S. pyogenes*, *S. aureus* and other bacteria. Erythromycin is a poor choice for treating otitis given the prevalence of *H. influenzae* and the poor activity of erythromycin against this pathogen. Both azithromycin and clarithromycin have shown good *in vitro* activity against the pathogens causing middle ear infections (**Table 1**). A randomized clinical trial comparing 3–5-day courses of azithromycin was compared with a 10-day course of amoxicillin/clavulanate and was found to be clinically equivalent in the management of acute OM in the pediatric population. However, side effects were statistically less commonly associated with azithromycin. Clinical cure in acute OM has also been reported in studies comparing clarithromycin and amoxicillin or amoxicillin/clavulanate or cephalosporins. Recently, several studies have reported bacteriological failures with the newer macrolides. In 1996, McLinn and Williams published a report showing that 34 confirmed *H. influenzae* cases treated with azithromycin failed to bacteriologically eradicate the pathogen in 71% of children; however, clinical cure rates were similar [122]. Similar bacteriological failure has been shown with penicillin.

A recent pediatric trial investigating the efficacy, safety and tolerability of a 3-day course of azithromycin with a 10-day course of amoxicillin/clavulanate resulted in a cure or clinically improved rate of 91 and 87%, respectively [123]. Significantly more related GI adverse events were found in the amoxicillin/clavulanate group ($p = 0.01$). This short-course therapy (3 days) data corroborates other clinical results observed.

More recently, three studies (Arguedas and colleagues, Dunne and colleagues, Block and colleagues) evaluated single-dose (30 mg/kg) azithromycin therapy for the treatment of uncomplicated OM [124–126]. Comparator regimens in two of the studies were ceftriaxone (50 mg/kg intramuscular single dose) and amoxicillin clavulanate (22.5 mg/kg twice daily, 45 mg/kg/day) (**Table 12**). Clinical success rates in the azithromycin-treated patients ranged from 64–97% compared with 57–98% and varied depending on patients age (aged <2 or >2 years) and day(s) of the measure of clinical response (10–32 days). In all three studies, there was no statistical differences in clinical efficacy between treatment groups. However, there was a statistical difference in compliance ($p > 0.001$) for patients taking azithromycin compared with amoxicillin/clavulanate [126]. In a review of these three studies, Arguedas and colleagues concluded that a single dose of azithromycin (30 mg/kg) is safe and effective for the treatment of uncomplicated OM in children [127]. For a more comprehensive overview of the diagnosis and treatment of acute OM, readers are referred to recently published clinical practice guidelines [128].

Clinical use in adults

Lower RTIs

Community-acquired pneumonia

From some of the initial pneumonia guidelines from the American Thoracic Society in 1993, macrolides (azithromycin and clarithromycin) were recommended as first-line agents in the treatment of CAP in patients aged under 60 years and without comorbidities, and they were amongst the agents of choice for treating patients with atypical pneumonia [129–132]. A review of selected clinical trials involving macrolides for treating CAP are summarized in **Table 4**.

The 2001 American Thoracic Society guidelines, 2003 Canadian guidelines, the 2003 Infectious Diseases Society of America (IDSA) guidelines and the results of several comparative clinical studies suggests that azithromycin and clarithromycin should be considered as first-line agents in the treatment of adults with suspected CAP and should be the agents of choice in patients with an established or suspected diagnosis of pneumonia owing to atypical pathogens [129,131–135]. Other first-line empiric agents to be considered in the empiric treatment of CAP include the newer fluoroquinolones (gatifloxacin, gemifloxacin and moxifloxacin) and doxycycline; however, the recent withdrawal of gatifloxacin in North America leaves only gemifloxacin and moxifloxacin as 'new' respiratory fluoroquinolones. It has been recommended that hospitalized patients with CAP admitted to a general medical ward and intensive care unit should be empirically treated with a β-lactam agent with or without a macrolide or newer fluoroquinolone as a single agent. Those with severe pneumonia admitted to an intensive care unit should be treated with a β-lactam agent in combination with a macrolide or fluoroquinolone. The benefit of combination therapy included potentially lowering mortality (severe *P. pneumonia* [136,137]), an expanded spectrum of activity to include both typical and

Table 6. Initial empirical therapy for suspected bacterial CAP in immunocompetent adults.

Patient variable	Preferred treatment options
Outpatient: previously healthy	
No recent antibiotic therapy	A macrolide* or doxycycline
Recent antibiotic therapy‡	A respiratory fluoroquinolone§ alone, an advanced macrolide¶ plus high-dose amoxicillin# or an advanced macrolide plus high-dose amoxicillin-clavulanate**
Comorbidities (chronic obstructive pulmonary disease, diabetes, renal or congestive heart failure or malignancy)	
No recent antibiotic therapy	An advanced macrolide¶ or a respiratory fluoroquinolone
Recent antibiotic therapy	A respiratory fluoroquinolone§ alone or an advanced macrolide plus a β-lactam‡‡
Suspect aspiration with infection	Amoxicillin–clavulanate or clindamycin
Influenza with bacterial superinfection	A β-lactam‡‡ or a respiratory fluorouqinolone
Inpatient: medical ward	
No recent antibiotic therapy	A respiratory fluoroquinolone alone or an advanced macrolide plus a β-lactam§§
Recent antibiotic therapy	An advanced macrolide plus a β-lactam or a respiratory fluoroquinolone alone (regimen selected will depend on nature of recent antibiotic therapy)
Intensive care unit	
Pseudomonas infection is not an issue	A β-lactam§§ plus either an advanced macrolide or a respiratory fluoroquinolone
Pseudomonas infection is not an issue but patient has a β-lactam allergy	A respiratory fluoroquinolone with or without clindamycin
Pseudomonas infection is an issue¶¶	Either an antipseudomonal agent## plus ciprofloxacin or an antipseudomonal agent plus an aminoglycoside*** plus a respiratory fluoroquinolone or a macrolide
Pseudomonas infection is an issue but the patient has a β-lactam allergy	Either aztreonam plus levofloxacin‡‡‡ or aztreonam plus moxifloxacin or gatifloxacin with or without an aminoglycoside
Nursing home	
Receiving treatment in nursing home	A respiratory fluoroquinolone alone or amoxicillin–clavulanate plus an advanced macrolide
Hospitalized	Same as for medical ward and intensive care unit

**Erythromycin, azithromycin or clarithromycin.*

‡The patient was given a course of antibiotic(s) for treatment of any infection within the past 3 months, excluding the current episode of infection. Such treatment is a risk factor for drug-resistant Streptococcus pneumoniae *and possibly for infection with Gram-negative bacilli. Depending on the class of antibiotics given recently, one or other of the suggested options may be selected. Recent use of a fluoroquinolone should indicate selection of a nonfluoroquinolone regimen and* vice versa*.*

§Moxifloxacin, gatifloxacin, levofloxacin or gemifloxacin (oral gemifloxacin only, approved by the US FDA on April 4, 2003 and is the only fluoroquinolone approved for multidrug-resistant S. pneumoniae*, not yet marketed).*

¶Azithromycin or clarithromycin.

#Dosage 1 g per oral *three times a day.*

***Dosage 2 g* per oral *twice daily.*

‡‡High-dose amoxicillin, high-dose amoxicillin–clavulanate, cefpodoxime, cefprozil and cefuroxime.

§§Cefotaxime, ceftriaxone, ampicillin–sulbactam or ertapenem; ertapenem was recently approved for such use (in once-daily parenteral treatment), although there is little experience thus far.

¶¶The antipseudomonal agent chosen reflect this concern. Risk factors for Pseudomonas *infection include severe structural lung disease (e.g., bronchiectasis) and recent antibiotic therapy or stay in hospital (especially in the intensive care unit) for patients with community-acquired pneumonia (CAP) in the Intensive Care Unit, coverage for* S. pneumoniae *and* Legionella *species must always be assured. Piperacillin–tazobactam, imipenem, meropenem and cefepime are excellent β-lactams and are adequate for most* S. pneumoniae *and* Haemophilus influenzae *infections. They may be preferred when there is concern for relatively unusual CAP pathogens, such as* Pseudomonas aeruginosa*,* Klebsiella *species and other Gram-negative bacteria.*

##Piperacillin, piperacillin–tazobactam, imipenem, meropenem or cefepime.

****Data suggest that elderly patients receiving aminoglycosides have worse outcomes.*

‡‡‡Dosage for hospitalized patients 750 mg once daily.

Reproduced with permission from [139].

atypical agents and with some combinations, the possibility of synergistic activity. Readers are referred to the complete guideline publications to fully appreciate the specific recommendations and the rational/data used to arrive at these recommendations [138,139].

Table 7. Empirical antibacterial selection for CAP: advantages and disadvantages .

Patient group, drug(s)	Advantages	Disadvantages
Outpatient		
Macrolides (azithromycin, clarithromycin and erythromycin)	Active against most common pathogens, including atypical agents	Macrolide resistance is reported for 20–30% of *Streptococcus pneumoniae* and *in vitro* resistance has emerged during therapy
	S. pneumoniae resistance *in vitro* may be deceptive since the M phenotype may not be clinically relevant and alveolar lining fluid or intracellular levels may be more important than serum levels used to determine *in vitro* activity	Breakthrough pneumococcal bacteria with macrolide-resistant strains appear to be more common than with β-lactams or fluoroquinolones
	Clinical trial data have shown consistently good results, including activity against strains resistant *in vitro*	Erythromycin is poorly tolerated and is less effective against *Haemophilus influenzae*
	Azithromycin and clarithromycin have the advantage of once-daily therapy and are well tolerated	
Amoxicillin	Amoxicillin is the preferred drug for oral treatment of susceptible strains of *S. pneumoniae*	Lacks activity against atypical agents and β-lactamase-producing bacteria
	Active against 90–95% of *S. pneumoniae* strains when used at a dosage of 3–4 g/day	High dosages (3–4 g/day) required to achieve activity against greater than 90% of *S. pneumoniae*
	Standard in many European CAP Guidelines for empiric treatment of outpatients as well as CDC guidelines	The number of recent publications documenting efficacy is modest
Amoxicillin-clavulanate	Compared with amoxicillin, spectrum *in vitro* includes β-lactamase-producing bacteria such as most *H. influenzae*, methicillin-susceptible *Staphylococcus aureus* and anerobes	Lacks activity against atypical agents
	Clinical trials reported to document efficacy	More expensive and more gastrointestinal intolerance compared with amoxicillin
	Standard in many European CAP guidelines for empiric treatment of outpatients as well as CDC guidelines	The number of recent publications documenting efficacy is relatively modest
Oral cephalosporins (cefpodoxime, cefprozil and cefuroxime axetil)	Active against 75–85% of *S. pneumoniae* and virtually all *H. influenzae*	All cephalosporins (and all β-lactams) are inactive against atypical agents
	Clinical trial data support efficacy in outpatients with CAP	Amoxicillin is more predictably active against *S. pneumoniae* (cefprozil and cefpodoxime are more active than cefuroxime)
Doxycycline	Active against 90–95% of strains of *S. pneumoniae*. Also active against *H. influenzae*, atypical agents and category A bacterial agents of bioterrorism	Very limited recent published clinical data on CAP and few clinicians use it
	At least one recent report showing good outcomes in hospitalized patients with CAP	
Fluoroquinolones (gatifloxacin, levofloxacin, moxifloxacin and gemifloxacin)	Active against greater than 98% of *S. pneumoniae* strains in the USA, including penicillin-resistant strains	Concern for abuse with risk of increasing resistance by *S. pneumoniae*. This includes clinical failures attributed to emergence of resistance during therapy and selection of resistant strains, such as 23F, that may be prevalent in selected areas and are usually also resistant to macrolides and β-lactams

CAP: Community-acquired pneumonia. Reproduced with permission from [139].

Table 7. Empirical antibacterial selection for CAP: advantages and disadvantages (cont.).

Patient group, drug(s)	Advantages	Disadvantages
	Substantial comparative clinical trial data to confirm equivalence or superiority to alternative commonly used regimens and a meta-analysis of trials demonstrated significantly better outcomes than for β-lactams or macrolides	Expensive compared with some alternatives, such as doxycycline or erythromycin
	Active against *H. influenzae*, atypical agents, methicillin-susceptible *S. aureus* and category A bacterial agents of bioterrorism	
	Regimens have advantage of once-daily administration and are well tolerated	
Clindamycin	Active against 90% of *S. pneumoniae*	Not active against *H. influenzae* or atypical agents
	Good *in vitro* activity and established efficacy in anerobic bacterial infections and favored for toxic shock associated with pneumonia due to group A streptococci	Limited published data on use for CAP
		High rates of diarrhea and *Clostridium difficile*-associated colitis
Macrolide plus amoxicillin–clavulanate	Macrolide adds activity against agents to spectrum of amoxicillin–clavulanate (described above)	Limited published data for outpatients
		Requires high dosages of amoxicillin–clavulanate (4 g/day)
		High rates of gastrointestinal intolerance anticipated
		Unlikely to be effective against fluoroquinolone-resistant strains of *S. pneumoniae*
Hospitalized patients		
Fluoroquinolones (gatifloxacin, levofloxacin, moxifloxacin and gemifloxacin)	Broad spectrum of activity against likely agents of CAP (summarized above)	Concern for increasing resistance (summarized above)
	Extensive published data, including retrospective analyses of hospitalized medicare patients, showing significantly lower mortality than for macrolides alone or cephalosporins alone	Clinical outcome attributed to resistant strains reported
	Efficacy in serious infections, including bacteremic *Pneumococcal pneumonia*, established	
	Available in oral and parenteral formulations (except for gemifloxacin, for which only oral formulations are available) facilitating intravenous-to-oral switch	
Macrolides (azithromycin, erythromycin)	*In vitro* spectrum summarized above	Retrospective analysis of 14,000 hospitalized medicare recipients for 1998–1999 shows mortality rate for macrolide alone was significantly greater than that for cephalosporin plus a macrolide or a fluoroquinolone alone
	Extensive clinical trail data and clinical experience to document efficacy	Increasing *in vitro* resistance by *S. pneumoniae*, as summarized above
	Azithromycin is included as an appropriate choice in many current CAP guidelines, including the guidelines of the American Thoracic Society	Breakthrough bacteremia due to resistant strains of *S. pneumoniae* is unusual but appears to be more common with macrolides than with other agents

CAP: Community-acquired pneumonia. Reproduced with permission from [139].

Table 7. Empirical antibacterial selection for CAP: advantages and disadvantages (cont.).

Patient group, drug(s)	Advantages	Disadvantages
Cephalosporins (ceftriaxone and cefotaxime)	Considered the parenteral drugs of choice (as well as penicillin G) for CAP caused by susceptible strains of *S. pneumoniae*	Not active against atypical agents or category A agents of bioterrorism
	Active *in vitro* against 90–95% of *S. pneumoniae*. Also active against *H. influenzae* and methicillin-resistant *S. aureus*	Retrospective analysis of 14,000 medicare patients showed higher mortality for cephalosporins alone than for cephalosporins plus macrolides or fluoroquinolones alone
	Extensive clinical trial experience to document efficacy	Increasing resistance by *S. pneumoniae*
Fluoroquinolones plus cephalosporin	May increase antimicrobial activity against *S. pneumoniae*	No documented benefit compared with fluoroquinolone alone
Macrolide plus cephalosporin	Cephalosporin provides better *in vitro* activity against *S. pneumoniae* and macrolide adds activity against atypical agents	Data suggesting that the macrolide–cephalosporin combination is superior to monotherapy in pneumococcal bacteremia are uncontrolled and inconsistent
	Retrospective analyses demonstrate reduced mortality for this combination compared with single-agent therapy in patients with pneumococcal bacteremia and for empiric treatment of pneumonia	
Penicillin G	Preferred agent (along with ceftriaxone, cefotaxime and amoxicillin) for proven penicillin-susceptible strains of *S. pneumoniae*	Limited spectrum of activity against common pulmonary pathogens other than *S. pneumoniae*
	Published experience to document clinical efficacy is extensive	
New agents		
Telithromycin	Active *in vitro* against most *S. pneumoniae*, including macrolide-resistant strains. Also active against *H. influenzae* and atypical agents	Available in oral formulation only
	Favorable pharmacokinetics	Clinical trial data are considered preliminary
	Clinical trials in CAP show equivalence to high-dose amoxicillin, macrolides and trovafloxacin, including CAP caused by β-lactam-resistsant strains of *S. pneumoniae*	
Gemifloxacin	Most active of the 'respiratory fluoroquinolone' against *S. pneumoniae in vitro*	High rate of rash, especially in women aged under 40 years and with use for more than 10 days
	Clinical trial data for CAP show good results	Available only in oral formulation
Ertapenem	Clinical efficacy for empiric treatment of CAP comparable to ceftriaxone	Parenteral formulation only
	Once-daily parenteral dosing	Inactive against atypical agents and less active than imipenem against *P. aeruginosa*
	In vitro activity against *S. pneumoniae* is similar to ceftriaxone and cefotaxime	
Linezolid	Active *in vitro* against most Gram-positive bacteria, including multidrug-resistant *S. pneumoniae* and *S. aureus*	Lacks established activity against atypical agents
	Efficacy comparable to ceftriaxone for treatment of *P. pneumonia*	Alternative antimicrobials have more established role in CAP
	Oral and parenteral formulations	Concern regarding abuse, expense, drug–drug interaction and toxicity

CAP: Community-acquired pneumonia. Reproduced with permission from [139].

A substantial number of comparative clinical trials using β-lactam and fluoroquinolone agents have confirmed the efficacy of azithromycin and clarithromycin in the treatment of patients with CAP. The clinical and bacteriological results of selected trials are summarized in **Table 4** [140–150]. Overall, clinical success rates ranging from 81–100 and 86–97% were observed with azithromycin and clarithromycin, respectively; bacteriological success ranged from 80–94 and 89–95% respectively. O'Doherty and Muller compared the clinical and bacteriological efficacy of azithromycin and clarithromycin and reported the rates of clinical and bacteriological success were similar and greater than 94% for each agent [151]. However, azithromycin attains lower serum concentrations (discussed earlier) than clarithromycin, which has raised concerns regarding its use in patients with possible bacteremic *P. pneumonia* and the potential impact this may have on resistance selection [152].

D'Ignazio and colleagues reported on the clinical results comparing a single-dose microsphere formulation of azithromycin (2 g oral dose) versus 7 days of levofloxacin (500 mg/day orally) therapy for treatment of mild-to-moderate CAP in adults [153]. Clinical response at test of cure (days 13–24) was the primary end point and each arm of the study had approximately the same number of subjects (213 vs 214, respectively). Clinical cure rates were 89.7% for azithromycin-treated patients compared with 93.7% for patient receiving levofloxacin (bacteriological success was 90.7 vs 92.3%, respectively). A total of 19.9% of patients treated with azithromycin experienced treatment-related adverse events compared with 12.3% of patients on levofloxacin. The authors concluded that a single 2.0 g dose of azithromycin microsphere was at least as effective as 7 days of levofloxacin in the treatment of mild to moderate CAP in adult outpatients. For a review of the azithromycin microsphere formulation, readers are referred to a recent summary by Tatum and Amsden [154].

Table 8. Risk classification and suggested antimicrobial therapy for acute exacerbations of chronic bronchitis.

Group	Basic clinical state	Symptoms and risk factors	Probable pathogens	First choice	Alternatives for treatment failure
0	Acute tracheobronchitis	Cough and sputum without previous pulmonary disease	Usually viral	None unless symptoms persist for over 10–14 days	Macrolide or tetracycline
I	Chronic bronchitis with risk factors (simple)	Increased cough and sputum, sputum purulence and increased dyspnea	*Haemophilus influenzae*, *Haemophilus* spp., *Moraxella catarrhalis* and *Streptococcus pneumoniae*	Second-generation macrolide, second- or third-generation cephalosporin, amoxicillin, doxycycline or trimethoprim-sulfamethoxazole	Fluoroquinolone or β-lactam/β-lactamase inhibitor
II	Chronic bronchitis with risk factors (complicated)	As in group I plus (at least one of): FEV_1 less than 50% predicted, more than four exacerbations/year, cardiac disease, use of home oxygen, chronic oral steroid use or antibiotic use in the past 3 months	As in group I plus *Klebsiella* spp and other Gram-negatives, increased probability of β-lactam resistance	Fluoroquinolone or β-lactam/β-lactamase inhibitor	May require parenteral therapy. Consider referral to a specialist or hospital
III	Chronic suppurative bronchitis	As in group II with constant purulent sputum: some have bronchiectasis, FEV_1, usually less than 35% predicted, or multiple risk factors (e.g., frequent exacerbations and FEV_1 less than 50%)	As in group II plus *Pseudomonas aeruginosa* and multiresistant *Enterobacteriaceae*	Ambulatory patients: tailor treatment to airway pathogen, *P. aeruginosa* common (ciprofloxacin). Hospitalized patients: parenteral therapy usually required	

FEV_1: Forced expiratory volume in 1 s.

Reproduced with permission from [195].

Table 9. Summary of selected antimicrobial comparator trials in adult patients with acute bacterial exacerbations of chronic bronchitis.

Treatment	Dosage	Duration	End of treatment		Ref.
			Clinical outcome (%)	Bacteriological outcome (%)	
Azithromycin					
Azithromycin	500 mg daily	3	100		[164]
Amoxicillin	500 mg three-times a day	5	92		
Azithromycin	2 g-microsphere	Single dose	94.5	*S. pneumoniae* (97.3) *H. influenzae* (96.3) *M. catarrhalis* (1000)	[180]
Levofloxacin	500 mg once a day	10	92.8	*S. pneumoniae* (92.3) *H. influenzae* (100) *M. catarrhalis* (90.9)	
Azithromycin	500 mg daily x 1, then 250 mg daily x 4 days	5	88	94	[165]
Moxifloxacin	400 mg daily	5	88	95	
Azithromycin	2g OD	Single dose	93.6	*S. pneumoniae* (95) *H. influenzae* (94.7) *M. catarrhalis* (92)	[171]
Levofloxacin	500 mg OD	7	92.7	*S. pneumoniae* (100) *H. influenzae* (90.5) *M. catarrhalis* (81.3)	
Clarithromycin					
Clarithromycin	500 mg twice daily	10	90	96	[166]
Ciprofloxacin	750 mg twice daily	10	91	98	
Clarithromycin	500 mg twice daily	10		*S. pneumoniae* (91) *H. influenzae* (74) *H. parainfluenzae* (100) *M. catarrhalis* (100)	[167]
Moxifloxacin	400 mg daily	5		*S. pneumoniae* (100) *H. influenzae* (89) *H. parainfluenzae* (100) *M. catarrhalis* (85)	
Moxifloxacin	400 mg daily	10		*S. pneumoniae* (96) *H. influenzae* (96) *H. parainfluenzae* (100) *M. catarrhalis* (94)	
Moxifloxacin	200 mg daily	10		*S. pneumoniae* (89) *H. influenzae* (96) *H. parainfluenzae* (100) *M. catarrhalis* (100)	
Cefuroxime	500 mg twice daily	10		*S. pneumoniae* (89) *H. influenzae* (81) *H. parainfluenzae* (89) *M. catarrhalis* (70)	
Clarithromycin	500 mg twice daily	≤14	94	92	[168]
Cefaclor Cefuroxime Cefixime	500 mg three-times a day 500 mg twice daily 400 mg daily	≤14	91	87	
Clarithromycin	500 mg twice daily	≤14	88	91	[169]

**p < 0.05 – Open-label study.*

Table 9. Summary of selected antimicrobial comparator trials in adult patients with acute bacterial exacerbations of chronic bronchitis.

Treatment	Dosage	Duration	End of treatment		Ref.
			Clinical outcome (%)	Bacteriological outcome (%)	
Cefuoxime	500 mg twice daily	≤14	90	90	
Azithromycin vs clarithromycin					
Azithromycin	500 mg daily	3	97	93*	[170]
Clarithromycin	250 mg twice daily	7	87	75	

$p < 0.05$ – Open-label study.

Drehobl and colleagues comapred single-dose azithromycin microspheres (2 g) with that of extended-release clarithromycin (1 g/day for 7 days) for the treatment of mild to moderate CAP in adults [155]. This was a Phase III, multinational, multicenter, randomized, double-blind, double-dummy study where the primary end point was clinical response at the test of cure (days 14–21). Clinical cure rates were 92.6% for azithromycin treated patients and 94.7% for those given clarithromycin (pathogen eradication rates were 91.8 and 90.5%, respectively, and treatment-related adverse events were 26.3 and 24.6%, respectively). The authors concluded that both therapies were effective in the treatment of adults with mild-to-moderate CAP.

Stahl and colleagues studied the effect of macrolides on length of hospital stay in patients with CAP and suggest an important role for these compounds in initial empirical therapy [156]. For 76 hospitalized patients with CAP, prospective evaluation of their antibiotic therapy by simple regression techniques examined the correlation between initial therapy (i.e., ceftriaxone or a macrolide) and length of stay and mortality. The length of stay was 50% shorter (2.75 vs 5.3 days) for 12 patients given a macrolide (alone or in combination) within the first 24 h of hospitalization than for patients receiving other antimicrobial compounds ($p = 0.01$). However, this association was only observed when the macrolide was administered within the first 24 h. There were no significant differences in patient risk factors (age, sex, distribution, mortality risk or social factors) for those receiving a macrolide compared with other antibiotics. Interestingly, patients who received a macrolide were less likely to have a pathogen identified, compared with those receiving other antimicrobials, within the first 24 h of admission ($p \leq 0.06$). It was concluded that the findings from this study reinforce guidelines recommending macrolide therapy for empiric therapy of CAP. Regardless of the use of these compounds either alone or in combination, their activity against atypical pathogens (*M. pneumoniae*, *C. pneumoniae* and *L. pneumophila*) was beneficial to patient care and may provide a plausible explanation for the above noted observation. The results of this study suggest that a randomized, prospective trial would be worthwhile.

Gleason and colleagues investigated initial antimicrobial therapy and outcome for elderly patients hospitalized with pneumonia [157]. In this study, the authors sought to determine an association between 30-day mortality and initial antimicrobial therapy in elderly patients hospitalized for CAP. This was a retrospective study reviewing hospital records for over 12,000 hospitalized patients (≥65 years) with pneumonia. A Cox proportional hazards model was used to assess association between 30-day mortality and the initial antimicrobial regimen [135,158]. Adjustments were made for illness severity, care processes and patient characteristics. The reference group for antimicrobial regimen comparisons was patients who received a nonpseudomonal third-generation cephalosporin.

The following initial treatments were independently associated with a lower 30-day mortality rate:

- A second-generation cephalosporin plus a macrolide (29%)
- A nonpseudomonal third-generation cephalosporin plus a macrolide (26%)
- A fluoroquinolone alone (30%)

The mortality rates with the above three regimens become significantly lower than those observed with the reference group beginning 2, 3 and 7 days, respectively, after hospitalized admission. Increased 30-day mortality was associated with:

- Use of a β-lactam/β-lactamase inhibitor plus a macrolide
- Aminoglycoside plus another agent

Table 10. Summary of selected studies of azithromycin and clarithromycin in the treatment of adults with pharyngitis.

Treatment	Dosage	Duration (days)	End of treatment		Ref.
			Clinical outcome	Bacteriological outcome	
Azithromycin					
Azithromycin	500 mg day 1 and 250 mg daily on days 2–5	5	99	91	[172]
Penicillin VK	250 mg once daily	10	99	96	
Azithromycin*	2 g-microsphere	Single dose	99	86.3	[176]
Azithromycin	500 mg once daily	3	96.7	81.4	
Clarithromycin					
Clarithromycin	500 mg twice daily	10–14	95–100	88–100	[173]
Penicillin VK	250 mg once daily	10–14	92–100	91–97	
Clarithromycin	250 mg twice daily	≤10	97	95	[177]
Penicillin VK	250 mg three times a day	≤10	97	87 (p = 0.009)	
Azithromycin vs clarithromycin					
Azithromycin	500 mg day 1 and 250 mg daily on days 2–5	5	90 (p = 0.002 vs clarithromycin)	77 (p > 0.001 vs clarithromycin)	[189]
Clarithromycin	250 mg twice daily	10	98	94	

*Adults and adolescents.

Gleason and colleagues concluded that decreased 30-day mortality was associated with initial antimicrobial regimens with activity against common typical and atypical pathogens (i.e., *S. pneumoniae*, *H. influenzae, Legionella* species, *M. pneumoniae*, *C. pneumoniae* and *C. burnetti*) and that atypical pathogens amongst the hospitalized elderly patients with CAP may be a more significant problem than most appreciate. Modifying existing initial antimicrobial prescribing may help improve the care of hospitalized elderly patients with pneumonia [157]. Some data suggest the incidence of atypical pneumonia leading to hospitalization is as high as 44% (*M. pneumoniae* 33% and *C. pneumoniae* 9%) and that *C. pneumoniae* has been associated with deadly outbreaks of pneumonia in nursing home residents [159–163]. In a recent review of the etiology of CAP, Blondeau and Tillotson reported that atypical pathogens were being found more often and, as such, may represent increasing prevalence, better or more aggressive diagnostic testing or study designs attempting to document atypical pathogen prevalence rates [5].

Limitations of this study as identified by the authors were:

- Observational study design and, therefore, antimicrobial treatment selection biases were possible
- Route of drug administration, dose and discontinuation data were not recorded
- The definition of initial antimicrobial therapy consisted of all agents prescribed within 48 h of hospital arrival and does not reflect the influence of subsequent changes in therapy or patient outcome;
- No microbiological culture or sensitivity data were available and it was not possible to definitely correlate association between antimicrobial therapy, microbiological etiology, antimicrobial susceptibility and patient outcome;
- Do not resuscitate orders were not systematically recorded and patients with such orders may not have been aggressively treated with antimicrobials in light of patient and/or family wishes.

Even with the obvious limitations, this data suggest that combination therapy with a macrolide (plus either a second or third [nonpseudomonal] generation cephalosporin) or a fluoroquinolone alone were associated with a lower 30-day mortality in elderly patients hospitalized with pneumonia and, thus, provide potential opportunities to reduce mortality and improve the quality of care for elderly patients.

Table 5 is a copy of the antimicrobial drug recommendations in the Canadian guidelines for the empiric antimicrobial therapy of adult patients with CAP [138]. **Table 6** is copied from the

Infectious Diseases Society of America guidelines on the management of CAP in immunocompetent adults [139]. Macrolides continue to be recommended as the preferred treatment options in previously healthy outpatients with no recent antimicrobial therapy or in combination with high-dose amoxicillin or high-dose amoxicillin–clavulanate for previously healthy outpatients that have received recent antibiotic therapy. Macrolides also factor prominently for other clinical scenarios, depending on patient variables (**Table 5**). While the guidelines as presented are an accurate reflection of the data available at the time of publication, the increasing prevalence of infection caused by methicillin-resistant *S. aureus*, extended-spectrum β-lactamase-producing Gram-negative bacilli and multidrug class-resistant organisms require additional consideration in subsequent guidelines.

Table 7 is also copied from the recent IDSA guidelines and summarizes the advantages and disadvantages of various antimicrobial compounds used to treat CAP.

Acute bacterial exacerbations of chronic bronchitis

It has been estimated that between 5 and 6% of the US population are affected by acute bacterial exacerbations of chronic bronchitis (ABECB). Among all patient groups, the elderly and those with compromised immune systems are at highest risk of ABECB. Pathogens most commonly recovered from patients during episodes of ABECB include *H. influenzae*, *M. catarrhalis*, *S. pneumoniae* and *H. parainfluenzae*, and all are within the spectrum of macrolide therapy and macrolides have been shown to be highly effective. **Table 10** summarizes the clinical and bacteriological response rates, each of which is greater than 87%, observed in selected studies involving azithromycin and clarithromycin for the treatment of ABECB [164–170]. Numerous antimicrobial regimens have been studied in patients with chronic lung disease and ABECB.

Recently, Zervos and colleagues reported on the 2-g oral dose of azithromycin microspheres (single dose) compared with 500 mg once daily of levofloxacin for 7 days in the treatment of patients with ABECB [171]. In this study, subjects had Anthonisen Type 1 exacerbations, were aged over 50 years and had a greater than 50 pack/year smoking history. The primary end point in this study was clinical response at test of cure visit (days 14–21) and the secondary end point was bacterial response at test of cure visit in subjects in whom a baseline pathogen had been identified. Clinical cure rates for patients treated with azithromycin was 93.6%, as compared with 92.7% in patients treated with levofloxacin. Both treatments were well tolerated in this study and the authors concluded that the microsphere formulation of azithromycin was as effective as a 7-day course of levofloxacin in the treatment of acute exacerbations of chronic bronchitis. A summary of treatment guidelines are reproduced in **Table 9**.

Upper RTIs

Pharyngitis

Approximately 33% of pharyngitis cases are due to bacteria, with *S. pyogenes* (group A *Streptococcus*) being the primary pathogen identified in these cases. While 40% or more of all cases of pharyngitis are viral in origin, differentiation between viral and bacterial etiologies is clinically difficult owing to symptom overlap. Laboratory testing to differentiate between viral and bacterial etiologies is essential and encouraged to ensure appropriate antimicrobial use, since judicious use of antimicrobial agents is necessary. Serious consequences of bacterial pharyngitis include acute rheumatic fever, and it is necessary to reduce the period of contagion and limit the spread of the infection to others that mandate empiric antimicrobial therapy be initiated to those patients most likely to have a bacterial etiology, such as *S. pyogenes*.

Penicillin remains the treatment of choice for pharyngitis. However, studies have found azithromycin and clarithromycin to be highly effective alternative agents and macrolides are useful in patients with a penicillin allergy. In the study by Hooton, 5 days of azithromycin therapy was found to be clinically equivalent to 10 days of penicillin V [172]. Similarly, clarithromycin 250 mg twice daily for 10 days was comparable with penicillin V 500 mg once daily. Clinical and bacteriological success rates exceeded 90% for both treatment groups [173,174]. In a comparative study of the two agents, clarithromycin produced significantly higher rates of clinical and bacteriological cure compared with azithromycin (98 vs 90% and 94 vs 77%, respectively; $p > 0.002$) [175].

Recently, the single-dose azithromycin microsphere formulation was compared with 3 days of azithromycin for the treatment of group A β-hemolytic streptococci pharnyngitis/tonsillitis in adults and adolescents [176]. This was a Phase III multicenter, randomized, double-blind, plecebo-controlled trial conducted in North

America, Europe and India, where the primary end point was bacteriological response at test of cure (day 24–28) and the secondary end points were clinical response at test of cure. In this study, bacteriological eradication was achieved in 86.3 and 81.4%, respectively in the azithromycin microsphere compared with 3-day azithromycin groups. Clinical cure was observed in 99% of patients receiving the microsphere formulation, compared with 96.7% in the 3-day azithromycin therapy group. In both treatment arms, therapy was well tolerated and most adverse events were mild to moderate in intensity. The authors concluded that a single 2-g dose of azithromycin microspheres was as effective and well tolerated as 3 days of azithromycin (500 mg once daily) for treating group A β-hemolytic *S. pharyngitis* in adults and adolescents. The results of selected studies are summarized in **Table 10** [172,173,175,177].

Acute bacterial rhinosinusitis

Antibacterial rhinosinusitis is a common infectious disease with up to at least 13% of the US population affected. Common pathogens associated with sinusitis infection include *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* with the former two pathogens being nearly equiprevalent. Comparative trials in acute maxillary sinusitis in adults have shown that agents, such as phenoxymethylpenicillin, amoxicillin, erythromycin, clarithromycin and azithromycin, are effective. In an open-label, noncomparative trial using azithromycin administered over 5 days (1.5 g total) resulted in 86% clinical efficacy. Similar clinical efficacy was observed in short-course therapy (3 days with azithromycin vs 10 days with amoxicillin/clavulanate). In studies investigating clarithromycin, clinical response rates ranged from 87 to 93% compared with bacterial response rates of 87–97% (**Table 11**). Clarithromycin is the only macrolide currently approved for use in sinusitis. Readers are referred to treatment guidelines for more comprehensive recommendations on therapy for acute bacterial rhinosinusitis [178,179].

Azithromycin (2 g single-dose microsphere) was compared with 500 mg once-daily levofloxacin for 10 days for the treatment of acute bacterial sinusitis in adults [180]. The primary end point was clinical efficacy at test of cure (17–24 days). Clinical success rates were 94.5% for azithromycin-treated patients versus 92.8% in the levofloxacin group. The authors concluded that the single-dose azithromycin formulation was as effective as 10 days of levofloxacin for the effective treatment of acute bacterial sinusitis.

Otitis media

Otitis media is a common infection among children and adults and, in 1995, approximately 22 million Americans experienced an acute ear infection [181]. Pathogens most commonly associated with OM include *S. pneumoniae* (implicated in up to 45% of infections), *H. influenzae*, *M. catarrhalis* and Group A *Streptococcus*. Macrolides (azithromycin administered for 3 days or clarithromycin for 10 days) were equivalent to amoxicillin/clavulanate (10 days) in clinical studies (**Table 12**) [182–185]. Ramet compared 5 days of

Table 11. Summary of selected antimicrobial comparator trials in adult* patients with sinusitis.

Treatment	Dosage	Duration (days)	End of treatment		Ref.
			Clinical outcome (%)	Bacteriologic outcome (%)	
Azithromycin					
Azithromycin	500 mg once daily x 1 day, 250 mg x 4 days	5	100	100	[190]
Amoxicillin	500 mg thrice daily	10	100	100	
Clarithromycin					
Clarithromycin	500 mg twice daily	7–14	92		[191]
Amoxicillin	500 mg thrice daily	7–14	91		
Clarithromycin	500 mg twice daily	14	93		[192]
Levofloxacin	500 mg once daily	14	96		
Clarithromycin	500 mg twice daily	≤14	87	97	[193]
Amoxicillin/clavulanate	500 mg thrice daily	≤14	90	93	

**Adults and adolescents.*

treatment with azithromycin or clarithromycin and found equivalent cure rates of 99% in each treatment group [185].

Expert commentary & outlook

The ongoing inclusion of macrolide compounds in pneumonia and bronchitis treatment guidelines and the recognition of impacting lengths of hospitalization stay and 30-day mortality in the elderly confirm the importance of these compounds for infected patients. Initially, macrolides were seen as an important alternative therapy to β-lactams for infected patients, first against Gram-positive pathogens and subsequently for atypical organisms, thereby, expanded their utility. Expanding the spectrums of azithromycin and clarithromycin to include some Gram-negative pathogens (most notably *H. influenzae*) aligned these agents to be more suitable to treat RTIs (i.e., infections caused by Gram-positive, Gram-negative and atypical pathogens). In numerous clinical trials comparing macrolides with various other compounds has shown the macrolides to be clinically and bacteriologically equivalent for various infections of the upper and lower respiratory tract.

Antimicrobial agents are used to treat patients with infectious diseases caused by organisms considered susceptible to the treatment drug. Antimicrobial resistance has reshaped our thinking on the use of antibacterial compounds. In the earlier days of drug-resistant bacteria, the strategy for dealing with the problem was to find new drugs that remained active against the pathogen(s) and not negatively affected by that particular mechanism of resistance. Similar approaches would remain relevant today; however, there clearly appears to be fewer new antimicrobial drugs in development than there was just several years ago. Given that simply ignoring the problem of drug-resistant bacteria is no longer an option, one approach to this problem may be to improve our understanding of the factors that contribute to resistance and to determine whether modifying these factors impacts on slowing, reducing or reversing resistance trends. Such factors may include the propensity of a particular drug class or specific drug to disproportionately be associated with a resistance trend. Such arguments have been debated previously for fluoroquinolones and *S. pneumoniae*, and it now appears that similar data exist for the macrolides, as mentioned previously [44,186]. Based on the evidence summarized, it indicates that azithromycin is more likely to select for macrolide-resistant *S. pneumoniae* than clarithromycin. Whether this observation extends to other bacterial pathogens remains to be determined through further investigation.

The mutant or resistance prevention concentrations described by Blondeau and colleagues, and its subsequent application to the macrolides,

Table 12. Summary of selected studies of azithromycin and clarithromycin in the treatment of patients with otitis media.

Treatment	Dosage	Duration (days)	Clinical outcome (%)	Ref.
Azithromycin				
Azithromycin	10 mg/kg once daily	3	94	[182]
Amoxicillin/clavulanate	250 mg three times a day	10	100	
Azithromycin	30 mg/kg	Single dose	94–97	[124]
Azithromycin	20 mg/kg once daily	3	92–95	
Ceftriaxone	50 mg/kg intramuscular	Single dose	97–98	
Azithromycin	30 mg/kg	Single dose	77–91	[125]
Azithromycin	30 mg/kg	Single dose	64–93	[125]
Amoxicillin/clavulanate	22.5 mg/kg twice daily	10	57–88	
Clarithromycin				
Clarithromycin	7.5 mg/kg twice daily	10	90	[183]
Amoxicillin/clavulanate	13.3 mg/kg three times a day	10	92	
Clarithromycin	7.5 mg/kg twice daily	10	93	[184]
Amoxicillin/clavulanate	13.3 mg/kg three times a day	10	94	
Azithromycin vs clarithromycin				
Azithromycin	10 mg/kg day 1 and 5 mg/kg daily on days 2–5	5	99	[185]
Clarithromycin	7.5 mg twice daily	5	99	

show a convincing differential impact of various macrolides to select for resistant bacterial subpopulations for high-density bacterial inoculum [44]. The concept of MPC or resistance prevention concentration is based on preventing mutants from being selectively amplified under selective drug pressure. The concept is not based on mutation prevention. As such, it appears clear that, for both fluoroquinolones and macrolides, appropriate drug selection for therapy of pathogens, such as *S. pneumoniae*, also involves selection of an agent that is less likely to select for resistance, in addition to a favorable clinical outcome.

Since the early 1990s, consensus treatment guidelines for the empiric therapy of CAP and, ultimately, ABECB recommend macrolide antimicrobial agents, depending on the clinical presentation and a number of different variables or cofactors. Also, depending on disease severity in association, macrolides are recommended for either monotherapy or combination therapy with compounds from other drug classes in both CAP and ABECB. In some specific instances, azithromycin and clarithromycin are specifically recommended over erythromycin. The reports by Gleason and colleagues [156] and Stahl and colleagues [157] suggests macrolides, in combination with other agents, may have wider benefits than previously recognized (i.e., decreased length of stay and reduced 30-day mortality.

There is little doubt that increasing antimicrobial resistance is impacting on all classes of antimicrobial compounds. In particular, drug-resistant *S. pneumoniae* is a global concern. Penicililin-resistant pneumococci are cross- or co-resistant to other β-lactams, macrolides, tetracycline and trimethoprim/sulfamethoxazole, and the level of cross- or coresistance is affected by the level of penicillin resistance. Surveillance studies for determining current levels of susceptibility/resistance are important epidemiologically. However, this data must be carefully correlated with clinical success and failures and modeled with accepted pharmacological principals in order to fully appreciate the full impact of increasing drug-resistant bacteria.

Macrolides continue to be important antimicrobial compounds and their best use in RTIs may be based on:

- Appropriate use (i.e., nonviral infections), as with all drugs;
- Monotherapy for mild-to-moderate disease or in combination with suitable agents in accordance with guideline recommendations;
- Based on local susceptibility/resistance data specifically highlighting the principal respiratory tract pathogens;
- The patients antibiotic history and it's potential impact on the selection of a macrolide agent, as per the findings of Vanderkooi and colleagues [51];
- Considering the potency against the targeted pathogen(s) and choosing an agent less likely to select for resistance.

It is becoming clearer that the role or clinical utility of the macrolide agents is continuing to be defined.

Finally, in the clinical world, drug approval is based on clinical trials showing noninferiority between an investigational compound and some appropriate compound that is already approved for the same indication. What would be the design of a clinical evaluation of a drug if, in addition to clinical outcome, microbiological and pharmacological outcomes were also made based on some defined criteria or breakpoint. Clearly, long-term societal consequences must be considered. If a favorable clinical outcome and the selection of drug-resistant bacteria are capable of being two independent events, which criteria should be used for drug approval? If, in fact, the patient gets better, should that be sufficient? If, on the other hand, selection of drug-resistant bacterial subpopulations occurs, is this acceptable given that a drug class could be ultimately compromised over time. Such a finding could shorten the life expectancy of a particular drug or drug class and deter future research efforts. In an ideal world, pathogen-specific therapy would

Highlights

- The study by Vanderkooi identifying risk factors for having antibiotic-resistant pathogens provides an important link with drug use and resistance.
- The side effects and pharmacological profiles of azithromycin and clarithromycin are more favorable than those for erythromycin.
- Macrolides continue to be clinically efficacious therapy for community-acquired respiratory tract infections (RTIs).
- Azithromycin may more readily select for macrolide resistance in Streptococcus pneumoniae than clarilthromycin.
- Treatment guidelines for community-acquired RTIs still recommend macrolide therapy depending on disease severity and patient variables.
- Mutant prevention or resistance prevention concentration testing has been applied to macrolide compounds.
- Macrolides are considered to be safe compounds.
- Antimicrobial-resistant organisms may impact clinical outcome.
- Erythromycin is a poor agent for *Haemophilus influenzae*.

be based on comprehensive and sensitive laboratory testing that would ensure the right drug for the task. Perhaps we need to acknowledge that prevention of resistance should also be a goal of antimicrobial therapy. Given the relative scarcity of new antimicrobial compounds being developed for the treatment of a variety of both community- and hospital-acquired infections, perhaps a greater appreciation of the factors leading to the selection of antimicrobial resistance, in addition to the prevention of the selection of antimicrobial-resistant subpopulations, should be reviewed more vigorously. Doern suggests that drug potency was of paramount importance to this whole equation [187]. Perhaps he is right.

Acknowledgements

I thank Deb Hills for excellent clerical assistance. Segments of this manuscript were previously used in an editorial and are reproduced within, mostly unchanged [41].

Bibliography

1. Whitman MS, Tunkel AR. Azithromycin and clarithromycin: an overview and comparison with erythromycin. *Infect. Control Hosp. Epidemiol.* 13, 357–368 (1992).
2. Zuckerman JM, Kaye KM. The newer macrolides – azithromycin and clarithromycin. *Infect. Dis. Clin. North Am.* 9, 731–745 (1995).
3. Amsden GW. Erythromycin, clarithromycin and azithromycin: are the differences real? *Clin. Ther.* 18, 56–72 (1996).
4. McKenna S, Evans GA, The Canadian Infectious Disease Society Antimicrobial Agents Committee. Macrolides: a Canadian Infectious Disease Society position paper. *Can. J. Infect. Dis.* 12, 218–231 (2001).
5. Blondeau J, Tillotson GS. A critical review of the changing etiology of community-acquired pneumonia and the clinical impact of antimcrobial resistance. *Chest* 118, S235 (2000).
6. Blondeau BJ. The evolution and role of macrolides in infectious diseases. *Expert Opin. Pharmacother.* 3, 1131–1151 (2002).
7. Blondeau BJ, DeCarolis E, Metzler KL, Hansen G. The macrolides. *Expert Opin. Investig. Drugs* 11, 189–215 (2002).
8. Kirst HA, Sides GD. New directions for macrolide antibiotics: structure modifications and *in vitro* activity. *Antimicrob. Agents Chemother.* 33, 1413–1418 (1989).
9. Drew RH, Gallis HA. Azithromycin – spectrum of activity, pharmacokinetics and clinical applications. *Pharmacotherapy* 12, 161–173 (1992).
10. Fiese EF, Steffen SH. Comparison of the acid stability of azithromycin and erythromycin A. *J. Antimicrob. Chemother.* 25, 39–47 (1990).
11. Periti P, Mazzie T, Mini E, Novelli A. Clinical pharmacokinetic properties of the macrolide antibiotics. Effects of age and various pathophysiological states. *Clin. Pharmacokinet.* 16, 193–214 (1989).
12. Retsema JA, Girard AE, Girard D, Milisen WB. Relationship of high tissue concentrations of azithromycin to bactericidal activity and effiacy *in vivo*. *J. Antimicrob. Chemother.* 25, 83–89 (1990).
13. Piscitelli SC, Danziger LH, Rodvold KA. Clarithromycin and azithromycin: new macrolide antibiotics. *Clin. Pharm.* 11, 137–152 (1992).
14. Fernandes PB, Hardy DJ. Comparative *in vitro* potencies of nine new macrolides. *Drugs Exp. Clin. Res.* 14, 445–451 (1988).
15. Finberg RW, Moellering Jr RC, Tally FP *et al.* The importance of bactericidal drugs: future directions in infectious disease. *Clin. Infect. Dis.* 39, 1314–1320 (2004).
16. Brisson-Noel A, Trieu-Cuot P, Courvalin P. Mechanism of action of spiramycin and other macrolides. *J. Antimicrob. Chemother.* 22, 13–23 (1988).
17. Weisblum B. Inducible resistance to macrolides, lincosamides and streptogramin type B antibiotics: the resistance phenotype, its biological diversity and structural elements that regulate expression – a review. *J. Antimicrob. Chemother.* 16, 63–90 (1985).
18. Menninger JR. Functional consequences of binding macrolides to ribosomes. *J. Antimicrob. Chemother.* 16, 23–34 (1985).
19. Retsema JA, Girard AE, Schelkly W *et al.* Spectrum and mode of action of azithromycin (CP-62,993), a new 15-membered-ring macrolide with improved potency against gram-negative organisms. *Antimicrob. Agents Chemother.* 31, 1939–1947 (1987).
20. Eisenberg E, Barza M. Azithromycin and clarithromycin. *Curr. Clin. Top. Infect. Dis.* 14, 52–79 (1994).
21. Eady EA, Ross JI, Cove JH. Multiple mechanisms of erythromycin resistance. *J. Antimicrob. Chemother.* 26, 461–465 (1990).
22. Amsden GW. Pneumococcal macrolide resistance – myth or reality? *J. Antimicrob. Chemother.* 41, 1–6 (1999).
23. Foster TJ. Plasmid-determined resistance to antimicrobial drugs and toxic metal ions in bacteria. *Microbiol. Rev.* 47, 361–409 (1983).
24. Fernandes PB, Baker WR, Freiberg LA *et al.* New macrolides active against Streptococcus pyogenes with inducible or constitutive type of macrolide–lincosamide–streptogramin B resistance. *Antimicrob. Agents Chemother.* 33, 78–81 (1989).
25. Blondeau JM. *Appropriate Antibiotic Use – Past Lessons Provide Future Directions.* International Congress and Symposium Series, Royal Society of Medicine Press Limited 1–10 (2001).
26. Hoban DJ, Wierzbowski AK, Nichol KA, Zhanel GG. Macrolide-resistant *Streptococcus pneumoniae* in Canada during 1998–1999: prevalence of mef(A) and erm(B) and susceptibilities to ketolides. *Antimicrob. Agents Chemother.* 45, 2147–2150 (2001).
27. Sahm DF, Jones ME, Hickey ML, Diankun DR, Mani SV, Thornsberry C. Resistance surveillance of *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* isolated in Asia and Europe, 1997–1998. *J. Antimicrob. Chemother.* 45, 457–466 (2000).
28. Blondeau JM, Vaughan D, Laskowski R, Borsos S, Group TCAS. Susceptibility of Canadian isolates of *Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pneumoniae* to oral antimicrobial agents. *Int. J. Antimicrob. Agents* 17, 457–464 (2001).
29. Thornsberry C, Ogilvie P, Kahn J, Mauriz Y, Group TLI. Surveillance of antimicrobial resistant in *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* in the United States in 1996–1997 respiratory season. *Diagn. Microbiol. Infect. Dis.* 29, 249–257 (1997).
30. Jones RN, Jacobs MR, Washington JA, Pfaller MA. A 1994–95 survey of *Haemophilus influenzae* susceptibility to ten orally administered agents: a 187 clinical laboratory center sample in the United States. *Diagn. Microbiol. Infect. Dis.* 27, 75–83 (1997).

31. Felmingham D, Robbins MJ, Tesfaslasie Y, Harding I, Shrimpton S, Gruneberg RN. Antimicrobial susceptibility of community-acquired lower respiratory tract bacterial pathogens isolated in the UK during the 1995–1996 cold season. *J. Antimicrob. Chemother.* 41, 411–415 (1998).
32. Felmingham D, Washington JA, Group TAP. Trends in the antimicrobial susceptibility of bacterial respiratory tract pathogens – findings of the Alexander Project 1992–1996. *J. Chemother.* 11, 5–21 (1999).
33. Mathai D, Lewis MT, Kugler K, Pfaller MA, Jones RN, SENTRY Participants Group of North America. Antibacterial activity of 41 antimicrobials tested against over 2773 bacterial isolates from hospitalized patients with pneumonia: I-results from the SENTRY Antimicrobial Surveillance Program (North America, 1998). *Diagn. Microbiol. Infect. Dis.* 39, 105–116 (2001).
34. Felmingham D, Gruneberg RN. *Comparative in vitro activity of 16 antimicrobials against 5442 community-acquired, lower respiratory tract pathogens: the Alexander Project 1997*, in 36th IDSA, Denver, CO, USA (1998).
35. Doern GV, Heilmann KP, Huynh HK, Rhomberg PR, Coffman SL, Brueggemann AB. Antimicrobial resistance among clinical isolates of *Streptococcus pneumoniae* in the United States during 1999–2000, including a comparison of resistance rates since 1994–1995. *Antimicrob. Agents Chemother.* 45, 1721–1729 (2001).
36. Doern GV, Richter SS, Miller A *et al.* Antimicrobial resistance among *Streptococcus pneumoniae* in the United States: have we begun to turn the corner on resistance to certain antimicrobial classes? *Clin. Infect. Dis.* 41, 139–148 (2005).
37. Shortrige D, Urban C, Rahal JJ, Mariano N, Ramer N, Tanaka SK. Prevalence of ermA and mefE in penicillin resistant *Streptococcus pneumoniae*. In: *4th International Conference on the Macrolides, Azalides, Streptogramins and Ketolides*, Wallace Communications Inc, Atlanta, GA, Barcelona, Spain (1998).
38. Marchese A, Schito GC, Tomasz A. Preponderance of multidrug-resistant clones among penicillin resistant isolates of *Streptococcus pneumoniae* from Italy., in *4th International Conferenece on the Macrolides, Azalides, Streptogramins and Ketolides.* Wallace Communications Inc. Atlanta, GA, Barcelona, Spain (1998).
39. Tonoli E, Marchese A, Debbia EA, Schito GC. Prevalence and characterization of the mechanisms of macrolide resistance in 830 penicillin-susceptible *Streptococcus pneumoniae* isolated in Italy during 1993–1997. In: *4th International Conference on the Macrolides, Azalides and Ketolides*, Wallace Communications, Inc. Atlanta, GA, Barcelona, Spain (1998).
40. Baquero F. Evolving resistance patterns of *Streptococcus pneumoniae*: a link with long-acting macrolide consumption? *J. Chemother.* 11, 35–43 (1999).
41. Blondeau JM. Differential impact on macrolide compounds in the selection of macrolide nonsusceptible *Streptococcus pneumoniae. Therapy* 2, 813–818 (2005).
42. Blondeau JM, Metzler KL, Hedlin P, Hansen G, Drlica K. Comparison of the mutant prevention concentration of gatifloxacin, garenoxacin, gemifloxacin, levofloxacin and moxifloxacin against clinical isolates of *Streptococcus pneumoniae* collected prior to (1994–97) and after 1997 (1997–2003). In: *14th European Congress of Clinical Microbiology and Infectious Diseases*, Prague, Czech Republic (2004).
43. Blondeau JM, Borsos S, Hesje C, Blondeau LD. The killing of multidrug resistant *Streptococcus pneumoniae* (MDRSP) by gatifloxacin (GA), gemifloxacin (GM), levofloxacin (Lfx) and moxifloxacin (Mfx) over a range of bacterial inoculums using 2 different drug concentrations. In: *World Conference on Magic Bullets* – to Celebrate Paul Ehrlich's 150th Birthday, Nurnberg, Germany (2004).
44. Blondeau JM, Hansen G, Metzler KL, Hedlin P. The role of PK/PD parameters to avoid selection and increase of resistance: mutant prevention concentration. *J. Chemother.* 16, 1–19 (2004).
45. Zhanel GG, Palatnick L, Nichol KA, Bellyou T, Low DE, Hoban DJ. Antimicrobial resistance in respiratory tract *Streptococcus pneumoniae* isolates: results of the Canadian Respiratory Organism Susceptibility Study, 1997 to 2002. *Antimicrob. Agents Chemother.* 47, 1867–1874 (2003).
46. Bingen E, Lambert-Zechovsky N, Mariani-Kurkdjian P *et al.* Bacterial counts in cerebrospinal fluid of children with meningitis. *Eur. J. Clin. Microbiol. Infect. Dis.* 9, 278–281 (1990).
47. Feldman W. Concentrations of bacteria in cerebrospinal fluid of patients with bacterial meningitis. *J. Pediatr.* 88, 549–552 (1976).
48. Mitchison DA. Drug resistance in mycobacteria. *Br. J. Bull.* 50, 84–90 (1984).
49. Firsch AW, Tripp JT, Barrett Jr CD, Pidgeon BE. Specific polysaccaride content of pneumoni lungs. *J. Exp. Med.* 76, 505–510 (1942).
50. Blondeau JM, Borsos S. Comparative minimum inhibitory and resistance prevention concentrations (RPC) of azithromycin (AZ), clarithromycin (C) and erythromycin (E) against 191 susceptible strains of *Streptococcus pneumoniae* (SP). In: *45th Interscience Conference on Antimicrobial Agents and Chemotherapy*, American Society of Microbiology, Washington, DC, USA (2005).
51. Vanderkooi OG, Low DE, Green K, Powis JE, McGeer A. Predicting antimicrobial resistance in invasive pneumococcal infections. *Clin. Infect. Dis.* 40, 1288–1297 (2005).
52. Garcia-Rey C, Aguilar L, Baquero F, Casal J, Martin JE. Pharmacoepidemiological analysis of provincial differences between consumption of macrolides and rates of erythromycin resistance among Streptococcus pyogenes isolates in Spain. *J. Clin. Microbiol.* 40, 2959–2963 (2002).
53. Pihlajamaki M, Kotilainen P, Kaurila T, Klaukka T, Palva EPH. Macrolide-resistant *Streptococcus pneumoniae* and use of antimicrobial agents. *Clin. Infect. Dis.* 33, 483–488 (2001).
54. Granizo JJ, Aguilar L, Casal J, Garcia-Rey C, Dal Re R, Baquero F. *Streptococcus pneumoniae* resistance to erythromycin and penicillin in relation to macrolide and B-lactam consumption in Spain (1979–1997). *J. Antimicrob. Chemother.* 46, 767–773 (2000).
55. Reinert RR, Lahham AL, Lemperle M *et al.* Emergence of macrolide and penicillin resistance among invasive pneumococcal isolates in Germany. *J. Antimicrob. Chemother.* 49, 61–68 (2002).
56. Kastner U, Guggenbichler JP. Influence of macrolide antibiotics on promotion of resistance in the oral flora of children. *Infection* 5, 251–256 (2001).
57. Davidson RJ, Chan CCK, Doern GV, Zhanel GG. Macrolide-resistant *Streptococcus pneumoniae* in Canada: correlation with azithromycin use. *Clin. Microbiol. Infect.* 9, 240–241 (2003).
58. Davidson RJ, Cavalcanti R, Brunton JL *et al.* Resistance to levofloxacin and failure of treatment of *pneumococcal pneumonia*. *N. Engl. J. Med.* 346, 747–750 (2002).
59. Doern GV. Antimicrobial use and the emergence of antimicrobial resistance with *Streptococcus pneumoniae* in the United States. *Clin. Infect. Dis.* 33, S187–S192 (2001).
60. Diekema DJ, Brueggemann AB, Doern GV. Antimicrobial-drug use and changes in resistance in *Streptococcus pneumoniae*. *Emerg. Infect. Dis.* 6, 552–556 (2000).

61. Leach AJ, Shelby-James TM, Mayo M *et al.*: A prospective study of the impact of community-acquired azithromycin treatment of trachoma on carriage and resistance of *Streptococcus pneumoniae*. *Clin. Infect. Dis.* 24, 356–362 (1997).
62. Edelstein PH. Predicting the emergence of antimicrobial resistance (correspondence). *Clin. Infect. Dis.* 34, 1418 (2002).
63. Doern GV. Predicting the emergence of antimicrobial resistance (reply). *Clin. Infect. Dis.* 34, 1418–1420 (2002).
64. Ghaffar F, Muniz LS, Katz K *et al.* Effects of amoxicillin/clavulanate or azithromycin on nasopharyngeal carriage of *Streptococcus pneumoniae* and *Haemophilus influenzae* in children with acute otitis media. *Clin. Infect. Dis.* 31, 875–880 (2000).
65. Gray GC, Witucki PJ, Gould MT *et al.* Randomized placebo-controlled clinical trial of oral azithromycin prophylaxis against respiratory infections in a high-risk, young adult population. *Clin. Infect. Dis.* 33, 983–990 (2001).
66. Hyde TB, Gay K, Stephens DS *et al.* Macrolide resistance among invasive *Streptococcus pneumoniae* isolates. *JAMA* 286, 1857–1862 (2001).
67. Garcia-Rey C, Aguilar L, Baquero F *et al.* Importance of local variations in antibiotic consumption and differences in erythromycin and penicillin resistance in *Streptococcus pneumoniae*. *J. Clin. Microbiol.* 40, 159–164 (2002).
68. Foulds G, Shepard RM, Johnson RB. The pharmacokinetics of azithromycin in human serum and tissues. *J. Antimicrob. Chemother.* 25, 73–82 (1990).
69. Patel KB, Xuan D, Tessier PR *et al.* Comparison of bronchopulmonary pharmacokinetics of clarithromycin and azithromycin. *Antimicrob. Agents Chemother.* 40, 2375–2379 (1996).
70. Conte Jr JE, Golden J, Duncan S *et al.* Single dose intrapulmonary pharmacokinetics of azithromycin, clarithromycin, ciprofloxacin and cefuroxime in volunteer subjects. *Antimicrob. Agents Chemother.* 40, 1617–1622 (1996).
71. Rodvold KA, Gotfried M, Danziger LH, Servi R. Intrapulmonary steady-state concentrations of clarithromycin and azithromycin in healthy adult volunteers. *Antimicrob. Agents Chemother.* 41, 1399–1402 (1997).
72. Gordon EM, Blumer JL. Rationale for single and high dose treatment regimens with azithromycin. *Pediatr. Infect. Dis. J.* 23, S102–S107 (2004).
73. Cornish P. The new macrolides: azithromycin and clarithromycin. *J. Clin. Pharmacol.* 2, 153–166 (1995).
74. Girard AE, Girard A, English AR *et al.* Pharmacokinetic and *in vivo* studies with azithromycin (CP-62,993), a new macrolide with an extended half-life and excellent tissue distribution. *Antimicrob. Agents Chemother.* 31, 1948–1954 (1987).
75. Cooper MA, Nye K, Andrews JM *et al.* The pharmacokinetics and inflammatory fluid penetration of orally administered azithromycin. *J. Antimicrob. Chemother.* 26, 533–538 (1990).
76. Thakker K, Caridi F, Powell M, Chung M. Multiple dose pharmacokinetics of azithromycin following 1 hour intravenous infusions in hospitalized patients with community-acquired pneumonia (abstract). *Antimicrob. Agents Chemother.* 37, 24 (1997).
77. Gladue RP, Snider ME. Intracellular accumulation of azithromycin by cultured human fibroblasts. *Antimicrob. Agents Chemother.* 34, 1056–1060 (1990).
78. Lalak NJ, Morris DL. Azithromycin clinical pharmacokinetics. *Clin. Pharmacokinet.* 25, 370–374 (1993).
79. Bermudez LE, Inderlied C, Young LS. Stimulation with cytokines enhances penetration of azithromycin into human macrophages. *Antimicrob. Agents Chemother.* 35, 2625–2629 (1991).
80. Gladue RP, Bright GM, Isaacson RE, Newborg MF. *In vitro* and *in vivo* uptake of azithromycin (CP-62, 993) by phagocytic cells: possible mechanism of delivery and release at sites of infection. *Antimicrob. Agents Chemother.* 33, 277–282 (1989).
81. Chu S, Deaton R, Cavanaugh JC. Absolute bioavailability of clarithromycin after oral administration in humans. *Antimicrob. Agents Chemother.* 36, 1147–1150 (1992).
82. Neu HC. The development of macrolides: clarithromycin in perspective. *J. Antimicrob. Chemother.* 27, 1–9 (1991).
83. Ferrero JL, Bopp BA, Marsh KC *et al.* Metabolism and disposition of clarithromycin in man. *Drug Metab. Dispos.* 18, 441–446 (1990).
84. Le Bel M. Clinical pharmacokinetics of new macrolides. *Can. J. Infect. Dis.* 4, 10A–12A (1993).
85. Chu S, Park Y, Locke C, Wilson DS, Cavanaugh JC. Drug–food interaction potential of clarithromycin, a new macrolide antimicrobial. *J. Clin. Pharmacol.* 32, 32–36 (1992).
86. MacLeod C, Schotzinger RJ, Van Hove GF, Bachand RT. Pharmacokinetics and safety of a once-daily clarithromycin formulation. *Adv. Ther.* 11, 11–27 (1999).
87. Periti P, Mazzie T. Clarithromycin: pharmacokinetic and pharmacodynamic interrelationships and dosage regimen. *J. Chemother.* 11, 11–27 (1999).
88. Hardy DJ, Guay DRP, Jones RN. Clarithromycin, a unique macrolide: a pharmacokinetic, microbiological and clinical overview. *Diagn. Microbiol. Infect. Dis.* 15, 39–53 (1992).
89. Chu S, Granneman GR, Pichotta P, Decourt JP, Girault J, Fourtillan JB. Effect of moderate or severe hepatic impairment on clarithromycin pharmacokinetics. *J. Clin. Pharmacol.* 33, 480–485 (1993).
90. Kohno Y, Yoshida H, Suwa T, Suga T. Comparative pharmacokinetics of clarithromycin (TE-031), a new macrolide antibiotic, and erythromycin in rats. *Antimicrob. Agents Chemother.* 33, 751–756 (1989).
91. Kohno Y, Yoshida H, Suwa T, Suga T. Uptake of clarithromycin by rat lung cells. *J. Antimicrob. Chemother.* 26, 503–513 (1990).
92. Kohno Y, Ohta K, Suwa T, Suga T. Autobacteriographic studies of clarithromycin and erythromycin in mice. *Antimicrob. Agents Chemother.* 34, 562–567 (1990).
93. Suwa T, Yoshida H, Fukushima T, Nagate T. Metabolic fate of TE-031 (A-56268) I. Comparative pharmacokinetics of TE-031 and erythromycin stearate in rats and mice. *Chemotherapy* 36, 198–204 (1988).
94. Hopkins S. Clinical toleration and safety of azithromycin. *Am. J. Med.* 91, 40S–45S (1991).
95. Guay DRP. Pharmacokinetics of new macrolides. *Infect. Med.* 9, 31–38 (1992).
96. Alvarez-Elcoro S, Enzler MJ. The macrolides: erythromycin, clarithromycin and azithromycin. *Mayo Clin. Proc.* 74, 613–634 (1999).
97. Hopkins S. Clinical toleration and safety of azithromycin in adults and children. *Rev. Contemp. Pharmacother.* 5, 383–389 (1994).
98. Guay DRP, Patterson DR, Seipman N, Craft JC. Overview of the tolerability profile of clarithromycin in preclinical and clinical trials. *Drug Saf.* 8, 350–364 (1993).
99. Anderson G, Esmonde TS, Coles S, Macklin J, Carnegie C. A comparative safety and efficacy study of clarithromycin and erythromycin stearate in community-acquired pneumonia. *J. Antimicrob. Chemother.* 27, 117–124 (1991).

100. Wallace Jr RJ, Brown BA, Griffith DE. Drug intolerance to high-dose clarithromycin among elderly patients. *Diagn. Microbiol. Infect. Dis.* 16, 215–221 (1993).
101. Yew WW, Chau CH, Lee J, Leung CW. Cholestatic hepatitis in a patient who received clarithromycin therapy for a *Mycobacterium chelonae* lung infection (letter). *Clin. Infect. Dis.* 18, 1025–1026 (1994).
102. Shaheen N, Grimm IS. Fulminant hepatic failure associated with clarithromycin. *Am. J. Gastroenterol.* 91, 394–395 (1996).
103. Liviu L, Yair L, Yehuda S. Pancreatitis induced by clarithromycin (letter). *Ann. Intern. Med.* 125, 701 (1996).
104. Pijpers E, Van Rijswijk RE, Takx-Kohlen B, Schrey G. A clarithromycin induced myasthenic syndrome. *Clin. Infect. Dis.* 22, 175–176 (1996).
105. Periti P, Mazzie T, Mini E, Novelli A. Pharmacokinetic drug interactions of macrolides. *Clin. Pharmacokinet.* 23, 106–131 (1992).
106. Watkins VS, Polk RE, Stotka JL. Drug interactions of macrolides: emphasis on dirithromycin. *Ann. Pharmacotherapy* 31, 349–356 (1997).
107. Ludden TM. Pharmacokinetic interactions of the macrolide antibiotics. *Clin. Pharmacokinet.* 10, 63–79 (1985).
108. Nawarskas JJ, McCarthy DM, Spinler SA. Digoxin toxicity secondary to clarithromycin therapy. *Ann. Pharmacotherapy* 31, 864–866 (1997).
109. Spicer ST, Liddle C, Chapman JR *et al.* The mechanism of cyclosporine toxicity induced by clarithromycin. *Br. J. Clin. Pharmacol.* 43, 194–186 (1997).
110. Brown BA, Wallace Jr. RJ, Griffith DE, Warden R. Clarithromycin-associated digoxin toxicity in the elderly. *Clin. Infect. Dis.* 24, 92–93 (1997).
111. Paar D, Terjung B, Sauerbruch T. Life-threatening interaction between clarithromycin and disopyramide (letter). *Lancet* 349, 326–327 (1997).
112. Grau E, Real E, Paster E. Interaction between clarithromycin and oral anticoagulants (letter). *Ann. Pharmacotherapy* 30, 1495–1496 (1996).
113. Gillum JG, Israel DS, Scott RB, Climo MW, Polk RE. Effect of combination therapy with ciprofloxacin and clarithromycin on theophylline pharmacokinetics in healthy volunteers. *Antimicrob. Agents Chemother.* 40, 1715–1716 (1996).
114. Bedford TA, Rowbotham DJ. Cisapride: drug interactions of clinical significance. *Drug Saf.* 15, 167–175 (1996).
115. Yeates RA, Laufen H, Zimmermann T. Interaction between madazolam and clarithromycin: comparison with azithromycin. *Int. J. Clin. Pharmacol. Ther.* 34, 400–405 (1996).
116. Sketris IS, Wright MR, West ML. Possible role of the intestinal P-450 enzyme system in a cyclosporine–clarithromycin interaction. *Pharmacotherapy* 16, 301–305 (1996).
117. Vance E, Watson-Bitar M, Gustavson LE, Kazanijan P. Pharmacokinetics of clarithromycin and zidovudine in patients with AIDS. *Antimicrob. Agents Chemother.* 39, 1355–1360 (1995).
118. Gustavson LE, Chu SY, Mackenthum A, Gupta SD, Craft JC. Drug interaction between clarithromycin and oral zidovudine in HIV-1 infected patients (abstract). *Clin. Pharmacol. Ther.* 53, 163 (1993).
119. Vance E, Guzman J, Bitar M, Kazanijan P. Clarithromycin and zidovudine pharmacokinetic study (abstract). Presented at: International Conference on AIDS, pp. 201 (1994).
120. Polis MA, Piscitelli SC, Vogel S *et al.* Clarithromycin lowers plasma zidovudine levels in persons with human immunodeficiency virus infection. *Antimicrob. Agents Chemother.* 41, 1709–1714 (1997).
121. Gillum JG, Bruzzese VL, Israel DS, Kaplowitz LG, Polk RE. Effect of clarithromycin on the pharmacokinetics of 2′, 3′-dideoxyinosine in patients who are seropositive for human immunodeficiency virus. *Clin. Infect. Dis.* 22, 716–718 (1996).
122. McLinn S, Williams DJ. Incidence of antibiotic resistant *Streptococcus pneumoniae* and β-lactamase-positive *Haemophilus influenzae* in clinical isolates from patients with otitis media. *Pediatr. Infect. Dis. J.* 15, S3–9 (1996).
123. Ferwarda A, Moll HA, Hop WC *et al.* Efficacy, safety and tolerability of 3 day azithromycin versus 10 day co-amoxiclav in the treatment of children with acute lower respiratory tract infections. *J. Antimicrob. Chemother.* 47, 441–446 (2001).
124. Arguedas A, Loaiza C, Perez A, Gutierrez A, Herrera ML, Rothermel CD. A pilot study of single-dose azithromycin versus 3-day azithromycin or single-dose ceftriaxone for uncomplicated acute otitis media in children. *Curr. Ther. Res. Clin. Exp.* 64, A-16–29 (2003).
125. Dunne MW, Khurana C, Mohs AA *et al.* Efficacy of single dose azithromycin in the treatment of acute otitis media in children receiving a baseline tympanocentesis. *Antimicrob. Agents Chemother.* 47, 2663–2665 (2003).
126. Block SL, Arrieta A, Seibel M, McLinn S, Eppes S, Murphy MJ. Single-dose (30 mg/kg) azithromycin compared with 10-day amoxicillin/clavulanate for the treatment of uncomplicated acute otitis media. *Curr. Ther. Res. Clin. Exp.* 64, A30–42 (2003).
127. Arguedas A, Loaiza C, Soley C. Single dose azithromycin for the treatment of uncomplicated otitis media. *Pediatr. Infect. Dis. J.* 23, S108–S114 (2004).
128. Subcommittee on Management of Acute Otitis Media: Diagnosis and management of acute otitis media. *Pediatrics* 113, 1451–01465 (2004).
129. American Thoracic Society: Guidelines for the initial management of adults with community-acquired pneumonia: diagnosis, assessment of severity and initial antimicrobial therapy. *Am. Rev. Respir. Dis.* 148, 1418–1426 (1993).
130. Fang GD, Fine M, Orloff J *et al.* New and emerging etioilogies for community-acquired pneumonia with implications for therapy: a prospective multicenter study of 359 cases. *Medicine (Baltimore)* 69, 307–316 (1999).
131. Bartlett JG. Empirical therapy of community-acquired pneumonia: macrolides are not ideal choices. *Semin. Respir. Infect.* 12, 329–333 (1997).
132. Vergis EN, Yu VL. Macrolides are ideal for empiric therapy of community-acquired pneumonia in the immunocompetent host. *Semin. Respir. Infect.* 12, 322–328 (1997).
133. Bartlett JG, Dowell SF, Mandell LA, File Jr TM. Practice guidelines for the management of community-acquired pneumonia in adults. *Clin. Infect. Dis.* 31, 347–382 (2000).
134. Bartlett JG, Breiman RF, Mandella LA *et al.* Community-acquired pneumonia in adults: guidelines for management. *Clin. Infect. Dis.* 26, 811 (1998).
135. Lubin JH. Analysis under Cox's failure time model using weighted last squares. *Biometrics* 36, 307–312 (1980).
136. Baddour LM, Yu VL, Klugman KP *et al.*, International Study Group. Combination antibiotic therapy lowers mortality among severely ill patients with pneumococcal bacteremia. *Am. J. Respir. Clin. Care Med.* 170, 440–444 (2004).
137. Waterer GW, Somes GW, Wunderink RG. Monotherapy may be suboptimal for severe bacteremic *pneumococcal pneumonia*. *Arch. Intern. Med.* 161, 1837–1842 (2001).
138. Mandell LA, Marrie TJ, Grossman RF, Chow AW, Hyland RH, The Canadian Community-Acquired Pneumonia Working

Group: Canadian guidelines for the initial management of community-acquired pneumonia: an evidence-based update by the Canadian Infectious Diseases Society and the Canadian Thoracic Society. *Clin. Infect. Dis.* 31, 383–421 (2000).

139. Mandell LA, Bartlett JG, Dowell SF, File Jr TM, Musher DM. Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. *Clin. Infect. Dis.* 37, 1405–1433 (2003).
140. Balmes P, Clerc G, Dupont B *et al.* Comparative study of azithromycin and amoxicillin/clavulanic acid in the treatment of lower respiratory tract infections. *Eur. J. Clin. Microbiol. Infect. Dis.* 10, 437–439 (1991).
141. Dark D. Multicenter evaluation of azithromycin and cefaclor in acute lower respiratory tract infections. *Am. J. Med.* 91, 31S–35S (1991).
142. Schonwald S, Gunjaca M, Kolacny-Babic L, Car V, Gosev M. Comparison of azithromycin and erythromycin in the treatment of atypical pneumonia. *J. Antimicrob. Chemother.* 25, 123–126 (1990).
143. Kinasewitz G, Wood RG. Azithromycin versus cefaclor in the treatment of acute bacterial pneumonia. *Eur. J. Clin. Microbiol. Infect. Dis.* 10, 872–877 (1991).
144. Bohte R, Van'Twout JW, Lobatto S *et al.* Efficacy and safety of azithromycin versus benzylpenicillin or erythromycin in community-acquired pneumonia. *Eur. J. Clin. Microbiol. Infect. Dis.* 14, 182–187 (1995).
145. Ramirez J, Unowsky J, Talbot GH, Zhang H, Townsend L. Sparfloxacin versus clarithromycin in the treatment of community-acquired pneumonia. *Clin. Ther.* 21, 103–117 (1999).
146. Fogarty C, Grossman C, Williams J *et al.* Efficacy and safety of moxifloxacin vs clarithromycin for community-acquired pneumonia. *Infect. Med.* 16, 748–763 (1999).
147. Patel T, Desai R, Duff J *et al.* Comparison of grepafloxacin with clarithromycin in the treatment of community-acquired pneumonia. Presented at: *37th Interscience Conference on Antimicrobial Agents and Chemotherapy, American Society for Microbiology*, Washington, DC, Toronto, Ontario, Canada (1997).
148. Sullivan J, Gezon D, Hopkins WW. A double-blind, randomized, multicenter study in ambulatory community-acquired pneumonia comparing trovafloxacin with clarithromycin. Presented at: *37th Interscience Conference on Antimicrobial Agents and Chemotherapy, American Society of Microbiology*, Washington, DC, Toronto, Ontario, Canada (1997).
149. Chien SM, Pichotta P, Siepman N, Canada-Sweden Clarithromycin Pneumonia Study Group *et al.* Treatment of community-acquired pneumonia: a multicenter, double-blind randomized study comparing clarithromycin with erythromycin. *Chest* 103, 697–701 (1993).
150. Neu HC, Chick TW. Efficacy and safety of clarithromycin compared to cefixime as outpatient treatment of lower respiratory tract infections. *Chest* 104, 1393–1399 (1993).
151. O'Doherty B, Muller O. Randomized, multicenter study of the efficacy and tolerance of azithromycin versus clarithromycin in the treatment of adults with mild to moderate community-acquired pneumonia – Azithromycin Study Group. *Eur. J. Clin. Microbiol. Infect. Dis.* 17, 828–833 (1998).
152. Charles L, Segreti J. Choosing the right macrolide antibiotic. A guide to selection. *Drugs* 53, 349–357 (1997).
153. D'Ignazio J, Camere MA, Lewis DE, Jorgensen D, Breen JD. Novel, single-dose microsphere formulation of azithromycin versus 7-day levofloxacin therapy for treatment of mild to moderate community-acquired pneumonia in adults. *Antimicrob. Agents Chemother.* 49, 4035–4041 (2005).
154. Tatum M, Amsden GW. Novel, single-dose microsphere formulation of azithromycin extended-release for the treatment of respiratory tract infections. *Therapy* 3, 357–363 (2006).
155. Drehobl MA, De Salvo MC, Lewis DE, Breen JD. Single-dose azithromycin microspheres vs clarithromycin extended release for the treatment of mild to moderate community-acquired pneumonia in adults. *Chest* 128, 2230–2237 (2005).
156. Stahl JE, Barza M, Desjardin J, Martin R, Eckman MH. Effect of macrolides as part of initial empiric therapy on length of stay in patients hospitalized with community-acquired pneumonia. *Arch. Intern. Med.* 159, 2576–2580 (1999).
157. Gleason PP, Meehan TP, Fine JM, Galusha DH, Fine JM, Fine MJ. Associations between initial antimicrobial therapy and medical outcomes for hospitalized elderly patients with pneumonia. *Arch. Intern. Med.* 159, 2562–2572 (1999).
158. Prentice RL, Kalbfleisch JD. Hazard rate models with covariates. *Biometrics* 35, 25–39 (1979).
159. Marston BJ, Plouffe JF, File Jr TM, The Community Based Pneumonia Incidence Study Group *et al.* Incidence of community-acquired pneumonia requiring hospitalization: results of a population-based active surveillance study in Ohio. *Arch. Intern. Med.* 157, 1709–1718 (1997).
160. Stephenson J. Studies suggest a darker side of "benign" microbes. *JAMA* 38, 1873–1878 (1997).
161. Taylor-Robinson D. Infections due to species of Mycoplasma and Ureaplasma: an update. *Clin. Infect. Dis.* 23, 671–684 (1996).
162. Hammerschlag MR. Antimicrobial susceptibility and therapy of infections caused by *Chlamydia pneumoniae*. *Antimicrob. Agents Chemother.* 38, 1873–1878 (1994).
163. Troy CJ, Peeling RW, Ellis AG *et al.* Chlamydia pneumoniae as a new source of infectious outbreaks in nursing homes. *JAMA* 277, 1214–1218 (1997).
164. Mertens JCC, Van Barneveld PWC, Asin HRG *et al.* Double-blind randomized study comparing the efficacies and safeties of a short (3-day) course of azithromycin and a 5-day course of amoxicillin in patients with acute exacerbations of chronic bronchitis. *Antimicrob. Agents Chemother.* 36, 1456–1459 (1992).
165. De Abate CA, Mathew CP, Warner JH, Heyd A, Church D. The safety and efficacy of short course (5-day) moxifloxacin versus azithromycin in the treatment of patients with acute exacerbation of chronic bronchitis. *Resp. Med.* 94, 1029–1037 (2000).
166. Anzueto A, Niederman MS, Tillotson GS, Bronchitis Study Group. Etiology, susceptibility and treatment of acute bacterial exacerbations of complicated chronic bronchitis in the primary care setting: ciprofloxacin 750 mg bid versus clarithromycin 500 mg bid. *Clin. Ther.* 20, 885–890 (1998).
167. De Abate CA, Herman-Gnjidic Z, Aneiro L, Haverstock DC, Church D. Moxifloxacin in acute exacerbations of chronic bronchitis – a bacteriological meta-analysis. Presented at: *21st International Congress of Chemotherapy*, Birmingham, England July 3rd–4th (1999).
168. Notario G, Siepman N, Devcich K, Guay DRP. Comparative safety and efficacy of clarithromycin and three oral cephalosporins in the treatment of outpatients with bacterial bronchitis. *Curr. Ther. Res. Clin. Exp.* 54, 628–640 (1993).
169. Anzueto A, Jenkinson SG, Clarithromycin Chronic Bronchitis Study Group. Safety and efficacy of clarithromycin versus cefuroxime

axetil in the treatment of acute bacterial exacerbation of chronic bronchitis. *Immunol. Infect. Dis.* 3, 231–237 (1993).
170. Pozzi E, Grossi E, Pecori A, The Azithromycin Research Group. Azithromycin verus clarithromycin in the treatment of acute exacerbations of chronic bronchitis. *Curr. Ther. Res. Clin. Exp.* 55, 759–764 (1994).
171. Zervos M, Breen JD, Jorgensen D, Goodrich JM. Novel, single-dose microsphere formulation of azithromycin versus levofloxacin for the treatment of acute exacerbations of chronic bronchitis. *Infect. Dis. Clin. Pract.* 13, 115–121 (2005).
172. Hooten TM. A comparison of azithromycin and penicillin V for the treatment of streptococcal pharyngitis. *Am. J. Med.* 91, 23–26 (1991).
173. Bachand RT. A comparative study of clarithromycin and penicillin VK in the treatment of outpatients with streptococcal pharyngitis. *J. Antimicrob. Chemother.* 27, 75–82 (1991).
174. Bachand RT. Comparative study of clarithromycin and ampicillin in the treatment of patients with acute exacerbations of chronic bronchitis. *J. Antimicrob. Chemother.* 27, 91–100 (1991).
175. Gooch WM, Gan VN, Corder WT *et al.* Clarithromycin and cefaclor suspensions in the treatment of acute otitis media in children *Pediatr. Infect. Dis. J.* 12, S128–133 (1993).
176. Kegel S, McCoig CC, Jorgensen D. Single-dose azithromycin in microspheres versus three-day azithromycin for the treatment of group A β-haemolytic streptococcal (GABHS) pharyngitis/tonsillitis in adults and adolescents. Presented at: *15th European Society of Clinical Microbiology and Infectious Diseases (ECCMID)*, Copenhagen, Denmark, April 2nd–5th (2005).
177. Schrock CG. Clarithromycin versus penicillin in the treatment of streptococcal pharyngitis. *J. Fam. Pract.* 35, 622–626 (1992).
178. Hadley JA, Benninger MS, Osquthorpe JD. Antimicrobial guidelines for acute and chronic rhinosinusitis: an update from the sinus and health partnership in conjunction with ARS in celebration of its 50th anniversary. *Otolaryngol. Head Neck Surg.* 131, 62 (2004).
179. Klossek JM, Federspil P. Update on treatment guidelines for acute bacterial sinusitis. *Int. J. Clin. Pract.* 59, 230–238 (2005).
180. Murray JJ, Emparanza P, Lesinskas E, Tawadrous M, Breen J. Efficacy and safety of a novel, single-dose azithromycin microsphere formulation versus 10 days of levofloxacin for the treatment of acute bacterial sinusitis in adults. *Otolaryngol. Head Neck Surg.* 133, 194–200 (2005).
181. Benson V, Marano MA. Current estimates from the National Health Interview Survey, 1995. *Vital Health Stat.* 10, 199 (1998).
182. Dunn CJ, Barradell LB. Azithromycin: a review of its pharmacological properties and use as 3-day therapy in respiratory tract infections. *Drugs* 51, 483–505 (1996).
183. McCarty JM, Phillips A, Wiisanen R. Comparative safefty and efficacy of clarithromycin in the treatment of acute otitis media in children. *Pediatr. Infect. Dis. J.* 12, S122–127 (1993).
184. Aspin MM, Hoberman A, McCarty JM *et al.* Comparative study of the safety and efficacy of clarithromycin and amoxicillin-clavulanate in the treatment of acute otitis media in children. *J. Pediatr.* 125, 136–141 (1994).
185. Ramet J. Comparative safety and efficacy of clarithromycin and azithromycin suspensions in the short course treatment of children with acute otitis media. *Clin. Drug Investig.* 9, 61–66 (1995).
186. Blondeau JM, Tillotson GS. Antibiotic dosing: do we dose to cure the individual or do we treat the greater societal needs? *Therapy* 2, 511–516 (2005).
187. Doern GV. How using a potent antibiotic reduces the risk of resistance. *J. Resp. Dis.* 35, S9–S14 (2004).
188. Carbon C, Poole MD. The role of newer macrolides in the treatment of community-acquired respiratory tract infection. A review of experimental and clinical data. *J. Chemother.* 11, 107–118 (1999).
189. McCarty JM, Hedrick J, Gooch WM. Clarithromycin suspension vs penicillin V suspension in children with streptococcal pharyngitis. *Adv. Ther.* 17, 14–26 (2000).
190. Casiano RR. Azithromycin and amoxicillin in the treatment of acute maxillary sinusitis. *Am. J. Med.* 91, 83–90 (1991).
191. Calhoun KH, Hokanson JA. Multicenter comparison of clarithromycin and amoxicillin in the treatment of acute maxillary sinusitis. *Arch. Fam. Med.* 2, 837–840 (1993).
192. Adelglass J, Jones TM, Ruoff G *et al.* A multicenter, investigator-blinded, randomized comparison of oral levofloxacin and oral clarithromycin in the treatment of acute bacterial sinusitis. *Pharmacotherapy* 18, 1255–1263 (1998).
193. Dubois J, Saint-Pierre C, Tremlay C. Efficacy of clarithromycin vs amoxicillin/clavulanate in the treatment of acute maxillary sinusitis. *Ear. Nose Throat J.* 72, 804–810 (1993).
194. Blondeau JM, Borsos S. Killing of Streptococcus pneumoniae by azithromycin, clarithromycin, telithromycin and gemifloxacin using the minimum inhibitory and mutant prevention drug concentration. *15th European Congress of Clinical Microbiology and Infectious Diseases.* Copenhagen, Denmark, 2–5 April, 2005. Poster session III.
195. Balter SM, La Forge J, Low DE, Mandell L, Grossman RF and the Chronic Bronchitis Working Group, on behalf of the Canadian Thoracic Society and the Canadian Infectious Disease Society: Canadian guidelines for the management of acute exacerbations of chronic bronchitis. *Can. Respir. J.* 10(Suppl. B), B3–B32 (2003).

Affiliation

Joseph M Blondeau
Department of Clinical Microbiology, Royal University Hospital & Saskatoon Health Region and Departments of Microbiology & Immunology & Pathology, University of Saskatchewan, 103 Hospital Drive, Saskatoon, Saskatchewan, S7N 0W8, Canada
Tel.: +1 306 655 6943
Fax: +1 306 655 6947
joseph.blondeau@saskatoonhealthregion.ca