

Macrolides: A Canadian Infectious Disease Society position paper

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Since the introduction of erythromycin in 1965, no new compounds from the macrolide antimicrobial class were licensed in Canada until the 1990s. Clarithromycin and azithromycin, since their introduction, have become important agents for treating a number of common and uncommon infectious diseases. They have become prime agents in the treatment of respiratory tract infections, and have revolutionized the management of both genital chlamydial infections, by the use of single-dose therapy with azithromycin, and nontuberculous mycobacterial infections, by the use of clarithromycin. The improvement of clarithromycin and azithromycin over the gastrointestinal intolerance of erythromycin has led to supplanting the use of the latter for many primary care physicians. Unfortunately, the use of these agents has also increased the likelihood for misuse and has raised concerns about a resultant increase in the rates of macrolide resistance in many important pathogens, such as *Streptococcus pneumoniae*. This paper reviews the pharmacology and evidence for the current indications for use of these newer agents, and provides recommendations for appropriate use.

Key Words: *Azithromycin; Clarithromycin; Erythromycin; Macrolides; Review; Therapeutic use*

Macrolides : Énoncé de position de la Société canadienne des maladies infectieuses

RÉSUMÉ : Depuis l'introduction de l'érythromycine en 1965, aucune nouvelle molécule de la classe des macrolides n'a été brevetée, soit depuis les années 1990. Depuis leur lancement, la clarithromycine et l'azithromycine sont devenues d'importants agents thérapeutiques pour de nombreuses maladies infectieuses courantes ou rares. On les utilise en effet comme agents de premier recours pour le traitement des infections respiratoires et elles ont révolutionné le traitement des infections génitales à Chlamydia par le recours à des posologies monodoses avec azythromycine, et les infections mycobactériennes non tuberculeuses par le recours à la clarithromycine. L'amélioration que représentent la clarithromycine et l'azythromycine par rapport à l'érythromycine, dont les effets secondaires gastro-intestinaux sont importants, a relégué cette dernière au second rang pour de nombreux omnipraticiens. Malheureusement, l'emploi de ces agents a également fait augmenter le risque de leur utilisation à mauvais escient et soulève des problèmes d'augmentation des taux de résistance aux macrolides que manifestent de nombreux agents pathogènes importants, comme *Streptococcus pneumoniae*. Cet article passe en revue les aspects pharmacologiques et les preuves sur lesquelles s'appuient les indications actuelles des agents plus récents et formule des recommandations pour leur utilisation appropriée.

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Erythromycin A is a naturally occurring, microbiologically active compound of the macrolide class of antibiotics. Chemical modification of erythromycin A's 14-membered lactone ring has led to the formation of semisynthetic derivatives with not only improved bioavailability and tolerability, but also expanded spectrums of microbiological activity and improved pharmacokinetic profiles. Such modifications produced clarithromycin, classified as a macrolide because it retains the central 14-membered lactone ring (1,2), and azithromycin, classified as an azalide due to its 15-membered aglycone ring (1). The latter two compounds are the newest agents in the macrolide class licensed for use in Canada. Roxithromycin and dirithromycin are available in other countries.

These compounds are clinically active against Gram-positive and Gram-negative cocci, and Gram-negative bacilli (primarily *Haemophilus influenzae*, *Legionella* species, *Moraxella catarrhalis*, *Campylobacter jejuni*, *Bordetella pertussis* and *Helicobacter pylori*). Azalides such as azithromycin have exhibited superior activity against Gram-negative pathogens and are generally less active against Gram-positive pathogens. Intracellular pathogens such as *Chlamydia* species, *Mycoplasma* species, *Ureaplasma* species, *Borrelia* species and nontuberculous mycobacteria species show varying susceptibilities. On the basis of their microbial activity, both the macrolides and azalides have been shown to be clinically useful in the treatment of uncomplicated skin and soft tissue infections, upper and lower respiratory tract infections, sexually transmitted *Chlamydia trachomatis* infection and peptic ulcer disease. Additionally, the improved pharmacokinetic profiles and acid stability exhibited by the newer agents may lead to enhanced patient adherence through less frequent dosing and improved bioavailability in the presence of food.

MECHANISMS OF ACTION AND RESISTANCE

Macrolides and azalides exert their antimicrobial activity by inhibiting translocation of aminoacyl transfer RNA through reversible binding to the 50S ribosomal subunit. In this manner, bacterial protein synthesis is inhibited (2). Generally, these agents are considered to be bacteriostatic. However, bactericidal activity has been demonstrated in vitro against certain strains of *Streptococcus pyogenes* and *Streptococcus pneumoniae*. Additionally, clarithromycin (and its active 14-hydroxy metabolite) and azithromycin have exhibited bactericidal activity against *H influenzae* (2). The antibacterial activity of clarithromycin and azithromycin is most likely enhanced by unique tissue distribution and elimination profiles, which result in high and sustained tissue levels relative to those produced with the use of erythromycin (3). These pharmacokinetics provide a probable explanation for the enhanced clinical activity of the newer agents against intracellular pathogens such as *Chlamydia* species (2,3).

Microbial resistance to macrolides and azalides may be either intrinsic or acquired in nature (4). At physiological pH, macrolides exhibit a low degree of ionization. The intrinsic resistance of the vast majority of Gram-negative bacilli and

enterococci to these hydrophobic drugs is believed to be due to outer membrane impermeability (2). Acquired resistance occurs most frequently via either the induction of enzymes causing ribosomal methylation, a target site modification or active efflux. Ribosomal target site modification is mediated by one of a number of *erm* genes (*ermA*, *ermB*, *ermC*, *ermTR*). These genes modify the ribosome through methylation of a specific adenine residue in a conserved region of the 23S ribosome that interacts with macrolide, lincosamide and streptogramin type B antibiotics, conferring the so-called 'MLS_B' phenotype (5). Macrolide, lincosamide and streptogramin (MLS) resistance typically results in high levels of resistance to all macrolides leading to erythromycin minimum inhibitory concentrations (MICs) of 64 mg/L or greater. Active efflux of macrolides and azalides has been demonstrated in both staphylococci and streptococci, and generally confers low level resistance to these drugs (4,6). In *Staphylococcus aureus*, efflux is mediated through *msrA* and *msrB* genes encoding an adenosine triphosphate-dependent efflux pump, and results in both macrolide and streptogramin resistance or the MS phenotype. In *S pneumoniae* and *S pyogenes*, the genes *mefE* and *mefA*, respectively, encode for two transporter efflux pumps (MefE and MefA) that confer resistance only to macrolides and azalides (6). The latter is referred to as the M phenotype. Macrolide modification or inactivation (eg, *Escherichia coli* production of erythromycin esterase) does occur but is rare in *S aureus*, and has not been described in *S pneumoniae* or *S pyogenes*. Macrolide resistance rates in Canada remain low and have not exceeded 10% among isolates of *S pneumoniae* (6). In a 1999 Canadian study of 121 macrolide-resistant *S pneumoniae* isolates, 50.4% possessed the M phenotype (*mefA*), while 45.5% demonstrated MLS resistance (*ermB*). Both resistance genes were found in 3.3% of isolates, while neither genetic determinant was found in 0.8% (7). In North America, macrolide resistance in *S pyogenes* remains at less than 3% (6).

IN VITRO ACTIVITY

Table 1 lists published MICs of erythromycin, clarithromycin and its active metabolite, where relevant, and azithromycin, for pathogens of clinical interest. Streptococci are usually susceptible to the macrolides and azalides; however, erythromycin and clarithromycin are generally more active than azithromycin. As noted previously, susceptibility of staphylococcal strains is extremely variable due to several possible mechanisms of resistance.

In certain cases, the in vivo activity of clarithromycin and azithromycin against Gram-negative and intracellular pathogens has been shown to be better than anticipated on the basis of in vitro data. For example, the activity of clarithromycin against *H influenzae* is enhanced in vivo by the microbiological activity of its metabolite, 14-hydroxycarithromycin. Other factors that may confound the interpretation of in vitro MIC data include the postulated postantibiotic effect, the effect of serum and the variability of activity according to the pH at the site of action (2).

TABLE 1
Published minimum inhibitory concentrations (mg/L) of erythromycin, clarithromycin (and 14-hydroxylclarithromycin [14-OH]) and azithromycin for pathogens of clinical interest

Pathogen	Erythromycin	Clarithromycin	Azithromycin
Gram-positive cocci			
<i>Staphylococcus aureus</i> (susceptible)	0.06 to 0.25	0.03 to 0.25 (same for 14-OH metabolite)	0.06 to 0.5
<i>S aureus</i> (inducible resistance)	4 to >128	4 to >128 (same for 14-OH metabolite)	4 to >128
<i>S aureus</i> (constitutive resistance)	>128	>128 (same for 14-OH metabolite)	>128
<i>Streptococcus pneumoniae</i>	0.01 to 0.06	<0.01 to 0.03	0.03 to 0.12
<i>Streptococcus agalactiae</i>	0.01 to 0.06	0.01 to 0.03	0.06 to 0.12
<i>Streptococcus pyogenes</i>	0.01 to 0.03	<0.01 to 0.03	0.03 to 0.12
Gram-negative cocci			
<i>Neisseria gonorrhoeae</i>	0.06 to 1	0.06 to 0.5	0.03 to 0.06
Gram-negative bacilli			
<i>Haemophilus influenzae</i>	0.5 to 4	1 to 8 (0.5 to 4 for 14-OH metabolite)	0.25 to 1
<i>Haemophilus ducreyi</i>	0.001 to 0.01	No data	0.001 to 0.004
<i>Moraxella catarrhalis</i>	0.03 to 0.25	0.03 to 0.25	0.03 to 0.06
<i>Bordetella pertussis</i>	0.008 to 0.03	0.008 to 0.03	0.01 to 0.03
<i>Helicobacter pylori</i>	0.12 to 0.25	0.03 to 0.06	0.25
Intracellular microorganisms			
<i>Legionella</i> species	0.25 to 2	0.03 to 0.06	0.03 to 0.5
<i>Mycoplasma pneumoniae</i>	0.008 to 0.03	0.002 to 0.008	<0.002 to 0.004
<i>Mycoplasma hominis</i>	>32	8 to 64	2 to 16
<i>Ureaplasma urealyticum</i>	0.12 to 2	0.015 to 0.25	0.12 to 1
<i>Chlamydia pneumoniae</i>	0.06 to 0.125	0.015 to 0.03 (0.015 for 14-OH metabolite)	0.06 to 1
<i>Chlamydia trachomatis</i>	0.06 to 1.02	0.007 to 0.008	0.032 to 1.02
<i>Mycobacterium avium</i> complex*	>8	0.25 to >8	>8
<i>Mycobacterium tuberculosis</i> *	>8	0.125 to >8	>8
<i>Mycobacterium kansasii</i> *	>8	0.5 to >8	4 to >8
<i>Mycobacterium chelonae</i> *	>8	0.5 to >8	>8
<i>Mycobacterium fortuitum</i> *	4 to >8	0.25 to >8	4 to >8
<i>Borrelia burgdorferi</i>	0.03 to 0.16	0.015 to 0.06	0.015 to 0.04

Unless otherwise specified, data taken from references 2, 8 and 93. *Data from reference 94

Inherent difficulties in the determination of MICs for intracellular pathogens also emphasize the need for cautious interpretation (8).

Mycoplasma pneumoniae is generally susceptible to the aforementioned macrolides and azithromycin. Both clarithromycin and azithromycin are active against certain pathogens involved in sexually transmitted disease; namely, *C trachomatis* and *Haemophilus ducreyi*.

Organisms of the *Mycobacterium avium* complex (MAC) are susceptible to both clarithromycin and azithromycin. Other nontuberculous mycobacteria, including *Mycobacterium kansasii*, *Mycobacterium simae*, *Mycobacterium xenopi* and *Mycobacterium malmoense*, have been shown to be susceptible in vitro to both azithromycin and clarithromycin in a beige mouse model of infection (9). Clarithromycin has been shown to possess broad in vitro activity against many nontuberculous mycobacteria, including *Mycobacterium scrofulaceum*, *Mycobacterium szulgai*, *M xenopi*, *Mycobacterium fortuitum* complex and *Mycobacterium marinum* (10). Neither new macrolide nor related compounds possess significantly important clinical activity against *Mycobacterium tuberculosis*.

Clarithromycin exhibits the greatest activity against *H pylori*, whereas both clarithromycin and azithromycin are active against *Borrelia burgdorferi*. Clarithromycin and azithromycin are each more active than erythromycin against *Legionella pneumophila*.

PHARMACOKINETICS

The oral bioavailability of erythromycin is variable, and depends on the presence of food and formulation administered. Erythromycin degrades rapidly in the presence of acid to form products devoid of antimicrobial activity. Unlike erythromycin, clarithromycin and azithromycin are stable in the presence of acid. Both are readily absorbed after oral administration. Food delays the time to peak serum concentrations of clarithromycin but does not affect the extent of absorption (bioavailability of 55%) (2,11). The bioavailability of azithromycin is approximately 37%; however, food can decrease this value by as much as 50%.

Erythromycin attains a peak serum concentration (C_{max}) of 1.8 mg/L approximately 1.7 h after oral administration (12). Clarithromycin reaches a C_{max} of 2.1 mg/L after a similar period of time. The peak concentration of azithromycin is

0.4 mg/L, achieved approximately 2.5 h after oral administration. Erythromycin and azithromycin are also available commercially in parenteral formulations. At steady state, the C_{max} of parenteral erythromycin, administered in 500 to 1000 mg doses four times daily, is approximately 10 to 17 mg/L (13). Azithromycin, administered in 500 mg doses intravenously once daily, reaches a steady state C_{max} of 3 mg/L (14).

Clarithromycin and azithromycin are more extensively distributed than erythromycin (volume of distribution of erythromycin = 0.64 L/kg; volume of distribution of clarithromycin = 3.4 L/kg; volume of distribution of azithromycin = 23 L/kg) (11). High concomitant serum concentrations are maintained with clarithromycin, while low serum concentrations with concomitant high and persistent tissue concentrations occur with azithromycin. Peak clarithromycin concentrations in the lung have been shown to exceed that in plasma by sixfold. Two- to sixfold tissue to plasma clarithromycin concentrations also occur in the nasal mucosa and tonsils (2). Similarly, azithromycin tissue concentrations are 10- to 100-fold higher than those in plasma (15). In comparison, erythromycin exhibits a tissue to plasma concentration ratio of only 0.5- to fivefold (10). Azithromycin becomes highly concentrated in various cells (eg, polymorphonuclear leukocytes, monocytes, alveolar macrophages and fibroblasts) and is subsequently released slowly into the extracellular space. In adults, a single oral 500 mg dose of azithromycin has been shown to produce tissue drug concentrations that are in excess of the minimum inhibitory concentration for many pathogens at sites of infection (bronchial epithelial lining fluid, sputum and bronchial mucosa) for up to 96 h postdose (12). Tonsillar levels exceed plasma concentrations by over 150-fold up to 84 h after two oral doses of 250 mg every 12 h (16).

Clarithromycin and azithromycin exhibit 45% to 50% and 7% to 50% protein binding, respectively, in human serum compared with 65% to 90% for erythromycin base (17). Due to the saturable nature of azithromycin binding, increased free drug concentrations are noted with increased total serum drug concentrations (12).

The elimination half-lives of erythromycin, clarithromycin and azithromycin are 2 h, 4 h and 68 h, respectively, after administration of a single 500 mg oral dose (11). Clarithromycin undergoes extensive hepatic metabolism, and there is a substantial first pass effect. The major metabolic pathway is hydroxylation, which results in the formation of the active 14-hydroxyl metabolite. Both unchanged clarithromycin and its metabolites are eliminated in the feces and the urine. Clarithromycin's pharmacokinetics are nonlinear due to a saturable metabolism; therefore, increased half-life and decreased metabolic clearance occur with increased doses (2). Azithromycin is primarily eliminated unchanged, principally, in the feces and, to a lesser extent, in the urine (12).

CLINICAL TRIALS

Respiratory tract infections: Several randomized clinical trials have shown clarithromycin and azithromycin to be as effective as erythromycin and other conventional antibiotics

in the treatment of upper and lower respiratory tract infections (Table 2).

Upper respiratory tract infections: Clinical response to clarithromycin and azithromycin therapy was found to be similar to the response found with the use of penicillin V in the treatment of group A beta-hemolytic streptococcal pharyngitis in children (18-20) and adults (21). However, bacteriological cure rates were variable. Compared with penicillin V, eradication rates were higher in clarithromycin-treated groups and lower in azithromycin-treated groups. One study found azithromycin 10 mg/kg daily for three days to be clinically inferior to penicillin V 50,000 U/kg/day administered in two divided doses for 10 days in children with group A beta-hemolytic streptococcal pharyngitis (22). Clinical response rates comparable with that of penicillin V have been reported using azithromycin 12 mg/kg/day daily for five days (23,24).

Acute maxillary sinusitis in adults appears to respond equally well to clarithromycin 500 mg orally twice daily, amoxicillin 500 mg orally three times daily or amoxicillin (combined with clavulanate) 500 mg orally three times daily (25,26). Similarly, an open-label, noncomparative study for this indication demonstrated the effectiveness of azithromycin 500 mg orally on the first day followed by 250 mg orally for four more days (27). Azithromycin 500 mg orally for three days was found to be clinically as effective as amoxicillin/clavulanate 500 mg administered three times daily for 10 days in the treatment of nonsevere, acute maxillary or ethmoidal sinusitis (28).

Clinical response to therapy with azithromycin or amoxicillin/clavulanate was found to be equivalent in the treatment of acute otitis media in paediatric patients (29). However, bacteriological failures with azithromycin recently have been demonstrated. Amoxicillin/clavulanate therapy was associated with higher middle ear fluid bacterial pathogen eradication rates and increased likelihood of clinical improvement in culture-positive patients compared with azithromycin (30). Similarly, bacteriological failure has been demonstrated in a study comparing azithromycin with cefaclor (31). Clinical cure or improvement has been documented in trials comparing clarithromycin and amoxicillin (32,33), amoxicillin/clavulanate (34,35) or cefaclor (36).

Acute exacerbations of chronic bronchitis: Studies of the treatment of mild to moderate acute exacerbations of chronic bronchitis in adults have demonstrated acceptable clinical response rates to clarithromycin administered for five to 10 days or cefaclor for seven days (37,38). Clarithromycin 500 mg has also been compared with oral ciprofloxacin 500 mg, each administered twice daily for 14 days in the treatment of acute bacterial exacerbations of bronchitis. Ciprofloxacin therapy was associated with a longer infection-free interval (median 142 days versus 51 days for clarithromycin, $P=0.15$). There were trends toward better clinical response and bacteriological response rates with ciprofloxacin than with clarithromycin (90% versus 82% [not significant] and 91% versus 77% [$P=0.01$], respectively) (39). This finding is in contrast to an earlier trial that demonstrated similar clinical

TABLE 2
Comparative clinical trials: Respiratory tract infections

Reference	Patient population	Agents compared	Results
Still et al, 1993 (18)	Paediatric Group A beta-hemolytic streptococcal pharyngitis (n=506)	Clarithromycin 7.5 mg/kg by mouth bid for 10 days Penicillin VK 13.3 mg/kg by mouth tid for 10 days	Clinical response Clarithromycin 96% Penicillin VK 94% (NS) Bacterial eradication Clarithromycin 92% Penicillin VK 81% (P=0.004)
Schaad and Heynen, 1996 (19)	Paediatric Group A beta-hemolytic streptococcal pharyngitis (n=343)	Azithromycin 10 mg/kg by mouth daily for three days Penicillin V 100,000 U/kg by mouth tid for 10 days	Clinical response Azithromycin 93% Penicillin V 90% (NS) Bacterial eradication Azithromycin 55% Penicillin V 80% (P<0.001)
McCarty et al, 2000 (20)	Paediatric Group A beta-hemolytic streptococcal pharyngitis (n=528)	Clarithromycin 7.5 mg/kg by mouth bid for five days Penicillin VK 13.3 mg/kg by mouth tid for 10 days	Clinical response Clarithromycin 97% Penicillin VK 94% (NS) Bacterial eradication Clarithromycin 94% Penicillin VK 78% (P<0.001)
Bachand, 1991 (21)	Adult Group A beta-hemolytic streptococcal pharyngitis (n=128)	Clarithromycin 250 mg by mouth bid Penicillin VK 250 mg by mouth four times daily	Clinical response Clarithromycin 86% Penicillin VK 77% (NS) Bacterial eradication Clarithromycin 88% Penicillin VK 91% (NS)
Pacifico et al, 1996 (22)	Paediatric Group A beta-hemolytic streptococcal pharyngitis (n=154)	Azithromycin 10 mg/kg by mouth daily for three days Penicillin V 50,000 U/kg/day bid for 10 days	Clinical response Azithromycin 75% Penicillin V 91% (P<0.05) Bacterial eradication Azithromycin 53.9% Penicillin V 85.8% (P<0.0001)
Still, 1994 (23)	Paediatric (three to 12 years old) Group A streptococcal pharyngitis (n=342)	Azithromycin 12 mg/kg by mouth daily for five days Penicillin V 250 mg by mouth tid for 10 days	Clinical response Azithromycin 95% Penicillin V 78.5% (P<0.001) Bacterial eradication Azithromycin 79.3% Penicillin V 67.2% (P=0.035)
Calhoun and Hokanson, 1993 (25)	Adult Acute maxillary sinusitis (n=142)	Clarithromycin 500 mg by mouth bid for seven to 14 days Amoxicillin 500 mg by mouth tid for seven to 14 days	Clinical response Clarithromycin 91% Amoxicillin 89% (NS)
Dubois et al, 1993 (26)	Adult Acute maxillary sinusitis (n=497)	Clarithromycin 500 mg by mouth bid Amoxicillin/clavulanate 500 mg by mouth tid	Clinical response Clarithromycin 97% Amoxicillin/clavulanate 93% (NS) Bacterial eradication Clarithromycin 87% Amoxicillin/clavulanate 90% (NS)
Clement and de Gandt, 1998 (28)	Adult Acute maxillary or ethmoidal sinusitis (nonsevere) (n=254)	Azithromycin 500 mg by mouth daily for three days Amoxicillin/clavulanate 500 mg by mouth tid for 10 days	Clinical response Azithromycin 87.5% Amoxicillin/clavulanate 83.7% (NS)
Principi, 1995 (29)	Paediatric Acute otitis media (n=484)	Azithromycin 10 mg/kg by mouth once daily for three days Amoxicillin/clavulanate 13.3 mg/kg by mouth tid for 10 days	Clinical response Azithromycin 92.6% Amoxicillin/clavulanate 93.9% (NS)

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TABLE 2 (continued)
Comparative clinical trials: Respiratory tract infections

Reference	Patient population	Agents compared	Results
Dagan et al, 2000 (30)	Paediatric Acute otitis media (n=238)	Azithromycin 10 mg/kg by mouth on day 1, then 5 mg/kg by mouth once daily on days 2 to 5 Amoxicillin/clavulanate 45/6.4 mg/kg by mouth in two divided doses for 10 days	Clinical response in culture-positive patients: Azithromycin 70% Amoxicillin/clavulanate 86% (P=0.023)
Dagan et al, 2000 (31)	Paediatric Acute otitis media (n=122)	Azithromycin 10 mg/kg by mouth once daily for three days Cefaclor 40 mg/kg by mouth in three divided doses for 10 days	Clinical response Azithromycin 82% Cefaclor 85% (NS) Bacteriological response <i>Haemophilus influenzae</i> Azithromycin 53% Cefaclor 52% (NS) <i>Streptococcus pneumoniae</i> Azithromycin 29% Cefaclor 37% (NS)
Pukander, 1993 (32)	Paediatric Acute otitis media (n=79)	Clarithromycin 7.5 mg/kg (maximum 500 mg) by mouth bid for seven to 10 days Amoxicillin 20 mg/kg (maximum 750 mg) by mouth bid for seven to 10 days	Clinical response Clarithromycin 93% Amoxicillin 90% (NS)
Coles et al, 1993 (33)	Paediatric Acute otitis media (n=259)	Clarithromycin Weight <25 kg: 125 mg by mouth bid Weight >25 kg: 250 mg by mouth bid for five days Amoxicillin Weight <25 kg: 125 mg by mouth tid Weight >25 kg: 250 mg by mouth tid for five days	Clinical response Clarithromycin 96% Amoxicillin 96% (NS)
Aspin et al, 1994 (34)	Paediatric Acute otitis media (n=180)	Clarithromycin 15 mg/kg/day by mouth in two divided doses for 10 days Amoxicillin/clavulanate 40 mg/kg/day by mouth in three divided doses for 10 days	Clinical response Clarithromycin 93% Amoxicillin/clavulanate 95% (NS)
McCarty et al, 1993 (35)	Paediatric Acute otitis media (n=338)	Clarithromycin 7.5 mg/kg (maximum 500 mg) by mouth bid for 10 days Amoxicillin/clavulanate 13.3 mg/kg (maximum 500 mg) by mouth tid for 10 days	Clinical response Clarithromycin 90% Amoxicillin/clavulanate 92% (NS)
Gooch et al, 1993 (36)	Paediatric Acute otitis media (n=379)	Clarithromycin 7.5 mg/kg (maximum 500 mg) by mouth bid for 10 days Cefaclor 20 mg/kg (maximum 500 mg) by mouth bid for 10 days	Clinical response Clarithromycin 86% Cefaclor 90% (NS)
Wettengel et al, 1993 (37)	Adult Acute bronchitis of bacterial etiology (mild to moderate) (n=207)	Clarithromycin 250 mg by mouth bid for seven days maximum Cefaclor 500 mg by mouth tid for seven days maximum	Clinical response Clarithromycin 99.5% Cefaclor 97.9% (NS) Bacteriological cure Clarithromycin 94.6% Cefaclor 90.3% (NS)
Adam, 1993 (38)	Adult Purulent bronchitis (n=221)	Clarithromycin 250 mg by mouth bid for five days Clarithromycin 250 mg by mouth bid for 10 days	Clinical response Clarithromycin (five days) 98% Clarithromycin (10 days) 99% (NS) Bacteriological cure Clarithromycin (five days) 100% Clarithromycin (10 days) 94% (NS)

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TABLE 2 (continued)
Comparative clinical trials: Respiratory tract infections

Reference	Patient population	Agents compared	Results
Neu and Chick, 1993 (41)	Adult Community-acquired lower respiratory tract infections (bacterial pneumonia, acute bacterial exacerbations of chronic bronchitis or asthmatic bronchitis) (n=213)	Clarithromycin 500 mg by mouth bid for seven to 14 days Cefixime 400 mg by mouth daily for seven to 14 days	Clinical response Clarithromycin 86% Cefixime 88% (NS) Bacteriological eradication Clarithromycin 91% Cefixime 90% (NS)
Fong et al, 1995 (42)	Adult Lower respiratory tract infections (acute bronchitis or exacerbation of chronic bronchitis, or pneumonia) (n=95)	Clarithromycin 250 or 500 mg by mouth bid for seven to 14 days Cefaclor 250 or 500 mg by mouth tid for seven to 14 days	Clinical response Clarithromycin 94.7% Cefaclor 90.2% (NS) Bacteriological eradication Clarithromycin 72.2% Cefaclor 70% (NS)
Chodosh et al, 1998 (39)	Adult Acute bacterial exacerbations of chronic bronchitis (n=234)	Clarithromycin 500 mg by mouth bid for 14 days Ciprofloxacin 500 mg by mouth bid for 14 days	Clinical response Clarithromycin 82% Ciprofloxacin 90% (NS) Bacteriological eradication Clarithromycin 77% Ciprofloxacin 91% (P=0.01)
Anzueto et al, 1998 (40)	Adult Complicated and/or severe acute exacerbations of chronic bronchitis (n=2180)	Clarithromycin 500 mg by mouth bid for 10 days Ciprofloxacin 750 mg by mouth bid for 10 days	Clinical response Clarithromycin 90% Ciprofloxacin 93% (NS) Bacteriological eradication Clarithromycin 96% Ciprofloxacin 96% (NS)
Bradbury, 1993 (43)	Adult Lower respiratory tract infections (acute bronchitis, acute infective exacerbations of chronic bronchitis or pneumonia) (n=510)	Azithromycin 500 mg by mouth daily for three days Clarithromycin 250 mg by mouth bid for 10 days	Clinical response Azithromycin 97% Clarithromycin 100% (NS) Bacteriological response Azithromycin 100% Clarithromycin 95% (NS)
Biebuyck, 1996 (44)	Adult Acute tracheobronchitis or acute infectious exacerbations of chronic bronchitis (n=759)	Azithromycin 500 mg by mouth daily for three days Amoxicillin/clavulanate 625 mg by mouth tid for five to 10 days	Clinical response Azithromycin 89.7% Amoxicillin/clavulanate 80.2% (P=0.0003)
Jang et al, 1995 (47)	Adult Community-acquired pneumonia (n=40)	Clarithromycin 250 mg by mouth bid for 14 days Erythromycin 500 mg by mouth four times daily for 14 days	Clinical response Clarithromycin 95% Erythromycin 90% (NS)
Chien et al, 1993 (48)	Adult Community-acquired pneumonia (n=268)	Clarithromycin 250 mg by mouth bid for seven to 14 days Erythromycin stearate 500 mg by mouth four times daily for seven to 14 days	Clinical response Clarithromycin 97% Erythromycin 96% (NS) Bacteriological response Clarithromycin 88% Erythromycin 100% (NS)
Rizzato et al, 1995 (49)	Adult Community-acquired pneumonia (low to moderately severe) (n=40)	Azithromycin 500 mg by mouth daily for three days Clarithromycin 250 mg by mouth bid for eight to 12 days	Clinical response Azithromycin 20% Clarithromycin 17% (NS) Bacteriological response Azithromycin 100% Clarithromycin 100% (NS)

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TABLE 2 (continued)
Comparative clinical trials: Respiratory tract infections

Reference	Patient Population	Agents Compared	Results
Bohte et al, 1995 (50)	Adult Community-acquired pneumonia (hospitalized) (n=108)	Azithromycin 500 mg by mouth bid for one day, then 500 mg by mouth daily for 4 days, versus Benzylpenicillin 1 MU intravenously four times daily until afebrile for five days, or Erythromycin 500 mg by mouth four times daily for 10 days	Clinical response Pneumococcal Azithromycin 83% Benzylpenicillin 66% (NS) Nonpneumococcal Azithromycin 79% Erythromycin 76% (NS)
Vergis et al, 2000 (51)	Adult Community-acquired pneumonia (hospitalized) (n=145)	Azithromycin 500 mg intravenously daily for two to five days, then 500 mg by mouth daily to complete seven to 10 days, versus [Cefuroxime 750 mg intravenously every 8 h for two to seven days, then cefuroxime axetil 500 mg by mouth bid to complete seven to 10 days, and Erythromycin 500 to 1000 mg intravenously by mouth every 6 h for up to 21 days]	Clinical response Azithromycin 91% Cefuroxime and erythromycin 91% (NS)
Plouffe et al, 2000 (52)	Adult Community-acquired pneumonia (hospitalized) (n=403)	Azithromycin 500 mg intravenously daily for two to five days then 500 mg by mouth daily to complete seven to 10 days, versus [Cefuroxime 750 mg intravenously every 8 h for two to seven days, then cefuroxime axetil 500 mg by mouth bid to complete seven to 10 days with or without Erythromycin 500 by mouth or 500 to 1000 mg intravenously every 6 h for up to 21 days]	Clinical response Azithromycin 77% Cefuroxime with or without erythromycin 74% (NS) Bacterial eradication <i>Haemophilus influenzae</i> Azithromycin 94% Cefuroxime with or without erythromycin 73% (NS)
Uzun et al, 1994 (53)	Adult Community-acquired pneumococcal pneumonia (n=25)	Azithromycin 1000 mg by mouth on first day, then 500 mg by mouth daily on following two days	Clinical response 96% Bacterial response 93%

NS Not significant

cal success and overall bacteriological response rates in patients treated with oral clarithromycin 500 mg or ciprofloxacin 750 mg twice daily (40). Compared with cefixime as a seven- to 14-day outpatient treatment, both therapies were found to be effective for the treatment of mild to moderate pneumonia and acute bacterial exacerbations of chronic bronchitis caused by *H influenzae*, *M catarrhalis* or *S pneumoniae* in adults (41). Comparison of clarithromycin with cefaclor for the same indication showed similar favourable clinical response and bacteriological eradication rates in both groups (42). An open-label study employing clarithromycin (250 mg orally twice daily for 10 days) or azithromycin (500 mg orally once daily for three days) for the treatment of lower respiratory tract infections, including acute bronchitis, acute infective exacerbations of chronic bronchitis and pneumonia, showed similar effectiveness for both drugs (43). Azithromycin has also been shown to have a statistically significant higher overall clinical response rate than amoxicillin/clavulanate for the treatment of acute tracheobronchitis or acute infectious exacerbations of chronic bronchitis (44).

Pertussis: Only two clinical trials have been published that have evaluated the use of either azithromycin or clarithromycin for the treatment of pertussis in children (45,46). Small numbers of subjects in each trial make it difficult to

recommend these agents as first-line therapy. It is likely that the newer agents are equivalent to standard therapy, such as erythromycin, for this infection.

Community-acquired pneumonia: The empirical treatment of community-acquired pneumonia (CAP) with the macrolides has been well studied. Clarithromycin 250 mg orally bid has been shown to be just as effective as erythromycin 500 mg orally four times daily as a seven- to 14-day therapy for this condition in adults (47,48). Oral azithromycin has also compared favourably with oral clarithromycin (49) and oral erythromycin (50) for the treatment of CAP. More recently, azithromycin (500 mg intravenously once daily for two days followed by 500 mg orally once daily; total duration of seven to 10 days) was compared with the combination of cefuroxime (750 mg intravenously every 8 h for two to seven days followed by 500 mg orally twice daily; total duration seven to 10 days) and erythromycin (500 to 1000 mg intravenously or orally every 6 h; total duration up to 21 days) in hospitalized patients (51). Clinical cure rates were similar (91% in each group, $P=0.95$). Another open-label trial comparing intravenous-to-oral azithromycin therapy with cefuroxime therapy with the addition of erythromycin therapy, if deemed necessary by the clinician, has been published (52). Clinical cure or improvement was noted in 77% of

TABLE 3
Frequency of gastrointestinal adverse effects of macrolides at recommended doses

Adverse effect	Erythromycin (%) [*]	Clarithromycin (%) [†]	Azithromycin (%) [‡]
Diarrhea	5.3	3	4.3
Dyspepsia	5 to 7 [§]	2	<1
Abdominal pain	6.9	2	2.6
Vomiting	2.9	1	1.3
Nausea	5.5	4	3.5

Data from references ^{*}87, [†]95, [‡]14, [§]12

the azithromycin group and 74% of the cefuroxime with or without erythromycin group (not significant). Until further information is available, the treatment of patients with bacteremic *S pneumoniae* pneumonia with azithromycin monotherapy should be undertaken with caution due to low serum concentrations relative to beta-lactam agents. An open-label study in 25 patients using a three-day course of the azalide reported that a patient with *S pneumoniae* bacteremia and pneumonia failed to respond to antibiotic therapy and died in respiratory failure (53).

The effectiveness of azithromycin for CAP has also been studied in children. Clinical response was similar when azithromycin was compared with amoxicillin/clavulanate (age five years or younger) or erythromycin estolate (age older than five years) (90.6% and 87.1%, respectively) (54). *Chlamydia pneumoniae* and *M pneumoniae* eradication was at least as successful with azithromycin as with the comparator antimicrobial (81% and 100% for azithromycin versus 100% and 57% for amoxicillin/clavulanate, respectively).

Skin and skin structure infections: The efficacy of clarithromycin in the treatment of mild to moderate skin and skin structure infections has been assessed in adults and children. Clarithromycin (500 mg twice daily for five to 14 days) produces clinical response rates comparable with erythromycin (250 mg four times daily for less than 14 days) and cefadroxil (500 mg twice daily for five to 14 days) (55). Similarly, children treated with clarithromycin 7.5 mg/kg (maximum 500 mg) twice daily responded equally well to cefadroxil 15 mg/kg (maximum 1000 mg) twice daily (56).

Azithromycin (500 mg orally on the first day followed by 250 mg for four more days) has been shown to be as effective as oral erythromycin (500 mg four times daily for seven days) (57,58), cephalexin (500 mg twice daily for 10 days) (59,60) and cloxacillin (500 mg twice daily for seven days) (58) in the treatment of mild to moderate acute bacterial infections of skin or soft tissue in adults. In children aged six months to 12 years, therapy with azithromycin 10 mg/kg for three days was shown to be as effective as cefaclor 20 mg/kg/day in three divided doses for the treatment of mild to moderate dermatological conditions and abscesses (61).

Sexually transmitted diseases: Several clinical trials have demonstrated the effectiveness of azithromycin for the treatment of sexually transmitted chlamydial infections. A single

1000 mg dose of oral azithromycin was shown to be effective and well tolerated compared with doxycycline 100 mg orally twice daily for seven days in men treated for either uncomplicated gonococcal urethritis and/or urethritis caused by *C trachomatis* and *Ureaplasma urealyticum* (62). Similarly, other trials have shown chlamydial cervicitis and nongonococcal urethritis to respond equally well to either azithromycin or doxycycline (63,64) and clarithromycin 250 mg orally twice daily for seven days or doxycycline (65). However, in the latter trial, doxycycline was more effective than clarithromycin in eradicating *U urealyticum*. Treatment of chlamydial infection in pregnant women and their sexual partners with single-dose azithromycin has been shown to be superior to therapy with standard course erythromycin for women, combined with tetracycline for their sexual partners. The proportion of positive cultures for *C trachomatis* at four weeks was significantly lower in women and partners randomized to single dose azithromycin (4.5%) than in those randomized to standard dose erythromycin or tetracycline (21.1%) (66). In this same study, adverse effects were significantly less in the azithromycin group (7.4%) compared with the group receiving erythromycin (38.8%) or tetracycline (28.6%).

Nontuberculous mycobacterial infections – MAC prophylaxis and therapy: Clarithromycin and azithromycin have been studied in the prophylaxis and treatment of HIV-infected patients with MAC infections. Clarithromycin reduced the incidence of disseminated infection by 10% and improved survival (hazard ratio 0.75, P=0.026) in patients with advanced AIDS compared with a placebo (67). Clarithromycin when used as a monotherapy has also been shown to be as effective as when used in combination with rifabutin for primary prophylaxis in HIV-infected patients (68). A comparison of azithromycin (1200 mg once weekly) alone, rifabutin (300 mg daily) alone or both for MAC prophylaxis showed that the combination produced the lowest cumulative incidence of disseminated MAC infection (2.8%) at one year of prophylactic therapy (69).

Clarithromycin in doses of 500 to 1000 mg twice daily has been demonstrated to eradicate MAC bacteremia and improve symptomatology (70,71). In disseminated MAC, however, macrolide monotherapy can lead to drug resistance (72). Therefore, the use of combination therapy is advocated (73). The addition of ethambutol to macrolide-containing regimens for MAC bacteremia has been shown to decrease the emergence of resistance (74). A clarithromycin-based three-drug regimen was superior to a four-drug regimen without clarithromycin in resolving MAC bacteremia and increasing survival rates in patients with AIDS (75). Most recently, a trial demonstrated that a combination of clarithromycin and ethambutol was superior to azithromycin and ethambutol for the treatment of MAC bacteremia in HIV-infected patients (76). Median time to clearance of bacteremia was significantly faster in the clarithromycin group (4.38 weeks versus longer than 16 weeks in the azithromycin group). Bacteremia resolved in a greater proportion of patients randomized to the clarithromycin group at 16 weeks (85.7% versus 37.5%).

TABLE 4
Potential clinically significant drug interactions involving erythromycin, clarithromycin and azithromycin

Interacting drug	Effect when administered with macrolide indicated		
	Erythromycin	Clarithromycin	Azithromycin
Theophylline and related drugs	Increased serum theophylline level with possible toxicity	Increased serum theophylline level with possible toxicity	No interaction observed but caution advised
Carbamazepine	Increased serum carbamazepine level with possible toxicity	Increased serum carbamazepine level with possible toxicity	No interaction reported
Cisapride (no longer marketed in Canada)	Increased serum cisapride level with possible cardiotoxicity (QT prolongation)	Increased serum cisapride level with possible cardiotoxicity (QT prolongation)	No interaction reported
Cyclosporine, tacrolimus	Increased serum immunosuppressant level with possible toxicity	Increased serum immunosuppressant level with possible toxicity	No interaction reported
Astemizole, terfenadine (no longer marketed in Canada)	Increased serum level of antihistamine leading to possible cardiotoxicity (QT prolongation)	Increased level on antihistamine leading to possible cardiotoxicity (QT prolongation)	No interaction reported
Alprazolam, diazepam, midazolam, triazolam	Increased serum level of benzodiazepines that undergo oxidative metabolism with possible toxicity	No interaction reported	No interaction reported
Buspirone	Increased serum buspirone level with possible toxicity	No interaction observed but caution advised	No interaction reported
Ergot alkaloids (including bromocriptine)	Increased risk of peripheral ischemia	Increased risk of peripheral ischemia	No interaction reported
Lovastatin	Possible severe myopathy or rhabdomyolysis; caution advised with all 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors	No interaction observed but caution advised	No interaction observed but caution advised
Rifabutin, rifampin	Possible decrease in antimicrobial effects	Possible decrease in antimicrobial effects	No interaction reported
Disopyramide	Increased serum disopyramide level with possible toxicity	Increased serum disopyramide level with possible toxicity	No interaction reported
Digoxin	Increased serum digoxin level with possible toxicity	Increased serum digoxin level with possible toxicity	No interaction reported
Warfarin	Reduction in warfarin clearance leading to potentiation of anticoagulant effect	Reduction in warfarin clearance leading to potentiation of anticoagulant effect	No interaction reported

Data from reference 96

However, it is possible that, in this study, the dose of azithromycin (600 mg once daily) studied was too low.

Infections with other nontuberculous mycobacteria: Clarithromycin therapy in combination with other agents may be effective for the treatment of nontuberculous, non-MAC mycobacterial infections. If required due to protease inhibitor drug interactions, clarithromycin or rifabutin may be added to isoniazid and ethambutol instead of rifampin for the treatment of *M. kansasii* pulmonary disease. This recommendation is based on the excellent in vitro susceptibility of *M. kansasii* to clarithromycin (77). Excellent in vitro susceptibility to clarithromycin has also led to this agent being recommended as one of the treatments for cutaneous infections with *M. marinum*, for pulmonary infections with *M. xenopi* and for cutaneous or pulmonary infections with *Mycobacterium abscessus* or *M. fortuitum* (77). Clarithromycin is also recommended for the treatment of cervical lymphadenitis caused by nontuberculous mycobacteria in patients with extensive disease or poor response to surgical excision (77). Long term clarithromycin monotherapy has been shown to be effective for the treatment of cutaneous infection with *M. chelonae* in an open-label, noncomparative trial (78). Promising results were also observed in a small trial assessing improvement in clinical and laboratory parameters; patients with previously untreated *Mycobacterium leprae* infection received clarithromycin monotherapy (79).

Peptic ulcer disease and *H. pylori* infection: The association of *H. pylori* with peptic ulcer disease is now well established. There have been six published meta-analyses on regimens for *H. pylori* eradication (80-85). All have shown that three drug regimens using clarithromycin and a proton pump inhibitor in combination with amoxicillin or metronidazole have eradication rates between 80% to 90% assessed by intention-to-treat analysis. In one meta-analysis examining the role of high versus low dose clarithromycin administered with a proton pump inhibitor and amoxicillin or metronidazole, the best treatment results by intention-to-treat analysis were seen with 500 mg twice daily compared with 250 mg twice daily (amoxicillin, 86.6% versus 78.2%; metronidazole, 88.3% versus 86.7%) (82). Azithromycin for *H. pylori* infection has not been as well studied as clarithromycin and is not currently recommended.

ADVERSE EFFECTS

Erythromycin is one of the safest antibiotics in clinical use. Gastrointestinal upset is the most common adverse event associated with macrolide therapy and is dose-related (Table 3). Macrolides act as gastric prokinetic agents through stimulation of motilin receptors in the gastrointestinal tract. It is believed that erythromycin's high affinity for these receptors, relative to that of clarithromycin and azithromycin, results in the higher incidence of gastrointestinal upset observed during

TABLE 5
Oral dosing of select macrolides and azalides

	Erythromycin base	Clarithromycin	Azithromycin
Dose (adult)	250 to 500 mg by mouth four times daily for 10 days	250 to 500 mg by mouth bid for 10 days	500 mg by mouth on first day followed by 250 mg by mouth daily on the following four days
Cost per course (adult)*	\$1.81 to \$3.62	\$29.58 to \$59.16	\$29.60
Dosing in renal and/or hepatic failure	No adjustment in renal impairment; use with caution if there is hepatic impairment	Reduce dose and/or frequency in renal impairment (creatinine clearance <0.5 mL/s)	No dose adjustment if there is mild to moderate renal or hepatic impairment; use with caution if creatinine clearance <0.5 mL/s; avoid if there is severe hepatic disease
Administration	1 h before or 2 h after food or antacids; stability in presence of acid varies with formulation administered	With or without food	Capsules and suspension: 1 h before or 2 h after food or antacids Tablets (with or without food):
Paediatric dosing	7.5 to 12.5 mg/kg/dose by mouth administered four times daily	3.75 to 7.5 mg/kg/dose by mouth administered twice daily (maximum 1000 mg/day)	10 mg/kg/day by mouth on the first day followed by 5 mg/kg/day by mouth administered as a single dose on the following four days (12 mg/kg/day for five days for pharyngitis/tonsillitis)

*Drug acquisition costs for solid oral dosage forms, from reference 97

TABLE 6
Parenteral dosing of erythromycin and azithromycin

	Erythromycin lactobionate	Azithromycin dihydrate (reference 14)
Dose (adult)	500 to 1000 mg intravenously every 6 h	500 mg intravenously every 24 h
Cost per day (adult)*	\$8.60 to \$17.20	\$20.00
Dosing in renal and/or hepatic failure	Use with caution in renal and hepatic impairment	No dose adjustment if mild to moderate renal or hepatic impairment; use with caution if creatinine clearance <0.5 mL/s; avoid if severe hepatic disease
Administration	Dilute each dose in 250 to 500 mL sodium chloride 0.9% to achieve concentration of ≤ 4 mg/L; infuse each dose over at least 30 minutes	Dilute each dose in 250 to 500 mL sodium chloride 0.9% or dextrose 5%; infuse each dose over 1 h
Pediatric dosing	7.5 to 12.5 mg/kg/dose by mouth administered four times daily	Not approved for use

*Hospital drug acquisition costs

therapy with this macrolide (86). The incidence of significant gastrointestinal effects (ie, nausea, diarrhea, abdominal pain and vomiting) is reported to be 20% to 35% with erythromycin and 10% to 15% for clarithromycin or azithromycin (87). Venous irritation and phlebitis occur commonly with parenteral erythromycin therapy, and may be minimized with a reduction in the concentration and/or infusion rate (88). Parenteral azithromycin appears to be better tolerated with an incidence of infusion site reactions of 3% to 6% (14). Other adverse effects reported during clinical trials with a frequency of less than 2% include headache, hepatic dysfunction, changes in neutrophil or leukocyte counts, and skin rash. Taste perversion has been reported in patients receiving clarithromycin therapy at a frequency of 2%. Bilateral, sensorineural ototoxicity has been reported with each of the macrolide derivatives. It is typically reversible with drug discontinuation and appears to be related to high serum concentrations arising from aggressive dosing, or hepatic or renal dysfunction (13,89).

DRUG INTERACTIONS

Several pharmacokinetic drug interactions have been documented with erythromycin, an inhibitor of the cytochrome P450 (subset CYP3A) enzyme system through inactivation by

the formation of an inactive complex (Table 4). The clearance of theophylline, carbamazepine, non-sedating antihistamines (ie, terfenadine, astemizole and, potentially, loratidine), ergot alkaloids, cyclosporine and warfarin may decrease if erythromycin is administered concomitantly. Clinically significant toxicity may ensue. Clarithromycin forms microsomal complexes to a lesser extent, and azithromycin does not appear to inactivate cytochrome P450 at all. Clarithromycin may cause clinically significant increases in carbamazepine, terfenadine and theophylline concentrations via inhibition of CYP3A-mediated metabolism (2). Concomitant use should be avoided or monitored closely. Azithromycin appears to have no clinically significant pharmacokinetic effect on drugs metabolized by cytochrome P450 (90).

When physical complexes are formed with antacids or food, there may be a reduction in the bioavailability of erythromycin. Food and antacids do not appear to cause a clinically significant interaction when administered with clarithromycin. However, peak azithromycin serum levels may be reduced when administered as a capsule or oral suspension concomitantly with food or antacids (14). Therefore, this drug is recommended for administration on an empty stomach in the absence of antacids.

DOSING AND ADMINISTRATION

The recommended dosages and recommendations regarding dosing adjustment in renal and/or hepatic failure are presented in Table 5. Estimated drug acquisition costs for total regimen are also provided. Only erythromycin and azithromycin are available in parenteral forms for intravenous administration. Parenteral azithromycin therapy may be a useful alternative to parenteral erythromycin when a reduction in fluid administration or frequency of administration is desired. A dosing comparison of these agents is provided in Table 6.

CONCLUSIONS AND RECOMMENDATIONS

The macrolide clarithromycin and the azalide azithromycin offer potential therapeutic and tolerability advantages over erythromycin. For the majority of patients treated (eg, those suffering from community-acquired respiratory tract infections), these drugs offer a more tolerable gastrointestinal adverse event profile and a simpler dosing regimen. The antimicrobial spectrum and clinical trial evidence support the use of either azithromycin or clarithromycin as first-line agents or alternatives to erythromycin in the treatment of CAP in the ambulatory setting. Both agents are acceptable for the treatment of hospitalized patients with CAP in combination with second- or third-generation cephalosporins. The introduction of azithromycin injection offers an alternative to parenteral erythromycin in this setting. The extended antimicrobial coverage of clarithromycin versus MAC and other nontuberculous mycobacteria is clinically relevant. For peptic ulcer disease caused by *H pylori*, triple-drug regimens containing clarithromycin are considered first-line therapy. In the treatment of uncomplicated genital tract chlamydial infection and nongonococcal urethritis, single dose azithromycin is now the standard. For the treatment of skin and skin structure infections, more effective and less expensive agents exist, rendering these agents to second-line status.

The evidence cited in these recommendations has been classified into five levels, which have been used in the development of other clinical practice guidelines (91).

- Level I evidence is based on randomized, controlled trials (or meta-analysis of such trials) of adequate size to ensure a low risk of incorporating false-positive or false-negative results.
- Level II evidence is based on randomized, controlled trials that are too small to provide level I evidence. These may show either positive trends that are not statistically significant or no trends, and are associated with a high risk of false-negative results.
- Level III evidence is based on nonrandomized, controlled or cohort studies, case series, case-controlled studies or cross-sectional studies.
- Level IV evidence is based on the opinion of respected authorities or that of expert committees as indicated in published consensus conferences or guidelines.

- Level V evidence expresses the opinion of those individuals who have written and reviewed these guidelines, based on their experience, knowledge of the relevant literature and discussion with their peers.

Taking into account the differences in drug acquisition cost and spectrums of activity between erythromycin, clarithromycin and azithromycin, the following recommendations are made.

First-line therapy

- CAP in ambulatory patients (in combination with beta-lactam if modifying risk factors) (Level I)
- CAP in hospitalized patients in combination with beta-lactam (Level I)
- Single-dose treatment of uncomplicated nongonococcal urethritis or cervicitis (azithromycin 1 g orally) (Level I)
- For eradication of *H pylori* infection in combination with a proton pump inhibitor and either amoxicillin or metronidazole (clarithromycin 500 mg twice daily) (Level I)
- For treatment of infection with MAC (clarithromycin in combination with ethambutol with or without rifabutin) (Level I)
- For treatment of infection caused by susceptible nontuberculous mycobacteria (clarithromycin in combination with other agents) (Level IV)
- For prophylaxis of infection with MAC in HIV-infected patients azithromycin 1200 mg once weekly (with or without rifabutin) (Level I)

Alternate therapy

- For treatment of infection with MAC (azithromycin in combination with ethambutol with or without rifabutin) (Level II)
- For prophylaxis of infection with MAC in HIV-infected patients (clarithromycin) (Level II)
- For patients experiencing or who have a history of severe gastrointestinal adverse effects while receiving any oral erythromycin formulation or conventional beta-lactam antibiotics (eg, penicillins and cephalosporins) for community-acquired respiratory tract infections (Level III)
- For patients who are likely to be nonadherent with standard erythromycin or conventional beta-lactam antibiotic regimen (Level IV)
- For prophylaxis of bacterial endocarditis for dental, oral, respiratory or gastrointestinal endoscopic procedures in patients with a history of beta-lactam hypersensitivity as recommended by the American Heart Association (92) (Level IV)

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