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The use of macrolides in respiratory tract infections

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Macrolides have enjoyed continued use for over 40 years, being increasingly used for the treatment of respiratory tract infections. Newer macrolides have been introduced that show improved absorption after oral administration, better gastrointestinal tolerance, and delivery of increased amounts of drug to the infection site. Macrolides are commonly used in community-acquired pneumonia, as well as in atypical pneumonia and legionellosis. The newer macrolides, in comparative studies, have been shown to be as effective as the conventional therapies for treating acute otitis media, acute sinusitis and acute pharyngitis, with a low incidence of side-effects. However, dosing can be simplified because of their unique pharmacokinetic properties. Limitations in the use of macrolides for respiratory infections include rather marginal activity in the most severe cases of Haemophilus influenzae infections, lack of activity against Klebsiella and other coliforms, which precludes their use as single agents in the therapy of pneumonia in patients with significant underlying disease or in the elderly, and development of resistance in streptococci and staphylococci.

Key words: Macrolides; Respiratory tract infections; New compounds; Modified compounds

Introduction

Macrolides are so named after the macrocyclic lactose nucleus they contain (Table 1). Erythromycin, the first agent of this class, was described in 1952. It is derived from a strain of Streptomyces erythreus discovered in a soil sample from the Philippines. Macrolides have been widely used during the last

| TABLE 1 |
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| Representative macrolides; prototype of each class is underlined |
| 14-membered | 15-membered | 16-membered |
| Erythromycin | Azithromycin | Spiramycin |
| Oleandomycin | | Josamycin |
| Flurithromycin | | S-5556 |
| Clarithromycin | | Tylosin |
| Megalomycin | | Rosaramicin |
| Lankamycin | | Turimycin |
| Dirithromycin | | Miocamins |

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four decades, mainly in out-patients with respiratory tract infections. In recent years, their use in clinical practice has become even more extensive, the renewed interest in macrolide antibiotics having several causes. Their value for the treatment of lower respiratory tract infections has been increasingly appreciated, since their antibacterial spectrum matches almost exactly that required for the therapy of pulmonary infections caused by more recently recognized pathogens (*Legionella* spp., *Chlamydia pneumoniae*, *C. trachomatis*). Molecules have been developed that overcome some of the disadvantages associated with erythromycin: irregular and limited absorption after oral administration; and frequent adverse gastrointestinal side-effects. In addition, newer agents that assure increased amounts of drugs in infected tissues have been recently introduced including, in particular, 14-membered macrolides such as roxithromycin, dirithromycin, florithromycin and clarithromycin, and the 15-membered azithromycin which results from the insertion of a methyl-substituted nitrogen into the erythromycin molecule, producing a new class of macrolides, the azalides.

### Table 2

| Activity                      | Microorganism                      |
|-------------------------------|------------------------------------|
| **Usually susceptible**       | *Actinomyces israelii*             |
| *Bordetella pertussis*        | *Fusobacterium necrophorum*        |
| *Chlamydia pneumoniae*        | *Legionella* spp.                  |
| *Chlamydia psittaci*          | *Moraxella catarrhalis*            |
| *Chlamydia trachomatis*       | *Mycoplasma pneumoniae*            |
| *Corynebacterium diptheriae*  | *Streptococcus pneumoniae*         |
|                               | *Streptococcus pyogenes*           |
| **Less regularly susceptible**| *Haemophilus influenzae*           |
| *Mycobacterium* sp.           | *Staphylococcus aureus*            |
| *Nocardia asteroides*         | *Staphylococcus epidermidis*       |
| **Usually resistant**         | *Bacteroides fragilis*             |
| *Coxiella burnetti*           | *Francisella tularensis*           |
| *Enterobacteriaceae*          | *Rickettsia conorii*               |
|                               | *Rickettsia rickettsii*            |
| **Still under investigation** | *Pneumocystis carinii*             |
|                               | *Toxoplasma gondii*                |

**In vitro activity of macrolides against respiratory pathogens**

Macrolides are broad-spectrum antibiotics with activity against both Gram-positive and Gram-negative species (Table 2). The antimicrobial activity is due to the binding of the macrolide molecule to the 50S ribosomal subunit, effectively blocking the ribosomal P site and resulting in the inhibition of RNA-dependent protein synthesis. Due to very different ribosomal structures, this binding cannot occur in eucaryotic cells, which accounts for the low toxicity of macrolides in humans. Of particular interest in the context of respiratory tract infection therapy is the fact that macrolides exhibit consistent activity against atypical bacteria frequently involved in pneumonia (e.g. *Mycoplasma pneumoniae* and *Chlamydia* spp.) whereas β-lactams and aminoglycosides are ineffective. Macrolides also possess excellent potency against *Legionella* spp., *Bordetella pertussis* and *Corynebacterium diptheriae*, as well as having certain antimycobacterial activities which can be helpful in the context of the recent increased prevalence, and the multiple-resistance problems of these diseases.

Erythromycin has been shown to be bactericidal towards groups A streptococci, *Streptococcus pneumoniae* and *Haemophilus influenzae* (at high concentrations), and a post-antibiotic effect has been demonstrated against these species [1]. By contrast, the antistaphylococcal effect is essentially bacteriostatic, and a post-antibiotic effect is only shown after prolonged exposure to high concentrations [2].

The *in vitro* activity of macrolides exhibits certain differences when various compounds are compared [3]. In general, 14-membered macrolides are more active against streptococci and *B. pertussis* than is azithromycin (a 15-membered azalide), which in turn is more active than the 16-membered macrolides. Clarithromycin is the most active compound against *Streptococcus pyogenes*, pneumococci and *Corynebacterium* spp. Azithromycin exhibits greatly enhanced potency (eight-fold or more) against Gram-negative species, including *H. influenzae*, *Moraxella catarrhalis*, *Campylobacter jejuni* and Enterobacteriaceae, probably as a result of the insertion of the second basic site of protonation into the macrocyclic nucleus which improves the outer membrane...
permeability [4]. Clarithromycin yields similar minimal inhibitory concentrations (MICs) against *H. influenzae* as erythromycin but is metabolized in vivo, leading to the production of a 14-hydroxy metabolite that is a little more active than the parent compound and with which it generates an additive effect [5].

Resistance to macrolides may result from reduced permeability in Enterobacteriaceae, drug inactivation (notably in *Staphylococcus aureus* and *Escherichia coli* [6]) or, most importantly, alteration of the target site. The last mechanism involves a demethylation of adenine residues in 23S ribosomal RNA leading to a reduction in the affinity between the antibiotic and the 50S fraction of the ribosome. As a result, the activity of macrolides, lincosamides and streptogramin B (the so-called MLS$_B$ phenotype) is affected [7]. This alteration can be inducible [8], in which case the resistance is apparently dissociated, the 14- and 15-membered macrolides being clearly inactive, whereas the MICs of 16-membered macrolides are less than 1 mg/l [3]. The clinical efficacy of 16-membered macrolides in infections caused by strains possessing the inducible MLS$_B$ phenotype, however, remains to be solidly documented and some authorities feel it would be preferable to avoid the use of all macrolides in such cases. MLS$_B$ resistance can also be constitutive, with clear cut resistance to all antibiotics of the group. MLS$_B$ resistance has been shown in many bacterial species, including staphylococci, streptococci, *C. diphtheriae* and *Legionella* spp. [9,10]. The erythromycin resistance methylase gene (*erm*) responsible for the MLS$_B$ phenotype can be located on a plasmid, a transposon, or the chromosome.

The prevalence of resistance to macrolides shows great geographical variations. Resistance of methicillin-susceptible *S. aureus* ranges from 1% to 50%, community isolates being more frequently susceptible than hospital isolates, and the majority of methicillin-resistant staphylococci are resistant to macrolides [2]. Prevalence of erythromycin resistance in pneumococci is also variable and has tended to increase during recent years. The percentage of resistance seems to peak in South Africa, reaching more than 50% in one report [11] and pockets of high incidence have been reported in France [12], Belgium and Spain. In many other areas, resistance has been reported to be lower than 5% [11]. Some of the pneumococcal isolates are especially troublesome because of multiple resistance, affecting practically all drugs available except vancomycin [13]. Resistance in *S. pyogenes* is generally less than 5% in most parts of the world, with some notable exceptions, such as Japan, where a prevalence exceeding 50% has been reported [14]. Resistance in *Legionella* spp. and mycoplasmas is very infrequent, and remains rare in *C. diphtheriae* [7].

### Tissue specificity of macrolides

All macrolides can be administered orally and, because of improved acid stability, greater oral bioavailability has been obtained with newer compounds compared with erythromycin. Excellent tissue penetration is the pharmacokinetic hallmark of macrolides; they penetrate well into the host cells, particularly phagocytes, and once within the cells, the macrolides only slowly egress. As a consequence of this, tissue:plasma antibiotic ratios are well above 1 over the complete time course following ingestion, high macrolide concentrations are found in most tissues and body fluid (with the exception of the cerebrospinal fluid), tissue and plasma half-lives are prolonged (Table 3), and apparent volumes of distribution are relatively large. In practical terms, this unique pharmacokinetic profile has allowed simplified dosing schedules, with the possibility of once-

### Table 3

| Macrolide    | Oral dose (mg) | C$_{max}$ (mg/l) | T$_{max}$ (h) | T$_{1/2}$ (h) | AUC (mg/l·h) |
|--------------|----------------|------------------|--------------|--------------|--------------|
| Azithromycin | 500            | 0.4              | 2.0          | 35.0         | 4.5          |
| Clarithromycin | 500           | 2.4              | 1.7          | 4.9          | 18.9         |
| 14-OH metabolite | —            | 0.7              | —            | 7.2          | 6.0          |
| Flurithromycin | 500            | 1–2              | 1–2          | 8.0          | 16.0         |
| Roxithromycin | 300            | 10.8             | 1.6          | 12.0         | 81.0         |

C$_{max}$ maximum concentration in serum; T$_{max}$ time to maximum concentration in serum; T$_{1/2}$ serum half-life; AUC, area under the serum concentration–time curve.
daily administration for roxithromycin, dirithromycin and azithromycin [17,18]. Tissue specificity depends on the compound and appears to be especially remarkable in the case of azithromycin, a feature thought to be due to the insertion of a second nitrogen capable of protonation in the molecule. After oral administration, azithromycin produces relatively low plasma concentrations, but a number of animal models of localized infections have demonstrated that efficacy of azithromycin correlates with its extravascular pharmacokinetics and not with blood concentrations [19].

With regard to respiratory tract infections, macrolides assure high concentrations in the corresponding tissues and body fluids, including the tonsils, sputum, bronchial secretions, middle ear fluid, nasal and bronchial mucosa, epithelial alveolar lining fluid and alveolar macrophages, where the highest lung concentrations of macrolides occur (Table 4).

**Favourable safety profiles of newer macrolides**

Since macrolides are often used in ambulatory patients with mild or moderately severe respiratory tract infections, the safety profile is extremely important, notably as a guarantee of good compliance. In general, macrolides have been extensively used during the last four decades with little serious associated toxicity, and erythromycin can be used in pregnant women at any gestational stage. Erythromycin, however, generates a rapid increase in gastric and upper intestinal motility when administered either by the oral or the intravenous route, and this can produce serious discomfort in patients and a high incidence of vomiting [22]. This pharmacological effect is thought to be related to intramolecular cyclization of the drug, which can be inhibited by modification of the functional groups that participate in the degradation reaction. Modifications of the ketone group at C-9 produce, for example, derivatives including the 16-membered macrolides, azithromycin, roxithromycin and dirithromycin that are less prone to intramolecular cyclization [17] and that create fewer gastrointestinal effects. Other alterations such as the alkylation of the hydroxyl group at C-6 have produced the same beneficial effects [17]. The alkylated derivative clarithromycin, for example, is also associated with fewer gastrointestinal effects than erythromycin stearate [23].

**Macrolides for treating respiratory tract infections**

As a consequence of improved absorption after oral administration, ability to assure increased amounts of drug at the site of infection and greater gastrointestinal tolerance, it is likely that the newer macrolides will progressively replace erythromycin.

**Acute group A streptococcal pharyngitis**

Pharyngitis is one of the most common diseases treated by general practitioners and approximately 15% of all cases of pharyngitis are due to *S. pyogenes*. Antibiotic therapy of streptococcal pharyngitis is important for the prevention of supplicative complications, notably otitis, and reduction of the risk of acute rheumatic fever. The gold standard for treating the disease is a 10-day course of an oral penicillin, or in poor areas, a single intramuscular injection of

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**TABLE 4**

Site concentrations ± s.d. of macrolides within the human lung [20,21]

| Macrolide  | Oral dose and frequency | Serum (mg/l) | Bronchial biopsy (mg/kg) | Epithelial lining fluid (mg/l) | Alveolar macrophages (mg/kg) |
|------------|-------------------------|--------------|--------------------------|-------------------------------|-------------------------------|
| Clarithromycin | 250 mg, b.i.d. 2 days    | 1.2 ± 0.04   | —                        | 10.4 ± 0.7                    | 86.5 ± 3.6                    |
| Azithromycin   | 500 mg 1 day            | 0.13 ± 0.05  | 3.9 ± 1.2                | 2.2 ± 0.9                     | 23.0 ± 5.1                    |
1.2 \times 10^6 \text{ IU benzathin penicillin.} There are some problems, however, associated with these schedules: possible serious allergic reactions; the need for oral administration every 6–8 h, or a painful injection; and a high incidence of therapeutic failure manifested by recurrent symptomatic illness. As an alternative, a 10-day course of erythromycin is traditionally used to treat streptococcal pharyngitis in patients allergic to penicillin.

Some of the newer macrolides may, however, challenge the traditional regimens, due to their attractive pharmacokinetic properties, allowing simplified dosing, and their excellent tolerance. Several studies have shown that drugs like josamycin, clarithromycin, roxithromycin or azithromycin are as efficacious and better tolerated than traditional comparators (Table 5). In these studies, the newer regimens were simplified, which may have led to a better patient compliance. With this regard, the efficacy obtained with a 3-day course of azithromycin was especially impressive.

**Acute otitis media**

Acute otitis media is an extremely frequent illness in children, peaking in the first 3 years of life, and it may generate serious sequelae if not properly treated. The microbiology of otitis media has been documented by cultures of middle ear effusions obtained by needle aspiration. The four leading causes are *S. pneumoniae*, *H. influenzae*, *S. pyogenes* and *M. catarrhalis*, which represent the main targets for antimicrobial therapy. Amoxycillin and ampicillin are still the drugs of choice in many geographical areas, but the emergence of β-lactamase-producing *H. influenzae* and *M. catarrhalis* may lead to alternatives being preferred such as amoxycillin–clavulanate, cefaclor or co-trimoxazole (trimethoprim–sulphonamide). Erythromycin is also used, notably in children with an allergy to penicillin, but its marginal activity against *H. influenzae* has led to the recommendation that it be used in combination with a sulphonamide.

Newer macrolides like roxithromycin, dirithromycin and flurithromycin possess the same potency against *H. influenzae* as erythromycin [30], but their higher tissue specificity may create a therapeutic advantage; this still needs to be firmly established. The additive effect of clarithromycin and its 14-hydroxy metabolite, and the greater *in vitro* potency of azithromycin against *H. influenzae* represent a potential advantage of these antibiotics for the treatment of otitis media due to this species [4,31].

A variety of comparative studies have shown that

| Table 5 |
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| Representative studies on streptococcal pharyngitis comparing macrolide therapy with conventional drugs |

| Macrolide therapy | Comparator drug | Cure rate (%) | Bacteriological response (%) | Patients with side-effects (%) | Reference |
| --- | --- | --- | --- | --- | --- |
| Roxithromycin 150 mg b.i.d. for 10 days | Erythromycin 500 mg q.i.d. for 10 days | 87 vs 88 | 88 vs 92 | 11.8 vs 26.6* | [24] |
| Clarithromycin 7.5 mg/kg b.i.d. for 10 days | Penicillin V 13.3 mg/kg b.i.d. for 10 days | 96 vs 94 | 92 vs 81b | Similar | [25] |
| Clarithromycin 250 mg b.i.d. for 10 days | Penicillin V 250 mg q.i.d. for 10 days | 96 vs 98 | 100 vs 97 | 6 vs 9 | [26] |
| Clarithromycin 250 mg b.i.d. for 10 days | Penicillin V 250 mg q.i.d. for 10 days | 95 vs 91 | 88 vs 91 | 43 vs 27 | [27] |
| Josamycin 1 g b.i.d. for 5 days | Penicillin V 1 MU t.i.d. for 10 days | 95 vs 96.7 | 94 vs 88 | Similar | [28] |
| Azithromycin 10 mg/kg once daily for 3 days | Penicillin V 125 or 250 mg q.i.d. for 10 days | 90 vs 94 | 95 vs 93 | 4 vs 0 | [29] |

*a Significant difference at the level of \( P < 0.05 \).

*b Significant difference at the level of \( P < 0.01 \).
the newer macrolides are, in general, as effective as the conventional therapies for treating acute otitis media and are sometimes associated with a lower incidence of side-effects [30]. Furthermore, the dosing schedules are simpler than conventional therapies, especially in the case of azithromycin (one oral dose daily for 3 days). For other macrolides, very recent studies have tended to reduce the therapeutic regimen to a 5-day course.

Acute sinusitis

Acute sinusitis is usually a complication of a viral infection of the upper respiratory tract, allergic rhinitis, or is associated with dental infections. This is a potentially severe disease which can lead to meningitis or an intracranial abscess. The bacterial species most often responsible for acute sinusitis include S. pneumoniae (the main agent), H. influenzae and various anaerobic bacteria belonging to the oral flora; S. aureus, S. pyogenes and M. catarrhalis have also been implicated. The efficacy of antimicrobial therapy is well established in this disease and conventionally includes any of the drugs used to treat otitis media. Significant efficacy has been obtained using macrolides but classic studies have shown that patients with sinusitis due to H. influenzae responded more slowly to therapy with erythromycin than did those with streptococcal sinusitis [32]. Until recently, therefore, the relatively poor activity against H. influenzae justified the macrolides not being considered as first-line drugs in sinusitis. The newer compounds, which ensure improved penetration into the appropriate tissues and fluids, may reverse this trend. Illustrating this statement, clarithromycin has been found to be as effective and well tolerated as amoxycillin in the treatment of acute sinusitis [33], and azithromycin for 3 days yielded similar results to clarithromycin given for 10 days [34].

Acute community-acquired pneumonia

Although pneumonia is no longer regarded as 'captain of the men of death', this disease remains the most common cause of infection-related mortality in developed countries. There are multiple microbiological causes of pneumonia and, since the exact aetiology is difficult to determine in many cases, the physician must use a management strategy that does not rely on a precise diagnosis in each case. Macrolides are part of this strategy for several reasons: they are the drugs of first choice in Mycoplasma pneumoniae infections which are the main bacterial cause of so-called 'atypical pneumonia'; erythromycin is also the established standard therapy for legionellosis; it is often recommended as an alternative therapy in pneumococcal pneumonia, notably in patients allergic to penicillin; and macrolides, but not β-lactams, are active against C. trachomatis resulting in pneumonia in infants, and are used as an alternative to tetracycline in the treatment of Chlamydia psittaci infections. In addition, macrolides are probably effective in the newly recognized infections caused by C. pneumoniae. Erythromycin or its derivatives, therefore, are recommended as empirical therapy for community-acquired pneumonia in normal hosts [35], especially when the clinical background corresponds to a 'viral-like illness' or if legionnaire's disease is suspected or proven. In some cases, a β-lactam such as ampicillin or amoxycillin–clavulanate is combined with the macrolide. Complications can arise in certain patient groups, e.g. patients of advanced age (especially if staying in nursing homes) or those with an underlying disease that changes the aetiological considerations, in which case Gram-negative bacteria, including Klebsiella pneumoniae, H. influenzae or even Pseudomonas aeruginosa, become a significant risk and the macrolides are not recommended. In addition, in any patient with clinical signs and symptoms that are highly suggestive of pneumococcal pneumonia, penicillin G should be used provided the patient is not allergic to the drug.

Until recently, the most commonly used macrolide for community-acquired pneumonia has been erythromycin, but some studies seem to indicate that newer macrolides would be preferable in terms of tolerance and ease of administration, although similar in terms of efficacy [23,36]. Roxithromycin and clarithromycin, with a 14-day maximum duration of treatment, performed equally well as erythromycin [37], as did clarithromycin (10 days) and azithromycin (3 days) [Washton H, personal communication].

Acute bronchitis

The majority of acute bronchitis cases are caused
by respiratory viruses (rhinovirus, coronavirus, influenza, adenovirus) so that the value of antibiotics is uncertain. A small proportion of cases, however, are of bacterial aetiology, including *M. pneumoniae*, *B. pertussis* and *C. pneumoniae*, and a macrolide is indicated for severe mycoplasma infections. Early studies have indicated that once a cough has begun, macrolides do not alter the course of the disease but, if given early, they may have a favourable effect [38]. In pertussis, macrolides have been used successfully as chemoprophylaxis of asymptomatic contacts [39], but in the case of *C. pneumoniae* infections, the macrolides have yet to be formally evaluated.

### Acute exacerbations of chronic bronchitis

The pathogenesis of acute exacerbations of chronic bronchitis (AECB) remains unclear in many respects, and the role of bacterial infection is controversial. Chronic colonization of the airways with unencapsulated strains of *H. influenzae*, *S. pneumoniae* or *M. catarrhalis* is frequent, but the role of these bacteria in the genesis of AECB is debatable; *M. pneumoniae* is another possible cause. Despite this obscure background, antibiotics are often used in AECB because it is felt that they may improve symptoms, although the overall benefit is unknown. Erythromycin, or other macrolides, represent a possible choice in this difficult context, notably because of their antimycoplasmal efficacy.

### Special issues

#### Very severe respiratory infections

In patients with very severe respiratory infections, blood cultures are frequently positive and the cerebrospinal fluid can be infected, especially during *S. pneumoniae* and *H. influenzae* infections. Since macrolides only poorly penetrate the cerebrospinal fluid, it is probably not advisable to use them as single antimicrobial agents in such cases. Of course, this observation is not valid in legionellosis, which can be extremely severe but is rarely complicated with meningitis. Macrolides are not recommended in severe staphylococcal infections due to limited bactericidal potency.

### Specific *H. influenzae* infections

Most of the studies presented here describe empirical therapy of respiratory infections, but in some patients *H. influenzae* is formally recognized or highly suspected as being the invasive pathogen (e.g. acute epiglottitis in a young child). In general, macrolides possess marginal potency against *H. influenzae*, with MIC₉₀ s typically of 4 or 8 mg/l and, thus, cannot be recommended. In contrast, β-lactams or quinolones are more active and have good clinical records in this setting. Multiple studies, however, involving the use of macrolides, especially the newer compounds, against various respiratory tract infections including diseases where *H. influenzae* was recognized as the pathogen responsible after initiation of therapy have shown good efficacy. So the use of macrolides as empirical antimicrobial therapy can assure an acceptable coverage of *H. influenzae* infections. The 14-hydroxy metabolite of clarithromycin and overall azithromycin (typical MIC₉₀ s: 0.5–2 mg/l) possess improved activity against *H. influenzae* compared with the other drugs of the group, but it is presently considered that further clinical studies specifically addressing this problem are required for a definitive opinion on the clinical benefit of this enhanced potency.

### Macrolides as chemoprophylaxis of respiratory tract infections

As discussed above, macrolides have been successfully used in the prevention of whooping cough, and erythromycin is the drug of choice for the eradication of *C. diphtheriae*. Studies on the efficacy of macrolides against *N. meningitidis* are awaited.

### References

1. Bundzen RW, Gerber AV, Cohn DJ., Craig WA. Post-antibiotic suppression of bacterial growth. Rev Infect Dis 1981;3:28–37.
2. Neu HC. The development of macrolides: clarithromycin in perspective. J Antimicrob Chemother 1991;27(suppl A):1–9.
3. Hardy DJ, Hensley DM, Beyer JM, Vojtko C, McDonald EJ, Fernandes PB. Comparative in vitro activities of new 14-...
15-, and 16-membered macrolides. Antimicrob Agents Chemother 1988;32:1710–1719.

4 Williams JD. Spectrum of activity of azithromycin. Eur J Clin Microbiol Infect Dis 1991;10:818–820.

5 Olsson-Liljequist B, Hoffman BM. In vitro activity of clarithromycin combined with its 14-hydroxy metabolite A-62671 against Haemophilus influenzae. J Antimicrob Chemother 1991;27(suppl A):11–17.

6 Barthélémyn P, Autusier D, Gerbaud G, Courvalin P. Enzymatic hydrolysis of erythromycin by a strain of Escherichia coli. J Antimicrob (Tokyo) 1984;37:1692–1697.

7 Ounissi H, Courvalin P. Heterogeneity of macrolide lincomamide streptogramin B-type antibiotic resistance determinants. In: Schlessinger D, ed. Microbiology 1992. Washington, DC: American Society for Microbiology, 1992.

8 Horiouchi S, Weisblum B. Post-transcriptional modification of mRNA conformation: mechanisms that regulate erythromycin-induced resistance. Proc Natl Acad Sci USA 1980;77:7079–7083.

9 Buu-Hoi A, Bieth G, Horand T. Broad host range of streptococcal macrolide resistance plasmids. Antimicrob Agents Chemother 1984;25:289–294.

10 Dowling IN, McDevitt DA, Pasculle WA. Isolation and preliminary characterization of erythromycin-resistant variants of Legionella micdadei and Legionella pneumophila. Antimicrob Agents Chemother 1985;24:277–279.

11 Klugman KP. Pneumococcal resistance to antibiotics. Clin Microbiol Rev 1990;3:171–196.

12 Geslin P, Buu-Hoi A, Fremaux A, Acar JF. Antimicrobial resistance in Streptococcus pneumoniae: an epidemiological survey in France, 1970–1990. Clin Infect Dis 1992;15:95–98.

13 McDougal LK, Facklam R, Reeves M et al. Analysis of multiple antimicrobial-resistant isolates of Streptococcus pneumoniae from the United States. Antimicrob Agents Chemother 1992;36:2176–2184.

14 Maruyama S, Yoshioka H, Fujioka K, Takimoto M, Satake Y. Sensitivity of group A streptococci to antibiotics. Am J Dis Child 1979;133:1143–1148.

15 Kirst HA, Sides GD. New directions for macrolide antibiotics: pharmacokinetics and clinical efficacy. Antimicrob Agents Chemother 1989;33:1419–1422.

16 Nielsen OO. Comparative pharmacokinetics of macrolides. J Antimicrob Chemother 1987;20(suppl B):81–88.

17 Kirst HA, Sides GE. New directions for macrolide antibiotics: structural modifications and in vitro activity. Antimicrob Agents Chemother 1989;33:1413–1418.

18 Pechère JC. Clinical evaluation of roxithromycin 300 mg once daily as an alternative to 150 mg twice daily. Diagn Microbiol Infect Dis 1992;15:1115–1175.

19 Pechère JC. The activity of azithromycin in animal models of infection. Eur J Clin Microbiol Infect Dis 1991;10:821–827.

20 Loos U, Kees F. Pulmonary disposition of clarithromycin (abstract 441). In: Abstracts of the 17th International Congress of Chemotherapy, Berlin 1991. Munich: International Society of Chemotherapy, 1991.

21 Baldwin DR, Wise R, Andrews JM, Ashby JP, Honeybourne D. Azithromycin concentrations at the sites of pulmonary infection. Eur Respir J 1990;3:886–890.

22 Pilot MA, Qin XY. Macrolides and gastrointestinal motility. J Antimicrob Chemother 1988;22(suppl B):201–206.

23 Anderson G, Esmonde TS, Coles S, Macklin J, Carnegie G. A comparative safety and efficacy study of clarithromycin and erythromycin stearate in community-acquired pneumonia. J Antimicrob Chemother 1991;27(suppl A):117–124.

24 Herron JM. Roxithromycin in the therapy of Streptococcus pyogenes throat infections. J Antimicrob Chemother 1987;20(suppl B):139–144.

25 Still JG. Comparative safety and efficacy of clarithromycin and penicillin V suspensions in the treatment of children with streptococcal pharyngitis and/or tonsillitis (Abstract 1677). In: Program and Abstracts of the 32nd Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, DC: American Society for Microbiology, 1992.

26 Levenstein JH. Clarithromycin versus penicillin in the treatment of streptococcal pharyngitis. J Antimicrob Chemother 1991;27(suppl A):67–74.

27 Bachand RT Jr. A comparative study of clarithromycin and penicillin UK in the treatment of outpatients with streptococcal pharyngitis. J Antimicrob Chemother 1991;27(suppl A):75–82.

28 Portier H, Hoorzie S, Kazmierzak A, Lucht F, Ross A. Five days josamycin 1 g b.i.d. vs 10 days peni V IMIU t.i.d. for streptococcal pharyngitis/tonsillitis in adults and children over 8 years (Abstract 1678). In: Program and Abstracts of 32nd Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, DC: American Society for Microbiology, 1992.

29 Hamil MC. Multicentre evaluation of azithromycin versus erythromycin in the treatment of paediatric pharyngitis or tonsillitis caused by group A streptococci. J Antimicrob Chemother 1993;31(suppl E):89–94.

30 Bahal N, Nahata MC. The new macrolide antibiotics: azithromycin, clarithromycin, and roxithromycin. Ann Pharmacother 1992;26:46–55.

31 Barrett MS, Jones RN. Clarithromycin in vitro activity enhanced by its major metabolite, 14-hydroxy-clarithromycin. Diag Microbiol Infect Dis 1992;15:259–266.

32 Kalm O, Kamme C, Bergström B, Lölkvist T, Norman O. Erythromycin stearate in acute maxillary sinusitis. Scand J Infect Dis 1975;7:209–217.

33 Karma P, Pukander J, Penttilä M et al. The comparative efficacy and safety of clarithromycin and amoxicillin in the treatment of outpatients with acute maxillary sinusitis. J Antimicrob Chemother 1991;27(suppl A):83–90.

34 Müller O. Comparison of azithromycin versus clarithromycin in the treatment of patients with upper respiratory tract infection. J Antimicrob Chemother 1991;27(suppl E):137–146.

35 Pennington JE. Community-acquired pneumonia and acute bronchitis. In: Pennington JE, ed. Respiratory Infections: Diagnosis and Management. New York: Raven Press, 1989.

36 Huck W, Guthrie EH, Smits P, Black S, Ferendo R, Harris J.
Dirithromycin vs erythromycin base in lobar pneumonia/bronchopneumonia due to Mycoplasma, Legionella or Chlamydia infection (abstract 1680). In: Program and Abstracts of 32nd Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington: American Society for Microbiology, 1992.

37 Poirier R. Comparative study of clarithromycin and roxithromycin in the treatment of community-acquired pneumonia. J Antimicrob Chemother 1991;27(suppl A):109–116.

38 Altemeir WA, Ayoub EM. Erythromycin prophylaxis for pertussis. Pediatrics 1977;59:623–625.

39 Bass JW. Erythromycin for treatment and prevention of pertussis. Pediatr Infect Dis J 1986;5:154–157.