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# Comparative Tolerability of Erythromycin and Newer Macrolide Antibacterials in Paediatric Patients

*Nicola Principi* and *Susanna Esposito*

Paediatric Department IV, University of Milan, L. Sacco Hospital, Milan, Italy

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## Abstract

The macrolides are a well established group of antibacterials frequently used in general practice. The most frequently used macrolides in paediatric patients are erythromycin, a naturally occurring compound, and clarithromycin and azithromycin, recently developed macrolides.

Overall adverse effect rates of 7 to 26% for erythromycin, 14 to 26% for clarithromycin, and 6 to 27% for azithromycin have been described in children. Adverse gastrointestinal effects, including nausea, vomiting, diarrhoea and abdominal cramps, are the most common problems in children. Allergic reactions, hepatotoxicity, ototoxicity and adverse effects involving the central and peripheral nervous systems have also been observed in children. Stevens-Johnson, Schönlein-Henoch and Churg-Strauss syndromes have been rarely described in children.

Treatment-related laboratory abnormalities have been recorded in 2 to 4% of erythromycin- and in 0 to 1% of both clarithromycin- and azithromycin-treated children. Elevation in liver function tests was the most common abnormality cited.

Increased macrolide use in children in recent years has resulted in a growing potential for drug interactions between them and other pharmacologically active agents via the inhibition of cytochrome P450 (CYP) microsomal enzymes. Drug interactions with theophylline, cyclosporin, carbamazepine, terfenadine and warfarin limit erythromycin use. Clarithromycin is a weak inducer of CYP and exhibits fewer drug-drug interactions than erythromycin. However, its use with theophylline, carbamazepine and terfenadine is contraindicated. In contrast, no significant interactions have been reported with azithromycin to date.

Macrolides have been proven to be well tolerated in the treatment of upper and lower respiratory tract infections, skin and soft tissue infections, and also in less frequent infections occurring in paediatric patients. In addition, clarithromycin and azithromycin have shown good tolerability profiles in immunocompromised paediatric patients.

*In conclusion*, macrolides antibacterials have proven to be well tolerated in paediatric patients. Although the incidence of adverse effects is similar with the use of erythromycin and the newer macrolides, drug interactions occur significantly less when clarithromycin or azithromycin are administered.

The macrolides are a well established group of antibacterials frequently used in general practice.[1,2] Erythromycin, a naturally occurring compound, is the most well known member of this group and is probably one of the better tolerated antibacterials in common use.[3,4] The 2 forms of erythromycin used in paediatric practice are erythromycin ethylsuccinate and erythromycin estolate, which are both well tolerated. However, higher peak serum concentrations and half-lives for the estolate form has been noted after administration of multiple doses.[5] Clinical findings suggest that erythromycin in both ethylsuccinate and estolate forms is the drug of choice for infants and children with pertussis, lower respiratory tract infections caused by *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Chlamydia trachomatis*, *Legionellosis*, and enteritis caused by *Campylobacter jejuni*. They are also indicated for treatment of syphilis; for streptococcal, staphylococcal and pneumococcal infections; genital infections caused by *Ureaplasma urealyticum*; and for the prevention of rheumatic fever and endocarditis in patients who are allergic to β-lactam antibacterials.[6,7]

The newer macrolides recently developed offer advantages over the erythromycin forms.[8-11] Azithromycin and clarithromycin are more active than erythromycin against *Haemophilus influenzae*.[1,2] These 2 drugs are also active against *Borrelia burgdorferi*, *Helicobacter pylori*, *Plasmodium falciparum*, *Mycobacterium avium-intracellulare* complex, *Cryptosporidium* spp. and *Toxoplasma gondii*.[11] These agents may also provide alternatives to erythromycin for the management of several other paediatric infections, including *Bordetella pertussis* infection, trachoma and neonatal *U. urealyticum*.[11] Moreover, they have fewer interactions with commonly used drugs.[10]

Only erythromycin, clarithromycin and azithromycin have been selected for review in this article, the former being the natural product and the latter two being the most often used semisynthetic newer products.

## 1. Overview of Tolerability

Data from clinical trials conducted worldwide show that macrolides are one of the most innocuous antibacterial classes in use. The relatively few studies that compared different macrolides in the same clinical conditions showed that erythromycin, clarithromycin and azithromycin are well tolerated and can be used for the treatment of acute bacterial infections in infants and children of all ages. Overall adverse effect rates of 7 to 26% for erythromycin,

**Table I.** Comparison of the incidence of treatment-related adverse effects of macrolides in paediatric patients

| Reference | Indication | Treatment (days) | No. of patients | Adverse effect [no. (%)] | | |
|---|---|---|---|---|---|---|
| | | | | gastrointestinal | allergic reactions | others |
| Block et al.[17] | CAP | E 13.3 mg/kg tid (10) | 110 | 29 (26.3) | 0 | 0 |
| | | CLR 7.5 mg/kg bid (10) | 124 | 32 (25.8) | 1 (0.8) | 0 |
| Roord et al.[15] | LRTI | E 13.3 mg/kg tid (10) | 40 | 6 (15) | 0 | 0 |
| | | AZM 10 mg/kg od (3) | 45 | 12 (26.6) | 0 | 0 |
| Weippl[14] | PH | E 10-16.6 mg/kg tid (10) | 47 | 6 (12.7) | 0 | 0 |
| | | AZM 10 mg/kg od (3) | 46 | 4 (8.6) | 0 | 1[a] (2.1) |
| Principi et al.[16] | CAP | E 13.3-16.6 mg/kg tid (10) | 67 | 5 (7.4) | 1 (1.4) | 0 |
| | | AZM 10 mg/kg od (3) | 78 | 2 (2.5) | 0 | 0 |
| Treadway & Pontani[12] | URTI/LRTI/SSTI | E 13.3 mg/kg tid (10) | 270 | 18 (6.7) | 4 (1.4) | 0 |
| | | CLR 7.5 mg/kg tid (10) | 7 | 0 | 0 | 0 |
| | | AZM 10 mg/kg od (3) | 2655 | 140 (5.4) | 29 (1.1) | 6[b] (0.2) |
| Arguedas et al.[18] | AOM | CLR 7.5 mg/kg bid (10) | 47 | 10 (21.2) | 1 (2.1) | 0 |
| | | AZM 10 mg/kg od (3) | 50 | 5 (10) | 0 | 0 |

a Headache.

b Headache, dizziness.

**AOM** = acute otitis media; **AZM** = azithromycin; **bid** = twice daily; **CAP** = community-acquired pneumonia; **CLR** = clarithromycin; **E** = erythromycin; **LRTI** = lower respiratory tract infection; **od** = once daily; **PH** = pharyngitis; **SSTI** = skin and soft tissue infection; **tid** = 3 times daily; **URTI** = upper respiratory tract infection.

14 to 26% for clarithromycin and 6 to 27% for azithromycin have been described for children.[12-18] The majority of adverse effects were mild to moderate, and only rarely was therapy prematurely discontinued. In addition, it should be recalled that adverse effect rates are always higher under the strict conditions of clinical trials than in daily practice.

Data on the tolerability of erythromycin ethylsuccinate versus erythromycin estolate in comparative paediatric trials are scanty; the rates of occurrence of adverse effects with the 2 drug preparations seem to be similar. The incidence of adverse effects is similar with the use of erythromycin and that of the other macrolides. However, compared with both erythromycin forms, newer macrolides demonstrate an improved pharmacokinetic profile allowing less frequent administration, increased and more consistent serum concentrations against the organisms usually associated with the commonest bacterial infections encountered in paediatric patients and a better microbiological profile.[12-18] A comparison of the incidence of treatment-related adverse effects of the different macrolides in paediatric patients is shown in table I.

Treadway and Pontani[12] treated 2655, 7 and 270 children with azithromycin, clarithromycin and erythromycin, respectively. The incidence of treatment-related adverse effects was 8.1% for erythromycin, 0% for clarithromycin (there were only 7 children studied) and 8.7% for azithromycin. In all treatment groups, the majority of the adverse effects were classed as being of only mild or moderate severity and were gastrointestinal in nature. Therapy was discontinued in 3% of the erythromycin- and in 1.3% of the azithromycin-treated children.

In a review of 6655 patients aged 6 months to 94 years, Hopkins[13] confirmed these results comparing the safety and tolerability of azithromycin with that of other antimicrobials, including erythromycin. There was no difference in safety and tolerability between azithromycin and the comparative agents. The incidence of treatment-related adverse effects was 8.4% for azithromycin and 12.9% for the comparative agents considered all together. Premature discontinuation due to adverse effects was observed in 0.6% of azithromycin- and in 0.9% of erythromycin-treated children.

In several clinical studies,[14-17] erythromycin showed comparable tolerability and tolerance to both clarithromycin and azithromycin. Moreover, it was shown that clarithromycin and azithromycin had similar tolerability profiles.[18]

Macrolide-related adverse effects can be classified into 7 categories. Because of the scarcity of studies comparing different macrolides, the incidence of treatment-related adverse effects classified in each category can be drawn only from studies that have evaluated the tolerability of a single macrolide in comparison with antimicrobials of other classes.

### 1.1 Gastrointestinal Adverse Effects

Adverse gastrointestinal effects including nausea, vomiting, diarrhoea and abdominal cramps, are the most common problems in patients receiving macrolide therapy.[12-23] Gastrointestinal adverse effect rates of 7 to 26% for erythromycin, 14 to 26% for clarithromycin, and 3 to 27% for azithromycin have been observed.[12-18] Gastrointestinal intolerance may be related to a promotility effect of the macrolides on gastrointestinal smooth muscle, caused by the macrolide acting as an agonist at the motilin receptor.[24] These gastrointestinal complaints may occur more frequently when the medication is administered on an empty stomach and/or in excessive dosage. Several approaches to reduce the incidence or severity of these effects have been proposed, such as temporarily reducing the daily dose, using the oral suspension formulation in small doses at frequent intervals, administering the drug with food or milk and drinking water every 15 minutes for 2 to 3 hours after each dose.[25] However, these measures may not be effective and may compromise therapy by reducing the dose administered and/or absorbed, or by reducing compliance.

### 1.2 Allergic Reactions

Allergic reactions, characterised by rash, fever, eosinophilia and joint pain, have been observed.[12-18] However, in contrast to other antibacterial classes, especially the ß-lactams, hypersensitivity to the macrolides occurs rarely. The incidence of anaphylaxis for erythromycin is less than 1 per million patients and newer macrolides have demonstrated similar figures.[12-18] However, other adverse effects that might be associated with possible allergic reactions have been observed in 0 to 5% of children treated with erythromycin, clarithromycin and azithromycin.[12-18] Even this small incidence is probably spuriously high since no systematic search has been made for other causes of hypersensitivity. Some of them might have been viral or due to a response caused by the infection, rather than the medication.[12-18]

### 1.3 Hepatotoxicity

Macrolide-associated cholestatic hepatotoxicity may produce mild to severe signs and symptoms, with the more severe symptoms mimicking acute cholecystitis. Altogether, cholestatic hepatitis is a very rare event: all macrolide antibacterials have been associated with this adverse reaction, but erythromycin is by far the most frequently implicated. In the past, the rate of occurrence of hepatotoxicity with erythromycin estolate was considered higher than with erythromycin ethylsuccinate; recent data indicate that the frequency of cholestatic hepatitis is similar for the 2 paediatric forms of erythromycin.[20,26-30] However, for the paediatric age group as a whole, the risk of hepatic toxicity with macrolides is very small; after puberty, the frequency of toxicity appears to increase modestly.[20,26-30]

Individuals experiencing hepatic adverse effects from macrolides complain of abdominal pain, nausea and vomiting; acholic stools and dark urine have also been described. Fever occurs in approximately 50% of patients; jaundice and pruritus are prominent in 20%. Hepatic enlargement may occur, and various pleomorphic rashes are occasionally observed. Eosinophilia is present in at least two-thirds of patients and serum bilirubin and alkaline phosphatase levels are increased in about half of affected individuals, whereas transaminases are uniformly elevated. This reaction, which usually occurs after 10 to 21 days of treatment (sooner on rechallenge), is thought to occur by a combined hypersensitivity-toxicity mechanism.[20,28-30]

### 1.4 Ototoxicity

Reversible sensorineural bilateral hearing loss, which is most likely to occur at high doses in patients with decreased renal function, has also been reported.[31-33] Typical findings include moderate perceptive hearing loss with greater impairment above 4000Hz and low-pitched tinnitus. The ototoxic symptoms usually appear within the first days of drug administration and recovery of hearing generally begins almost immediately once the drug is withdrawn. Macrolide ototoxicity results from excessive drug serum concentrations and is thought to involve central auditory pathways.[31-33]

Haydon et al.[31] reported 22 cases of ototoxicity due to erythromycin. All occurred among adults, who had a median age of 61 years. The youngest patients were 2 young women aged 17 and 18 years, and both were experiencing renal failure. Of the 22 reported cases, most had received erythromycin intravenously; in 2 instances the drug had been added to peritoneal dialysate. Defective excretion of erythromycin has been found to be a major factor in the production of deafness.[31]

Hearing loss has also been described in HIV-positive adults receiving long term daily regimens of azithromycin.[33] Of 21 patients treated for disseminated *Mycobacterium avium* infection with a regimen containing azithromycin, clofazimine, and ethambutol, 14% developed transient bilateral sensorineural hearing loss documented by audiological assessments. Because of azithromycin ototoxicity, Wallace et al.[33] treated *M. avium* with a 3-drug regimen of clarithromycin, clofazimine, and ethambutol. None of the 26 patients on clarithromycin who were followed for 2 to 12 months reported any ototoxicity.

It is unclear whether deafness may also be possible in paediatric patients receiving long term high dose macrolide therapy. However, children receiving macrolides on a long term basis should be monitored for hearing problems.

### 1.5 Reactions Limited to Parenteral Products

Thrombophlebitis secondary to intravenous administration of erythromycin is a significant adverse effect that may be reduced in incidence or severity by decreasing the infusion rate and/or the drug concentration in the infusate.[20] Another adverse effect in infants and children that may be related to the intravenous route of administration of erythromycin is cardiotoxicity,[34] manifested by bradycardia, hypotension, cardiac arrest and torsade de pointes (polymorphous ventricular tachycardia). There have been case reports of newborn and infant mortality due to cardiac disturbances after intravenous injection of erythromycin.[35,36] Consequently, the intravenous administration of erythromycin is not recommended to premature babies, infants and young children.

### 1.6 Miscellaneous Adverse Effects

As would be expected with any medication that is commonly prescribed, a number of adverse effects have been reported on rare occasions which are almost certainly spurious. In most instances, these changes were part of the natural history of the disease that was being treated or occurred when the drug was administered but the underlying disease was still unrecognised.

Adverse effects involving the central and peripheral nervous systems have been observed (with an incidence of 0.2 to 1.3% for all macrolides, predominantly manifesting as headache, insomnia

and/or dizziness).[12-18] Stevens-Johnson, Schönlein-Henoch and Churg-Strauss syndromes have also been described in association with macrolide use.[37-39]

Clinically insignificant abnormalities in laboratory tests have been reported, with treatment-related laboratory abnormalities recorded in 2 to 4% of erythromycin- and in 0 to 1% of both clarithromycin- and azithromycin-treated participants.[2-18,40] Elevation in liver function tests have been the most commonly reported (table II). All laboratory values were found to return to normal at follow-up.[2-18,40]

### 1.7 Pharmacological Drug Interactions

Increased macrolide use in recent years has resulted in a growing potential for drug interactions between these agents and other drugs. Most of these interactions involve inhibition of drug metabolism via cytochrome P450 (CYP) microsomal enzymes. This occurs via the induction of 1 or more CYP enzymes that in turn convert the macrolide to a nitrosalkalane metabolite that forms a stable inactive complex with the iron of CYP. Interactions have been reported between macrolides and other widely used or widely available compounds. Consequently, all patients have to be questioned carefully and cautioned before antibacterials are prescribed.[41-44] Macrolide drug interactions that may cause clinical symptoms in children are shown in table III.

**Table II.** Liver function abnormalities occurring during macrolide therapy

| | Erythromycin[40] | Clarithromycin[22] | Azithromycin[12] |
|---|---|---|---|
| **AST/ALT** | | | |
| No. of patients evaluated | 166 | 1101 | 598 |
| No. (%) with values ONL | 7 (4.2) | 5 (0.4) | 3 (0.5) |
| **Alkaline phosphatase** | | | |
| No. of patients evaluated | 166 | 1676 | 486 |
| No. (%) with values ONL | 6 (3.6) | 0 | 2 (0.5) |
| **Total bilirubin** | | | |
| No. of patients evaluated | 166 | 1077 | 489 |
| No. (%) with values ONL | 3 (1.8) | 1 (0.09) | 1 (0.2) |

**ALT** = alanine aminotransferase (SGPT); **AST** = aspartate aminotransferase (SGOT); **ONL** = outside normal limits .

Erythromycin has been noted for a wide range of interactions with other therapeutic agents. Many of these interactions can be severe and have resulted in erythromycin's use being restricted among certain patient groups receiving concomitant therapies. Drug interactions with theophylline, cyclosporin, carbamazepine, terfenadine and warfarin limit erythromycin use.[2,41-44]

Children receiving concurrent therapy with erythromycin and theophylline were found to have markedly increased serum concentrations of theophylline, and this was often associated with bouts of vomiting.[45] Parish et al.[46] reported a case of a child who was taking carefully monitored doses of theophylline for chronic asthma and who experienced seizure activity when she was placed on erythromycin therapy for bronchitis.

Cyclosporin is extensively metabolised by the CYP system and so, as with theophylline, there is considerable potential for interaction with erythromycin. This is particularly important because, since immunosuppressants reduce the ability of the body to fight infection, antibacterial therapy is often required.

A number of cases of carbamazepine toxicity have been described in children with epilepsy who were also receiving erythromycin. Signs of toxicity, including confusion, somnolence, ataxia, vertigo, nausea and vomiting started shortly after beginning erythromycin therapy and disappeared rapidly on withdrawal of the antibacterial.[50-52] Thus, if avoidance of this drug combination is not possible, modification of carbamazepine dosage and/or monitoring blood concentrations is desirable.[50,52]

Terfenadine, when administered with erythromycin, may accumulate and serious cardiovascular adverse effects may occur. These reactions include

**Table III.** Pharmacological drug interactions of macrolides: clinical effects observed in children

| Macrolide | Interacting drug | Clinical effect | Reference |
|---|---|---|---|
| E, CLR | Theophylline | Nausea, vomiting, convulsions, supraventricular tachycardia | 44-47 |
| E | Cyclosporin | Renal failure | 48,49 |
| E, CLR | Carbamazepine | Nausea, vomiting, confusion, somnolence, ataxia, vertigo | 50-52 |
| E, CLR | Terfenadine | Ventricular arrhythmias, torsade de pointes, cardiac arrest, death | 53 |
| E | Warfarin | Haemorrhage | 44 |
| E | Corticosteroids | Myopathy, nervousness, insomnia, osteoporosis, osteonecrosis | 44,54 |
| E | Digoxin | Atrial or ventricular arrhythmias, cardiac arrest, death, nausea, vomiting, diarrhoea, headache | 55 |
| E | Ergot alkaloids | Nausea, vomiting, hypoaesthesia, paraesthesia | 44,56 |
| E | Benzodiazepines | Nausea, vomiting, confusion, somnolence, ataxia, vertigo | 44,56 |

**CLR** = clarithromycin; **E** = erythromycin.

ventricular arrhythmias, torsade de pointes, cardiac arrest and death.[53] Erythromycin can also decrease warfarin clearance and consequently can markedly increase prothrombin time. In patients receiving concomitant therapy it is recommended that prothrombin time is monitored.[44]

There are also several reports of erythromycin interacting with a range of other drugs including corticosteroids, bromocriptine, digoxin, ergot alkaloids and benzodiazepines.[44,53,54] In the case of digoxin, the interaction is thought to occur via enhancement of the bioavailability of the drug secondary to inhibition of digoxin-metabolising bacteria in the large bowel.[55]

Modifications of the macrocyclic lactone ring structure and of the substituent groups in erythromycin have resulted in macrolide compounds with different drug interaction potentials.[2,44]

Clarithromycin is a weak inducer of CYP and exhibits fewer drug-drug interactions than erythromycin. However, its use with theophylline, carbamazepine and terfenadine is contraindicated.[21,47,52] There have been no reports of clarithromycin interacting with cyclosporin.[57,58]

No significant interactions have been reported with azithromycin to date.[23,44] These data may be explained by the absence of CYP interactions with azithromycin. Consequently, azithromycin can be administered to patients receiving theophylline, carbamazepine, terfenadine and warfarin without need for dosage adjustment.[23,44] However, a single recent case report showed a marked increase in serum concentrations of cyclosporin 2 days after the start of a 5-day course of azithromycin in a renal transplant recipient. Monitoring of serum cyclosporin concentrations is therefore recommended in patients who receive both drugs.[59] Data on interactions between azithromycin and digoxin or ergot derivatives are unavailable at present. Therefore, serum digoxin concentrations should be monitored in patients who are prescribed azithromycin together with digoxin and concurrent administration of azithromycin and ergot derivatives are not recommended because of the theoretical risk of ergotism.[56,60]

Although the absorption of the capsule formulation of azithromycin is significantly reduced by coadministration with food, the paediatric oral suspension and tablet formulations are not, and can be taken without regard to meals.[44]

Interestingly, interactions have been observed between azithromycin and aluminium/magnesium combination antacids. Although the mean maximum serum concentrations of azithromycin were significantly reduced by concurrent antacid administration, the extent of total azithromycin absorption was unaffected. This finding probably has little clinical implication as the activity of

azithromycin is not directly dependent on serum concentration.[23]

The data presented in references 41 to 60 highlighted that an advantage of the newer macrolides is their lower incidence of drug interactions than erythromycin. However, it is important to remember that investigations on possible drug interactions are usually conducted in healthy volunteers, so that experimental conditions are controlled and confounding factors are avoided. Clinical practice can present a different picture. There are several groups of patients in whom the risks of interactions are greater, and it is important that the medical community is first alerted to a potential interaction through a case report. In particular, it is important to carefully observe immunocompromised patients who are at increased risk of antibacterial-related interactions because they receive aggressive antibacterial regimens as therapy for difficult-to-treat pathogens.

## 2. Macrolide Tolerability in Different Clinical Conditions

*In vitro* susceptibility testing has demonstrated a good activity of macrolides against Gram-positive and Gram-negative pathogens, as well as atypical organisms involved in the aetiology of upper and lower respiratory tract infections and skin and soft tissue infections. Moreover, newer macrolides have proven to be useful for therapy of *Helicobacter pylori* infections, mycobacterial and odontogenic infections and prophylaxis against chloroquine-resistant strains of *Plasmodium falciparum*.[8-11]

### 2.1 Upper Respiratory Tract Infections

The group A β-haemolytic streptococcus (*Streptococcus pyogenes*) remains an important cause of acute pharyngitis, especially among school-aged children. Parenteral or oral penicillins are the drugs of choice in the treatment of this disease; macrolides are considered the most useful alternative agents except in countries where the frequency of erythromycin-resistant *S. pyogenes* strains is relevant.[1,2,10] The tolerability of macrolides in children with upper respiratory tract infections is shown in table IV.

It has been shown that phenoxymethylpenicillin (penicillin V) and macrolides are both well tolerated in upper respiratory tract infections.[61-63] Still et al.[61] compared clarithromycin and phenoxymethylpenicillin potassium (penicillin VK) suspensions. It was observed that the 2 drugs were equally well tolerated. The incidence and nature of adverse effects were similar in the clarithromycin and penicillin groups, except for gastrointestinal complaints reported in 14% of the clarithromycin recipients compared with 5% in the penicillin recipients ($p < 0.01$). There were no significant changes in haematological or serum chemistry parameters in either group.

In a multicentre trial, Hamill[62] compared azithromycin once daily for 3 days with phenoxymethylpenicillin 4 times daily for 10 days in children with acute pharyngitis or acute tonsillitis. Only 2 patients (4%) in the azithromycin group complained of adverse effects. One patient had moderate headache and dizziness, and vomited once (4 weeks after the end of treatment): this event was unlikely to be related to the study treatment. The second patient had moderate diarrhoea on the last day of treatment, but this resolved within 1 day. No adverse effects were reported in the group treated with phenoxymethylpenicillin. Laboratory test abnormalities were observed in 13% and in 9% azithromycin- and phenoxymethylpenicillin-treated patients, respectively, but none was judged to be clinically significant. Most of the abnormalities recorded were haematological (low neutrophil count, elevated white blood cell count); in 1 patient liver enzymes were elevated but no follow-up was required. It was concluded that the shorter azithromycin course was as well tolerated as the standard 10-day penicillin course. Other studies have yielded similar results.[21,63]

Apart from pharyngitis, one of the commonest infectious diseases in childhood is acute otitis media. It is predominantly of bacterial aetiology: *Streptococcus pneumoniae* is the most frequently recognised pathogens, followed by *Haemophilus*

**Table IV.** Tolerability of macrolides in children with upper respiratory tract infections

| Diagnosis | Dosage (mg) | Treatment duration (days) | No. of evaluable patients | Adverse events (%) | Overall gastrointestinal problems (%) | Reference |
|---|---|---|---|---|---|---|
| **Comparisons with phenoxymethylpenicillin [penicillin V (PV)]** | | | | | | |
| PG | CLR 7.5 mg/kg bid | 10 | 176 | 52 | 14[a] | 61 |
| | PV 13.3 mg/kg tid | 10 | 191 | 46 | 5 | |
| PG | AZM 10 mg/kg od | 3 | 49 | 4 | 0 | 62 |
| | PV 125-250 mg qid | 10 | 47 | 0 | 0 | |
| PG | AZM 10 mg/kg od | 3 | 160 | 14 | NA | 21 |
| | PV 18 mg/kg tid | 10 | 160 | 9 | NA | |
| PG | AZM 10 mg/kg od | 3 | 93 | 8.6 | 7.5 | 63 |
| | PV 14 mg/kg tid | 10 | 90 | 5.5 | 4.4 | |
| **Comparison with amoxicillin (AMX)** | | | | | | |
| AOM | CLR 7.5 mg/kg bid | 7-10 | 27 | 25.6 | 15.4 | 64 |
| | AMX 20 mg/kg bid | 7-10 | 20 | 17.5 | 12.5 | |
| AOM | AZM 10 mg/kg od | 3 | 77 | 3 | 3 | 65 |
| | AMX 10 mg/kg tid | 10 | 77 | 4 | 4 | |
| AOM prevention | AZM 5-10 mg/kg od | 180 | 74 | 0 | 0 | 75 |
| | AMX 20 mg/kg od | 180 | 74 | 0 | 0 | |
| **Comparison with amoxicillin-clavulanic acid (AMC)** | | | | | | |
| AOM | CLR 7.5 mg/kg bid | 10 | 161 | 31.1[a] | 21.1[a] | 66 |
| | AMC 13.3 mg/kg tid | 10 | 177 | 41.8 | 36.7 | |
| AOM | CLR 7.5 mg/kg bid | 10 | 90 | 32[a] | 20[a] | 67 |
| | AMC 13.3 mg/kg tid | 10 | 90 | 51 | 51 | |
| AOM | AZM 10 mg/kg od | 3 | 197 | 11.7[a] | 7.6[a] | 68 |
| | AMC 13.3 mg/kg tid | 10 | 192 | 22.4 | 18.7 | |
| AOM | AZM 10 mg/kg od | 3 | 215 | 4.5[a] | 3.2[a] | 69 |
| | AMC 13.3 mg/kg tid | 10 | 198 | 8.3 | 5.8 | |
| AOM | AZM 5-10 mg/kg od | 5 | 85 | 3.5[a] | 3.5[a] | 70 |
| | AMC 13.3 mg/kg tid | 10 | 84 | 31 | 28.6 | |
| AOM | AZM 5-10 mg/kg od | 5 | 341 | 8.8[a] | 7.9[a] | 71 |
| | AMC 13.3 mg/kg tid | 10 | 336 | 30.8 | 28.7 | |
| AOM | AZM 5-10 mg/kg od | 5 | 263 | 7.2[a] | 6.1[a] | 72 |
| | AMC 13.3 mg/kg tid | 10 | 263 | 17.1 | 14.8 | |
| **Comparison with cefaclor (CEC)** | | | | | | |
| AOM | CLR 7.5 mg/kg bid | 10 | 199 | 15.1 | 11.4 | 73 |
| | CEC 10 mg/kg bid | 10 | 180 | 17.2 | 13.3 | |
| AOM | AZM 10 mg/kg od | 3 | 125 | 5 | 5 | 74 |
| | CEC 6.6 mg/kg tid | 10 | 134 | 6 | 5 | |

a $p < 0.05$ versus comparator agent.

**AOM** = acute otitis media; **AZM** = azithromycin; **bid** = twice daily; **CLR** = clarithromycin; **NA** = not available; **od** = once daily; **PG** = pharyngitis; **qid** = 4 times daily; **tid** = 3 times daily.

*influenzae* and *Moraxella catarrhalis*. Therapy with an appropriate antibacterial, coupled with clinical follow-up, remains the cornerstone of effective therapy. The recent emergence of penicillin-resistant *S. pneumoniae* and the increasing frequency of ß–lactamase-producing strains of *M. catarrhalis* and *H. influenzae* are creating concerns regarding the use of amoxicillin as traditional first line empiric therapy for acute otitis media. Thus, alternative agents have been employed.

Newer macrolides have proven to be clinically and bacteriologically equivalent to amoxicillin,

amoxicillin-clavulanic acid, or cefaclor for the treatment of acute otitis media in children, with a comparable safety profile and low incidence of adverse effects.[64-75]

Pukander et al.[64] showed that clarithromycin and amoxicillin, both twice daily for 7 to 10 days, were similarly effective and well tolerated for the treatment of acute otitis media in children. No significant differences in the incidence rates of adverse effects and laboratory abnormalities were found. In both treatment groups gastrointestinal disorders were the most common complaint. Comparable tolerability was also observed between azithromycin and amoxicillin.[65]

Mohs et al.[65] compared azithromycin once daily administered for 3 days with amoxicillin administered 3 times daily in the treatment of acute or recurrent otitis media. Both drugs were well tolerated by the children, with no discontinuations due to adverse effects in either group. All adverse effects were gastrointestinal in nature.

Randomised, multicentre trials have also compared the safety and efficacy of clarithromycin and azithromycin with that of amoxicillin-clavulanic acid in the treatment of acute otitis media in children.[66-72] Data have indicated that the efficacy of clarithromycin oral suspension was comparable with that of amoxicillin-clavulanic acid oral suspension; however, clarithromycin was better tolerated with a lower incidence of gastrointestinal adverse effects.[66,67] Also, azithromycin was as effective as amoxicillin-clavulanic acid both clinically and bacteriologically, but was significantly better tolerated.[68-72] Neither drug caused serious adverse effects, and no patients were withdrawn from therapy as a result of laboratory test abnormalities in any study. Of note, however, azithromycin was associated with a significantly lower incidence of adverse effects in the comparative trials, as well as a markedly lower incidence of withdrawals because of adverse effects than amoxicillin-clavulanic acid.[68-72]

In an nonblind multicentre study[69] carried out in 484 children between the ages of 6 months and 12 years with acute otitis media, the differences between azithromycin and amoxicillin-clavulanic acid in terms of tolerability were statistically significant: treatment-related adverse effects were recorded in 4.5% of azithromycin recipients and in 8.3% of amoxicillin-clavulanic acid recipients. No patients in the azithromycin-treatment group were withdrawn from treatment, whereas 6 amoxicillin-clavulanic acid–treated patients, including two patients who were <2 years of age, discontinued treatment prematurely because of moderate gastrointestinal disturbances ($p < 0.05$).

In 11 of 243 azithromycin-treated patients, a total of 14 adverse effects that may or may not have been treatment related were recorded.[69] Of these 14 effects 11 involved the digestive system as follows: 4 cases of mild and 2 of moderate diarrhoea; 2 cases of moderate vomiting; 1 case of mild abdominal pain; 1 case of mild dyspepsia; and 1 case of moderate jaundice. Nongastrointestinal adverse effects consisted of moderate rash in 1 patient with moderate diarrhoea, moderate anorexia in 1 child, who also experienced mild vomiting and diarrhoea, and mild cough in 1 patient.

In 20 of 240 amoxicillin/clavulanate-treated patients a total of 30 adverse effects that may or may not have been treatment related were recorded.[69] Of these, 24 involved the digestive system as follows: 13 cases of diarrhoea, 7 cases of vomiting, 3 cases of nausea and 1 case of mild dyspepsia. Other adverse effects included 2 cases of moderate and 1 case of mild abdominal pain, and moderate rash and moderate facial oedema in 1. No significant difference was detected between treatment groups in the proportion of patients with laboratory abnormalities or abnormal liver function tests when all patients or the subgroup who were <2 years old were considered.

Other studies have confirmed that azithromycin is as effective as amoxicillin-clavulanic acid but produces a significantly lower incidence of adverse effects.[68,70-72]

Moreover, no statistically significant differences were observed between clarithromycin or a 3-day regimen of azithromycin and cefaclor suspension in the treatment of acute otitis media in

children.[73,74] Gooch et al.[73] showed that adverse effects associated with the digestive system were the most frequently reported among treatment groups: diarrhoea was the most common gastrointestinal complaint in the clarithromycin treatment group, whereas vomiting was the most common gastrointestinal complaint in the cefaclor group. No clinically significant differences in laboratory values were observed between the 2 treatment groups.

Rodriguez[74] performed an nonblind, multicentre study involving 259 children between 6 months and 13 years of age to assess the efficacy and tolerability of azithromycin and to compare it with cefaclor as treatment of acute otitis media. Patients were randomised to receive either azithromycin 10 mg/kg once daily for 3 days or cefaclor 40 mg/kg daily in divided doses every 8 hours for 10 days. The results showed that the 2 treatments had comparable clinical efficacy with comparable tolerability, with none of the observed adverse effects considered to be severe. Moreover, no abnormalities in laboratory data were noted in any of the evaluable patients.

It is also well known that, because of possible short and long term sequelae of recurrent otitis media, prevention is desirable. Among the various approaches which have been proposed, chemoprophylaxis has been considered the first option. Azithromycin, with its good activity against pathogens that commonly cause acute otitis media and its peculiar pharmacokinetic properties, if given periodically, is theoretically as effective as antibacterials traditionally recommended if given continuously. We performed a study in which a 6-month course of once-weekly azithromycin 5 or 10 mg/kg was compared with that of once-daily amoxicillin 20 mg/kg.[75] We observed that both drugs were well tolerated and no laboratory or clinical adverse effects were observed. Although in our study no substantial modification of the nasopharyngeal flora was noted at the end of prophylaxis in both antimicrobial groups, accurate selection of children eligible for prophylaxis is mandatory to avoid the risk of emergence of resistant strains.[75]

### 2.2 Lower Respiratory Tract Infections

Practitioners have developed a functional algorithm, based on limited data from past studies, about the most important organisms by age group for empiric treatment of community-acquired pneumonia in children. These causative organisms are believed to be mainly respiratory viruses and *S. pneumoniae* in young children and *S. pneumoniae*, *M. pneumoniae* and *C. pneumoniae* in older children.[76] When the diagnosis of *S. pneumoniae* pneumonia seems to be likely, macrolides are not recommended due to the high resistance rate to these antibacterials among *S. pneumoniae* isolates. On the other hand, when *M. pneumoniae* and *C. pneumoniae* are believed to be the aetiological agents of lower respiratory tract infections, macrolides are considered to be the therapy of choice.[77]

In these infections there are only comparative clinical trials of tolerability between different macrolides and not between macrolides and antimicrobials of other classes. All the macrolides appear to be well tolerated.

Block et al.[17] found that clarithromycin and erythromycin were similarly effective for the treatment of radiographically proven, community-acquired pneumonia in children older than 2 years. The majority of adverse effects were mild to moderate and related to the gastrointestinal tract; these effects occurred in 24% of clarithromycin- and 23% of erythromycin-treated patients. The majority of nongastrointestinal adverse effects reported were thought to be secondary to concurrent conditions related to the patients' pneumonia and not caused by the study drug therapy. Clinically insignificant asymptomatic elevations in liver function tests, which did not require a change in therapy, were observed in 1 patient in each treatment group but all laboratory values returned to normal at follow-up visits.

In children with community-acquired pneumonia,[15,16] azithromycin 10 mg/kg/day once daily for 3 days was compared to erythromycin 40 to 50 mg/kg/day 3 times/day for 10 days. It was observed that azithromycin was well tolerated and had a

**Table V.** Tolerability of macrolides in children with skin and soft tissue infections

| Reference | Diagnosis | Dosage (mg/kg) | Treatment duration (days) | No. of evaluable patients | Adverse events (%) | Overall gastrointestinal problems (%) |
|---|---|---|---|---|---|---|
| Hebert et al.[81] | SSTI | CLR 7.5 bid | 10 | 118 | 15.3 | 11 |
| | | CFR 15 bid | 10 | 113 | 19.5 | 15 |
| Montero[82] | SSTI | AZM 10 od | 3 | 100 | 3 | 0 |
| | | CEC 6.6 tid | 10 | 100 | 2 | 0 |
| Rodriguez-Solares et al.[83] | SSTI | AZM 10 od | 3 | 30 | 4 | 4 |
| | | DCX 3-6 qid or FCX 125-400mg qid | 7 | 30 | 4 | 4 |

**AZM** = azithromycin; **bid** = twice daily; **CEC** = cefaclor; **CFR** = cefadroxil; **CLR** = clarithromycin; **DCX** = dicloxacillin; **FCX** = flucloxacillin; **od** = once daily; **qid** = 4 times daily; **SSTI** = skin and soft tissue; **tid** = 3 times daily.

more rapid onset of action than the comparator drug. Most adverse effects were gastrointestinal complaints (diarrhoea, abdominal discomfort and vomiting) in both treatment groups. The shorter treatment course of azithromycin, however, might have an additional beneficial effect on compliance.

### 2.3 Skin and Soft Tissue Infections

Skin and soft tissue infections are common infections, usually caused by *Staphylococcus* and *Streptococcus* species.[78,79] Many antibacterials have been used to treat these infections, but their success has been limited by drug resistance or by adverse reactions. Newer macrolides have shown improved tolerability and efficacy profiles, but optimal therapy has not yet been defined.[80] Results of paediatric multicentre trials, in which macrolides have been studied for skin and soft tissue infections, are shown in table V.

Hebert et al.[81] reported results of a multicentre trial of clarithromycin or cefadroxil administered for 10 days to children ages 6 months to 12 years with infections of the skin and skin structures. Clarithromycin oral suspension appeared to be a well tolerated and effective alternative to cefadroxil for the treatment of paediatric skin and skin structures infections. Adverse effects were mild or moderate and were reported in 25% of clarithromycin and in 35% of cefadroxil patients ($p > 0.05$). In both groups adverse effects involved primarily the digestive tract. The most common gastrointestinal effects event in both treatment groups was vomiting. No significant laboratory changes were noted.

An nonblind, multicentre study[82] was carried out in 200 paediatric patients between 6 months and 12 years of age with skin and/or soft tissue infections (mild-to-moderate dermatological conditions and abscesses) to compare the efficacy and safety of azithromycin and cefaclor oral suspensions. Patients were randomly assigned to receive either azithromycin 10 mg/kg once daily for 3 days or cefaclor 20 mg/kg/day in 3 divided doses for 10 days. The clinical efficacy and the tolerability profile of both treatments were comparable. In particular, the incidence of adverse effects was low (3% in the azithromycin group and 2% in the cefaclor group) and no patient in either treatment group withdrew from the study because of adverse effects. There were, however, significant differences in the treatment regimens of both antibacterials, with advantages in favour of azithromycin because of the once-daily dosing and the short duration of treatment.

Rodriguez-Solares et al.[83] in an nonblind, randomised multicentre trial compared azithromycin 10 mg/kg/day once daily, over 3 days with 2 cloxacillin esters, dicloxacillin 12.5 to 25 mg/kg/day, depending upon infection severity, administered in 4 equal doses daily over 7 days, and flucloxacillin 500 to 1000 mg/day for patients aged 2 to 10 years, and 1000 to 2000 mg/day for patients aged >10 years, administered in 4 equal doses daily over 7 days. Azithromycin was shown to be at least as effective and well tolerated as alternative treatments. Adverse effects, all of which affected the gastrointestinal system, were all rated as mild and

occurred in 4% of the children in each treatment group.

### 2.4 Other Infections

The antimicrobial spectrum of clarithromycin and azithromycin has suggested a number of further uses for these newer macrolides.[8-11]

It has been observed that a 1-week course of treatment with colloidal tripotassium dicitrato bismuthate (bismuth subcitrate), combined with metronidazole and clarithromycin, can eradicate *H. pylori* infection in children and is well tolerated.[84] Among the 22 children who entered into the study, 15 noted no adverse effects apart from black stools, which was expected due to the inclusion of a bismuth-containing compound in the regimen. Two children (9%) had significant adverse effects. One of these children complained of multiple symptoms, including a burning sensation of the tongue, vomiting for 1 day, persistent diarrhoea, and nightmares. A second child vomited or spat out approximately 10 doses of elixir, and was noted to be irritable during the period of treatment. Milder adverse effects were observed by 5 children. Four (18%) complained of a bad taste or burning sensation on the tongue. The fifth child was nauseated for 2 days. None of children withdrew from the study due to adverse effects.

Safety data are also available from a study[85] in paediatric patients receiving clarithromycin plus rifabutin for the treatment of nontuberculous mycobacterial lymphadenitis. This drug combination was associated with a good tolerability profile and caused resolution of discharge and chronic sinus formation.

Azithromycin and spiramycin were compared in the treatment of odontogenic infections in an nonblind, randomised study.[86] Both drugs were well tolerated; azithromycin, however, was significantly more effective than spiramycin in reducing the numbers of anaerobic bacteria in the oral microflora. Moreover, azithromycin has antimalarial activity and favourable pharmacokinetic properties as a prophylactic antimalarial agent.[87,88] Prophylactic azithromycin may offer advantages over doxycycline. Firstly, azithromycin may be better tolerated than doxycycline prophylaxis because gastrointestinal complaints are reported more frequently with the latter drug. Secondly, the long half-life of azithromycin suggests effectiveness when given once or twice a week, whereas doxycycline has a short half-life of 18 hours and must be taken every day to prevent malaria.

Clinical data are unavailable for some diseases caused by organisms that are susceptible *in vitro* to newer macrolides such as *B. pertussis*.[89] However, because of their ease of administration, newer macrolides might be of value for therapy or prophylaxis of cases and contacts of whooping cough.

## 3. Tolerability in Selected Groups of Patients

In the last 20 years, more than at any time in the past, the practice of medicine has had to face the challenge of infections in the immunocompromised host. With the onset of ablative chemotherapy, the widespread use of immunosuppressive regimens, and the occurrence of the AIDS epidemic, illnesses unknown to prior generations have been seen. Depletion of CD4+ lymphocytes prevents the host from activating monocytes and macrophages and, as a consequence, a variety of opportunistic pathogens become capable of causing disease. Antibacterials which accumulate within the cell can serve to compensate for this deficit in phagocytic function.[90]

In addition to their activity against Gram-positive and a number of Gram-negative pathogens, newer macrolides are effective *in vitro* and in animal models[91-96] against *Cryptosporidium parvum*, *T. gondii*, *P. carinii*, *Rhodococcus equi*, *Bartonella* (*Rochalimaea*) species and the *Mycobacterium avium-intracellular* complex. The combination of these drugs' broad antibacterial spectra and their proclivity to concentrate within infected cells makes them particularly attractive agents for use in therapy of the immunocompromised patient.[8-10]

The activity of azithromycin and clarithromycin in the treatment of HIV-seropositive children infected with *Mycobacterium avium-intracellular*

complex has recently been described.[97] Both drugs were well tolerated: adverse effects that were sometimes described included diarrhoea, nausea, vomiting, abdominal pain, headache, dizziness, serum aminotransferase elevations and ototoxicity.

In an experimental study Rehg[98] found azithromycin to be the most effective macrolide in decreasing the parasitic load in the ileum of immunosuppressed experimental animals infected with *Cryptosporidium*. These data have been confirmed *in vivo* by Vargas et al.[99] who observed, in 2 children with cancer and cryptosporidiosis, that administration of azithromycin 40 mg/kg once daily for 21 days was followed by prompt clinical improvement.

## 4. Conclusions

Selection between specific macrolides and between macrolides and other antibacterials in the paediatric population is likely to depend, at least for the immediate future, on separate comparisons of product availability, cost, effectiveness and tolerability profiles.

An abbreviated treatment period is likely to result in better compliance as well as less exposure of the patient to the drug, which might be expected to reduce the risk of adverse effects and further improve compliance.[100,101] Moreover, palatability can affect compliance and thus clinical outcome: it has been observed that the bitter taste of some antibacterial suspensions may reduce compliance and lead to premature discontinuation of therapy.[102] Consequently, even if erythromycin is still the reference macrolide for the treatment of many paediatric infections, its use is associated with disadvantages such as interactions with other drugs and frequent administration.[1,2] The pharmacokinetics of clarithromycin and azithromycin permit a reduction in dose frequency and duration while maintaining tolerability and efficacy comparable to that of conventional 7- to 10-day 3 or 4 times daily regimens.[9,21,22] Consequently, taking into account the simpler administration regimens, it is clear that treatment with newer macrolides carries a substantial clinical advantage in terms of likely patient compliance with, and completion of, the administration regimen.

*In conclusion*, macrolides represent a class of antibacterials characterised by a good tolerability profile. Erythromycin still plays an important role in the therapeutic approach of infections in children. Although the incidence of adverse effects is similar with the use of erythromycin and that of the newer macrolides, drug interactions occur significantly less frequently when clarithromycin or azithromycin are administered. These advantages, coupled with the better compliance of the latter drugs, should be considered in the choice of antibacterial treatment for paediatric patients.

## References

1. Klein JO. History of macrolide use in pediatrics. Pediatr Infect Dis J 1997; 16: 427-31
2. Guay DRP. Macrolide antibiotics in paediatric infectious diseases. Drugs 1996; 5: 515-36
3. Washington JA II, Wilson WR. Erythromycin: a microbial and clinical perspective after 30 years of clinical use (first of two parts). Mayo Clin Proc 1985; 60: 189-203
4. Washington JA II, Wilson WR. Erythromycin: a microbial and clinical perspective after 30 years of clinical use (second of two parts). Mayo Clin Proc 1985; 60: 271-8
5. Butler DR, Kuhn RJ, Chandler MHH. Pharmacokinetics of antiinfective agents in paediatric patients. Clin Pharmacokinet 1994; 26: 374-95
6. Brittain DC. Erythromycin. Med Clin North Am 1987; 71: 1147-54
7. Smilack JD, Wilson WR, Cockerill III FR. Tetracyclines, chloramphenicol, erythromycin, clindamycin, and metronidazole. Mayo Clin Proc 1991; 66: 1270-80
8. McCraken GH. Microbiologic activity of the newer macrolide antibiotics. Pediatr Infect Dis J 1997; 16: 432-7
9. Nightingale CH. Pharmacokinetics and pharmacodynamics of newer macrolides. Pediatr Infect Dis J 1997; 16: 438-43
10. Jacobs RF, Schutze GE, Young RA, et al. Antimicrobial agents. In: Long SS, Pickering LK, Prober CG, editors. Principles and practice of pediatric infectious diseases. New York: Churchill Livingstone, 1997: 1604-62
11. Tarlow MJ, Block SL, Harris J, et al. Future indications for macrolides. Pediatr Infect Dis 1997; 16: 457-62
12. Treadway G, Pontani D. Paediatric safety of azithromycin: worldwide experience. J Antimicrob Chemother 1996; 37 Suppl. C: 143-9
13. Hopkins SJ. Clinical toleration and safety of azithromycin in adults and children. Rev Contemp Pharmacother 1994; 5: 383-9
14. Weippl G. Multicentre comparison of azithromycin versus erythromycin in the treatment of paediatric pharyngitis or tonsillitis caused by group A streptococci. J Antimicrob Chemother 1993; 31 Suppl. E: 95-101
15. Roord JJ, Wolf BHM, Goossens MMHT, et al. Prospective open randomized study comparing efficacies and safeties of a 3-day course of azithromycin and a 10-day course of erythromycin in children with community-acquired acute lower respiratory

tract infections. Antimicrob Agents Chemother 1996; 40: 2765-8
16. Principi N, Marchisio P, Biasini G, et al. Azithromycin versus erythromycin in the treatment of paediatric community-acquired pneumonia. Eur J Clin Res 1993; 4: 127-33
17. Block S, Hedrick J, Hammerschlag MR, et al. *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* in pediatric community-acquired pneumonia: comparative efficacy and safety of clarithromycin vs erythromycin ethylsuccinate. Pediatr Infect Dis J 1995; 14: 471-7
18. Arguedas A, Loaiza C, Rodriguez F, et al. Comparative trial of 3 days of azithromycin versus 10 days of clarithromycin in the treatment of children with acute otitis media with effusion. J Chemother 1997; 9: 44-50
19. Kramer MS, Hutchinson TA, Naimark L, et al. Antibiotic-associated gastrointestinal symptoms in general pediatric outpatients. Pediatrics 1985; 76: 365-70
20. Eichenwald HF. Adverse reactions to erythromycin. Pediatr Infect Dis 1986; 5: 147-50
21. Langtry HD, Brogden RN. Clarithromycin. A review of its efficacy in the treatment of respiratory tract infections in immunocompetent patients. Drugs 1997; 53: 973-1004
22. Craft JC, Siepman N. Overview of the safety profile of clarithromycin suspension in pediatric patients. Pediatr Infect Dis J 1993; 12 Suppl. 3: 142-7
23. Dunn CJ, Barradell LB. Azithromycin. A review of its pharmacological properties and use as 3-day therapy in respiratory tract infections. Drugs 1996; 51: 483-505
24. Zara GP, Thompson HH, Pilot MA, et al. Effects of erythromycin on gastrointestinal tract motility. J Antimicrob Chemother 1985; 16 Suppl. A: 175-9
25. Latare PA, Setness PA. Using erythromycin. Postgrad Med 1989; 86: 55-9, 63
26. Braun P. Hepatotoxicity of erythromycin. J Infect Dis 1969; 119: 300-6
27. Tolman KG, Sannella JJ, Freston JW. Chemical structure of erythromycin and hepatotoxicity. Ann Intern Med 1974; 81: 58-60
28. Periti P, Mazzei T, Mini E, et al. Adverse effects of macrolide antibacterials. Drug Saf 1993; 9: 346-64
29. Yew WW, Chau CH, Lee J, et al. Cholestatic hepatitis in a patient who received clarithromycin therapy for a *Mycobacterium chelonae* lung infection [letter]. Clin Infect Dis 1994; 18: 1025-6
30. Pessayre D, Larrey D, Funk-Brentano C, et al. Drug interactions and hepatitis produced by some macrolide antibiotics. J Antimicrob Chemother 1985; 16 Suppl. A: 181-94
31. Haydon RC, Thelin JW, Davis WE. Erythromycin ototoxicity: analysis and conclusions based on 22 case reports. Otolaryngol Head Neck Surg 1984; 92: 678-84
32. Brummett RE. Ototoxicity liability of erythromycin and analogues. Otolaryngol Clin North Am 1992; 26: 811-9
33. Wallace MR, Miller LK, Nguyen MT, et al. Ototoxicity with azithromycin [letter]. Lancet 1994; 343: 241
34. Farrar HC, Walsh-Sukys MC, Kyllonen K, et al. Cardiac toxicity associated with intravenous erythromycin lactobionate: two case reports and a review of the literature. Pediatr Infect Dis J 1993; 12: 688-91
35. Benoit A, Bodiou C, Villain E, et al. QT long et arrêt circulatoire après une injection dérythromycine chez un nouveau-ne. Arch Fr Pediatr 1991; 48: 39-41
36. Brandriss MW, Richardson WS, Barold SS. Erythromycin-induced QT prolongation and polymorphic ventricular tachycardia (torsades de pointes): case report and review. Clin Infect Dis 1994; 18: 995-8
37. Handa SP. The Schonlein-Henoch syndrome: glomerulonephritis following erythromycin. South Med J 1972; 65: 917-20
38. Wong KY, Boose GM, Issitt CH. Erythromycin-induced hemolytic anemia. J Pediatr 1981; 98: 647-9
39. Hubner C, Dietz A, Stremmel W, et al. Macrolide-induced Churg-Strauss syndrome in a patient with atopy [letter]. Lancet 1997; 350: 563
40. Ginsburg CM, and the Multicenter Pneumonia Study Group. A prospective study on the incidence of liver function abnormalities in children receiving erythromycin estolate, erythromycin ethylsuccinate or penicillin V for treatment of pneumonia. Ped Infect Dis J 1986; 5: 151-3
41. Periti P, Mazzei T, Mini E, et al. Clinical pharmacokinetic properties of the macrolide antibiotics: part I. Clin Pharmacokinet 1989; 16: 193-214
42. Periti P, Mazzei T, Novelli A, et al. Clinical pharmacokinetic properties of the macrolide antibiotics: part II. Clin Pharmacokinet 1989; 16: 261-82
43. Periti P, Mazzei T, Mini E, et al. Pharmacokinetic drug interactions of macrolides. Clin Pharmacokinetic 1992; 23: 106-31
44. Nahata M. Drug interactions with azithromycin and the macrolides: an overview. J Antimicrob Chemother 1996; 37 Suppl. C: 133-42
45. Rieder MJ, Spino M. The theophylline-erythromycin interaction. J Asthma 1988; 25: 195-204
46. Parish RA, Haulman J, Burns RM. Interaction of theophylline with erythromycin base in a patient with seizure activity. Pediatrics 1983; 72: 828-9
47. Tinel M, Descatoire V, Larrey D, et al. Effects of clarithromycin on cytochrome P-450. Comparison with other macrolides. J Pharmacol Exp Ther 1989; 250: 746-51
48. Sands M, Brown RB. Interactions of cyclosporin with antimicrobial agents. Rev Infect Dis 1989; 11: 691-7
49. Baciewicz AM, Baciewicz FA. Cyclosporine pharmacokinetic drug interactions. Am J Surg 1989; 157: 264-71
50. Kutt H. Interactions between anticonvulsants and other commonly prescribed drugs. Epilepsia 1984; 25 Suppl. 2: 118-31
51. Baciewicz AM. Carbamazepine drug interactions. Ther Drug Monitor 1986; 8: 305-17
52. OConnor NK, Fris J. Clarithromycin-carbamazepine interaction in a clinical setting. J Am Board Fam Pract 1994; 7: 489-92
53. Honig PK, Woosley RL, Zamani K, et al. Changes in the pharmacokinetics and electrocardiographic pharmacodynamics of terfenadine with concomitant administration of erythromycin. Clin Pharmacol Ther 1992; 52: 231-8
54. Orme MLE, Back DJ. Interactions between oral contraceptive steroids and broad-spectrum antibiotics. Clin Exp Dermatol 1986; 11: 327-31
55. Rodin SM, Johnson BF. Pharmacokinetic drug interactions with digoxin. Clin Pharmacokinet 1988; 15: 227-44
56. Von Rosenstiel NA, Adam D. Macrolide antibacterials: drug interactions of clinical significance. Drug Saf 1995; 13: 105-22
57. Gersema LM, Porter CB, Russell EH. Suspected drug interaction between cyclosporine and clarithromycin. J Heart Lung Transplant 1994; 13: 343-5
58. Sketris IS, Wright MR, West ML, et al. Possible role of the intestinal P-450 enzyme system in a cyclosporine-clarithromycin interaction. Pharmacotherapy 1996; 16: 301-5

59. Ljutic D, Rumboldt Z. Possible interaction between azithromycin and cyclosporin: a case report. Nephron 1995; 70: 130
60. Association of the British Pharmaceutical Industry. Zithromax. In: Walker G, editor. ABPI data sheet compendium 1994-95. London: Datapharm Publications Ltd., 1994: 1285-6
61. Still JG, Hubbard WC, Poole JM, et al. Comparison of clarithromycin and penicillin VK suspensions in the treatment of children with streptococcal pharyngitis and review of currently available alternative antibiotic therapies. Pediatr Infect Dis J 1993; 12 Suppl. 3: 134-41
62. Hamill J. Multicentre evaluation of azithromycin and penicillin V in the treatment of acute streptococcal pharyngitis and tonsillitis in children. J Antimicrob Chemother 1993; 31 Suppl. E: 89-94
63. Pacifico L, Scopetti F, Ranucci A, et al. Comparative efficacy and safety of 3- day azithromycin and 10-day penicillin V treatment of group A beta-hemolytic streptococcal pharyngitis in children. Antimicrob Agents Chemother 1996; 40: 1005-8
64. Pukander JS, Pero JP, Kaprio EA, et al. Clarithromycin vs amoxicillin suspensions in the treatment of pediatric patients with acute otitis media. Pediatr Infect Dis J 1993; 12 Suppl. 3: 118-21
65. Mohs E, Rodriguez-Solares A, Rivas E, et al. A comparative study of azithromycin and amoxycillin in paediatric patients with acute otitis media. J Antimicrob Chemother 1993; 31 Suppl. E: 73-9
66. McCarty JM, Phillips A, Wiisanen R. Comparative safety and efficacy of clarithromycin and amoxicillin/clavulanate in the treatment of acute otitis media in children. Pediatr Infect Dis J 1993; 12 Suppl. 3: 122-7
67. Aspirin MM, Hoberman A, McCarty J, et al. Comparative study of the safety and efficacy of clarithromycin and amoxicillin-clavulanate in the treatment of acute otitis media. J Pediatr 1994; 125: 136-41
68. Schaad UB. Multicentre evaluation of azithromycin in comparison with co-amoxiclav for the treatment of acute otitis media in children. J Antimicrob Chemother 1993; 31 Suppl. E: 81-8
69. Principi N. Multicentre comparative study of the efficacy and safety of azithromycin compared with amoxicillin/clavulanic acid in the treatment of paediatric patients with otitis media. Eur J Clin Microbiol Infect Dis 1995; 14: 669-76
70. Aronovitz G. A multicenter, open label trial of azithromycin vs amoxicillin/clavulanate for the management of acute otitis media in children. Pediatr Infect Dis J 1996; 15 Suppl. 9: 15-9
71. McLinn S. A multicenter, double blind comparison of azithromycin and amoxicillin/clavulanate for the treatment of acute otitis media in children. Pediatr Infect Dis J 1996; 15 Suppl. 9: 20-3
72. Khurana CM. A multicenter, randomized, open label comparison of azithromycin and amoxicillin/clavulanate in acute otitis media among children attending day care or school. Pediatr Infect Dis J 1996; 15 Suppl. 9: 24-9
73. Gooch III WM, Gan VN, Corder WT, et al. Clarithromycin and cefaclor suspensions in the treatment of acute otitis media in children. Pediatr Infect Dis J 1993; 12 Suppl. 3: 128-33
74. Rodriguez AF. An open study to compare azithromycin with cefaclor in the treatment of children with acute otitis media. J Antimicrob Chemother 1996; 37 Suppl. C: 63-9
75. Marchisio P, Principi N, Sala E, et al. Comparative study of once-weekly azithromycin and once-daily amoxicillin treatments in prevention of recurrent acute otitis media in children. Antimicrob Agents Chemother 1996; 40: 2732-6
76. Denny FW. Acute respiratory infections in children: etiology and epidemiology. Pediatr Rev 1987; 9: 135-46
77. Dagan R. Antibiotic treatment of pediatric community-acquired lower respiratory tract infections: challenges and possible solutions. Respiration 1993; 60 Suppl. 1: 28-44
78. Finch R. Skin and soft-tissue infections. Lancet 1988; 1: 164-8
79. Ferrante JA. Infectious skin diseases. Prim Care 1990; 17: 867-81
80. Bass JW. Treatment of skin and skin structure infections. Pediatr Infect Dis J 1992; 11: 152-5
81. Hebert AA, Still JG, Reuman PD. Comparative safety and efficacy of clarithromycin and cefadroxil suspensions in the treatment of mild to moderate skin and skin structure infections in children. Pediatr Infect Dis J 1993; 12 Suppl. 3: 112-7
82. Montero L. A comparative study of the efficacy, safety and tolerability of azithromycin and cefaclor in the treatment of children with acute skin and/or soft tissue infections. J Antimicrob Chemother 1996; 37 Suppl. C: 125-31
83. Rodriguez-Solares A, Pérez-Gutiérrez F, Prosperi J, et al. A comparative study of the efficacy, safety and tolerance of azithromycin, dicloxacillin and flucloxacillin in the treatment of children with acute skin and skin-structure infections. J Antimicrob Chemother 1993; 31 Suppl. E: 103-9
84. Walsh D, Goggin N, Rowland M, et al. One week treatment for *Helicobacter pylori* infection. Arch Dis Child 1997; 76: 352-5
85. Berger C, Pfyffer GE, Nadal D. Treatment of nontuberculous mycobacterial lymphadenitis with clarithromycin plus rifabutin. J Pediatr 1996; 128: 383-6
86. Lo Bue AM, Sammartino R, Chisari G, et al. Efficacy of azithromycin compared with spiramycin in the treatment of odontogenic infections. J Antimicrob Chemother 1993; 31 Suppl. E: 119-27
87. Kuschner RA, Heppner DG, Andersen SL, et al. Azithromycin prophylaxis against a chloroquine-resistant strain of *Plasmodium falciparum*. Lancet 1994; 343: 1396-7
88. Anderson SL, Berman J, Kuschner R, et al. Prophylaxis of *Plasmodium falciparum* malaria with azithromycin administered to volunteers. Ann Intern Med 1995; 123: 771-3
89. Hardy DJ, Hensey DM, Beyer JM, et al. Comparative *in vitro* activities of new 14-, 15- and 16-membered macrolides. Antimicrob Agents Chemother 1988; 32: 1710-9
90. Dunne MW, Williams DJ, Young LS. Azithromycin and the treatment of opportunistic infections. Rev Contemp Pharmacother 1994; 5: 373-81
91. Kimata I, Uni S, Iseki M. Chemotherapeutic effect of azithromycin and lasalocid on *Cryptospridium* infection in mice. J Protozool 1991; 38: S232-3
92. Chamberland S, Kirst HA, Current WL. Comparative activity of macrolides against *Toxoplasma gondii* demonstrating utility of an *in vitro* microassay. Antimicrob Agents Chemother 1991; 35: 903-9
93. Hughes WT. Macrolide-antifol synergism and anti-*Pneumocystis carinii* therapeutics. J Protozool 1991; 38 Suppl. 6: S160
94. Giner C, De Rafael L, Ruiz LM, et al. *Rhodococcus equi*: antimicrobial susceptibility pattern [abstract]. Programme and Abstracts of the 32nd Interscience Conference on Antimicrobial Agents and Chemotherapy: 1992 11-14 October; Anaheim, California. American Society for Microbiology, 1992: 334
95. Maurin M, Raoult D. Antimicrobial susceptibility of *Rochalimaea quintana*, *Rochalimaea vinsonii*, and the newly recognised *Rochalimaea henselae*. J Antimicrob Chemother 1993; 32: 587-94

96. Naik S, Ruck R. *In vitro* activities of several new macrolide antibiotics against *Mycobacterium avium* complex. Antimicrob Agents Chemother 1989; 33: 1614-6
97. Masur H, the Public Health Service Task Force on Prophylaxis and Therapy for *Mycobacterium avium* complex. Recommendations on prophylaxis and therapy for disseminated *Mycobacterium avium* complex disease in patients infected with the human immunodeficiency virus. N Engl J Med 1996; 329: 898-904
98. Rehg JE. Activity of azithromycin against cryptosporidia in immunosuppressed rats. J Infect Dis 1991; 163: 1293-6
99. Vargas SL, Shenep JL, Flynn PM, et al. Azithromycin for treatment of severe *Cryptosporidium* diarrhea in two children with cancer. J Pediatr 1993; 123: 154-6
100. Eisen SA, Miller DK, Woodward RS, et al. The effect of prescribed daily dose frequency on patient medication compliance. Arch Intern Med 1990; 150: 1881-4
101. Nightingale CH, Belliveau PP, Quintiliani R. Cost issues and considerations when choosing antimicrobial agents. Infect Dis Clin Pract 1994; 3: 8-11
102. Powers JL. Properties of azithromycin that enhance the potential for compliance in children with upper respiratory tract infections. Pediatr Infect Dis J; 1996; 15 Suppl. 9: 30-7

Correspondence and reprints: Dr *Nicola Principi*, Paediatric Department IV, University of Milan, L. Sacco Hospital, Via G.B.Grassi 74, 20157 Milan, Italy.