

# The appropriate use of **macrolides**

## What are macrolides and how do they work?

Macrolides are a class of antibiotic that includes erythromycin, roxithromycin, azithromycin and clarithromycin. They are useful in treating respiratory, skin, soft tissue, sexually transmitted, *H. pylori* and atypical mycobacterial infections. Macrolides share a similar spectrum of antimicrobial activity with benzylpenicillin making them useful alternatives for people with a history of penicillin (and cephalosporin) allergy. Bacteria often display cross-resistance between the macrolides.

Macrolides interfere with bacterial protein synthesis and, depending on concentration and bacterial species, are either bactericidal (kill bacteria), or bacteriostatic (inhibit growth of bacteria). Macrolides also have immunomodulatory and anti-inflammatory effects, which can be beneficial in some situations, e.g. when they are used in the treatment of cystic fibrosis.<sup>1</sup>

## Which infections should macrolides be used for?

Macrolides are effective against gram-positive (excluding enterococci) and some gram-negative bacteria. They are also active against *Mycoplasma pneumoniae*, *Treponema pallidum*, *Bordetella pertussis*, *Chlamydia trachomatis*, *Chlamydophila pneumoniae*, *Legionella spp.*, *Campylobacter spp.* and *Borrelia spp.*<sup>1</sup>

First-line indications for macrolides for common infections are listed in Table 1. There are numerous infections in which macrolides would be considered for second-line treatment.

**Table 1:** Common first-line indications for macrolides

| Infection                     | First-line treatment                                                                   | Second-line treatment                                      |
|-------------------------------|----------------------------------------------------------------------------------------|------------------------------------------------------------|
| Pertussis                     | Erythromycin                                                                           | –                                                          |
| Community acquired pneumonia  | Amoxicillin alone<br>or<br>Amoxicillin + <b>erythromycin</b> (for atypical infections) | Erythromycin, roxithromycin, doxycycline or co-trimoxazole |
| <i>H. pylori</i>              | Amoxicillin + <b>clarithromycin</b> + omeprazole                                       | Metronidazole + clarithromycin + omeprazole                |
| Chlamydia                     | <b>Azithromycin</b>                                                                    | Doxycycline, amoxicillin, erythromycin                     |
| Acute non-specific urethritis | <b>Azithromycin</b>                                                                    | Doxycycline                                                |

## Prescribing erythromycin

Erythromycin is available in New Zealand as erythromycin ethyl succinate (fully subsidised), erythromycin lactobionate (fully subsidised, injection only) and erythromycin stearate (partially subsidised).

The usual oral adult dose of erythromycin is 1 – 2 g daily, in two to four divided doses. The dose may be increased up to 4 g per day according to the severity of the infection. As erythromycin ethyl succinate is now the only fully subsidised oral option, dosing recommendations in this article are altered to take into account the tablet dosages available.

Erythromycin ethyl succinate is available in 400 mg tablets, and two strengths of liquid formulation – 200 mg/5 mL and 400 mg/5 mL. The usual adult dose is 400 mg, four times daily. Alternatively, 800 mg, twice daily, may be a more convenient dose regimen for some patients. In severe infections, the dose may be increased up to a maximum of 4 g per day. Tablets may be taken with or without food.

The usual dose for infants and children is 10 mg/kg, four times daily, although this may be doubled in severe infections. The daily dose may be divided into twice daily or three times daily dosing if desired. Children aged over eight years may be given the usual adult dose.<sup>2</sup>

 The erythromycin doses expressed in this article refer to prescribing of erythromycin ethyl succinate. Therefore, some dosing recommendations may differ slightly from those listed in the bpac<sup>nz</sup> antibiotic guide.

## First-line indications for macrolides

### Pertussis



Erythromycin 10 mg/kg (400 mg for adults), four times daily, for 14 days

Cases of pertussis (whooping cough) persist in New Zealand, despite the vaccine being part of the National Immunisation Schedule. Antibiotics are ineffective at reducing the duration or severity of symptoms if given more than seven days after the infection begins. However, antibiotics are still useful, if started within three to four weeks of infection, to prevent transmission to others. Women diagnosed with pertussis in the third trimester of pregnancy, should be given antibiotic treatment regardless of the time of onset of infection.<sup>4</sup>

Prophylactic antibiotic treatment should be offered to household contacts of a person with pertussis, if the household includes a child who has not completed a course of pertussis vaccination.<sup>4</sup>

Erythromycin is considered the medicine of choice for treatment and prophylaxis of pertussis as it is active against the causative organism – *Bordetella pertussis*. Infants aged under three months treated with erythromycin are at increased risk of developing pyloric stenosis. As the risk associated with pertussis in a young infant is considerably greater, erythromycin is still indicated, but the infant should be monitored for complications for four weeks after completion of treatment.<sup>4</sup>

### Community-acquired pneumonia: atypical infection



Amoxicillin 500 – 1000 mg, three times daily, for seven days + erythromycin 400 mg, four times daily (or 800 mg, twice daily), for seven days

Severe cases of pneumonia require hospitalisation. The first-line treatment choice for pneumonia treated in the community is amoxicillin (to cover *Streptococcus pneumoniae*). Erythromycin (or roxithromycin) should be added to the treatment regimen when atypical infection is known to be circulating in the community. Erythromycin and roxithromycin provide coverage for *Mycoplasma pneumoniae*, *Legionella spp.* and *Chlamydophila pneumoniae*.

Resistance of *S. pneumoniae* to macrolides is a worldwide problem. In 2010, resistance of *S. pneumoniae* (non-invasive disease) to erythromycin in New Zealand was 19%.<sup>5</sup>

## Pneumonia in children

Amoxicillin (25 mg/kg, three times daily, for seven days) is the first-line antibiotic for the treatment of pneumonia in children managed in the community. Erythromycin (10 mg/kg, four times daily, for seven days) may be used instead of amoxicillin in children aged over five years, if treatment fails or if atypical infection is known to be circulating in the community. Atypical infection is unlikely in children aged less than five years.<sup>6</sup>

If there is no response to treatment within 24 – 48 hours, review the diagnosis and consider referral to hospital.

Erythromycin may also be used as an alternative to amoxicillin in any child with an allergy to penicillin.

## *Helicobacter pylori* infection



Clarithromycin 500 mg, amoxicillin 1 g and omeprazole 20 mg, twice daily, for seven days

The rate of eradication of *H. pylori* with “triple therapy” (amoxicillin, clarithromycin and omeprazole) is over 85%.<sup>7</sup> Post-treatment “test of cure” is not required unless the patient has a peptic ulcer, significant co-morbidities or non-resolution of symptoms.<sup>7</sup>

Resistance to clarithromycin is increasing worldwide, therefore it is recommended that clarithromycin should not be used as part of “triple therapy” if it has been used in the last year for any other infection.<sup>8</sup>

## Chlamydia



Azithromycin 1 g stat

Azithromycin is the treatment of choice for *Chlamydia trachomatis* infection. Alternatives include doxycycline (100 mg, twice daily, for seven days), amoxicillin (500 mg, three times daily, for seven days) or erythromycin (800 mg, four times daily, for seven days).<sup>9</sup>

A “test of cure” should be requested four to five weeks after treatment with azithromycin if the patient is pregnant, has a rectal infection or if amoxicillin or erythromycin have been used for treatment.<sup>9</sup>

Sexual contacts from the past two months of a symptomatic person and from the past six months of an asymptomatic person who has tested positive for chlamydia should also be

## Prescribing roxithromycin

Roxithromycin may be considered as an alternative to erythromycin. However, its use is generally reserved for mild to moderate respiratory infections, such as mild to moderate atypical community acquired pneumonia (in combination with amoxicillin). Roxithromycin is generally well tolerated, but does not have any major advantages over erythromycin.<sup>3</sup> The usual dose of roxithromycin is 150 mg, twice daily or 300 mg, once daily. Roxithromycin tablets (150 mg, 300 mg) are fully subsidised. A liquid form is not available in New Zealand.

treated.<sup>9</sup> Patients should be advised not to have unprotected sex for one week after treatment and until partners have completed treatment.<sup>9</sup>

Resistance of *Chlamydia trachomatis* to azithromycin is increasing, although the extent to which this is occurring is unknown.<sup>10</sup> Some guidance suggests that doxycycline should be considered first-line instead of azithromycin, in order to avoid overuse.<sup>10</sup>

Azithromycin is also added to the treatment regimen for gonorrhoea (ceftriaxone 250 mg IM + azithromycin 1 g stat) because co-infection with chlamydia is common. Monotherapy with azithromycin 1 g is not adequate treatment for both pathogens.

## Acute non-specific urethritis



Azithromycin 1 g stat

Non-specific urethritis is a diagnosis of exclusion. Symptoms include erythema, discomfort and pain in the urethra and penile discharge.

A first void urine sample and urethral swab\* should be taken to test for gonorrhoea and chlamydia. Empirical treatment with azithromycin is given on the presumption that the patient has uncomplicated urethritis, due to *Chlamydia trachomatis*. If a purulent discharge is present, treat as for gonorrhoea (i.e. add ceftriaxone 250 mg IM stat).

Sexual contacts from the past two months should also be treated and tested. This is still necessary if chlamydia and gonorrhoea tests are negative as false negative results are possible and treating the female partner reduces the chance of recurrence in affected males.<sup>9</sup>

\* Check with your local laboratory, a swab may not be necessary depending on urinalysis method

## Campylobacteriosis

In the majority of cases of campylobacteriosis, antibiotic treatment is not required as diarrhoea will resolve with symptomatic treatment only. Antibiotics have limited effect on the duration and severity of infection, but can remove the infection from the stool and therefore reduce transmission to others.

Treatment with erythromycin 400 mg (children 10 mg/kg), four times daily, for five days, is indicated for people with severe or prolonged infection, in pregnant women nearing term and may be considered for food handlers, childcare workers and people caring for patients who are immuno-compromised.

## Second-line indications for macrolides

Erythromycin is an alternative antibiotic for people with a history of penicillin allergy in the treatment of otitis media, pharyngitis and boils (when treatment is indicated for these conditions), cellulitis, mastitis and syphilis.

Azithromycin (1 g stat or 500 mg, once daily, for three days) can be used instead of ciprofloxacin as a second-line treatment for severe traveller's diarrhoea, when antibiotics are required. Azithromycin is recommended for pregnant women (ciprofloxacin is contraindicated) or in areas where there is quinolone resistance, e.g. South East Asia. Azithromycin (10 mg/kg, once daily for three days) is also recommended for young children with traveller's diarrhoea (ciprofloxacin is not recommended in children), but a liquid formulation is not available in New Zealand. Erythromycin is an alternative. N.B. Azithromycin is not funded for this indication.

Azithromycin 1 g stat can be used instead of doxycycline to treat pelvic inflammatory disease (plus ceftriaxone 250 mg, IM stat and metronidazole 400 mg, twice daily, for two weeks), when chlamydia is present, especially if compliance is likely to be a problem.

## Adverse effects of macrolides

The most common adverse effects associated with macrolides are gastrointestinal, such as abdominal discomfort and cramp, nausea, vomiting and diarrhoea. Symptoms are dose dependent and are more common in children.<sup>1</sup> Erythromycin is associated with a higher incidence of gastrointestinal adverse effects than other macrolides, with 5 – 30% of patients reporting symptoms.<sup>2</sup> Erythromycin ethyl succinate has a lower incidence of gastrointestinal adverse effects compared to other forms of erythromycin. More frequent daily dosing may alleviate gastrointestinal effects.

## Endorsement is required when prescribing azithromycin or clarithromycin

Prescriptions for azithromycin must be endorsed to qualify for a full subsidy. An endorsement requires the prescriber to write "certified condition" on the prescription, to indicate that the patient meets the criteria for subsidy. Azithromycin is fully-subsidised for people with uncomplicated urethritis or cervicitis proven or presumed to be due to chlamydia infection, and their sexual contacts. Azithromycin is also available via Practitioners Supply Order, which must be endorsed.

Clarithromycin is fully subsidised with endorsement for *H. pylori* eradication. Endorsement occurs automatically

if clarithromycin, amoxicillin (or metronidazole) and a proton pump inhibitor are concurrently prescribed as "triple therapy". A maximum of 14 tablets per prescription is allowed. Special Authority criteria also applies for relevant practitioners to prescribe clarithromycin for mycobacterial infections.



See pharmaceutical schedule for full details  
[www.pharmac.govt.nz](http://www.pharmac.govt.nz)

Macrolides, particularly erythromycin and clarithromycin, have been associated with prolongation of the QT interval and should be used cautiously in patients at risk of developing arrhythmias.<sup>1, 3</sup> The risk of prolongation of the QT interval may also be increased when macrolides are taken with other medicines that may affect cardiac function or reduce the rate of macrolide clearance (see “Medicines interactions”).

Macrolides should be avoided in people with severe liver impairment.

Other rare adverse effects include hypersensitivity (e.g. anaphylaxis, fixed drug eruptions, Stevens-Johnson syndrome and interstitial nephritis), cholestatic hepatitis, pancreatitis, *Clostridium difficile*-associated infection, blood dyscrasias (e.g. blood thrombocytopenia), psychiatric disturbances and ototoxicity.<sup>1, 2, 3</sup>

### Medicines interactions

Macrolides are potent hepatic cytochrome P450 enzyme inhibitors. They also have an inhibitory effect on transporter proteins, as well as affecting gastrointestinal flora and gastric emptying.<sup>1, 2</sup> These actions have the potential to cause adverse interactions with other medicines. Erythromycin and clarithromycin are more commonly associated with medicine interactions than other macrolides. Elderly people and those with renal or liver impairment are more likely to be affected by medicines interacting with macrolides. If possible, it is recommended that the interacting medicine be withheld, or the dose reduced during the course of antibiotics while monitoring for signs of toxicity.

**Calcium channel blockers** taken at the same time as erythromycin or clarithromycin have been shown to increase the short-term risk of hypotension or shock amongst elderly people.<sup>11</sup> Verapamil may increase the concentration of erythromycin, resulting in an increased risk of QT interval prolongation.<sup>1</sup>

Other medicines that may increase the risk of QT prolongation include; amiodarone, methadone, lithium, amitriptyline and citalopram.<sup>1</sup>



For a full list of medicines that increase QT prolongation see: [www.azcert.org/index.cfm](http://www.azcert.org/index.cfm)

N.B. this is a US based reference so may not include all medicines available in New Zealand

## Safety in pregnancy and breast feeding

**Erythromycin** – Category A\*; safe to use, but consider an alternative in the first trimester (unconfirmed reports of an association with congenital cardiac malformations)

**Roxithromycin** – Category B1; considered safe to use

**Azithromycin** – Category B1; considered safe to use

**Clarithromycin** – Category B3; uncertain safety in pregnancy, consider an alternative

Erythromycin, roxithromycin and azithromycin are safe to use while breast feeding, clarithromycin is considered safe to use while breast feeding.<sup>1</sup>

\* Australian Therapeutic Goods Administration Pregnancy Categories

**Warfarin and dabigatran** may have increased anticoagulant properties when taken with clarithromycin and erythromycin.<sup>12</sup> If possible, an alternative antibiotic should be used. Warfarin may need to be temporarily stopped or the dose reduced if there is no alternative. The INR should be monitored if warfarin and macrolides are taken at the same time. Little information is available on interactions with dabigatran, but patients should be monitored for signs of bleeding. This effect may be more pronounced in elderly people, or when renal function is reduced.

**Statin** metabolism, in particular simvastatin and atorvastatin, may be affected by macrolides inhibiting CYP3A4 enzymes. This can result in an increased risk of statin-induced rhabdomyolysis. Azithromycin interacts less with CYP3A4 enzymes, however, there have also been occasional reports of rhabdomyolysis in patients taking azithromycin.<sup>13</sup> Patients can be advised not to take simvastatin or atorvastatin while completing a course of a macrolide antibiotic. Pravastatin is not significantly metabolised by CYP3A4, therefore is less likely to be affected by concurrent macrolide use.

**Digoxin** is known to interact with clarithromycin, which can lead to digoxin toxicity.<sup>14</sup> When these medicines are taken in combination the digoxin dose should be reduced by half and the patient monitored for symptoms of toxicity.<sup>15</sup>

**Other medicines** that may have significant interactions with macrolides in elderly people or those with significant co-morbidities include; benzodiazepines, carbamazepine, cimetidine, clozapine, colchicine and theophylline.<sup>14</sup>

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