

## Azithromycin for empiric treatment of community acquired pneumonia

CDHB's adult antimicrobial guidelines are reviewed annually. These are informed by local sensitivity data, international guidelines and local clinical specialists. Choosing the appropriate antimicrobial drug and dosing regimen improves clinical outcomes, and minimises resistance, adverse reactions and cost. In the latest antimicrobial guidelines ("Pink Book" - Preferred Medicines List, 18<sup>th</sup> edition, 2014), oral azithromycin is introduced as a treatment for community acquired pneumonia (CAP). This bulletin compares oral azithromycin to alternative macrolides in CAP.

**TABLE: Empiric treatment of CAP (see the Pink Book, 18<sup>th</sup> edition, 2014)**

Mild disease (CURB-age 0-1)	Moderate (CURB-age 2)	Severe (CURB-age 3-4)	Extremely severe (CURB-age 4-5)
amoxicillin 500 mg po tds OR azithromycin 500 mg po stat then 250 mg po daily for 4 days*	amoxicillin 1 g iv q8h  <i>Mild penicillin allergy:</i> cefuroxime 1.5 g iv q8h  <i>Severe penicillin allergy:</i> azithromycin 500 mg po stat then 250 mg po daily for 4 days*	amoxicillin/clavulanate 1.2 g iv q8h AND clarithromycin 500 mg iv q12h (with early switch to oral azithromycin) OR azithromycin 500 mg po daily (where oral treatment is sufficient)  <i>Mild penicillin allergy:</i> cefuroxime 750 mg-1.5 g iv q8h AND clarithromycin OR azithromycin (use as outlined above)  <i>Severe penicillin allergy:</i> consult infectious diseases, microbiology or respiratory departments	clarithromycin 500 mg iv q12h followed by an early switch to azithromycin 500 mg po daily AND ceftriaxone 2 g iv q12h AND gentamicin 5 mg/kg iv (initial dose – see p161 of the Pink Book)  <i>Penicillin allergy:</i> consult infectious diseases, microbiology or respiratory departments
*an accepted alternative approach is to use 500 mg po daily for 3 days (total course is 1.5 g)	*an accepted alternative approach is to use 500 mg po daily for 3 days (total course is 1.5 g)		

Azithromycin is in wide use internationally for the treatment of CAP. It has good activity against common Gram-positive respiratory pathogens (eg. *S. pneumoniae*), but compared with erythromycin it has improved activity against Gram-negative (eg. *H. influenzae*) and atypical organisms (eg. *Legionella pneumophila*).

Two advantages that azithromycin has over other macrolides are that it has better tissue penetration and a longer half-life (~60h versus 2h for erythromycin, 4h for clarithromycin and 12h for roxithromycin). After a 500 mg oral dose, concentrations in pulmonary tissue remain well above the minimum inhibitory concentrations for common pathogens for ~4 days<sup>1</sup>. These features mean that azithromycin can be given once daily and for a shorter length of time than alternate antibiotics, which may help compliance.

### Dosing

In *mild to moderate CAP*, azithromycin can be prescribed as 500 mg po on day 1 followed by 250 mg po daily on days 2 to 5. Another approach is to give 500 mg po daily for 3 days (both regimens provide a total course of 1.5 g and are similarly effective). For *severe CAP* where oral treatment is sufficient, azithromycin 500 mg po daily may be given with an appropriate  $\beta$ -lactam iv (see Table above). Very unwell patients requiring iv therapy should be initiated on clarithromycin iv (plus  $\beta$ -lactam and gentamicin iv – see Table) with the view to changing to oral azithromycin as soon as possible (iv azithromycin is not licensed in NZ). Note: this use of iv clarithromycin may be outside of PHARMAC's Hospital Medicines List where it states it should not be used as a first-line macrolide in CAP.

### Duration of treatment

Patients are often treated with antibiotics for longer than necessary. Assuming a good response, a 5 to 7 day antimicrobial course will usually suffice for most patients with *mild to moderate CAP*. For azithromycin, a shorter course of 1.5 g over 3 to 5 days has proven comparable to 10 days of

oral agents like clarithromycin<sup>2</sup>. Patients should usually be afebrile for 48 to 72 h and clinically stable before stopping. For legionella, 7 to 10 days with azithromycin should be adequate except where the patient has been particularly unwell or is immunocompromised (Note: oral doxycycline is also an option for legionella infection).

### Adverse effects

The discontinuation rate due to adverse effects with azithromycin in lower respiratory tract infections is low at <1%<sup>3</sup>. The most common side effects involve the gut (eg. nausea, vomiting, diarrhoea), although rash, headache and dizziness are also reported. Azithromycin may cause QT prolongation although the risk appears less than with erythromycin or clarithromycin (see Clinical Pharmacology bulletin No 004\_13 on the intranet). Selecting oral azithromycin over parenteral clarithromycin avoids adverse effects like phlebitis that are associated with iv macrolide use.

### Interactions

Azithromycin interacts with fewer drugs than erythromycin or clarithromycin as it does not appreciably inhibit cytochrome P450 3A (CYP3A). This means that it is unlikely to increase concentrations of CYP3A substrates like statins (some) and calcium channel blockers (see the Pink Book p187). Azithromycin has been implicated in increasing ciclosporin and digoxin concentrations, and occasionally the INR in warfarinised patients - monitoring is required.

### Funding

For treatment of CAP in hospitalised patients, azithromycin tablets (250 mg and 500 mg) and oral liquid (40 mg/mL) may be prescribed for up to five days' treatment with a review required at five days. The cost is ~\$2.84 per 500mg dose (cf ~\$30 per 500 mg vial of clarithromycin). For outpatients, up to 5 days' treatment are funded per prescription (usual co-payment of \$5 for adults applies).

References: 1.Eur Resp J 1990;3:886-90. 2.Eur J Clin Microbiol Infect Dis 1998;17: 828. 3.J Antimicrob Chemother 2001;48:691.