Canterbury District Health Board
Te Poari Hauora ō Waitaha

Antimicrobial Stewardship Bulletin

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Macrolides in Community Acquired Pneumonia (CAP) – the pros and cons

CDHB guidelines **(Pink Book, 18th ed, 2014)** for the treatment of CAP encourage the use of azithromycin orally instead of clarithromycin intravenously, when a macrolide is indicated **(green box)**. Azithromycin has some important advantages over clarithromycin but recent studies have highlighted cardiovascular and resistance concerns. This bulletin outlines the place of each macrolide in the treatment of CAP, and compares their advantages and disadvantages.

Which macrolide in CAP?

Azithromycin orally is our first choice macrolide for the treatment of CAP, except in the severely ill (see below). Its advantages include:

- **Good activity against likely respiratory pathogens.**
- **Improved compliance through once daily dosing and shorter treatment courses**. The long half-life (~60h vs 4h for clarithromycin) of azithromycin means the duration of treatment should be *several days less* than for other antimicrobials. For mild to moderate CAP (CURB 0 – 2), azithromycin 500 mg daily for 3 days is approximately equivalent in efficacy to 7-10 days of oral clarithromycin.
- **Fewer drug interactions.** Azithromycin has few pharmaco-kinetic interactions whereas clarithromycin increases the concentrations of many drugs (eg. benzodiazepines, 'statins') by inhibition of cytochrome P450 3A (refer Pink Book (2014), p187). Note: azithromycin may occasionally increase the INR in patients taking warfarin (clarithromycin is more likely to do this) – increased INR monitoring is required.
- **No phlebitis.** Prescribing azithromycin orally avoids phlebitis which is common with the iv macrolides.
- **Lower cost.** Azithromycin costs less than clarithromycin at $0.63 vs $60 per day, respectively. Clarithromycin also has additional costs eg. infusion bags, giving sets & nursing time.

Clarithromycin iv is a valid choice for those who are/have:

- **Compromised gastrointestinal absorption.**
- **Severely ill (CURB 3 – 5).** Minimise iv use (eg. 1 or 2 doses) then switch to azithromycin po when able. One approach is to give **one** dose of clarithromycin iv at the **same time** as the first dose of azithromycin. For example:
  - Clarithromycin iv **stat** (one dose) on the front of the drug chart AND
  - Azithromycin po **regularly** to start at the same time as clarithromycin

If initiating azithromycin after a few doses of clarithromycin iv, start it when the next dose of clarithromycin would have been due

Cardiovascular risks with macrolides

Macrolide antimicrobials are established causes of QT interval prolongation and torsade de pointes. Recent studies have focussed attention on azithromycin as a possible cause of cardiovascular death. Unfortunately, the studies are difficult to interpret because of conflicting findings and methodological flaws. Overall, the absolute risk for cardiovascular mortality with azithromycin is low in the absence of risk factors for QT prolongation. Available data are inadequate to determine with precision if there is a difference in risk between macrolides.

Key points for prescribers

- Ensure that the indication for the macrolide is appropriate.
- Consider alternate antimicrobials* in patients with risk factors for QT prolongation eg. hypokalaemia, bradycardia.
- Macrolides are best avoided with other drugs that prolong the QT interval eg. most antipsychotics, domperidone, amiodarone.
- Clarithromycin (but not azithromycin) increases concentrations of many QT prolonging drugs by inhibiting their metabolism which further increases the risk of arrhythmias.
- In vulnerable patients check the QT interval on ECG and if borderline repeat the ECG during treatment.
- Refer to your Ward Pharmacist, Drug Information (ext 80900) or the Pink Book (2014), p174 for further information.

*Fluoroquinolones are also rare causes of QT prolongation and torsade de pointes. Consider consulting with Infectious Diseases/Microbiology if unsure about your options.

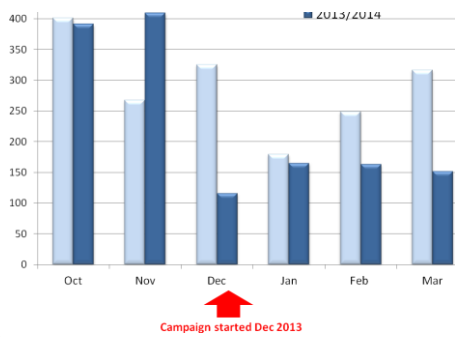
Antimicrobial resistance with azithromycin

The downside of azithromycin's long half-life is that persistent concentrations below the minimum inhibitory concentration increase antimicrobial resistance. This has been seen overseas where azithromycin use is widespread (40 million scripts were written in the US in 2011!). Avoid inappropriate use of antimicrobials (including azithromycin) and unnecessarily long courses.

Clarithromycin

A decrease in CDHB usage - well done!

Figure: Clarithromycin iv usage (number of vials)



- In December 2013, we launched a campaign to decrease unnecessary iv clarithromycin use.
- This was in response to the:
  - advantages of azithromycin as outlined above,
  - desire to move away from iv as the "default" method of giving antimicrobials in hospital,
  - need to comply with PHARMAC's Hospital Medicines List (HML).
- The campaign had the support of the Departments of Infectious Diseases, Respiratory, General Medicine, Clinical Pharmacology and Pharmacy.
- Methods included verbal presentations, bulletins and changes to ward imprest (removal of clarithromycin iv from most areas and replacement with azithromycin tablets).
- The campaign was associated with a 54% decrease in the use of clarithromycin iv (number of vials) over the past four months (Dec 13 – Mar 14) compared with the previous year.
- Clarithromycin use will be monitored over winter to see if more improvements can be made.