Azithromycin: use it wisely

Growing use of azithromycin in New Zealand means that we are in danger of increasing bacterial resistance to macrolide antibiotics, as has been the case in other countries. Macrolides are particularly important in New Zealand given our high rates of pertussis and rheumatic fever. It is not too late to act; azithromycin should only be prescribed for specific indications to make sure it works when we need it the most.

Azithromycin is an effective antibiotic, but it's use must be preserved

Azithromycin is a macrolide antibiotic with a broad spectrum of activity. While azithromycin has a number of indications, infectious diseases experts recommend that in New Zealand, azithromycin only be used in the following situations:*

- **First-line indications:** pertussis in children, chlamydia, gonorrhoea (for treatment of presumed co-infection with chlamydia), acute non-specific urethritis
- **Second-line indications:** pelvic inflammatory disease as an alternative to doxycycline when chlamydia is present, pertussis in adults when erythromycin is unable to be tolerated

* bpac^{nz}. Antibiotic choices for common infections. 2013. Available from: www.bpac.org.nz

Internationally, particularly in the United States, azithromycin is a widely used antibiotic. This has led to rapidly increasing levels of resistance among some common pathogens, e.g. *Streptococcus pneumoniae*.[1] In December, 2012, PHARMAC widened subsidised access to azithromycin to allow for the treatment of pertussis in children. While this has been beneficial for managing the pertussis epidemic we need to remain cautious with the use of azithromycin to avoid an increase in macrolide resistance in New Zealand, as has been the case overseas.

How does antimicrobial resistance occur?

All use of antibiotics contributes to resistance, but suboptimal use of antibiotics is the most important cause of the emergence and spread of resistant organisms. Prescribing antibiotics when they are not indicated (e.g. for viral infections), prescribing a broad spectrum antibiotic when a narrow spectrum option would be adequate and prescribing antibiotics at an inappropriate dose or duration of treatment all result in increased resistance.

Azithromycin in particular is more likely to contribute to the development of resistance because of its long half-life of approximately three days.[2] This results in low (i.e. sub-inhibitory) concentrations of the drug at sites of microorganism carriage for several days, which promotes the selection of resistant strains of bacteria. Nasopharyngeal carriage of macrolide-resistant streptococci following treatment with azithromycin has been observed in a number of studies.[3]

Cardiovascular risks with azithromycin

In March, 2013, the US Food and Drug Administration (FDA) warned that there is an increased risk of QT-prolongation and potentially fatal arrhythmia with azithromycin use, particularly in people who are already at increased cardiovascular risk.[10] Other macrolide antibiotics are associated with cardiovascular adverse effects, but until recently it was thought that azithromycin had minimal cardiotoxicity.[11]

People at risk of azithromycin-induced arrhythmia include those with existing prolonged QT interval, bradycardia, low blood levels of potassium or magnesium and those currently taking antiarrhythmic medicines or other medicines which prolong the QT interval, e.g. antipsychotics, citalopram.

This risk of cardiovascular adverse effects with azithromycin was first raised in 2012 when a United States study found that there was a small increased risk of cardiovascular death and death from any cause during five days treatment with azithromycin compared to treatment with amoxicillin, ciprofloxacin or no medicine.[11] The risk was greatest in those with a high baseline risk of cardiovascular disease.[11] This means that for every 21 000 prescriptions written for azithromycin for patients in the community, one extra cardiovascular death occurred when compared to the same number of amoxicillin prescriptions. This risk increased to one extra cardiovascular death per 4100 prescriptions for azithromycin in patients with existing high cardiovascular risk (compared to amoxicillin).[12] There have been mixed results in subsequent studies of the cardiovascular risk associated with azithromycin, however, the evidence was considered robust enough to prompt the FDA warning.[12]

Along with macrolides, QT-prolongation is associated with other antibiotics such as fluoroquinolones. This should be taken into consideration when making the decision to prescribe any antibiotic, especially in patients with cardiovascular risk factors and cases where antibacterial treatment has limited benefits.[12]

Azithromycin use in the United States: A cautionary tale

Azithromycin is used much more extensively in the United States, for a wider range of infections, than in New Zealand. Azithromycin is perceived to have potential advantages over other macrolides because it has fewer adverse gastrointestinal effects, requires less frequent dosing (once a day), and it usually requires a shorter duration of treatment (e.g. five days). For these reasons, azithromycin became the most commonly prescribed antibiotic in the United States in 2011.[4] However, resistance is increasingly of concern, with recent studies showing high rates of azithromycin resistance, particularly in pneumococci. Currently 30 – 35 % of pneumococci in the United States are resistant to macrolides.[5] Resistance rates to macrolides began to increase sharply in the 1990s, coinciding with the introduction of clarithromycin in the United States in 1991 and azithromycin in 1992. In the early 1990's rates of macrolide resistance in pneumococci were approximately 10%, however, by the early 2000's resistance rates had reached 30%.[5]

International studies have linked increasing use of macrolides, particularly azithromycin, with the increasing prevalence of resistance in *Streptococcus pyogenes*[6] and in *Streptococcus pneumoniae*.[7] While the direct consequences of increasing rates of macrolide resistance are difficult to quantify, there have been cases of breakthrough bacteraemia in patients treated with macrolides who were subsequently found to be infected with macrolide-resistant strains of *S. pneumoniae*.[8] Other cases highlight problems with macrolide resistance in *Streptococcus pyogenes*, e.g. two cases of children in the United States who developed rheumatic fever following treatment of streptococcal pharyngitis with azithromycin. Macrolide resistance was proven in one case and presumed in the other.[9]

Azithromycin use in New Zealand: halting the surge

Concerns about increasing macrolide resistance were raised prior to the funding change in December, 2012, which widened access to azithromycin. This change allowed for funded treatment of pertussis using a liquid formulation of azithromycin suitable for children (as well as tablets). Previously, funding for azithromycin had been restricted to a maximum of two 500 mg tablets per prescription, for the treatment of infections due to *Chlamydia trachomatis*. Following consultation, PHARMAC added a restriction of five days supply to the new azithromycin listing.

The number of azithromycin prescriptions in New Zealand has been increasing since the widening of access in December 2012 (Figure 1). While some increase may be expected due to the use of azithromycin for pertussis, Figure 1 shows that pertussis rates began to decrease in early 2013, but dispensed azithromycin did not. Rates of chlamydia and gonorrhoea also appear to be stable or decreasing.

ESR collects annual surveillance data on antimicrobial resistance rates in New Zealand. Data is not reported specifically on azithromycin, but latest figures from 2012 show that 19.2% of *S. pneumoniae* and 3.9% of *S. pyogenes* were resistant to erythromycin.[13]

The final word

Unlike some other countries where macrolide resistance is already out of control, it is not too late to preserve the effectiveness of macrolides in New Zealand. By prescribing azithromycin only for the conditions it is recommended for (i.e. first-line antibiotic treatment for pertussis in children and first-line treatment for chlamydia, and second-line antibiotic treatment for pelvic inflammatory disease) we can ensure that macrolide antibiotics remain effective when they are needed the most. Wise use of antibiotics means prescribing the right antibiotic, for the right indication, to the right person.

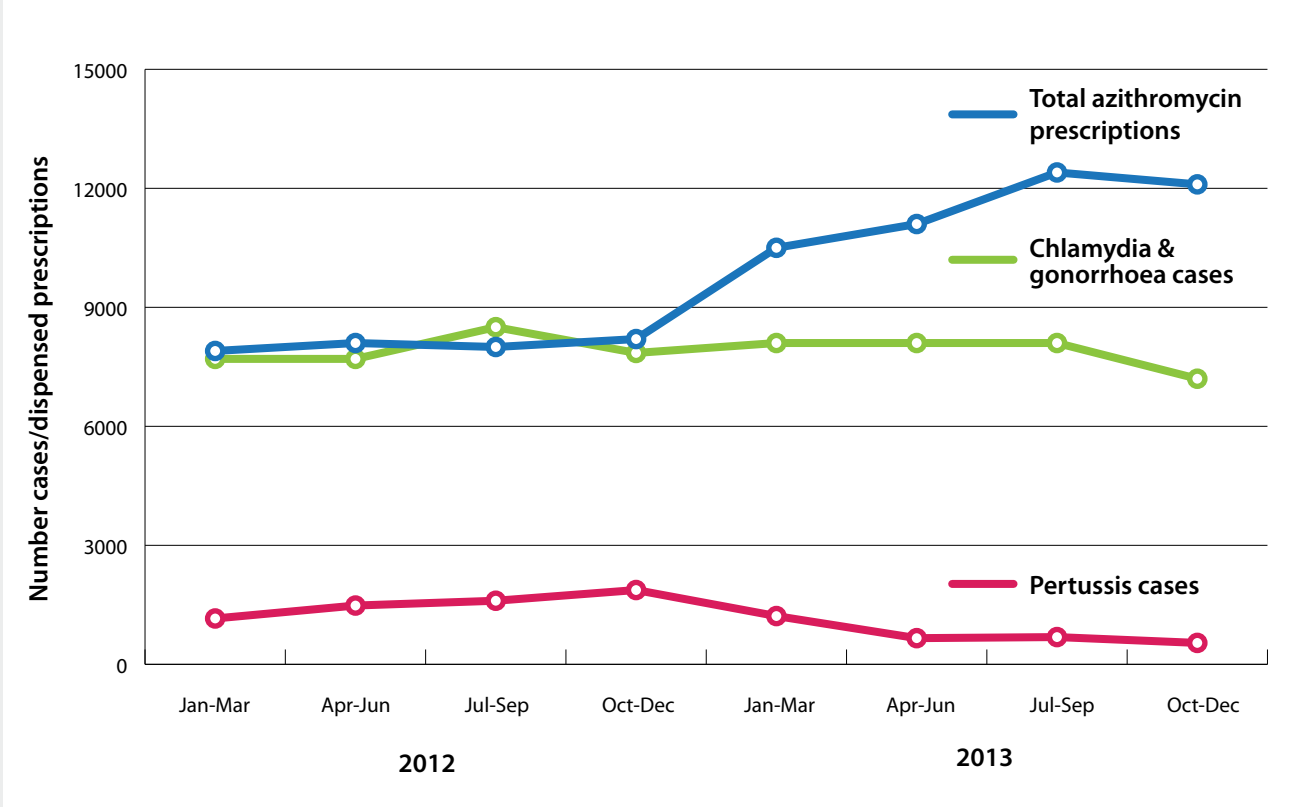

Figure 1: Number of dispensed azithromycin prescriptions and number of cases of pertussis and gonorrhoea and *Chlamydia* (combined), 2012 – 2013.

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