AZITHROMYCIN
Prophylactic use in COPD and Bronchiectasis

Initiation: Secondary Care and only appropriate for frequent exacerbations (> 2 / year)
Note: patients must be warned to stop treatment if they notice any hearing impairment

Baseline monitoring (to be undertaken by specialist in secondary care):
- LFT and U+E. Avoid in severe liver disease and renal disease (eGFR < 10ml/min)
- 3 sputum samples to exclude mycobacterium infection
- ECG (check no QT prolongation)

Dose:
- 250mg THREE times per WEEK initially, increased to 500mg THREE times per WEEK if ineffective
- Prescribe as Tablets not Caps (28 day treatment costs based on 3 x weekly dose 250mg caps £27.78, 250mg tabs £8.55, 500mg tabs £9.04. Drug tariff March 2013)

Duration of Treatment:
- Trial period 6-12 months
- If no reduction in exacerbations discontinue treatment
- If exacerbations reduce continue treatment
- Review treatment every 6 months to confirm continued efficacy

During Treatment:
- Monitor efficacy by encouraging patients to record exacerbations (ideally in hand held record)
- Monitor LFTs every 6 months
- Patients should be warned to stop treatment if they notice any hearing impairment
- Screen sputum for acid-fast bacilli if clinical or radiological suspicion of mycobacterial infection

Treating Breakthrough Exacerbations:
- Temporarily stop azithromycin
- Give 2 week course of antibiotics for bronchiectasis or 1 week course of antibiotics for COPD
- Culture sputum if no response to initial antibiotic course

Background Information

Azithromycin is a macrolide antibiotic with both antimicrobial and anti-inflammatory effects. It has a similar spectrum of antibacterial activity to penicillin but has enhanced activity against some gram negative organisms, including Haemophilus influenzae. Contraindications include severe liver disease, severe renal impairment (eGFR <10ml/min) and a prolonged QT interval. Side-effects include liver dysfunction and sensorineural deafness. Prior to initiating azithromycin, non-tuberculous mycobacterial infection must be excluded in anyone with a clinical or radiological suspicion of this as macrolide monotherapy is inappropriate for these conditions.

Prophylactic use in COPD

Patients with COPD fall into two distinct phenotypes: frequent exacerbators and infrequent exacerbators. Exacerbations are a sustained worsening of a patients condition which lead to a prolonged period of ill-health (usually several weeks) and loss of lung function which is sometimes never recovered. They can have a major impact on quality of life and utilization of health resources.

Several medicines have been shown to reduce exacerbation rates including high dose inhaled corticosteroids, long-acting beta 2 agonists and tiotropium. Prophylactic antibiotics have generally been avoided due to concerns about the emergence of drug resistance. However there is now a landmark paper from the New England Journal of Medicine which has shown significant positive outcomes from prophylactic azithromycin.

A large trial of azithromycin 250mg once daily for 12 months was conducted: 1142 patients were randomised to azithromycin or placebo (1:1) in addition to usual treatments. Patients had a history of steroid use in the last 12 months or had very severe disease and were on long-term oxygen therapy. All had a history of exacerbations. The median time to first exacerbation was increased from 174 to 266 days (p<0.001), and the frequency of exacerbations was reduced from 1.83 to 1.48 (p=0.01) per year in the azithromycin group. Hearing decrement occurred in 25% of the azithromycin group compared to 20% in the placebo group (p=0.04) and there was an increased rate of colonisation with macrolide-resistant organisms in the macrolide group.

The COPD NICE guidelines 2010 do not recommend azithromycin prophylaxis but this study has demonstrated that among selected subjects, azithromycin taken daily for 1 year, when added to usual treatment, can decrease the frequency of exacerbations and improve quality of life. However, as the long-term effect of this intervention on microbial resistance patterns is not known, local antibiotic resistance patterns should be closely monitored and use should be restricted to selected individuals until such time that further information supports more widespread use.

Prophylactic use in Bronchiectasis

Bronchiectasis is a disorder characterised by neutrophilic airways inflammation, chronic bacterial infection and recurrent exacerbations. Large volumes (>30mls) of purulent sputum are often produced on a daily basis. Organisms isolated from sputum include Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Pseudomonas aeruginosa and Staphylococcus aureus.

Azithromycin has been used successfully in cystic fibrosis patients to reduce exacerbation rates and is now increasingly used in non-CF bronchiectasis.

The EMBRACE² trial, published recently in The Lancet, provides further data on the efficacy of azithromycin prophylaxis in bronchiectasis. 141 patients were randomised to placebo or azithromycin 500mg alternate days for 6 months. There was a further follow-up period for 6 months. In the treatment period, the rate of exacerbations was 0.59 per patient in the azithromycin group compared with 1.57 per patient in the placebo group, corresponding to a 62% relative risk reduction. The annual rate of exacerbations was 1.58 in the azithromycin group and 2.73 in the placebo group, corresponding to a 42% risk reduction.

The long-term use of azithromycin is not recommended in the 2010 BTS Bronchiectasis Guidelines but these guidelines pre-date the publication of the EMBRACE study quoted above. Due to concerns about emerging drug resistance with long-term azithromycin use, duration of treatment should be tailored individually; there is no long –term data from clinical trials available at the present time.