NHS
Greater Glasgow and Clyde

CLINICAL GUIDELINE

Long Term Azithromycin in COPD and Bronchiectasis in Adults

A guideline is intended to assist healthcare professionals in the choice of disease-specific treatments.

Clinical judgement should be exercised on the applicability of any guideline, influenced by individual patient characteristics. Clinicians should be mindful of the potential for harmful polypharmacy and increased susceptibility to adverse drug reactions in patients with multiple morbidities or frailty.

If, after discussion with the patient or carer, there are good reasons for not following a guideline, it is good practice to record these and communicate them to others involved in the care of the patient.

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Important Note:

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Any printed copies should therefore be viewed as 'Uncontrolled' and as such, may not necessarily contain the latest updates and amendments.

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Introduction

Long term macrolide antibiotic therapy in COPD and bronchiectasis may reduce the number of exacerbations, improve quality of life and have other beneficial effects in lung disease. Initiation of long term macrolide therapy should be undertaken with caution due to potential adverse effects including QT prolongation, ototoxicity and development of antibiotic resistance.

This guidance covers only the use of long term azithromycin in COPD and bronchiectasis in adults as this is the macrolide of choice for this indication within NHSGGC.

Long term azithromycin therapy must be initiated, and prescribed by or under the direction of a respiratory consultant

Indications

Patients with COPD or bronchiectasis and:
More than 3 exacerbations / year requiring antibiotic and/or steroid therapy,
OR chronic persistent symptoms of airways inflammation (chronic production of purulent phlegm), despite optimising therapy (see below).
All therapy must be initiated on the advice of a respiratory consultant.

Optimise Therapy

The following aspects of therapy should be assessed and optimised prior to initiation of long term azithromycin as per available local and national (BTS, NICE) guidelines:

Bronchial hygiene:

- Review by respiratory physiotherapist
- Trial of oral mucolytic therapy (and nebulised saline 7% in bronchiectasis if tolerated / not contra-indicated)

Steroid therapy (oral and inhaled) reviewed (optimise steroid therapy if asthmatic - consider monitoring FeNO; minimise steroid therapy if not asthmatic):

- Review spirometry / reversibility / consider formal steroid trial; FeNO; sputum eosinophilia to identify asthmatic component / eosinophilic bronchitis.
- Ensure meets guidelines for use of ICS in COPD (if COPD); consider change from more potent to less potent ICS (refer to NHSGGC COPD inhaler device guide). Consider trial of withdrawal of steroid therapy if no asthma and does not meet COPD criteria for ICS.

Prior to initiation the following antimicrobial colonisation must be excluded or treated:
Exclusion of allergic bronchopulmonary aspergillosis (aspergillus specific IgE and IgG, skin prick testing)

Exclusion of pathogenic colonising / exacerbating organism (eg haemophilus, streptococcus, moraxella)

- 2 weeks appropriate oral or IV therapy to eradicate if present
- Consider longer course of oral antibiotics (up to 8 weeks) if no clinical response. This advice is based on local experience.
- Not all colonising organisms are pathogenic and need eradicated – discuss with microbiologist if unsure

Exclusion of pseudomonal colonisation.

- Adequate attempts at eradicating airways colonisation by pseudomonas if present with oral or IV antibiotic therapy / maintenance inhaled antibiotics (see BTS guidelines on the management of non-cystic fibrosis bronchiectasis for details).

Exclusion of MSSA and MRSA colonisation.

- Eradication with 2 weeks appropriate oral or IV antibiotics if present

Exclusion of non tuberculosis mycobacteria (NTM) colonisation.

- At least 3 sputum samples in last year excluding NTM colonisation.
- At least 3 sputum samples in last year for bacteriology associated with exacerbations.
- Successful treatment of NTM airways infection if present.

Other measures:
Immuno-deficiency excluded or treated (Immunoglobulins and functional antibodies). HIV excluded.

Smoking cessation (if appropriate).

Pulmonary rehabilitation (if appropriate).

Contra-Indications

Hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic, or to any of the excipients listed

ECG QTc > 450ms . A baseline ECG must be performed prior to initiation

Electrolyte disturbances (predisposition to QT interval prolongation);

May aggravate myasthenia gravis

Drug interactions

The potential for drug interactions with azithromycin should be assessed before treatment is commenced, the BNF (www.medicinescomplete.com) and Summary of Product Characteristics (SPC) (www.medicines.org.uk) provide details of known interactions.

In addition, azithromycin can prolong the QT interval and should be used with caution in patients taking other medicines that are known to cause QT interval prolongation. Medicines Update Extra bulletins are available with advice on evaluating and managing this type of interaction and suggested ways to address common clinical scenarios involving QT prolonging drugs – they can be found on http://www.ggcprescribing.org.uk/. Alternatively click here for a direct link.
If azithromycin is deemed not to be appropriate please discuss alternative approaches with respiratory Consultant.

Initiation and Dosage

Baseline audiometry not necessary unless pre-existing hearing problems not fully documented. Advise all patients of loss of hearing as a potential side effect and to report promptly any deterioration in hearing.

Baseline FBC, U&Es, LFTs prior to treatment.

Azithromycin should be used with caution in patients with severe renal impairment (GFR<10ml/min).

Azithromycin should not be used in patients with severe liver disease as the main route of metabolism is via the liver. There have been cases of hepatitis reported with azithromycin therefore it is recommended that the drug should be stopped if liver dysfunction occurs.

ECG at baseline. Refer to GGC QT prolongation bulletin for advice on ECG evaluation, any modifiable risk factors for QT prolongation should be corrected prior to azithromycin initiation Discuss with cardiology if further advice is required.

Initiate azithromycin 500mg three times a week. An alternative dose schedule of 250mg daily can be considered if better tolerated. Note this is an off label indication for azithromycin but is supported by guidelines (NICE,BTS).

The initial recommendation to commence azithromycin must be made by a respiratory physician. Ongoing monitoring and review should be at a respiratory clinic.

During an acute exacerbation an antibiotic from a different class should be used. Although it may be reasonable to continue azithromycin during an exacerbation, there may be an increased risk of drug interactions and prolonged QTc in unwell patients so consider stopping for the duration of the exacerbation and restarting if safe to do so thereafter. There is no rational for substituting another macrolide e.g. clarithromycin to treat an exacerbation in a patient on long term azithromycin.

Follow Up

- Repeat ECG after 2-3 weeks.
  - Also repeat ECG if further QTc prolonging drug is added.
  - Consider stopping if there is a significant change in QTc interval or if QTc interval is >450ms

- Repeat FBC, U&Es and LFTs at 2 weeks and at clinic review thereafter.

- Consultant review at 3-6 months initially and minimum yearly thereafter to assess tolerability and clinical response
  - Document response to therapy (reduction of frequency of steroid / antibiotic courses).Consider cessation of long term macrolide therapy over summer if seasonal (winter) pattern of exacerbations
  - Enquire about potential hearing problems at each review visit and refer to audiometry if symptoms develop.

Criteria for stopping treatment

Development of significant side effects, prolongation of QTc or contraindication to ongoing therapy

Loss of clinical response as evidenced by failure to reduce exacerbation rate, or an increase in exacerbation rate again following a previous good clinical response.

Background

1: Altenburg J, de Graaff CS, Stienstra Y, et al. Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non-cystic fibrosis bronchiectasis: the BAT randomized controlled trial.
JAMA (2013);**309**:1251-9.

2: Wong C, Jayaram L, Karalus N, et al. Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): A randomised, double-blind, placebo-controlled trial.
The Lancet (2012); **380**: 660-667.

3: Serisier DJ, Martin ML, McGuckin MA, et al. Effect of long-term, low-dose erythromycin on pulmonary exacerbations among patients with non-cystic fibrosis bronchiectasis: the BLESS randomized controlled trial.
JAMA (2013); **309**:1260-7.

4: Hill AT, Sullivan AL, Chalmers JD, et al. Thorax 2019;74 (Suppl 1):1–69.

5: Albert RK, Connett J, Bailey WC, et al. Azithromycin for Prevention of Exacerbations of COPD. NEJM (2011); 365: 689–698.

6. Cochrane review: Macrolide antibiotics for bronchiectasis. Kelly C et al. March 2018