Herefordshire and Worcestershire Medicines and Prescribing Committee

NHS Herefordshire and Worcestershire Clinical Commissioning Group

Prescribing Guideline for Long Term Off-Label use of Prophylactic Azithromycin for Patients with COPD, Asthma and Bronchiectasis

Guideline Objective

To define safe and effective procedures for prescribing and monitoring of long term off-label azithromycin therapy by primary and secondary care practitioners for eligible COPD, asthma, or bronchiectasis patients, in line with the British Thoracic Society Guidelines 2020.

Areas of Prescribing Responsibility

Azithromycin should only be started following discussion and shared decision-making between the patient and a respiratory specialist.

This local prescribing guideline outlines the responsibilities for prescribing azithromycin, and the subsequent management of patients, by the respiratory specialist* and general practitioner (GP) or non-medical prescriber in primary care. GPs are invited to participate and if not confident to undertake these roles, then the total clinical responsibility for the patient remains with the specialist. **If a specialist asks the GP to prescribe this treatment, the GP should reply to this request as soon as practicable.** The prescriber legally assumes clinical responsibility for the drug and the consequences of its use.

*Respiratory Specialist defined as: Respiratory Consultant, GP with Specialist Interest, Specialist Nurse Prescriber, COPD Team

Inclusion criteria:

- **COPD or bronchiectasis patients** who have 3 or more exacerbations per year requiring steroid therapy and at least one exacerbation requiring hospital admission per year.

  Exacerbation defined as: sustained episode (>48h) of symptoms exceeding normal variability; 2 or more of increased sputum purulence, increased sputum volume or constitutional symptoms for >3 days.
- **Asthma patients** who have ongoing symptoms despite adherence to high-dose inhaled steroids and at least one exacerbation requiring oral steroids in the past year, following secondary care review.

Exclusion criteria:

- Cystic fibrosis
- Children, pregnancy, or breast feeding
- Allergy to macrolide antibiotics or excipients
- LFTs more than 2 x upper limit of normal at baseline or known liver disease.
- eGFR less than 10 ml/min /1.73m^2
- Atypical mycobacterial infection on sputum culture
- QTc greater than >450 ms for men and >470 ms for women
- Risk of prolonged QTc due to co-prescribing drugs known to prolong QTc

Joint Responsibilities of All Clinicians Involved in Patient Care

Ensure optimal pharmacological and non-pharmacological treatment prior to commencing azithromycin, in particular:

- Smoking cessation advice and signposting to community pharmacist for support.
- Ensure optimisation of therapies: correct inhaler choice, dose and technique.
- Encourage regular chest clearance, such as active cycle breathing techniques and consider mucolytic therapy.
- Regular sputum cultures if change in colour or consistency, or antibiotics prescribed.

Responsibilities of Initiating Clinician

Initiation by Respiratory Specialist* **OR**

Initiation by GP on Respiratory Specialist Advice, with GP Agreement

- Discuss with patient the intended benefits of treatment, side effects and 'off label' use of azithromycin.
- Explain the intention for shared care and the possible involvement of the specialist nursing team.
- Prescribe the first month's treatment and appropriate blood monitoring (See '*Baseline Evaluation and Monitoring'* overleaf).
- Provide patient with patient information leaflet.
- If initiated by respiratory specialist, request GP participation to prescribe azithromycin after first month, recommended for minimum trial of 6 months.
- Patients remain under specialist care for **at least 12 months** but may be discharged from regular annual specialist follow-up if they remain stable with azithromycin regime for over 12 months (on a case by case basis, with GP agreement).

Responsibilities of Clinician Prescribing On-going Treatment

- Reply to specialist care prescribing request as soon as practicable.
- After the first month of treatment by the specialist, continue to prescribe azithromycin at the dose recommended for a minimum trial of 6 months.
- Monitor in line with 'On-going management' on page 4 overleaf.

Seek advice from the specialist in the following circumstances:

- Patient has a recurrent or non-resolving exacerbation whilst on azithromycin, except where there is a clear reason e.g. acute viral infection.
- Patient is non-compliant with optimal therapy.
- When there is a significant drug interaction with essential therapy.

Patient / Carer Responsibilities

- Report to the specialist or GP if they do not have a clear understanding or have any concerns about the treatment.
- Should comply with any investigation schedule (including blood tests) advised by GP or specialist.
- Report any adverse effects to the GP or specialist:

  Patients should immediately report any signs of tinnitus or deafness, yellowing of the whites of their eyes or skin or unusual bruising to GP or specialist.

Baseline Evaluation and Monitoring

Baseline Checklist

- Document current/baseline symptoms, exacerbation frequency and nature of exacerbations, including:
  - breathlessness, MRC dyspnoea score
  - new or increased sputum production
  - purulent nature of sputum
- Chest X-ray (CT thorax may be required to confirm diagnosis of bronchiectasis)
- FBC, U&Es and liver function tests (LFTs)
- ECG to record QTc interval.

  Avoid azithromycin if QTc >450 ms men; >470 ms women; consider cardiology referral if any concerns.

  Caution in patients with low serum potassium or on concomitant medicines that prolong QTc interval. *See www.crediblemeds.org for full list.*
- Sputum sample for routine MC&S
- 3 good sputum samples for AFB / Mycobacterial culture (non-consecutive days) to exclude non-tuberculosis mycobacterium (NTM)

  Macrolide monotherapy should be avoided if an NTM is identified.
- Assess for interactions with concomitant medications - *see BNF.*

  Further advice can be sought through ***Worcestershire Acute Hospitals NHS Trust Medicines Information: 01527 505776*** or ***Wye Valley NHS Trust Medicines Information 01432 364017*** (Mon-Fri 9am-5pm)
- Consider audiometry referral, especially if patient has a history of baseline hearing impairment or tinnitus. If known impairment, await results before prescribing.

Prescribing Checklist for initiation:

- Document informed patient consent for use of azithromycin 'off-label'
- Provide patient with patient information leaflet (and copy to GP)
- **Prescribe**: azithromycin 250mg tablets three times per week (suggest taken Monday, Wednesday, Friday) for first month. (*In certain situations, under specialist instruction 500mg prescribed or daily use; titration according to clinical response*)
- Encourage patient to complete symptom diary (hand-held written record of admissions to hospital, antibiotic courses, and exacerbations); *consider patient passport.*
- Advise patients that the medicine should be stopped if they develop any signs of hearing impairment or tinnitus, jaundice, itching or vomiting.
- Counsel patient about potential adverse effects including: Gastrointestinal upset, hearing and balance disturbance, cardiac effects, and microbiological resistance.
- Provide forms for LFTs 4 weeks after initiation of treatment, as bloods may need to be taken in community and monitor LFT results for first month.
- **Arrange 6-month specialist review. If the patient has not been followed up within 6 months, it is the responsibility of the specialist to chase.**

On-Going Management

Checklist Post Azithromycin Initiation

After 4 weeks from initiation:

- **Repeat LFTs** (*specialist to provide forms when treatment is commenced as bloods may need to be taken in community; specialist to check results*)
- **Repeat ECG** to assess for any new QTc prolongation (*see "Baseline Checklist" on page 3 for guidance*).

On-going management, after 6-month specialist review:

- Ensure regular sputum MC&S sent to monitor antibiotic resistance *(at least every 2 months if productive)*.
- LFTs at 6-month intervals *(to be checked in specialist clinic or by GP if discharged)*.
- Annual clinical review if patient stable and patient discharged with GP agreement.

- **STOP** azithromycin if LFTs increase more than 2 x upper limit and refer immediately back to specialist.

- **STOP** azithromycin prophylaxis when patients are receiving oral or IV antibiotics with the potential to prolong the QT interval and recommence once antibiotics treating infection or exacerbation have been stopped.

- **Trial OFF treatment:** If requested by the specialist, offer patient a '*drug holiday'* in summer months. This is often recommended where there are significant seasonal variations in exacerbations or symptoms specific to winter.

  Treatment should then recommence for winter months. Further blood monitoring on recommencement of prophylaxis is not required unless there are any specific concerns.

6 Month Specialist Review and Annual Review Thereafter:

- **Review**: symptoms, exacerbations, compliance with therapy.
- **Check**: LFTs, sputum cultures.
- **Assess efficacy**: ongoing treatment should be guided by clinical response based on specific outcome measures including exacerbation frequency, symptoms and quality of life assessed at baseline, e.g. via MRC, CAT or ACQ scores.
- ***If patient has not benefitted from treatment****:* reassess at each appointment and stop treatment if no benefit.
- ***If treatment is to continue beyond 6 months****,* annual review is required; if patient stable and discharged from specialist care with GP agreement, this annual review will fall to Primary Care.
- LFTs should be checked at 6-month intervals while on treatment.

Additional Prescribing Note: Azithromycin and Statins
Azithromycin has potentially been implicated in cases of rhabdomyolysis with statins. Use extra caution when considering the use of azithromycin and statins. This combination is considered lower risk than combinations with other macrolides (clarithromycin, erythromycin). If azithromycin is co-prescribed with a statin, the patient should be monitored closely for evidence of toxicity (e.g. muscle aches and pains, and renal dysfunction). Patient should be counseled to promptly report muscle pain or weakness.

References:

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