NHS
Greater Manchester
Integrated Care

Long-Term Azithromycin in Adults with Chronic Respiratory Disease: Guidance for Primary Care.

1.0 Background

Azithromycin is a macrolide antibiotic with good antimicrobial activity against the usual respiratory pathogens (gram positive, some gram-negative and atypical organisms e.g. legionella, mycoplasma and mycobacterial species). In addition to their antimicrobial effects, it has been recognised that macrolide antibiotics also possess anti-inflammatory/immunomodulatory effects[1]. Consequently, low dose, long-term macrolides may provide a potential treatment strategy in several chronic inflammatory airway conditions.

In 2020, the British Thoracic Society (BTS) published guidance[1] on the use of long-term macrolides in adults with respiratory disease. The BTS recommendations on the prescribing of long-term azithromycin in adults with a diagnosis of asthma, COPD or bronchiectasis are summarised in the table in appendix 1. The use of long-term azithromycin in this context is unlicensed and current trial data only provides evidence of benefit and risk up to 12 months for bronchiectasis and COPD and 48 weeks for asthma[1].

Good practice points are set out in appendix 2 and should be considered in both primary and secondary care when prescribing long-term azithromycin to patients.

1.1 Antimicrobial Stewardship

Antibiotics should only be prescribed when there is likely to be a clear clinical benefit to ensure:

- their use is safe and effective and
- to minimise the emergence of bacterial resistance.

The possible side effects and risk of resistance should be discussed with patients prior to starting low-dose azithromycin therapy. Long-term antibiotics therapy must be regularly reviewed to determine that benefits are balanced against risks of continuing treatment.

1.2 Limitations

Other respiratory, and non-respiratory indications, plus the above indications in individuals under 16 years of age are not covered by this guidance.

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2.0 Initiation of therapy

Long-term azithromycin should only be initiated by or on the advice of a respiratory specialist for patients with a confirmed diagnosis of asthma, COPD or bronchiectasis.

2.1 Responsibility of respiratory specialist:

The initial steps of the process should be undertaken by a specialist in respiratory medicine and the patient should not be discharged from their care until all these steps are completed. See appendix 1 for details.

1. Identifying suitability for treatment with long-term azithromycin
2. Identifying any contra-indications to long-term azithromycin therapy
3. Perform all safety checks before initiating azithromycin
4. Ensuring patient is sufficiently counselled.

Azithromycin has been classified as a **GREEN drug with specialist advice** by GMMMG, therefore, the specialist may request a patients' GP to initiate long-term prescribing on their recommendation. The specialist is expected to communicate, in writing, to the GP:

a. That the first 4 steps have been performed (including results of any tests performed).
b. Provide information on:
    i. the dosage regimen
    ii. follow up plan, including date of next review, who is to carry out the review & if discharged under what circumstances the patient should be re-referred back to specialist care.

NB in certain circumstances the respiratory specialist may deviate from the recommendations given by BTS in appendix 1. In these instances, it is **essential that the specialist can clearly communicate the rational for the deviation to the GP**, not doing so may risk treatment being delayed.

2.2 Responsibility of GP:

- GPs should be satisfied that the initial steps have been completed by the specialist before they take on prescribing responsibility (details in appendix 1).
- A prescription for 28 days' supply should be added to the patient's repeat medication for **one authorisation only** and in line with recommendations from the patient's consultant.
- Add the **Snomed code 422181004** (administration of prophylactic antibiotic) or **READ code 65N4** (antibiotic prophylaxis) to the patient's record.

- Long-term antibiotics should have the next review date, 'REVIEW dd/mm/yy', included in the dosing directions. This is to ensure that antibiotics are not issued long-term without regular review.

3.0 Monitoring and review

3.1 Monitoring during therapy

Ongoing therapy will need to be regularly monitored. Details of what should be monitored, when, and who by can be found in appendix 1 and table 1.

Table 1:

What	When	Who	Action
LFTs	After 1 month and every 6 months	• Clinician undertaking prescribing at 1 month. • GP 6 monthly, thereafter. GP.	Azithromycin administration should be stopped if liver dysfunction has emerged[2]
ECG	After 1 month & after initiating any new drug that may prolong QTc interval	• Clinician undertaking prescribing at 1 month. • Clinician responsible for initiating the new drug, thereafter.	As below in appendix 1
Side effects	6 to 12 months at review (initial review at 3 months for patients with COPD[3])	GP at least every 12 months at annual review / Respiratory specialist at each review.	If GI upset - consider dose reduction to 250mg three times a week (or stopping if already on this dose).
Medication review			Review for drug interactions and potential QTc prolongation
Standard Sputum in patients able to expectorate		At annual review GP should ensure that sputum has been monitored at least once in previous 12 months. Respiratory specialist may do more often as appropriate	Can be used to detect changes in microbial growth & highlight resistance which should be considered when reviewing ongoing treatment (see below 3.2.2).

3.2 Review

An initial review of treatment should be undertaken by the specialist after 3 to 6 months to determine evidence of improvement (reduction in exacerbation rate & improvement in symptoms). Patients should also be reviewed for adverse drug reactions/ intolerance to treatment and for any new drug interactions. See appendix 1 & table 1 for details.

If, after this initial review, it is deemed appropriate for treatment to continue the responsibility of ongoing monitoring & review will depend on the indication being treated and whether the patient is still under regular respiratory follow up, see below.

3.2.0 Responsibilities of respiratory specialist:

Bronchiectasis – these patients will remain under respiratory follow up and on-going use of azithromycin should be considered at each review and communicated to the patient's GP[4].

Asthma & COPD – these patients should ideally have their initial 3 to 6 month review performed by their respiratory consultant. Any patient discharged from specialist follow up will need to have a detailed plan for monitoring/review determined by the specialist and communicated to the GP.

3.2.1 Responsibilities of general practice:

Bronchiectasis, Asthma & COPD – at annual review and as part of a structured medication review patients should be reviewed for:

- continued respiratory input (as appropriate),
- exacerbation rate,
- symptoms (use of a validated scoring tool may be useful),
- side effects & intolerances,
- new drug interactions – particularly drugs that could cause QTc prolongation,
- LFTs are being monitored every 6 months,
- changes in sputum microbiology.

Asthma & COPD - for patients who have been discharged from ongoing respiratory follow up these patients should have their azithromycin reviewed at least annually with the aim of stopping treatment to test benefit. If patients are still having regular exacerbations despite optimal therapy, they will need to be re-referred to respiratory for advice.

3.2.2 Criteria for stopping treatment in primary care.

Clinical judgement of effectiveness should be used to determine if the benefits of treatment are outweighed by the risks from continuing azithromycin (see 'Review therapy in 6-12 months section' of table in appendix 1). The following should be

considered:

1. Does the patient believe the azithromycin has improved their symptoms? In particular ask if it has:
    a. Helped their breathing and exercise tolerance?
    b. Reduced their sputum volume or tenacity (i.e. made it easier to clear their chest)?
    c. Reduced their frequency of exacerbations? Does this correlate to the number of antibiotics prescribed for acute exacerbations/ rescue packs issued?
    d. For asthma, ask specifically about improvement in wheeze as well as tenacity and volume of sputum.

    If there is no benefit, treatment should be stopped.

2. Is the patient a current smoker?
    a. Azithromycin should only be considered for people with COPD who **do not smoke**[3].
    b. Patients with COPD who are current smokers should have their azithromycin stopped and be referred back to the specialist for review.
    c. Offer smoking cessation advice and referral to local stop smoking services to all patients.

3. Enquire about **adverse drug reactions**, specifically ask patient about:
    a. Ototoxicity (tinnitus, hearing and balance upset). Stop azithromycin and refer back to specialist.
    b. Gastrointestinal upset (nausea, vomiting, abdominal pain, anorexia, diarrhoea). Dose reduction may improve tolerability (stop if already on 250mg 3 times a week). Consider if diarrhoea could be due to Clostridium difficile. Stop azithromycin in confirmed/suspected cases and consult microbiology for advice.
    c. Other perceived issues the patient may have.

4. Also consider **drug interactions and results from sputum cultures.** Check the patient's record for newly prescribed drugs and sputum microbiology since their last review. If culture and sensitivity testing show resistance to azithromycin there are no suitable alternative antibiotics to switch to. However, ongoing clinical benefit may be attributed to anti-inflammatory/ immunomodulatory effects. Consider referral back to the specialist for a decision on whether treatment should be continued in this case.

    If the risk of continuing azithromycin outweighs any benefits seen

treatment should be stopped.

Even if benefit is seen, after 12 months of sustained improvement, consideration should be given to trialling stopping treatment. Either stop azithromycin completely or for a period each year (drug holiday), which should usually be attempted in the warmer summer months e.g., April to September.

References

1. Smith, D, Du Rand I, Addy CL, *et al*. British Thoracis Society guideline for the use of long-term macrolides in adults with respiratory disease. *Thorax* 2020(0), 1-35.
2. Medicines.co.uk. (2021). Azithromycin 500mg Film-coated Tablets Summary of Product Characteristics (SmPC) – (eMC). Retrieved from https://www.medicines.org.uk/emc/product/11681/smpc
3. Nice Guidance (2019) NG115 Chronic obstructive pulmonary disease in over 16s: diagnosis and management retrieved from https://www.nice.org.uk/guidance/ng115
4. Hill AT, Sullivan AL, Chalmers JD *et al*. British Thoracis Society Guideline for bronchiectasis in adults. *Thorax* (2019);74 (Suppl 1): 1-69

Document history

Date	Version	Section	Details
20/07/21	1.1	2.1	Addition of specialist deviation from BTS guidance
20/07/21	1.1	3.1	Table 1: LFTs & ECG monitoring. Change in who is responsible for monitoring at 1 month for LFTs and if new drug initiated for ECG.
20/07/21	1.1	Appendix 1	Addition of more details around monitoring of sputum prior to initiation.
20/07/21	1.1	3.2.1	Added exacerbation rate and symptoms
13/08/21	1.2	3.2	Added that responsibility for initial review remains with specialist for bronchiectasis to ensure constancy throughout document.
19/10/2022	1.3	3.2.2	Addition of a section of considerations for stopping azithromycin/trialling azithromycin holiday in primary care.
19/10/22	1.3	2.1, table 1 & appendix 1	Added asterisk to dose regimen (2.1), follow up ECG (table 1) & 3x sputum for AAFB as feedback from specialist is that they may deviate from BTS recommendations in certain circumstances.
15/12/22	1.4	2.1, table 1 & appendix 1	Asterisk and statement re 3x sputum for AAFB removed as this will be determined in secondary care prior to initiation by the specialist and any deviations communicated to GP as per section 2.1.
15/12/22	1.4		Moved to NHS GM Integrated Care template.

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01/03/2022	1.5	1.0	Specified difference in trial evidence length for COPD/bronchiectasis and asthma. Added reference to statement on anti-inflammatory/immunomodulatory effects.
01/03/2022	1.5	2.2	Added that details of initial steps can be found in appendix 1
01/03/2022	1.5	3.2 & 3.2.0	Initial review to be carried out 3-6 months by the specialist.
01/03/2022	1.5	3.2.2	Re-written paragraph on stopping treatment and drug holidays.
19/07/2023	1.6	2.1	Decision on RAG status of azithromycin for this indication added
19/07/2023	1.6	3.1 table 1	Information on sputum samples changes to patients who can expectorate and removed information about NTM.
19/07/2023	1.6	3.2.2	Added actions if ototoxicity occurs Added note to consider Clostridium difficile infection in patients with diarrhoea and action if this shown. Added actions if resistance is shown on C&S testing.
12/09/23	1.8	2.1	Removed the instruction for specialist to initiate treatment as RAG status now GREEN specialist advice.
12/09/23	1.8	3.2.2	Added information about reviewing smoking status for all patients at review and stopping azithromycin and referring back to specialist for patients with COPD in line with NICE guidance NG115.
12/09/23	1.8	3.1 table 1	Changed wording around responsibility of monitoring at 1 month and when initial review should take place for COPD patients.

Appendix 1: Summary of Recommendations for Long Term Azithromycin Use in Adults with Respiratory Disease

Supplementary 1:

Quick reference guide for azithromycin

	Asthma	COPD	Bronchiectasis
Identify if suitable for Azithromycin therapy	Confirmed diagnosis of asthma Symptomatic despite >800mcg/BED At least 1 exacerbation in previous 12 months Inhaled therapies optimised including inhaler technique and adherence review	Confirmed diagnosis of COPD 3 or more exacerbations in previous 12 months OR 1 or more severe exacerbation with hospitalisation/morbidity Inhaled therapies optimised including inhaler technique and adherence review, smoking cessation and pulmonary rehabilitation completed	Confirmed diagnosis of bronchiectasis. 3 or more exacerbations in previous 12 months Optimisation of other interventions such as airway clearance and pulmonary rehabilitation
Identify Contra-indications to macrolide therapy	Absolute Contra-indication: Previous allergy/intolerance to macrolides History of prolonged QTc Active NTM disease		Relative Contra-indications: Hearing or balance problems History of NTM disease Abnormal liver function tests
Perform safety checks before starting therapy	Baseline ECG— If QTc prolonged (>450msec for men, >470msec for women) do not give macrolide Baseline liver function tests	Standard sputum for baseline culture if able to expectorate If bronchiectatic or clinical concern of NTM infection investigate to exclude (following BTS guideline on NTM disease).	Review concomitant medications for potential interactions
Start Azithromycin therapy	Azithromycin (250mg/500mg)thrice weekly Plan to treat for 6-12 months Warn of potential side effects	Azithromycin 500mg thrice weekly or 250mg daily Plan to treat for 6-12 months Warn of potential side effects	Azithromycin 500mg thrice weekly or 250mg daily Plan to treat for 6-12 months Warn of potential side effects
Monitoring during therapy	Liver function tests at 1 month and every 6 months Repeat ECG at 1 month—if QTc prolonged (>450msec for men, >470msec for women) stop macrolide	Enquire about side effects, especially GI upset and hearing and balance problems Standard sputum for culture at review if able to expectorate	Medication review for potential drug interactions and QT prolongation
Review therapy at 6-12 months	Objective evidence of improvement: Reduction in exacerbation rate Improvement in symptoms Change in sputum microbiology including NTM growth Medication review for potential interactions	Objective evidence of improvement: Reduction in exacerbation rate Improvement in symptoms, QoL or CAT score Change in sputum microbiology including NTM growth Medication review for potential interactions	Objective evidence of improvement: Reduction in exacerbation rate Improvement in symptoms, QoL Change in sputum microbiology including NTM growth Medication review for potential interactions
Decide if suitable for ongoing therapy	Perform individual risk/benefit analysis	If therapy continued ensure ongoing monitoring and annual review of therapy	Consider treatment break for 3-6 months each year to reduce treatment burden (and possibly reduce microbiological resistance)

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Appendix 2: Good practice points to consider – as per BTS Guidelines for use of Long-term Macrolides in adults with respiratory disease

Asthma: Could be used to reduce exacerbation frequency in adults (50-70 yrs) with ongoing symptoms despite adherence to high dose inhaled steroids and at least one exacerbation requiring oral steroids in the last year.

- Considered for a **minimum of 6 -12 months** to assess evidence of efficacy. Then review.
- SHOULD NOT be offered as a way to reduce oral steroid dose.
- **Good practice points** – other asthma therapies should be optimised first, and patients referred to respiratory specialist to reduce exacerbation frequency. See **GMMMG Asthma Management Plan**
- Justification of ongoing treatment should be guided by clinical response based on specific outcome measures – including exacerbation frequency, symptoms and QoL assessed at baseline.
- If azithromycin therapy is considered for symptom reduction, this should be for a defined period **(6–12 months)** and stopped if no symptomatic improvement is seen. Use of a validated symptom score (e.g. Asthma Control score (ACQ) may be useful to make this less subjective.
- If desired clinical outcome is achieved, consider breaks in therapy, to reduce treatment burden.

COPD: Long-term azithromycin therapy could be considered for patients with COPD with more than three acute exacerbations requiring steroid therapy and at least one exacerbation requiring hospital admission per year to reduce exacerbation rate.

- Considered for a **minimum of 6 months and up to 12 months** to assess the impact on exacerbation rate.
- **Good practice points:** Non-pharmacological and pharmacological therapies should be optimised prior to considering long-term azithromycin therapy. This includes smoking cessation, optimised inhaler technique, optimised self-management care plan, airway clearance techniques and attendance at pulmonary rehabilitation courses. See **GMMMG COPD Management Plan**
- Microbiological assessment of sputum should be performed before therapy, including investigation for NTM.
- Accurate assessment of baseline exacerbation rate should be determined before starting long-term azithromycin for patients with COPD and a CT scan should be considered to exclude a possible diagnosis of bronchiectasis

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- Objective measure such as exacerbation rate, CAT score or QoL using a validated assessment tool should be used to determine benefit**. If no benefit derived stop treatment.**
- It is not necessary to stop prophylactic azithromycin during an acute exacerbation of COPD unless another antibiotic with potential to affect the QTc interval has also been prescribed.

Bronchiectasis: Long-term azithromycin treatment could be offered to reduce exacerbations in those with high exacerbation rates (i.e. 3 or more per year).

- When using azithromycin to reduce exacerbation rates, therapy should be **offered for a minimum of 6 months.**
- Azithromycin can be considered with the aim of improving quality of life **but may require a long period of therapy (e.g., 1 year)** for significant effects
- **Good practice points:** Therapies should be optimised in accordance with BTS Bronchiectasis Guidelines[2] before considering long-term azithromycin therapy (e.g. airway clearance techniques and attendance at pulmonary rehabilitation courses).
- Azithromycin should only be started following discussion and shared decision-making between the patient and a respiratory specialist.
- Microbiological assessment of sputum should be performed before therapy, including investigation for NTM.
- Accurate assessment of baseline exacerbation rate should be determined before initiation.
- Subsequent follow-up at 6 months and 12 months should determine whether benefit is being derived from therapy. **If there is no benefit, treatment should be stopped.**
- **Even if benefit is seen, consideration should be given to stopping treatment for a period each year, for example, over the summer. Such a drug holiday may help with reducing the development of resistance while maintaining efficacy because the vicious cycle has been broken.**