BMJ Open Respiratory Research

British Thoracic Society guideline for the use of long-term macrolides in adults with respiratory disease

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To cite: Smith D, Du Rand IA, Addy C, *et al*. British Thoracic Society guideline for the use of long-term macrolides in adults with respiratory disease. *BMJ Open Resp Res* 2020;**7**:e000489. doi:10.1136/bmjresp-2019-000489

Received 5 September 2019
Accepted 6 September 2019

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ABSTRACT

The full British Thoracic Society (BTS) guideline for the use of long-term macrolides in adults with respiratory disease is published in Thorax. The following is a summary of the recommendations and good practice points. The sections referred to in the summary refer to the full guideline. The appendices are available in the full guideline and online appendices are available on the BTS website. This is the first BTS guideline to use the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach as part of the process of guideline development and the guideline was used to pilot the new methodology.

INTRODUCTION

The full guideline for the use of long-term macrolides in adults with respiratory disease is published in Thorax.[1] The key features of the methodology and guideline are highlighted in a short article published to accompany the full guideline.[2] The following is a summary of the recommendations and good practice points (GPPs). The sections referred to in the summary refer to the full guideline.

BACKGROUND

The aim of this guideline was to examine the evidence for the use of long-term, low-dose macrolide agents used in the therapy of adult respiratory diseases, to develop guidance for clinicians in the use of these agents.

The guideline covers the use of macrolide in adults (>16 years) where the duration of treatment exceeds that usually employed to treat an acute infection and the dosage is less than that usually employed to treat an acute infection. Such usage is considered to be exerting an effect through mechanisms other than a direct antibacterial one, commonly described as immunomodulatory mechanisms. We have characterised this as long-term, low-dose usage.

In addition, the Guideline Development Group (GDG) has looked at safety issues surrounding the long-term use of macrolides at both patient and population levels to help to formulate pragmatic guidance in this area based on the best available evidence combined with clinical experience.

TARGET AUDIENCE FOR THE GUIDELINE

The guidelines will be of interest to the UK-based clinicians caring for adults with respiratory disease, including respiratory physicians, acute/general medicine physicians and respiratory specialist nurses. The guidelines may also be of interest to general practitioners, community matrons and practice nurses, hospice staff and community respiratory teams, physiotherapists, microbiologists, pathologists, pharmacists, haematologists and lung transplant teams.

AREAS COVERED BY THE GUIDELINE

This guideline covers the following respiratory conditions: asthma, bronchiectasis, chronic obstructive pulmonary disease (COPD), bronchiolitis obliterans, chronic cough, organising pneumonia and diffuse panbronchiolitis.

The guideline excludes paediatric practice. The use of macrolides in cystic fibrosis has not been included recognising the parallel work of the National Institute for Health and Care Excellence [3] in this area. Long-term macrolides for chronic rhinosinusitis have not been included. The use of macrolides as antibacterial agents to treat respiratory infection is excluded.

METHODOLOGY

This is the first British Thoracic Society (BTS) guideline to use the GRADE approach as

Table 1 Summary of outcome measures

Population	Intervention	Control	Outcomes
Adults with asthma Adults with bronchiectasis Adults with COPD Adults with bronchiolitis obliterans Adults with chronic cough Adults with organising pneumonia Adults with diffuse panbronchiolitis	Long-term, low-dose macrolides	Placebo	▶ Quality of life measures ▶ Symptom improvement/symptom score ▶ Exacerbation rates ▶ Hospital admission rate ▶ Disease progression and changes in lung function tests ▶ Mortality ▶ Exercise capacity/tolerance ▶ Sputum volume/colour/character and microbiological resistance/dysbiosis ▶ Drug monitoring/side effects/toxicity

COPD, chronic obstructive pulmonary disease.

part of the process of guideline development. Previous guidelines have used the SIGN methodology. BTS has made this change to reflect common practice in guideline development internationally across all medical specialities. The advantages of the GRADE approach are described in detail in the GRADE handbook and the BTS GRADE guideline production manual (https://www.brit-thoracic.org.uk/quality-improvement/guidelines/).

An accompanying article has been published in Thorax which provides additional background.[2]

CLINICAL QUESTIONS, PATIENT CENTRED OUTCOMES AND LITERATURE SEARCH

Clinical questions were formulated in the PICO (patient, intervention, comparison and outcome) format. The PICO framework was used to define the scope of the guideline and formed the basis of the literature search. The initial search was completed in February 2017, with a subsequent search perfumed later in 2017 by York University. Systematic electronic database searches were conducted to identify all papers which might potentially be included in the guideline. For each question, the following databases were searched: Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database, Cochrane Central Register of Controlled Trials, MEDLINE and MEDLINE In-Process, Embase and PubMed. The search strategy is available for review in online appendix 1.

In line with GRADE, a series of patient-centred outcomes were identified by the group when the scope was agreed (see table 1).

APPRAISAL AND GRADING OF EVIDENCE

Each relevant paper was appraised by outcome(s), to generate the best estimate of the effect on each outcome and an index of the uncertainty associated with that estimate where possible. An evidence profile entry was completed for each outcome which included grading of the quality of the evidence. The type of evidence available for each outcome varied from systematic reviews to case series; for each outcome, the highest-quality evidence available was included. GRADEpro was used to generate the evidence profiles, published online on the BTS website where they are available for review (see online appendix 2). The GRADE approach to rating the quality of evidence begins with the study design (table 2) and then, through a process of considered judgement, applies five reasons to possibly rate down the quality of evidence and three reasons to possibly rate up the quality (table 3).

In assessing the evidence, the GDG combined low and very low evidence into one category (low) as the body of evidence was limited.

DRAFTING THE GUIDELINE AND MAKING RECOMMENDATIONS

The GDG reviewed each clinical question during the regular meetings and consensus was reached. Having

Table 2 Categories of evidence

	Characteristics	Confidence
High	Based on consistent results from well-performed randomised controlled trials	Further research is very unlikely to change the estimate of the effect
Moderate	Based on randomised controlled trials where there is evidence of bias, or from other well-conducted study types (eg, well-executed observational studies)	Further research is likely to have an impact on the estimate of the effect
Low	Based on observational evidence, or from controlled trials with several serious limitations	Further research is likely to have an important impact
Very low	Based on case studies or expert opinion	Estimates of effect are far from certain and more research is needed

Table 3 Decreasing and increasing the grade of evidence

Decrease grade if*	► Serious or very serious limitation to study quality ► Important inconsistencies in results ► Some or major uncertainty about directness of the evidence ► Imprecise or sparse data (relatively few participants and/or events) ► High probability of reporting bias
Increase grade if	► Magnitude of the treatment effect is very large and consistent ► Evidence of a large dose-response relation ► All plausible confounders/biases would have decreased the magnitude of an apparent treatment effect

*Each quality criterion can reduce the quality by one or, if very serious, two levels. See BTS GRADE guideline production manual for further details (https://www.brit-thoracic.org.uk/quality-improvement/guidelines/).
BTS, British Thoracic Society.

Table 4 Explanation of the terminology used in BTS recommendations

Strength	Benefits and risks	Implications
Strong. It is recommended and so 'offer'	Benefits appear to outweigh the risks (or vice versa) for the majority of the target group	Most service users would want to or should receive this intervention
Conditional. It is suggested and so 'consider'	Risks and benefits are more closely balanced, or there is more uncertainty in likely service users values and preferences	The service users should be supported to arrive at a decision based on their values and preferences

BTS, British Thoracic Society.

generated evidence profiles for each of the clinical questions, the GDG as a whole then considered the importance of each of the outcomes for each clinical question and proceeded to grade the overall body of evidence for critical and important outcomes.

The GDG went on to decide on the direction and strength of recommendations considering the quality of the evidence, the balance of desirable and undesirable outcomes, and the values and preferences of patients and others. GRADE specifies two categories of strength of a recommendation as presented in table 4.

From the outset, it was acknowledged that there would be little high-quality evidence for some of the clinical questions identified. GPPs were developed by consensus in areas where there was no quality evidence but the GDG felt that some guidance based on the clinical experience of the GDG might be helpful to the reader. These are indicated as shown below.

► Recommended best practice based on the clinical experience of the guideline development group

DECLARATIONS OF INTEREST

All members of the GDG made declarations of interest in line with BTS policy and further details can be obtained on request from BTS. Guideline Group members are listed in appendix 1 to the full guideline.

STAKEHOLDER ORGANISATIONS

Stakeholders were identified at the outset and were notified when the guideline was available for public consultation.

SUMMARY OF RECOMMENDATIONS AND GPPS

Asthma

Recommendations

- Oral macrolide therapy could be considered to reduce exacerbation frequency in adults (50–70 years) with ongoing symptoms despite >80% adherence to high-dose inhaled steroids (>800 µg/day) and at least one exacerbation requiring oral steroids in the past year. This recommendation reflects the population within the AMAZES randomised controlled trial (RCT) which represents the highest-quality evidence of macrolide therapy leading to a significant reduction in exacerbations. (Conditional)
- Treatment with azithromycin should be considered for a minimum of 6–12 months to assess evidence of efficacy in reducing exacerbations. (Conditional)
- Oral macrolide therapy should not be offered as a way to reduce oral steroid dose; in some individuals, this may result as a consequence of a reduction in exacerbations or symptoms. (Strong)

GPPs (also see quick reference guide in online supplementary file 1)

- Optimisation of other asthma therapies, including establishing good adherence to inhaled therapies, should be performed before considering a trial of oral macrolide therapy.
- Referral to a respiratory specialist or specialist asthma service should be considered prior to initiation of macrolide therapy aimed at reducing exacerbation frequency.
- For safety purposes, an ECG should be performed prior to initiation of macrolide therapy to assess QTc interval. If QTc is >450 ms for men and >470 ms for

women then this is considered a contraindication to initiating macrolide therapy. Baseline liver function tests (LFTs) should also be measured.
- Patients should be counselled about potential adverse effects before starting therapy, including gastrointestinal upset, hearing and balance disturbance, cardiac effects and microbiological resistance.
- Microbiological screening of sputum before and during macrolide therapy may be clinically helpful in patients who are able to expectorate sputum. This would allow monitoring for the development of resistance and detect changes in microbial growth to direct appropriate antibiotic therapy if required. However, the resource implications of this approach have not been assessed.
- If oral macrolide therapy is considered, justification for ongoing treatment should be guided by clinical response based on specific outcome measures, including exacerbation frequency, symptoms and quality of life assessed at baseline.
- A risk:benefit profile should be considered in each individual if significant side effects from oral macrolide therapy develop. If gastrointestinal side effects occur at the higher dose of azithromycin (500 mg three times a week), a dose reduction to azithromycin 250 mg three times a week could be considered if macrolide therapy has been of clinical benefit.
- Liver function tests should be checked one month after starting treatment and then every 6 months. An ECG should be performed one month after starting treatment to check for new QTc prolongation. If present, treatment should be stopped.
- Symptom improvement with macrolide treatment may be minimal and not consistent across all people with asthma. If macrolide 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, such as the ACQ, may be useful to help to make this assessment less subjective.
- If the desired clinical outcome is achieved, the possibility of breaks in therapy may be considered to reduce the treatment burden for patients. It is unclear whether this may also reduce antimicrobial resistance rates.

Bronchiectasis

Recommendations

- Long-term macrolide treatment could be offered to reduce exacerbations in those with high exacerbation rates (ie, three or more per year). (Strong)
- The dosing regimens with the greatest supportive evidence, when using macrolides to reduce exacerbation rates, are azithromycin 500mg three times a week, azithromycin 250mg daily, and erythromycin ethylsuccinate 400mg twice a day. Astarting dose of azithromycin 250mg three times a week could be used to minimise side effect risk with subsequent titration according to clinical response (Conditional)
- When using macrolides to reduce exacerbation rates, therapy should be offered for a minimum of 6 months. (Strong)
- Macrolides can be considered with the aim of improving quality of life but may require a long period of therapy (eg, 1 year) for significant effects. (Conditional)

GPPs (also see quick reference guide in online supplementary file 1

- Therapies should be optimised in accordance with BTS Bronchiectasis Guidelines before considering long-term macrolide therapy (eg, airway clearance techniques and attendance at pulmonary rehabilitation courses).
- Macrolides should only be started following discussion and shared decision-making between the patient and a respiratory specialist.
- For safety purposes, an ECG should be performed prior to initiation of macrolide therapy to assess QTc interval. If QTc is >450 ms for men and >470 ms for women then this is considered a contraindication to initiating macrolide therapy. Baseline LFTs should also be measured.
- Patients should be counselled about potential adverse effects before starting therapy, including gastrointestinal upset, hearing and balance disturbance, cardiac effects and microbiological resistance. Microbiological assessment of sputum should be performed before therapy, including investigation for NTM. Macrolide monotherapy should be avoided if an NTM is identified. When evaluating for NTM infection, macrolides should not be used for 2 weeks before microbiological testing.
- Accurate assessment of baseline exacerbation rate should be determined before starting long-term macrolides for bronchiectasis.
- Liver function tests should be checked one month after starting treatment and then every 6 months. An ECG should be performed 1 month after starting treatment to check for new QTc prolongation. If present, treatment should be stopped.
- Subsequent follow-up at 6 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 whilst maintaining efficacy because the vicious cycle has been broken.

Chronic obstructive pulmonary disease

Recommendations

- Long-term macrolide 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. (Conditional)
- Long-term macrolide therapy could be considered for a minimum of 6 months and up to 12 months to assess the impact on exacerbation rate. (Conditional)

GPPs (also see quick reference guide in online supplementary file 1

- Non-pharmacological and pharmacological therapies should be optimised prior to considering long-term macrolide therapy. This includes smoking cessation, optimised inhaler technique, optimised self-management care plan, airway clearance techniques and attendance at pulmonary rehabilitation courses.
- Macrolides should only be started following discussion and shared decision-making between the patient and a respiratory specialist.
- For safety purposes, an ECG should be performed prior to initiation of macrolide therapy to assess QTc interval. If QTc is >450 ms for men and >470 ms for women then this is considered a contraindication to initiating macrolide therapy. Baseline LFTs should also be measured.
- Patients should be counselled about potential adverse effects before starting therapy, including gastrointestinal upset, hearing and balance disturbance, cardiac effects and microbiological resistance.
- Microbiological assessment of sputum should be performed before therapy, including investigation for NTM. Macrolide monotherapy should be avoided if an NTM is identified. Repeat assessments are recommended with clinical decline or during exacerbations to monitor resistance patterns.
- Accurate assessment of baseline exacerbation rate should be determined before starting long-term macrolides for patients with COPD and a CT scan should be considered to exclude a possible diagnosis of bronchiectasis.
- A risk:benefit profile should be considered in each individual if significant side effects from oral macrolide therapy develop. If gastrointestinal side effects occur at the higher dose of azithromycin (500 mg three times a week), a dose reduction to azithromycin 250 mg three times a week could be considered if macrolide therapy has been of clinical benefit.
- Liver function tests should be checked one month after starting treatment and then every 6 months. An ECG should be performed one month after starting treatment to check for new QTc prolongation. If present, treatment should be stopped.
- Subsequent follow-up at 6 and 12 months should determine whether benefit is being derived from therapy using objective measures, such as the exacerbation rate, CAT score or quality of life as measured by a validated assessment tool, such as SGRQ. If there is no benefit, treatment should be stopped.
- It is not necessary to stop prophylactic azithromycin during an acute exacerbation of COPD unless another antibiotic with potential to affect the QT interval has also been prescribed.

Bronchiolitis obliterans (including post-transplantation)

Recommendations

- Low-dose, long-term azithromycin (250 mg three times a week) could be considered to prevent the occurrence of BOS post-lung transplantation. (Conditional)
- Low-dose azithromycin (250 mg alternate days for a trial period of 3 months) could be considered to treat BOS occurring in lung transplant recipients. (Conditional)

THE USE OF MACROLIDES IN OTHER RESPIRATORY CONDITIONS

Cough

Recommendations

- Long-term macrolide antibiotics should not be used to manage patients with unexplained chronic cough. (Conditional)

Organising pneumonia

There is insufficient evidence to make a recommendation.

SAFETY ISSUES

Gastro-intestinal effects

Good practice points

- Prior to initiating low-dose macrolide therapy, patients should be warned of the possibility of gastrointestinal side effects.
- Gastrointestinal side effects may be ameliorated by dose reduction, although this may also reduce clinical efficacy.
- Clinicians should carefully consider the risk-to-benefit balance when considering therapy for those with pre-existing gastrointestinal symptomatology.

Cardiac effects

Good practice points

- Prior to initiating low-dose macrolide therapy, patients should be asked if they have a history of heart disease, previous low serum potassium measurements, a slow pulse rate, a family history of sudden death or known prolonged QT interval. Patients with such a history should not receive low-dose macrolide therapy without careful consideration and counselling of the increased risk of adverse cardiac effects.

- Prior to initiating low-dose macrolide therapy, a drug history looking for agents that might prolong the QTc interval should be sought (see appendices 3 and 4). Patients taking such agents should not receive low-dose macrolide therapy.
- Prior to initiating low-dose macrolide therapy, an ECG should be performed to exclude a prolonged QTc interval defined as >450 ms for men and >470 ms for women (see section √Methodology in appendices). Patients with a prolonged QTc interval should not receive low-dose macrolides.
- One month after initiating low-dose macrolide therapy, a second ECG should be performed to exclude the development of a prolonged QTc interval. Patients who develop a prolonged QTc interval on low-dose macrolides should stop the macrolide.
- If any new drug that could potentially prolong QTc time is started or if dose increases are made, repeat ECG assessment.

Ototoxicity

Good practice point

- Prior to initiating low-dose macrolide therapy, patients should be asked if they have a history of hearing or balance difficulties. Such patients should be made aware of the potential for a further, almost always reversible, deterioration in hearing or balance with macrolide therapy. Patients with pre-existing hearing or balance difficulties who wish to proceed with treatment should be asked to report any change in hearing or balance promptly.

Other side effects

Good practice points

- Prior to initiating low-dose macrolide therapy, baseline LFTs should be checked.
- LFTs should be checked after one month of treatment and then every six months thereafter for the duration of therapy.

ANTIMICROBIAL RESISTANCE

Good practice points

- The risks associated with increasing antimicrobial resistance should be discussed with patients prior to starting low-dose macrolide therapy. Patients should understand the risk that there may not be an effective antibiotic for them, or someone else, when needed in the future.
- Prior to initiating low-dose macrolide monotherapy, patients should be asked if they have a history of previous or current NTM infection or disease. Current NTM infection should be managed with reference to BTS guidance and precludes low-dose macrolide monotherapy. Successfully treated NTM disease should not preclude low-dose macrolide monotherapy.
- If there is any clinical suspicion of possible NTM disease, patients should be screened via examination of sputum samples prior to starting therapy. If positive for recognised potential pathogenic species, low-dose macrolide prophylaxis is contraindicated.

DISCLAIMER

Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply recommendations for the management of patients. The recommendations presented here are a guide and may not be appropriate for use in all situations. The guidance provided does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

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Contributors DS and IDR chaired the Guideline Group, and as lead authors led the drafting and revision of the document. All the authors drafted sections of the full guideline and undertook revisions of the paper. DS and IDR had final responsibility for the guideline and the summary paper submitted to BMJORR.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests CA, TC, IDR, PM, DS and RS had no funding to declare. SH declared funding from Chiesi. NR declared funding from Rocket Medical, UK, Lung Therapeutics and BD.

Patient consent for publication Not required.

Provenance and peer review Commissioned; internally peer reviewed.

Data availability statement There are no data in this work.

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