Use of Azithromycin in Children with Non-Cystic Fibrosis Bronchiectasis or Chronic Suppurative Lung Disease

Purpose

This Guideline provides recommendations for the use of azithromycin as prophylaxis in paediatric patients with non-CF bronchiectasis or chronic suppurative lung disease.

Scope

This Guideline provides information for Children’s Health Queensland (CHQ) staff caring for paediatric patients with non-CF bronchiectasis or chronic suppurative lung disease.

Related documents

Procedures, Guidelines, Protocols

- CHQ Procedure_01035 Antimicrobial Restriction Procedure
- CHQ Antimicrobial Restriction list
- CHQ Paediatric Respiratory Antiobiocard - Empirical antimicrobial therapy for patients with Cystic Fibrosis and Non-CF Bronchiectasis
Background

Early and effective management reduces short and long-term morbidity in people with bronchiectasis.[1,2] In children, airway injury is superimposed upon the physiological changes involving lung growth and development.[3]

Appropriate use of antibiotics is one of the key treatment principles. Use of maintenance antibiotics should be restricted to selected children with bronchiectasis and when doing so, the child should be closely monitored with consideration to cease these antibiotics after a period of 6-24 months.

Azithromycin is a macrolide antibiotic with anti-inflammatory and immuno-modulatory properties. Evidence in Indigenous children indicate that 12 to 24 months of continuous azithromycin decreased the frequency of exacerbations in children with non-cystic fibrosis (non-CF) bronchiectasis or chronic suppurative lung disease (CSLD) by 50% (95% CI 35%, 71%, p<0.0001).[4] Data have also shown that use of the prolonged courses of macrolides (6-12 months) improves lung function and health-related quality of life in adults with non-cystic fibrosis bronchiectasis (summarised in [5]), Furthermore, despite the development of macrolide resistance in the resident nasopharyngeal microbiota, the use of antibiotics for non-pulmonary infections was significantly lower in the children who received azithromycin compared to those on placebo (incidence rate ratio 0.50; 95% CI 0.31–0.81; p=0.005).[4]

There are however, significant concerns around macrolide use and antibiotic resistance, with a consistent association with long-acting macrolide use and increased population-level macrolide resistance rates for several types of respiratory bacteria, including S pneumoniae (both invasive and clinical isolates) and S pyogenes, in many different countries. Although twice daily macrolides (e.g., clarithromycin) have also been implicated in increases in macrolide resistance rates, azithromycin has been most strongly associated in most investigations, with erythromycin least.[5]

More worryingly macrolides also have a strong selection pressure for other multidrug resistant (MDR) pathogens, including increased risk of penicillin resistance[6] or community acquired MRSA[7]. The direct clinical consequences of macrolide resistance are difficult to quantify, and few data are available, however the global rise of all classes of antibiotic resistance is of great concern, thus judicious use of azithromycin is necessary.

Based on current evidence, a trial of azithromycin therapy for 6-24 months to reduce respiratory exacerbations in carefully selected children with non-CF bronchiectasis can be justified under the circumstances presented below [8,9].
Guideline for Azithromycin prophylaxis in children with non cystic fibrosis (non-CF) bronchiectasis or chronic suppurative lung disease (CSLD)

Prior to initiation of azithromycin as maintenance therapy, the following are required:

- Presence of bronchiectasis or CSLD
- Child has had ≥3 exacerbations and/or ≥2 hospitalisations in previous 12 months
- Child has been reviewed by a respiratory consultant
- Child has failed a trial of long term non-macrolide antibiotics (such as trimethoprim/ sulfamethoxazole) for a period of at least three months
- Previous documented absence of non-tuberculous mycobacteria in the lower airways. If child can produce sputum, culture the sputum for acid fast bacilli.
- Child is regularly followed up with other standard therapies for non-CF bronchiectasis optimised
- Consider doing liver function test and ECG if other risk factors are present.

Exclusion criteria

- Patients with microbiological evidence of non-tuberculous mycobacterial infection
- Allergy to macrolides
- Abnormal liver function tests
- Clinically significant drug interaction with existing therapy (eg QT prolongation in patients receiving anti-arrhythmics, neurotoxicity in patients receiving Vinca-alkaloids (CyP3A4 interaction).

At follow-up (minimum at 6 months post initiation)

- Review effect of azithromycin on frequency of exacerbations and other clinical aspects
- Consider repeating liver function test
- Repeat sputum (if sputum can be obtained)

Azithromycin prophylaxis dosing schedule

- Patient less than 25kg weight: 30mg/kg per week (may be given in divided doses on a daily basis, three times weekly or as a single weekly dose)
- Patient 25-40kg weight: 250mg/dose three times weekly
- Patient >40kg weight: 500mg/dose three times weekly
Assessing benefit

- Patients requiring azithromycin for more than 6 months will require 6 monthly review and assessment of ongoing benefit and safety monitoring.
- Formal review by a Paediatric Respiratory Consultant at 12 months to assess benefit:
  - Reduction in frequency and/or severity of exacerbations, wet cough or sputum
  - Improvement in respiratory function
  - Improvement in general well-being (eg weight gain, school loss, behaviour)
  - Patient or family demonstrated capacity for regular review while on long term therapy
  - Surveillance of macrolide resistance patterns on microbiology results (if sputum can be obtained)

Ceasing azithromycin after 6 to 24 months (or earlier)

- Not tolerating the medication
- No clinical benefit demonstrated after a 6 month trial of the antibiotic
- Anticipated spontaneous clinical improvement based upon prior history (e.g. over summer)
- Discontinue azithromycin for a trial 3 to 6 month period after 24 months of continuous use, since there is limited long-term safety and efficacy data and the condition frequently shows improvement over time.
- If after a trial of cessation (3 to 6 months off azithromycin), the child fulfils the criteria of deterioration (≥3 exacerbations and/or ≥2 hospitalisations in previous 12 months, pro-rata), azithromycin may be recommenced for up to 6 months, with formal review by a Paediatric Respiratory Consultant to assess benefit at 6 months.

Consultation

Key stakeholders who reviewed this version:

- Paediatric Respiratory Consultant Team
- Paediatric Infectious Diseases Consultant team
- Antimicrobial Stewardship Pharmacist
### Definition of terms

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<thead>
<tr>
<th>Term</th>
<th>Definition</th>
<th>Source</th>
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<tbody>
<tr>
<td>Chronic suppurative lung disease (CSLD)</td>
<td>A clinical syndrome of respiratory symptoms and/or signs. Symptoms of chronic endobronchial suppuration are a continuous, wet or productive cough for more than 8 weeks, with or without other features, such as exertional dyspnoea, symptoms of reactive airway disease, recurrent chest infections, growth failure, clubbing, hyperinflation or chest wall deformity.</td>
<td>Thoracic Society of Australia and New Zealand and Australian Lung Foundation Position Statement. Med J Aust 2010; 193: 356-365</td>
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### References and suggested reading

## Guideline revision and approval history

<table>
<thead>
<tr>
<th>Version No.</th>
<th>Modified by</th>
<th>Amendments authorised by</th>
<th>Approved by</th>
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<tbody>
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<td>1.0</td>
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<td>Medicines Advisory Committee (MAC)</td>
<td>Executive Director of Medical Services</td>
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<td>Executive Director Medical Services</td>
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### Keywords
- Azithromycin, macrolide, non-cystic fibrosis bronchiectasis, non-CF, chronic suppurative lung disease, CSLD, antimicrobial stewardship, antimicrobial resistance, 01061

### Accreditation references
- NSQHS Standards (1-10): Standard 3 – Preventing and Controlling Healthcare Associated Infections