Guideline

Non-Cystic Fibrosis Bronchiectasis - Antimicrobial Therapy for Children

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Applicable to	All Children's Health Queensland Staff				
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Purpose

This guideline provides Children's Health Queensland (CHQ) recommendations regarding best practice for empirical antimicrobial therapy for paediatric patients with non-cystic fibrosis (non-CF) bronchiectasis including inpatient and outpatient management.

Scope

This guideline provides information for CHQ staff involved in the care of paediatric respiratory patients with non-CF bronchiectasis.

Related documents

- CHQ Guideline: Paediatric Therapeutic Drug monitoring of Tobramycin and Gentamicin
- CHQ@Home Outpatient Parenteral Antimicrobial Therapy Prescribing, Administration and monitoring guideline
- CHQ-PROC-01036 Antimicrobial: Prescribing and Management
- CHQ Antimicrobial Restriction list
- CHQ-GDL-01221 Immunisation Guideline for Medically at Risk Children

Guideline

Empirical Antimicrobial Therapy for Children with Non-Cystic Fibrosis Bronchiectasis

Part 1. Summary table of empirical antimicrobial therapy for children with Non-CF bronchiectasis

- Acute Exacerbation (empirical)
- Recurrent Exacerbation (empirical)
- Acute Exacerbation with Methicillin Sensitive Staphylococcus Aureus (MSSA)
- Acute Exacerbation with Methicillin Resistant Staphylococcus Aureus (MRSA)
- Pseudomonas aeruginosa
  - First/new isolation without exacerbation
  - First/new isolation with exacerbation
  - Chronic Pseudomonas aeruginosa (PsA) with exacerbation

Part 2. Summary table of antibiotic doses recommended in patients with Non CF bronchiectasis

- Additional monitoring whilst on intravenous (IV) antibiotics
- Intravenous antibiotics
- Oral antibiotics
- Inhaled or nebulised antibiotics

Part 3. Hospital In The Home (HITH)

Part 4. Use of Azithromycin in Children with Non-Cystic Fibrosis Bronchiectasis or Chronic Suppurative Lung Disease

Part 1.

Table 1: Summary table of empirical antimicrobial therapy for infants over 1 month of age; children and adolescents with non-CF bronchiectasis

For neonates or patients with renal/liver disease, seek specialist advice. For patients with a history of immediate or delayed type penicillin and/or cephalosporin hypersensitivity, please consult the Infectious Diseases team (ID) for advice on treatment options prior to commencement of antibiotics.

Clinical Scenario	Setting	Antibiotic (Dosing recommendations – see Part 2)	Duration	Alternative antibiotic	Comments
Acute Exacerbation (empirical)	**Inpatient** **OR** **HITH***	**IV Ceftriaxone*** OR **IV Cefotaxime**	**10 to 14 days**	IV Amoxicillin-clavulanate	IV Amoxicillin-clavulanate is not suitable for HITH
	Outpatient	**Oral Amoxicillin-clavulanate**	**2 to 4 weeks**	(1) Oral Cefuroxime if non severe penicillin hypersensitivity. (2) Oral Azithromycin if non severe or severe penicillin hypersensitivity	If improving, adjustment of antibiotic therapy based on the results of sputum culture is **not** required. If not improving, check microbiology for directed antibiotic therapy.
Recurrent Exacerbation (empirical)	**Outpatient**	**Oral Azithromycin (as anti-inflammatory)** [10 mg/kg three times a week, on Mondays, Wednesdays and Fridays; maximum 500 mg/dose]			Exclude non-tuberculous mycobacteria infection. See Part 4 below
Acute Exacerbation with Methicillin Resistant Staphylococcus Aureus (MRSA)	**Inpatient or Outpatient**	**Tailor to susceptibility**			**Discuss with Paediatric Infection Specialist**

Table 1: Summary table of empirical antimicrobial therapy for infants over 1 month of age; children and adolescents with non-CF bronchiectasis (continued)

Clinical Scenario	Setting	Antibiotic (Dosing recommendations – see Part 2)	Duration	Alternative antibiotic	Comments
First/new isolation of *Pseudomonas aeruginosa (PsA)* without exacerbation	**Outpatient**	**(1) Oral Ciprofloxacin** OR **Inhaled tobramycin (preservative free)** OR **both** ***Followed by*** **(2) Inhaled tobramycin (preservative free)**	**14 days** **4 to 12 weeks**		Treat Pseudomonas isolated on **lower airway specimen** only (lavage or sputum). 2nd attempt at clearance: Use or repeat dual therapy.
First/new isolation of *Pseudomonas aeruginosa (PsA)* with exacerbation	**Inpatient** **OR** **HITH***	**IV Piperacillin/Tazobactam*** OR **IV Ceftazidime*** ***With or without either*** **IV Tobramycin** OR **Inhaled tobramycin (preservative free)** ***Followed by*** **Inhaled Tobramycin (preservative free)**	**14 days** **14 days** **4 to 12 weeks**	If *PsA* resistant to Tobramycin and failure of first line eradication regimen, can consider 12 weeks nebulised colistin. ID approval required.	Dual anti-pseudomonal antibiotic therapy is controversial. Consider the harms and benefits of combination therapy and check for contraindications and precautions before prescribing aminoglycosides.
	Outpatient	**(1) Oral Ciprofloxacin** OR **Inhaled tobramycin (preservative free)** OR **both** ***Followed by*** **(2) Inhaled tobramycin (preservative free)**	**14 days** **4 to 12 weeks**	.	2nd attempt at clearance: use or repeat dual therapy.

Table 1: Summary table of empirical antimicrobial therapy for infants over 1 month of age; children and adolescents with non-CF bronchiectasis (continued)

Clinical Scenario	Setting	Antibiotic (Dosing recommendations – see Part 2)	Duration	Alternative antibiotic	Comments
Chronic *Pseudomonas aeruginosa (PsA)* with exacerbation	**Outpatient**	**Inhaled tobramycin (preservative free)** ***With or without* Oral Ciprofloxacin**	**2 to 4 weeks**		Treat Pseudomonas isolated on lower airway specimen only (lavage or sputum). Where lower airway specimens unable to be obtained (eg Cerebral palsy / neuromuscular disorders) pseudomonas often reflects upper airway colonisation and first line exacerbation therapy should be: Oral Amoxycillin/clavulanic acid OR IV Ceftriaxone as per **Acute Exacerbation (empirical) above** .
	Inpatient	**IV Piperacillin/Tazobactam* OR IV Ceftazidime*** ***With or without either*** **IV Tobramycin** **OR Inhaled tobramycin (preservative free)**	**14 days**	Use IV tobramycin instead of inhaled tobramycin if already used previously and no or limited response to inhaled therapy	

Part 2. Table 3: Summary table antibiotic doses recommended for paediatric patients with non CF bronchiectasis with normal renal function (including oral, IV and inhaled antibiotics)

Some IV medications require therapeutic drug monitoring (TDM). See table for recommendations. Consider impact of patient/disease factors that may impact on TDM results, for example:

- Liver disease (risk of hepato-renal syndrome).
- Concomitant nephrotoxic medications (e.g. Tacrolimus, NSAIDs).
- Hydration status (consider oral fluid intake, fasting status, input/output including diarrhoea/vomiting).
- Age (impact of hormonal changes on body composition and organ function during adolescence).

Antimicrobial	Recommended starting doses for infants, children and adolescents with non CF bronchiectasis (For neonates or patients with renal/liver disease, seek specialist advice)	ID approval required for patients with non CF bronchiectasis
Amoxicillin-clavulanate	**Oral:** 25 mg/kg/dose twice daily (maximum 875 mg/dose amoxicillin component)	No
	Intravenous: 25 mg/kg/dose IV 6-hourly (maximum 1 g/dose amoxicillin component)	Yes
Azithromycin	**Oral: (treatment):** 10 mg/kg once daily (Maximum 500 mg/day) for 5 days Note: Azithromycin has a very long half-life (54.5 hours in children)	Yes
	Oral: (anti-inflammatory for chronic lung disease) Patient less than 25 kg weight : 30 mg/kg per week (may be given in divided doses on a daily basis, three times weekly or as a single weekly dose) Patient 25 to 40 kg weight: 250 mg/dose three times weekly Patient >40kg weight: 500 mg/dose three times weekly	No. See Part 4 for eligibility criteria.
Cefotaxime	**Intravenous:** 50 mg/kg/dose 6-hourly (maximum 2 g/dose)	No (up to 14 days)
Ceftazidime	**Intravenous:** 50 mg/kg/dose 8-hourly (maximum 2 g/dose)	No (inpatient – if used according to guideline criteria) Yes (HITH)
Ceftriaxone	**Intravenous:** 100mg/kg once daily (maximum 4 g/day)	No (up to 14 days)
Cefuroxime	**Oral:** 15 mg/kg (maximum 500 mg) twice daily	No
Ciprofloxacin	**Oral:** 10 mg/kg/dose twice daily (12 hourly) (maximum 750 mg /dose) Oral ciprofloxacin has poor palatability, consider rounding doses to the nearest 125 mg (if appropriate based on weight) to reduce need to manipulate the dose form. For children unable to swallow tablets whole, discuss options to improve adherence with the Pharmacist. Monitor compliance closely.	No (if used according to guideline criteria)
Colistin	**Nebulised:** 1 to 2 years of age: 1 million units inhaled 12 hourly 2 to 18 years of age: 1 to 2 million units inhaled 12 hourly (for eradication: 2 million units inhaled 12 hourly) The dose administered of Colistin depends mostly on the concentration of the drug used and the tidal volume of the patient however the nebuliser characteristics are also very important and maintenance of the nebuliser is also critical (29). Seek Respiratory consultant advice on nebulised dosing.	Yes

Table 3: Summary table antibiotic doses recommended for paediatric patients with non CF bronchiectasis with normal renal function (including oral, IV and inhaled antibiotics) (continued)

Antimicrobial	Recommended starting doses for infants, children and adolescents with non CF bronchiectasis (For neonates or patients with renal/liver disease, seek specialist advice)	ID approval required for patients with non CF bronchiectasis
Flucloxacillin	**Intravenous:** 50 mg/kg/dose 6-hourly (maximum 2 g/dose)	No
	Oral: 25 mg/kg/dose four times a day (6-hourly) (maximum 1 g/dose)	No
Piperacillin/ Tazobactam	**Intravenous: More than 1 month of age:** 100 mg/kg/dose 6-hourly (maximum 4 g/dose piperacillin component)	No (inpatient – if used according to guideline criteria) Yes (HITH)
Tobramycin	**Intravenous: Dose based on ideal body weight.** **More than 1 month old to 10 years of age:** 7.5 mg/kg once daily (maximum 320 mg/day for initial dose) **Over 10 years of age:** 6 mg/kg once daily (maximum 560 mg/day for initial dose) **Perform TDM:** Tobramycin 2 and 6 hour post dose levels should be taken after dose 1 of therapy (for AUC calculation) and at least once a week during IV antibiotic course. Repeat Tobramycin 2 and 6 hour post dose levels should be taken after each dose adjustment. **Tobramycin TDM targets:** **Pseudomonas eradication (Non CF):** Aim for Cmax 25 to 35 mg/L and AUC 70 to 90, with Cmin (C24 predicted) less than 0.5 mg/L **Chronic Pseudomonas colonisation (Non CF):** Aim for Cmax 25 to 35 mg/L and AUC 70 to 90, with Cmin (C24 predicted) less than 0.5 mg/L. For more information, please refer to the CHQ Paediatric Tobramycin / Gentamicin Therapeutic Drug Monitoring	No (inpatient – if used according to guideline criteria) Yes (HITH)
	Inhaled: **Option 1:** All ages – Tobramycin 300mg inhaled twice daily • Use Tobramycin 300mg/5mL preservative free ampoules for inhalation • Patients treated at Queensland Children's hospital (QCH): No ID approval or Individual patient approval (IPA) required if managed according to criteria detailed in this guideline. Outside this criteria, ID approval required. • Patients receiving treatment at another Queensland Health hospital: Individual patient approval (IPA) required to facilitate supplies (non LAM indication for this formulation). ID approval as per local practices. **Option 2:** All ages - Tobramycin 160 mg inhaled twice daily • Use Tobramycin 80mg/2mL preservative free ampoules • Meets LAM criteria – No IPA required.	No (QCH – if used according to guideline criteria) Other sites: ID approval as per local practices
Trimethoprim/ Sulfametho-xazole	**Oral:** 4 mg/kg/dose 12-hourly (maximum 160 mg/dose Trimethoprim component). For MRSA eradication, please consult ID team for advice on dose.	No

Part 3: Hospital In The Home (HITH)

- Contact the CHQatHome pharmacist/ AMS pharmacist for advice on drug stability and suitable administration device/method. For more information, please refer to Table 1 - Suitability of parenteral antimicrobials for HITH use in paediatrics on the HITH section of the CHQ Antimicrobial Stewardship Website.
- For more information on paediatric dosing, administration and monitoring of HITH antimicrobial therapy, refer to: CHQ@Home Outpatient Parenteral Antimicrobial Therapy Prescribing, Administration and monitoring guideline (available via CHQ AMS Website).
- **The following pre-approved HITH antimicrobial options are available for patients with non-CF bronchiectasis:**
  - IV ceftriaxone (one daily) for up to 14 day course. ID approval is required for more than 14 days of treatment.
- **The following HITH antimicrobial options for patients with non-CF bronchiectasis require ID approval:**
  - For Pseudomonas eradication:
    - IV Piperacillin/Tazobactam (as continuous infusion via ambulatory device) +/- IV Tobramycin (once daily – infused over 30 minutes) for up to 14 day course.

      OR
  - IV Ceftazidime (as 8-hourly dosing – each dose administered over 30 minutes via Intermate® ambulatory device) +/- IV Tobramycin (once daily infused over 30 minutes) for up to 14 day course.
    - Ceftazidime doses administered by parent/carer after successful completion of CHQ competency training package "Guide to giving your child's IV antibiotic at home – for children with PICC lines") for up to 14 day course.
- All other home parenteral antimicrobial therapy requires ID approval prior to making (HITH) referral. Written confirmation of ID approval needs to accompany CHQ@Home (HITH) referral form and/or electronic medical record (ieMR).

Part 4: Use of Azithromycin in Children with Non-Cystic Fibrosis Bronchiectasis or Chronic Suppurative Lung Disease

Background

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 to 24 months.

Azithromycin is a macrolide antibiotic with anti-inflammatory and immuno-modulatory properties. Based on current evidence, a trial of azithromycin therapy for 6 to 24 months to reduce respiratory exacerbations in carefully selected children with non-CF bronchiectasis can be justified under the circumstances presented below [9,10].

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 amoxicillin/clavulanate or 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 25 kg weight: 30 mg/kg per week (may be given in divided doses on a daily basis, three times weekly or as a single weekly dose)
- Patient 25 to 40 kg weight: 250 mg/dose three times weekly
- Patient >40kg weight: 500 mg/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 (2 months or more 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 with formal review by a Paediatric Respiratory Consultant to assess benefit at 6 months and every 6 months for a further 12 months.
- Every 12 months, a 2 month or longer trial of azithromycin cessation should be tried to assess continued clinical requirement. Azithromycin may be continued in this way with Paediatric Respiratory Consultant review.

ALERT

Azithromycin increases the risk of diarrhea and abdominal pain

Azithromycin increases population-level macrolide resistance rates for several types of respiratory bacteria, including S pneumoniae (both invasive and clinical isolates) and S pyogenes also has a strong selection pressure for other multidrug resistant (MDR) pathogens, including increased risk of penicillin resistance [11, 12] or community acquired MRSA [13].

Consultation

Key stakeholders who reviewed this version:

- Paediatric Respiratory Consultant and Fellow Team (CHQ)
- Paediatric Infectious Diseases Consultant and Fellow team (IMPS, CHQ)
- Clinical Pharmacist Lead - Antimicrobial Stewardship (CHQ)
- CHQ Medical Advisory Committee endorsed 26/07/2021

List of abbreviations

Abbreviation	Definition
AMS	Antimicrobial Stewardship
CHQ	Children's Health Queensland
CKN	Clinician's Knowledge Network
HITH	Hospital in the Home
IMPS	Infection Prevention and Management Service
ID	Infectious Diseases Team
IV	Intravenous
LAM	Queensland Health List of Approved Medicines
MRSA	Methicillin Resistant Staphylococcus Aureus
MSSA	Methicillin Sensitive Staphylococcus Aureus
Non CF	Non cystic fibrosis
PBS	Pharmaceutical Benefit Scheme
PO	Per oral
PsA	Pseudomonas aeruginosa
QCH	Queensland Children's Hospital
SAS	Special Access Scheme
TDM	Therapeutic Drug Monitoring
WHO	World Health Organization

References and suggested reading

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Guideline revision and approval history

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1.0 20/12/2018 (supersedes CHQ-GDL-01059)	Paediatric Respiratory Consultant Team (CHQ) Paediatric Infectious Diseases Consultant team (CHQ) Antimicrobial Stewardship Pharmacist (CHQ)	Divisional Director Medicine	Executive Director Clinical Services (QCH)
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2.1 30/06/2020	Director - Respiratory and Sleep Medicine (CHQ) Director – Infection Management and Prevention service (CHQ) Pharmacist Advanced - Antimicrobial Stewardship (CHQ)	Divisional Director Medicine	Executive Director Clinical Services (QCH)
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Accreditation references	National Safety and Quality Health Service Standards (1-8): • Standard 3: Preventing and Controlling Healthcare-Associated Infection • Standard 4: Medication Safety		