Guideline

Empirical antimicrobial therapy for children with Cystic Fibrosis

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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 for empirical antimicrobial therapy for children with Cystic Fibrosis (CF), for inpatient and outpatient management.

Scope

This guideline provides information for CHQ staff caring for paediatric CF patients.

Related documents

Procedures, Guidelines, Protocols

- CHQ Paediatric Therapeutic Drug Monitoring – Tobramycin/Gentamicin
- CHQ Paediatric Therapeutic Drug Monitoring - Vancomycin
- CHQ@Home Outpatient Parenteral Antimicrobial Therapy Prescribing, Administration and monitoring guideline
- CHQ-PROC-01035 Antimicrobial Restrictions – Antimicrobial Stewardship (AMS)
- CHQ-PROC-63223 Management of patients with cystic fibrosis
- CHQ-GDL-01061 Immunisation Guideline for Medically at Risk Children

Other

- CHQ Antimicrobial Restriction list

Guideline

Empirical antimicrobial therapy for patients with Cystic Fibrosis

Part 1. Summary table of empirical antimicrobial therapy for children with Cystic Fibrosis (CF)

- Pulmonary Exacerbation - Pseudomonas aeruginosa (PsA) negative
- Pulmonary Exacerbation - PsA eradication
- Chronic PsA colonisation – exacerbation
- Chronic PsA colonisation – maintenance therapy
- Methicillin Resistant Staphylococcus Aureus (MRSA) eradication – outpatient treatment
- MRSA Pulmonary optimisation – inpatient treatment
- Burkholderia cepacia complex eradication – inpatient treatment
- Non-tuberculous mycobacterium (NTM) – induction and maintenance treatment (Quick reference guide)

Part 2. Hospital In The Home (HITH)

Part 3. Non-tuberculous mycobacterium (NTM) eradication – induction and maintenance treatment

Part 4. Fungal infections

- Allergic bronchopulmonary aspergillosis (ABPA)

Part 5. Summary table of antibiotic doses recommended in Cystic Fibrosis (CF)

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

Part 1. Summary table of empirical antimicrobial therapy for children with Cystic Fibrosis

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		Antibiotic	Duration	Alternative antibiotic	Comments
Cystic Fibrosis **Exacerbation** ***Pseudomonas aeruginosa* (PsA) negative**	**Inpatient** **or** **HITH**	**Piperacillin/Tazobactam IV** 100 mg/kg/dose 6-hourly (maximum 4 g Piperacillin component/dose) **PLUS** **Tobramycin IV*** More than 1 month old to 12 years: 10 mg/kg once daily (maximum 640 mg initial dose) More than 12 years: 7.5 mg/kg once daily (maximum 640 mg initial dose) *(or previously optimised dose from a recent admission (within last three months), speak to a Pharmacist for advice)*	**14 days**	Ceftazidime (plus IV Tobramycin) is an alternative if **no** *S.aureus* isolated **Ceftazidime IV** 100 mg/kg/dose 8-hourly (maximum 4 g/dose) **If ceftazidime used and *S.aureus* present, add in Flucloxacillin:** **Flucloxacillin IV** 50 mg/kg/dose 6-hourly (maximum 2 g/dose) **or** **Oral Flucloxacillin** 25 mg/kg/dose four times daily (maximum 1 g/dose)	**Monitoring:** Baseline and then weekly Full blood count (FBC) & Electrolytes and liver function tests (eLFTS or CHEM20), vestibular toxicity monitoring whilst on IV Tobramycin ***See Part 5 for IV Tobramycin therapeutic drug monitoring (TDM)** **Pre-approved HITH:** **IV Tobramycin (once daily) and IV Piperacillin/ Tazobactam (continuous infusion via ambulatory device) or Ceftazidime (via intermate device) for 14 days.**
Cystic Fibrosis **Exacerbation** ***Pseudomonas aeruginosa* (PsA) negative**	**Outpatient**	**Amoxycillin-clavulanic acid** (DUO preparation) 25 mg/kg/dose orally 12-hourly (maximum 875 mg Amoxycillin component/dose)	**14 days** **to** **6 weeks**	**Trimethoprim/Sulfamethoxazole Oral** 8 mg/kg/dose twice daily (maximum 320 mg/dose Trimethoprim component)	**Monitoring:** FBC and CHEM20 once a month whilst on high dose Trimethoprim/Sulfamethoxazole

Clinical Scenario		Antibiotic	Duration	Alternative antibiotic	Comments
Cystic Fibrosis – Pseudomonas aeruginosa (PsA) **Eradication**	**Inpatient** **or** **HITH**	**Piperacillin/Tazobactam IV** 100 mg/kg/dose 6-hourly (maximum 4 g Piperacillin component/dose) **PLUS** **Tobramycin IV*** More than 1 month old to 12 years: 10 mg/kg once daily (maximum 640 mg initial dose) More than 12 years: 7.5 mg/kg once daily (maximum 640 mg initial dose) *(or previously optimised dose from a recent admission (within last 3 months), speak to a Pharmacist for advice)* **Followed by Tobramycin inhaled**: 0 to 18 years: 300 mg nebulised 12 hourly	**14 days** **4 weeks**	**Ceftazidime (plus IV Tobramycin)** an alternative if **no** *S.aureus* isolated **Ceftazidime IV** 100 mg/kg/dose 8-hourly (max 4 g/dose) **If Ceftazidime used and *S.aureus* present, add in Flucloxacillin:** **Flucloxacillin IV** 50 mg/kg/dose 6-hourly (max 2 g/dose) **or** **Oral Flucloxacillin** 25 mg/kg/dose four times daily (max 1 g/dose)	**Monitoring:** Baseline and then weekly FBC & CHEM20, vestibular toxicity monitoring whilst on IV Tobramycin ***See** Part 5 **for IV Tobramycin TDM** **Pre-approved HITH:** **IV Tobramycin (once daily) and IV Piperacillin/ Tazobactam (continuous infusion via ambulatory device) or Ceftazidime (via intermate device) for 14 days.**
Cystic Fibrosis – Pseudomonas aeruginosa (PsA) **Eradication**	**Outpatient**	**Tobramycin inhaled** (use preservative free formulation) 0 to 18 years: 300 mg 12-hourly **If treatment failure or Tobramycin resistant:** **Oral Ciprofloxacin** 20 mg/kg/dose orally 12-hourly (maximum 1 g/dose) **PLUS** **Inhaled Colistin (Tadim®)** 1 to 2 years: 1 million units inhaled 12-hourly 2 to 18 years: 2 million units inhaled 12-hourly	**4 weeks** **4 weeks** **12 weeks**		Eradication should be attempted for all children on first/new isolation of *Pseudomonas aeruginosa* Consider the impact of type of nebuliser when choosing Colistin dose see Part 5 (*29*) Prescription for Sodium Chloride 0.9% ampoules also required when prescribing Inhaled Colistin (required for reconstitution).

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Clinical Scenario		Antibiotic	Duration	Alternative antibiotic	Comments
Cystic Fibrosis Exacerbation **Chronic *Pseudomonas aeruginosa* colonisation**	**Inpatient** **or** **HITH**	**Piperacillin/tazobactam IV** 100 mg/kg/dose 6-hourly (maximum 4 g Piperacillin component/dose) **PLUS Tobramycin IV*** More than 1 month old to 12 years: 10 mg/kg once daily (maximum 640 mg initial dose) More than 12 years: 7.5 mg/kg once daily (maximum 640 mg initial dose) *(or previously optimised dose from a recent admission (within last 3 months), speak to a Pharmacist for advice)*	**14 days**	**Ceftazidime (plus IV Tobramycin)** an alternative if **no** *S.aureus* isolated. **Ceftazidime IV** 100 mg/kg/dose 8-hourly (maximum 4 g/dose) **If Ceftazidime used and *S.aureus* present, add in Flucloxacillin:** **Flucloxacillin IV** 50 mg/kg/dose 6-hourly (maximum 2 g/dose) **OR Oral Flucloxacillin** 25 mg/kg/dose four times daily (maximum 1 g/dose)	**Monitoring:** Baseline and then weekly FBC & CHEM20, vestibular toxicity monitoring whilst on IV Tobramycin. ***See Part 5 for IV tobramycin TDM** **Pre-approved HITH: IV Tobramycin (once daily) and IV Piperacillin/ Tazobactam (continuous infusion via ambulatory device) or Ceftazidime (via intermate device) for 14 days.**
Cystic Fibrosis Exacerbation – Chronic *Pseudomonas aeruginosa* colonisation	**Outpatient**	**Tobramycin inhaled** (use preservative free formulation): 0 to 18 years: 300 mg nebulised 12-hourly **or** More than 6 years old: **TOBI®** podhaler 112 mg (4 caps) 12-hourly	**4 weeks**	**If on cyclical inhaled Tobramycin may consider adding oral Ciprofloxacin** 20 mg/kg/dose twice daily (maximum 1 g/dose) for two weeks.	
Cystic Fibrosis – Chronic Pseudomonas aeruginosa Maintenance therapy	**Outpatient**	**Alternate month Tobramycin inhaled** (use preservative free formulation)**:** 0 to 18 years: 300 mg nebulised 12-hourly **Or** More than 6 years: **TOBI®** podhaler 112 mg (4 caps) 12-hourly	**Long term**	If resistant organism or intolerant of **TOBI®** consider **alternate month inhaled Colistin** plus **Oral Ciprofloxacin** (2 to 4 weeks). If deterioration consistently in the month off inhaled antibiotics or frequent exacerbations (three or more/ year) consider continuous alternating inhaled therapy (CAIT) using **inhaled Tobramycin** alternating with **inhaled Colistin** plus **oral Ciprofloxacin** for two of the four weeks.	Consider the impact of type of nebuliser when choosing Colistin dose see Part 5 (*29*) Prescription for Sodium Chloride 0.9% ampoules also required when prescribing Inhaled Colistin (required for reconstitution)

Clinical Scenario		Antibiotic	Duration	Alternative antibiotic	Comments
Methicillin Resistant Staphylococcus Aureus (MRSA) **Eradication**	**Outpatient**	**Oral Rifampicin** 15 mg/kg/dose once daily (maximum 600 mg/dose) (see note) **PLUS, *either*** **Oral Trimethoprim/Sulfamethoxazole** 8 mg/kg/dose twice daily (max 320 mg/dose trimethoprim component) **or** **Oral Sodium Fusidate** 12 mg/kg/dose orally 8-hourly (max 500 mg/dose) (Sodium Fusidate 250 mg tablets are available in Australia) **Fusidic acid oral suspension** is not TGA registered and only available via the Special Access Scheme (SAS). The suspension is not bioequivalent to Sodium Fusidate tablets. **Fusidic Acid oral suspension**15 mg/kg/dose orally 8-hourly (maximum 750 mg/dose) Use in conjunction with CHQ-GDL-01063 Recurrent Boils (furunculosis): Guidelines for management and Staphylococcal decolonisation (MRSA and MSSA). This includes Triclosan 1% body washes and Nasal Mupirocin 2% (Bactroban®) for at least 5 days and enhanced household cleaning. *Repeat course if respiratory sample MRSA positive at end of 14 days or incomplete clinical improvement* **or** *Admit for IV therapy if MRSA positive at end of 14 days and clinical requirement for pulmonary optimisation*	**14 days**	**Check MRSA antibiotic susceptibilities prior to treatment and discuss with ID** Rifampicin can interact with numerous medications. Pharmacy review prior to commencement. **Do not use Rifampicin if on Ivacaftor or Lumacaftor.** **If unable to use Rifampicin substitute with oral Clindamycin** 10 mg/kg/dose three times daily (maximum 600 mg/dose) (maximum 40 mg/kg/day; maximum 1.8 g/day) Oral Clindamycin has poor palatability, consider rounding doses to the nearest 150mg if appropriate to reduce need to obtain part doses from capsules. For children unable to swallow capsules whole, monitor compliance closely. Sodium Fusidate/Fusidic acid: Food delays absorption. Give on an empty stomach if possible. Alternative method to reduce gastrointestinal side effects: give with or soon after food.	**Isolation of MRSA**: MRSA on BAL or induced/lower respiratory sample on one sample **or** MRSA on upper respiratory sample (e.g. cough swab) on two samples more than one week apart. **Consider MRSA Eradication therapy:** At first isolation of MRSA, or if previously cleared of MRSA, aim for eradication. **Upon completion of two weeks of oral antibiotics**: Repeat respiratory sample MRSA negative: repeat testing as clinically indicated (usually three monthly) **Monitoring:** Baseline and then 2 to 4 weekly FBC & CHEM20

Clinical Scenario		Antibiotic	Duration	Alternative antibiotic	Comments
MRSA Pulmonary Optimisation	**Inpatient**	**Admission for IV antibiotics that target MRSA only** **Lincomycin IV** 15 mg/kg/dose 6-hourly (maximum 1.2 g/dose) **PLUS** **Rifampicin PO** 15 mg/kg/dose once daily (maximum 600 mg once daily) (see note*) **PLUS** **Inhaled Tobramycin** (use preservative free formulation) 0 to 18 years: 300 mg nebulised 12 hourly **Followed by:** 2 weeks of dual oral eradication therapy	**14 days** **14 days**	**Check MRSA antibiotic susceptibilities prior to treatment and discuss with ID** **Do not use if also targeting other pathogens. Discuss with ID.** <u>Note*:</u> Rifampicin can interact with numerous medications. Pharmacy review prior to commencement. **Do not use Rifampicin if on Ivacaftor or Lumacaftor. Seek ID advice for alternatives.** **If Lincomycin resistant: Teicoplanin IV** 10 mg/kg/dose 12-hourly (maximum 800 mg/dose) for 3 doses (Loading dose), then 10 mg/kg IV once daily (maximum 800 mg/day).	**Eradication of MRSA achieved when:** More than 3 months has elapsed since the last positive sample No exposure to antibiotics or antiseptic body washes for the two weeks prior to screening Two negative samples from the site that have previously been MRSA positive, taken one week apart **Monitoring:** Baseline and then 2 to 4 weekly FBC & CHEM20

Clinical Scenario		Antibiotic	Duration	Alternative antibiotic	Comments
Burkholderia cepacia complex **Eradication**	**Inpatient**	**With ID advice and approval only** **Trimethoprim/Sulfamethoxazole IV** 5 mg/kg/dose 8-hourly (max 160 mg/dose Trimethoprim component) **PLUS** **Meropenem IV** 40 mg/kg/dose 8-hourly (maximum 2 g/dose) **or** **Ceftazidime IV** 100 mg/kg/dose 8-hourly (maximum 4 g/dose) **PLUS** **Tobramycin IV*** More than 1 month of age to 12 years of age: 10 mg/kg IV once daily (max 640 mg/day as initial dose) More than 12 years of age: 7.5 mg/kg IV once daily (max 640 mg/day as initial dose)	**14 to 21 days**	**May still use Trimethoprim / Sulfamethoxazole even if *B. cepacia* shows in-vitro resistance** **Check antibiotic susceptibilities prior to commencement and discuss with ID**	*B. multivorans* and *B. cenocepacia* (Bcc) most common. Success rate of eradication therapy is reportedly less than 50% Follow on oral and/or inhaled antibiotic therapy post eradication should be discussed with ID prior to discharge **Monitoring:** Baseline and then weekly FBC & CHEM20, vestibular toxicity monitoring whilst on IV Tobramycin. ***See Part 5 for IV Tobramycin TDM** # T**rimethoprim/ Sulfamethoxazole IV** 5 mg/kg/dose 8-hourly (maximum 160 mg/dose Trimethoprim component) for 48 hours. If renal function remains stable and urine pH > 5.5, consider optimizing to dose to 5 mg/kg/dose 6-hourly (maximum 160 mg/dose Trimethoprim component). Monitor renal function and hydration status closely. Risk for renal toxicity and crystalluria.

Clinical Scenario		Antibiotic	Duration	Alternative antibiotic	Comments
Mycobacterium abscessus (MABSC) **Eradication**	**Intensive** **Inpatient**	**With ID advice and approval only** **Oral Azithromycin** **Amikacin* IV** **Imipenem IV** or **Cefoxitin IV** if macrolide resistant (constitutive or inducible) **PLUS** **Tigecycline IV** (> 8 years old)	**3 to 4 weeks**	**With ID advice and approval only** **Adjust as per sensitivities** If macrolide resistant (constitutive or inducible) and <8 years old, consider Clofazimine in induction.	***See Table 1 (Part 3) for amikacin TDM** **Refer to Table 1 (Part 3) for dosing and monitoring**
	Consolidation **Outpatient**	**Amikacin Inhaled (use preservative free formulation)** **Oral Clofazimine** **Oral Azithromycin**	**12 to 18 months**	**With ID advice and approval only** Oral Moxifloxacin may also be considered	**Refer to Table 2 (Part 3) for dosing and monitoring**

Part 2. Hospital In The Home (HITH)

- Contact the CHQ@Home 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 Cystic Fibrosis:
  - IV Tobramycin (once daily) and IV Piperacillin/Tazobactam (as continuous infusion via ambulatory device) for up to 14 day course. ID approval is required for more than 14 days of treatment.
  - IV Tobramycin (once daily) and IV Ceftazidime (as 8-hourly dosing – each dose administered over 30 minutes via Intermate® ambulatory device. 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. ID approval is required for more than 14 days of treatment.
  - 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 3. Mycobacterium abscessus (MABSC) eradication

Non-tuberculous mycobacteria (NTM) are universal environmental organisms that can cause chronic pulmonary infection, particularly in individuals with pre-existing inflammatory lung disease such as CF. Pulmonary disease caused by NTM, particularly MABSC, has emerged as a major threat to the health of individuals with CF but remains difficult to diagnose and problematic to treat (27). The clinical significance of *M.avium* (MAC) or other NTM isolates in children with CF are even less certain than MABSC and rarely require antibiotic treatment.

ALERT

Macrolide monotherapy should be stopped on first identification of NTM in child with CF.

Diagnosis requires a combination of clinical and microbiological criteria (Algorithm 1).

Clinical criteria for diagnosis of NTM (28):

1. Pulmonary symptoms, nodular or cavitary opacities on chest radiograph, or a high-resolution computed tomography scan that shows multifocal bronchiectasis with multiple small nodules.

   and

2. Appropriate exclusion of other diagnoses.

Microbiologic criteria:

1. Positive culture results from at least two separate sputum samples.
   or
2. Positive culture result from at least one bronchial wash or lavage.
   or
3. Transbronchial or other lung biopsy with mycobacterial histopathologic features (granulomatous inflammation or acid fast bacilli (AFB)) and positive culture for NTM.

Making the diagnosis of NTM lung disease does not, per se, necessitate the initiation of therapy. Decision to initiate and timing of treatment is based on potential risks and benefits of treatment for the individual patient in discussion with respiratory and ID consultants.

MABSC eradication – intensive and consolidation treatment

There are no drug regimens of proven or predictable efficacy for treating MABSC. Guidelines are based on expert opinion and in practice treatments vary considerably. Suggested regimens include an *intensive phase* of 3 to 12 weeks of IV antibiotics (usually Amikacin, Cefoxitin or Imipenem/Cilastatin ± Tigecycline) plus an oral macrolide, with duration based on clinical and microbiological response. This is followed by a *consolidation* phase, that includes oral drugs (usually a macrolide, plus others based on antibiograms, tolerability and experience) and an inhaled IV formulation of Amikacin, for 3 to more than 12 months.

MABSC treatment

Antibiotic plan is dependent on MABSC sensitivities. Sensitivity results must be available prior to elective admission for IV antibiotics for MABSC treatment. Individual treatment plans will be provided by ID.

Suggested intensive phase (inpatient): 3 - 4 weeks

- Oral Azithromycin, Amikacin* IV, Imipenem/Cilastatin IV **or** Cefoxitin IV
- +/- Tigecycline IV** (More than 8 years old) **or** oral Clofazimine (Less than 8 years old)
  - May be added if macrolide resistant (constitutive or inducible) or if clinically otherwise indicated.
- **Tigecycline: May be considered in patients younger than 8 years where benefits outweigh risks after ID and respiratory consultant discussion, and parent consultation.
- Refer to Table 1 for dosing recommendations.

Consolidation phase (outpatient): 12 to 18 months

- Oral Azithromycin, oral Clofazimine, Amikacin inhaled (use preservative free formulation).
- Oral Moxifloxacin **or** oral Linezolid may be additionally considered.
- Refer to Table 2 for dosing recommendations.

MAC treatment: 6 to 12 months

Individual treatment plans will be provided by ID.

Usually all oral regime, however if severe disease and high mycobacterial load **Amikacin IV** may be added for up to 4 weeks initially.

- **Oral Azithromycin** 10 mg/kg once daily (maximum 500 mg/day).
- **Oral Rifampicin** 10 to 20 mg/kg once daily (maximum 450 mg if less than 40kg, maximum 600 mg if more than 40 kg).
  - Rifampicin can interact with numerous medications. Pharmacy review prior to commencement. Do not use Rifampicin if on Ivacaftor or Lumacaftor. Seek ID advice for alternatives.
- **Oral Ethambutol** 15mg/kg once daily (maximum 1.2 g/day, dose based on lean body weight).
- **Oral Clofazimine may be considered** 1 to 5 mg/kg orally once daily (maximum 100 mg/day)

Pre-treatment screening:

- Baseline audiology and ECG (to check for QT prolongation).
- Baseline ophthalmology and 3 monthly when on Ethambutol.
- Baseline CHEM20 and FBC.
- Baseline lactate. Repeat weekly when on Linezolid (high risk of lactic acidosis).
- Please review all the patient's medications and supplements for potential medication interactions with the Clinical Pharmacist before commencement of eradication therapy.

Algorithm 1. Investigation of NTM pulmonary disease in patients with CF

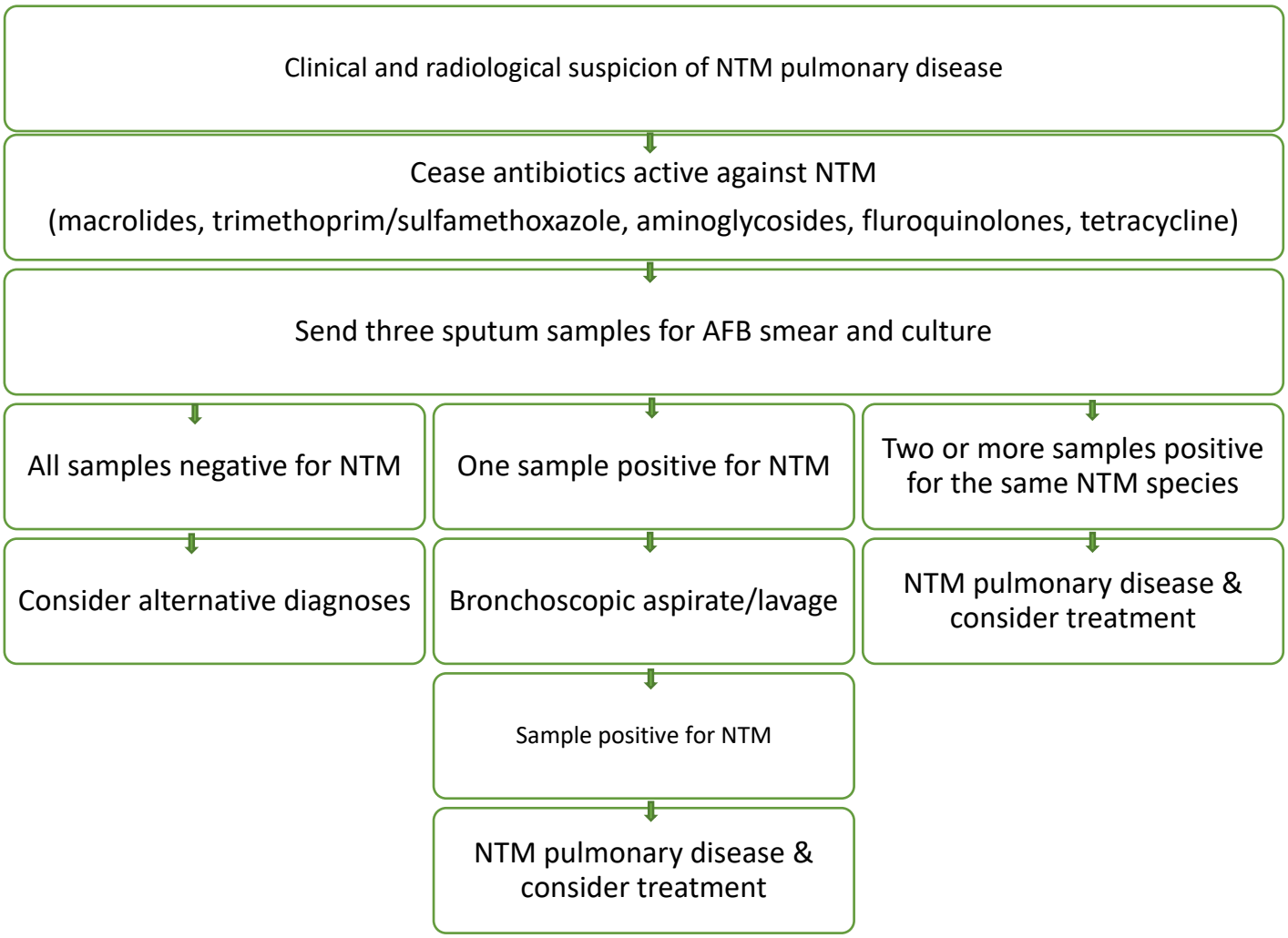

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Table 1. NTM Intensive phase (3-4 weeks – inpatient treatment)

Use a three or four drug combination based on sensitivities and Infectious diseases team advice.

Drug	Recommended starting doses for infants, children and adolescents with CF	Monitoring
Amikacin IV	**1 month to 12 years:** 30 mg/kg IV once daily (maximum 1.25 g/day as starting dose) **Over 12 years of age:** 15 mg/kg IV once daily (maximum 1.25 g/day as starting dose) Please note: Dose based on ideal body weight.	Baseline audiology and CHEM20 Repeat audiology and CHEM20 weekly Amikacin 2 and 6 hour post dose levels on day 1, then at least once a week (if dose/levels/condition stable) or after each dose change. TDM target: Aim for Amikacin Cmax 80 to 100mg/L and C24 less than 1 mg/L. No Amikacin AUC target.
Tigecycline IV **(> 8 years of age)**	**Day 1: (50% of optimal dose)** 0.6 mg/kg IV 12-hourly **Day 2: (75% of optimal dose)** 0.6 mg/kg IV in the morning (max 50mg/dose) and 1.2 mg/kg IV at night (max 50mg/dose) **Day 3: (100% of optimal dose)** 1.2 mg/kg IV 12-hourly (maximum 50 mg/dose, maximum 100 mg/day). If tolerated, continue this dose.	Please chart Ondansetron to be given 15 to 30 minutes before each tigecycline dose. High incidence of nausea/vomiting – Tigecycline dose titration trialled in other patients with good effect. Second and third line anti-emetics may be required in some patients.
Imipenem / Cilastatin IV	**Day 1 to 2 (75% of optimal dose)** 25 mg/kg/dose IV 8-hourly (maximum 1g Imipenem component per dose) **Day 3 (100% of optimal dose)** 25 mg/kg/dose IV 6-hourly (maximum 1 g imipenem component per dose) (maximum 4 g imipenem component per 24 hours)	Infuse each dose over 1 to 3 hours to reduce incidence of nausea/vomiting. Note: CF PKPD differences necessitate using higher mg/kg doses. Suggest giving regular anti-emetics 15 to 30 minutes before each Imipenem/Cilastatin dose. Additional anti-emetics may be required. Assess on an individual patient basis. Monitor CHEM20 and FBC weekly.
Cefoxitin IV	40 mg/kg/dose IV 6-hourly (maximum 2 g/dose)	Infuse each dose over 3 hours to optimize Time > MIC.
Oral Clarithromycin	7.5 mg/kg/dose orally twice daily (maximum 500 mg/dose)	Check inducible resistance test results before commencing treatment. Risk of QT prolongation. Strong CYP3A4 inhibitor - treatment modifications may be required Please review all the patient's medications and supplements for potential **medication interactions** with the Clinical Pharmacist before commencement of eradication therapy. Monitor CHEM20.
Oral Azithromycin	10 mg/kg (max 500 mg/day) orally once daily	Risk of QT prolongation Monitor CHEM20

Table 2. NTM maintenance phase (12 months – outpatient treatment)

Use nebulised Amikacin plus two oral medications based on sensitivities and Infectious diseases team advice.

Drug	Recommended starting doses for infants, children and adolescents with CF	Monitoring
Inhaled Amikacin (use preservative free formulation)	More than 6 years: Inhale 500 mg twice daily **Use after physiotherapy**	Monitor for bronchospasm. Consider using Salbutamol MDI pre-inhaled antibiotics as bronchodilator. Prescription for Sodium Chloride 0.9% ampoules also required when prescribing inhaled Amikacin (required for dilution).
Oral Clofazimine	1 mg/kg to 5 mg/kg orally once daily (maximum 100 mg/day) Please note: Children: Limited data, WHO recommendations for MDR-TB and XDR-TB are based on experience and expert opinion, and suggest 3 to 5 mg/kg/day (max 100 mg/day) (28)	Risk of QT prolongation Monitor CHEM20 Only available as 50mg and 100mg capsules Only available through TGA Special Access Scheme Program – additional approvals required
Oral Moxifloxacin	10 mg/kg orally once daily (maximum 400 mg/day)	Risk of QT prolongation Monitor CHEM20
Oral Clarithromycin	7.5 mg/kg/dose orally twice daily (maximum 500 mg/dose)	Check inducible resistance test results before commencing treatment Risk of QT prolongation Strong CYP3A4 inhibitor - Treatment modifications may be required. Please review all the patient's medications and supplements for potential medication interactions with the Clinical Pharmacist before commencement of eradication therapy. Monitor CHEM20
Oral Azithromycin	10 mg/kg orally once daily (maximum 500 mg/day)	Risk of QT prolongation Monitor CHEM20

Part 4. Fungal infections

Treatment of allergic bronchopulmonary aspergillosis (ABPA) in patients with cystic fibrosis

- **Itraconazole** dosing (Sporanox® brand):
  - **Less than 12 years of age:** Itraconazole oral 5 mg/kg/dose (max 200 mg/dose initially) twice daily (10 mg/kg/day) as starting dose.
  - **More than 12 years of age:** Itraconazole oral 2.5 mg/kg/dose (max 200 mg/dose initially) twice daily (5 mg/kg/day) as starting dose.
  - ID approval required for itraconazole for ABPA treatment exceeding six (6) months.
  - Prescribers to specify brand name and generic name on prescription to avoid confusion.
    - Sporanox® 100mg capsules and 10 mg/mL liquid are available on the List of approved medicines (LAM) and Pharmaceutical Benefit Scheme (PBS).
    - Lozanoc® (itraconazole 50mg) capsules are not interchangeable with Sporanox® (itraconazole 100mg) capsules or liquid.
    - The manufacturer of Lozanoc® reports that this product has higher bioavailability than other itraconazole capsules (e.g. Sporanox®). One capsule of Lozanoc 50 mg is therapeutically equivalent to one 100 mg capsule of conventional itraconazole capsules. The recommended dose for Lozanoc® is therefore half the recommended dose for conventional itraconazole capsules. However, this has not been studied extensively in the paediatric population.

Optimising azole absorption and levels

- Due to significant difference in bioavailability, itraconazole capsules and liquid can't be used interchangeably.
- **For Sporanox ® liquid preparation:**
  - Take on empty stomach with an acidic drink (coca cola, orange juice).
- **For Sporanox® capsule preparation:**
  - Take with food and an acidic drink (coca cola, orange juice).
- Acid suppressing medications will affect stomach pH and reduce itraconazole absorption, consider clinical need for this agent if there is difficulty in obtaining therapeutic levels
- Consider compliance and how dose is being taken in relation to food/acidic drink if there is difficulty in obtaining therapeutic levels.

Therapeutic drug monitoring

- Itraconazole trough (pre-dose) level, 7 to 10 days from commencement of therapy as well as and 5 to 7 days after each dose adjustment.
- Aim for trough level (taken 30 minutes before the morning dose) of 500 to 1000 microgram/L.

Drug interactions

- Itraconazole is a potent inhibitor of CYP450 3A4 isoenzyme.
- Treatment modifications may be required. Please review all the patient's medications and supplements for potential medication interactions with the Clinical Pharmacist before commencement of therapy.

Recommended adjustments

- **Ivacaftor (Kalydeco®)**

  Reduce the dose of Ivacaftor when initiating strong inhibitors of CYP3A4 (e.g. ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin and clarithromycin). Ivacaftor should be administered at a dose of:

  - Children less than 14kg: 50 mg twice a week only (space doses apart during week).
  - Children 14kg to 25kg: 75 mg twice a week only (space doses apart during week).
  - Children more than or equals to 25 kg: 150 mg twice a week only (space doses apart during week).
  - With close monitoring of Itraconazole, Voriconazole or Posaconazole levels.
  - Remember to re-review the Ivacaftor dose when the interacting drug is stopped.

  When co-administered with moderate inhibitors of CYP3A4 (e.g. fluconazole, erythromycin), Ivacaftor should be administered at a dose of:

  - Children less than 14kg: 50 mg once daily.
  - Children 14kg to 25kg: 75 mg once daily.
  - Children more than or equal to 25 kg: 150 mg once daily.
  - Remember to re-review the Ivacaftor dose when the interacting drug is stopped.

- **Ivacaftor/lumacaftor (Orkambi ®)**

  Consider alternative antifungal treatment options – seek Infection Specialist (ID) advice. Anecdotal experience suggests high risk of itraconazole treatment failure in patients taking concomitant Ivacaftor / Lumacaftor.

- **Cyclosporin, tacrolimus, sirolimus, warfarin, phenytoin**

  Monitor itraconazole levels and adjust accordingly.

- **Corticosteroids**

  Risk of growth failure in patients with CF on itraconazole reported (severe adrenal suppression observed). Monitor adrenal response carefully (31).

- Useful drug interaction resources for comprehensive drug interaction information:
  - Flockhart Cytochrome P450 Drug Interaction Table, Division of Clinical Pharmacology, Indianna University
  - Micromedex ® 2.0 Drug Interactions search. Truven Health Analytics ® (Available via CKN)
  - UpToDate Drug Interaction search.
  - For new disease modifying agents, such as Ivacaftor or Ivacaftor / Lumacaftor, refer to Product information for up to date drug interaction information and advice on dose adjustments.
- Alternative azole treatment options may include oral Voriconazole or oral Posaconazole.
  - Discuss treatment options with ID team prior to commencing or changing therapy.
  - Therapeutic drug monitoring required – discuss therapeutic target levels with ID team.
  - ID approval required for oral Voriconazole and oral Posaconazole.
  - Please review all the patient's medications and supplements for potential medication interactions with the Clinical Pharmacist before commencement of therapy.

Part 5. Summary table antibiotic doses recommended for paediatric CF patients 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 CF and normal renal function *(For neonates or patients with renal/liver disease, seek specialist advice)*	ID approval required for patients with CF
Amikacin (Refer to Part 3 for more information)	**Intravenous:** **1 month to 12 years:** 30 mg/kg IV once daily (maximum 1.25 g/day as starting dose) **More than 12 years of age:** 15 mg/kg IV once daily (maximum 1.25 g/day as starting dose). Dose based on ideal body weight. Perform TDM.	Yes
	Nebulised (use preservative free formulation): Less than 6 years: Seek specialist advice. Over 6 years of age: Inhale 500 mg twice daily **Use after physiotherapy** Prescription for Sodium Chloride 0.9% ampoules also required when prescribing inhaled Amikacin (required for dilution).	
Amoxycillin / 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:** 10 mg/kg orally three times a week (anti-inflammatory for chronic lung disease) (max 500 mg/dose)	No
	Oral: 10mg/kg orally once daily (maximum 500 mg/day) (NTM treatment)	Yes
Aztreonam	**Intravenous:** 50 mg/kg/dose 6-hourly (maximum 2 g/dose)	Yes
	Nebulised (Aztreonam lysine for inhalation): More than 7 years of age: 75 mg inhaled three times a day	Yes (and SAS approval: Category A and B)
Cefalexin	**Oral:** 30 mg/kg/dose three times daily (8 hourly) (maximum 1 g/dose)	No
Cefazolin	**Intravenous:** 50 mg/kg/dose 8-hourly (maximum 2 g/dose)	No

Antimicrobial	Recommended starting doses for infants, children and adolescents with CF and normal renal function *(For neonates or patients with renal/liver disease, seek specialist advice)*	ID approval required for patients with CF
Cefepime	**Intravenous:** 50 mg/kg/dose 6-hourly (maximum 2 g/dose)	Yes
Cefoxitin	**Intravenous:** 40 mg/kg/dose 6-hourly (maximum 2 g/dose)	Yes
Ceftazidime	**Intravenous:** 100 mg/kg/dose 8-hourly (maximum 4 g/dose)	No (up to 14 days)
Ciprofloxacin	**Intravenous:** 10 mg/kg/dose 8-hourly (maximum 400 mg/dose)	Yes
	Oral: 20 mg/kg/dose twice daily (12 hourly) (maximum 1 g/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
Clarithromycin	**Oral:** 7.5 mg/kg/dose twice daily (max 500 mg/dose) (NTM treatment)	Yes
Clindamycin	**Oral:** 10 mg/kg/dose three times daily (8 hourly) (maximum 600 mg/dose). Oral Clindamycin has poor palatability, consider rounding doses to the nearest 150 mg (if appropriate based on weight) to reduce need to obtain part doses from capsules. For children unable to swallow capsules whole, discuss options to improve adherence with the Pharmacist or consider alternative treatment options – discuss with ID team. Monitor compliance closely.	Yes
Clofazimine	**Oral:** 1 to 5 mg/kg orally once daily (maximum 100 mg/day) Note: Children: Limited data, WHO recommendations for MDR-TB and XDR-TB are based on experience and expert opinion, and suggest 3 to 5 mg/kg/day (maximum 100 mg/day) (28)	Yes (and SAS approval: Category A and B)
Colistin	**Intravenous:** More than 5 years of age: 2 mg/kg/dose 8-hourly (Maximum 150 mg/dose) (maximum 8 mg/kg/day for severe infections). Monitor for nephrotoxicity. Weekly CHEM20 and twice weekly urine dipsticks (monitor for proteinuria)	Yes
	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 CF consultant advice on nebulised dosing.	No (If PsA resistant to Tobramycin **or** failure of first line eradication regimen)
Doxycycline	**Oral:** More than 8 years of age: 2 mg/kg twice daily (maximum 100 mg/dose) Seek ID specialist advice for use in children less than 8 years of age.	Yes
Ethambutol	**Oral:** 15 mg/kg once daily (Maximum 1.2 g/day) Dose based on lean body weight.	Yes

Antimicrobial	Recommended starting doses for infants, children and adolescents with CF and normal renal function *(For neonates or patients with renal/liver disease, seek specialist advice)*	ID approval required for patients with CF
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)	
Imipenem / Cilastatin	**Intravenous:** 25 mg/kg/dose IV 6-hourly (maximum 1g imipenem component per dose) High incidence of nausea/vomiting – Imipenem / Cilastatin dose titration trialled in other patients with good effect. Pre-medicate with anti-emetics.	Yes
Itraconazole **(Refer to Part 4 for more information)**	**Oral (Sporanox®):** Less than 12 years of age: 5 mg/kg/dose (maximum 200 mg/dose initially) orally twice daily (10 mg/kg/day) as starting dose. More than or equal to 12 years of age: 2.5 mg/kg/dose (maximum 200 mg/dose initially) orally twice daily (5 mg/kg/day) as starting dose. Due to significant difference in bioavailability, Itraconazole capsules and liquid can't be used interchangeably. **For Sporanox ® liquid preparation:** Take on empty stomach with an acidic drink (coca cola, orange juice) **For Sporanox® capsule preparation:** Take with food and an acidic drink (coca cola, orange juice) **TDM:** Take trough (pre-dose) level 7 to 10 days from starting therapy. Aim for trough level (taken 30 minutes before the morning dose) of 500 to 1000 microgram/L	No (up to 6 months)
Lincomycin	**Intravenous:** 15 mg/kg/dose 6-hourly (max 1.2 g/dose)	Yes
Linezolid	**Intravenous/ Oral:** Less than 12 years of age: 10 mg/kg/dose 8-hourly (maximum 600 mg/dose) More than or equal 12 years of age: 10 mg/kg/dose 12-hourly (maximum 600 mg/dose)	Yes
Meropenem	**Intravenous:** 40 mg/kg/dose 8-hourly (maximum 2 g/dose) Monitor for thrush (oral and vaginal) in susceptible individuals	Yes
Minocycline	**Oral:** More than 8 years of age: 4 mg/kg/dose (maximum 200 mg) as loading dose, then 2 mg/kg twice daily (Maximum 100 mg/dose). Seek ID specialist advice for use in children less than 8 years of age.	Yes
Moxifloxacin	**Intravenous:** 10 mg/kg 24-hourly (maximum 400 mg/day)	Yes
	Oral: 10 mg/kg once daily (maximum 400 mg/day)	

Antimicrobial	Recommended starting doses for infants, children and adolescents with CF and normal renal function *(For neonates or patients with renal/liver disease, seek specialist advice)*	ID approval required for patients with CF
Piperacillin/ Tazobactam	**Intravenous: More than 1 month of age:** 100 mg/kg/dose 6-hourly (maximum 4 g/dose piperacillin component)	No (up to 14 days)
Rifampicin	**Oral:** 10 to 20 mg/kg/dose once daily (maximum 450 mg/day if less than 40kg; maximum 600 mg/day if more than 40kg)	Yes
Sodium fusidate	**Oral : Sodium fusidate (tablets):** 12 mg/kg/dose orally 8-hourly (maximum 500 mg/dose)	Yes
	Oral: Fusidic acid suspension: 15 mg/kg/dose orally 8-hourly (maximum 750 mg/dose) Fusidic acid oral suspension is not TGA registered and only available via the special access scheme (SAS). The suspension is <u>not</u> bioequivalent to sodium fusidate tablets.	Yes (and SAS approval: Category A and B)
Teicoplanin	**Intravenous:** 10 mg/kg/dose 12-hourly (maximum 800 mg/dose) for 3 doses (loading dose), then 10 mg/kg IV once daily (maximum 800 mg/day) for MRSA eradication. Therapeutic drug monitoring (TDM) can be utilised if concerns about response to treatment. Please discuss with Infectious diseases team as TDM target may be dependent on MIC results.	Yes
Tigecycline	**Intravenous:** High incidence of nausea/vomiting – Tigecycline dose titration trialled in other patients with good effect. Pre-medicate with anti-emetics. **Day 1: (50% of optimal dose):** 0.6 mg/kg IV 12-hourly (maximum 50 mg/dose) **Day 2: (75% of optimal dose)** 0.6 mg/kg IV in the morning (maximum 50 mg/dose) 1.2 mg/kg IV at night (maximum 50 mg/dose) **Day 3: (100% of optimal dose)** 1.2 mg/kg IV 12-hourly (maximum 50 mg/dose, maximum 100 mg/day). If tolerated, continue on this dose.	Yes
Tobramycin	**Intravenous:** Dose based on ideal body weight. **More than 1 month old to 12 years of age**: 10 mg/kg once daily (maximum 640 mg/day for initial dose) **Over 12 years of age**: 7.5 mg/kg once daily (maximum 640 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: Aim for Cmax 25 to 35mg/L and AUC 90 to 110, with Cmin (C24 predicted) less than 0.5mg/L • Chronic Pseudomonas colonisation: Aim for Cmax 25 to 35mg/L and AUC 80 to 100, with Cmin (C24 predicted) less than 0.5mg/L For more information, please refer to the CHQ Paediatric Tobramycin / Gentamicin Therapeutic Drug Monitoring	No (up to 14 days)

Antimicrobial	Recommended starting doses for infants, children and adolescents with CF and normal renal function *(For neonates or patients with renal/liver disease, seek specialist advice)*	ID approval required for patients with CF
Tobramycin inhaled	**Nebulised / inhaled (use Tobramycin preservative free preparation)**: **0 to 18 years of age:** 300 mg inhaled twice daily (12-hourly) **or** **More than 6 years of age**: TOBI® podhaler 112 mg (4 capsules) inhaled twice daily (12-hourly)	No
Trimethoprim / Sulfamethoxazole	**Intravenous:** 5 mg/kg/dose 8-hourly (maximum 160 mg/dose Trimethoprim component) for 48 hours If renal function remains stable and urine pH more than 5.5, consider optimizing to dose to 5 mg/kg/dose IV 6-hourly (maximum 160 mg/dose Trimethoprim component). Monitor renal function and hydration status closely. Risk for renal toxicity and crystalluria.	Yes
	Oral: MRSA eradication/severe infection: 8 mg/kg/dose 12-hourly (maximum 320 mg/dose Trimethoprim component)	No
Vancomycin	**Intravenous:** Severe infection/ MRSA: 15 mg/kg/dose 6-hourly (maximum 750 mg/dose as starting dose) Dose based on actual body weight. Perform TDM. Please refer to the CHQ Guideline: Vancomycin Therapeutic Drug Monitoring for more information.	Yes

Consultation

Key stakeholders who reviewed this version:

- Paediatric Respiratory Consultant and Fellow Team (CHQ)
- Paediatric Infectious Diseases Consultant and Fellow team (IMPS, CHQ)
- Pharmacist Advanced - Antimicrobial Stewardship (CHQ)
- Senior Clinical Pharmacist – Respiratory (CHQ)

List of abbreviations

Abbreviation	Definition
ABPA	Allergic bronchopulmonary aspergillosis
AFB	Acid fast bacilli
AMS	Antimicrobial Stewardship
AUC	Area Under the Curve
Bcc	Burkholderia cepacia complex
CF	Cystic fibrosis
CHEM20	A comprehensive metabolic panel is a group of blood tests, including electrolytes and liver function tests
CHQ	Children's Health Queensland
CKN	Clinicians Knowledge Network
Cmax	A pharmacokinetic measure used to determine drug dosing. Cmax is the maximum (or peak) serum concentration that a drug achieves in a specified compartment of the body after the drug has been administrated
Cmin	C24 predicted. A pharmacokinetic measure used to determine drug dosing. Cmin is the lowest concentration of a drug in the blood after a dose is given
ECG	Electrocardiogram
FBC	Full blood count
HITH	Hospital In The Home
IMPS	Infection Prevention and Management service
ID	Infectious diseases Team
IV	Intravenous
LAM	Queensland Health List of Approved of Medicines
MIC	Minimum Inhibitory Concentration is the lowest concentration of a chemical, usually a drug, which prevents visible growth of a micro-organism.
MRSA	Methicillin Resistant Staphylococcus Aureus
NSAIDs	Non-steroidal anti-inflammatory drugs
NTM	Non tuberculous mycobacteria
PBS	Pharmaceutical Benefit Scheme
PKPD	Pharmacokinetics and pharmacodynamics
PsA	Pseudomonas Aeruginosa
QCH	Queensland Children's Hospital
QT	QT prolongation is a measure of delayed ventricular repolarisation. Excessive QT prolongation can predispose the myocardium to the development of early after-depolarisations, which in turn can trigger re-entrant tachycardias such as Torsades de Pointes.
SAS	Special Access Scheme
TDM	Therapeutic drug monitoring
TOBI® podhaler	Inhaled Tobramycin 28mg capsule
WHO	World Health Organization

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Guideline revision and approval history

Version No.	Modified by	Amendments authorised by	Approved by
1.0 (replaces CHQ-GDL-01059)	Paediatric Respiratory Consultant and Fellow Team (CHQ) Paediatric Infectious Diseases Consultant and Fellow team (CHQ) Antimicrobial Stewardship Pharmacist (CHQ)	Divisional Director Medicine	Executive Director Clinical Services (QCH)

Keywords	cystic fibrosis, exacerbation, inpatient management, outpatient management, pseudomonas aeruginosa, allergic bronchopulmonary aspergillosis, antimicrobial stewardship, HITH, hospital in the home, tobramycin, TOBI, amoxycillin-clavulanic acid, trimethoprim-sulfamethoxazole, piperacillin-tazobactam, ceftazidime, ciprofloxacin, colistin, ABPA, itraconazole, NTM, non tuberculous mycobacteria, Bcc, burkholderia cepacia, MRSA, methicillin resistant staphylococcus aureus, lincomycin, clindamycin, rifampicin, sodium fusidate, fusidic acid, amikacin, clofazimine, moxifloxacin, azithromycin, clarithromycin, cefoxitin, ethambutol, imipenem/cilastatin, meropenem, minocycline, doxycycline, flucloxacillin, cephalexin, vancomycin, aztreonam, cefepime, moxifloxacin, teicoplanin, 01073
Accreditation references	**National Safety and Quality Health Service Standards** – • Standard 3: Preventing and Controlling Healthcare-Associated Infection • Standard 4: Medication Safety