Antibiotics in the Treatment of Cystic Fibrosis Lung Disease

Sites where Clinical Guideline applies
HNE facilities which care for Cystic Fibrosis patients

This Clinical Guideline applies to:

1. Adults Yes
2. Children up to 16 years Yes
3. Neonates – less than 29 days No
   Approval gained from the Children Young People and Families Network on 5 October 2015

Target audience
All clinical staff who provide care to Cystic Fibrosis patients

Description
An acute pulmonary exacerbation (APE) in Cystic Fibrosis (CF) is a critical event. Most adults with CF have chronic growth or presence of organisms such as Pseudomonas or Staphylococcus aureus in their airways.

Keywords
Cystic Fibrosis, CF, antibiotics, Pseudomonas, Burkholderia cepacia complex, chest infection

Document registration number
HNELHD CG 15_43

Replaces existing document?
No

Related Legislation, Australian Standard, NSW Ministry of Health Policy Directive or Guideline, National Safety and Quality Health Service Standard (NSQHSS) and/or other, HNE Health Document, Professional Guideline, Code of Practice or Ethics:

- PD2013_043 Medication Handling in NSW Public Health Facilities
- PD2013_043: PCP 5 Storage of Refrigerated Medications in Patient Care Areas
- PD2007_084: PCP 1 Management of Multi-resistant Organisms and Clostridium difficile
- HNELHD DPG 14_27 Adult Nebulised Antibiotic Prescribing Guideline
- PD2007_036LPCP 3 and PD2007_084-PCP 2 Allocation of Isolation Rooms and use of patient Cohorting for Designated Infectious Diseases
- GNAH_0159: Aminoglycoside dosing and monitoring
- GNAH_0461 Adult Vancomycin DPG

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**Antibiotics in the Treatment of Cystic Fibrosis Lung Disease HNELHD CG 15_43**


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**GLOSSARY**

<table>
<thead>
<tr>
<th>Acronym or Term</th>
<th>Definition</th>
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</thead>
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<tr>
<td>APE</td>
<td>Acute pulmonary exacerbation</td>
</tr>
<tr>
<td>AST</td>
<td>Antimicrobial susceptibility testing</td>
</tr>
<tr>
<td>CF</td>
<td>Cystic Fibrosis</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Neb</td>
<td>Nebulised</td>
</tr>
<tr>
<td>BD</td>
<td>Twice daily</td>
</tr>
<tr>
<td>TDS</td>
<td>Three times daily</td>
</tr>
<tr>
<td>PICC</td>
<td>Peripherally inserted central catheter</td>
</tr>
<tr>
<td>MRSA</td>
<td>Methicillin resistant Staphylococcus aureus</td>
</tr>
<tr>
<td>NTM</td>
<td>Non-tuberculous mycobacteria</td>
</tr>
<tr>
<td>ABPA</td>
<td>Allergic bronchopulmonary aspergillosis</td>
</tr>
<tr>
<td>MIC</td>
<td>Minimum inhibitory concentration</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under curve</td>
</tr>
</tbody>
</table>

**Risk Statement:**

These guidelines have been developed to provide guidance to staff, and to ensure Cystic Fibrosis patients who present with a respiratory infection are assessed and treated with appropriate antibiotics.

Any unplanned event resulting in, or with the potential for, injury, damage or other loss to patients/staff/visitors as a result of this procedure must be reported through the Incident Information Management System and managed in accordance with the Ministry of Health Policy Directive: Incident management PD2014_004. This would include unintended injury that results in disability, death or prolonged hospital stay.

**Risk Category:** Clinical care and patient safety
GUIDELINE SUMMARY

This document establishes best practice for HNE Health. While not requiring mandatory compliance, staff must have sound reasons for not implementing standards or practices set out within the guideline, or for measuring consistent variance in practice.

An acute pulmonary exacerbation (APE) in Cystic Fibrosis (CF) is a critical event. Most adults with CF have chronic growth or presence of organisms such as *Pseudomonas* or *Staphylococcus aureus* in their airways.

The general approach to APE treatment involves aggressive antibiotic treatment of resident respiratory bacterial pathogens and, in the event of poor response, consideration of other differential diagnoses, especially infection with other pathogens (viruses, atypical organisms) that are not detected without special microbiological testing.

**It is important to distinguish the different objectives of antibiotic treatment at different phases of illness as this influences the endpoints of therapy and duration of use:**

- **Eradication therapy** (used for patients that have been newly detected with *Pseudomonas aeruginosa* or MRSA) requires intensive treatment protocols that last up to 3 months with a culture-based endpoint.

- **Treatment of exacerbation** (patients chronically colonised) is designed to reduce the bacterial load and attendant inflammation; eradication is impossible due to the presence of biofilm. Duration is determined by clinical response; typically 10–14 days. There is no proven utility in prolonging therapy once clinical response has occurred and antibiotic treatment may not in fact be the primary factor in response, especially when exacerbations have been caused by viral infection or other causes.

Interval protocols for monthly rotating nebulised antibiotics are designed to reduce the bacterial load. Whether provision of antibiotic-free periods is beneficial is unknown.

**Clinical factors that should routinely be assessed during treatment** are:

1. Improvement in pulmonary function testing
2. Improvement in symptoms of cough, sputum production and dyspnoea
3. Improvement in inflammatory markers – total white cell and neutrophil count, C-reactive protein (CRP) and improvement in radiography (chest X-ray or CT)

**Objectives of treatment for APE** include:

1. Return of lung function back to baseline
2. Reduction of chest symptoms back to baseline for that patient
3. If relevant, eradication of certain newly-acquired respiratory pathogens

**All patients should receive annual influenza vaccination.**

**Introduction**

The main objective when treating people who have cystic fibrosis (CF) is to prevent, eradicate or control all types of respiratory infection, particularly endobronchial and pulmonary infection with *Staphylococcus aureus*, *Haemophilus influenzae*, *Pseudomonas aeruginosa* and *Burkholderia cepacia* complex.

The common respiratory viruses are important in initiating and exacerbating the chest infection and contribute to the associated damaging inflammatory processes.

In CF, chronic and progressive lower respiratory tract infection is early and inevitable, leading to death in early childhood unless antibiotic treatment is used. In adults, failure to treat infection leads to irreversible and progressive loss of lung function resulting in death or the need for lung transplantation (Courtney, Bradley et al. 2007, de Boer, Vandemheen et al. 2011).

Treatment of CF exacerbations must be accompanied by effective escalation of psychological, physiotherapeutical and nutritional support with strong involvement/participation by the patient’s carers and family.
Pathogens in CF

Pseudomonas aeruginosa

*Pseudomonas aeruginosa* remains the major pathogen of most patients with CF and a majority become chronically infected by their early teens. The non-mucoid form classically infects the airways prior to the subsequent emergence of the mucoid alginate-producing variants that are associated with biofilm production. Once the transition to the mucoid form has occurred, infection becomes chronic and is associated with intermittent exacerbations and progressive lung disease. The presence of the non-mucoid form is frequently asymptomatic, may be intermittent and requires regular screening and attempts at early eradication.

Regimens of inhaled tobramycin or colistimethate sodium (the form of colistin sulfate used for parenteral or inhalational use) together with oral ciprofloxacin have been shown to lead to an inability to detect *Pseudomonas* for up to 12 months in > 60% of children treated and some short-term improvements in lung function (Taccetti, Bianchini et al. 2012). It is not clear that success would be similar in adults with CF and is not known whether eradication leads to improved long-term clinical outcomes. In an adult who has not previously had *Pseudomonas* isolated and now has a new isolate, it is reasonable to discuss with them the implications of this and consider eradication therapy.

At this stage there is no clear evidence that one regimen is superior to another – in particular it is not clear that IV therapy is better than oral or inhaled therapy. Usually a combination of two agents with activity against *Pseudomonas* is used. The antibiotic susceptibility of the non-mucoid isolate(s) should be checked prior to design of the therapeutic regimen. Cultures are taken during and after treatment to document eradication. Continued surveillance for relapse should also take place.

For treatment of acute exacerbations of CF airways disease, antimicrobial choices should be based on the treatment guidelines below rather than the antimicrobial susceptibility results which may be unreliable and are not predictive of treatment response.

Burkholderia cepacia complex and B. cenocepacia

The *B. cepacia* complex includes 9 species; including *B. cenocepacia* (also termed *Burkholderia cepacia genomovar III*). *B cenocepacia* acquisition is associated with worsened clinical outcomes and a heightened risk of systemic sepsis and rapid deterioration. Mortality in the immediate post-lung transplantation phase is also considerably higher than for patients with other pathogens. At this stage carriage of *B. cenocepacia* is likely to preclude listing for lung transplantation.

Intrinsic and acquired antimicrobial resistance is even greater in *B. cepacia* complex than in *P. aeruginosa* (see table below), and it is frequent to see isolates with apparent resistance to all antibiotics. *Burkholderia cepacia* complex presents a major problem, associated with the spread of highly transmissible strains.

For this reason there are strict segregation policies for patients with *B. cepacia* complex from all other CF patients.

Stenotrophomonas maltophilia

*Stenotrophomonas maltophilia* is one of the most common emerging multi-drug resistant organisms found in the lungs of people with CF and has recently been shown to be an independent predictor of pulmonary exacerbation requiring hospitalisation and antibiotics. However, the role of antibiotic treatment of *Stenotrophomonas maltophilia* infection in people with CF is still unclear and clinicians need to rely upon their clinical judgement in deciding when to treat patients and what antibiotics should be used. (Amin and Waters 2014).

Antibiotics that have potential activity are limited and include:

- Sulfamethoxazole + trimethoprim
- Ticarcillin + clavulanic acid
- Ciprofloxacin
- Colistimethate (colistin sulfate)

NB. This species is intrinsically resistant to all other beta-lactams, aminoglycosides and piperacillin + tazobactam (see Table).

Achromobacter xylosoxidans

The role of this organism is not as well defined in CF but is being isolated intermittently and chronically in patients with CF. Cross-infection of patients has been reported and elevated serum antibodies have been associated with a faster decline in FEV1.
Antibiotics that have potential activity based on in vitro testing include:
- Piperacillin + tazobactam
- Minocycline
- Meropenem
- Chloramphenicol

Other non-fermentative Gram-negative species
Gram-negative species such as Chryseobacterium indologenes, Pandoraea and Ralstonia species may be isolated intermittently or chronically from sputum. The significance of these isolates needs to be assessed clinically and other possible causes of APE excluded. Treatment options are usually limited in any case. In the absence of symptomatic deterioration or lack of response to usual treatments, no special treatment is required.

Non-tuberculous mycobacteria (NTM)
Both M. abscessus and Mycobacterium avium complex (MAC) are opportunistic pathogens in CF that seriously affect morbidity and mortality. Since 2013 it has become clear that CF patient-to-patient transmission occurs with M. abscessus. M abscessus is most often associated with morbidity, accelerated loss of lung function and is likely to increase mortality. It has also been associated with serious complications post-transplantation, resulting in some centres no longer listing affected patients.

Evidence for NTM infection should be looked for at least annually and especially if there is unexplained deterioration or lack of expected improvement with appropriate IV antibiotics. To detect the organism, patients may need to withhold both azithromycin and inhaled aminoglycosides.

Patients colonised or infected with M. abscessus are an infection control risk. For this reason there are strict segregation policies for all CF patients.

Treatment of NTM is difficult, with highly resistant organisms that require prolonged treatment for at least 12 months. Even with this, successful eradication in CF is often not achieved. Treatment regimens currently are based on those recommended by the ATS 2007. If treatment is clinically indicated, then seek treatment advice from Infectious Diseases.

Allergic bronchopulmonary aspergillosis (ABPA)
ABPA should be suspected if there is a poor response to IV antibiotics, markedly increased or new-onset wheeze, deterioration in lung function despite treatment, pleuritic chest pain, or when there is an elevation in the serum total IgE and evidence of specific IgE or IgG to Aspergillus.

Viral pathogens
Viral respiratory tract infections are often associated with an APE in infants (Hiatt, Grace et al. 1999) as well as older children and adults (Wark, Tooze et al. 2012). If a viral respiratory tract infection is suspected then an R10 (extended viral PCR assay) viral throat or nose swab should be obtained for testing.

Antimicrobial susceptibility testing (AST)
The non-fermentative Gram-negative pathogens that colonise CF patients have many intrinsic resistances. There is no value in performing AST against intrinsically resistant agents or using the information to guide therapeutic agents (Sherrard, Tunney et al. 2014).

The role of AST of Pseudomonas species is controversial (Hurley, Ariff et al. 2012). Many different strains colonise the respiratory tract, phenotypic expression of antibacterial resistance by one strain may vary widely making reliable representative testing impossible and no clinical studies have demonstrated that availability of such AST results enables selection of clinically more effective antibiotic treatment(s).

Multiple antibiotic synergy (chequerboard) testing has not been shown to provide useful clinical information and is not recommended.

There are no reliable or standardised methods for testing susceptibility of Burkholderia cepacia complex. Different testing methods give highly variable results that are of unproven clinical relevance.

Our recommendation for AST in this setting is that it should be done in the following situations:
1. All newly-isolated organisms
2. Chronic isolates on an annual basis, at the time of annual review (specify ‘annual CF respiratory culture review’ on the request form). Isolates will be stored by the laboratory (Pathology North)
3. At the commencement of treatment for an APE in case of a less than ideal clinical response
Table 1: Intrinsic antibiotic resistance amongst non-fermentative Gram-negative bacteria

<table>
<thead>
<tr>
<th>Organism</th>
<th>Ampicillin</th>
<th>Amoxicillin</th>
<th>Ceftazidime</th>
<th>Piperacillin</th>
<th>Ceftriaxone</th>
<th>Ciprofloxacin</th>
<th>Tobramycin</th>
<th>Gentamicin</th>
<th>Polymyxin E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acinetobacter baumannii</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
</tr>
<tr>
<td>A. calcoaceticus</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
</tr>
<tr>
<td>A. baumannii</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
</tr>
<tr>
<td>A. lwoffii</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
</tr>
<tr>
<td>E. vulneris</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
</tr>
<tr>
<td>E. coli var.</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
</tr>
<tr>
<td>S. maltophilia</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
<td>Resistant</td>
</tr>
</tbody>
</table>

Principles of treatment of acute pulmonary exacerbations in CF

These guidelines have been based on the Cystic Fibrosis Foundation (CF) USA recommendations (Flume, Mogayzel et al. 2009).

An APE requires five main areas of attention in the management of patient with CF:

1. The use of suitable antibiotics to treat infection
2. If IV antibiotics are required, then the patient requires suitable venous access
3. A physical therapy plan to enhance airway clearance
4. A nutritional plan to support enhanced nutritional requirements during an APE
5. A social support plan to assist the patient and their carers during the APE

Treatment for APE can be delivered either in hospital or in the home. Home intravenous (IV) antibiotic therapy can be delivered through referral to the Hunter New England Out and About program. Paediatric patients require admission to hospital for commencement of antibiotic therapy prior to consideration of the use of the Out and About service. For home therapy to be successfully administered there need to be reliable utilities (electricity, telephone and plumbing) in the home and, as well, the patient must live within a practical distance to attend the Infusion Lounge and collect their medications.

Reliable venous access is required for patients needing IV antibiotics. This can be delivered through a permanently inserted venous access device (such as a PORT-A-CATH®) or a PICC line. A PICC line will need to be inserted at the commencement of therapy and this requires a written referral to the IV Access Team. Insertion of PICC lines in young paediatric patients is by the paediatric anaesthetists in theatre under a light anaesthetic, or if old enough to be done on the ward without requirement for anaesthetic, by the IV Access Team. This decision is made by the paediatric treating team in conjunction with child/family and anaesthetists or IV Access Team.

The US CFF guidelines recommend that APE be treated with two antipseudomonal antibiotics, each with a different mechanism of action, in an effort to enhance antibacterial activity and reduce resistance (Flume, Mogayzel et al. 2009). There was a trend to higher rates of resistance with monotherapy.

Beta-lactam antibiotics exhibit time-dependent, bactericidal activity against susceptible bacteria (Fig 1). These agents achieve maximal microbiological efficacy at concentrations at the infecting site that are low multiples of the minimum inhibitory concentration (MIC) for the relevant pathogen (i.e., 3–4 times MIC). Maximum efficacy occurs when the non-protein bound concentrations of antibiotic remain above the MIC for at least 50% of the dosing interval. For this reason and in view of the very high tissue levels of beta-lactam antibiotics that may be required to reach the airways in CF there has been a trend towards the use of continuous intravenous infusions or providing short 2–3 hour infusions with each intermittent dose.

Beta-lactams may be combined with other antipseudomonal antibiotics [i.e., aminoglycosides, fluoroquinolones or colistimethate sodium (colistin sulfate)] which exhibit different mechanisms of action and concentration-dependent bactericidal activity, quantified by examining the ratio of the area under the serum concentration curve to the MIC of the organism (AUC:MIC ratio) (Fig 1).
Fig 1: Pharmacodynamic parameters of efficacy for antipseudomonal antibiotics. Drug concentration versus time curve. T > MIC is the time that serum concentrations exceed the MIC (this parameter best predicts microbiologic efficacy for the beta-lactams). Whilst there are clinical data relating the Cmax:MIC ratio to aminoglycoside effectiveness, the — AUC:MIC ratio (area under the serum concentration versus time curve to the MIC) is now the accepted best predictor for aminoglycosides as well as fluoroquinolones and colistimethate sodium (colistin sulfate). In practice, the AUC and peak (Cmax) are usually linearly related to the dose.

Anti-pseudomonal aminoglycosides exhibit a wide range of antimicrobial activity against aerobic Gram-positive and Gram-negative bacteria, including *P. aeruginosa*.

Aminoglycosides may very rarely cause idiosyncratic ototoxicity after a single dose although this is debated. Prolonged exposure may also cause irreversible vestibular (or much more rarely, cochlear) toxicity as well as reversible nephrotoxicity. Toxicity is reduced by giving single daily doses, altering dosage in accord with renal function and serum drug concentrations and by minimising duration of treatment. Toxicity can also be reduced by using the nebulised route by preference.

The development of loss of balance, vertigo, tinnitus or hearing loss should be regularly enquired about and aminoglycosides ceased at least temporarily as soon as this occurs. The dynamic visual acuity test is a simple bedside test that clinicians can carry out to screen for aminoglycoside-induced ototoxicity. The patient views an eye chart (Snellen chart) and visual acuity is measured with the head still. Then one moves the patient’s head horizontally at 2 Hz for 30 degrees. If there is bilateral vestibular damage the patient will lose > 2 lines of visual acuity (Longridge and Mallinson 1987). Any persistence of symptoms should be investigated formally by referral for ENT assessment including an audiogram.

**Aminoglycoside computerised monitoring for directed therapy**

The Hunter Drug Information Service (HDIS) provides a computerised monitoring service to adjust doses of tobramycin and gentamicin using AUC and Cmax. The medication must be given at a carefully recorded time, best at 0600, and preferably as a push over 5 minutes. In the paediatric wards this is given diluted in 50–100 mL and infused over 15–30 minutes, with timings accurately recorded. Bloods are then collected for the concentration within 4–6 hours of the dose and electrolytes and creatinine are measured simultaneously. A standard request form must be completed with these results and include the patient’s height and weight. HDIS will then notify the submitting clinician of the next dose and when the next concentration is required. The HDIS request form and aminoglycoside policy is available on the intranet at: http://intranet.hne.health.nsw.gov.au/__data/assets/pdf_file/0008/119618/GNAH_0159_Aminoglycosides_guideline.pdf

For a further detailed account of the use of antibiotics in CF please see the following references (Zobell, Young et al. 2012, Stockmann, Sherwin et al. 2013, Young, Zobell et al. 2013, Young, Zobell et al. 2013, Zobell, Waters et al. 2013, Zobell, Young et al. 2013).

Antibiotic Treatment Guidelines

A. Eradication protocols
Eradication of *Pseudomonas aeruginosa* isolates should be performed in all newly detected *Pseudomonas* respiratory tract infections within 30 days of screening (expectorated sputum or throat swab;), defined as either the first lifetime documented culture positive for *Pseudomonas* or first positive culture after ≥ 1 year history of ≥ 2 negative cultures/year.

Table 2 Eradication therapy for newly acquired *Pseudomonas aeruginosa* (Langton Hewer and Smyth 2014)

<table>
<thead>
<tr>
<th>Regimen in preferred order of use</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Nebulised or inhaled tobramycin ± oral ciprofloxacin</td>
<td>28 days</td>
</tr>
<tr>
<td>2. Nebulised colistimethate + oral ciprofloxacin</td>
<td>28 days</td>
</tr>
<tr>
<td>3. IV ± oral antibiotic regime with 2 agents active against the colonising <em>Pseudomonas</em></td>
<td>Not defined</td>
</tr>
</tbody>
</table>

Successful eradication will be judged to have occurred if the patient has ≥ 2 negative and no positive cultures between 4 and 12 weeks following completion of the protocol.

If the initial eradication protocol fails, the clinician, in consultation with the patient/family, should discuss whether an alternative protocol should be considered for implementation.

Table 3 Eradication therapy for newly acquired MRSA

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>PO sulfamethoxazole 800 mg + trimethoprim 160 mg bd or doxycycline 100 mg bd [Paediatric dose: Sulfamethoxazole 20 mg + trimethoprim 4 mg/kg (max 800 mg/160 mg) every 12 hours] + PO rifampicin 300 mg bd [Paediatric dose: 10 to 20 mg/kg daily in 1 to 2 divided doses, max 600 mg daily] + chlorhexidine 2% or triclosan 1% body wash + intranasal mupirocin tds + home environmental measures</td>
<td>28 days</td>
</tr>
</tbody>
</table>

Clearance screens – 1, 3 and 6 months – should include nose, throat, sputum, perianal swabs. Six months after last positive, two sets are taken and separately tested.


NB. Household members are also decolonised during the process (not tested)


B. Interval suppressive therapy

Table 4 Suppression of chronic *Pseudomonas* infection (Flume, O’Sullivan et al. 2007)

<table>
<thead>
<tr>
<th>Regimen in preference of use</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Nebulised or inhaled tobramycin</td>
<td>28 days on and 28 days off</td>
</tr>
<tr>
<td>2. Inhaled colistimethate</td>
<td>28 days on and 28 days off</td>
</tr>
<tr>
<td>3. Nebulised aztreonam</td>
<td>28 days on and 28 days off</td>
</tr>
</tbody>
</table>
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C. Treatment of pulmonary exacerbations in cystic fibrosis (Flume, Mogayzel et al. 2009)

1) Decide on the most appropriate setting for treatment and the delivery of antibiotics
   a) Outpatient treatment with oral ± inhaled antibiotics
   b) Hospital in the home with IV antibiotics ± inhaled or oral antibiotics
   c) Inpatient treatment

2) Most exacerbations will resolve with treatment for 10 days, but a longer duration of treatment may be required. Treatment duration should depend upon clinical response in terms of improvement of symptoms, return of lung function to baseline and improvement in systemic markers of inflammation

3) Antibiotic choice should be based on the guideline sequence below and patient tolerance. If there is a lack of clinical response at the 10 day point, escalation to the next option should be considered. Other potential factors should also be considered such as NTM infection or ABPA

4) For most situations, at least two agents are required to reduce the emergence of resistance during treatment and subsequently.

i) *Pseudomonas aeruginosa* (independent of measured susceptibilities):

<table>
<thead>
<tr>
<th>Agent 1</th>
<th>Agent 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Oral ciprofloxacin</td>
<td>Nebulised tobramycin or colistimethate</td>
</tr>
<tr>
<td>2. IV piperacillin + tazobactam</td>
<td>Nebulised tobramycin</td>
</tr>
<tr>
<td>3. IV ceftazidime</td>
<td>Nebulised colistimethate or tobramycin</td>
</tr>
<tr>
<td>4. IV meropenem</td>
<td>IV tobramycin ± nebulised colistimethate</td>
</tr>
</tbody>
</table>

ii) *B. cepacia* complex (independent of measured susceptibilities):

<table>
<thead>
<tr>
<th>Agent 1</th>
<th>Agent 2</th>
<th>Agent 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. PO sulfamethoxazole 800 mg + trimethoprim 160 mg bd [Paediatric dose: Sulfamethoxazole 20 mg + trimethoprim 4 mg/kg (max 800 mg/160 mg) every 12 hours]</td>
<td>Nebulised tobramycin</td>
<td>PO doxycycline</td>
</tr>
<tr>
<td>2. IV ceftazidime</td>
<td>PO sulfamethoxazole 800 mg + trimethoprim 160 mg bd [Paediatric dose: Sulfamethoxazole 20 mg + trimethoprim 4 mg/kg (max 800 mg/160 mg) every 12 h]</td>
<td>PO doxycycline</td>
</tr>
<tr>
<td>3. IV ceftazidime</td>
<td>IV meropenem</td>
<td>Nebulised tobramycin</td>
</tr>
</tbody>
</table>

iii) MRSA (dependent on measured susceptibilities):

<table>
<thead>
<tr>
<th>Agent 1</th>
<th>Agent 2</th>
<th>Agent 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. PO doxycycline 100 mg bd [Paediatric dose refer to AMH children’s dosing companion]</td>
<td>PO sulfamethoxazole 800 mg + trimethoprim 160 mg bd [Paediatric dose: Sulfamethoxazole 20 mg + trimethoprim 4 mg/kg (max 800 mg/160 mg) every 12 hours]</td>
<td>PO doxycycline</td>
</tr>
<tr>
<td>2. PO rifampicin 300 mg bd [Paediatric dose: 10 to 20 mg/kg daily in 1 to 2 divided doses, max 600 mg daily] + PO sulfamethoxazole 800 mg + trimethoprim 160 mg bd [Paediatric dose: Sulfamethoxazole 20 mg + trimethoprim 4 mg/kg (max 800 mg/160 mg) every 12 hours] OR doxycycline</td>
<td>Nebulised vancomycin</td>
<td></td>
</tr>
<tr>
<td>3. IV vancomycin</td>
<td>Plus two orally active agents</td>
<td></td>
</tr>
</tbody>
</table>

NB.
- Consider MRSA decolonisation when first detected – see below
- Doxycycline NOT for use in children < 8 years of age

iv) Other predominant organisms – seek expert advice
### Table 4 Recommended doses for frequently used antibiotics in CF (Zobell, Waters et al. 2013)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Paediatric Dose</th>
<th>Adult Dose</th>
<th>Max adult dose</th>
<th>Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piperacillin + tazobactam (IV)</td>
<td>90 mg/kg to 150 mg/kg (piperacillin) 6 hourly (Max 4 g 6 hourly)</td>
<td>4.5 g 6 hourly</td>
<td>4.5 g 4 hourly</td>
<td>13.5 g over 24 h</td>
</tr>
<tr>
<td>Ceftazidime (IV)</td>
<td>50 mg/kg to 100 mg/kg 8 hourly (Max 2 g 8 hourly)</td>
<td>2 g 8 hourly</td>
<td>2 g 4 hourly</td>
<td>6–8 g over 24 h</td>
</tr>
<tr>
<td>Ciprofloxacin (PO)</td>
<td>15 mg/kg 12 hourly Not routinely used in children but 250–500 mg 12 hourly has been used</td>
<td>750 mg 12 hourly</td>
<td>750 mg 12 hourly</td>
<td></td>
</tr>
<tr>
<td>Meropenem (IV)</td>
<td>40 mg/kg 8 hourly (max 2g 8 hourly)</td>
<td>2 g 8 hourly</td>
<td>2 g 8 hourly</td>
<td></td>
</tr>
<tr>
<td>Vancomycin (IV)*</td>
<td>15 mg/kg (max 750 mg) 6 hourly or 30 mg/kg (max 1.5 g) 12 hourly</td>
<td>Start with loading dose of 25 mg/kg and see dosing table below</td>
<td>Dosing is based on actual body weight</td>
<td></td>
</tr>
<tr>
<td>Tobramycin (IV)**</td>
<td>Commence 7 to 10 mg/kg</td>
<td>Commence 7 to10 mg/kg (slow IV push over minimum of 5 min)</td>
<td>Refer HDIS for dose adjustment</td>
<td></td>
</tr>
</tbody>
</table>

*Vancomycin dosing and timing of trough concentration for children, see Therapeutic Guidelines: Antibiotic, Therapeutic Guidelines, Melbourne, Victoria 2014*

**Refer to Aminoglycoside guidelines on PPG directory
**VANCOMYCIN (This is only for adult patients)**

Refer to Vancomycin guidelines on PPG directory. Maximum infusion rate 10 mg/min. **First dose at 25–30 mg/kg.** Before giving any single dose of vancomycin in excess of 2 g, consult the Infectious Diseases Team.

Subsequent vancomycin maintenance dosage and timing of trough concentration measurements for adults:

<table>
<thead>
<tr>
<th>Creatinine clearance (mL/min)</th>
<th>Subsequent dose and interval</th>
<th>Timing of trough concentration (if given for longer than 48 hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 90</td>
<td>20 mg/kg 12 hourly</td>
<td>Before fourth dose</td>
</tr>
<tr>
<td>60 to 90</td>
<td>15 mg/kg 12 hourly</td>
<td>Before fourth dose</td>
</tr>
<tr>
<td>20 to less than 60</td>
<td>15 mg/kg 24 hourly</td>
<td>Before fourth dose</td>
</tr>
<tr>
<td>&lt; 20</td>
<td>15 mg/kg 48 hourly</td>
<td>48 hours after first dose</td>
</tr>
</tbody>
</table>

Target concentration is 15–20 mg/L but may vary with clinical situation. See Therapeutic Guidelines: Antibiotic, Therapeutic Guidelines, Melbourne, Victoria 2014 pages 577–583.

**Table 5 Recommended doses for frequently used inhaled antibiotics in CF (Zobell, Waters et al. 2013)**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Reconstitution</th>
<th>Max dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aztreonam</td>
<td>500 mg to 1000 mg BD Reconstitute vial with 4 mL water for injection 500 mg dose: Nebulise 2.6 mL 1 g dose: Nebulise entire contents of vial</td>
<td>2 g daily</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>1 to 2 g BD to TDS (Paediatric dose 1 to 2 g BD) Reconstitute vial with 3 mL 0.9% sodium chloride. Nebulise entire contents of vial</td>
<td>6 g</td>
</tr>
<tr>
<td>Colistimethate for inhalation (Tadim)</td>
<td>1 to 2 million units BD to TDS (Paediatric dose &gt; 2 yo 1 to 2 million units BD) Reconstitute vial with 1 million unit dose: Reconstitute vial with 4 mL water for injection. 2 million unit dose: Reconstitute each 1 million unit vial with 2 mL water for injection. Gently swirl whilst reconstituting to prevent excessive frothing</td>
<td>6 million units daily</td>
</tr>
<tr>
<td>Ticarcillin + clavulanate</td>
<td>3.1 g BD (Paediatric dose BD 0–5 yo 1 g 5–10 yo 1.5 g &gt; 10 yo 2 g) Reconstitute vial with 3 mL 0.9% sodium chloride and nebulise entire contents (or as directed in paediatrics)</td>
<td>6.2 g daily</td>
</tr>
<tr>
<td>Tobramycin solution (Tobi)</td>
<td>300 mg neb BD (only for children &gt; 6 yo) None</td>
<td>600 mg daily</td>
</tr>
<tr>
<td>Tobramycin powder (Tobi Podhaler)</td>
<td>112 mg BD (only for children &gt; 6yo) None</td>
<td>224 mg daily</td>
</tr>
<tr>
<td>Tobramycin 80 mg/2 mL (contains metabisulfite)</td>
<td>Paediatric dose BD &lt; 5 yo 80 mg 5–12 yo 160 mg &gt; 12 yo 240 mg Optimal volume 4 mL Add 0.9% sodium chloride to make up to volume</td>
<td></td>
</tr>
</tbody>
</table>

Refer to Nebulised Antibiotic Prescribing Guidelines on PPG directory.
**Staff Preparation**

It is mandatory for staff to follow relevant: “Five moments of hand hygiene”, infection control, moving safely/safe manual handling, documentation practices and to use HAIDET for patient/carer communication: 
**Hand hygiene Acknowledge, Introduce, Duration, Explanation, Thank you or closing comment.**

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**IMPLEMENTATION PLAN**

The guidelines will be:

- Circulated to all HNE clinicians who care for Cystic Fibrosis patients.
- Be included in orientation and education programs for medical and nursing staff who care for Cystic Fibrosis patients.

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**MONITORING AND AUDITING PLAN**

The use of the guidelines will be monitored through auditing medical records (See Appendix 1) and IMMS data, related to medication errors in prescribing.

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**CONSULTATION WITH KEY STAKEHOLDERS**

- Dr John Ferguson, Director of Infection Prevention Service, John Hunter Hospital
- Dr Jodi Hilton, Paediatric Respiratory and Sleep, John Hunter Children’s Hospital
- Ms Jennifer MacDonald, Director Pharmacy, John Hunter Hospital
- Dr Josh Davies, Immunology & Infectious disease, John Hunter Hospital
- Dr Rodney Givney, Microbiology, Pathology
- Ms Felicity Prior, Director Hunter Drug Information Service, Calvary Mater Hospital
- Prof Michael Hensley, Director of Medical Services, John Hunter Hospital
- Dr Mark Loewenthal, Director Infusion lounge, Immunology & Infectious disease, John Hunter Hospital
- Ms Lisa Harris, Pharmacist, John Hunter Hospital

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**FEEDBACK**

Any feedback on this document should be sent to the Contact Officer listed on the front page.
REFERENCES


## Clinical Audit Tool

(National Standard 1: 1.7.2 The use of agreed clinical guidelines by the clinical workforce is monitored)

<table>
<thead>
<tr>
<th>Criterion no.</th>
<th>Criterion</th>
<th>Exceptions</th>
<th>Definition of terms and/or general guidance</th>
<th>Data source</th>
<th>Frequency</th>
<th>Position Responsible</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Compliance with the guidelines</td>
<td>None</td>
<td>Compliance with the guidelines to be monitored through audit of medical records. Audit period 3 months (includes both inpatients and outpatients)</td>
<td>Patient medical records</td>
<td>12 months</td>
<td>CF Pharmacist</td>
</tr>
</tbody>
</table>