Specialised Services Clinical Access Policy:
Inhaled Therapy for Patients 6 years and older with Cystic Fibrosis

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1. POLICY STATEMENT

The Welsh Health Specialised Services Committee (WHSSC) will fund inhaled therapies for the management of patients with Cystic Fibrosis in line with this policy.

Clinicians are requested to take this policy into account when discussing treatment options with patients. The monitoring of quality and outcome measures specified in this document are mandatory for any centre treating Welsh patients.

2. CLINICAL INDICATIONS

It is recommended that all patients with evidence of chronic or intermittent Pseudomonas aeruginosa pulmonary infection should receive therapy with inhaled anti-Pseudomonas antibiotics in line with the product summary characteristics.

Colistimethate sodium, tobramycin and aztreonam lysine are effective in treating chronic or intermittent Pseudomonas infection resulting in improvements in lung function, quality of life, and disease progression.

This policy does not specifically cover the role of inhaled therapies in the eradication of Pseudomonas aeruginosa.

3. CLINICAL ASSESSMENT

Inhaled anti-pseudomonal therapies are usually initiated for eradication of pseudomonas aeruginosa, and may be commenced by the CF centre, by the local hospital or by primary care in a shared care arrangement. Eradication therapy can include either nebulised colistimethate sodium or tobramycin.

The first line therapy for chronic or intermittent pseudomonas aeruginosa infection is nebulised colistimethate sodium. Second line therapy should only be initiated by a specialist cystic fibrosis centre. For Colistimethate sodium DPI (Colobreathe®), Tobramycin DPI (Tobi podhaler®) and nebulised Aztreonam (Cayston®), continued supplies of treatment may be prescribed by the specialist centre or via a homecare agreement in line with the patient access scheme in NHS Wales. For nebulised colistimethate sodium (colomycin®, Promixin®), nebulised Tobramycin (TOBI® and Bramitob®), continued supplies of treatment may be prescribed by the specialist centre or by patient’s general practitioner via Shared Care Agreement where applicable.
Treatment choice is determined by clinical response. Failed eradication or Pseudomonal regrowth whilst on inhaled antibiotics may necessitate a change in antibiotic therapy.

In the event of intolerance/allergy to an antibiotic eg Colistimethate sodium, then an alternative should be tried. Tobramycin should be regarded as second line therapy and Aztreonam Lysine as third line.

All patients should be prescribed a supervised test dose in the hospital environment before commencing therapy. An inhaled or nebulised bronchodilator should be administered before the test dose if this is part of the patient's current regimen. The test dose should be supervised by a nurse, physiotherapist or lung function technician.

The test dose may be repeated at least 24 hours later if wheezing or bronchoconstriction occurs, after the administration of inhaled or nebulised bronchodilator (if not administered before the first test dose). If the patient tolerates the repeated test dose, they should use the inhaled/nebulised bronchodilator before each subsequent dose.

The patient should have a pre and post dose FEV\textsubscript{1} and FVC measured on their test dose. The patient should also be monitored for post-dose wheezing and bronchoconstriction.

3.1 **Specific monitoring for Tobramycin**

As small amounts of the drug are absorbed from the lung into the systemic circulation there is a potential for patients with pre-existing renal disease or those with pre-existing high cumulative doses of systemic tobramycin to suffer ototoxicity. The CF team should make patients aware of potential side effects such as ringing in the ears and ensure therapy is stopped if this occurs. At risk patients may require baseline audiometry when starting therapy.

4. **TREATMENT**

Management of the pulmonary component of cystic fibrosis includes a range of measures to aid clearance of respiratory secretions and to decrease inflammation and bacterial growth in the respiratory tract, such as chest physiotherapy, inhaled bronchodilators, inhaled mucolytics (such as rhDNase and hypertonic saline) and antibiotic treatment. The aim of treatment is to delay or slow deterioration in lung function, measured by forced expiratory volume in 1 second (FEV\textsubscript{1}).
Treatment with the following inhaled treatments will be routinely funded for adults and children (over the age of 6) with a confirmed diagnosis of Cystic Fibrosis (CF) who meet clinical criteria for their use:
- Colistimethate sodium (Colomycin, Promixin, Colobreathe)
- Tobramycin (Tobi, Bramitob, Tobi Podhaler)
- Aztreonam Lysine (Cayston)

A stepwise approach is recommended and this is detailed in the treatment algorithm in diagram 1 below.

All patients should have regular review of airway microbiology to ensure continued appropriate ongoing treatment. If *Pseudomonas* has not been isolated or has been replaced by a new organism (ie *Burkholderia cepacia complex*) then a change of therapy should be considered.

All patients should have a regular assessment of lung function to ensure ongoing treatment tolerance and identification of adverse effects.

The following diagram details the treatment algorithm for the clinical criteria using these inhaled therapies.
**Inhaled/Nebulised Antibiotics Algorithm**

Chronic Pseudomonas colonisation in Cystic Fibrosis patients aged 6 and over

Incorporating NICE TA276, AWMSG 0813 & NHSBC/A01/PS/a

**Nebulised colistimethate sodium**

- Intolerant
- Deteriorating

**Colistimethate sodium DPI**

- Intolerant
- Deteriorating

**Nebulised tobramycin or tobramycin DPI + Nebulised aztreonam lysine**

**Nebulised colistimethate sodium + Nebulised tobramycin or tobramycin DPI**

**Nebulised colistimethate sodium DPI + Nebulised tobramycin or tobramycin DPI**

- Deteriorating

**Colistimethate sodium DPI + Nebulised aztreonam lysine**

Where two antibiotics are advised, these should be used on an alternating monthly regimen

DPI = Dry Powder for Inhalation

* Oral macrolide treatment should be considered for all patients

* FEV₁ decline >1% predicted per year or more than one course of IV antibiotics in previous year

† FEV₁ decline >2% predicted per year or more than two courses of IV antibiotics in previous year

October 2013
4.1 Stopping Criteria

4.1.1 Medical Adherence

Intolerance is defined as the inability to continue taking, or difficulty in continuing to take, a medication because of an adverse side effect that is not immunity-medicated. This may be self-reported and documented side-effects or evidenced by a fall in lung function on trial.

In all patients actual and perceived benefits (see Section 6.2) and adherence to therapies (either self-reported and/or where possible by evidence from prescription collection/delivery records) should be assessed. In patients where there is no actual or perceived benefit and adherence is under 50%, reasons for non-adherence should be discussed: it may thereafter be reasonable to consider stopping therapy.

4.1.2 Bronchoconstriction and/or Intolerance

If there is evidence of bronchoconstriction or intolerance (ie a fall in FEV\textsubscript{1} of >10% predicted at trial, or other documented side effects) associated with on going therapy, then the inhaled antibiotic should be discontinued and an alternative tried.

Colistimethate sodium has not been shown to improve lung function in studies therefore if there is continued loss of lung function (more than 1% per year) alternative antibiotics should be considered. Likewise, lack of effectiveness of an inhaled therapy should lead to escalation to second or third line therapies as per treatment algorithm. Patients may have to be considered for lung transplant assessment as appropriate, if there is further deterioration whilst continuing on optimal inhaled therapies and other complicating factors assessed for and managed.

5. RELATIONSHIP WITH OTHER POLICIES AND SERVICE SPECIFICATIONS

This document should be read in conjunction with the following documents:

- All Wales Policy: Making Decisions on Individual Patient Funding Requests (IPFR).

6. DEFINITIONS

**Cystic Fibrosis** – Cystic fibrosis affects over 8500 children and young adults in the UK and has an incidence of 1 in 2500 live births. About 1 in 25 people in the UK of white European origin are carriers of an affected CFTR gene. It is much less common in people of African-Caribbean and Asian origin. Cystic fibrosis is a progressive condition that reduces life expectancy. In 2010, the cystic fibrosis registry recorded 103 deaths in UK patients; the median age at death was 29 years. However, prognosis is improving with the treatments now available and around half of the current cystic fibrosis population are expected to have a life expectancy of over 38 years.

**CF Pulmonary exacerbation**—episode of acute or sub-acute worsening of respiratory symptoms from patient’s baseline. People with cystic fibrosis have problems with their respiratory system and digestion, including prolonged diarrhoea that can affect growth and body mass index. They are prone to lung infections by a range of pathogens including *Staphylococcus aureus, Haemophilus influenzae, Pseudomonas aeruginosa* and *Burkholderia cepacia*. This is thought to be because the thick mucus makes it difficult for the body to clear inhaled bacteria, and because people with cystic fibrosis have an increased airway inflammatory response to pathogens. Chronic inflammation and progressive lung destruction from chronic infection can lead to bronchiectasis, altered pulmonary function and respiratory failure.

**FEV<sub>1</sub>** – FEV<sub>1</sub> is the maximal amount of air forcefully exhaled in one second. Absolute values are standardised by expressing them as a percentage of normal corrected for age, sex, height and ethnic origin. FEV<sub>1</sub> is a marker for the degree of airway obstruction, and its decline is an important prognostic indicator of life expectancy in CF:
- FEV<sub>1</sub> greater 80% of predicted = normal
- FEV<sub>1</sub> 60% to 79% of predicted = Mild obstruction
- FEV<sub>1</sub> 40% to 59% of predicted = Moderate obstruction
- FEV<sub>1</sub> less than 40% of predicted = Severe obstruction

FEV<sub>1</sub> is measured by spirometry, and the percent predicted is calculated automatically by the spirometer based on normal values and the individual demographics of the patient.

**Therapy Intolerance** - the inability to continue taking, or difficulty in continuing to take, a medication because of an adverse side effect that is not immunity-mediated. This may be self-reported and documented side-effects or evidenced by a fall in lung function on trial. Examples may include significant prolonged cough, nausea, chest tightness and dysgeusia.
7. **CLINICAL CODING**

**ICD-10**

E84.9 Cystic Fibrosis, unspecified

*Cystic fibrosis with pulmonary manifestations*

E84.0 is a billable ICD-10-CM code that can be used to specify a diagnosis.

Description

Synonyms
- Cystic fibrosis of the lung
- Cystic fibrosis with pulmonary manifestation
- Cystic fibrosis, pulmonary

Use Additional code to identify any infectious organism present, such as:
- Pseudomonas (B96.5)

8. **PATIENT PATHWAY**

Referrers should refer the patient to the appropriate specialist cystic fibrosis centre that manages the care of the patient.

Ultimately, patients may become eligible for lung transplantation. The care of most patients in the UK is coordinated by a tertiary cystic fibrosis centre with formal shared care with local clinics.

9. **EXCLUSIONS**

Treatments are not licensed for use in children under the age of 6 years. Please refer to the separate guidance on inhaled anti-pseudomonal therapy in children aged less than 6 years with CF.

10. **QUALITY AND OUTCOME MEASURES**
The Provider must work to written quality standards and provide monitoring information to the lead purchaser. Providers are expected to comply with the following:

- CF Core Standards as outlined by WHSSC
- Proportion of patients seen by specialist team for specialist annual review
- All providers should submit the minimum dataset data to the UK CF Registry within the required timescales. There is an expectation that data from all of Welsh CF patients would be entered onto the CF registry, but where it is not possible to obtain consent for registration and data entry the reasons should be documented for future audit.
- Serious incidents reported externally to STEIS, Welsh Government or equivalent must be shared at time of reporting
- Annual information to be received regarding:
  - Number of serious incidents reported externally
  - Number of concerns received, response timescales, lessons learnt and action plans
  - Compliance with safety notices e.g. NRLS Rapid Response Reports

For those patients on inhaled therapies providers should provide the following for every patient:

- Baseline FEV$_1$ in year prior to commencing therapy
- Baseline number of courses in IV in year prior to commencing therapy
- Baseline hospitalisations in year prior to commencing therapy
- Baseline BMI or BMI SDS/percentages in year prior to commencing therapy
- FEV$_1$ every 2 months for first 6 months and annually thereafter
- BMI or BMI SDS/percentage annually
- Courses of IV each year after commencing therapy
- Number of hospitalisations each year after commencing therapy
- Monitor adverse events
- Monitor acute exacerbations

10.1 Clinical Audit

An annual audit day will be held between providers and WHSSC to review the quality of services.
10.2 Patient Experience

Providers should use a validated patient experience tool for monitoring patient experience on an annual basis (e.g. CAREs tool (http://www.caremeasure.org/))

10.3 Quality of Life

Measurement of the Quality of Life using the Cystic Fibrosis Revised Questionnaire Quality of Life tool with patients on inhaled antibiotic therapies is expected as a regular component of the annual review of patients.

11. EQUALITY IMPACT ASSESSMENT

The Equality Impact Assessment (EQIA) process has been developed to help promote fair and equal treatment in the delivery of health services. It aims to enable Welsh Health Specialised Services Committee to identify and eliminate detrimental treatment caused by the adverse impact of health service policies upon groups and individuals for reasons of race, gender re-assignment, disability, sex, sexual orientation, age, religion and belief, marriage and civil partnership, pregnancy and maternity and language (welsh).

This policy has been subjected to an Equality Impact Assessment.

The Assessment demonstrates the policy is robust and there is no potential for discrimination or adverse impact. All opportunities to promote equality have been taken.

12. REFERENCES

3. Tappenden P, Harnan S, Uttley L et al., Colistimethate sodium powder and tobramycin powder for inhalation for the treatment of
Pseudomonas aeruginosa lung infection in cystic fibrosis, March 2012 (ScHARR).


15. Tobramycin Inhalation Solution, USP.