Title	Mucolytic Therapy
Version	1

1. Introduction

- Mucolytics 'mucus thinners' are used in Cystic Fibrosis to loosen thick sticky airway mucus and aid clearance with physiotherapy & coughing and are routinely offered to patients with clinical evidence of lung disease.
- NICE guidance recommends Pulmozyme (DNase) as first mucolytic choice and if clinical evaluation of lung function testing indicates an inadequate response to then consider DNase with Hypertonic saline (HTS) or HTS alone.
- A more recent publication suggests that early use of mucolytic therapy (HTS) age 3-6 years may help improve Lung Clearance Index in children with CF.
- Mannitol dry powder for inhalation is recommended by NICE as a treatment option for adult patients with Cystic Fibrosis who cannot use DNase due to ineligibility, intolerance or inadequate response or adult patients whose lung function is declining (FEV1 greater than 2% annually).
- Carbocysteine & other thiol derivatives whilst helpful in other lung conditions have no evidence to support their use in CF by oral or nebulised route.

2. Pulmozyme (Dornase Alpha/DNase/rhDNase)

2.1. Introduction

- In the response to infection and inflammation large amounts of DNA are released from degenerating white cells which then accumulate within the airways, resulting in highly viscoelastic sputum.

2.2. Mechanism of action

- The released DNA, which thickens the mucus, is broken down into smaller molecules by Pulmozyme. This results in "thinner", less viscoelastic sputum.

2.3. Indications and Dose

- Licensed for the management of cystic fibrosis patients with a forced vital capacity (FVC) of greater than 40% of predicted to improve pulmonary function (see 2.5 below).
- Child: 5-17 years: 2.5mg daily via a nebuliser. Given at a younger age if felt clinically appropriate.
- Adult: 2.5mg daily via a nebuliser, pts over 21 years may benefit from twice daily dosage.

2.4. Directions for administration

- Licensed for administration at least one hour prior to airway clearance via a nebuliser (Portaneb, e-Flow or Ineb)
- Best timing of administration is unclear from evidence and can be tailored to patient need/response e.g. ½ hour/just prior to airway clearance or some hours prior
- Alternate day treatment with DNase has been shown to be as effective as daily treatment in some patients and so potentially helping to reduce treatment burden (Rand 2013)
- Inhalation in the morning may produce a faster daytime muco-ciliary clearance and help the clearance effects of daytime activities such as exercise. However, inhalation in the evening may increase the dwell time in the airways since muco-ciliary clearance and cough are suppressed overnight (Rand et al 2013)

2.5. **Side-effects**

- Chest pain, conjunctivitis, dyspepsia, dyspnoea, fever, increased risk of infection, skin reactions, hoarse voice, sore throat.
- There is no clear evidence that rhDNase directly causes haemoptysis, although treatment should be stopped in those patients with moderate to significant bleeding as it may exacerbate the situation by dislodging mucus plugs (see also 2.7 below)

2.6. **Clinical Effectiveness**

- Recommended as first-line mucolytic in CF (Cochrane review)
- DNase is effective and safe at all stages of lung disease
- DNase is effective with long term use

2.7. Recommendations

- **Pulmozyme Trial.** NWMCF Centre recommends a trial DNase from age 6 years/school age and continued of of clinical benefit after up to 3 months treatment
- **First Dose.** Undertaken as out-patient or in-patient in the hospital environment. Requires pre- and post-assessment (using nebulised trial sheet/local protocol and any bronchoconstriction or ADR documented)
- **Haemoptysis.** NWMCF Centre recommends stopping DNase (and hypertonic saline and any Positive expiratory pressure devices which are used for airway clearance). Once a patient is 48 hours clear of any further haemoptysis then they can restart DNase nebs and then after a further 24 hours clear of any further haemoptysis then patients can restart their PEP devices.

3. Hypertonic Sodium Chloride

3.1. Introduction

- The airway surface liquid (ASL) is normally kept at the height of the cilia that line the airways. These beat in a synchronised fashion to clear the lungs of debris and keep them free of infection.
- Dysfunction of the cystic fibrosis transmembrane conductance regulator (CFTR) protein results in failure of chloride and reduced the volume of the ASL, causing excess viscosity (stickiness) of the airway mucus and failure of muco-ciliary clearance
- Retained viscous mucus is a focus for infection

3.2. Mechanism of action

- HTS increases the ion concentration in the ASL and osmotically draws fluid into the airway lumen, thereby replenishing the fluid layer and accelerating mucus clearance.
- Neutrophil DNA released at cell breakdown binds with mucoprotein in the airways, increasing sputum viscosity by preventing mucoprotein breakdown and removal from the lung.
- Hypertonic saline separates DNA/mucoprotein complex allowing normal degradation to occur
- Inhalation of hypertonic saline usually causes coughing. This aids mucus clearance by stimulating large shear stresses and promoting the separation of mucus plaques from the airway walls.

3.3. Clinical Effectiveness

- Cochrane Review 2017 reports:
  - Regular nebulised hypertonic saline by adults and children over the age of 12 years with CF results in an improvement in lung function after four weeks (very low-quality evidence from three trials), but not sustained at 48 weeks (low-quality evidence from one trial).
  - nebulised hypertonic saline reduced the frequency of pulmonary exacerbations (insufficient evidence for this outcome under six years of age) and may have a small effect on improvement in quality of life in adults.
  - rhDNase may lead to better lung function at three months
  - Hypertonic saline does appear to be an effective adjunct to physiotherapy during acute exacerbations of lung disease in adults.

- 2019 SHIP study supports the use of 7% HTS as an early intervention strategy in children aged 3-6 years with cystic fibrosis but due to the minimal clinical improvements recommended that clinicians discuss with families to weigh up treatment effect versus treatment burden.

3.4. Dose, Concentration and Timing

- Child 6 to 17 years and Adult: 4mls 2 to 4 times a day.
- The relative importance of variations in saline volume and inhalation frequency are not fully understood and have not been subject to direct comparison in clinical trials. With greater concentrations mucus clearance is increased but at the expense of an increase in adverse events.
- HTS is available in different concentrations. 7% HTS is used first-line, but 3% may be better tolerated particularly if asthmatic, or if 7% cases bronchoconstriction or excessive cough
- Timing of delivery makes little difference to effects. It is usually given immediately prior to airway clearance (or simultaneously with appropriate device)

3.5. Side Effects

- Coughing bouts precipitated by inhalation of hypertonic saline preclude its use in some patients. Patients may also suffer bronchoconstriction, especially if they have a history of asthma.
- Cough, chest tightness and pharyngitis may resolve after a few doses or after a temporary break in treatment.
- Some patients cannot tolerate the salty taste.
- 8% of patients are not able to tolerate HTS

3.6. Practicalities of treatment

- Bronchodilator inhalation is recommended before administration of hypertonic saline.
- Patients require an initial supervised test dose with pre and post dose monitoring of lung function in hospital
- Patients do not like inhalation of large volumes (10mls) or frequent (>4) inhalations.
- Treatment with hypertonic saline is a significant additional burden for the patient.

4. Mannitol (Bronchitol)

4.1. Introduction

- Bronchitol is an inhaled dry powder which can be used as a treatment option to augment airway clearance for adult patients with Cystic Fibrosis.

4.2. Criteria

- Patients who cannot use DNase due to ineligibility, intolerance or inadequate response to DNase
- Patients whose lung function is rapidly declining (FEV1 decline greater than 2% annually)
- For patients whereby other osmotic agents are not considered appropriate

4.3. **Mechanism of action**

Bronchitol is a muco-active agent that causes water to enter the airway lumen and hydrate airway secretions. This reduces the viscosity of the secretions and can stimulate a cough and so will improve secretion clearance and pathogenic bacteria.

4.4. **Dose**

- Bronchitol is a dry powder and is inhaled from a hand-held, breath activated device
- Dose: 400mg twice a day (10 x 40mg powder capsules) or lower dose depending on response/tolerance

4.5. **Clinical Effectiveness**

- Long term use of inhaled Bronchitol can result in a significant and clinically meaningful improvement in lung function relative to the control in adult cystic fibrosis subjects.
- Improvements seen irrespective of DNase, tobramycin or colistin use.
- Can reduce number and frequency of chest infections and pulmonary exacerbations.

4.6. Side–effects

Bronchitol can cause chest discomfort, condition-aggravated cough, haemoptysis, headache, throat complaints and vomiting

4.7. **First dose**

- This is completed in hospital as an out-patient or as an in-patient.
- It is advised that a BIDA (Bronchitol initiation dose assessment) is completed as a test dose in hospital. Please click on link: http://www.bronchitol.info/assets/Uploads/2018-05-15-Bronchitol-HCP-Leaflet-UK-V2.2.pdf
- The patient should be seated for the test and the procedure explained.
- The patient should be pre-medicated with a bronchodilator 5-15 minutes prior to the initiation dose but after the baseline FEV1 and SpO2 (Oxygen saturation in the blood) measurement. All FEV1 measurements and SpO2 monitoring should be performed 60 seconds after dose inhalation.
- Training the patient to practice correct inhaler technique during the initiation dose assessment is important.
- The initiation dose assessment must be performed according to the following steps:
  Step 1: Patients baseline FEV1 and SpO2 is measured prior to the initiation dose
  Step 2: Patient inhales 40 mg (1x40 mg capsules) and SpO2 is monitored
  Step 3: Patient inhales 80 mg (2x40 mg capsules) and SpO2 is monitored
  Step 4: Patient inhales 120 mg (3x40 mg capsules), FEV1 is measured and SpO2 is monitored
  Step 5: Patient inhales 160 mg (4x40 mg capsules), FEV1 is measured and SpO2 is monitored
  Step 6: Patients FEV1 is measured 15 minutes post initiation dose.
- Patients with asthma may experience reversible temporary mild bronchospasm after passing the initiation dose assessment and therefore all patients should be monitored until their FEV1 has returned to baseline levels.
- If the patient shows any signs of significant bronchoconstriction such as wheezing or shortness of breath during the test, measure FEV1 and treat accordingly.
- There are three possible outcomes to the BIDA, pass, fail or incomplete.

5. References

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