South East London Integrated Guideline for the Use of Nebulised Antibiotics in the Management of *Pseudomonas aeruginosa* in Adult Non-Cystic Fibrosis Bronchiectasis

This guideline has been developed by the South East London Responsible Respiratory sub-group – a sub-group of the SEL Integrated Medicines Optimisation Committee (SEL IMOC).

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South East London Integrated Medicines Optimisation Committee (SEL IMOC). A partnership between NHS organisations in South East London Integrated Care System: NHS South East London (covering the boroughs of Bexley/Bromley/Greenwich/ Lambeth/Lewisham and Southwark) and GSTFT/KCH /SLaM/ Oxleas NHS Foundation Trusts and Lewisham & Greenwich NHS Trust

South East London Integrated Guideline for the Off-Label Use of Nebulised Antibiotics in the Management of *Pseudomonas aeruginosa* in Adult Non-Cystic Fibrosis Bronchiectasis*

NHS South East London

This is a specialist pathway for use in adult patients. All prescribing, supply and monitoring of treatment will be managed by the hospital team

Aims, Diagnosis and Initial treatment

- Nebulised antibiotics in non-cystic fibrosis (non-CF) bronchiectasis are indicated to reduce exacerbations, minimise symptoms and improve overall health. They should be considered for patients experiencing ≥3 infective exacerbations per year and those with significant associated morbidity (e.g. chronic purulent sputum with evidence of colonisation / infection), despite otherwise optimised management (see **Investigations** side-bar to right)
- *Some patients without bronchiectasis may be colonised with pseudomonas and the same principles of care should apply (e.g. tracheostomy patients or in very severe COPD).
- Where appropriate, eradication should by attempted initially with oral or intravenous antibiotics for a new growth of P. aeruginosa (first isolation or regrowth in the context of intermittently positive cultures):
  - **First line eradication treatment choice**: ciprofloxacin 500–750mg orally twice a day for 2 weeks;
  - **Second line eradication treatment choice**: IV antipseudomonal beta-lactam ***check allergy status*** ± an IV aminoglycoside for 2 weeks
- Eradication with 3 months of nebulised antibiotic should almost always follow oral or IV treatment (as above)
- 1st line colistin (Colomycin®); 2nd line gentamicin; 3rd line tobramycin. 2nd and 3rd line options may be appropriate in cases of treatment failure, intolerance or where regime complexity (e.g. reconstitution/administration) is a concern
- Longer term suppression therapy with the same nebulised antibiotic may follow eradication. The decision to start suppression therapy should based on clinical picture, including exacerbation history and risk, and sputum cultures
- Refer to the BTS guidance for further information https://www.brit-thoracic.org.uk/document-library/guidelines/bronchiectasis/bts-guideline-for-bronchiectasis-in-adults/

Investigations

Patients must be adequately investigated and therapies optimised prior to initiation of nebulised antibiotics. This includes:

- Pharmacotherapy such as mucolytics, bronchodilators (if appropriate), nebulised saline and prophylactic oral antibiotics (e.g. macrolide)
- Airway clearance optimised by physiotherapy +/- adjunct (e.g. OPEP)
- Sputum culture (including AFB for non-tuberculous mycobacteria)
- Consideration of need for fungal investigations
- Lung function
- Radiological investigations

Considerations before prescribing Nebulised Antibiotics

Good Antimicrobial Stewardship and Sensitivity Testing

- Prescribing nebulised antibiotics:
  - Initiation must be by a clinician experienced in the management of *Pseudomonas aeruginosa* in non-CF bronchiectasis
  - Counsel patients on potential major side effects of long-term antibiotics and advise patients to seek medical attention if side effects develop, e.g. ototoxicity with gentamicin or recurrence/worsening of symptoms suggestive of antimicrobial resistance
  - Nebulised antibiotics are not licensed to treat non-CF bronchiectasis and thus use for this indication is off-label
- Role of microbiology sensitivity testing:
  - Treatment should be guided by antibiotic sensitivity results, but where necessary antibiotic choice can be empiric or based on previous sputum bacteriology
  - To identify resistance to acute or long-term antibiotic treatment
  - Some patients with an infective exacerbation may respond to antibiotic treatment despite resistance to that drug in vitro

Airway Clearance and Initial Management

- Initial management includes:
  - airways clearance techniques (+/- adjunct)
  - pulmonary rehabilitation
  - Influenza, pneumococcal and COVID vaccinations,
  - optimised oral mucolytic therapy (e.g. carbocisteine or acetylcysteine),
  - prompt and appropriate antibiotic treatment for acute exacerbations, alongside a self-management plan
- If a patient has ≥3 exacerbations a year, consider adding a nebulised mucolytic:
  - Sodium chloride 3% or 7% (hypertonic saline). 3% up to four times daily, 7% up to twice a day
- Before initiating hypertonic saline a test dose of the nebulised drug needs to be administered

Nebuliser Supply and Maintenance

Nebuliser equipment supply, servicing & repair: the hospital (e.g. lung function department or equipment store, depending on trust) issue all equipment including compressor, mouthpiece/mask, tubing, antibiotic handset/attachment, nebuliser chamber and filters. They carry out the annual service of *trust* issued compressors and can deal with any issues relating to nebuliser function or part replacement. The use of privately purchased equipment should be discouraged. Privately purchased nebuliser equipment also require maintenance and annual service. This cannot be provided by the trust, rather it is the patient's responsibility to arrange this independently.

Supporting Patient Literature: The patient should be provided with information (written and verbal) about nebuliser compressor equipment, servicing, and how to obtain ongoing advice or support regarding the maintenance of their nebuliser. They should also be offered the patient information leaflet on nebuliser use and maintenance, and the patient information leaflet, developed alongside this guideline, on the nebulised medication they are to be issued.

Nebulised Treatment for *Pseudomonas aeruginosa* (eradication and suppression)

The 1st dose must be administered by a trained respiratory physiotherapist/nurse/physiologist or lung function technician (where possible this should involve a test dose with pre- and post-spirometry within the lung function department to exclude significant bronchoconstriction (please see below))

First Line

Colistin (Colomycin®) (Off-label Indication)

- **Dose**: **2 million International Units (IU) nebulised twice a day**
- NB 1 million units may be used for maintenance in some patients
- **Presentation**: 2 million IU powder for reconstitution in glass vial with 'flip off' lilac cap
- **Diluent:** 4mL water for injection (WFI) OR 4mL sodium chloride 0.9% neb OR 2.5mL salbutamol 2.5mg/2.5mL neb
- **Additional equipment:** syringes (if WFI, sodium chloride 0.9%). Green filter needles can be used with syringes but is not mandatory unless using glass ampoules. A sharps bin must be provided with needles
- **Administration:**
  - Prepare a clean surface, wash and dry hands before mixing dose
  - Each vial of Colomycin® 2 million IU = one vial per dose
  - Pull back the lid on the vial, peel off the metal ring around the top of the vial and remove the rubber bung
  - Add the diluent (chosen from the options above) to the vial of Colomycin®
  - DO NOT SHAKE THE VIAL. This causes the solution to froth and adversely affects its nebulisation. Rather gently roll the vial until the powder in the vial is dissolved
  - Pour the solution within the vial into the medication chamber of the nebulisers antibiotic handset e.g., Sidestream® Plus or PARI LC PLUS
  - Safely dispose of the diluent syringe, metal cap and vial
- **Potential Side-effects:** Wheezing, chest tightness, bronchospasm, skin reactions, sore throat, sore mouth, oral candidiasis, increased cough.
- **Prior to prescribing, consider the following cautions to Colistin use:**
  - Neuromuscular disorders, severe heamoptysis, porphyria, renal impairment, pregnancy or breast-feeding
- **Monitoring:**
  - Sputum cultures (after 3 months of eradication treatment and otherwise as advised by respiratory specialist)
  - Efficacy of treatment
  - Signs or symptoms of toxicity (e.g. nephrotoxicity and neurotoxicity (colistin specific)
  - Renal function - perform at the start of treatment and then repeat routinely during treatment

Refer to the Colomycin® Summary of Product Characteristics for further information

Other information: For maximum effect, a nebulised antibiotic should be administered after chest physiotherapy and other nebulised therapies or inhaled bronchodilators. Prior use with bronchodilators is not necessary if reconstituting with salbutamol. Nebulised antibiotics should not be mixed (other than with the diluents listed above)

Second Line

Gentamicin (Off-label Indication)

- **Dose: 80mg nebulised twice a day**
- **Presentation:** 80mg in 2mL solution in glass ampoule
- **Diluent:** none required for vial reconstitution. Sodium chloride ampoule 0.9% for dilution
- **Additional equipment:** syringes, green filter needles, sharps bin
- **Administration:**
  - Prepare a clean surface, wash and dry hands before mixing the dose
  - Attach a needle to the syringe
  - Each ampoule of gentamicin contains 80mg in 2mL. Use one ampoule for each dose
  - Open the plastic ampoule of sodium chloride 0.9%
  - Carefully snap open the glass gentamicin ampoule
  - Draw up the contents of the gentamicin ampoule vial using the needle and syringe
  - Draw up 2mL sodium chloride0.9% from the ampoule into the syringe. This dilutes the gentamicin to make a total volume of 4mL
  - Put the contents of the syringe into the nebuliser chamber of the antibiotic handset/attachment
  - Safely dispose of the needle, syringe and glass ampoule in your sharps bin
- **Potential side effects:** Cough, bronchospasm. Ototoxicity (including tinnitus and hearing loss) and nephrotoxicity.
- **Prior to prescribing, consider cautions as for colistin plus the following:**
  - Creatinine clearance <30mL/min, concomitant nephrotoxic medications, patient needing a hearing aid or with considerable balance issues
- **Monitoring:** As for colistin, plus audiometry testing if suspicion of ototoxicity

Third Line

Tobramycin (300mg/5mL generic) (Off-label Indication)

- **Dose: Eradication: 300mg nebulised twice a day for 84 days. Suppression: 300mg nebulised twice a day for 28 days, followed by 28 days off treatment. Continue a cycle of 28 days on/off treatment**
- **Presentation:** plastic ampoule, nebulised solution. No further dilution required
- **Additional equipment:** a hand-held PARI LC PLUS reusable nebuliser antibiotic handset with a suitable, compatible compressor (SideStream® Plus not licensed)
- **Potential side effects; as for gentamicin plus:** laryngitis, rhinitis, dysphonia, myalgia, malaise
- **Prior to prescribing, consider cautions as for colistin and gentamicin**
- **Monitoring:** As for colistin and gentamicin

Refer to Tobramycin 300 mg/ 5 ml nebuliser solution - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

Nebuliser Trial/Test Dose: A trial dose is administered to confirm the patient's tolerance of nebulised treatment and to ensure there is no deterioration in lung function. The test dose is deemed unsuccessful if the patient experiences a drop in FEV_1 of ≥15%, a significant increase in respiratory rate, a decrease in SpO_2 or they develop a wheeze or signs of distress. The healthcare professional administering the test dose must document the details and outcome of the trial in the medical notes.

Initial Prescription: Following the test dose, the first month of nebulised antibiotic is prescribed by the hospital respiratory team. It will include the medication, diluent and necessary ancillaries

Subsequent Prescriptions: Follow up prescriptions are written by the hospital respiratory team for dispensing, and where required delivery to the patient, by either the hospital outpatient pharmacy or a homecare company.

The hospital team remain responsible for the prescribing, supply and monitoring of medication.