

<p>Nebulised Colistin – Colistimethate sodium (Colomycin®) for the treatment of Pseudomonas Aeruginosa colonisation and infection in adult patients with non-Cystic Fibrosis bronchiectasis or bronchial sepsis</p>	<p>Wye Valley  NHS Trust</p>
<p>Classification: Shared care protocol Authors: Dr Ingrid du Rand (Consultant Physician Respiratory Medicine) Dr Alison Johnson (Consultant Microbiologist), Ms Sue Vaughan (Pharmacist) Authors Division: Wye Valley NHS Trust Agreed at FWG date 13th June 2017 Issue number: 1 Expiry Date: June 2019</p>	

Contents

Section	Page
Key Points	2
Licensed indication	3
Dosage, prescribing & administration	3-4
Roles and responsibilities	5-6
Monitoring	6
Adverse effects, contra-indications. Interactions	6-7
Standards & references	7-8
Appendices – template letters	9-11

Who should read / have access to this document?

Respiratory Physicians
Advanced Practitioner in Respiratory
Respiratory Specialist Nurses
General Practitioners
GP Practice Nurses & Nurse Practitioners
Pharmacists community & hospital, Dispensers dispensing practices

What is new in this version?

This is a new agreed document with no changes made

Key Points

- Shared Care Policy for the prescribing of nebulised Colistimethate sodium (Colomycin®) in the treatment of lung colonisation or infection with *Pseudomonas Aeruginosa* in adult patients with non-cf bronchiectasis or bronchial sepsis. Shared care has been defined as the mechanism of sharing patient care between primary and secondary care providers. This document sets out the responsibilities from initial diagnosis to the on-going support.
- Shared care is an agreement between the GP and the consultant
- This shared care document has been developed to facilitate the safe and appropriate prescribing, supply and monitoring of nebulised Colistimethate sodium (Colomycin®) in primary and secondary care. It is aimed at all healthcare professionals involved in prescribing, dispensing and monitoring of nebulised Colistimethate sodium (Colomycin®)
- Colomycin® must be prescribed by brand to ensure the patient receives the correct brand for nebulisation
- It has been produced as a result of improved local services for patients with bronchiectasis. Reducing the bacterial load can potentially prevent admissions to the hospital by reducing the severity and frequency of infective exacerbations and impact on morbidity and mortality.

Guideline

Licensed indication

Nebulised Colistimethate sodium (Colomycin®) is indicated for the treatment of colonisation and infections due to *Pseudomonas aeruginosa* in patients with bronchiectasis or bronchial sepsis. The licensed dose for children >2 years and adults is 1-2 million international units (MIU) every 12 hours.

Therapeutic use and background

Pseudomonas Aeruginosa is a pathogen that causes severe lung damage and subsequent loss of functioning lung in patients who become colonised and then chronically infected. Patients with bronchiectasis and bronchial sepsis are at risk of significant morbidity and mortality from the damage caused by this pathogen. Nebulised antipseudomonal antibiotic treatment has been shown to improve lung function, slow the rate of respiratory decline and reduce the frequency of infective exacerbations in these patients. Nebulised antibiotics are able to achieve high local concentrations with low systemic absorption and toxicity as opposed to intravenous antibiotics, where there is high risk of developing adverse effects from systemic absorption.

Colomycin®

Nebulised Colistimethate sodium (Colomycin®) is indicated for chronic pulmonary *Pseudomonas aeruginosa* infection in adults with non-cf bronchiectasis or bronchial sepsis. It is also indicated for eradication of first pulmonary colonisation with *Pseudomonas aeruginosa* for a period of three weeks – three months (initially with high dose ciprofloxacin)

Colomycin® powder for nebulisation is reconstituted with 0.9% sodium chloride and inhaled using an air compressor and nebuliser. This equipment is provided by the

Respiratory Department at the hospital. The equipment will be recalled for service as per manufacturer guidance.

All the consumables including the filters, ventstream and sidestream nebulisers are replenished by the hospital annually or as required. The hospital provides a helpline within office hours for support with the equipment and consumables (01432 364416).

When a Consultant Respiratory Physician initiates Colomycin® a letter for prescribing of Colomycin® powder for nebulisation solution will be sent to the GP. The Respiratory team will prescribe the initial dose and invite the patient for an observed test dose, to ensure the patient does not experience bronchospasm. This will take place in a controlled safe environment within the hospital and will be supervised by a member of the Respiratory team. If no adverse effects are experienced by the patient they will be provided with all the necessary equipment, consumables; information booklet and contact details for a helpline. The patient will then receive a fourteen day supply of Colomycin® for home administration from the hospital. The patient will thereafter request repeat prescriptions for all the necessary therapy from their General Practitioner and redeem their prescription at their local pharmacy.

The patient will remain under the shared care of the GP and Respiratory Team. Any adverse effects experienced will be dealt with promptly and alternative treatments will be explored for that individual patient.

Dosage regimen

Initial colonisation with *Pseudomonas aeruginosa* should be treated with an oral agent if tolerated in the first instance. If eradication is not achieved and the pathogen is sensitive to colistimethate sodium this may be considered as step 2 for eradication.

Eradication regimen STEP 1 CIPROFLOXACIN 750mg tablet BD: 2 weeks (repeat sputum specimen) (NB If eradication has not been achieved then consider one of the step 2 options)		
STEP 2	STEP 2	STEP 2
I.V. anti pseudomonal antibiotics – 2 weeks	Further 4 weeks of Ciprofloxacin 750mg BD Plus 2 million units Nebulised Colomycin® BD for 3 months	2 million units Nebulised Colomycin® BD – 3 months

Eradication of first growth of *Pseudomonas Aeruginosa* (step 2) Colomycin®

Age ≥ 2 years and adults: Colomycin® 2 million units are mixed with 2 - 4ml 0.9% sodium chloride nebulised BD for 3 months. (2.5mg salbutamol can be nebulised 20 minutes prior to nebulised Colomycin), Ciprofloxacin twice daily is co-administered usually for 6 weeks. Dose as outlined below.

Chronic Colonisation (Three or more positive cultures of *Pseudomonas aeruginosa* sensitive to colistimethate sodium in a 12 month period) may require long-term therapy with 1 to 2 million units once or twice daily. Additional parenteral or oral antibiotics may need to be administered to treat acute exacerbations of pulmonary infection.

Prophylaxis

Colomycin® is nebulised once or twice daily on a continual basis.

Availability

Colomycin® can be obtained on prescription and supplied via the community pharmacist.

Route of administration: Nebulisation

Colomycin®

The dose of Colomycin® administered depends on the individual patient and the frequency and severity of infective exacerbations along with their response to treatments. The patient may be instructed to administer one nebulised dose of a bronchodilator via the nebuliser prior to administration of the Colomycin®. Colomycin® is prepared by mixing and diluting the powder with 2-4mls of sodium chloride 0.9% (4 mls in total). This should be stated clearly on the prescription. The patient will administer the antibiotic via a nebuliser unit that is provided by the hospital. It is important that the patient receives a prescription for 5ml plastic ampoules of 0.9% sodium chloride injection in order to be able to effectively mix the therapy without using a syringe which can be problematic for some patients.

Cost (prices June 2017 C&D)

Colomycin®

Each 2 million unit vial costs £3.24

A month's supply of Colomycin® 2 million unit vials (60) is £194 BD dose. 12 months £2,333

For some patients as instructed by the Consultant Physician in Respiratory Medicine:

Each 1 million unit vial costs £1.80

A month's supply of Colomycin® 1 million unit vials (60) is £108

OD dose (OD dose is 30 vials a month) £648 a year

The 0.9% sodium chloride for injection (to be used as diluent) costs £2.11 for 10x5ml (costs for plastic ampoules may vary depending on brand available)

Nebulised Colomycin® should be administered after physiotherapy techniques and other inhaled treatments, where indicated. Other inhaled therapies may include agents to reduce the viscoelasticity of sputum and bronchodilators. These will be specified by the hospital team.

The dosage is determined by the severity and type of infection.

The dose may be varied across this range depending on the condition being treated, tolerability of the patient and response to treatment.

Summary Table 1: Colomycin® (colistimethate sodium)

Drug Nebulised	Equivalent dose	Preparation of drug used	Diluents and volume	Volume used in nebuliser
Colomycin® (colistimethate sodium)	1 million units BD	1 x 1 million unit vial	Sterile 0.9% sodium chloride 2-4ml	4mls four millilitres
	2 million units BD	1 x 2 million unit vial	Sterile 0.9% sodium chloride 2-4ml	4mls four millilitres

Responsibilities of initiating specialist: Consultant and Respiratory Team

- Diagnosis of *Pseudomonas aeruginosa* infection or colonisation in patients diagnosed with bronchiectasis or bronchial sepsis based on a timely and comprehensive assessment
- Organise the test dose and, if the patient tolerates, a prescription for the first 14 days
- Advise the patient's GP that *Pseudomonas aeruginosa* has been isolated and inform them a test dose and initial supply has been made
- Liaison with the GP to discuss a clear shared care agreement
- Supplying the initial sundries where required
- Monitor response and indications of adverse drug reactions (ADRs) during the first test/challenge dose and the subsequent initial follow up period by organising appropriate follow up tests, spirometry, samples
- Evaluate evidence of ADR's or any other concerns raised by the GP and discuss alternative treatment options where appropriate
- Advise GP about possible drug interactions
- Advise the GP if there are any supply issues related to Colomycin®
- In relation to eradication therapy, secondary care will supply the patient with sputum collection pots and advise the patient to send the specimens to their GP for processing in the laboratory at the appropriate time intervals or bring into the chest clinic where appropriate
- The secondary care respiratory team will follow up the results of sputum cultures after the three months' eradication therapy and relay relevant information to the GP
- Respiratory team will ensure patient has a self-management plan and information for managing bronchiectasis.

Responsibilities of the GP

- Authorisation of the prescribing of Colomycin® powder for nebulised solution and sodium chloride diluent
- Monitoring the patient's overall health and well being as usual
- Report any evidence of ADR's or drug intolerance to the Specialist
- Provision of repeat prescriptions of Colomycin® and diluent and any necessary drugs for pre-dosing
- Ensuring advice is sought from the secondary care clinician if there is any significant change in the patient's health status
- Reducing and/or stopping treatment in line with secondary care clinicians directive
- For eradication therapy, GP should ensure sputum samples from the patient are sent for processing two weeks after patient has completed the three-month eradication therapy period, and send any further samples for processing upon request
- If the patient lives outside Herefordshire or tests are analysed in laboratories outside WVT the GP will arrange for sputum specimen results to be forwarded to the secondary care respiratory team within an appropriate timeframe.

Secondary care contact information (Bronchiectasis Team)

Drs Ingrid du Rand, Phil Ryan and Aled Phillips Consultant Respiratory Physicians
 Wye Valley NHS Trust Hereford County Hospital
 01432 3655444 x 5767 or 01432 364210

Julie Manning
 Resp. Specialist Nurse WVT
 01432 364416

Responsibilities of the patient

The patient is responsible for safe administration of the therapy in line with demonstration and instruction provided both verbally in the clinic and written guidance for home reference. The patient must clean and maintain the equipment and seek advice where necessary if equipment fails. Any unused drug must be handed to the pharmacist or GP dispensary for safe disposal.

Patients must order prescriptions in advance as supplies may take a few days to obtain in primary care.

The patient must attend their regular clinic appointments with the specialist for ongoing monitoring and management. They should seek medical assessment from their GP if any side effects occur, or phone the respiratory nurse for advice, or attend the ED if severe adverse effects noted.

Monitoring

Regular monitoring during treatment is essential to detect adverse reactions at an early stage and patients will be counselled by the specialist team about the risk factors and told to report all signs and symptoms of toxicity. Monitoring will be a shared responsibility between the respiratory team in secondary care and the General Practitioner depending on where the patient is seen. Monitoring in the practice may include sputum specimens, oxygen saturation levels and patient reported symptoms depending on the patients management plan. The GP/PN will arrange for sputum specimens to be collected in line with the individualised management plan. Spirometry and oxygen saturation levels will be assessed at every clinic visit, where indicated. Patients will be provided with a contact number where they can report any adverse effects or indeed query any aspects of this service and their individual care.

Adverse Effects

The commonest undesirable effects following nebulisation of Colomycin® are coughing and bronchospasm (indicated by chest tightness which may be detected by a decrease in FEV1) in approximately 10% of patients.

Adverse reactions are tabulated below by system organ class and frequency. Frequencies are defined as Very common ($\geq 1/10$): common ($\geq 1/100$ to $< 1/10$): uncommon ($\geq 1/1,000$ to $< 1/100$): rare ($\geq 1/10,000$ to $< 1/1,000$) and very rare ($< 1/10,000$), not known (cannot be estimated from the available data)

Body System	Frequency	Reported adverse reaction
Immune system disorders	Not known	Hypersensitivity reactions such as skin rash
Respiratory, thoracic and mediastinal disorders	Very common	Cough, chest tightness, bronchoconstriction or bronchospasm
General disorders and administration site conditions	Not known	Sore throat and sore mouth

Nebulised Colistimethate Sodium, Colomycin® can potentially cause bronchoconstriction in some patients, which may lead to discontinuation. This may be relieved in some patients by using an inhaled/nebulised bronchodilator prior to nebulisation of Colomycin®.

Contra-indications, Precautions and Warnings

- Colomycin® is contra-indicated in patients with known hypersensitivity to colistimethate sodium
- Colomycin® is known to reduce the amount of acetylcholine released from the pre-synaptic neuromuscular junction and therefore should not be used in patients with myasthenia gravis
- Use with caution in renal impairment
- Should be used with extreme caution in patients with porphyria

Drug interactions

Nebulised antibiotics should not be given within an hour of dornase-alfa (Pulmozyme®). Concomitant use of inhaled colistimethate sodium with other medications that are nephrotoxic or neurotoxic (e.g. cephalothin sodium, aminoglycosides, non-depolarising muscle relaxants) including those which are administered by the IV or IM routes should only be undertaken with the greatest caution.

Pregnancy

There is evidence that colistimethate sodium crosses the placenta and consequently there is potential for foetal toxicity if used during pregnancy. Clinical use suggests it is probably safe when used by inhalation. Colomycin® should only be given during pregnancy if the benefits outweigh any potential risk. Advising patients and carers is the responsibility of the specialist service.

Breast feeding

Present in milk but poorly absorbed from gut; manufacturers advise avoid (or use only if potential benefit outweighs risk).

Pharmacokinetic Properties Absorption

Gastrointestinal absorption is negligible hence the swallowing of colistimethate sodium deposited in the nasopharynx is unlikely to add to the systemic exposure. Absorption following lung administration is influenced by the nebuliser system, aerosol droplet size and disease state of the lungs.

Pharmacokinetics

A study in healthy volunteers, who inhaled colistimethate sodium, demonstrated the C_{max} of polymyxin E1 (the active moiety) varied between 40.0 and 69.9 ng/mL and the AUC varied between 350 and 668 ng/mL/h depending on the nebuliser and the fill volume and concentration, which varied the dose from 0.3 million IU to 2 million IU. The half-life was approximately 5.2 hours. The absolute bioavailability was calculated to vary between 5% and 18% depending on the nebuliser. The AUC following an intravenous dose of 0.5 million IU was 3,352 ng/ml/h and the C_{max} was 1,232 ng/mL.

Standards

This shared care protocol must be adhered to by all medical, nursing, pharmacy and other staff who are involved in the care of patients who are suitable for shared care, as agreed by both the GP and hospital specialist caring for the patient.

Monitoring and review

This shared care protocol will be reviewed on a two yearly basis or in the intervening period if new research is published, or changes to the drug license that means an update is required before the two years have passed.

References and Supporting Documents

1. BTS guidance on non CF bronchiectasis <https://www.brit-thoracic.org.uk/standards-of-care/guidelines/>
2. Banerjee D, Stableforth D. (2000) The treatment of respiratory pseudomonas infection in cystic fibrosis: what drug and which way? *Drugs* Nov; 60(5): 1053-64.
3. Boe, J. Dennis J. H. and O'Driscoll, B. R. et. al. (ERS TASKFORCE) (2000) European Respiratory Society Guidelines on the use of nebulizers. *European Respiratory Journal*; 18:228-242.
4. Cole, P. J. (2001) The role of nebulised antibiotics in treating serious respiratory infections. *J. Chemother*; 3(4): 354-62.
5. Conway, S. P. (2005) Nebulised antibiotic therapy: the evidence. *Chron Respir Dis.*; 2(1): 35-41. Review.
6. Prober-C-G, Walson-P-D, Jones-J. (2000) Technical report: precautions regarding the use of aerosolized antibiotics. *Committee on Infectious Diseases and Committee on Drugs. Pediatrics, {Pediatrics}*, Dec, vol. 106, no. 6, p. E89, 48 refs, ISSN: 1098-4275.
7. Steinfort DP, Steinfort C. (2007) Effect of long-term nebulized colistin on lung function and quality of life in patients with chronic bronchial sepsis. *Intern Med J.* 2007 Jul;37(7):495-8.

Roles and responsibilities

All staff are responsible for checking that their practice complies with the guidance. The respiratory team is responsible for keeping up-to-date with current research and best practice and disseminating this information.

Appendices

- Appendix 1- GP Shared care agreement letter
- Appendix 2 – Patient shared care agreement letter
- Appendix 3 – GP outcome of drug challenge and ongoing management letter

Appendix 1

GP Shared care agreement letter

Shared care is an agreement between the GP and the hospital consultant. This letter is a request by the consultant to share the suggested pathway of your patient. If you are unable to agree to the sharing of care and continued prescription of the suggested medication, please make this known to the Consultant within 14 days, stating the nature of your concern.

Your patients respiratory consultant has recommended nebulised Colomycin® antibiotic therapy for your patient. The evidence indicates that this therapy is able to reduce the bacterial load in an attempt to reduce the frequency and severity of infective exacerbations of bronchiectasis and reduce the decline in lung function and improve the patient's quality of life as a result.

If you approve the shared care of this therapy, then I will make arrangement for an appointment for your patient to attend the out patients department for a challenge first dose. Your patient will be given a full demonstration of how to make up the drug, have an assessment of their most effective breathing pattern and receive cleaning and equipment maintenance instructions. If they do not experience significant side effects following the first test/challenge dose, they will be provided with all the necessary equipment, information booklet and helpline number.

I have summarised the list of drugs and consumable this patient will require on repeat prescription if there are no significant side effects noted. We will supply the first 14 days of treatment.

Summary of drugs and equipment required from the surgery

Colomycin® two million international unit vial (MIU) 1 BD - 60 per month
Sodium chloride 0.9% 5ml plastic ampoules 2-4ml BD - 60 per month

Yours sincerely

Julie Manning
Respiratory Specialist Nurse
Respiratory Medicine

Dr Ingrid du Rand
Consultant Respiratory Physician
Clinical Lead for Bronchiectasis

Appendix 2

Patient shared care agreement letter

Patient Information Letter

Dear (Insert patients name & hospital number),

As you are aware Dr (insert Dr's name) has recommended that you start on treatment with nebulised Colomycin® antibiotic therapy

Your GP has agreed to prescribe this treatment. We will arrange an appointment for you to attend the Oxford Suite at the Hospital for instruction on how to take the treatment and observation of your response to the therapy. A date and time for the appointment will be sent through the post within the next few days. If you are not able to come, then please let me know so that someone else can use that time slot in clinic.

You will be given all the necessary equipment and 14 days supply of the treatment from the hospital. Your GP will then provide the treatment on repeat prescription in the usual way.

If you have any queries, please contact Julie Manning 01432 364416

Yours sincerely

Insert name of consultant
Consultant Respiratory Physician
Valley NHS Trust

Julie Manning
Specialist nurse Wye
Respiratory Medicine

Appendix 3

GP outcome of drug challenge and ongoing management letter

Dear Dr [insert Doctors name here]

Patient name:[insert Patients name here] Date of birth:
[insert date of birth] Diagnosis: [insert diagnosis here]

This patient is suitable for treatment with (insert name of drug) for the treatment of (insert name of indication)

This drug has been accepted for Shared Care.

Treatment was started on [insert date started] at a dose of [insert dose]

Summary of drugs and equipment required from the surgery

- Colomycin® two (2) million international unit vial (MIU) BD
- Normal Saline plastic ampules (5ml) use 2-4ml BD (diluent)

The patient was provided with all the necessary equipment, information booklet, helpline number and 14 day supply of Colomycin® antibiotic therapy and diluent.

Next review with this department: [insert date]

The patient will not be discharged from out-patient follow-up while taking nebulised Colomycin® antibiotic therapy.

Ongoing prescribing will depend on attendance at clinics as requested by the clinicians.

The Consultant or Respiratory Nurse Prescriber is responsible for any dose adjustment.

Thank you.

Yours sincerely

Consultant name to be inserted
Consultant Respiratory Physician
Wye Valley NHS Trust

Julie Manning
Respiratory
Specialist Nurse