ADULT PROTOCOL FOR INTRAPLEURAL ALTEPLASE AND DORNASE ALFA FOR THE TREATMENT OF EMPYEMA

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Please record brief details of the changes made alongside the next version number. If the procedural document has been reviewed **without change**, this information will still need to be recorded although the version number will remain the same.

Version	Date Issued	Brief Summary of Changes	Author
Version 2	Aug 26	New agreement to give concurrent intrapleural instillation of tissue plasminogen activator and Dornase Alfa Re-format of original guidelines	Dr A Holbourn
Version 1	Dec 23	Original Copy	Helen Meynell Dr Moe Kyi

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ADULT PROTOCOL FOR INTRAPLEURAL ALTEPLASE AND DORNASE ALFA FOR THE TREATMENT OF EMPYEMA

Introduction

Reported mortality rates from pleural infection are between 10-20%. Standard medical management with drainage through a chest drain and administration of antibiotics fail in approximately one third of patient. Such patients are often referred for thoracic surgery, but many patients are not suitable due to co-morbidities or frailty.

Intrapleural fibrolytics with a combination of alteplase (tissue plasminogen activator (tPa)) and Dornase Alpha (DNase) have been shown in a randomised trial (MIST2) to reduce rate of referral for surgery and duration of hospital stay for patients with pleural infections treated with antibiotics and chest drain insertion.

It is currently unclear how the use of intrapleural fibrinolytic therapy should be used in the context of thoracic surgery, however if a patient fails to improve after 24-48 hours of treatment with chest tube drainage and antimicrobials, intrapleural fibrinolytics can be used at the discretion of a Respiratory Consultant. If used, it should be administered early in the disease course.

The MIST2 protocol involved the administration of intrapleural medications separated by a minimum of two hours, however the concurrent instillation has been demonstrated to be safe and effective (Majid et al. 2016 and Kheir et. Al 2018).

The protocol for administration for intra-pleural fibrinolytics in included in the British Thoracic Society Guidelines for pleural disease (2023) online Appendix 12 Intrapleural treatment guides. This protocol is based on these recommendations and the MIST 2 eligibility criteria.

Protocol

Indications

- Clinical evidence of pleural infection
    - Macroscopically purulent pleural fluid OR pleural fluid positive for bacteria on gram stain or culture OR pleural fluid with a pH <7.2 with clinical evidence of infection or clinical evidence of infection with imaging indicated complex parapneumonic effusion or empyema
- Radiological evidence of persistent infected effusion despite 24hr of attempted drainage with an appropriately sited and patent drain and appropriate therapy AND an inadequate or incomplete clinical response to appropriate antibiotic treatment

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Contraindication:

Absolute contraindications

- If use of intrapleural fibrinolytics would results in a delay to appropriate surgical intervention
- Allergy to alteplase or Dornase alpha
- <18 years of age
- Active pleural bleeding
- Acute stroke
- Current major chest haemorrhage or trauma including intercostal artery injury
- Major surgery in the preceding 5 days
- Previous pneumonectomy on the infected side
- Pregnancy or breastfeeding

Relative Contraindications

- Previous treatment with intrapleural fibrinolytic agents, dornase or both for empyema
- Risk factors for pleural bleeding (for example uncorrected coagulopathy)
- Severe hepatic or renal impairment
- Patients on anticoagulation inc. warfarin, treatment dose LMWH and DOAC

Informed Consent

In all cases, informed consent should be obtained and patients should be informed of the risks and benefits of the procedure as this is an unlicensed treatment. Written consent should be taken prior to the first administration. Specific risks that should be discussed are:

- Intrapleural bleeding: Haemorrhagic fluid is common but frank intrapleural bleeding is rare (4%). Rarely a blood transfusion may be required as a result
- Discomfort/ pain: 5 % patients may experience pain related to administration, it is often mild and may require analgesia
- Fever: mild transient fever can occur after instillation
- Potential allergic reaction
- Infection
- Blockage/ dislodgement of drain
- Failure of procedure

Medication Regime

Drug Name	Dose (via intrapleural)	Frequency	Duration
Alteplase	10mg in 30ml of 0.9% sodium chloride	Twice a day (at least 6 hours apart)	Max of 3 days
Dornase alpha (DNase)	5000units in 30ml 0.9% sodium chloride		

The Respiratory Consultant treating the patient may consider a reduction in dose in the context of significant bleeding risk. The 'half-dose' prescription is Alteplase 5mg and DNase 5000units twice a day for 3 days

If significant response to initial doses of intrapleural fibrinolytics the responsible Respiratory Consultant made reduce the duration of treatment if they are satisfied there has been a complete clearance of the pleural space.

Prescribing the medication

These medications can only be prescribed by a consultant chest physician or on the recommendation of a consultant chest physician.

These medications must be prescribed on Wellsky electronic prescribing system.

The prescription can be found under the 'Protocol section: Alteplase Intrapleural fibrinolysis'

This will default to prescribe:

- Alteplase 10mg injection twice daily for a 3 day course

  AND
- Dornase alfa 2500 units nebules 5000 units twice daily for a 3 day course

Administration

These medications should only be administered by a doctor who has been trained in the administration of intrapleural fibrinolytic medication.

Patients should be managed in areas with registered nurses who are experienced in managing chest drains.

Prior to administration

- Consultant Respiratory Physician approval obtained
- Patient consent obtained and procedure explained
- Ensure IV access
- Confirm chest drain in in the pleural space and patent
- Ensure 3-way tap attached to the chest drain tubing

Equipment

- 10mg alteplase
- 5000units DNase
- 100ml 0.9% sodium chloride
- 2 x 50ml luer lock syringes
- 1 x 20ml luer lock syringe
- Dressing pack
- Sterile gloves
- Cleaning wipes
- 3x Drawing up needles

Procedure

- Prepare and label syringes aseptically:
    - Syringe 1: 10mg alteplase in 30ml 0.9% sodium chloride
    - Syringe 2: 5000 units Dornase Alfa in 30ml 0.9% sodium chloride
- Ensure 3-way tap is off to the side port (ie. Open from pleural space through to underwater seal)
- Remove side-port bung and clean the side port with a chlorhexidine wipe
- Attach 50ml syringe 1 containing Alteplase and 30ml 0.9% sodium chloride to side port. Turn 3-way tap off to the underwater seal (i.e. open from pleural space to side port) and inject alteplase into the pleural space.
- Ensure 3-way tap is off to the side port (ie. Open from pleural space through to underwater seal)
- Attach second 50ml syringe containing Dornase Alfa and 30ml 0.9% sodium chloride to side port. Turn 3-way tap off to the underwater seal (i.e. open from pleural space to side port and inject dornase alfa into the pleural space
- Ensure 3-way tap is off to the side port (ie. Open from pleural space through to underwater seal)
- Attach 20ml syringe containing 20ml 0.9% sodium chloride to side port. Turn 3-way tap off to the underwater seal (i.e. open from pleural space to side port) and inject the saline flush into the pleural space.
- Leave the drain off to the underwater seal for 1 hour
- Following 1 hour the drain can be turned on and free drainage allowed from the pleural space to the underwater seal.

Post-Administration

- The nurse responsible for the patient must be informed following administration that the drain has been turned off and instructed to open the drain in 1hr times
- The medication must be signed as administered on WellSky

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Monitoring and Follow-up

Patients who are being treated with intrapleural fibrinolytics must be reviewed by a Respiratory Consultant or Respiratory Specialty Registrar daily

All patients should be monitored for adverse events, such as allergic reactions or signs of bleeding e.g. intrapleural haemorrhage, haemoptysis, gastrointestinal bleeding. All adverse events should be recorded via the DATIX system and reported via the yellow card system monitored by the MHRA.

Treatment should be discontinued in the event the patient clinically deteriorates.

Alternative Agent

In the event of a national shortage, urokinase can be used as an alternative to Alteplase. The recommended dose is:

- Urokinase 100,000 units + Dornase Alfa 5000 units twice daily for 3 days

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