Royal Cornwall Hospitals
NHS Trust

Loculated Empyema: Administration of Intrapleural Thrombolytics in Adults Clinical Guideline

V2.0

July 2024

1. Aim/Purpose of this Guideline

1.1. Pleural infections are becoming an ever-increasing problem within thoracic medicine, with a high associated morbidity and mortality rate. Prompt clinical evaluation and therapeutic intervention is vital in helping to reduce this, whilst also providing additional reductions in healthcare costs and inpatient stays.

1.2. An estimated half of all patients with pleural infections develop parapneumonic effusions; primary treatment for these infected effusions is drainage, but this can be complicated by the presence of loculation or thickened fluid.

1.3. It is estimated that medical management will fail in 30% of patients, requiring referral for surgical drainage and obliteration of the pleural cavity.

1.4. The aim of intrapleural thrombolytics is to encourage successful drainage by thinning the infected intrapleural fluid and uniting these loculated fluid pockets.

1.5. This intervention is intended for use in patients deemed unfit for thoracic surgery or where transfer delays require interim measures to be taken.

1.6. This version supersedes any previous versions of this document.

1.7. Acronyms:

- COPD - Chronic Obstructive Pulmonary Disease.
- CRP - C-reactive protein.
- CT - computed tomography.
- CXR – Chest x-ray.
- GI – Gastrointestinal.
- Hb – Haemoglobin.
- MIST - Medical Illness Simulating Trauma.
- NaCI - Sodium Chloride.
- PE – Pulmonary Embolism.
- pH - Potential of Hydrogen.
- RCHT – Royal Cornwall Hospital Trust.
- TDS - Take three times a day.
- VATS - Video Assisted Thoracoscopic Surgery.
- WCC – White Cell Count.
- WFI - Water for Injection.

Data Protection Act 2018 (UK General Data Protection Regulation – GDPR) Legislation.

The Trust has a duty under the Data Protection Act 2018 and UK General Data Protection Regulations 2016/679 to ensure that there is a valid legal basis to process personal and sensitive data. The legal basis for processing must be identified and documented before the processing begins. In many cases we may need consent; this must be explicit, informed, and documented. We cannot rely on opt out, it must be opt in.

Data Protection Act 2018 and UK General Data Protection Regulations 2016/679 is applicable to all staff; this includes those working as contractors and providers of services.

For more information about your obligations under the Data Protection Act 2018 and UK General Data Protection Regulations 2016/679 please see the Information Use Framework Policy or contact the Information Governance Team.

Royal Cornwall Hospital Trust rch-tr.infogov@nhs.net

2. The Guidance

2.1. All treatment initiation should be agreed with a respiratory consultant or specialist registrar (on the recommendation of a consultant chest physician).

2.2. In all cases informed consent must be obtained and the patient should be made aware that this treatment is unlicensed. All outcomes of this consultation should be documented both on the electronic system and in the medical notes.

2.3. Specific risks that should be discussed include discomfort and pain (likely to be mild but may require analgesia) and the risk of intrapleural bleeding (this is a rare side effect differing from the haemorrhagic pleural fluid commonly seen in these procedures).

2.4. Nutrition and effective thrombosis prophylaxis should be discussed and prescribed alongside this regimen. Patients with pleural infections may suffer catabolic consequences which may hinder effective recovery. Hypoalbuminemia is also associated with poor outcomes.

2.5. There have been a handful of studies looking into the substitution and utilisation of 5mg Alteplase instead of the recommended 10mg. Although these studies have produced promising results, due to the lack of clinical evidence available, the reduction of the alteplase dose is a decision that must be made by the respiratory consultant or specialist registrar.

Dosing regimens included in this guideline:

Alteplase 10mg + Dornase Alpha 5mg via intrapleural administration, both TWICE DAILY for 3 days

Or

(Where shortages in alteplase impact it's use in this setting)

Urokinase 100,000 units + Dornase Alpha 5mg via intrapleural administration, both TWICE DAILY for 3 days

2.6. **Eligibility**

2.6.1. **Patient Suitability Criteria** (adapted from MIST 2 criteria).

2.6.2. The parameters below should be used following radiological evidence of persistent infective effusions despite 24 hours of attempted drainage. Confirmation of appropriate antibiotic therapy, site of drain and patency of drain itself should also be sought.

2.6.3. Perform an USS thorax – identify a loculated empyema with chest drain in situ within pleural cavity.

Eligible Patients:

- Evidence of infection; including raised CRP, presence of fever or an elevated WCC.
- Pleural effusion on CXR/CT.
- Patient is not fit for thoracic surgery or transfer delays require interim measures to be taken.

Pleural fluid is either:

- Macroscopically purulent.
- Positive for bacterial infection on culture / Gram stain.
- pH<7.2.

Exclusion Criteria:

- Recent treatment with intrapleural fibrinolytic agents or dornase alpha for empyema.
- Use of this regimen would result in a delay to appropriate thoracic surgical intervention.
- Known sensitivity to either alteplase, urokinase or dornase alpha.
- Current coincidental stroke, current major haemorrhage/ trauma, or a major surgery within the previous 5 days.
- Previous pneumonectomy on the infected side.
- Pregnancy or lactation.
- Patient is a surgical candidate for a VATs procedure (discuss with Derriford cardiothoracics if unsure).

Potential Risks of Treatment	Potential Benefits of Treatment
Haemorrhage.	Drainage of collection/resolution of empyema.
Infection.	Lower risk than surgery for frail patients.
Allergic reaction.	Reduced average hospital stay.
Failure of procedure to work.	

2.7. **Regimen**

Equipment List: (For each administration).

- Sterile dressing pack and gloves.
- Chlorhexidine wipes.
- 50ml syringes x 2.
- 30ml syringe x 1 (Initial NaCl 0.9% flush).
- Needles to draw up medication.
- NaCl 0.9% flushes (10ml).
- Dornase alpha 5mg (fridge item) – dilute with 30ml of water for injection (WFI).
- Alteplase 10mg (reconstituted with WFI) – dilute with 30ml of NaCl 0.9%.

OR

- Urokinase 100,000 units (reconstituted with NaCl 0.9%)– dilute with 30ml of NaCl 0.9%.

Please note the alteplase supply is **restricted at RCHT**, so contact your pharmacist to obtain stock. **Do NOT use the 50mg vials** of alteplase as these are reserved specifically for massive PE and stroke patients.

The regimen below uses alteplase; this should be substituted for urokinase if stock cannot be obtained due to shortages:

10am	11am	4pm (allows 6 hours in between doses)	5pm
• Flush drain with 30mls saline. • Alteplase 10mg in 30mls saline. • Flush with 10ml saline. • Dornase alpha 5mg in 30mls WFI.	• Unclamp drain (open drainage) for 1 hour.	• Flush drain with 30mls saline. • Alteplase 10mg in 30mls saline. • Flush with 10ml saline. • Dornase alpha 5mg in 30mls WFI.	• Unclamp drain (open drainage) for 1 hour.

10am	11am	4pm (allows 6 hours in between doses)	5pm
• Flush with 10ml saline. • Clamp for 1 hour.		• Flush with 10ml saline. • Clamp for 1 hour.	

No.	Procedure:
1.	Ensure all equipment has been gathered and medications are prescribed correctly on WellSky (ensuring administration is set as intrapleural).
2.	Check positioning and patency of the intercostal drain (complete with 3-way tap) has been confirmed with imaging and by flushing the drain with 30ml of NaCl 0.9% (with no leakages around the tube).
3.	Use a sterile dressing pack and disinfectant wipe to clean and protect the drain tap.
4.	Attach the syringe containing the alteplase to the side port and then ensure the 3-way tap has been turned off to the underwater seal. Inject the contents of the syringe into the pleural space and then flush the line with 10ml of NaCl 0.9%. Once completed turn the 3-way tap off to the patient whilst you prepare your second syringe.
5.	Attach your second syringe containing the dornase alpha and then administer using the same process as above, including flush. Turn the 3-way tap off to the patient.
6.	Leave the drain clamped for 1 hour.
7.	Unclamp the drain and leave on free drainage for 1 hour. (There may be large volumes of blood-stained fluid from the drain once treatment has commenced, which is to be expected. Treatment should only be stopped if frank blood is seen). Once this is complete re-clamp the drain and repeat the above steps at the next administration (leaving at least 6 hours between doses).
8.	Total of 6 administrations over 3 days.

Please note our Trust has a strict no vial sharing policy; so, to administer the 10mg twice daily alteplase, please contact pharmacy to source the most appropriate vial size and reduce wastage.

2.8. **Nurse Administration**

All doses must be drawn up, administered, and charted by either a doctor or nurse who has documented experience administering this therapy.

All nursing staff will be required to complete the sign off below as proof of experience/ competency administering this regimen. Sign-off to be completed by a Doctor or Nurse who has already completed this training.

Stage of sign off:	Date:	Signature of Witness:
Witness / aid in administration.		
Solo administration with supervision.		

2.9. **Antimicrobial Cover**

Patients should continue antibiotic cover for at least 4 weeks after treatment (usually 6 weeks total including intravenous antibiotics in hospital). **All regimens should still cover for anaerobes.**
Empirical intravenous options (whilst awaiting microbiology input):

- Piperacillin-tazobactam 4.5g TDS.
- Meropenem in patients who cannot tolerate penicillin (excluding anaphylaxis). See Micro guide for renal dosing recommendations.
- Teicoplanin IV plus ciprofloxacin IV 400mg every 12 hours in penicillin anaphylaxis.

Oral switch:

- 4/52 co-amoxiclav 500/125mg TDS or,
- 4/52 1000mg amoxicillin + metronidazole 400mg TDS.
- Unless otherwise specified by Microbiology.

In the case of **penicillin allergy,** the following are good oral alternatives. Dosing of which should be prescribed as per the Microguide or microbiology:

- Cefalexin (with exception of penicillin anaphylaxis) and metronidazole.
- Clindamycin.

Important factors to consider when deciding on antimicrobial agents:

- If the patient is diabetic, has COPD or has experienced a long stay in hospital it is recommended that co-amoxiclav is used rather than amoxicillin and metronidazole, as there is an increased chance of Gram-negative bacteria and S. aureus.
- If the patient has confirmed bronchiectasis, you may elect to cover Pseudomonas if they had been chronically colonised.
- Someone otherwise healthy presenting from the community almost certainly has pneumococcus, so unless they had just returned from foreign travel amoxicillin and metronidazole will be sufficient.

- The patient doesn't necessarily need to have definite radiological resolution, as the fluid may be sterilised before being reabsorbed. However, it is key that the consulting physician is satisfied that there has been a sustained clinical response and should monitor for relapse.

2.10. **Monitoring**

Ongoing monitoring for the patient should include:

- Pleural fluid samples should be sent for pH and cytology.
- Cultures and Biochemistry.
- Monitor drainage volume and nature.
- Repeat CXR after treatment.
- Continued monitoring of CRP, WCC, Hb and signs of bleeding (intrapleural haemorrhage, haemoptysis, GI bleeding).

3. Monitoring compliance and effectiveness

Information Category	Detail of process and methodology for monitoring compliance
Element to be monitored	All patients should be monitored for adverse events, these all need to be reported via the Datix system and reported to the MHRA. Treatment should cease if the patient clinically deteriorates.
Lead	Lead Respiratory Consultant.
Tool	Audit, individual review, peer review.
Frequency	Annually or earlier if indicated.
Reporting arrangements	Audit Lead. Respiratory Consultants, Department Audit and Guidelines meeting.
Acting on recommendations and Lead(s)	Respiratory Consultants, Department Audit and Guidelines meeting.
Change in practice and lessons to be shared	Required changes to practice will be identified and actioned within 3-6 months. A lead member of the team will be identified to take each change forward where appropriate. Lessons will be shared with all the relevant stakeholders.

4. Equality and Diversity

4.1. This document complies with the Royal Cornwall Hospitals NHS Trust service Equality and Diversity statement which can be found in the Equality Diversity And Inclusion Policy or the Equality and Diversity website.

4.2. Equality Impact Assessment

The Initial Equality Impact Assessment Screening Form is at Appendix 2.

Appendix 1. Governance Information

Information Category	Detailed Information
Document Title:	Loculated Empyema: Administration of Intrapleural Thrombolytics in Adults Clinical Guideline V2.0
This document replaces (exact title of previous version):	Administration of Intrapleural Alteplase and Dornase Alfa for the Treatment of Loculated Empyema Clinical Guideline V1.0.
Date Issued/Approved:	May 2024
Date Valid From:	June 2024
Date Valid To:	June 2027
Directorate / Department responsible (author/owner):	Danielle Best, Respiratory, HIV and Cystic Fibrosis Pharmacist.
Contact details:	01872 252588
Brief summary of contents:	Guidance on the administration of both Alteplase and Dornase alfa in the treatment of empyema. The aim of intrapleural Alteplase and Dornase alfa treatment is to thin this fluid and unite these separate fluid pockets, to help encourage successful drainage. Prompt therapeutic intervention with a treatment such as this has been shown to reduce morbidity and mortality as well as hospital stays and healthcare costs.
Suggested Keywords:	Dornase alfa, Alteplase, Empyema, Drainage.
Target Audience:	**RCHT:** Yes **CFT:** No **CIOS ICB:** No
Executive Director responsible for Policy:	Chief Medical Officer
Approval route for consultation and ratification:	Medicines Practice Committee. Respiratory Governance.
Manager confirming approval processes:	Racheal Pearce
Name of Governance Lead confirming consultation and ratification:	Siobhan Hunter
Links to key external standards:	None required

Information Category	Detailed Information
Related Documents:	**References** BTS guidance on pleural disease 2010: (https://www.brit-thoracic.org.uk/document-library/clinical-information/pleural-disease/pleural-disease-guidelines-2010/pleural-disease-guideline/. MIST2 trial 2011: (https://www.nejm.org/doi/full/10.1056/NEJMoa1012740) Pleural infection-current diagnosis and management 2012; Rosenstengel A: (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3378219/ Luton and Dunstable University Hospital; Adult protocol for intrapleural (IP) Alteplase and Dornase Alfa for the treatment of empyema. Dec 2017.
Training Need Identified?	No
Publication Location (refer to Policy on Policies – Approvals and Ratification):	Internet and Intranet
Document Library Folder/Sub Folder:	Clinical/Respiratory.

Version Control Table

Date	Version Number	Summary of Changes	Changes Made by
20/04/2020	V1.0	Initial issue	Danielle Best, Respiratory, HIV and Cystic Fibrosis Pharmacist. Dr Douglas Meehan, Respiratory Medicine.
May 2024	V2.0	Full update and transposed to new trust template.	Danielle Best, Respiratory, HIV and Cystic Fibrosis Pharmacist.

All or part of this document can be released under the Freedom of Information Act 2000.

All Policies, Strategies and Operating Procedures, including Business Plans, are to be kept for the lifetime of the organisation plus 6 years.

This document is only valid on the day of printing.

Controlled Document.

This document has been created following the Royal Cornwall Hospitals NHS Trust The Policy on Policies (Development and Management of Knowledge Procedural and Web Documents Policy). It should not be altered in any way without the express permission of the author or their Line Manager.

Appendix 2. Equality Impact Assessment

Section 1: Equality Impact Assessment (EIA) Form

The EIA process allows the Trust to identify where a policy or service may have a negative impact on an individual or particular group of people.

For guidance please refer to the Equality Impact Assessment Policy (available from the document library) or contact the Equality, Diversity, and Inclusion Team rcht.inclusion@nhs.net

Information Category	Detailed Information
Name of the strategy / policy / proposal / service function to be assessed:	Loculated Empyema: Administration of Intrapleural Thrombolytics in Adults Clinical Guideline V2.0
Directorate and service area:	Respiratory.
Is this a new or existing Policy?	Existing.
Name of individual completing EIA (Should be completed by an individual with a good understanding of the Service/Policy):	Danielle Best, Respiratory, HIV and Cystic Fibrosis Pharmacist.
Contact details:	01872 252588

Information Category	Detailed Information
1. Policy Aim - Who is the Policy aimed at? (The Policy is the Strategy, Policy, Proposal or Service Change to be assessed)	Clear guidance on the administration of intrapleural Alteplase and Dornase alfa for the treatment of empyema in adults.
2. Policy Objectives	Clear guidance on the administration of intrapleural Alteplase and Dornase alfa for the treatment of empyema in adults.
3. Policy Intended Outcomes	Evidenced based standardised practice.
4. How will you measure each outcome?	Audit and review.
5. Who is intended to benefit from the policy?	Patients and staff members.

Information Category	Detailed Information
6a. Who did you consult with? (Please select Yes or No for each category)	• Workforce: Yes • Patients/ visitors: No • Local groups/ system partners: No • External organisations: No • Other: No
6b. Please list the individuals/groups who have been consulted about this policy.	**Please record specific names of individuals/ groups:** Medicines Practice Committee
6c. What was the outcome of the consultation?	Guideline approved
6d. Have you used any of the following to assist your assessment?	**National or local statistics, audits, activity reports, process maps, complaints, staff, or patient surveys:** No.

7. The Impact

Following consultation with key groups, has a negative impact been identified for any protected characteristic? Please note that a rationale is required for each one.

Where a negative impact is identified without rationale, the key groups will need to be consulted again.

Protected Characteristic	(Yes or No)	Rationale
Age	No	
Sex (male or female)	No	
Gender reassignment (Transgender, non-binary, gender fluid etc.)	No	
Race	No	
Disability (e.g. physical or cognitive impairment, mental health, long term conditions etc.)	No	
Religion or belief	No	
Marriage and civil partnership	No	

Protected Characteristic	(Yes or No)	Rationale
Pregnancy and maternity	No	
Sexual orientation (e.g. gay, straight, bisexual, lesbian etc.)	No	

A robust rationale must be in place for all protected characteristics. If a negative impact has been identified, please complete section 2. If no negative impact has been identified and if this is not a major service change, you can end the assessment here.

I am confident that section 2 of this EIA does not need completing as there are no highlighted risks of negative impact occurring because of this policy.

Name of person confirming result of initial impact assessment: Danielle Best, Respiratory, HIV and Cystic Fibrosis Pharmacist.

If a negative impact has been identified above OR this is a major service change, you will need to complete section 2 of the EIA form available here:
Section 2. Full Equality Analysis