1. **Introduction**

1.1 Pneumonia accounts for 1.3 million hospitalisations annually and of those 36% to 66% have pleural effusions. Mortality increases from 7% to 33% as effusions evolve to become infective (1).

1.2 The role of fibrinolytics in management of pleural infection

   a) Drainage of infected fluid is key to successful treatment. However, infected pleural fluid can be difficult to drain due to the presence of fibrous septations and the high fluid viscosity. The standard treatment with antibiotics and tube drainage of infected pleural fluid fail in approximately one third of patients, who then require surgical drainage [2,3]. Surgery has recognised morbidity and is often restricted to those with low peri-operative risk.

   b) Observational data suggest that intrapleural administration of fibrinolytic drugs reduces the frequency of failed drainage and requirement for surgery by cleaving intrapleural fibrinous septations and improving chest-tube drainage [3,4] but a large Multicentre Intrapleural Sepsis Trial (MIST1) and subsequent meta-analysis showed no benefit of intrapleural streptokinase [5,6]. The presence of extracellular DNA and other bacterial components in the infected pleural space increases viscosity and permit biofilm formation [7]. Simpson et al. proved the principle that addition of Dornase alpha (DNase) allowed significantly faster passage of infected pleural fluid and hence a potential treatment for pleural infection [8].

   c) The MIST-2, published in 2011, is a randomized, double-blind, placebo-controlled trial involving 196 adult patients (mean age 59 years, 72% men) with pleural infection. This trial shows that combination intrapleural tissue plasminogen activator (t-PA, Alteplase®) and Dornase alpha DNase therapy improves the drainage of pleural fluid in patients with pleural infection and that such treatment is associated with reductions in the hospital stay and the need for thoracic surgery that are likely to be clinically significant [8]. Another multicentre open-label series evaluated the “real life” application of t-PA/DNase treatment in 107 patients with (mostly community-acquired) pleural infection. In 84% of patients, t-PA/DNase was initiated as a “rescue therapy” >24 hours after chest drain insertion when the patient failed to improve. In addition, three quarters of the patients had ≥1 comorbidity and up to 15% had major life-limiting diseases (e.g., cancer or end stage renal failure) - patients who are often poor candidates for surgery. In this cohort of patients 92.3% were successfully managed with t-PA/DNase. No patients died from pleural infection. The median hospital stay from first intrapleural treatment dose was 10 (IQR, 6-17) days [10]. This combined treatment may therefore be useful in patients in whom standard medical management has failed and thoracic surgery is not a treatment option [11].

1.3 This guideline is for use by all respiratory physicians and thoracic surgeons involved in looking after adult patients who are admitted with or develop pleural infection during their hospital stay.
1.4 This guideline is not designed to be used in paediatric population (<18 years of age)

2. Guideline Standards and Procedures

2.1 Inclusion criteria for intrapleural fibrinolytics:
   a) A clinical presentation compatible with pleural infection
   b) Has pleural fluid requiring drainage which is either:
      - Purulent or
      - Gram stain positive or
      - Culture positive or
      - Acidic with a pH <7.2
   c) Treatment failure with antibiotics and tube drainage of pleural fluid after 24 hours
   d) Patient is not fit for surgery or patient can’t wait for surgery – this will be at discretion of respiratory physicians and thoracic surgeons
   e) Written informed consent must be obtained from patient

2.2 Exclusion criteria:
   The following patients will be excluded from this treatment:
   a) Age of less than 18 years
   b) Known sensitivity to DNase or t-PA
   c) Coincidental stroke
   d) Major haemorrhage or major trauma
   e) Significant bleeding diathesis
   f) Major surgery in the previous 5 days
   g) Previous pneumonectomy on the infected side
   h) Bronchopleural fistula
   i) Pregnancy or lactation
2.3 Administration Protocol:

a) Intrapleural Alteplase and Dornase Alpha (DNase) will be administered by ST3+ grade doctors under the supervision of the Consultant.

b) The prescribing doctor will prescribe using the pre-printed prescription label provided by the ward pharmacist, which will be applied to the patient’s drug chart. Each dose administered must be signed for by the doctor and second signature by nurse overseeing administration.

c) Nursing staff will order medicines from the department of pharmacy (within pharmacy working hours).

d) Insert chest drain (the minimum size of the chest drain is 12F; there is no maximum limit) in accordance with the UHL Pleural procedures/Chest drain policy[13].

e) Flush chest drain with 20 ml sodium chloride 0.9% and confirm its patency.

f) Prepare Alteplase 10mg in 30 ml sodium chloride 0.9% and administer it into the chest tube followed by a flush with 20 ml sodium chloride 0.9%.

g) Close the chest tube using a three way tap or clamp for one hour and then open it.

h) Prepare DNase 5mg in 30 ml sterile water. Administer it into the chest drain two hours after the dose of Alteplase. Flush the drain with 20ml sodium chloride 0.9%.

i) Close the chest tube using a three way tap or clamp for one hour.

j) Release the three-way tap/clamp and allow draining.

k) Repeat every 12 hours for a total of 3 days (Total course: 6 doses)

2.4 Adverse effects:

From the published data on clinical use of t-PA/DNase, the treatment appears safe. Major adverse events in MIST-2 were not significantly different between the t-PA/DNase and placebo groups. The following possible side effects are well documented:

a) Chest pain - typically a dose of t-PA stimulates the accumulation of >500 mL of pleural fluid. This sudden expansion of fluid within 60 minutes and the lysis of adhesions may generate pain. This will require initiation or escalation of analgesia. In the trial conducted by Picollo F et al in ~4% of patients the pain was severe enough to terminate treatment [10]

b) Intrapleural bleeding - production of a large volume of haemorrhagic pleural fluid is a common observation after intrapleural administration of fibrinolytics. Significant pleural bleeding, defined as a reduction of haematocrit necessitating blood transfusion, is rare. In MIST-2 there were two intrapleural haemorrhages and one episode of haemoptysis in the t-PA/DNase treated group (n=48). Cessation of
therapy and supportive measures (e.g., transfusion) are adequate in managing most cases of fibrinolytic-induced pleural bleeding [11].

2.5 Monitoring

Assess the response to Alteplase/DNase by:

a) Daily imaging (CXR/ultrasound) to assess successful drainage of fluid
b) Daily monitoring of volume and appearance of pleural fluid drained
c) Daily monitoring of inflammatory markers (e.g., fever, white cell count, CRP)
d) Daily monitoring of serum haematocrit and Hb levels to detect significant blood loss through induced pleural haemorrhage.

3. Education and Training

There are no additional educational requirements for this guideline

4. Monitoring Compliance

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5. Supporting References


12. University Hospitals of Leicestershire. Pharmacy Central Purchasing Price (VAT inclusive) from Boehringer Ingelheim Ltd (Alteplase) and Roche Products Ltd (DNase) 1st June 2017

13. UHL Pleural Procedures Policy, Trust Reference B9/2012

6. Key Words

Pleural infection, empyema, intrapleural, fibrinolytics, chest drain, dornase alpha, DNase, alteplase