Comparative Analysis *of Intrapleural **Al**teplase-**T**yloxap**o**l vs Intrapleural Alteplase-D**N**ase in **P**leural **I**nfection (ALTON-PI)*

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CHAPTER 1: INTRODUCTION

Pneumonia, thought to be the chief aetiological process in the development of pleural space infection, is defined as an infection of the lung parenchyma with an estimated annual incidence rate of 5–11 cases per 1000 population, with around 50,000 hospital admissions in the U.K. per year (1). Parapneumonic effusions caused by an infection of the pleural membranes occur in 40–57% of cases of pneumonia. A variable percentage (10–20%) of parapneumonic effusions progresses to empyema (pus) and/or abscess formation (encapsulation). Pleural infection is associated with significant morbidity and mortality, which may be as high as 20–35% in immunocompromised patients. (1)

Standard treatment of these collections in adults involves antibiotic therapy, adequate drainage of infected fluid, and surgical intervention if conservative management fails. Appropriate treatment is adequate drainage via an intercostal catheter (ICC) with antibiotic therapy for parapneumonic effusions requiring clearance. Frequently, simple ICC drainage is ineffective due to the presence of loculations, formed predominantly by fibrinous material deposited in the fibrinopurulent phase of empyema, preventing free drainage of infected pleural fluid (2). The presence of fibrinous septae in the pleural space, known as loculations, may result in inadequate drainage of effusions and, therefore, nonresolution of infection and systemic sepsis. Surgical intervention (VATS or open) is usually required to clear loculations and resolve infection without adequate intercostal catheter drainage.

Nonsurgical treatment options to reduce the impact of adhesions and loculi include (in addition to appropriate antibiotic therapy) single and multiple thoracocentesis, or single and multiple intercostal tube thoracostomies, with or without intrapleural fibrinolytic agents. Surgical options include direct vision and VATS adhesiolysis, limited and full thoracotomy with adhesiolysis, and decortication for severe pleural thickening (3).

Although the success rate of surgical intervention remains high, the morbidity and mortality of both VATS and open thoracotomy are of concern, particularly in a cohort of patients who may be older and with significant comorbidity. Less invasive therapies, which promote pleural space drainage and effective resolution of pleural infection, are therefore likely to be of considerable clinical utility.

Intrapleural fibrinolytic therapy (IPFT) in the management of complex parapneumonic effusions and thoracic empyema has been employed for over 50 years, with a mixture of agents including streptokinase/streptodornase, urokinase, alteplase, and a combination of streptodornase and alteplase (4-12). These medications are administered into the pleural space via an ICC.

Fibrinolytic agents, including streptokinase, urokinase, alteplase, and recombinant tissue plasminogen activator (rTPA), have been used safely and effectively intrapleurally for complicated pleural effusion and empyema (12-14). During the fibrinopurulent-purulent stage of empyema, there is an imbalance between fibrin activators and fibrin inhibitors, with elevated levels of plasminogen activator inhibitor (PAI-1) resulting from the presence of inflammation-induced tumour necrosis factor alpha, interleukin-8, and transforming growth factor beta, as well as lower levels of endogenous tissue plasminogen activator (tPA). This results in a profibrotic state, causing deposition of fibrin-forming loculations within the infected pleural space. Fibrinolytic agents activate plasmin, lysing fibrinous septations, thereby improving pleural fluid drainage and clearing infection without surgical intervention. (15, 16)

The MIST 2 trial has established intrapleural therapy as the mainstay of CPEE treatment, hence avoiding surgery and decreasing the length of hospitalization; however, little is known about the correct dosage needed for tPA and Dornase Alfa/Deoxyribonuclease (DNase) (8). Dose and duration of intrapleural therapy based on MIST 2 involve multiple dosing and can be time-consuming for health care providers(8, 17). Nevertheless, treatment of pleural infection with fibrinolytic therapy has been incorporated in the British Thoracic Society guideline 2023. (18)

Another study in 2022 by Cheong et al. used a modified regimen of intrapleural alteplase 16 mg t-PA with 5 mg DNase for three doses administered sequentially within 24 h. In this study, a modified regimen of t-PA and DNase offers an alternative therapeutic option for patients who are unfit or refuse surgical intervention but have persistent pleural infection (19). They have demonstrated similar treatment success comparable to other studies, as evidenced by improved pleural fluid drainage and reduced pleural opacity on day 7 chest x-ray, approximately 50% from the baseline (8, 20, 21). The mechanism of action of t-PA and DNase in the pleural cavity remains unclear. Studies suggested that IPFT may trigger the monocyte chemoattractant protein 1 (MCP-1) pathway, which promotes pleural fluid formation and subsequently causes a therapeutic lavage effect that increases pleural fluid drainage(22).

The respiratory unit in Hospital Canselor Tuanku Muhriz (HCTM) Universiti Kebangsaan Malaysia (UKM) has used intrapleural fibrinolysis therapy with varying doses since 2017. Tyloxapol was also explored in managing pleural infection, as DNase is not readily available in certain centres.

Tyloxapol (Tacholiquin) is a synthetic mucolytic surfactant traditionally used to aid the clearance of bronchopulmonary secretions. (23) Unlike DNase, its intrapleural use for pleural infection is not established; to date, Provan et al. provide the only published report, describing intrapleural tyloxapol—used with chloramphenicol—for empyema. (24) Limited case-series experience with adjunctive saline irrigation appears promising but remains preliminary. (25)

In 2024, Mohamad Jailaini et al first reported cases on the combination of intrapleural saline irrigation and intrapleural tyloxapol as an alternative treatment for pleural infection, apart from parenteral antibiotics as the pillar of the treatment. These two cases were then referred to decortication. A good treatment outcome was shown in both cases upon follow-up, evidenced by clinical cure, biochemical recovery, and radiological improvement. (25)

This study retrospectively compares outcomes between tPA(alteplase)+DNase and tPA+Tyloxapol across two centres. Given the scarce evidence in the literature, this study was conducted to support further the evidence on the safety and efficacy of IP tacholiquin as an alternative treatment for pleural infection.

CHAPTER 2: PROBLEM STATEMENT

Pleural infection carries substantial morbidity, and standard chest-tube drainage often fails due to septations and viscous pus. While intrapleural alteplase+DNase improves drainage, its cost, bleeding concerns, and availability limit universal adoption; alteplase combined with the surfactant-mucolytic tyloxapol (Tacholiquin) is increasingly used but supported only by small case series. Robust, real-world head-to-head data comparing alteplase(t-PA)+DNase versus alteplase (t-PA)+tyloxapol are

lacking, prompting this two-centre retrospective study to evaluate their comparative effectiveness and safety.

CHAPTER 3: RESEARCH OBJECTIVES & HYPOTHESIS

3.1 Research Questions:

- Is there a difference in efficacy and safety between a combination of intrapleural alteplase (5 mg + tacholiquin, with intrapleural alteplase 5mg and DNase (Pulmozyme) 5mg in managing pleural infection?

3.2 Primary Objective:

- To compare the reduction of pleural opacity (in percentage) on chest radiograph from baseline (0-24 hours pre-intervention) to day 7 post-intervention between group A (alteplase + DNase) and group B (alteplase + tacholiquin)

3.3 Secondary Objectives:

- To compare the absolute and percentage change in inflammatory markers (WBC/CRP) from baseline (0-24 hours pre-intervention) to day 7 between the two groups
- To compare the volume of pleural effusion drainage (in mL) 72 hours following post-intervention between the two groups
- To compare the outcome between the two groups:
  - Length of hospital stay (in days) after the intervention for each group
  - The need for surgical intervention within 30 days
  - Adverse effects following alteplase/DNase and talteplase +Tacholiquin
  - Mortality rate at 30 days

3.4 Study Hypothesis

- The mean reduction in pleural opacity (%) from baseline (0–24 h pre-intervention) to day 7 is the same in both groups.
- The mean change in WBC/CRP from baseline to day 7 is the same in both groups.
- The mean pleural effusion drainage volume in both groups over the first 72 hours post-intervention is the same.
- The mean length of hospital stay (days) post-intervention is the same in both groups.
- The proportion requiring surgical intervention within 30 days is the same in both groups.
- The proportion experiencing adverse effects is the same in both groups.
- The 30-day mortality proportion is the same in both groups.

CHAPTER 4: METHODOLOGY

4.1 Study Design

Retrospective, observational cohort; on patients with pleural infection exposure defined by intrapleural regimen received (Alteplase+DNase vs Alteplase+Tyloxapol) DNase from June 2023 to June 2025 in HCTM UKM and University Malaya Medical Centre.

4.2 Study Population

Adult patients with pleural infection (complex pleural effusion or empyema) with poor outflow (≤ 150 cc) from chest drain after 24 Hours of insertion in medical and non-medical wards, HCTM UKM, and UMMC from June 2023 to June 2025.

4.3 Sample Size and Power of Study

Following the guidance of the UH Bristol and Weston Clinical Audit Team (Version 5), a pragmatic snapshot sample of 40 cases for each arm was deemed sufficient to measure current practice against the pre-defined standard, prioritizing feasibility over formal statistical representativeness.

Sampling Method
All cases (universal sampling) that fulfill the inclusion criteria will be included from 2023 to 2025.

4.4 Inclusion and Exclusion Criteria

Inclusion Criteria

1. Adult patient aged ≥ 18 years old
2. Patients with pleural infection (complex parapneumonic effusion or empyema) with poor pleural fluid drainage of ≤ 150 ml after 24 hours of chest drain insertion received either t-PA-DNAse or t-PA/Tyloxapol.
3. Clinical features consistent with pleural infection; fulfilling ≥ 2 of the following characteristics:
    i) Clinical evidence of infection, such as fever and or elevated C-reactive protein (CRP) or total white blood count (TWBC)
    ii) Complex pleural effusion proven by thoracic ultrasound is defined as the presence of fibrin strands or septations within the pleural cavity
    iii) Pleural fluid that fulfils at least one of the characteristics:

- Frank Pus,
- Exudative type of pleural effusion (according to light's criteria)
- Gram stain or culture positive
- Lactate dehydrogenase (LDH) > 900U/L
- Acidic with pH < 7.2
- Glucose level < 3.3 mmol/L

Exclusion criteria

1. Incomplete data.
2. Medical records that cannot be retrieved.

4.5 Recruitment/Data Collection

Data sources: Electronic medical records, chest drain charts, medication/pharmacy logs, radiology PACS (for Day 0 and Day 7 CXR), ultrasound notes.

• Outcome assessment: Radiographic % opacity measured by two blinded readers using a standardized digital polygon/planimetry method; discrepancies resolved by consensus; drainage volume calculated net of any volume infused

Medication Regimen:

t-PA (Alteplase) 5mg and DNase (Pulmozyme) 5mg

t-PA (Alteplase), which is available in our pharmacy, is 50mg per ampoule, and DNase (Pulmozyme) is 2.5mg per ampoule

The number of intrapleural t-PA/DNase installations depends on the treating physician's discretion (at least 6 hours apart between doses). 5mg of alteplase (t-PA) and 5mg DNase are diluted in each 50ml of 0.9% sodium chloride solution. T-PA and DNase are not mixed in one syringe. The detailed method of t-PA/DNase therapy administration is described in Appendix 1. In brief, both medications are administered sequentially, with t-PA first instilled intrapleurally, and the chest tube is then clamped for 45 minutes, then unclamped to allow free drainage for 45 minutes. The same procedure is then repeated for DNase. Selection of the timing of treatment and removal of the chest tube depends on the chest physician's judgment.

Patients who received t-PA/Tyloxapol (Tacholiquin) will be given 5-10 mg alteplase + 200 mg Tyloxapol—the detailed method as described in Appendix 2.

Both groups received standard care of treatment, which includes regular flushing of the chest drain to maintain patency using 20 mL of normal saline.

The primary outcome was to evaluate the percentage reduction in ipsilateral pleural opacity on chest radiograph at Day 7 compared with baseline (preintervention), quantified as % hemithorax occupied by effusion. The area of pleural opacity and the location of the ipsilateral hemithorax will be measured digitally by two radiologists using Horos Project Software, v3.2.1, as described previously in Multicentre Intrapleural Sepsis Trial 2 (MIST-2).

The secondary outcomes are measuring net pleural fluid drainage within 72 hours post first intrapleural dose (mL), change in inflammatory markers (CRP, WBC) from baseline to Day 7, length of stay (days) from first intrapleural dose to discharge, and the need for surgical intervention (VATS/open decortication) within 30 days. Adverse events: pleural/systemic bleeding, Hb drop ≥10%, chest pain requiring escalation, hemoptysis, hemodynamic instability, and 30 day all cause mortality and readmission for pleural infection.

Monitoring Parameters:

a. TPA-Tacholiquin Group

Parameter	**Day0**	**Day1**	**Day2**	**Day3**	**Day7**	**Day30**
Investigations						
• Full blood count (FBC) o WBC o Hemoglobin	√				√	
• C C-reactive protein (CRP)	√				√	
• Chest X-ray	√				√	
• Ultrasound Thorax	√	√	√	√		
Adverse effects						
• Chest pain requires escalation of analgesics.		√	√	√		
• Gastrointestinal bleed		√	√	√		
• Bleeding from the chest drain site		√	√	√		
• Intrapleural hemorrhage		√	√	√		
• Hemoptysis		√	√	√		
• Clinical deterioration – hypotension, dyspnea		√	√	√		
• Hb drop >10% requires transfusion of blood.		√	√	√		
• Death related to intrapleural saline irrigation.		√	√	√		
Others Outcome						
• Mortality						
• Surgical intervention						

Net volume of pleural fluid drained (ml) post pleural irrigation	**Baseline**	**Day 1**	**Day 2**	**Day 3**
	√	√	√	√
Cumulative pleural fluid drained post-pleural irrigation.				√

b. Intrapleural fibrinolytic group

Parameter	Day0	Day1	Day2	Day3	Day7	Day30
Investigations						
• Full blood count (FBC) o WBC o Hemoglobin	√	√	√	√	√	
• C C-reactive protein (CRP)	√				√	
• Chest X-ray	√				√	
• Ultrasound Thorax	√	√	√	√		
Adverse effects						
• Chest pain requires escalation of analgesics.		√	√	√		
• Gastrointestinal bleed		√	√	√		
• Bleeding from the chest drain site		√	√	√		
• Intrapleural hemorrhage		√	√	√		
• Hemoptysis		√	√	√		
• Clinical deterioration – hypotension, dyspnea		√	√	√		
• Hb drop >10% requires transfusion of blood.		√	√	√		
• Death related to intrapleural therapy.		√	√	√		
Others Outcome						
• Mortality						
• Surgical intervention						

Net volume of pleural fluid drained (ml) post IPFT	Baseline	Day 1	Day 2	Day 3
	√	√	√	√
Cumulative pleural fluid drained post IPFT				√

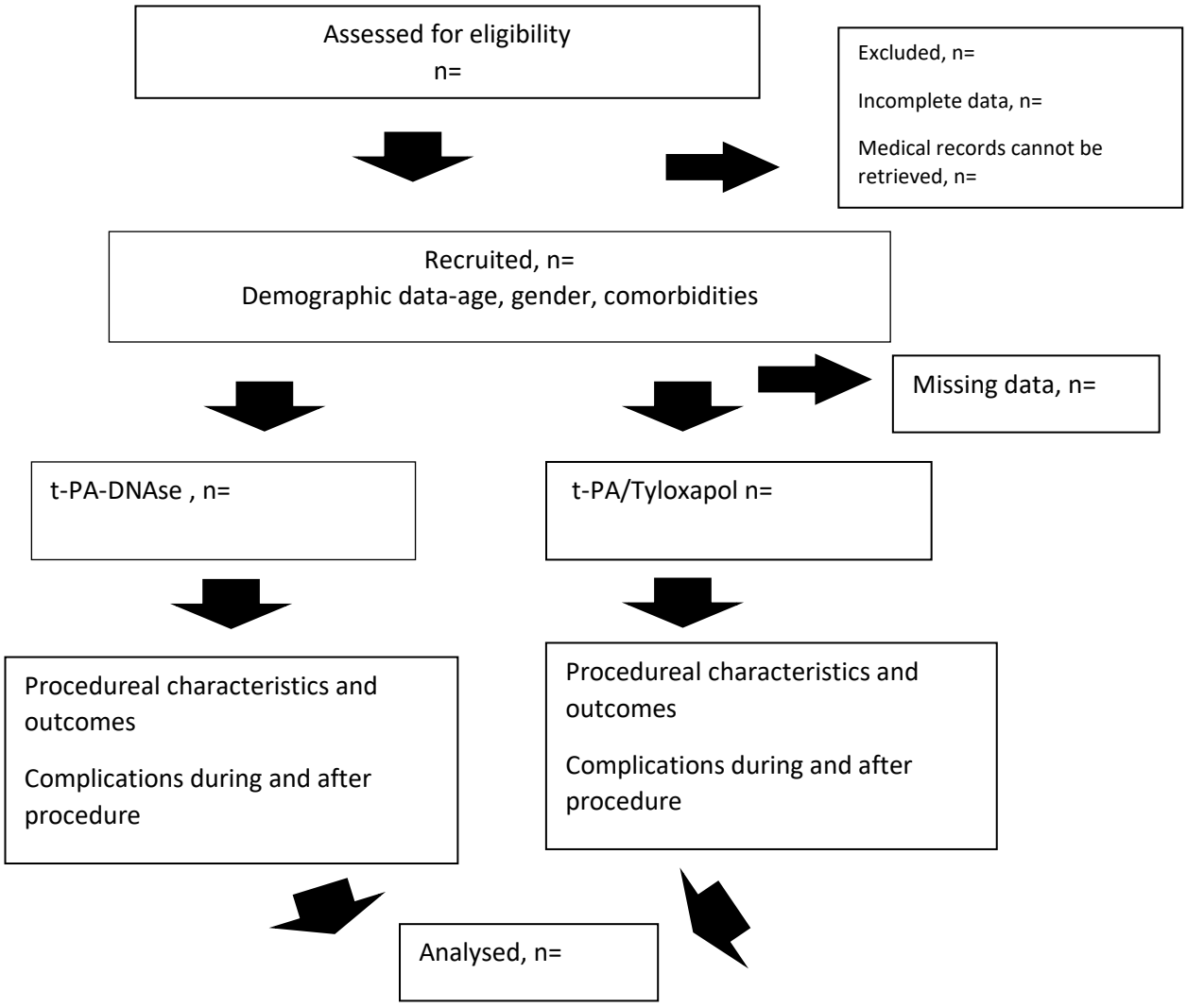
Operational Definition:

- Treatment success will be assessed at two predefined time points: day 7 and day 30. At day 7, success is defined as adequate pleural drainage post-intervention with resolution of septations on thoracic ultrasound, a reduction in chest radiograph opacity by more than 50%, and resolution of inflammatory markers. On day 30, success is defined as no surgical intervention.
- Treatment failure:

- Poor drainage from chest drain, failure of resolution of pleural effusion or empyema, at least 50% reduction in opacity on chest x-ray, and clinical evidence of ongoing infection that requires surgical intervention within 30days post-intervention or death before discharge.

Data will be collected retrospectively by reviewing patient demographics, clinical data on length of hospital stay, pleural fluid analysis, intrapleural therapy, radiographic characteristics, and adverse events.

4.6 Study protocol /flow chart



4.7 Statistical Analysis

• Descriptive statistics by arm; normality via Shapiro-Wilk.

• Primary endpoint: two sample t- test (or Mann-Whitney U) on % reduction Day 7; report mean/median difference and 95% CI. Sensitivity analysis using ANCOVA, adjusting for baseline % opacity and matched/weighted cohorts.

• Secondary endpoints:

- ✓ Net drainage 72h: t-test/Mann-Whitney; linear regression with adjustment.
- ✓ Change in CRP/WBC Day7: t-test/Mann-Whitney.
- ✓ LOS: Mann-Whitney; competing risk sensitivity if death before discharge.
- ✓ Surgery within 30 days: chisquare/Fisher's exact; logistic regression to adjust confounders; time to event via Kaplan-Meier and Cox model.

• • Adverse events & 30-day mortality: chisquare/Fisher's exact.

• Multiplicity: secondary outcomes interpreted as exploratory; $p<0.05$ (two sided) for primary endpoint.

4.8 Estimated cost of study

Not applicable

4.9 Research ethics

Ethics: To be submitted to the UKM Research Ethics Committee and the UMMC MREC. Retrospective design with minimal risk; request for informed consent waiver and data use agreement; strict de-identification; secure storage on institutional servers.

CHAPTER 4: GANTT CHART

Progression / Timeline	July 2025-September 2025	November 2025-December 2025	January 2026-December 2026	January 2027- June 2027	July 2027-December 2027	January 2028-July 2028
Formulating a research title and literature review						
Proposal write-up and editing.						
Proposal presentation and modification						
Proposal submission and ethics committee approval						
Commencement of study and data collection						
Data analysis						
Thesis write-up / Dissertation preparation.						
Dissertation presentation and submission						

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APPENDIX 1 :

DRUG ADMINISTRATION OF INTRAPLEURAL t-PA (ALTEPLASE) & DNase (PULMOZYME)

<table>
<tr><td>Drugs dosage</td><td>Intrapleural t-PA 5mg per dose
Intrapleural DNase 5mg (2 ampoules of 2.5mg) per dose
at least 6 hrs apart
Timing of administration: 8-9 am, 4-5 pm & next day, 8-9 am.</td></tr>
<tr><td>Patient undergoing hemodialysis</td><td>No dosage adjustment provided. Suggest heparin-free dialysis while receiving t-PA and DNase.</td></tr>
<tr><td>Patient on anticoagulant</td><td>No standard guideline. Physician to assess patient‘s thrombotic risk & bleeding risk and decide if need to withhold anticoagulant.
<table>
<tr><td></td><td>Elimination half-life</td></tr>
<tr><td>Warfarin</td><td>20-60 hours</td></tr>
<tr><td>Rivaroxaban</td><td>5-9 hrs; Elderly: 11-13 hrs; renal impairment: 8.7-9.5 hrs; hepatic impairment: 10.1-10.4 hrs)</td></tr>
<tr><td>Apixaban</td><td>~12 hrs (8-15 hrs)</td></tr>
<tr><td>Dabigatran</td><td>12 -17 hrs; Elderly: 14-17 hrs; Mild-to-moderate renal impairment: 15-18 hrs; Severe renal impairment: 28 hrs</td></tr>
</table></td></tr>
</table>

MATERIAL REQUIREMENT:

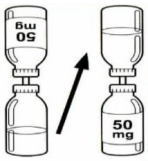
1. Drugs as prescribed
2. Dressing pack
3. Sterile gloves
4. Povidone iodine 10% or Chlorhexidine in 70% alcohol or alcohol swab
5. 2 x 50ml leur lock syringes (for Alteplase & Pulmozyme)
6. 2 x 10ml syringes (to flush)
7. 2 x Blunt-ended drawing up needles
8. 0.9% NaCl total 750ml
9. 3-way tap connector
10. Rubbish bag
11. Dressing trolley

1. PREPARATION CHART t-PA (ALTEPLASE)/ACTILYSE®:

A) Reconstitution

1) Wipe the top of the vial with a 60-70% alcohol swab.
2) Insert cannula into **Sterile Water Vial** (provided in the box).

3) Empty water into **Actilyse® 50mg Vial**.

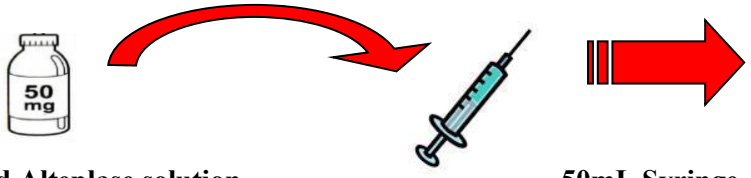


4) Mix by gentle swirling/ slow inversion. **DO NOT** shake. Allow to stand if foam is present. Final concentration = **1mg/mL (50mL)**.

B) Administration

STEP 1

Syringe out **dose** required (eg, if 16 mg = 16 ml)



Reconstituted Alteplase solution 1mg/mL (50mL)

50mL Syringe

Further dilute with normal saline up to **a final volume of 50ml**

STEP 2

Wrap the balance Alteplase solution with parafilm, label the date and time opened, and keep in the fridge. (stable for 24 hours)

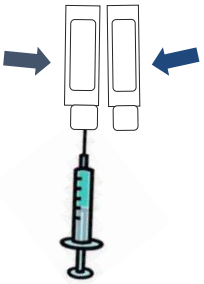
2. PREPARATION CHART – DNase (PULMOZYME) :

- DNase (Pulmozyme) must be stored **in the refrigerator** at **2-8°C** and protected from light & heat.
- Do not use the medicine if it has been at room temperature for more than 24 hours.
- The solution should be discarded if it is cloudy or discoloured.
- DNase (Pulmozyme) contains no preservative; the entire ampoule must be used or discarded once opened.

a) Open the foil pouch and remove only **two ampoules (2x2.5mg=5mg)** of DNase (Pulmozyme) from its pouch each time before instillation. Keep the other ampoules back in the fridge.

b) Hold the tab at the base of the ampoule of DNase (Pulmozyme) firmly, taking care not to squeeze the body of the ampoule, and twist off th

c) Syringe out the full dose of the drug from 2 ampoules of DNase (Pulmozyme) (2 x 2.5ml) until the ampoule is empty.



Turn the ampoule upside down and gently squeeze.

Syringe the contents from 2 ampoules (2x 2.5ml=5ml =5mg) into the syringe.

50mL Syringe

Further dilute with normal saline to **a final volume of 50ml**

d) Wrap the 50ml syringe with diluted DNase (Pulmozyme) with parafilm, label the date and time of preparation. Do not use the medicine if it has been at room temperature for more than 24 hours.

PROCEDURE OF INSTILLATION OF t-PA/DNase

1. Premedication (Tramadol) for pain relief before each dose. Medication to be given at least 20 minutes before the procedure.
2. Draw up Alteplase & DNase as prescribed (Refer to Sections 6 & 7 of the protocol). Prepare 2 x 10ml 0.9% NaCl in syringes for flushing purposes.
3. Check all connections are secure.
4. Uncap the outer port.
5. Clean the port thoroughly with Chlorhexidine, Povidone iodine 10% or alcohol swab.
6. Turn the 3-way tap to the off position.
7. Attach the 10cc syringe filled with NS to the outer port and turn the three-way tap towards the chest.
8. Flush the drain with 5 mL NaCl (pre-Alteplase) to check patency.
9. Turn the three-way tap to the off position on the chest.
10. Attach a 50cc syringe containing diluted alteplase, turn back the three-way tap towards the chest, and inject slowly within 1-2 minutes.
11. Disconnect and flush with 5ml NaCl towards the chest (post-Alteplase).
12. After flushing, keep the 3-way tap turned off to the chest and clamp for 45 minutes.
13. Attach a new bung to the outer port.
14. After clamping, open the 3-way tap to drain towards the bottle for 45 minutes, and record drainage before the second instillation.
15. After 45 minutes of drainage, repeat the process with DNase (Pulmozyme). Flush the drain with 5 ml NS (pre-Pulmozyme).
16. Turn the 3-way tap to the off position.

17. Attach a 50cc syringe containing diluted DNase (Pulmozyme), turn back the 3-way tap towards the chest, and inject slowly within 1-2 minutes. Followed by a 5ml NS flush (post-Pulmozyme).
18. After flushing, keep the 3-way tap turned off to the chest.
19. After 45 minutes of clamping, open the 3-way tap to drain towards the bottle and record the drainage until the next instillation.

OBSERVATION AFTER ADMINISTRATION OF t-PA (ALTEPLASE) & DNase (PULMOZYME)

1. Observe the patient for:
    a. deterioration in clinical condition
    b. tension pneumothorax
    c. hemorrhage from the site or excessive drainage (in excess of 1L per hour) in the drainage bottle

2. Monitor for:
    a. Bedside ultrasound of thorax (by chest physician) daily with curvelinear probe (ultrasound Mindray, model Z5) by measuring the maximum distances between the parietal and visceral pleura.
    b. Serial chest x-ray (baseline x-ray, day 7 post t-PA/DNase and pleural irrigation)
    c. Serum CRP level (baseline, day 7 post t-PA/DNase and pleural irrigation)
    d. FBC (baseline, day 1- 3, day 7 post t-PA/DNase and pleural irrigation). A drop of hemoglobin by less than 10% from baseline is acceptable.
    e. Systemic bleeding/ Pleural bleeding
    f. Drainage of pleural effusion daily

3. Stop the t-PA & DNase if there is a significant drop in haemoglobin (>10% drop in Hb) with clinical signs of shock or significant haemorrhagic fluids drained. Consider CTA and blood transfusion in those cases.