Official Title of the study:

Fibrinolysis Compared to Thoracoscopy for Pleural Infection

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Patient Population

Subjects (> 18 years of age) with either CPPE or empyema will be screened for inclusion. Screening logs recording reasons for non-trial entry will be kept.

CPPE is defined as non-purulent effusions in a patient with clinical evidence of infection such as fever and/or elevated blood leukocyte count and/or elevated CRP, with pleural fluid pH ≤ 7.2 (measured by blood-gas analyzer), or pleural fluid glucose < 60 mg/dl or pleural fluid LDH >1000 IU/L. Empyema is defined as pus within the pleural space and/or presence of bacteria on pleural fluid Gram stain or culture.

For patients to be considered for the trial they need to fulfill one of the following criteria: 1) CPPE along with evidence of septated pleural effusion on pleural ultrasonography and/or chest CT scan [26] (Figure 1) with entrapped lung or 2) empyema.

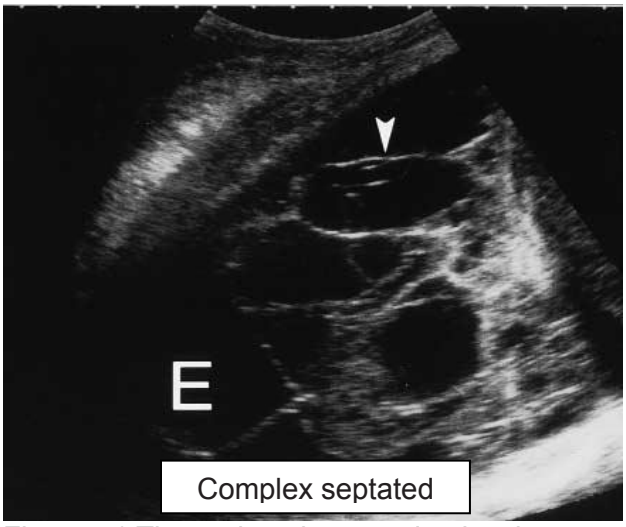

Figure 1.Throracic ultrasound showing complex pleural effusion along with septation (arrowhead)

Study exclusion criteria are: 1) age <18 years; 2) pregnant women 3) inability to give informed written consent; 4) previous thoracic surgery or thrombolytic therapy for pleural infection; 5) medical thoracoscopy cannot be performed within 48 hours; 6) inability to tolerate procedure due to hemodynamic instability or severe hypoxemia; 7) unable to correct coagulopathy, 8) presence of a homogeneously echogenic effusion on pleural US[26] (Figure 2) and 9) evidence of non-expanadable lung (air in pleural space) after initial thoracentesis or small bore chest tube on chest CT imaging.

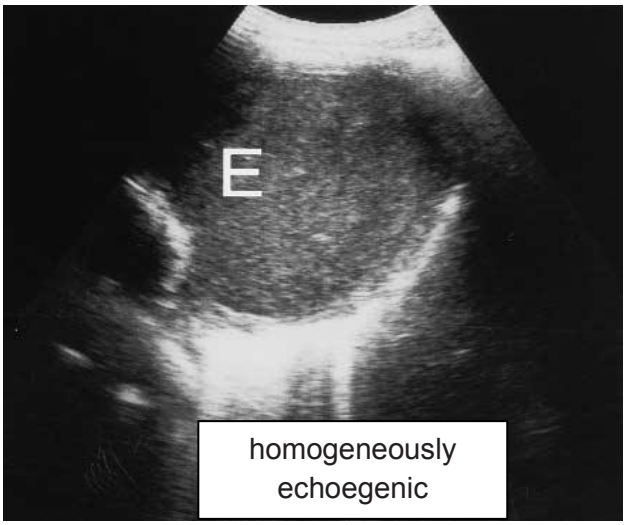

Figure 2. Thoracic ultrasound showing homogeneously echogenic loculated effusion

All patients will undergo diagnostic thoracentesis and chest computed tomography as part of routine care, prior to the enrollment in the study. Women of childbearing potential will have a pregnancy test as part of standard of care and pregnant women will be excluded from the study. Intravenous antibiotics will be changed to oral consolidation therapy by the managing consultant in light of the clinical response. Antibiotic therapy will be continued between 2 and 6 weeks, as required.

Patients who accept to be involved in the trial will sign an informed consent and then will be randomized to either Medical Thoracoscopy (Treatment Arm) or Fibrinolytic Therapy (Control Arm). (Figure 3)

Chest computed tomography (CT) will be done prior to randomization (day 0),prior to chest tube removal and at 12 weeks follow up visit respectively as part of standard of care protocol .On chest CT without contrast, pleural effusion will be defined as loculated if it had (1) lobulated shape with a convex boarder or (2) compartmentalized, accumulated in a fissure or a non-dependent portion of the pleura. On chest ultrasound pleural effusion will be defined as fibrin strands or septa floating inside the anechoic/hypoechoic pleural effusions along with presence of defined multiple pockets in the pleural cavity[27]

Operative Technique

I-Medical Thoracoscopy (Thoracoscopy Arm)

Patients will undergo medical thoracoscopy (rigid or semi-rigid) within 48 hours of randomization. Under ultrasound guidance, a single port (with a maximum of 2 ports) will be placed and thoracoscopy will be performed under moderate sedation in the operating room or endoscopy suite with continuous monitoring as per standard protocols, with the patient in a lateral decubitus position. The pleura will be carefully inspected through the thoracoscope under direct visualization. With the closed biopsy forceps, step by step, fibrinous septate will be disrupted with fluid and fibrinopurulent material aspirated and removed from the pleural cavity. A suction irrigator device) will be used at the discretion of the operator. Following adhesiolysis , a pleural lavage with a liter of warmed saline will be done. At the end of the procedure, a drain

(24Fr) will be inserted and connected to underwater seal suction with a negative pressure suction of 20 cm H2O. A chest CT without contrast will be performed and if there was no evidence of significant residual pleural effusion and chest tube drainage is <75ml/day the chest drain will be removed. The fluid volume will be calculated by measuring the maximum perpendicular distance between the surface and the chest wall right above the diaphragm with at maximum inspiration in the most dependent position.[28]

II-Fibrinolytic Therapy (Fibrinolytic Arm)

A chest tube (14-French Seldinger or less) under ultrasonography guidance will be inserted into the most dependent area of the pleural effusion or into the largest loculation in patients with multiloculated effusions. The dose of DNase (Pulmozyme, Genentech, USA) is 5 mg and the dose of tPA (Actilyse, Genentech, USA) is 10 mg, each in 50 ml of 0.9% NaCl. tPA and DNase will not be mixed together in one syringe. Concurrent tPA and DNase will be administered intrapleurally through the chest tube followed by 60 ml saline flush. The tube will then be clamped for 120 minutes before the chest tube will be opened to -20 cmH20 of wall suction. Therapy will be given twice daily for a maximum of 6 doses. A chest CT without contrast will be performed and if there was no evidence of significant pleural effusion [28] and chest tube drainage is <75 ml/day, the catheter will be removed.

Study Outcome

Primary outcome measure:

- Duration of hospital stay after intervention

Secondary outcome measures:

- Total length of hospital stay
- Failure rate of assigned treatment (persistent fever, leukocytosis evidence of loculation 48 hours post intervention) necessitating intervention defined as any of the following:
  1-Surgical intervention (VATS, open thoracotomy) in the medical thoracoscopy or fibrinolytic therapy arm
  2-Need of additional chest tube and/or fibrinolytic therapy in the medical thoracoscopy arm due to clinical non-responsiveness
  3-Need of additional chest tube in the fibrinolytic therapy arm due to clinical non-responsiveness
- Adverse events
  - Pleural bleeding defined as drop in serum hematocrit requiring blood transfusion or causing hemodynamic instability
  - Significant pain requiring escalation of analgesia
- In hospital and 30 day mortality

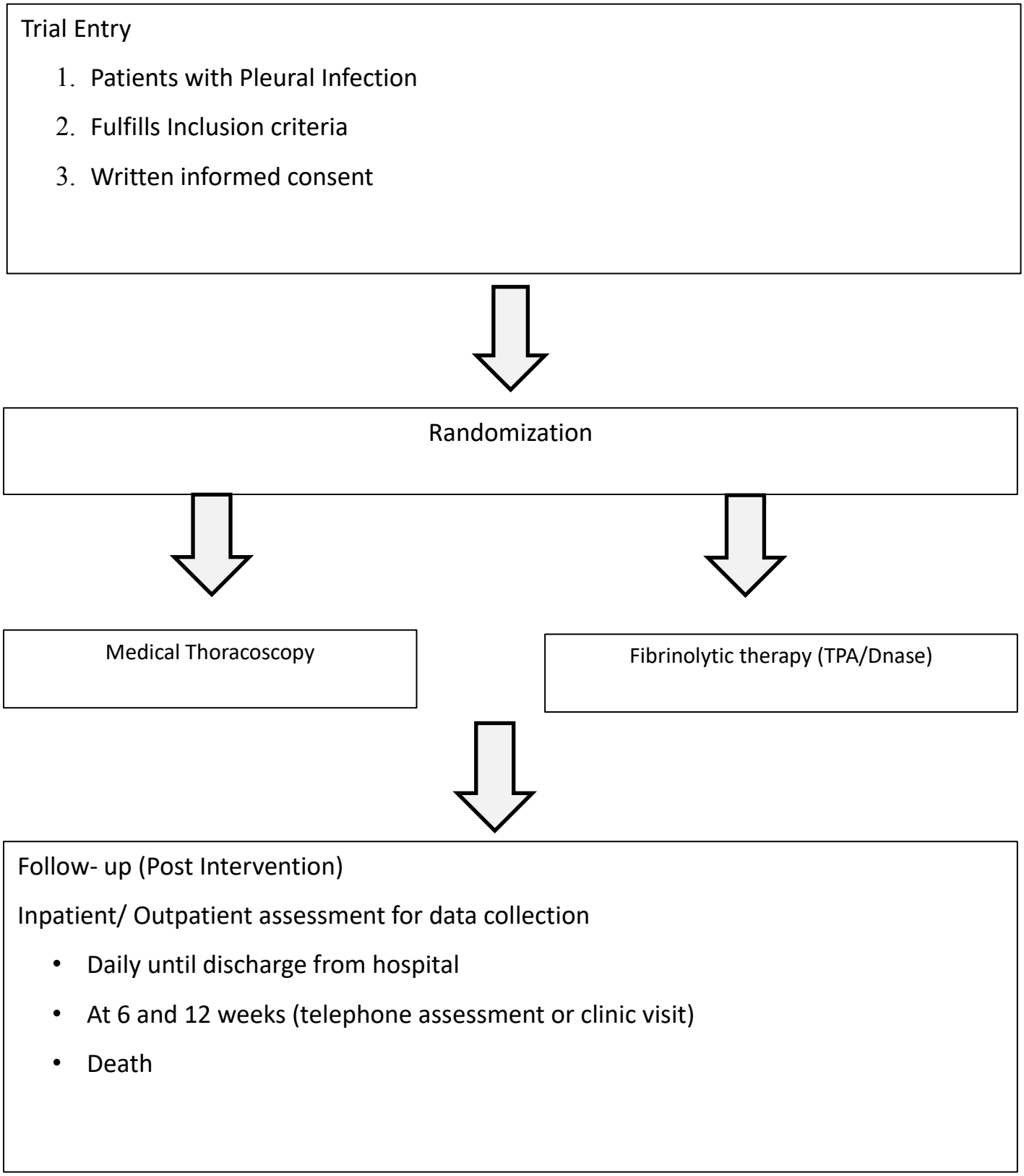

Figure 3. Proposed Study Protocol