COMIRB Protocol

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Protocol #: 17-0857
Project Title: Early Intervention for Complicated Parapneumonic Effusion: Randomized Controlled Trial for Fibrinolytic Therapy vs. VATs Decortication
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I. Hypotheses and Specific Aims

Early VATS decortication in patients with complicated parapneumonic effusion unable to be drained by image thoracostomy tube reduces hospitalization time and is more cost effective than fibrinolytic therapy.

Specific aims:
1: Standardize a method for identifying patients with complicated parapneumonic effusions that require a secondary intervention to clear infection from pleural space

2: Contrast outcomes in patients who undergo early VATS decortication vs. fibrinolytic therapy for complicated parapneumonic effusion

3: Contrast the cost of early VATS decortication vs. fibrinolytic therapy for complicated parapneumonic effusion

4: Contrast the complications associated with early VATS decortication vs. fibrinolytic therapy for complicated parapneumonic effusion

5: Assess patient's coagulation status while undergoing each intervention

II. Background and Significance

Introduction

The treatment of parapneumonic infections (infection in the pleural space) at the Denver Health Medical Center is not standardized, and timing for advanced interventions such as fibrinolytic therapy or surgical decortication remain unclear. The definitive treatment strategy in these patients may be sub-optimal, and lead to prolonged hospitalization and morbidity. This is concerning as the mortality rate of

community acquired pneumonia triples in the presence of a parapneumonic process (5-15%) and can reach over 25% if it becomes bilateral(1). Prompt recognition of pleural space infections is essential for reducing morbidity and mortality. This is attributable to the progression of the disease from a simple fluid collection amenable to pleural space drainage, to necrotizing empyema requiring thoracotomy decortication and open drainage. The keys to management of parapneumonic effusions are early diagnosis, appropriate therapeutic intervention, and recognition of failure of conservative management. We propose that a standardized pathway for identifying and treating parapneumonic effusions will be an important quality improvement. A key gap in the literature remains if patients with parapneumonic infections that cannot be drained with a chest tube should undergo a trial in intrapleural fibrinolytic therapy, or if they should go directly to video assisted thoracic surgery (VATS) for decortication of all infectious material.

Physiology of Pleural Space Fluid Shifts

Appreciation of the pleural space physiology helps conceptually understand the progression of pleural space disease. This is an active region of fluid exchange due to the leaky pleural membrane and negative pressure of the pleural space(2). The fluid originates predominantly from the parietal capillaries because of hydrostatic pressure, augmented by the negative pressure of the pleural space. Less fluid is produced by the visceral pleura because the hydrostatic pressure is attenuated by pulmonary venous drainage. However, the visceral surface will add more pleural fluid with increased pulmonary interstitial pressure. A small volume of fluid is normal in the pleural space, but healthy individuals should have less than 4 mm of dependent pleural fluid on decubitus ultrasound.(3)

Clearance of fluid from the pleural space is accomplished by lymphatics. The visceral mesothelium of the pleural space is intricately connected to the lung parenchyma, whereas the parietal layer is more loosely connected to the thoracic structures separated by a variable fatty layer. The parietal pleura has specialized areas known as stoma, and an extensive lymphatic network exists below which is the predominant route of fluid resorption located at the dependent portion of the chest cavity(4). Under normal conditions, it is estimated that each pleural cavity generates 0.2 to 0.4 mL/kg per hour. The capacity for pleural fluid absorption is thought to exceed 500 mL of fluid from each cavity with an intact lymphatic system. Overall, the accumulation of pleural fluid is the result of a dynamic system of fluid production and absorption. Pathology of the pleural space tends to shift extra fluid into the region from increased oncotic drive due to increased particulate, increased permeability of the pleural membrane, and decreased lymphatic clearance.

Evolution of Pleural Space Infection to Empyema

Complicated parapneumonic effusions, and ultimately empyema, develop in three conceptual phases(5, 6). The early phase is a sterile effusion caused by parenchymal inflammation that activates mesothelial cells and enhances capillary permeability, termed exudative (days 2–5). This is thought to be driven by proinflammatory cytokines, including interleukin 8 and tumor necrosis factor-[alpha].(6) Ultimately, the volume of fluid traversing into the pleural cavity exceeds the capacity to reabsorb the fluid and an effusion develops. The second phase is termed fibropurulent, which is initiated by bacterial infection (days 5–10). At this point, the immune system is activated and the once hypocoagulable environment is changed dramatically.

Bacterial and neutrophil activity acidify the fluid, consume glucose, increase protein content, and release lactate dehydrogenase (LDH) from cellular apoptosis and necrosis. The environment now becomes hypercoagulable because of the integrated responses of the innate immune and coagulation systems.(7, 8) These findings are directly relevant to the evolution of complicated effusions because the exuberant fibrin deposition is a concerted effort to control progressive infection. The final state of a complicated effusion is referred to as the organization phase (days 10–21). Fibroblasts migrate into the pleural space and create a dense fibrotic lining of the visceral and parietal surfaces. This phase is thought to be driven by regenerative cytokines, for example, transforming growth factor-[beta] and platelet-derived growth factor released primarily from activated mesothelial cells.(9) The net result is a progressive rind that encases the lung, reducing ventilatory capacity and sequestering bacteria.

Risk Factors and Bacteriology of Pleural Space Infection

There are over a million patients hospitalized for pneumonia a year and 10% of these patients will develop a pleural space infection(10). Patients who present to the hospital with pneumonia have an increased risk for pleural space infection if they have a history of IV drug use and alcohol abuse(11), age less than 60(12), and male gender(13). Nosocomial pneumonia have a higher rate of pleural space infection and have reported needs for operative intervention in up to a third of patients(14). The incidence of pleural infection in trauma patients with thoracic injuries is around 3%.(15) Risk factors for developing a post-traumatic empyema include multiple rib fractures, thoracostomy tube placed in the emergency department, and underlying pulmonary contusion. Another risk factor is placement by non-surgical specialty (16). This has clinical significance as a retained post-traumatic hemothorax has the highest risk for empyema, with an infection rate of over 25%(17).

A Gram stain and culture of the pleural fluid is often beneficial in directing management in pleural space infection, although 20% to 40% of the time, there is no reported identifiable pathogen.(12, 18, 19). However, the patient's history is often helpful when directing empiric antibiosis while waiting for gram stains and cultures to finalize. In empyema associated with community-acquired pneumonia, the most

common pathogen *Streptococcus milleri* (32%), whereas if hospital acquired, it was methicillin-resistant *Staphylococcus aureus* (28%). Patient characteristics, including diabetes, alcoholism, age older than 60 years, and trauma are associated with more anaerobic and resistant gram-positive organisms.(20) Hospital-acquired empyema is reported to have a fourfold greater risk of death compared with community acquired.(12) *S. milleri* is a commonly identified pathogen in patients who have undergone surgical intervention of the chest or upper digestive tract and often require decortication.(21) Because of the differences in bacteriology of pleural space infections an adequate history of patients with parapneumonic processes (community vs. hospital acquired pneumonia, vs. chest space intervention) is essential for guiding early antibiosis.(22) Of note, although most antibiotics penetrate the pleura well, aminoglycosides may be inactivated at a lower ph.(23)

Diagnosis of Pleural Space Infection

Radiographic identification of an effusion in a patient with a systemic inflammatory response syndrome (SIRS) does not necessarily correlate with a pleural space infection. Only 1 in 4 patients with an effusion associated with a CAP ultimately require drainage of the pleural space.(1) The next step in management of an effusion is quantifying the volume of fluid. The standard method to estimate the amount of pleural fluid has been the lateral decubitus chest x-ray(24). Recent comparative studies indicate that ultrasound is a more reliable method to quantitate a pleural effusion (24-26). As previously mentioned, an effusion measured up to 4 mm is considered normal.(3) Clinical studies by Light et al.(10) indicated that infections involving an effusion of less than 10 mm will resolve with antibiotics alone, and this has been supported by subsequent series.(27, 28). Therefore patients with large effusions on upright films or CT images should proceed to drainage of the pleural space with a chest tube. Patient with smaller effusions should have a bedside estimate of the volume of fluid in their chest with ultrasound, and those with fluid levels less than 10 mm in height are likely to have resolution of their symptoms with antibiotic therapy alone.

If the decision is made to perform a thoracentesis of the pleural space, the fluid removed should undergo evaluation for an active infection. Gross purulence (empyema) at the time of thoracentesis is unusual but constitutes an indication for prompt video-assisted thoracoscopic surgery (VATS) decortication.(5) In all other circumstances, the pleural fluid should be submitted for laboratory analysis. The traditional technique to distinction an exudative versus transudative effusion is via Light's criteria: protein greater than 0.5 serum, LDH greater than 0.6 serum, or LDH greater than two-thirds normal serum.(29) However, the most cost-effective means to analyze this is to measure the pH of the pleural fluid using a standard blood gas analyzer, available in most intensive care units. A pH less than 7.2 is the threshold, although less than 7.3 is considered high risk. (30-32) An exception is a *Proteus* infection where the pH may exceed 7.4 because of ammonia production.(6) An alternative diagnostic criterion is a pleural fluid glucose less than 60 mg/dL when infection is suspected.(6) Because the evolution of an empyema may extend for days to weeks and the early phase is a sterile effusion, a repeat diagnostic thoracentesis

should be done in any patient with a persistent unexplained SIRS and unilateral pleural effusion.(5)

Early Management of Pleural Space Infection

Those patients with fluid tested in the chest space concerning for pleural infection require empiric antibiotic treatment to cover suspected pathogens in addition to tube thoracostomy drainage. The exception is in patients with gross purulence aspirated from the pleural space that should under go prompt operative decortication. The optimal size of the chest tube remains debated,(33, 34) but a 18F seems effective in removing this hypercoaguable fluid. This is a grade B recommendation. These smaller chest tubes are associated with less chest wall pain than blunt dissection–inserted tubes, without compromise in clinical outcome. The position of the chest tube, however, is important.(34) The tube should be placed in the posterior (dependent) pleural space and not within a pulmonary fissure. We have observed that the typical "trauma" chest tube introduced through the fifth intercostal space (ICS), at the mid–axillary line, favors fissure placement. Consequently, we recommend ultrasonography-guided tube insertion via the sixth intercostal space. But this is based on our unpublished experience. A Gram stain and culture of the pleural fluid should be obtained at the time of tube thoracostomy to differentiate the organism, although as previously mentioned up to 40% if the time no pathogen may be found. More recent techniques such as countercurrent electrophoresis, latex agglutination, or bacterial DNA detection by polymerase chain reaction could in theory improve pathogen identification, but are not currently standard of care in the clinical setting.(30)

After tube placement vigilant follow up of chest tube output and changes in radiographic appearance are critical. Pleural collections persisting for more than 24 hours warrant prompt computed tomographic (CT) imaging for evaluation of the entire thoracic space.(9, 29). Delay in diagnosis of an undrained simple fluid collection allows progression to a complex multilocular process and the final organization stage.(35) As Sahn and Light(28) stated in 1989, "the sun should never set on a parapneumonic effusion"; early diagnosis and treatment of complicated pleural infection is essential for optimal outcomes. CT images are crucial for the next step in the management of pleural space infections that have not resolved with tube drainage as this dictates operative versus fibrinolytic therapy.

Fibrinolysis Therapy for Treating Pleural Space Infections

The rationale for obtaining a CT scan 24 hours after failure of appropriate tube drainage for a pleural infection is for recognition of a persistent pleural collection trapped via thin fibrin septa. This fibrin deposition likely had an initial protective role. The prehistoric horseshoe crab uses a unique protease, Factor C, to initiate coagulation in the presence of endotoxin, trapping and killing pathogens(36). This has been extrapolated to animal models, in which it has been demonstrated that anti-fibrinolysis is protective in gram-negative infection(37). However excessive fibrin deposition maybe pathologic and impaired fibrinolysis has recently been

described ventilated patients(38). It has become increasingly apparent that the majority of patients with sepsis(39) or sustaining significant injury(40) have resistance to fibrinolytic activity and prone to developing organ failure from what is believed to be micro vascular fibrin deposition. This translates to the pleural space, where fibrin deposition is appreciated during inflammation and infection.(41) This early fibrin deposition may help contain the pathogen with impending progressive infection. Pathologic fibrin deposition occurs when the body is unable to clear the pathogen and the speta become thickened, rendering chest tube drainage ineffective. The proposed therapeutic option is to medically breakdown these fibrin depositions by up regulating the fibrinolytic system.

The first report of fibrinolytic therapy in the pleural space was by Tillett and Sherry(42) in 1949. They infused purified hemolytic streptococcal concentrates, presumed to contain streptokinase and deoxyribonuclease (DNase). Although apparently safe, there was no documented improvement in patient outcome during the ensuing 60 years. The first randomized trial, by Davies et al.(43) in 1997, demonstrated radiographic improvement in 24 patients but no discernible clinical benefit. This was followed by a number of underpowered randomized studies in Europe, suggesting that urokinase demonstrated a therapeutic value.(44, 45) These conflicting results led to the MIST I study(46) involving 52 hospitals in the United Kingdom with 412 randomized patients. The data indicated that 72 hours of streptokinase treatment resulted in no improvement in mortality, rate of surgery, or length of stay and was associated with an increased rate of serious adverse events. This study was criticized for including a heterogeneous mix of patients with different comorbidities and different stages of pleural disease.(47) A subsequent Cochrane review in 2008(48) noted that there was a discordance between earlier studies and the MIST I data and concluded that fibrinolytics should be used selectively because there has not been a proven benefit in high-quality trials; however, the authors acknowledged that there may be certain subgroups of patients who benefit from this therapy. Clinical studies in other arenas indicated that tissue plasminogen activator (tPA) was a more effective and safer agent than streptokinase or urokinase as a fibrinolytic agent.(49) Other studies suggested that the addition of DNase to streptokinase improves evacuation of an empyema.(50, 51) Subsequently, MIST II, using tPA with or without DNase, has been completed.(52) Unfortunately, this study (n = 210; four study groups) was only powered sufficiently to evaluate radiographic changes. But consistent with MIST I, tPA showed no benefit over any fibrinolytic treatment. The combination of tPA and DNase, however, was beneficial in both the primary end point (radiographic clearance) and secondary end points (need for thoracotomy, hospital length of stay). The authors responsibly conclude, “Our study shows that combination intrapleural t-PA and DNAse therapy improves the drainage of pleural fluid in patients with pleural infection… This combined treatment may therefore be useful in patients in whom standard medical management has failed and thoracic surgery is not a treatment option. However, appropriate trials are needed to accurately define the treatment effects.”

Thus, the debate continues regarding the role of fibrinolytics in the management of pleural collections. Most intensivists have observed effective eradication of early empyema in some patients but agree that the appropriate population remains

ill defined. On the basis of the pathophysiology of empyema and the morbidity of thoracotomy for delayed intervention, most think that fibrinolytic treatment should be attempted for early empyema with simple collections separated by thin septa documented by CT scan if tube thoracotomy drainage fails. Image-guided direct infusion of fibrinolytics into the collection is superior to delivery via the failed chest tube. The precise agent, dosage, and timing of infusion remain to be analyzed; the combination of tPA and DNase seems to be the most effective regimen at this time.(52) Large case series have emerged since the publication of MIST II. Piccolo et al(53) reported a three-year experience using the MIST II protocol (5mg DNase and 10mg tPA BID for up to six doses) in 10 different centers. Inclusion criteria were patients with a pleural PH < 7.2 and clinical evidence of infection. The majority of these patients were male (69%) had CAP (97%), middle aged (median 56 yrs.), and received 2 days of therapy. Of the 107 patients included in the analysis 93% had successful fibrinolytic/DNAse to avoid surgery. Of note 23% of patients had increased pain associated with infusion and required additional analgesic medication, which should be taken into consideration when starting therapy. A smaller case series from Mehta et al.(54) evaluating 55 patients using once a day therapy for 3 days had similarly positive results with 93% of patients not requiring surgical intervention. They also appreciated that 15% of patients required additional analgesics during treatments.

Surgical Decortication

There are no randomized control trials evaluating VATs vs. fibrinolytic therapy in adults. However in adolescents a small trial demonstrated equivalency in fibrinolytic therapy and VATS in clearing infection, but the surgical intervention group had 3 fewer days with a chest tube and 3 fewer hospital days(55). This is important to take into the context of the patient's physiologic status. There is a need for a prospective randomized control trial to determine if VATS or fibrinolytic therapy is the optimal treatment of patients with complicated parapneumonic effusions who are physically fit to undergo surgery. In addition there are also patents that should proceed to decortication and avoid attempts at fibrinolysis therapy. Multiloculated empyema with an established pleural peel evident on CT scanning should undergo prompt VATS.(48) Although "medical" VATS using local anesthesia has been reported,(56) the standard procedure is lateral decubitus positioning with dual lung ventilation to facilitate comprehensive evaluation of the involved pleural cavity and systematic decortication. A key maneuver is to enter the pleural space without injuring the underlying lung because of extensive pleural adhesions. An initial incision in the upper thorax, where the empyema is least developed, is usually the safest strategy. In most cases, we have used the existing chest tube site to free the lung for placement of the initial port. With the thorascope in position and the lung at least partially deflated, additional working ports are added under direct vision. The sites for these ports are chosen to match the chest wall entrance of the chest tubes after VATS.

The objectives of VATS are to unroof all loculated collections, including those in the fissures, and to free the lung of the visceral pleural fibrous encasement.

Usually, the decortication is initiated in the upper lobe, where the process is more limited, and ultimately, the fibrous debris is removed as much as possible from the lung surface to enable re-expansion. Dissection must be done carefully on the mediastinal side to avoid injury to the phrenic nerve and pulmonary vasculature. Similarly, clearing the diaphragm must be done cautiously to avoid perforation. In fact, the diaphragm does not need to be systematically debrided as long as the lower lobe is freed. After extensive decortication, the thorax is usually drained with three relatively large chest tubes (28F) to facilitate removal of debris and blood associated with the procedure. The most inferior tube is usually an angled tube positioned in the posterior dependent recess of the chest.

In the event of a dense fibrous peel that precludes clearance via VATS, a limited lateral muscle-sparing thoracotomy ("mini thoracotomy") is performed to accomplish decortication. Transecting the posterior rib facilitates exposure of the fibrous cavity. Advanced empyemas often require scalpel incision to free the lung for re-expansion; inspection of the lung with periodic re-inflation should be done to avoid extensive pulmonary parenchymal air leaks. In the unusual case of a chronic empyema, a standard posterolateral thoracotomy is required. Often, the safest approach is to develop an extrapleural plane and directly enter the empyema cavity before any further thoracic dissection is done. After these extensive decortications, the thorax is drained with three relatively large chest tubes (28F), and the most inferior tube is usually an angled tube positioned in the posterior dependent recess of the chest. Occasionally, these tubes are simply transected to provide external drainage for outpatient management of extended processes.

Treatment of an advanced process caused by a necrotic infected lung with associated major air leaks in a severely immunocompromised patient warrants open thoracic drainage. The Eloesser flap, thoracic cavity marsupialization via segmental rib resection and suturing the skin to the underlying parietal surface, has been the standard for these complicated cases.(57) But recently, simple open drainage with suturing the skin margin to the chest wall, thoracostomy, and the application of a vacuum-assisted wound closure has been popularized.(58, 59) Ultimately, some of these wounds will heal by secondary intention, and the remaining can be closed with thoracomyoplasty.(60)

Significance

Infection of the pleural space is a morbid condition requiring prompt intervention. The keys to optimal care in these patients are 1) early identification 2) antibiotics and 3) clearance of infection from the pleural space. When a chest tube has incompletely drained the pleural space within 24 hours CT imaging to better characterize the pleural space is essential. The Western Trauma Association has published a critical decision algorithm for determining which patients should proceed to decortication versus fibrinolytic therapy(61). It is important to note that there have been no randomized trials in adults comparing early VATs to fibrinolytic therapy in patients who can tolerate surgery. Future studies are warranted to address this gap in knowledge, as pediatric literature supports early decortication may be more cost effective and beneficial to the patient. Failure to appropriately treat pleural space

infection resulting in empyema results in highly morbid open operations requiring prolonged hospitalization and lengthy recovery.

III. Preliminary Studies/Progress Report:

We have previous completed a retrospective study at Denver Health evaluating Strep Milleri associated pleural infections(62). Over the 70-month period evaluated, 39 patients had S Milleri infections of the pleural space; 26 (67%) patients underwent operative intervention. The majority (72%) were men with a mean age of 46 (range 22 to 63); the underlying etiology in those patients requiring operation was pneumonia (26 patients; 67%), trauma (9 patients; 23%), postoperative infection (2 patients), foreign body ingestion (1 patient), and malignancy (1 patient). The average duration of chest tube drainage prior to operation was 4.4 days (95% confidence interval [CI] 2.6 to 6.2) and antibiotic treatment was 6.0 days (95% CI 3.8 to 8.2). Thirteen patients (50%) underwent video-assisted thoracoscopic surgery (VATS) and 13 patients required thoracotomy. VATS was performed more often when operative intervention occurred early (average hospital day 6.2) compared to initial thoracotomy or conversion from VATS to thoracotomy (average hospital day 9.8). Hospital length of stay was less in the operative group (average 24 days; 95% CI 17 to 31) than in the non-operative group (34 days; 95% CI 19 to 49), discharge to home was greater in the operative group (77% vs. 16%), and mortality was less in operative group (0% vs. 23%).

While this data was published before the routine use of antibiotics, it demonstrates key aspects of the current proposed study; 1) decreasing time to surgical consultation and chest tube placement 2) early operative intervention when indicated allowing for minimally invasive surgery 3) decreased hospitalization time in patients when operative intervention is performed. This study only included patients with Strep Milleri, which in regards to historic literature represents 1/3rd of all pleural space infections.

IV. Research Methods

A. Outcome Measure(s):

Primary: Length of stay (determined by when treating team deems medically fit for discharge, and excludes extended stay for social work related issues)

Secondary:
- ICU free days
- Ventilator free days
- Days with chest tube in place after intervention
- Total cost - post intervention
- Pain scores
- Chest tube drainage post intervention
- Incentive spirometry volume post intervention for 5 days
- Days to wean off supplemental oxygen

Days to resolution of fever
Days of antibiotic therapy after intervention
Days to normalization of WBC
Change in TEG variables after initiating intervention

Covariates: Age, BMI, Diabetes, Duration of symptoms, Steroid use

Adverse events: Air leak, bleeding requiring transfusion, need for additional chest tube, and need for secondary operation/intervention, mortality

B. Description of Population to be Enrolled:

Adults ≥18 admitted with pleural effusion diagnosed by chest x-ray or computed tomography, that undergo thoracentesis or chest tube drainage by any service.

If the patient has a pleural fluid PH < 7.3, the patient will be screened for potential study enrollment. If the patient does not have any exclusion criteria (listed below) the patient will be followed for study enrollment. If there is a persistent effusion 24 hours after chest tube insertion, diagnosed by morning chest X ray, and no exclusion criteria identified, the patient may then undergo CT scan to characterize the effusion. If CT scan is done and confirms a loculated fluid collection or if an additional CXR is grossly abnormal, despite chest tube drainage, these patients will then be approached for consent and randomized to either bedside fibrinolytic therapy through their chest tube versus operative VATS decortication. The patients that undergo VATS decortication, will subsequently be transferred to the surgery service for the remainder of their hospital stay.

Exclusion:

- Intrathoracic malignancy
- Any existing malignancy causing malignant effusion
- Prehospital pulmonary symptoms over 14 days prior to admission
- Prior instrumentation of the chest during same admission
- Malignant cells from initial pleural fluid sample
- End stage liver disease (Child's B or greater)
- Coagulopathy
- Unable to tolerate surgical procedure
- Frank purulent drainage (needs OR regardless)
- Recent surgery of abdomen or thorax precluding the use of tPA
- Pre-existing and permanent neurologic impairment

C. Study Design and Research Methods

This study is a proposed pragmatic prospective randomized open label clinical trial to treat patients with complicated parapneumonic effusion. Complicated parapneumonic effusion is defined as fluid collection in the pleural space with a fluid pH<7.3.

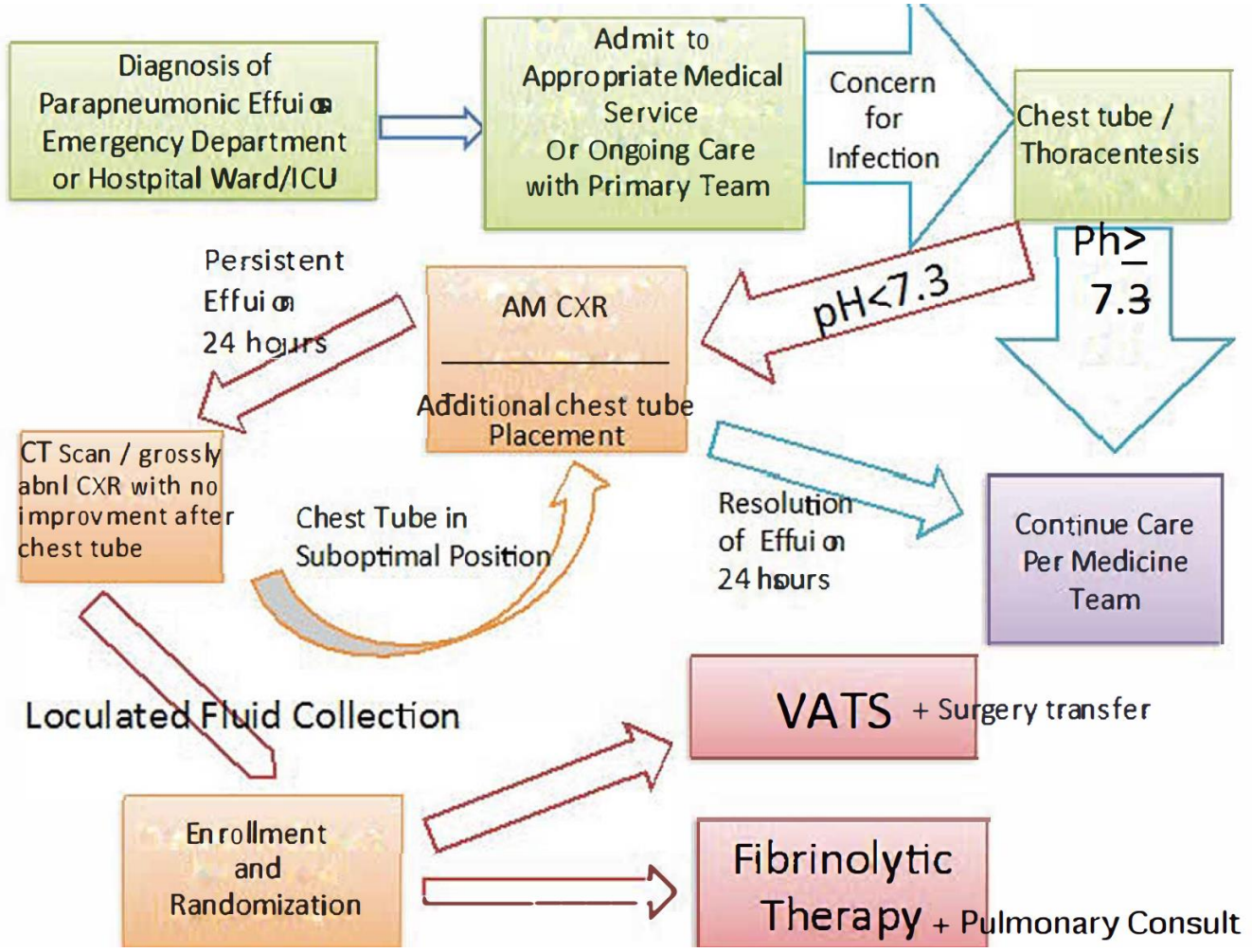
Standard of Care Procedure prior to study eligibility:
Patients with parapneumonic effusions identified on chest x-ray or CT will be admitted to the medicine service and started on the appropriate therapy. The medicine/pulmonary service will then perform a thoracentesis or place a chest tube in patients that there is a concern for an infectious process. Pleural fluid sampling will undergo pH testing, and those patients with a low pleural pH (pH <7.3) will continue to be observed over the next 24 hours. Those patients who have persistent fluid collections >24 hours from chest tube placement identified by a morning chest X ray, will undergo a CT scan of the chest to further characterize the pleural space. These eligible patients will be approached by a study team member for study consent to enroll and randomized into a treatment group (Fibrinolytic therapy vs. early VATS Decortication).

Study Procedures:
Eligible patients will be screened for study participation and after consenting will be randomized to *early surgical decortication via VATs* versus *fibrinolytic therapy (FT)* based off of the current MIST II protocol, currently utilized at Denver Health. Should the patient be randomized into the FT group, initiation of fibrinolytic therapy will start within 24 hours of CT scan,. Conversely, if the patient is randomized into the surgery group, VATS decortication will occur as soon as the operating room is available. The fibrinolytic therapy will be delivered by a member of the treatment team per current standard of care for 3 days. Removal of chest tubes is dependent on the mutual agreement of both the surgical and pulmonary attending involved with the patients care. Per standard clinical care, labs will be collected daily (determined by the medical team, but usually include complete blood count and basic metabolic panel). In addition to the standard of care labs, pleural fluid will be collected for study purposes and extra blood samples will be collected for thrombelastography (TEG) analysis. TEG assesses changes in clot strength in both plasma and pleural samples by measuring proteins related to coagulation with proteomic analysis. Thrombo Therapeutics, Inc. is not involved in this study. tPA-challenged TEG assay is used for research purposes only. The data from this test is not accessible for the clinical care providers and does not affect the patient care. We are using this assay to study the clot sensitivity and as a marker for massive blood transfusion. The results of tPA-challenged TEG assay will not be used for any clinical decision or research subject assignment. At the moment there is no plan to submit tPA-challenged TEG data to the FDA.This study blood and pleural fluid will be drawn by the phlebotomy service or medical team member (nurse or physician to draw pleural fluid) and will be collected by a professional research assistant (PRA) trained in both running the TEG assay and in processing of blood for plasma analysis. Blood and pleural fluid samples will be 3.5ml each.

Study blood will be drawn prior the intervention and then for 3 sequential days after (for a total of 4 draws). This blood will be assayed by TEG with and without the t-PA challenge. This modified TEG assay (t-PA challenge) is completed by taking 500 microliters of patient blood out of the citrated tube and adding it to a pre made

glass container with lypohylized t-PA. This blood is mixed with a defined concentration of t-PA is then added to a TEG cup for analysis. This will quantify the patient's systemic blood to fibrinolysis resistance. In addition to the blood draws, pleural fluid will be drawn from the patient's chest tube in the morning prior to the intervention, and then after the intervention for 3 days (same days that blood samples are obtained, for a total of 4 pleural fluid samples). Pleural fluid samples will only be drawn from chest tubes already in place. In the event the chest tube is removed prior to 3 days post-intervention pleural fluid samples will be unattainable. The pleural fluid would otherwise be discarded as human waste. We will also conduct a novel assay to determine if the pleural space content is fibrinolytic resistant. This will be accomplished by an ex vivo diluting of the patient's blood (from the collected citrated tube) by 25% with normal saline and conducting a t-PA challenge versus a 25% dilution of the patient's blood (from the collected citrated tube) with their pleural fluid. The relative differences in the lysis at 30 minutes between these two assays will give a crude estimate of fibrinolytic inhibition. Remaining blood after TEG analysis will be spun down to plasma and flash frozen for future measurements, such as elastase activity and a targeted cohort for proteins related to coagulation with proteomic analysis. These results paired with proteomic analysis will enable correlations between fibrinolysis resistance and relative protein concentrations to identify potential mechanistic culprits driving fibrinolysis resistance. This study blood will be collected by PRA (drawn by the nurse and handed off to thePRA) trained in both running the TEG assay and in processing blood for plasma analysis.

Data collection will be done prospectively by a member of the research team. Data



will be stored in a secure excel sheet accessible only to the study team members.
Randomization

Intervention

VATS decortication
Vs.
tPA and DNASE per MISTII protocol

D. Description, Risks and Justification of Procedures and Data Collection Tools:

The adverse events of the standard of care fibrinolytic therapy include pain, fever, bleeding, and failure to effectively clear infection from the pleural space requiring

surgery, which tend to be higher risk due to disease progression. The VATS decortication is a slightly more invasive procedure, as it requires general anesthesia and single lung ventilation. Complications from surgery include injury to lung causing an air leak, bleeding, pain, and need for conversion to an open operation. The VATS surgery uses small holes in the thoracic cavity that are similar in diameter to a chest tube. This requires 1 or 2 additional holes in the chest cavity compared to the patients who already have one chest tube receiving fibrinolytic therapy. The benefits of VATS over fibrinolytic therapy are reduction in chest tube time and overall reduction in hospitalization time. In children VATS reduced the requirement of a chest tube by 3 days and associated with hospital discharge 3 days earlier with resolution of symptoms 3 days earlier. This is logical as the chest is cleared of all infected material with the VATS operation, while fibrinolysis is dependent on the medication breaking down all of the loculated fluid collections. The second benefit may be a reduction in cost to the patient, and improvement in resource utilization of the hospital. Three days of hospitalization out weighs the cost of the operating room. All clinical outcomes will be monitored by a research team member who will be collecting blood on a daily basis for 3 days post intervention and inputting data into a RED CAP data bank designed for the study. As this study is associated with an operative arm a data safety monitoring board (DSMB) will be created to assess patient outcomes after enrollment of 10 patients or once a year, even if enrollment has not increased by 10. This will not include an interim analysis on primary outcome, as this will decrease power and necessitate additional patients for enrollment. We anticipate that roughly 2 patients per month will be eligible for enrollment in this study and would expect completion of the study within 18 months.

E. Potential Scientific Problems:

This study is established as a pragmatic study as it is anticipated that some patients would prefer conservative fibrinolytic therapy to surgery. We have adjusted for this in our power calculation (see below). In addition the timing of availability of the operating room staff is not predictable. There may be a delay in taking the patient to the operating room. The importance of performing this study is that it is perceived that fibrinolytic therapy should be the standard of care for treating these patients. However, pediatric literature supports that optimal care of these patients may be an early surgical intervention. This is similar to an operative intervention for appendicitis. While it is possible to treat patients with appendicitis with antibiotics and avoid surgery, it results in longer hospitalizations, in addition if medical treatment fails the appendical perforation can result in life threatening sepsis and require surgery or additional procedures. This parallels complicated parapneumonic infections, in which surgery can be avoided, but result in prolonged hospitalization and if fibrinolytic therapy fails, surgery becomes a riskier endeavor.

F. Data Analysis Plan:

Power analysis

Using the pediatric literature assume effect size of reduction in 3 days of hospitalization requirement with variability of 2.3 days with alpha of 0.05 and 1:1 group allocation would require 12 patients per arm (24 total) to power the study to 80%. Anticipating up to 30% of patients may decline surgery we would seek to enroll 17 patients per arm. Will conduct an analysis based on intention to treat (included patients who declined surgery) in addition the treatment the patients received.

Table 4
Postoperative results of the cases.

	STK	VATS	P
Post-therapy days of O^2 support	2.3±1.4	2.1±2.0	0.911
Afebrile days after intervention	3.9±2.1	3.4±2.4	0.782
Analgesia doses	22.1±18.9	25.4±13.1	0.561
Chest tube removal time	9.48±2.50	6.56±1.55	0.0001
Duration of hospital stay	10.37± 2.29	7.41±1.45	0.0001
Duration of symptoms after intervention	6.78±1.69	3.78±1.25	0.0001
Fluid drainage			
Initial drainage amount	394.93±220.65	379.19±230.14	0.786
Postoperative drainage amount	850.59±301.91	865.78±444.41	0.884

Statistical analysis will be performed using SPSS 22 software (Microsoft, Armonk, NY). Normally distributed data will be described as mean and standard deviation and non-normally distributed data were described as the median value with the 25th to 75th percentile values (IQR). Outcomes will be contrasted between intervention arms with a T test (normal distribution) or Mann Whitney U test (non normal distribution) for continuous variables or chi square analysis for dichotomous outcomes. Kaplan-Meier plot will be generated to identify the timing of chest tube removal from intervention, and time to hospital discharge from intervention.

G. Summarize Knowledge to be Gained:

Complicated parapneumonic effusions are life-threatening infections that are progressive and if mistreated can result in prolonged hospitalization and open thoracic surgery. The optimal care of adult patients remains controversial, and there may be a role for early operative intervention versus conservative fibrinolytic therapy. VATS is a minimally invasive procedure that allows complete removal of all infected material from the chest cavity. We believe that the benefit of a quicker recovery and definitive management of this disease process with VATS outweighs

the risk of undergoing surgery and may be superior to fibrinolytic therapy is at risk of incompletely removing infected material. This study is also a quality improvement project to standardize the identification of patients at risk of complicated parapneumonic processes to guide the medical service to early diagnosis and interventions the manage this process with guidance for when to initiate advance therapy in regard to fibrinolytic therapy versus operative intervention.

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