Efficacy of Intrapleural Fibrinolytic Therapy as First Line Treatment in Complicated Pleural Effusions or Empyema

Kailey Oxenforth BSc., BSc. RT, RRT, PA-S

7687175

oxenfork@myumanitoba.ca

Rebecca Mueller, MSc, PA-C and Elisa Chand CCPA

A capstone project submitted to the Faculty of Graduate Studies of
The University of Manitoba in partial fulfillment of the requirements for the degree of
MASTER OF PHYSICIAN ASSISTANT STUDIES

Master of Physician Assistant Studies
University of Manitoba

May 29th, 2020

Abstract

BACKGROUND: There are various treatment options for empyema and complicated pleural effusion, most of them requiring an invasive procedure. The use of intrapleural fibrinolytic therapy may prevent a more invasive surgical procedure.

OBJECTIVES: To determine if intrapleural fibrinolytic therapy is an effective treatment in empyema or complicated pleural effusions.

METHODS: A primary systematic literary search was conducted using the online databases Embase and MEDLINE. A secondary search was then conducted from the references of primary search results. Five articles were used within analysis and were either randomized controlled trials or retrospective reviews.

RESULTS: A total of five studies were used from the primary and secondary search out of the original 65 articles found.

DISCUSSION: A total of five studies were used within the review, three were randomized controlled trials and two were retrospective reviews. Three out of the five studies included showed statistical significance in the use of intrapleural fibrinolytic therapy as treatment for illness and prevention of surgical intervention.

CONCLUSION: Intrapleural fibrinolytic therapy has been shown to be statistically significant in treatment of empyema and complicated pleural effusions as well as reduction in need of surgical intervention, however there are limitations to the results.

KEYWORDS: Empyema, Complicated Pneumonia, Tissue Plasminogen Activator, Dornase Alpha.

Table of Contents

Introduction

In Canada, pneumonia is a leading cause of death and hospitalization for immunocompromised populations and elderly individuals, however it can affect people of all ages (1). Within Canadian Emergency Departments (ED) pneumonia is 1 of the top 10 reasons for an ED visit (2). The Canadian Institute for Health Information (CIHI) identified 135,000 ED visits related to pneumonia in 2017-2018 (2). Pneumonia can progress to cause complications within the pleural space in the form of a complicated parapneumonic effusion or empyema (3). The purpose of this review is to evaluate the efficacy and safety of using intrapleural fibrinolytic therapy to treat the intrapleural complications of pneumonia in adults.

Background

Pneumonia has been defined as an infection of the lower respiratory tract by bacteria, viruses, fungi or parasites causing inflammation of the lung parenchyma and associated consolidation of the alveolar spaces (4,5). The most common cause of pneumonia is *Streptococcus pneumoniae,* a gram-negative diplococcal bacterium (4). *S. pneumoniae* makes up 60-75% of community acquired infections and 3-9% of nosocomial infections (4). Currently the recommended treatment for a community-acquired pneumonia is 7-10-day course of a macrolide antibiotic or fluroquinolone if the patient has other co-morbidities (4). Providers can use the CURB-65 guidelines (See Table 2) to determine if a patient can recover at home or require admission to hospital (6). Not all patients will recover from a course of antibiotics and some will go on to develop complications of pneumonia. Approximately 20-40% of hospitalized pneumonia patients develop complicated parapneumonic effusions and 5-10% of these patients go on to develop an empyema (3).

Complicated Parapneumonic Effusions and Empyema

A chest radiograph that should have been obtained to diagnose the pneumonia, should be used to help identify and quantify the presence and size of an effusion. The fluid in the pleural space (unless loculated) should settle in a gravity dependent position. On an anteroposterior radiography the effusion can be seen as >175mL with blunting of the lateral costophrenic angle (3). A lateral decubitus radiograph can show as little as 10ml of fluid, however it is not deemed sufficient enough to proceed with a thoracentesis till there is ≥ 1cm of fluid layered out on the film (3,7) Under ultrasound guided technique some individuals will still attempt a thoracentesis with <1cm layered out as there are no official guidelines with ultrasound as of yet (3). In some instances, a chest radiograph or ultrasound may not be sufficient in the diagnosis of an empyema. In these cases, a CT scan of the chest is obtained. The CT typically has fluid density collections within the pleural space and may contain locules of gas (8). The split pleura sign is used to distinguish between an empyema and peripheral lung abscess. The split pleura sign is seen at the margin of the empyema where the pleura can be seen dividing into the parietal and visceral layers (8).

Parapneumonic effusions are defined as an exudative pleural effusion that occur secondary to a pneumonia or lung abscess (9). To determine if the effusion is exudative Lights Criteria is used (10). A complicated parapneumonic effusion occurs when the standing parapneumonic effusion requires invasive intervention for treatment, or when bacterial cultures from the effusion are positive, however the pleural fluid is non-purulent (11). There are many different definitions and criteria for the diagnosis of an empyema, but the consensus is that one can be diagnosed with empyema when a patient has pus within the pleural space or organisms are seen on a Gram stain or culture of the pleural fluid (5). There are differing opinions on the

acidity level of the pleural fluid for diagnosis however pH <7.2 should be considered diagnostic (11). There does not need to be a positive culture for the diagnosis however it would be beneficial to have a culture and sensitivity to provide organism-directed treatment (5). The pleural fluid from a diagnostic thoracentesis can be used to help determine the category of effusion (complicated or empyema) and be used to determine treatment options. The category scale is from 1 to 4, with 4 being the most severe. See table 3 for the categorization. Diagnosis of a category 1 or 2 may not require any drainage (12). When the effusion escalates to a category 3 or 4, drainage is required and possible addition of other forms of therapy (12). Types of current therapy for treatment of an empyema or complicated parapneumonic effusion are as follows; video-assisted thorascopic surgery (VATS), tube thoracostomy, therapeutic thoracentesis, intrapleural fibrinolytics, decortication, open thoracotomy, and intrapleural fibrinolytics (11).

Diagnostic/Therapeutic Thoracentesis and Chest Tube Thoracostomy

In order to evaluate the pleural fluid for Lights Criteria (10), a diagnostic thoracentesis is required (13). As previously discussed, the pleural fluid is sent for laboratory evaluation. A thoracentesis is when a small thoracentesis catheter is introduced into the pleural space under sterile technique to get a sample of the pleural fluid. The amount of fluid removed does vary but typically no more than 1000ml to 1500ml is removed at any given time (14). There are possible complications with a thoracentesis such as bleeding, re-expansion pulmonary edema, pneumothorax or diaphragm perforation (14). The procedure should be terminated if the patient develops intractable chest discomfort or the clinician is unable to evacuate anymore fluid (14). To evaluate the success of the thoracentesis and assess for any pneumothorax post procedure a chest radiograph should be obtained (14). If the thoracentesis were to cause a pneumothorax or the effusion were to reaccumulate a tube thoracostomy would be indicated. This entails inserting

a chest tube under sterile conditions into the pleural space and securing it in place. For drainage of empyema or complicated a large bore chest tube >28F is indicted typically (15). There are risks associated with the insertion of both a chest tube and performing a thoracentesis, common risks/complications are as follows; bleeding, diaphragmatic injury, bowel injury, pneumothorax, pain with insertion/procedure and infection (14,16).

Fibrinolytic Therapy

Fibrinolytic therapy is commonly used for treatment of stroke and myocardial infarctions by activating plasminogen to form plasmin that goes on to cleave fibrin cross-links resulting in thrombus breakdown (17). However, in this context fibrinolytic therapy is used to dissolve fibrinous clots and/or membranes within the pleural space and prevent fluid sequestration to ultimately improve pleural fluid drainage (18).

Objective

The objective of this literary review was to set out and determine if treatment of complicated pleural/parapneumonic effusions and empyema with intrapleural fibrinolytic therapy was sufficient in resolution of illness and/or prevention of invasive surgical procedures for treatment.

Methodology

A preliminary search was conducted using Embase and MEDLINE in January 2020. Keywords included in search “Empyema”, “Pleural Effusion”, “Parapneumonic Effusion”, “Complicated Pneumonia”. These were used to select the desired population, to select the desired intervention keywords “Alteplase”, “Tissue Plasminogen Activator”, “DNase”,

"Deoxyribonucleases", "Dornase Alpha", were used. This search originally produced 63 records. The search was then limited to English Language, Humans, Randomized Controlled Trials and Retrospective Reviews only which brought the record countdown to 13. A secondary search of reference lists was conducted, and 2 articles were put forward to have full-text review. The full-text articles were then analyzed, and the record was reduced to 5 articles included in the review. The articles excluded were for the wrong study design, no outcome measured, or study not completed.

Results

A double-blind randomized cross over trial was conducted by Thommi et al. (19) set out to determine the "Efficacy of intrapleural instillation of Alteplase vs. Placebo in empyema and complicated parapneumonic effusions" (19). This study was conducted at 1 hospital in the United States over a five-year period. During this study individuals had the Placebo or Alteplase treatment which was 25mg of "drug" in 100mls of normal saline (NS), divided into two 60mls syringes and then instilled intrapleurally once daily for three days (19). After the instillation of the treatment the chest tube was flushed with 50mls NS and clamped for 60 minutes then unclamped and 60 minutes later placed on suction. If failed after three days participants could switch to the second arm of trail and receive whichever "drug" they did not receive originally for another three days (19). Failure was determined if the pleural fluid did not decrease by at least 50% on CT scans on day four (19).

To be included in this trial participants needed to be diagnosed with empyema or complicated pleural effusion (CPE), be over 18 years of age, have no bleeding disorders or, recent cerebral vascular accident, bronchopleural fistula, uncontrolled hypertension or be coagulopathic. 108 patients were assessed for eligibility, however 68 individuals ended up

participating in the trial. In the first arm of the trial 35 individuals were allocated to the alteplase group and 32 to the placebo group. In this first arm 32/35 (91%) participants in the alteplase group had successful treatment versus 4/32 (12.5%) in the placebo group. In the cross over portion 26/26 (100%) participants in the alteplase group had resolution versus 0/1 (0%) in the placebo group (2 individuals refused to continue with the cross over). The trial was able to conclude that alteplase therapy was significantly more effective than Placebo therapy (95% vs. 12%; p value <0.001) in treatment of empyema and CPE (19).

Rahman et al. (20) conducted a blinded 2-by-2 factorial trial which involved 210 participants. This study set out to determine the success of interpleural fibrinolytic therapy, which was evaluated by change in pleural opacity, identified as a percentage of hemithorax occupied by effusion on day 7 compare to day 1. The study took place over 11 centers within the United Kingdom over a 3-year time period. Individuals were assigned to one of four treatment groups, t-PA + DNase, DNase + placebo, t-PA + placebo or placebo + placebo. For each group the medication doses remained the same 5mg of DNase and 10mg t-PA (20). These medications were given intrapleurally twice daily for three days, after each dose was given the chest tube was clamped for 60 minutes prior to allowing drainage.

To be enrolled in the trial one had to have a complicated pleural effusion or empyema determined by pleural fluid sample being positive on culture for bacteria or Gram's staining or pH < 7.20. Out of the 210 individuals enrolled only 193 were used within the trial. 51 received double placebo, 48 received tPA only, 46 received DNase only and 48 received both tPA and DNase. When comparing the mean difference in pleural opacity from day 7 to day 1 for the three treatment groups in comparison to the double placebo (-17.2%) only the t-PA-DNase (-29.5%) group had clinical and statistically significant differences (-7.9%; 95% Confidence Interval [CI]).

The conclusion of this study was intrapleural t-PA-DNase therapy improved fluid drainage in patients with pleural infection compare to placebo (95% CI; P=0.005) (20).

Maskell et al. (21) compared the use of intrapleural streptokinase to placebo in a double-blind, randomized trial conducted within 52 centers in the United Kingdom. The purpose of this study was to evaluate efficacy of streptokinase as a treatment, failure was determined by death or need for surgical intervention within three months of randomization. Individuals were randomly assigned to either the streptokinase or placebo group. The dose of 250,000 IU of streptokinase or equivalent placebo were administered in 30mls of NS, which was then injected into the pleural space through the patient's chest tube. Individuals were given a dose every 12 hours for 3 days (total 6 doses).

454 individuals were selected for the trial however only 427 completed the study. To be eligible one had to have infected pleural fluid determined by positive culture for bacteria, positive Gram's stain for bacteria or pH < 7.2. Individuals were randomly placed into the streptokinase group (206) or placebo group (221). There was no clinical or statically significant difference in the number of individuals who 'failed' the trial in the streptokinase 64/206 (31%) versus the placebo 60/221 (27%). The study concluded that intrapleural administration of streptokinase does not improve mortality, rate of surgery or length of hospitalization for patients with pleural infections (21).

In another study conducted by Bishwakarma et al. (22) coadministration of tPA/DNase in complicated parapneumonic effusions and empyema was evaluated through a retrospective observational study. This review evaluated a 3-year time frame at the University of Texas Medical Branch and included 39 participants. The study was trying to determine if coadministration of tPA/DNase would be successful in treating complicated pleural effusion or

empyema both clinically and radiographically without the need for surgical intervention prior to hospital discharge. Individuals would be given 10mg tPA and 5mg DNase simultaneously through their chest tube into the pleural space followed by 20-30mL of saline as a flush. The chest tube would be clamped for 2 hours so the medications could remain in the pleural space before being opened for drainage (22).

Participants were identified and enrolled if they met the following criteria: exudative and loculated effusion in a patient with community or hospital-acquired pneumonia, Gram stain or culture positive, macroscopically purulent (22). This study was able to conclude that intrapleural coadministration of tPA/DNase appeared effective and safe in treatment of patients with complicated pleural effusions and empyema as 85% of individuals were successfully treated, 15% failed treatment, 7.6% referred for surgery and 7.6% of participants died (22). Bishwakarma et al. (22) did have two notable limitations in their study. The first being they only had repeat chest radiographs for 35/39 participants, showing that 29/35 (83%) did have improvement on pleural effusion opacity on 3-7 days after initiating intrapleural treatment. The second profound limitation is that this study was a retrospective observational study conducted at only 1 site.

McClune et al. (23) conducted a retrospective review at two institutions over a 2.5-year period to determine if extended dose therapy with intrapleural fibrinolytics in patients with empyema or complicated pleural effusions improved outcomes or decreased need for surgical intervention. Neither site had a specific protocol for t-PA or DNase administration, but both did generally reflect the MIST II protocol (20), indicating they administered t-PA (10mg) and DNase (5mg) intrapleurally twice daily for three days (6 doses total). However, the dose and frequency for the extended therapy was up to the discretion of the administering physician (23).

To be a participant in this study one had to have a confirmed or suspected empyema/complicated pleural effusion requiring chest tube placement and undergo inpatient intrapleural fibrinolytic therapy, in addition individuals could not have previously undergone pleural interventions for previous infections or have an incomplete medical record. Originally 173 patients were identified, only 101 met the criteria for the trial and were included in this study. Of the 101 individuals 81 received standard intrapleural fibrinolytic therapy (6 doses total) and 20 received extended intrapleural fibrinolytic therapy (mean number of doses 9.8). This study concluded that the use of extended dosing intrapleural fibrinolytic therapy compare to standard dosing was not statistically significant at reducing the need for surgical intervention ($p = 0.821$), complications ($p = 0.056$ to 0.924) or any outcome differences ($p = 0.200$ to 0.975) (23).

Discussion

There were five studies included in this review, of those studies three (19,20,22) were able to demonstrate intrapleural fibrinolytic therapy being statically significant at treatment of illness and reduction of surgical intervention. Three (19,20,21) of the five studies were randomized controlled studies with two (22,23) being retrospective reviews. The duration of the studies ranged from 2.5 to 5 years and were conducted in either the United States of America (19,22,23) or the United Kingdom (20,21). The studies ranged from being conducted in 1 center to 52 centers. Within these studies the number of participants varied from 39-427 with the largest treatment group allocation being 206 (21) participants.

Each of the five studies required a medical diagnosis of empyema or complicated pleural effusion however, all five studies had specific guidelines for what they defined as empyema or complicated pleural effusion. Thommi et al. (19) used the diagnosis of empyema to be pleural

fluid glucose <60mg/dl with normal or high blood glucose values, pH <7.2 or pleural fluid culture positive or frank pus was found. They diagnosed CPE if pleural fluid was exudative and CT scan or Ultrasound of the chest showed multiple loculations with a pneumonic process (19). Two other studies (20,21) also had the criteria for enrollment being pleural fluid sample positive on culture for bacteria or Gram's staining or pH <7.20. Bishwarkarma et al. (22) had similar guidelines of pleural fluid being positive on culture or Gram's stain however did not document a pH level for enrollment instead used macroscopically purulent pleural fluid to be called empyema. Lastly McClune et al. (23) defined empyema as macroscopic pus or presence of bacteria on culture or Gram stain and CPE was clinical evidence of infection and pleural fluid biochemical profile consistent with CPE. The biochemical profile they are referring to was not explicitly stated to be but table 1 documented this as Lactate dehydrogenase, Protein and Glucose (23).

The protocol for administration of the treatment and the drug of choice for treatment varied among the five studies. One study used 25mg t-PA (19), one study used 250,000 UI Streptokinase (21) three studies used a combination of 10mg t-PA and 5mg DNase (20,22,23). These studies used t-PA as the fibrinolytic medication and DNase to break down the viscosity of the pleural fluid (24). The degradation of leukocytes within the pleural fluid causes deoxyribonucleoprotein which contributes to the viscosity of the pleural fluid, the use of DNase (recombinant deoxyribonuclease) has been shown to be effective in reducing the viscosity of the pleural fluid (24). In addition, two studies (19,20) required 60 minutes of chest tube clamping post treatment administration, one study (22) required 180 minutes of chest tube clamping post treatment and the other two studies (21,23) did not comment on length of chest tube clamping required after administration of treatment. Of important note McClune et al. (23) did not

specifically have set guidelines for the administration of drug or dosing as it was a retrospective review they stated the MIST I (19) guidelines were generally used indicating not always and other dosing within the trial was left to the discretion of the administering physician. Although the studies did not necessarily conduct their research with the same dosages nor the same drug as treatment. The results of this literary review were able to identify t-PA and DNase did show statically significant results for use as intrapleural treatment of empyema or complicated pleural effusion. The use of streptokinase was shown to be of no statically significant improvement as a treatment option.

McClune et al. (23) did not directly set out to determine if intrapleural fibrinolytic therapy was sufficient at treatment of empyema or complicated pleural effusion but rather set out to determine if extended dosing of such intrapleural therapy would further the efficacy of the treatment (23). However, within this study it was shown 101 individuals were enrolled, 81 of which received standard dosing which they loosely defined as 5mg DNase and 10mg t-PA, with the other 20 individuals receiving extended dosing which was not defined. When evaluating the study, it did show that 68/81(84%) 'standard' participants did not go on to require surgery and 17/20 (85%) 'extended' participants did not go on to require surgery. So, although the use of extended intrapleural fibrinolytic therapy was not statistically significant this study was still able to show that intrapleural fibrinolytic therapy is statically significant at reducing the need for surgical intervention.

It is important to note the results regarding prevention of the need for surgical intervention. Surgical intervention comes with many of its own risks, such as reaction to anaesthetics, infections, death, and prolonged recovery time to name a few. Having an intervention such as fibrinolytic therapy that can be used to not only treat the empyema or

complicated pleural effusion but also prevent the need for surgery is beneficial to the patient as well as the Canadian medical system.

Limitations and Future Research

We acknowledge several limitations within this literary review. This review set out to determine the efficacy of interpleural fibrinolytic therapy in empyema and complicated pleural effusions as well as the success of preventing surgical intervention. However, there was very little quality research on this topic.

Within the studies included two were retrospective in nature with their results being observational in nature. The sample sizes of all five of these studies were on the smaller side with the largest study included having no statistically significant results.

The five studies included in the review did not set out to determine the same fibrinolytic drug to be used as treatment nor did they all agree on the dosages of the medications to use. Future research would be warranted to determine the adequate dosage of drug as well as which specific fibrinolytic drugs should be indicated for intrapleural treatment.

A limitation of this review that is warranted mentioning is that every study included was conducted on individuals older than 18 years of age. So, although there is statistically significant data showing that intrapleural fibrinolytic therapy is successful at treatment of empyema/complicated pleural effusion and prevention of surgical intervention it is unclear if this data can be extrapolated to the pediatric population. Additional research is required to determine efficacy and safety of interpleural fibrinolytic therapy within the pediatric population.

Relevance to Physician Assistant Profession

Physician Assistants (PA) are highly skilled health care professionals educated in the medical model who practice medicine (25). Sine PAs have such a wide range of knowledge they are utilized within many fields of medicine (25). Within the hospital patients who get admitted with empyema or complicated pleural effusions will usual enter the system through the emergency department and later be transferred to a surgical or internal medicine team depending on the hospital and staff comfort level with such patients. Within Canada PAs work in the emergency departments, surgical teams and internal medicine. In some areas the PA may be inserting the chest tube themselves or administering intrapleural fibrinolytic treatments depending on the scope of the physician they work with and autonomy level within the position (25). Because of this the use of intrapleural fibrinolytic therapy in complicated pleural effusions or empyema becomes very relevant to a PA practicing within these certain fields of medicine.

Conclusion

Intrapleural fibrinolytic therapy with the use of DNase and/or t-PA has the potential to be statistically significant in treatment of empyema and complicated pleural effusions as well as reduction in needed surgical intervention. As there are multiple limitations of this review, further research is required to confidently change medical practice.

References

1. Pneumonia [Internet]. the lung association BREATHE. [cited 2020Mar26]. Available from: https://www.lung.ca/lung-health/lung-disease/pneumonia
2. Pneumonia a leading cause of emergency department visits in Canada last year [Internet]. CIHI. 2020 [cited 2020Mar26]. Available from: https://www.cihi.ca/en/pneumonia-a-leading-cause-of-emergency-department-visits-in-canada-last-year
3. Strange C. Epidemiology, clinical presentation, and diagnostic evaluation of parapneumonic effusions and empyema in adults [Internet]. UpToDate. [cited 2020May1]. Available from: https://www.uptodate.com/contents/epidemiology-clinical-presentation-and-diagnostic-evaluation-of-parapneumonic-effusion-and-empyema-in-adults?search=complicated parapneumonic effusion&source=search_result&selectedTitle=1~35&usage_type=default&display_rank=1
4. Benjamin IJ. Andreoli and Carpenters Cecil essentials of medicine. Philadelphia, PA: Elsevier, Saunders; 2016.
5. Shafarenko M, Tofighi T. Toronto notes 2019: comprehensive medical reference and review for the Medical Council of Canada qualifying exam part 1 and the United States Medical Licensing Exam step 2. Toronto: Toronto Notes for Medical Students Inc; 2019.
6. Jones BE, Jones J, Bewick T, Lim WS, Aronsky D, Brown SM, et al. CURB-65 Pneumonia Severity Assessment Adapted for Electronic Decision Support. Chest. 2011;140(1):156–63.
7. Yu H. Management of Pleural Effusion, Empyema, and Lung Abscess. Seminars in Interventional Radiology. 2011;28(01):075–86.
8. Weerakkody Y. Thoracic empyema: Radiology Reference Article. Radiopaedia Blog RSS. https://radiopaedia.org/articles/thoracic-empyema-1 (accessed May 20, 2020).
9. Light R. Parapneumonic Effusions and Empyema. Seminars in Respiratory and Critical Care Medicine. 1987;9(01):37–42.
10. Saguil A, Wyrick K, Hallgren J. Diagnostic Approach to Pleural Effusion [Internet]. American Family Physician. 2014. Available from: https://www.aafp.org/afp/2014/0715/p99.html
11. Shen KR, Bribriesco A, Crabtree T, Denlinger C, Eby J, Eiken P, et al. The American Association for Thoracic Surgery consensus guidelines for the management of empyema. The Journal of Thoracic and Cardiovascular Surgery. 2017;153(6).
12. Shebl E. Parapneumonic Pleural Effusions And Empyema Thoracis [Internet]. StatPearls [Internet]. U.S. National Library of Medicine; 2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK534297/
13. Heffner J, Maldonado F. Diagnostic evaluation of a pleural effusion in adults: Initial testing [Internet]. UpToDate. [cited 2020May4]. Available from: https://www.uptodate.com/contents/diagnostic-evaluation-of-a-pleural-effusion-in-adults-initial-testing
14. Huggins J, Chopra A. Large volume (therapeutic) thoracentesis: Procedure and complications [Internet]. UpToDate. [cited 2020May4]. Available from: https://www.uptodate.com/contents/large-volume-therapeutic-thoracentesis-procedure-and-complications

15. Filosso PL, Sandri A, Guerrera F, Ferraris A, Marchisio F, Bora G, et al. When size matters: changing opinion in the management of pleural space—the rise of small-bore pleural catheters. Journal of Thoracic Disease. 2016;8(7).
16. Stawicki SA, Kwiatt M, Tarbox A, Seamon M, Swaroop M, Cipolla J, et al. Thoracostomy tubes: A comprehensive review of complications and related topics. International Journal of Critical Illness and Injury Science. 2014;4(2):142.
17. Fibrinolytic Therapy (Thrombolytic Therapy) Topic Review: LearntheHeart.com [Internet]. Fibrinolytic Therapy (Thrombolytic Therapy) Topic Review | LearntheHeart.com. [cited 2020May]. Available from: https://www.healio.com/cardiology/learn-the-heart/cardiology-review/topic-reviews/fibrinolytic-therapy-thrombolytic-therapy
18. Singh G;Pitoyo CW;Nasir AU;Rumende CM;Amin Z; Update on the Role of Intrapleural Fibrinolytic Therapy in the Management of Complicated Parapneumonic Effusions and Empyema [Internet]. Acta medica Indonesiana. U.S. National Library of Medicine; [cited 2020May]. Available from: https://pubmed.ncbi.nlm.nih.gov/22983084/
19. Thommi G, Shehan JC, Robison KL, Christensen M, Backemeyer LA, McLeay MT. A double blind randomized cross over trial comparing rate of decortication and efficacy of intrapleural instillation of alteplase vs placebo in patients with empyemas and complicated parapneumonic effusions. Respir Med [Internet]. 2012;106(5):716–23. Available from: http://dx.doi.org/10.1016/j.rmed.2012.02.005
20. Rahman NM, Maskell NA, West A, Teoh R, Arnold A, Mackinlay C, et al. Intrapleural use of tissue plasminogen activator and DNase in pleural infection. N Engl J Med. 2011;
21. Maskell NA, Davies CWH, Nunn AJ, Hedley EL, Gleeson F V., Miller R, et al,U.K.controlled trial of intrapleural streptokinase for pleural infection. N Engl J Med. 2005;
22. Bishwakarma R, Shah S, Frank L, Zhang W, Sharma G, Nishi SPE. Mixing It Up: Coadministration of tPA/DNase in Complicated Parapneumonic Pleural Effusions and Empyema. J Bronchol Interv Pulmonol. 2017;
23. McClune JR, Wilshire CL, Gorden JA, Louie BE, Farviar AS, Stefanski MJ, et al. Safety and efficacy of intrapleural tissue plasminogen activator and DNase during extended use in complicated pleural space infections. Can Respir J. 2016;
24. Yap KH, Tan GP, Abisheganaden J. Intrapleural tissue plasminogen activator (tPA) and deoxyribonuclease (DNAse) for pleural infection in an Asian population: Similar outcomes between 5mg and 10mg regimen. Respiratory infections. 2018;
25. What is a Physician Assistant? [Internet]. Canadian PA. 2020 [cited 2020May19]. Available from: https://canadianpa.ca/whatisapa/

Appendix

	Light's Criteria	Modified Light's Criteria
Protein- Pleural/Serum	>0.5	>0.5
LDH- Pleural/Serum	>0.6	>0.6
Pleural LDH	>2/3 upper limit of N serum LDH	>0.45 upper limit of N serum LDH

Table 1: Light's Criteria

CURB-65 Pneumonia Severity Score	
Confusion	Abbreviated mental score ≤ 8 or orientation < 3 (time, place, self) (1 point)
Urea	BUN ≥ 20 mg/dL (1 point)
Respiratory Rate	≥ 30 breaths/min (1 point)
Blood Pressure	Diastolic < 60mmHg, Systolic < 90mmHg (1 point)
Age	≥ 65 years (1 point)
Score of 0 or 1: Mild to Moderate pneumonia, may consider outpatient management Score of ≥ 2: Severe pneumonia, Recommend hospitalization	

Table 2: CURB-65 Pneumonia Severity Score

Category of Effusion	Description	Treatment	Risk of Poor Outcome
1	- Small effusion, <10mm thickness on lateral decubitus, CT or Ultrasound - Free flowing effusion	No thoracentesis is performed	Very low
2	- Small to moderate effusion, equal to 10mm thickness and ½ the hemithorax - Free flowing effusion	Thoracentesis is performed, Gram stain and culture of pleural fluid are negative, pleural fluid pH >7.20	Low
3	Must meet one of the following: - Effusion occupies more than ½ hemithorax - Loculated - Associated with a thickened parietal pleura	Thoracentesis is performed, Gram stain or culture is positive or pleural fluid <7.20, or pleural fluid glucose <60mg/dl.	Moderate
4	Pleural fluid consists of pus	Drainage required	High

Table 3: Categorization of Pleural Effusion

Authors	Study Design	Sample Size	Sample Type	Objectives	Primary Outcomes	Conclusion
Thommi et al.	Double blind randomized placebo controlled cross over study	108 individuals >18 years old underwent randomization, only 68 completed the trial	-Empyema or CPE -No bleeding, HTN, >18 years of age, coagulopathy	Determine efficacy and safety of intrapleural alteplase vs. placebo in comparison to decortication	40% reduction in surgical intervention	-Intrapleural instillation of Alteplase is significantly more effective than Placebo in patients with empyema or CPE -No participants went on to have surgery
Rahman et al.	Blinded, 2-by-2 factorial trial	210 individuals enrolled, primary analysis included 193 individuals.	Empyema or CPE diagnosed as positive on culture for bacteria or Gram's staining or pH < 7.20.	Determine intrapleural fibrinolytic therapy (t-PA) alone, vs placebo vs with DNase	Change in pleural opacity, measured as % of hemithorax occupied by effusion on CXR day 7 vs day 1.	-Intrapleural t-PA-DNase therapy improved fluid drainage in patients with pleural infection and reduced frequency of surgical referral and duration of hospital stay
Maskell et al.	Double-blind trial	454 individuals enrolled, 430 completed the trial	-Infected pleural fluid, positive on culture for bacteria, positive on Gram stain or pH <7.2	To determine the therapeutic role of intrapleural streptokinase	The number of patients who died or required surgical intervention for infected pleural fluid within three months of randomization	-Intrapleural administration of streptokinase does not improve mortality, rate of surgery, or the length of hospital stay among patients with pleural infection
Bishwakarma et al	Retrospective observational study	39 individuals originally, only 35 followed through with trial	Criteria was exudative and loculated effusion in a patient with community or hospital-acquired pneumonia, Gram stain or culture positive, macroscopically purulent	To determine if coadministration of t-PA and DNase is effective as intrapleural treatment	-Clinically and radiographically without the need for surgical intervention prior to hospital discharge	-Intrapleural coadministration of tPA/DNase appeared effective and safe in treatment of patients with complicated pleural effusions and empyema
MClune et al.	Retrospective Review	173 enrolled, 101 individuals completed	-Confirmed or suspected empyema/complicated pleural effusion requiring chest tube placement, undergo inpatient intrapleural fibrinolytic therapy and be at least 18 years of age	To determine if extended use of intrapleural t-PA and DNase is more beneficial at prevention of surgical intervention than standard dosing	Reduction in surgical intervention	-No statistically significant difference in using 'standard' verses 'extended' use of intrapleural fibrinolytics

Table 4: Summary of Articles within Review.

Figure 1: Flow Diagram of Included Articles