

Pleural Effusions:
A Focus on Parapneumonic Effusions
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Introduction

Pleural effusions are described as excess pleural fluid localized between the pleural membranes which line the lung, or visceral membrane, and chest wall, or parietal membrane. On average, the total volume of pleural fluid in a 70-kg non-smoking human is 18mL¹. The function of pleural fluid is to lubricate the visceral and parietal pleural membranes so as to aid in breathing. Additionally, pleural fluid functions to fill the intrapleural space and maintain a negative intrathoracic pressure to prevent lung collapse during breathing. Production of pleural fluid occurs on the parietal membrane and is absorbed by the lymphatic system in the visceral membrane. The lymphatics of the visceral membrane have the capacity to absorb up to 20-40times the amount of fluid that the parietal membrane normally produces. The accumulation of pleural fluid can occur with a great variety of systemic and localized diseases. The fluid that accumulates in the pleural space is classically divided into “transudative” or “exudative” effusions. Transudative effusions occur due to systemic diseases altering the formation or reabsorption of pleural fluid. This alteration is related to increased hydrostatic pressure or decreased oncotic pressure, also known as Starling forces². Exudative effusions are more commonly associated with localized diseases and related to damage or disruption of pleural membranes or vasculature². The focus of this study is to explore exudative effusions that are associated with pneumonias, or Parapneumonic Effusions.

Evaluation of Effusion

The evaluation of a patient with a pleural effusion begins with a detailed history and thorough physical exam. Patients occasionally note symptoms such as dyspnea or cough, but frequently are without symptoms. On physical exam, the clinician may note localized decreased breath sounds, dullness to percussion, or absent tactile fremitus on pulmonary exam. Typically, imaging is performed to elucidate size and location of a possible pleural effusion. Upright Posteroanterior and Lateral Chest Films can demonstrate the general size of an effusion. Ideally, a Lateral Decubitus Chest Film will be obtained to further determine if the fluid is loculated and better estimate the size of the effusion. Other imaging including CT

or Ultrasound is even higher quality in helping to determine the number of loculations and more accurately quantify size of the effusion. If a pleural effusion is greater than 1.0cm on lateral decubitus film when measured from the inner chest wall, then the effusion is thought to be accessible to pleural fluid sampling

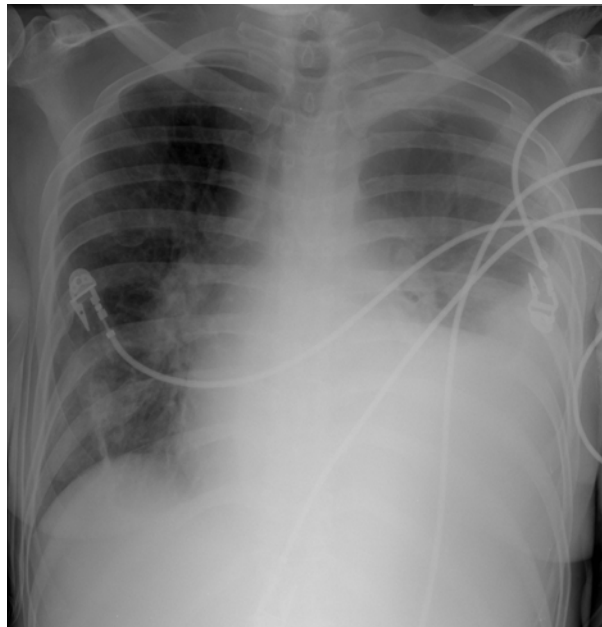


Figure 1: Anterior projection of a Left-sided pleural effusion.

with thoracentesis³. Pleural fluid sampling is typically performed if the etiology of the effusion is unclear or if the patient is not responding to appropriate therapy. When a thoracentesis is performed, the fluid is typically sent for Protein and LDH, historically known as Light's Criteria to demonstrate transudative effusions from exudative

effusions². Additional studies are available for further information, including gram stain and culture, pH, glucose, and cell count with differential. These studies can further aid in determining the cause of the effusion.

Parapneumonic Effusions

Parapneumonic effusions are those which are associated with pneumonias or lung abscesses. It is believed that effusions typically occur with 20-40% of pneumonias which require hospitalization, noting of course that pleural effusions are included in the Pneumonia Outcomes Research Trial (PORT) Score to assess need for hospitalization⁵. There are three types of parapneumonic effusions: (1) Uncomplicated, (2) Complicated, and (3) Empyema. Uncomplicated parapneumonic effusions are those which resolve with appropriate antibiotic therapy. Complicated parapneumonic effusions are those with

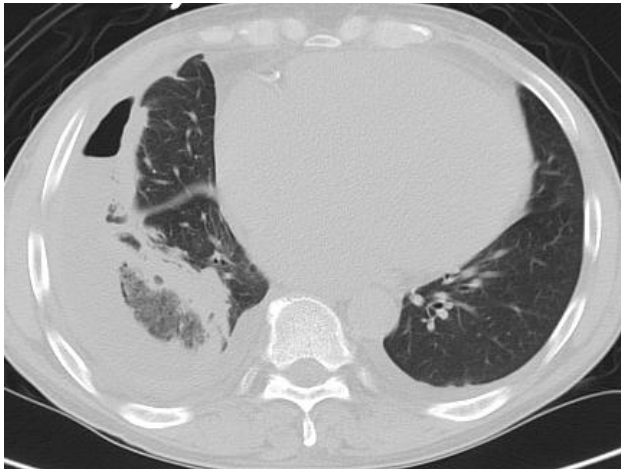


Figure 2: Empyema formation with air-fluid levels.

do not resolve with appropriate antibiotic therapy alone, but require drainage through repeat thoracentesis or tube thoracostomy. Empyema is described as frank pus seen on thoracentesis, however this definition has been broadened to include effusions with positive gram stain or

culture. Empyemas require drainage through tube thoracostomy but may also require additional treatment with fibrinolytics or Video Assisted Thoracic Surgery (VATS).

The problems presented by parapneumonic effusions include the need and timing of tube thoracostomy for complicated effusions and empyema. Light et al performed a prospective observational study on 90 patients to assess characteristics of complicated versus uncomplicated pleural effusions³. The study showed that many effusions resolved with appropriate antibiotic therapy. However, the effusions that did not resolve with antibiotics alone had a positive gram stain or culture, a significantly elevated LDH, a pH of less than 7.20, or glucose less than 60mg/dL. These effusions required tube thoracostomy for resolution. Even with tube thoracostomy, not all pleural effusions resolved with antibiotic therapy and some required surgical intervention for complete resolution.

To understand why these pleural effusions did not all resolve with appropriate drainage using tube thoracostomy, we must first understand the natural evolution of the parapneumonic effusion. On initial formation of an infiltrate, there is extensive localized pleural inflammation. This inflammation leads to the first stage, the Exudative Stage,

during which there is a rapid accumulation of sterile serous fluid with a normal pH and normal glucose. Without appropriate antibiotic therapy initiated during the Exudative Stage, the second stage, or Fibrinopurulent Stage, can develop. During the Fibrinopurulent Stage there is an



Figure 3: Fibrinopurulent Stage loculations in a parapneumonic effusion.⁹

accumulation of fibrin, polymorphonuclear cells, and bacteria in the pleural fluid. Pleural

fluid sampled during this stage typically has a low pH, low glucose, and elevated LDH, which worsen during the progression of this stage. Loculations can form in the pleural effusion during this stage given the presence of fibrin deposits. Tube thoracostomy late in this stage is of limited effect given loculations which inhibit complete drainage. The third stage, or Organization Stage, is noted by the migration of fibroblasts into the exudate creating an inelastic membrane around the lung called a pleural peel.

Additionally during the Organization Stage, the effusion can drain through the chest wall or lung tissue, forming empyema necessitatis or bronchopleural fistula, respectively.

Commonly during the third stage, definitive surgery is required to correct the defect created given the advanced disease. The physician should be aware of the natural evolution of the pleural effusion and treat early to prevent the significant complications associated with advanced disease.

Fibrinolytics

Limited drainage from a tube thoracostomy in the presence of a large effusion is typically due to loculations or fibrin deposits. Many clinical trials have been performed to assess the utility of breaking up these adhesions to promote adequate drainage.

Surgical intervention is a viable option but limited in patients who are poor surgical candidates or in hospital systems without available resources. Alternative therapies including the use of fibrinolytics have been evaluated, the concept that breaking down the fibrin loculations would allow for a greater ability to drain the pleural effusion.

Fibrinolytics evaluated include Streptokinase and Urokinase. Davies et al performed a randomized controlled trial involving 24 patients and with cohorts of intrapleural

streptokinase compared to intrapleural normal saline. The study showed a significant increase in drainage and improvement in radiographic appearance for the streptokinase cohort¹¹. Bouros et al also performed a randomized controlled trial but with 31 patients and comparing intrapleural urokinase to intrapleural normal saline. This study showed complete drainage in the entire urokinase group and only 4 of 12 control patients. The 12 remaining control patients were then all given intrapleural urokinase which aided in the complete resolution of 6 effusions, the final 6 effusions required VATS for complete resolution¹². Additionally, Mithos et al performed a prospective study which showed significantly decreased rates for surgical intervention and decreased mortality in patients treated with intrapleural streptokinase. The three above studies all show that complicated parapneumonic effusions can be treated effectively with tube thoracostomy and fibrinolytic therapy for complete resolution.

However, Maskell et al performed a double-blinded randomized controlled trial involving 454 patients and comparing streptokinase with placebo. This study did not show a significant decrease in mortality, rate of surgery, radiographic improvement, or hospital stay¹³. Given the large number of patients and fact that it was a double-blinded randomized control trial, the results of Maskell et al strongly point against the use of fibrinolytics in complicated parapneumonic effusions or empyema. A follow up meta-analysis performed by Tokuda et al also did not support the routine use of fibrinolytics for complicated parapneumonic effusions or empyema, however it was likely that this study was greatly powered by the Maskell study¹⁴. There is hope that newer fibrinolytics might be more effective in the lysis of adhesions such as DNase or tissue plasminogen activator (tPA). As such, the current recommendations for the use of fibrinolytics include

poor surgical candidates and patients who do not have the resources available for surgical debridement.

Thoracoscopy and Thoracotomy

In patients whom there is persistent effusion despite adequate chest tube placement or those with extensive loculations limiting effective drainage, surgical debridement is necessary. Utilizing Video Assisted Thoracic Surgery (VATS), the pleural space can be completely drained and loculations can be broken down without an open thoracotomy. VATS, in the hands of the experienced surgeon, can also be used for removal of the pleural peel which can form during the Organization Stage. In a

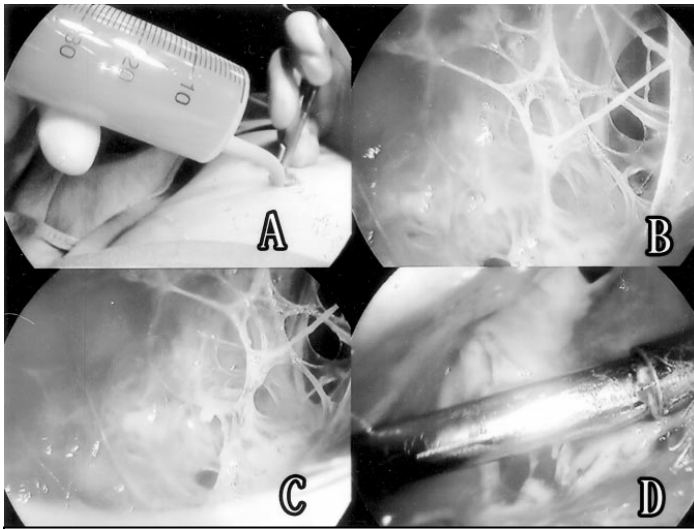


Figure 4: Lysis of adhesions using VATS.¹⁵

retrospective study, Luh et al found that early intervention with VATS resulted in better clinical results with decreased hospital stays and more rapid radiographic resolution of the effusion¹⁵. Occasionally, the pleural sepsis is severe enough to require Decortication which

involves the removal of all fibrous tissue from the visceral and parietal pleura. This allows the lung to re-expand, however this procedure is performed with a full thoracotomy so its utility in poor surgical candidates is limited. Additionally, open drainage of the area can be performed but ideally is performed late in the evolution of the

complicated effusion so as to allow the fusion of the visceral and parietal pleura at the edge of the empyema and prevent collapse of the lung with the open procedure. VATS, Decortication, and Open Drainage should be evaluated based on surgical risk for individual patients, at present VATS provides a good option for lysis of adhesions and complete drainage of a complicated parapneumonic effusion or empyema.

Future Testing of Pleural Fluid

To date, many studies have been performed to re-evaluate Light's Criteria and the criteria to differentiate complicated from uncomplicated parapneumonic effusions. Additional studies are currently being performed to look for alternative factors that may better help determine causes for exudative effusions, whether it be parapneumonic, tuberculosis, or malignancy related. The inflammatory marker, C-reactive protein, has been shown to be elevated in serum in accordance with systemic inflammation. In a recent study by Chen et al, it has been shown to have a high sensitivity and high specificity in pleural fluid when evaluated in combination with LDH^{18, 19}. Other markers including pleural TNF-alpha and pleural Adenosine Deaminase have been showed to be significantly elevated in Tuberculosis Effusions, whereas pleural VEGF has been showed to be elevated in malignant pleural effusions. Much research is still to be performed regarding the ideal supplements to Light's Criteria for further evaluation of pleural fluid.

Summary

Pleural effusions occur with a wide variety of systemic and localized diseases. Parapneumonic effusions can be divided into three types including uncomplicated,

complicated, and empyema. A thoracentesis should be performed on any parapneumonic effusion $>1.0\text{cm}$ on lateral decubitus film at diagnosis. A chest tube should be placed if the effusion is determined to be complicated or empyema based on pleural fluid analysis including pH, glucose, or gram stain and culture. If drainage with tube thoracostomy is unsuccessful then VATS should be utilized with minimal delay. In general, definitive treatment is more successful with utilized early in disease course. Future research is ongoing to help determine complicated effusions earlier so as to improve the physician's ability to intervene earlier in the natural history of parapneumonic effusions.

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