Update on the Role of Intrapleural Fibrinolytic Therapy in the Management of Complicated Parapneumonic Effusions and Empyema

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ABSTRACT

A parapneumonic effusion is the collection of exudative fluid in the pleural space associated with a concurrent pulmonary infection. Parapneumonic effusions account for approximately one-third of all effusions, and about 40% of patients with pneumonia develop a concomitant effusion. Patients with pneumonia who develop an effusion have an increased risk of morbidity and mortality. Some of the excess mortality is due to mismanagement of the parapneumonic effusion. Bacterial and white cell metabolism can rapidly turn a simple exudative parapneumonic effusion into a multiloculated purulent empyema with low pH and high lactate dehydrogenase levels. The optimal approach to treating parapneumonic effusions and pleural empyemas remains controversial. Accepted management consists of systemic antibiotics and drainage of the pleural cavity, which is achieved by either medical chest tube drainage or surgery. Several investigators have studied the efficacy and safety of intrapleural fibrinolytics in the treatment of pleural effusion and empyema. Intrapleural instillation of fibrinolytic agents is undertaken to dissolve fibrinous clots and membranes, to prevent fluid sequestration, and hence to improve drainage. Recombinant deoxyribonuclease has been reported to improve drainage in a single patient who did not respond to fibrinolytic therapy.

Key words: parapneumonic effusions, empyema, intrapleural fibrinolytics, recombinant deoxyribonuclease.
INTRODUCTION

Pleural infections represent an important group of disorders that is characterized by the invasion of pathogens into the pleural space and the potential for rapid progression to frank empyema.\(^1\) Pleural effusion develops in about 36% to 57% of patients with pneumonia. Of these patients, about 10% develop empyema or complicated parapneumonic effusion, which has a 14% to 20% mortality rate. The classification by Hamm and Light is particularly useful because it correlates closely with the correct approach to treatment of pleural infection. The 4 stages are as follows: (1) pleuritis sicca, ie, pleural inflammation without effusion; (2) exudative, ie, pleural effusion with normal pH; (3) fibropurulent, ie, pleural fluid with any combination of pH less than 7.20, frank pus, or bacteria by Gram stain or culture; and (4) organizational, ie, organized fibrin membranes with pleural peels.\(^2\)

Previous epidemiologic studies have indicated that empyema is increasing in prevalence, which underscores the importance of urgent diagnosis and effective drainage to improve clinical outcomes. Unfortunately, limited evidence exists to guide clinicians in selecting the ideal drainage intervention for a specific patient because of the broad variation that exists in the intrapleural extent of infection, presence of locules, comorbid features, respiratory status, and virulence of the underlying pathogen. Moreover, many patients experience delays in both the recognition of infected pleural fluid and the initiation of appropriate measures to drain the pleural space.\(^1\) Emphyema and large or loculated effusions need to be formally drained, as well as parapneumonic effusions with a pH <7.20, glucose <3.4 mmol/l (60 mg/dl) or positive microbial stain and/or culture.\(^3\)

Several investigators have studied the efficacy and safety of intrapleural fibrinolytics in the treatment of pleural effusion and empyema. These researchers report a 38–100% success rate (defined as improvement of symptoms, improvement of X-ray imaging, no need for surgical intervention). One group stressed the importance of accurate staging of empyema when choosing to initiate intrapleural fibrinolytic therapy. They found Computed Tomography (CT) scan evidence of a pleural peel was predictive of failure with fibrinolytic therapy. However, some patients with a complicated pleural effusion (CPE) may benefit from adjunct approaches, such as intrapleural fibrinolytics, to reduce the need for surgical interventions.\(^4\)

The present article provides review on the pathogenesis and interventional therapy of pleural infections with an emphasis on the role of intrapleural administration of fibrinolytic agents for the treatment of complicated parapneumonic effusions and empyema.

EPIDEMIOLOGY AND RISK FACTORS

Complicated parapneumonic effusions and empyema are more common at both extremes of age. At least two thirds of patients will have an identifiable risk factor at presentation, which may include immunosuppressive states (most frequently Human Immunodeficiency Virus infection, diabetes mellitus and malnutrition), alcohol or intravenous drug abuse, bronchial aspiration, poor dental hygiene, gastro-esophageal reflux, and chronic parenchymal lung disease. Microbial virulence and idiosyncrasies of the immune system are often also implicated, principally in individuals with no apparent predisposition.\(^3\)

PATHOPHYSIOLOGIC CLASSIFICATION AND CLINICAL STAGING OF PLEURAL FLUID

Pleural effusions develop when the balance of pleural fluid formation and removal is altered. Pleural effusions secondary to pneumonia are termed parapneumonic effusions. Most of these effusions remain sterile and resolve with antibiotic therapy (termed uncomplicated parapneumonic effusions), but infections of the pleural space develop in a small subset of patients and require drainage for full recovery (termed complicated parapneumonic effusions). Without effective drainage, complicated parapneumonic effusions progress to frank intrapleural pus, which defines the presence of an empyema. This progression may occur rapidly over a few days and necessitate surgical drainage (Figure 1).\(^1\)

Progression to empyema occurs in three phases. The exudative phase develops when inflammatory fluid enters the pleural space across vascular and visceral pleural membranes that have increased permeability due to pneumonia. Pleural fluid is nonviscous, free-flowing, and readily drained by thoracentesis or chest tube.
Unremitting inflammation deposits fibrin that coats the visceral pleura and promotes the formation of locules that impede lung reexpansion during attempts at fluid drainage. Pleural fluid becomes purulent and increasingly viscous (Figure 2).

This fibrinopurulent phase may respond to therapy with antibiotics and chest tube drainage but often requires intervention to break down adhesions. If a fibropurulent effusion remains undrained, fibroblasts eventually deposit fibrotic tissue that encases the lung in inelastic peels. At this organizing phase, resolution of the empyema requires surgical procedures to drain pus, obliterate the empyema space, and reexpand the lung. Parapneumonic effusions represent the most common cause of exudative effusions and occur in 20 to 57% of hospitalized patients with pneumonia. Empyemas occur in 1 to 5% of hospitalized patients with 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 1.0 cm on lateral decubitus film when measured from the inner chest wall, then the effusion is thought to be accessible to pleural fluid sampling with thoracentesis. 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 effusions. 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. A positive result from either the Gram stain or culture, or a pH of <7.20 is associated with a worse outcome and indicates the need for drainage. If the pleural fluid pH is unavailable, the pleural fluid glucose may serve as a surrogate. A glucose level >3.4 mmol/l (60 mg/dl) is associated with a better prognosis.

OPTIONS FOR MANAGEMENT OF PLEURAL FLUID

There are several options available for the management of the pleural fluid in patients with parapneumonic effusion, range from non-invasive antibiotic therapy and observation, to semi-invasive techniques such as therapeutic aspiration, tube thoracostomy and intrapleural fibrinolytics, to invasive interventions such as thoracoscopy, thoracotomy or open drainage.

In practical terms, however, the initial evaluation should focus on three critical questions, namely:

Figure 1. Serial chest radiographs and CT scan images demonstrating rapid progression of infected pleural fluid to an empyema that required surgical drainage. A: a chest radiograph obtained at hospital admission demonstrates a right pleural effusion and parenchymal density at the right lung base. Therapy with antibiotics was begun, but thoracentesis was not performed. The effusion became massive 3 days later (B) when a noncontrasted CT scan (C) demonstrated multiple locules that contained viscous pus during surgical drainage. Without contrast, the CT scan could not clearly differentiate in some areas between loculated fluid and lung consolidation.

Figure 2. Fibrinopurulent Stage loculations in a parapneumonic effusion.
Table 1. ACCP system for staging pleural infections and recommending drainage

<table>
<thead>
<tr>
<th>Effusion stage</th>
<th>Pleural space features</th>
<th>Bacteriology</th>
<th>Pleural fluid</th>
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<tr>
<td></td>
<td></td>
<td>Chemistery</td>
<td>Thoracentesis/drainage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>pH unknown</td>
<td>No/No</td>
</tr>
<tr>
<td>I (uncomplicated parapneumonic)</td>
<td>Minimal, free-flowing effusion (&lt;10 mm on lateral decubitus)</td>
<td>Culture and Gram stain results unknown</td>
<td></td>
</tr>
<tr>
<td>II (uncomplicated parapneumonic)</td>
<td>Small-to-moderate free-flowing effusion (&gt;10 mm and less than one-half hemithorax)</td>
<td>Negative culture and Gram stain</td>
<td>pH &gt;7.20 or glucose &gt;60 mg/dL</td>
</tr>
<tr>
<td>III (complicated parapneumonic)</td>
<td>Large, free-flowing effusion (one-half hemithorax or greater); loculated effusion; effusion with thickened parietal pleura</td>
<td>Positive culture or Gram stain</td>
<td>pH &lt;7.20 or glucose &lt;60 mg/dL</td>
</tr>
<tr>
<td>IV (empyema)</td>
<td>Pus</td>
<td>Tests not indicated</td>
<td>Yes/Yes</td>
</tr>
</tbody>
</table>

(1) Should the pleural space be drained? (2) How should the pleural space be drained? (3) Should fibrinolytics be instilled? Table 1 is adapted from the American College of Chest Physicians’ (ACCP) consensus statement that categorizes parapneumonic effusions according to the need for drainage. It is important to realize that the pleural space anatomy (best visualized by means of ultrasonography), pleural fluid appearance and smell, as well as pleural pH are often the only useful criteria for initial decision making, as all other laboratory tests need time for processing. Frank pus on aspiration, large effusions greater than half of one hemithorax, effusions with loculations, or fluid with a pH <7.20 all herald the need for immediate drainage. Further indications include a positive Gram stain, a positive microbial culture and pleural fluid glucose of <3.4 mmol/l (60 mg/dL).3

INTRAPLEURAL FIBRINOLYTICS

When an infected pleural space progresses to the fibrinopurulent phase, fibrin creates intrapleural locules that impede chest tube drainage. Intrapleural instillation of fibrinolytic drugs offers a theoretical benefit for lysing fibrin adhesions, promoting pleural drainage, and avoiding surgery. Small studies have reported the beneficial effects of therapy with streptokinase, urokinase, and tissue plasminogen activator(rtPA) for avoiding surgery, promoting catheter drainage, and improving the radiographic appearance of loculated effusions.1 Based on early reports of efficacy, the British Thoracic Society (BTS)11,12 and the ACCP guidelines10 recommend fibrinolytic drugs as management options.

Numerous case series and controlled trials have shown that intrapleural fibrinolysis is safe, increases drainage and improves radiological appearance. A randomized controlled study by Davies et al.13 established that systemic fibrinolysis or bleeding complications did not occur with streptokinase, and that patients who were given intrapleural streptokinase drained significantly more pleural fluid both during the days of treatment (n = 24; mean 391 vs. 124 ml, p<0.001) and overall. Patients who received fibrinolytics also showed greater improvement on the chest radiograph at discharge. Bouros et al.14 demonstrated that urokinase was a safe intrapleural fibrinolytic. The same group showed that streptokinase and urokinase were clinically and radiologically equally effective as intrapleural fibrinolytics15, and that intrapleural urokinase decreased the duration of hospitalization, duration of pleural drainage and time to defervescence. Furthermore, Bouros et al.16 were able to show that urokinase’s effect in empyema was through the lysis of pleural adhesions, rather than the volume effect of instilled urokinase and saline.

The largest prospective double-blind controlled study on the role of intrapleural streptokinase for pleural infection was published in 2005 (Multicenter Intrapleural Sepsis Trial - MIST 1).17 In this study 454 patients with pleural pus, pleural sepsis with a pH <7.2 or bacterial invasion of the pleural space were randomly assigned to receive streptokinase or placebo. The
patients included were older than in most other studies (average age 60 years) and had a high prevalence of comorbidities. The MIST 1 study could not substantiate the role of streptokinase in pleural infections: There was no difference in mortality, need for surgery, radiographic outcome or length of hospitalization. The design and execution of this study, however, were criticized. The lack of image-based selection criteria meant that patients with pleural sepsis were included irrespective of presence, quantity and quality of loculations. Questions were raised about the reproducibility of clinical management decisions taken across 52 study centres, many of which lacked on-site surgical expertise and contributed only small numbers of patients. The study permitted small-bore chest tubes, but did not report on pleural drainage volumes, which casts doubt on the efficacy of the drainage techniques used. Furthermore, owing to the decentralized and blinded design streptokinase/placebo was shipped to the study centres after randomization causing delays in the initiation of treatment. The value of mortality as an endpoint was also questioned, as patients with serious concomitant illnesses that made survival beyond 3 months unlikely were excluded from the study. The 3-month mortality after hospitalization for pneumonia among middle-aged and older patients is more closely associated with the fact that an episode of pneumonia often identifies a fragile underlying health status than with the severity of the acute episode of pneumonia itself. Intrapleural streptokinase may therefore not have been given a fair chance to improve the short-term mortality. These deficiencies do not invalidate this large randomized trial, but concerns remain about the validity of its results with regard to younger, more severely ill patients and in different health care settings.

The most recent and second largest prospective study was conducted by Misthos et al. In their study, patients were randomized to a group managed solely with tube thoracostomy or a group treated with a combination of tube thoracostomy and streptokinase instillation (no placebo control). They found that tube thoracostomy was successful in 67.1% of cases, whereas the installation of streptokinase led to a favourable outcome in 87.7% (p<0.05) and significantly shortened hospital stay. The mortality rate was also significantly lower in the fibrinolytic group, and streptokinase was found to decrease the rate of surgical interventions and the length of hospital stay.

Some centers now use rtPA for fibrinolysis. Walker et al. first reported the apparent benefits of rtPA in a patient with empyema. Subsequently, Skeete et al. instilled rtPA through surgical chest tubes into 42 patients with a variety of pleural conditions, of which 12 were empyemas. They reported accelerated radiographic improvement and clinical benefit. Levinson and Pennington used fibrinolytic therapy for 30 patients with largely multiloculated pleural infections; 20 patients received rtPA through small-bore, image-guided chest tubes. The mean length of hospital stay was 11 days, and no patient required surgical drainage. Gervais et al. reported their experience with rtPA instilled through image-guided 8.5F to 16F catheters in 66 patients, of whom 53 had empyemas or complicated parapneumonic effusions. In the study by Gervais et al. patients were selected for fibrinolysis if the initial pleural fluid drainage was incomplete. The overall success rate was 86%, although the outcomes were not specifically reported for the 53 patients with pleural infections. Based on CT imaging studies obtained before chest tube insertion that demonstrated multiple locules, the authors opined that rtPA successfully drained effusions that would otherwise have required surgery. The suggested dosages of the current fibrinolytics in use are summarized in Table 2.

<table>
<thead>
<tr>
<th>Fibrinolytic</th>
<th>Dose</th>
<th>Instillation</th>
<th>Duration</th>
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<tbody>
<tr>
<td>Streptokinase</td>
<td>250,000 IU</td>
<td>100–200 ml saline</td>
<td>Daily for up to 7 days (until drainage &lt;100 ml/day)</td>
</tr>
<tr>
<td>Urokinase2</td>
<td>100,000 IU</td>
<td>100 ml saline</td>
<td>Daily for up to 3 days</td>
</tr>
<tr>
<td>tPA</td>
<td>10-25 mg</td>
<td>100 ml saline</td>
<td>Twice daily for up to 3 days</td>
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</table>

Fibrinolytic drugs have negligible effects on decreasing the viscosity of empyema pus in contrast to agents that depolymerize DNA, such as human recombinant deoxyribonuclease. The viscosity of pus is largely attributable to its deoxyribose nucleoprotein content. Recombinant deoxyribonuclease has been reported to improve drainage in a single
patient who did not respond to fibrinolytic therapy. Clinical trials on the efficacy of recombinant tPA and DNase are currently being performed. An interesting ex vivo observation by Light et al. was that DNase combined with streptokinase (known as Varidase) was superior to either streptokinase or urokinase at liquefying empymic pleural material obtained from rabbits. When thick empymic material from rabbits is incubated with either streptokinase or urokinase, there is no significant liquefaction of the fluid. In contrast, when the fluid is incubated with Varidase, the fluid becomes completely liquefied over 4 h. Although Varidase is presently not available in the United States, recombinant human DNase (Pulmozyme; Genentech, San Francisco, CA) is available. It was postulated that the streptodornase (DNase) was necessary for the liquefaction of the deoxyribose nucleoproteins, which make up a sizable proportion of the solid sediment of purulent exudates. Simpson and coworkers have recently demonstrated that recombinant DNase by itself is very effective at reducing the viscosity of human empyma fluid.

At the present time, there is another multicenter trial underway in the United Kingdom in which patients with complicated parapneumonic effusions are randomized to saline, 10 mg tPA, 1 mg recombinant DNase, or the combination of tPA and DNase twice a day. Until the results of this trial are available, the use of intrapleural fibrinolytics should be reserved for patients in centers without access to video-assisted thoracic surgery and for patients who are not surgical candidates.

**CONCLUSION**

Modern principles of managing pleural space infections emphasize the importance of the early detection of effusions in patients with pneumonia, and the prompt drainage of complicated parapneumonic effusions and empyemas. Delays in effective drainage increase morbidity and mortality. It is recommended that a stepwise approach be taken with patients with parapneumonic effusions. The treatment options are therapeutic thoracentesis, tube thoracostomy, tube thoracostomy with intrapleural fibrinolytics, thoracoscopy, and thoracotomy. The use of fibrinolytics remains controversial, although evidence suggests a role for the early use in complicated, loculated parapneumonic effusions and empyema, particularly in young, acutely ill patients, poor surgical candidates and in centres with inadequate surgical facilities. Recombinant deoxyribonuclease has been reported to improve drainage in a single patient who did not respond to fibrinolytic therapy.

**REFERENCES**

9. Dittmar PC. Pleural effusions: A focus on parapneumonic effusions. (Published online 24 July, 2009).