Intrapleural Fibrinolytics in Management of Empyema Thoracis*

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**Study objective:** To determine the success and complication rates of fibrinolytic therapy (FL) in the treatment of thoracic empyema.

**Design and patients:** Between December 1992 and November 1994, all patients referred with empyema thoracis (ET) were offered FL. FL consisted of streptokinase (275,000±170,000 IU) or urokinase (121,000±57,000 IU) daily for a mean of 6.2±2.1 days.

**Setting:** The University of New Mexico Health Sciences Center and the Albuquerque Veterans Affairs Medical Center.

**Results:** Twenty-six patients were treated. Sixty-two percent (16/26) had complete resolution (CR) of symptoms, near or complete normalization of chest radiographic findings, and required no surgery or empyema tubes. Eight percent (2/26) had relief of symptoms and partial resolution (PR) of radiographic abnormalities and were discharged from the hospital with empyema tubes in place. All patients with PR had empyema tubes removed within 30 days of hospital discharge. Thirty-one percent (8/26) of patients failed to completely improve clinically or radiographically (nonresponse) and were treated with decortication or empyema tubes for greater than 30 days. Bleeding occurred in a single patient (4%). There was no mortality associated with FL use.

**Conclusions:** The use of FL is associated with resolution of ET in 69% (18/26) of patients. This modality is safe, effective, and spares most patients with empyema the morbidity and mortality of thoracotomy.

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**Key words:** empyema; streptokinase; urokinase

**Abbreviations:** CR=complete responder; ET=empyema thoracis; FL=fibrinolytic therapy; LDH=lactate dehydrogenase; NR=nonresponder; PR=partial responder; PT=prothrombin time; PTT=partial thromboplastin time

Empyema thoracis (ET) represents a continuum of disease ranging from thin pleural fluid microscopically contaminated by organisms to gross purulence with dense deposition of fibrin and scar within the pleural space. The management of ET must be tailored to the character of changes within the pleural space and the patient condition. Most commonly, management of ET has consisted of administration of systemic antibiotics, with observation, thoracentesis, insertion of a chest tube, or decortication.

The use of intrapleural enzymatic agents for dissolution of ET was first described by Tillett and Sherry in 1949. Streptokinase and streptodornase were used. More recently, other reports have described using purified streptokinase or urokinase to decrease the frequency of side effects. However, these reports have been sporadic and in small groups of patients. We describe a large consecutive group of patients treated with fibrinolytic therapy (FL) for ET.

**Materials and Methods**

All patients referred for decortication for ET between December 1992 and November 1994 were considered for FL. ET was defined as the presence of documented infection by Gram’s stain or culture, the presence of grossly purulent pleural fluid, complicated parapneumonic effusion (two of the following: pH<7.20, lactate dehydrogenase [LDH]>400 IU/L, or glucose <40 mg/dL), or pleural effusion and clinical sepsis without other etiology. All patients had failed to respond to antibiotic therapy and chest tube placement, and they were candidates for surgical decortication. History and physical examination were performed prior to FL.

Standard posteroanterior and lateral chest radiographs were obtained daily. Chest CT scans were performed prior to, during, and after FL. Prothrombin time (PT), partial thromboplastin time (PTT), and platelet counts were measured prior to initiating therapy and during the period of FL administration.

Patients were not treated with FL if they had coagulation abnormalities, trauma, or surgery within 7 days, prior reaction to streptokinase or urokinase, or if they refused or were noncompliant with therapy. Patients were also excluded if a bronchopleural fistula (air leak) was present or if severity of sepsis required urgent operation. If abnormalities in the PT, PTT, or platelet count developed, therapy was terminated. A patient with empyema...
had no hospital discharge. With a small residual pleural cavity, patients were discharged home from the hospital without surgical intervention, but with empyema tubes in place (Fig 2). All patients in this group had removal of empyema tubes within 30 days of completion of FL.

Nonresponders (NR) were patients who underwent decortication or empyema tube drainage for greater than 30 days after completion of FL (Fig 3). NRs were compared with responders (CRs and PRs) for age, duration of empyema, initial temperature and WBC count, number of tubes and catheters, dosage of FL, number of treatments, length of hospitalization, fluid chemistries, and whether cultures grew organisms or were sterile. Platelet count, PT, and PTT before and after treatment were compared to determine whether coagulopathy had developed. Data were analyzed using the Student's *t* test with Satterthwaite's approximation for continuous variables, the two-sample Wilcoxon test with exact *p* value for ordinal variables and as a nonparametric method for nonnormal distributions, and Fisher's Exact Test for binary variables. For paired data (premeasurement and postmeasurements), paired *t* tests were performed. Results are presented as means±1 SD.
RESULTS

A total of 26 patients are described. Nineteen patients were treated with streptokinase, 7 with urokinase. Mean age was 41.8±17.1 years. Twelve percent (3/26) were female, and the remainder (23/26) were male.

The mean duration of ET symptoms prior to treatment was 2.9±2.6 weeks. The mean temperature maximum immediately prior to treatment was 38.4±1.2°C, the mean WBC count prior to initiating FL was 15.0±5.3×10³ cells/mm³.

Empyema fluid had a mean pH of 6.96±0.34, a mean glucose level of 51.9±51.1 mg/dL, a mean LDH level of 6,989±6,478 IU/L, a mean total protein (TP) level of 4.95±1.13 g/dL, and a mean WBC count of 36,963±68,449 cells/mm³. Cultures grew organisms in 42% (11/26) of patients. The most common organisms were Staphylococcus, Streptococcus, and anaerobic bacteria.

Patients required 1.36±0.7 chest tubes, and 0.42±0.58 radiographically placed catheters. All patients received at least one chest tube. Sixty-five percent of patients (17/26) received chest tubes only; the remainder received catheters as well. The average number of treatments was 6.19±2.08. Patients without other reason for hospitalization (decortication, trauma, pancreatitis, renal failure, etc) were discharged from the hospital after completing FL. The mean hospitalization was 13.1±11.5 days. Twenty-three percent (6/26) of patients received thoracotomy. No patient with significant clinical improvement after only 7 days of FL chose decortication at that time. No patient required thoracotomy for deteriorating clinical status while receiving FL.

The mean pretreatment PT was 11.81±0.73 s; posttreatment it was 11.89±1.02 s (p=0.33). The PTT pretreatment was 29.11±2.45 s; posttreatment it was 29.29±3.47 s (p=0.53). The platelet count pretreatment was 551±196 cells/mm³; posttreatment it was 688±240 cells/mm³ (p=0.015).

There was no significant difference (p>0.1) between patients with complete responses or partial responses and those with nonresponses in age; number of FL treatments; pH, LDH, total protein (TP), WBC, or RBC count of empyema; temperature prior to treatment; WBC count; number of chest tubes; whether
cultures were positive or sterile; or dosage of urokinase.

There was a trend toward significance in the duration of empyema prior to treatment, with NRs having longer durations (mean 4.50±3.25 vs 2.15±1.86 weeks; p=0.088), and in the empyema glucose, with NRs having lower levels (mean 27.83±17 vs 63.10±58 mg/dL; p=0.062).

Patients with nonresponses received fewer interventional catheters (p=0.02) and higher doses of streptokinase than PRs or CRs (385,000±214,572 vs 208,333±118,386 IU; p=0.04). Responders had significantly shorter hospitalizations following initiation of FL than NRs (9.29±3.56 vs 21.13±17.84 days; p=0.006) (Table 1).

There were no deaths. A significant complication occurred in only 1 patient (4%). He required 2 thoracotomies for oozing from rib fractures sustained 1 month prior to FL. This patient had coagulation studies prior to FL, results of which were normal. Minor complications included discomfort during instillation of FL easily managed with narcotics. Fever was present in most patients but did not result in discontinuation of FL in any patient.

Follow-up was a minimum of 30 days from hospital discharge or removal of tubes, which ever was later. There was no recurrence of ET in any patient during this period. Patients were subsequently followed up by the medical and pulmonary services. However, no patient has been referred with recurrence subsequent to the 30-day surgical follow-up.

**DISCUSSION**

ET is thought to proceed through several well-described stages during maturation. In the exudative stage, a parapneumonic effusion develops and becomes secondarily infected. As infection progresses, the initially serous fluid becomes thick and purulent with organisms, fibrin, and WBCs. Loculations develop: the fibropurulent stage. Additional time and inadequate treatment result in organization with fibroblasts and scar encasing the empyema, lung, and pleural space.

The therapy for ET is determined by stage. In the exudative stage, antibiotics and thoracentesis or chest tube placement usually results in cure. In the fibropurulent stage, antibiotics with properly positioned chest tube drainage may resolve the ET. Failures are due to improperly positioned tubes, loculations, increased fluid viscosity, or early peels on the lung. Failures are traditionally managed with decortication or prolonged open drainage. The organized stage requires antibiotics and either decortication or open drainage.

Thoracoscopy is useful for early loculated ET by allowing lysis of adhesion within the pleural space. However, general anesthesia is required, and the result achieved is the same as draining each loculation with a tube or catheter. In patients with trapped lung due to debris and early peel, neither complete drainage nor pneumolysis will be effective. Either chemical dissolution using FL or mechanical removal by decortication is required.

FL decreases empyema viscosity and dissolves loculations within the pleural space and therefore may resolve ET in patients in whom nonsurgical treatment has otherwise failed. Both streptokinase and urokinase convert plasminogen to plasmin. Plasmin dissolves fibrin and produces dissolution of loculations and early peels. Combined with chest tube drainage, this allows evacuation of fibropurulent empyemas that fail chest tube drainage alone. Both urokinase and streptokinase have been used in treatment of empyema. Urokinase is used most commonly because of the lower risk of anaphylaxis or other complication.

The efficacy of FL therapy for treatment of ET has been well documented in small series. In one recent series, Robinson et al described 13 patients with ET treated with streptokinase or urokinase intrapleural instillations. Although they reported 77% complete success, only 4 of 13 (31%) fulfilled our criteria for CR, ie, hospital discharge without empyema tubes. Six of 13 (46%) of their patients were discharged home from the hospital with empyema tubes in place. None of these tubes were removed within 30 days and would be considered nonresponsive by our criteria. Three of 13 (23%) were considered failures and required thoracotomy.

Moulton et al described 118 patients with complicated pleural disease. Fifty-seven patients had documented empyema based on culture, Gram’s stain, or purulent drainage. Twenty-seven patients had sterile complicated parapneumonic effusions. FL was used in 98 (83%) of the entire group. The overall success rate

**Table 1—Comparison Between NRs and CRs or PRs**

<table>
<thead>
<tr>
<th>Variable</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Duration</td>
<td>0.088</td>
</tr>
<tr>
<td>Temperature</td>
<td>&gt;0.1</td>
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<tr>
<td>WBC</td>
<td>&gt;0.1</td>
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<tr>
<td>Glucose</td>
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<tr>
<td>Empyema fluid pH, LDH, TP, WBC, RBC</td>
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<tr>
<td>No. of interventional catheters</td>
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</tr>
<tr>
<td>No. of chest tubes</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Length of hospitalization after initiation of FL</td>
<td>0.006*</td>
</tr>
<tr>
<td>Dose of streptokinase</td>
<td>0.04*</td>
</tr>
<tr>
<td>Dose of urokinase</td>
<td>&gt;0.1</td>
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<tr>
<td>No. of FL treatments</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Culture results</td>
<td>&gt;0.1</td>
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*Statistically significant.
with or without FL was 94%, mean duration of drainage was 6 days, and mean hospitalization was 20 days. Details for patients with empyema were not specified further. Other smaller series have reported success rates of up to 92%.4-9

In this study, the CR rate was 62%, the PR was 8%, and the NR was 31%. Thus, more than two thirds of patients with traditional indication for decortication for ET were treated successfully with FL and without thoracotomy.

NRs had longer duration of symptoms and lower empyema glucose levels than responders, consistent with more advanced infections. The mean duration of symptoms in responders was 2 weeks (fibropurulent stage); these patients are expected to respond to FL. NRs had a mean duration of symptoms of 4.5 weeks (organized stage); they are less likely to respond to FL. These findings are similar to those reported by Moulton et al.3 Because the range of duration was wide in each group, duration of empyema should not be used as an exclusion criterion in patients being considered for FL.

NRs received significantly higher mean streptokinase dosages than responders. The failure to resolve empyemas in these patients suggests that doses of more than 250,000 IU are not necessary. The optimal dose of streptokinase per treatment is unknown.

Since responders had significantly more interventional catheters than NRs, improved drainage of localizations may have been partially responsible for the improved results compared with the NRs. However, all patients had CT scan verification of properly positioned drains and at least 24 h of 20 cm H2O suction prior to initiation of FL. This suggests that FL rather than catheters produced the response.

Although most responders had some residual pleural thickening radiographically, the natural history and significance of these findings are unknown. At least some of the patients showed continued radiographic improvement after removal of tubes in limited follow-up.

Our FL of choice during the study changed from streptokinase to urokinase. Both are relatively inexpensive ($87.88/250,000 IU vs $124.20/100,000 IU, respectively), but urokinase, unlike streptokinase, is a native protein and therefore less likely to produce antibodies, allergic reaction, or anaphylaxis. The cost of urokinase treatment, based on the mean of 6.19 treatments per patient in this study, is estimated to be $768.80.

FL is associated with low morbidity and mortality and should be considered in the treatment of patients with ET. We suggest the following algorithm in treatment of patients with ET and without contraindications to FL: (1) drainage of all localizations using chest tubes or radiographically placed catheters using criteria above; (2) if this fails to completely expand the lung after 24 h of 20 cm H2O suction as documented with repeated CT scan, perform FL using 100,000 IU of intrapleural urokinase; FL is administered daily for 7 days, or less if radiographic resolution occurs, using the technique already described; drains are removed when CT scan confirms complete resolution of pleural fluid and cavities; (3) if no response results, proceed to empyema tube drainage or decortication; if partial improvement has occurred, perform FL for an additional 7 days, or less if CT documented resolution is achieved; and (4) if after 14 days of FL complete improvement is not reached, convert drains to empyema tubes or proceed to decortication.

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REFERENCES