Intrapleural Urokinase in the Treatment of Loculated Pleural Effusions*

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The purpose of this study was to assess the value of intrapleural urokinase (UK) instillations in enhancing tube drainage of loculated, complex pleural effusions. Tube thoracostomy has variable success in the treatment of complex pleural effusions, with limitations because of viscous fluid, improper tube position or kinking, and, most importantly, loculation. In the past, intrapleural administration of streptokinase has been used to lyse locules. In this study, eight patients with nine loculated pleural processes were treated with intrapleural instillations of UK. Six patients had previously undergone unsuccessful conventional tube drainage. Loculation was suggested by persistent fluid despite an adequate trial of simple drainage, radiographic demonstration of septation, or drainage of a volume of fluid far less than expected by a computed tomography scan. After instillation of a UK solution, the tubes were clamped for 30 to 180 min and then placed back to suction. Five pleural cavities with disease 6 to 18 days old showed complete resolution, and clinical improvement occurred. Three pleural processes showed improvement and one showed no improvement, with disease ranging from 23 days to 3 months. No complications were seen. These results suggest that UK instillations may enhance tube drainage of loculated pleural fluid in the early phase, before fibrosis has developed.

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SK = streptokinase; UK = urokinase

Conventional indications for tube thoracostomy in the setting of infection include empyema with frank pus, complicated parapneumonic effusion (pH less than 7.0 to 7.2, glucose less than 40 mg/dl, or lactate dehydrogenase greater than 1,000)U/L, or positive pleural Gram stain or culture.[1] Additionally, laboratory values may be misleading in the presence of loculation, and tube drainage may be indicated in that situation despite normal values.[2] These pleural processes may result from an adjacent pneumonia, prior trauma or thoracic surgery, or extension from an intra-abdominal process.

Failure to control the pleural process can lead to persistent sepsis, bronchopleural or bronchocutaneous fistulae, restrictive lung disease, and, occasionally, death.[3] Factors that may lead to progressive disease include improper antimicrobial therapy, a resistant pneumonia (such as one from an endobronchial obstruction), and inadequate drainage. Simple drainage may be inadequate because of the presence of viscous fluid with fibrinous debris or clots clogging the tube, loculation of the fluid, improper tube position, or kinking of the tube. Solutions to these problems are the use of image-guidance to repositioning tubes or place new tubes,[4-6] instillation of streptokinase (SK) through the tube, chronic open tube thoracostomy, or surgical drainage.[1] Recently, two reports have appeared concerning the use of intrapleural urokinase (UK) to dissolve fibrinous debris and loculi to enhance drainage.[7,8] Below, we describe our experience with UK in eight patients with nine loculated effusions refractory to conventional tube thoracostomy.

Material and Methods

Eight patients with loculated pleural effusions in 9 hemithoraces were treated from December 1990 to July 1992. This consists of all patients with loculated effusions referred to the interventional radiology section during this time who met the criteria for UK therapy described below with the exception of one pregnant woman. This last patient was not treated because of concern over potential *in utero* bleeding should significant amounts of the drug be absorbed.

There were 7 men and 1 woman, ages 29 through 63. Indications for initial therapy with closed thoracostomy drainage were persistent fever despite antibiotics in five patients, respiratory compromise in four patients, two of whom were ventilator-dependent, and complicated fluid identified on prior thoracentesis in six patients. The pleural fluid consisted of gross pus in one postoperative patient, serous, complicated parapneumonic effusions (pH less than 7.0, glucose less than 40 mg/dl and straw-colored fluid) in four pleural cavities in three patients, and infected, loculated hemothorax in one patient. The sixth patient (seventh hemithorax) had a large hemothorax that developed in the setting of a small, pre-existent, complicated parapneumonic effusion. This occurred 10 days after starting anticoagulation therapy for a pulmonary embolism. The seventh patient (eighth hemithorax) had serous, multiloculated fluid that was the residual of a 2- to 3-month-old tuberculous empyema. The last patient (ninth pleural space) had a chronic loculated process with a history of pus that was drained by conventional chest tubes starting 81 days earlier.

Six patients had prior unsuccessful attempts at treatment by conventional drainage with large bore surgical tubes (30 to 40F tubes placed using traditional external anatomic landmarks); the remaining two patients were referred directly for image-guided tube placement due to marked obesity and obvious loculation as

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indicated by numerous air bubbles on chest radiography.

Eight pleural spaces were treated by placement of 10F to 14F VTC locking pigtail drainage catheters (Medi-tech, Watertown, Mass) into the fluid by using image guidance. These catheters are relatively thin walled, with inner diameters ranging from 7.5 to 10.4F, and large, skived, sideholes with diameters of 3 to 6 mm each. A combination of fluoroscopy, ultrasound, and computed tomography (CT) permitted precise placement of the tube into the fluid. The Seldinger technique was usually used, in which preliminary placement of a needle was followed by a guidewire and then exchanged for the drainage catheter. The drain was positioned such that it would traverse the greatest distance within the pleural collection. The postoperative empyema already had a conventional, large-bore chest tube located properly, as depicted by CT. All tubes were placed to water-seal suction.

The estimated time from the onset of the pleural process to the use of UK was from 6 to 81 days. Criteria for the use of UK were (1) persistent fluid and poor tube drainage despite an appropriately positioned, patent drain, (2) multiple loculi depicted by CT scan, ultrasonography, or fluoroscopy with contrast injection, or (3) presumed multiloculation indicated by initial drainage of a volume of fluid far less than expected by imaging studies.

Urokinase (Abbokinase, Abbott Laboratories, North Chicago, Ill) was instilled as a solution of 1,000 to 2,500 U/ml in volumes of 100 to 500 ml of normal saline solution. After injection, the tube was clamped for 30 to 180 min during which time the patient was instructed to shift position to promote even distribution of the drug. The catheter was then placed back to suction. The initial doses ranged from 180,000 to 250,000 U with two patients receiving this as divided instillations 12 h apart. All patients except one had a follow-up CT scan within 5 days with decisions concerning further treatment based on the findings. The patient with morbid obesity exceeded the table limit for the CT scanner.

Associated medical conditions included unstable angina in one patient, severe coronary artery disease and heart failure (ejection fraction of 23 percent) in one patient, HIV positivity in two patients, morbid obesity in one patient, and diabetes and hypothyroidism in one patient.

Results

The treatment of the pleural effusions with UK was successful in completely resolving the pleural disease in five of the nine cavities (four of eight patients) including the one postoperative empyema and the infected hematoma. Significant improvement in the volume of fluid was seen in three of the remaining pleural spaces, and no significant improvement was seen in one. The results are summarized in Table 1.

Resolution of Pleural Disease

The five pleurae showing resolution (patients 1, 2, 4, and 5) had complex exudates that were 6 to 18 days old. The fluid completely resolved in 2 to 7 days, documented by CT scans (Fig 1 A-C). Three of these five pleural processes resolved with one instillation of UK while two required a second instillation, given after an interim scan showed persistent fluid. The UK was used immediately after chest tube placement and maximal aspiration of fluid in two of these five pleural cavities, both of which were the ones requiring retreatment. In one of these, there was a loculus separate from the position of the chest tube.

Drainage before the use of UK ranged from 10 to 945 ml over 0 to 14 days. Net drainage after treatment was 240 to 1,260 ml with a sharp rise in net output of several hundred milliliters. In all cases, net drainage was maximal in the first 12 to 24 h after each UK instillation and then tapered off. In the three spaces initially draining straw-colored fluid, 50 to 150 ml of thick, proteinaceous (fibrinous) material was recovered. All four patients (five pleural spaces) showed significant clinical improvement with resolution of infection.

Case Example

The patient with the postoperative empyema was a 57-year-old man with a history of diabetes, schizophrenia, hypothyroidism, and gout. On admission, he had *Mycoplasma pneumoniae* and a complicated pleural exudate (pH 6.9, WBC 14,000, and culture

Table 1—*Results of Urokinase Instillation in Nine Loculated Pleural Effusions*

Patient	Pleural Space*	Age of Effusion†	Cause of Effusion	UK Dose, 1,000 U	Outcome: Pleural Fluid	Outcome: Clinical Improvement‡	Comments
1	R	13	Parapneumonic	750	Resolution	Y	
	L	13	Parapneumonic	250	Resolution	Y	
2	R	6	Parapneumonic	400	Resolution	Y	
3	R	42	Parapneumonic	500	Persistent	N	Open tube drainage
4	R	18	Postoperative empyema	500	Resolution	Y	
5	R	11	Infected hemothorax	250	Resolution	Y	
6	R	23	Parapneumonic + hemothorax	750	Minimal residual	Y	
7	R	90	Residual tuberculous empyema	1250	Persistent	Y	Trapped lung
8	L	81	Residual pyogenic empyema	750	Minimal residual	N	Infected pleural peel

*R = right, L = left.
†Estimated age in days.
‡Y = yes, N = no.

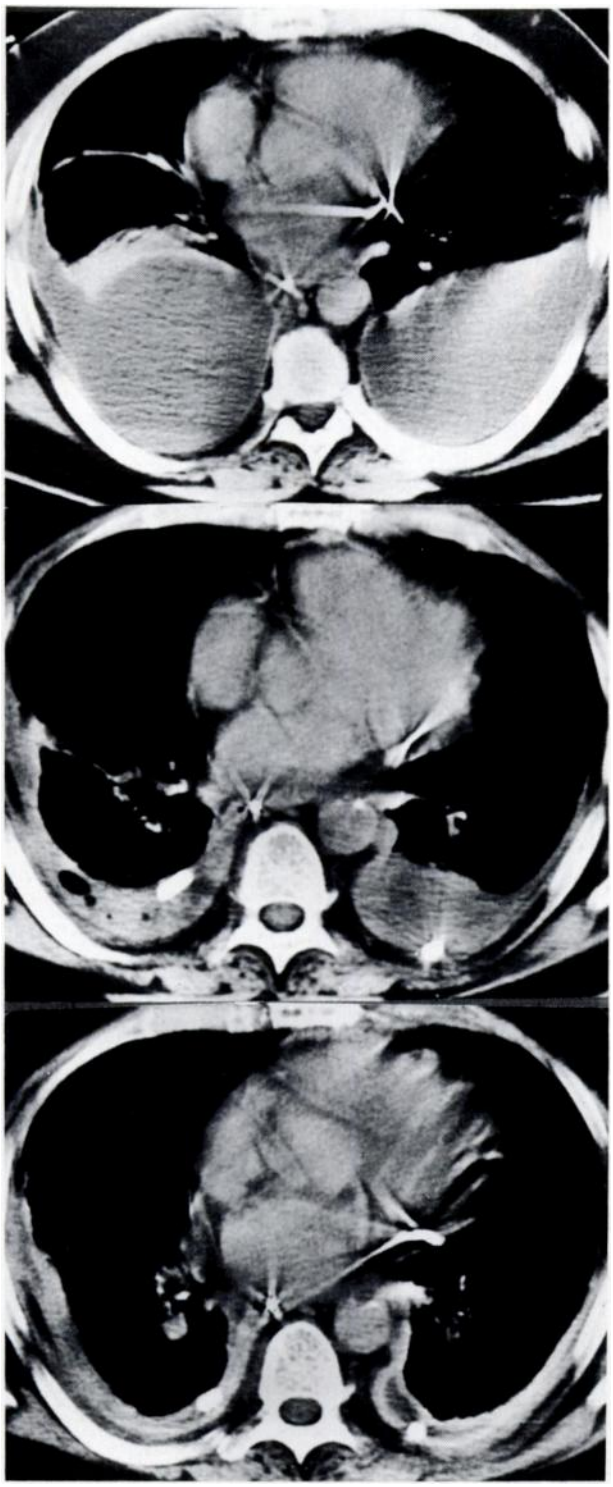

FIGURE 1. A 55-year-old man is ventilator-dependent and has unstable angina, bilateral pneumonia, and large, complicated parapneumonic exudates refractory to conventional chest tubes. *Top*, CT scan showing bilateral effusions before radiologic guided placement of a 14F drain on each side. Urokinase was given immediately on the right because of the demonstration of numerous septae on ultrasonography and a relatively low initial output of only 300 ml. After an additional output of 700 ml on the right side over the next 24 h, both tubes stopped draining. *Center*, CT scan 48 h later shows significant improvement but still residual fluid, greater on the left than on the right. Urokinase was readministered on the right and given for the first time on the left side. After an additional 250 ml of drainage on the right side and 300 ml on the left side, output again became scant. *Bottom*, CT scan at 6 days shows minimal residual fluid and slight pleural thickening. The patient had been extubated and defervesced the next day, at which time the tubes were removed.

negative), and developed respiratory failure requiring intubation 17 days later. The patient had continued sepsis and culture from a repeat thoracentesis 51 days after admission, which yielded enterococcus. Another culture obtained at the time of placement of a chest tube on day 74 grew coagulase negative Staphylococcus. Follow-up imaging studies showed persistence of pleural fluid and the patient had a thoracotomy, decortication, and rib resection on day 81. A No. 40 chest tube was placed at that time. Four days after surgery, the patient developed a fever spike, and a CT scan showed the tip of the chest tube appropriately positioned in a pleural fluid collection despite scanty output: initially 30 to 60 ml/d of purulent drainage, then 10 to 20 ml/d. He remained ventilator dependent, and a repeat CT scan 15 days after surgery showed a persistent collection around the chest tube (Fig 2, top) that had been irrigated in the interval. On the 18th postoperative day, 250,000 U of UK in 125 ml of saline solution was injected and the tube clamped for 1.5 h. This procedure was repeated the next day as well. Over the next 2 days, the patient drained 230 ml of purulent material, and a repeat CT scan showed atelectasis and moderate pleural thickening but no pleural fluid. Pleural cultures now revealed Klebsiella and Pseudomonas and his antibiotic regimen was altered accordingly. The tube continued to drain 20 to 50 ml/d over the next 6 days, after which output became scant. He defervesced on the fourth day and showed continued clinical improvement. He was discharged several weeks later with the chest tube to be advanced 1 inch per week. A follow-up CT scan 36 days after UK therapy showed minimal fluid and residual pleural thickening about the tip of the chest tube (Fig 2, bottom).

Incomplete Responses

The three patients (patients 6, 7, and 8) showing incomplete responses had disease ranging from 23 days to 3 months. Clinical improvement occurred in two patients. The first patient (patient 6) had respiratory compromise related to a hemothorax developing 10 days after anticoagulation therapy for pulmonary embolism. Additionally, an underlying parapneumonic effusion related to *Staphylococcus aureus* bacteremia was present. A chest tube placed 23 days later drained 2,600 ml of fluid then stopped despite significant residual fluid. Two instillations of UK over the next few days netted another 750 ml and resulted in a much smaller effusion. The patient clinically was doing well, so the tube was removed without further attempts to fine-tune his treatment.

The second patient (patient 7) had a 3-month-old tuberculous pleural effusion with numerous air bubbles visible on chest radiographs. Severe cardiac insufficiency contraindicated surgery, so tube drainage was requested. Only 90 ml drained over the first 24 h, so UK was instilled, resulting in a net output of 365 ml over the next day and then a drop in drainage. Radiographs showed coalescence of the pleural process into a single air-fluid level, but the space did not resolve despite two more instillations

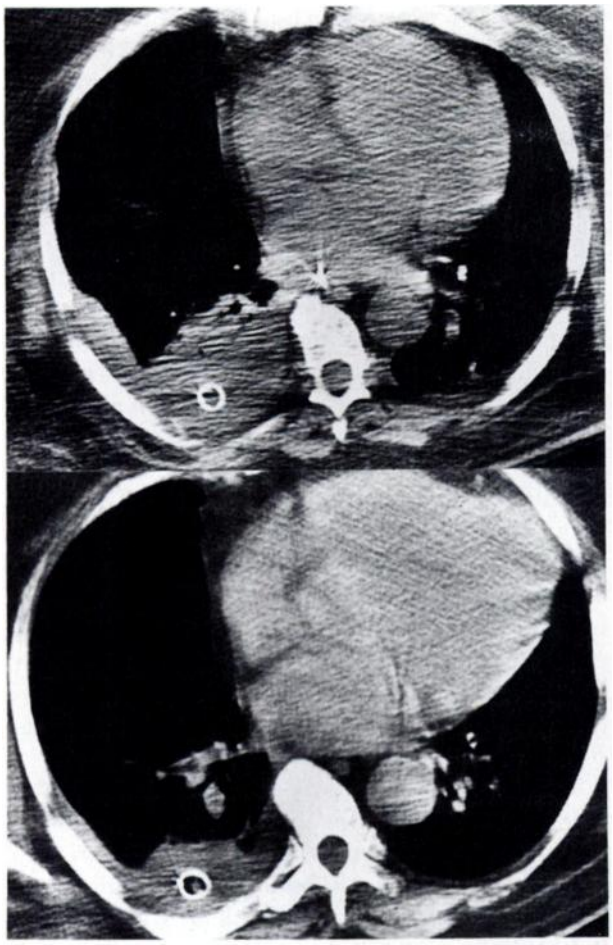

FIGURE 2. *Top*, CT scan of a postoperative empyema 15 days after decortication and rib resection for a 3-month-old infected pleural space. Three days later, UK was instilled through the appropriately positioned chest tube. *Bottom*, CT scan after UK therapy shows only residual pleural thickening.

of UK. A CT scan revealed adjacent lung disease, and thoracoscopy with a flexible endoscope showed extensive pleural scarring giving a trapped lung and preventing spontaneous collapse of this space. The tube was removed and he has remained stable with regard to his pulmonary disease for 5 months by receiving continued antituberculous medication.

The third incomplete response (patient 8) was in a patient who had a basilar pleural effusion with extensive surrounding pleural thickening 81 days after presenting with a tension pyothorax. Three UK instillations each accumulated several hundred milliliters over the next 24 h, after which the drainage would decline. A follow-up CT scan showed only slight residual fluid at the base but no change in the extensive pleural peel elsewhere. He had no clinical improvement despite drainage of this fluid and was thought to have an infected pleural peel.

No Response

Patient 3 showed no benefit. He had a straw-colored, *Haemophilus influenzae* parapneumonic empyema that was culture-positive and had been present for at least 42 days despite treatment with a conventional 32F chest tube for the last 33 days. A 12F catheter was placed into residual fluid under CT and fluoroscopic guidance followed by instillation of a total of 500,000 U of UK over the next 5 days. Less than 100 ml of additional fluid drained. The patient was not considered to be a surgical candidate due to poor overall medical condition, and both chest tubes were removed after the patient defervesced. He returned 17 days later with recurrent symptoms and enlargement of the pleural effusion. This was treated by repeat drainage, with the initial closed tube thoracostomy eventually converted to open tube drainage.

No specific complications in relation to UK were seen in any of the patients.

Discussion

Failure of tube thoracostomy treatment for complex pleural exudates is related to several factors, of which the most critical are believed to be loculation and viscosity. Closed tube thoracostomy has reported success rates of 35 to 80 percent with poorer results in secondary empyemas (postoperative and posttraumatic) than in primary, parapneumonic empyemas.[9,10] Death rates of 8 to 51 percent have been reported for thoracic empyema[9,11] with poorer outcomes again seen in secondary lesions. Open tube thoracostomy or surgical drainage may be necessary, especially in resistant effusions,[1,9-11] although thoracoscopy holds promise as a less invasive alternative for managing these.[12]

Streptokinase and streptodornase instillations were first used by Tillett in 1949 to lyse fibrinous pleural material and break down loculi,[13] but this method has received limited attention in the literature over the past two decades.[14,15] Problems encountered with this regimen were allergic reactions and antibody neutralization of SK with prolonged therapy.

Streptokinase is a bacterial-derived protein that indirectly activates the fibrinolytic system.[16] It first binds a molecule of plasminogen after which this complex cleaves a second plasminogen molecule resulting in plasmin. It is plasmin that degrades fibrin as well as fibrinogen and other coagulant factors. Urokinase is a direct plasminogen activator initially isolated from human urine. Unlike SK, there is a one-to-one relationship of plasmin production for each molecule of UK, thereby making more efficient use of pre-existent plasminogen. Furthermore, UK is not antigenic and the rare reactions seen with it are probably related to contaminants (pyrogens) in the solution.

Recently, two reports concerning the use of UK

for pleural disease have appeared, both with encouraging results. Moulton et al[7] treated 13 hemorrhagic and nonhemorrhagic processes, including 5 infected hemothoraces and 6 parapneumonic empyemas. They initiated UK instillation in patients with persistent loculated fluid 1 to 22 days after tube thoracostomy with complete resolution of 12 fluid collections. The one failure was in a critically ill patient in whom further therapy was discontinued. Lee et al[8] had equally impressive results in ten empyemas (nine parapneumonic, one tuberculous), all of which were completely drained with one recurrence successfully treated by needle aspiration. While Moulton et al[7] treated some of their patients with several drains, Lee et al[8] treated theirs with only a single chest tube with resolution even with loculi not in direct communication with the drain. Lee et al[8] limited this technique to patients with disease less than 6 weeks old based on indications that a fibrotic pleural peel would develop at that time. Organized, fibrotic tissue would not be expected to respond to fibrinolytic medication.

No complications occurred in either series, nor in ours. Patients maintained stable vital signs and hematocrits, and no significant amount of bleeding through the tubes was observed. Moulton et al[7] waited at least 3 days after the bleeding event before giving UK to patients with infected hemothoraces.

Our limited series appears to substantiate these results. The four patients with disease up to 18 days old in five pleural spaces all had rapid and dramatic responses to UK instillation. Additionally, even the patients with partial responses showed significant elevations in drainage after UK therapy. Perhaps the most impressive example of this treatment is the response seen in the patient with the postoperative empyema: within only 2 days of therapy, a CT scan showed resolution of the loculated fluid collection. Conventional teaching is that postoperative empyemas should be treated surgically given the poor outcome when more conservative measures are used.[9]

Our failure to completely resolve the four more chronic processes supports the reluctance of Lee et al[8] to treat pleural disease older than 6 weeks. Still, clinical improvement was seen in two of these patients, and significant improvement in the volume of pleural fluid in three patients. Organization of fibrinous pleural deposits into fibrosis occurs to varying degrees by 6 weeks, limiting the efficacy of fibrinolytic agents. Thus, while UK was able to resolve multiloculated fluid collections in two patients, their extensive pleural peels remained, preventing complete collapse of the pleural cavity in one (trapped lung) and presumably acting as the source of continued infection in the other.

Our basic indication for the use of UK in pleural effusions is the presence or expectation of inadequate drainage. The criteria we use follow: (1) poor drainage despite an appropriately positioned, patent chest tube; (2) multiple loculi as depicted by septations on CT scan, ultrasonography, or fluoroscopy with contrast injection; or (3) presumed multiloculation as indicated by the initial drainage of a volume of fluid far less than expected by imaging studies. While the radiographic distinction of complete from incomplete septation may be difficult, the presence of any septation likely implies a more complex process that will be difficult to treat with simple drainage. Indeed, while five of our complete or partial responses were treated immediately after initial drainage (based on the second or third criteria), all of these required retreatments to effectively reduce the volume of pleural fluid; therefore, they all eventually met the first criterion as well. While there appears to be little or no systemic effect of UK, active bleeding, surgery in the past few days, and pregnancy should be considered relative contraindications.

The optimal dosage for UK is not known, and the methods in this retrospective study varied depending on the physician, the expected volume of the pleural collection, and the infusion volume symptomatically tolerated by the patient. Currently, we tailor our therapy to the patient with the following regimen: (1) 250,000 U of UK are mixed in 250 ml of normal saline solution; (2) as much of this as the patient can tolerate without discomfort is instilled into the pleural collection (small collections will frequently be limited to less than 250 ml); and (3) the chest tube is then capped for 1.5 to 2 h and the patient is encouraged to shift positions to evenly distribute the solution. Any remaining solution is refrigerated and used for repeat instillations at 8- to 12-h intervals (UK in solution can be refrigerated up to 24 h), to give the total dose of 250,000 U of UK within the first day. Repeat treatments are guided by the appearance of the effusion on follow-up imaging studies. The CT scanning is frequently necessary for loculated processes not easily assessed by plain chest radiographs.

Potential alternate explanations for the responses seen in our patients are the use of image-guidance to place a catheter directly into the bulk of the pleural fluid and the mechanical effect of the large fluid instillations on the loculations. Several reports have shown the efficacy of image-guided drainage both after unsuccessful conventional chest tube placement and as the primary modality.[4-6] While new catheters were placed by this method in most of our patients, there was a clear response to the UK

instillations as indicated by the increase in the volumes of drainage and follow-up CT scans. It is difficult to assess the contribution of the large volumes of fluid used to deliver the UK.

This small series suggests that UK is a useful adjunct for patients with loculated pleural effusions that have not progressed to the stage of fibrosis, and it may obviate the need for surgical drainage procedures in such patients. Prior work suggests that fibrosis may develop at 6 weeks and, indeed, our three patients with disease older than this did not completely respond to fibrinolytic therapy. Advantages of UK over SK are a more effective use of plasminogen and the rare occurrence of adverse reactions.

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