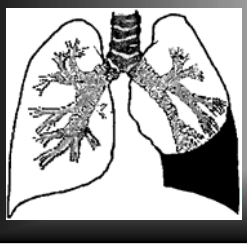
International Pleural Newsletter



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Fibrinolysis for the Management of Empyema: *Pros and Cons*

The Pros:

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"If a pleurisy lasts 20 days then it forms an empyema and if it does not rupture then death will occur".

Hippocrates taught physicians a universal truth: pus needs to be evacuated. Hewitt showed us how to drain the pleural space: in 1876 he described a closed drainage system using a rubber tube and a water seal. Tillett and Sherry were responsible for the introduction of intrapleural fibrinolysis as a supplement to antimicrobial therapy as early as 1949. The theoretical advantage of fibrinolytics certainly seemed obvious: complicated parapneumonic effusions and empyemas are characterized by the progressive development of dense layers of fibrin and pleural fluid loculation. Constructing an evidence base has, however, proven to be challenging.

Numerous case series and controlled trials[1-4] have shown that intrapleural fibrinolysis is safe, increases drainage and improves radiological appearance. A randomized controlled study by Davies et al[1] established that systemic fibrinolysis or hemorrhage did not occur. Bouros et al showed that streptokinase (SK) and urokinase (UK) were equally effective as intrapleural fibrinolytics. The same authors[2] published a randomized double-blind study that proved the efficacy of intrapleural UK (in loculated empyema) in decreasing the duration of hospitalization, duration of pleural drainage and time to defervescence. Patients who received intrapleural UK showed superior radiological improvement and also required less operative intervention (13.5% *vs* 37.5%, $p<0.05$).

The most meaningful clinical endpoint, that of the necessity for surgical intervention, was only recently addressed in randomized controlled studies. Tuncozgur et al[4]

found a significantly lower decortication rate (60% *vs* 29.1%, p<0.01) and shorter duration of hospitalization (14 days *vs* 21 days, p<0.01) with UK than with placebo. A single-center, randomized, placebo-controlled study by Diacon et al[5] used structured clinical protocols for inclusion and evaluation and demonstrated that intrapleural SK resulted in faster resolution of infection, reduced need for surgery (13.6% *vs* 45.5%, p=0.018) and improved clinical outcome in patients with loculated empyema.

The recently published multicenter MIST-1 study[6] could not substantiate the role of SK in pleural infections. The design and execution of this study has been criticized. The lack of image-based criteria meant that patients with pleural sepsis were included irrespective of number and quality of loculations. Questions were raised about the reproducibility of clinical management decisions taken across 52 study centers, 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 serious doubt on the efficacy of the drainage techniques used. Albeit the largest randomized trial by far, the negative result of the MIST-1 study stands alone against the majority of smaller, well conducted trials.

Though we acknowledge that the indiscriminate use of fibrinolysis in uncomplicated pleural sepsis should be discouraged, we maintain that the current evidence base clearly favors the use of this modality in the management of *loculated* parapneumonic effusions and empyema. We trust that well-designed future studies utilizing modern agents such as rTPA or DNase will further clarify the role of intrapleural fibrinolysis.

The Cons:

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The rationale for fibrinolytic therapy is strong. Deposition of fibrin within the pleural space is an early event in pleural infection that sets the stage for maturation to an organized empyema, which prolongs hospital stay and requires surgical drainage. Early instillation of fibrinolytics would theoretically lyse adhesions, promote drainage of infected fluid, and prevent progression to an empyema.

Unfortunately, little evidence exists to support this utility. A comprehensive review of the literature identifies only five randomized controlled studies of fibrinolytic therapy[1,2,4-6] that meet established criteria for methodologic quality[7]. Among these studies (patient n=575), four enrolled small numbers of patients (range of n in each study = 22 to 49) from single study sites[1,2,4,5], one included patients with tuberculous pleuritis[5], only one study had an intention-to-treat design[3], and each of the five studies used different criteria to determine radiographic improvement and enrolled different populations of patients with varying inclusion criteria and stages of their pleural infections. The MIST-1 study[6] is the largest (n=427) and the only one with a multicenter design and information on how long patients were followed to assess outcomes. This negative study, however, used small chest tubes (median 12F, 12-20F), left the determination of outcomes to treating clinicians without rigorous protocols, and did not stage empyemas with CT imaging.

If we ignore the design problems and consider the studies' conclusions, we learn that no study demonstrated improved mortality, which may not be an achievable endpoint of fibrinolytic therapy because empyemas may not be an attributable cause of death among hospitalized pneumonia patients. Indeed, only 64 deaths occurred among the 575 patients (11% mortality) in the five trials, and 62 of these deaths occurred in the largest study[6], which was negative for all endpoints.

The second outcome in these five trials was effect on decreasing the need for surgical drainage. Taken in aggregate, the five studies showed no efficacy with an absolute risk reduction (ARR) for surgery of 6.5% (95% CI 0.1% to 12.9%) with a number needed to treat (NNT) of 16 (95% CI 8 to 709). The largest study (n=427) clearly demonstrated no effect with a risk ratio of 1.07 right down the middle of equivalency[6]; however, the four small trials showed either a trend[1-2] or significant risk reduction[4-5] with fibrinolysis. In aggregate, these four small studies had an ARR of 28.9% (95% CI 14.8% to 43.0%). These studies, however, had an unusually high rate of need for surgery for the control patients (45.3%) that was higher (45.5% and 60%) in the two studies that showed significant effect compared to the two studies that only showed a trend (25.0% and 37.5%). The fifth and largest trial[6], which was negative, reported that only 14.5% of control patients required surgery. These observations suggest that centers showing efficacy of fibrinolysis either somehow biased control patients toward surgery or had some yet-to-be-defined way of selecting patients on the basis of their high likelihood of responding to fibrinolysis and high risk for surgery if fibrinolysis is not provided. If the latter is true, the two small, positive studies do not provide sufficient information to generalize their patient selection techniques.

Pending future research, no high quality data establish the value of fibrinolytic therapy for empyema. Fibrinolysis should not be used routinely for pleural infections but reserved for patients in the fibropurulent stage of empyema formation who appear at high risk for surgery yet likely to respond to fibrinolytic drugs. Definitive surgical drainage should not be delayed, however, for prolonged trials of fibrinolytic therapy, which remains on shaky investigative grounds.

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DNase in Pleural Infection

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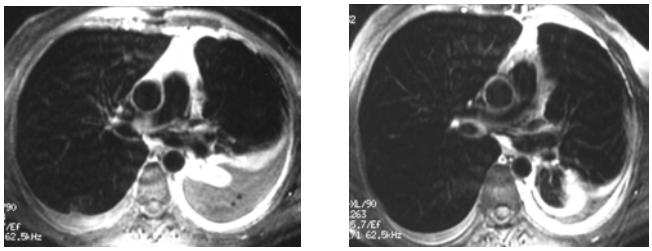
Open thoracic drainage was the only treatment option in empyema until the innovation of closed tube drainage, and the principles of drainage established almost 100 years ago still stand today. Despite the widespread use of drainage and antibiotics, mortality and morbidity from pleural infection remains high. Up to 30% of patients will fail treatment with chest tube drainage and antibiotics alone, and 15% of UK cases result in death, with over 20% of cases requiring surgery[1]. Many patients with pleural infection are elderly with co-morbid disease (up to 70%) precluding surgical options. Empyema is a good model in which to study abscess disease in general, a common condition globally which often fails percutaneous catheter drainage alone. Morbidity from surgery is high, with a mortality of up to 10% in the worst cases. Treatment allowing more effective drainage of pus via percutaneous catheters is likely to decrease morbidity and mortality not only in empyema, but also in abscess disease in general.

Failure of single chest tube drainage is attributed to several factors. Firstly, with deactivation of the normal pleural fibrinolytic system, fibrin adhesions form and create a loculated, non-free flowing pleural cavity. Secondly, due to release of DNA from bacteria and leukocytes, pus is viscid and unable to pass easily down a chest tube.

Many case series and four small randomized trials support the use of intrapleural fibrinolytics to aid chest tube drainage[2]. However, the largest randomized study to specifically address the question of whether intrapleural fibrinolytics affect clinically significant outcomes found no difference in terms of mortality, need for surgery, chest x-ray appearance or hospital stay between placebo and streptokinase[1].

While fibrinolytics are effective in dividing pleural septations and creating a free flowing space, the remaining pus may be too viscid to travel down the chest tube. In fact the original reported use of intrapleural fibrinolytics in the 1940s used a combination of streptococcal fibrinolytic and an enzyme capable of lysing strands of DNA – streptodornase. Further support is derived from two *in vitro* experiments which elegantly demonstrate the ability of DNase to decrease pus viscosity and allow it to pass through a filter or thin tube, whereas fibrinolytics alone have no effect on viscosity[3;4].

There are a few examples of use of DNase in human cases. In Oxford, we have documented four cases of successful use of DNase in patients after failed treatment with fibrinolytics (figures 1 and 2). Simpson et al[5] have reported a single case of a patient successfully treated with intrapleural DNase after failed fibrinolytic therapy. Fujiwara et al[6] reported a series of 15 patients treated with a combination of streptodornase and streptokinase, with a 93% success rate and no adverse events.



CT thorax of a patient who had a left-sided empyema before (Fig 1, left) and after (Fig 2, right) six doses of intrapleural DNase treatment. The clinical signs of sepsis resolved and surgery was avoided.

Therefore, intrapleural use of a combination of a fibrinolytic agent (to divide adhesions) and DNase (to decrease pus viscosity) may promote efficient drainage of pus in empyema. Larger trials are needed to address this issue, and a randomized controlled trial (the 2nd Multi-center Intrapleural Sepsis Trial, MIST-2) is about to start recruitment in the UK.

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CASE: *Massive Pleural Effusion in a Patient with Beta-Thalassemia Intermedia*

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A 50-year old woman with beta-thalassemia intermedia and chronic atrial fibrillation treated by adenocoumarol presented with a five-day history of dyspnea. Clinical and radiological (fig 1) examination revealed a large right pleural effusion. Laboratory workup showed a prolonged prothrombin time (58 sec). Thoracentesis yielded a bloody lymphocytic exudate with 12% erythroblasts. CT revealed bilateral intrathoracic paravertebral masses (fig 2) and bone marrow scan revealed increased tracer activity on the right lower mediastinum (fig 3).

***Fig 1**: Chest x-ray on admission revealed a unilateral massive right sided pleural effusion.*

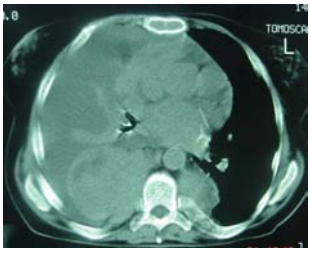

***Fig 2**: CT of the chest demonstrated on the right side two lobulated paravertebral masses surrounded by pleural fluid. A smaller mass was seen on the left side.*

Diagnosis: ***Extra-medullary hemopoiesis (EMH)*** was confirmed by open biopsy of the paravertebral masses. A bleomycin pleurodesis was undertaken successfully (fig 4) with no recurrence of the effusion one year later.

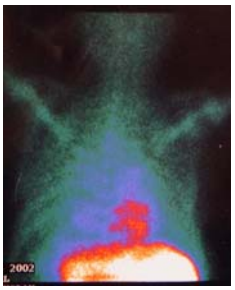

***Fig 3**: Technetium 99m bone marrow scan showed increased tracer activity (red color) throughout the lower mediastinum, spleen and along the diaphragm, a finding consistent with EMH.*

***Fig 4**: Chest x-ray after pleurodesis revealed complete resolution of the effusion as well as bilateral intrathorasic masses due to EMH.*

Discussion: Pleural effusion can be a feature of intrathoracic EMH in patients with chronic bone marrow insufficiency or longstanding hemolytic anemia. Pleural effusion is rare in beta-thalassemia intermedia. Pleural involvement, sepsis, trauma and spontaneous laceration of the heterotopic marrow have all been associated with the development of an effusion in EMH[1]. Over-anticoagulation was a contributing factor to the effusion formation in our patient.

Pleural effusions from EMH can be lymphocyte- or neutrophil-predominant, and the appearance can vary from sanguineous to bloody[2]. Detection of erythroid or myeloid precursor cells and megakaryocytes is diagnostic[3]. Treatment of EMH is warranted when complications, eg effusions, arise. Low dose radiation (1.5Gy) to the site has been used to control symptomatic EMH. Sclerotherapy is effective[4], but tetracycline pleurodesis has been reported to accelerate bleeding[2]. In our patient, there was no adverse event with bleomycin pleurodesis.

In conclusion, pleural effusion can be a feature of intrathoracic EMH. Precautions should be taken when these patients are given anticoagulation treatment.

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