Fibrinolytics in Parapneumonic Effusions/Empyemas

To the Editor:

We read with interest the point/counterpoint debate by Drs Corcoran, Rahman, Colice, and Idell in *CHEST* (January 2014)¹⁻⁴ regarding thrombolytics in parapneumonic effusions (PPEs)/empyemas. We have treated > 400 patients with PPEs and empyemas with intrapleural tissue plasminogen activator (tPA), and only four patients with chronic empyema needed decortication. We published two articles; one was a randomized placebo-controlled double-blinded crossover trial that was approved by the US Food and Drug Administration and ClinicalTrials.gov.^{1,2,5,6} We agree with

Drs Colice and Idell regarding the optimum tPA dose, and our pilot determined that 25 to 50 mg of tPA was necessary for viscous purulent effusions.³⁻⁶ We do not agree that the risk of bleeding is high, and studies have shown that systemic effects of thrombolytics are negligible.³⁻⁷ Most cases that reported significant bleeding complications did not perform coagulation studies, or patients were on therapeutic anticoagulation. Platelet function assay (PFA) is the most useful coagulation test, and if within normal limits or mildly elevated the risk of significant bleeding is < 1%. We recommend that the international normalized ratio and partial thromboplastin time be below 4 and 50, respectively. Failure to respond to these viscous effusions may also be related to chest tube size.^{5,6}

Figure 1 – Algorithm for management of parapneumonic effusions/empyema. CXR = chest radiograph; INR = international normalized ratio; PFA = platelet function assay; PTT = partial thromboplastin time; TPA = tissue plasminogen activator; VATS = video-assisted thoracic surgery.

We agree with Drs Colice and Idell that the major flaw in the first Multicenter Intrapleural Sepsis Trial (MIST1) and subsequent MIST2 trial is using chest radiographs to document response to thrombolytic therapy.^{3,4} Chest radiographs cannot differentiate fluid, consolidated lung, pleural thickening, pulmonary infiltrates, or a mass.⁶ The primary end point in the MIST2 trial was pleural opacity changes on chest radiographs and not surgery. If referral to surgery was the primary end point there would be no significant difference between tPA alone and tPA/deoxyribonuclease (three of 48 vs two of 48). Therapy with deoxyribonuclease appears to have little or no thrombolytic activity, as this group had more surgical referrals than placebo (18 of 46 vs eight of 51).⁸ Several authors have shown tPA to be effective as a single agent in parapneumonic effusions and empyemas in adults and children.^{5,6}

Critically ill patients who are high surgical risks respond well with minimal complications when treated with tPA instillation, yet we do not give the same option to young and stable patients. We recommend that patients with PPE/empyema be treated initially with intrapleural tPA if PFA and coagulation studies are acceptable (Fig 1). Delaying surgery for 2 days would not be detrimental but could prevent morbidity and mortality associated with surgery and general anesthesia.

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Response

To the Editor:

We thank Dr Thommi and colleagues for their comments regarding our point/counterpoint debate¹⁻⁴ on the use of fibrinolytics in managing complicated parapneumonic effusions. There are two points raised in this letter that should be considered. First, the effective dosing regimen for intrapleural administration of tissue plasminogen activator (tPA) in managing complicated parapneumonic effusions has not been confirmed by appropriate phase 1/2 dose escalation and phase 2 dose-response studies. While determination of the dosing regimen for any drug can be challenging, it is especially important when using intrapleural tPA to manage complicated parapneumonic effusions. This is because both dose and dosing interval must be considered; dosing efficacy requires precise definition, and tPA inhibitors, including plasminogen activator inhibitor-1 that is typically increased in these effusions, may affect outcomes.² Unfortunately, studies in this area have not adequately addressed these issues.

The second Multicenter Intrapleural Sepsis Trial (MIST2) studied only a single dosing regimen of tPA: 10 mg bid administered intrapleurally for 3 days.⁵ A justification for this dose and dosing interval was not provided. Dr Thommi and colleagues should be applauded for exploring the effect of higher doses of tPA. They administered intrapleural tPA doses ranging from 10 mg to 100 mg once daily for 3 days.⁶ We are perplexed, though, by the approach used to determine the dosing regimen. Apparently, doses of tPA were adjusted upward for more turbid pleural effusions and downward for complicated malignant effusions. Also, tPA dosing could have been continued for > 3 days based on clinical response. Using objective measures to

determine dosing adjustments in these studies would have been preferred. In a later study, Thommi et al⁷ administered 25 mg of tPA once daily for 3 days, but did not explain why this dose was chosen.⁷ Further studies of fibrinolysis for managing complicated parapneumonic effusions in adults are reasonable, particularly if an appropriate dosing regimen is validated.

Second, the risk/benefit balance for intrapleural tPA should be carefully evaluated. There are safety concerns with intrapleural administration of tPA related to bleeding risk. In a retrospective review, four of 57 patients (7%) treated with intrapleural tPA for a parapneumonic effusion (PPE) or empyema suffered a bleeding complication, some of which were serious.⁵ Although in their letter Dr Thommi and colleagues advise against use of tPA in patients with coagulopathy, thrombocytopenia, and/or platelet dysfunction, in their own experience and despite using these exclusion criteria, they reported that two of 68 patients (3%) had clinically meaningful bleeding after intrapleural tPA.⁷ Balanced against the bleeding risk with tPA, Rahman et al⁵ concluded in the well-performed MIST2 that intrapleural administration of “tPA alone was ineffective.” With possible risk but no consistent benefit, we do not favor routine administration of intrapleural tPA for adults with a PPE requiring drainage.

Our recommended approach is straightforward. Evaluate patients with pneumonia for a PPE. If a PPE is present, determine whether drainage is recommended. If drainage would provide benefit, perform tube thoracostomy and consult thoracic surgery. If there is clear, rapid clinical improvement in the PPE with tube thoracostomy and antibiotics, no further steps may be needed. If, however, tube thoracostomy does not provide adequate pleural drainage and the clinical picture does not improve, the next step should be video-assisted thoracoscopic surgery to effectively break down loculations and drain the pleural space under direct vision. In patients with limiting comorbid conditions or in whom surgery is not an option, administration of intrapleural tPA/DNase should be considered.

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Response

To the Editor:

We would like to thank Dr Thommi and colleagues for their letter regarding our point/counterpoint debate¹⁻⁴ on fibrinolytic treatment in pleural infection, in which they discuss the use of intrapleural tissue plasminogen activator (tPA) in the treatment of adult and pediatric pleural infection. We agree that the risks of intrapleural bleeding with intrapleural therapy is small, and this has also been demonstrated in the first Multicenter Intrapleural Sepsis Trial (MIST1)⁵ and subsequent MIST2⁶ trial, in which there was no statistically significant increase in bleeding events compared with placebo with either fibrinolytics alone or tPA plus deoxyribonuclease (DNase).

The authors suggest that failure to drain viscous effusions may be related to chest tube size. We do not agree that there is strong evidence to support this statement; the largest study to directly address this issue, although not a randomized dataset, analyzed clinically important outcomes from the MIST1 trial by initial chest tube size used and demonstrated that there was no difference in outcome comparing chest tubes of varying sizes.⁷ Indeed, this study demonstrated a statistically significant improvement in outcome with the use of smaller chest tubes in the purulent (and, therefore, more viscous) subgroup.⁷ As this was nonrandomized data, we do not take this as evidence of smaller tubes being more effective in the treatment of purulent fluid. However, this does provide compelling evidence that larger tube sizes are not likely to be more effective in the treatment of pleural infection. In addition, our analysis of factors predictive of outcome in pleural infection⁸ did not demonstrate a significant effect of chest tube type.

We disagree with the authors that chest radiograph outcomes are a flaw in the MIST1 and MIST2 trials. Chest radiographs are the most common clinical surrogate used in decision-making in pleural infection, although we agree that they cannot differentiate consolidation from pleural effusion. However, the MIST1⁵ trial primary and secondary outcomes were not radiologic (death, surgery, lung function, and hospital stay). In the MIST2 trial⁶ and in acceptance of the previous point, the digital chest radiograph measurement system used was shown to have very high correlation with the amount of pleural fluid change as measured by CT scan. The quoted article from the authors describing a randomized, crossover trial using tPA⁹ also uses a radiologic outcome (CT scan), and we do not believe that a crossover trial is the correct design for addressing the efficacy of intrapleural agents in pleural infection.

The authors suggest that if surgical outcome was the primary outcome measure in the MIST2 trial, there would be no difference between the tPA and tPA plus DNase groups. However, there was a statistically significant improvement in surgical referral in the tPA plus DNase group (OR, 0.17; $P = .03$) and not in the tPA group (OR, 0.29; $P = .1$) compared with placebo. The differences were small (down to one patient); however, these were secondary outcomes, and any treatment effect should be treated with caution. If all data from the trial are taken together, it is clear that the tPA plus DNase group demonstrates consistent improvement in several outcomes (chest radiograph,

surgical referral, hospital stay, and reduction of fever) compared with placebo, whereas tPA only shows a modest effect in surgical referral that is statistically nonsignificant. This, in parallel to the MIST1 trial result, suggests that fibrinolytics alone are not effective in the treatment of pleural infection. Our view remains that the published data suggest that combination tPA and DNase has been shown to be superior to placebo and the agents individually and that further large trials are required to provide precise data on the treatment effect on surgical, hospital stay, and mortality outcomes.

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