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Counterpoint: Should Fibrinolytics Be Routinely Administered Intrapleurally for Management of a Complicated Parapneumonic Effusion? No

In this debate, the question involves three key terms: fibrinolytics, routine administration intrapleurally, and complicated parapneumonic effusion (PPE). Fibrinolytics promote lysis of fibrin by generating plasmin. The only currently available fibrinolytic in the United States is tissue plasminogen activator (tPA). Routine use implies that administration of intrapleural fibrinolytic therapy represents a standard approach. Complicated PPE is a term introduced by Light[1] to describe a PPE that evolved into the fibropurulent stage with a higher pleural fluid lactate dehydrogenase level, a lower pleural fluid glucose level, and a higher likelihood of a positive pleural fluid Gram stain. Light[1] suggested that complicated PPE would not resolve with antibiotic treatment but would require drainage. Instead of the term complicated PPE, we prefer the approach adopted by the American College of Chest Physicians consensus panel for the management of PPE for identifying those PPEs in need of effective drainage.[2] This consensus panel divided PPE into four different groups with varying risks for poor outcomes based on pleural space anatomy, pleural fluid bacteriology, and pleural fluid chemistry criteria (Table 1). The groups at increased risk for poor outcomes, such as those with large or loculated effusions, empyema, or a pleural fluid pH < 7.20, would benefit from drainage.

With the question defined, there are three reasons why fibrinolytics should not be administered intrapleurally as part of standard procedure for managing PPEs at increased risk for poor outcomes. Dosing regimens for fibrinolytics do not ensure effective intrapleural fibrinolysis. Clinical trials in adults have failed to demonstrate consistent clinical benefit with administration of intrapleural fibrinolytics. An alternative approach, surgical drainage by video-assisted thoracoscopic surgery (VATS), provides effective drainage of the pleural space with improved clinical outcomes.

Developing any agent for human use requires determining the effective dose and dosing interval. The dose and dosing interval of intrapleural fibrinolytic agents has been and remains empirical. tPA usually is administered intrapleurally at a 10-mg dose once or twice daily for several days.[3] However, tPA is subject to rapid inhibition by plasminogen activator inhibitor 1, the levels of which may be markedly increased in the pleural fluid of patients with pleural infection, as previously reviewed.[4] We are not aware of evidence-based indicators to guide clinicians about how much more fibrinolysin to give if adequate pleural drainage is not initially achieved. To our knowledge, no US Food and Drug Administration-approved fibrinolytic agents for intrapleural use are currently available. In addition, no formal toxicology studies have been done to identify the optimal and safest dosing in animals as the basis for determining a safe starting dose for clinical safety trials, nor have dose escalation phase 1 and 2 safety trials of fibrinolytic agents in patients with PPE been conducted prior to broad clinical application. These considerations likely underlie the wide variability in patient outcomes in trials of intrapleural fibrinolytic therapy.

Small case series in the 1990s suggested that intrapleural administration of streptokinase provide clinical benefit in managing PPE requiring drainage.[2,5] The first Multicenter Intrapleural Sepsis Trial (MIST1), published in 2005, was an important step forward because it included a large number of well-characterized patients with PPE requiring drainage randomized to either intrapleural streptokinase or placebo.[6] The results disagreed with previous work and showed no clinical benefit with intrapleural fibrinolytics compared with placebo (Table 2). A Cochrane review of intrapleural fibrinolytic therapy in 2008, largely based on the results of MIST1, did not find consistent benefit for these agents.[7] The subsequent MIST2 trial was smaller and included four possible treatment options, one of which was intrapleural administration of tPA.[3] Again, the results demonstrated no clinical benefit with the use of intrapleural fibrinolytics vs placebo (Table 3). A systematic review and meta-analysis evaluated outcomes with intrapleural fibrinolytic therapy for managing PPE in 801 patients from seven placebo-controlled trials.[8] Although the authors concluded that there was a potential benefit with intrapleural fibrinolytics in reducing treatment failures (surgical intervention and death), concerns exist about this analysis. There were no differences in treatment failures between intrapleural fibrinolytics and placebo in the two largest trials included in the analysis: MIST1 and MIST2. In the next largest trial, calculations of treatment failures might have been affected by a critical methodological flaw.[9] Of the 65 patients randomized to streptokinase, eight (12%) were lost to follow-up because the protocol was not followed. None of the 70 patients managed

Table 1—*Categorizing Risk for Poor Outcome in Patients With PPE*

Pleural Space Anatomy		Pleural Fluid Bacteriology		Pleural Fluid Chemistry[a]	Category	Risk of Poor Outcome	Drainage
A_0 minimal, free-flowing effusion (<10 mm on lateral decubitus)[b]	AND	B_x culture and Gram stain results unknown	AND	C_x pH unknown	1	Very low	No[c]
A_1 small to moderate, free-flowing effusion (>10 mm and $<1/2$ hemithorax)	AND	B_0-negative culture and Gram stain[d]	AND	C_0 pH ≥ 7.20	2	Low	No[e]
A_2 large, free-flowing effusion ($\geq 1/2$ hemithorax),[f] loculated effusion,[g] or effusion with thickened parietal pleura[h]	OR	B_1-positive culture or Gram stain	OR	C_1 pH <7.20	3	Moderate	Yes
		B_2 pus			4	High	Yes

PPE = parapneumonic effusion. Reprinted with permission from Colice et al.[2]

[a] pH is the preferred pleural fluid chemistry test, and pH must be determined with a blood gas analyzer. If a blood gas analyzer is not available, pleural fluid glucose should be used (P_0 glucose ≥ 60 mg/dL; P_1 glucose <60 mg/dL). The American College of Chest Physicians Parapneumonic Effusions Panel cautions that the clinical utility and decision thresholds for pH and glucose have not been well established.

[b] Clinical experience indicates that effusions of this size do not require thoracentesis for evaluation but will resolve.

[c] If thoracentesis were performed in a patient with A_0 category pleural anatomy and P_1 or B_1 status found, clinical experience suggests that the P_1 or B_1 findings might be false positive. Repeat thoracentesis should be considered if effusion enlarges or clinical condition deteriorates.

[d] Regardless of prior use of antibiotics.

[e] If clinical condition deteriorates, repeat thoracentesis and drainage should be considered.

[f] Larger effusions are more resistant to effective drainage possibly because of the increased likelihood that large effusions will also be loculated.

[g] Pleural loculations suggest a worse prognosis.

[h] Thickened parietal pleura on contrast-enhanced CT scan suggests presence of empyema.

by thoracostomy alone were lost to follow-up. Consequently, it is not possible to determine the true frequency of treatment failures in this study. Overall, the currently available information does not document a clear clinical benefit for intrapleural fibrinolytic therapy in managing PPE in adults.

Two caveats must be considered, though. These studies considered only adults. Sonnappa et al[10] randomized 30 children with empyema to VATS and 30 to treatment with intrapleural urokinase. There was no difference between the treatment groups in the primary outcome measure of length of hospital stay, and five patients in each group required additional surgery because of treatment failure. Treatment costs, though, were higher with VATS. Faber et al[11] performed a retrospective analysis of 44 cases of pediatric empyema, with 18 treated with early decortication and 26 with streptokinase. All children had complete recovery, and length of hospital stay was similar. A consensus panel of pediatric surgeons advised the use of tPA as chemical debridement for first-line therapy in pediatric empyema, with surgical debridement reserved for patient failures.[12] Interestingly, a retrospective database analysis of 14,936 children hospitalized from 2003 through 2008 for empyema or PPE found that the use of fibrinolytics was uncommon (0.1% of patients received fibrinolytic therapy) and did not confer benefit in addition to tube thoracostomy.[13] The MIST2 trial included a treatment arm of combination therapy with intrapleural tPA and DNase.[3] The use of DNase with tPA was prompted by ex vivo work showing that DNase might complement fibrinolysis and facilitate intrapleural drainage by reducing pus viscosity.[14] Preclinical work found efficacy with the combination.[15] The primary outcome in MIST2—change in the extent of chest radiographic pleural opacification—was significantly better with tPA plus DNase than with placebo.[3] The clinical significance of this finding, though, is uncertain. There were numerically more serious adverse events from bleeding complications in the tPA plus DNase group than in the placebo group, but there were numerically more patients in the placebo group than in the tPA plus DNase group who underwent subsequent surgical drainage.

Direct surgical drainage by VATS is an alternative approach to intrapeural fibrinolytics for managing a patient with a PPE requiring drainage. The value of VATS in managing PPE has been demonstrated by

Table 2—*Clinical Outcomes in the First Multicenter Intrapleural Sepsis Trial*

Outcome	Streptokinase (n = 206)	Placebo (n = 221)	*P* Value
Death (3 mo)	32 (16)	30 (14)	.66
Surgical intervention (3 mo)	32 (16)	32 (14)	.87
Median hospital stay, d	13	12	.16
Serious adverse events	14 (7)	6 (3)	.08

Data are presented as No. (%) unless otherwise indicated.

Table 3—*Clinical Outcomes in the Second Multicenter Intrapleural Sepsis Trial*

Outcome	Tissue Plasminogen Activator	Placebo	*P* Value
Change in pleural opacification, %	− 17.2 ± 24.3	− 17.2 ± 19.6	NS
Death (3 mo)	4 of 48 (8%)	6 of 46 (13%)	NS
Surgical intervention (3 mo)	3 of 48 (6%)	6 of 51 (12%)	.025
Hospital stay, d	16.5 ± 22.8	24.8 ± 56.1	.21
Serious adverse events	0 of 52 (0%)	1 of 55 (2%)	NS

Data are presented as mean ± SD unless otherwise indicated. NS = not significant.

two small randomized trials. Wait et al[16] randomly allocated 20 patients requiring drainage for a PPE to either VATs (n = 11) or to intrapleural streptokinase (n = 9). Patients randomized to VATS had a significantly higher rate of primary treatment success and significantly shorter hospital stays. Bilgin et al[17] randomized 35 patients with parapneumonic empyema to immediate VATS drainage and 35 patients to tube thoracostomy drainage. The length of hospital stay was significantly shorter and the likelihood of clinical recovery numerically greater in the group undergoing VATS drainage. Retrospective case series of patients managed for empyema have shown that the initial drainage procedure is the most important determinant of ultimate therapeutic success.[18,19] Directed surgical drainage through either VATs or thoracotomy was associated with a significantly greater likelihood of ultimate success, including fewer deaths, than simple drainage.[18,19] A retrospective series showed that patients aged > 80 years with empyema (and a high frequency of severe cardiac comorbidity) tolerated early VATS, with recovery in 97% and only one death.[20] These clinical results are intuitively reasonable. Effective drainage of pus under direct vision, if it can be performed safely, is a well-recognized clinical axiom. Although VATS for PPE requiring drainage should generally be considered, this approach might not be appropriate for all. For instance, if the PPE completely resolves after thoracentesis or tube thoracostomy, VATS will not be necessary. Patients with severe comorbid disease would, in our view, be reasonable candidates for attempted drainage with intrapleural tPA plus DNase at this time.

To summarize, there are compelling reasons why tPA intrapleurally should not be administered routinely to patients with a PPE that requires drainage. The dosing regimen used for tPA does not ensure that effective fibrinolysis will actually occur in the pleural space. Clinical trials have not confirmed reliable clinical benefit with intrapleural fibrinolytics in adults. Tube thoracostomy alone may be effective, but when additional measures are required in these patients, VATS is, in experienced hands, a clinically effective and safe approach to managing a PPE that requires drainage.

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Rebuttal From Drs Corcoran and Rahman

In their counterpoint editorial, Drs Colice and Idell[1] reject the routine administration of intrapleural fibrinolytics for complicated parapneumonic effusions (pleural infection) on two key grounds: (1) There is no evidence of clinical benefit or efficacy for usual dosing regimens of fibrinolytics in isolation and (2) an alternative approach with video-assisted thoracoscopic surgery (VATS) offers both effective drainage of the pleural space and improved clinical outcomes. We addressed this latter point and demonstrated there is no robust, randomized evidence that surgical intervention for pleural infection offers any advantage with respect to clinical outcomes. While acknowledging that VATS is more attractive as an interventional prospect than open thoracotomy,[2] it remains a procedure with both immediate and long-term complications that should not be considered benign in a population where the majority of cases can already be successfully managed medically.[3,4] Drs Colice and Idell[1] do acknowledge the pediatric randomized studies that have shown a greater financial cost and no clinical advantage of VATS compared with medical management of pleural infection, but currently there are no robust data indicating that the situation in adult patients is any different.

The adult studies referenced in support of their counterpoint are small single-center studies with no predefined primary outcome measure and inadequate power.[5,6] The populations enrolled are not representative of that usually seen in pleural infection and demonstrate selection bias, with a mean age of 43[5] and 47[6] years as opposed to 60[3] and 59[4] years. Neither study clearly defines how medical patients were managed, and both use a thoracostomy technique that is no longer considered the standard of care in an era of ultrasound-guided, narrow-bore chest drains.[7] We recognize the potentially life-saving role of surgery in pleural infection; but how, when, and in whom it should be used remain unclear and in need of clarification through properly designed prospective studies. There is certainly no randomized trial data to support its use as a frontline intervention, and consequently, advocating surgery as an alternative to fibrinolytics is not logical if a lack of evidence is the main criticism of the latter approach.

Nonetheless, it is clear that we agree with Drs Colice and Idell on a number of points. We recognize that the first and the second Multicenter Intrapleural Sepsis Trial (MIST) studies[3,4] demonstrated no clinical benefit for the use of individual intrapleural fibrinolytics in isolation (be that streptokinase or tissue plasminogen activator [tPA]) in adult pleural infection. Equally, we agree that further in vitro and in vivo research is needed to better define dosing regimens and mechanisms of action for intrapleural fibrinolytics. There is consensus that in patients with pleural infection in whom simple tube thoracostomy failed and who are unfit for surgery because of comorbid disease or physiologic compromise, combination intrapleural therapy with tPA and deoxyribonuclease (DNase) represents a reasonable intervention on the basis of the results of the MIST2 study.[4] We would contend that taking this one step further and extending the availability of combination intrapleural therapy to all adult patients with pleural infection may represent no greater risk than the surgical alternative Drs Colice and Idell propose.

In the absence of high-quality randomized data to show that surgery has a place in the immediate treatment pathway for adults with pleural infection, we can, therefore, assume that all patients will be managed medically at presentation. The MIST2 study[4] showed that combination intrapleural therapy with a fibrinolytic (tPA) and DNase improves chest radiographic opacification (primary outcome correlating with clearance of pleural collections) and significantly reduced