hospital stay and the need for surgical clearance (secondary outcomes). The use of combination intrapleural therapy following tube thoracostomy, therefore, improves clearance of the infected material and may minimize hospital stay and the need to subject a patient to more invasive and perilous interventions, such as VATS or thoracotomy, at a later stage. Furthermore, combination intrapleural therapy, such as tube thoracostomy, would be available to all patients and all clinicians in all centers of care, unlike VATS, which Drs Colice and Idell¹ acknowledge requires “experienced hands” and, therefore, a specialist service that can never be delivered universally.

We would welcome further large-scale clinical trials to better define the role of different therapeutic interventions, including combination intrapleural therapy and VATS, in pleural infection, although these should be robustly designed and open to all-comers to ensure adequate representation of the population presenting with this disease. In the absence of such data, we remain of the opinion that medical management and combination intrapleural tPA-DNase therapy represent the most rational treatment option available to improve key clinical outcomes in adults with pleural infection.

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Rebuttal From Drs Colice and Idell

Drs Corcoran and Rahman¹ emphasized that clinical use of a therapeutic agent should be determined by its risk/benefit profile. Let us consider the risk/benefit profile of intrapleural fibrinolytics. Because streptokinase and urokinase are not currently available in the United States, we will focus on the tissue plasminogen activator (tPA). Use of tPA is associated with the risk of bleeding. In a retrospective review, four of 57 patients (7%) treated with intrapleural tPA for a parapneumonic effusion (PPE) or empyema experienced bleeding complications, some of which were serious.² Balanced against the bleeding risk with tPA, clinicians should appreciate that Rahman et al³ concluded in the second Multicenter Intrapleural Sepsis Trial (MIST2) that intrapleural administration of tPA alone was ineffective. Besides the lack of clinical benefit with tPA in this study, there was no difference in the change in intrapleural opacification between placebo and tPA. This observation indicates that tPA did not effectively cause intrapleural fibrinolysis and pleural drainage when used at an empirical intrapleural dose of 10 mg. With possible risk but no evident benefit, we do not favor routine administration of intrapleural fibrinolytics to adults with a PPE requiring drainage.

Drs Corcoran and Rahman¹ stated that use of intrapleural fibrinolytics in children is firmly established. Although a number of studies support this position, information about clinical practice patterns in the United States does not agree with this point. A large retrospective US database analysis examined treatments and outcomes in 14,936 children hospitalized with empyema or PPE.⁴ Database analyses provide an invaluable perspective into actual clinical practice. Only 0.1% of these children were treated with intrapleural fibrinolytic therapy, but 8% underwent video-assisted thoracoscopic surgery (VATS). These results indicate that use of VATS, rather than intrapleural fibrinolytics, is firmly established in US management of pediatric patients requiring drainage of a PPE. This clinical

Table 1—Deaths After VATS in Randomized Controlled Clinical Trials in Adults and Children With PPE Requiring Drainage

Study	Patient Group	Deaths in VATS Group	Deaths in Control Group	P Value
Wait et al ⁵	Adults	1 of 11 (9%)	1 of 9 (11%)	NS
Bilgin et al ⁶	Adults	0 of 35 (0%)	1 of 35 (3%)	NS
Sonnappa et al ⁷	Children	0 of 30 (0%)	0 of 30 (0%)	NS
St Peter et al ⁸	Children	0 of 18 (0%)	0 of 18 (0%)	NS
Total	...	1 of 94 (1%)	2 of 92 (2%)	...

NS = not significant; PPE = parapneumonic effusion; VATS = video-assisted thoracoscopic surgery.

approach is supported by outcomes reported in this study. Mortality and length of stay were no different with intrapleural fibrinolytics than with standard treatment with tube thoracostomy alone but were significantly improved with VATS compared with tube thoracostomy.

The statement that the outcomes of MIST2 support use of intrapleural tPA with deoxyribonuclease (DNase) is based on results that are not convincing.¹ Although change in pleural opacification, a primary outcome in MIST2, significantly favored tPA/DNase over placebo, the difference was modest (mean decrease, 7.9% vs placebo), especially when considering that the chest radiograph measurement strategy predicted only 71% of the exact, CT scan-determined pleural collection.³ The small amount of additional pleural fluid drainage provided by tPA/DNase did not result in significant differences between the tPA/DNase and placebo groups in the clinically relevant outcomes of death and need for eventual surgery, although length of stay with tPA/DNase was shorter. Although these results are promising, the tPA/DNase approach is based on empirical dosing of both components. Further exploration of the relationship between dose of tPA/DNase and pleural drainage is needed.

Drs Corcoran and Rahman¹ attributed a mortality rate of around 5% to surgical drainage of a PPE, but this statistic is misleading. In the few (small) randomized controlled clinical trials evaluating VATS in patients requiring drainage of a PPE, mortality rates after VATS were very low and similar to control groups⁵⁻⁸ (Table 1). Farjah et al⁹ reported a mortality rate of 5.4% after surgical drainage of pleural space infection, but this was significantly lower than the mortality rate for patients not undergoing surgery (16.6%). As we discuss in our counterpoint editorial,¹⁰ recent studies have shown that choosing surgery as the initial pleural drainage procedure after failed tube thoracostomy will result in significantly better outcomes than other pleural drainage approaches. Surgical pleural space drainage can be performed with excellent outcomes even in very elderly patients with significant comorbidity.¹⁰ Early use of VATS to drain PPEs has been associated with a shorter hospital length of stay than other drainage approaches.^{11,12}

Our recommended approach is straightforward. Evaluate patients with pneumonia for a PPE. If a PPE is present, follow the approach described in our counterpoint editorial¹⁰ to 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 VATS 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, combination tPA/DNase therapy should be considered.

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