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Point: Should Fibrinolytics Be Routinely Administered Intrapleurally for Management of a Complicated Parapneumonic Effusion? Yes

Abbreviations: DNase = deoxyribonuclease; MIST = Multicenter Intrapleural Sepsis Trial; PPE = parapneumonic effusion; tPA = tissue plasminogen activator; VATS = video-assisted thoracoscopic surgery

The introduction of a therapeutic intervention into everyday clinical practice must always be given careful consideration by physicians regarding the risks and benefits the intervention poses to patients. Factors to be taken into account are the incidence of the condition being targeted, the morbidity and mortality associated with the condition, the adequacy of preexisting therapeutic approaches, the side-effect profile of the proposed intervention, and the additional financial cost incurred during the care of the patient. In this regard, one can make a strong and valid argument for the routine administration of intrapleural fibrinolytics for pleural infection (complicated parapneumonic effusion or empyema thoracis) in adults.

Infection of the pleural space is a serious respiratory disease for which the case incidence is rising in adult and pediatric populations without a clearly identifiable cause.[1-3] Current data predict > 80,000 new cases per year of adult pleural infection in the United Kingdom and United States alone at a financial cost of > $500 million in health-care services.[1,4,5] Furthermore, despite apparent improvements in the diagnostic and therapeutic tools available to physicians over the past 3 decades, there has been little or no impact on the morbidity and mortality associated with pleural infection,[1,6,7] a poor return compared with such conditions as coronary vascular disease where mortality has been significantly reduced over the same time frame. The greatest increase in caseload has been in patients aged > 65 years,[1] a population in whom physicians manage an ever-expanding range of medical comorbidities and where the mortality rate at 3 months from pleural infection remains steadfastly > 30%.[6] These facts highlight the need to consider and develop new therapeutic strategies in adult pleural infection given the apparent inadequacy of those we already possess.

Current and widely accepted guideline statements for the management of pleural infection in adults and children[8-10] advocate the combination of early drainage of the infected pleural space with appropriate antibiotic therapy as critical. Failure to adhere to this advice (eg, through a delay in diagnosis or intervention) is directly associated with a poorer outcome for the patient.[1,2,7,8] This has led some to advocate early thoracic surgical intervention as the best means by which to ensure both adequate clearance of infected material and a better clinical outcome.[2,11,12] However, this argument has several fundamental flaws.

Although surgery is vital and lifesaving in selected patients, the majority of adult patients with pleural infection can be successfully managed medically, with this approach failing in only 18%[5] and 11%[6] of patients in two large prospective randomized studies. Adopting an unselected approach to surgical drainage would consequently impose an unnecessary procedure on the majority of patients alongside the perioperative and anesthetic risks of this intervention, which include a 28-day mortality of around 5%, complication rates of up to 20%, and chronic pain in up to 50% of patients at 1 year.[2,11,13] Furthermore, two large surgical case series from the United States[2] and United Kingdom[11] showed that patients undergoing surgery for pleural infection are younger (aged approximately 50 vs 60 years) and have fewer comorbidities than an unselected patient population.[5,6] Given that the highest mortality from pleural infection is seen in elderly patients with comorbidities,[6] the possibility is raised that selection bias is augmenting the apparent survival advantage claimed for surgical intervention and that patients being selected for thoracic surgery would have a better outcome regardless. Most critical, however, is the absence of any robust prospective trial data to support a role for

universal frontline surgical intervention in pleural infection. Frequently cited studies in adults[14,15] suffer from inadequate power, unorthodox medical management in control arms, and a lack of objective decision-making criteria, whereas studies in children have shown no clinical or financial gain from a more radical front door surgical approach.[4,16]

Accepting that medical management is, therefore, most appropriate for the majority of patients with pleural infection, finding a means to ensure that clearance of the infected collection through an intercostal drain is as swift and complete as possible should be a priority to minimize both hospital stay and long-term morbidity. Targeting the fibrinolysis pathway to enhance drainage and prevent progression of pleural infection from exudative to fibrinopurulent and fibrotic stages represents one potential option that has been pursued by chest physicians for more than half a century.[17] Early studies using streptokinase and urokinase in adults showed promise without ever providing conclusive data,[18] ultimately leading to the first Multicenter Intrapleural Sepsis Trial (MIST1).[6] This large randomized controlled trial (N = 454) in adults surprised many clinicians by failing to show any benefit between streptokinase and placebo for a number of key clinical outcomes, including mortality, surgical referral rate, and hospital stay. This result was in direct contrast to results for pleural infection in children, where the role of intrapleural fibrinolytics was already well established and remains so even now.[10,19]

Pediatric empyema is predominantly community acquired (notably from *Streptococcus pneumoniae*), whereas adult cases have a higher proportion of nosocomial or mixed infections, including anaerobes, staphylococci, and gram-negative organisms.[3,4,7,11] This variation in etiology and microbiology may explain the differing results in adult and pediatric studies of intrapleural streptokinase in pleural infection. Adequate clearance of an infected pleural collection requires not only the breakdown of septations that might otherwise obstruct drainage but also a reduction in fluid viscosity and biofilm formation. In this regard, streptokinase (or urokinase) may be the wrong fibrinolytic agent for adults with pleural infection given its inability to influence these factors in an in vitro setting.[20]

The MIST2 study[5] used a novel combination of a direct tissue plasminogen activator (tPA) and deoxyribonuclease (DNase) to address this. tPA exerts a direct fibrinolytic effect to break down septations, bypassing the need for streptokinase to combine with plasminogen in vivo and rendering the former vulnerable to depleted levels of the latter in the pleural space. DNase targets uncoiled DNA to reduce both fluid viscosity and biofilm formation that might otherwise encourage retention of infected material in the pleural space and relapsing sepsis. Through a double-dummy, double-placebo, randomized controlled trial design (N = 210), MIST2 demonstrated a highly significant effect ($P = .005$) of combination tPA-DNase therapy vs placebo for the primary outcome of relative change in chest radiograph pleural opacity (Fig 1), as validated against CT scan as a measure of successful drainage of pleural collections. Among the secondary outcomes, both surgical referral rate and hospital stay were also significantly reduced in the combination therapy arm, whereas no increase in adverse events compared with the placebo arm were found.

The combination of intrapleural tPA and DNase in pleural infection clearly improves chest radiographic appearance compared with placebo and may reduce hospital stay and the requirement for surgery, all of which are clinically significant outcomes important to both physicians and patients. This benefit (accepting the sample size limitations of MIST2) was realized in the absence of any increase in adverse events and was independent of purulence of pleural fluid (as demonstrated in the balanced subgroup analysis). Given this evidence demonstrating potential treatment benefit, and when no other treatment has been demonstrated against placebo to have such benefit, the routine use of intrapleural tPA and DNase can be considered rational and has more of an evidence base than other

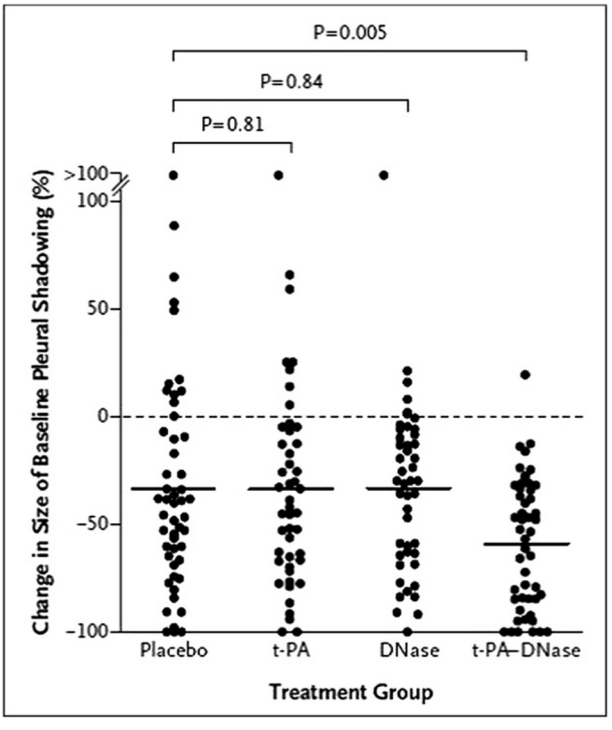

FIGURE 1. Relative change in chest radiograph pleural opacity by treatment arm in the Multicenter Intrapleural Sepsis Trial 2 study on d 7 vs d 1 and expressed as a percentage of hemithorax occupied. DNase = deoxyribonuclease; t-PA = tissue plasminogen activator. (Reprinted with permission from Rahman et al.[5])