September, 2011 Pulmonary Journal Club

Rahman NM, Maskell NA, West A. Intrapleural use of tissue plasminogen activator and DNAse in pleural infection. N Engl J Med 2011;365:518-26.

The use of intrapleural fibrinolytics in the management of pleural space infections and loculated effusions has been in contestation for nearly 20 years. In 2004 a Cochrane review of the 4 Randomized controlled trials demonstrated a potential benefit of intrapleural streptokinase therapy vs. placebo in the management of pleural space infections and loculated effusions. The follow up study …Multicenter Intrapleural Sepsis Trial (MIST1) was supposed to answer the question on the efficacy intrapleural fibrinolytic therapy but its results were discordant with prior data, showing NO benefit of streptokinase compared to placebo in reducing hospital days, surgical referrals, or mortality. The discordant results have been challenged on various levels including time to therapy (which was 14 days), and subjective radiographic criteria in enrollment. The study also questioned the pathophysiology behind failure of fibrinolytic monotherapy and whether an additional agent to promote DNA cleavage is needed. The study *Intrapleural Use of Tissue Plasminogen Activator and DNase in Pleural Infecti*on looks to compare the efficacy of combination therapy of TPA + DNase vs. Placebo vs. TPA or DNase as monotherapy.

The study was a double-blinded, randomized, controlled trial performed at 11 centers in the United Kingdom. Inclusion criteria were clinical evidence of infection and pleural fluid showing any one of the following: positive culture, purulence, pH< 7.2 or a positive gram stain. A total of 210 pts were enrolled and received either placebo (55 pts), TPA (52 pts), DNase (51 pts) or TPA + DNase (52 pts). Treatment was given as twice daily pleural instillations for 3 days. The primary outcome was a radiographic change in pleural opacity on day 7 vs. day 1. Secondary outcomes looked at rates of surgical referral, length of hospital days, and volume of fluid drained by day 7.

The results showed the that combination therapy with TPA + DNase showed a decrease in pleural opacity, decreased surgical referral (4% vs. 14% in placebo) and decrease in hospital days by 6.7 days when compared to placebo. Monotherapy with either TPA or DNase showed no benefit when compared to placebo.

Our review of the study showed that it was well done and prompted a discussion on our own experiences. Several of our faculty has noted marked clinical and radiographic response when using TPA or Streptokinase as monotherapy, myself included. The development of loculations within the plural space occurs as early as 72 hours so the duration to the first dose of intrapleural treatment at 14 days remains questionable and may explain the failure of fibrinolytic therapy in MIST 1 as well as in this study. The study did reinforce several beliefs. First, chest tube drainage as stand alone therapy may become obsolete in the management of pleural space infection; second, the time to drainage is still beyond what is pathophysiologically sound; and finally, the use of intrapleural therapy has not been associated with significant adverse events. Whether chest tube drainage + TPA + DNase will become the new gold standard in the

management of pleural space infections is doubtful, however, it is conceivable that this may now become first line therapy especially in higher surgical risk patients.

Manoj Mathew MD, FCCP, MCCM
Associate Editor, Pulmonary Journal Club