Concurrent Versus Sequential Intrapleural Instillation of Tissue Plasminogen Activator and Deoxyribonuclease for Pleural Infection

Fayez Kheir, MD, MSCR,† George Cheng, MD, PhD,‡*
Estefania Rivera, MD, Alejandro Folch, MD,§ Erik Folch, MD, MsC,‖*
*Sebastian Fernandez-Bussy, MD,¶ Colleen Keyes, MD,‖ Mihir Parikh, MD,**
Colleen Channick, MD,‖ Alex Chee, MD, and Adnan Majid, MD, FCCP**

Background: **Treatment of pleural infection with instillation of sequential intrapleural tissue plasminogen activator (tPA) and human recombinant deoxyribonuclease (DNase) twice daily for a total of 6 doses has been shown to decrease surgical referral and improve radiographic imaging. This labor-intensive regimen was empirically chosen. Thus, it remains unclear whether the 2 drugs can be administered immediately one after the other (concurrent administration) instead of instilling them separately with a 1-hour to 2-hour interval in between (sequential administration). The aim of this study was to compare the efficacy and safety of sequential versus concurrent tPA/DNase therapy in patients with pleural infection.**

Methods: **This was a prospective observational study. Consecutive patients with pleural infection who received concurrent and sequential tPA/DNase were included. The initiation and number of doses of tPA/DNase therapy were based on the amount of pleural fluid drainage, clinical response and radiographic findings.**

Results: **A total of 38 patients with pleural infection received tPA/DNase treatment: 18 in the sequential group and 20 in the concurrent group. Treatment was successful in 77.7% in the sequential group and 75% in concurrent group ($P = 0.57$). There was no statistically significant difference between the 2 treatment groups (sequential and concurrent) in median pleural fluid drainage ($P = 0.45$), median volume of pleural effusion estimated on chest computed tomography scan ($P = 0.4$) or median hemithorax occupied by effusion on chest radiography ($P = 0.83$) following intrapleural therapy. One patient required a blood transfusion for gradual pleural blood loss in each treatment group. Pain needing escalation of analgesia affected 3 patients in each arm but none required cessation of therapy.**

Conclusion: **A simpler regimen of concurrent administration of intrapleural tPA/DNase as compared with sequential intrapleural therapy is safe, effective, and represents a viable option for the management of pleural infection.**

Key Words: tissue plasminogen activator, deoxyribonuclease, pleural infection, empyema, complicated parapneumonic effusion

(*J Bronchol Intervent Pulmonol* 2018;25:125–131)

Pleural infection [empyema or complex parapneumonic effusion (CPPE)] represents one of the most common clinical diagnoses encountered in clinical practice in the United States and worldwide. The incidence of pleural infection continues to rise with an annual incidence of approximately ~65,000 in the United States and the United Kingdom.[1] It is associated with substantial morbidity and mortality as well as increased hospital costs despite advances in medical diagnostic and therapeutic strategies.[2–4] The overall mortality of pleural infection approaches 20% and it is above 30% in elderly patients over 65 years and immunocompromised patients.[1,3,5–7]

Treatment of CPPE or empyema requires antibiotics and drainage of the pleural cavity.[3] However, approximately 30% of patients have difficulty draining fluid, because of loculations,

Received for publication May 10, 2017; accepted October 4, 2017.
From the *Department of Thoracic Surgery and Interventional Pulmonology, Beth Israel Deaconess Medical Center, Harvard Medical School; §Department of Internal Medicine, Boston University School of Medicine; ‖Department of Pulmonary and Critical Care Medicine, Massachusetts General Hospital Harvard Medical School, Boston, MA; †Critical Care and Environmental Medicine, Tulane University Health Sciences Center, Division of Pulmonary Diseases, New Orleans, LA; ‡Division of Pulmonary, Allergy and Critical Care, Duke University School of Medicine, Durham, NC; and ¶Section of Interventional Pulmonology, Clinica Alemana, Universidad Del Desarrollo, Santiago, Chile.
F.K. and G.C. contributed equally.
Funded by American Association of Bronchology and Interventional Pulmonology.
Disclosure: There is no conflict of interest or other disclosures.
Reprints: Adnan Majid, MD, FCCP, Section of Interventional Pulmonology Beth Israel Deaconess Medical Center, Associate Professor of Medicine Harvard Medical School, 185 Pilgrim Road, Deaconess -201, Boston, MA 02215 (e-mail: amajid@bidmc.harvard.edu).

DOI: 10.1097/LBR.0000000000000461

septations, and increased viscosity of the pleural fluid.[8,9] In the last few years, intrapleural therapy with combined tissue plasminogen activator (tPA) and human recombinant deoxyribonuclease (DNase) have been shown to improve the chest radiographic appearance, reduce the need for surgical intervention and decrease the length of hospital stay in patients with pleural infection.[9–13] However, the optimal administration (concurrent or sequential) and duration of intrapleural therapy remains unclear. In the randomized controlled Multi-Center Intrapleural Sepsis Trial (MIST-2) sequential tPA (10 mg) and DNase (5 mg) were instilled intrapleurally twice-daily up to a maximum of 6 doses over 3 days.[9] Following each medication, chest tube was clamped for up to 60 minutes to allow drugs to remain in the pleural space. However, such protocol is cumbersome for the medical team, nurses, and patients as it requires access to the chest tube 4 times per day (maximum of 12 in 3 d) and lengthens the treatment time to 3 hours per instillation, making such regimen difficult to implement in a busy medical ward. A recent report by our group describes the findings of a single-arm study using concurrent tPA/DNase immediately after each other (hereafter referred to as concurrent) in patients with pleural infection. The safety and effectiveness were in-line with previously described sequential tPA/DNase studies.[9–13]

In this study, we aim to compare the efficacy and safety of sequential versus concurrent tPA/DNase therapy in patients with CPPE or empyema.

METHODS

We conducted a prospective observational study. The study was approved by the institutional review board for data collection and analysis of Beth Israel Deaconess Medical Center (IRB 2015P-000034). If patients agreed to participate, informed consent was obtained. Consecutive patients who received concurrent and sequential intrapleural tPA/DNase therapy for pleural infection were enrolled in the study. The use of a sequential or concurrent intrapleural tPA/DNase regime was determined by the treating physician.

The definition of pleural infection included empyema and complex parapneumonic effusion, defined as clinical evidence of infection, such as fever and/or elevated blood leukocyte count, with pleural fluid fulfilling one or more of the following characteristics: purulent fluid, pH ≤ 7.2 (measured using a blood gas analyzer), pleural fluid glucose <60 mg/dL, pleural fluid lactate dehydrogenase > 1000 IU/L, presence of microorganism(s) on gram-stain and/or bacterial culture.[3] With ultrasonographic guidance, a chest tube was inserted into the most dependent area of the pleural effusion or into the largest loculation in patients with multiloculated effusions.

Following chest tube insertion, suitability, and timing of intrapleural tPA/DNase therapy was determined by the interventional pulmonary attending on the basis of pleural fluid drainage (< 200 mL within 24 h) and radiographic evidence of (1) septations on chest ultrasound (US) (defined as fibrin strands floating inside the anechoic/hypoechoic pleural effusions along with presence of multiple pockets of fluid in the pleural cavity) and/or (2) loculations on low-dose chest computed tomography (CT) (defined as a lobulated shape with a convex border or compartmentalized and accumulated in a fissure or a nondependent portion of the pleura).[14–16]

Per our protocol, chest ultrasound was performed on all patients before initial insertion of a chest tube for drainage, as well as before and after each administration of intrapleural fibrinolytic therapy. In addition, all patients with dry tap or fluid drainage <200 mL in 24 hours underwent low-dose chest CT 24 hours before the administration of tPA-DNase to ensure adequate chest tube position. After completion of treatment, all patients underwent a second low dose chest CT within 24 hours after last dose of treatment to quantify the change in pleural fluid volume.

The dose of DNase (Pulmozyme, Genentech) was 5 mg and of tPA (Actilyse, Genentech) 10 mg. Each mixed in 50 mL of 0.9% sodium chloride solution. The detailed method of tPA/DNase therapy administration in each group (sequential and concurrent) has been previously described.[9,11] Briefly, for the concurrent group, tPA and DNase were injected concurrently using different syringes through the chest tube followed by a 20 mL saline flush. The chest tube was then clamped for 60 minutes before being opened to -20 cm H_20 of wall suction. For the sequential group, tPA was instilled by the chest tube, followed by a 30 mL saline flush. The chest tube was then clamped for 60 minutes, then unclamped and connected to wall suction at –20 cm H_2O, allowing free drainage for 60 minutes. The same procedure was then repeated for DNase. In both groups, therapy was given twice daily for a maximum of 6 doses.

Data were collected prospectively for each of the cases. We reviewed patient demographics, clinical data on length of hospital stay, pleural fluid analysis, intrapleural therapy, radiographic characteristics, and adverse events. Intrapleural therapy data included: number of chest tubes, duration of chest tube in pleural cavity (total and from insertion to first dose of tPA/DNase), cumulative volume of pleural fluid drained 24 hours before and 24 hours after last dose of tPA/DNase therapy. Radiographic data reviewed was change in the volume of pleural effusion on low-dose chest CT imaging. All adverse events were registered including pleural bleeding (defined as drop in serum hemoglobin requiring blood transfusion or causing hemodynamic instability), significant pain requiring escalation of analgesia and 30-day mortality. Treatment success was defined as radiographic and clinical improvement without the need for surgical intervention.

The change in the percentage of hemithorax occupied by effusion was measured on chest radiographs using a method described previously in the MIST2 trial.[9] The pleural effusion volume was quantified using OsiriX digital analysis program (OsiriX Imaging Software, v3.6.1, OsiriX Foundation, Geneva, Switzerland) reconstructed from patients' low-dose chest CT scans as described previously.[11]

Statistical analysis was performed using STATA version 14.2 (Stata Corp, TX), with a *P*-value of <0.05 defined as significant. Results were expressed as median with interquartile range (IQR). The Wilcoxon signed-rank test was used to compare pleural fluid drainage, volume of pleural effusion on chest CT, and percentage of hemithorax chest x-ray occupied by effusion before and after tPA/DNase administration. Fisher exact test was used to compare treatment success between the 2 groups. Power calculation was performed using a noninferiority test for binary outcomes. A treatment success rate of 96% was assumed based on the MIST 2 trial, to a power of 80%, significance level of 5%, and a 10% difference cut-off. This resulted in an estimated sample size calculated of 90 patients. An interim analysis was performed after enrolling around 40 patients. When the results were reviewed and analysis of the primary outcome was undertaken, the study was terminated early because of no difference between groups.

RESULTS

A total of 38 patients with pleural infection received tPA/DNase treatment: 18 in the sequential group and 20 in the concurrent group (Fig. 1). The baseline demographic and clinical

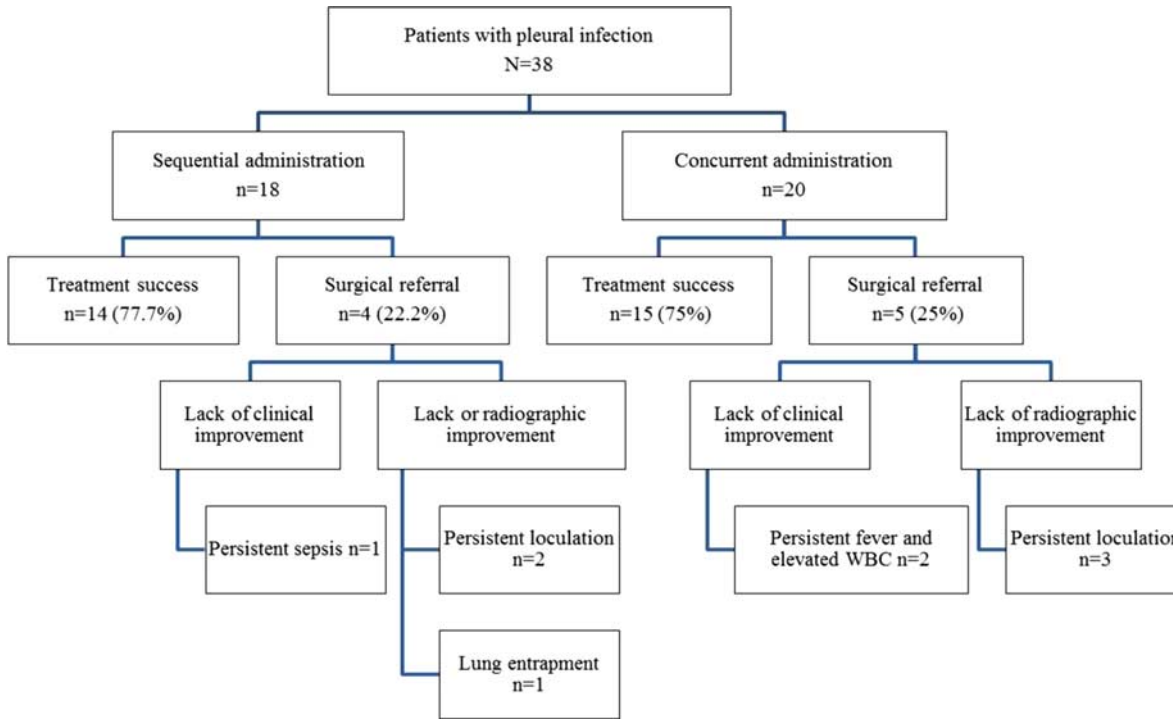

FIGURE 1. Patient flowchart.

TABLE 1. Demographic and Clinical Characteristics

	n (%)	
	Sequential	**Concurrent**
Median age (IQR) (y)	62 (55.7, 72.5)	66 (55, 82)
Men	13 (72)	14 (70)
Comorbid cancer diagnosis	4 (22)	4 (20)
Median peripheral leukocyte count ($\times 10^9$/L) (IQR)	15.3 (10.65,19.85)	14 (12.3, 19.85)
Chest tube size		
14 Fr	16 (89)	15 (75)
8 Fr	1 (5)	1 (5)
12 Fr	—	1 (5)
24 Fr	1 (5)	3 (15)
Ultrasonographic evidence of loculations	9 (50)	12 (60)
Chest tube location—right	11 (61.1)	13 (65)
Positive bacterial Gram's stain or culture of pleural fluid	4 (22.22)	5 (25)
Positive fungal culture	0 (0)	0 (0)
Median pleural fluid percentage of neutrophils (IQR)	85 (54, 96)	92.5 (52,97)
Geometric mean pleural-fluid pH	7.1	7.04
Median pleural-fluid glucose (mg/dL) (IQR)	64.5 (12.5, 100)	35 (11,68)
Median lactate dehydrogenase in pleural fluid (IU/L) (IQR)	705.5 (356, 1757)	999 (694,2010)

IQR indicates interquartile range.

characteristics were similar across both groups (Table 1).

Sequential Group

The median number of doses of tPA/DNase was 2 (IQR, 1 to 3). One patient completed 6 doses of tPA/DNase without clinical improvement. Therapy was successful in 77.7% (14/18) patients. Four patients (22.2%) required surgical intervention. Two patients had persistently loculated effusion on chest CT, one had persistent sepsis, and one had lung entrapment.

Surgery was performed after a median of 1.5 days (IQR, 1 to 5) following the last tPA/DNase dose because of lack of clinical improvement and persistence of multiloculated pleural effusion on chest CT. Fibrinolytic therapy increased the volume of pleural fluid drained from a median of 355 mL (IQR, 188 to 585) 24 hours before treatment to a median of 730 mL (IQR, 278 to 1281) 24 hours following therapy. Median length of hospital stay was 13 days (IQR, 10 to 15) Median time from diagnosis to administration of intrapleural fibrinolytic therapy was 4 days (IQR, 2 to 6) (Table 2).

Concurrent Group

The median number of tPA/DNase doses was 2.5 (IQR, 2 to 3). Two patients completed 6 doses of tPA/DNase, both with treatment success. Therapy was successful in 75% (15/20) of patients. Five patients (25%) required surgical intervention after a median of 3 days (IQR, 1.5 to 3.5) following the last tPA/DNase dose. Two patients had no clinical improvement with persistent fever and elevated white blood count; the other 3 had persistent loculation on repeat chest CT. Pleural fluid drainage increased from a median of 250 mL (IQR, 25 to 500) 24 hours before treatment to a median of 670 mL (IQR, 300 to 1693) 24 hours after fibrinolysis. Median length of hospital stay was 12 days (IQR, 5 to 16) Median time from diagnosis to administration of intrapleural fibrinolytic was 3 days (IQR, 2 to 6) (Table 2).

Treatment Outcomes

There was no statistically significant difference between the two treatment groups in success rate ($P = 0.57$), median pleural fluid drainage ($P = 0.45$), median volume of pleural effusion estimated on chest CT scan ($P = 0.4$) or median hemithorax occupied by effusion on chest radiography ($P = 0.83$) following intrapleural therapy.

Two patients died in each treatment arm secondary to pleural infection. All fatalities had major life-limiting disease or underlying advanced malignancy and occurred after attempt of treating the pleural infection with antibiotics and fibrinolytic therapy. In the sequential group, one patient had advanced lung cancer whereas the other had end-stage alcoholic liver cirrhosis with heart failure. In the concurrent group, one patient had metastatic hepatocellular carcinoma whereas the other had endocarditis with multiorgan failure.

TABLE 2. Clinical Outcomes

Demographic and Clinical Characteristics	n (%)	
	Sequential	Concurrent
Intrapleural therapy with treatment success	14 (77.7)	15 (75)
Median number of doses (IQR)	2 (1,3)	2.5 (2,3)
Patients who received first dose ≤24 h after chest tube insertion	10 (55.5)	11 (55)
Median days from presentation to administration of 1st dose of tPA/DNase (IQR)	4 (2,6)	3 (2,6)
Median days from chest tube insertion to 1st dose of tPA/DNase (IQR)	1 (1,3)	1 (1,4)
Median days of chest tube in pleural cavity	8 (5,10)	6 (4,11)
Median days of hospital stay	13 (10,15)	12 (5,16)
Pain that required escalation of analgesics	3 (16.6)	3 (15)
Hemorrhage that required transfusion	1 (5.5)	1 (5)
Mortality because of pleural infection	2 (11.11)	2 (10)
Median pleural drainage after therapy (mL) (IQR)	305 (70, 867)	510 (40, 1383)
Median volume reduction in CT (%) (IQR)	39.5 (24,68)	46 (38, 79)
Median reduction in % of hemithorax with effusion (%) (IQR)	13.8 (1, 25)	12.2 (2, 27)

CT indicates computed tomography; tPA/DNase, tissue plasminogen activator/human recombinant deoxyribonuclease; IQR, interquartile range.

Two patients experienced pleural hemorrhage that required packed RBC transfusion, one in the sequential and one in the concurrent group. Both patients were receiving anticoagulation, one for pulmonary embolism and the other for atrial fibrillation. However, at the time of intrapleural therapy, both patients had normal platelets, coagulation profiles, and anticoagulation therapy was held during intrapleural therapy. Chest pain requiring escalation of analgesia occurred in 6 patients, 3 in the sequential group and 3 in the concurrent group. None of them required termination of intrapleural therapy.

DISCUSSION

Our data showed that intrapleural instillation of tPA/DNase either concurrent or sequential for pleural infection seemed to have comparable efficacy and safety profile (Table 2). The clinical success was supported by significant improvements in radiographic clearance, pleural fluid drainage, and clinical improvement. Treatment with either the concurrent or sequential methods was well tolerated. Although the incidence of complications (bleeding and pain) were comparable, small sample size and the overall low incidence of complication with fibrinolytic therapy, it would be difficult to find differences between 2 groups.

Even though prior publications show that sequential intrapleural tPA/DNase therapy for a total of 6 doses in 3 days in patients with pleural infection resulted in a significant reduction in surgical referral and length of hospital stay over conventional therapy,[9] the implementation of such protocols remains problematic. This is because of the (1) frequency needed to access chest tube 4 times per day (maximum of 12 in 3 d), (2) significant time commitment needed from health care providers (nurses and physicians) to administer each therapy, and (3) drug costs. This will potentially lead to decreased compliance with a twice daily regimen, as demonstrated by a compliance rate of around 70% in the MIST-2 trial[9] and potentially even lower in real world settings. The complexity of treatment regimens is often associated with poor adherence,[17] in the same manner, simplification of therapeutic regimens is frequently associated with improved adherence.

The use of concurrent rather than sequential therapy offers many advantages in everyday clinical settings as (1) it decreases the frequency needed to access chest tube and (2) shortens the treatment duration per instillation without affecting success rate or adverse events, making such a protocol easier to implement. Furthermore, the optimal dose and frequency of intrapleural fibrinolytic therapy is still unknown. In the MIST-2 protocol, tPA and DNase doses and frequency were chosen empirically, and the optimal dose of tPA required to lyse loculations remains unclear. Akin to our previous study,[11] the decision to start and guide fibrinolytic therapy was based upon clinical as well as radiographic (pleural US or low dose chest CT) evidence rather than initiated upon admission or as a rescue therapy.[9,10] This translated into a smaller number of required doses (2 in sequential

and 2.5 in concurrent) per patient. Given the high cost of tPA/DNase, it may be feasible to guide the timing and number of doses based on clinical and radiographic response, leading to fewer doses and less cost as shown in our previous study.[11]

To our knowledge, this is the first study to compare consecutive patients presenting with pleural infection using 2 different methods of drug administration. Also, our results are generalizable as we included all patients with pleural infection, regardless of expected prognosis or comorbidities, thus providing a more realistic and conservative estimate of safety and mortality.

The study has several limitations. First, similar to other studies addressing tPA/DNase therapy so far, there were no standard criteria for defining conservative treatment failure, and the decision of surgical referral was left to the discretion of the attending physician. Our treatment success rate in sequential and concurrent groups was 77.7% and 75%, respectively. This was lower than other reported studies.[9–12] A probable explanation is that our therapy is guided by pleural US and/or chest CT rather than chest radiography, the former have a higher sensitivity to identify small pockets of pleural fluid. In addition, we have a low threshold for referral to thoracic surgery given our local expertise and the fact that video-assisted thoracic surgery (VATS) is still considered a first-line treatment for pleural infection refractory to medical management.[18–23] Thus, per our institution protocol a residual pocket of >200 mL on chest CT or US without clinical response are preferably drained using VATS early in the course of pleural infection. This could potentially lead to bias in surgical referral. Also, perhaps our surgical rate would be lower (in both groups) if a full regimen was delivered. Second, our study was a prospective nonblinded study of a single institution. Future studies are needed to evaluate optimal administration of tPA/DNase treatment, minimum number of doses required and timing of treatment initiation. Also, direct comparative studies are needed to evaluate VATS or medical thoracoscopy with intrapleural therapy in this subgroup of patients who have failed conservative treatment. Currently there is an ongoing randomized clinical trial comparing early medical thoracoscopy versus intrapleural therapy for pleural infection (NCT #02973139).

In conclusion, concurrent intrapleural tPA/DNase therapy as compared with sequential therapy in patients with CPPE and empyema guided by clinical and radiographic response is comparable in safety and effectiveness. These findings support the use of a concurrent therapy in patients with pleural infection.

REFERENCES

1. Light RW, Girard WM, Jenkinson SG, et al. Parapneumonic effusions. *Am J Med*. 1980;69:507–512.
2. Grijalva CG, Zhu Y, Nuorti JP, et al. Emergence of parapneumonic empyema in the USA. *Thorax*. 2011;66:663–668.
3. Davies HE, Davies RJ, Davies CW. The BTS Pleural Disease Guideline Group. Management of pleural infection in adults: British Thoracic Society pleural disease guideline 2010. *Thorax*. 2010;65(suppl 2):ii41–ii53.
4. Søgaard M, Nielsen RB, Nørgaard M, et al. Incidence, length of stay, and prognosis of hospitalized patients with pleural empyema: a 15-year Danish nationwide cohort study. *Chest*. 2014;145:189–192.
5. Ferguson AD, Prescott RJ, Selkon JB, et al. The clinical course and management of thoracic empyema. *Q J Med*. 1996;89:285–289.
6. Davies CW, Kearney SE, Gleeson FV, et al. Predictors of outcome and long-term survival in patients with pleural infection. *Am J Respir Crit Care Med*. 1999;160:1682–1687.
7. Alemán C, Alegre J, Monasterio J, et al. Association between inflammatory mediators and the fibrinolysis system in infectious pleural effusions. *Clin Sci*. 2003;105:601–607.
8. Maskell NA, Davies CW, Nunn AJ, et al. First Multicenter Intrapleural Sepsis Trial (MIST1) Group. U.K. controlled trial of intrapleural streptokinase for pleural infection. *N Engl J Med*. 2005;352:865–874.
9. Rahman NM, Maskell NA, West A, et al. Intrapleural use of tissue plasminogen activator and DNase in pleural infection. *N Engl J Med*. 2011;365:518–526.
10. Piccolo F, Pitman N, Bhatnagar R, et al. Intrapleural tissue plasminogen activator and deoxyribonuclease for pleural infection: an effective and safe alternative to surgery. *Ann Am Thorac Soc*. 2014;11:1419–1425.
11. Majid A, Kheir F, Folch A, et al. Concurrent intrapleural instillation of tissue plasminogen activator and DNase for pleural infection. a single-center experience. *Ann Am Thorac Soc*. 2016;13:1512–1518.
12. Mehta HJ, Biswas A, Penley AM, et al. Management of intrapleural sepsis with once daily use of tissue plasminogen activator and deoxyribonuclease. *Respiration*. 2016;91:101–106.
13. Bishwakarma R, Shah S, Frank L, et al. Mixing it up: coadministration of tPA/DNase in complicated parapneumonic pleural effusions and empyema. *J Bronchol Interv Pulmonol*. 2017;24:40–47.
14. Tsai TH, Yang PC. Ultrasound in the diagnosis and management of pleural disease. *Curr Opin Pulm Med*. 2003;9:282–290.

15. Yang PC, Luh KT, Chang DB, et al. Value of sonography in determining the nature of pleural effusion: analysis of 320 cases. *AJR Am J Roentgenol*. 1992;159:29–33.
16. Arenas-Jimenez J, Alonso-Charterina S, Sanchez-Paya J, et al. Evaluation of CT findings for diagnosis of pleural effusions. *Eur Radiol*. 2000;10:681–690.
17. Bangalore S, Kamalakkannan G, Parkar S, et al. Fixed-dose combinations improve medication compliance: a meta-analysis. *Am J Med*. 2007;120:713–719.
18. Marks DJ, Fisk MD, Koo CY, et al. Thoracic empyema: a 12-year study from a UK tertiary cardiothoracic referral centre. *PLoS One*. 2012;7:e30074.
19. Suchar AM, Zureikat AH, Glynn L, et al. Ready for the frontline: is early thoracoscopic decortication the new standard of care for advanced pneumonia with empyema? *Am Surg*. 2006;72:688–692.
20. Solaini L, Prusciano F, Bagioni P. Video-assisted thoracic surgery in the treatment of pleural empyema. *Surg Endosc*. 2007;21:280–284.
21. Chung JH, Lee SH, Kim KT, et al. Optimal timing of thoracoscopic drainage and decortication for empyema. *Ann Thorac Surg*. 2014;97:224–229.
22. Schweigert M, Solymosi N, Dubecz A, et al. Surgical management of pleural empyema in the very elderly. *Ann R Coll Surg Engl*. 2012;94:331–335.
23. Shen KR, Bribriesco A, Crabtree T, et al. The American Association for Thoracic Surgery consensus guidelines for the management of empyema. *J Thorac Cardiovasc Surg*. 2017;153:e129–e146.