Intrapleural Fibrinolytic Therapy versus Early Medical Thoracoscopy for Treatment of Pleural Infection

Randomized Controlled Clinical Trial

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Abstract

Rationale: Pleural infection is frequently encountered in clinical practice and is associated with high morbidity and mortality. Limited evidence exists regarding the optimal treatment. Although both early medical thoracoscopy (MT) and tube thoracostomy with intrapleural instillation of tissue plasminogen activator and human recombinant deoxyribonuclease are acceptable treatments for patients with complicated pleural infection, there is a lack of comparative data for these modes of management.

Objectives: The aim of this study was to compare the safety and efficacy of early MT versus intrapleural fibrinolytic therapy (IPFT) in selected patients with multiloculated pleural infection and empyema.

Methods: This was a prospective multicenter, randomized controlled trial involving patients who underwent MT or IPFT for pleural infection. The primary outcome was the length of hospital stay after either intervention. Secondary outcomes included the total length of hospital stay, treatment failure, 30-day mortality, and adverse events.

Results: Thirty-two patients with pleural infection were included in the study. The median length of stay after an intervention was 4 days in the IPFT arm and 2 days in the MT arm ($P = 0.026$). The total length of hospital stay was 6 days in the IPFT arm and 3.5 days in MT arm ($P = 0.12$). There was no difference in treatment failure, mortality, or adverse events between the treatment groups, and no serious complications related to either intervention were recorded.

Conclusions: When used early in the course of a complicated parapneumonic effusion or empyema, MT is safe and might shorten hospital stays for selected patients as compared with IPFT therapy. A multicenter trial with a larger sample size is needed to confirm these findings.

Clinical trial registered with ClinicalTrials.gov (NCT02973139).

Keywords: medical thoracoscopy; intrapleural fibrinolytic therapy; pleural infection

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Pleural infection is a common clinical diagnosis encountered in clinical practice in the United States and worldwide. The incidence of pleural infection continues to rise, with an annual incidence of ~80,000 in the United States and 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 (1–3). The overall mortality of pleural infection approaches 20%, reaching more than 30% in

patients over 65 years of age and immunocompromised patients (2, 4–6).

Treatment of pleural infection requires antibiotics and chest tube drainage of the pleural cavity (2). However, ∼30% of patients experience difficulty in draining fluid owing to loculations, septations, and increased viscosity of the pleural fluid, and ∼20% will need a surgical intervention to adequately treat their pleural infection (7, 8).

The intrapleural therapy of combined tissue plasminogen activator (tPA) and human recombinant deoxyribonuclease (DNase) for the management of pleural infection was shown to improve the chest radiographic appearance of infected effusion in MIST2 (Multicenter Intrapleural Sepsis Trial 2) as compared with either medications or placebo (8). However, this approach is expensive and requires a substantial hospital stay (10–14 d) (8).

Medical thoracoscopy (MT) is a minimally invasive procedure that can be used to treat pleural infection by improving clearance via mechanical lysis of adhesions and targeted drain placement. MT can also be used in patients who are not fit for general anesthesia because it can be performed using local anesthesia and moderate sedation. MT has been shown in observational studies to be safe and effective for the treatment of pleural infection (9–12). However, there are currently no randomized controlled trials addressing the potential role of early MT versus intrapleural fibrinolytic therapy (IPFT) in pleural infection.

The goal of this study was to compare the efficacy of early MT versus IPFT in patients with complicated parapneumonic effusion (CPPE) or pleural empyema.

A portion of the work contained in this manuscript was previously presented as an oral presentation (13).

Methods

Study Design

This randomized trial recruited patients at three academic medical centers (Tulane University Medical Center, New Orleans, LA; University of Florida, Gainesville, FL; and Beth Israel Deaconess Medical Center, Boston, MA. The institutional review boards of all institutions approved the trial (Tulane University Medical Center: 1070390; University of Florida: 201700012; and Beth Israel Deaconess Medical Center: 2016P000307). The trial was registered at ClinicalTrials.gov (Identifier: NCT02973139). All of the centers have a dedicated pleural service that evaluates all patients admitted to the hospital for pleural effusion and dictates further diagnostic and treatment plans along with the primary team.

Patient Population

Subjects (>18 yr of age) who were referred or initially admitted for suspicion of either CPPE or empyema were screened for inclusion in the trial.

CPPE was defined as nonpurulent effusions in a patient with clinical evidence of infection such as fever and/or elevated blood leukocyte count and/or elevated CRP (C-reactive protein), with pleural fluid pH ⩽ 7.2 (measured by blood-gas analyzer), pleural fluid glucose < 60 mg/dl, or pleural-fluid lactate dehydrogenase (LDH) > 1,000 IU/L (8, 14). Empyema was defined as pus within the pleural space and/or presence of bacteria on pleural fluid Gram stain or culture (8, 14).

For patients to be considered for the trial, they had to meet one of the following criteria: *1*) CPPE along with evidence of septated pleural effusion on pleural ultrasonography and/or chest computed tomography (CT) scan (15) (Figure 1) with evidence of minimal (pleural space < 2 cm) or no lung entrapment, or *2*) empyema that failed to drained completely with a chest tube. MT could be performed within 48 hours from the time of chest tube placement in either of the inclusion criteria conditions.

The study exclusion criteria were *1*) age <18 years, *2*) pregnancy, *3*) inability to give written informed consent, *4*) previous thoracic surgery or IPFT therapy for pleural infection, *5*) inability to tolerate a procedure due to hemodynamic instability or severe hypoxemia, *6*) uncorrectable coagulopathy, *7*) presence of a homogeneously echogenic effusion on pleural ultrasound (US) (16) (Figure 1), and *8*) evidence of nonexpandable lung (air in pleural space) after initial thoracentesis or small-bore chest tube on chest imaging.

Patients who met the inclusion criteria and agreed to be involved in the trial signed an informed consent and then were randomized to either MT or IPFT in a 1:1 ratio using a minimization method and opaque sealed envelopes. The minimization criteria were the presence of purulent pleural fluid, septated pleural effusion, effusion size, and the presence of a hospital- or community-acquired infection.

Study Intervention

All patients underwent small-bore (⩽14 French [Fr]) chest tube insertion under US guidance along with intravenous antibiotics as part of routine care before enrollment in the study. Antibiotics therapy (oral and intravenous), as well as the duration of the therapy, was managed by the primary medical team according to the clinical response and local microbiology cultures.

On chest CT without contrast, pleural effusion was defined as loculated if it *1*) had a lobulated shape with a convex border, or *2*) was compartmentalized, if it accumulated in a fissure or a nondependent portion of the pleura (15). For chest US examination, the patients were in a sitting position. The phased-array US probe was moved in a cranial direction (longitudinal plane) in the midscapular line with interpleural separation on end-expiration of ⩾20 mm. On chest US, pleural effusion was defined as fibrin strands or septa floating inside the anechoic/hypoechoic pleural effusions along with the presence of defined multiple

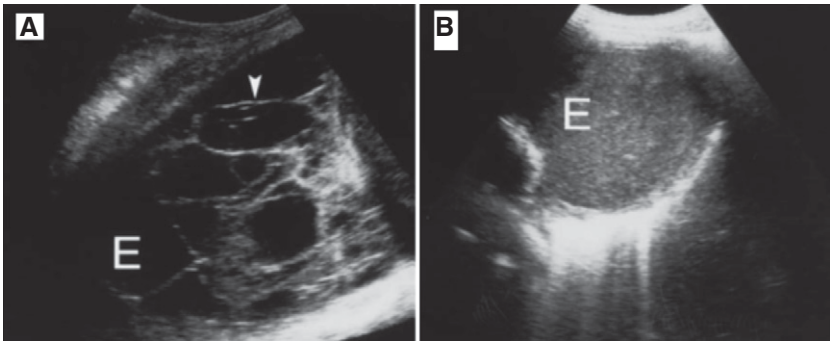

Figure 1. (*A*) Thoracic ultrasound showing complex pleural effusion along with septations (arrowhead). (*B*) Thoracic ultrasound showing homogeneously echogenic loculated effusion. E = effusion.

pockets in the pleural cavity. Effusion size was estimated by measuring the maximal distance between the mid-height of the diaphragm, and visceral pleura (D) was measured after freezing the image in end-expiration using the formula V (ml) = [16 × D (mm)] (17).

Operative Technique

MT. Patients underwent MT (rigid or semirigid) within 48 hours of randomization. Under US guidance, a single port (with a maximum of two ports) was placed and thoracoscopy was performed under moderate sedation and local anesthesia in the operating room or endoscopy suite with continuous monitoring as per standard protocols, with the patient in a lateral decubitus position. The pleura was carefully inspected with the thoracoscope under direct visualization. With closed biopsy forceps, step by step, fibrinous septate was disrupted with fluid and fibrinopurulent material was aspirated and removed from the pleural cavity. A suction irrigator device was used at the discretion of the operator. After adhesiolysis, a pleural lavage with a liter of warmed saline was performed. At the end of the procedure, a drain (24 Fr) was inserted and connected to an underwater seal drain with a negative pressure suction of 20 cm H_2O. A chest CT without contrast or pleural US was performed, and if there was no evidence of significant residual pleural effusion (<200 ml) and chest tube drainage was <75 ml/d, the chest drain was removed.

Intrapleural fibrinolytic therapy. A chest tube (≤14 Fr Seldinger) under ultrasonography guidance was inserted into the most dependent area of the pleural effusion or into the largest loculation in patients with multiloculated effusions. The dose of DNase (Pulmozyme; Genentech) was 5 mg and the dose of tPA (Actilyse; Genentech) was 10 mg, each in 50 ml of 0.9% NaCl. Concurrent tPA and DNase were administered intrapleurally through the chest tube followed by a 60-ml saline flush. The tube was then clamped for 2 hours before the chest tube was opened to −20 cm H_2O of wall suction. Therapy was given twice daily and response was assessed clinically and radiographically (chest X-ray and pleural US) as previously described by our group, for a maximum of six doses (18). A chest CT without contrast or pleural US was performed, and if there was no evidence of significant residual pleural effusion (<200 ml) and chest tube drainage was <75 ml/d, the chest drain was removed.

Study Outcomes

Primary outcome. The primary outcome was the duration of hospital stay after each intervention.

Secondary outcomes. The secondary outcomes were as follows:

1. Total length of hospital stay.
2. Failure rate of assigned treatment (any of the following: persistent fever, leukocytosis, and evidence of loculation 48 h after intervention) necessitating intervention, defined as any of the following:
   a. Surgical intervention (video-assisted thoracic surgery [VATS], open thoracotomy) in the MT or IPFT arm.
   b. Need for additional chest tube and/or fibrinolytic therapy in the MT arm due to clinical nonresponsiveness.
   c. Need for additional chest tube in the IPFT arm due to clinical nonresponsiveness.
3. Adverse events, defined as follows:
   a. Pleural bleeding (defined as a drop in serum hematocrit requiring blood transfusion or causing hemodynamic instability).
   b. Significant pain requiring escalation of analgesia.
   c. In-hospital and 30-day mortality.
   d. Visceral pleural injury (pneumothorax with air leak lasting >1 h after the procedure).
   e. Prolonged air leak (pneumothorax with air leak lasting >5 d).
   f. Cellulitis or chest wall infection at the port/chest tube site requiring antibiotic therapy.
   g. Clinically significant subcutaneous emphysema (defined as the presence of crepitus on physical exam and subcutaneous air collection on chest radiograph).

Each case was then reviewed by an independent reviewer blinded to the patient's trial treatment before data analysis.

Statistical Analysis

We believe that a difference of 2 days in the length of the postintervention hospital stay between the two treatment arms would be clinically important. This rationale is based on a previous randomized study that compared VATS and streptokinase therapy in empyema (18). In that study, the number of chest tube days after VATS was 5.8 ± 1.1 days, as compared with 9.8 ± 1.3 days in the streptokinase group. Furthermore, a case series from MT trials reported an average postoperative stay of 7–8 days (9–12), as compared with an average of 10–13 days in IPFT trials (7, 8). According to a two-sided type I error of 0.05 and 80% power, the sample size was 16 patients in each group. All analyses were performed using GraphPad Prism (version 7.0; GraphPad Software). Descriptive statistics were used to summarize the patients' characteristics. The *t* test was used to examine differences between groups with parametric data and the Mann-Whitney *U* test was used for nonparametric data. Fisher's exact test was used for categorical variables. A *P* value of ≤0.05 was considered statistically significant.

Results

Between November 2017 and July 2019, 114 patients were screened and 32 were recruited to the trial. A flow chart showing the enrollment, assignment, and follow-up of patients in the primary analysis is presented in Figure 2. Seventy-one patients were not recruited because they did not meet the inclusion criteria, and 11 refused to participate. Overall, the antibiotics used for patients with pleural infection included vancomycin (*n* = 20, 62.5%), quinolones (*n* = 13, 40.63%), macrolides (*n* = 5, 15.63%), carbapenems (*n* = 3, 9.38%), piperacillin-tazobactam (*n* = 13, 40.63%), ceftriaxone (*n* = 3, 9.38%), cefepime (*n* = 7, 21.88%), and metronidazole (*n* = 11, 34.38%). The median number of days the patients were hospitalized before randomization was 1 (IQR, 1–2.75) for both groups. The baseline demographics and clinical characteristics are shown in Table 1.

Patients

In the IPFT group, the median age was 58 years (interquartile range [IQR], 49–65) and 62.5% were men. The median pleural fluid pH, LDH, and glucose levels were 7.02 (IQR, 6.69–7.09), 1,003 IU/L (IQR, 697–1,959.5), and 46.5 mg/dl (IQR, 12.5–74.5), respectively. The effusions were purulent in 25% of the patients and 18.75% had a positive Gram stain or fluid culture result. Microbiology culture yielded

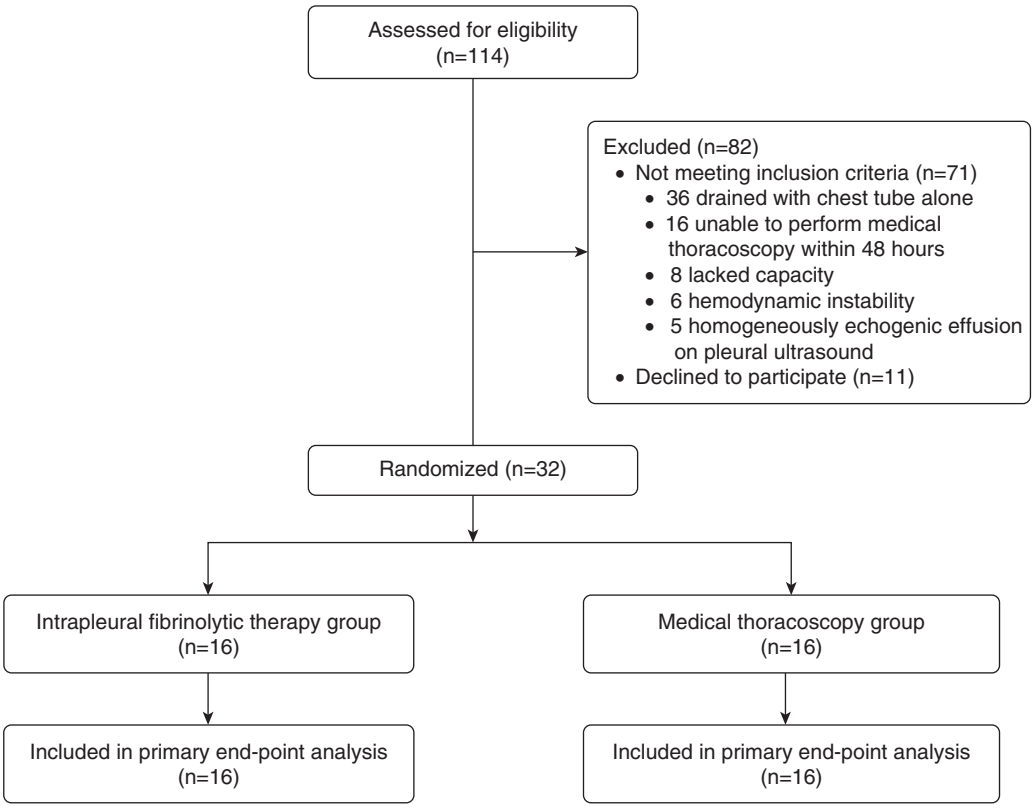

Figure 2. Consort diagram for the medical thoracoscopy versus intrapleural fibrinolytic therapy trial.

Streptococcus milleri ($n = 1$), *S. aureus* ($n = 1$), and *S. anginosus* ($n = 1$).

In the MT group, the median age was 65 years (IQR, 62.5–72.5) and 87.5% were men. The median pleural fluid pH, LDH, and glucose levels were 7.05 (IQR, 6.94–7.12), 982 IU/L (IQR, 450–1,819), and 37 mg/dl (IQR, 14–74), respectively. The effusions were purulent in 18.75% of the patients and 25% had a positive Gram stain or fluid culture result. An additional two patients had a positive pleural biopsy. Microbiology culture yielded viridans streptococci ($n = 2$), *S. milleri* ($n = 1$), *Pseudomonas aeruginosa* ($n = 1$), *S. anginosus* ($n = 1$), and *Staphylococcus epidermidis* ($n = 1$). Overall, the characteristics of the treatment arms were similar (Table 1).

Table 1. Baseline demographics and clinical characteristics of the participants

	IPFT ($n = 16$)	MT ($n = 16$)
Median age, yr (IQR)	58 (49–65)	65 (62.5–72.5)
Men, *n* (%)	10 (62.5)	14 (87.5)
Antibiotics duration, d (IQR)	27.5 (24–30.75)	26.5 (22–32.25)
Ultrasonographic estimated pleural effusion volume, *n* (%)		
Moderate (⩾500 ml)	13 (81.25)	13 (81.25)
Large (⩾1,000 ml)	3 (18.75)	3 (18.75)
Median peripheral leukocyte count, $\times 10^9$/L (IQR)	16.2 (12.9–25)	8.2 (6.3–13.5)
Purulent pleural fluid, *n* (%)	4 (25)	3 (18.75)
Side of pleural collection, right/left	12/4	11/5
Type of infection, community/hospital, *n* (%)	12 (75)/4 (25)	12 (75)/4 (25)
Positive Gram stain or culture of pleural fluid, *n* (%)	3 (18.75)	4 (25)
Median pleural-fluid pH (IQR)	7.02 (6.69–7.09)	7.05 (6.94–7.12)
Median pleural-fluid lactate dehydrogenase, IU/L (IQR)	1003 (697–1959.5)	982 (450–1819)
Median pleural-fluid glucose, mg/dl (IQR)	46.5 (12.5–74.5)	37 (14–74)

Definition of abbreviations: IPFT = intrapleural fibrinolytic therapy; IQR = interquartile range; MT = medical thoracoscopy.

Treatment Outcomes

The median length of hospital stay after the intervention was 4 days (IQR, 4–4.5) in the IPFT group as compared with 2 days (IQR, 2–5) in the MT group ($P = 0.026$). The median total length of hospital stay in the IPFT group was 6 days (IQR, 5–8.5) as compared with 3.5 days (IQR, 2–10) in the MT group ($P = 0.12$). All patients were followed up in the pleural clinic at 4–6 weeks after hospital discharge. No patients were readmitted within 30 days after the intervention in either arm. All patients in both groups had a chest radiograph upon clinic follow-up, and no additional pleural interventions were necessary in either group. The total median antibiotic duration was 27.5 days (IQR, 24–30.75) in the IPFT

Table 2. Clinical outcomes

	IPFT (*n* = 16)	MT (*n* = 16)	*P* Value
Median length of hospital stay after intervention, d (IQR)	4 (4–5.5)	2 (2–5)	0.026
Median total length of hospital stay, d (IQR)	6 (5–8.5)	3.5 (2–10)	0.12
Therapeutic failure, *n* (%)	3 (18.75%)	4 (25%)	>0.99
Adverse events, *n* (%)	1 (6.25%)	1 (6.25%)	>0.99
Mortality, *n* (%)	0	1 (6.25%)	>0.99

Definition of abbreviations: IPFT = intrapleural fibrinolytic therapy; IQR = interquartile range; MT = medical thoracoscopy.

arm and 26.5 days (IQR, 22–32.25) in the MT arm.

IPFT was successful in 13 patients (81.25%). The median number of fibrinolytic therapies administered was 4 (IQR, 3–6). Three patients failed treatment: one required an additional chest tube because the first chest tube got dislodged, one required an additional chest tube for a loculated fluid pocket, and one underwent an open thoracotomy. One patient had hemothorax without hemodynamic instability and did not need transfusion, but was monitored in the intensive care unit overnight. There was no mortality in the IPFT arm.

MT was successful in 12 patients (75%). Four patients failed the treatment: one required an additional chest tube for a loculated fluid pocket, two patients needed IPFT, and one patient required an additional chest tube and IPFT. One patient had intraprocedural hypoxia that resolved with insertion of a supraglottic airway tube and oxygen therapy. One patient died on Day 21 after the procedure, related to an acute coronary event. Three patients developed nonclinically significant subcutaneous emphysema that eventually resolved. Otherwise, there were no other related adverse events. Table 2 summarizes the clinical outcomes.

Discussion

VATS has been suggested as a surgical invasive approach to clear potentially infected material from the pleural space. In small randomized and nonrandomized prospective trials comparing VATS with intercostal drainage plus intrapleural streptokinase, VATS was associated with decreased hospital stays (19, 20). However, large cases series (21, 22) have shown that VATS is usually performed on younger individuals with fewer comorbidities (i.e., highly selected patients) compared with the unselected population of patients (who are usually sicker, elderly, and have multiple comorbidities) with pleural infection seen in the fibrinolytic studies (7, 8). Also, VATS or open thoracotomy has been used when patients fail to respond to IPFT. In this scenario, surgery allows adequate drainage of the pleural cavity and removal of the visceral pleural rind, thus improving lung restriction and compliance (2). This operation frequently leads to a higher complication rate (9–40%) and 30-day mortality (2–6%) (23, 24). Moreover, VATS was compared with intrapleural streptokinase. The intrapleural activity of endogenous PAI-1 (plasminogen activator inhibitor 1) in the pathogenesis of pleural infection is important because this mediator not only directly inhibits streptokinase but also contributes to the severity of loculation and poor outcomes with IPFT (25–27).

IPFT with tPA and DNase has been commonly used to treat patients with complicated pleural infection through a combination of chemical adhesion lysis, reduction of viscosity, biofilm degradation, and possible lavage component–induced pleural fluid formation mediated by monocyte chemotactic protein (28).

Recently, the use of MT for the management of pleural infection has gained interest (9, 10, 12). MT has the advantage of mechanically breaking loculations and septations in the pleural space, which will facilitate pleural fluid drainage, lavage, and targeted placement of the chest tube. In addition, pleural biopsies, which have been shown to increase diagnostic sensitivity for identifying the infectious agent, can be obtained. Furthermore, this minimally invasive procedure can be done under moderate sedation and local anesthesia, without the need for single lung ventilation or general anesthesia. Also, MT can be performed successfully by any operator (interventional pulmonologist or thoracic surgeon) who has completed dedicated training in the procedure.

However, the MT modality has not previously been directly compared with IPFT. The results of this study suggest that MT might shorten hospital stays after the intervention as compared with IPFT. This is probably because the mechanical breakage of adhesions can expedite infected pleural effusion drainage as compared with chemical adhesion lysis through IPFT. Moreover, the overall length of hospital stays was shorter in the MT arm (3.5 d) than in the IPFT arm (6 d), which is clinically relevant as well.

The two interventions had similar treatment success without an increase in adverse events, confirming previous findings regarding the safety and efficacy of both modalities. Furthermore, pleural biopsies increased the microbiology diagnostic yield by 12.5% in the MT arm, which confirms the results of a recent published trial of pleural biopsy in pleural infection (29). This represents an additional advantage over IPFT alone, as pleural biopsies can accurately dictate the use of personalized rather than empiric antibiotics. It is also important to recognize that the antibiotics used in this study were given empirically for patients with pleural infection. However, once a pathogen was identified or the patient's clinical condition improved, the antibiotics were modified accordingly.

The rate of complications related to MT in our study was slightly lower than those reported in the literature (6.25% vs. 7–17%) (9, 10, 12). This is because the primary outcome of the study was powered to detect the length of stay after hospitalization and not complications. Furthermore, only 16 patients were included in the MT arm, and the procedure was performed by an experienced practitioner.

In this study, we did not directly compare the average costs of IPFT and MT. However, four doses of IPFT cost approximately $12,032 USD, and MT (including 2 h of operating room time, sedation, and professional fees) costs approximately $9,682 USD. This could translate to lower overall costs for patients admitted with pleural infection.

There are several limitations to this study. The primary outcome of the study

was the length of hospital stay after either intervention. This could potentially lead to a bias toward MT over IPFT. However, we defined treatment failure as ongoing infection with loculations at 48 hours after either intervention, and previous studies showed that a median of two to three doses was enough to achieve clinical success (18, 30, 31). Furthermore, all of the centers have dedicated interventional clinicians with experience in MT, and initially evaluate/comanage all admitted patients with pleural effusion regardless of etiology; thus, the results are limited to centers with similar expertise. Our exclusion criteria were very selective. For instance, we only included patients with early-stage pleural infection based on chest US who were initially admitted or referred for evaluation concerning an infected pleural space and did not develop an effusion during their hospitalization. In addition, they were hemodynamically stable, able to provide written informed consent, and did not receive IPFT, which contributed to the high success rate.

This could also explain the shorter postintervention shorter hospital stays in both arms as compared with previous studies, but would not affect the comparison between the groups. Also, the median age for patients undergoing MT was 65 years as compared with 58 years in the IPFT arm, which could have affected our results. However, this proves that MT can be safely offered and is effective in elderly patients without causing an increase in adverse events. In addition, leukocyte counts were lower in the MT arm than in the IPFT arm, which also could be a confounder. However, a previous study showed that patients with sepsis and lower leukocyte counts had more severe outcomes, including mortality, than those with higher counts (32). This was not evident in our study. Moreover, patients who were randomized to the MT arm had up to two ports placed and a 24-Fr chest tube introduced through the exiting port and positioned at the end of the procedure, whereas patients in the IPFT arm had a small-bore chest tube was inserted, which might translate to an increased level of pain or discomfort postoperatively. We did not calculate objective pain scores because we assumed that it would not be clinically meaningful to compare them between the IPFT and MT arms. Finally, the study included only 32 patients; a larger sample size is probably needed to achieve greater precision.

In conclusion, MT is a minimally invasive procedure that is safe and effective for the treatment of early pleural infection in a select population, and might shorten hospital stays as compared with IPFT when performed in high-volume pleural centers by experienced interventional pulmonologists. A multicenter trial with a larger sample size is needed to confirm our findings. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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