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Review Article

Management in Pleural Infection and Role of Intrapleural Fibrinolytic Therapy

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Pleural infection was first described by the ancient Egyptians, and its treatment has been recognized since the era of Hippocrates[1]. Pleural infection is a major cause of morbidity and mortality; previous reports indicate 30-day mortality rates of 9-13% and 12-month mortality rates of 22-32% following the infection[2-4]. Mortality may be higher in immunocompromised host and often reaching approximately 40%[5]. Bacterial pleural infection most commonly arises from pneumonia[2,5-8]. Two-thirds of patients with pneumonia present with an associated pleural effusion, of which 5–7% patients developed a pleural infection such as simple or complicated parapneumonic effusion or empyema[2,7]. Light and colleagues previously established Light's criteria for classifying pleural fluid, which uses a pH cutoff of 7.2 to indicate the requirement for chest tube drainage[9]. The 2023 British Thoracic Society (BTS) guideline for pleural disease recommended the use of biomarkers such as pleural fluid pH, LDH, and glucose to consider chest tube thoracostomy or surgical management. To date, novel biomarkers such as soluble urokinase-plasminogen activator receptor (suPAR) and plasminogen activator inhibitor-1 (PAI-1) have been used to assess the prognosis and severity of peural infection[9]. The management of pleural infection consists of antibiotics, chest tube drainage (thoracostomy), intrapleural fibrinolytic therapy, intrapleural saline irrigation, medical thoracoscopy, and surgery which usually via video-assisted thoracoscopic surgery (VATS), though open thoracotomy may be required in more complex cases when the infection is not effectively controlled[10]. However, surgery is associated with significant morbidity, including perioperative and anesthetic mortality[11]. Intrapleural fibrinolytic therapy instillation plays a role in complicated parapneumonic effusion, empyema, and hemothorax by breaking down fibrin septations and reducing the rates of failed chest tube drainage and surgical referral[12-15]. The therapeutic use of intrapleural fibrinolytics was first reported in 1949 by Tillett WS and Sherry S[16]. They applied intrapleural fibrinolytic enzyme instillations, which included streptokinase and streptococcal deoxyribonuclease (streptodornase), in cases of hemothorax and postpneumonic empyema[5,16-19]. Over seven decades, there have been several reports of intrapleural fibrinolytic therapy in pleural infection;

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however, the results showed no benefit for the use of intrapleural streptokinase in pleural infection[20-21]. In 2011, the Second Multicenter Intrapleural Sepsis Trial (MIST-2 trial), a randomized trial, was a landmark study that established combined intrapleural enzyme therapy, tissue plasminogen activator (t-PA) and deoxyribonuclease (DNase), as a standard, non-surgical management for pleural infection[22]. Currently, the literature reports a wide range of dosages used for intrapleural fibrinolytic therapy instillation, and the optimal dosing regimen for each fibrinolytic drug remains controversial[12,14,16,18-19,21,23-28]. The aim of this review article is to provide an update on the diagnosis, management, and role of intrapleural fibrinolytic therapy in pleural infection.

Pathophysiology and Epidemiology

Approximately 20%-57% of patients with community-acquired pneumonia develop para-pneumonic effusion[6]. Pneumonia, mostly resulting from the aspiration of organisms from the oropharynx, is a major cause of pleural infection[29]. Pleural effusion occurs due to the presence of bacterial infection in the pleural space, which increases capillary permeability secondary to endothelial injury activated by neutrophils. Untreated parapneumonic effusion may transform into the fibrinopurulent stage, which is characterized by fibrinous adhesions and fibroblasts entering the pleural space, leading to pleural septation. Over the subsequent 2-3 weeks, the fibrinopurulent stage of parapneumonic effusion transitions to the organized or empyema stage, characterized by f ibroblast proliferation and the formation of a thick pleural peel that limits lung expansion, causing trapped lung or lung entrapment[18,29-30]. The common organisms in community-acquired pleural infection include gram-positive bacteria such as *Streptococcus* spp. (~52%), with viridans group streptococci as the most common causative agent, and *Staphylococcus aureus* (11%), followed by anaerobes (20%) and gram-negative aerobes (9%), which include Enterobacteriaceae and *Escherichia coli*. In the hospital-acquired pleural infection setting, the most common organism is methicillin-resistant *Staphylococcus aureus* (MRSA) (25%), followed by gram negative aerobes (~17%) (*Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella* spp.) and anaerobes. The mortality rate is up to 40% in cases of gram-negative, *Staphylococcus aureus*, and mixed aerobic pleural infections. In addition, 90-day mortality correlates with nosocomial infection[3-4,23,31-34]. Atypical pathogens often cause pneumonia but are a less likely cause of pleural infection[2,35].

Clinical presentation

The incidence of pleural infection has been identified in both young and elderly populations. Clinical presentation may include fever, chest pain, pleuritic chest pain, cough, purulent sputum, and dyspnea. Elderly patients may also present with non-specific symptoms such as anorexia and weight loss[2,31]. The duration from the infected period to the development of parapneumonic effusion varies from a few days to 1-2 weeks, and the transformation of pleural infection to the organized stage or empyema takes approximately 2-3 weeks[29].

Risk factors for pleural infection are similar to those for pneumonia, such as alcohol abuse, diabetes, poor oral hygiene, intravenous drug use, and gastro-esophageal reflux[8,35-36]. To date, there is no literature evaluating clinical tools for predicting the progression of pneumonia to pleural infection[2].

Imaging

Chest radiography

Chest radiography (CXR) is the first modality for detecting pleural effusion. A blunt costophrenic angle appears on the posteroanterior view when pleural fluid accumulation is greater than approximately 200 ml. in the pleural cavity[37]. CXR detects large pleural effusions, defined as approximately 350 ml. of fluid, with a sensitivity of 92% and a specificity of 89%. In contrast, CXR often fails to diagnose small and medium-sized pleural effusions, with sensitivities of 55% and 67%, respectively[38]. Furthermore, some patients with subpulmonic pleural effusions may have a normal costophrenic angle on CXR because a large amount of pleural effusion, up to 1000 ml, can remain in the subpulmonic area without extending to the chest wall[39].

Chest ultrasound

Lung ultrasound has a higher accuracy rate for diagnosing pleural effusion than conventional CXR, with a sensitivity ranging from 43-100% and a specificity ranging from 80-100%[38]. Furthermore, lung ultrasound demonstrated a higher sensitivity (86%) and specificity (100%) than chest CT scans for detecting pleural septations, defined as fibrin strands in the pleural cavity, which are associated with poor outcomes[40]. For chest examinations, two types of probes can be applied to the chest wall. The convex probe is a low-frequency transducer (3-7 MHz) that creates a deep, wide image with low resolution, which is appropriate for evaluating pleural effusion. The linear probe is a high-frequency transducer (7-15 MHz) that creates high-resolution images with less depth, making it suitable for examining the diaphragm, costophrenic angles, and the pleural line, as well as detecting small pleural effusions, pneumothorax, and pleural thickening[41].

Computed tomography scan (CT-scan)

Thoracic CT scans can play a role in distinguishing between uncomplicated parapneumonic effusion, complicated parapneumonic effusion, and empyema. Enhanced CT scans show a sensitivity of 59.8% and a specificity of 87% for diagnosing pleural infection[40]. The split pleura sign defined as the thickening and separation of the visceral and parietal pleural layers by effusion that demonstrates a high diagnostic yield for distinguishing uncomplicated parapneumonic effusion from complicated parapneumonic effusion or empyema[42]. A retrospective study including 83 patients with parapneumonic effusion demonstrated that the split pleura sign and a total pleural effusion volume of 30 ml. had high diagnostic accuracy for discriminating between these conditions[42]. Porcel et al. proposed a CT scoring system for validating the role of chest tube drainage in pleural effusion; this study showed that pleural contrast enhancement, pleural microbubbles, increased attenuation of extra-pleural fat, and a pleural fluid volume of 400 ml. were identified more frequently in patients with complicated parapneumonic effusion or empyema than in those with simple pleural effusion[43]. However, to date, there are no prospective studies validating the CT score in clinical practice.

Thoracentesis

Thoracentesis is a mandatory modality for diagnosing pleural infection. The aspiration of macroscopically purulent pleural fluid that including pus or fluid with positive gram stain or culture results indicates a need to drain the pleural infection. In contrast, non-purulent pleural fluid requires further investigation, such as testing for pleural pH, LDH, and glucose[2,29]. In 2010, the BTS guideline recommended that all

patients with parapneumonic effusion, recent trauma or surgery, or ongoing sepsis require thoracentesis if the pleural effusion is > 10 mm. in depth. Furthermore, small pleural effusions, defined as < 10 mm. in thickness on ultrasound imaging, often resolve with antibiotics alone[1].

Pleural fluid biomarkers

Over 40 years ago, Light and colleagues established Light's criteria that including pleural fluid lactate dehydrogenase (LDH) and pleural fluid protein to distinguish between transudative and exudative pleural fluid, and used a pleural pH cutoff of < 7.2 to indicate the need for chest tube drainage[9]. The latest BTS guideline for pleural disease (2023) proposes that a pleural pH 7.2 in patients with suspected complicated parapneumonic effusion requires chest tube drainage if lung ultrasound shows adequate pleural fluid volume and safe access to the pleural space[44]. Although pleural pH is a highly accurate biochemical marker for considering chest tube drainage, it may be altered by factors such as residual air, heparin, lidocaine, and delayed analysis. Pleural pH is significantly increased by residual air and delayed analysis; while it remains stable at room temperature for one hour, it increases significantly at 4 and 24 hours. Conversely, pleural fluid pH is decreased by residual heparin and lidocaine[45-46]. Additionally, pleural pH is applied to discriminate between the exudative phase (defined by normal pH and glucose) and the fibrinopurulent phase (defined by a pleural pH < 7.2 and glucose < 40 mg/dL), according to the American Thoracic Society staging system for pleural empyema[10], as summarized in Table 1.

Table 1. Characteristics of pleural infection and management as recommended by American Thoracic Society staging system and the British Thoracic Society guidelines for complicated parapneumonic effusion/empyema.

Stage	Characteristics	Pleural fluid biomarkers	Management
Stage I: Exudative phase	Clear fluid, neutrophilic response	Normal pH and glucose, consider LDH (via BTS)	Antibiotics, ± thoracentesis drainage, chest tube drainage if pH >7.2 and < 7.4 and LDH > 900 IU/L
Stage II: Fibrinopurulent phase	Turbid or purulent fluid, septations and loculations	pH < 7.2, glucose < 40 mg/dL (or glucose ≤ 72 mg/dL via BTS)	Chest tube drainage, surgical interventions (VATs debridement/decortication) ± fibrinolytic therapy, ± saline irrigation,
Stage III: Organizing phase	Fibroblast proliferation, thick pleural peel	Thick pleura, may be trapped lung	Chest tube drainage, VATs (± open surgery), ± fibrinolytic therapy, ± saline irrigation

BTS: The British Thoracic Society guideline, LDH: Lactate dehydrogenase, VATs: Video-Assisted Thoracic Surgery.

Novel pleural fluid biomarkers

Novel pleural fluid biomarkers, such as soluble urokinase plasminogen activator receptor (suPAR) and plasminogen activator inhibitor-1 (PAI-1), may play a role in predicting pleural septation formation and the requirement for chest tube insertion[9,30].

PAI-1

Pleural infection is associated with pleural inflammation, in which intrapleural fibrin accumulates due to mesenchymal and myeloid cell infiltration. Additionally, pleural mesenchymal cells and lung myofibroblasts increase PAI-1 levels in response to proinflammatory mediators released by pleural inflammation. Subsequently, excessive PAI-1 levels increase pleural septation and block intrapleural fibrinolytic activity[13]. A prospective study, including 214 pleural fluid samples, demonstrated that pleural fluid PAI-1 was associated with septation formation, septation severity, increased length of stay, and 12-month mortality[30]. However, a randomized trial showed that plasminogen deficiency-caused by the presence of neutrophil elastase, which cleaves plasminogen in several locations is a more significant factor influencing intrapleural fibrinolytic failure than the pleural fluid PAI-1 level, as the majority of PAI-1 in that trial was inactive[15]. Nevertheless, large future multicenter prospective or randomized trials will be required to determine the utility of PAI-1 and neutrophil-mediated inflammatory plasminogen degradation in clinical practice.

suPAR

suPAR is the soluble form of uPAR (urokinase type plasminogen activator receptor), which binds to endogenous uPA (urokinase) that converts plasminogen to plasmin, which in turn dissolves fibrin. Both suPAR and PAI-1 are regulated by pleural mesothelial cells[13]. An observational study demonstrated that suPAR levels were significantly higher in pleural infections and loculated malignant pleural effusions. Pleural suPAR alone was superior to pleural fluid pH alone for predicting the need for chest tube drainage in pleural infection. Similarly, pleural suPAR was superior to all conventional biomarkers combined-including pleural pH, LDH, and glucose for determining the role of intrapleural fibrinolytic therapy or surgical intervention[9]. Multicenter trials are required to assess the utility of pleural suPAR in pleural infection.

Microbiology

Conventional Gram stain and culture results are negative in approximately 40% of pleural infection cases. A prospective study showed that the use of blood culture bottles for pleural fluid culture increased the microbiological yield when at least 5-10 ml of infected pleural fluid was instilled into the bottle[32]. Another prospective study showed that 16S rRNA sequencing can identify polymicrobial organisms in pleural infection[2,47]. Thus, 16S rRNA might improve the diagnostic yield of pathogen identification in culture-negative pleural infection.

Procalcitonin

Procalcitonin has been revealed as a specific biomarker for bacterial infection. A prospective study involving 80 patients with pleural infection demonstrated that serum procalcitonin is not superior to C-reactive protein (CRP) or white blood cell count for the diagnosis of bacterial pleural infection, in neither patients who received antibiotics nor those who did not received antibiotics[48]. Robust prospective

studies are necessary to evaluate the value of procalcitonin in pleural infection.

Management

Antibiotics

Patients with pleural infection should receive broad-spectrum antibiotics based on local antibiotic policies, resistance patterns, and the source of the infection (community-acquired or hospital-acquired)[1-2]. Penicillins, penicillins combined with β-lactamase inhibitors, metronidazole, and cephalosporins have good pleural penetration. In contrast, aminoglycosides should be avoided due to their low efficacy caused by inactivation in the low pleural pH environment[1,29]. In penicillin-allergic patients, clindamycin alone or a combination of clindamycin with ciprofloxacin or a cephalosporin are alternative drugs. In hospital-acquired settings, antipseudomonal antibiotics and coverage for MRSA and anaerobes should be recommended[2]. The optimal length of antibiotic treatment remains controversial. The duration of antibiotics varies between 2-6 weeks according to clinical response, though at least 4 weeks of total antibiotic therapy is usually recommended. Currently, stepping down from intravenous to oral antibiotics should be considered when features of sepsis, radiological findings, and inflammatory biomarkers have improved. Most infected pleural patients receive 5-7 days of intravenous antibiotics to achieve clinical improvement. In cases where bacterial sensitivities and drug allergies are unknown, ambulatory intravenous treatment should be considered[1-2,44].

Repeated therapeutic thoracentesis

The management of pleural infections involves mandatory antibiotic therapy and chest tube drainage. Moreover, complex cases of infected pleural space require surgical management, which can lead to discomfort, reduced mobility, and a longer hospital stay. Thoracentesis is a simple procedure that reduces the risk of chest tube dislodgement and, under ultrasound guidance (USG), allows for the drainage of infected fluid from different loculated areas[49]. In 2015, Jouneau S. and colleagues reviewed the success and mortality rates of repeated therapeutic thoracentesis (RTT) in pleural infection studies. Their review, which included 329 patients across nine studies, demonstrated that the success rate for complicated parapneumonic effusion or empyema varied between 41-100%, with a mortality rate of 5-14% and a median of three thoracentesis procedures[49]. A recent randomized trial comparing therapeutic thoracentesis with chest tube insertion showed that RTT resulted in a significantly shorter hospital stay (5.4 days in the RTT group versus 13 days in the chest tube group). The median number of procedures was similar in both groups (1.4 in the RTT group versus 1.2 in the chest tube group), and there was no difference in the rate of surgical referrals. However, this study had limitations, including a small sample size of only 10 patients due to the impact of the COVID-19 pandemic. Additionally, patients with severe septations or loculations on pleural ultrasound, signs of ongoing sepsis, or recent thoracic surgery were excluded[50]. Therefore, repeated therapeutic thoracentesis should be considered for selected patients with non-severe infected pleural spaces.

Chest drain insertion

Chest tube insertion has been the standard of care for complicated parapneumonic effusion and empyema. Historically, there was a traditional

preference for large-bore chest tubes in pleural infection due to concerns regarding the evacuation of viscous pleural fluid and potential tube obstruction. Chest tube sizes are typically divided into small-bore (≤14 French) and large-bore (>14 French). For nearly two decades, small-bore catheters have been increasingly used for a wider range of pleural diseases, such as malignant pleural effusion with pleurodesis, pleural infection, and some cases of traumatic hemothorax, hydrohemothorax, or pneumothorax. Several studies demonstrate that small-bore chest tubes have successful outcomes in pleural fluid drainage and are non-inferior to large-bore chest tubes[51-53]. Although the MIST1 trial showed negative results of streptokinase in pleural infection, retrospective data from the trial demonstrated that small-bore chest tube insertion via the Seldinger technique (guidewire-inserted) reduced insertion-related discomfort and pain compared to blunt dissection techniques, particularly the blunt dissection used for large-bore catheter insertion[21,52]. Furthermore, studies have shown no significant difference in the frequency of chest tubes becoming displaced but some literature indicates that small-bore chest tubes have a trend toward unintentional displacement[54]. Further studies should analyze the rate of chest tube displacement across different sizes and its effect on treatment outcomes. To date, the 2023 British Thoracic Society guidelines recommend small-bore chest tubes for pleural infection drainage over large-bore chest tubes, as large-bore tubes may increase pain both during and after the procedure.

Intrapleural fibrinolytic therapy

Parapneumonic effusion is caused by pneumonia and may progress to complicated parapneumonic effusion or empyema, which is associated with a significant increase in pleural inflammatory mediators-such as tissue plasminogen activator (tPA) inhibitors-and other inflammatory mediators that lead to decreased fibrinolytic activity and increased septations and loculations[2,13].

For nearly a century, it has been known that Tillett and Garner discovered an active mediator for clot lysis from Streptococcus species, named streptokinase. In 1949, Tillett and Sherry reported the first intrapleural fibrinolytic instillation, using streptokinase and streptococcal deoxyribonuclease (DNase) in patients with pleural infections and hemothorax. They found significantly low levels of plasminogen in empyema and noted that DNase has the potential to reduce pleural fluid viscosity; this viscosity is attributed to high DNA concentrations resulting from the DNA degradation of phagocytes, bacteria, and intrapleural cells[16, 18]. The initial use of non-purified streptokinase showed a trend toward adverse events, including chest pain, febrile reactions, leukocytosis, and allergies. Some literature reported systemic and intrapleural hemorrhage requiring thoracotomy following intrapleural streptokinase instillation[18]. In 2005, a large randomized controlled trial, the MIST1 trial, demonstrated that intrapleural streptokinase instillation showed no significant difference in mortality, surgical rates, radiological resolution, or length of hospital stay compared to a placebo. Furthermore, the study showed that adverse events were more common in the streptokinase group.

Urokinase is also known as urokinase-type plasminogen activator (uPA). It is released in the urine and derived from the epithelial cells lining the straight parts of both the proximal and distal tubules[55]. Its function is to convert plasminogen into plasmin, which breaks down fibrin. Urokinase was initially used for intrapleural fibrinolysis in 1987 and has been

frequently used instead of streptokinase due to concerns regarding the adverse events and immunologic side effects of streptokinase[2,56]. Additionally, the efficacy of urokinase is not diminished by antibody production because it is produced from cultured human embryonic kidney cells[18]. The literature has shown that urokinase significantly increases pleural fluid volume drainage and improves radiological findings, but its effects on mortality and the rate of surgery remain unknown[57]. In 1997, a randomized controlled trial demonstrated that urokinase was as effective as streptokinase for the drainage of complicated parapneumonic effusions and empyema and might reduce the need for surgical intervention. In this study, 100,000 IU of intrapleural urokinase in 100 ml of normal saline was instilled via chest tube and compared to 250,000 IU of intrapleural streptokinase (SK) in 100 ml of normal saline. The total number of fibrinolytic instillations required for a therapeutic response was six in both groups, and the chest tubes were clamped for 3 hours before reopening the suction[58]. A single-center, controlled prospective cohort study of 93 patients hospitalized with pleural infection compared the efficacy of intrapleural urokinase (250,000 units in 30 ml of 0.9% NaCl twice daily for 5 days) and tissue plasminogen activator/DNase (tPA/DNase) (10 mg tPA and 5 mg DNase injected together in 30 ml of 0.9% NaCl twice daily for 3 days). The results demonstrated that the success rate of fibrinolysis, the rate of additional procedures, surgical referrals, drainage duration, and length of hospital stay did not differ significantly between the groups. However, the tPA/DNase group showed a significantly greater decrease in CRP levels by day 7 and was associated with a higher rate of non-serious hemothorax, which was hemodynamically stable, no reduction in hemoglobin, and necessitated no further interventions[27]. In contrast, a prospective randomized controlled trial showed that rt-PA (alteplase) resulted in a significantly greater change in pleural opacity than urokinase, while common adverse events, such as pain and hemothorax, were not significantly different between the groups[19]. Recently, a meta-analysis reviewed the efficacy and safety of urokinase in various etiologies of pleural effusion, mostly parapneumonic/empyema and TB pleurisy, using varying doses of intrapleural urokinase ranging from 100,000 to 250,000 units per dose. The analysis found that urokinase significantly improved treatment success rates, increased total pleural fluid drainage, shortened the length of hospital stay, and reduced residual pleural thickening[59]. In conclusion, intrapleural urokinase may serve as an alternative drug for pleural infection therapy; however, the optimal dose and duration of treatment remain controversial. Further large, multicenter randomized controlled trials are mandatory to evaluate the efficacy of urokinase in pragmatic pleural infection management.

Tissue plasminogen activator (tPA), also known as recombinant tissue plasminogen activator (rt-PA) or Alteplase, was first used as an intrapleural fibrinolytic instillation for pleural infection in 2003 by Walker and colleagues[60-61]. In 2011, the MIST-2 trial, a landmark randomized controlled study of intrapleural fibrinolytic therapy in pleural infection, utilized 10 mg of intrapleural tPA in 30 ml of normal saline and 5 mg of DNase (Pulmozyme) in 30 ml of water, followed by clamping the chest tube for one hour. The trial demonstrated that the combined tPA-DNase regimen was associated with improved pleural fluid drainage, a reduction in pleural opacity, a decreased rate of surgical referral, and a shortened length of hospital stay. In contrast, neither tPA alone nor DNase alone achieved the aforementioned outcomes. Notably, the

DNase-alone group had an increased rate of surgery. These results were consistent with a systematic review and meta-analysis which demonstrated a significant decrease in surgical intervention among patients who received both intrapleural fibrinolytics and DNase compared to patients who were given DNase alone[26]. The authors hypothesized that DNase monotherapy might lead to clinical deterioration due to the systemic absorption of bacteria and inflammatory components following DNase-mediated biofilm disruption in cases where pleural space drainage remains ineffective because of undisrupted pleural septations or loculations. However, the mortality rate showed no significant difference among the tPA-DNase, tPA-alone, DNase-alone, and placebo groups. Regarding the optimal timing for initial fibrinolytic agents, the MIST-2 trial did not establish an optimal timeframe from chest tube insertion to the start of intrapleural fibrinolytic therapy.

Combined tPA and DNase have good outcomes for pleural infection treatment. However, intrapleural bleeding associated with tPA has been reported in approximately 1.8-12% of cases, requiring blood transfusions in about 5% of patients treated with 10 mg of tPA and 28% of patients treated with 20 mg of tPA. Therefore, literature including the ADAPT-1 and ADAPT-2 trials was established to evaluate the efficacy and safety of a de-escalated dose of intrapleural tPA therapy. The ADAPT-1 trial, an observational open-label study, administered 5 mg of intrapleural tPA and 5 mg of DNase diluted with 30 ml of 0.9% NaCl twice daily, followed by clamping the chest tube for 40–60 minutes. Each institution followed individual protocols: tPA was instilled intrapleurally via a chest tube and then clamped and unclamped for pleural fluid drainage, after which DNase was instilled (sequential instillation), or both tPA and DNase were instilled directly after each other before the chest tube was clamped (concurrent instillation). The results showed that most patients (91.8%) did not require surgery within 3 months, and there was a reduction of pleural opacity at least 72 hours after intrapleural fibrinolytic instillation. Additionally, there was increased pleural fluid drainage, a decrease of approximately half in CRP levels by day 4, and a median length of stay (LOS) of 7 days[62]. Similarly, the ADAPT-2 trial, which used a de-escalated dose of 2.5 mg of intrapleural tPA and 5 mg of DNase, demonstrated that the 2.5 mg tPA dose with 5 mg of DNase had efficacy similar to the results of the ADAPT-1 trial[63].

Since the MIST-2 trial, several studies have investigated alternative intrapleural fibrinolytic drugs. The types of fibrinolytic drugs, frequency of administration, method of delivery (concurrent or sequential instillation), and optimal doses have varied among these studies. A retrospective study showed that tPA alone was effective in reducing surgical intervention, and cumulative doses of tPA ≤ 10 mg versus > 10 mg in tPA only group showed no significant difference in the need for surgical referral[14]. Some retrospective studies also indicated that the concurrent intrapleural instillation of combined tPA/DNase and once-daily tPA/DNase were effective in decreasing surgical intervention compared to sequential and twice-daily regimens[64-65]. A review of the dosage, frequency, and types of fibrinolytic drugs is summarized in Table 2.

Intrapleural fibrinolytic usage has been limited in some countries. In our institution, we have used only intrapleural tPA without DNase because DNase is not available in our country. We applied varying

Table 2. Review studies of intrapleural fibrinolytic therapy for complicated pleural effusion/empyema.

Study	Number of patients	Interventions	Outcomes	Median LOS (day)	Surgical intervention rate
Bouros D. et al (RCT; 1997)	50	Urokinase (UK; 100,000 IU) vs Streptokinase (SK; 250,000 IU)	Similar pleural fluid drainage, LOS, rate of surgical intervention	UK: 11.28 SK: 10.48	UK: 8% SK: 8%
Bouros D. et al (RCT; 1999)	31	Urokinase (UK; 100,000 IU) vs Normal saline (100 ml)	UK: shorten of fever duration and LOS, improved radiological imaging, reduced rate of surgery	UK: 13 Normal saline: 18	UK: 13.5% Saline: 37.5%
Bédat B. et al (single-center, prospective cohort study; 2019)	93	Urokinase (250,000 units twice daily x 5 days) vs tPA/DNase (10 mg tPA and 5 mg DNase twice daily x 3 days)	Similar drainage duration, LOS, required additional procedures, rate of surgical referral	UK: 18 tPA/DNase: 18	Overall 13% underwent VATS (OR 0.52; 95% CI: 0.14-2.02; P 0.35)
Adhikari S. et al (RCT; 2024)	50	Urokinase (100,000 IU thrice daily x 2 days) vs Alteplase (10 mg twice daily x 2 days)	Similar changed pleural opacity on chest imaging, side effects (fever and pain)	-	-
Jiang T. et al (meta-analysis; 2026)	1,990 (25 RCTs)	Urokinase vs Normal saline	UK: increased total drainage volume, shorten LOS and radiological resolution, no significant difference in adverse events	Median -6.94 days (95% CI: -9.37 to -4.51; P < 0.001)	-
Maskell N. A. et al (MIST-1 trial) (RCT; 2005)	427	Streptokinase (250,000 IU twice daily x 3 days) vs placebo	No significant difference in degree of reduction pleural opacity and pleural thickening, rate of surgical referral, mortality	SK: 13 Placebo: 12	SK: 16% Placebo: 14%
Rahman N. M. et al (MIST-2 trial) (RCT; 2011)	210	tPA/DNase (10 mg tPA+ 5 mg DNase) vs tPA (10 mg) vs DNase (5mg) vs placebo (All regimens were given twice daily x 3 days)	tPA/DNase: reduction of pleural opacity, ruduced rate of surgical intervention, shorten length of stay	tPA/DNase: 11.8 tPA: 16.5 DNase: 28.2 Placebo: 24.8	tPA/DNase: 4% tPA: 6% DNase: 39% Placebo: 16%
Popowicz N. et al (ADAPT-1 trial) (retrospective; 2017)	61	tPA/DNase (5 mg tPA+ 5 mg DNase; duration base on clinician)	Increased pleural fluid drainage, reduction of serum CRP level, few surgical referral	De-escalated dose: 7 10 mg tPA/DNase: 8	Overall 8.2%
Popowicz N. et al (ADAPT-2 trial) (prospective cohort study; 2022)	69	tPA/DNase (2.5 mg tPA+ 5 mg DNase; duration base on clinician)	Increased pleural fluid drainage, reduction of serum CRP level, few surgical referral (median total dose of tPA was 12.5 mg per patient)	12	2.8%
Bedawi E. O. et al (MIST-3 trial) (Multicenter RCT; 2023)	60	Standard care vs IPFT (10 mg tPA + 5 mg DNase twice daily; maximum 6 doses; median times to IPFT were 1 day) vs early VATS (within 5 days)	Similar LOS in IPFT and VATS groups, no significant difference in mortality rate among all groups	Standard care: 10 IPFT: 7 VATS: 7	Standard care: 19% IPFT: 10.5% VATS: 10% (further IPFT+VATS)

IPFT: intrapleural fibrinolytic therapy, VATS: Video-Assisted Thoracic Surgery.

initial doses of tPA ranging from 2-5 mg per dose, with cumulative doses (total dose of tPA) ranging from 2-8 mg, and instilled the intrapleural fibrinolytic once daily to shorten the procedure time. The total dose of tPA was not similar to that used in the MIST-2 trial because our patients showed clinical and radiological improvement after the first or second dose; furthermore, some patients developed adverse events related to tPA, such as nausea, vomiting, and transient confusion. Nevertheless, all patients were able to be discharged and had satisfactory outcomes during their follow-up periods. The results from our institution were similar to those of other studies, indicating that varied doses and frequencies of tPA can produce effects comparable to the original tPA protocol of the MIST-2 trial[14,26,62-63,65].

Recently, combined intrapleural fibrinolytic and enzyme therapy, including tPA and DNase, has been widely used as an alternative treatment to surgery. The most common side effect of intrapleural fibrinolytic therapy is chest pain, which occurs in 17-38% of patients receiving tPA/DNase, 13% receiving tPA alone, and 16% receiving DNase alone, followed by nausea, transient confusion, and erythema or rash. Moreover, dose de-escalation of tPA does not result in a significant difference in the rate of chest pain[22,62-63]. Both local and systemic hemorrhage are concerns regarding intrapleural fibrinolytic therapy. Some literature has found that intrapleural tPA instillation, with or without DNase, infrequently results in systemic bleeding, but the rate of intrapleural bleeding is approximately 1.8-12%. Intrapleural bleeding from tPA rarely leads to hemodynamic compromise. Some patients may require blood transfusions, but the majority of patients do not require surgical intervention. The risk of bleeding is increased with dose-dependent intravenous tPA administration. However, some retrospective studies have demonstrated that dose de-escalation of tPA and the use of concurrent or sequential administration of intrapleural fibrinolytic agents show no significant difference in the rate of intrapleural bleeding[62,66]. The incidence of intrapleural bleeding is higher in patients who continue anti-coagulation during treatment compared to those who withhold it (with a median discontinuation duration of 2 days); therefore, systemic anticoagulation should be withheld, or an international normalized ratio (INR) of < 2 should be achieved in the case of warfarin, before intrapleural fibrinolytic instillation. In the case of anti-platelet agents used with intrapleural fibrinolytic drugs, one cohort study found no evidence of intrapleural bleeding, but the authors suggested withholding anti-platelet agents due to the small number of patients in the study who were receiving them. Regarding comorbidities, liver disease is not associated with a significant bleeding risk; conversely, end-stage renal disease is associated with an increased rate of intrapleural bleeding. Furthermore, studies have shown that patients with a platelet count of 50 to 100 × 10^9/L have a significantly increased risk of intrapleural bleeding compared to those with a platelet count > 100 × 10^9/L[66].

Tenecteplase is another recombinant tissue plasminogen activator, similar to alteplase, which is a fibrin-specific fibrinolytic agent. It exhibits increased fibrin binding and greater resistance to PAI-1, has a longer half-life than alteplase, and promotes the breakdown of fibrin. Some studies demonstrate that tenecteplase is associated with a significant increase in pleural fluid drainage, a decreased rate of surgical referral, and a reduction in CRP levels. In these

studies, the total number of tenecteplase instillations ranged from 2 to 5 doses (mean 3.2 doses). The intrapleural bleeding rate for tenecteplase was approximately 7%, while systemic bleeding was not reported[12,67]. Robust studies are required to evaluate the efficacy and safety of tenecteplase in pleural infection management.

The majority of patients with intrapleural f ibrinolytic bleeding improved with the withholding of anticoagulants and observation; however, blood transfusions were required in some cases. Approximately 21% of patients with intrapleural bleeding required surgical intervention for hemothorax evacuation, as well as prompt decortication or debridement for definitive pleural infection treatment[62,65- 66]. Consensus has not been reached regarding the contraindications for intrapleural fibrinolytics. The literature proposes that bronchopleural fistula is the most common absolute contraindication. Other absolute contraindications include any trauma, surgery, or major hemorrhage within the previous 48 hours, as well as a history of allergic reactions to the drugs. Relative contraindications involve coagulopathy or therapeutic anticoagulation, invasive thoracic or abdominal surgery within the previous two weeks, a history of cranial hemorrhage, cranial surgery or trauma in the previous two weeks, and chronic empyema[68,69].

To date, VATS is a modern surgical technique and a minimally invasive approach for the decortication or debridement of early-stage infected pleural space[10,70]. A prospective multicenter RCT, the MIST-3 trial, showed that early VATS was associated with a shortened length of stay compared with the standard care group, but there was no significant difference when compared with the intrapleural fibrinolytic group (median LOS was 10 days in the standard care group and 7 days in both the intrapleural fibrinolytic and early VATS groups). The mean duration until intervention was 1.0 day in the intrapleural fibrinolytic group and 3.5 days in the VATS group. The requirement for readmission and/or further intervention at the 6-month follow-up was similar between the intrapleural fibrinolytic therapy and VATS arms. The mortality rate trended higher in the VATS arm compared with standard care and intrapleural fibrinolytic therapy (20%, 4.8%, and 5.3%, respectively). However, this study had a small sample size; therefore, large multicenter RCT studies are required to assess the optimal timing for VATS in pleural infection[70].

Normal saline irrigation

Intrapleural normal saline instillation is a simple, quick, and safe procedure. In a pilot study, normal saline irrigation which consisting of 250-ml. bags of 0.9% sodium chloride administered through the chest drain into the thoracic cavity by gravity (without an infusion pump and with no pressure applied) over one hour then allowed to drain using a three-way stopcock three times a day for three days (total nine irrigations) was associated with improved pleural fluid drainage and reduced surgical referral compared to standard care, which involved 30 ml normal saline flushes three times a day for three days[71].

However, because of the small number of patients in this study, robust trials are needed to confirm the efficacy of saline irrigation in pleural infection. To date, the 2023 BTS guidelines recommend using normal saline irrigation in patients with infected pleural space who have contraindications to intrapleural

fibrinolytic agents or are unsuitable for surgical intervention.

Medical thoracoscopy/pleuroscopy

Medical thoracoscopy (MT), also known as pleuroscopy, was established over 100 years ago. The procedure is performed under local anesthesia and moderate conscious sedation. Both rigid and semi-rigid or flexible thoracoscopes can be used in medical thoracoscopy[72-73]. MT is useful for the mechanical breakdown of fibrin and pleural septations or loculations. A few studies have shown that medical thoracoscopy might be superior to intrapleural fibrinolytic and DNase agents, as it shortened the length of stay (4 days in the intrapleural fibrinolytic therapy group versus 2 days in the MT group)[17,74]. Furthermore, MT combined with intrapleural fibrinolytic therapy was associated with a shorter duration of pleural fluid drainage, reduced intravenous antibiotic use, a shorter length of stay, and a reduction in subsequent interventions compared to intrapleural fibrinolytics with chest tube drainage alone. Specifically, patients with early stage complicated parapneumonic effusion (stages I and II) or empyema who underwent medical thoracoscopy had better outcomes than those treated in stage III (the organized phase)[75-76]. However, there were no significant differences in mortality, treatment failure, or adverse events. In cases of organized phase of empyema, medical thoracoscopy may be associated with poor outcomes due to thickened fibrous bands and severe adhesions or septations. Therefore, such patients should require VATS decortication or conversion to open thoracotomy. Unless patients are too frail to undergo surgery, MT should be considered in stages I and II of complicated parapneumonic effusion or empyema, as it is a safe and minimally invasive procedure for pleural infection management[72,76].

Surgery

Current guidelines recommend surgical consultation within 48 hours for patients who do not respond to antibiotics and chest tube drainage, defined as a lack of improvement in clinical status, radiological imaging, or inflammatory markers. Surgical intervention is the mainstay of treatment for pleural infection stage II, III, and empyema thoracis. In the past, open thoracotomy was significantly associated with morbidity and mortality. Currently, with advances in surgical techniques, Video-Assisted Thoracic Surgery (VATS) has become a modern and minimally invasive technique that reduces pain, shortens operative times, and decreases the length of hospital stay. The VATS procedure is usually performed under general anesthesia with single-lung ventilation via double-lumen intubation or a single-lumen tube. However, VATS has also been performed with sedation and local anesthesia[72]. In cases of complex, complicated parapneumonic effusion or empyema which a thick fibrous peel limits lung expansion, VATS may be insufficient for breaking down septations or accessing the thoracic cavity. Open decortication via thoracotomy remains the definitive treatment for patients who fail VATS and are suitable for surgery[10].

Intrapleural antibiotic instillation

Intrapleural antibiotic administration was established over 50 years ago as a prophylactic measure for postpneumonectomy empyema and as a therapeutic modality for patients with complicated parapneumonic effusion or empyema who do not

respond to chest tube drainage or systemic antibiotics and are unfit for surgery. Some studies show that intrapleural antibiotics might enhance the elimination of bacterial infection in the pleural space and prevent pleural infection after lung resection; furthermore, complications from intrapleural antibiotics have not been reported. Nevertheless, most of the data are from retrospective studies. Further studies are necessary to confirm the value of intrapleural antibiotics in pleural infection management [77-79].

Indwelling pleural catheter (IPC)

Indwelling pleural catheters (IPCs) play a role in ambulatory chest drainage for recurrent malignant pleural effusion and non-expandable lung. IPC insertion is associated with a spontaneous pleurodesis rate of approximately 51.3%, and talc pleurodesis can also be applied via IPC to bring the parietal and visceral pleura attached to each other. Additionally, IPCs have been introduced for pleural fluid drainage in pleural infection, and intrapleural fibrinolytic agents have been instilled via IPCs to break down fibrin and increase the rate of drainage. However, major complications that including empyema, loculations, dislodgement, leakage, and pneumothorax are found in approximately 1-2% of cases[62,80-84]. Currently, there is a lack of consensus on IPC implementation as a standard treatment for pleural infection. IPCs should be considered a bridging therapy for patients with chronic pleural infection who are not candidates for standard drainage or surgical intervention.

Conclusion

Complicated parapneumonic effusion and empyema can lead to significant morbidity and mortality. Intrapleural fibrinolytic agents and pulmozyme are alternative treatments for patients with an infected pleural space who are not candidates for surgical intervention and do not have contraindications to intrapleural fibrinolytic therapy. Currently, the type and standard dose of tPA used in the MIST-2 trial are recommended. However, research indicates that various types, doses, and frequencies of intrapleural tPA instillation might be as effective as the standard protocol. Further robust studies are necessary to confirm the efficacy and safety of various types and doses of tissue plasminogen activator, as well as the optimal time for initiating fibrinolytic therapy after chest tube insertion.

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