



# Current status and prospect of medical and surgical management for thoracic empyema

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**Abstract:** We sometimes encounter patients with chronic empyema of their thoracic cavity with or without air leakage. These patients often experience mental and physical problems because of restrictions in daily life and long-term treatment. Thoracic empyema is classified as acute or chronic empyema. The former is treated by antibiotics, thoracic drainage, fibrinolysis, or debridement under video-assisted thoracic surgery (VATS), while the latter is treated by managing the infection and reducing the dead space of the thoracic cavity. In this review, we summarize the procedures for various treatment methods and technical skills in the management of thoracic empyema. Chest physicians should consider the advantages and disadvantages of each method and choose an appropriate technique or possibly a combination of techniques to obtain an optimal outcome in the treatment of thoracic empyema. The techniques and knowledge described in this review will be useful for many physicians' clinical work. Treatment methods differ among institutions, and a guideline for thoracic empyema is needed to standardize treatment of this entity in future.

**Keywords:** Empyema; chest drainage; fibrinolysis; video-assisted thoracic surgery (VATS); open surgery

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## Introduction

Thoracic empyema, which is defined as purulent collections within the thoracic cavity due to a pleural space infection, is associated with severe morbidity and mortality in both adults and children despite optimal treatment (1-4). This entity was first described in the fifth century B.C. by Hippocrates in his aphorisms, who proposed drainage as a treatment (5). For hundreds of years thereafter, empyema was treated using open drainage. However, most cases are now initially treated using antibiotics with or without repeated thoracentesis or tube drainage. Surgical approaches including video-assisted thoracic surgery (VATS) or open thoracotomy are usually reserved for patients with a deteriorated clinical condition following

failed conservative treatment. VATS has been shown to result in earlier and more complete resolution of empyema than tube drainage alone (6,7). Fibrinolysis has also been shown to be superior to tube drainage alone (8-10). The management of thoracic empyema is empirical, and its treatment strategy is controversial. Furthermore, limited data from controlled clinical trials are available to guide the management of thoracic empyema. This review highlights significant findings in empyema management to help readers comprehend the current status of this field.

## Epidemiology

Recent epidemiologic studies have indicated that the incidence of empyema has been increasing during the last

few decades (11). In 2016 in Japan, 2,833 cases of empyema were reported and hospital mortality rate was 6.9% (12). In the United States, the estimated incidence of parapneumonic empyema is 6 cases per 100,000 people, and the hospital mortality rate in the adult population is approximately 16.1% (13). Risk factors of empyema include diabetes mellitus, gastroesophageal reflux, poor dental hygiene, chronic lung disease, alcohol abuse, and so on. Empyema may develop as a complication of pulmonary infection, thoracic and abdominal surgery, trauma, and iatrogenic procedures. However, pleural infection may also occur as a primary infection without pneumonia.

## Pathophysiology and classification

### *Acute empyema*

Thoracic empyema is the accumulation of purulent collections within the pleural cavity. Empyema is classified as acute or chronic and is also classified as localized or diffuse. Empyema is divided into three stages (14): stage I is an acute exudative phase in which the visceral pleura remains elastic and the dimensions of the thoracic cavity are maintained. Stage II is a subacute fibrinopurulent phase characterized by turbid, infected fluid with fibrin deposits constructing bridges that separate the effusions. Stage III is chronic organizing phase in which this construct is replaced by formal granulation tissue. Successful treatment of acute empyema requires immediate treatment with adequate antibiotics and tube drainage to prevent recurrence and chronicity. Most affected patients have small and uncomplicated effusion that can be treated conservatively with continued antibiotics, thoracentesis and observation. However, patients with loculated pleural effusion or purulent effusion on thoracentesis should be considered prompt insertion of a chest tube. Patients with loculated parapneumonic effusion (stage II, subacute phase), particularly those patients whose lung fails to re-expand, should be considered for early VATS procedure or intrapleural fibrinolytics (15,16).

### *Chronic empyema*

Empyema lasting  $\geq 4$  weeks is classified as chronic empyema (17). At stage III empyema, the cloudy fluid begins to organize and form granulation tissue. The continuous inflammation of the infectious process involves in the formation of a fibrin peel on the visceral and

parietal pleural surface. Continuation of this process also contributes contraction of the affected thorax in addition to a mediastinal shift toward the affected side and rib space narrowing. In general, chronic empyema is characterized by thickened visceral and parietal fibrin peels that hamper the ability of the affected lung to re-expand. At stage III empyema, chest tube drainage is no longer effective, therefore, chronic condition of pleural cavity needs surgical procedure. The purpose of surgical treatment is to remove purulent effusion, infected tissue and thickened pleura, and finally to close the empyema space to avoid recurrence. The selection of the initial treatment depends on the conditions of the patient's pleural cavity and lung parenchyma.

### *Classification by American Thoracic Society*

The American Thoracic Society proposed a classification system in 1962 based on the natural history of empyema (*Table 1*) (14). In this classification, empyema is divided into three stages: exudative phase, fibrinopurulent phase and organized phase. The exudative phase lasts for several days and is characterized by a free-moving effusion in the pleural space. The fibrinopurulent phase is characterized by a reduced intrapleural fibrinolysis that causes fibrin deposition on the visceral and parietal pleura and is also characterized by a cloudy, viscous fluid. The organized phase is characterized by the fibrin and collagen deposition, resulting in fibrous thickening of the pleura. This classification is useful in practice and is still employed because the method of treatment is totally different in each stage or phase.

### *Light's classification*

According to Light (18), thoracic empyema is classified into seven categories as shown in *Table 2*. This classification has four variables: fluid bacteriology, fluid property, fluid chemistry, and fluid pH. According to this classification, a typical parapneumonic effusion meets the following criteria: the thickness of the pleural fluid is  $>10$  mm, the pleural glucose concentration is  $>40$  mg/dL, the pleural fluid pH is  $>7.20$ , the pleural fluid lactate dehydrogenase concentration is  $<1,000$  IU/L, and Gram stain and culture are negative. A borderline complicated parapneumonic effusion meets the following criteria: the pleural fluid pH is 7.00 to 7.20, the pleural fluid lactate dehydrogenase concentration is  $>1,000$  IU/L, the pleural fluid glucose concentration is  $>40$  mg/dL, and Gram stain and culture

**Table 1** Three-stage classification by the American Thoracic Society

	Exudative phase (stage I)	Fibrinopurulent phase (stage II)	Organized phase (stage III)
Characteristics of pleural effusion or pus	Inflammatory processes extend to the pleura and result in immediate outpouring of fluid	Frank pus accumulates especially laterally and dorsally	Thick and sedimented exudate
Pathophysiology of pleural effusion and pleura	Low cell content	High cell content and fibrin depositions over the pleural surfaces and fibrinous strands within the fluid	Fibroblast growth and fibrosis
Intrathoracic condition	Re-expandable lung	Tendency for development of loculations and formations of membranes Beginning constriction of the lung	Inelastic membranes over the pleural surfaces Trapped lung

**Table 2** Light's classification

Class	Characteristics of effusion	Bacteriology	Imaging findings	Biochemistry	pH	Treatment
Class 1	Nonsignificant parapneumonic effusion	Gram stain and culture negative	<10 mm thick on decubitus X-ray	–	–	No thoracentesis indicated
Class 2	Typical parapneumonic effusion	Gram stain and culture negative	>10 mm thick	Glucose >40 mg/dL	pH >7.20	Antibiotics alone
Class 3	Borderline complicated parapneumonic effusion	Gram stain and culture negative	Not loculated, no frank pus	Glucose >40 mg/dL, LDH >1,000 IU/L	7.00 < pH <7.20	Antibiotics plus serial thoracentesis
Class 4	Simple complicated parapneumonic effusion	Gram stain and culture positive	Not loculated, no frank pus	Glucose <40 mg/dL	pH <7.00	Tube thoracotomy plus antibiotics
Class 5	Complex complicated parapneumonic effusion	Gram stain and culture positive	Multiloculated	Glucose <40 mg/dL	pH <7.00	Tube thoracotomy plus thrombolytics
Class 6	Simple empyema	Frank pus present	Single locule or free-flowing	–	–	Tube thoracotomy ± decortication
Class 7	Complex empyema	Frank pus present	Multiple locules	–	–	Tube thoracotomy plus thrombolytics; VATS or decortication often required

LDH, lactate dehydrogenase; VATS, video-assisted thoracic surgery.

are negative. A simple complicated parapneumonic effusion meets the following criteria: the pleural fluid pH is <7.00, the pleural fluid glucose concentration is >40 mg/dL, and Gram stain is positive; however, the fluid is not loculated and does not appear to be frank pus. A complex complicated parapneumonic effusion meets the criteria for a simple

complicated parapneumonic effusion with multiloculation of the pleural fluid. In a simple empyema, the pleural fluid is frank pus and the fluid is free-flowing without loculi. If the pleural fluid is frank pus and the fluid is multiloculated, these conditions are called to have complex empyema. This classification is widely accepted and is useful for physicians

**Table 3** Categorization of risk for poor outcome among patients with parapneumonic effusion and empyema by the American College of Chest Physicians

Category	Risk of poor outcome	Pleural space anatomy		Pleural fluid bacteriology		Pleural fluid chemistry	Drainage
1	Very low	A0: Minimal, free-flowing effusion (<10 mm on lateral decubitus view)	and	Bx: Culture and Gram stain results unknown	and	Cx: pH unknown	No
2	Low	A1: Small to moderate free-flowing effusion (>10 mm and less than one-half hemithorax)	and	B0: Negative culture and Gram stain	and	C0: pH $\geq$ 7.20	No
3	Moderate	A2: Large, free-flowing effusion (at least one-half hemithorax) loculated effusion, or effusion with thickened parietal pleura	or	B1: Positive culture and Gram stain	or	C1: pH <7.20	Yes
4	High	–	–	B2: Pus	–	–	Yes

to choose the optimal treatment of thoracic empyema because each classification recommends a therapeutic option.

#### *Guidelines by the American College of Chest Physicians*

The American College of Chest Physicians proposed guidelines on the medical and surgical treatment of parapneumonic effusions in 2000 (19). This guideline has three variables: pleural space anatomy, pleural fluid bacteriology, and pleural fluid chemistry. These variables are used to categorize patients into four separate risk levels: category 1 (very low-risk), category 2 (low-risk), category 3 (moderate-risk), and category 4 (high-risk) (Table 3).

#### **Diagnostic methods**

##### *Imaging*

A staging assessment based mainly on the start of symptoms is not easily implemented in some cases. A chest roentgenogram, ultrasound examination, and chest computed tomography (CT) scan are all required and are considered as the primary imaging modalities for effusion (20). Imaging plays three important roles in empyema management: confirmation and characterization of effusions; decision for treatment, including thoracentesis, drainage, and surgical interventions; and follow-up of the patients after treatment.

##### **Chest roentgenogram**

Imaging techniques play a fundamental role in the management of empyema. In spite of advances in imaging modalities, the chest X-ray still plays a basic role in establishing the presence and amount of pleural effusion and guiding management during follow-up of patients. Asymmetric pleural effusion with blunting of the costophrenic angle can be recognized and smaller-volume effusions are detectable with a lateral-view roentgenogram.

##### **Chest CT**

Chest CT with intravenous contrast is optimal and has high diagnostic yield for empyema. Furthermore, a CT scan provides additional information about detailed anatomy including the mediastinum and hila. A CT scan is also necessary in some cases to confirm the characteristics of the effusion, determine the presence of pleural thickening or adhesions, and identify associated lesions such as tumors (21).

##### **Ultrasonography**

Ultrasound is an accessible, radiation-free method of visualizing free versus loculated pleural effusions. A previous study showed that ultrasound had better sensitivity for diagnosing pleural effusion than did plain radiographs (22). In the absence of clear loculation on ultrasonography, simple thoracentesis or chest tube drainage can be the standard treatment; however, patients with clear loculation require a form of thoracoscopy as an

initial treatment (23).

### ***Thoracentesis and pleural fluid analysis***

Diagnostic thoracentesis is crucial to demonstrate the presence of pus, which identifies the empyema. Additionally, pleural fluid sampling via thoracentesis is needed for fluid analysis and diagnosis of pleural effusion (20). For patients with a known pleural infection, intercostal drainage is required for appropriate treatment, and thoracentesis without pleural tube drainage is not recommended (24). Patients with empyema who have non-purulent pleural fluid with a low pH or glucose concentration can be managed with antibiotics alone (25,26). However, most patients who have purulent collections in their pleural cavity require VATS or open thoracotomy (27). Light (18) proposed a classification system that assists the physician in determining the aggressiveness of the initial therapy. We have described the details of this classification in the previous section of this review.

## **Treatment modalities**

### ***Antibiotics***

Although the choice of antibiotics should be essentially on the basis of culture in pleural effusion, antibiotic therapy is started empirically; in only a minority of cases is the antibiotic therapy adapted to the laboratory results because of the low rate of positive bacteriology results. Broad-spectrum antibiotics are used for most patients with suspected or confirmed thoracic empyema. Antibiotics should be tailored to target pathogens based on epidemiology, antibiotic resistance patterns, cause of acquisition, and whether the affected patients are from a community versus healthcare setting. In community-acquired empyema, the antibiotic regimen should target common pathogens including *Staphylococcus* and *Streptococcus* species. Appropriate antibiotics include a third-generation cephalosporin plus metronidazole or a beta-lactam/beta-lactamase inhibitor combination. In hospital-acquired empyema, antimicrobial therapy should be directed at providing coverage for methicillin-resistant *Staphylococcus aureus* and *Pseudomonas*. Reasonable options include vancomycin plus metronidazole and antipseudomonal cephalosporin. Intravenous administration of antibiotics is often appropriate initially; however, the administration route can be changed to oral when objective clinical (e.g.,

improvement in temperature) and biochemical improvement (e.g., C-reactive protein) has been observed. Continuation of antibiotic therapy is generally recommended for 2 to 6 weeks depending on the degree of aforementioned infection and clinical response to the treatment (28).

### ***Chest tube drainage***

A poor response to antibiotics requires chest tube drainage. The optimal size of the chest tube and duration of tube drainage are not determined. A large multicenter study on the chest drain diameter in the treatment of plural infection showed no significant differences in any impairment in clinical outcome except insertion discomfort between small- and large-diameter drains (29). Clinically, the location of the chest tube is more relevant than the tube size, and inappropriate positioning of the chest tube can cause treatment failure. The appropriate removal time of the chest tube depends on two factors: radiological confirmation of successful pleural drainage and objective evidence of infection resolution. However, the presence of loculations frequently makes the effusion difficult to discharge from pleural cavity with chest tube drainage. In the situation, intrapleural fibrinolysis, VATS, or open surgery is needed.

### ***Fibrinolysis***

Intrapleural fibrinolytic therapy was first reported in the late 1940s. Tillett and Sherry (30) used a partially purified streptococcal concentrate containing streptokinase and streptococcal deoxyribonuclease (DNase) intrapleurally in patients with fibrinopurulent pleura and empyema. To date, 11 randomized controlled trials have been performed since 2000, including both adults and children (*Table 4*). Of these trials, the largest are Multicenter Intrapleural Sepsis Trials 1 and 2 (MIST-1 and MIST-2) (31,41). MIST-1 showed that streptokinase at 250,000 IU twice daily for 3 days increased the amount of pleural fluid drainage, however, which was not associated with reduced mortality, lower surgical referral, or duration of hospital stay (41). MIST-2 was a randomized double-blinded, placebo-controlled trial for adult patients with pleural infection (34). This study showed that combined intrapleural tissue plasminogen activator (tPA)/DNase resulted in a significant reduction of pleural effusion in radiograph, a lower frequency of surgery, and decreased duration of hospital stay compared with placebo.

**Table 4** Randomized controlled trials of fibrinolytic treatment reported since 2000

Study	Year	Sample size	Age group	Intervention	Outcomes
Tuncozgun <i>et al.</i> (31)	2001	49	Adult	Urokinase (100,000 IU)	Pleural fluid drainage Length of stay Rate of surgical intervention
Diacon <i>et al.</i> (32)	2004	53	Adult	Streptokinase (250,000 IU)	Rate of surgical intervention
Misthos <i>et al.</i> (33)	2005	127	Adult	Streptokinase (250,000 IU)	Rate of surgical intervention Length of stay
MIST-1 (34)	2005	454	Adult	Streptokinase (250,000 IU)	Rate of surgical intervention Mortality
Kurt <i>et al.</i> (7)	2006	18	Child	Fibrinolytics versus VATS	Hospital length of stay Number of chest tube days
Sonnappa <i>et al.</i> (35)	2006	60	Child	Urokinase (10,000–40,000 IU) versus VATS	Number of hospital days after intervention Number of chest drain days
St Peter <i>et al.</i> (36)	2009	36	Child	tPA (4 mg) versus VATS	Length of postoperative hospitalization
Cobanoglu <i>et al.</i> (37)	2011	54	Child	Streptokinase (250,000 IU) versus VATS	Continuity of symptoms after the operation Duration of thoracic tube
MIST-2 (38)	2011	210	Adult	tPA (10 mg) plus DNase (5 mg)	Rate of hemothorax occupied by effusion Rate of surgical intervention Mortality
Thommi <i>et al.</i> (39)	2012	68	Adult	tPA (25 mg)	Rate of surgical intervention
Marhuenda <i>et al.</i> (40)	2014	103	Child	Urokinase (40,000 IU) versus VATS	Length of hospital stay after treatment Total length of hospital stays

VATS, video-assisted thoracic surgery; tPA, tissue plasminogen activator; DNase, deoxyribonuclease. MIST, Multicenter Intrapleural Sepsis Trial.

### Streptokinase

The most commonly used fibrinolytic in the clinical setting is streptokinase, and several prospective studies have proven the efficacy of this agent for thoracic empyema (Table 4) (32,38). A total of 250,000 IU of streptokinase was administered into the pleural space for 3 to 7 days. However, the optimal dosage and required number of daily washings of streptokinase are still controversial. Furthermore, according to the negative results of MIST-1, streptokinase is giving way to other fibrinolytics such as urokinase, tPA, and DNase.

### Urokinase

Urokinase is a thrombolytic agent derived from human neonatal kidney cells. Some case reports have shown that urokinase therapy improves pleural fluid drainage and reduces the need for further surgical intervention (33,42).

In addition to these retrospective studies, some randomized clinical trials have shown that urokinase therapy increases pleural fluid drainage and reduces the referral rate for surgery (43,44). Tuncozgun *et al.* (45) also showed that intrapleural instillation of urokinase (100,000 IU/day) provided a better outcome and reduced the need for decortication (Table 4). These randomized trials have increased the level of clinical evidence.

### Ozone

The benefits of ozone therapy have been studied for more than a century. Ozone has been demonstrated to be a forceful and reliable antimicrobial agent against bacteria, fungi, and viruses (31). Ozone induces the destruction of cytoplasmic membranes of bacteria and fungi by acting on glycoproteins, glycolipids, and other amino acids as

well as by inhibiting key enzymes in the cells. Through these actions, microbial cell death occurs (31). Ozone can also be widely spread into the abscess cavity, resulting in abscess wall dehydration and expand the distribution of drug solutions (31). A retrospective study showed that combined treatment with ozone and urokinase is useful in the management of empyema and can safely reduce the rate of surgical referrals and the duration of hospital stay (46). The authors injected 50,000 U of urokinase diluted in 20 mL of normal saline into the pleural cavity through a pigtail catheter. In addition to urokinase, 10 to 20 mL of an oxygen-ozone gas mixture (ozone concentration of 25 mcg/mL) was administered through the catheter per day (46). A randomized prospective study is needed to assess the role of ozone in the treatment of this entity.

### DNase

DNase synergizes with tPA or streptokinase *in vitro* and in animal models of empyema (47). MIST-2 (34) (Table 4) demonstrated that the combination of intrapleural tPA (10 mg twice a day for 3 days) and DNase (5 mg twice a day for 3 days) resulted in statistically significant clinical improvement in pleural fluid drainage and a reduction in the length of hospital stay compared with the other three treatments (tPA, DNase, and placebo). Furthermore, a 75% reduction of surgical referral at 3 months was achieved in the tPA-DNase group compared with the placebo group (34). Six serious adverse events occurred in the study: two cases of intrapleural hemorrhage (both in the tPA-DNase group), one case of hemoptysis (in the placebo group), two episodes of gastrointestinal bleeding (both in the DNase group), and one case of clinical deterioration (in the placebo group). The frequency of adverse events did not significantly differ among the groups (34). Thommi *et al.* (48) also showed the efficacy and safety of tPA for thoracic empyema in their double-blind randomized crossover trial.

### VATS

VATS can be performed in patients whose chest tube drainage has failed or when the lung does not re-expand well after medical management. One retrospective study showed fewer complication and higher success with early treatment by VATS when compared with delayed surgery (39). In other studies, VATS debridement resulted in shorter hospital stays and superior empyema improvement rates when compared with chest tube drainage (49,50). Current guidelines advocate the use of surgery

when an advanced fibrinopurulent phase is suspected by the presence of extensive pleural thickening that requires decortication (20). The need for surgery is usually assessed 5 to 7 days after initial treatment for empyema (51,52). Currently, VATS is considered as the primary treatment option for stage II empyema. However, the guidelines are based on low-quality evidence, and there are no reliable data to identify which patients are likely to benefit from surgical treatment or determine the optimal time point for referral to a surgeon. The recently proposed RAPID score enables clinicians to prognosticate at the time of presentation (53). VATS or open intervention remains the standard option for treating complicated pleural effusion or empyema. The American Association for Thoracic Surgery consensus guidelines for the management of empyema recently classified VATS as a class IIa recommendation (24). According to this recommendation, VATS is considered to be the primary treatment in stage II (fibrinopurulent phase) patients (level of evidence B), and intrapleural fibrinolytics should not be used primarily for both complicated pleural effusion and early empyema (level of evidence B) (24). The European Association of Cardiothoracic Surgery expert consensus statement for surgical management of pleural empyema demonstrated benefits of VATS decortication for stage II and III empyema, which are tolerable conditions for treatment with an operative procedure (54). A recent systematic review and meta-analysis compared VATS and chest drainage with fibrinolysis in the management of pediatric empyema (55). The authors evaluated previous randomized trials (7,35-37,40) and found that VATS and chest drainage with fibrinolysis for empyema in children have a similar incidence of perioperative complications and that VATS tends to reduce the need for re-intervention and is associated with a shorter postoperative hospital stay (55).

### Open surgery

#### Decortication

For several decades, open decortication remained the only surgical treatment for complicated empyema (56). Open decortication has been adapted to remove fibrous tissue and peel from the parietal and visceral pleura in order to improve lung expansion, resulting in a greater lung vital capacity and improvement in symptoms. A recent analysis demonstrated equivalent effectiveness of VATS decortication in the management of advanced stage II or III empyema (57). However, the study showed no superior results with VATS versus open surgery decortication in

the treatment of thoracic empyema. Therefore, VATS and open thoracotomy decortication can be recommended in the surgical management of thoracic empyema. However, in advanced empyema patients, VATS can be easily led to the conversion to an open surgery. According to these research findings, open decortication is saved for unresolved empyema.

### Open window thoracotomy (fenestration)

Dr. Leo Eloesser, the surgeon who developed the surgical procedure associated with his name, reported in 1935 its use as an alternative to existing treatment for acute tuberculous empyema that were associated with high mortality (58). In his original report of the operation (Eloesser's method), he constructed the window with a flap so that it functioned as a one-way valve, carrying out the fluid from pleural cavity while preventing air from entering the pleural cavity and causing lung collapse. This procedure requires partial resection of two to three ribs and creation of a U-shaped soft tissue flap that is folded into the chest cavity. Thourani *et al.* (59) subsequently proposed the modified Eloesser flap, which uses an inverted U-shaped muscle flap. Open window thoracotomy still remains a life-saving treatment option for patients with pleural cavity infection, especially in patients with bronchopleural fistulas (BPFs). This method requires resection of two to three ribs and careful separation of the chest wall muscles, which results in a segmental defect of the chest wall and a poor cosmetic appearance. Novel prosthetic devices for open thoracotomy, which require only a 3 cm resection in one rib, have been shown to be effective for resolving chronic empyema (60,61). These prostheses are self-retained silicone tubes, which drain out into a small plastic bag. Another novel device, the vacuum-assisted closure device (negative-pressure wound therapy), might help the management of patients with empyema by hastening recovery (62,63). However, the previous American Association for Thoracic Surgery expert consensus guidelines warned that the vacuum-assisted closure method should be used with caution in the presence of a BPF or visceral pleural fistula (24). This open window thoracotomy technique has a specific advantage in the successful closure of BPF (64,65). In patients with a BPF, bronchial occlusion is necessary and an Endobronchial Watanabe Spigot (Novatech, Grasse, France) is sometimes used to decrease air leakage and thus avoid fenestration (66).

### Management of residual thoracic space

Three approaches are used for treatment of the residual

thoracic space. The first is a permanent open thoracotomy window. Second, the space can be closed and filled with antibiotic solution (Clagett procedure) (67) after achieving good control of the infection. The third approach requires plombage (pneumolysis) of the thoracic cavity with a pedicle muscle or omental flap with or without a partial thoracoplasty. The choice of biomaterials varies and depends on the surgeon's preference, location of the residual thoracic space, and previous damage of muscles by prior surgery. The latissimus dorsi muscle, anterior serratus muscle, major pectoral muscle, greater omentum, or a combination of these organs are frequently used and can achieve successful results (68). Thoracomyoplasty is being increasingly used as a definitive approach to manage complicated empyema, especially in patients with a BPF (69-71).

### Recent topics and forward agenda

Currently, the most reliable infection biomarkers are C-reactive protein and procalcitonin. In addition to these, soluble triggering receptor expressed on myeloid cells (STREM-1) is a promising biomarker in diagnosing pleural infection and deciding whether to use chest tube drainage (72,73). A large prospective study is urgently needed to evaluate this biomarker in the near future.

The development of fibrinolytic agents is remarkable in the field of fibrinolytic therapy. In the coagulation cascade, a crucial factor of this reaction is the resolve of plasminogen into plasmin by tPA, which competes with inhibitory substances such as plasminogen activator inhibitor (PAI)-1 and -2 (74). The PAI-1 concentration is elevated within locules and is therefore likely to contribute to the formation of pleural septations (75). These facts have encouraged to target this specific pathway. PAI-1-targeting monoclonal antibodies can be used as adjunctive therapy (76). Lansley *et al.* (77) theorized that the injection of tPA itself induces pleural fluid production. Their experiment on mice revealed that monocyte chemoattractant protein-1 (MCP-1) involved in tPA-induced pleural effusion formation. They also found that MCP-1 antagonists could inhibit large effusion formation with intrapleural fibrinolysis (77). No prospective studies have yet been performed to evaluate fibrinolytic agents (*Table 4*), although some prospective studies comparing various fibrinolytics or surgical intervention versus fibrinolytics are ongoing (*Table 5*). These studies will contribute to the establishment of future guidelines.

**Table 5** Ongoing prospective randomized controlled trials

ClinicalTrials.gov Identifier	Phase	Sample size	Age group	Status	Intervention	Primary outcome	Country	Study start date	Study completion date
NCT03478933	4	32	Adult	Recruiting	tPA and DNase	Duration of hospital stay after intervention	United States	November 1, 2017	December 1, 2019
NCT02165891	3	40	Child	Recruiting	Urokinase versus VATS	Duration of drainage	Belgium	February 1, 2015	June 1, 2020
NCT02014077	NA	100	Adult	Recruiting	VATS versus thoracotomy tube	Duration of hospital stay	South Africa	January 1, 2014	March 31, 2020
NCT03716375	NA	80	Child	Not yet recruiting	Urokinase	Length of hospital stay	China	November 1, 2018	April 30, 2020
NCT03873766	NA	30	Adult	Recruiting	IPFT versus surgery	Feasibility of the proposed study algorithm	United States	April 1, 2019	September 1, 2020
NCT03859206	NA	60	Adult	Not yet recruiting	Medical thoracoscopy versus tube thoracostomy	Medical cure without secondary intervention	Egypt	March 1, 2019	May 1, 2021
NCT03584113	NA	70	Adult	Not yet recruiting	tPA versus VATS	Rate of re-intervention	Canada	November 1, 2019	July 31, 2021
NCT04095676	NA	184	Adult	Not yet recruiting	DNase versus VATS	Hospitalization time	Denmark	March 1, 2020	September 1, 2023
NCT03583931	NA	36	Adult	Enrolling by invitation	tPA and DNase versus VATS	Hospital length of stay	United States	July 26, 2018	April 30, 2024

NA, not applicable; tPA, tissue plasminogen activator; DNase, deoxyribonuclease; VATS, video-assisted thoracic surgery; IPFT, intrapleural fibrolytic therapy.

## Conclusions

The pathophysiology of thoracic empyema varies, and affected patients' general conditions are poor. Therefore, physicians must evaluate the patients' conditions and choose the treatment strategy early in the clinical course. Thoracic empyema is undoubtedly a complex issue of which some aspects have been clarified; however, many aspects are still under discussion, such as the methods of removing loculated effusions (various fibrinolytics versus VATS), the drainage techniques (open surgery versus VATS), the best timing of these treatments, and so on. For these reasons, thoracic empyema has thus not been treated on the basis of evidence from prospective studies as on the empirical basis. Multicenter controlled clinical trials are needed to resolve these problems, and widely accepted guidelines for the treatment of empyema must be established.

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