



Review

# Management of Pleural Infection: A Historical Review and Updates

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**Abstract:** Pleural infection, including empyema, continues to have a high morbidity. A deep understanding of the pathobiology and appropriate medical management is crucial to avoid complications and progression to the need for surgery. Over the last several decades, we have learned much about the pathophysiology, microbiology, and epidemiology of pleural infections. Management has changed considerably over the years with more recent clinical practices favoring minimally invasive interventions over surgery. Here we discuss in detail the pathophysiology of parapneumonic effusions as they progress from uncomplicated parapneumonic effusions to empyema and how this relates to their diagnosis and management. We review the microbiology and how it relates to recommended empiric antibiotic regimens. As intrapleural fibrinolytic therapy has become the cornerstone of management, we outline the literature on this topic dating back decades up to the most recent clinical trials and give our recommendations for management based on the literature.

**Keywords:** empyema; parapneumonic effusion; intrapleural fibrinolytics; pleural infection; thoracoscopy



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## 1. Introduction

Pleural effusion, an abnormal accumulation of fluid in the pleural space, is a commonly encountered entity. The abnormal accumulation of pleural fluid in the setting of a pneumonia is termed parapneumonic effusion, which can be seen in up to 50% cases of pneumonia [1]. While most parapneumonic are “simple” or uncomplicated, about 15% of them can become infected, and progress to complicated parapneumonic pleural effusions and empyema. Empyema is a subcategory of complicated parapneumonic effusions characterized by positive pleural fluid cultures or with overt purulent exudate within the pleural cavity [2]. Empyema is usually a complication in up to 2–3% of the cases of pneumonia, and its incidence in the US has been increasing with about 32,000 case per year [3–5]. Empyema can also be seen in cases with mediastinitis, spinal infections, bronchogenic carcinoma, esophageal rupture, bronchopleural fistula, trauma, and post-surgical complications [5]. The aim of this article is to provide a comprehensive review of pleural infections in the context of parapneumonic effusions including the underlying pathophysiology, microbiology, diagnostic testing, and management.

### 1.1. Pathophysiology

The development of empyema in the context of a parapneumonic effusion occurs over three stages: [6].

**Stage I: Exudative Phase:** This phase is characterized by an increased production of inflammatory cytokines with increased fluid accumulation due to increased vascular permeability. The exudative fluid is typically sterile at this stage and is often termed a simple parapneumonic effusion. Medical management with antibiotics is generally sufficient [7–9].

Stage II: Fibrinopurulent Phase: This stage is marked by the bacterial invasion of the pleural space. This further enhances the inflammatory response and leads to the activation of the coagulation cascade, which in turn promotes fibrin deposition. Overtime, membrane formation may occur and loculations may form [7]. Pleural fluid studies during this stage may demonstrate high white blood cell count, pH < 7.20, glucose concentration of <40 mg/dL, and a lactate dehydrogenase concentration of >1000 IU/L [10]. An elevated white blood cell count contributes to the presence of frank pus which is pathognomonic for empyema.

Stage III: Organizing Phase: As the name suggests, this stage is characterized by the organization of the pleural fluid collection to form granulation tissue. This, along with the proliferation of fibroblasts from the pleural surfaces into the exudate, leads to the formation of an inelastic membrane also known as “pleural peel” [8,11]. Overtime, this process leads to the formation of a thick pleural layer and trapped lung preventing re-expansion despite adequate fluid drainage [12]. The persistent pleural space created due to this process poses an ongoing risk of infection [13].

### 1.2. Microbiology

Community-acquired empyema is frequently caused by Gram-positive aerobes, especially Streptococcal species (accounting for approximately 50% of the community-acquired cases) and Staphylococcus aureus. Gram-negative and atypical organisms are less common causes of community-acquired empyema [14,15]. In contrast, commonly implicated bacteria in a hospital-acquired empyema include drug-resistant Gram-positive organisms (including methicillin-resistant Staphylococcus aureus (MRSA)) and Gram-negative organisms such as Escherichia coli, Enterobacter, and Pseudomonas. Anaerobic organisms are common in both community- and hospital-acquired empyema, typically as a co-infection with aerobic bacteria, but they can also cause monomicrobial infection. Anaerobic pleural infections can have an insidious onset and may not always be detected on cultures [14,16,17]. Polymicrobial infections with Gram-positive, Gram-negative, and anaerobic organisms are common in all settings even if single isolates are cultured. The exception is with streptococcus pneumoniae, which is often the only causative organism if identified on cultures [15,18].

There is considerable geographic variation in the causative organisms. Streptococcus pneumoniae is more common in the tropics whereas Strep. viridans is more prevalent in temperate regions. Staphylococcus aureus is the most widely reported causative organism worldwide and is becoming increasingly prevalent in both community- and hospital-acquired settings [18].

Fungal causes of empyema are exceedingly rare, with an incidence of about 1–3%. Most cases are attributed to Candida, followed by Aspergillus [19]. Although fungal isolates often represent contamination, they are an important cause of pleural infection especially in immunocompromised individuals, in the setting of a recent abdominal or thoracic surgery [18–23].

### 1.3. Epidemiology

Each year, about one million patients are hospitalized in the United States with pneumonia. Of these, 20–40% cases progress to develop a parapneumonic effusion and 5–10% of these effusions evolve into empyema [4]. A recent epidemiologic study found that empyema constituted about 6–7% of all adult hospitalizations due to pleural disease and comprised about 10% of the total health-care cost related to pleural disease in the United States [24]. Males are about twice as likely to develop empyema compared to females. Additionally, those aged  $\geq 45$  years are more likely to develop empyema [24,25]. Other risk factors include those with a history of alcohol or intravenous drug use [26]. Biochemical findings that have been associated with the development of empyema include serum albumin < 3 g/dL, sodium < 130 mmol/L, and C-reactive protein (CRP) > 100 mg/L [26].

## 2. Evaluation

### 2.1. Imaging

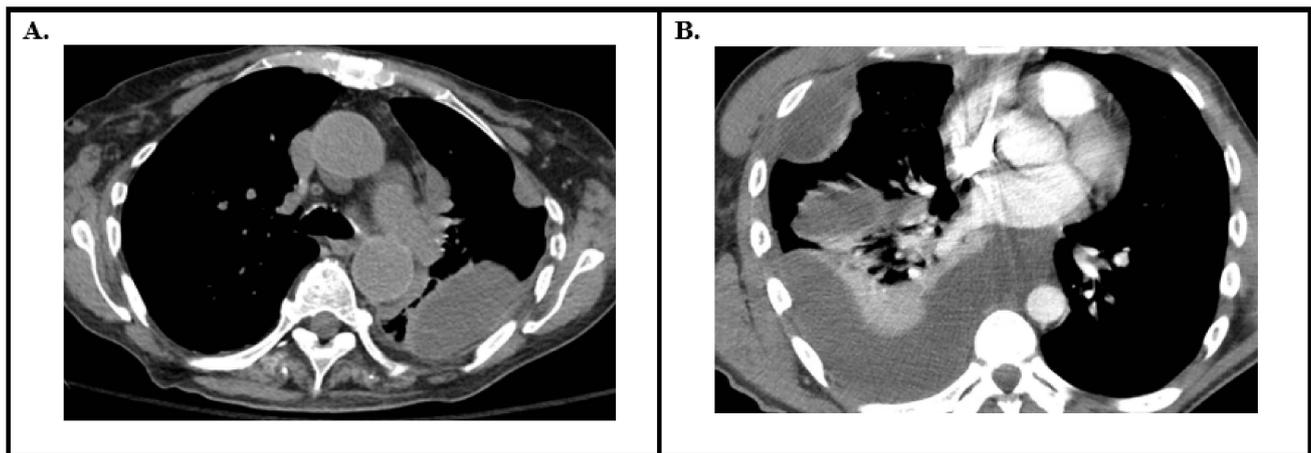
The initial imaging of pleural effusions is often performed with plain radiographs followed by thoracic US and CT chest (Table 1). Effusions with less than 1 cm depth in the lateral decubitus or <5 cm in height in the lateral erect position are found to be small and patients may improve without drainage even if parapneumonic effusions are suspected [9,27].

**Table 1.** Summary of characteristic findings on common imaging modalities that should trigger interventions such as tube thoracostomy.

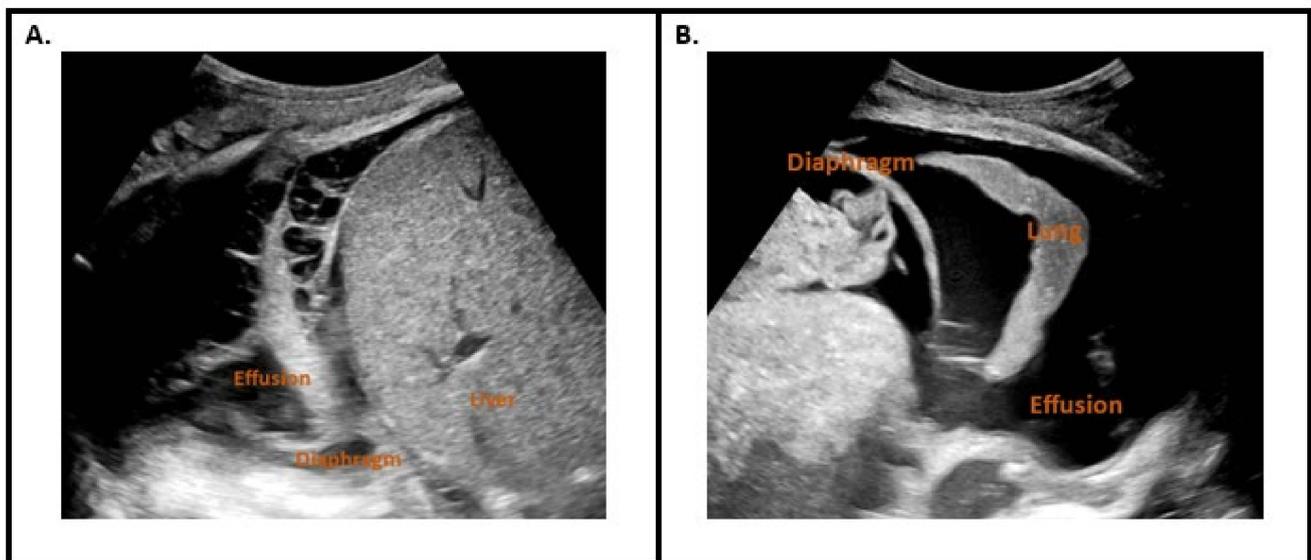
Imaging Modality	Characteristic Findings Suggestive of a Parapneumonic Effusion or That Intervention Is Needed
Chest Radiography	Minimum size to drain: >5 cm height on upright or >1 cm depth on lateral decubitus
Computed Tomography of the Chest	Minimum size to drain: >2.5 cm depth High risk findings: “Split Pleura” sign Increased attenuation of extra-pleural fat
Thoracic Ultrasound	Large volume effusion Pleural thickening High risk findings: Homogenous echogenicity Hyperechoic septation Thickened parietal pleura

Contrast-enhanced Computed Tomography (CT) chest performed in the tissue phase may be useful in cases where the diagnosis is unclear (such as empyema versus lung abscess) or if an associated pulmonary etiology is being investigated [13]. Small pleural effusions are defined by a depth of less than 2.5 cm which has been correlated to chest X-ray cut offs of less than 1 cm in the lateral decubitus and less than 5 cm in the lateral erect positions [28]. The “split pleura” sign on CT chest is characteristic of parapneumonic effusions and empyema; there is an increased thickening and enhancement of the parietal and visceral pleura, and the two surfaces are separated by a fluid collection. Other features suggestive of empyema include lenticular collections, loculations, and the increased attenuation of extra-pleural fat or thickening of more than 2 mm [29–31]. Pleural peel formation in the organizing phase may be seen as pleural thickening on CT chest, and can persist for several weeks before resolving, either with medical or surgical intervention [12]. Findings that may persist despite the adequate treatment of empyema include pleural calcification and the thickening of extra-pleural tissues. Certain findings on CT chest may be indicative of poor prognosis and can predict the need for further intervention in addition to medical management (drain placement, surgical intervention, etc.). These include the split pleura sign (Figure 1), the increased attenuation of extra-pleural fat, large volume effusion, and pleural thickening [32,33].

Ultrasonography is the preferred modality to evaluate pleural effusion given that it is readily accessible and highly specific in estimating the volume of any pleural effusion [5,34]. Complex septated and complex homogenous effusions are highly predictive of exudative effusions, with a specificity of 94% and a positive predictive value of 94% [35]. Although transudative effusions are typically anechoic in nature, exudative effusions can also appear anechoic [36]. Homogenous echogenic effusions on ultrasound are highly suggestive of underlying hemorrhage or empyema [37]. Other characteristic findings include echogenic swirling, septations, and loculations [38] (Figure 2). Additionally, ultrasonography is also useful in guiding both diagnostic and therapeutic aspirations [39].



**Figure 1.** (A) Left-sided loculated effusion with split pleura sign. (B) Left-sided loculated effusion.



**Figure 2.** (A) Complex septated effusion. This is highly suggestive of an exudative effusion and possibly empyema. (B) Simple effusion. The black space is without echogenicity or septations suggesting that the space may be transudative and is not infected.

Magnetic Resonance Imaging (MRI) is just as sensitive as CT chest in detecting empyema, and may be useful in cases where there is a contraindication to contrast or ionizing radiation (such as contrast allergy, pregnancy, etc.) [13].

## 2.2. Pleural Fluid Sampling

Although the clinical and radiological findings may support the diagnosis of empyema, they are not sensitive and do not reliably differentiate empyema from the other causes of pleural effusion. Pleural fluid studies remain the test of choice for accurately diagnosing empyema [5,26]. A diagnostic thoracentesis is recommended in all patients with suspected pneumonia, recent surgery, chest trauma, or with moderate–large effusions (more than 1 cm or 2.5 cm depth on lateral decubitus X-ray or CT, respectively, or more than 5 cm in height on lateral erect X-ray) [9,27,28]. Thoracentesis should be performed under ultrasound guidance to improve the diagnostic yield and decrease the risk of procedural complications [40,41].

## 2.3. Diagnosis

A diagnosis of empyema usually follows imaging demonstrating pleural fluid and a decision to sample revealing frank pus or positive pleural fluid culture. Because empyema

can only be diagnosed based on pleural fluid sampling, it is possible that some smaller effusions which may be due to empyema are underdiagnosed as they are not sampled.

The cultures of the pleural fluid and the blood are frequently obtained, but studies have demonstrated low sensitivity (about 60% for pleural fluid cultures and 14% for blood cultures) of these tests in diagnosing empyema [14,18]. Techniques that can be considered to improve culture yield include the use of thoracoscopic or image-guided parietal pleural biopsy and the inoculation of pleural fluid into blood culture media [42].

Complicated parapneumonic effusions are defined by pleural fluid chemistry (see Table 2). Given the poor sensitivity of pleural fluid cultures, complicated parapneumonic effusion are often grouped in their classification as a pleural infection with empyema and managed similarly.

**Table 2.** Summary of pleural effusion including simple effusions, parapneumonic, and empyema with common diagnostic features. Of note, pleural infections are defined as complicated parapneumonic effusions or empyema [2].

<u>Pleural Effusion</u>		<u>Diagnosis</u>
Simple Pleural Effusion		Lung Parenchyma Imaging: No pneumonia Effusion Imaging: simple Pleural Fluid Analysis: Transudative
Uncomplicated Parapneumonic Effusion		Lung Parenchyma Imaging: Pneumonia ipsilateral to the pleural effusion Effusion Imaging: May appear simple or complex Pleural Fluid Analysis: Exudative, pH > 7.2, and glucose > 2.2 mmol/L
Pleural Infection	Complicated Parapneumonic Effusion	Lung Parenchyma Imaging: Pneumonia ipsilateral to the pleural effusion Effusion Imaging: More often complex Pleural Fluid Analysis: Exudative, pH < 7.2, or glucose < 2.2 mmol/L
	Empyema	Lung Parenchyma Imaging: Most often there is a pneumonia ipsilateral to the pleural effusion. In rare cases of empyema outside of parapneumonic effusions, i.e., spontaneous bacterial empyema, this may not be the case Effusion Imaging: Complex Pleural Fluid Analysis: Frank pus or positive pleural fluid culture

### 3. Management

The mainstay of treatment for a pleural infection is antibiotic therapy and pleural fluid drainage via tube thoracostomy. Additional strategies, such as intrapleural fibrinolytics and surgical decortication, should be considered in cases of incomplete drainage [43].

#### 3.1. Antimicrobial Therapy

Selecting an adequate antimicrobial regimen is crucial in the management of empyema given the high risk of associated mortality. Antibiotic therapy should be initiated empirically and should not be delayed till culture results [42]. The initial choice of antibiotics is dependent on the clinical presentation (underlying pneumonia, spontaneous bacterial empyema, and penetrating trauma), setting (community- versus hospital-acquired infection), comorbidities, and local resistance patterns.

Aminopenicillins with beta-lactamase inhibitor are usually effective in patients in whom the risk of MRSA and drug-resistant Gram-negative infection is low. Alternatives for community-acquired empyema include second- or third-generation cephalosporins along with metronidazole or clindamycin for anaerobic coverage. Even in the presence

of a known, culture-positive aerobic infection, it is recommended to continue anaerobic coverage given that these organisms are frequently implicated in empyema and are not always detected [2,42]. *Streptococcus pneumoniae* typically causes monomicrobial infection and hence, the antibiotic course may be tailored accordingly [15,42].

Hospital-acquired pleural infections frequently arise due to drug-resistant organisms (~60%) and thus require prompt and more aggressive management [14]. It is recommended to add MRSA coverage (for example, vancomycin) in addition to antipseudomonal coverage (cefepime, piperacillin/tazobactam, and meropenem). Cephalosporin therapy is augmented by anaerobic coverage (metronidazole or clindamycin), as is the case in the treatment of community-acquired empyema. Aminoglycosides are not recommended in empyema as they are inactivated in the pleural fluid [42]. Antimicrobial coverage may be narrowed once culture results are available. If antifungal therapy is indicated, nonliposomal formulations are preferred as they have higher penetration into the pleural fluid [44].

The duration of antibiotic therapy is guided by culture results and treatment response but is generally 2 to 6 weeks after drainage and defervescence [5,42]. Longer durations may be favorable as demonstrated in a retrospective cohort analysis by Birkenkamp et al. which observed more instances of treatment failure among patients treated for ~2 weeks [45]. A shorter course of antibiotics could theoretically be considered in patients undergoing surgical intervention, although the high incidence of drug-resistant organisms in such patients might warrant a prolonged course of treatment [46]. Current guidelines do not address the ideal duration of therapy in this subset of patients.

Patients are usually transitioned to an oral regimen once symptomatic improvement is noted and source control has been achieved, as radiologic changes may lag clinical improvement. Follow up with imaging is recommended at 2–4 weeks to assess for treatment failure and at 8–12 weeks to confirm disease resolution [2].

The intrapleural administration of antibiotics has not been shown to be superior to parenteral antibiotics. Additionally, there have been no head-to-head studies comparing oral versus intravenous treatment for empyema to date. Currently, the use of intrapleural antibiotics is limited to certain surgical scenarios such as postpneumonectomy empyema [47,48].

### 3.2. Tube Thoracostomy

Fluid drainage along with antibiotics is the mainstay of treatment for empyema, though there is evidence that empyema secondary to pneumococcal pneumonia may resolve with antibiotics alone [49]. Nonetheless, pleural drain placement is recommended for all cases of suspected empyema [2,5,42].

Tube thoracostomy is considered the initial procedure of choice [50]. The presence of septations or loculations on imaging may be an additional indication for early tube thoracostomy [2,51]. Traditionally, large-bore catheters (>14F) have been used but there is growing evidence to support the use of small-bore catheters ( $\leq$ 14F) and they are now an accepted first-line alternative [2,13]. Chest tube bore size has not been shown to impact the mortality rate, the need for thoracic surgery, or the length of stay (LOS), but bore size  $\leq$  14F is associated with less post-procedural pain [52]. Chest tube sized <12F are avoided due to the risk of blockage [2]. If a small catheter is used, regular flushing with normal saline is recommended to prevent occlusion and improve drainage [53].

Tube thoracostomy placement should be closely followed by CT chest with contrast to confirm successful drainage. Additional drains or more intensive management should be considered in patients with an incomplete drainage of fluid. Chest drains may be removed once successful drainage is confirmed on imaging and clinical improvement is observed. Patients are routinely observed for 24 h after drain removal prior to discharge from the hospital [42].

In cases where the pleural fluid sample is not suggestive of empyema (not frankly purulent or culture positive), pleural fluid pH (<7.2) or lactate dehydrogenase (>1000 IU/L) along with glucose (<40 mg/dL) concentrations are recommended to help predict the need for chest tube placement [5,10,13]. Pleural CRP concentration >100 mg/dL has also been

shown to have comparable accuracy as pleural fluid pH and glucose concentration [54]. Serum CRP concentration >200 mg/L, in addition to the pleural fluid glucose concentration of <60 mg/dL is highly specific for detecting CPPE and predicting the need for chest drainage [55].

### 3.3. Fibrinolytics

Expert consensus has deemed therapeutic thoracentesis or tube thoracostomy alone to be insufficient treatment for empyema and complicated parapneumonic effusions, and suggest that fibrinolytics, video-assisted thoracoscopic surgery (VATS), and surgery including thoracotomy with or without decortication and rib resection are all acceptable approaches in the setting of empyema to reduce the risk of mortality and need for a second intervention [56].

In the setting of parapneumonic effusions and empyema, fibrinolytics are frequently used as a salvage therapy in patients who do not respond to chest tube drainage alone to improve treatment response and reduce the need for surgery. Fibrinolytic therapy is typically started within 48 h in patients who fail to show clinical, biochemical, or radiologic signs of improvement despite antibiotics and chest tube drainage [2].

In recent years, fibrinolytic monotherapy has fallen out of favor as it has not been shown to improve mortality, need for surgery, or hospital LOS [53,57]. Current practice supports the use of combination Intrapleural fibrinolytic (tissue plasminogen activator [tPA]) and Enzyme (DNase) therapy, also referred to as IET. The Second Multicenter Intrapleural Sepsis Trial (MIST-2) is the largest trial to date that compares IET to placebo and demonstrated that it improves radiographic clearance, need for surgery, and LOS, but no significant difference in overall mortality was found [58]. Either therapy alone was not proved to be more effective than the placebo.

The regimen used in the MIST-2 trial comprised 10 mg tPA and 5 mg DNase twice a day for three days. Although there have been further studies since then investigating the efficacy of different tPA dosing, frequency of administration, and duration of therapy [59–63], the general consensus is to adhere to the regimen used in the MIST-2 trial as it is most extensively studied, and because the other iterations of IET have not demonstrated any added benefit [64]. One accepted deviation from this regimen is in the administration of therapy; tPA and DNase therapies were administered sequentially in the MIST-2 trial, but more recent evidence demonstrates that concurrent administration is equally safe and efficacious as sequential therapy [65].

There are some deviations from the above-mentioned protocol that have been tried. For instance, a trial by Mehta et al. using once daily administration rather than twice a day resulted in similar outcomes [62]. Similarly, a reduced dose of 5 mg alteplase instead of 10 mg also resulted in similar outcomes with a dose escalation required in only a minority of patients [59].

Although generally considered safe, IET carries an associated risk of pain requiring the escalation of analgesia (~15%) [58,62], and bleeding (2–17%) [66,67]. Contraindications to the procedure include major hemorrhage or trauma, recent major surgery, a history of pneumonectomy on the affected side, coincidental stroke or a history of intracranial bleed [2]. In such cases, pleural saline irrigation may be considered as it has been shown to improve drainage and reduce the need for surgery [68]. See Table 3 for a chronological summary from early case reports to recent clinical trials investigating the use of fibrinolytics in empyema and parapneumonic effusion. See Table 4 for a summary our recommended dosing and schedule for fibrinolysis in empyema and parapneumonic effusions.

**Table 3.** This table lists both initial case reports/series with subsequent trials and studies through the years evaluating the safety and effectiveness of intrapleural enzymatic therapy. Initial interest in intrapleural lytic therapy started in the mid-twentieth century with urokinase and streptokinase. Although single-agent lytic therapy appeared promising, a large trial of streptokinase vs. placebo in 2005 demonstrated no benefit. The subsequent MIST-2 trial which combined agents in fibrinolytic therapy with both DNase and tPA did, however, demonstrate benefit.

Study	Study Type	Interventions	Highlighted Outcomes
Tillett et al. 1949 [69]	Prospective Observational 23 Subjects	Intrapleural Streptokinase	Reduced fibrinogen levels, increased proteolysis, and reduced viscosity No bleeding complications reported
Mitchell et al. 1989 [70]	Case Series 9 Subjects	Intrapleural Streptokinase	“of nine patient” there was “obvious increase in chest tube output in 6”
Moulton et al. 1989 [71]	Case Series 11 Subjects	Intrapleural Urokinase	A total of 12/13 collections drained completely. No bleeding complications reported
Lee et al. 1991 [72]	Prospective Cohort 10 Subjects	Intrapleural Urokinase	A total of 9/10 subjects had complete drainage
Rosen et al. 1993 [73]	Case Series 5 Subjects (pediatric)	Intrapleural Streptokinase	Increased chest tube drainage and clinical improvement in all five subjects
Taylor et al. 1994 [74]	Case Series 11 Subjects	Intrapleural Streptokinase	Increased chest tube drainage in all patients. A total of 8/11 demonstrated complete resolution of empyema. In total two patients underwent decortication No bleeding complications reported
Jerjes-Sanchez et al. 1996 [75]	Prospective Cohort 48 Subjects	Intrapleural Streptokinase	A total of 44/48 subjects had increased drainage with clinical improvement. Only four required surgery. No bleeding complications reported
Bouros et al. 1997 [76]	Randomized Double Blind Clinical Trial 50 Subjects	Intrapleural Streptokinase vs. Urokinase	No difference in efficacy. Both result in increased drainage No bleeding complications reported
Davies et al. 1997 [77]	Randomized Double Blind Placebo Controlled Trial 24 Subjects	Intrapleural Streptokinase vs. Saline	Intrapleural streptokinase resulted in greater pleural fluid drainage, radiographic improvement, and no decortication (three in saline group)
Bouros et al. 1999 [78]	Randomized Double Blind Placebo Controlled Trial 31 Subjects	Intrapleural Urokinase vs. Saline	Urokinase resulted in increased radiographic improvement, and the volume of pleural fluid drained
Thomson et al. 2002 [79]	Randomized Placebo Controlled Trial (pediatrics) 60 Subjects	Intrapleural Urokinase vs. Saline	Urokinase resulted in reduced hospital length of stay
Simpson et al. 2003 [80]	Case Report 1 Subject	Intrapleural Deoxyribonuclease (DNase)	Increased chest tube drainage and improved lung expansion
Diacon et al. 2004 [81]	Randomized Placebo Controlled Trial 53 Subjects	Intrapleural Streptokinase vs. Saline	Streptokinase resulted in fewer surgical referrals and increased treatment success No bleeding complications reported
Skeete et al. 2004 [82]	Case Series 41 Subjects	Intrapleural t-PA	All patients managed nonoperatively and had radiographic improvement following the administration of t-PA

**Table 3.** *Cont.*

Study	Study Type	Interventions	Highlighted Outcomes
Maskell et al. 2005 [53]	Double Bline Placebo Controlled Trial 454 Subjects	Intrapleural Streptokinase vs. Saline	No difference in mortality, the rate of surgery, radiographic changes, or the length of stay No increase in bleeding between groups
Thommi et al. 2007 [83]	Retrospective Cohort 120 Subjects	Intrapleural Alteplase	In total, >90% had complete or partial response with favorable safety profile Two subjects had bleeding complications at doses of 25 mg and 50 mg each
Rahman et al. 2011 [58]	Double Blind 2 × 2 Factorial Trial 210 Subjects	Intrapleural Placebo vs. t-PA + DNase vs. t-PA vs. DNase	The combination of intrapleural t-PA and DNase resulted in greater radiographic improvement, fewer surgical referrals, and a shorter hospital length of stay Two subjects had intrapleural bleeding and one had hemoptysis in the t-PA + DNase group. No such events in the control arm
Thommi et al. 2012 [84]	Randomized Double Blind Placebo Controlled Trial 68 Subjects	Intrapleural Alteplase vs. Saline	Alteplase resulted in improved clinical resolution
Piccolo et al. 2014 [85]	Retrospective Cohort 107 Subjects	Intrapleural t-PA + DNase	Regimen is safe and effective in real world use Two subjects had intrapleural bleeding complications requiring transfusion
Majid et al. 2016 [86]	Retrospective Cohort 73 Subjects	Simultaneous Intrapleural t-PA + DNase	Simultaneous administration is safe and efficacious Four subjects had intrapleural bleeding complications requiring transfusion
Popowicz et al. 2017 [59]	Observational Open-label Study 61 Subjects	Reduced Dose t-PA (5 mg) + DNase	Reduced dose resulted in increased pleural fluid drainage and reduced CRP. Three patients still underwent surgery Three subjects had intrapleural bleeding complications requiring transfusion

**Table 4.** Illustrates suggested dosing regimens based on the MIST-2 trial and subsequent observational studies. Note that prior studies suggested that bleeding complications are dose responsive. A 2017 observational study suggests similar efficacy with reduced dose tPA and therefore this may be a more well-tolerated regimen in those at an increased risk of bleeding.

Dosing	Schedule	Suggested Usage
Simultaneous administration of 5 mg DNase and 10 mg tPA followed by a flush and clamped for 60–120 min [58,85,86]	Twice daily for up to six doses	Standard dosing for patients with low risk of bleeding
Simultaneous administration of 5 mg DNase and 5 mg tPA followed by a flush and clamped for 40–60 min [59,83]	Twice daily, duration determined by clinical response	Alternative dosing for patients with increased risk of bleeding (i.e., on systemic anticoagulation, synthetic liver dysfunction etc.)

### 3.4. Surgical Management

Surgical decortication (via either VATS or open thoracotomy) as well as fibrinolytic therapy are both associated with a lower mortality risk and reduced need for repeat intervention compared to chest tube drainage [56]. However, there is a dearth of evidence supporting the use of surgical interventions in the initial management of empyema, so patients should initially be managed medically with chest tube placement.

When surgical management is performed, VATS is increasingly favored over open thoracotomy given that it carries a lower risk of complications such as post-operative pain, blood loss, and respiratory compromise [50]. VATS is also associated with a lower risk of peri-operative complications, shorter hospital LOS, and a lower risk of morbidity and 30-day mortality compared to open thoracotomy [87,88]. Both approaches carry a similar risk of requiring repeat intervention, although the overall risk of a second operation is low.

Factors that have been shown to increase the risk of the conversion of VATS to open thoracotomy include delay in surgical intervention (which may, in part, be due to delay in surgery referral), fever, and the presence of pleural thickening (>2 mm) on CT chest [87]. Most patients require surgical intervention if they are deemed to have failed medical management; however, there is no set criteria for when surgical consultation should be sought [42]. Given that delays in referral may lead to increased conversion from VATS to open thoracotomy and its associated complications, the early involvement of thoracic surgery consultants may be optimal.

## 4. Prognosis

Among patients with pneumonia, the presence of parapneumonic effusions alone increases the risk of 30-day mortality by 2-fold and are associated with a longer duration of hospitalization [1].

Empyema continues to pose a substantial risk of morbidity and mortality despite the advancements made in its management. The reported average LOS is about 13–19 days. Of all hospitalizations related to pleural disease, empyema is associated with the highest healthcare expenditure per case [24,89]. Up to 15% patients may need surgical drainage [53]. Empyema carries an in-hospital mortality rate of 4–7%, and a 12-month mortality rate of up to 22% [53,89,90]. Adults aged > 65 years are at a disproportionately elevated risk, with an in-hospital mortality rate of about 16% and a 12-month mortality rate of as high as 30–45% [89,91].

Epidemiologic studies over the past few decades demonstrate a 40–60% increase in the number of hospitalizations related to empyema across all age groups, although Gupta et al. reported a decrease in hospitalizations by about 25% in more recent years [50,89]. There have been modest improvements in the associated mortality, overall LOS, and hospitalization costs, although some studies have shown a slight increase in the 30-day readmission rate [24,25,50,89,92].

### *Predictors of Outcomes*

#### Clinical

Patients with a prior history of lung resection and those with concomitant cancer have been shown to have longer LOS, higher hospitalization costs, and mortality. Other factors that have been associated with a high risk of mortality among patients with empyema include age, diabetes mellitus, atrial fibrillation, alcohol abuse, hypertension, hyperlipidemia, malnutrition, and the presence of a fistula [2,26,93,94].

The RAPID scoring system is a useful tool derived from the First Multicenter Intrapleural Sepsis Trial (MIST-1) to predict poor clinical outcomes in pleural infection [53,95]. The scoring system stratifies patients into low-risk (0–2), medium-risk (3–4), and high-risk (5–7) groups based on their Renal profile, Age, Purulence of pleural fluid, Infection source (community- versus hospital-acquired), and Dietary factors (serum albumin). The RAPID score has since been validated in the MIST-2 trial, the Pleural Infection Longitudinal Outcome (PILOT) study, and several studies since [58,96]. High-risk patients had a statistically

significant increase in 3-month mortality compared to low-risk patients. Higher scores were also associated with a longer duration of hospital stay, though this association was not statistically significant.

Positive pleural fluid cultures are associated with a longer duration of pleural fluid drainage, hospital LOS, a higher risk of complications, and mortality [91,97]. The Oxford Pleural Infection Metagenomics Studies (TORPIDS) study investigated pleural fluid samples from the PILOT study and found that anaerobic infections or those caused by *Streptococcus anginosus* were associated with higher patient survival, whereas infections secondary to *Staphylococcus aureus* and *Enterobacteriaceae* were associated with less favorable outcomes [15].

#### Radiological

Certain radiological findings can also be used to stratify patients at high risk of complications from empyema. The presence of septations on ultrasound is a predictor of an increased need for thoracic surgery, the rate of ICU admission, hospital LOS, the risk of treatment failure, and overall increased mortality [98]. Pleural contrast enhancement, pleural microbubbles, increased extra-pleural fat attenuation, and fluid volume  $\geq 400$  mL or  $>40\%$  of the hemithorax predict the presence of complicated parapneumonic pleural effusion and are associated with a high risk of mortality and need for surgery [33]. Finally, pleural fluid leukocyte count of  $\leq 6400/\mu\text{L}$  has also been shown to be an independent predictor of failure of tube thoracostomy drainage [51].

There is no correlation between pleural thickness on CT chest and tube thoracostomy outcomes or need for surgery [99].

#### Microbiological

The causative organism is another positive predictor of clinical outcomes in patients with empyema. *Enterobacteriaceae* and *Staphylococcus Aureus*-related pleural infections pose a higher risk of mortality, whereas *Streptococcus anginosus* and anaerobes are associated with improved survival rates [15]. Fungal empyema is associated with a 30-day mortality rate of about 20% [100], with higher mortality rates among cancer patients ranging 30–70%. Though, studies conducted outside the US report a mortality rate as high as 73% [19,22,23]. Thus, it is recommended to obtain pleural fluid fungal cultures in immunocompromised individuals [2]. It is worth noting that the presence of culture-positive pleural infection is independently associated with an increased length of stay, as well as increased risk of complications [97].

## 5. Conclusions

Pleural infections and empyema are a heterogeneous group of diagnosis with multiple etiologies and responses to treatment. The most common pathobiology stems from the progression of a parapneumonic effusion to an empyema. Over the decades treatment has been variable with increasing reliance on minimally invasive measures in addition to systemic antibiotics. The current treatment paradigm usually requires the placement of a thoracostomy tube and the instillation of intrapleural fibrinolytics. Nonresponsive effusions may require surgical decortication. Ultimately, the prognosis of empyema and pleural infections is variable and future research should focus on identifying which patients may benefit from early surgical interventions.

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