Management of Parapneumonic Effusion and Empyema

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KEYWORDS

• Pleural infection • Parapneumonic effusions (PPEs) • Chest tube drainage
• Intrapleural enzyme therapy (IET) • RAPID score

KEY POINTS

- Pleural infection is common with a rising incidence and significant mortality rate.
- Management of pleural infection is multifaceted and includes antibiotics, chest drainage, intrapleural enzyme therapy, and surgical intervention, tailored according to the severity and progression of disease.
- Risk stratification tools such as the RAPID score may help guide intensity of treatment and improve clinical outcomes.

INTRODUCTION AND DEFINITIONS

Pleural infection is defined as bacterial entry and replication in the pleural space.[1] While most cases are linked to pneumonia, about 30% are "primary" with no associated pneumonic illness.[2] Parapneumonic effusions (PPEs), which are pleural effusions associated with pneumonia, occur in about 20% to 57% of pneumonia cases and can be classified as either "simple" or "complicated."[3] Around 5% to 7% of these effusions progress to pleural infection.[4] "Empyema" refers to the presence of purulent fluid in the pleural space and represents a severe form of pleural infection.[5] Modern literature and the authors, therefore, prefer the term "pleural infection" as it includes both "complicated PPE" and "empyema."

Pleural infection is a common condition with a combined incidence of over 80,000 cases per annum in the United States and United Kingdom.[6] Recent studies indicate that the incidence of pleural infection is rising, particularly in the elderly.[7–9] Although this condition has been described over 5000 years ago,[10] clinical outcomes continue to remain poor. While pleural infection itself has a 12-month mortality as high as 32%,[2] "simple PPEs" are also associated with a high 30-day mortality and prolonged hospital stay.[11] Therefore, both PPEs and pleural infection contribute to significant health burden.

This review aims to provide an overview of the management of PPE and pleural infection, emphasizing recent developments in these areas. Additionally, it highlights current knowledge gaps and potential future research directions.

PATHOGENESIS

The evolution of pneumonia to pleural infection occurs in 3 stages. Initially, microorganisms invade

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Abbreviations	
DNase	deoxyribonuclease
IET	intrapleural enzyme therapy
LAT	local anesthetic thoracoscopy
PPE	parapneumonic effusion
TT	therapeutic thoracocentesis
VATS	video-assisted thoracoscopic surgical

the lung parenchyma leading to increased capillary permeability of the visceral pleura.[12] This causes leakage of fluid and inflammatory cells in the pleural space, giving rise to a "simple PPE."[13] If untreated, the "fibrinopurulent" stage follows, where bacterial invasion and reduced fibrinolytic activity create septations and loculations, requiring drainage.[14] This stage can evolve into empyema. The final "organizing" stage involves fibroblast proliferation and pleural peel formation, impairing lung expansion and function.

The progression of pneumonia to pleural infection is influenced by a complex interplay between host and microbial factors, causing variability in disease progression among patients.[15] Some may develop multiloculated effusions while others develop frank pus, thereby challenging the notion of a strictly "linear" progression.

DISCUSSION

Management of Parapneumonic Effusion

At the "simple PPE" stage, the pleural fluid is not deemed to be "infected" and fluid drainage is not recommended. If the patient presents to a health care provider with infective respiratory symptoms at this stage, treatment is with antibiotics alone. However, as simple PPEs can progress to pleural infection and are associated with poor patient outcomes, monitoring high-risk patient groups appears prudent.

There are currently no validated clinical risk prediction tools that predict the development of pleural infection from pneumonia. A large prospective study of 1269 patients identified 7 clinical factors that independently predicted the development of pleural infection from pneumonia, namely low serum albumin, low serum sodium, elevated platelet count, high C-reactive protein, history of alcohol abuse, and intravenous drug use.[4] Another study prospectively analyzed 4715 patients with pneumonia and determined 5 clinical factors that could predict the development of pleural infection, namely young age (<60 years), alcoholism, pleuritic chest pain, tachycardia, and leukocytosis.[16] Neither of these "scores" have been prospectively validated. A reliable prediction tool for pleural infection in patients with pneumonia would allow early identification of high-risk patients, thereby allowing close monitoring and early detection and management to improve outcomes.

Management of Pleural Infection

Antibiotic therapy

Antibiotics and chest drainage remain the cornerstone of treatment. Broad spectrum antibiotics should be commenced once pleural infection is suspected[10,17]; the choice of antibiotic should be determined by the source of infection, local resistance patterns, and local antimicrobial policies. Community-acquired pleural infections are commonly caused by gram-positive aerobic organisms and anaerobes.[18] Hence, appropriate antibiotic cover includes either aminopenicillins, β-lactamase inhibitors, or second-generation cephalosporins in combination with metronidazole. For patients with penicillin allergy, clindamycin alone, or in combination with ciprofloxacin or a cephalosporin would provide appropriate coverage.[10,17] In monomicrobial infection with *Streptococcus pneumoniae*, antimicrobial choice can be narrowed as anaerobic cover is rarely required.[19,20]

Hospital-acquired pleural infections often arise due to surgery, nosocomial infection, and trauma. Therefore, antipseudomonal antimicrobials with anaerobic coverage are recommended, and the regimen should also cover drug resistant gram-negative pathogens and methicillin-resistant *Staphylococcus aureus*.[18,21] An example is vancomycin/linezolid and meropenem, or an antipseudomonal antibiotic such as piperacillin-tazobactam. Most classes of antibiotics are deemed to have good penetration into the pleural space, based on extrapolation from animal studies.[22,23] However, recent pharmacologic studies have suggested that the effectiveness of antibiotics in inhibiting bacterial proliferation in the pleural space is uncertain.[24] Further studies are required in this area.

Comparative studies between intravenous and oral antibiotics are lacking, and most guidelines recommend converting intravenous to oral antibiotics based on treatment response.[6,17] There is a paucity of data to definitively guide treatment duration, and the optimal duration of treatment remains unclear. In general, between 2 and 6 weeks of antibiotic treatment is recommended for pleural infection, with early follow-up to ensure treatment response and eventually clinical resolution.[6]

Chest tube drainage

Closed tube drainage of the thoracic cavity has been the standard of care for patients with pleural infection since the establishment of the "Empyema Commission" during World War I,[25] when this intervention reduced mortality from 30% to

3.4%. Chest drainage should be performed once pleural infection is suspected or confirmed by pleural fluid sampling.[6,17] There may be a role for conservative management without drain insertion in a select group of patients, particularly those with a small effusion or pH biochemistry consistent with intermediate likelihood of pleural infection.[6] However, close follow-up is necessary to ensure adequate clinical response to treatment, including early repeat imaging to reassess the need for drainage.

The optimal size for chest tube drainage remains controversial. While previous recommendations suggested large bore chest drain insertion to reduce the risk of tube blockage by viscous fluid, pleural infections are now increasingly managed with small-bore drains ($\leq$14 F).[26] This shift in management has been guided by several studies, including a retrospective analysis of the (multicentre intrapleural sepsis trial [MIST-1]), reporting higher pain scores with large-bore drains, and no difference in mortality or the need for surgery.[27] In a subgroup analysis of the MIST-2 trial, no association was found between small-bore drains and reduced treatment success.[28] A recent systematic review by Federico and colleagues reported similar findings with no difference in clinical outcomes and complications between large-bore and small-bore drains in pleural infection.[29] Nevertheless, routine flushing of small-bore drains to maintain drain patency is still commonly practiced, with some studies showing a high rate of drain blockage of up to 64% when small-bore (12 F) drains are used,[30,31] which is reduced with regular saline flushes.[32]

Therapeutic thoracocentesis

Repeated therapeutic thoracocentesis (TT) has been shown to have acceptable treatment success in several studies with shorter hospital stay compared with chest tube drainage.[33–35] However, these studies are largely retrospective case series. Lethuelle and colleagues demonstrated a reasonable success rate of repeated TT in an observational study (81%, median of 3 procedures) but prospective trial data are lacking.[36] Pragmatically, therapeutic aspiration seems reasonable as the initial diagnostic/therapeutic procedure for small uncomplicated effusions, but large effusions occupying more than one-half of the hemithorax are more likely to need tube drainage.[37] A recently concluded feasibility randomized controlled trial (RCT) comparing TT versus chest tube drainage similarly reported shorter hospital days with the former but was limited by small number of patients (n = 10), raising questions of feasibility of a full-scale trial.[38] Further prospective studies evaluating the outcomes of patients with repeated TT compared with chest drainage are needed, and therefore, repeated TT is not routinely included as a management strategy in international guidelines as yet.

Intrapleural enzyme therapy

Infected pleural fluid has a tendency to loculate and become more viscous and purulent over time, making drainage challenging. This occurs due to the presence of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-alpha) and plasminogen activator inhibitors in the pleural space, which activate the inflammatory cascade and lead to increased deposition of fibrin clots. Current evidence indicates that up to 27% patients treated with antibiotics and chest tube insertion alone will still require surgical intervention to treat their pleural infection.[39]

The concept of instilling intrapleural enzyme therapy (IET) to break down viscous pleural exudations is not new. Tillet and Sherry first published their work in 1949,[40] detailing their research involving the injection of streptokinase and deoxyribonuclease (DNase) into the pleural cavity to break down sediments which they found were largely made up of "deoxyribose nucleoprotein." Their demonstration of its utility in reducing fluid viscosity and increasing drainage effectiveness helped lay the foundation for the application of IET in pleural infections. Unfortunately, its use fell out of favor for decades due to concerns around triggering an acute inflammatory response,[41] with the original extract using hemolytic group C Streptococci.[42] IET was reintroduced in the 1980s when purified urokinase and streptokinase became available for clinical use.

Since then, the effect of IET on clinical outcomes has been studied more extensively. Initial research centered around the use of either streptokinase, urokinase, or alteplase as IET monotherapy. In a Cochrane review of 12 RCTs,[43] the IET arm demonstrated a reduction in surgical intervention and treatment failure, but did not demonstrate significant difference in mortality (OR 0.37, 95% CI 0.21–0.68 and 0.16, 95% CI 0.05–0.58, respectively). It is important to note that the trials included in the systematic review included heterogenous cohorts and varying outcome measures; for example, the largest trial (MIST-1) recruited all patients with pleural infection, while others specified patients with complicated PPEs only and evidence of loculation or failure to progress with tube drainage.

The MIST-2 trial,[28] which utilized a combination of alteplase tissue plasminogen activator (tPA) and DNase therapy, was the first RCT to demonstrate that combined IET led to better outcomes than monotherapy alone. TPA increases the production

of plasmin which causes degradation of fibrin clots, and DNase reduces the viscosity of the fluid; this synergistic effect results in better drainage and resolution of pleural infection. The authors demonstrated statistically significant reduction in surgical referral (77%) and length of hospital stay (6.7 days) compared with placebo, in addition to improving radiographic resolution. This has now become the standard of care for nondraining pleural infections.[6]

If alteplase is not available, urokinase can be used. It has a similar efficacy and safety profile, as demonstrated in a prospective cohort study comparing the outcomes of patients receiving TPA/DNase or urokinase/DNase for pleural infections.[44] There was no difference in surgical referrals (OR 0.52, 95% 0.14–2.02), or need for additional drainage procedures (OR 0.69, 95% CI 0.25–1.91). Thirteen percent of the subjects failed IET therapy and required further surgery.

One of the major concerns associated with the administration of IET is the risk of bleeding. In a multicenter retrospective study of a large cohort of patients with pleural infection,[45] overall bleeding risks were low (4.2%), similar to the results reported in the original MIST-2 study. When bleeding events did occur, most were managed with blood transfusion alone and did not require invasive intervention. Factors such as systemic anticoagulation and high RAPID score were independently associated with a higher risk of bleeding complications. Therefore, patients should have their anticoagulation withheld prior to administration of IET, and for high risk cohorts, dose reduction can be considered. Early involvement of hematology and surgical colleagues is also recommended.

Surgery

The main goal of surgery in pleural infections is to achieve complete evacuation of potentially infected fluid and complete re-expansion of the lung. Surgery for pleural infection ranges from video-assisted thoracoscopic surgical (VATS) to more invasive surgical procedures such as open thoracotomy (decortication), thoracoplasty, and open window thoracotomy.[46,47] With the landmark, MIST-2 trial establishing the benefit of IET, and subsequent prospective studies reporting promising outcomes, surgery is now generally considered only after an initial trial of IET.[6] Nevertheless, the proportion of patients who fail medical therapy is not an insignificant number, with up to 15% to 20% of cases eventually requiring surgery.[28] This delay to surgery is not without consequence and has been consistently shown to be associated with the highest risk of conversion to open thoracotomy,[48,49] with longer recovery times and increased morbidity.[50–52] However, determining which patients will benefit most from early or upfront surgery remains a challenge.

Contributing to this uncertainty is the fact that patients do not present with, or progress into distinct stages of empyema, but rather fall anywhere along a continuum of free-flowing exudative effusions to heavily organized infected pleural space with a fibrinous pleural peel and nonexpandable lung. The recently published MIST-3 trial, which was designed to be a feasibility trial, randomized 60 patients recruited over 8 centers in the United Kingdom to early VATS, early IET, or standard care.[53] The trial established feasibility of a future definitive study, and there were no differences found in length of stay, readmission, and further intervention rates, which was expected as the study was inadequately powered for these outcomes. The IET arm had a larger improvement in 2-month quality of life scores compared with early VATS, but this requires validation in a definitive RCT.

Saline irrigation

Besides keeping chest drains patent, large volume saline flushes have been shown to improve pleural fluid drainage and reduce surgical referral rates in a single center RCT involving 35 patients.[54] Saline irrigation was performed by administration of 250-mL bags of 0.9% sodium chloride by gravity (on a drip stand) via the chest tube, followed by clamping for 1 hour and then opened to allow free drainage. This was performed 3 times a day for a total of 9 irrigations and is a reasonable alternative for patients with contraindications to IET, or if surgery is not a viable option.[26]

Local anesthetic thoracoscopy

Also referred to as medical thoracoscopy or pleuroscopy, local anesthetic thoracoscopy (LAT) is a well-tolerated procedure, with a wealth of data supporting its safety profile and diagnostic yield in undiagnosed pleural effusions.[55,56] LAT can be performed under conscious sedation and allows for disruption of pleural loculations and drainage, commonly with a single access port and rigid or semirigid instruments. However, unlike VATS or thoracotomy, LAT does not accommodate interventions such as debridement and decortication to achieve lung re-expansion.

The evidence supporting LAT in pleural infections is limited to retrospective case series, which report success rates ranging from 75% to 90%.[57–59] Poorer outcomes are seen in patients with organized effusions as compared with free-flowing or multiloculated effusions. Post-thoracoscopy intrapleural urokinase was also administered in patients

with residual multiloculated or organized effusions in several studies.[57,59] It is, therefore, unclear if treatment success can be attributed to thoracoscopic disruptions of loculations and drainage, intrapleural fibrinolytics, or both. Almost all studies used rigid thoracoscopy, and the data supporting semirigid thoracoscopy in pleural infections are lacking.[60] Kheir and colleagues performed an RCT comparing early LAT with IET.[61] The study enrolled 32 patients with either septated pleural effusions or pleural infection that failed to drain completely with a chest tube. The primary outcome was length of hospital stay. Although the study reported shorter stay in the LAT arm (median length of stay of 4 days in IET arm and 2 days in LAT arm), the primary outcome was measured from the point of intervention, thereby making the results less robust. There were no differences observed in secondary outcomes including treatment failure and 30-day mortality. While larger RCTs are required to establish the role of LAT in pleural infections, a recently concluded (Studying Pleuroscopy in Routine Pleural Infection Treatment [SPIRIT]) feasibility randomized trial (ISRCTN98460319) demonstrated failure of feasibility of this approach.

Indwelling pleural catheter

For patients with a chronically infected pleural space, surgical intervention is the mainstay of treatment. The aims of surgery, like with acute empyema, are drainage and importantly, obliteration of the pleural space to prevent recurrence with debridement and/or decortication. In severe or persistent cases with or without a bronchopleural fistula, placement of tissue flaps to obliterate the infected pleural space, or creation of an open thoracic window (as a staged or definitive procedure) for chronic drainage may be undertaken.[17] An alternative is the placement of a chest tube for continued drainage,[62] and in this regard, there may be some role for the use of indwelling pleural catheters (IPCs) for long-term drainage of a chronically infected space that is not readily treatable in other ways or for patients who are not fit for surgery.[63] However, robust evidence to recommend this approach is lacking.

It is worth mentioning that IPC-related pleural infections (pleural infection as a complication of IPC insertion) can occur in about 5%–10% of patients with IPCs, but unlike standard pleural infection, have a much lower overall mortality risk of about 0.3%.[64,65] Most patients will not require removal of the IPC but can be successfully treated with an extended duration of antibiotics and pleural drainage via the IPC.[66] If required, IET with intrapleural alteplase and DNase may also be employed in IPC-related pleural infections.[67]

Risk Stratification

Despite advancements in managing pleural infections, morbidity and mortality rates over the past 20 years have remained largely unchanged. The existing universal approach to treating pleural infections, from chest drain insertion to IET and surgical referral, may not be suitable for all patients. Implementing risk stratification from the outset could allow for tailored management, potentially improving clinical outcomes. A large cohort study from the Danish Pleural Empyema Group found that a 2-day delay in pleural drainage from time of diagnosis led to higher mortality rates at 30 and 90 days.[68] Delayed surgical referrals were also linked to poor outcomes, including higher rates of conversion to open surgery and therefore, increased mortality in this group of patients.[69]

The RAPID score, which was derived from and validated in the MIST-1 and MIST-2 studies, uses 5 parameters (**Table 1**) to classify patients into risk categories, correlating with mortality rates.[70] The RAPID score is the only prospectively validated risk prediction score and appears robust in large-scale prospective validation.[71] Although the RAPID score's role in routine care is still being explored, it shows promise in guiding choice and intensity of management based on patient risk.

Table 1
Components and categories of the RAPID score for risk stratification of patients with pleural infection

Clinical Parameter	Points		
	0	1	2
*R*enal (blood urea), mmol/L	<5	5–8	>8
*A*ge, years	<50	50–70	>70
*P*urulence of pleural fluid	Yes	No	–
*I*nfection source	Community	Hospital	–
*D*ietary (serum albumin), mmol/L	≥27	<27	–
Risk categories:	0–2: Low	3–4: Moderate	5–6: High
Mortality rates:	1.5%	17.8%	47.8%

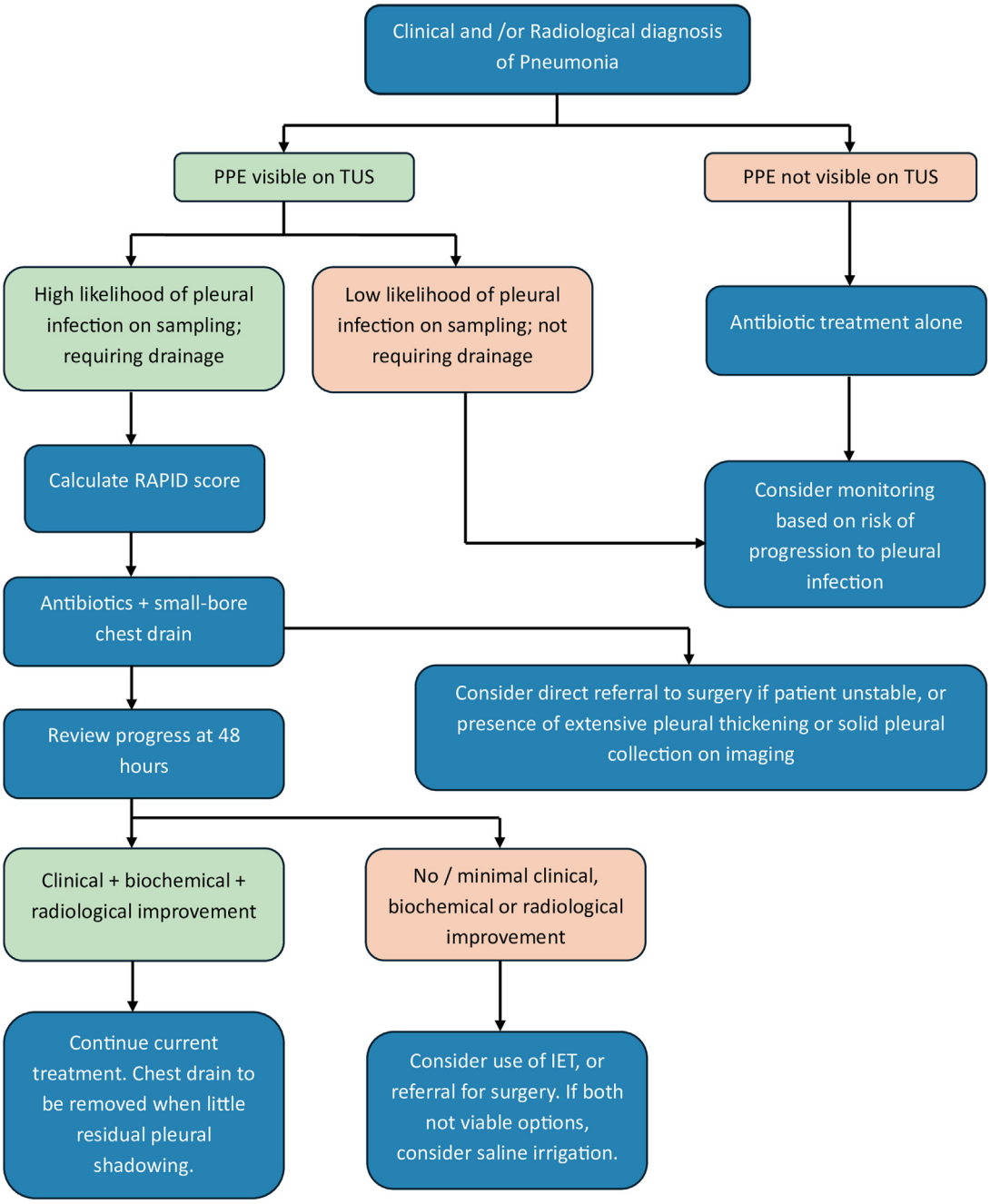

Fig. 1. Proposed algorithm for management of PPE and pleural infection. PPE, parapneumonic effusion, TUS, thoracic ultrasonography, LET, intrapleural enzyme therapy.

SUMMARY

In summary, pleural infection poses a significant challenge. Management is multifaceted and involves antibiotic therapy alongside pleural fluid drainage by means of chest drain insertion, repeated TT, IET, or surgical approaches. These approaches have been highlighted in Fig. 1. Empirical antibiotic regimens, tailored to local resistance patterns, play a crucial role, while chest drain insertion remains the mainstay of treatment. IET helps facilitate improved drainage and surgical options are largely reserved for advanced cases. With the help of predictive and risk stratification tools such as the RAPID score, we are now entering an era of precision medicine in this field.

This comprehensive and tailored approach may hold the key to tackling the persistent challenges presented by pleural infections.

CLINICS CARE POINTS

- Broad-spectrum antibiotics should be initiated as soon as pleural infection is suspected. Antibiotic choice is dictated by local policies and resistance patterns but in general, community-acquired infections require gram-positive and anaerobic cover, and hospital-acquired infections require gram-negative, antipseudomonal, anaerobic, and MRSA cover.
- Standard care for pleural infections involves chest tube drainage. Small-bore drains ($\leq$14 F) cause less pain and similar outcomes to large-bore drains, and are therefore, preferred in modern-day practice. Regular saline flushes of small-bore drains are recommended to prevent blockage and maintain patency.
- Intrapleural enzyme therapy (IET) in the form of combined tPA and DNase, is effective in breaking down loculated, viscous pleural fluid, facilitating better drainage. Combined IET reduces surgical referral rates and hospital stays, and large well-designed randomized trials demonstrate that fibrinolytic monotherapy is ineffective. However, caution is advised in the use of IET due to the potential albeit low risk of bleeding, especially in patients on anticoagulation or with high RAPID scores.
- The RAPID score, based on parameters like serum urea, patient age, pleural fluid purulence, infection source, and serum albumin, helps classify patients into low-risk, medium-risk, and high-risk categories. This stratification correlates with mortality rates and can guide the intensity of management, improving clinical outcomes by tailoring treatment approaches to individual patient risks.

DISCLOSURE

The authors have nothing to disclose.

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