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Expert Review on Nonsurgical Management of Parapneumonic Effusion: Advances, Controversies, and New Directions

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Abstract

Parapneumonic effusion and empyema are rising in incidence worldwide, particularly in association with comorbidities in an aging population. Also driving this change is the widespread uptake of pneumococcal vaccines, leading to the emergence of non-vaccine-type pneumococci and other bacteria. Early treatment with systemic antibiotics is essential but should be guided by local microbial guidelines and antimicrobial resistance patterns due to significant geographical variation. Thoracic ultrasound has emerged as a leading imaging technique in parapneumonic effusion, enabling physicians to characterize effusions, assess the underlying parenchyma, and safely guide pleural procedures. Drainage decisions remain based on longstanding criteria including the size of the effusion and fluid gram stain and biochemistry results. Small-bore chest drains appear to be as effective as large bore and are adequate for the delivery of intrapleural enzyme therapy (IET), which is now supported by a large body of evidence. The IET dosing regimen used in the UK Multicenter Sepsis Trial -2 has the most evidence available but data surrounding alternative dosing, concurrent and once-daily instillations, and novel fibrinolytic agents are promising. Prognostic scores used in pneumonia (e.g., CURB-65) tend to underestimate mortality in parapneumonic effusion/empyema. Scores specifically based on pleural infection have been developed but require validation in prospective cohorts.

Keywords
- parapneumonic effusion
- pleural infection
- empyema
- intrapleural enzyme therapy

Epidemiology

Pleural infection represents a common and often life-threatening condition. Clinical studies show that more than half of the patients with pneumonia develop pleural effusion. The estimated incidence across the United Kingdom and the United States was 80,000 cases per year in 2011.[1] The reported mortality rate was 10.5% at 30 days[2] and 19% at 1 year.[3,4] Parapneumonic effusion and empyema are also associated with a significant increase in the cost of care,[5] with annual estimates from the United States in 2010 being in excess of US$500 million[1] including costs of pleural interventions and thoracic surgery.[6]

The incidence of empyema began rising worldwide in the early 21st century in both developed and developing countries and across all age groups.[7,8] The annual empyema-associated hospitalization rates increased approximately 70% between 1997 and 2006 in children in the United States.[8]

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Similar trends have been found in children in Israel,[9] Taiwan,[10] and New Zealand.[11] As observed in children, increased pleural infection rates were documented in adults after 2000 in developed nations such as Canada,[12] United States[13], France,[14] and England.[15] In France, empyema incidence rose from 7.15 to 7.75 cases per 100 000 inhabitants between 2013 and 2017.[14] Analysis from England found the number of cases of empyema across the National Health System increased significantly from 4,447 in 2008 to 7,268 in 2017.[15] In adults in the United States, hospitalizations for empyema increased by 37.5% between 2007 and 2016.[16] A sixfold rise in empyema mortality rates was also reported in Utah between 1950 and 2004.[7]

The etiology of the increased prevalence of empyema is hypothesized to be multifactorial. The aging population of developed countries increases the prevalence of risk factors for empyema such as older age,[15] chronic obstructive pulmonary disease (particularly when associated with diabetes, cancer, and other comorbidities),[17] and chronic renal and liver failure.[18,19] The introduction of the 7-valent conjugate pneumococcal vaccine (PCV-7)[20] has led to a serotype shift toward serogroups 1 and 3,[14,21,22] which are associated with a greater frequency of empyema. However, the introduction of PCV-13, which has activity against serogroups 1 and 3, has brought a fall in empyema rates in the United States,[23] Scotland,[24] and Spain,[25] although not in Australia.[26] As pneumococcal serotypes continue to evolve in response to changes in conjugate vaccines, the prevalence of empyema will need to be carefully monitored.

Pathogenesis

A parapneumonic effusion is a pleural effusion secondary to a pulmonary infection of viral or bacterial origin (pneumonia or lung abscess) and is considered complicated when an invasive procedure is required (i.e., chest tube insertion).

In pneumonia, the inflammatory response can extend to the visceral pleura causing the accumulation of inflammatory mediators, such as interleukin-8 and tumor necrosis factor α, the activation of somatic pain receptors responsible for pleuritic pain, and formation of an exudative pleural effusion (exudative stage). In some cases, the inflammatory response can progress to a fibrinopurulent stage characterized by the deposition of fibrin membranes and bacterial migration into the pleural space. The consequent promotion of inflammatory response triggers the extrinsic coagulation cascade and neutrophil activation/phagocytosis.

In some cases, despite antibiotic therapy, the effusion can progress to the organizing phase, characterized by large fibroblastic activation that leads to fibrotic pleural peels and, potentially, to "trapped lung." This can lead to a variety of complications from severe respiratory failure (reduced gas exchange efficiency) to chronic empyema.

Excessive fibrin deposits should be degraded by plasmin, a serine protease that is derived from plasma plasminogen. Plasminogen can be transformed into its active form by urokinase (uPA) and tissue-type plasminogen activators (t-PA) by binding to specific receptors (e.g., soluble uPA-type plasminogen activator receptor [suPAR]). The proenzyme single chain uPA (scuPA) can also be found in plasma while local mesothelial cells produce t-PA. The plasminogen activator inhibitor (PAI)-1 regulates plasminogen activation by irreversibly inhibiting both uPA and t-PA. Increased PAI-1 expression can be the main cause of pleural fibrosis, as confirmed by different animal models.[27,28]

The microbiology of parapneumonic effusion differs from pneumonia as it is also influenced by the acidic and hypoxic environment of the infected pleural space. While *Streptococcus pneumoniae* remains one of the commonest causes of both parenchymal and pleural infections, poor dental hygiene and aspiration of organisms from the oropharynx have classically been associated with pleural infection caused by anaerobic or facultative anaerobic pathogens that rarely cause parenchymal infection.[29,30] Hematogenous spread of bacteria can induce pleural infection without evidence of pulmonary infiltrates.

Etiology

The prevalence of causative organisms of pleural infection varies depending on the source of infection (community vs. hospital-acquired empyema), host factors (patient age and immune status), and geographic region (►**Table 1**).[31] The UK Multicenter Intrapleural Sepsis Trial (MIST)-1 confirmed streptococcal species as the most prevalent organisms isolated in adult community-acquired cases of pleural infection, with the *Streptococcus milleri* group accounting for one-third

Table 1 Common causes of empyema by group (subject to geographical differences)

Pediatric	Community-acquired adult	Nosocomial
Streptococcus pneumoniae	Viridans streptococci[a]	*Staphylococcus aureus* (MRSA > MSSA)
Staphylococcus aureus (MSSA > MRSA)	*Streptococcus pneumoniae*	Enterobacteria
Streptococcus pyogenes	*Staphylococcus aureus* (MSSA > MRSA)	Enterococci
Viridans streptococci[a]	Enterobacteria	Viridans streptococci[a]
Mycobacterium tuberculosis	Klebsiella species	Pseudomonas species
	Pseudomonas species	Klebsiella species
	Mycobacterium tuberculosis	

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive Staphylococcus aureus.
[a]*Streptococcus milleri* being the most common pathogen in this group.

of cases.[32] *Streptococcus pneumoniae* is the second most common pathogen in community-acquired adult empyema and the most common in pediatric empyema.[29,31,33] Other commonly occurring microbes include anaerobes and Staphylococci, the latter accounting for 46% of hospital-acquired cases.[32] Conversely, *Klebsiella pneumoniae* was the most frequent cause of community-acquired empyema or complicated parapneumonic effusion in Taiwanese adults treated during the period 2001–2008.[34] *Mycobacterium tuberculosis* is also an important cause of pleural infection in the developing world but is very uncommon in developed economies.[4,31,35,36] Fungal pathogens, most commonly Candida species, are rare causes of empyema, typically seen in patients with significant immune compromise.[37] Detection of microbes especially anaerobes has been enhanced with the guideline-endorsed practice of direct inoculation of pleural fluid into blood culture bottles.[38–40] Further improvements in culture positivity rates occur when a pleural biopsy is performed at the time of drain insertion.[41]

Radiology in Parapneumonic Effusion

Radiography

Chest radiography (CXR) is typically performed in suspected pneumonia and can detect small-volume parapneumonic effusions.[42] However, CXR is inaccurate in separating lung consolidation and pleural effusions and is insensitive to the detection of small effusions.[43] Patients with pneumonia who have ongoing fever or fail to respond to therapy, therefore, need additional imaging modalities such as computed tomography (CT) or thoracic ultrasound (TUS).

Computed Tomography

Cross-sectional imaging with CT can identify collections that are not visible on CXR or TUS (e.g., paramediastinal or fissural locules). CT can also evaluate the lung parenchyma and may identify an unexpected alternative etiology such as esophageal perforation. A CT scoring system for parapneumonic effusions, incorporating the presence of the split pleura sign, visible microbubbles, increased extrapleural fat attenuation, and fluid volume greater than 400 mL (3 cm), has an 81% diagnostic accuracy for complicated effusions, although clinical utility of the score has not been prospectively proven (►**Fig. 1**).[44]

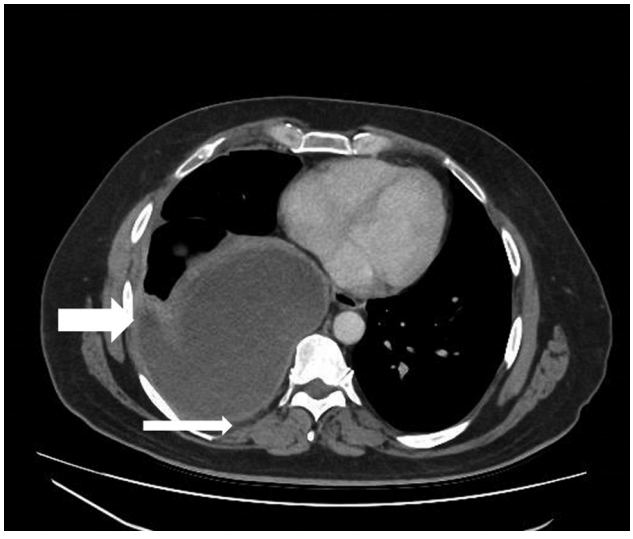

Fig. 1 CT thorax showing a loculated pleural effusion with pleural enhancement, the split pleura sign (*broad white arrow*), and increased extra-pleural fat attenuation (*thin white arrow*). Pleural phase CT demonstrates visceral and parietal pleural enhancement, resulting in the "split pleura" sign. CT, computed tomography.

Thoracic Ultrasound

TUS is an increasingly useful imaging modality for the identification of pleural effusion at any volume.[45,46] TUS can evaluate effusion characteristics that can assist with prognostication and management decisions (e.g., echogenicity[47,48] and septations[49]) and the underlying etiology (e.g., lung consolidation/abscess). The sensitivity of TUS in the identification of septations far exceeds CT (44 vs. 6%).[49] Although neither TUS nor CT findings of septations predicted the need for surgery in one study, all included patients were aggressively managed with chest tube drainage and intrapleural fibrinolytics.[49] Whether the presence of septations predicts the need for fibrinolytics warrants further investigation.

Patients with complex septations on TUS have increased requirements for ICU and a lower likelihood of survival.[50] Furthermore, routine use of ultrasonography in critically ill patients decreases the number of radiographic and CT investigations, reducing patient and staff exposure to ionizing radiation.[51] Its increasing use as a point-of-care bedside investigation has resulted in its recommendation as the first-line imaging modality in cases of suspected pleural infection where available.[52]

Pediatric studies have demonstrated the superiority of MRI over CXR in the identification of empyema[53] and excellent correlation with findings on CT[54] but is unlikely to surpass TUS from practicality and cost-effectiveness standpoints.

Systemic Therapies for Parapneumonic Effusion

Systemic Antibiotic Therapy

Early administration of antibiotics is advised in suspected pleural infection, and adequacy of antimicrobial therapy independently correlates with mortality.[7,55] The appropriate choice of empiric antibiotic therapy depends on several factors such as community- versus hospital-acquired infection,[4,29] host characteristics, pathogens identified, and local antimicrobial resistance patterns due to the significant geographical variation described above. Initial empiric therapy may need to be adjusted according to the results of microbiological testing that is mandatory in all patients with pleural effusion.

Patient characteristics, for instance, age, comorbidities, and previous hospitalization and/or antibiotic treatments, can influence choice, as well as the risk of intolerance to antibiotics (side effects, pharmaceutical interactions), and the risk of multidrug-resistant (MDR) pathogens or unusual pathogens such as anaerobic or fungal infections.

MDR pathogens are frequent causes of pleural effusion. Towe et al found that 37% of isolates in community-acquired infections and 77% of isolates in hospital-acquired infections were resistant to at least one antibiotic commonly used to treat respiratory infections.[56] The factors that significantly increase the risk of MDR infections are chronic renal disease, cancer, diabetes mellitus, cerebrovascular diseases, and recent antibiotic therapy.[57] Immunosuppression is associated with an increased risk of unusual pathogens. For instance, uncontrolled HIV infection is associated with a higher risk of *Pneumocystis jirovecii, Toxoplasma gondii*, or *Nocardia* species.[58–60]

Multiple studies have demonstrated that many cases of pleural effusion are polymicrobial and, therefore, require broad-spectrum antibiotics.[29,61] Empirical antibiotics can be recommended based on currently available pathogen data from large comprehensively assessed cohorts such as the MIST-1 trial population (►**Fig. 2**).[29,32] Atypical organisms are rarely associated with pleural infection, and routine use of macrolides is not recommended.[52] Fungal infections, although rare (approximately 3%), are usually caused by candida and aspergillus species and require specific coverage if confirmed.[37,62,63]

Antibiotic cessation or deescalation can be considered after 2 to 3 weeks.[64,65] The Optimal Duration of Antibiotics in Parapneumonic Effusion study demonstrated noninferiority of a 2-week (vs. 3-week) course of coamoxiclav in non-ICU cases who had achieved clinical stability at Day 14 of treatment,[66] but a longer duration of treatment (3–6 weeks) is usually recommended in nosocomial or postsurgical infections.[67,68]

Corticosteroids in Parapneumonic Effusion

Considering evidence for the significant role inflammation plays in the generation of pleural fluid, corticosteroids have been suggested as an adjunct treatment. In a large cohort of patients presenting with CAP, those who were prescribed regular inhaled corticosteroids (ICS) preadmission were less likely to develop a parapneumonic effusion and when an effusion occurred, it was smaller and less inflammatory than those not using ICS. A randomized controlled trial (RCT) of 60 children with parapneumonic effusions demonstrated that intravenous dexamethasone shortened the time to clinical stability (median [95% confidence interval] 109 [37–180] versus 177 [115–238] hours, $p = 0.037$),[69] especially for those who had simple (rather than complex) parapneumonic effusions.

The Steroid Therapy and Outcome in Parapneumonic Pleural Effusion placebo-controlled RCT, however, did not find benefits with intravenous dexamethasone in adults with community-acquired parapneumonic effusion.[70]

Drainage of Pleural Fluid

Pleural fluid drainage is usually critical to the resolution of complicated parapneumonic effusion. Delays in drainage are associated with increased mortality[71] and clinical guidelines mandate timely drainage where possible.[52,72,73] However, determining whether an effusion is complicated and requires drainage is not always straightforward. A free-flowing but large effusion may require drainage for symptom relief alone.[52,72,73] Loculations and septations seen on chest X-ray or ultrasound are associated with poorer outcomes[50,74–76] and are considered an indication for chest tube insertion in all guidelines.[52,72,73]

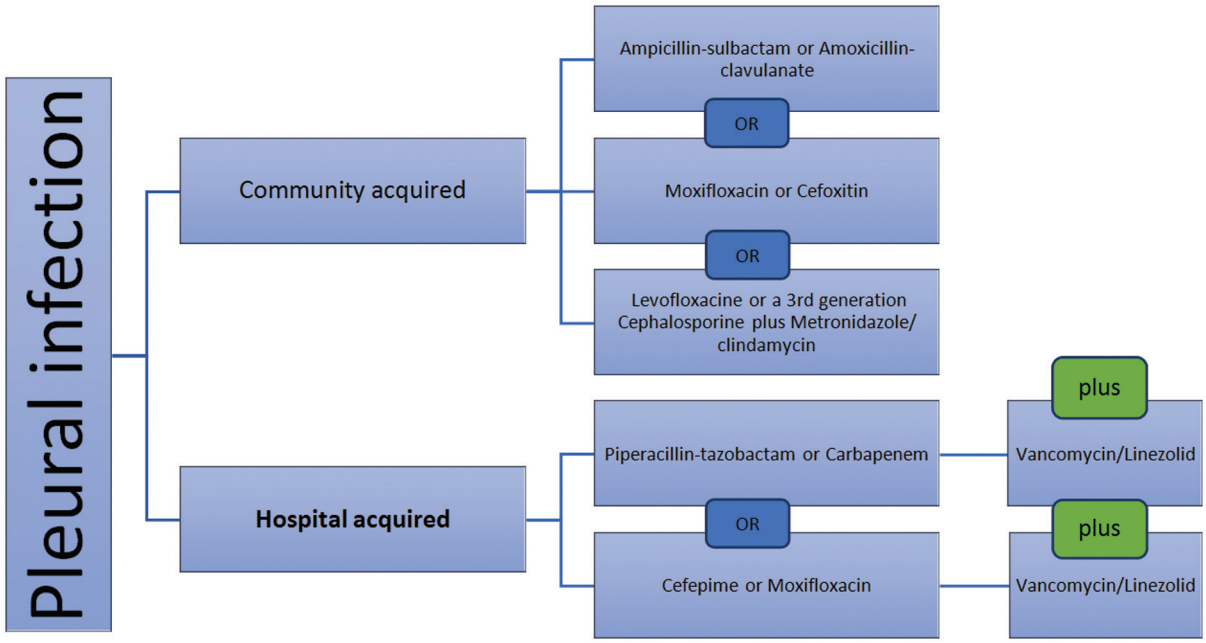

Fig. 2 Suggested empirical antibiotics for (**A**) community-acquired infections aiming to cover gram positive, gram negative, and anaerobic infections and (**B**) hospital-acquired infections aiming to include cover for pseudomonas ± methicillin-resistant *Staphylococcus aureus* (MRSA).[52,63,64] Modifications may be required depending on local microbiology guidelines and resistance patterns.

Purulent fluid should be drained as it is associated with increased failure of medical management and risk of death.[52,77] Pleural fluid gram stain or culture positivity, or pH of <7.2, also indicates the need for chest tube drainage.[52,74,78] Pleural fluid pH is only reliable if sampled in a manner that prevents exposure to lignocaine or air and analyzed with a blood gas analyzer.[79,80]

Although a large meta-analysis did not find that lactate dehydrogenase (LDH) improved diagnosis of pleural infection over pH alone,[78] LDH >1,000 IU/L can be a useful indicator of complexity and, hence, indicate drainage requirement.[73] Furthermore, pleural fluid glucose <3.3 mmol/L is the consensus value believed to equate to a pH of <7.2 and can be of value when pH is unavailable or unreliable. In a large cohort of well-phenotyped effusions, pH and glucose were concordant in more than 90% of cases.[81]

Increased concentrations of suPAR are associated with loculated pleural effusions and the need for chest tube drainage, intrapleural fibrinolytics, and surgery.[82] Furthermore, elevated levels of PAI-1, the major inhibitor of fibrinolysis in the inflamed/infected pleural space, appear to be associated with the development of septations and their severity, length of hospital stay, and mortality.[83] PAI-1 is known to inhibit the activity of uPA and t-PA; it is possible that levels of PAI-1 rise over time and reduce the efficacy of intrapleural enzyme therapy (IET).[84] In the future, it may be that baseline levels of PAI-1 could be used to guide the need for drainage, the procedure chosen, and choice and dose of fibrinolytic agents (see below).[84]

The optimal approach to drainage of a parapneumonic effusion has not been empirically defined.[85] Therapeutic thoracentesis (TT) may be performed at the time of the diagnostic aspirate in small free-flowing effusion as fluid may not always reaccumulate.[86] The Aspiration versus Chest Tube (ACTion) trial demonstrated the feasibility of TT in 10 patients with complicated parapneumonic effusion without significant loculations.[87] This approach will need evaluation in larger studies.

Controversy regarding the choice of catheter size for drainage in pleural infection persists. Early studies of Seldinger chest drains inserted for effusions of varying etiologies demonstrated a higher incidence of tube blockage and failure in empyema cases.[88,89] A post-hoc analysis of patients from the MIST-1 study, however, demonstrated that small-bore chest tubes (<16 Fr) were as effective as large-bore ones, with no difference in clinical outcomes (radiographic resolution, LOS, progression to surgery, or mortality) but caused significantly less pain, particularly in comparison to those inserted using blunt dissection.[90] Regular flushing is advised to maintain the patency of small-bore tubes.[52] Specific position of the tube in the chest is not likely to significantly impair drainage.[91] Often US- or CT-guided placement of several catheters for the drainage of noncommunicating collections is necessary.[92] Cases of indwelling pleural catheter (IPC) use for chronic empyema in patients unfit for surgery have been reported.[93]

Intrapleural Enzyme Therapy

The presence of loculations can preclude adequate drainage. Fibrinolytic agents can breakdown fibrinous septations allowing fluid drainage. Recombinant tissue plasminogen activator (rtPA and alteplase) combined with deoxyribonuclease (dornase α and DNase) reduces the need for surgical referrals for pleural infection in comparison to either therapy alone or placebo.[94] This approach has revolutionized the management of pleural infection worldwide. Numerous studies have demonstrated real-world success[95] and trialed various methods of administration (e.g., combined vs. sequential instillation, once daily dosing), with generally high rates of success.[96–98] Long-term follow-up studies assessing the radiological (CXR), physiological (spirometry), and functional (quality of life) effects of tPA/DNase treatment, revealed no significant adverse effects.[99] Novel fibrinolytic agents such as scuPA plasminogen activator, resistant to the endogenously produced PAI-1, are under investigation.[100] In consideration of the positive results of phase I clinical trial, a phase II trial is currently evaluating the fibrinolytic efficacy of scuPA in patients with loculated pleural infection (identifier: NCT04159831).

Complications of IET are rare; however, the risk of pleural bleeding remains a concern. A large retrospective study found an overall bleeding rate of 4.1%.[101] Bleeding rates were significantly higher in patients who were therapeutically anticoagulated, had low platelets ($<100 \times 109$), or elevated urea levels.[101] Dosing of tPA in the original trials (10 mg/instillation) was arbitrary and the usual dose escalation studies, to which novel drugs are subjected, were not performed. The Alteplase Dose Assessment for Pleural Infection Therapy project assessed lower doses of tPA (5 and 2.5 mg) and demonstrated similar success rates, although dose escalation to 10 mg was required in 12 and 24%, respectively.[102] Case reports of ultra-low dose tPA (1 mg) have been published.[103] Overall bleeding risk was not reduced using lower doses when compared with standard 10 mg regimens.[101] Consensus expert opinion is that anticoagulants should be withheld before and during intrapleural therapy where possible. If withholding these medications is not possible, a lower dose tPA should be considered.[63]

The increased drainage of fluid following the administration of tPA occurs in part due to the induction of exudative fluid generation by the drug itself. Animal models have demonstrated that this fluid generation is monocyte chemotactic protein-1 dependent[104] and may additionally provide a lavage effect to clear the pleural space. Similarly, saline irrigation of the infected pleural cavity showed some benefits in a small trial[105] and may be of benefit in those for whom tPA poses an unacceptable bleeding risk.

The recent upsurge in the use of IPCs has given rise to a novel challenge of IPC-related pleural infection. Compared with de novo parapneumonic effusion, the complexity of the pleural environment, in which malignant pleural infiltration of the pleura has occurred, is much greater. Expert consensus recommends keeping the catheter in situ while treating the infection with systemic antibiotics.[106] If the effusion becomes loculated and drainage ceases, intrapleural administration of tPA/DNase via the IPC itself has been successful and safe in retrospective studies.[107,108]

Clinical Scoring Systems

Several scoring tools have been published and validated in pleural infection. Currently, these remain largely used as research tools with limited clinical application.

Unsurprisingly scores that pick up on frailty such as the Charlson comorbidity index do predict worse outcomes in the setting of empyema.[109] The RAPID score,[110] a 0 to 7 scale based on renal function, age, purulence of the pleural fluid, the infection source (community or nosocomial), and serum albumin (diet), was shown to be useful in identifying patients at increased risk of mortality and prolonged hospitalization both retrospectively[111] and prospectively.[3] This is largely driven by identifying elderly patients with significant comorbidity and/or frailty.

Commonly used in sepsis, the Sequential Organ Failure Assessment (SOFA)[112,113] and quick SOFA (qSOFA)[114] indices also help identify patients with empyema at a high risk of death.[115] Notably, a score $\geq$2 in either index indicated a much higher risk of a pathogen resistant to common empiric antibiotics.[115] It is important to note that the performance of SOFA or qSOFA to predict antibiotic-resistant pathogens will be highly dependent on the overall prevalence of these resistant pathogens.

Comparison of the utility of the pneumonia severity index, CURB-65, CRB-65, Acute Physiology and Chronic Health Evaluation (APACHE) II, and standardized early warning score in a large population with community-acquired pneumonia (n = 1269) found none of these scores useful in predicting the development of complicated parapneumonic effusion or empyema.[116] In fact, evidence suggests the CURB-65 score dramatically underestimated mortality in pneumonia complicated by parapneumonic effusion.[117] However, multivariate analysis of the 1,269 patients did allow the development of a 6-point scoring system (Chalmer's score) based on serum albumin, sodium, platelet count, c-reactive protein, and a history of alcohol or illicit drug use that achieved a receiver operator characteristic curve of 0.84 for these outcomes.[116] This requires prospective evaluation before inclusion in clinical guidelines but if validated is likely to be of clinical value.

Conclusion

The incidence of pleural infection complicating community-acquired pneumonia is increasing, predominantly due to the aging, increasingly comorbid population at higher risk of empyema and likely in part the emergence of nonvaccine-type pneumococci and other bacteria. Early identification of complicated parapneumonic effusion requiring drainage is essential. Application of novel scores can allow us to identify those at risk earlier and, in combination with improved imaging with TUS, allows for the rapid institution of nonsurgical interventions that are proving to be efficacious and safe in both the short- and long-term.

Future directions include further investigation of causative bacteria in different settings, particularly in the context of novel genetic sequencing, which will assist with choosing appropriate antibiotic therapy. Individualization of treatment such as specific choice and dosing of intrapleural fibrinolytic therapy based on TUS findings and novel biomarkers predictive of loculations may become possible. A prospective comparison of these nonsurgical interventions and surgery for pleural infection is ongoing (ISRCTN18192121), and the results will further improve our management of this high morbidity and mortality condition.

Conflict of Interest
None declared.

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