The word complicated, when used to describe a pleural effusion, can be applied in several contexts. The various descriptions encompass fluid collections that have begun to develop visible fibrin deposition, have become abnormally acidic, or require medical intervention to ensure resolution. Although changes such as these may be caused by pleural malignancy, or even by some benign processes, the term complicated pleural effusion has become synonymous with the commonest cause: pleural space infection.

The incidence of pleural infection seems to be increasing worldwide, but despite continued advances in the management of this condition, morbidity and mortality have essentially remained static over the past decade. The quest for improvements in this field has resulted in an active international research community, which continues to
work to further the understanding of the underlying pathophysiology. Beneficial effects on the provision of health care are also anticipated from new techniques for early detection and risk stratification. This article summarizes the current evidence and opinions on the epidemiology, etiology, and management of complicated pleural effusions caused by infection, including empyema. Although many parallels may be drawn between children and adults in such cases, most trials, guidelines, and series regard pediatric patient groups and those more than 18 years of age as separate entities. This review focuses mainly on the treatment of adult disease.

HISTORICAL PERSPECTIVE
The first historical references to pleural infection have been credited to the ancient Egyptians, around 5000 years ago. However, it was Hippocrates who first described empyema through his revolutionary bedside-based and dissection-based approach to medicine around 400 BC. Medical practices were not significantly challenged again until the late nineteenth century when French physicians revisited the Hippocratic method with a modern eye. Until this time, open thoracic drainage of empyema was the standard of care, however there was a 70% mortality rate with this treatment. Closed tube drainage was described but not adopted widely until the formation of an Empyema Commission shortly after World War I, when the ravages of the influenza pandemic and its inevitable pleural sequelae forced the introduction of significant management changes. A landmark paper by Graham charted the successes seen during this time, with short-term mortality plummeting to 3.4% in certain treatment camps. He went on to describe in great detail the etiology, physiology, microbiology, and outcomes of empyema thoracis and its treatment at the time, laying the foundation for modern approaches. The ensuing 90 years were punctuated by further significant advances in the management of pleural infection, although perhaps not to the degree that was hoped for. Widespread availability of antibiotics, vaccination programs, and video-assisted surgery have had an impact on both microbiology and long-term morbidity, with further improvements hopefully still to be gained by the use of intrapleural fibrinolytic therapy.

EPIDEMIOLOGY
Despite these advances, recent literature has shown that the incidence of infection-related complicated pleural effusion is increasing. This seems to be the case for both children and adults, and although most data are derived from populations in the developed world, this pattern has been replicated worldwide. Between 20% and 57% of patients who develop pneumonia go on to develop a parapneumonic effusion, and although most of these patients do not require invasive treatment or investigation, a small subgroup may experience serious complications. Of the approximately 1 million cases of hospitalized pneumonia each year in the United States, around 60,000 develop frank empyema. A further 25,000 are estimated to develop empyema for other reasons, including trauma and iatrogenic instrumentation. These figures do not necessarily take into account effusions deemed complicated due to bacterial isolation or fibrous septations, which almost certainly makes the true burden of pleural infection much greater. Grijalva and colleagues recently examined the trends in parapneumonic empyema in the United States over a 13-year period in a recent publication. This study relied heavily on disease coding practices in hospitals but was still able to demonstrate a doubling in the rate of hospitalization due to empyema between 1996 and 2008, from 3.04 to 5.98 per 100,000. Similar results were demonstrated by a Canadian study, which also confirmed the significant disparity in empyema incidence between those aged 65 years or more (17–20 per 100,000) and those aged 19 years or less (2–4 per 100,000). Taking into account the average number of bed days for such patients, the average cost of managing patients with pleural infections in the United States and the United Kingdom probably exceeds $300 million per year.

Mortality rates from empyema also seem to be on the increase. A study looking at the population of Utah showed a marked increase in mortality between 2000 and 2005 compared with the relatively stable rates between 1950 and 1999. Absolute percentage mortality was low (<4%) in this group, but figures from other series have recorded mortality among standard inpatients up to 18% in the short-term, with those in intensive care experiencing mortality as high as 41%. In a large multicenter trial from the United Kingdom, in which the average patient age was 59 years, the 1-year mortality rate after treatment for empyema ranged between 8% and 20%.

MICROBIOLOGY
Understanding of pleural infection microbiology has traditionally involved extrapolation from the organisms implicated in pneumonia. Theoretic evidence supports this, at least in part, as
exemplified in a recent study by Wilkosz and colleagues who demonstrated a murine model for the transfer of upper airway bacterial isolates into the pleural space. Although there are undoubtedly patients who experience something similar, mounting evidence suggests that the bacteriology of pleural infection, and perhaps the condition itself, should be considered as a distinct entity. The infected pleural space has significant differences in acidity and oxygenation compared with aerated lung, lending itself to invasion by certain organisms more than others. Furthermore, there is incomplete radiographic correlation between pneumonia and pleural infection, and an inability for many traditional pneumonia severity scores to accurately predict the outcome of pleural infection. Similar differences exist between pleural infections acquired in the community and those acquired in health care settings; the latter group is occasionally further subdivided into those who have iatrogenic intervention and those who have passive exposure to infection.

The first major shift in the type of bacteria causing pleural infection occurred after the introduction of antibiotics. Before this, around two-thirds of community-acquired cases were attributable to Streptococcus pneumonia; this figure subsequently dropping to around 10%. Precise definition of the cause is challenging, however. Ex vivo culture is difficult, particularly with the early and aggressive use of antibiotics, which can mask bacterial isolates. The highest yield using standard culture techniques seems to be around 60%, with the inoculation of standard blood culture bottles the most convenient method for achieving this. A large study of patients in the United Kingdom with pleural infection combined standard methods with nucleic acid amplification to discern causative organisms; a 74% overall identification rate was attained. Cloning techniques were also applied to a small number of cases (3%), limited by cost. DNA studies were able to identify an organism in 38% of the culture-negative samples; the same organism was found by both culture and nucleic acid amplification (or cloning) in 35% of cases. Of these, culture was only able to provide more complete information about the organism 6% of the time and DNA studies 8% of the time. A technique was deemed superior when it was able to find an organism not picked up by the other. Using this rule, culture was better in 26% of cases and nucleic acid amplification in 13% of cases. In 12%

<table>
<thead>
<tr>
<th>COMMUNITY ACQUIRED</th>
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<tr>
<td>AEROBES 73%</td>
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<td>STREPTOCOCCI 72%</td>
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<tr>
<td>Strep. milleri group 46%</td>
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<tr>
<td>Strep. pneumoniae 40%</td>
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<td>Strep. pyogenes 5%</td>
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<tr>
<td>Other streptococci 9%</td>
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<tr>
<td>STAPHYLOCOCCI 14%</td>
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<tr>
<td>S. aureus 77%</td>
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<td>MRSA 20%</td>
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<td>S. epidermidis 3%</td>
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<td>GRAM NEGATIVE 12%</td>
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<td>OTHER 2%</td>
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<td>ANAEROBES 22%</td>
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<td>OTHER 5%</td>
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<tr>
<th>HOSPITAL ACQUIRED</th>
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<td>STAPHYLOCOCCI 40%</td>
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<td>MRSA 71%</td>
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<td>S. aureus 29%</td>
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<td>GRAM NEGATIVE 26%</td>
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<td>STREPTOCOCCI 21%</td>
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<td>ENTEROCOCCI 13%</td>
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<tr>
<td>ANAEROBES 8%</td>
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<td>OTHER 4%</td>
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*Anaerobes* includes Fusobacterium, Bacteroides, Peptostreptococcus, Unclassified mixed anaerobes, Prevotella spp., Clostridium spp., Mycobacterium tuberculosis and Actinomyces spp.

*Other* includes *Escherichia coli*, *Enterobacter* spp. and *Pseudomonas aeruginosa*.

*Gram negative* includes *Escherichia coli*, *Enterobacter* spp., *Pseudomonas aeruginosa*.

*Other* includes *Burkholderia cepacia*, *Eikenella*, *Haemophilus influenzae*, oral bacterium, *Pasteurella multocida*, and *Klebsiella* spp.

Fig. 1. Description of the bacteriology of pleural infection. Figures are derived from the total number of bacterial isolates achieved using standard culture and DNA amplification techniques (n = 336 for community-acquired, n = 60 for hospital-acquired). Of 434 individual cases analyzed, 88 (20%) were polymicrobial.
of cases there was conflicting information from the tests and so a clear assessment could not be made.

In this cohort, the *Streptococcus anginosus* group (formerly *S. milleri* group) was the predominant set of bacteria. These and other gram-positive aerobes were implicated in 65% of cases, confirming the inherent differences in etiology compared with pneumococcal pneumonia. Other organisms included *Staphylococci* (11%), gram-negative aerobes such as *Escherichia coli* (9%), and anaerobes (20%). Poly-microbial samples were identified in 20% of cases, but this may well underestimate the true incidence, as suggested by the cloning techniques used in the study and the fact that anaerobes have been identified in up to three-quarters of cases of community-acquired pleural infection in other series.

Hospital-acquired pleural infection made up only 15% of the UK cohort, but the differences between these cases and community-acquired cases was marked. Most (58%) cases were attributed to gram-negative organisms or *Staphylococci*; more than 70% of the latter were caused by methicillin-resistant *Staphylococcus aureus* (MRSA). Similar gram-negative predominance has been found among patients admitted to the intensive care setting. These findings have led to a shift in the antibiotics suggested for empirical treatment of pleural infections, and to the development of specific guidelines for their management. Although necessarily region specific, the recommendations acknowledge the likelihood of *Streptococcal* and anaerobic coinfection in community-acquired disease, and for the higher proportion of multidrug-resistant *Staphylococci* in hospital-associated disease.

The heptavalent pneumococcal vaccine, which was introduced in 2000, may also be playing a role in the evolution of pleural infection bacteriology. Numerous investigators have noted a shift in the predominant serotypes causing disease toward those not covered by the vaccine. This phenomenon has been described in both the adult and pediatric populations, and seems to correlate with the significant increase in the incidence of empyema, suggesting a degree of heightened virulence in the new organisms. This makes it all the more important that the approach to, and understanding of, complicated pleural effusions is based on current evidence, and that descriptive series continue to be attempted alongside the interventional.

**PATHOGENESIS AND TERMINOLOGY**

As alluded to earlier, confusion may occasionally arise from the terms used to describe the processes and conditions involved in pleural infection. The phrase complicated pleural effusion and the word empyema are sometimes used interchangeably, and although convenient, this approach presupposes the lack of disease spectrum and potential significant clinical differences between patients. A useful clinical classification describes infection-related effusions as being complicated when invasive or semi-invasive intervention becomes necessary because of the presence of bacteria in the fluid, or when biochemical markers within it suggest the development of significant inflammation. The term empyema should be used based on visual appearances, with the presence of pus in the chest as its defining feature. This typically represents a later, and often more therapeutically challenging, degree of pleural involvement.

The processes that lead to pneumonia-associated empyema are typically broken down into 3 phases (Fig. 2), with the transition between them varying greatly from one patient to the next. The trigger is usually the aspiration of oropharyngeal bacteria and the development of pneumonic changes over approximately 1 week. Primary pleural infection, without pneumonia, probably arises as a result of hematogenous spread from similar areas. An uncomplicated effusion may develop over the next few days, representing an exudative stage, which becomes complicated during the subsequent fibrinopurulent stage. An empyema forms during the longer-lasting organizational stage, reflected in the indolent clinical course in some of those affected. The overall timeframe for the development of empyema can depend on several factors, including the patient’s own immunity and the virulence of the infecting organism. This means that, although some patients may progress rapidly, it is also not unusual to find others deteriorating over 4 to 6 weeks.

Initial pleural fluid formation is usually a direct consequence of localized inflammation and immune system activation. The processes involved may be likened to those involved in wound healing and begin with increased capillary vascular permeability as a result of endothelial injury caused by activated neutrophils, which form the bulk of the immune cells in early complicated effusions. This allows fluid to move into the pleural space, which in normal circumstances contains around 10 mL of liquid with the resulting accumulation caused by an imbalance in the ratio of production to lymphatic drainage. At this stage, pleural fluid sampling reveals an exudative effusion, but does not demonstrate significant acidity (pH is >7.2), a notable decrease in glucose, or an increase in lactate dehydrogenase (LDH).

Ongoing pleural insult leads to the development of the fibrinopurulent phase, with activation of
### SUMMARY OF CHARACTERISTICS FOR PLEURAL INFECTION DIAGNOSIS AND MANAGEMENT

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>PATHOPHYSIOLOGY</th>
<th>CLINICAL APPEARANCES</th>
<th>BIOCHEMISTRY</th>
<th>MICROBIOLOGY</th>
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<tr>
<td></td>
<td>PLEURAL INJURY</td>
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<td></td>
<td>Early inflammation</td>
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<td></td>
<td>Neutrophil chemotaxis</td>
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<td></td>
<td>Increased vascular and pleural permeability (mediated by cytokines, e.g. VEGF)</td>
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<td></td>
<td>Increasing fluid accumulation</td>
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<tr>
<td></td>
<td>ONGOING INFLAMMATION AND BACTERIAL TRANSLLOCATION (mediated by cytokines, e.g. IL-8, TNF-α, TGF-β)</td>
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<td></td>
<td>Activation of coagulation cascade</td>
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<td></td>
<td>Increasing pleural fibrin deposition and fibrin remodelling</td>
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<td></td>
<td>Down-regulation of local fibrinolytic pathways</td>
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<td></td>
<td>BUILD-UP OF BACTERIAL AND INFLAMMATORY CELL DEBRIS</td>
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<td></td>
<td>Fibroblast chemotaxis</td>
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<td></td>
<td>Development of fibrosis</td>
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<td></td>
<td>Formation of complex, organized pleural peel</td>
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<td></td>
<td>SIMPLE PARAPNEUMONIC EFFUSION</td>
<td>Free-flowing fluid</td>
<td>pH &gt; 7.20</td>
<td>NO ORGANISMS PRESENT</td>
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<td></td>
<td></td>
<td></td>
<td>GLUCOSE &gt; 60 mg/L</td>
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<td></td>
<td></td>
<td></td>
<td>LDH &lt; 1000 IU/L</td>
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<td></td>
<td>COMPLICATED PARAPNEUMONIC EFFUSION</td>
<td>Increasingly turbid fluid +/− fibrinous septations and loculations</td>
<td>pH &lt; 7.20</td>
<td>ORGANISMS POSSIBLY FOUND</td>
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<td></td>
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<td>GLUCOSE &lt; 60 mg/L</td>
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<td></td>
<td>LDH &gt; 1000 IU/L</td>
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<tr>
<td></td>
<td>EMPYEMA</td>
<td>Pus</td>
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**Fig. 2.** The pathophysiology, appearance, diagnostic parameters, and treatment options of infected pleural effusions.
proinflammatory and profibrotic components, as well as initiation of the coagulation cascade. The local inflammatory response is amplified by the presence of various cytokines, such as transforming growth factor (TGF)-β, tumor necrosis factor (TNF)-α, and interleukin (IL)-8, which stimulate neutrophil and fibroblast chemotaxis. Membrane permeability makes recordable bacterial translocation most likely during this period, and the later stages of this process can lead to the expected visual appearance of empyema due to the presence of cell breakdown products and bacterial remnants. The high level of cellular respiration and lactic acid are reflected in the fluid biochemistry, which by definition now has a low pH (<7.2), low glucose level, and LDH level 3 times normal. A notable exception to this are effusions caused by Proteus species, which can secrete enzymes that cause a more alkaline environment. The overall intrapleural effect of the cellular infiltration is to downregulate fibrinolysis, thus increasing fibrin formation using locally available substrate. A major component in this process is plasminogen, which can normally be cleaved to the active compound plasmin by enzymes such as urokinase plasminogen activator or tissue plasminogen activator (t-PA). This forms the basis for modern fibrinolytic therapy. Plasmin normally functions to degrade fibrin clots, and so its inhibition can lead to many of the changes seen in the pleural space during complicated pleural processes, typified by fibrous septation and fluid loculation. Studies have demonstrated high levels and increments of inhibitory compounds, such as plasminogen activator inhibitors (PAI)-1 and PAI-2, in patients with pleural injury. Left unchecked, these processes can progress to the organizational phase, in which complex pleural fibrosis can form over both the parietal and visceral pleural surfaces because of increased fibroblast infiltration (likely mediated by TGF-β), and can make management of patients extremely difficult without surgical intervention. The overall balance of the various mechanisms is complex and subtle, and is likely to vary significantly between patients. Nonetheless, ongoing clarification of these processes continues, with the ultimate aim of being able to identify sensitive and specific biomarkers, and to provide efficacious treatments to patients at all stages of disease.

CLINICAL PRESENTATION AND EARLY RISK STRATIFICATION

Although there have been some extremely unusual cases, the classic presentation of prolonged pleural infection is difficult to separate from that of pneumonia, whereby patients suffer with dyspnea, cough, fever, malaise, and perhaps pleuritic chest pain. A significant number of patients go on to develop a parapneumonic effusion but clues to its existence are rare in terms of symptoms. Furthermore, there is no symptomatic discriminator between patients with complicated and uncomplicated effusions. A high index of suspicion should be maintained for those patients who fail to improve within a few days of initiating antibiotic therapy or who exhibit persistent fever or signs of sepsis; further investigations should follow rapidly. In the long term, patients with indolent pleural infection can mimic the course of those with malignant processes, often describing significant weight loss, sweats, and loss of appetite.

The ability to identify patients who are most likely to develop complicated effusions, or those likely to have the worst outcomes, could enable physicians to target these groups for more aggressive initial management or potent therapies. Although there are likely to be complex interactions between the genetic and environmental factors that contribute to the development of pleural infection, these have not yet been determined. There are, however, certain patient risk factors, particularly chronic alcohol excess and intravenous drug use, which likely increase the risk due to gastric aspiration. In addition, Chalmers and colleagues described 4 other independent risk factors that seem to predict the development of pleural infection: serum albumin less than 30 g/L; serum C-reactive protein (CRP) greater than 100 mg/L; platelet count greater than 400 × 10⁹/L; and serum sodium less than 130 mmol/L. This study noted than none of the routinely used pneumonia or sepsis scores were adequate in determining this outcome, and suggested a score based on these 6 factors, although this still requires validation. Patients with chronic obstructive pulmonary disease were found to be at lower risk of developing pleural infection, perhaps due to a background level of generalized inflammation causing an attenuated response to a pleural bacterial challenge.

For those patients who are confirmed to have pleural infection, those at greatest risk of poor outcome may be identified. In a large multicenter cohort of patients with pleural infection recruited to the UK Multicenter Intrapleural Sepsis Trial (MIST) 1 trial, the RAPID score was developed and subsequently validated using a second cohort from the MIST2 trial. Of the 32 baseline characteristics analyzed, 5 presenting factors (age, serum urea, serum albumin, fluid purulence, and likely origin of infection) could predict the eventual outcome,
with patients divided into low-risk, medium-risk, or high-risk groups based on a score out of 7. Patients in the lowest risk group were found to have a mortality rate of less than 5% at 3 months, whereas those in the highest were found to have a mortality rate approaching 50% over the same period. The main potential advantage of this stratification system is that it allows physicians to institute fibrinolytics or surgery earlier in the clinical presentation when they are perhaps more likely to be successful.

**IMAGING TECHNIQUE FOR PLEURAL INFECTION**

Radiological tests form the cornerstone for the initial diagnosis and management of complicated pleural effusion. Radiographs, computed tomography (CT), ultrasonography (US), and other tools can detail the size, extent, nature, and potentially the cause of pleural effusions before any other intervention is undertaken. The standard chest radiograph is a valuable screening tool because of its ubiquity and low radiation dose. Fluid collections greater than 250 mL are usually appreciable although the cause of the fluid may not be apparent. The suspicion of a complicated pleural process should be raised if the lung seems to be indented by pleural shadowing in a way that is not consistent with the expected effects of gravity on fluid (Fig. 3).52

CT and US have become part of the standard approach to many pleural conditions. The use of US enables a radiation-free bedside assessment of fluid echogenicity, an approximation of volume, and can guide thoracentesis or chest tube placement. The degree of septation and loculation can be better appreciated than on CT scans (Fig. 4), allowing a strong inference of the presence of a complicated effusion or empyema in the right clinical setting.53 US can also be used to improve the safety and accuracy of pleural sampling and drain insertion,54,55 because images are viewed in real time.

Imaging of the pleura is best undertaken using CT. In addition, the ability to reconstruct images allows for a greater appreciation of the overall fluid burden as well as potential parenchymal causes such as pneumonia or obstructing lesions.56 By obtaining images approximately 20 to 60 seconds after contrast administration, with slices of 1 to 3 mm, a clear delineation between lung and pleural tissue can usually be made, especially if the lung is atelectatic.57 Features suggestive of pleural infection include the presence of air in the pleural space (in the absence of recent instrumentation) (Fig. 5) and smooth pleural thickening that spares the mediastinal surfaces. In cases of empyema or otherwise infected pleural fluid, the split pleura sign can often be appreciated due to visceral and parietal pleural enhancement surrounding a fluid collection (Fig. 6), occasionally in conjunction with increased attenuation of extrapleural fat.58 Despite a strong case for their regular use in the assessment of pleural infection, and despite some physicians’ tendencies,59 currently neither CT nor US can reliably predict the outcome of an effusion after chest tube insertion or fibrinolytic therapy,60 nor which patients should be selected for a particular surgical intervention.61

As a result of the accuracy achieved by these imaging modalities, the role for others, such as magnetic resonance imaging (MRI) and positron emission tomography (PET), is restricted. MRI is capable of similar diagnostic accuracy to CT scans but the images are easily degraded by
respiratory motion and the scan is often more challenging for patients. Nonetheless, MRI may find use if spinal or rib involvement is suspected due to the infective process.53 PET scanning in pleural infection is usually limited to when other modalities or tests have been unable to distinguish infection from pleural malignancy, because, although subtle, contrast uptake between these 2 conditions can differ.62

PLEURAL FLUID INVESTIGATION

Concerning signs, symptoms, or blood tests in the context of a suggestive radiograph should lead to confirmation of effusion and early fluid sampling. However, in a small retrospective series by Skouras and colleagues,63 the investigators suggested that parapneumonic effusions less than 2 cm in depth on US can be treated without further sampling as they are unlikely to become complicated or require intervention. Even if confirmed in larger prospective studies, such patients require close monitoring and appropriate antibiotic therapy.

Once the effusion has been sampled, routine tests should include fluid pH, protein, LDH, and glucose. Increased levels of cellular respiration and breakdown within the fluid cause dynamic changes in these values, with the development of a complex parapneumonic effusion suggested by the presence of a pH value less than 7.2, an LDH level greater than 1000 IU/L, and a glucose level less than 60 mg/dL (3.4 mmol/L).6 As described earlier, the yield from sending a sample for Gram stain and bacterial culture may be significantly improved by inoculating a blood culture bottle with a few milliliters of the initial aspirate.29 If there is a suspicion of mycobacterial involvement, adenosine deaminase levels along with stain and culture for acid-fast bacilli may be of diagnostic use; extended viral or fungal studies may also be useful in patients who are significantly immunocompromised. In addition, because repeated thoracentesis is itself a risk-factor for pleural infection, and because there are occasions when primarily malignant effusions can mimic complicated infective effusions, recommendations state that fluid be sent for cytologic examination along with these other baseline tests.64 The discovery of a neutrophil-predominant or macrophage-predominant effusion may guide management toward that of infection, whereas malignant processes tend to produce lymphocytic exudates.65 A degree of diagnostic caution should always be maintained, however, as inflammatory effusions are likely to transition from being neutrophil-predominant or macrophage-predominant to lymphocyte-predominant if present for more than 2 weeks.

The best solitary discriminator for a complicated pleural process during initial investigations is fluid pH level. Many studies demonstrate better patient outcomes when drainage is instituted based on the early biochemical changes related to infection.66 Current guidelines regard a pH of 7.2 as diagnostic of complexity, making this the definitive cutoff value below which drainage should take place.6 Samples for pH can typically be processed within a few minutes using a blood gas analyzer, although samples that appear frankly purulent need not be tested for pH in this way because the visual appearance of empyema should prompt intervention irrespective of acidity.1 Fluid pH values may be appreciably altered by minor variations in sampling and processing techniques, which can

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Fig. 5. CT scan showing a left-sided empyema (arrow). Note how the fluid (darker gray) contains numerous bubbles (black), indicating the presence of gas-forming organisms. The fact that the bubbles have not coalesced suggests significant loculation, but this is not easily visualized using this modality.

Fig. 6. The split pleura sign. CT scan showing a significant right-sided empyema. Note how the pleural fluid (F) is outlined by markedly thickened visceral (V) and parietal (P) pleural membranes, which are seen as a result of a delayed contrast scan protocol. A chest drain (D) is in situ.
therefore have significant effects on management strategy. A study by Rahman and colleagues re-produced several common scenarios that may occur during the testing of pleural fluid, and were able to demonstrate that even small amounts of residual heparin or local anesthetic in a sample syringe can dramatically lower pH results. The opposite was found when residual air was left in the syringe; pH increased by an average of 0.08 if 2 mL of fluid was exposed to 1 mL of air. This represented a clinically significant change in more than two-thirds of patients.

ADDITIONAL FLUID INVESTIGATIONS

Glucose, LDH, and pH measurements determine whether an effusion is complicated and have been shown to be extremely sensitive discriminators. However, a retrospective analysis by Porcel and colleagues showed that these tests were not particularly specific when it came to establishing the need for chest tube drainage in nonpurulent effusions, meaning a subset of patients may undergo unnecessary treatments. Other fluid biomarkers have been investigated to help guide diagnostics and therapeutic interventions.

In recent years, many potential markers have been tested focusing on different parts of the inflammatory and infective cascades. These include complement products (C5b-9), enzymes (myeloperoxidase), acute phase reactants (CRP and procalcitonin), markers of oxidative stress, and cytokines (TNF-α and IL-8). It has also been suggested that the absolute neutrophil count in fluid can be useful. Both pleural fluid CRP and vascular endothelial growth factor have been suggested as long-term predictors for developing residual pleural thickening. Although the sensitivity and specificity of some of these tests can be extremely good, none have so far been proved to be superior in differentiating between uncomplicated and complicated effusions compared with the existing methods. Further clarification and experimentation is needed before any new marker can be adopted, although skepticism exists on whether the ideal biomarker will ever be found.

BASIC THERAPIES

Antibiotics and Chest Drainage

The need for supportive and preventative care is great in those with pleural infection, as many are toward the severe end of the sepsis spectrum and will perhaps be more immobile after intervention. Early institution of thromboembolic prophylaxis is recommended for most medical inpatients, and the use of calorie supplements should not be delayed if needed, remembering that empyema is more common in groups who are predisposed to nutritional impairment. As discussed earlier, the empirical use of antibiotics or other antimicrobials should be based on local guidelines and patient-specific risks. Patients often show signs of generalized sepsis at presentation, and systemic antibiotics are frequently administered before pleural fluid cultures can be taken or analyzed.

Previous studies have shown that the concentrations of parenterally administered penicillins and cephalosporins within a parapneumonic effusion are up to 75% of those found in serum, and similarly high pleural levels of metronidazole were found in an animal model of empyema. These antibiotics allow a broad spectrum of coverage, including anaerobes. Alternative antibiotic classes and agents that have shown good pleural penetration, albeit rarely in true clinical scenarios, are carbapenems, ciprofloxacin, clindamycin, and chloramphenicol. Because of these results, little work has been done to explore intrapleural antibiotic instillation despite it being intuitively appealing, especially as little is known about antibiotic levels in fluid surrounded by thickened pleura. There is also limited understanding regarding the activity of such antibiotics in highly acidic environments, circumstances that may explain why studies have shown amino-glycoside levels to be undetectable in empyema when given intravenously.

Historically, patients suspected of having pleural infection had larger chest drains inserted. Although never formally proved, this recommendation was largely based on the fear of small tubes becoming blocked with the viscous fibrous products likely to be drained in these situations. However, current practice has begun to shift toward the use of smaller drains because evidence of their noninferiority has begun to mount. A large Taiwanese series used small (10–16 French) pigtail catheters to manage a range of pleural conditions. Most of these were used for cases of pleural infection, with a reported success rate of 72%. A retrospective analysis of the large MIST1 cohort demonstrated no significant difference in the rates of surgical referral or mortality depending on drain size. This same analysis showed patients with larger drains were more likely to suffer pain from their tube, although there may have been bias introduced because the drain size was not randomized (drain size was determined by local physicians, meaning those with empyema, and perhaps more inflamed pleura, may have received larger drains).

The lack of formal randomized studies means that there is as yet no formal consensus on the issue of optimal drain size, but the latest British
Thoracic Society guidelines now suggest 10 to 14 French chest tubes can be used first line in cases of complicated pleural effusion. These drains can usually be inserted safely using the Seldinger technique and are best managed after insertion with regular sterile flushes to ensure drain patency. Some European centers use regular saline irrigation to manage complex effusions with the aim of removing pleural debris in conjunction with systemic therapy. Such a concept is plausible, even if the only studies thus far relate to postoperative infected pleural collections; these studies have also tested the idea of pleural sterilization using antibiotic irrigation.

**Fibrinolytic Therapy**

Early knowledge of the fibrotic processes underlying complicated pleural effusions led to the first use of intrapleural streptokinase more than 60 years ago. However, it is only in the last 10 to 15 years that significant advances have been made in determining the most appropriate role for this class of medication in pleural infection; more work is still needed.

Davies and colleagues were able to begin to allay long-standing safety fears regarding intrapleural thrombolysis in a small series of 24 patients; improvements in clinical outcomes were also noted in those given streptokinase. Other studies tended to focus more on the use of urokinase in loculated effusions; benefits were demonstrated in terms of treatment failure (as judged by surgical referral or death), surgical outcome, and length of hospital stay. However, these studies tended to be small trials or case series, which limited their generalizability.

The MIST1 trial recruited 454 patients with pleural infection from around the United Kingdom to receive either streptokinase or placebo. Entry criteria reflected real-world practice with a strong reliance on diagnosis by a local physician, antibiotic choice, chest tube use, and surgical referral. The trial was unable to show any significant benefit from the use of streptokinase in either levels of surgical referral or death, and was supported by a subsequent meta-analysis. However, a Cochrane review found that intrapleural fibrinolytics conferred benefit in both treatment failure and the need for surgical intervention in loculated effusions or empyema, but not mortality. Criticism of the MIST1 trial largely stemmed from its design. The use of small-bore chest tubes was questioned, as was the inclusion of patients who did not have loculated effusions, and because centralized drug distribution may have led to treatment delays. The choice of streptokinase as the primary lytic may also have contributed to these results, because its mechanism of action relies on using a proportion of the intrapleural plasminogen to form an active complex before the rest can be converted to plasmin. Nonetheless, the 2010 British Thoracic Guidelines went on to state that intrapleural fibrinolytics should not be used routinely, but may be considered in select cases.

The MIST2 trial was published in 2011 by Rahman and colleagues. It hypothesized that the addition of intrapleural deoxyribonuclease (DNase) to standard fibrinolytic therapy (recombinant t-PA) would confer extra benefit in the treatment of empyema and complicated pleural effusions. This hypothesis was based on previous observations that similar combinations in animal models had resulted in reduced empyema viscosity, presumably through the supplemental breakdown of DNA-based debris within the fluid. Recruitment took place over 3 years from 11 UK centers and patients were selected on clinical criteria. A higher proportion (91.4%) of patients had loculated effusions at baseline compared with those in MIST1. The primary end point was change in radiographic pleural opacification and patients were randomized to receive 1 of 4 treatments: double placebo, DNase plus placebo alone, t-PA plus placebo, or t-PA plus DNase. Although the actual numbers of patients receiving each treatment were small, those who received DNase and t-PA in combination were found to have significantly improved radiographic outcomes, lower rates of surgical referral at 3 months, and a mean hospital stay of almost a week less than those receiving placebo alone. The finding that isolated treatment with either of the study drugs produced results similar to placebo potentially supports the findings of the earlier MIST trial, and led the investigators to suggest that future studies should be directed toward larger-scale combination trials. This sentiment was echoed in a 2012 meta-analysis that included the results of this study. They reported similar findings to the previous Cochrane review, noting significant heterogeneity in study results, but suggesting potential benefits by reducing treatment failure with antifibrin treatment. A summary of the double-blind placebo-controlled trials that have looked at fibrinolytic therapy is shown in Fig. 7.

As the documented evolution of the use of thrombolytic therapy demonstrates, there is undoubtedly a great deal left to discover regarding their true role in the management of complicated pleural effusions. Work continues to try and refine thrombolytic molecules, with a plasmin-activated urokinase precursor demonstrating, in animal models, reduced susceptibility to PAI-1 inhibition, increased
### SUMMARY OF DOUBLE-BLIND, PLACEBO-CONTROLLED TRIALS OF FIBRINOLYTIC THERAPY

<table>
<thead>
<tr>
<th>STUDY</th>
<th>STUDY SIZE</th>
<th>INCLUSION</th>
<th>DRAIN SIZE</th>
<th>TREATMENT</th>
<th>MORTALITY (%)</th>
<th>SURGICAL REFERRAL RATE (%)</th>
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Fig. 7. Summary of double-blind placebo-controlled trials of fibrinolytic therapy.
fibrin selectivity, and a half-life that would potentially allow for single-dose administration.37

**Surgical Options**

Referral for surgical intervention usually occurs after failed medical treatment (antibiotics, chest drain insertion, and fibrinolytics), or with late presentations with highly organized empyemas showing marked pleural fibrosis. Practice tends to vary, but some centers have an extremely low threshold for early surgery, especially as the overall costs can be comparable with medical treatments.100 The point at which medical management is deemed to have failed is necessarily ill-defined; the risks of a particular surgical procedure are highly dependent on individual patient factors. Surgical involvement should be considered with significant loculation, which may predispose to long-term respiratory impairment, and/or ongoing signs of sepsis despite adequate antibiotic therapy.

Surgical options are varied and may be tailored to the individual. Video-assisted thoracoscopic surgery (VATS) typically requires general anesthetic and single-lung ventilation, but these requirements can be relaxed in the face of significant comorbidities. Although originally used for thorough pleural debridement,101 VATS can now be used to perform decortication in particularly advanced or chronic empyema, although the latter situation may reduce the chance of a successful outcome.102 Despite this, the overall success rate for VATS exceed 85%.

Open decortication for empyema was formerly a mainstay of treatment, but as evidence has emerged to show that VATS is at least comparable, and perhaps even superior,103 its role is likely to become increasingly marginalized, being used only when the less invasive approach has failed. Decortication after thoracotomy allows complete mobilization of the lung, which is particularly useful in cases of trapped lung.104 It may ensure that maximum symptomatic benefit is gained from 1 operation, although this may be at the expense of a more prolonged recovery. A study from 1996 described a mortality rate of about 3% for this operation.105

For patients who have recurrent or particularly complex empyema, small prosthetic devices may be inserted between ribs to maintain a permanent drainage route. The more extreme way to achieve this effect is to perform an open-window thoracotomy. This procedure involves the resection of 2 or 3 ribs to create a direct opening to the thoracic cavity, which affords the opportunity to pack the pleural space at the expense of creating an aesthetic alteration to the chest wall.106 Should methods such as these fail, a thoracomyoplasty may become necessary, whereby a large muscle is used to pack the thoracic cavity. This procedure is usually reserved for patients with bronchopleural fistulae, trapped lung, or postoperative empyema.104

**SUMMARY**

The treatment of complicated pleural effusions caused by infection continues to evolve. The worldwide incidence is increasing with a changing spectrum of causative organisms and underlying causes. Although often related to a pneumonic illness, there is little correlation between organisms typically found in the pleural space and those usually associated with parenchymal lung infections, suggesting primary pleural infection is far more common than previously believed, and that the term parapneumonic effusion is therefore often not an accurate label. Thus, there is an ever-growing appreciation of the complex processes involved and pleural infection is increasingly being recognized as an entirely separate entity. Specialized tools have now been developed and validated to allow physicians to more accurately predict the likely progress of patients and the potential to target treatment.

Early recognition and instigation of simple therapies such as antibiotics, nutritional supplements, and chest drainage remains the cornerstone of good management. However, for an important subgroup of patients, fibrinolytic therapy seems to enable full recovery without surgical methods. Larger randomized trials are needed in this area to fully clarify their role, but recent evidence suggests that combination therapy with DNase is likely to lead to the best outcomes for patients.

**REFERENCES**

Treatment of Complicated Pleural Effusions in 2013


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