Task force report

ERS/ESTS statement on the management of pleural infection in adults

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**Conflicts of interest**
EOB, SR, MH, MRG, RA, OCA, KA, MB, SP, EKH,SE, RK, AM, NAM, EP, JMP, LY, EPB, IO and NMR have no conflicts of interest to disclose

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### List of Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>ATS</td>
<td>American Thoracic Society</td>
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<tr>
<td>AUC</td>
<td>Area under the curve</td>
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<td>AUC_{pf/s}</td>
<td>AUC for concentration of a given antibiotic in the pleural fluid to that in the serum</td>
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<td>BPF</td>
<td>Bronchopleural fistula</td>
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<tr>
<td>CCI</td>
<td>Charlson Comorbidity Index</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>COPD</td>
<td>Chronic Obstructive Pulmonary Disease</td>
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<td>CPPE</td>
<td>Complicated Parapneumonic Effusion</td>
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<td>CRP</td>
<td>C-reactive Protein</td>
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<td>CT</td>
<td>Computed Tomography</td>
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<td>DM</td>
<td>Diabetes Mellitus</td>
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<tr>
<td>DNase</td>
<td>Deoxyribonuclease</td>
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<td>ERS</td>
<td>European Respiratory Society</td>
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<td>ESTS</td>
<td>European Society of Thoracic Surgeons</td>
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<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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<tr>
<td>IDSA</td>
<td>Infectious Diseases Society of America</td>
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<tr>
<td>IET</td>
<td>Intrapleural Enzyme Therapy (combination tPA and DNase)</td>
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<td>IPC</td>
<td>Indwelling Pleural Catheter</td>
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<tr>
<td>ISS</td>
<td>Injury Severity Score</td>
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<tr>
<td>LDH</td>
<td>Lactate Dehydrogenase</td>
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<tr>
<td>LMWH</td>
<td>Low Molecular Weight Heparin</td>
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<tr>
<td>LOS</td>
<td>Length of hospital stay</td>
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<tr>
<td>MIST</td>
<td>Multicentre Intrapleural Sepsis Trial</td>
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<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<tr>
<td>MRSA</td>
<td>Methicillin Resistant Staph Aureus</td>
</tr>
<tr>
<td>ODAPE</td>
<td>Optimal Duration of Antibiotics in Parapneumonic Effusions trial</td>
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<td>OR</td>
<td>Odds Ratio</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>OWT</td>
<td>Open Window Thoracostomy</td>
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<tr>
<td>PCT</td>
<td>Procalcitonin</td>
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<tr>
<td>PF / pf</td>
<td>Pleural Fluid</td>
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<td>PILOT</td>
<td>Pleural Infection Longitudinal Outcome Study</td>
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<td>RAPID</td>
<td>Renal (serum urea), Age (in years), Purulence, Infection source, Diet (serum albumin)</td>
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<tr>
<td>RCT</td>
<td>Randomised Controlled Trial</td>
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<td>s</td>
<td>Serum</td>
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<tr>
<td>SARS</td>
<td>Severe Acute Respiratory Syndrome</td>
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<td>SPC</td>
<td>Summary of medicinal product characteristics</td>
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<tr>
<td>SPIRIT</td>
<td>Studying Pleuroscopy in Routine Pleural Infection Treatment (SPIRIT) Trial</td>
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<tr>
<td>STS</td>
<td>Society of Thoracic Surgeons</td>
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<tr>
<td>suPAR</td>
<td>Soluble urokinase plasminogen activator receptor</td>
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<td>TF</td>
<td>Taskforce</td>
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<tr>
<td>tPA</td>
<td>Tissue plasminogen activator</td>
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<tr>
<td>UK</td>
<td>United Kingdom</td>
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<tr>
<td>UPPE</td>
<td>Uncomplicated parapneumonic effusion</td>
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<tr>
<td>US</td>
<td>Ultrasound</td>
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<tr>
<td>USA</td>
<td>United States of America</td>
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<tr>
<td>VAC</td>
<td>Vacuum Assisted Closure</td>
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<td>VATS</td>
<td>Video Assisted Thoracoscopic Surgery</td>
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Abstract

Pleural infection is a common condition encountered by respiratory physicians and thoracic surgeons alike. The European Respiratory Society (ERS) and European Society of Thoracic Surgeons (ESTS) established a multidisciplinary collaboration of clinicians with expertise in managing pleural infection with the aim of producing a comprehensive review of the scientific literature.

Six areas of interest were identified including the epidemiology of pleural infection, the optimal antibiotic strategy, diagnostic parameters for chest tube drainage, the status of intrapleural therapies, the role of surgery and the current place of outcome prediction in management.

The literature revealed that recently updated epidemiological data continue to show an overall upwards trend in incidence, but there is an urgent need for a more comprehensive characterization of burden of pleural infection in specific populations such as immunocompromised hosts. There is a sparsity of regular analyses and documentation of microbiological patterns at a local level to inform geographical variation and ongoing research efforts are needed to improve antibiotic stewardship.

The evidence remains in favour of a small-bore chest tube optimally placed under image guidance as an appropriate initial intervention for most cases of pleural infection. With a growing body of data suggesting delays to treatment are key contributors to poor outcomes, this suggests that earlier consideration of combination intrapleural enzyme therapy (IET) with concurrent surgical consultation should remain a priority. Since publication of the MIST-2 study, there has been considerable data supporting safety and efficacy of IET, but further studies are needed to optimise dosing using individualised biomarkers of treatment failure.

Pending further prospective evaluation, the MIST-2 regimen remains the most evidence based. Several studies have externally validated the RAPID score, but it requires incorporating into prospective intervention studies prior to adopting into clinical practice.
Introduction

It is estimated that 2.5 million people globally died due to pneumonia in 2019, approximately 250,000 in Europe [1]. Up to 50% of pneumonia cases develop a pleural effusion, an occurrence which in itself is associated with a 3-6 fold increase in mortality [2]. While the majority of these ‘simple’ parapneumonic effusions resolve with antibiotics and optimal medical therapy, approximately 15% progress to bacterial invasion of the pleural space and become true ‘pleural infection’ – defined as a pleural collection in the context of infective symptoms with a pH<7.2, or a low glucose (<2.2 mmol/L, in the presence of normal serum blood glucose), a pleural collection that is culture positive, or an ‘empyema’ when frank pus accumulates in the pleural space.

Presentation is often delayed due to a subacute onset, and the reported median length of hospital stay (LOS) of 14-19 days [3–8] is associated with significant healthcare resource utilisation with the potential requirement for prolonged antibiotics, chest tube drainage, intrapleural therapy and/or surgery. This culminates in this condition being linked to the overall highest average cost per case (approximately €21,822 per admission in Europe [4]) among pleural disease and other acute lung conditions. Most worryingly, patient outcomes have not significantly improved, with average 30-day and 3-month mortalities at approximately 10% [9, 10] and 1-year mortality at 20% rising up to 35% in the elderly and immunocompromised [11]. New treatment strategies are urgently needed.

Existing pleural infection guidelines are outdated[12, 13] and there are significant variations in practice across the world with regard to standard care, use of intrapleural therapy and surgery. Despite the sparsity of large multicentre randomised controlled trials (RCTs), several important additions to the literature in recent years have informed our understanding of the underlying pathology, microbiology, and advances in intrapleural treatment. One example is the recent finding that a significant subgroup of patients (up to a third) present with ‘primary pleural infection’ without radiological evidence of pneumonia [14] and appear to have a microbial profile similar to the oral cavity, supporting spread to the pleural space via alternative routes, potentially haematogenously [15, 16]. Innovations in surgery with experience using less invasive techniques such as Video Assisted Thoracoscopic Surgery (VATS) have made this modality safer and more accessible in later stage disease and to an older, frailer population.

This statement aims to form a narrative review of the current evidence with regards to adult pleural infection management. It does not make clinical practice recommendations but in specific areas where the evidence is scarce or mixed, these limitations are described and the practice of the taskforce (TF) members is mentioned for information, but not with the aim of guiding clinical practice.
Methods

A TF was assembled with the goal of producing a Statement that represented a comprehensive, scientific review of the literature, identified by systematic searches with conclusions supported by accompanying references. Membership of the taskforce was based on recommendations of the European Respiratory Society (ERS) Scientific Committee in collaboration with the European Society of Thoracic Surgeons (ESTS) Board and included representation from seven European countries, the United States (USA), South America and North Africa. The taskforce was comprised of nine respiratory physicians (with subspecialist expertise in pleural disease, respiratory infection, and interventional pulmonology), three thoracic surgeons, a clinical epidemiologist, a clinical pharmacist, with the support of four early career ERS members and two early career ESTS members.

Prior to the conception of this statement, informal meetings were held with an established pleural infection patient focus group (led by the Oxford Respiratory Trials Unit; EOB and NMR) to identify patient priorities to ensure these were incorporated into the scope of the statement. Specifically, issues such as the inconvenience of prolonged antibiotics, earlier diagnosis, optimal intervention and inability clinicians to provide an individualised prognosis were highlighted.

The final scope of the statement was agreed at the initial meeting in January 2021, specifically that it would be limited to adult pleural infection and would not include paediatric pleural infection or tuberculous pleuritis as it was agreed that these were distinct clinical entities. Six clinically relevant, patient centred areas of pleural infection research were chosen by consensus with specific research questions built around these.

The literature search was undertaken by allocated subgroups to each clinical question with access to an ERS methodologist and a librarian (EKH). MEDLINE (National Library of Medicine, USA), EMBASE (Elsevier, the Netherlands) and Scopus databases were searched using a combination of appropriate MeSH headings and keywords. Search results were limited to the last 15 years (with older studies for reference only). The full search strategy for each clinical question is shown in the online supplement. Once the search had been run, further potentially eligible articles were identified by reviewing the reference lists of identified papers. The search was repeated in February 2022 to identify recently published papers.

Abstracts were screened independently for inclusion by subgroup members and were included based on pre-specified eligibility criteria (online supplement). Any queries or disagreements were resolved through discussion at taskforce virtual meetings, with final word to the taskforce chairs (EOB, IO, and NMR).

Subgroups prepared drafts summarising the relevant literature for their clinical question, which underwent review by the full taskforce before being revised and submitted to the chairs. The taskforce chairs collated the drafts into a complete
statement and the final draft was approved by all members prior to submission to the ERS and hence represents a statement of the entire taskforce. Future research recommendations reflecting some of the gaps in the literature from each focus area have been summarised in the online supplement.
Results

Question 1: What is the current burden of pleural infection?

Despite a lack of reliable characterisation of trends globally, recent epidemiological data [3–5] have demonstrated trends in rising incidence similar to those observed at the turn of the last decade [17–19]. In the UK, there was a year-on-year increase from 6.44/100,000 to 8.3/100,000 in between 2008 and 2017[3]. In France, Bobbio et al observed a similar incidence, increasing from 6.7/100,000 to 7.7/100,000 in the short period between 2013 and 2017 [4]. In the USA, Mummadi et al recently reported a 37.5% relative increase in pleural infection related hospitalisation between 2007 and 2016 [5]. This represents a worrying upwards trend compared to the increase from 3.4 to 5.8 cases per 100,000 between 1996 and 2008 reported by Grijalva et al in the US in 2011[18] or the 26% relative increase in Denmark between 1997 and 2011[9].

These rising trends are likely the result of variable interplay between an ageing population living longer with chronic comorbidities (such as the increased prevalence of diabetes mellitus (DM) [8, 20]) acting as risk factors, the increased prescribing of immunosuppressive agents, the natural evolution of bacterial pathogens, as well as improved access to sensitive imaging [computed tomography (CT) and bedside ultrasound (US)].

Age and gender distribution

Similar to previous reports [19], the increases were highest among the over 60s with almost a doubling across the decade studied (2008-2017) [3]. However, it is important to note that at least 40% of adult pleural infection hospitalisations in the UK and Europe are still represented in the 18-64 age group, rising to 60% in the US [3–5]. The marked male predominance remains consistent at approximately 2.3:1 (70%)[3–6, 19, 21]. Interestingly, this appears to begin after adolescence (equal gender distribution in children), rises gradually and peaks in the >60 age group. The reasons for this are not fully understood but plausible hypotheses include gender differences in health-seeking behaviours (delayed presentation in males), worse dental hygiene trends and male predominance of pre-existing comorbidities.

Comorbidities

A recent systematic review reporting data from over 225,000 patients, found that the prevalence of pre-existing comorbidity in pleural infection is high (up to 72%) [8, 22] with chronic respiratory and cardiovascular conditions having the highest contribution (table 1.2). The French national database study found a median Charlson
Comorbidity Index (CCI) of 5 in patients with pleural infection (CCI 3 in those without cancer or recent surgery) [4].

Independent of other risk factors, patients with DM were twice as likely to develop pleural infection and within pleural infection cohorts, the prevalence of DM was 5-times higher than the general population[20]. Malnutrition and alcohol abuse are also important risk factors [23], stressing the significance of dietary supplementation during therapy. Concurrent malignancy rates as high as 30% have been reported[4] (average 12-13% [8, 24]), emphasising the importance of avoiding diagnostic anchoring, particularly during a protracted clinical course.

While a decreased risk of pleural infection in chronic obstructive pulmonary disease (COPD) has been hypothesised to be related to the use of inhaled corticosteroids, resulting in a dampened pleural inflammatory response [23, 25], other studies have reported conflicting findings [26]. It is plausible that hyperexpanded lungs and a higher intrinsic pressure results in smaller effusions. It is noteworthy that patients with COPD often have other comorbidities that increase their risk of developing pleural infection. A recent nationwide cohort study with propensity-matched controls found schizophrenia to be a risk factor for developing pleural infection [27], although a relationship between mental health illness and increased risk of infections generally has been reported and is complex [28, 29].

Immunosuppressive states acquired through diseases such as human immunodeficiency virus (HIV) infection, or iatrogenically-induced by treatments (steroids, immunomodulatory, chemotherapeutic agents) have been reported to be associated with pleural infection [30, 31] but data on these are poorly collected in recent epidemiological studies [8]. Future studies should focus on routine collection of these data to allow a better understanding of the course and outcomes of pleural infection in these specific groups where the microbiology and immune response are likely to differ from immunocompetent states.

**COVID-19, seasonal variation, and the role of viruses**

With reference to the COVID-19 pandemic, a recent meta-analysis found that approximately 10% of patients developed pleural effusions[32]. Although SARS-CoV-2 virus has been isolated in pleural fluid [33], in most cases effusions are expression of comorbidities such as heart failure, and have been shown to be associated with increased risk of COVID-19 severity and mortality. To date there is no convincing evidence of ‘viral empyema’ as a direct complication of severe COVID-19 pneumonia.

Viruses are rarely considered as a potential etiological factor of pleural infection. A spike in cases of secondary bacterial pneumonia with empyema was well documented following the 1918 Spanish influenza epidemic and more recently in
Utah following the 2009 influenza A pandemic[34]. The potential role of viruses in the epidemiology of pleural infection was recently explored by Arnold et al[3]. Overall, pleural infection diagnoses increased by 25% in the winter months and in 9 of the 10 years studied, the highest annual point incidence of influenza coincided with the highest admission rate for empyema (with a 2-week lag), with an approximately 1.8x increase in admissions noted. These data suggest that there may be a seasonal variation in pleural infection incidence and a temporal association with influenza. However, a direct causative role of viruses in the pathogenesis of pleural infections has yet to be clearly established and we conclude that shared risk factors for both diseases may, at least in part, explain their concomitant onset.
**Question 2: In adults with pleural infection, what is the optimal antibiotic strategy?**

Extensive and inappropriate use of antibiotics has been associated with increased mortality and duration of hospitalisation [35], resulting in the emergence of antibiotic resistant pathogens, a severe public health threat [36]. Focused and narrower spectrum antibiotics are difficult to achieve in pleural infection due to the poor yield of pleural fluid cultures using the current "gold standard" (culture-based pathogen detection methods). In a recent systematic review of over 10,000 patients, the yield from standard culture was only 56% [37]. This is likely due to a combination of prior receipt of antimicrobials, low bacterial concentration in pleural fluid and nutritionally fastidious microorganisms that are difficult to isolate due to stringent requirements[38, 39].

An overview of the bacteriology and methods of optimising the microbiological yield in pleural infection are presented in the online supplement.

**Antibiotics and the pleura**

In pharmacokinetic studies the penetration of antibiotics into the pleura is expressed by calculating the ratio between the area under the curve (AUC) for concentration of a given antibiotic in the pleural fluid to that in the serum (AUC\(_{PF/S}\)) [40]. In a rabbit model of empyema, penicillin had the highest AUC\(_{PF/S}\) (2.31) followed by metronidazole (0.98), ceftriaxone and clindamycin. Gentamicin had the lowest AUC\(_{PF/S}\) in this study [40] and, therefore, due to low pleural penetration and tendency of aminoglycosides to be inactivated in the acidic medium of the infected pleural space[41] this group is not recommended for managing pleural infections [12].

In a study of humans with parapneumonic effusions, ceftriaxone concentration remained above the minimum inhibitory concentration for most susceptible organisms for 53 hours after a single parenteral dose [42]. In patients with methicillin resistant *Staphylococcus aureus* (MRSA) mediastinitis receiving linezolid, the drug had an AUC\(_{PF/S}\) of 1.64 [43], suggesting it is likely to be a suitable option in resistant pleural infection. One study evaluating the pharmacokinetics of carbapenems in pleural fluid demonstrated the most favourable results for the use of meropenem[44]. In both rabbit [45] and human [46] studies, moxifloxacin has also demonstrated favourable pleural penetration as an oral treatment option[45].

In patients with fungal pleural infection, non-liposomal formulations of antifungal therapy are preferred to liposomal due to their superior pleural penetration [47, 48].
Antibiotic regimens for pleural infection

The initial antibiotic regimen for pleural infection is almost always empirical because of the importance of prompt initiation of antimicrobial therapy. In usual practice, complete microbiological workup is carried out at the earliest opportunity to ensure the treatment is appropriate and to allow narrowing of the spectrum once the results of culture and antibiogram become available. It is noteworthy that even in situations where an anaerobic organism is not identified on microbiological tests, it is still recommended to continue anaerobic coverage given the difficulty in culturing these organisms that commonly infect the pleural space [49].

The choice of the regimen is usually based on whether the infection is community- or hospital-acquired, together with the local prevalence of microorganisms and antibiotic resistance patterns [12]. Individual factors to be taken in consideration include age, comorbidities, previous hospitalization and/or antibiotic treatments. Pleural infection by antibiotic-resistant pathogens is relatively common and, in a study, 37% of isolates in community-acquired infections and 77% of isolates in hospital-acquired infections were resistant to at least one of the antibiotics commonly prescribed for respiratory infections [50].

An example antibiotic protocol is presented in the online supplement (table S3).

Difficult to treat infections/special situations

Factors associated with bacterial resistance include the presence of chronic kidney disease, DM, malignancy and recent antibiotic therapy [51]. In a systematic review of 134 studies of unselected cohorts of adults with pleural infection, the incidence of immune compromising conditions was relatively low, with median prevalence of DM 17%, malignancy 12%, chronic kidney disease 7%, long-term steroid use 4%, and chemotherapy 4% [52]. However, patients with immune compromise (particularly with HIV disease) are at increased risk of developing parapneumonic effusions as a complication of pneumonia [53] and are prone to infections by unusual organisms. For example, patients with HIV have been reported to suffer from pleural infections by organisms such as Pneumocystis jirovecii [54] Nocardia spp [55] and Toxoplasma gondii [56].

Fungal aetiology of pleural infection is uncommon with an incidence ranging between 1.75% in community-acquired infections and 2.68% in hospital-acquired infections [11, 51, 57–60]. In up to 40% of instances where a fungus is isolated from pleural fluid, it represents contamination rather than true infection [61, 62]. However, in 708 pleural fluid positive cultures from patients with cancer, 18% grew fungi [63] hence this is not an insignificant clinical issue.

The most common species are Candida spp followed by Aspergillus spp [61, 63]. In series of patients with fungal empyema, 60–79% had immune compromising
conditions [61, 64]. Other risk factors for fungal empyema included recent thoracic or abdominal invasive procedures [63, 64]. Besides the challenges with treating these infections that require long courses of toxic antimicrobials, the 6-week mortality of fungal empyema in patients with cancer was as high as 34%[63]. Some infections that are endemic in certain geographic areas (e.g. parasitic infections[65] and melioidosis[66]) can cause pleural infections that are challenging to diagnose or treat, but detailed description of these conditions is outside the scope of this document.

The evidence from tuberculosis and recurrent bacterial pneumonia can be extrapolated and HIV screening is routinely performed in pleural infection. In current practice, pleural fluid fungal cultures are used in patients with known malignancy and immunocompromising conditions.

**Antibiotic duration and strategy**

The duration of antibiotic treatment in pleural infection has not been specifically assessed in adequately powered RCTs. The complexity is due to a heterogeneity of factors potentially influencing a favourable outcome including drug penetration into the pleural space, host immune response, infection setting, and microbial sensitivity to antibiotics. Treatment strategies are generally extrapolated from lung abscess, with a general consensus of at least 3 weeks, based on clinical, biochemical and radiological response[12, 67].

One recent study, the ODAPE trial, was a non-inferiority double-blind RCT assessing a 2-week vs 3-week antibiotic strategy[68]. The study was underpowered as it had to terminate early due to under-recruitment but showed excellent success rates in the small group (n=25) treated with a 2-week course, provided successful drainage and clinical stability had been achieved. This preliminary data is encouraging and sets the scene for further large prospective studies specifically targeting a pleural infection population.

An initial intravenous course of antibiotics of 5-7 days is usually administered to dampen the initial systemic inflammatory response and while no studies have specifically addressed this in pleural infection, extending the initial intravenous component would not appear to confer additional benefit extrapolating from evidence in other deep seated infections[69, 70].

Patients who have been surgically treated for pleural infection may require shorter post-operative courses but antibiotic resistance remains an important consideration[71]. Even within this cohort specifically, some potentially multidrug-resistant pathogens, such as *Enterobacteriaceae* or MRSA have been associated with increased risk of mortality and prolonged hospital stay[72]. Conversely, some pleural infection microorganisms such as *Streptococcus pneumoniae* do not tend to
partake in pleural ‘co-infection’; therefore, where these are isolated, they are likely to be the dominant pathogen and it may be reasonable to narrow the antibiotic spectrum by e.g., stopping metronidazole, potentially also improving tolerance and compliance. In practice, longer antibiotic courses are used for nosocomial infections or infections occurring post-surgical interventions, although we would emphasise that there are specific situations, such as a post-pneumonectomy infected space, where the data suggests that these should not be treated as standard empyema and where earlier thoracic surgery intervention may be required [73, 74].

Monitoring treatment response

The ATS/IDSA 2007 criteria for clinical stability of community-acquired pneumonia have demonstrated good performance in guiding clinical decision-making around switching to oral therapy, discharge or re-evaluation of patients at risk of treatment failure [75]. A substantial proportion of pleural infections are parapneumonic in aetiology, hence these criteria, despite not being specifically validated for pleural infection, can be extrapolated from pneumonia. It is important to note that many cases of pleural infection present sub-acutely without ‘sepsis’ features and in up to a third, without evidence of parenchymal infection [14]. In such cases, assessing treatment response can be more complicated, placing greater weight on radiological assessment of pleural drainage and biochemical response.

Based on the evidence to date, the C-reactive protein (CRP) appears to be sufficient as a biochemical marker of treatment response, particularly due to its cheap cost and availability [76]. The use of procalcitonin (PCT) in monitoring treatment response has been addressed in a small comparative surgical study (n=22) to evaluate the postoperative course in pleural infection [77] and in another small single centre medical study (n=53), both demonstrating favourable performance compared to CRP [78]. However, further prospective trials with larger study groups are required to clarify a role for PCT in monitoring pleural infection progress. Although radiological improvement is often considered to evaluate response to treatment, complete resolution of pleural abnormalities on imaging (chest radiograph/CT) is often delayed compared to clinical response.

In current practice, inpatient treatment and early response are guided predominantly by clinical and biochemical parameters with suggested follow up timepoints at 2-4 weeks to detect early treatment failure and 8-12 weeks to ensure complete resolution of the radiology.
Question 3: In adults with pleural infection, what are the optimal diagnostic parameters predicting need for chest tube drainage?

Can we refine the diagnostic approach to pleural infection?

Pleural fluid analysis is vital to achieving the correct diagnosis and guiding the appropriate subsequent intervention. In the presence of a clinical history or biochemical picture compatible with infection, current guidelines [13, 79] recommend using a pleural fluid pH<7.2 [or in the absence of pH, a combination of glucose concentration <40 mg/dL (2.2 mmol/L) with a lactate dehydrogenase [LDH] >1000 IU/L[80] as the most important predictors of chest tube drainage. The same groups agree that the presence of pus and/or microorganisms on Gram stain or culture should necessitate chest tube drainage.

Several factors can affect both biochemical and cytological features of pleural fluid. The residual syringe volume of lidocaine or heparin can falsely lower the pH, whilst the presence of air in the syringe or pleural fluid protease-producing organisms can lead to a false elevation in pH [81]. While most cytological examinations of pleural infection fluid will show ‘acute inflammation’ with neutrophilic predominance, it should be noted that early antibiotic administration can convert pleural fluid characteristics into a lymphocyte predominant picture [82].

A binary ‘pH’ biomarker in a condition that represents a progression along a spectrum lends itself to flaws. To this end, other markers have been assessed in terms of their ability to discriminate a complicated parapneumonic pleural effusion (CPPE) requiring urgent tube drainage from an uncomplicated (simple) parapneumonic pleural effusion (UPPE) often responding to antimicrobial treatment alone.

Serum CRP (sCRP)>200mg/L had low sensitivity (58%) and specificity (81%), however, the combination of sCRP with pleural fluid analysis increased the diagnostic yield, resulting in specificity as high as 98% for sCRP>200 mg/L and pleural fluid glucose<60 mg/dL (<3.3mmol/L) [83]. A recent narrative review of serum PCT (sPCT) in pleural infection found sPCT sensitivity and specificity for diagnosing pleural infection ranged from 69-83% and from 80-94%, respectively. The authors concluded that the current evidence does not support the routine use of serum PCT for the diagnosis or as a predicting factor for drainage in pleural infection[84].

With regards to additional PF testing, pleural fluid CRP level >100 mg/L was found to have the same performance characteristics (AUC=0.81) in differentiation between a CPPE and UPPE as the widely accepted biochemical parameters, including pH and glucose [85]. Combinations of pleural fluid CRP with pH or glucose resulted in further increase in discriminative value, with 75-80% sensitivity and 97% specificity for CPPEs. Pleural fluid PCT (pf-PCT) has not been shown to have a significant
diagnostic role in differentiation between infectious vs non-infectious pleural effusion and to date, there have been no studies on the role of PCT in discrimination between CPPE and UPPE[84].

Based on the evidence, in a clinical context suggestive of infection, the authors would perform urgent pleural fluid sampling of a unilateral effusion to confirm/exclude a diagnosis of pleural infection. Pleural fluid pH remains the most accurate predictor for chest tube drainage. The current evidence does not show utility for the routine use of sPCT.

Imaging

Pleural US is a widely available and easy-to-use diagnostic method. Important features include the presence of echogenic swirling (often signifying strong exudate or pus) and fibrin strands seen as septations or fully enclosed loculations[86]. Robust prospective comparative studies were not identified in the literature but a recent study comparing chest radiograph, CT and US appeared to demonstrate the latter to outperform the discriminative yield of CT in ruling in CPPE. US had a sensitivity and specificity of 69.2% and 90% respectively, compared to chest CT sensitivity of 76.9% and specificity of 65% [87]. The positive likelihood ratio of US to diagnose CPPE was significantly higher than those for CT and chest radiograph (6.92, 2.20 and 1.54 respectively; p<0.05) [87]. It should be noted that the presence of septations should warn about possible differences in pH between different fluid locules which may affect management decisions.

The classic CT signs regarded to be typical for CPPE/empyema include thickening and enhancement of the parietal pleura, increase in the thickness and attenuation of the adjacent extrapleural fat, and enhancement of both the visceral and parietal pleura (‘split pleura sign’), presence of multiple bubbles in the effusion (signifying anaerobic ‘gas producing’ bacteria), and pleural septations. These signs have good sensitivity, but low specificity [88]. A CT scoring model designed to distinguish CPPE and UPPE was generated and validated in a retrospective series, with a sum score of ≥4 yielding 84% sensitivity, 75% specificity, 81% diagnostic accuracy, and an AUC of 0.83 for labelling CPPE [89]. An easier method to differentiate between CPPE and UPPE based on the presence of the split pleura sign combined with a distance between both pleural layers (occupied by pleural fluid) ≥30 mm has been proposed and was characterized by a reasonable diagnostic accuracy (AUC 0.80) [90].

To date, the literature does not define a role for Magnetic Resonance Imaging (MRI) in adult pleural infection, although its role as a radiation-free non-invasive imaging modality is being explored in paediatric pleural infection, where further cross-sectional imaging is specifically required [91, 92]. Of note, most of the aforementioned CT features have MRI correlates, such as the increased extrapleural fat attenuation which may be seen as increased signal on fat suppressed T2
weighted (T2W) images. Infectious pleural effusions have a typical fluid appearance of low signal on T1W and high signal on T2W images. MRI outperforms CT in visualisation of septations [93].

The authors conclude that US is adequate for initial assessment, clinical decision making and guiding diagnostic sampling. Based on the current evidence, the TF members would adopt a lower threshold for pleural drainage in the presence of septations, echogenicity and larger pleural collections. In current practice, where pleural sepsis persists beyond the initial 48h of drainage, evaluation with a contrast-enhanced CT scan (in the venous “pleural” phase) can be helpful in revealing malpositioned chest tubes, lung abscesses, adjacent subdiaphragmatic abscesses and bronchopleural fistulas.

Distinguishing pleural infection from an inflammatory malignant pleural effusion

Pleural infection in patients with malignant pleural effusion (MPE) is of particular importance since a significant proportion of these patients are immunocompromised (due to malignant disease, chemo- and/or radiation therapy) and are exposed to repeated pleural interventions. The diagnosis of pleural infection in MPE patients may be challenging due to the non-specific results of pleural fluid analysis (e.g., low pH and low glucose can be attributed to both pleural malignancy and pleural infection). The data on pleural infection superimposed on MPE is scarce and somewhat ambiguous, largely due to the low yield of pleural fluid culture, the pre-test probability of pleural infection at time of sampling patients with MPE and the size of the effect of iterative thoracenteses in increasing the risk of pleural infection [94].

The inflammation associated with MPE can raise commonly used biomarkers including LDH, CRP, and adenosine deaminase, but to date, no biomarker was studied for the specific application of diagnosing infected MPE. In one study, PCT was found to be a relatively specific marker distinguishing between pleural infection and non-infective pleural effusions matched for systemic inflammation as measured by CRP. In contrast to CRP, PCT remained stable even in the presence of intense non-infective inflammation caused by talc pleurodesis [95].

Diagnosis of pleural infection in patients with MPE can be complex. In practice, a lower threshold for antimicrobial initiation is used followed by close observation. In this specific scenario, the authors feel sPCT may have some utility but acknowledge that this is based on low level evidence.

Chest tube size

‘Small bore’ chest drains are usually defined as <14F [96, 97] or <16F [98], albeit the definition varies across studies and is therefore somewhat equivocal. In this document, small-bore drains are defined as ≤14F and large-bore chest drains are
defined as ≥18F. Traditionally, large-bore chest drains have been used to drain pus or viscous fluid. A retrospective analysis of the MIST-1 RCT (n=405) [21] is the only direct comparison study of chest tube size in pleural infection [99]. Patients treated with a range of chest drain sizes (from <10F to >20F) showed no difference in primary and secondary outcomes (death, need for thoracic surgery, LOS, chest radiograph appearance and lung function at 3 months) according to chest drain size. Moreover, large-bore chest drains were associated with more pain [99]. This data therefore shows that small-bore chest drains are sufficient as a first line intervention for pleural infection. There is concern that smaller bore chest drains tend to become occluded with fibrin or pus. In the MIST-1 trial, chest tube patency was maintained with three-times-daily 30ml saline flushes. One retrospective study reported that only 1/58 drains flushed with 20ml sterile saline every 6 hours became blocked (vs 6/19 non-flushed drains) [96]. Care is usually taken to ensure that all the fenestrations on the chest drain are located intrapleurally to work effectively and minimise risk of infected fluid leakage into subcutaneous tissue.

There is sufficient evidence that 12-14F chest tubes are efficient as a first line intervention in pleural infection, with regular saline flushes. In their practice, the TF members prioritise correct placement using radiological guidance (US or CT) targeting the largest locule where these are present with securement/fixation sutures and bespoke dressings. Chest drains <12F are usually avoided to minimise risk of blockage and dislodgement.

Do all cases need draining? The evidence for conservative approach and alternative/less invasive strategies

Small parapneumonic effusions that are <5 cm on an erect lateral chest X-ray [100] or <2.5 cm on CT scan [101] can be managed without thoracentesis, although where diagnostic sampling is feasible this may be helpful to confirm diagnosis and microbiology. A recent retrospective study confirmed that some patients with small pleural collections can be managed successfully with antibiotics alone with slightly higher but statistically insignificant infection-related mortality rate [102]. This suggests that for very small or difficult to access pleural infection collections, it may be possible in selected patients to treat with antibiotics treatment alone without drainage of fluid, although we recommend caution with regular review.

Ambulatory management / Iterative thoracenteses

In some centres, iterative or repeated therapeutic thoracenteses are used as standard first line treatment [102]. Four case series of patients with CPPE or empyema who underwent iterative thoracocenteses were summatively analysed (n=250) [103–106] in a review of minimally invasive management of pleural infection,
and a 76% successful treatment rate was reported with repeated thoracocentesis [107]. The advantages proposed by advocates of this technique are that the patients are more mobile than they would be with a chest drain *in situ*, different locules may be targeted at each aspiration procedure, and that there is a possibility of outpatient management reducing hospital stay and cost [105]. One recently published retrospective comparative study of two successive cohorts of patients with CPPE or pleural empyema in whom repeated thoracentesis with intrapleural urokinase (n=52) vs. intrapleural urokinase plus DNase (n=81) was applied as the first line treatment, showed a failure rate of 17% and 19% respectively [108]. It would seem a reasonable option for lower risk patients without evidence of systemic sepsis and small-moderate volume effusions; however, to date there is no RCT data to support this as a first line option and it is currently not recommended by any guidelines [13, 79]. Importantly, the associated healthcare resource utilisation and the potential increased risk of repeated procedure-related complications have not been adequately studied.

### Indwelling pleural catheters and pleural infection

In the context of pleural infection, indwelling pleural catheters (IPCs) are relevant in two ways; firstly catheter-related pleural infection as a complication of IPC insertion, and secondly IPCs as a therapeutic option for the outpatient management of chronic pleural infection, especially with trapped lung.

In a recent Modified Delphi Consensus Statement on the management of IPCs, two types of infectious complications were defined: local IPC-related infections (including catheter associated cellulitis, exit site infection, tunnel tract infection) and IPC-related pleural space infection [109, 110].

In a large multicentre retrospective review of 1,021 patients treated with IPC, pleural space infections specifically, developed in 50 (4.9%) patients with an overall mortality risk of 0.3% [111], significantly lower than standard pleural infection. In another large multicentre series (n=1318), Wilshire et al recently found a similar infection rate (6-7%) but importantly also showed that the risk of IPC-related infection did not appear to be increased by antineoplastic therapy use or an immunocompromised state. In multivariable competing risk analyses they found longer IPC *in-situ* duration to be associated with a higher risk of infection [112].

IPC-related infections generally tend to occur around 6 weeks post insertion [111, 112], which goes against them being directly procedure-related, however studies investigating the mechanisms leading to pleural space infections in this group are lacking [113]. They are most frequently reported in association with *Staphylococcus aureus* organisms, followed by *Pseudomonas aeruginosa* but to date, there are no studies specifically evaluating the bacteriology and significance of bacterial colonisation in this cohort [52].
Most patients can be successfully treated with oral antibiotics (3-4 weeks) and attaching the catheter to an underwater seal drainage bottle for continuous drainage, without need for IPC removal or replacement[109, 111]. Although this condition rarely requires surgical intervention [114], early discussion with thoracic surgical teams is usually conducted if the patient is receiving systemic chemotherapy. An additional chest drain and surgical intervention is sometimes considered especially if there is evidence of undrained collections contributing to systemic sepsis [54]. Longer antibiotic courses are frequently required and intrapleural enzyme therapy (IET) via the IPC is another therapeutic option for patients who are not surgical candidates [109, 110].

Recurrent or chronic pleural infection creates difficult management issues, especially in those with trapped lung and where there is no surgical option. Small studies and case series have shown IPC’s to be a potentially useful treatment strategy for achieving longer term sepsis control in those candidates who are not fit for surgery or those who decline it [115, 116].
Question 4: In adults with pleural infection, what is the role of intrapleural therapy?

Is there a role for fibrinolytic monotherapy?

Prior to 2011, there was no alternative to fibrinolytic monotherapy as medical treatment for non-draining empyema. The MIST-1 study, to date the largest multicentre RCT in pleural infection, showed that streptokinase resulted in no improvement in outcomes to patients who fail standard care[117]. Looking at other trials of monotherapy, a recent prospective RCT by Alemán et al comparing tissue plasminogen activator (tPA, alteplase) versus urokinase found no difference in the mortality rate, surgical referral rate, or a composite of both[118].

In 2019, a Cochrane review of RCTs of fibrinolytic monotherapy, concluded that monotherapy may be associated with a reduction in the requirement for surgical intervention and overall treatment failure but importantly there was considerable heterogeneity between the studies reviewed and only MIST-1 had an overall low risk of bias[119]. The meta-analysis confirmed no evidence of change in mortality compared with placebo (OR1.24 [95%CI 0.74–2.07]).

There is no evidence-based role for fibrinolytic or deoxyribonuclease (DNase) monotherapy in adult pleural infection.

Effect of fibrinolytics on clinical outcomes?

The landmark MIST-2 RCT demonstrated that the combination of tPA with DNase (henceforth referred to as IET) led to improvements in radiographic clearance (primary outcome) and statistically significant reductions in surgical referral (77%) and LOS (6.7 days) compared to placebo (secondary outcome) [6].

We examined ten studies following MIST-2 (between 2011 to 2020) that also evaluated the role of IET on surgery and LOS (table 4.1). We could not identify other directly comparative RCTs of IET vs placebo but the 2 largest series by Piccolo and Popowicz reported a requirement for surgical intervention of 7.7% and 4.9% with combination therapy, in contrast with 15% of patients from the placebo groups in MIST-1 and MIST-2 trials. No studies to date have shown a mortality benefit.

What is the optimal IET strategy?

In the MIST-2 study, patients were randomly assigned to IET (or one of the other arms) immediately after chest tube insertion. The relatively small number of patients in the IET arm of MIST-2 meant that aspects such as safety and adverse events
were not adequately evaluated and hence overall, IET was not justified in being immediately incorporated into ‘standard care’ for all patients based on MIST-2 data alone. However, since then multiple non-comparative studies have confirmed IET to be safe and effective (online supplement S4).

Based on the placebo controlled randomised study and subsequent case series, IET is considered by most TF members as ‘rescue’ therapy i.e., after failing to respond to a period of initial antibiotics and chest tube drainage, as judged by clinical (ongoing fever, tachycardia), biochemical (failure of CRP to fall by >50%) and radiological (persistent effusion on chest radiograph or ultrasound) parameters.

There is good evidence that treatment delays are associated with worse outcomes. On this basis, most TF members would initiate IET within 48 hours of standard care (chest tube drainage and antibiotics), as a potentially surgery-sparing modality if there is ongoing evidence of treatment failure. In the absence of head-to-head superiority data, a surgical referral is usually considered in parallel to IET commencement.

IET dosing and schedule

In most studies of IET (table 4.2), the dosing that has been used is tPA 10mg and DNase 5mg, based on the MIST-2 trial. It should be noted that this was chosen empirically by the MIST-2 investigators and was not the result of dose-finding studies. Lower dosing regimens of tPA (5mg and 2.5mg) have been investigated in small observational series (without comparator data) with similar safety and efficacy[120, 121], with 12% (tPA 5mg) and 24% (tPA 2.5mg) of these study populations ultimately requiring dose escalation [120].

It is noteworthy that any cost benefit of lower dosing is dependent on vial size manufacturer supply (varies by country) as the tPA summary of product characteristics (SPC) suggest that the reconstituted solution is for single use only and from an infection control perspective, should be used immediately after reconstitution.

Most studies using IET administer agents twice daily [6, 122] for a maximum of 3 days (total of 6 doses of both medications) as per the MIST-2 regime. Case series data have shown that once daily administration and extended dosing regimens may be suitable alternatives in terms of efficacy and safety, respectively, although comparative trials are needed [123–125].

The authors conclude that optimal IET dosing and schedule has not yet been rigorously studied. Until dose-ranging studies occur, being the only dose and schedule tested in a double-blinded RCT setting, the regimen with the highest-level evidence for efficacy is 10mg tPA and DNase 5mg intrapleurally twice a day for 6 doses [6].
Preparation and administration regimen

Sequential administration of IET was used in the MIST-2 study based on the tPA SPC suggesting that mixing of this solution with other drugs (such as DNase) could lead to adverse structural and/or functional changes in tPA or the admixed compound. This suggests that sequential administration of tPA and DNase is safer pharmacologically than concurrently. However, it is unknown whether concurrent intrapleural administration of tPA and DNase affects the pharmacokinetics of either drug. There are data showing that concurrent and sequential administration may be equally safe and effective [126]. In practice, concurrent dosing also decreases the amount of cumulative time that the chest tube remains clamped and reduces the frequency needed to access the chest tube. These changes may result in improved provider compliance and reduced risk of iatrogenic infection.

In current practice, concurrent administration is preferred due to convenience and decreased risk of iatrogenic infection, but the evidence does not favour one over the other.

A suggested protocol for IET preparation, administration and monitoring is included in the online supplement (S4.1)

IET safety and adverse events

The MIST-2 study recruited 52 participants in the tPA/DNase combination arm and reported 2 bleeding events (3.8%) [6]. Subsequently, a number of smaller studies have reported rates of pleural bleeding with intrapleural administration of tPA (with or without DNase) in the context of pleural infection of between 1.8 and 12% [118, 122, 124–128]. Other than the heterogeneity between these studies, the key limitation was the small study populations and therefore low event rates.

Bleeding risk and complications were specifically evaluated recently in the largest series of IET in pleural infection (>1800 patients) [129]. Overall bleeding rate was 4.1% and in the 172 patients who received a lower dose tPA regimen (median 5mg), the bleeding rate was not significantly reduced. Moreover, in a multivariate regression analysis, their data showed that the use of concurrent systemic anticoagulation, increasing RAPID score, elevated urea and platelets <100x10^9 were associated with a significant increase in bleeding risk [129]. Hold systemic treatment-dose anticoagulation prior to commencing IET for up to 48 hours (or maintaining INR<2 in case of warfarin) was shown to mitigate the additional bleeding risk.

In patients with a perceived higher than average risk of bleeding (for whom surgical intervention for pleural infection is not an option), most TF members would
commence with a reduced dose of tPA (5mg) and escalate according to response. In cases where it may be unsafe to withhold anticoagulation (e.g. recent pulmonary embolism), TF members may opt to use split dose LMWH alongside IET but appreciate that these cases are complex and require careful, multidisciplinary consideration.

The commonest side effect with IET is pain requiring escalation of analgesia, in up to 36% (table S4.1), particularly following the first dose, hence most TF members ensure premedication with analgesia to improve compliance.

A summary of other studies reporting data on IET-related side effects, complications and mortality is summarised in table S4.2a. Suggested contraindications to IET use are presented in table S4.2b.

**Intrapleural saline irrigation**

If fibrinolytics are contraindicated, pleural saline irrigation has been shown to be a potentially useful therapeutic option. In 2015, Hooper et al. conducted the first RCT of pleural irrigation with normal saline versus standard care alone in patients with pleural infection. The administration regimen consisted of a 250 ml bottle of 0.9% sodium chloride erected from a drip stand and run through a giving set connected to the chest tube, into the pleural space. The tube was then clamped for an hour before being open to free drainage. This was repeated 3 times a day for a total of nine irrigations and demonstrated a superior resolution of CT pleural fluid volume (primary outcome) over the course of the treatment compared to standard care alone, as well as a reduction in surgical referrals (secondary outcome) [130]. It is noteworthy that the 50% surgical requirement in the control group is very high compared to other RCTs, and this was an unblinded study. Two retrospective studies [131, 132] have also demonstrated that intrapleural saline irrigation may be useful in the management of pleural infection but further studies are required in larger multicentre RCT settings.

*Until larger multicentre RCTs consolidate the evidence base, currently most TF members would consider saline irrigation in pleural infection on a case-by-case basis where there are strong contraindications to IET (e.g., therapeutic anticoagulation which cannot be stopped), and where surgery is not a viable option.*

**Intrapleural antibiotics**

Direct administration of antibiotics may have the theoretical advantage of reducing systemic side effects and antibiotic resistance. However, the efficacy of intrapleural treatment may be hampered by non-uniform distribution across often septated or multiloculated pleural spaces (in comparison with parenteral administration). Existing
guidelines therefore either take an equivocal position [133] or recommend against[12, 134] the use of intrapleural antibiotics in acute pleural infection due to the lack of evidence for their efficacy.

In current practice, intrapleural antibiotics are reserved for managing post lung resection pleural infections which often require prolonged courses of parenteral antibiotics [135–137]. An antibiotic-eluting chest tube has been trialled in a rabbit model and was shown to allow steady release of antibiotics for up to 14 days [138, 139]. Safety and efficacy of such technology is yet to be proven in human studies.

There is currently no evidence for the role for intrapleural antibiotics in the routine management of pleural infection outside specific surgical scenarios.
**Question 5: In adults with pleural infection, what is the role of surgery and other interventions?**

**Role of surgery and choice of approach**

Improvements in medical therapy have reduced the requirement for surgical management of pleural infection; however, a significant minority (15-20%) of patients continue to require surgical intervention where sepsis and residual collection persist [6, 7], or the patient presents with late stage disease [6, 133]. In the absence of prospective, comparative studies directly addressing the question, the role of empyema stage (table S6) in predicting success or failure of image-guided drain placement remains unclear [13]. An additional complicating factor, and the cause of some heterogeneity in the reported literature, is that in clinical practice, empyema staging is continuum of pathology with patients rarely presenting with ‘pure’ stage II pleural infection, but rather a ‘mixed stage’ with areas of fibrin organisation on the pleural surface.

The principles of surgery are drainage, deloculation, debridement and obliteration of the pleural space, ideally by decortication. In the era of VATS, surgeons have developed the required skills to achieve these principles via minimal access surgery and its role in empyema is now well established. Two small, randomised studies demonstrated superior outcomes when VATS was compared to chest tube with or without fibrinolytics in organised empyema [140, 141]. Case series have shown VATS success rates of 82—92% [142, 143]. A best evidence review demonstrated that VATS was equivalent to thoracotomy in terms of resolution, and superior in terms of reduced LOS, where most studies included mixed and late-stage disease [144]. More recently, international guidelines have moved to supporting a more pragmatic approach of considering VATS in most cases [13, 79, 145].

Reduction in morbidity, arguably as important to patients as disease resolution, is superior with VATS compared to open surgery [146]. Reduced operative time [147–150], LOS [142, 147–153], pain [142, 149, 150], air leak [148, 150], duration of tube drainage [154] are more favourable with VATS. Greater satisfaction [12] and earlier return to work [150] have also been reported.

These studies are supported by the largest patient cohort available to date in the Society of Thoracic Surgeons (STS) General Thoracic Surgery Database review of over 7300 patients undergoing decortication. The STS reported a statistically significant difference in mortality between open surgery (3.7%) and VATS (2.8%), with thoracotomy also associated with increased morbidity, discharge to care other than home, and prolonged LOS [146].

In 4,435 patients who underwent a VATS approach there was a 14.2% (95%CI 13.2%-15.3%) conversion rate to open thoracotomy. Conversion rates are stage
related with higher conversion rates seen in stage III disease [146, 147, 151]. Other risk factors for conversion include delayed surgical referral over two weeks, thickness of pleura and a Gram–negative causative organism [155].

Stage III empyema was previously an indication for proceeding directly to open surgery; however, is now regarded as a predictor of risk for conversion, rather than a contraindication to VATS. Early referral to the thoracic surgical team is therefore recommended to facilitate likelihood of proceeding to VATS without requirement for conversion, to confer its attendant benefits [155]. Several authors have stated that the time to referral is the commonest independent factor influencing need for conversion [151, 156]. Moreover, improved overall outcomes have been demonstrated when surgery is undertaken within four weeks from onset of symptoms, where early surgery resulted in decreased post-operative LOS, reduced operative time and fewer prolonged air leaks [154]. In the STS database data, adverse outcomes in terms of readmission, major morbidity, prolonged LOS, and discharge to transitional care were all higher when preoperative hospitalization extended beyond 5 days [146]. In the largest randomised study of pleural infection to date the median duration of symptoms prior to presentation was 2 weeks [21].

*The evidence to date demonstrates the potential for improved outcomes with surgical referral and discussion being initiated as early as possible, with the aim of surgery (if required) occurring within 10 days of medical presentation. In their current practice, most TF members would consider surgical referral at day 3 post initial chest tube if ongoing sepsis, radiological persistence and/or clinical deterioration.*

Amongst the major determinants of surgical approach is the ability to successfully perform decortication where lung expansion is required for space obliteration. Decortication beyond space obliteration to facilitate improved lung function is of less certain benefit. There is evidence that decortication is associated with increased lung perfusion and spirometry, although function of the affected lung may not return to normal [157]. In a study of the added benefit of decortication over debridement, there was no difference in eventual cavity size [158]. Perioperative morbidity and mortality after decortication are significant, with reported 90-day mortality of 7.6% and postoperative morbidity of 35.7%, both significantly associated with increasing antibiotic resistance to the infecting organism(s) [71].

**Post-traumatic empyema**

Post-traumatic empyema is reported to occur in up to 25% of patients with retained haemothorax [159]. The Injury Severity Score (ISS) correlates with mortality, morbidity, and hospitalization time after trauma and has been widely adopted to assess chest wall trauma severity, with a score of >15 being defined as major trauma [160]. Risk factors for the development of post traumatic empyema include
the presence of rib fractures, ISS >25, lung contusion and the requirement for additional interventions to evacuate retained blood from the thorax [159, 161–163].

The use of prophylactic antibiotics promptly upon hospitalization for thoracic trauma significantly decreases the incidence of post-traumatic empyema [164]. Current trauma guidelines endorse the use of VATS drainage for the treatment of retained haemothorax and prevention of empyema [165]. Early VATS, within 5 days after trauma, results in complete resolution in 87% of cases (75%-100%), with a conversion to thoracotomy rate of 11% [166].

Whether medical management in the form of fibrinolytics or medical thoracoscopy has a role in retained traumatic haemothorax is yet to be determined. In a systematic review and meta-analysis of lytic therapy for retained traumatic haemothorax, avoidance of surgery following treatment with fibrinolytic agents was 87% (95%CI 81%-92%) [167]. Of note, however, the average LOS was 14.8 days (95%CI 12.8-16.8). In one non-randomised study, Oğuzkaya et al. found that VATS was associated with shorter hospital stay and reduced requirement for thoracotomy compared to intrapleural streptokinase [168]. Historical referral patterns encourage direct surgical intervention and whether avoidance of surgery has clinical and cost benefits in the setting of trauma is not known.

In current practice, surgical intervention remains first line management in patients with retained haemothorax and post-traumatic empyema, however, medical management including intrapleural fibrinolytics may be considered in patients at high operative risk.

**Medical thoracoscopy**

Medical thoracoscopy is well established in the management of pleural effusion, however, its role in pleural infection is less clearly defined. Advocates of medical thoracoscopy have demonstrated success rates of 79.3%-97.7% in multi-loculated organising empyema [169–172]. A recent meta-analysis of non-randomised studies reported a pooled treatment success rate of 85% when utilised as first-line therapy or after failure of chest tube, with a complication rate of 9% [147]. Higher success rates were associated with bacteriological negative effusions and administration of adjuvant intrapleural fibrinolysis [147]. A recent RCT of medical thoracoscopy versus intrapleural fibrinolytic therapy showed a shorter LOS post intervention associated with the thoracoscopy arm [173]. The small numbers within the trial and the limitations of the primary outcome require further studies to establish the true role of medical thoracoscopy in empyema. The SPIRIT feasibility randomised trial (ISRCTN98460319) demonstrated failure of feasibility of this approach in the context of UK thoracoscopy services.
In their practice, most TF members occasionally consider medical thoracoscopy as a treatment option in multi-loculated pleural infection in elderly and frail patients considered to be high surgical risk, where there is local expertise including sufficient access to local anaesthetic thoracoscopy, thoracic surgery and anaesthetic support.

Management of persistent pleural space and post-pneumonectomy empyema

The prognosis of empyema is generally good in young and fit patients where early treatment is instituted. Overall surgical mortality rates, however, remain high, reported to be between 0-10% [140–142, 174]. It is noteworthy that where aggressive intervention cannot be undertaken, mortality rates approach that of untreated empyema [175].

Drainage, deloculation, debridement and decortication will achieve space obliteration in most cases, a prerequisite for achieving resolution in closed empyema surgery [176]. The combination of insufficient diaphragmatic or mediastinal shift and incomplete lung expansion as markers of chronicity, or previous lung resection may contribute to a persistent space. Where a residual space is an issue, the use of muscle or omental flaps can provide space obliteration and heal small bronchopleural fistulae. In the nowadays rare scenario where muscle flaps are inadequate to facilitate space obliteration, or have been unsuccessful, interventions including open window thoracostomy (OWT) or thoracoplasty are considered [177].

OWT is occasionally utilised as part of staged management, or as a definitive measure, where previous intervention has failed or when patients are not fit for more major intervention, in the presence of chronic empyema and where broncho-pleural fistula (BPF) is present. Previous techniques have been described by Eloesser and Clagett [178, 179]. Mortality of thoracostomy in modern series is around 6% with success rates of up to 95% in patients with post-surgical and post-pneumonic aetiology, with and without BPF [180, 181].

The accelerated ‘iterative thoracotomy’ technique consists of repeated debridement and packing with povidoneiodine dressings under general anaesthesia every 48 hours [190]. BPF is closed where necessary using techniques described above. The chest cavity is obliterated with an antibiotic solution, and the thoracotomy definitively closed when macroscopically clean. The largest series evaluating this technique (n=75) found it to be safe and effective, reporting successful treatment in 97.3% of patients with 94.6% having a definitively closed chest within 8 days. Median hospitalisation time was 18 days, and 90-day mortality was 4%. [184]

Intrapleural vacuum assisted closure (VAC) wound therapy, which stimulates angiogenesis and fibroblasts to facilitate healing, is a more recent adjunct to OWT (OWT-VAC) that has the added advantage of achieving rapid source control and suction to aid lung re-expansion. This has been associated with reduced morbidity, hospital stay and total treatment times [182–184]. In their practice, the TF members would consider its use in patients with residual lung in situ and in post-
pneumonectomy patients, with and without BPF. Caution is recommended in the post-pneumonectomy and BPF patients where pain, hypotension and requirement for surgical removal of foam is described [185–187].

Mini-VAC therapy (without OWT) has been described to treat complex empyema with primary closure in patients both with and without BPF. In a small study of patients receiving mini-VAC therapy, all six patients [184] were discharged with a closed chest at a mean of 22+/-11 days without further recurrence and remaining integrity of the chest cavity [188]. The additional instillation of intra-pleural antiseptic fluid (Mini-VAC-Instill) was associated with a further reduction in treatment time and shorter LOS (15+/-4.8 days; p=0.027) [186].

Thoracoplasty facilitates space obliteration by excision of the upper ribs and can be combined with muscle flaps or omental transposition. Significant associated morbidity, including chronic pain, progressive scoliosis, and the resulting cosmetic appearance, limits first line use of thoracoplasty in the modern era. However, it continues to provide a useful solution in specific situations where flaps and OWT have failed [13]. Recent series report an operative mortality of around 5% with success rates of up to 90% [189].

Pleural infection after surgical resection is a specialist area which always requires involvement of surgical services from the point of diagnosis. Where empyema occurs following lung resection, it is usual practice that tube drainage is instigated, and bronchoscopy undertaken to confirm or refute BPF. In current practice, re-operation with closure of the fistula and space obliteration utilising tissue flaps is preferred in the early post-operative phase and in patients who remain fit for re-operation. In cases of late presentation, persistent BPF or patients unfit for further operation, most TF members would consider OWT +/- VAC as a favourable option.
Question 6: In adults with pleural infection, what is the role of risk stratification and outcome prediction?

Data from a large Danish cohort [191] found that delayed pleural drainage by more than 2 days from diagnosis was associated with both a worse 30-day and 90-day mortality. Delayed surgical referral has been shown to be associated with risk of conversion and worse outcomes, with each additional preoperative hospital day (up to 5 days) being associated with 1.2x increased risk of mortality per day [146]. The current practice of sequential progression of therapies from chest tube drainage to intrapleural therapies to consideration of surgical intervention, in a ‘one size fits all’ approach may be to the detriment of certain patients.

Whilst the evidence clearly does not justify upfront intrapleural and surgical therapies for all patients with pleural infection, one or both may eventually be necessary in at least a third of patients [6]. Despite advances in both these treatment modalities in the last decade, the lack of improvement in outcomes may lie in our inability to identify the patients who would benefit from them at an earlier stage in their disease.

Clinical predictors of poor outcome

The RAPID score was developed as the first prognostic risk model specifically for pleural infection [192]. Using 5 baseline parameters, the RAPID score could predict 3-month mortality. Since its publication, the RAPID score has undergone prospective external validation in the PILOT study [7] and has been assessed in a number of single centre, retrospective studies in the USA, New Zealand and Japan, which have all further validated its clinical applicability and association with mortality [193–196].

An overview of the RAPID score is provided in the online supplement.

Despite the PILOT study specifically excluding patients with an expected survival of less than 3 months due to pre-existing (non-pleural infection) comorbidity, a majority of deaths occurred within the first three months following diagnosis of pleural infection, as has been seen in previous studies [21, 197], suggesting that mortality is disease-specific and potentially amenable to improvement.

Whilst the RAPID score represents a major step forward in the ability to specifically prognosticate patients with pleural infection, it cannot yet direct clinical care or decision making. The main goal now should be to incorporate it into future prospective studies assessing the safety and efficacy of new treatment paradigms – perhaps using less invasive, ambulatory strategies in the low-risk RAPID population [107] and early invasive treatment such as surgery or IET in the high-risk groups. RAPID may also be used to inform clinicians’ discussions of the likely outcome from pleural infection at presentation and the balance of risk or benefit from any planned medical or surgical intervention.
The CCI has been shown to be a good predictor of outcome in 3 pleural infection cohorts [4, 9, 24]. Other clinical factors shown to be associated with adverse outcomes in pleural infection may also be helpful in overall prognostication and rationalisation of further intervention in individual cases. These include multimorbidity, malignancy, alcohol excess and cardiovascular disease, the latter having also been associated with prolonged LOS in the RAPID study. An important caveat here is that, in contrast to the RAPID criteria, the majority of these are derived from hospital episode statistics from administrative databases that are flawed by coding inaccuracies and thus represent a lower level of evidence.

The studies containing the largest patient cohorts and their main findings are summarised in table 6.1.

**Radiological biomarkers**

Radiological parameters predicting outcomes have been challenging to study in pleural infection, mostly because studies to date have been largely small, retrospective and have demonstrated that radiology tends to predict clinician behaviour rather than true outcome from pleural infection [198–200].

The presence of sonographic septations, or enclosed ‘loculations’, is often assumed to be associated with the need for more aggressive upfront drainage therapy such as intrapleural fibrinolytics or surgical drainage. However, the evidence linking this to worse outcomes in pleural infection is limited to small retrospective case series [199, 201]. To date, the largest pleural infection trials [6, 21] were conducted prior to the era of commonplace US and hence the RAPID model did not address these.

In a smaller retrospective study (n=145), aimed at developing a CT scoring system to predict parapneumonic effusions requiring drainage, Porcel et al identified that the presence of the ‘split pleura’ sign on CT or pleural fluid volume ≥500ml, were independent predictors of surgery and in-hospital mortality [89]. Bobbio et al additionally identified the CT evidence of a fistula (present in 31% of their large cohort) to be independently predictive of mortality (OR 2.09 99%CI 1.88-2.32) [4].

As IET in pleural infection becomes more routine, in their retrospective study (n=84) using statistical modelling and machine learning (not externally validated), Khemasuwan et al identified pleural thickening and abscess or necrotizing pneumonia as risk factors for IET failure in both models [202].

**Microbiology**

Culture-positive pleural infection has been proven to be associated with higher mortality [11], longer LOS and worse surgical outcomes [203]. Association between
bacterial pattern and 1-year survival was amongst the primary outcomes of the recent largest metagenomics analysis of pleural infection bacteriology [16]. The presence of anaerobes or bacteria of the *Streptococcus anginosus* group (*Strep anginosus, Strep intermedius, Strep constellatus*) was associated with better patient survival. The presence or dominance of *Staphylococcus aureus* was linked with lower survival, while dominance of *Enterobacteriaceae* was associated with higher risk of death perhaps due to being more resistant to antibiotic therapy. Given that *Staph aureus* was recently found to be the most common organism isolated regardless of study or setting with increasing prevalence of methicillin resistance [37], most TF members would opt for earlier escalation of therapy and vigilant follow up in this patient group.

**Novel biomarkers**

Recently, Arnold et al demonstrated that pleural fluid suPAR more accurately predicted the need for more invasive management compared to conventional biomarkers, as assessed by referral for intrapleural fibrinolytic therapy or thoracic surgery [204]. suPAR is the soluble form of uPAR (urokinase type plasminogen activator receptor), which, once bound to endogenous uPA (urokinase), catalyses the conversion of plasminogen to plasmin (a potent fibrinolytic). To make a firm statement about the clinical relevance of suPAR will require an external prospective validation cohort with predetermined criteria for intrapleural fibrinolytic therapy and/or surgery. However, this study adds credence to the role of baseline pleural fluid biomarkers of fibrinolytic activity, perhaps through regulation of the development of pleural loculation, in predicting clinically important outcomes.
Conclusions

Recent updated data on epidemiology of pleural infection continue to show an overall upwards trend in incidence. There is an urgent need for a more comprehensive characterization of burden and trends of pleural infection across Europe. Large microbiology studies have resulted in a clearer understanding of the pleural microbiome and the aetiopathogenesis of pleural infection, e.g., the abundance of anaerobes found in the oral cavity likely seeding through aspiration or haematogenously. Regular analysis and documentation of microbiological patterns at a local level should remain a priority. Beyond the pleural fluid pH, ongoing efforts are needed to refine the diagnostic approach. Simple parapneumonic effusions are poorly studied and shifting our focus downstream in the coming years is vital.

For those with an established diagnosis, an optimally placed chest tube with ongoing evidence of infection, there is now a plethora of evidence beyond the MIST-2 study IET is safe and effective. Surgery continues to hold a vital role in the management of pleural infection, outcomes from VATS are favourable and early referral should remain a priority.

To date, the RAPID score remains the only externally validated risk stratification model that has been shown to be predictive of outcomes in different pleural infection populations. The incorporation of this tool in future studies is suggested to define its utility in clinical practice.
Figures and tables

Figure 1.1 Trends in incidence of pleural infection in different countries from the world literature
Table 1.1 Prevalence of pre-existing comorbidities in patients with pleural empyema

<table>
<thead>
<tr>
<th>Pre-existing comorbidities</th>
<th>% Prevalence (interquartile range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any comorbidity</td>
<td>72 (58-83)</td>
</tr>
<tr>
<td>Specific disease</td>
<td></td>
</tr>
<tr>
<td><em>Hypertension</em></td>
<td>23 (17–38)</td>
</tr>
<tr>
<td><em>Diabetes</em></td>
<td>17 (11–27)</td>
</tr>
<tr>
<td><em>Stroke</em></td>
<td>13 (5–20)</td>
</tr>
<tr>
<td><em>Ischemic heart disease</em></td>
<td>11 (5–16)</td>
</tr>
<tr>
<td><em>Chronic obstructive pulmonary disease</em></td>
<td>11 (6–20)</td>
</tr>
<tr>
<td><em>Chronic kidney disease</em></td>
<td>7 (5–13)</td>
</tr>
</tbody>
</table>

*Adapted with permission from Cargill et al [8]*
<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Years</th>
<th>n</th>
<th>Age</th>
<th>Male</th>
<th>Mortality</th>
<th>LOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bobbio et al, 2021</td>
<td>France</td>
<td>2013-2017</td>
<td>25512</td>
<td>62.4±15.6</td>
<td>71.7%</td>
<td>17.1%</td>
<td>19 (IQR 11-35)</td>
</tr>
<tr>
<td>Arnold et al, 2020</td>
<td>UK</td>
<td>2008-2018</td>
<td>51057</td>
<td>64 (IQR 51-75)</td>
<td>68.5%</td>
<td></td>
<td>In-hospital 14.9%</td>
</tr>
<tr>
<td>Søegard et al, 2014</td>
<td>Denmark</td>
<td>1997-2011</td>
<td>6878</td>
<td>Non aggregated data</td>
<td>65.8%</td>
<td></td>
<td>30-day 10.5% in 1997 vs 9% in 2011</td>
</tr>
<tr>
<td>Mummadi et al, 2021</td>
<td>US</td>
<td>2007-2016</td>
<td>2735</td>
<td>Non aggregated data</td>
<td>68.0%</td>
<td></td>
<td>In-hospital 7.1%</td>
</tr>
<tr>
<td>Grupta et al, 2021</td>
<td>US</td>
<td>2005-2014</td>
<td>150496</td>
<td>58.3±0.1</td>
<td>67.9%</td>
<td></td>
<td>12.3 ± 0.1</td>
</tr>
<tr>
<td>Grijalva et al, 2011</td>
<td>US</td>
<td>1996-2008</td>
<td>157094</td>
<td>48.4 (95% CI 47.4-49.4)</td>
<td>64.2%</td>
<td></td>
<td>In-hospital 7.2%</td>
</tr>
<tr>
<td>Farjah et al, 2007</td>
<td>US</td>
<td>1987-2004</td>
<td>4424</td>
<td>57.0±18.6</td>
<td>66.8%</td>
<td></td>
<td>30-day 10.8%</td>
</tr>
<tr>
<td>Finley et al, 2008</td>
<td>Canada</td>
<td>1995-2003</td>
<td>11294</td>
<td>ND</td>
<td>69%</td>
<td>ND</td>
<td>21.8 ± 33.9</td>
</tr>
</tbody>
</table>
Table 4.1 Effects of IET on surgery and length of stay

<table>
<thead>
<tr>
<th>Author and country</th>
<th>Type of study</th>
<th>n</th>
<th>Dosage</th>
<th>Surgery, n (%)</th>
<th>Cause of surgical referral</th>
<th>Comments</th>
<th>LOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rahman et al, 2011. UK</td>
<td>RCT</td>
<td>48/210</td>
<td>10 mg tPA; 5 mg DNase</td>
<td>2/48 (4.2) vs placebo 8/51 (16.0)</td>
<td>Clinical evidence of worsening infection</td>
<td>Surgical referral at 3 months in the tPA-DNase group was lower than in the placebo group. A 6.7-day reduction in LOS was observed</td>
<td>11.8 ± 9.4 (mean±SD)</td>
</tr>
<tr>
<td>Piccolo et al, 2014. Australia, UK and New Zealand</td>
<td>P Obs</td>
<td>107</td>
<td>10 mg tPA; 5 mg DNase</td>
<td>8 (7.7)</td>
<td>Failure to respond to treatment with persistent clinical and laboratory evidence of active infection</td>
<td>The median time from first fibrinolytic dose to surgery was 3 days (IQR 3-4.75)</td>
<td>10 (IQR 6-17) From first intrapleural treatment</td>
</tr>
<tr>
<td>Popowicz et al, 2017. Australia, UK and New Zealand</td>
<td>P Obs</td>
<td>61</td>
<td>5 mg tPA; 5 mg DNase</td>
<td>3 (4.9)</td>
<td>Persistent infection in two patients. An open decortication of thick residual visceral pleural rind and resultant trapped lung</td>
<td>One underwent VATS, another a mini-thoracotomy and the third the thoracotomy</td>
<td>7 (IQR 5-10)</td>
</tr>
<tr>
<td>Bédat et al, 2019. Switzerland</td>
<td>P Obs</td>
<td>41/93</td>
<td>10 mg tPA; 5 mg DNase</td>
<td>4 (10)</td>
<td>Absence of clinical response to the initial fibrinolysis</td>
<td>Multiple pleural collections and large-bore drain could predict the need for an additional chest tube or surgery</td>
<td>18 (IQR 11-32)</td>
</tr>
<tr>
<td>Kheir et al, 2018. US and Chile</td>
<td>P Obs</td>
<td>38 (20 sequential and 18 concurrent)</td>
<td>10 mg tPA; 5 mg DNase (concurren t vs sequential)</td>
<td>4 (22) for sequential and 5 (25) for concurrent</td>
<td>Sequential: 2 persistently loculated effusion, 1 persistent sepsis and 1 lung entrapment. Concurrent: 2 no clinical improvement; 3 with persistent loculation</td>
<td>Surgery was performed after a median of 1.5 days (IQR 1-5) following the last dose and after 3 days (IQR 1.5-3.5) in the sequential and concurrent groups</td>
<td>13 (IQR 10-15) for sequential vs 12 (IQR 5-16) for concurrent</td>
</tr>
<tr>
<td>Jiang et al, 2020. US</td>
<td>R</td>
<td>56 (concurrent therapy)</td>
<td>10 mg tPA; 5 mg DNase</td>
<td>2 (3.6)</td>
<td>Treatment failure. VATS was carried out with success</td>
<td>There were two patients with refractory septic shock considered no candidates for VATS</td>
<td>15 (IQR 11-28)</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>n</td>
<td>Treatment</td>
<td>Duration</td>
<td>Outcome Description</td>
<td>Duration</td>
<td>Notes</td>
</tr>
<tr>
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<td>-------------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Khemasuw et al. 2018, US</td>
<td>R</td>
<td>84</td>
<td>10 mg tPA; 5 mg DNase (concurrent therapy)</td>
<td>27 (32.1)</td>
<td>Worsening sepsis regardless of radiographic abnormality in 6; ongoing infection and worsening follow-up chest CT scan in 19 and haemothorax in 2.</td>
<td>No</td>
<td>9 (IQR 6-12) From drain insertion</td>
</tr>
<tr>
<td>Majid, et al. 2016, US, UK and Chile</td>
<td>R</td>
<td>73</td>
<td>10 mg tPA; 5 mg DNase (concurrent)</td>
<td>7 (9.6)</td>
<td>No radiographic response</td>
<td>No</td>
<td>7 (IQR 5-11)</td>
</tr>
<tr>
<td>McClune, et al. 2016, US</td>
<td>R</td>
<td>101</td>
<td>10 mg tPA; 5 mg DNase. Six doses (&gt; 6 days vs standard use*)</td>
<td>3 (15) vs 13 (16)</td>
<td>ND</td>
<td>No</td>
<td>17 (IQR 9-25) vs 13 (IQR 9-19)</td>
</tr>
<tr>
<td>Metha et al. 2016, US</td>
<td>R</td>
<td>55</td>
<td>10 mg tPA; 5 mg DNase. Once daily (3 doses)</td>
<td>4 (7.3)</td>
<td>Persistent fluid collection and/or treatment failure with persistent sepsis in 2 and inability of the lung to fully re-expand in 2.</td>
<td>One of the four patients who underwent surgery died within 30 days of intrapleural tPA-DNase instillation</td>
<td>13 (IQR 11-18)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Type</th>
<th>C / NC</th>
<th>No. of pts. treated with active combination</th>
<th>Agents Used and Dosing</th>
<th>Total no. of Doses</th>
<th>Concurrent or Sequential?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rahman et al – 2011</td>
<td>Randomised</td>
<td>C</td>
<td>52 / 210</td>
<td>5mg DNase + 10mg t-PA b.d.</td>
<td>6 doses of each agent</td>
<td>Sequential</td>
</tr>
<tr>
<td>_piccolo et al – 2014</td>
<td>Prospective</td>
<td>NC</td>
<td>107 / 107</td>
<td>5mg DNase + 10mg t-PA b.d.</td>
<td>Maximum of 6 doses of each agent</td>
<td>Sequential</td>
</tr>
<tr>
<td>Majid et al – 2016</td>
<td>Retrospective</td>
<td>NC</td>
<td>73 / 73</td>
<td>5mg DNase + 10mg t-PA b.d.</td>
<td>Maximum of 6 doses of each agent</td>
<td>Concurrent</td>
</tr>
<tr>
<td>McClune et al - 2016</td>
<td>Retrospective</td>
<td>NC</td>
<td>101 / 101</td>
<td>5mg DNase + 10mg t-PA b.d. for 3 days</td>
<td>6 doses of each agent</td>
<td>Sequential</td>
</tr>
<tr>
<td>Mehta et al – 2016</td>
<td>Retrospective</td>
<td>NC</td>
<td>55 / 55</td>
<td>5mg DNase + 10mg t-PA o.d.</td>
<td>Maximum of 3 doses of each agent</td>
<td>Concurrent</td>
</tr>
<tr>
<td>Popowicz et al – 2017</td>
<td>Prospective</td>
<td>NC</td>
<td>61 / 61</td>
<td>5mg DNase + 5mg t-PA b.d. for a median of 6 doses</td>
<td>Average of 6 doses of each agent</td>
<td>Concurrent</td>
</tr>
<tr>
<td>Kheir et al – 2018</td>
<td>Prospective</td>
<td>C</td>
<td>38 / 38</td>
<td>5mg DNase + 10mg tPA b.d..</td>
<td>Maximum of 6 doses of each agent</td>
<td>Sequential (n=18)</td>
</tr>
<tr>
<td>Khemasuwan et al – 2018</td>
<td>Retrospective</td>
<td>NC</td>
<td>84 / 84</td>
<td>5mg DNase + 10mg tPA b.d. for a maximum of 6 doses.</td>
<td>Maximum of 6 doses of each agent</td>
<td>Concurrent</td>
</tr>
<tr>
<td>Jiang et al - 2020</td>
<td>Retrospective</td>
<td>NC</td>
<td>56 / 56</td>
<td>5mg DNase + 10mg t-PA o.d. Med. no. of days = 3 days</td>
<td>Average of 3 doses of each agent</td>
<td>Concurrent</td>
</tr>
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</table>

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<td>non</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>comparative</td>
</tr>
</tbody>
</table>

Table 6.1 – Summary of studies exploring outcome predictors in pleural infection
<table>
<thead>
<tr>
<th>Year and Country</th>
<th>Publication</th>
<th>Type of Study</th>
<th>Population (n)</th>
<th>Primary Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CCI score Malnutrition or cachexia Alcohol abuse Cardiovascular disease</td>
</tr>
<tr>
<td>2019 Australia</td>
<td>Brims et al</td>
<td>Bacteriology and clinical outcomes of patients with culture positive pleural infection in Western Australia: A 6-year analysis</td>
<td>Western Australia public hospitals electronic records</td>
<td>601</td>
<td>Bacteriology and clinical outcomes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3-month mortality Female gender, age, CRP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1-year mortality Age, active cancer, renal failure</td>
</tr>
<tr>
<td>2018 Taiwan</td>
<td>Wu J. et al</td>
<td>Assessment of the Charlson Comorbidity Index score, CHADS2 and CHA2DS2-VASc scores in predicting death in patients with thoracic empyema</td>
<td>National database</td>
<td>484</td>
<td>Predictive scores for risk of dead</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CCI Score CHADS2 and CHA2DS-VASc scores not predictive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Advanced age previous malignancies, institutional care, alcoholism, malignant aetiology</td>
</tr>
<tr>
<td>2016 Korea</td>
<td>Park CK. et al</td>
<td>Microbiological Characteristics and Predictive Factors for Mortality in Pleural Infection: A Single-Centre Cohort Study in Korea.</td>
<td>Retrospective single centre study</td>
<td>164</td>
<td>Predictive factors/scores for 30 days mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Scores: CURB-65 ≥ 2 , PSI risk class IV-V, SOFA score &gt;2 Factors: structural lung disease, hospital acquired infection, withholding intrapleural fibrinolytics</td>
</tr>
</tbody>
</table>

References


ERS/ESTS PLEURAL INFECTION TASKFORCE – STATEMENT

SUPPLEMENTARY MATERIALS

S2. Brief overview of bacteriology
S3. Suggested antibiotic regimen for pleural infection
S4. Intrapleural Enzyme therapy (IET)
   S4.1 Suggested protocol for IET preparation, administration and monitoring
   S4.2 IET-related adverse events
S5. ATS staging definition of empyema
S6. Brief overview of the RAPID score
S7. Future research recommendations
S8. Search strategies
S2. Brief overview of pleural infection bacteriology

Despite the aetiology of most cases being parapneumonic, the bacteriology of pleural infections has important differences to that of pneumonia [1–3]. The “milleri” group (more recently named ‘strept anginosus group’) are the most common pathogens in community acquired pleural infection, based on data from Europe, North America and Australia. Furthermore, ‘atypical’ pathogens, such as *Mycoplasma, Legionella* and *Chlamydombilla*, that are commonly considered in pneumonia, do not have a significant role in pleural infection [4, 5]. Recently, in the largest exploratory metagenomics analysis, using Next Generation Sequencing (NGS), pleural infection was found to be polymicrobial in up to 80% of cases [6], previously significantly underestimated by standard culture techniques [1].

Pleural infection bacteriology also varies with age, geographical area, setting of infection (community- vs hospital-acquired), and comorbidities [1]. In the aforementioned systematic review, community-acquired pleural infections were more often due to Gram-positive aerobes (65.1%), followed by anaerobes (17.8%), and Gram-negative aerobes (17.1%). By contrast, the causes of hospital-acquired pleural infections included Gram-negative organisms (37.5%), followed by *Staphylococcus aureus* (35%; of which 58% were methicillin-resistant), and anaerobes (11%) (Fig. 1).

**Optimising microbiological yield**

Blood cultures are positive in approximately 17% of the cases and in 1 in 10 patients, may represent the only positive microbiology [7–9].

Bedside inoculation of pleural fluid in blood culture bottles in addition to standard cultures increases the proportion of patients with identifiable pathogens by roughly 20% (from 37.7% to 58.5%) [10] and has now become a common practice. Additionally, the AUDIO study demonstrated that culture of pleural tissue biopsies substantially increased the microbiological yield as compared with pleural fluid and blood specimens (45% vs 20% vs 10%, respectively) in 20 patients with clinically established pleural infection [11]. This suggests that bacteria may preferentially invade pleural tissues rather than the hypocellular, hypoxic environment of pleural fluid. Beyond demonstrating feasibility, a recommendation for including pleural biopsy in the routine work-up of suspected pleural infections is premature pending larger, prospective multicentre data.

Nucleic acid amplification testing (NAAT) on pleural fluid specimens has shown potential for a rapid (a few hours) and precise identification of microorganisms [12], particularly when patients have received antibiotics, or an anaerobic infection is suspected [13]. The standard method involves polymerase chain reaction (PCR) amplification of the 16S rRNA gene (conserved regions are common to all bacteria),
followed by sequencing and comparison to known databases for genus and species identification. In a series of 723 pleural fluid samples, of which 82 corresponded to infections, 16S PCR increased bacterial identification 1.5 times as compared to conventional cultures (from 54.9% to 81.7%) [14]. However, in addition to costs and the need for adequate laboratory equipment, the clinical impact of identifying multiple pathogens or interpreting culture-PCR discrepancies is uncertain [2, 14, 15]. One of the limitations of the NAAT is its inability to discriminate pathogens driving disease from bystander bacteria. Finally, the use of commercially available multiplex bacterial PCR assays is hampered by the lack of dedicated panels covering the common pathogens involved in pleural infection [16].

Until NAAT techniques become more widely available and there is greater evidence on their treatment implications, in their current practice TF members would ensure pleural fluid is cultured in aerobic and anaerobic media, including blood culture bottles as routine when infection is suspected as well as separately obtaining blood cultures.
Relative contribution of bacterial groups and organisms in the aetiology of community-acquired pleural infections. Klebsiella spp. are expressed separately from other Enterobacteriales to highlight the importance of this organism in the pathogenesis of pleural infection particularly in certain geographic areas.
Relative contribution of bacterial groups and organisms in the aetiology of hospital-acquired pleural infections. Klebsiella spp. are expressed separately from other Enterobacteriales to highlight the importance of this organism in the pathogenesis of pleural infection particularly in certain geographic areas.
Table S3: Example empiric antibiotic regimen for pleural infection*

<table>
<thead>
<tr>
<th>Type of infection</th>
<th>Target groups/organisms</th>
<th>Suggested antibiotic</th>
<th>Alternatives (allergy, or local resistance patterns)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community acquired</td>
<td>Gram positive and negative aerobes</td>
<td>Penicillin with β-lactamase inhibitor (e.g., ampicillin-sulbactam$ or amoxicillin-clavulanate$)</td>
<td>Quinolones, e.g. - Moxifloxacin$ - Levofoxacin Injectable 2nd or 3rd generation cephalosporin, e.g.: - Cefoxitin - Ceftriaxone + Metronidazole or clindamycin#</td>
</tr>
<tr>
<td></td>
<td>Anaerobes%</td>
<td>+ Metronidazole or clindamycin#</td>
<td></td>
</tr>
<tr>
<td>Hospital-acquired</td>
<td>Gram positive and negative aerobes (including Pseudomonas spp)</td>
<td>Antipseudomonal penicillin with β-lactamase inhibitor (e.g., piperacillin-tazobactam) or Carbapenem (e.g., meropenem)</td>
<td>Anti-pseudomonal cephalosporin (e.g., cefepime) or quinolone (moxifloxacin or levofloxacin).</td>
</tr>
<tr>
<td></td>
<td>MRSA</td>
<td>+ Linezolid</td>
<td>+ Vancomycin + Metronidazole or clindamycin#</td>
</tr>
<tr>
<td></td>
<td>Anaerobes*</td>
<td>(Covered by above antibiotics)</td>
<td></td>
</tr>
</tbody>
</table>

* This is a description of TF members’ practice and is not intended as a clinical practice recommendation. Local microbiology guidelines where available should always take precedence.

% Even if an anaerobic organism is not identified on microbiological tests, most TF members would include anaerobic coverage in antibiotic regimens given the difficulty in culturing these organisms that commonly infect the pleural space.

# Clindamycin and metronidazole have comparable anti-anaerobic spectrum, although the latter may have a lower incidence of bacterial resistance and better penetration into the pleura.

$ These agents possess anaerobic coverage and some TF members would consider for use as single agents in community-acquired infection (especially if needed to improve...
tolerance/compliance) but higher-than-standard doses may be required for some agents. In most cases, TF members would prefer anaerobic cover with a specific agent.
S4.1 Example* protocol for IET preparation, administration and monitoring

*This protocol is intended to depict TF members’ practice and is for information only. It is not intended as a clinical practice recommendation. The TF would always encourage clinicians to adapt IET protocol to local service and practice.

Drug Preparation

1. Disconnect the chest drain from the tubing by either:
   - Closing 3-way tap; or
   - Clamping large bore chest tube and disconnecting drain from the tubing at connection site

2. Alteplase (Actilyse®) Preparation:
   - This drug should always be given first.
   - Add the contents of the provided vial of solvent (Water for injection) to the alteplase vial using the transfer cannula (if provided) to give a final concentration of 1mg/ml.
   - During reconstitution, agitate the vials gently until the contents are dissolved. Do NOT shake. If foaming occurs then allow solution to settle for several minutes
   - In a 50ml syringe, add the 10mg* of alteplase and make up to a total volume of 30ml with sodium chloride 0.9%.
   - After reconstitution, use immediately

3. Dornase alfa (Pulmozyme®):
   - Note: This medication is stored in the refrigerator prior to use.
   - Check the contents of the dornase alfa nebules prior to use. The solution must be clear and colourless, otherwise it must be disposed of in a sharps bin.
   - In a 50ml syringe, add 5mg of dornase alfa (two of the 2.5mg/2.5ml nebules) and make up to a total volume of 30ml with water for injections.
   - Dornase alfa is an unbuffered aqueous solution and should not be diluted or mixed with other drugs or solutions. Mixing of this solution could lead to adverse structural and/or functional changes in dornase alfa or the admixed compound. Therefore, after diluting the dornase alfa for administration intrapleurally, it should be used immediately
**Administration:**

- Inject the Alteplase intrapleurally, followed by a 10ml flush of sodium chloride 0.9% then
- Inject the Dornase alfa intrapleurally, followed by a 10ml flush of sodium chloride 0.9%
- Clamp for 1 hour then free drainage.

Repeat the process 12 hours later, e.g.

<table>
<thead>
<tr>
<th></th>
<th>8-10am</th>
<th>6-8pm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First drug</strong></td>
<td>10mg Alteplase + 10ml sodium chloride 0.9% flush</td>
<td>10mg Alteplase + 10ml sodium chloride 0.9% flush</td>
</tr>
<tr>
<td><strong>Followed by second drug</strong></td>
<td>5mg Dornase alfa + 10ml sodium chloride 0.9% flush</td>
<td>5mg Dornase alfa + 10ml sodium chloride 0.9% flush</td>
</tr>
<tr>
<td><strong>Followed by</strong></td>
<td>Clamp for 1 hour then free drainage</td>
<td>Clamp for 1 hour then free drainage</td>
</tr>
</tbody>
</table>

Repeat the procedure twice daily for 3 days, until a total of 12 doses of drugs (6 doses of alteplase and 6 doses of dornase alfa) have been given.

**Monitoring:**

- Monitor chest drain site for erythema and rash
- If anaphylactic reactions occur, discontinue administration of medication, and treat appropriately
- Offer analgesia early (preferably premedicate) and monitor for pain
- Monitor for evidence of significant intrapleural bleeding – some blood staining of the pleural fluid is expected, however the drainage of significant amounts of heavily blood-stained fluid or complete cessation of drainage AND any evidence of haemodynamic instability (tachycardia, hypotension, reduction in serum Hb concentration) should be investigated with a thoracic ultrasound +/- CT scan and a specialist opinion sought.

**S4.2 IET-related adverse events**

A list of contraindications to IET is provided below (table S4.2). Use of fibrinolytics (including alteplase) and dornase alfa intrapleurally for pleural infection remains off-licence. These contraindications are based on manufacturer summary product characteristics (SPC), Safety Data Sheets and trial exclusion criteria.
Table S4.2a Side effects, complications, and mortality of IET

<table>
<thead>
<tr>
<th>Author and country</th>
<th>Type of study</th>
<th>N</th>
<th>Agent(s)</th>
<th>Overall bleeding n (%)</th>
<th>Pleural bleeding</th>
<th>Pain with escalation of analgesia</th>
<th>Other adverse events/ complications</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rahman et al, 2011. UK</td>
<td>RCT</td>
<td>52/210</td>
<td>10 mg tPA; 5 mg DNase</td>
<td>3 (6%)</td>
<td>2 (4.2%)</td>
<td>6 (11.5%)</td>
<td>Serious adverse events; Haemoptysis Gastrointestinal bleeding Non-serious adverse events; Nausea Transient confusion Erythema Rash</td>
<td>4 (8.3%) at three months</td>
</tr>
<tr>
<td>Piccolo et al, 2014. Australia, UK, and New Zealand</td>
<td>P Obs</td>
<td>107</td>
<td>10 mg tPA; 5 mg DNase</td>
<td>2 (1.8%)</td>
<td>2 (1.8%)</td>
<td>21 (19.6%)</td>
<td>ND</td>
<td>3 (2.8%) at 30 days</td>
</tr>
<tr>
<td>Popowicz et al, 2017. Australia, UK, and New Zealand</td>
<td>P Obs</td>
<td>61</td>
<td>5 mg tPA; 5 mg DNase</td>
<td>3 (4.9%)</td>
<td>3 (4.9%)</td>
<td>36.0% (none required cessation of therapy)</td>
<td>ND</td>
<td>1 (1.6%) at 30 days</td>
</tr>
<tr>
<td>Bédat et al, 2019. Switzerland</td>
<td>P Obs</td>
<td>93</td>
<td>tPA- DNase Urokinase</td>
<td>7/41 (17%) with tPA-DNase; None with urokinase</td>
<td>7/41 (17%) with tPA-DNase; None with urokinase (p=0.002)</td>
<td>ND</td>
<td>ND</td>
<td>2 (5%) with tPA- DNase. 4 (8%) with urokinase at 30 days</td>
</tr>
<tr>
<td>Kheir et al,</td>
<td>P</td>
<td>38</td>
<td>10 mg tPA; 5 mg</td>
<td>1 (5%) for</td>
<td>1 (5%) for</td>
<td>3 (15%) for</td>
<td>ND</td>
<td>4 due to</td>
</tr>
<tr>
<td>Year</td>
<td>Location</td>
<td>Study Type</td>
<td>Treatment Details</td>
<td>Concurrent DNase (10 mg tPA; 5 mg DNase) (%)</td>
<td>Sequential DNase (10 mg tPA; 5 mg DNase) (%)</td>
<td>Concurrent DNase (10 mg tPA; 5 mg DNase) (%)</td>
<td>Sequential DNase (10 mg tPA; 5 mg DNase) (%)</td>
<td>Complications</td>
</tr>
<tr>
<td>------------------------</td>
<td>---------------------</td>
<td>------------</td>
<td>--------------------------------------------------------</td>
<td>---------------------------------------------</td>
<td>---------------------------------------------</td>
<td>---------------------------------------------</td>
<td>---------------------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>2018. US and Chile</td>
<td></td>
<td>Obs</td>
<td>DNase (concurrent vs sequential)</td>
<td>16.1%</td>
<td>16.1%</td>
<td>ND</td>
<td>ND</td>
<td>pleural infection (2 in each arm) at 30 days</td>
</tr>
<tr>
<td>Jiang et al, 2020. US</td>
<td>R</td>
<td>56 (concurrent therapy)</td>
<td>10 mg tPA; 5 mg DNase</td>
<td>9 (16.1%)</td>
<td>9 (16.1%)</td>
<td>ND</td>
<td>ND</td>
<td>2 (3.6%) due to pleural infection at 30 days</td>
</tr>
<tr>
<td>Khemasuwan et al, 2018. US</td>
<td>R</td>
<td>84</td>
<td>10 mg tPA; 5 mg DNase (concurrent therapy)</td>
<td>4 (4.7%)</td>
<td>4 (4.7%)</td>
<td>13 (15.5%)</td>
<td>Increased oxygen requirement in 3. Minor complications in 20 patients</td>
<td>1 (1.2%) due to septic shock at 30 days</td>
</tr>
<tr>
<td>Majid et al, 2016. US, UK, and Chile</td>
<td>R</td>
<td>73</td>
<td>10 mg tPA; 5 mg DNase (concurrent therapy)</td>
<td>4 (5.4%)</td>
<td>4 (5.4%)</td>
<td>11 (15.1%)</td>
<td>ND</td>
<td>2 (2.7%) as a result of pleural infection at 30 days</td>
</tr>
<tr>
<td>McClune et al, 2016. US</td>
<td>R</td>
<td>101 (20 extended and 81 standard therapy)</td>
<td>10 mg tPA; 5 mg DNase. Six doses (&gt; 6 days versus standard use*)</td>
<td>2 (10%) for extended and 2 (3%) for standard therapy</td>
<td>ND</td>
<td>16 (80%) for extended and 46 (57%) for standard therapy</td>
<td>Readmission (10% vs 16%). Outpatient pleural drainage (10% vs 12%). Tube dislodgement (15% vs 4%)</td>
<td>ND</td>
</tr>
<tr>
<td>Mehta et al, 2016. US</td>
<td>R</td>
<td>55</td>
<td>10 mg tPA; 5 mg DNase. Once daily (3 doses)</td>
<td>No major bleeding events</td>
<td>None</td>
<td>8 (15%)</td>
<td>4 erythema and swelling along the drainage site</td>
<td>3 (5.4%) at 30 days</td>
</tr>
</tbody>
</table>

Table S4.2b Suggested contraindications to IET

<table>
<thead>
<tr>
<th>Absolute</th>
<th>Relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Known sensitivity to the drug</td>
<td>Known haemorrhagic diathesis/uncorrectable coagulopathy</td>
</tr>
<tr>
<td>Coincidental stroke</td>
<td>Broncho-pleural fistula</td>
</tr>
<tr>
<td>Major haemorrhage or trauma</td>
<td>Severe renal disease</td>
</tr>
<tr>
<td>Major surgery in the previous five days</td>
<td>Anticoagulation therapy and/or antiplatelet agents*</td>
</tr>
<tr>
<td>Previous pneumonectomy on the infected side</td>
<td>Neoplasm with increased bleeding risk</td>
</tr>
<tr>
<td>Known history of or suspected intracranial bleeding</td>
<td>Severe liver disease</td>
</tr>
<tr>
<td>Pregnancy or lactation</td>
<td>Recent obstetrical delivery</td>
</tr>
<tr>
<td></td>
<td>Recent (less than 10 days) traumatic external heart massage</td>
</tr>
<tr>
<td></td>
<td>Recent puncture of a non-compressible blood vessel (e.g., subclavian, or jugular vein puncture)</td>
</tr>
</tbody>
</table>

#In practice, and when appropriate to do so, most TF members hold anticoagulation therapy and/or antiplatelet agents (with the exception of low doses of aspirin and prophylactic doses of low molecular weight heparin) before and during administration of intrapleural fibrinolytics.
S5. ATS Stage definition of Pleural empyema

<table>
<thead>
<tr>
<th>Exudative phase (stage I)</th>
<th>Fibrinopurulent phase (stage II)</th>
<th>Organized phase (stage III)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory processes extend to the pleurae and result in immediate outpouring fluid</td>
<td>Frank pus accumulates especially laterally and dorsally</td>
<td>Thick and sedimented exudate</td>
</tr>
<tr>
<td>Low cell content</td>
<td>High cell content (PMN) and fibrin depositions over the pleural surfaces and fibrinous strands within the fluid</td>
<td>Fibroblast growth Fibrosis</td>
</tr>
<tr>
<td>Re-expandable lung</td>
<td>Lung is less expandable</td>
<td>Trapped lung</td>
</tr>
<tr>
<td>Tendency to loculations and formations of membranes</td>
<td>Inelastic membranes over the pleural surfaces</td>
<td></td>
</tr>
</tbody>
</table>
S6. Brief overview of the RAPID score

The RAPID score was derived from data obtained from the MIST-1 study [17] and validated in the MIST-2 cohort [18]. Of 22 baseline characteristics recorded at initial presentation, using multivariate modelling, five parameters were strongly independently associated with poor outcome (figure 1), specifically 3-month mortality and a prolonged length of hospital stay.

The RAPID score recently underwent prospective external validation in the international multicentre observational (PILOT) study (n=546) [19], where patients were treated according to standard guidelines and local practice. PILOT demonstrated robust clinical ability of the RAPID score to stratify patients into different categories according to increasing risk of three-month mortality (figure 2).

One interesting observation from the PILOT study was the higher rate of surgical referral in the low-risk group (19%) compared to the high-risk group (5.9%). No significant differences were observed in rates of intrapleural therapy between the 3 groups, but the overall rate of intrapleural fibrinolytic therapy in this study was low, making it difficult to draw conclusions.

Figure S6.1 – Parameters of the RAPID Score

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Measure</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Renal</strong></td>
<td>Urea</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;5mmol/L</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>5-8 mmol/L</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&gt;8 mmol/L</td>
<td>2</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>Age</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;50 years</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>50-70 years</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&gt;70 years</td>
<td>2</td>
</tr>
<tr>
<td><strong>Purulence of fluid</strong></td>
<td>Purulent</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-purulent</td>
<td>0</td>
</tr>
<tr>
<td><strong>Infection Source</strong></td>
<td>Community acquired</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Hospital acquired</td>
<td>1</td>
</tr>
<tr>
<td><strong>Dietary Factors</strong></td>
<td>Albumin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;27mmol/L</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&lt;27mmol/L</td>
<td>1</td>
</tr>
</tbody>
</table>

| Risk categories         |                |       |
|                        | Score 0-2      | Low risk |
|                        | Score 2-4      | Medium-Risk |
|                        | Score 5-7      | High Risk  |
Figure S6.2 – Kaplan Meier survival plot based on RAPID stratification (taken from the PILOT study) (Corcoran et al ERJ 2020)
S7. Future research recommendations

1. Detailed characterisation of patients presenting with pleural infections to gain further understanding of the host factors contributing to the increased burden
   Further exploration of the role of viruses in adult pleural infection epidemiology

2. Additional benefit from a pleural-infection-specific multiplex PCR assay in improving pathogen identification and antimicrobial stewardship
   Strategy of de-escalation and duration of oral antimicrobial therapy after ‘medical’ and surgical’ control of pleural infection
   Optimal biomarker to monitor treatment response in acute pleural infection
   Further studies on the added yield from microbiological testing of pleural biopsy in the setting of pleural infection.

3. Biomarkers targeting reliable diagnosis of pleural infection in complex clinical circumstances, such as post pleurodesis or pleural infection superimposed on MPE, with or without IPC in-situ.
   Ambulatory management of small volume pleural infection in lower risk patients with treatment modalities including antibiotic treatment only – failure rates, need for intervention and how outcomes differ in this setting compared to upfront intervention.

4. Comparative studies addressing the optimal dosing and schedule for IET
   Studies addressing the effect of fibrinolysis inhibitors (such as PAI-1) on IET outcomes
   Effects of chest tube dwell/clamp time impact on IET success
   Large observational studies addressing the significance of bronchopleural fistulas in the context of IET
   Studies addressing the most important radiological predictors of IET failure

5. The role and efficacy of medical thoracoscopy versus VATS drainage of empyema
   The role of intrapleural fibrinolytics in the setting of traumatic retained haemothorax and empyema prevention

6. Prospective data on long term pleural infection outcomes beyond 12 months
   The role of RAPID score together with surgical risk calculation (e.g. ASA-score) in evaluation of the risk-benefit from surgery more precisely
   The role of RAPID score in altering treatment paradigms at baseline
   The role of PAI-1 and other pleural fibrinolytic biomarkers in phenotyping patients, directing treatments and predicting outcome
S8. Search strategies

Results restricted to those involving only adult humans and those in the English language.
The search was initially set from present to 2006 (15 years).

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systematic reviews</td>
<td>Opinion pieces</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>Editorials</td>
</tr>
<tr>
<td>RCTs</td>
<td>Informal reviews</td>
</tr>
<tr>
<td>Comparative studies (non randomised)</td>
<td>Case reports</td>
</tr>
<tr>
<td>Observational studies (retrospective or prospective)</td>
<td>Paediatric studies</td>
</tr>
<tr>
<td>Case series</td>
<td>Animal studies</td>
</tr>
</tbody>
</table>

**Question 1 – What is the current burden of pleural infection?**


**Question 2 – In adults with pleural infection, what is the optimal antibiotic strategy?**

((cavity, pleural[MeSH Terms]) OR (empyema, pleural[MeSH Terms])) AND ((antibiotics[MeSH Terms]) OR (6640, antibiotic[MeSH Terms]) OR (agents, antimicrobial[MeSH Terms])) AND (cavity, pleural[MeSH Terms]) OR (empyema, pleural[MeSH Terms]) AND ((antibiotics[MeSH Terms]) OR (6640, antibiotic[MeSH Terms]) OR (agents, antimicrobial[MeSH Terms])) AND (english[Language])
Question 3 – In adults with pleural infection, what are the optimal diagnostic parameters predicting need for chest tube drainage?


(“pleura”[MeSH Terms] OR “pleura”[All Fields] OR “pleural”[All Fields]) AND (“fluids”[All Fields] OR “fluid”[All Fields]) AND (“analysis”[MeSH Subheading] OR “analysis”[All Fields])


Question 4 – In adults with pleural infection, what is the role of intrapleural therapy in pleural infection?


Question 5 – In adults with pleural infection, what is the role of surgery in pleural infection?

P Patients with pleural infection
I Surgical drainage and debridement
C Video-assisted Thoracoscopic Surgery (VATS), thoracotomy, decortication, open window thoracostomy, thoracoplasty, vacuum devices, medical thoracoscopy
O Resolution of symptoms, conversion rates, pain, air leak, length of stay, mortality, reintervention
Mesh descriptor
- Empyema pleural / surgery
- Thoracic Surgery, Video-Assisted
- Thoracotomy / methods
- Debridement
- Pneumonectomy / adverse effects
- Bronchial fistula / surgery
- Surgical Flaps
- Thoracoplasty/ adverse effects
- Hemothorax / surgery

Methods
A MEDLINE search of the MeSH database was performed based on PICO elements ‘empyema, pleura’, ‘empyema, pleural, surgery’, ‘empyema, pleural, decortication’, ‘empyema, pleural, VATS’, ‘empyema pleural, thoracoplasty’, ‘empyema pleural, medical thoracoscopy’

Question 6 – what is the role of outcome prediction in pleural infection?

("Empyema, Pleural"[Mesh]) OR ("pleural infect"[Title/Abstract] OR parapneumonic*[Title/Abstract] OR para-pneumonic*[Title/Abstract] OR empyema*[Title/Abstract])) AND ((prognos*[Title/Abstract] OR model*[Title/Abstract] OR “risk factor”*[Title/Abstract] OR prediction*[Title/Abstract] OR score*[Title/Abstract] OR outcome*[Title/Abstract]) OR (((“Prognosis”[Mesh]) OR “Risk Factors”[Mesh]) OR “Treatment Outcome”[Mesh]))
References


