



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

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Intrapleural fibrinolytic-based therapy has revolutionised pleural infection management, but surgical intervention remains vital in select patients. Studies into early and targeted escalation of treatment based on risk stratification are now required. <https://bit.ly/3y6rZ8a>

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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: 1) epidemiology of pleural infection, 2) optimal antibiotic strategy, 3) diagnostic parameters for chest tube drainage, 4) status of intrapleural therapies, 5) role of surgery and 6) 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 characterisation of the 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

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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⁻¹, 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 hospital length of 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 EUR 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 regard to adult pleural infection management. It does not make clinical practice recommendations; however, in specific areas where the evidence is scarce or mixed, these limitations are described and the practice of the Task Force members is mentioned for information (as denoted by the italic text), but not with the aim of guiding clinical practice.

Methods

A Task Force 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 Task Force 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 USA, South America and North Africa. The Task Force was comprised of nine respiratory physicians (with subspecialist expertise in pleural disease, respiratory infection and interventional pulmonology), three thoracic surgeons, a clinical epidemiologist and 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 (E.O.B. and N.M.R.)) 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 of 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 subgroups allocated to each clinical question with access to an ERS methodologist and a librarian (E.K.H.). MEDLINE, Embase and Scopus databases were searched using a combination of appropriate MeSH (Medical Subject Headings) terms and key words. 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 supplementary material S8. 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 (supplementary material S8). Any queries or disagreements were resolved through discussion at Task Force virtual meetings, with final word to the Task Force chairs (E.O.B., I.O. and N.M.R.).

Subgroups prepared drafts summarising the relevant literature for their clinical question, which underwent review by the full Task Force before being revised and submitted to the chairs. The Task Force chairs collated the drafts into a complete statement and the final draft was approved by all members prior to submission to the ERS and ESTS, and hence represents a statement of the entire Task Force. Future research recommendations reflecting some of the gaps in the literature from each focus area have been summarised in supplementary material S7.

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 (figure 1.1 and table 1.1) Summary of epidemiological studies of pleural infection [17–20]. In England, there was an increase from 6.44 to 8.38 per 100 000 hospital admissions between 2008 and 2017 [3]. In France, BOBBIO *et al.* [4] observed a similar incidence, increasing from 7.15 to 7.75 per 100 000 in the short period between 2013 and 2017. In the USA, MUMMADI *et al.* [5] reported a 37.5% relative increase in pleural infection-related hospitalisation between 2007 and 2016. This represents a worrying upwards trend compared to the increase from 3.04 to 5.98 cases per 100 000 between 1996 and 2008 reported by GRIJALVA *et al.* [18] in the USA in 2011 or the 36% relative increase in Denmark between 1997 and 2011 [9].

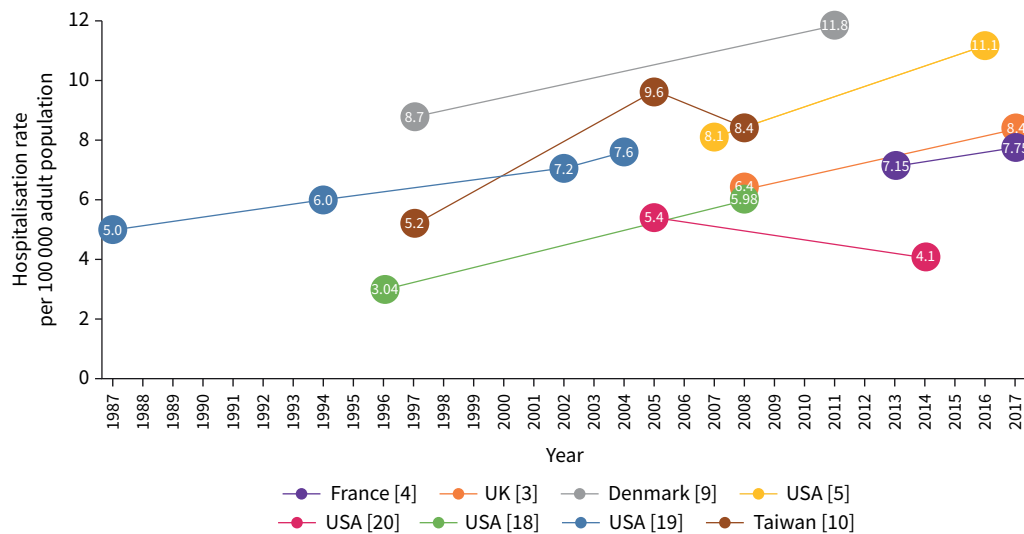


FIGURE 1.1 Trends in incidence of pleural infection in different countries from the world literature.

TABLE 1.1 Summary of epidemiological studies of pleural infection

First author [ref.], year	Country	Years	Population, n	Age, years	Male, %	Mortality, %	Hospital length of stay, days
BOBBIO [4], 2021	France	2013–2017	25 512	62.4±15.6	71.7	17.1	19 (IQR 11–35)
ARNOLD [3], 2021	UK	2008–2018	51 057	64 (IQR 51–75)	68.5	In-hospital: 14.9	15 (IQR 6–28)
SØGAARD [9], 2014	Denmark	1997–2011	6878	Nonaggregated data	65.8	30-day: 10.5 in 1997 versus 9 in 2011	22 (IQR 12–43) in 1997 versus 17 (IQR 10–28) in 2011
MUMMADI [5], 2021	USA	2007–2016	2735	Nonaggregated data	68.0	In-hospital: 7.1	13.8 (95% CI 13.3–14.2)
GUPTA [20], 2021	USA	2005–2014	150 496	58.3±0.1	67.9	In-hospital: 4.4; 2.6 in 2014	12.3±0.1
GRIJALVA [18], 2011	USA	1996–2008	157 094 (26 125 ≤18 years old)	48.4 (95% CI 47.4–49.4)	64.2	In-hospital: 7.2 (>16.1 in ≥65 years old)	15.2
FARJAH [19], 2007	USA	1987–2004	4424	57.0±18.6	66.8	30-day: 10.8	14.1±11.8
FINLEY [17], 2008	Canada	1995–2003	11 294 (children included)	<1–>90	69	ND	21.8±33.9
SHEN [10], 2012	Taiwan	1997–2008	26 385	60 (45–72) in 1997/8 versus 65 (49–77) in 2007/8	76.6	In-hospital: 17.6 (1997/8) versus 16.0 (2007/8)	21 (13–34) in 1997/8 versus 19 (12–31) in 2007/8

IQR: interquartile range; ND: no data.

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 [8, 21]) 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).

Age and gender distribution

Similar to previous reports [19], the increases were highest among those aged >60 years 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 years age group, rising to 60% in the USA [3–5]. The marked male predominance remains consistent at approximately 2.3:1 (70%) [3–6, 19, 22]. Interestingly, this appears to begin after adolescence (equal gender distribution in children), rises gradually and peaks in the >60 years 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, 23], with chronic respiratory and cardiovascular conditions having the highest contribution (table 1.2) Prevalence of pre-existing comorbidities in patients with pleural empyema. The French national database study found a median Charlson Comorbidity Index (CCI) of 5 in patients with pleural infection (compared with a CCI of 3 in those without cancer or recent surgery) [4].

Independent of other risk factors, patients with diabetes mellitus were twice as likely to develop pleural infection and within pleural infection cohorts, the prevalence of diabetes mellitus was 5 times higher than the general population [21]. Malnutrition and alcohol abuse are also important risk factors [24], stressing the significance of dietary supplementation during therapy. Concurrent malignancy rates as high as 30% have been reported [4] (average 12–13% [8, 25]), emphasising the importance of avoiding diagnostic anchoring, particularly during a protracted clinical course.

While a decreased risk of pleural infection in COPD has been hypothesised to be related to the use of inhaled corticosteroids, resulting in a dampened pleural inflammatory response [24, 26], other studies have reported conflicting findings [27]. 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 in Taiwan with

TABLE 1.2 Prevalence of pre-existing comorbidities in patients with pleural empyema

Pre-existing comorbidities	Prevalence, % (interquartile range)
Any comorbidity	72 (58–83)
Specific disease	
Hypertension	23 (17–38)
Diabetes	17 (11–27)
Stroke	13 (5–20)
Ischaemic heart disease	11 (5–16)
COPD	11 (6–20)
Chronic kidney disease	7 (5–13)

Adapted with permission from CARGILL *et al.* [8].

propensity-matched controls found schizophrenia to be a risk factor for developing pleural infection [28], although a relationship between mental health illness and increased risk of infections generally has been reported and is complex [29, 30].

Immunosuppressive states acquired through diseases such as HIV infection or iatrogenically induced by treatments (steroids, immunomodulatory and chemotherapeutic agents) have been reported to be associated with pleural infection [31, 32], 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.

Coronavirus disease 2019, seasonal variation and the role of viruses

With reference to the coronavirus disease 2019 (COVID-19) pandemic, a recent meta-analysis found that approximately 10% of patients developed pleural effusions [33]. Although the severe acute respiratory syndrome coronavirus 2 virus has been isolated in pleural fluid [34], 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 aetiological 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 in the USA following the 2009 influenza A pandemic [35]. 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 nine 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 1.8 times 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 [36], resulting in the emergence of antibiotic-resistant pathogens, a severe public health threat [37]. 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% [38]. 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 [39, 40].

An overview of the bacteriology and methods of optimising the microbiological yield in pleural infection are presented in supplementary material S2.

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 the concentration of a given antibiotic in the pleural fluid to that in the serum ($AUC_{PF/S}$) [41]. 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 [41]; therefore, due to low pleural penetration and the tendency of aminoglycosides to be inactivated in the acidic medium of the infected pleural space [42], 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 h after a single parenteral dose [43]. In patients with methicillin-resistant *Staphylococcus aureus* (MRSA) mediastinitis receiving linezolid, the drug had an $AUC_{PF/S}$ of 1.64 [44], 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 [45]. In both rabbit [46] and human [47] studies, moxifloxacin has also demonstrated favourable pleural penetration as an oral treatment option [46].

In patients with fungal pleural infection, nonliposomal formulations of antifungal therapy are preferred to liposomal formulations due to their superior pleural penetration [48, 49].

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 culture results 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 [50].

The choice of 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 hospitalisation and/or antibiotic treatments. Pleural infection by antibiotic-resistant pathogens is relatively common and, in one 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 [51].

An example antibiotic protocol is presented in supplementary material S3.

Difficult to treat infections/special situations

Factors associated with bacterial resistance include the presence of chronic kidney disease, diabetes mellitus, malignancy and recent antibiotic therapy [52]. 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 diabetes mellitus 17%, malignancy 12%, chronic kidney disease 7%, long-term steroid use 4% and chemotherapy 4% [8]. 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, 52, 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 include 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 noninferiority double-blind RCT assessing a 2-week versus 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. These preliminary data are encouraging and set 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 [51]. 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 LOS [71]. 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, *e.g.* by 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 suggest that these should not be treated as standard empyema and where earlier thoracic surgery intervention may be required [72, 73].

Monitoring treatment response

The American Thoracic Society/Infectious Diseases Society of America 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 [74]. 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 subacutely 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, C-reactive protein (CRP) appears to be sufficient as a biochemical marker of treatment response, particularly due to its low cost and availability [75]. The use of procalcitonin (PCT) in monitoring treatment response has been addressed in a small comparative surgical study (n=22) to evaluate the post-operative course in pleural infection [76] and in another small single-centre medical study (n=53), both demonstrating favourable performance compared to CRP [77]. 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 radiography/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 time-points 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 [12, 13] recommend using a pleural fluid pH <7.2 (or in the absence of pH, a combination of glucose concentration <40 mg·dL⁻¹ (2.2 mmol·L⁻¹) with lactate dehydrogenase (LDH) >1000 IU·L⁻¹) [78] 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 [12, 13].

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, while the presence of air in the syringe or pleural fluid protease-producing organisms can lead to a false elevation in pH [79]. 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 [80].

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) >200 mg·L⁻¹ had low sensitivity (58%) and specificity (81%); however, the combination of sCRP with pleural fluid analysis increased the diagnostic yield, resulting in a specificity as high as 98% for sCRP >200 mg·L⁻¹ and pleural fluid glucose <60 mg·dL⁻¹ (<3.3 mmol·L⁻¹) [81]. A recent narrative review of serum PCT (sPCT) in pleural infection found sPCT sensitivity and specificity for diagnosing pleural infection ranged from 69% to 83% and from 80% to 94%, respectively. The Task Force members 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 [82].

With regard to additional pleural fluid testing, pleural fluid CRP level >100 mg·L⁻¹ 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 [83]. Combinations of pleural fluid CRP with pH or glucose resulted in a further increase in discriminative value, with 75–80% sensitivity and 97% specificity for CPPEs. Pleural fluid PCT has not been shown to have a significant diagnostic role in differentiation between infectious *versus* noninfectious pleural effusion and to date, there have been no studies on the role of pleural fluid PCT in discrimination between CPPE and UPPE [82].

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 ultrasound 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 [84]. Robust prospective comparative studies were not identified in the literature, but a recent study comparing chest radiography, CT and ultrasound appeared to demonstrate the latter to outperform the discriminative yield of CT in ruling in CPPE. Ultrasound had a sensitivity and specificity of 69.2% and 90%, respectively, compared to chest CT sensitivity of 76.9% and specificity of 65% [85]. The positive likelihood ratio of ultrasound to diagnose CPPE was significantly higher than those for CT and chest radiography (6.92, 2.20 and 1.54, respectively; p<0.05) [85]. 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 [86]. 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 AUC 0.83 for labelling CPPE [87]. 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 characterised by a reasonable diagnostic accuracy (AUC 0.80) [88].

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 noninvasive imaging modality is being explored in paediatric pleural infection, where further cross-sectional imaging is specifically required [89, 90]. 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 images. Infectious pleural effusions have a typical fluid appearance of low signal on T1-weighted and high signal on T2-weighted images. MRI outperforms CT in visualisation of septations [91].

The authors conclude that ultrasound is adequate for initial assessment, clinical decision making and guiding diagnostic sampling. Based on the current evidence, the Task Force 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 48 h 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 nonspecific results of pleural fluid analysis (e.g. low pH and low glucose can be attributed to both pleural malignancy and pleural infection). Data on pleural infection superimposed on MPE are scarce and somewhat ambiguous, largely due to the low yield of pleural fluid culture, the pre-test probability of pleural infection at the time of sampling patients with MPE and the size of the effect of iterative thoracenteses in increasing the risk of pleural infection [92].

The inflammation associated with MPE can raise commonly used biomarkers including LDH, CRP and adenosine deaminase, but to date, no biomarker has been 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 noninfective pleural effusions matched for systemic inflammation as measured by CRP. In contrast to CRP, PCT remained stable even in the presence of intense noninfective inflammation caused by talc pleurodesis [93].

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 PCT may have some utility but acknowledge that this is based on a low level of evidence.

Chest tube size

“Small-bore” chest drains are usually defined as <14 F [94, 95] or <16 F [96], albeit the definition varies across studies and is therefore somewhat equivocal. In this document, small-bore drains are defined as ≤ 14 F and large-bore chest drains are defined as ≥ 18 F. Traditionally, large-bore chest drains have been used to drain pus or viscous fluid. A retrospective analysis of the MIST-1 RCT (n=405) [22] is the only direct comparison study of chest tube size in pleural infection [97]. Patients treated with a range of chest drain sizes (from <10 F to >20 F) 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 [97]. These data therefore show 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 [22], chest tube patency was maintained with 3-times-daily 30 mL saline flushes. One retrospective study reported that only one out of 58 drains flushed with 20 mL sterile saline every 6 h became blocked (versus six out of 19 nonflushed drains) [94]. Care is usually taken to ensure that all the fenestrations on the chest drain are located intrapleurally to work effectively and minimise the risk of infected fluid leakage into subcutaneous tissue.

There is sufficient evidence that 12–14 F chest tubes are efficient as a first-line intervention in pleural infection, with regular saline flushes. In their practice, the Task Force members prioritise correct

placement using radiological guidance (ultrasound or CT) targeting the largest locule where these are present with securement/fixation sutures and bespoke dressings. Chest drains <12 F are usually avoided to minimise risk of blockage and dislodgement.

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

Small parapneumonic effusions that are <5 cm on an erect lateral chest radiograph [98] or <2.5 cm on CT scan [99] 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 a slightly higher but statistically insignificant infection-related mortality rate [100]. *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 [100]. Four case series of patients with CPPE or empyema who underwent iterative thoracenteses were summatively analysed (n=250) [101–104] in a review of minimally invasive management of pleural infection and a 76% successful treatment rate was reported with repeated thoracentesis [105]. 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 LOS and cost [103]. 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) *versus* intrapleural urokinase plus DNase (n=81) was applied as the first-line treatment showed a failure rate of 17% and 19%, respectively [106]. 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 [12, 13]. 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: 1) catheter-related pleural infection as a complication of IPC insertion and 2) 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 and tunnel tract infection) and IPC-related pleural space infection [107, 108].

In a large multicentre retrospective review of 1021 patients treated with IPC, pleural space infections specifically developed in 50 (4.9%) patients with an overall mortality risk of 0.3% [109], significantly lower than standard pleural infection. In another large multicentre series (n=1318), WILSHIRE *et al.* [110] 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 [110].

IPC-related infections generally tend to occur around 6 weeks post-insertion [109, 110], which goes against them being directly procedure related; however, studies investigating the mechanisms leading to pleural space infections in this group are lacking [111]. They are most frequently reported in association with *S. aureus* organisms followed by *Pseudomonas aeruginosa*; however, to date, there are no studies specifically evaluating the bacteriology and significance of bacterial colonisation in this cohort [8].

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 the need for IPC removal or replacement [107, 109]. Although this condition rarely requires surgical intervention [112], 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 [107, 108].

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 IPCs 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 surgery [113, 114].

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 nondraining empyema. The MIST-1 study, to date the largest multicentre RCT in pleural infection, showed that streptokinase resulted in no improvement in outcomes for patients who fail standard care [22]. Looking at other trials of monotherapy, a recent prospective RCT by ALEMÁN *et al.* [115] comparing tissue plasminogen activator (tPA; alteplase) *versus* urokinase found no difference in the mortality rate, surgical referral rate or a composite of both.

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 [116]. The meta-analysis confirmed no evidence of change in mortality compared with placebo (OR 1.24 (95% CI 0.74–2.07)).

There is no evidence-based role for fibrinolytic or 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 10 studies following MIST-2 (between 2011 and 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 *versus* placebo, but the two largest series by POPOWICZ *et al.* [117] and PICCOLO *et al.* [118] reported a requirement for surgical intervention of, respectively, 7.7% and 4.9% with combination therapy, in contrast to 15% of patients from the placebo groups in the 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; 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 noncomparative studies have confirmed IET to be safe and effective (supplementary material S4).

Based on the placebo controlled randomised study and subsequent case series, IET is considered by most Task Force 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 and tachycardia), biochemical (failure of CRP to fall by >50%) and radiological (persistent effusion on chest radiography or ultrasound) parameters.

There is good evidence that treatment delays are associated with worse outcomes. On this basis, most Task Force members would initiate IET within 48 h 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 10 mg and DNase 5 mg, 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 (5 and 2.5 mg) have been investigated in small observational series (without comparator data) with similar safety and efficacy [117, 119],

TABLE 4.1 Effects of intrapleural enzyme therapy on surgery and hospital length of stay (LOS)

First author [ref.], year	Country	Study type	Population, n/N or n	Dosage	Surgery, n/N (%) or n (%)	Cause of surgical referral	Comments	LOS, days
RAHMAN [6], 2011	UK	RCT	48/210	10 mg tPA; 5 mg DNase	2/48 (4.2) versus placebo 8/51 (16.0)	Clinical evidence of worsening infection	Surgical referral at 3 months in tPA/DNase group lower than in placebo group; 6.7 days reduction in LOS observed	11.8±9.4 (mean±sd)
PICCOLO [118], 2014	Australia, UK and New Zealand	Prospective observational	107	10 mg tPA; 5 mg DNase	8 (7.7)	Failure to respond to treatment with persistent clinical and laboratory evidence of active infection	Median time from first fibrinolytic dose to surgery 3 (IQR 3–4.75) days	10 (IQR 6–17) from first intrapleural treatment
POPOWICZ [117], 2017	Australia, UK and New Zealand	Prospective observational	61	5 mg tPA; 5 mg DNase	3 (4.9)	Persistent infection in two patients; an open decortication of thick residual visceral pleural rind and resultant trapped lung	One underwent VATS, another a mini-thoracotomy and the third the thoracotomy	7 (IQR 5–10)
BÉDAT [199], 2019	Switzerland	Prospective observational	41/93	10 mg tPA; 5 mg DNase	4 (10)	Absence of clinical response to initial fibrinolysis	Multiple pleural collections and large-bore drain could predict need for additional chest tube or surgery	18 (IQR 11–32)
KHEIR [123], 2018	USA and Chile	Prospective observational	38 (20 sequential; 18 concurrent)	10 mg tPA; 5 mg DNase (concurrent versus sequential)	4 (22) for sequential; 5 (25) for concurrent	Sequential: two persistently loculated effusion, one persistent sepsis and one lung entrapment; concurrent: two no clinical improvement; three persistent loculation	Surgery performed after median 1.5 days (IQR 1–5) following last dose and after 3 days (IQR 1.5–3.5) in sequential and concurrent groups	13 (IQR 10–15) for sequential versus 12 (IQR 5–16) for concurrent
JIANG [200], 2020	USA	Retrospective	56	10 mg tPA; 5 mg DNase (concurrent)	2 (3.6)	Treatment failure; VATS carried out with success	Two patients with refractory septic shock considered not candidates for VATS	15 (IQR 11–28)
KHEMASUWAN [196], 2018	USA	Retrospective	84	10 mg tPA; 5 mg DNase (concurrent)	27 (32.1)	Worsening sepsis regardless of radiographic abnormality in six; ongoing infection and worsening follow-up chest CT scan in 19; haemothorax in two	No	9 (IQR 6–12), from drain insertion
MAJID [124], 2016	USA, UK and Chile	Retrospective	73	10 mg tPA; 5 mg DNase (concurrent)	7 (9.6)	No radiographic response	No	7 (IQR 5–11)
McCLUNE [122], 2016	USA	Retrospective	101	10 mg tPA; 5 mg DNase (6 doses (>6 days versus standard use [#]))	3 (15) versus 13 (16)	ND	No	17 (IQR 9–25) versus 13 (IQR 9–19)
MEHTA [121], 2016	USA	Retrospective	55	10 mg tPA; 5 mg DNase (once daily (3 doses))	4 (7.3)	Persistent fluid collection and/or treatment failure with persistent sepsis in two; inability of the lung to fully re-expand in two	One of the four patients who underwent surgery died within 30 days of intrapleural tPA/DNase instillation	13 (IQR 11–18)

RCT: randomised controlled trial; tPA: tissue plasminogen activator; IQR: interquartile range; VATS: video-assisted thoracoscopic surgery; CT: computed tomography; ND: no data. [#]: standard use defined as ≤6 days.

TABLE 4.2 Summary of dosing and administration regimens used in intrapleural enzyme therapy studies

First author [ref.], year	Study type	Comparative or noncomparative	Patients treated with active combination, n/N	Agents used (dosing)	Total number of doses	Concurrent or sequential?
RAHMAN [6], 2011	RCT	Comparative	52/210	5 mg DNase; 10 mg tPA (twice daily)	6 doses of each agent	Sequential
PICCOLO [118], 2014	Prospective observational	Noncomparative	107/107	5 mg DNase; 10 mg tPA (twice daily)	Maximum 6 doses of each agent	Sequential
MAJID [124], 2016	Retrospective	Noncomparative	73/73	5 mg DNase; 10 mg tPA (twice daily)	Maximum 6 doses of each agent	Concurrent
MCCLUNE [122], 2016	Retrospective	Noncomparative	101/101	5 mg DNase; 10 mg tPA (twice daily for 3 days)	6 doses of each agent	Sequential
MEHTA [121], 2016	Retrospective	Noncomparative	55/55	5 mg DNase; 10 mg tPA (once daily)	Maximum 3 doses of each agent	Concurrent
POPOWICZ [117], 2017	Prospective observational	Noncomparative	61/61	5 mg DNase; 5 mg tPA (twice daily)	Median 6 doses of each agent	Concurrent
KHEIR [123], 2018	Prospective observational	Comparative	38/38	5 mg DNase; 10 mg tPA (twice daily)	Maximum 6 doses of each agent	Sequential (n=18); concurrent (n=20)
KHEMASUWAN [196], 2018	Retrospective analysis	Noncomparative	84/84	5 mg DNase; 10 mg tPA (twice daily)	Maximum 6 doses of each agent	Concurrent
JIANG [200], 2020	Retrospective cohort	Noncomparative	56/56	5 mg DNase; 10 mg tPA (once daily)	Median 3 doses of each agent	Concurrent

RCT: randomised controlled trial; tPA: tissue plasminogen activator.

with 12% (tPA 5 mg) and 24% (tPA 2.5 mg) of these study populations ultimately requiring dose escalation [117].

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 (www.medicines.org.uk/emc/product/898/smpc) suggests 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, 118] for a maximum of 3 days (total of six 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 [120–122].

The authors conclude that optimal IET dosing and schedule have 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 tPA 10 mg and DNase 5 mg intrapleurally twice a day for six doses [6].

Preparation and administration regimen

Sequential administration of IET was used in the MIST-2 study based on the tPA Summary of Product Characteristics 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 [123]. 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 supplementary material S4.1.

IET safety and adverse events

The MIST-2 study recruited 52 participants in the tPA/DNase combination arm and reported two 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% [115, 118, 121–125]. 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 (over 1800 patients) [126]. The overall bleeding rate was 4.1% and in the 172 patients who received a lower dose tPA regimen (median 5 mg), the bleeding rate was not significantly reduced. Moreover, in a multivariate regression analysis, the data showed that the use of concurrent systemic anticoagulation, increasing RAPID score, elevated urea and platelets $<100 \times 10^9 \text{ L}^{-1}$ were associated with a significant increase in bleeding risk [126]. Hold systemic treatment-dose anticoagulation prior to commencing IET for up to 48 h (or maintaining international normalised ratio <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 Task Force members would commence with a reduced dose of tPA (5 mg) and escalate according to response. In cases where it may be unsafe to withhold anticoagulation (e.g. recent pulmonary embolism), Task Force members may opt to use split-dose low-molecular-weight heparin 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% (supplementary table S4.1), particularly following the first dose; hence, most Task Force members ensure *pre-medication with analgesia to improve compliance*.

A summary of other studies reporting data on IET-related side-effects, complications and mortality is provided in supplementary table S4.2a. Suggested contraindications to IET use are presented in supplementary 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.* [127] 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 on a drip stand and run through a giving set connected to the chest tube, into the pleural space. The tube was then clamped for 1 h 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) [127]. It is noteworthy that the 50% surgical requirement in the control group was very high compared to other RCTs and this was an unblinded study. Two retrospective studies [128, 129] 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 Task Force 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 nonuniform distribution across often septated or multiloculated pleural spaces (in comparison with parenteral administration). Existing guidelines therefore either take an equivocal position [130] or recommend against [12, 13] 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 [131–133]. 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 [134, 135]. Safety and efficacy of such technology are 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, 130]. In the absence of prospective, comparative studies directly addressing the question, the role of empyema stage (supplementary table S5) 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 [136, 137]. Case series have shown VATS success rates of 82–92% [138, 139]. 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 [140]. More recently, international guidelines have moved to supporting a more pragmatic approach of considering VATS in most cases [12, 13, 141].

Reduction in morbidity, arguably as important to patients as disease resolution, is superior with VATS compared to open surgery [142]. Reduced operative time [143–146], LOS [138, 143–149], pain [138, 145, 146], air leak [144, 146] and duration of tube drainage [150] are more favourable with VATS. Greater satisfaction [12] and earlier return to work [146] 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 [142]. 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 [142].

In 4435 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 [142, 143, 147]. Other risk factors for conversion include delayed surgical referral over 2 weeks, thickness of pleura and a Gram-negative causative organism [151].

Stage III empyema was previously an indication for proceeding directly to open surgery; however, it 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 [151]. Several authors have stated that the time to referral is the commonest independent factor influencing need for conversion [71, 147]. Moreover, improved overall outcomes have been demonstrated when surgery is undertaken within 4 weeks from onset of symptoms, where early surgery resulted in decreased post-operative LOS, reduced operative time and fewer prolonged air leaks [150]. In the STS database data, adverse outcomes in terms of readmission,

major morbidity, prolonged LOS and discharge to transitional care were all higher when pre-operative hospitalisation extended beyond 5 days [142]. In the largest randomised study of pleural infection to date the median duration of symptoms prior to presentation was 2 weeks [22].

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 Task Force members would consider surgical referral at day 3 post-initial chest tube if ongoing sepsis, radiological persistence and/or clinical deterioration.

Among 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 [152]. In a study of the added benefit of decortication over debridement, there was no difference in eventual cavity size [153]. Peri-operative morbidity and mortality after decortication are significant, with reported 90-day mortality of 7.6% and post-operative morbidity of 35.7%, both significantly associated with increasing antibiotic resistance to the infecting organism(s) [51].

Post-traumatic empyema

Post-traumatic empyema is reported to occur in up to 25% of patients with retained haemothorax [154]. The Injury Severity Score (ISS) correlates with mortality, morbidity and hospitalisation time after trauma, and has been widely adopted to assess chest wall trauma severity, with a score of >15 being defined as major trauma [155]. 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 [154, 156–158].

The use of prophylactic antibiotics promptly upon hospitalisation for thoracic trauma significantly decreases the incidence of post-traumatic empyema [159]. Current trauma guidelines endorse the use of VATS drainage for the treatment of retained haemothorax and prevention of empyema [160]. 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% [161].

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%) [162]. Of note, however, the average LOS was 14.8 (95% CI 12.8–16.8) days. In one nonrandomised study, OĞUZKAYA *et al.* [163] found that VATS was associated with shorter LOS and reduced requirement for thoracotomy compared to intrapleural streptokinase. 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 multiloculated organising empyema [164–167]. A recent meta-analysis of nonrandomised studies reported a pooled treatment success rate of 85% when utilised as first-line therapy or after chest tube failure, with a complication rate of 9% [143]. Higher success rates were associated with bacteriological negative effusions and administration of adjuvant intrapleural fibrinolysis [143]. A recent RCT of medical thoracoscopy *versus* intrapleural fibrinolytic therapy showed a shorter LOS post-intervention associated with the thoracoscopy arm [168]. 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 (ISRCTN Registry: ISRCTN98460319) demonstrated failure of feasibility of this approach in the context of UK thoracoscopy services.

In their practice, most Task Force members occasionally consider medical thoracoscopy as a treatment option in multiloculated 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% and 10% [136–138, 169]. It is noteworthy that where aggressive intervention cannot be undertaken, mortality rates approach that of untreated empyema [170].

Drainage, deloculation, debridement and decortication will achieve space obliteration in most cases, a prerequisite for achieving resolution in closed empyema surgery [171]. 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 [172].

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 bronchopleural fistula (BPF) is present. Previous techniques have been described by ELOESSER [173] and CLAGETT and GERACI [174]. 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 [175, 176].

The accelerated “iterative thoracotomy” technique consists of repeated debridement and packing with povidone-iodine dressings under general anaesthesia every 48 h [177]. 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% [178].

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, LOS and total treatment times [178–180]. *In their practice, the Task Force 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 [181–183].*

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 [178] were discharged with a closed chest at a mean±SD of 22±11 days without further recurrence and remaining integrity of the chest cavity [184]. The additional instillation of intrapleural antiseptic fluid (Mini-VAC-Instill) was associated with a further reduction in treatment time and shorter LOS (15±4.8 days; p=0.027) [182].

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% [185].

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 Task Force 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 [72] found that delayed pleural drainage by >2 days from diagnosis was associated with worse 30- and 90-day mortality. Delayed surgical referral has been shown to be associated with risk of conversion and worse outcomes, with each additional pre-operative hospital day (up to 5 days) being associated with 1.2 times increased risk of mortality per day [142]. 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.

While 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 [186]. Using five 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 [187–190].

An overview of the RAPID score is provided in supplementary material S6.

Despite the PILOT study specifically excluding patients with an expected survival of <3 months due to pre-existing (nonpleural infection) comorbidity, a majority of deaths occurred within the first 3 months following diagnosis of pleural infection, as has been seen in previous studies [22, 191], suggesting that mortality is disease specific and potentially amenable to improvement.

While 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 [105] 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 three pleural infection cohorts [4, 9, 25]. 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 [192–194].

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 [193, 195]. To date, the largest pleural infection trials [6, 22] were conducted prior to the era of commonplace ultrasound 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.* [87] identified that the presence of the “split pleura” sign on CT or pleural fluid volume ≥ 500 mL were independent predictors of surgery and

TABLE 6.1 Summary of studies exploring outcome predictors in pleural infection

First author [ref.], year	Country	Type of study	Population, n	Primary outcome	Results
BOBBIO [4], 2021	France	National healthcare database (2012–2017)	25 512	Hospital length of stay, mortality and hospitalisation costs	CCI score; malnutrition or cachexia; alcohol abuse; cardiovascular disease
BRIMS [11], 2019	Australia	Western Australia public hospitals electronic records	601	Bacteriology and clinical outcomes	3-month mortality: female gender, age, CRP; 1-year mortality: age, active cancer, renal failure
WU [201], 2018	Taiwan	National database	484	Predictive scores for risk of death	CCI Score; CHADS2 and CHA2DS-VASc scores not predictive
KAHN [202], 2018	Finland	Retrospective long-term follow-up, single-centre study; gender/age matched with healthy controls from national database	191 (1910 controls)	Prognostic factors for adverse outcome	Advanced age; previous malignancies; institutional care; alcoholism; malignant aetiology
PARK [60], 2016	Korea	Retrospective single-centre study	164	Predictive factors/scores for 30-day mortality	Scores: CURB-65 ≥ 2 , PSI risk class IV–V, SOFA score >2 ; factors: structural lung disease, hospital-acquired infection, withholding intrapleural fibrinolytics

CCI: Charlson Comorbidity Index; CRP: C-reactive protein; PSI: Pneumonia Severity Index; SOFA: Sequential Organ Failure Assessment.

in-hospital mortality. BOBBIO *et al.* [4] 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)).

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.* [196] identified pleural thickening and abscess or necrotising pneumonia as risk factors for IET failure in both models.

Microbiology

Culture-positive pleural infection has been proven to be associated with higher mortality [11], longer LOS and worse surgical outcomes [197]. Association between bacterial pattern and 1-year survival was among 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 (*S. anginosus*, *S. intermedius* and *S. constellatus*) was associated with better patient survival. The presence or dominance of *S. 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 S. aureus was recently found to be the most common organism isolated regardless of study or setting with increasing prevalence of methicillin resistance [38], most Task Force members would opt for earlier escalation of therapy and vigilant follow-up in this patient group.*

Novel biomarkers

Recently, ARNOLD *et al.* [198] demonstrated that pleural fluid soluble urokinase plasminogen activator receptor (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. suPAR is the soluble form of uPAR, which, once bound to endogenous 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 characterisation of the 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.

There is now a plethora of evidence, beyond the original MIST-2 study, that 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.

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