



# Advances in pleural infection and malignancy

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**Pleural infection and malignancy are amongst the most common causes of pleural disease and form the mainstay of pleural practice. There has been significant increase in scientific understanding in these areas in the last decade.** <https://bit.ly/2zOV0KE>

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**ABSTRACT** Pleural infection and malignancy are among the most common causes of pleural disease and form the mainstay of pleural practice. There has been significant research and increase in scientific understanding in these areas in the past decade. With regard to pleural infection, the rising incidence remains worrying. An increased awareness allowing earlier diagnosis, earlier escalation of therapy and the use of validated risk stratification measures may improve outcomes. In pleural malignancy, research has enabled clinicians to streamline patient pathways with focus on reducing time to diagnosis, definitive management of malignant pleural effusion and achieving these with the minimum number of pleural interventions. Trials comparing treatment modalities of malignant pleural effusion continue to highlight the importance of patient choice in clinical decision-making. This article aims to summarise some of the most recent literature informing current practice in these two areas.

## Advances in pleural infection

Pleural infection can be defined as bacterial invasion of the pleural space, forming an effusion that requires urgent drainage. It may be fibrinopurulent in the case of a “complicated parapneumonic effusion” (also known as stage 2) or frank pus where it is termed an “empyema”, associated with pleural organisation and scarring of the pleural membranes with consequent lung restriction (stage 3). It is important to note that even when pleural effusion is considered reactive (*i.e.* without bacterial invasion), in so-called “simple” parapneumonic effusion (stage 1), the mortality is 3–6-fold higher than pneumonia without effusion [1].

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Pleural infection most commonly occurs as secondary infection in the context of severe or undertreated pneumonia, but recently and increasingly, primary pleural infection is being recognised without evidence of parenchymal infection (up to 30%; unpublished data), possibly due to advances in imaging and earlier computed tomography (CT) scanning. Despite the recent advances in understanding of the aetiology, pathogenesis and management, pleural infection continues to be associated with poor outcomes; with a median hospital stay of 10–12 days and 1-year mortality rates of 10–20%.

The following section will address some of the recent advances in the field of pleural infection with a focus on diagnostics, management and risk stratification.

### *Evolving epidemiology and rising incidence of pleural infection*

In the early 21st century, a plethora of evidence emerged demonstrating a rise in the rates of pneumococcal disease with resultant increases in the incidence of pneumonia and pleural infection [2–4]. There appears to have been a shift in the age distribution towards a more elderly cohort being consistently reported [3]. Studies have suggested that widespread vaccination programmes might have caused a replacement phenomenon with nonvaccine serotypes becoming increasingly responsible for disease [5]. Early studies on the consequent effects on pleural infection incidence have been inconclusive [6, 7] and data from large epidemiological studies are eagerly awaited.

Nonetheless, the change in the epidemiology of pleural infection is not sufficiently explained by nonvaccine serotypes alone, and does not adequately cover nonpneumococcal pleural infection as well as pleural infection without pneumonia. An ageing population may explain the increasing incidence of pleural infection in older patients with comorbidities living longer with an increased risk of aspiration of oropharyngeal commensals, which is previously under-recognised. The use of more specific imaging such as CT and ultrasound is likely to have contributed to more accurate diagnoses. This is not to underestimate the role of increased awareness of pleural infection amongst clinicians, increasing involvement of specialist pleural services and growing research initiatives.

### *Diagnosis*

#### *Biomarkers in pleural infection*

Despite much research in this area, the established pleural fluid pH continues to be the best predictor of need for drainage. Recent large, multicentre data have demonstrated high concordance rates of pleural fluid glucose with pH [8], which is particularly helpful in settings with no immediate access to a blood gas analyser or where contamination by air or local anaesthetic is suspected. The role of more novel biomarkers such as procalcitonin (PCT) in decision-making in pleural infection has been of interest. To date, serum PCT has not been shown to be superior to white cell count or C-reactive protein (CRP) in any aspect of diagnosis or management. Similarly, studies looking at pleural fluid PCT have also demonstrated low sensitivity and specificity [9, 10]. Studies have been somewhat limited by heterogeneous control populations and small numbers [10].

A number of other biomarkers, including inflammatory cytokines (tumour necrosis factor- $\alpha$ , interleukin (IL)-8, IL-6 and IL-1 $\beta$ ), enzymes (neutrophil elastase, myeloperoxidase, metalloproteinases, lipopolysaccharide binding protein, soluble triggering receptor expressed on myeloid cells-1 as well as CRP itself have been evaluated but so far none have been proven to outperform traditional criteria [11, 12]. Bactericidal permeability-increasing protein, a neutrophil granule protein with antimicrobial activity against bacteria, has shown positive results in a recent pleural fluid proteome profiling study but performance in a real-life clinical setting is yet to be demonstrated [13].

Novel pleural infection biomarker studies, in particular, are prone to incorporation bias, which occurs when a clinician makes the diagnosis of pleural infection based on routinely used tests, such as pleural fluid pH, making it more difficult to show superiority of newer laboratory markers [14]. The findings of a large prospective series of 308 pleural fluid samples from PORCEL *et al.* [15] are summarised in table 1.

#### *Microbiological analysis*

Despite having a clearly distinct microbiology from pneumonia [16, 17], the positive microbiology yield in pleural infection is similarly poor and in over half of cases, the culprit organisms remain unknown, and as a result, targeted antibiotic therapy remains a challenge. Theories for this low culture yield in pleural infection are likely to include a combination of low bacterial concentrations in hypoxic and acidic pleural fluid, initiation of antibiotic therapy prior to diagnostic sampling, as well as possibly causal microbes that are difficult to isolate in laboratories in routine practice due to stringent requirements. The current minimum standard should include obtaining pleural fluid samples for analysis in standard culture and BACTEC blood culture bottles [18], as well as obtaining serum blood cultures [19].

TABLE 1 Characteristics of pleural fluid tests distinguishing non-purulent uncomplicated and complicated parapneumonic effusions

| Biomarker                              | Sensitivity % | Specificity % | AUC %            |
|--|---------------|---------------|------------------|
| pH $\leq 7.20$                         | 57 (44–70)    | 93 (85–100)   | 0.83 (0.75–0.91) |
| Glucose $\leq 60$ mg·dL <sup>-1</sup>  | 59 (46–71)    | 90 (82–98)    | 0.80 (0.72–0.88) |
| LDH $\geq 1000$ U·L <sup>-1</sup>      | 75 (63–86)    | 82 (71–92)    | 0.82 (0.75–0.90) |
| CRP $\geq 80$ mg·L <sup>-1</sup>       | 68 (56–79)    | 75 (63–87)    | 0.81 (0.63–0.88) |
| sTREM-1 $\geq 180$ pg·mL <sup>-1</sup> | 72 (61–83)    | 82 (71–92)    | 0.79 (0.70–0.86) |
| PCT $\geq 0.25$ ng·mL <sup>-1</sup>    | 33 (21–45)    | 72 (59–86)    | 0.59 (0.49–0.70) |
| LBP $\geq 17$ $\mu$ g·mL <sup>-1</sup> | 76 (64–87)    | 81 (70–92)    | 0.84 (0.76–0.91) |

AUC: area under the curve; LDH: lactate dehydrogenase; CRP: C-reactive protein; sTREM-1: soluble triggering receptor expressed on myeloid cells-1; PCT: procalcitonin; LBP: lipopolysaccharide binding protein. Reproduced from [15] with permission.

Nucleic acid amplification testing, based on extracting and deep sequencing the of the 16S rRNA bacterial gene, is an established, reliable and sensitive method of pathogen detection [20, 21]. In contrast to conventional PCR, it uses a real-time PCR, also known as quantitative PCR (qPCR), which monitors the amplification of a targeted DNA molecule during the PCR instead of at the end. This was shown to be a feasible technique in pleural infection samples acquired in the recent AUDIO study [22]. Given the unacceptable delays posed by current culture techniques, the capability of returning a result within a few hours of receiving clinical samples is of great interest. However, this is an area where further research is needed to explore the expected challenges to clinicians in the interpretation of multiple pathogen isolation, separating true polymicrobial infection and how this can potentially guide antibiotic stewardship in pleural infection [23].

The AUDIO study also demonstrated that in a single centre pilot, ultrasound-guided pleural biopsies could be safely conducted as part of the same chest drain insertion procedure using a cutting needle (figure 1) after diagnostic aspiration confirmed the diagnosis. Importantly, this increased the microbiological yield by a further 25% and was independent of previous antibiotic therapy [22]. Further large prospective studies are needed to determine how this simple, yet clearly important, step can be incorporated into future practice guidelines.

### Management of pleural infection

*Standard care: antibiotics, drain and support*

Optimal and timely drainage of infected pleural collections to achieve sepsis control continues to be the priority of care in pleural infection. It is imperative that drainage is preceded by appropriate supportive



FIGURE 1 Real-time ultrasound-guided cutting-needle biopsy.

measures, including fluids, thromboprophylaxis and nutritional support, as even when not always apparent, pleural infection represents a significant catabolic state.

Antibiotic choice should be dictated by local prescribing policies and often empirically with adequate aerobic and anaerobic cover unless culture results are available. The role of antibiotics in pleural infection has been recently reviewed [24]. The duration of course and timing of the switch from intravenous to oral has not been evaluated in randomised clinical trials, but generally should be governed by clinical response and experts would advocate a total of 4 weeks of antibiotic therapy.

The question of optimal chest tube size has not been studied in randomised trials specifically designed to address it. Retrospective analysis of large prospective data would suggest that small bore drains (<15 F) are noninferior in terms of efficacy and outcomes, and significantly more comfortable [25]. Attention should be paid to attaching a three-way tap to facilitate regular saline flushes (e.g. 30 mL three times a day) to overcome the potential blockage by frank pus. In clinically stable patients with a small empyema, chest tube drainage may be impractical, in which case prolonged antibiotic therapy and vigilant observation may suffice.

This combination of “medical therapy” will successfully resolve approximately two in three cases of pleural infection. In those with medical “treatment failure”, defined as persistent sepsis, persistent collection or nonresolving inflammatory markers (failure of CRP to fall by >50%), other rescue therapies should be considered [26].

#### *Intrapleural enzyme therapy*

The MIST-2 trial [27] represents one of the biggest advances in pleural infection in the last decade. This randomised control trial (RCT) demonstrated a clear advantage in radiographic clearance of infection in 52 participants in the combination tissue plasminogen activator and deoxyribonuclease (DNase) arm. Since its publication, over 400 patients in the literature have been successfully treated with intrapleural enzyme therapy (IET) [28–31]. These have included large case series of over 100 patients, studies involving dose alteration, and modification of the administration regimen and course duration [32–34]. The theory for the success of this combination therapy, as opposed to previous studies looking at fibrinolytics alone [19, 35], is that it works through the synergistic effects of direct fibrinolytics to disrupt septations, and DNase to reduce fluid viscosity. DNase has also been shown to interfere with biofilm of the bacteria, which may potentially enhance the effect of antibiotics and contribute to its action in the infected pleural space [36]. Additionally, there is a clear therapeutic lavage effect of IET that has been demonstrated in human and animal studies [37], evidenced by a 10-fold increase in fluid production seen in the experiments, as well as the initial acceleration of drainage seen clinically when these agents are used. This was assumed to be driven by cytokine, monocyte chemoattractant protein 1 (MCP-1), expression and protein release by mesothelial cells but recent data has demonstrated that pleural fluid MCP-1 levels did not correlate with drainage volume, suggesting there are likely to be additional pathways at play [38].

#### *Saline irrigation*

On the subject of therapeutic lavage, the Pleural Irrigation Trial [39] recently reported positive results in a single centre pilot RCT involving 35 participants. The protocol involved administering 250-mL bags of 0.9% sodium chloride directly into the thoracic cavity. The saline bags were hooked onto a drip stand and run through a giving set, at free flow rate by gravity, *via* a chest tube connected to a three-way tap. The tube was then clamped for 1h and then opened to allow free drainage. This was repeated three times a day for a total of nine irrigations. The primary end-point was reduction in pleural collection volume on CT, compared to standard care, which reached statistical significance. Saline irrigation was shown to reduce referrals to surgery but did not impact on length of hospital stay.

#### *Therapeutic thoracentesis*

Whilst more established in the algorithm of malignant pleural effusion management, there is some recent data to suggest that in select patients this approach may be a reasonable alternative to chest tube drainage [40, 41]. In “low-risk” patients with no evidence of systemic sepsis and who are otherwise well, iterative thoracentesis using aspiration catheters may facilitate early mobilisation and discharge with continued management in an outpatient or “ambulatory” setting.

#### *Thoracoscopy*

There has been growing interest in the role of medical local anaesthetic thoracoscopy (LAT) in pleural infection performed by physicians. Some European centres, as well as others around the world, advocate early LAT in pleural infection and have been practicing this for some time [42–44]. It is not a recommendation of established guidelines [26] and the evidence for this approach is largely based on case

series. Theoretically, it would seem logical as a therapeutic option to allow catheter drainage of fluid, mechanical disruption of septations, followed by a chest tube placed under direct vision.

BRUTSCHE *et al.* [42] reported on a retrospective series of 127 patients over 14 years with multiloculated empyema treated with LAT. They demonstrated a success rate (not requiring any further treatment interventions) of 91%, although half of these also had intrapleural fibrinolytics as adjuvant therapy. A complication rate of 9% was observed with 6% requiring conversion to thoracotomy. A similar success and complication rate was observed in the subsequent smaller series from RAVAGLIA *et al.* [45], with both studies concluding that LAT is a safe and feasible treatment option in multiloculated empyema.

Large, prospective, multicentre studies are needed, with sonographic stratification by stage of empyema to confirm the role of LAT in pleural infection. In 2017, the Studying Pleuroscopy in Routine Pleural Infection Treatment (SPIRIT) trial was set up as a multicentre, feasibility RCT to assess whether health services in the UK could deliver LAT as a therapeutic modality in a timely fashion for pleural infection, within their current set up. The study has been completed and results are likely to be published in 2021.

### *Surgery*

Despite surgical literature in pleural infection being largely confined to case series and retrospective studies, there is clearly a group of patients who benefit from surgical intervention. Advances in video-assisted thoracoscopic surgery (VATS) techniques have improved the safety of the technique. In comparison with open techniques, studies have reported at least equivalent outcomes in mixed populations with stage 2/3 empyema [46, 47], most importantly in relation to postoperative pain and length of hospital stay. Yet these nonrandomised data should always be interpreted with caution. Delays to surgery have been associated with the highest risk of conversion to open thoracotomy with a reported rise in probability of 22–86%, between an interval of 12 and 16 days, respectively [48]. To date, there are no RCT data to inform patient selection, timing of surgery or whether surgery can truly improve clinical outcomes.

### ***Predicting outcomes: risk stratification and scoring***

Pleural infection represents significant heterogeneity. As well as affecting a variable population from young and fit, to older with comorbidities, the added difficulty in predicting outcomes is related to the variable presentations, from acute sepsis, to subacute indolent infection with weight loss and anorexia over weeks. There is undoubtedly a cohort of patients that would benefit from earlier aggressive treatment such as surgical intervention or IET as poor outcomes have been consistently attributed to delays in effective treatment [48, 49]. The surgical literature would suggest that there is still a clear selection bias giving preference to younger patients with fewer comorbidities (rather than severity of their condition) whom, by virtue of their underlying fitness, may have had a greater chance of overcoming their illness [3, 46]. We recently reported that regions with higher income economies, patients with pleural infection were older with higher in-hospital mortality [50]. The increasing use of IET means that fewer patients are now referred to surgery but despite evidence of it being cost-effective in a recent health economics analysis of MIST-2 [51], it still does carry a significant cost, which means it is difficult to justify for all patients. So how can clinicians risk stratify which patients may need early aggressive therapy?

Traditional predictors of outcome, such as fluid purulence, have not been borne out in clinical studies and large randomised data has shown that such pleural fluid characteristics cannot be used to predict poor outcomes. A robust clinical prediction model that could enable clinicians to triage patients in terms of risk would help direct aggressive and expensive therapy to the patients with the poorest outcomes or at least, facilitate earlier discussions. The RAPID score [52] is the first prognostic risk model specific to pleural infection, enabling outcome prediction at presentation. It was derived from examination of the baseline characteristics of the MIST-1 cohort [19] and validated on the MIST-2 cohort [27]. Five characteristics (renal (serum urea), age, purulence, infection source (community *versus* hospital) and dietary state (serum albumin)) were found to be strongly independently associated with poor outcome. The presence of each of these would result in a score giving an estimation of 3-month mortality.

### ***Future directions***

There remain many areas of unmet clinical need in pleural infection. Microbiological diagnosis remains challenging and whether the increased yield from pleural biopsy can alter the treatment paradigm and improve antibiotic stewardship is of great interest. Research into antibiotics in pleural infection is lacking and has been somewhat overshadowed by a focus on optimising fluid drainage. There are still key questions into antibiotic penetration, route, duration of therapy and assessing adequacy of treatment, that remain unanswered. Studies looking at measuring antibiotic penetration to pleural fluid with perhaps the potential to individualise dosing are also intriguing and eagerly awaited.

Ongoing research into the role of iterative thoracentesis is likely to inform future guidelines on patient selection (*e.g.* defining low risk based on RAPID score) [52], and whether this can be incorporated into outpatient treatment pathways.

The currently recruiting MIST-3 trial is a multicentre, UK-based, RCT assessing the feasibility of randomising patients with pleural infection to early VATS *versus* early IET, and should begin to add some important insights into patient selection for surgery and inform future head to head trials.

Ongoing research into IET is now focusing on a personalised approach to optimise the MIST-2 regime. IET is rapidly inactivated by plasminogen activator inhibitor (PAI)-1 and it is now understood that this is present in variable concentrations in pleural fluid of adults with pleural infection, as demonstrated by the variability of the fibrinolysin inhibitor profile in the MIST-2 population. It is plausible that individual PAI-1 measurements in the future guiding dosing of IET could enhance both safety and efficacy. Although the MIST-2 dosing schedule was shown to be cost-effective in a recent health economics analysis [51], personalised dosing would certainly enhance this further.

New targets for IET that are less prone to PAI-1 activation are also on the horizon. Single chain urokinase plasminogen activator has proven durability with promising results in a recent phase 1 study [53], and may be an important advance in IET use in the near future. The RAPID score has undergone prospective validation in the international, multicentre observational study PILOT (unpublished data) and if the results of the validation cohort can be replicated, this could become a very useful tool to clinicians in the day-to-day management of pleural infection.

### **Conclusion**

There has been an acceleration in studies addressing key management issues in pleural infection, and much of the treatment that was previously based on expert opinion is now evidence based. The key event in most cases of pleural infection appears to be translocation of bacteria from the infected lung into the pleural space, an environment suited to bacterial replication. It would seem plausible that there are variations in bacterial virulence and inflammatory milieu of the host that govern why some patients present with simple parapneumonic effusions and others with complex parapneumonic effusions and empyema. A better understanding of these factors would allow us to better explain the different phenotypes seen in clinical practice and target treatment modalities accordingly. Risk stratification and earlier aggressive treatment may help improve the persistently poor outcomes of this morbid condition. Advances in IET may prove crucial for an increasing incidence amongst an ageing population whose fitness precludes access to surgical intervention.

### **Advances in pleural malignancy**

Malignant pleural effusion (MPE) is a common clinical problem affecting thousands of people in Europe and the USA each year [54, 55]. The majority of MPE arises from lung cancer, breast cancer and lymphoma [56, 57], and it is estimated that more than one-third of patients with lung cancer suffer from an MPE during the course of their disease [58]. MPE is associated with a poor prognosis, even in the case of small, asymptomatic effusions that are not amenable to aspiration [58]. Median survival with an MPE is 3–12 months and individualised estimates can be made using the LENT scoring system (pleural lactate dehydrogenase rate, neutrophil-to-lymphocyte ratio, tumour type and Eastern Cooperative Oncology Group performance status) [55] or the PROMISE score that performed better to predict 3-month survival [59]. MPE most commonly presents with dyspnoea, chest pain or discomfort that often profoundly impacts patients' quality of life (QoL). MPE can be challenging to manage and is associated with high mortality and healthcare burden. An estimated 126 000 hospital admissions are due to pleural malignancy each year in the USA [60], incurring high treatment costs, with an estimated 11.6% inpatient mortality. Despite major advances in cancer treatments, management options remain palliative and are directed at improving symptoms and QoL. Several factors should be taken into account in the management of MPE, including Eastern Cooperative Oncology Group performance status, primary tumour site and the presence of trapped lung. Over the past decade, several RCTs have led to a paradigm shift in the management of MPE, and shed light into the need to incorporate precision medicine into the field of pleural malignancy. This section summarises the recent advances in the management of pleural malignancy through an overview on diagnosis and treatment aspects, with a focus on new concepts.

### ***New concepts in the diagnosis of malignant pleural effusion***

#### ***Imaging***

Thoracic imaging is usually the first step that leads to suspicion of pleural malignancy. Thoracic ultrasound (TUS) has become the standard of care in the past decade for the evaluation of pleural effusion [61]. TUS can provide valuable information as it can estimate the quantity of pleural fluid and

detect parietal pleural thickening, as well as visceral and/or parietal nodules, highly suggestive of underlying malignancy [62]. Septations or loculations are also better detected by TUS, guiding subsequent pleural manoeuvres. It is now well recognised that thoracentesis should always be performed under real-time ultrasound, or by marking at the bedside, significantly reducing the rate of post-procedural pneumothorax [63]. New concepts have emerged concerning the ability of TUS to diagnose MPE. Ultrasound elastography gives information on tissue elasticity and stiffness, and thus could be used as a diagnostic tool. In the recent study by JIANG *et al.* [64], two-dimensional shear wave elastography was applied to the parietal pleura in a cohort of patients presenting with malignant and benign pleural effusions. It consisted of applying a stress using an acoustic radiation force impulse on the tissue, with the purpose to identify a stiffer tissue and therefore increase the accuracy of ultrasound elastography for differentiating MPE from benign pleural effusion. Pleural ultrasound elastography seemed to be helpful in differentiating MPE from benign pleural disease, with a sensitivity and specificity of 84% and 91%, respectively. Although this is a novel and potentially promising technique, further studies are needed to establish its role in the workup of suspected malignant effusion. TUS can also be helpful in predicting lung expansion after pleural drainage, hence diagnosing trapped lung. Several ultrasound features, such as a decreased transmission of cardiac pulsations using tissue movement in M mode or deformation using speckle-tracking images, can identify a nonexpandable lung (NEL) [65]. If appropriately validated, these could supersede the classic radiographic description of NEL, defined as <50% pleural re-apposition on post-drainage radiograph, which has a poor interobserver agreement [66].

Contrast-enhanced CT is able to identify features suggestive of pleural malignancy, such as pleural thickening (*e.g.* circumferential parietal pleural or mediastinal, thickening >1 cm) and pleural nodules [67]. A CT score has been proposed to distinguish malignant from benign effusions [68] with a sensitivity and specificity of 88% and 94%, respectively, including items such as pleural lesions, lung nodule, liver metastases, abdominal mass and absence of cardiomegaly, pericardial effusions and pleural loculations. However, due to its low negative predictive value in the absence of pleural abnormalities, further investigations have to be done in case of suspicion of pleural malignancy. Concerning the role of positron emission tomography (PET), a recent meta-analysis reported a sensitivity of 81% but a low specificity of 74% [69]. Therefore, due to the high rate of false positives cases (*e.g.* inflammatory pleuritis or post-talc pleurodesis), PET should not be used as a standard of care for the diagnosis of MPE. Hence, to date, no imaging modality has been shown to diagnose a malignant effusion without the need for further cytological examination.

#### *Thoracentesis: the cornerstone in the initial management of MPE*

In cases of suspected MPE, thoracentesis should be the first step in the diagnostic process to obtain fluid for analysis, whilst concurrently aspirating a sufficient volume to provide a therapeutic effect. It is crucial to observe the symptomatic effect of this drainage. A recently published RCT demonstrated comparable levels of procedural comfort and dyspnoea improvement between active (manual) aspiration and gravity drainage [70]. Shortness of breath, one of the cardinal symptoms of pleural effusion, is rarely due to a lung problem, but rather attributable to diaphragmatic dysfunction secondary to compression by volume, leading to modification of diaphragm shape [71]. Thus, in the absence of symptomatic improvement with pleural drainage, alternative causes should be considered (*e.g.* pulmonary embolism, lymphangitis carcinomatosa). Thoracentesis can also identify NEL, when pleural aspiration is associated with negative pleural pressure and result in chest pain or post-procedure pneumothorax. Measurement of pleural pressure can be done using a pleural manometer, that allows an understanding of the impact of pleural effusion drainage on pleural pressure. In a normal lung, pleural pressure is negative (from  $-3$  to  $-5$  cmH<sub>2</sub>O) at the functional residual capacity, and becomes positive in the presence of a pleural effusion. While evacuating the fluid, pleural pressure decreases and become slightly negative at the end of the drainage. In contrast, patients with NEL have a different modifications and changes of pleural pressure. Indeed, in malignant condition, an entrapped lung, due to either proximal endobronchial obstruction, or more frequently visceral pleural thickening, can be seen. In these cases, pleural pressure is also positive prior to drainage, but rapidly become excessively negative ( $<-20$  cmH<sub>2</sub>O) during the effusion removal, and thus could lead to patient's symptoms. Albeit a useful tool, a recent study reported that manometry measuring pleural pressure during thoracentesis does not reduce the risk of post-procedure chest pain or discomfort [72]. However, identify patients with NEL is crucial and, in this setting, pleural manometry could be an useful tool. Moreover, if adequate lung expansion occurs following drainage (either with thoracentesis or a chest tube) pleurodesis can be considered.

It has previously been assumed that repeated pleural fluid sampling increased the sensitivity after a first negative procedure [56], but the results of a recent prospective study have refuted this [73]. Overall, the sensitivity of pleural fluid cytology to detect a malignant effusion is 46%, with significant variability among tumour type. The highest cytological yield is observed for ovarian carcinoma (>95%), lung adenocarcinoma

(>80%) and breast cancer (71%), with the poorest yield being for malignant mesothelioma (6%) [56, 73]. Therefore, the choice of investigation after a first negative thoracentesis should take into account the known or suspected primary tumour, so as to avoid futile interventions and not delay care. Through advances in precision medicine, identification of oncogenic driver mutations leading to targeted therapy has now become standard practice in nonsmall cell lung cancer. For the detection of EGFR, KRAS, BRAF, ALK and ROS1, pleural fluid cell-block seems to be adequate for mutation analysis (using DNA or next generation sequencing and fluorescence *in situ* hybridisation) [74–77]. Since the relative development of immunotherapy, analysis of programmed death ligand-1 (PD-L1) is crucial to select appropriate candidates for anti PD-L1 treatment [78–80]. Despite recent reports of good correlation between PD-L1 expression from pleural fluid cell-blocks specimen, compared to histological biopsies [81–83], the strength of evidence remains insufficient to negate the need to undertake histological biopsies, unless these are not feasible due to patient fitness.

#### *Pleural biopsies*

In cases of suspected MPE, histological analysis obtained through pleural biopsies is recommended, especially after negative pleural cytology [84]. Image-guided (CT or ultrasound) cutting-needle pleural biopsy can be safely performed under local anaesthesia with excellent diagnosis yields in cases of pleural abnormalities (e.g. pleural nodules or thickening) [85]. CT-guided biopsies have been shown to be superior to blind needle techniques with respective sensitivities of 87% *versus* 47% [86], possibly due to focal and patchy pleural involvement, as well as the obvious risk reduction in complications. PET-CT is routinely reserved for early stage disease but, in theory, it can be used to identify targets to better guide pleural biopsies. Whether or not this approach adds diagnostic value has been studied in the recently completed randomised multicentre TARGET trial that directly compared PET-CT *versus* CT-guided pleural biopsies in patients with suspected malignancy who have had one nondiagnostic biopsy [87].

There is an increasing evidence base relating to the diagnostic use of TUS-guided biopsies over the past 15 years. These can be easily and safely performed by pulmonologists with a diagnostic yield similar to those obtained with CT-guided biopsies, including for mesothelioma, and especially when the suspect lesion is >20 mm [88]. However, it should be noted that in the absence of pleural lesions such as thickening or nodularity, the diagnostic yield of image-guided biopsy significantly decreases and thoracoscopic pleural biopsies under direct vision should be performed where possible.

Both VATS and medical thoracoscopy can be performed to obtain sufficient pleural tissue with a similar diagnostic yield (>90%) for MPE [89–91], especially in cases of suspected malignant pleural mesothelioma [92]. Despite advances in techniques, drawbacks of VATS include significant post-operative pain [93] and the need for general anaesthesia with single lung ventilation. Medical thoracoscopy can be a safe alternative, performed under local anaesthesia or conscious sedation using a single port of entry. In the absence of adequate effusion, pneumothorax induction can be safely performed in a spontaneously breathing patient, to facilitate entry into the pleural space [94]. However, in a situation of pleural symphysis or adhesions that do not allow an easy access to the pleural cavity, VATS should be preferred. Forceps biopsies can be performed on the parietal pleura using a rigid thoracoscope through a 5- or 7-mm trocar. Flexi-rigid medical thoroscopes can also be used as an alternative with a similar diagnostic yield to those obtained with a rigid instrument [95]. Tissue samples obtained with flexible forceps are smaller, but yield can potentially be increased using cryobiopsies, although the evidence for the latter in the pleura remains limited to safety and feasibility [96]. Moreover, thoracoscopy facilitates a “one-stop” diagnostic and therapeutic procedure including the option of instillation of sclerosing agents in the pleural cavity.

#### ***Management of malignant pleural effusion: what is new?***

Despite new advances in the treatment of cancer, management options of MPE remain palliative and are primarily aimed at improving QoL. Few pleural malignancies can be controlled with systemic treatment but in most cases, MPE control requires a pleural intervention. Repetitive thoracentesis are recommended only when life expectancy is short (<1 month), due to the high rate of recurrence. Since the publication of the 2010 British Thoracic Society guidelines [97], talc pleurodesis has been the established first-line definitive treatment for MPE. Pleurodesis aims to perform a diffuse inflammatory pleural reaction with an activation of the coagulation system leading to fibrin deposition and adhesion between parietal and visceral pleura, in order to avoid the fluid accumulation [98]. Several sclerosing agents have been evaluated to obtain a pleurodesis but a recent review of literature emphasised the superiority of graded talc [99–101]. Placement of indwelling pleural catheters (IPCs) was initially only advocated in patients unsuitable for pleurodesis in cases of trapped lung or after pleurodesis failure.

In the past 10 years, several RCTs and good quality data have led to a paradigm shift in the management options of MPE and the publication of new practical guidelines and a statement from the European



Respiratory Society/European Society of Thoracic Surgeons and the American Thoracic Society. They both emphasise the superiority of talc over other sclerosing agents [84, 102] and suggest that talc poudrage may be more effective than talc slurry [84]. This has now been superseded by the very recent publication of the TAPPS trial, which compared thorascopic talc poudrage *versus* talc slurry *via* chest tube and demonstrated overall equivalence in these two techniques, with no significant difference in the rate of pleurodesis failure at 90 days [103] ([www.isrctn.com](http://www.isrctn.com); ISRCTN47845793). IPC is also now recommended as a suitable alternative in first-line intervention [104, 105], bringing patient choice to the forefront of clinical decision-making. Patient-related outcome measures (PROMs) such as symptom palliation, hospitalisation length, functional status and QoL are now well recognised as treatment aims rather than pleural symphysis on radiological assessment.

#### *Indwelling pleural catheters as an alternative first therapeutic intervention*

IPC is a silicone tube of 15–16 Fr placed under local anaesthesia in the pleural cavity and tunneled subcutaneously with a one-way valve at the distal extremity. A profibrotic cuff secures the catheter to the skin and provides a “bacterial protection” to the pleural cavity. It can be inserted on an ambulatory basis and allows outpatient drainage performed by a nurse or trained family members according to patient’s symptoms. IPC related complications occur in approximately 10–20% of patients but are mostly minor (*e.g.* catheter malfunction and cellulitis) [106–110]. The main serious complication is infection of the pleural cavity (<5%), which in most cases does not require removal of the drain and may be controlled by antibiotics combined with frequent drainage. Interestingly, two-thirds of patients can develop pleurodesis after infection of the pleural cavity, mostly reported in case of *Staphylococcus aureus* infection [106].

In the past 7 years, RCTs have studied different outcomes of IPC for the management of MPE. Some of these studies have compared IPC *versus* talc slurry PROMs. They established that IPC improved breathlessness and QoL in a similar manner to talc slurry, as well as significantly reducing the initial length of hospitalisation (2.49 *versus* 4.98 days) and the pleural related days of hospitalisation for up to 12 months (10 *versus* 12 days) [109, 111].

Retrospective studies have previously reported a rate of spontaneous pleurodesis of ~43% with a high variation between tumour type [104]. Spontaneous pleurodesis was defined by three consecutive drainages <50 mL with no pleural effusion on chest radiography. Higher rates were observed for breast and ovarian cancer (>70%), whereas it was shorter for lung cancer (44%) [110]. In more recent prospective RCTs, rate of spontaneous pleurodesis appears to be lower using the symptom-guided approach but can increase depending on the frequency of IPC drainage [55, 58]. Indeed, both the ASAP [112] and AMPLE-2 [113] trials favoured daily IPC drainage that led to higher rate of spontaneous pleurodesis (47% and 37%, respectively) compared to symptom-guided drainage (24% and 17%, respectively). Both drainage regimens improved dyspnoea with no difference in term of post-drainage pain [109].

A recent cost-effectiveness analysis of IPC *versus* talc slurry was performed [114] alongside the TIME2 trial [109]. For patients presenting a limited survival (<14 weeks), IPC was more cost-effective, but became most costly when at least 2 h nursing time per week was assumed for catheter drainage. This might impact the results reported by the ASAP and AMPLE-2 trial which favoured daily IPC drainage, even though shortening the duration of IPC treatment through earlier pleurodesis could potentially reduce the cost of ambulatory treatment.

#### *Combined therapies using sclerosing agents and IPC*

The aim of combining therapeutic interventions is to obtain the highest chance of pleurodesis with the shortest hospital stay, whilst being as minimally invasive as possible. Rapid pleurodesis consists of performing a talc poudrage during a medical thoracoscopy followed by the placement of an IPC during the same operation, in order to reduce the length of hospital stay through ambulatory drainage, and was performed in two studies. Both studies reported high rate of pleurodesis (>90%), a short median hospitalisation time (1.79 and 3 days, respectively) and removal of the catheter at a median of 8 days [115, 116]. Instillation of talc slurry through an IPC initially reported a high rate of pleurodesis in an outpatient setting [117]. More recently, the IPC-PLUS RCT analysed outcomes of this regimen while excluding trapped lung [118]. Participants received either talc slurry or saline through IPC 10 days after catheter placement. At 35 days, the rate of pleurodesis was higher in the talc group (43% *versus* 23%) and increased at 70 days (51% *versus* 27%). Albeit promising, pleurodesis rates reported with the talc regimen were lower than expected, especially in an enriched population considered “fit for pleurodesis”. Moreover, the 27% rate of spontaneous pleurodesis observed at day 70 was lower than those observed in initial retrospective studies, and in line with spontaneous pleurodesis rates observed in other RCT without additional intervention [109, 112].

Combining therapy by coating the IPC with a sclerosing agent, such as silver nitrate has reported promising outcomes. Intrapleural instillation of silver nitrate has initially been reported to be effective in animal and human studies to obtain pleurodesis, but its use has been limited due to adverse effects reported with high dose. A new drug-eluting IPC has recently been developed, and experimented on in an animal study. Pleurodesis scores were higher in the silver nitrate-coated IPC animal group and no toxicity or mortality was due to a silver-coated catheter [119]. A prospective clinical study including nine patients [120] reported the safety and efficiency of silver nitrate-coated IPC for the management of MPE with an expandable lung obtaining an 89% rate of pleurodesis. An ongoing multicentre RCT is currently assessing the efficiency of silver nitrate-coated IPC in term of pleurodesis rate at 30 days (ClinicalTrials.gov identifier: NCT02649894).

### Conclusions

Identifying pleural involvement in malignancy is fundamental as it has both therapeutic and prognostic implications. Thoracentesis is useful in the initial diagnostic workup as it facilitates a simultaneous therapeutic opportunity and assessment. However, frequently negative pleural fluid cytology mandates the need for pleural biopsies and, increasingly, the feasibility of “direct to biopsy” pathways are being studied. According to the tumour characteristics and operators’ skills, both image-guided cutting-needle or thoracoscopic biopsies can lead to a diagnosis in most cases. There is now high-level evidence suggesting equivalence in IPC *versus* talc pleurodesis, as well as slurry *versus* poudrage, and options for combining techniques. The onus is on clinicians to allow patient choice and priorities to dictate first-line treatment. Our understanding of the genesis of MPE to identify future targets for both systemic or intrapleural

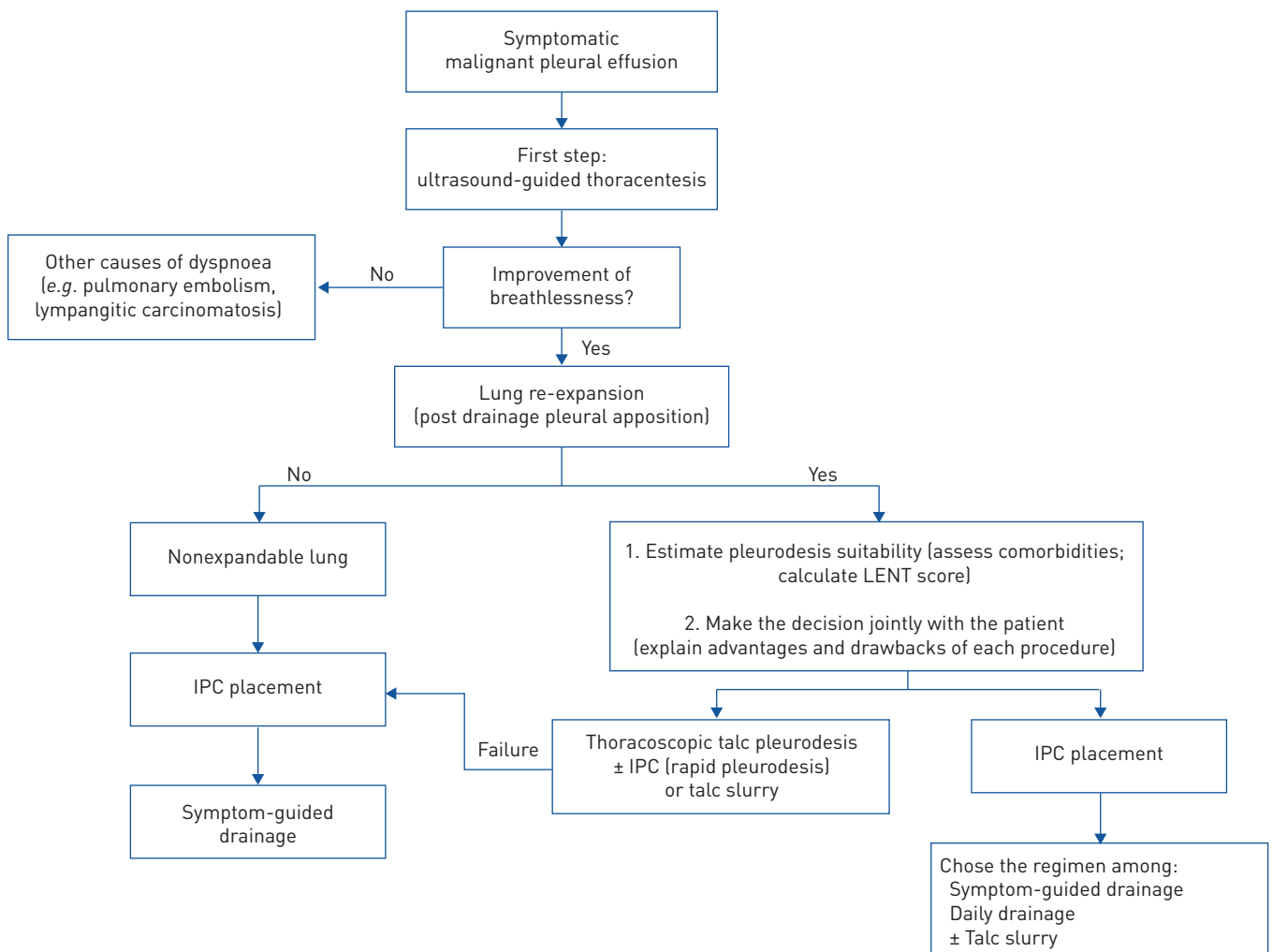


FIGURE 2 A practical algorithm for the management of malignant pleural effusion. IPC: indwelling pleural catheter; LENT: pleural lactate dehydrogenase rate, neutrophil-to-lymphocyte ratio, tumour type and Eastern Cooperative Oncology Group performance status.

treatments and the knowledge of predictive parameters for pleurodesis success have to be increased to optimise MPE management (figure 2).

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