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REVIEW ARTICLE

The role of interventional pulmonology in the diagnosis and management of undiagnosed pleural effusions

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ABSTRACT

In recent years, there has been an unprecedented drive for quality research in pleural disease, and advances in technology that have changed the landscape of interventional pulmonology, particularly for patients with undiagnosed pleural effusions. With a range of pleural procedures now available to the pulmonologist, the challenge is integrating these into a diagnostic and therapeutic pathway that is individualised to the patient's needs, while also providing expeditious diagnostic evaluation, limiting the number of procedures, and shifting care to the ambulatory setting. This review aims to summarise the important evidence related to pleural procedures, discuss their advantages and limitations, and describe their role in the management of undiagnosed pleural effusions.

Keywords: Interventional pulmonologists. Pleural infection. Pleural malignancy. Undiagnosed unilateral pleural effusion.

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INTRODUCTION

Pleural effusions are a common problem encountered in everyday practice. It can arise from more than 50 different diseases with both benign and malignant aetiologies[1,2]. With the rising incidence of malignant pleural disease and pleural infection[3,4], each associated with significant morbidity and mortality, the undiagnosed pleural effusion can often be a challenge to evaluate and treat. The management of pleural disease however has evolved significantly over the past two decades[5]. There is now an expansion of diagnostic and therapeutic interventions available to the pulmonologist. These have empowered physicians and pleural services to develop more efficient pathways for expeditious diagnosis and treatment, with a focus on ambulatory care and individualised management. The evolution of ultrasonography in recent years has also facilitated upfront diagnostic evaluation and enhanced procedural safety and planning[6,7].

However, determining the suitability of specific pleural interventions is often not straightforward, with several elements to be considered. These include procedural expertise and safety, the need for "actionable histology", expediting time to diagnosis and treatment, time spent out of hospital, and resource constraints. Patient values, preferences, and suitability for treatment are also key considerations before performing any pleural intervention. It is important to keep in mind that a holistic assessment with careful history taking, physical examination, and targeted investigations are still key for appropriate decision making. Several causes of pleural effusions such as heart failure, which remains one of the most common causes worldwide[8], can be diagnosed with careful assessment of the patient, without the need for advanced pleural interventions[9].

In this review, we aim to summarise the role of several advanced pleural procedures available to the modern pleural service. We will also explore the nuances of fundamental pleural interventions (e.g., pleural aspirations and drainage) and discuss how adjuncts including ultrasonography have influenced the current management of undiagnosed pleural effusions.

THORACIC ULTRASONOGRAPHY

The incorporation of thoracic ultrasound (TUS) into pleural disease has advanced our diagnostic capabilities and transformed how we perform pleural procedures. It should be considered an essential skill for all interventional pulmonologists. It has distinct advantages because of its widespread availability, lack of radiation, and being readily portable and relatively inexpensive. There is now strong evidence supporting its role in procedural guidance to increase diagnostic yield and reduce the risk of complications such as pneumothoraces and organ puncture[10,11].

The diagnostic utility of TUS in patients with pleural effusions is clear. It is far more sensitive than chest radiographs at detecting pleural effusions[12] and provides valuable information such as pleural effusion size, echogenicity, septations, pleural thickening and nodularity, diaphragmatic shape and movement, all of which help to streamline evaluation and treatment. TUS assessment is

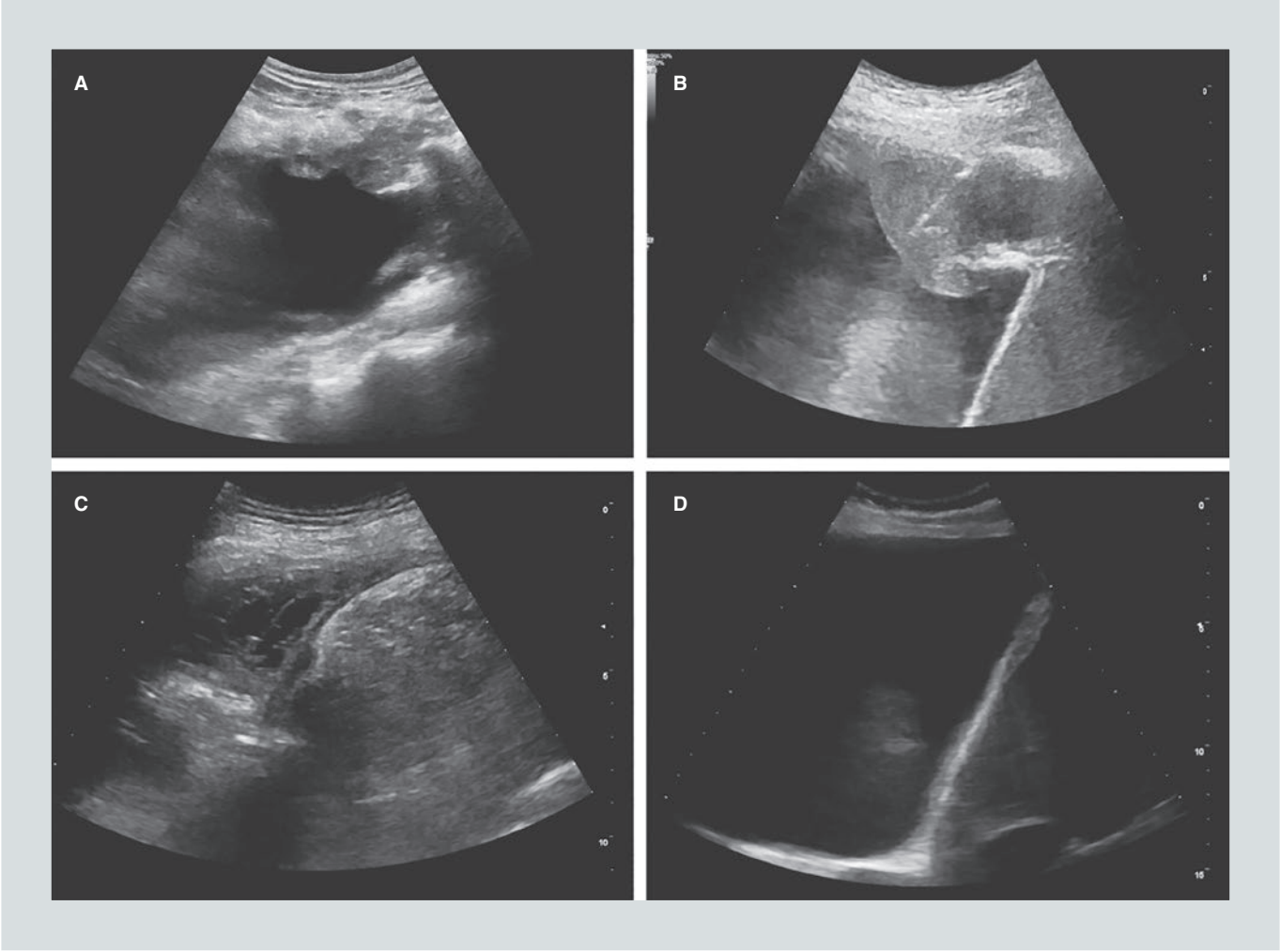

Figure 1. **A**: irregular nodularity of the parietal pleura consistent with a malignant process. **B**: real-time ultrasound guided pleural biopsy of a pleural based mass with a cutting needle. **C**: parietal pleural thickening and septations. **D**: large anechoic pleural effusion with a flattened diaphragm.

particularly helpful in malignant pleural effusions (MPE)[13]. A prospective study evaluating the diagnostic value of ultrasonography in 154 patients reported a diagnostic accuracy of up to 82%, with features such as pleural or diaphragmatic nodularity and thickness > 10 mm supporting a malignant etiology[14]. Visualisation of parietal nodularity or thickness also helps to guide image guided pleural biopsies (Figure 1A and 1B)[15]. In addition, the septations and loculations commonly seen with pleural infections are also readily identified with TUS (Figure 1C), with evidence supporting the superiority of TUS over computed tomography (CT) in identifying pleural septations[16]. There are advantages of CT imaging such as superior visualisation of the mediastinum, mediastinal pleura, and lung parenchyma, and therefore both imaging modalities should be viewed as complementary rather than exclusive[17].

The utility of ultrasound goes beyond diagnostic evaluation, also providing valuable information for procedural planning. TUS assessment for septations, or absence of lung

adhesions as suggested by the presence of lung sliding, is useful to evaluate suitability for thoracoscopy[18]. Abnormal diaphragmatic shape (Figure 1D) or paradoxical movement predicts symptom benefit from therapeutic pleural aspirations independent of expandable or non-expandable lung[19]. There has been data suggesting a role for ultrasonography in predicting non-expansile lung using M-mode imaging to characterise the transmission of cardiac impulses to adjacent atelectatic lung[20], and screening for intercostal vessels using colour doppler was shown to alter the site of procedural intervention in 30% of patients[21]. Finally, assessment of lung sliding following talc pleurodesis led to reduced hospitalisation days, by facilitating earlier removal of chest drains in a recent randomised trial[22].

One important limitation of ultrasonography is that it is ultimately operator dependent. Clearly, decisions made from incorrect interpretation of ultrasound images can lead to unnecessary risk to the patient. As more physicians adopt ultrasonography as a diagnostic and interventional adjunct, there is also a need for robust training standards and incorporation of ultrasonography in pulmonology training programs[10].

PLEURAL ASPIRATION AND DRAINAGE

Pleural fluid analysis is a cornerstone in the evaluation of pleural effusions. Pleural aspiration (also called thoracentesis) is a safe procedure, provides important diagnostic information and can provide therapeutic relief for symptomatic pleural effusions. Major complications such as bleeding and re-expansion pulmonary oedema are rare[23]. The largest case series reported an incidence of symptomatic re-expansion pulmonary oedema in only 0.5% of patients undergoing large volume thoracentesis of one litre or more[24].

Since its creation in 1971, Light's criteria remain a fundamental component of pleural fluid analysis, but there are important caveats to appreciate. Firstly, the criteria cut-offs perform with high sensitivity in identifying true exudates, at the cost of reduced specificity. This means that Light's criteria are less likely to miss true exudates like cancer but may "overcall" exudates arising from conditions like heart failure. This "overcalling" is particularly common where the pleural fluid protein criteria is a transudate and the pleural fluid lactate dehydrogenase is an exudate (or vice versa), also referred to as "discordant" exudative effusions. Discordant exudates account for up to 33% in a large case series and perform with a positive predictive value of 81.5% for exudative effusions, compared to 99.4% in concordant exudates[25]. Another challenge in interpreting Light's criteria is that up to 10-15% of MPEs are transudates on initial analysis[26-28], and careful clinical and radiological assessment is important to guide further management.

The main drawback of pleural fluid cytology is its limited sensitivity for MPEs, reported to be 46% in a large prospective cohort study of 921 patients[28]. The yield from pleural fluid cytology is further reduced when "actionable cytology" is considered. A retrospective study by Tsim et al.[29] showed that only 61% and 71% of pleural aspirations had adequate material for full molecular profiling

of non-small cell lung cancers and breast cancers respectively. Interestingly, the yield from pleural fluid cytology varies significantly based on cancer type, as high as 94.7% in ovarian cancer to only 6.1% in mesothelioma[28]. This makes upfront pleural biopsy with local anaesthetic thoracoscopy (LAT) a reasonable option for patients with a high suspicion for mesothelioma[5].

Treatment of pleural infection or talc pleurodesis are common reasons for chest drain insertion. Small bore chest drains (14 French or less) are widely used by physicians for the above indications[30]. In pleural infection, small bore chest drains are almost always adequate. A recent meta-analysis evaluating small (14 French or less) versus large bore drains showed no difference in surgical referral rate, mortality, and hospital length of stay[31]. The evidence to guide drain size for talc pleurodesis however is less clear. A meta-analysis evaluating chest drain sizes in pleurodesis efficacy reported a 73.8% versus 82.0% success rate for small versus large chest drains respectively[32]. The TIME1 trial randomised controlled trial (RCT) assessed the effect of chest drain size on pleurodesis efficacy and found a higher pleurodesis failure rate with 12 French chest drains (30 versus 24%), failing to meet the non-inferiority criteria. However, interpretation of this result is complicated by the large number of patients in the study who had undergone a thoracoscopy and large chest drain insertion, and hence could not be included in the analysis. Most guidelines recommend that chest drains inserted for talc pleurodesis should be at least 12 F with a caveat that 12-16 French chest drains may be more likely to get blocked with talc particles compared with larger bore drains[5].

IMAGE GUIDED PLEURAL BIOPSY

Considering the relatively low yield of pleural fluid cytology, pleural biopsies remain the gold standard for the diagnosis of MPEs. Pleural biopsies are also useful in other pleural diseases such as tuberculous pleuritis, where the diagnostic yield is as high as 95%[33]. There are several options for obtaining pleural biopsies. These include surgical pleural biopsy, LAT, and closed needle biopsy (either Abram's needle or cutting-needle biopsy) with or without image-guidance (CT or ultrasound).

Closed biopsy techniques without image-guidance, most commonly using Abrams needles, date back to decades ago and remain important in resource-poor countries with limited access to advanced pleural interventions. In regions of the world where tuberculosis is endemic, closed biopsy with an Abrams needle (without image-guidance) performs with a relatively high diagnostic sensitivity of up to 80% (when combined with pleural fluid culture) for tuberculous pleuritis[34] and is a practical low-cost option. This high performance is related to tuberculous (TB) pleuritis being a uniform and pan-pleural disease. However, such biopsies perform poorly for malignant disease (which unlike TB does not tend to affect the pleura diffusely) with significantly reduced diagnostic sensitivity compared to image-guided biopsy[35].

CT or ultrasound-guidance conversely allows the operator to identify focal pleural thickening or nodules as targets for biopsy. With cutting needles, image guided biopsies perform with a relatively high diagnostic yield for malignant disease, ranging from 75% to 90%.

A recent meta-analysis reported a pooled diagnostic yield of 84% for ultrasound-guided biopsy and 93% for CT-guided biopsy[36]. Whether CT-guided biopsies are superior to US-guided biopsies for diagnostic accuracy remains unclear, with only a few direct head-to-head comparisons between CT and US-guided biopsies. One RCT randomised patients to CT-guided core needle biopsy under direct imaging observation, and ultrasound-guided Abrams needle biopsy with ultrasound used to identify the site for biopsy (no direct imaging observation) and showed no difference in diagnostic accuracy (79.2% versus 72.3% respectively)[37]. Another RCT randomised patients with cytology negative exudates to CT-guided Abrams needle biopsy and US-guided core needle biopsy and reported a lower diagnostic sensitivity from US-guided biopsy (66.7% versus 82.4%)[38]. However, interpretation of both RCTs is difficult due to the different biopsy techniques (Abrams versus core needle) used. In the latter study by Metintas et al.[38], neither procedure was performed under real-time visualisation with imaging used only to identify the site for pleural biopsy.

Traditionally performed by interventional radiologists, ultrasound-guided pleural biopsy is now finding its way into the hands of pulmonologists. In recent years, several studies describing physician-led ultrasound-guided pleural biopsies using 14-18G cutting needles have reported a diagnostic sensitivity between 85-96%, and a good safety profile[17,39-40]. In the largest cohort study of 90 ultrasound guided pleural biopsies, there were two complications: one patient had pneumothorax requiring chest drain insertion and a three-day hospitalisation, and another patient had bleeding that resolved with the application of external pressure over the chest wall[39]. There are several potential advantages using ultrasound-guided biopsies; patient sedation is usually not required, there is no radiation risk to the patient, and ultrasound is a relatively accessible and requires minimal consumables. Doppler ultrasound screening of the intercostal vessels at the time of procedure can also be conducted.

Image guided pleural biopsies are also a useful alternative for patients with significant comorbidities and frailty, or patients with heavily septated pleural fluid or lung adhering to the chest wall, thus prohibiting LAT. Furthermore, in patients with suspected pleural infection, pleural biopsies increased the sensitivity of bacterial culture yield for pleural infections by up to 25% with no increased risk of adverse events as shown in the Pilot feasibility study in establishing the role of ultrasou2d-guided pleural biopsies in pleural infection (AUDIO study) [41]. However, image guided biopsies appear to be inferior to thoracoscopy biopsies specifically for the yield of molecular profiling and 'actionable histology' for cancer. In a retrospective analysis comparing the yield of actionable histology, the yield from thoracoscopic biopsies (95%) was significantly superior to CT scan guided biopsies (86%) and ultrasound guided biopsies (77%)[42].

THORACOSCOPY

Local anaesthetic thoracoscopy (also known as pleuroscopy) is a well-established diagnostic and therapeutic tool for undiagnosed pleural effusions. As the name suggests, it is performed under local anaesthesia and conscious sedation, and allows for careful inspection of the pleural cavity, pleural biopsies under direct

vision, and therapeutics such as talc poudrage, concurrent indwelling pleural catheter (IPC) insertion. A "one-stop" approach is therefore possible with LAT, particularly for suspected mesothelioma where the yield of pleural fluid cytology is less than 10%[28]. The increasing practice of day case LAT also increases the shift towards ambulatory care for these patients[43].

LAT differs from video-assisted thoracoscopic surgery (VATS) in that VATS is performed with single lung ventilation and general anaesthesia, and typically utilises multiple entry ports. But this allows for complete visualisation of the hemithorax and more advanced interventions such as lobectomy, lung biopsies and decortication. However, most pleural effusions, apart from heavily septated effusions or empyema in the organised phase, can be adequately evaluated with LAT, which has a good safety profile and diagnostic accuracy. For MPE, biopsies performed with LAT under direct visualisation lead to a diagnostic yield of up to 95%, significantly higher than image guided pleural biopsy techniques, and in particular pleural fluid cytology for malignancy. A recently published meta-analysis of 41 studies reported a pooled diagnostic sensitivity of 92.9% of LAT for MPE[44]. LAT is also a safe procedure in experienced hands, with a pooled rate of 1.8% of major complications including bleeding, empyema or persistent air leaks, and a combined mortality rate of 0.34% from 47 studies[45].

While rigid thoracoscopy has traditionally been used for LAT, an alternative is the semi-rigid thoracoscope. The semi-rigid thoracoscope has the advantage of increased manoeuvrability and a gentler learning curve for respiratory physicians already familiar with the flexible bronchoscope, but is more expensive, may require maintenance and repairs more often and is less adept at sampling densely thickened pleura and therapeutics such as controlling haemorrhage after biopsy[46]. RCTs comparing the efficacy and outcomes of rigid versus semi-rigid thoracoscopes clearly show that larger biopsy samples can be obtained with rigid thoracoscopes, but whether this results in increased diagnostic yield remains unclear. Two randomised studies have conflicting results. Rozman et al.[47] published the first randomised study with 84 patients and found similar diagnostic accuracy (100% with rigid thoracoscopy and 97.6% with semi-rigid thoracoscopy) despite having larger specimens obtained with the rigid forceps (24.7 versus 11.7 mm^2). In the second study by Dhooria et al.[48] with 90 patients, the diagnostic yield was higher with rigid thoracoscopy (97.8% versus 73.3%) on an intention-to-treat analysis but similar (100% versus 94.3%) in those with successful biopsy (excluding patients in whom thoracoscopy was not feasible due to extensive adhesions)[48]. Martinez-Zayas et al.[44] evaluated the outcomes of thoracoscopy in a recently published meta-analysis and reported similar diagnostic sensitivity for MPE between rigid and semi-rigid thoracoscopy (92.9% [95% CI: 90.8-94.8] versus 93.1% [95% CI: 88.0-97.1] respectively)[44].

An alternative to traditional forceps biopsy during LAT is pleural cryobiopsy. A flexible cryoprobe can be introduced through the working channel of the thoracoscope, and the tip cooled transiently while in contact with the pleura, to freeze adjacent tissue for biopsies. However, there is no convincing data to favour the use of cyrobiopsy over forceps

biopsies. A crossover randomised trial compared pleural cryobiopsy with flexible forceps biopsy in 200 patients and found no significant difference in diagnostic yield[49]. A recent meta-analysis of 15 studies concluded that there was no difference in diagnostic yield, even with significantly larger specimens obtained with pleural cryobiopsy[50].

The management of non-specific pleuritis (NSP) is worthy of mention, as it accounts for up to 35% of patients undergoing thoracoscopic biopsies[51]. defined as fibrinous or inflammatory pleuritis which cannot be attributed to a specific benign or malignant aetiology. As between 5-15% of patients with NSP are diagnosed with cancer (most commonly mesothelioma) at a median time of approximately 9-12 months[52-55], a common practice is therefore to follow up these patients for a minimum of 12-24 months.

In pleural infection, the role of LAT remains unclear. It appears as an attractive alternative to surgery and intrapleural fibrinolytic therapy, and allows for the mechanical breaking down of loculations, fluid drainage and pleural biopsies for increased microbiological yield. However, the data supporting LAT in pleural infections are largely from case series or retrospective observation studies and should be interpreted with caution[56]. One small, randomised trial of only 32 patients showed a signal towards reduced hospital length of stay with LAT compared to chest drainage and intrapleural therapy, but no difference in treatment failure or complications[57], and the study used the outcome of time in hospital from the point of intervention (as opposed to the point of randomisation). A multi-centre UK feasibility study (SPIRIT trial: 'Studying pleuroscopy in routine pleural infection treatment') randomising patients to LAT and chest drainage was attempted, but unfortunately demonstrated that adequate recruitment within the designed protocol was not possible in the UK given the thoracoscopy provision available.

What we currently practice, and propose, is a consideration for an "upfront" or "straight-to-thoracoscopy" approach in patients with suspected mesothelioma. Where a pleural biopsy is indicated, we also adopt a preference for thoracoscopic biopsy over image guided pleural biopsies except for patients who are unfit for LAT, or if LAT is technically not possible or anatomically challenging. This is based on the higher diagnostic yield (including actionable histology) and sensitivity for MPE with thoracoscopic biopsy, the ability for simultaneous pleural fluid control (complete fluid drainage, talc poudrage or IPC insertion) with LAT, and in the case of mesothelioma, identification of histological subtypes (e.g., biphasic mesothelioma) with separate site pleural biopsies during LAT.

INDWELLING PLEURAL CATHETER

The IPC is a multi-fenestrated tunnelled catheter made from flexible silicone, with a small polyester cuff enveloping the medial portion of the tube. It is placed percutaneously, and the procedure can be performed in an outpatient setting. The proximal end is connected to a one-way valve designed to be attached to proprietary vacuum drainage bottles or drainage bags. In the current British Thoracic Society (BTS) 2023 guidelines, IPCs are recommended as an option for first-line therapy for

the management of symptomatic malignant effusions. The main objective of this catheter is to relieve breathlessness via repeated drainage, with the additional benefit of auto-pleurodesis (in the absence of any sclerosing agent) reported in up to 51% of cases[58]. Daily application of vacuum bottle drainage has been shown to increase the rates of auto-pleurodesis, which has been shown in RCTs (Randomized trial of pleural fluid drainage frequency in patients with malignant pleural effusions [the ASAP trial] and Aggressive versus symptom-guided drainage of malignant pleural effusion via indwelling pleural catheters [AMPLE-2] trial)[59-60].

IPCs can be used for non-malignant recurrent pleural effusions as well, including chronic pleural infection, especially in the group of patients with trapped lung. Patients with recurrent and chronic pleural infections have difficult management issues. Surgical drainage is currently recommended for patients who have failed 'medical therapy' (i.e., chest tube insertion, and antibiotic therapy), but the options for patients who are not suitable candidates for surgery are limited and hence the IPC can be useful here.

Although IPCs are not routinely placed for undiagnosed pleural effusions, there is an evolving role for upfront insertion when the patient has suspected MPE. Conventionally, the IPC is inserted only after the diagnosis is proven after pleural fluid aspiration. However, patients treated with aspiration alone have a high chance of recurrent fluid accumulation and worsening symptoms, which results in recurrent unplanned medical visits, contributing to patient distress. To streamline this process, an ongoing randomised controlled trial (The randomised thoracoscopic talc poudrage and indwelling pleural catheters versus thoracoscopic talc poudrage only in malignant pleural effusion [TACTIC] trial) is investigating the hypothesis that in patients with suspected malignant effusions, upfront thoracoscopy, talc pleurodesis and IPC insertion reduces hospital length of stay, compared to thoracoscopy and talc pleurodesis alone[61]. It is thought that the potential advantages of this approach include reducing hospital length of stay, and shorter time to achieving pleurodesis, thereby also allowing earlier removal of the IPC.

The complication rates of IPCs are generally low. The main complication of IPC is thought to be infection, which occurs in up to 5% of patients[62]. In cases of MPE, catheter tract metastases can develop, which usually present as a tender nodule/mass near the IPC insertion site or tract. Catheter tract metastases have been reported in cases where the primary cancer originated from the lung, breast, ovary, or mesothelioma[63]. Other complications include bleeding, organ injury, pneumothorax, dislodgement, tube fracture on removal, which are not specific to IPC but associated with tunnelled line insertion.

TALC PLEURODESIS

Historically, the preferred treatment in managing malignant effusion is via the induction of pleurodesis, usually via the administration of sterile talc into the pleural cavity. Talc can be administered either via slurry (talc is made up with saline and inserted via the chest drain), or by insufflating it under direct vision as poudrage. Data from a meta-analysis

has confirmed that the use of talc is the most efficacious agent for achieving pleurodesis, with success rates of up to 82% reported[64]. Along with the insertion of an IPC, talc pleurodesis is a first line option for definitive management of symptomatic pleural effusions. The choice for talc pleurodesis or IPC insertion should be a shared decision between physician and patient, with each offering unique advantages and disadvantages. While the IPC can be performed in an outpatient setting, it is associated with complications such as pleural infection or IPC blockages requiring further intervention and can result in discomfort or problems with sleep, and require regular aftercare[65]. Talc pleurodesis on the other hand, requires a hospital admission and will not be suitable for non-expansile lung, which often is difficult to predict without a prior large volume thoracentesis, but will not require repeated drainages (sometimes associated with discomfort) or specific aftercare required for IPCs.

The Efficacy of indwelling pleural catheter placement versus placement plus talc sclerosant in patients with malignant pleural effusions managed exclusively as outpatients (IPC-PLUS) trial introduced the concept of administering talc pleurodesis via the IPC, employing a protocol wherein patients were discharged two hours after talc administration, and were not required to be admitted[66]. Patients were enrolled at the time of IPC insertion, and after ten days, they were randomised to either placebo or talc administration. The outcome was pleurodesis failure at day 35 after randomization. The study demonstrated that the rate of successful pleurodesis at day 70 was 51% in the group receiving talc compared to 27% of the placebo group. Although longer term follow-up data is not available, this data is clinically significant in this group with short median survival.

Our approach to definitive pleural fluid control is guided by shared decision making, after a discussion and understanding of each patient's preferences, concerns, and values. During these discussions, we also impress upon patients the understanding that the majority of IPCs will be lifelong (considering an auto pleurodesis rate of approximately 30-40%) and require regular care and drainage. Worth mentioning is the recently published OPTIMUM trial (The impact of outpatient versus inpatient management on health-related quality of life outcomes for patients with malignant pleural effusion) which randomised patients with symptomatic MPE into an inpatient arm with chest drain insertion and talc pleurodesis, versus an outpatient arm with IPC insertion and an option for talc pleurodesis[67]. There was no difference in the primary outcome of quality-of-life improvement indices, although notably with more trial-related adverse events in the IPC group, in part due to drainage-related discomfort and cutaneous infection.

INTRAPLEURAL THERAPY

For more than 70 years, intrapleural fibrinolytic therapy has been part of the treatment armamentarium to assist pleural drainage in patients with complicated parapneumonic effusions and empyema. Pleural infection results in worsening fibrin deposition and septations, and intrapleural therapy has been used to assist drainage and attempt to avoid the need for invasive surgery. The Multi-center

Intrapleural Streptokinase Trial (MIST-2) demonstrated that combination intrapleural fibrinolytic therapy and enzyme therapy (IET) improved the drainage of patients with pleural infection, reduction in the need for surgical referral, and increased the improvement in chest x-ray opacification[68]. IET should be considered if there is poor response to chest drainage and appropriate antimicrobial therapy at the 48-hour mark after drain insertion, defined as static or worsening pleural shadowing on imaging and measurement of inflammatory markers[5]. The recommended dosing of IET is alteplase (10mg) and Deoxyribonuclease (DNase) (5mg) twice daily via the chest tube, over three days. Dose reduction can be considered in those patients with potentially higher bleeding risk, or those who cannot pause their anticoagulation therapy. When IET is not available, and surgery is not an option, saline irrigation can be considered for the treatment of complicated pleural infection. This has been shown to reduce the size of the pleural collection on imaging and reduce the need for surgical referral[69].

MPEs often septate, diminishing the efficacy of drainage in patients with chest drains. The mechanism of formation of loculation and septation is due to the underlying malignancy stimulating a proinflammatory response. In patients with good performance status and good prognosis, surgery can be considered for palliation of symptoms, but a majority of patients do not qualify for surgery due to the extent of their underlying disease. Intrapleural fibrinolytics can be used to break down the fibrinous septations and improve the radiological lung expansion. In patients with nondraining MPE, it has been demonstrated that insertion of a chest drain and administration of intrapleural fibrinolytics does not significantly improve dyspnoea scores nor improve pleurodesis success[70]. However, in patients who have an existing IPC for malignant effusion, and identification of a septated, nondraining effusion, intrapleural fibrinolytics may be administered to break down the locules and possibly improve breathlessness. Further high-quality data is required before this treatment is used more widely.

FUTURE DIRECTIONS

The landscape of pleural interventions for undiagnosed pleural effusions has changed dramatically over the last two decades, with increasing adoption of a range of pleural procedures worldwide. Interventional pulmonologists have extended their practice into areas previously reserved for thoracic surgeons. With advanced imaging techniques such as narrow band imaging[71] and confocal laser endomicroscopy[72] for thoracoscopy, and ultrasound techniques including contrast enhanced ultrasound[73] and ultrasound elastography, the boundaries for improving safety and efficiency in many of these interventions continue to be pushed.

In the modern pleural service, the trend of pleural diagnostic and therapeutic pathways are increasingly designed to minimise interventions, time to diagnosis, and potentially an ambulatory one-stop-shop approach to MPE. This may require taking a step away from the traditional diagnostic pathway of a pleural aspiration for all undiagnosed pleural effusion, towards upfront pleural biopsies and concurrent therapeutic interventions. More studies are needed to explore the benefit of

upfront pleural biopsies, and even concurrent definitive therapy for fluid control such as insertion of an IPC, in patients with suspected MPEs. The earlier mentioned multicentre randomised trial comparing thoracoscopic talc poudrage versus thoracoscopic talc poudrage and IPC insertion for symptomatic MPE (TACTIC trial)[61] is underway and will inform us on yet another therapeutic combination to improve personalised care of these patients.

Another promising area of pleural diagnostics is the utility of pleural fluid supernatant cell-free DNA (cfDNA) for molecular profiling of cancer. There is increasing data supporting a high diagnostic yield of pleural fluid cfDNA for non-small cell lung cancer, superior to pleural fluid cytology and comparable to tumour biopsies[74-75]. This should not be viewed as an alternative to pleural biopsies but rather complementary to histology and cytology, particularly with the ever-increasing discovery of target mutations in cancer. This will be also particularly useful in patients who are not suitable for LAT because of co-morbidities or lung adhesions.

CONCLUSION

The approach and management of undiagnosed pleural effusions has evolved rapidly in recent years. Driven by advances in technology, expertise and a rapid expansion of quality research, respiratory physicians now can utilise a range of advanced pleural procedures that once belonged to the domain of surgeons and interventional pulmonologists. This has allowed pleural services to develop safer and more efficient diagnostic and therapeutic pathways, with a focus on individualised care, minimising time to diagnosis and number of procedures, all in the ambulatory setting. Not discussed in this review are also rapid access pleural clinics and expeditious pleural referral pathways, which will contribute to timely diagnostic and therapeutic intervention. It is important to remember that there should always be careful consideration for every pleural intervention, where any procedure should only be undertaken with the intention of either improving symptoms or providing information that will change clinical management. Finally, with the significant role of ultrasonography in diagnosis and procedural guidance, there is also a need for respiratory training programmes to ensure robust standards for ultrasonography and procedural competency for trainees.

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The authors do not have any conflict of interests to declare.

ETHICAL DISCLOSURES

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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