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Title:

Modern management of malignant pleural effusions

Authors:

Rachel M Mercer ^{1,2}, John P Corcoran ^{2,3}, Najib M Rahman ^{2,3,4}

Affiliations:

¹ Department of Respiratory Medicine, Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust, Bournemouth, UK

² University of Oxford Respiratory Trials Unit, Churchill Hospital, Oxford, UK

³ Oxford Centre for Respiratory Medicine, Oxford University Hospitals NHS Trust, Oxford, UK

⁴ NIHR Oxford Biomedical Research Centre, University of Oxford, Oxford, UK

Corresponding Author:

Dr Rachel M Mercer, University of Oxford Respiratory Trials Unit, Churchill Hospital, Oxford, UK OX3 7LE

Email: mda03rmm@doctors.org.uk; Phone: +44(0)1865 225205; Fax: +44(0)1865 857109

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MANUSCRIPT
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ABSTRACT

The development of a malignant pleural effusion (MPE) is diagnostic of advanced incurable cancer, and is seen with increasing frequency as the population ages and patients with malignancy survive for longer after diagnosis as a result of advances in oncological therapies. MPE is frequently associated with significant symptoms including dyspnoea, malaise and cough that have a negative impact on a patient's quality of life. Treatment is generally palliative with median survival following diagnosis varying from three to twelve months. There has been great progress made in recent years with respect to the management of MPE and both patients and clinicians are now faced with a wide range of therapeutic interventions, each of which has its own advantages. This review article aims to summarise the evidence that underpins our current understanding of MPE and its treatment, and offer an insight into how ongoing research may further impact on patient care in the future.

INTRODUCTION

The development of a malignant pleural effusion (MPE) is a common complication of advanced malignant disease, with an estimated incidence of more than 150,000 cases per year in the United States alone [1]. Lung, breast, gastric and ovarian cancers along with lymphoma account for more than 80% of all MPEs [2]. Malignant pleural mesothelioma (MPM) is an uncommon cause of MPE given the relative rarity of this particular malignancy, but it is worth noting that a high proportion (>90%) of patients with MM will develop a MPE during the course of their disease. The median survival following presentation with and diagnosis of any MPE is reported as being between 3 and 12 months [3] and reflects progressive metastatic and, at present, incurable disease. This may, in part, relate to the presenting symptoms of MPE which are frequently non-specific and insidious in onset; including dyspnoea, reduced exercise tolerance, fatigue, weight loss and cough.

Historically, the primary aim of MPE management was to achieve radiological resolution, usually with the use of an intercostal chest drain and pleurodesis agent. This focus on radiological outcomes led to the use of pleurodesis agents which were later shown to be potentially harmful, with increased morbidity and mortality (e.g. small particle talc). The recent volume of evidence-based research into pleural disease has led to many changes in clinical practice including the widespread use of large particle graded talc; the introduction of indwelling pleural catheters as a first-line therapeutic option; and ongoing research addressing methods of modifying pleural fluid production. The aim of treatment has also moved towards patient-related outcome measures rather than radiological resolution, recognising this is the aim of treatment intent, and that radiological change may not correlate with patient experience and symptoms. The benchmark for success is now an intervention that prevents further pleural procedures being necessary, rather than achieving radiological resolution, and is shown to improve symptoms and quality of life for the patient with MPE.

The management of an individual MPE is dependent on a number of factors including patient symptoms and wishes, co-morbidities and prognosis. This increasing individualisation of care has been facilitated by the increasing range of treatment options, which in the modern era of pleural medicine include repeated large-volume thoracentesis; intercostal chest drain insertion and pleurodesis with talc slurry or other sclerosing agent; thoracoscopy with talc poudrage; or indwelling pleural catheter (IPC) insertion. An increasing number of centres provide some or all of these interventions through bespoke pleural services, recognising the need for specialised care in this patient population. More invasive surgical options such as surgical pleurectomy or pleuroperitoneal shunting remain available, but are less frequently used in routine clinical practice.

There are a significant number of ongoing trials assessing novel treatment strategies in MPE, including “outpatient pleurodesis” (talc slurry instillation via IPC) or improving symptom control using adjuncts to drainage with IPCs [4,5]. The next natural step in this field will be to enhance our understanding of factors

that influence MPE formation and develop treatments that altering the mechanisms responsible for fluid production and absorption; a problem that may be addressed by research into specific biomarkers and targeted immunotherapies. This paper will review the evidence and indications for the currently available and future management options for patients with MPE.

AETIOLOGY

It is widely accepted that pleural fluid is produced by the parietal and visceral pleura and absorbed by the parietal pleura lymphatics in normal subjects [6]. The development of a pleural effusion occurs when there is either increased filtration or leakage of the pleural fluid, or decreased reabsorption. Increased transpleural pressure leading to increased filtration of pleural fluid normally causes a transudative effusion whilst increased vascular permeability causing fluid leakage often leads to an exudate [7]. Malignant invasion of the pleural surface increases capillary permeability which can lead to increased fluid leakage. There is also evidence that tumour cells secrete vasoactive mediators which further increase capillary permeability. Tumour infiltration into the parietal pleural lymphatic system can obstruct reabsorption of the fluid and thus lead to pleural fluid accumulation.

Not all patients with malignant pleural infiltration will develop a pleural effusion; this suggests that other factors influence the excess production or reduced absorption of fluid. Numerous cytokines such as vascular endothelial growth factor and angiopoietins have been shown to increase vascular permeability and subsequently investigated for their potential role in pleural fluid production [6]. Research to identify specific biomarkers linked to pleural fluid production may lead to a better understanding of the mechanism of fluid formation, and thereby treatments to block these pathways specifically and prevent pleural effusion development. There is currently no such targeted treatment available, but identification of such an agent would almost certainly have significant advantages over the non-specific mechanical drainage and pleurodesis techniques currently available.

DIAGNOSIS

The diagnosis of MPE is based on the identification of malignant cells in the pleural fluid or pleural tissue (8). Para-malignant effusions (where no malignant pleural involvement is seen) and concurrent effusions may be present and are typically associated with a better prognosis. However, they may also indicate the presence of other conditions requiring treatment such as heart failure; as such, the clinical differentiation of these conditions is important for both prognostic and therapeutic reasons [1]. Thoracentesis and pleural biopsies are typically used to obtain samples for cytology and histology respectively. It is worth noting that pleural fluid cytology has an approximate diagnostic yield of around 60% which only increases marginally if a second sample is taken. On this basis, repeated aspiration for diagnostic purposes is not recommended [3] and failure to obtain a clear diagnosis on the basis of pleural fluid cytology should prompt consideration of alternative diagnostic strategies where clinically appropriate, notably thoracoscopic or image-guided pleural biopsies. There is evidence to show that cytological analysis of 60 mL of pleural fluid is more sensitive than smaller volumes, whereas larger volumes than this have not been shown to further increase diagnostic yield [3].

Firm histocytological diagnosis of pleural malignancy is increasingly important for accurate prognostication and effective treatment, particularly with the introduction of newer targeted oncological treatments. Until recently, patients with poor performance status and advanced malignancy would often have not been suitable for disease modifying chemotherapy or radiotherapy, and therefore obtaining a precise histological diagnosis was not considered a requirement for oncological management. However, this has now changed with the increasing use of molecular targeted strategies. For example, the identification of epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) mutations in metastatic lung cancer is associated with a good response to tyrosine kinase inhibitors even in advanced non small cell lung cancer. The side-effect burden with these agents is low compared to conventional chemotherapy and they are commonly better tolerated, meaning they are suitable in a broader range of patients including those with poor performance status and multiple co-morbidities [9]. The identification of these specific mutations

requires adequate volumes of tissue or cellular material to be available in lung cancer and other malignancies. As personalised medicine advances and specific hormonal and immunological treatments become more widely available, the need for increasing volumes of cellular material for both immediate and future analysis is only likely to increase.

Another potential direction is the need for repeat sampling of tumours as new mutations often develop in response to treatments such as the tyrosine kinase inhibitors. This change in practice may lead to greater use of more advanced sampling techniques, such as endobronchial ultrasound (EBUS) and thoracoscopy, in patients where it was previously felt to be inappropriate. For patients with MPE this may be especially relevant since the pleural space is an area potentially amenable to repeated sampling (via thoracentesis, thorascopic or image guided biopsies) if required. The introduction of IPCs into routine clinical practice may also provide an opportunity for repeated, non-invasive sampling which may permit monitoring of the tumour characteristics and its response to treatment.

MANAGEMENT

Patient Selection

The management of MPEs has moved away from radiological evaluation as the sole determinant of both the need for intervention and subsequent success of any procedure, towards patient related outcome measures. The clinician's focus is now rightly centred on symptom management, patient choice, minimising the number of interventions, shorter inpatient stays and cost effectiveness of any intervention as a whole.

Large volume thoracentesis in patients with symptomatic MPE is an important first step, initially to aid diagnosis but also to provide information regarding the symptomatic benefit of any fluid drainage. Patients with advanced malignancy often have multifactorial breathlessness and the primary driver of symptoms may

not be the effusion. If the patient derives no benefit from fluid drainage it is reasonable to assume the effusion is not the primary cause of the patient's breathlessness and that further interventions are not necessary; there is no evidence to show clinical benefit from draining asymptomatic effusions [3]. Similarly, some very frail patients with advanced disease and a short life expectancy may not be suitable for invasive procedures, in which case symptoms can be managed with opiates or other pharmaceutical agents which have been shown to be effective in the control of dyspnoea [10]. However, it should be noted that in the presence of multiple causes of breathlessness (for example, lymphangitis, pulmonary embolus and airways disease), aspiration of even a relatively small amount of fluid (200 mL) can result in significant amelioration of breathlessness; as such, a trial drainage of any sizable effusion is nearly always indicated.

If a large volume therapeutic aspiration results in symptomatic benefit, further measures such as pleurodesis or IPC insertion should be automatically considered in the event of the effusion subsequently recurring. The development of an accurate means of assessing likely prognosis at the outset of treatment is therefore important to guide patients and clinicians during the discussion of future management options. The LENT score has recently been developed to predict prognosis in MPEs [11] and there is also ongoing work to identify both systemic and local biomarkers in MPE which might provide clinicians with greater information about prognostic and treatment outcomes. The LENT score was derived from and validated in large groups of patients with MPE, and is a prognostic algorithm using performance status, pleural fluid LDH, serum neutrophil to lymphocyte ratio and tumour type to stratify patients into low, moderate and high risk groups. The median survival in the high risk group was 44 days compared to 319 days in the low risk group [11]. The LENT score has yet to be validated in a large prospective study but the results will hopefully allow physicians to have frank discussions with patients regarding treatment options that might be appropriate given a greater degree of certainty regarding their prognosis. Other measures that might help to determine prognosis include co-morbidities and the composition of the effusion [11]. Biomarkers such as survivin, vascular endothelial growth factors (VEGF) and mesothelin in mesothelioma are currently being investigated for their prognostic ability. A previous study has shown higher levels of LDH and lower pleural pH were associated with a poorer

prognosis in non-mesothelioma MPEs, suggesting the biological activity within the pleural space may carry important prognostic information [12].

In patients with chemosensitive malignancies (e.g. lymphoma and small cell lung cancer), decisions around definitive pleural intervention are more complicated. Effusions in this situation can regress with chemotherapy and therefore may not require a definitive long-term strategy for drainage. Thoracentesis can be used as a bridging procedure if chemotherapy is to be initiated quickly and thought likely to control subsequent pleural fluid production. Some authorities believe that obliteration of the pleural space should be attempted regardless to prevent a pleural effusion developing later in the course of the disease, and one option now available to these patients is the first-line use of IPCs to control symptoms whilst chemotherapy is provided, meaning further and potentially risky pleural interventions are not necessary during the period of chemotherapy. There is robust evidence that the use of an IPC to control pleural fluid is safe during chemotherapy and should not be considered a barrier to oncological therapy (13, 14).

Thoracentesis

Thoracentesis provides short-term relief and is helpful in aiding diagnosis and assessment of whether removal of fluid improves dyspnoea. MPEs reaccumulate in more than 90% of cases within 30 days, and therefore isolated thoracentesis without a plan for future definitive treatment is not recommended in those with a life expectancy of greater than 1 month [3]. Repeated thoracentesis involves numerous hospital attendances; an increased risk of acute complications such as infection or bleeding; and may promote the development of intrapleural septations which will impair successful drainage of fluid in the future. The maximum recommended amount of pleural fluid to be drained in a single procedure is 1.5L due to the risk of re-expansion pulmonary oedema [3]. There is some controversy as to whether this arbitrary limit is meaningful with some groups preferring to drain as large a volume of pleural fluid as possible guided by patient symptoms and pleural manometry, and case series evidence suggesting that this is safe [15].

Initial thoracentesis is also valuable in identifying patients with a trapped, or unexpandable, lung which in turn influences future treatment decisions. This scenario occurs when the lung is unable to re-expand due to a fibrous visceral pleural peel and is often found in longstanding MPEs, affecting around 15% of cases. There are multiple ways of identifying such patients – for example, the presence of a hydropneumothorax on post-procedure x-ray after an otherwise uncomplicated thoracentesis; the development of significant negative intrathoracic pressure or a rapid change in the intrapleural pressure during drainage; or the development of significant symptoms such as central chest pain and intractable cough during drainage [16]. Several groups have promoted the use of pleural manometry to aid in the diagnosis of trapped lung, by transducing pressures from needles or intercostal chest tubes. However, these techniques require the drainage to stop whilst pressures are measured, although newer strategies such as using an epidural catheter passed through a drainage tube may allow continuous monitoring [17].

There remains controversy as to whether the physiological data obtained via pleural manometry provides information beyond that provided by a post-procedure chest x-ray or patient symptoms during and after aspiration. A non-invasive method of identifying trapped lung that does not require the drainage of any fluid is therefore a priority, with studies focusing on the potential utility of thoracic ultrasound. A recent study demonstrated that lung tissue movement and strain related to the cardiac impulse identified on thoracic ultrasound were significantly reduced in patients subsequently found to have trapped lung following large-volume thoracentesis [18]. This method, if the promising outcome can be replicated in subsequent studies, may be useful in identifying trapped lung and guiding physicians towards the appropriate treatment strategy prior to any intervention.

Large volume thoracentesis of 1.5L of fluid is often symptomatically effective even in massive MPEs where residual fluid remains in the hemithorax, leading to questions about what causes patients' symptoms in such

cases. The symptomatic benefit of thoracentesis in these circumstances is thought to be due to a reduction in intrapleural pressure and associated improvement in lung and chest wall compliance. In these patients, the diaphragm is often noted to be inverted on thoracic ultrasound leading to paradoxical movement on inspiration; aspiration of even a moderate volume of pleural fluid can allow the diaphragm to revert to its normal shape and movement. All of these factors affect a patient's experience of dyspnoea and thus incomplete drainage of a MPE can still result in symptomatic benefit even if there is no significant increase in FEV1 or FVC and no or minimal change in PaO₂ [19].

Intercostal drainage and pleurodesis

Intercostal drainage with instillation of a sclerosant has been found to be effective in preventing fluid re-accumulation in the majority of patients with MPE. The procedure currently involves insertion of a chest tube to remove the pleural fluid before instilling a sclerosing agent with the aim of creating an inflammatory reaction. This leads to fibrosis and the development of adhesions between the visceral and parietal pleura, preventing further re-accumulation of fluid. This process usually requires an inpatient hospital stay of between 5 and 7 days; there are well-recognised risks associated with the procedure including treatment failure; inflammation of the underlying lung with resultant hypoxaemia; and drain displacement or blockage which may prevent pleurodesis being performed.

The choice of chest tube to facilitate pleurodesis in MPE has been the cause of great debate between thoracic physicians and surgeons for a number of years. The current BTS guidelines for management of MPE, published in 2010, suggest that a small-bore drain (up to 14F) is "as effective" as a larger drain to conduct MPE pleurodesis, and may be associated with less pain for the patient [3]. This advice was based on evidence from three papers, all of which concluded that small-bore catheters were as effective as larger bore chest tubes with respect to pleurodesis success [20-22]. However, the studies all had small sample sizes that were

underpowered to be able to answer this important clinical question definitively, and the largest was a retrospective review of 102 patients rather than a randomised trial [20].

The TIME1 trial was a large randomised controlled study [23] that recently published its findings regarding the optimum size of chest drain for attempting pleurodesis in MPE, randomising 114 patients randomised to have either a 12F or 24F chest tube. Although the 12F tube was associated with marginally less pain than the 24F tube and this difference was statistically significant, it did not reach the minimum clinically significant difference for the outcome tool used (difference in 100mm visual analogue score 6mm, $p=0.04$, minimum clinically significant difference of 13mm [24]). However, the study did identify a higher rate of pleurodesis failure with smaller chest tubes (30% versus 20% with larger tubes) and therefore failed to demonstrate the non-inferiority of smaller chest drains for pleurodesis in MPE. In addition, the proportion of complications at insertion and drain fall out rates were higher with smaller as opposed to larger tubes. This study, which is the largest in the literature and the only one to be adequately powered to allow assessment of non-inferiority, has questioned the widely held belief among chest physicians that smaller tubes are “just as good” as larger drains when attempting chemical pleurodesis in MPE. Although further studies in this area are needed, this may lead to a reconsideration of the current recommendations regarding drain size.

The timing of instillation of the sclerosing agent is key to the success of the procedure. The agent should ideally be instilled when the pleural surfaces are apposed to promote effective pleurodesis. If the lung fails to re-expand it is often due to the lung being trapped which prevents pleural apposition. Pleurodesis can still be attempted if there is partial apposition although how this impacts on clinical outcome is uncertain. The BTS guidelines [3] advise attempting pleurodesis when the fluid drainage is <150mls per day and once there is no residual pleural fluid on x-ray. A study comparing these methods showed that the rates of successful pleurodesis are equivalent but the inpatient stay is often shorter using radiological guidance rather than the daily volume drained [25]. However, the evidence to support these recommendations is weak and based on small studies only. Ultrasound is more sensitive at detecting small amounts of fluid and assessing the

difference between pleural thickening and fluid [3], and thus there is increasing interest in confirming complete evacuation of the pleural space using bedside ultrasound. A multi-centre randomised controlled trial has recently started recruiting with the primary aim of assessing the utility of thoracic ultrasound in improving pleurodesis efficacy and reducing hospital stay [26].

There is ongoing work into maximising the efficacy of pleurodesis. One study compared draining a maximum of 1.5L of pleural fluid per day and attempting pleurodesis once there was less than 300mL drain output per day compared to a rapid pleurodesis method of draining 1L every 8 hours until full evacuation of the pleural cavity was achieved. Both required radiological confirmation and the study found that the successful pleurodesis rates were equivalent and the rapid pleurodesis method had an inpatient stay of 2.2 days compared to 9.0 days in the standard group [27]. However, this study was relatively small and underpowered. Rotating the patient once the sclerosing agent has been instilled has not been shown to increase the rates of successful pleurodesis so is not recommended [3]. After the agent has been instilled the drain is clamped for 1 hour before being released, although there is no objective evidence to support this practice. Common complications include pleuritic chest pain and mild fevers, whilst more severe complications such as hypoxaemia and respiratory failure have also been reported [28]. The optimal timing of drain removal post pleurodesis is not well established. A study investigating the timing of drain removal suggested there was no difference in rates of successful pleurodesis between drains which were removed at 24 or 48 hours [29], but this study was not powered as a non-inferiority trial. The BTS guidelines regarding drain removal after pleurodesis suggest the drain should be removed after 24-48 hours if there is less than 250mls drained in a 24 hour period although there is little evidence to support this practice [3].

The most important marker of successful pleurodesis in MPE is now generally agreed to be a lack of need for further pleural interventions. If there is radiological reaccumulation of fluid but it is not sufficient to cause symptoms, this can be accepted as a treatment success given the clinician's intent is to prevent the recurrence of an MPE which then requires intervention.

Pleurodesis agents

Multiple different agents have been used for pleurodesis. A meta-analysis of randomised trials reported that sterile talc, via poudrage, is the most effective pleurodesis agent [30, 31]. Sterile talc is the most commonly used agent worldwide for pleurodesis in MPE, due to its availability, low cost and side-effect profile. Graded talc with a particle size of $>15\mu\text{m}$ is recommended as there are safety concerns with smaller particles which are thought to cause complications such as systemic distribution of talc [32] and adult respiratory distress syndrome in the context of lung parenchymal infiltration and inflammation [33]. A study where talc was introduced in graduated doses into the pleural space of rats showed subsequent deposition of talc in every organ of the animals studied, suggesting an element of systemic absorption of the talc which could in turn lead to complications [34]. In a landmark randomised trial, graded and non-graded talc has been compared assessing the effect on surrogates of lung inflammation, and less systemic and lung inflammation demonstrated with graded talc [35]. A large prospective cohort of patients treated with graded talc poudrage pleurodesis demonstrated not a single instance of ARDS in over 500 cases [36]; however, a significant proportion of patients experienced unexplained lung infiltrates and increased oxygen requirements following talc application, suggesting that there was still some associated lung and systemic toxicity.

Intrapleural tetracyclines have also been used for pleurodesis until recently but due to increasing supply problems these have tended to be replaced by more accessible agents. A study of pleurodesis methods in five English speaking countries showed that sterile talc was the most commonly used first-line agent accounting for 68% of respondents, followed by tetracycline and bleomycin at 26% and 7% respectively. Although this method of pleurodesis has variable documented success rates this study estimated the success rate to be between 60-70% [37].

The majority of currently available pleurodesis agents are non-specific agents which work by causing pleural injury and inflammation, resulting ultimately in the development of pleural fibrosis and adhesions. There have been attempts at identifying alternative targeted strategies, based on the clinical observation that a pleurodesed space is frequently seen following pleural infection. On this basis, a number of bacterial cell wall components have been utilised as experimental pleurodesis agents, including OK432 [38], Staphylococcal superantigen [39] and lipoteichoic acid-T [LTA-T]. LTA-T has been further assessed in a prospective IPC based study and shown to reduce pleural fluid production compared to saline control [40]. Newer pleurodesis agents may therefore be developed in the future that prove more effective and less toxic than the commonly used current agents.

Analgesia

Creating an inflammatory response causes pain due to the nervous innervation of the parietal pleura so common practice includes instilling lidocaine and using an opiate based analgesic prior to pleurodesis. Guidelines recommend the use of 3mg/kg of intrapleural lidocaine, up to a maximum dose of 250mg [3]. The use of opiates rather than NSAIDs has been based on the theory that since NSAIDs reduce inflammation, their use may result in a lower rate of successful pleurodesis. This hypothesis was put to the test in the TIME1 trial [23] where opiates were directly compared to NSAIDs. A dose of between 10 and 20mg of oral morphine used four times daily was compared to 800mg of ibuprofen three times daily, with the results showing no statistical difference in pain scores using NSAIDs or opiates (with a slight excess of rescue medication required with NSAIDs) and importantly that the likelihood of pleurodesis being successful was not affected when using NSAIDs. NSAIDs were not proven to be superior to opiates but this study [23] shows they can be used in cases where opiates are contraindicated without reducing the efficacy of pleurodesis.

Fibrinolytics

In certain circumstances, complete fluid drainage in MPE is not possible due to fibrinous septations within the pleural space, which renders treatments such as talc pleurodesis incapable of resolving fluid production. In addition, with the increasing use of indwelling pleural catheters, septated effusions are more common in the setting of longer term and recurrent drainage, and may be associated with difficult to treat symptoms. There is consequently growing interest in the use of intrapleural fibrinolytics (e.g. urokinase, streptokinase and tissue-plasminogen activator) to improve pleural fluid drainage, in parallel to their use in pleural infection [41, 42]. A recent retrospective case series in patients with septated MPE and IPC in-situ using intrapleural fibrinolytic therapy demonstrated increased fluid drainage in 93% and improved symptoms in 83%. This was associated with a modest risk of bleeding (3%), and the results should be interpreted with a degree of caution given the bias inherent in retrospective case series [43].

A recent double blind, placebo controlled trial assessing intrapleural urokinase in septated malignant effusion (TIME3) has just reported its primary results [44]. This study demonstrated no improvement in dyspnoea or pleurodesis success using intrapleural urokinase compared to saline placebo, despite the urokinase improving the appearance of the chest radiograph. This result once again highlights the importance of assessing clinically relevant outcomes that directly affect the patient, as opposed to purely radiological measures. Further studies in the MPE population are required to assess if this treatment has clinically meaningful efficacy in specific clinical scenarios.

Thoracoscopy and talc poudrage

In patients with negative pleural fluid cytology but a continued suspicion of malignancy, obtaining diagnostic pleural biopsies via thoracoscopy is frequently the next investigation of choice [3]. For the respiratory physician this is increasingly done via local anaesthetic thoracoscopy (LAT), a technique which is acknowledged to be safe, well tolerated and with a diagnostic sensitivity of 92.6% [45]. The other approach is via video assisted thoracoscopic surgery (VATS) which is normally performed by a surgeon and requires a

general anaesthetic, making it less suitable for frail patients. The diagnostic yields, and indeed the physical techniques, of both methods are similar [46] with the exception of VATS requiring general anaesthesia and usually single lung ventilation.

LAT is mostly used when the diagnosis of malignancy is suspected but has not been proven with pleural fluid cytology. One advantage is that LAT offers both a diagnostic and therapeutic intervention and provides a larger volume of tissue for evaluation which is increasingly important with the use of targeted molecular therapies. Direct visualisation of the pleura can also provide information about the extent of disease spread. Talc poudrage can then be performed during thoracoscopy with the aim of inducing pleurodesis in a select group of patients if a diagnosis of malignancy is evident on macroscopic visualisation of the pleura (e.g. gross pleural nodularity) or where no further investigations would be appropriate. Once the fluid has been drained talc is insufflated into the pleural space and a chest drain left in situ post-procedure to allow lung re-inflation.

A study of 501 patients comparing talc slurry via chest tube to talc insufflation during thoracoscopy demonstrated no significant difference in pleurodesis outcome. Patients with trapped lung were not excluded in the main analysis which may have been a reason that the primary outcome of the study did not reach statistical significance. The study suggested that in selected subgroups talc insufflation during thoracoscopy was more effective than talc slurry pleurodesis once patients with trapped lung were excluded, and that it also presented a therapeutic advantage specifically in patients with MPE secondary to primary breast or lung cancer [33]. These findings require validation in further studies and a prospective, multicentre, randomised controlled trial is currently ongoing aiming to definitively answer whether talc poudrage is more effective than talc slurry pleurodesis in patients with MPE [47].

A more novel approach recently adopted in some centres is the use of IPCs placed at the time of thoracoscopy and poudrage, with the aim of a combined approach which increases efficacy of care and reduces time in

hospital. A small pilot study of the so called “rapid pleurodesis” technique included 30 patients and reported a 92% successful pleurodesis rate, with the IPC in situ for a median of 7.5 days and a median duration of hospital stay of 1.8 days [48]. This implies that the length of stay and duration of IPC in situ can both be reduced but a prospective randomised control trial is needed to fully assess the safety and efficacy of this technique versus standard care.

Indwelling pleural catheters

Indwelling pleural catheters are long-term, small bore (16F) chest drains which are inserted into the pleural space and tunnelled under the skin. These catheters are generally used in the outpatient setting to drain fluid in increments, with drainage regimens (frequency and volume) varying according to patient need and symptoms. The drainage is performed using a vacuum bottle system and each drainage usually only takes a few minutes. District nurses, family members or the patient can be shown how to perform the drainage procedure. In between drainages, the pleural catheter remains under dressings to promote sterility and minimise inconvenience to the patient.

Patients with MPE are increasingly being offered IPC insertion as an alternative to pleurodesis as a first-line management strategy; in the specific setting of trapped lung IPC insertion is the preferred option due to the almost certain failure of any attempt at pleurodesis due to lack of pleural apposition. The TIME2 trial demonstrated no difference in rates of dyspnoea or quality of life between patients with MPE undergoing chest drainage and pleurodesis and those who were managed using an IPC [49]. One major advantage to an IPC over standard chest drain insertion and pleurodesis is the reduced length of hospital stay [50]; the published data would also suggest the two approaches have equivalent safety profiles, although the TIME2 study did report an increased risk of delayed complications (blockage, infection) that would be specific to IPC usage [49,50]. The recently reported AMPLE trial [51] was a multicentre randomised controlled study comparing talc pleurodesis to IPC with outcome measures including number of inpatient days, adverse events

and quality of life scores. It showed that patients with MPE who were managed with an IPC spent significantly fewer days in hospital with no significant difference in either adverse events or mortality between the two groups. In view of the differing benefits of each treatment it should be considered best practice to offer both management options and allow the patient to choose their preferred strategy.

The TIME2 trial reported the rate of long-term auto-pleurodesis in association with IPC insertion as 51% [49] which was similar to a single centre study of 250 patients where a pleurodesis rate of 42.9% was found [52]. In patients where auto-pleurodesis is achieved, usually identified by a decreasing drainage output and radiographic and ultrasonographic resolution of fluid, the IPC should be removed promptly to prevent the development of unnecessary complications [53]. The outcome of auto-pleurodesis can still be achieved in patients with trapped lung as volume loss occurs within the affected hemithorax; however, this is less common and it is not unreasonable for an IPC to remain in situ until death in these circumstances. IPCs are still helpful in symptom control even when pleurodesis is not achieved as the regular drainage of fluid can positively influence lung and chest wall mechanics, relieving dyspnoea as a consequence.

A major worry with the introduction of IPCs was the possibility of subsequent infection. An IPC can remain in the pleural space for a significant amount of time, unlike the temporary chest drains used for pleurodesis. This has led to particular concern among oncologists as to whether systemic chemotherapy could be safely administered to a patient with an IPC. There are as yet no large prospective trials answering this question but a retrospective study of 78 patients including 23 who were undergoing systemic chemotherapy during the time the IPC was in situ showed no difference in infection rates between those receiving chemotherapy and those not [13]. A separate retrospective analysis of 43 patients undergoing chemotherapy also failed to find a significant difference in infection rates between the chemotherapy and non-chemotherapy groups [14].

There is now a substantial body of data to suggest that the rates of long-term pleural infection following IPC insertion are <5% [53]. Most IPC-related infections can be controlled or completely treated with antibiotics and do not require removal of the catheter or other invasive procedures. A recent retrospective international multicentre study showed pleurodesis rates following pleural infection in association with an IPC have been reported to be as high as 62% with an infection-related mortality of only 0.29%, well below the mortality seen with conventional community-acquired pleural infection [54]. It has been hypothesised that this may be due to a combination of early detection due to close monitoring; the ability to continually drain the pleural space and therefore make it more difficult for bacteria to settle; and the ability to instil fibrinolytics with ease to promote complete evacuation. Of particular interest are the results of another multicentre retrospective study which appear to indicate that pleural infection associated with IPCs used to manage MPE may in fact be associated with longer survival, particularly in patients with MPM [55]. It has been hypothesised that this may be the result of the immune response to infection also suppressing tumour activity, a theory that merits further assessment in both the laboratory and clinical settings.

There is ongoing evaluation of the comparative costs of IPC vs chest drain and pleurodesis. Penz et al showed that IPCs were most cost effective if the patient has less than a 14 week survival [56]. There are multiple studies that support the hypothesis that pleurodesis is more cost effective in patients with longer life expectancies but the timing of when this becomes apparent remains open to question [57,58].

Procedural tract metastases

After any pleural intervention, but particularly those that result in a more extensive chest wall injury (e.g. thoracoscopy), it is possible for the tumour to metastasise through the tract created by the procedure. Metastases often present as painful subcutaneous masses or nodules either at the site of insertion or anywhere along the deeper tract, and are usually treated with palliative radiotherapy alongside oral analgesics [59,60]. Pleural interventions for patients with MPM have a higher incidence than other metastatic

pleural malignancies of developing subsequent intervention site or tract metastases. The role of prophylactic procedural tract radiotherapy to prevent later metastatic disease in MPM has been the subject of much debate, with individual clinicians and centres demonstrating widely variable practice [59]. This question was addressed by the recently reported SMART trial which showed that symptom control and quality of life were not improved by the use of routine prophylactic radiotherapy to sites of pleural intervention in patients with MPM, when compared to patients undergoing careful clinical follow up and treatment as and when symptoms developed [60]. The PIT trial [61], designed with the same question in mind, is close to completion and should provide further information relevant to this area of clinical practice.

FUTURE DIRECTIONS

Clinicians and patients are entering an era of personalised and precision medicine, where treatment is tailored to an individual patient's condition, prognosis and preferences. This is already evident in the everyday care of patients with MPE, with a series of large randomised studies [5, 23, 26, 44, 47, 49, 51, 60, 61] focused on patient-centred outcomes now either published or actively recruiting. The range of interventions and treatment options available to patients with malignant pleural disease has grown enormously since the turn of the century, and the concurrent recognition of pleural disease as a sub-specialty in its own right within the field of respiratory medicine has helped ensure access to these choices in an increasing number of centres. As clinicians become more familiar with the different therapeutic options available, newer strategies of combining treatments are being explored; for example, the IPC-PLUS study is investigating whether the use of talc slurry in conjunction with an IPC can enhance rates of early pleurodesis in patients with MPE [62]. Alongside other alternative approaches to pleurodesis and MPE management that are aimed at minimising time spent in hospital [26, 47, 48], there appears to be a general direction of travel towards ambulatory care for these patients wherever possible.

At present, all our strategies for the management of MPE are universally interventional and mechanical in their outlook, focused on different means of draining the fluid and obliterating the potential space that is left behind. Increasing our understanding of the inflammatory and immune responses that underpin MPE formation may offer a different opportunity for targeted therapies that are aimed at switching off fluid production at source. It is increasingly recognised that markers of systemic and localised inflammation can be directly related to prognosis in patients with MPE; and equally that the production and levels of specific cytokines and biomarkers such as VEGF, osteopontin, interleukin-5 and tumour necrosis factor within the pleural space can be implicated in both the formation of MPE and likely prognosis. Pre-clinical studies targeting these biomarkers have shown promise in switching off MPE formation and are likely to lead onto early phase clinical trials in the near future [63].

In this respect, the introduction of IPCs into the management pathway of patients with MPE represents a unique and valuable experimental and therapeutic opportunity. The availability of pleural fluid over a prolonged timeframe should allow clinician scientists to develop a greater understanding of how the physiology and biochemistry of the malignant pleural space evolves over time, with early studies indicating that specific cytokines such as monocyte chemotactic protein 1 may have an important role in pathogenesis [64]. In turn, the IPC also provides clinicians with access to the pleural space in order to directly deliver therapeutic agents such as immunomodulating or chemotherapeutic drugs with the aim of both switching off fluid production and treating malignant disease [65]. However, it is crucial that any future research in this field remains focused on outcomes that are directly relevant to patients with MPE, thereby ensuring clinicians can draw appropriate conclusions as to what is best for their patients in everyday clinical practice.

CONCLUSION

There are multiple options for the treatment of MPE and the decision regarding which to use should be based on a combination of prognosis, performance status, patient choice and cost effectiveness. It is generally agreed that repeated thoracentesis should only be used in patients with a limited prognosis. On the basis of

the current evidence, it is reasonable to offer either pleurodesis or IPC insertion according to patient preference. IPCs have the advantage of being a day case procedure and efficacious in all patients including those with trapped lung. On the other hand, pleurodesis when successful offers a single procedure which does not require any continued outpatient care. Thoracoscopy provides an opportunity for both diagnosis and treatment, and given the volume of cellular material provided may become more important with advances in targeted therapies. Future research is likely to look at preventing pleural fluid formation through a better understanding of the underlying mechanisms; alongside optimising the efficacy of interventions already available, with newer techniques combining IPCs with pleurodesis or thoracoscopy potentially representing an alternative gold standard. It is to be hoped the basic scientific, translation and clinical research activity ongoing in MPE will continue to improve care for patients in the future.

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