INVITED REVIEW

Interventional therapies for malignant pleural effusions: The present and the future

RAJESH THOMAS,1,2,3 ROSLYN FRANCIS,2,4 HELEN E. DAVIES5 AND Y.C. GARY LEE1,2,3

1Department of Respiratory Medicine, Sir Charles Gairdner Hospital, 2School of Medicine and Pharmacology, University of Western Australia, 3Pleural Disease Unit, Lung Institute of Western Australia, 4Department of Nuclear Medicine, Sir Charles Gairdner Hospital, Perth, Western Australia, Australia, and 5University Hospital of Wales, Cardiff, Wales, UK

ABSTRACT
The approach to management of malignant pleural effusions (MPE) has changed over the past few decades. The key goals of MPE management are to relieve patient symptoms using the least invasive means and in the most cost-effective manner. There is now a realization that patient-reported outcome measures should be the primary goal of MPE treatment, and this now is the focus in most clinical trials. Efforts to minimize patient morbidity are complemented by development of less invasive treatments that have mostly replaced the more aggressive surgical approaches of the past. Therapeutic thoracentesis is simple, effective and generally safe, although its benefits may only be temporary. Pleurodesis is the conventional and for a long time the only definitive therapy available. However, the efficacy and safety of talc pleurodesis has been challenged. Indwelling pleural catheter (IPC) drainage is increasingly accepted worldwide and represents a new concept to improve symptoms without necessarily generating pleural symphysis. Recent studies support the effectiveness of IPC treatment and provide reassurance regarding its safety. An unprecedented number of clinical trials are now underway to improve various aspects of MPE care. However, choosing an optimal intervention for MPE in an individual patient remains a challenge due to our limited understanding of the underlying pathophysiology of breathlessness in MPE and a lack of predictors of survival and pleurodesis outcome. This review provides an overview of common pleural interventional procedures used for MPE management, controversies and limitations of current practice, and areas of research most needed to improve practice in future.

Key words: indwelling pleural catheter, malignant, mesothelioma, pleural effusion, pleurodesis.

INTRODUCTION
Over 150 000 patients develop a malignant pleural effusion (MPE) in the United States every year,1 while in Europe, more than 100 000 patients suffer from MPEs secondary to lung cancer alone.2 Patients with an MPE most commonly present with breathlessness that is often debilitating and can significantly impair quality of life (QoL).3 Chest pain4 and constitutional symptoms, for example anorexia, weight loss or tumour fever, are common, alongside symptoms from the underlying cancer. MPE and its management have a major impact on patients, carers and the health-care system.

Following traditional management algorithm, most patients with MPE will have to undergo several/
multiple pleural procedures for diagnostic and therapeutic purposes. Typically, these include diagnostic thoracentesis (often more than once), pleural biopsies (closed or thoracoscopic) followed by therapeutic thoracentesis, surgical or bedside pleurodesis (when MPE recurs), and additional procedures (e.g. indwelling pleural catheter (IPC) insertion or further thoracenteses) if pleurodesis fails. All pleural interventions have associated discomfort, risks of morbidity (e.g. infection, bleeding, pneumothorax, even death) and costs, although the incidences and severity of adverse events vary. Many procedures require hospitalization, often for several days, leading to increased cost and burden on health-care resources.

CHANGES IN DIRECTION

The past couple of decades has seen significant changes in the views and, thus approaches, to MPE management. MPE researchers historically focused on stopping the pleural fluid reaccumulation by aggressive measures (e.g. pleurectomy) to obliterate the pleural space. Many (if not most) clinical studies were directed to comparing sclerosing agents. ‘Absence of radiographic evidence of fluid recurrence’, usually in the first month, was the commonest endpoint in clinical trials—even though it means little to patients with pleural malignancies. Clinicians have since come to the recognition that the key goals of management of MPE are to relieve patient symptoms with the least invasive means, preferably out of hospital, and in the most cost-effective way. These changes will have profound implications on the directions of clinical care and research of MPE management in the years to come.

First, improving patient-reported outcome measures (PROM) are now recognized as the main goal in MPE management. The recently published Therapeutic Intervention in Malignant Effusion (TIME) study was among the first randomized trials in this field to use PROM (breathlessness, chest pain and QoL scores) as its key end-points. Other patient-relevant outcomes, for example days in hospital, number of pleural procedures endured, are now the focus of many ongoing studies. Second, an MPE usually heralds an incurable cancer, and palliation is the key. Over the years, aggressive procedures are increasingly replaced by less invasive strategies to minimize morbidity. Interventional pulmonologists have progressively replaced thoracic surgeons as the first port of referral for MPE patients. Third, as the median survival of MPE patients were measured in weeks to months, development of ambulatory therapies has gained significant momentum, with many innovative technologies being tested in early phase trials. This is important as MPE continues to grow as a global health-care burden; future therapies must be cost-efficient/effective. Reducing hospital-based interventions will be an important direction of research.

Traditional care pathways for MPE are based mainly on ‘evidence-free practice’ that had never been formally tested. The last few years have seen an increasing number of clinical trials putting accepted practices as well as new innovations to vigorous scientific scrutiny never before seen in MPE research. This has provided a solid platform for a growing number of studies in progress (and others in planning) that will examine, and hopefully improve, key aspects of MPE care.

This article provides an overview of the common interventional procedures employed for MPE management and their limitations. We highlight unanswered questions surrounding current practice and some of the research focuses that may change future practice.

KEY AND UNANSWERED QUESTIONS ON MPE MANAGEMENT

The quest for development of better management strategies for MPE patients has been challenging; progress has been far and few in between. Talc poudrage, for example, was first described in 1935 by Norman Bethune and has remained as a mainstay of practice. Very rarely in other walks of medicine do we manage patients in (almost exactly) the same way as clinicians did 80 years ago.

The easy percutaneous access from the chest wall to the malignant pleural fluid permits pleural interventions to be performed with relative technical ease. A variety of drainage procedures are now available, but few quality data exist to guide optimal choice and application of these procedures. Conventional teaching suggests that a therapeutic thoracentesis should be performed and, for patients who have symptomatic benefits, pleurodesis be considered when the effusion recurs. Various sclerosing agents and different delivery methods exist, with considerable debate on the optimal choice. IPC now challenges the paradigm; its position in the treatment algorithm varies drastically from being the ‘first-line procedure when the fluid is drained’ to ‘no place at all’.

In the era of personalized medicine when each cancer patient receives tailored therapy based on the individual’s tumour characteristics and host factors, MPE is still managed largely as a single disease. Treatment is often generic regardless of the patient factors (e.g. comorbidity), underlying cancer (e.g. type and stage) or the effusion characteristics (e.g. rate of fluid accumulation). Response assessment is often haphazard. This is akin to oncologists dispensing the same drugs for all patients irrespective of their malignancy or its stage, and without objective stratification of tumour response.

Fundamental to choice of pleural intervention for patients with MPE is their prognosis. Although studies have established a median survival of 4–6 months for metastatic pleural cancers and ~12 months for pleural mesothelioma, wide variation in life expectancy exists. The heterogeneity of the MPE cohort means that very large populations are needed to determine useful prognosticators.

Breathlessness is by far the commonest symptom, which pleural interventions aim to improve. Although
the effusion is often the most prominent feature on radiographs and computed tomography (CT) (Fig. 1). Breathlessness in MPE is often multifactorial. The severity of breathlessness correlates poorly with the size of the effusion. Drainage only improves dyspnoea in some, certainly not all, patients. Most pathophysiological studies of breathlessness in pleural effusions involved few (often ≤20) patients and focused on specific aetiological factors in isolation. Few/no studies have correlated physiological improvements with patient symptoms (the key indication for pleural intervention), and no established, or reliable, predictors exist on which patient management should be guided by the survival, the rate of fluid reaccumulation and the degree of symptoms it creates. Developing algorithms that can provide accurate predictors for the above factors should be an important focus of future research in MPE. Until then, heterogeneity in management will continue worldwide, and patients will be subjected to procedures that may or may not be beneficial as guided by the experience and/or instinct of their attending physician.

In ideal circumstances, individually tailored MPE management should be guided by the survival, the rate of fluid reaccumulation and the degree of symptoms it creates. Developing algorithms that can provide accurate predictors for the above factors should be an important focus of future research in MPE. Until then, heterogeneity in management will continue worldwide, and patients will be subjected to procedures that may or may not be beneficial as guided by the experience and/or instinct of their attending physician.

INTERVENTIONAL THERAPIES IN MPE
Therapeutic thoracentesis
Therapeutic thoracentesis is a simple, effective outpatient-based procedure, although its benefits may only be temporary. This is suitable for symptomatic patients who require short-term measures, particularly those with a short expected survival.

Breathlessness is often multifactorial in MPE patients. Underlying cardiopulmonary comorbidity (e.g. chronic obstructive pulmonary disease), concurrent lung pathologies (e.g. pneumonia) and cancer-related complications (e.g. pulmonary embolism, phrenic nerve palsy, endobronchial obstruction, or lymphangitis) can all contribute to the breathlessness (Fig. 2). In a patient with alternative cause(s) of dyspnoea to MPE, large volume thoracentesis is a useful initial procedure to establish the relative contribution of the effusion to the overall symptoms. It can also allow identification of underlying trapped lung and estimation of the rate of fluid reaccumulation. This information will serve to guide future management strategies.

In patients with a short expected survival and/or poor performance status, a repeat therapeutic thoracentesis may be preferable if the fluid reaccumulates.

A therapeutic thoracentesis to relieve immediate symptoms while awaiting treatment response is also justifiable in patients whose underlying malignancy may respond to targeted therapy or systemic chemotherapy, e.g. small cell carcinoma or lymphoma (Fig. 3). Patients with an MPE from lung adenocarcinomas with sensitizing epidermal growth factor receptor mutations can have a favourable response to tyrosine kinase inhibitors (e.g. gefitinib, erlotinib). Erlotinib, in particular, has excellent pleural penetration. More definitive treatment to minimize multiple invasive procedures should be considered in other cases of recurrent symptomatic MPEs.

Thoracentesis is generally safe, especially if performed with imaging guidance and by experienced operators. A large longitudinal study of patients undergoing ultrasound-guided (diagnostic and therapeutic) thoracentesis found that complications developed in only 86 (9%) of 941 procedures in 605 patients. Vasovagal events were rare and routine use of atropine is not recommended. Re-expansion pulmonary oedema can occur (although uncommonly) after removal of large volume of fluid (>1.5 L) rapidly. The risk of clinical re-expansion pulmonary oedema was estimated to be 0.5% in a series of 185 patients. Evacuation of larger amount of fluid is best performed with tube thoracostomy, which allows controlled rate of fluid removal.

Pleurodesis
Pleurodesis and placement of an IPC are the two most commonly used pleural interventions aimed to control recurrent pleural effusions.

Creation of a pleurodesis depends on symphysis of the visceral and parietal pleurae generated by either chemical or mechanical means. The exact
Figure 2  (a) Chest X-ray of a patient with malignant mesothelioma who presented with worsening breathlessness. Therapeutic pleural drainage produced only partial relief. (b) Subsequent computed tomography thorax (coronal view) revealed a large pericardial effusion but no pleural effusion. Echocardiogram confirmed pericardial tamponade. The patient’s breathlessness significantly improved following pericardiocentesis.

Figure 3  Top and bottom panel rows show computed tomography, transaxial 18-Fluoro-deoxyglucose (FDG) positron emission tomography and maximum intensity projection images of a patient with diffuse large B-cell lymphoma. Top row shows right pleural effusion and extensive FDG-avid lesions at time of diagnosis. Bottom row shows the response after 2 months of chemotherapy. The pleural effusion resolved completely without any pleural intervention.
mechanism underlying development of pleurodesis is poorly understood. Some researchers believe that an intact mesothelium is needed in inducing fibrosis and successful pleurodesis. The traditional belief however describes the induction of an acute pleural inflammatory response from the sclerosants that results in mesothelial cell denudement. Subsequent chronic inflammation and pleural fibrosis obliterates the pleural space and prevents fluid accumulation. As such, the more significant the injury is to the pleura, the more intense the inflammation and the likelihood of successful pleurodesis (Fig. 4), at the expense of more adverse effects (e.g. pain and fever) from the severe pleuritis.

Surgical pleurodesis can create extensive pleural damage through mechanical abrasion or parietal pleurectomy via thoracotomy or video-assisted thoracoscopic surgery (VATS). Open thoracotomy was once the standard procedure for control of pleural effusions. However, it requires general anaesthesia (with associated risks), large incisions and longer hospitalizations (~5–7 days or more). Chronic intercostal neuralgia at 6 months post-thoracotomy was reported by over 40% of patients. One-tenth of 56 patients in another study required daily analgesia, nerve blocks, acupuncture or specialist pain clinic visits. VATS has now largely replaced open thoracotomy as the preferred first-line surgical procedure.

Although VATS also requires general anaesthesia and single-lung ventilation (similar to open thoracotomy), it is performed via two to four small (~1 cm) portals of entry instead of a large thoracotomy incision. During VATS pleurodesis, the surgeons can employ various combinations of a range of available techniques including decortication, mechanical abrasion and poudrage. The effectiveness of different surgical pleurodesis techniques (except for poudrage alone) has not been directly compared with bedside instillation of pleurodesing agents. In principle, the more aggressive the surgical techniques employed, the more likely it will create a successful pleurodesis; however, this needs to be balanced against the risks of general anaesthesia, the higher likelihood of adverse events and costs. For example, a small study has shown a 10% recurrence rate of MPE after VATS parietal pleurectomy. Patient selection is a key factor and pleurectomy should be reserved for patients with excellent performance status and prognosis, as...
complications following VATS are not uncommon.\textsuperscript{32,35} Up to 15% patients develop major complications, for example bleeding, prolonged air leak, empyema, pneumonia and wound infection in the immediate postoperative setting following VATS surgery.\textsuperscript{32} Patients spend an average of 4–7 days in hospital following surgery.\textsuperscript{32} Following discharge, some studies have reported that over a third of the patients suffer from persistent pain or discomfort at the operation site for over 3 months.\textsuperscript{32} Larger randomized, controlled trials (RCT) comparing it with less invasive treatments such as talc slurry are needed.

Intrapleural instillation of a sclerosant (chemical pleurodesis) is the most widely used pleurodesis method. Although over 30 RCT have been performed, they often included small numbers of patients, and few studies reached statistical significance.\textsuperscript{36} (Table 1) Talc is the most commonly used agent worldwide.\textsuperscript{53} Tetracycline derivatives, cytotoxic agents such as bleomycin, OK432 (a preparation of Streptococcus pyogenes type A3 commonly reported in Japanese studies\textsuperscript{54}) and quinacrine (an antimalarial agent used in Scandinavian studies\textsuperscript{55}) are some of the alternative agents used. Iodopovidone\textsuperscript{56,57} and silver nitrate\textsuperscript{58} have been shown, albeit in small trials, to have comparable efficacy as talc poudrage for MPE control, with few complications. Considerable interests have focused on the use of bacterial products such as new sclerosant. Staphylococcus aureus super antigen and lipoteichoic acid\textsuperscript{57,58} have both shown promise in small uncontrolled trials.

Talc has been shown to be more effective on comparative trials against bleomycin,\textsuperscript{42,43,46} tetracycline derivatives\textsuperscript{50,51} and over non-sclerosant controls.\textsuperscript{37} A Cochrane meta-analysis supported use of talc as the sclerosant of choice.\textsuperscript{50} Talc can be administered as a dry powder (poudrage), usually during thoracoscopy or as slurry via a chest tube. Talc poudrage was first described in 1935\textsuperscript{12} and allows distribution of the insufflated talc over the entire pleural surface.

It was conventionally believed that talc poudrage is more effective than slurry. Until recently, talc poudrage has been advocated as a more effective method than talc slurry pleurodesis, supported by anecdotal series faulted by selection bias. This belief has now been refuted by all three randomized trials comparing talc poudrage and slurry pleurodesis.\textsuperscript{5,38,39} This highlights the critical lack of scientific evaluation of conventional pleural practice, and the urgent need to evaluate common MPE care strategies through high-quality clinical studies. Indeed, the largest randomized trial in MPE\textsuperscript{5} showed in 482 patients that success rate of fluid control at 30 days was not significantly different between surgical thoracoscopic talc poudrage and chest-tube talc slurry pleurodesis (78% vs 71%, respectively). Talc poudrage was associated with significantly more complications, including postoperative pneumonia, respiratory failure, bronchopleural fistulae and dysrythmia. An unplanned subgroup analysis suggested a better successful pleurodesis rate with thoracoscopic poudrage in patients with lung or breast cancer.\textsuperscript{5} This is being evaluated in a randomized trial (ISRCTN47845793) in the United Kingdom. A smaller randomized study involving 60 patients showed that full lung re-expansion was more common after thoracoscopic pleurodesis but did not change patient outcomes\textsuperscript{60} with no difference in QoL, hospitalization or pleurodesis success rates when compared with talc slurry. The third randomized study comparing thoracoscopic pleurodesis with talc slurry pleurodesis in 57 patients also reported similar findings with no significant difference in pleurodesis success or hospitalization rates.\textsuperscript{39}

The lack of research on MPE is highlighted in the case of talc pleurodesis. Despite its use worldwide over many decades, its usefulness and harm have only been uncovered by research studies in recent years. In some countries, talc was licensed as a device rather than a drug and avoided the scrutiny of pharmaceutical safety.\textsuperscript{60} Only in recent years had it come to light that many ‘talc’ preparations used around the world contained largely other compounds or even no talc at all. Even within genuine talc preparations, significant heterogeneity exists in their physical properties in different commercial products.\textsuperscript{61} Talc of small particle size can be systemically absorbed, presumably via parietal lymphatics, as shown in human and animal studies.\textsuperscript{62,63,65} This induces systemic and lung inflammation. Dresler et al.\textsuperscript{5} showed that 2.3% of patients died of the resultant respiratory failure, irrespective of whether talc was insufflated or administered as slurry. Large particle size talc preparations (median particle size >25 μm) are not available in some parts of the world; this becomes an important factor in the choice of MPE treatment.

There are wide variations in how talc slurry pleurodesis is performed. No consensus exists on the ideal timing for pleurodesis. The reported success rate for pleurodesis attempted at the time of initial MPE diagnosis is similar to pleurodesis deferred for symptomatic recurrence.\textsuperscript{5,38,39} Early intervention may reduce the risk of trapped lung that could preclude pleurodesis\textsuperscript{66} (Fig. 5). Conversely, nearly half of all MPEs may not recur and cause significant symptoms, thus arguing against routine pleurodesis on all new patients. The exact timing of instillation of sclerosant is unknown; few data support the traditional practice to defer instillation till daily fluid output falls below a specified rate (e.g. <150 mL/day).\textsuperscript{5,67} Pleurodesis when radiographic lung re-expansion occurs is an alternative, but direct comparison of the approaches is needed.\textsuperscript{67} Use of suction pre- and post-instillation of sclerosant to assist apposition of the pleural membranes is often tried, but supporting evidence is lacking.

No consensus exists about the optimal chest tube clamping time following sclerosant injection. In an international survey, a wide range of duration of 1–4 h were used.\textsuperscript{11,53} The ideal time of chest tube removal after pleurodesis is not known. Some advocate tube withdrawal independent of drainage volume, whereas others remove the tube when the drainage volume is <150 mL/day.\textsuperscript{53} One small randomized study showed that routinely removing drains at 24 h (instead of 72 h) post-pleurodesis could significantly reduce hospital stay (4 vs 8 days; P < 0.01)\textsuperscript{68} without impacting success rates.
<table>
<thead>
<tr>
<th>Authors</th>
<th>Number of patients</th>
<th>Outcome measure(s)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Talc slurry versus thoracentesis alone Sorensen et al.</td>
<td>31</td>
<td>Complete resolution of effusion and subjective improvement</td>
<td>Favoured talc 100% versus 58%</td>
</tr>
<tr>
<td>Thoracoscopic talc poudrage versus talc slurry Terra et al.</td>
<td>60</td>
<td>Clinical efficacy; symptomatic +/- radiological recurrence</td>
<td>No significant difference (25/30 vs 26/30 success)</td>
</tr>
<tr>
<td>Dresler et al.</td>
<td>501</td>
<td>30-day freedom from radiographic MPE recurrence</td>
<td>No significant difference (78% vs 71%)</td>
</tr>
<tr>
<td>Yim et al.</td>
<td>57</td>
<td>Pleural fluid recurrence, length of hospital stay, complication rate</td>
<td>No significant difference</td>
</tr>
<tr>
<td>Thoracoscopic talc poudrage versus tetracycline Fentiman et al.</td>
<td>41</td>
<td>Radiological control</td>
<td>Favoured talc (92% vs 48%, ( P = 0.022 ))</td>
</tr>
<tr>
<td>Thoracoscopic talc poudrage versus doxycycline Kuzdzal et al.</td>
<td>33</td>
<td>Radiological fluid recurrence; short- and long-term (until death or ( \leq 12 ) months)</td>
<td>Significantly favoured talc (short-term ( P = 0.009; ) long-term ( P = 0.00003 ))</td>
</tr>
<tr>
<td>Thoracoscopic talc poudrage versus bleomycin Hamed et al.</td>
<td>29</td>
<td>Radiological control ( \geq 1 ) month</td>
<td>Favoured talc (0% reaccumulation vs 33%, ( P = 0.057 ))</td>
</tr>
<tr>
<td>Diacon et al.</td>
<td>36</td>
<td>Radiological recurrence rate and cost-effectiveness</td>
<td>Favoured talc at 30 days ( (P = 0.12) ), 90 days ( (P = 0.01) ) and 120 days ( (P = 0.005) )</td>
</tr>
<tr>
<td>Talc slurry versus bleomycin</td>
<td></td>
<td></td>
<td>No significant difference between groups</td>
</tr>
<tr>
<td>Zimmer et al.</td>
<td>35</td>
<td>Radiological control</td>
<td>Favoured talc (90% vs 79%, ( P = 0.388 )) Significant cost advantage with talc ( ($12.36 vs $955.83) )</td>
</tr>
<tr>
<td>Ong et al.</td>
<td>50</td>
<td>Radiological control ( \geq 1 ) month. Cost analysis</td>
<td>Favoured talc (89% vs 70%, ( P = 0.168 )) Cost analysis favoured talc</td>
</tr>
<tr>
<td>Haddad et al.</td>
<td>71</td>
<td>No recurrence of pleural effusion or asymptomatic recurrence of small effusion. Cost analysis</td>
<td>No difference seen between groups at 30, 60 or 180 days ( (P = 0.724) ) Talc significantly cheaper ( (P &lt; 0.001) )</td>
</tr>
<tr>
<td>Thoracoscopic talc poudrage versus mustine Fentiman et al.</td>
<td>46</td>
<td>Radiological control</td>
<td>Favoured talc (90% vs56%, ( P = 0.025 ))</td>
</tr>
<tr>
<td>Talc slurry versus silver nitrate Paschoalini et al.</td>
<td>60</td>
<td>No recurrence of pleural effusion</td>
<td>No significant difference at 30 (84% vs 96%), 60, 90 or 120 days</td>
</tr>
<tr>
<td>Talc slurry versus thoracoscopic mechanical pleurodesis (TMP) Crnjac et al.</td>
<td>87</td>
<td>Radiological recurrence, time of chest tube drainage and hospital stay, morbidity and mortality at 6 months</td>
<td>No significant difference (74% vs 87%). Shorter length of drainage and hospital stay with TMP. No significant difference in complication or mortality rates</td>
</tr>
<tr>
<td>Thoracoscopic talc poudrage versus 10% povidone iodine Mohsen et al.</td>
<td>42</td>
<td>Efficacy (symptom control, effusion recurrence) and safety</td>
<td>No significant difference at 3 (87% vs 85%) or 6 (91% vs 85%) months. No significant difference in complication or mortality rates</td>
</tr>
<tr>
<td>Talc slurry versus indwelling pleural catheter (IPC) Davies et al.</td>
<td>106</td>
<td>Subjective dyspnoea control</td>
<td>No significant difference in dyspnoea control at day 42. 22% talc versus 6% IPC needed further pleural intervention</td>
</tr>
<tr>
<td>Demmy et al.</td>
<td>57</td>
<td>Combined success: consistent/reliable drainage/pleurodesis, lung expansion and 30-day survival</td>
<td>Favoured IPC (62% vs 46%; odds ratio 5.0; ( P = 0.064 ))</td>
</tr>
</tbody>
</table>

Adapted from Davies et al.\cite{52}
The TIME-1 study (ISRCTN33288337) is a multi-centre randomized trial that compares the use of large versus small bore chest drains for pleurodesis (another common controversy). TIME-1 also evaluates the impact (if any) of non-steroidal anti-inflammatory drugs (NSAIDs) on effectiveness of talc pleurodesis. This is an interesting question as animal studies have shown that steroids and NSAIDs can inhibit sclerosant-induced pleural inflammation and subsequent pleurodesis.69

Recent data have established that talc pleurodesis will fail in ~30% of patients (Fig. 6). In symptomatic patients, repeat pleurodesis with either the same or a different agent is often performed without any supporting evidence; in one study, the overall pleurodesis success rate was increased by only 3.6%.70 Repeated therapeutic thoracenteses is an alternative in symptomatic patients with poor performance status and short life expectancy (4–6 weeks). IPC is now the preferred choice in many centres.

**Figure 5** Computed tomography thorax (axial and coronal view) shows trapped lung in a patient with malignant pleural effusion. The left lung did not fully re-expand and precluded pleurodesis despite complete drainage of effusion via an intercostal catheter.

**Figure 6** Computed tomography thorax (coronal and axial views) shows left-sided, multiple, large loculations as a sequel to failed surgical pleurodesis in a patient with malignant mesothelioma. The locules are separated by thick septations that prevent adequate fluid drainage and lung re-expansion. This patient was managed with an indwelling pleural catheter that provided effective drainage and relief of breathlessness.
Use of IPC represents a major step towards the new directions of MPE care (see previous discussion). This is a type of silicone tube placed in the pleural cavity, tunneled subcutaneously and brought out through an exit site on the skin with a capped one-way valve at the distal end. It allows ambulatory drainage and thus minimizes hospitalization and costs. Importantly, it addresses patient symptoms by removing the fluid and shows that pleurodesis is unnecessary to achieve this goal.

Leading guidelines have advocated the use of IPC for use in patients with symptomatic MPE, particularly those who fail pleurodesis or are unsuitable for pleurodesis (e.g. with trapped lung). A recent systematic review (19 studies, 1370 patients) showed that IPC provided symptomatic improvement in ~95% cases of recurrent MPE and complications were uncommon. Even in patients with underlying trapped lung, IPC drainage improved symptoms in 48–90% of patients. Drainage is usually guided by symptoms, and it offers a greater sense of control to the patients.

Two randomized studies comparing IPC with pleurodesis have demonstrated equivalent symptom benefits from either treatment. Putnam et al. showed that IPC provided equivalent improvement in both dyspnoea and QoL to doxycycline pleurodesis in 144 patients. Davies et al. further confirmed that both therapies offered similar benefits in dyspnoea, measured using a visual analogue scale, and QoL in the first 42 days. IPC however was superior by the end of 6 months in improving breathlessness. In most (>90%) patients, IPC avoided further pleural interventions, and the associated risks and costs.

Patients with IPC also spent significantly fewer days in hospital, another important PROM, in a patient-choice study. Patients who received talc pleurodesis spent (median) 11.5 days more in hospital from any cause of admission than the IPC-treated ones. This is being verified in a multinational randomized trial, the Australasian Malignant Pleural Effusion study (NCT02045121), which compares IPC with talc slurry as frontline treatment in MPE. This is the first randomized trial in MPE to use total hospital days in the patients’ remaining lifespan as the primary endpoint. The results will have implication on patients’ choice of treatment in future, as well as health economics. Another RCT in United States (NCT01117740) compares IPC versus thoracoscopic pleurodesis with a primary outcome of quality-adjusted survival times post-intervention.

Spontaneous pleurodesis (SP) following IPC was seen in almost half (45.6%) of the 943 cases studied in the meta-analysis by Van Meter et al.—rates comparable with that of successful pleurodesis at 6 months (Fig. 7). The average time to pleurodesis was 52 days. SP is seen, although less frequently, even in the presence of trapped lung. The mechanism underlying SP is unknown but has been associated with positive pleural fluid cytology, cancer-specific subtype of cancer and degree of lung re-expansion after fluid removal. Requirement for further pleural intervention after catheter removal due to recurrence of effusion is low (<8%).

Figure 7 (a) Computed tomography (CT) scan (coronal view) shows a large right pleural effusion that required indwelling pleural catheter (IPC) drainage for malignant pleural effusion management. (b) CT scan performed a few weeks later shows complete resolution of the effusion following spontaneous pleurodesis. The IPC was removed with no recurrence of effusion on follow-up.
At least two randomized studies (NCT00978939 & NCT00761618) are comparing aggressive (daily) versus standard drainage (three times a week) regimens with IPC to determine the optimal drainage method that can best produce SP. Considerable effort now also focuses on combining the benefits of IPC and pleurodesis to maximize the advantages of both procedures and minimizing the adverse effects of bearing an IPC long term. Placement of IPC at the same time as thoracoscopic talc poudrage has been shown feasible in a pilot study to provide the IPC as a ‘safety net’ should the pleurodesis fails. Another concept is being investigated in the IPC-PLUS trial (ISRCTN73255764): MPE patients are fitted with an IPC and talc instilled intrapleurally in those without significantly trapped lungs to enhance the chances of pleurodesis. Another innovative way being explored is to coat IPC with a sclerosant. In sheep and rabbit models, silver nitrate-coated IPC appeared effective shown feasible in a pilot study to provide the IPC as a ‘safety net’ should the pleurodesis fails. Another concept is being investigated in the IPC-PLUS trial (ISRCTN73255764): MPE patients are fitted with an IPC and talc instilled intrapleurally in those without significantly trapped lungs to enhance the chances of pleurodesis. Another innovative way being explored is to coat IPC with a sclerosant. In sheep and rabbit models, silver nitrate-coated IPC appeared effective in promoting pleurodesis. This concept has yet to be tested in humans.

Recent data have provided reassurance on the safety of IPC use. IPC-related complications are minor and easily treatable, for example cellulitis, catheter blockage (Fig. 8), catheter malfunction and symptomatic loculation (Fig. 9). IPC-related pleural infection, the most concerning potential complication for clinicians, occurred only in <5% of over 1000 patients in a multicentre study and were usually controlled with appropriate antibiotics. The risk of mortality from pleural infection in an IPC patient was only 0.3%. Interestingly, bacterial infection provides effective pleurodesis in about two-thirds of the patients allowing removal of the IPC. Another series of 243 patients (262 IPC procedures) also echoed the results showing a 6.1% infection rate and a complication rate in the chemotherapy group that was similar to those who did not receive chemotherapy (5.2% vs 7.9%). Catheter tract metastases (CTM) developed in ~10% of 110 patients in a region of high incidence of mesothelioma (Fig. 10). Importantly, CTM can complicate both mesothelioma and metastatic carcinomas. The symptoms are generally mild and usually respond to radiotherapy.

**Pleuroperitoneal shunt**

Pleuroperitoneal shunt (PPS) is a device with two catheters placed within the pleural and peritoneal cavities, and connected by a one-way valve pump chamber that draws fluid from the pleural space into peritoneal cavity. It can provide effective palliation in ~95% patients and can be valuable in patients with a trapped lung or who failed pleurodesis. PPS has its own set of complications including a high (~25%) occlusion rate that often requires shunt revision, removal and/or replacement. Pain and infections can occur, and some patients complained of the need of having to activate the pump hundreds of times a day. The popularity of IPCs has diminished the interests in PPS.

**Management of MPE in special scenarios**

If the lung fails to expand upon complete evacuation of pleural fluid, pleurodesis is likely to fail. Incomplete lung re-expansion can be due to encasement of the lung by tumour involvement of the visceral pleura or from endobronchial obstruction. Thoracoscopic decortication of visceral pleura and/or breakdown of loculations are employed in the former in some centres, but this has not been subjected to comparative clinical trials.

Management is challenging in patients presenting with loculated but symptomatic MPEs. The use of intrapleural fibrinolytic therapy to break down septations before instilling talc slurry is being tested in a randomized study (TIME-3; ISRCTN12852177).

**FUTURE DIRECTIONS**

Current MPE management targets fluid control although the ultimate goal will be to eradicate or control the underlying pleural malignancy. While this may not be realistic at this point, the next important aim will be to diagnose and treat the MPE with minimal or no interventions. Exudative effusions are formed from plasma extravasation. Tumour neovascularization is particularly ‘leaky’. Active research now targets the angiogenesis and vascular hyperpermeability. Pilot studies targeting pleural fluid production, for example using zoledronic acid, are underway and may offer novel approaches in the future. Intrapleural delivery of chemotherapy, immune-modulators and gene therapy remain subjects of ongoing research.

There is increasing realization of the magnitude of the health-care burden posed by MPE. There are more interests now in developing and optimizing therapies for MPE patients than ever before. The lessons learned from talc (poor understanding of its safety...
concerns and overestimated success) in recent years emphasize the need to evaluate existing as well as new therapies in vigorous scientific trials to ensure patient safety and delivery of best patient care. Although still in its early days, the use of PROMs as clinical trial end-points has to be the focus in patient management.

MPE must be recognized as an ‘umbrella term’ encompassing a diverse patient population of different prognoses, aetiology and predicted clinical course. Patients are likely to respond differently to various therapies, and it is vital that the research (and clinical) community continues to search for parameters that will help guide the best treatment approach for individual patients.

REFERENCES

Interventions for MPE


