Official Journal of the Asian Pacific Society of Respirology
Respirology

INVITED REVIEW

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

RAJESH THOMAS,[1,2,3] ROSLYN FRANCIS,[2,4] HELEN E. DAVIES[5] AND Y.C. GARY LEE[1,2,3]

[1]*Department of Respiratory Medicine, Sir Charles Gairdner Hospital,* [2]*School of Medicine and Pharmacology, University of Western Australia,* [3]*Pleural Disease Unit, Lung Institute of Western Australia,* [4]*Department of Nuclear Medicine, Sir Charles Gairdner Hospital, Perth, Western Australia, Australia, and* [5]*University 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.

Abbreviations: CT, computed tomography; CTM, catheter tract metastasis; IPC, indwelling pleural catheter; MPE, malignant pleural effusion; NSAID, non-steroidal anti-inflammatory drug; PPS, pleuroperitoneal shunt; PROM, patient-reported outcome measure; QoL, quality of life; TIME, Therapeutic Intervention in Malignant Effusion; VATS, video-assisted thoracoscopic surgery.

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 pain[4] 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/

Correspondence: Y.C. Gary Lee, University Department of Medicine, QE II Medical Center, Perth, WA 6009, Australia. Email: gary.lee@uwa.edu.au

The Authors: Rajesh Thomas is an academic respiratory specialist with research interests in thoracic malignancy. His current research aims to study and help define the role of indwelling pleural catheters in the management of malignant pleural effusions. Roslyn Francis, Associate Professor of Molecular Imaging at University of Western Australia and Head of Department of Nuclear Medicine/WA PET Service, Sir Charles Gairdner Hospital, has a clinical research interest in functional imaging of malignant pleural disease, including novel PET imaging agents. Helen Davies' research and clinical interests include pleural diseases, in particular malignant pleural conditions, and the palliative management of patients with advanced respiratory disease. Y.C. Gary Lee is a clinician scientist who leads a translational research program focusing on pleural diseases, especially pleural malignancies and infection. The program includes a laboratory and a clinical research arm closely integrated with an active tertiary clinical pleural disease service that he directs.

Funding: Y.C.G.L. is a National Health and Medical Research Council (NHMRC) Career Development Fellow and receives project grant funding from the NHMRC, New South Wales Dust Disease Board, Sir Charles Gairdner Research Advisory Committee, LIWA Westcare Grants and the Cancer Council of Western Australia. RT receives research scholarship support from NHMRC, Western Australia Cancer and Palliative Care Network (WACPCN) and LIWA, Australia.

Conflict of Interest: Y.C.G.L. is on the advisory board of CareFusion and Sequana Med. No other authors have a conflict of interest to declare.

Received 9 April 2014; invited to revise 28 April 2014; revised 1 May 2014; accepted 1 May 2014.

Article first published online: 19 June 2014

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[5–7]) 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.[8]

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.[9]

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)-2[10] 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.[11] 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 challenge 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[12] 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;[13] 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[14] and ~12 months for pleural mesothelioma,[15] 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

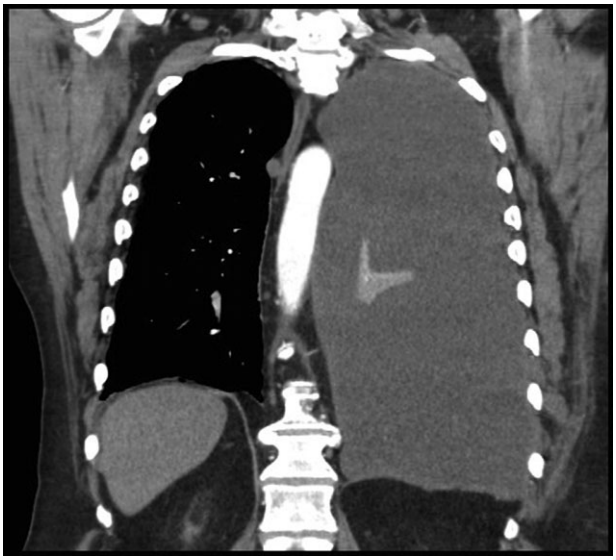

Figure 1 Computed tomography thorax (coronal view) shows a large left malignant pleural effusion causing flattening/inversion of the left hemi-diaphragm and expansion of the left chest wall; two mechanisms that may play an important role in the pathophysiology of breathlessness in pleural effusions.

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.[16–18] 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.[16–20] 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 will derive benefit. Patient selection is thus a principle area that needs to be addressed in future.

There are also no good predictors to determine in whom, and when, the effusion will recur after initial therapeutic drainage. Even in mesothelioma, when 95% of patients suffer from an effusion during their disease course, a recent review of the Western Australian mesothelioma registry over 5 years found that only 42% of the 320 patients needed pleurodesis for control of MPE.[21]

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).[22–24] Erlotinib, in particular, has excellent pleural penetration.[25] 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.[26] 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.[27] 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

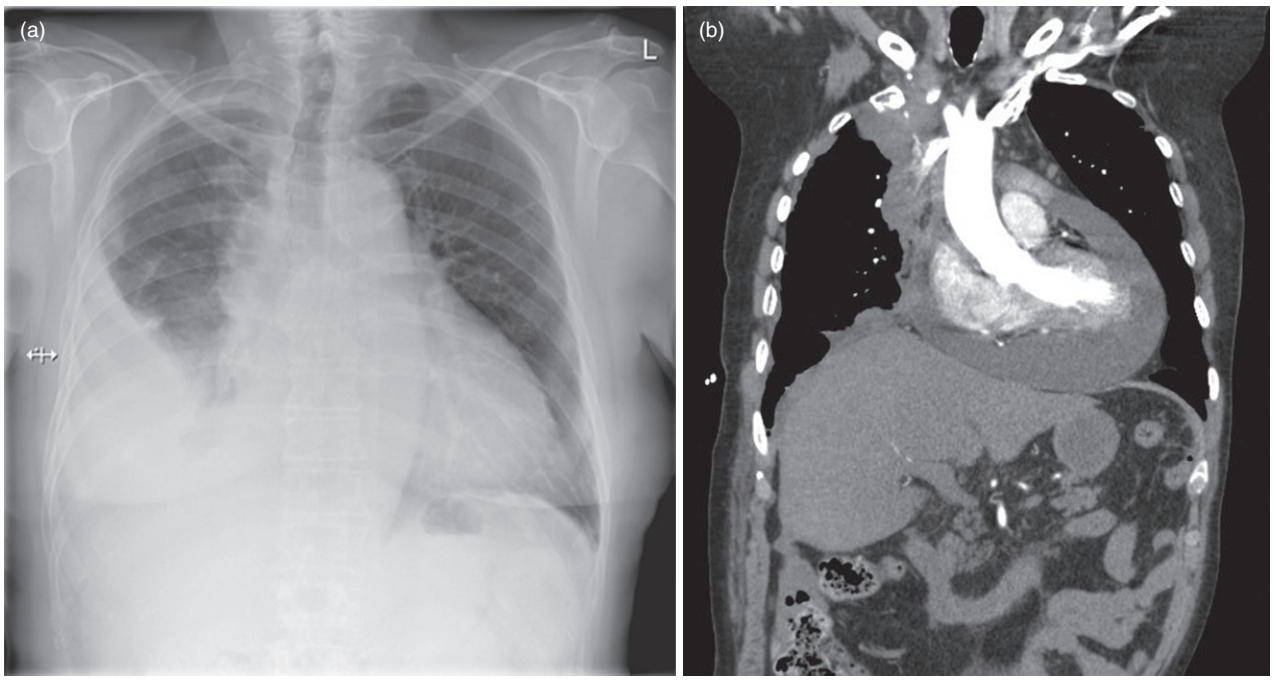

Figure 2 (a) Chest X-ray of a patient with malignant mesothelioma who presented with worsening breathlessness. Therapeutic pleural drainage produced only partial relief. (b) Subsequent computed tomography thorax (coronal view) revealed a large pericardial effusion but no pleural effusion. Echocardiogram confirmed pericardial tamponade. The patient's breathlessness significantly improved following pericardiocentesis.

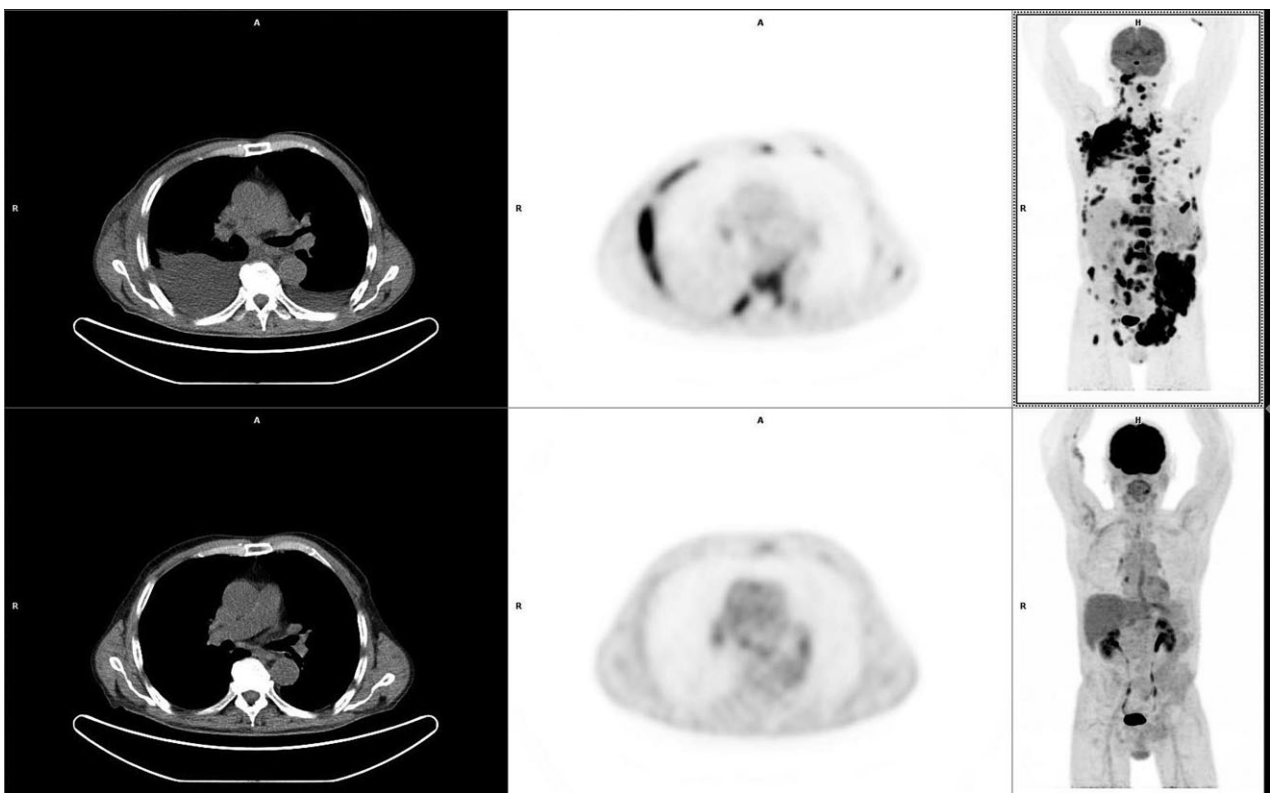

Figure 3 Top and bottom panel rows show computed tomography, transaxial 18-Fluoro-deoxyglucose (FDG) positron emission tomography and maximum intensity projection images of a patient with diffuse large B-cell lymphoma. Top row shows right pleural effusion and extensive FDG-avid lesions at time of diagnosis. Bottom row shows the response after 2 months of chemotherapy. The pleural effusion resolved completely without any pleural intervention.

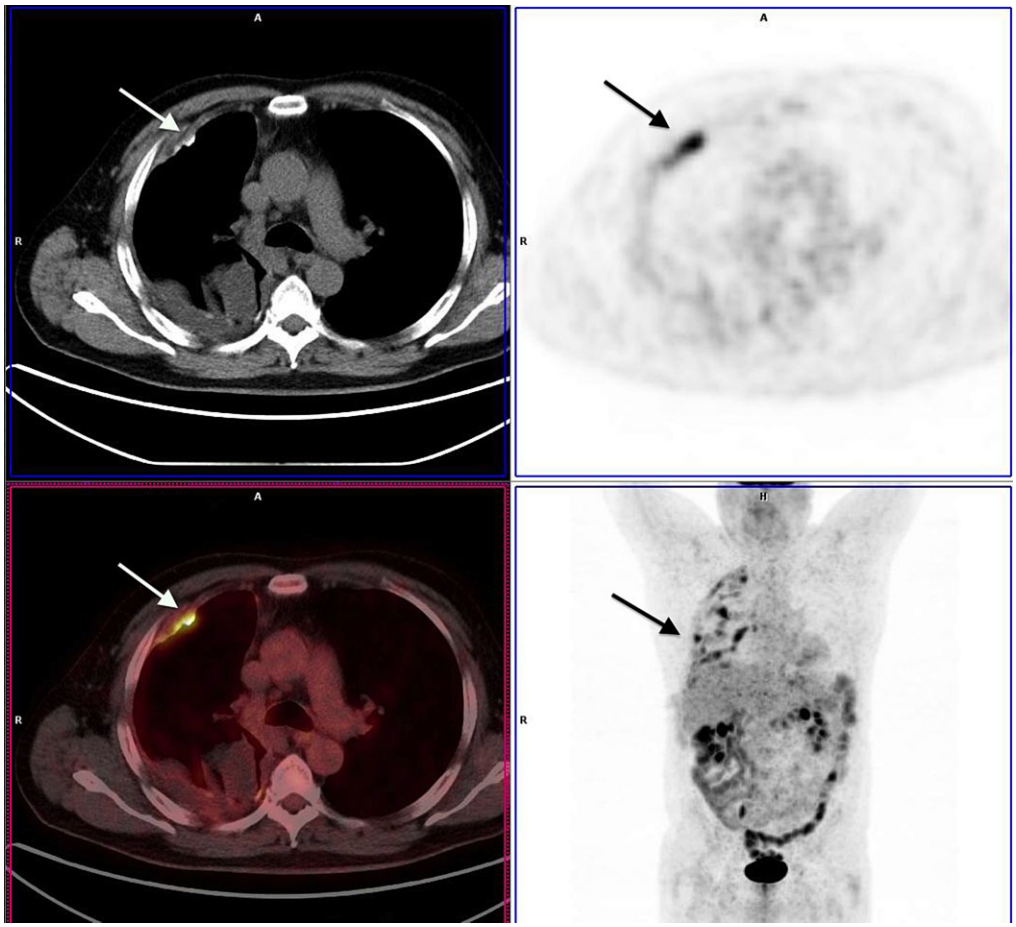

Figure 4 Transaxial computed tomography (CT), fluoro-deoxyglucose positron emission tomography (FDG PET), fused PET-CT and maximum intensity projection images in a patient who previously underwent talc pleurodesis. The talc can be seen as high-density material (arrow) on CT scan in the anterolateral pleural surface of the right lung. PET scan demonstrates focal FDG avidity around the talc deposition.

mechanism underlying development of pleurodesis is poorly understood. Some researchers believe that an intact mesothelium is needed in inducing fibrosis and successful pleurodesis.[28,29] 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).[30] 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).[31] Chronic intercostal neuralgia at 6 months post-thoracotomy[32] 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.[33] 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.[34] 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.[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.[35] Patients spend an average of 4–7 days in hospital following surgery.[35] 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.[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.[36] (Table 1) Talc is the most commonly used agent worldwide.[53] Tetracycline derivatives, cytotoxic agents such as bleomycin, OK432 (a preparation of *Streptococcus pyogenes* type A3 commonly reported in Japanese studies[54]) and quinacrine (an antimalarial agent used in Scandinavian studies[55]) are some of the alternative agents used. Iodopovidone[50,56] and silver nitrate[49] 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 as new sclerosant. *Staphylococcus aureus* super antigen and lipoteichoic acid[57,58] have both shown promise in small uncontrolled trials.

Talc has been shown to be more effective on comparative trials against bleomycin,[42,43,45,46] tetracycline derivatives[40,41] and over non-sclerosant controls.[37] A Cochrane meta-analysis supported use of talc as the sclerosant of choice.[59] 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[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.[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[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 dysrhythmia. An unplanned subgroup analysis suggested a better successful pleurodesis rate with thoracoscopic poudrage in patients with lung or breast cancer.[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[38] 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.[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.[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.[61] Talc of small particle size can be systemically absorbed, presumably via parietal lymphatics, as shown in human and animal studies.[62,63] This induces systemic and lung inflammation. Dresler *et al.*[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.[53,64,65] Early intervention may reduce the risk of trapped lung that could preclude pleurodesis[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).[53,67] Pleurodesis when radiographic lung re-expansion occurs is an alternative, but direct comparison of the approaches is needed.[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.[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.[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; $P < 0.01$)[68] without impacting success rates.

Table 1 Prospective randomized trials comparing talc with other agents

Authors	Number of patients	Outcome measure(s)	Results
Talc slurry versus thoracentesis alone			
Sorensen *et al.*[37]	31	Complete resolution of effusion and subjective improvement	Favoured talc 100% versus 58%
Thoracoscopic talc poudrage versus talc slurry			
Terra *et al.*[38]	60	Clinical efficacy: symptomatic +/– radiological recurrence	No significant difference (25/30 vs 26/30 success)
Dresler *et al.*[5]	501	30-day freedom from radiographic MPE recurrence	No significant difference (78% vs 71%)
Yim *et al.*[39]	57	Pleural fluid recurrence, length of hospital stay, complication rate	No significant difference
Thoracoscopic talc poudrage versus tetracycline			
Fentiman *et al.*[40]	41	Radiological control	Favoured talc (92% vs 48%, $P = 0.022$)
Thoracoscopic talc poudrage versus doxycycline			
Kuzdzal *et al.*[41]	33	Radiological fluid recurrence; short- and long-term (until death or ≤12 months)	Significantly favoured talc (short-term $P = 0.009$; long-term $P = 0.00003$)
Thoracoscopic talc poudrage versus bleomycin			
Hamed *et al.*[42]	29	Radiological control ≥1 month	Favoured talc (0% reaccumulation vs 33%, $P = 0.057$)
Diacon *et al.*[43]	36	Radiological recurrence rate and cost-effectiveness	Favoured talc at 30 days ($P = 0.12$), 90 days ($P = 0.01$) and 120 days ($P = 0.005$) Cost estimation favoured talc
Talc slurry versus bleomycin			
Noppen *et al.*[44]	26	Recurrent pleural fluid ≥50% of initial volume or requiring pleurocentesis	No significant difference between groups
Zimmer *et al.*[45]	35	Radiological control	Favoured talc (90% vs 79%, $P = 0.388$) Significant cost advantage with talc ($12.36 vs $955.83)
Ong *et al.*[46]	50	Radiological control ≥1 month. Cost analysis	Favoured talc (89% vs 70%, $P = 0.168$) Cost analysis favoured talc
Haddad *et al.*[47]	71	No recurrence of pleural effusion or asymptomatic recurrence of small effusion. Cost analysis	No difference seen between groups at 30, 60 or 180 days ($P = 0.724$) Talc significantly cheaper ($P < 0.001$)
Thoracoscopic talc poudrage versus mustine			
Fentiman *et al.*[48]	46	Radiological control	Favoured talc (90% vs56%, $P < 0.025$)
Talc slurry versus silver nitrate			
Paschoalini *et al.*[49]	60	No recurrence of pleural effusion	No significant difference at 30 (84% vs 96%), 60, 90 or 120 days
Talc slurry versus thoracoscopic mechanical pleurodesis (TMP)			
Crnjac *et al.*[30]	87	Radiological recurrence, time of chest tube drainage and hospital stay, morbidity and mortality at 6 months	No significant difference (74% vs 87%). Shorter length of drainage and hospital stay with TMP. No significant difference in complication or mortality rates
Thoracoscopic talc poudrage versus 10% povidone iodine			
Mohsen *et al.*[50]	42	Efficacy (symptom control, effusion recurrence) and safety	No significant difference at 3 (87% vs 85%) or 6 (91% vs 85%) months. No significant difference in complication rates
Talc slurry versus indwelling pleural catheter (IPC)			
Davies *et al.*[10]	106	Subjective dyspnoea control	No significant difference in dyspnoea control at day 42. 22% talc versus 6% IPC needed further pleural intervention
Demmy *et al.*[51]	57	Combined success: consistent/reliable drainage/pleurodesis, lung expansion and 30-day survival	Favoured IPC (62% vs 46%; odds ratio 5.0; $P = 0.064$)

Adapted from Davies *et al.*[52]

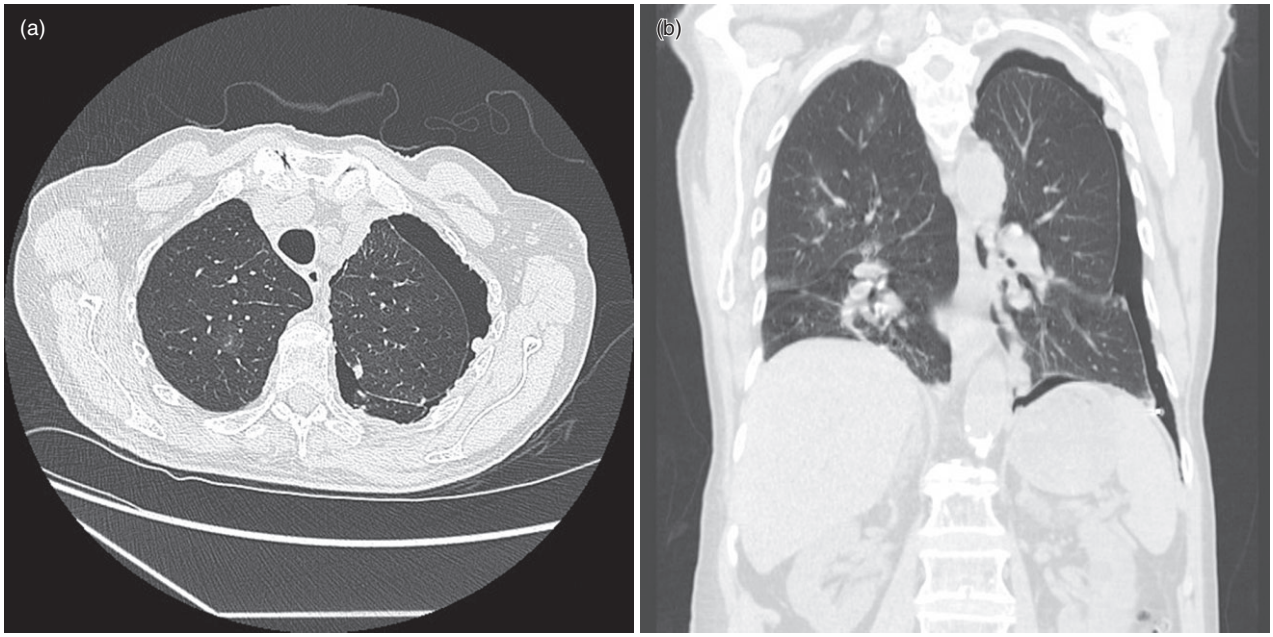

Figure 5 Computed tomography thorax (axial and coronal view) shows trapped lung in a patient with malignant pleural effusion. The left lung did not fully re-expand and precluded pleurodesis despite complete drainage of effusion via an intercostal catheter.

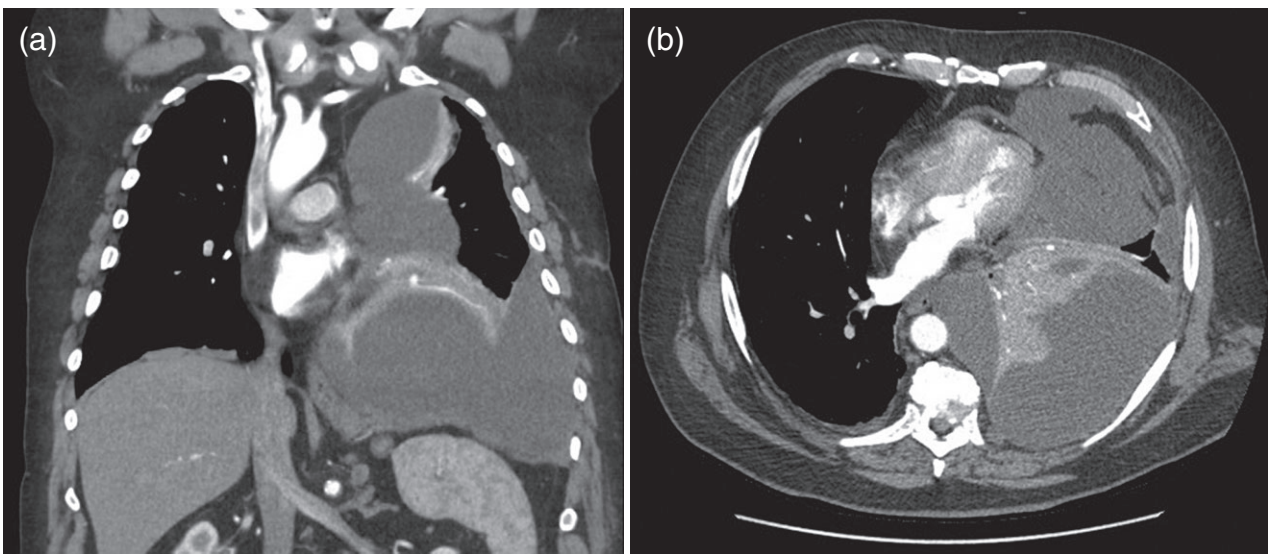

Figure 6 Computed tomography thorax (coronal and axial views) shows left-sided, multiple, large loculations as a sequel to failed surgical pleurodesis in a patient with malignant mesothelioma. The locules are separated by thick septations that prevent adequate fluid drainage and lung re-expansion. This patient was managed with an indwelling pleural catheter that provided effective drainage and relief of breathlessness.

The TIME-1 study (ISRCTN33288337) is a multicentre 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.

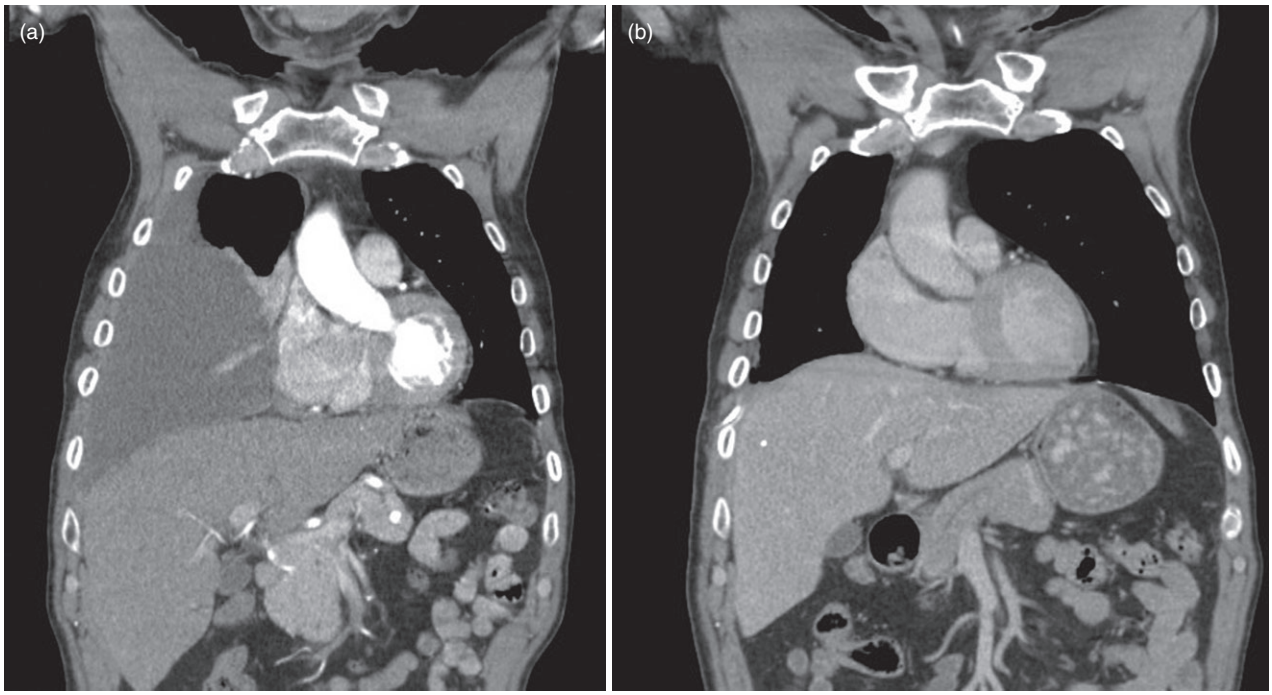

Figure 7 (a) Computed tomography (CT) scan (coronal view) shows a large right pleural effusion that required indwelling pleural catheter (IPC) drainage for malignant pleural effusion management. (b) CT scan performed a few weeks later shows complete resolution of the effusion following spontaneous pleurodesis. The IPC was removed with no recurrence of effusion on follow-up.

IPC

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, tunnelled 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,[11,71,72] particularly those who fail pleurodesis or are unsuitable for pleurodesis (e.g. with trapped lung). A recent systematic review (19 studies, 1370 patients)[73] 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.[8,74–76] 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.[8,10,51,77–81] Putnam *et al.*[77] showed that IPC provided equivalent improvement in both dyspnoea and QoL to doxycycline pleurodesis in 144 patients. Davies *et al.*[10] 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,[8,10,78] 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.[8] 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.*[72]—rates comparable with that of successful pleurodesis at 6 months[5] (Fig. 7). The average time to pleurodesis was 52 days. SP is seen, although less frequently, even in the presence of trapped lung.[75,76,82,83] 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.[84] Requirement for further pleural intervention after catheter removal due to recurrence of effusion is low (<8%).[73]

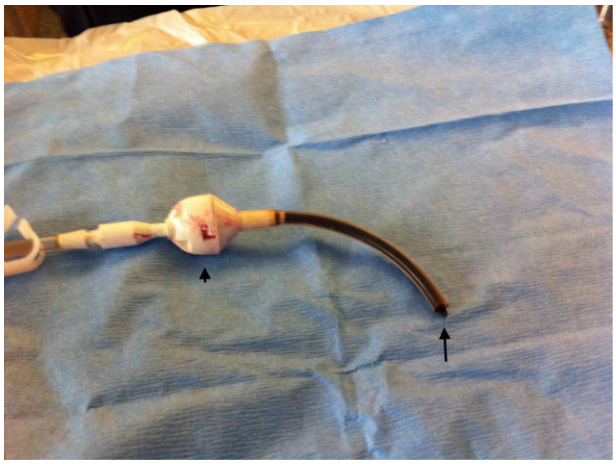

Figure 8 One-way valve (arrowhead) and distal end of an indwelling pleural catheter that was blocked by clotted blood (arrow). The clot could not be dislodged by saline flushing or by fibrinolytic therapy using tissue plasminogen activator. The distal end of the catheter was cut and replaced by a new valve following which normal catheter patency and pleural drainage were restored.

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[85] 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.[86] 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).[73] IPC-related pleural infection, the most concerning potential complication for clinicians, occurred only in <5% of over 1000 patients in a multicentre study[73,87] and were usually controlled with appropriate antibiotics.[87] The risk of mortality from pleural infection in an IPC patient was only 0.3%.[87] Interestingly, bacterial infection provides effective pleurodesis in about two-third 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%).[88] Catheter tract metastases (CTM) developed in ~10% of 110 patients in a region of high incidence of mesothelioma[89] (Fig. 10). Importantly, CTM can complicate both mesothelioma and metastatic carcinomas. The symptoms are generally mild and usually respond to radiotherapy.[89]

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.[90] PPS has its own set of complications including a high (~25%) occlusion rate that often requires shunt revision, removal and/or replacement.[91] 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.[92] 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 neovasculature is particularly 'leaky'.[93] Active research now targets the angiogenesis and vascular hyperpermeability.[94] Pilot studies targeting pleural fluid production, for example using zoledronic acid, are underway[95,96] and may offer novel approaches in the future. Intrapleural delivery of chemotherapy, immune-modulators and gene therapy[97–99] 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

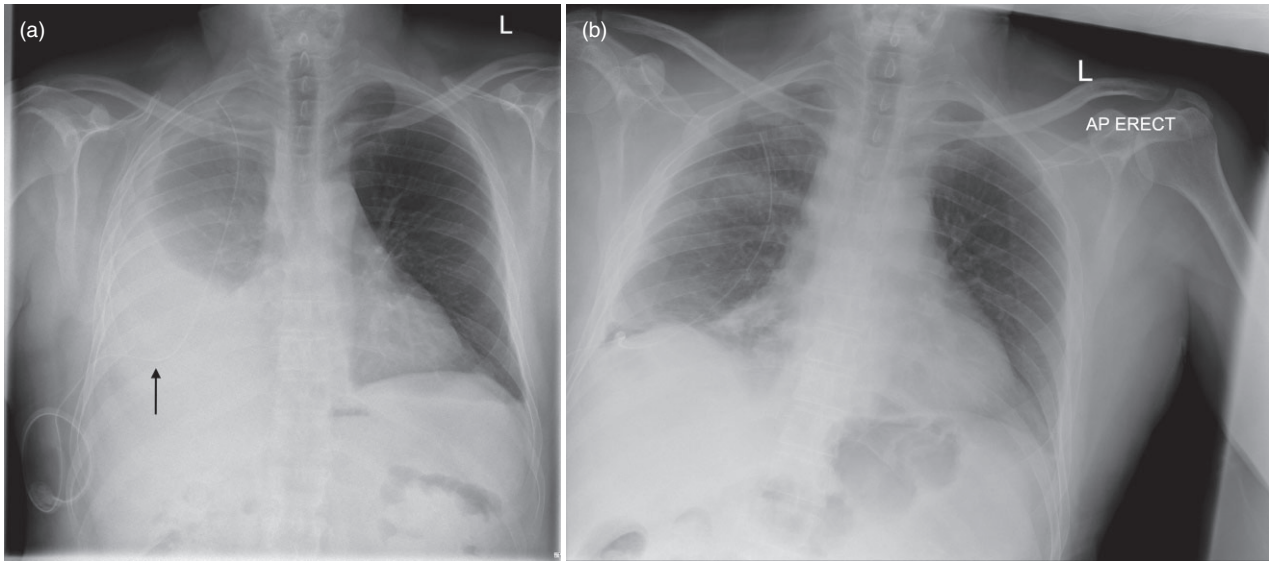

Figure 9 (a) Chest X-ray of a patient with indwelling pleural catheter *in situ* (arrow) for right-sided malignant pleural effusion who presented with symptomatic loculation (absent drainage, re-accumulation of effusion and recurrence of breathlessness). (b) Chest X-ray shows clearance of the pleural effusion after a single dose of tissue plasminogen activator.

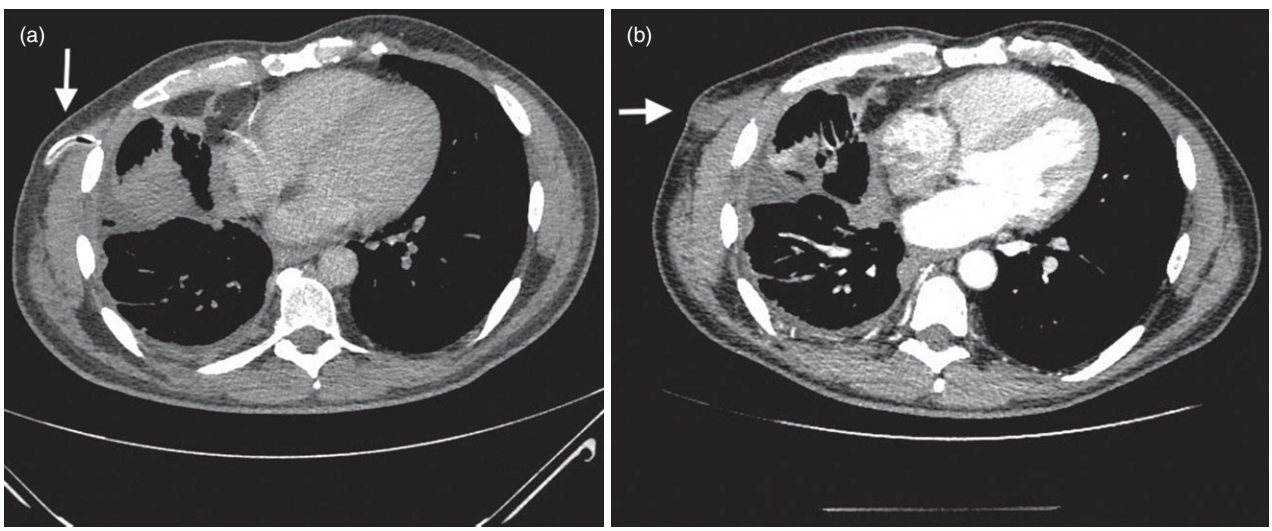

Figure 10 (a) Computed tomography (CT) thorax (axial view) showing right-sided indwelling pleural catheter *in situ* (arrow), which was later removed after spontaneous pleurodesis, in a patient with malignant mesothelioma. (b) CT thorax shows subcutaneous growth along the previous catheter tract (arrow), confirmed by fine needle aspiration cytology to be malignant tract metastasis.

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

1 Light RW. *Pleural Diseases*, 4th edn. Lippincott Williams & Wilkins, Philadelphia, 2001.
2 Ferlay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P. Estimates of the cancer incidence and mortality in Europe in 2006. *Ann. Oncol.* 2007; **18**: 581–92.

3 Lee YC, Light RW. Pleural effusion: overview. In: Laurent G, Shapiro S (eds) *Encyclopedia of Respiratory Diseases*, 4th edn. Elsevier, Oxford, UK, 2006; 353–8.
4 Marel M, Stastny B, Melinova L, Svandova E, Light RW. Diagnosis of pleural effusions. Experience with clinical studies, 1986 to 1990. *Chest* 1995; **107**: 1598–603.
5 Dresler CM, Olak J, Herndon JE 2nd, Richards WG, Scalzetti E, Fleishman SB, Kernstine KH, Demmy T, Jablons DM, Kohman L *et al*. Phase III intergroup study of talc poudrage vs talc slurry sclerosis for malignant pleural effusion. *Chest* 2005; **127**: 909–15.
6 Havelock T, Teoh R, Laws D, Gleeson F. Pleural procedures and thoracic ultrasound: British Thoracic Society Pleural Disease Guideline 2010. *Thorax* 2010; **65**(Suppl. 2): ii61–76.
7 National Patient Safety Agency. *Rapid Response Report: Risks of Chest Drain Insertion*. NPSA, London, 2008. [Accessed 3 June 2014.] Available from URL: http://www.12npsa.nhs.uk/nrls/alerts-and-directives/rapidrr/risks-of-chest-drain-insertion/.
8 Fysh ET, Waterer GW, Kendall PA, Bremmer PR, Dina S, Geelhoed E, McCarney K, Morey S, Millward M, Musk AW *et al*. Indwelling pleural catheters reduce inpatient days over pleurodesis for malignant pleural effusion. *Chest* 2012; **142**: 394–400.
9 Davies HE, Lee YC. Management of malignant pleural effusions: questions that need answers. *Curr. Opin. Pulm. Med.* 2013; **19**: 374–9.
10 Davies HE, Mishra EK, Kahan BC, Wrightson JM, Stanton AE, Guhan A, Davies CW, Grayez J, Harrison R, Prasad A *et al*. Effect of an indwelling pleural catheter vs chest tube and talc pleurodesis for relieving dyspnea in patients with malignant pleural effusion: the TIME2 randomized controlled trial. *JAMA* 2012; **307**: 2383–9.
11 Roberts ME, Neville E, Berrisford RG, Antunes G, Ali NJ. Management of a malignant pleural effusion: British Thoracic Society Pleural Disease Guideline 2010. *Thorax* 2010; **65**(Suppl. 2): ii32–40.
12 Bethune N. Pleural poudrage: a new technique for deliberate production of pleural adhesions as a preliminary to lobectomy. *J. Thorac. Surg.* 1935; **4**: 251–61.
13 Lee YC, Fysh ET. Indwelling pleural catheter: changing the paradigm of malignant effusion management. *J. Thorac. Oncol.* 2011; **6**: 655–7.
14 Heffner JE, Nietert PJ, Barbieri C. Pleural fluid pH as a predictor of pleurodesis failure: analysis of primary data. *Chest* 2000; **117**: 87–95.
15 Vogelzang NJ, Rusthoven JJ, Symanowski J, Denham C, Kaukel E, Ruffie P, Gatzemeier U, Boyer M, Emri S, Manegold C *et al*. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J. Clin. Oncol.* 2003; **21**: 2636–44.
16 Cartaxo AM, Vargas FS, Salge JM, Marcondes BF, Genofre EH, Antonangelo L, Marchi E, Teixeira LR. Improvements in the 6-min walk test and spirometry following thoracentesis for symptomatic pleural effusions. *Chest* 2011; **139**: 1424–9.
17 Estenne M, Yernault JC, De Troyer A. Mechanism of relief of dyspnea after thoracocentesis in patients with large pleural effusions. *Am. J. Med.* 1983; **74**: 813–19.
18 Wang JS, Tseng CH. Changes in pulmonary mechanics and gas exchange after thoracentesis on patients with inversion of a hemidiaphragm secondary to large pleural effusion. *Chest* 1995; **107**: 1610–14.
19 Krell WS, Rodarte JR. Effects of acute pleural effusion on respiratory system mechanics in dogs. *J. Appl. Physiol. (1985)* 1985; **59**: 1458–63.
20 Mulvey RB. The effect of pleural fluid on the diaphragm. *Radiology* 1965; **84**: 1080–6.
21 Fysh ET, Tan SK, Read CA, Lee F, McKenzie K, Olsen N, Weerasena I, Threlfall T, de Klerk N, Musk AW *et al*. Pleurodesis outcome in malignant pleural mesothelioma. *Thorax* 2013; **68**: 594–6.
22 Wu SG, Yu CJ, Tsai MF, Liao WY, Yang CH, Jan IS, Yang PC, Shih JY. Survival of lung adenocarcinoma patients with malignant pleural effusion. *Eur. Respir. J.* 2013; **41**: 1409–18.
23 Chen CH, Gow CH, Yu CJ, Shih JY, Hsu YC, Lee WY, Yang PC, Kuo SH. Clinical response of gefitinib on malignant pleural effusions in patients with non-small cell lung cancer. *J. Cancer Mol.* 2008; **4**: 23–8.
24 Guo H, Wan Y, Tian G, Liu Q, Kang Y, Li Y, Yao Z, Lin D. EGFR mutations predict a favorable outcome for malignant pleural effusion of lung adenocarcinoma with Tarceva therapy. *Oncol. Rep.* 2012; **27**: 880–90.
25 Masago K, Togashi Y, Fukudo M, Terada T, Irisa K, Sakamori Y, Kim YH, Mio T, Inui K, Mishima M. Plasma and pleural fluid pharmacokinetics of erlotinib and its active metabolite OSI-420 in patients with non-small-cell lung cancer with pleural effusion. *Clin. Lung Cancer* 2011; **12**: 307–12.
26 Jones PW, Moyers JP, Rogers JT, Rodriguez RM, Lee YC, Light RW. Ultrasound-guided thoracentesis: is it a safer method? *Chest* 2003; **123**: 418–23.
27 Feller-Kopman D, Berkowitz D, Boiselle P, Ernst A. Large-volume thoracentesis and the risk of reexpansion pulmonary edema. *Ann. Thorac. Surg.* 2007; **84**: 1656–61.
28 Genofre EH, Vargas FS, Antonangelo L, Teixeira LR, Vaz MA, Marchi E, Capelozzi VL. Ultrastructural acute features of active remodeling after chemical pleurodesis induced by silver nitrate or talc. *Lung* 2005; **183**: 197–207.
29 Marchi E, Vargas FS, Acencio MM, Antonangelo L, Genofre EH, Teixeira LR. Evidence that mesothelial cells regulate the acute inflammatory response in talc pleurodesis. *Eur. Respir. J.* 2006; **28**: 929–32.
30 Crnjac A, Sok M, Kamenik M. Impact of pleural effusion pH on the efficacy of thoracoscopic mechanical pleurodesis in patients with breast carcinoma. *Eur. J. Cardiothorac Surg.* 2004; **26**: 432–6.
31 Putnam JB Jr. *Lung, Chest Wall, Pleura, and Mediastinum*, 19th edn. Saunders Elsevier, Philadelphia, 2012.
32 Furrer M, Rechsteiner R, Eigenmann V, Signer C, Althaus U, Ris HB. Thoracotomy and thoracoscopy: postoperative pulmonary function, pain and chest wall complaints. *Eur. J. Cardiothorac Surg.* 1997; **12**: 82–7.
33 Dajczman E, Gordon A, Kreisman H, Wolkove N. Long-term postthoracotomy pain. *Chest* 1991; **99**: 270–4.
34 Waller DA, Morritt GN, Forty J. Video-assisted thoracoscopic pleurectomy in the management of malignant pleural effusion. *Chest* 1995; **107**: 1454–6.
35 Harris RJ, Kavuru MS, Mehta AC, Medendorp SV, Wiedemann HP, Kirby TJ, Rice TW. The impact of thoracoscopy on the management of pleural disease. *Chest* 1995; **107**: 845–52.
36 Tan C, Sedrakyan A, Browne J, Swift S, Treasure T. The evidence on the effectiveness of management for malignant pleural effusion: a systematic review. *Eur. J. Cardiothorac Surg.* 2006; **29**: 829–38.
37 Sorensen PG, Svendsen TL, Enk B. Treatment of malignant pleural effusion with drainage, with and without instillation of talc. *Eur. J. Respir. Dis.* 1984; **65**: 131–5.
38 Terra RM, Junqueira JJ, Teixeira LR, Vargas FS, Pego-Fernandes PM, Jatene FB. Is full postpleurodesis lung expansion a determinant of a successful outcome after talc pleurodesis? *Chest* 2009; **136**: 361–8.
39 Yim AP, Chan AT, Lee TW, Wan IY, Ho JK. Thoracoscopic talc insufflation versus talc slurry for symptomatic malignant pleural effusion. *Ann. Thorac. Surg.* 1996; **62**: 1655–8.
40 Fentiman IS, Rubens RD, Hayward JL. A comparison of intracavitary talc and tetracycline for the control of pleural effusions secondary to breast cancer. *Eur. J. Cancer Clin. Oncol.* 1986; **22**: 1079–81.
41 Kuzdzal J, Sladek K, Wasowski D, Soja J, Szlubowski A, Reifland A, Zielinski M, Szczeklik A. Talc powder vs doxycycline in the control of malignant pleural effusion: a prospective, randomized trial. *Med. Sci. Monit.* 2003; **9**: PI54–9.

42 Hamed H, Fentiman IS, Chaudary MA, Rubens RD. Comparison of intracavitary bleomycin and talc for control of pleural effusions secondary to carcinoma of the breast. *Br. J. Surg.* 1989; **76**: 1266–7.

43 Diacon AH, Wyser C, Bolliger CT, Tamm M, Pless M, Perruchoud AP, Soler M. Prospective randomized comparison of thoracoscopic talc poudrage under local anesthesia versus bleomycin instillation for pleurodesis in malignant pleural effusions. *Am. J. Respir. Crit. Care Med.* 2000; **162**: 1445–9.

44 Noppen M, Degreve J, Mignolet M, Vincken W. A prospective, randomised study comparing the efficacy of talc slurry and bleomycin in the treatment of malignant pleural effusions. *Acta Clin. Belg.* 1997; **52**: 258–62.

45 Zimmer PW, Hill M, Casey K, Harvey E, Low DE. Prospective randomized trial of talc slurry vs bleomycin in pleurodesis for symptomatic malignant pleural effusions. *Chest* 1997; **112**: 430–4.

46 Ong KC, Indumathi V, Raghuram J, Ong YY. A comparative study of pleurodesis using talc slurry and bleomycin in the management of malignant pleural effusions. *Respirology* 2000; **5**: 99–103.

47 Haddad FJ, Younes RN, Gross JL, Deheinzelin D. Pleurodesis in patients with malignant pleural effusions: talc slurry or bleomycin? Results of a prospective randomized trial. *World J. Surg.* 2004; **28**: 749–53, discussion 53–4.

48 Fentiman IS, Rubens RD, Hayward JL. Control of pleural effusions in patients with breast cancer. A randomized trial. *Cancer* 1983; **52**: 737–9.

49 Paschoalini Mda S, Vargas FS, Marchi E, Pereira JR, Jatene FB, Antonangelo L, Light RW. Prospective randomized trial of silver nitrate vs talc slurry in pleurodesis for symptomatic malignant pleural effusions. *Chest* 2005; **128**: 684–9.

50 Mohsen TA, Zeid AA, Meshref M, Tawfeek N, Redmond K, Ananiadou OG, Haj-Yahia S. Local iodine pleurodesis versus thoracoscopic talc insufflation in recurrent malignant pleural effusion: a prospective randomized control trial. *Eur. J. Cardiothorac Surg.* 2011; **40**: 282–6.

51 Demmy TL, Gu L, Burkhalter JE, Toloza EM, D'Amico TA, Sutherland S, Wang X, Archer L, Veit LJ, Kohman L. Optimal management of malignant pleural effusions (results of CALGB 30102). *J. Natl Compr. Canc. Netw.* 2012; **10**: 975–82.

52 Davies HE, Lee YCG. Pleurodesis. In: Light RW, Lee YCG (eds). *Textbook of Pleural Diseases*, 3rd edn. CRC Press, London, in press.

53 Lee YC, Baumann MH, Maskell NA, Waterer GW, Eaton TE, Davies RJ, Heffner JE, Light RW. Pleurodesis practice for malignant pleural effusions in five English-speaking countries: survey of pulmonologists. *Chest* 2003; **124**: 2229–38.

54 Kishi K, Homma S, Sakamoto S, Kawabata M, Tsuboi E, Nakata K, Yoshimura K. Efficacious pleurodesis with OK-432 and doxorubicin against malignant pleural effusions. *Eur. Respir. J.* 2004; **24**: 263–6.

55 Ukale V, Agrenius V, Hillerdal G, Mohlkert D, Widstrom O. Pleurodesis in recurrent pleural effusions: a randomized comparison of a classical and a currently popular drug. *Lung Cancer* 2004; **43**: 323–8.

56 Agarwal R, Paul AS, Aggarwal AN, Gupta D, Jindal SK. A randomized controlled trial of the efficacy of cosmetic talc compared with iodopovidone for chemical pleurodesis. *Respirology* 2011; **16**: 1064–9.

57 Ren S, Terman DS, Bohach G, Silvers A, Hansen C, Colt H, Sahn SA. Intrapleural staphylococcal superantigen induces resolution of malignant pleural effusions and a survival benefit in non-small cell lung cancer. *Chest* 2004; **126**: 1529–39.

58 Rahman NM, Davies HE, Salzberg M, Truog P, Midgely R, Kerr D, Clelland C, Hedley EL, Lee YC, Davies RJ. Use of lipoteichoic acid-T for pleurodesis in malignant pleural effusion: a phase I toxicity and dose-escalation study. *Lancet Oncol.* 2008; **9**: 946–52.

59 Shaw P, Agarwal R. Pleurodesis for malignant pleural effusions. *Cochrane Database Syst. Rev.* 2004; (1): CD002916.

60 Davies HE, Lee YC, Davies RJ. Pleurodesis for malignant pleural effusion: talc, toxicity and where next? *Thorax* 2008; **63**: 572–4.

61 Ferrer J, Villarino MA, Tura JM, Traveria A, Light RW. Talc preparations used for pleurodesis vary markedly from one preparation to another. *Chest* 2001; **119**: 1901–5.

62 Ferrer J, Montes JF, Villarino MA, Light RW, Garcia-Valero J. Influence of particle size on extrapleural talc dissemination after talc slurry pleurodesis. *Chest* 2002; **122**: 1018–27.

63 Werebe EC, Pazetti R, Milanez de Campos JR, Fernandez PP, Capelozzi VL, Jatene FB, Vargas FS. Systemic distribution of talc after intrapleural administration in rats. *Chest* 1999; **115**: 190–3.

64 Burrows CM, Mathews WC, Colt HG. Predicting survival in patients with recurrent symptomatic malignant pleural effusions: an assessment of the prognostic values of physiologic, morphologic, and quality of life measures of extent of disease. *Chest* 2000; **117**: 73–8.

65 Martinez-Moragon E, Aparicio J, Sanchis J, Menendez R, Cruz Rogado M, Sanchis F. Malignant pleural effusion: prognostic factors for survival and response to chemical pleurodesis in a series of 120 cases. *Respiration* 1998; **65**: 108–13.

66 Rodriguez-Panadero F, Antony VB. Pleurodesis: state of the art. *Eur. Respir. J.* 1997; **10**: 1648–54.

67 Villanueva AG, Gray AW Jr, Shahian DM, Williamson WA, Beamis JF, Jr. Efficacy of short term versus long term tube thoracostomy drainage before tetracycline pleurodesis in the treatment of malignant pleural effusions. *Thorax* 1994; **49**: 23–5.

68 Goodman A, Davies CW. Efficacy of short-term versus long-term chest tube drainage following talc slurry pleurodesis in patients with malignant pleural effusions: a randomised trial. *Lung Cancer* 2006; **54**: 51–5.

69 Teixeira LR, Wu W, Chang DS, Light RW. The effect of corticosteroids on pleurodesis induced by doxycycline in rabbits. *Chest* 2002; **121**: 216–19.

70 Dikensoy O, Light RW. Alternative widely available, inexpensive agents for pleurodesis. *Curr. Opin. Pulm. Med.* 2005; **11**: 340–4.

71 Simoff MJ, Lally B, Slade MG, Goldberg WG, Lee P, Michaud GC, Wahidi MM, Chawla M. Symptom management in patients with lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013; **143**: e455S–97S.

72 Antunes G, Neville E, Duffy J, Ali N. BTS guidelines for the management of malignant pleural effusions. *Thorax* 2003; **58**(Suppl. 2): ii29–38.

73 Van Meter ME, McKee KY, Kohlwes RJ. Efficacy and safety of tunneled pleural catheters in adults with malignant pleural effusions: a systematic review. *J. Gen. Intern. Med.* 2011; **26**: 70–6.

74 Efthymiou CA, Masudi T, Thorpe JA, Papagiannopoulos K. Malignant pleural effusion in the presence of trapped lung. Five-year experience of PleurX tunnelled catheters. *Interact Cardiovasc. Thorac. Surg.* 2009; **9**: 961–4.

75 Qureshi RA, Collinson SL, Powell RJ, Froeschle PO, Berrisford RG. Management of malignant pleural effusion associated with trapped lung syndrome. *Asian Cardiovasc. Thorac. Ann.* 2008; **16**: 120–3.

76 Pien GW, Gant MJ, Washam CL, Sterman DH. Use of an implantable pleural catheter for trapped lung syndrome in patients with malignant pleural effusion. *Chest* 2001; **119**: 1641–6.

77 Putnam JB Jr, Light RW, Rodriguez RM, Ponn R, Olak J, Pollak JS, Lee RB, Payne DK, Graeber G, Kovitz KL. A randomized comparison of indwelling pleural catheter and doxycycline pleurodesis in the management of malignant pleural effusions. *Cancer* 1999; **86**: 1992–9.

78 Tremblay A, Michaud G. Single-center experience with 250 tunnelled pleural catheter insertions for malignant pleural effusion. *Chest* 2006; **129**: 362–8.

79 Freeman RK, Ascioti AJ, Mahidhara RS. A propensity-matched comparison of pleurodesis or tunneled pleural catheter in patients undergoing diagnostic thoracoscopy for malignancy. *Ann. Thorac. Surg.* 2013; **96**: 259–63, discussion 63–4.

80 Hunt BM, Farivar AS, Vallieres E, Louie BE, Aye RW, Flores EE, Gorden JA. Thoracoscopic talc versus tunneled pleural catheters for palliation of malignant pleural effusions. *Ann. Thorac. Surg.* 2012; **94**: 1053–7, discussion 57–9.
81 Srour N, Amjadi K, Forster A, Aaron S. Management of malignant pleural effusions with indwelling pleural catheters or talc pleurodesis. *Can. Respir. J.* 2013; **20**: 106–10.
82 Sioris T, Sihvo E, Salo J, Rasanen J, Knuuttila A. Long-term indwelling pleural catheter (PleurX) for malignant pleural effusion unsuitable for talc pleurodesis. *Eur. J. Surg. Oncol.* 2009; **35**: 546–51.
83 Ohm C, Park D, Vogen M, Bendick P, Welsh R, Pursel S, Chmielewski G. Use of an indwelling pleural catheter compared with thorascopic talc pleurodesis in the management of malignant pleural effusions. *Am. Surg.* 2003; **69**: 198–202, discussion 02.
84 Tremblay A, Mason C, Michaud G. Use of tunnelled catheters for malignant pleural effusions in patients fit for pleurodesis. *Eur. Respir. J.* 2007; **30**: 759–62.
85 Reddy C, Ernst A, Lamb C, Feller-Kopman D. Rapid pleurodesis for malignant pleural effusions: a pilot study. *Chest* 2011; **139**: 1419–23.
86 Tremblay A, Dumitriu S, Stather DR, Maceachern P, Illanes O, Kelly MM. Use of a drug eluting pleural catheter for pleurodesis. *Exp. Lung Res.* 2012; **38**: 475–82.
87 Fysh ET, Tremblay A, Feller-Kopman D, Mishra EK, Slade M, Garske L, Clive AO, Lamb C, Boshuizen R, Ng BJ *et al*. Clinical outcomes of indwelling pleural catheter pleural infections: an international multicenter study. *Chest* 2013; **144**: 1597–602.
88 Mekhaiel E, Kashyap R, Mullon JJ, Maldonado F. Infections associated with tunnelled indwelling pleural catheters in patients undergoing chemotherapy. *J. Bronchology Interv. Pulmonol.* 2013; **20**: 299–303.
89 Thomas R, Budgeon CA, Kuok YJ, Read C, Fysh ET, Bydder S, Lee YC. Catheter tract metastasis associated with indwelling pleural catheters. *Chest* 2014. doi: 10.1378/chest.13-3057.
90 Little AG, Kadowaki MH, Ferguson MK, Staszek VM, Skinner DB. Pleuro-peritoneal shunting. Alternative therapy for pleural effusions. *Ann. Surg.* 1988; **208**: 443–50.
91 Genc O, Petrou M, Ladas G, Goldstraw P. The long-term morbidity of pleuroperitoneal shunts in the management of recurrent malignant effusions. *Eur. J. Cardiothorac Surg.* 2000; **18**: 143–6.
92 Lan RS, Lo SK, Chuang ML, Yang CT, Tsao TC, Lee CH. Elastance of the pleural space: a predictor for the outcome of pleurodesis in patients with malignant pleural effusion. *Ann. Intern. Med.* 1997; **126**: 768–74.
93 Lee YC, Wilkosz S. Malignant pleural effusions: fixing the leaky faucet. *Am. J. Respir. Crit. Care Med.* 2008; **178**: 3–5.
94 Stathopoulos GT, Kalomenidis I. Malignant pleural effusion: tumor-host interactions unleashed. *Am. J. Respir. Crit. Care Med.* 2012; **186**: 487–92.
95 Stathopoulos GT, Moschos C, Loutrari H, Kollintza A, Psallidas I, Karabela S, Magkouta S, Zhou Z, Papiris SA, Roussos C *et al*. Zoledronic acid is effective against experimental malignant pleural effusion. *Am. J. Respir. Crit. Care Med.* 2008; **178**: 50–9.
96 Veltman JD, Lambers ME, van Nimwegen M, Hendriks RW, Hoogsteden HC, Hegmans JP, Aerts JG. Zoledronic acid impairs myeloid differentiation to tumour-associated macrophages in mesothelioma. *Br. J. Cancer* 2010; **103**: 629–41.
97 Sterman DH, Haas A, Moon E, Recio A, Schwed D, Vachani A, Katz SI, Gillespie CT, Cheng G, Sun J *et al*. A trial of intrapleural adenoviral-mediated Interferon-alpha2b gene transfer for malignant pleural mesothelioma. *Am. J. Respir. Crit. Care Med.* 2011; **184**: 1395–9.
98 Sterman DH, Recio A, Carroll RG, Gillespie CT, Haas A, Vachani A, Kapoor V, Sun J, Hodinka R, Brown JL *et al*. A phase I clinical trial of single-dose intrapleural IFN-beta gene transfer for malignant pleural mesothelioma and metastatic pleural effusions: high rate of antitumor immune responses. *Clin. Cancer Res.* 2007; **13**: 4456–66.
99 Sterman DH, Recio A, Haas AR, Vachani A, Katz SI, Gillespie CT, Cheng G, Sun J, Moon E, Pereira L *et al*. A phase I trial of repeated intrapleural adenoviral-mediated interferon-beta gene transfer for mesothelioma and metastatic pleural effusions. *Mol. Ther.* 2010; **18**: 852–60.

