Management of Malignant Pleural Effusion with Indwelling Pleural Catheters

Dr Edward Fysh
MB BS BSc

This thesis is presented for the degree of Doctor of Philosophy of the University of Western Australia, School of Medicine.

June 2016
DECLARATION FOR THESES CONTAINING PUBLISHED WORK AND/OR WORK PREPARED FOR PUBLICATION

The examination of the thesis is an examination of the work of the student. The work must have been substantially conducted by the student during enrolment in the degree.

Where the thesis includes work to which others have contributed, the thesis must include a statement that makes the student’s contribution clear to the examiners. This may be in the form of a description of the precise contribution of the student to the work presented for examination and/or a statement of the percentage of the work that was done by the student.

In addition, in the case of co-authored publications included in the thesis, each author must give their signed permission for the work to be included. If signatures from all the authors cannot be obtained, the statement detailing the student’s contribution to the work must be signed by the coordinating supervisor.

Please sign one of the statements below.

<table>
<thead>
<tr>
<th>Statement</th>
<th>Signature</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. This thesis <strong>does not contain</strong> work that I have published, nor work under review for publication.</td>
<td></td>
</tr>
<tr>
<td>2. This thesis contains <strong>only sole-authored</strong> work, some of which has been published and/or prepared for publication under sole authorship. The bibliographical details of the work and where it appears in the thesis are outlined below.</td>
<td></td>
</tr>
<tr>
<td>3. This thesis contains published work and/or work prepared for publication, <strong>some of which has been co-authored</strong>. The bibliographical details of the work and where it appears in the thesis are outlined below. The student must attach to this declaration a statement for each publication that clarifies the contribution of the student to the work. This may be in the form of a description of the precise contributions of the student to the published work and/or a statement of percent contribution by the student. This statement must be signed by all authors. If signatures from all the authors cannot be obtained, the statement detailing the student’s contribution to the published work must be signed by the coordinating supervisor.</td>
<td></td>
</tr>
</tbody>
</table>

Student Signature ____________________________________________________________

Coordinating Supervisor Signature ____________________________________________
**Statement of Contribution by Candidate:**

All published work is referenced in the List of Publications as well as in the text. All coauthors of publications in this thesis are aware that these papers constituted part of Dr Fysh’s PhD thesis from the outset of the respective studies and have consented to their use as such. Dr Fysh contributed the majority of the work in each of the following components of all studies included in this thesis: conception, design, data collection, data storage and analysis, patient care, manuscript preparation and revision and final approval of the manuscripts.

Dr Edward Fysh (PhD Candidate)

Prof YC Gary Lee (PhD Supervisor)
## Contents:

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>List of Publications</td>
<td>v</td>
</tr>
<tr>
<td>List of Abbreviations</td>
<td>viii</td>
</tr>
<tr>
<td>Thesis Abstract:</td>
<td>ix</td>
</tr>
<tr>
<td>Acknowledgements:</td>
<td>xi</td>
</tr>
<tr>
<td>Introduction and Literature Review:</td>
<td>1</td>
</tr>
<tr>
<td>Part I: Pleurodesis or Indwelling Pleural Catheter?</td>
<td>24</td>
</tr>
<tr>
<td>Section I-1: Patient choice study of pleurodesis and IPC</td>
<td>26</td>
</tr>
<tr>
<td>Section I-2: Randomised comparison of pleurodesis and IPC</td>
<td>27</td>
</tr>
<tr>
<td>Section I-3: Pleurodesis success rates in mesothelioma</td>
<td>28</td>
</tr>
<tr>
<td>Part II: Complications of indwelling pleural catheters.</td>
<td>29</td>
</tr>
<tr>
<td>Section II-1: IPC related infection</td>
<td>31</td>
</tr>
<tr>
<td>Section II-2: Catheter tract metastasis</td>
<td>32</td>
</tr>
<tr>
<td>Section II-3: IPC fracture</td>
<td>33</td>
</tr>
<tr>
<td>Part III: Predicting Need for Definitive Therapy</td>
<td>34</td>
</tr>
<tr>
<td>Thesis Conclusion:</td>
<td>36</td>
</tr>
</tbody>
</table>
List of Publications:

*Publications incorporated in full in the body of this thesis:


8) A Prospective, Multinational Study of Predictors of Pleurodesis or Indwelling Pleural Catheter Therapy for Malignant Pleural Effusion. Fysh ETH, Bielsa S, Budgeon CA, et al. Chest. 2015;147(6):1629-34. (Used in full - Part III. Dr Fysh’s contribution >60%)

9) Comments on Predictors of Clinical Use of Pleurodesis and/or Indwelling Pleural Catheter Therapy for Malignant Pleural Effusion- Response. Chest. 2015;147(6):e233. (Used in full – Part III. Dr Fysh’s contribution >50%)

Other publications arising from and referenced in this thesis:


List of Abbreviations:

- MPE (Malignant Pleural Effusion)
- IPC (Indwelling Pleural Catheter)
- WA (Western Australia)
- TP (Talc Pleurodesis)
- QoL (Quality of Life)
- IQR (Interquartile Range)
- SD (Standard Deviation)
- MID (Minimum Important Difference)
- AMPLE (Australasian Malignant Pleural Effusion Trial)
- DNase (Deoxyribonuclease)
- tPA (Tissue Plasminogen Activator)
- CTM (Catheter Tract Metastasis)
- NTM (Needle Track Metastasis)
Thesis Abstract

Introduction: Malignant pleural effusion (MPE) is common and causes debilitating dyspnea and impairment of quality of life. Median survival is usually poor, ranging from 3 to 12 months depending on the underlying malignancy. Treatments aim to palliate symptoms, improve quality of life, and minimise hospital stay. Disease and symptom progression is highly variable and predictors of the need for definitive treatments are lacking.

Treatments: Pleurodesis aims to seal the pleural space, preventing reaccumulation of fluid. However, it requires admission to hospital, is associated with pain and other complications and has a significant failure rate. Tunneled, indwelling pleural catheters (IPC) represent a relatively novel therapy. IPC can usually be inserted without overnight hospital stay. IPC enable ambulatory drainage of the MPE and can remain in the pleural space for as long as needed. The introduction of IPC has opened up new possibilities, but new data is required to define their role in the management of MPE. Reevaluation of treatment indications, MPE management strategies and treatment benefits or complications is necessary.

Thesis Aims: First to develop a better understanding of the role of IPC as first line treatment for patients with MPE in comparison with TP; second to evaluate several of the potential complications of IPC use; and third to discern which patients may benefit most from this promising new therapy.

Conclusions: Part I - IPC-treated patients required significantly fewer days in hospital and fewer additional pleural drainage procedures than those who received pleurodesis. Safety profiles and symptom control were comparable. The protocol of our multinational
randomized trial is presented. This trial is underway and will further elucidate the relative merits of these two therapies. Pleurodesis (either surgical or bedside) has suboptimal efficacy in mesothelioma as well as metastatic MPE. This adds weight to the urgency to find novel treatment strategies.

**Part II**- The incidence of IPC-related pleural infection was low and the overall mortality risk from pleural infection in IPC-treated patients was only 0.28%. Catheter tract metastasis can occur in mesothelioma and also adenocarcinoma, but it is not always symptomatic and the symptoms are rarely difficult to treat. While infrequent, IPC fracture can occur and invasive removal of the retained fragment is unnecessary.

**Part III**- MPE patients with an effusion of low pleural fluid pH and large size on radiographs are more likely to be treated with pleurodesis and/or IPC. Further work is required to design and validate an algorithm to guide treatment decisions.

Overall, IPC-treated patients required fewer days in hospital and drainage procedures. Complications were uncommon and mortality low. MPE patients with acidic pleural fluid and large volumes are more likely to benefit from treatment.
Acknowledgements

My supervisor and mentor Gary Lee – you have introduced me to all sorts of possibilities and provided the motivation and guidance to make what seemed impossible attainable. Thank you for your long-suffering encouragement, support and precious time.

None of this work would have been possible without the extraordinary generosity of our patients and their family members, often at the most confronting and challenging times of their lives. I only hope that if I am faced with such awful diagnoses as malignant pleural effusion that I have the courage and magnanimity to show the same enthusiasm for someone else’s research in the trust that it will benefit others.

My many colleagues including clinical staff and co-authors have been a constant source of help and support – thank you all of you.

Many charitable or philanthropic organisations have provided the necessary funding to undertake my research. The State Health Research Advisory Committee, the National Health and Medical Research Committee, the Lung Institute of WA, the Cancer Council, and the New South Wales Dust Diseases Board have all provided generous funding without which I could not have dedicated the time and resources necessary to undertake this work.

Last but not least my family. My wife Fiona has been essential to my sanity and my ability to drop everything at home to undertake my research work, often on top of us both working incredibly busy clinical jobs. My three children have also involuntarily given up time with their Dad and I hope they will understand one day and see that it may have been worthwhile.
Introduction and Literature Review

Malignant pleural disease- relevance and global impact:

A malignant pleural effusion (MPE) is a cancer-induced collection of fluid in the pleural space. It is common and is the presenting feature of malignancy for approximately twenty percent of patients\(^{(1)}\). At post mortem, fifteen percent of patients who die of cancer have an MPE. After parapneumonic effusion, it is the second leading cause of exudative pleural effusion worldwide.

Epidemiological studies in Europe and the United States report the annual incidence of MPE to be approximately 660 cases per million of population\(^{(2)}\). Extrapolating this rate to Australia it is estimated that 15,000 patients develop malignant pleural effusions per year Australia-wide. The incidence of MPE is increasing, mostly because of a rise in the number of patients developing lung and breast cancer and also therapeutic advances that prolong survival in later stages of the disease.

Western Australia (WA) is no exception. Local Health Department coding data showed that in the five years leading up to this PhD project the inpatient care cost for the management of MPE in public WA Hospitals more than doubled from $5.4 to $11.7 million per year (Figure 1). The associated number of hospital admissions rose from 1522 to 2293 per year, an increase of 50.7%.
Figure 1. Graph depicting the rise in costs (AUD) attributed to the inpatient management of patients with MPE in Western Australia. (Source: WA Health Department coding data compiled and collated by Dr Fysh).

Pleural malignancy can be primary (arising *de novo* from the pleura in the case of mesothelioma) or, more commonly, secondary, caused by metastasis to the pleura or by direct invasion from adjacent structures. The aetiology of the MPE is confirmed by the detection of malignant cells on cytological examination of aspirated pleural fluid, or direct biopsy of the pleura. However, many of these patients are frail and recurrent painful procedures to obtain histocytological confirmation may be inappropriate and may delay effective therapy\(^{(3)}\). In this group the combination of known local or disseminated cancer and an exudative effusion may be sufficient for diagnostic purposes\(^{(4)}\).

The underlying pathology of MPE varies in prevalence from country to country. However, metastatic lung cancer is consistently the most frequent cause of MPE worldwide, responsible for over one third of all cases. Every year in Europe, as many
as 100,000 patients with lung cancer develop a pleural effusion. Breast cancer accounts for approximately 17% of cases, followed by lymphoma (12%), cancers of an unknown primary source (11%), genitourinary cancers (9%) and gastrointestinal cancers (7%)\(^{5}\).

Mesothelioma warrants special consideration, as 95% of patients (a far higher proportion) will develop a MPE and the associated median survival is longer than in the majority of secondary MPE at around 12 months, meaning the burden of MPE related to mesothelioma is potentially higher\(^{6}\). Moreover, mesothelioma rates in WA are the highest per capita in the world and are not expected to decline before 2017\(^{7,8}\). Over the last 10 years in WA the incidence of mesothelioma in males has been more than double that of the United States, at a rate of 4 to 5 per 100,000 population, per year as opposed to roughly 2/100,000 in the US\(^{9,10}\). Mesothelioma is also relevant globally because a “tsunami” of mesothelioma (and therefore MPE) is predicted in coming years from the heavily populated Asian nations because of their ongoing use of asbestos\(^{11}\).

MPE is a poor-prognostic indicator and usually heralds the incurable progression of the underlying malignancy\(^{1,12,13}\). Median survival ranges between three and twelve months depending on the type of cancer\(^{14}\). Focus on prompt palliation of symptoms and maintenance of independence from hospital is essential\(^{15,16}\).

The symptoms of MPE are frequently debilitating and may be the reason for initial cancer investigations\(^{5,17}\). Typically, symptoms start with breathlessness on exertion, which progresses as the effusion grows. Cough, pain and nausea are also frequently
encountered\textsuperscript{(18)}. Many patients have numerous comorbidities, and it can be difficult to determine which symptoms are attributable to the effusion and which are not. Indeed it is commonly the case that each symptom has multiple aetiologies at any one time, and patients are often not able to give clear descriptions and histories. Understanding the patients’ symptoms, however, is crucial when choosing between the various treatment options\textsuperscript{(19,20)}.

In summary, malignant pleural effusion, regardless of its aetiology, is a devastating disease that is growing in incidence around the globe. Effective advances in rapid symptom control are urgently needed. A thorough understanding of the pathophysiology of MPE development is needed to allow the necessary innovation in clinical care and a brief introduction to the physiology of the pleural space and the pathogenesis of MPE follows below.

\textit{Anatomy and Function of the Pleura:}

The pleural cavity is a sealed but expandable space between the visceral and parietal pleura, which are fibroelastic layers of tissue around 40\(\mu\)m thick in the healthy state. The visceral pleura coats the entire surface of the lung, while the parietal pleura lines the entire thoracic cage including the chest wall, mediastinum and the diaphragm. In humans the left and right pleural cavities are entirely separate from one another. Each pleural cavity is thought to contain around 1 to 15ml of fluid in healthy adult males\textsuperscript{(21,22)}, separating the pleural layers by at least 10 \(\mu\)m and allowing them to move freely across each other during respiration\textsuperscript{(4)}. The pleural surfaces are lined with mesothelial cells, which form microvilli that protrude into the pleural space. These are thought to
play a role in transcellular transport and in forming a lubricating layer of
glycoproteins that further encourage free movement of the pleural layers.

In health there is a balance between the production of fluid and drainage into the
lymphatic system. The vascular endothelial cell layers of the lungs and chest wall and
the mesothelial cells of the pleura control the movement of fluid between the systemic
circulation, the pulmonary interstitium and the pleural space. Around fifteen ml per
day of fluid enters the pleural space, predominantly filtering out from the parietal
capillaries. Fluid in the pleural space drains into the lymphatic system via stomata in
the parietal pleura, and valves in the major lymphatic channels regulate flow towards
regional lymph nodes. The rhythmic pumping motion of the chest wall, the diaphragm
and the lungs aids this flow during the respiratory cycle. Pleural pressure increases
during expiration, forcing fluid through the stomata and into the lymphatics. Pleural
pressure then falls during inspiration, but valves in the lymphatics close preventing
retrograde flow back into the pleural space.

The reabsorption capacity of the parietal lymphatic system is estimated to be 0.1-
0.2ml/kg/hr, although this is an extrapolation to humans from animal studies. The
reabsorption rate normally increases as pleural fluid levels, and hence pleural
pressures, increase. As a consequence, large disruptions of normal pleural fluid
homeostasis are required to produce a clinically significant effusion\(^{(23)}\).

In the diseased state the balance between pleural fluid production and drainage is
impaired. Inflammation results in increased permeability of the vascular endothelial
layers so leakage of fluid into surrounding tissues increases. The mesothelial cell
layers also become more permeable and hence regulation of fluid movement into the
pleural space becomes ineffective. This causes a significant increase in the production of pleural fluid. At the same time, the underlying pleural disease may cause obstruction of the stomata and the cellular content and viscosity of the fluid may also increase and hence the lymphatic flow decreases. This disruption of the balance between fluid production and drainage leads to the uncontrolled and sometimes rapid accumulation of a pleural effusion.

**Pathogenesis of Malignant Pleural Effusion:**

A post-mortem series of 191 individuals with one or more known malignancy found that 29% had pleural metastases\(^{(24)}\). Of these, 30 had pleural effusions at autopsy, i.e. 15% of the total number of malignancies, and 54.5% of those with pleural involvement. The distribution of pleural disease in these patients, i.e. predominantly affecting the visceral pleura in cases with a distant primary, indicated that pleural malignancies most commonly arise from embolisation of metastatic tumour to the visceral pleura, with subsequent seeding to the parietal pleura. The second most common route is direct invasion from adjacent structures, for example lung cancer from the lung parenchyma, breast cancer from the chest wall or ovarian cancer from diaphragmatic metastases. Primary *de novo* pleural malignancy such as mesothelioma represents a third, least common pathogenetic mechanism.

The precise mechanisms for production of the fluid are not yet fully understood and because of this, the differentiation between those effusions that will progress rapidly and those that will not is often very difficult. The majority of MPE are exudative as defined by Light’s criteria, although it is recognised that up to 8% can be transudates \(^{(25-27)}\). This would suggest an active manufacturing process either by cancer cells in
the pleural space, or stimulated by their effects on the pleura itself\(^{(28)}\). As mentioned previously, disequilibrium of pleural fluid formation and reabsorption often co-exist for an effusion to accumulate. Autopsy studies have shown that the presence of a pleural effusion correlates with lymphatic and mediastinal nodal infiltration rather than the extent of pleural metastases, suggesting impaired lymphatic drainage or reabsorption may be a second contributing factor\(^{(29,30)}\).

Increases in vascular and mesothelial membrane permeability, mediated by angiogenic cytokines secreted by tumour cells, appear to play a major role in this process. Mesothelial cells express the receptor for vascular endothelial growth factor (VEGF)\(^{(31)}\) and a number of studies have demonstrated significantly elevated levels of VEGF in malignant effusions\(^{(31-33)}\). VEGF also stimulates angiogenesis resulting in neovascularisation of the pleural surface and creation of an independent tumour vessel network. Haemorrhagic malignant effusions contain significantly higher levels of VEGF than non-haemorrhagic effusions\(^{(34)}\). One recent study found that increased levels of VEGF correlated with poorer survival in patients with MPE caused by non-small cell lung cancer, suggesting that VEGF may indeed play a key role in tumour progression\(^{(35)}\).

It should be noted, finally, that not all pleural effusions in patients with underlying malignancy are a direct consequence of neoplastic infiltration. Para-malignant effusions occur in the absence of malignant cells in the pleura\(^{(30)}\). These may arise as a result of local or systemic effect of the tumour (e.g. hypoproteinaemia, pulmonary embolism, pericardial involvement, endobronchial obstruction) or a complication of therapy (e.g. radiation-related pleuritis or chemotherapy agents). Chylothorax
develops when there is disruption of the thoracic duct and leakage of chyle-rich, lymphocytic fluid into the pleural space. This is most commonly found in patients with lymphoma.

**Survival and Symptom Recurrence:**

The next essential factor needed to allow innovation in the treatment of MPE is understanding of the prognosis and symptom progression of the patients.

Prognosis and prediction of symptom progression is of critical importance in consultations between patients with MPE and their physicians. It underpins most decisions that need to be made both in the patient’s life and in choices regarding treatment options. Early planning for the end of life is essential in ensuring effective palliation of symptoms and it reduces the anxiety and fear of both patients and their loved ones. Indeed in a significant recent study effective palliative care actually prolonged survival in patients with lung cancer\(^{36}\). The current lack of accurate prognostic indicators in patients with MPE means that clinicians remain unable to accurately counsel their patients and treatment choices may be made without supportive evidence.

MPE in itself is a bad prognostic indicator, usually precluding curative therapies. Few accurate prognostic markers exist, with median survivals varying greatly from 3 to 12 months depending on the stage and type of underlying malignancy\(^{12, 37, 38}\). In lung cancer with MPE patients’ mean length of survival is estimated at 3 months, while the prognosis for patients with breast carcinoma varies widely from 5-36 months, depending on susceptibility to more effective chemotherapy agents. Mesothelioma
patients tend to have a longer than average prognosis with a median survival of 9 to 12 months. Survival also differs significantly between patients with a good and those with a poor performance status. Burrows et al showed that in those with a Karnofsky score \( \leq 30 \) the median survival was 34 days compared to 395 days in patients with a score \( \geq 70 \)\(^{13}\).

The LENT score, standing for pleural \( \text{LDH, ECOG, Neutrophil to lymphocyte ratio in blood and Tumour type} \) was derived in part from this thesis data and validated in a second cohort from Bristol, UK. It combines the previously known predictors of survival (tumour type and performance status) with pleural fluid markers of disease activity and derives low, moderate and high risk categories that add much needed objective prognostic accuracy to clinical acumen\(^{39}\). However, predicted survival alone cannot define which patients will need aggressive MPE control and which treatment option is superior.

The clinical course and symptomatology of MPE patients varies greatly and this has an enormous impact on the quality of their remaining life. Some patients suffer from rapid recurrence of their fluid and symptoms. Many of these patients have to reattend hospital every few weeks. They endure multiple drainage procedures, which are uncomfortable and incur significant risk of complications. Other patients have no reaccumulation of fluid or recurrence of symptoms until death\(^{30}\). No quality data exist to predict this variable clinical course in individual patients. Evidently, this means there can be no “one size fits all” optimum strategy to control all MPE and the ability of clinicians and patients to choose the best treatment strategy is inadequate.
Current Treatment Options:

Repeated Thoracentesis: Some patients undergo repeated simple thoracentesis, which does not prevent recurrence of the fluid, and therefore usually incurs multiple procedures. As a result it greatly increases the rate of complications and the number of times the patient has to present to medical services\(^\text{(40)}\). It is therefore only advisable in patients who are in the final stages of their disease or whose fluid is accumulating very slowly, for example because of effective chemotherapy\(^\text{(30)}\). The majority of patients nowadays are offered treatments that attempt to better control the MPE, such as pleurodesis or indwelling pleural catheter\(^\text{(41)}\).

Pleurodesis: Pleurodesis is the iatrogenic obliteration of the pleural space to prevent recurrent accumulation of pleural fluid or air. It is usually performed chemically following intrapleural injection of a sclerosing agent, but mechanical pleurodesis may be achieved by pleural abrasion or parietal pleurectomy.

In the majority of centres chemical pleurodesis is still regarded as the first-line treatment for patients with a symptomatic MPE responsive to thoracentesis\(^\text{(42)}\). However, pleurodesis should be avoided in patients with a poor performance status (≥3), life expectancy of less than 6 weeks and failure of pleural apposition (i.e. ‘trapped’ lung)\(^\text{(3, 17)}\). No reliable clinical or biochemical predictors exist to guide patient selection although a low pleural fluid pH (<7.2) suggests pleurodesis is less likely to be successful\(^\text{(38, 43)}\).

The exact mechanism through which pleurodesis is induced is not yet fully understood. It is hypothesised that pleural injury, invoked by the sclerosant, initiates
a cascade of pleural inflammation and mesothelial cell denudement. This inflammatory response may progress with resultant fibrosis and pleural adhesion, or recede (in the instance of failed pleurodesis).

No universal consensus defines pleurodesis success. Many studies have focused on radiological fluid re-accumulation but have neglected to assess the effect on patients’ symptoms and quality of life. Success rates of different pleurodesis agents vary significantly\(^5\). Talc is the most commonly used pleurodesis agent worldwide, and a recent Cochrane meta-analysis supported its use as the sclerosant of choice (although large randomised trial comparisons with alternative newer agents have not yet been made)\(^{44}\). Talc may be instilled into the pleural space through a chest tube as ‘slurry’ (admixed with normal saline) or at the time of pleuroscopy as a powder (poudrage); there is no difference in 30 day freedom from radiological effusion recurrence between these techniques and the benefits of poudrage over slurry remain controversial\(^{45-47}\).

Side effects common to all sclerosing agents include chest pain and fever, however one major concern surrounding the use of talc is its association with development of the acute respiratory distress syndrome (ARDS)\(^{48}\). The aetiology is unknown, however it is hypothesised that the acute pneumonitis and resultant respiratory failure may be triggered by systemic uptake of talc particles through parietal pleural pores (systemic talc dissemination has been confirmed in animal studies)\(^{49, 50}\). The acute lung injury may also be initiated by potential contaminants i.e. endotoxin, bacteria, mineral dusts, which have persisted despite preparatory sterilization processes. The incidence of ARDS ranges between 0-9% and has been reported more commonly in
the USA where smaller particle talc is used (mean size 15µm), supporting the former hypothesis\(^{(48)}\). Larger, graded talc preparations (particles \(<10\mu m\) removed) are recommended\(^{(51)}\).

Tetracycline derivatives and antineoplastic agents (e.g. bleomycin) are alternative sclerosants, which should be considered in patients with pre-existing hypoxia when use of talc may be hazardous. Other agents used include OK-432 in Japan, and quinacrine which was used in Scandinavia\(^{(52)}\). In developing countries iodopovidone is an affordable, relatively effective option. Small studies report success rates between 86.5\% and 96\%\(^{(53, 54)}\). Pleuritic chest pain and hypotension have been described following its use and visual loss was reported in three patients following the thoracoscopic instillation of 200-500ml of 10\% iodopovidone; this complication has not been observed with use of the standard clinical dose (20ml of 10\% solution)\(^{(55)}\). Novel agents such as transforming growth factor-beta (TGF-beta) have shown promise in animal studies\(^{(56)}\).

Each bedside pleurodesis procedure requires an average of 6 bed days and carries significant costs\(^{(42, 57-59)}\). There have been trials of rapid pleurodesis where the agent is infiltrated as soon as the fluid is drained and the patient sent home within 48-72hrs but 20\% needed second procedures, and the fittest patients were selected, so they do not necessarily reflect standard practice overall\(^{(60, 61)}\).

Whilst in most Western centres talc pleurodesis is regarded as the gold standard\(^{(62)}\), it remains a crude treatment that aims to cause significant pleural injury, thereby inducing inflammation and pleural fibrosis. It is not surprising, therefore, that it is
often very painful, necessitating the use of significant doses of potent analgesic agents. It also has a failure rate of about 20% - 30%, and that is only in carefully selected patients, whose lungs fully reinflate after drainage\textsuperscript{(45, 46, 57, 63, 64)}. Nevertheless, when successful, one pleurodesis procedure can potentially provide freedom from any further fluid recurrence.

Over three quarters of a century after the description of talc poudrage\textsuperscript{(65)}, we are still searching for a viable alternative method of permanent fluid control, which avoids the instillation of potent pro-inflammatory sclerosants and the significant adverse events.

\textbf{Surgical Techniques:}

A relatively fit minority of patients may undergo surgery either via open thoracotomy or less invasive video-assisted thoracoscopic surgery (VATS). This usually includes decortication, which may have a higher success rate in inducing pleurodesis, but incurs more procedure-related morbidity. Up to 15% of patients (even after VATS) suffer major complications including bleeding, prolonged air leak, empyema, and severe pain\textsuperscript{(43, 66, 67)}.

Implantable pleuroperitoneal shunts are another surgical alternative, though these are rarely used and usually only in those who have failed other treatments or have significant trapped lung\textsuperscript{(68-70)}.

\textit{Indwelling Pleural Catheters:}
Indwelling, small-bore pleural catheters (IPC) are flexible silicon catheters that allow drainage whenever required by the patient (Figure 2). They can be curled up and dressed unobtrusively out of the way when not in use. They present an FDA-approved strategy that allows outpatient insertion and follow up. By removing the need for hospital admission and sclerosants, they are intended to avoid many of the side effects and costs of pleurodesis. They are the recommended treatment option in patients with significant trapped lung, and in those patients whose pleurodesis fails for other reasons\(^{71-73}\). IPC offer the potential for ambulatory care from start to finish, maintaining freedom from hospital and possibly maximizing time with family and friends for patients with incurable disease.

**Figure 2: Indwelling Pleural Catheter (IPC):** Flexible silicon catheter tunneled under the skin with a polyester cuff to promote ingrowth of fibroblasts, securing the catheter and providing a barrier to infection.

The use of IPC is still in its early phase and its exact role remains a hotly debated and studied topic\(^ {57, 74, 75}\). In the late 1990’s and the 2000’s small descriptive series and a
pilot randomized study demonstrated that they are effective, with >96% of patients getting symptom improvement and >90% never needing another ipsilateral pleural procedure in the largest series\textsuperscript{(58, 76-80)}. Another unintended but consistent benefit was that nearly half of the patients developed a spontaneous pleurodesis, not significantly lower than the long-term pleurodesis rate in the largest randomized trial of pleurodesis techniques\textsuperscript{(45)}. IPC demonstrated a similar safety record to pleurodesis also. However, direct comparisons of IPC use with other common treatments as the primary treatment option were lacking in number and quality to guide evidence based decisions. Moreover the critical information on hospital stay over the patient’s entire remaining life-span was not reported.

The original pilot study from the 1990’s that resulted in the FDA approving IPC for use in the USA was a comparison of 144 patients randomized in a 2:1 distribution to either IPC or doxycycline pleurodesis. It found that long-term effusion control was at least as good with IPC and that the initial hospital admission for IPC insertion was shorter than for bedside pleurodesis (1.0 as opposed to 6.5 days, \( p<0.001 \)). However, it did not assess the length of subsequent admissions for the rest of the patient’s life, so this second finding is not adequate to guide long-term treatment decisions for the patient with an MPE.

In May 2012 the findings of the TIME2 study (Second Therapeutic Intervention in Malignant Pleural Effusion) were published\textsuperscript{(81)}. This study randomized 106 patients with MPE in a 1:1 distribution to talc pleurodesis or IPC. The primary endpoint was dyspnea scores at six weeks. Secondary endpoints were: the proportion of patients less dyspnoeic at six weeks, and dyspnea scores at three months and six months; mean daily chest pain for the first 42 days and mean chest
pain at the same time points as dyspnea; nights spent in hospital from randomization to discharge; all cause mortality to one year; self-reported quality of life (EORTC-QLQ 30); and frequency of adverse events.

The TIME2 study did include initial stay in hospital as a secondary endpoint (0 vs. 4 days in favour of the IPC group, p<0.001), and the authors did attempt to address long-term “drainage related” stay in hospital in a post hoc analysis (1.0 vs. 4.5 days at 12 months, p<0.001). However, the most relevant data for the patient and their family is the time that they are going to be able to be independent from hospital. Moreover, when calculating the cost of the various treatments it is the all cause hospital admission data that is most relevant.

A third randomized clinical trial of talc pleurodesis or IPC therapy has recently been published that had to be stopped early because of difficulties in patient recruitment\(^{(82)}\). The target was to recruit 530 patients, however the study was stopped because of poor recruitment after only 57 patients had been randomized over two years. The primary endpoint of this study was a composite outcome at 30 days after trial intervention, consisting of: being alive; having no effusion recurrence; lung re-expansion of >90% on CXR; and completion of treatment by two weeks (removal of catheter for the pleurodesis arm or “proper function” of the IPC). While 62% of the IPC patients that were recruited achieved success in the primary endpoint versus 46% who received talc pleurodesis, this unsurprisingly did not achieve statistical significance (p=0.29).

This trial was significantly hampered by its failure to reach its target numbers derived from power calculations, but also by its focus on lung reexpansion/pleurodesis
success rather than more patient-centered outcomes. Indeed the investigators had to reduce their definition of successful lung reexpansion from the 90% cut off to 70% because almost none of the patients were achieving >90% despite highly meaningful success in terms of improved symptoms and quality of life. The authors, again, did not report the number or lengths of subsequent hospital admissions, leaving this issue as an important factor that needs to be addressed.

**PART 1 of this thesis aims to examine the role of Indwelling Pleural Catheters as initial treatment strategy for MPE:**

The advent of IPC has led to renewed critical appraisal of conventional approaches to MPE management. IPC offer ambulatory fluid drainage and primarily symptomatic therapy, thus prompting clinicians to reevaluate the goals of MPE care. IPC signal the arrival of symptom-directed palliative therapy in MPE. ‘Success’ must now be defined by patient-oriented parameters. The conventional measurement of ‘success’ by pleurodesis rate, often measured by absence of fluid on radiographs, is of peripheral importance. The priorities for most MPE patients are alleviation of dyspnea and optimization of quality of life. These parameters should be considered the key goals for MPE care and research.

Talc pleurodesis has been the mainstay of MPE management for decades, but its efficacy and safety have recently come under scrutiny. In the largest randomized trial in pleural disease (n=486), talc (poudrage or slurry) pleurodesis had a suboptimal success rate: only ~75% of MPE patients at one month and ~50% by six months had adequate fluid control. Adding the fact that many patients are unsuitable
for pleurodesis (e.g. with trapped lungs), talc pleurodesis benefits only a subset of all MPE patients. Randomized trials have also shown that talc induces lung and systemic inflammation\(^{(48)}\), and 2.3% of patients in a CALGB study died through talc-induced respiratory failure\(^{(45)}\). Although this acute lung injury can be avoided by using large particle size talc preparations\(^{(84)}\), such products are not readily available in many countries, including the USA.

These data have provoked debates and compelled the pleural community to revisit the principles of MPE care. The fundamental aim in MPE management is to improve dyspnea and quality-of-life (QoL), with minimal intervention and hospitalization. The timely introduction of IPCs which allow fluid evacuation from a single minimally-invasive procedure serves exactly this purpose and explains its rapid rise in popularity in the USA (over 39,000 units sold for pleural and peritoneal use in the USA per year\(^{(78)}\)).

IPC represents a new therapeutic ideology and clinicians are still adapting to the specific changes needed to realize the full potential of this device. First, the exact place of IPC in the paradigm of MPE management has yet to be defined. IPC is generally accepted for treatment of MPE patients in whom pleurodesis has failed or is contraindicated (especially trapped lungs)\(^{(85)}\). Many specialist centers now offer IPC as the first-choice therapy in place of talc pleurodesis, amid growing recognition of its limitations\(^{(41)}\). However, there are few head-on comparisons between these two strategies and patients and clinicians have needed to make choices between these therapies in an uninformed, often haphazard manner. This issue needed to be
addressed and was the major goal of the studies reported in Part I that compare the roles of IPC as opposed to talc pleurodesis as first-line therapy in MPE patients.

**PART II of this thesis aims to examine the complications of Indwelling Pleural Catheters:**

There is a lack of adequate studies examining the long-term complications of IPC use, which contributes to hesitance amongst some clinicians in employing IPC in patients with MPE. Many clinicians remain concerned about potential impacts on the patient of having a pleural catheter for several weeks or months. The possibilities of IPC use in particular acting as a portal for infection in patients on immunosuppressant chemotherapy, or allowing spread of tumour along the catheter track were not conclusively examined by the initial studies and further work was necessary to determine the importance of these concerns\(^{(74)}\). Part II of this thesis aims to address these ongoing concerns.

The reported complications related to IPC therapy are summarized in our review article in Current Opinion in Pulmonary Disease and are discussed in order of frequency\(^{(86)}\) (Table 1). As with standard chest tubes, mild pain post insertion is the most frequent reported event although less than 1% of patients experience ongoing pain requiring IPC removal\(^{(58, 76, 77, 80, 87, 88)}\). Around 5% of patients experience pain during drainage\(^{(58, 88)}\), most likely due to visceral pleural disease resisting lung re-expansion. Careful withdrawal of smaller volumes of pleural fluid can often prevent such pain during drainage.
Table 1: Complications associated with IPC insertion and use (summative statistics from published literature)\(^{(86)}\).

<table>
<thead>
<tr>
<th>Complication</th>
<th>Incidence (%)</th>
<th>Number of patients affected/total insertions from cited references</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild pain after insertion(^{(80, 94)})</td>
<td>35.7</td>
<td>20/56</td>
</tr>
<tr>
<td>Fluid leakage around catheter(^{(77, 80, 91)})</td>
<td>9.3</td>
<td>7/75</td>
</tr>
<tr>
<td>Symptomatic loculation(^{(58, 76, 87-92)})</td>
<td>7.1</td>
<td>44/621</td>
</tr>
<tr>
<td>Pain during drainage(^{(58, 88)})</td>
<td>5.4</td>
<td>8/147</td>
</tr>
<tr>
<td>Asymptomatic loculation(^{(76, 87, 89)})</td>
<td>5.1</td>
<td>17/332</td>
</tr>
<tr>
<td>Catheter occlusion(^{(58, 73, 77, 80, 88, 90-92, 94, 95)})</td>
<td>4.6</td>
<td>29/624</td>
</tr>
<tr>
<td>Pneumothorax(^{(58, 76, 77, 87, 88)})</td>
<td>3.4</td>
<td>15/438</td>
</tr>
<tr>
<td>Tumour seeding(^{(58, 76, 77, 87, 91, 92, 95, 99, 106)})</td>
<td>3.4</td>
<td>20/596</td>
</tr>
<tr>
<td>Unsuccessful insertion(^{(58, 76, 87, 90)})</td>
<td>3.0</td>
<td>12/400</td>
</tr>
<tr>
<td>Pleural infection(^{(58, 73, 76, 77, 80, 87, 88, 90-92, 94-99)})</td>
<td>2.7</td>
<td>29/1091</td>
</tr>
<tr>
<td>Soft tissue infection(^{(58, 73, 76, 77, 80, 87, 88, 90-92, 94, 96, 99)})</td>
<td>2.6</td>
<td>22/832</td>
</tr>
<tr>
<td>Bleeding post insertion/haemothorax(^{(58, 76, 87, 92, 97)})</td>
<td>1.0</td>
<td>5/498</td>
</tr>
<tr>
<td>Re-expansion pulmonary oedema(^{(58, 87)})</td>
<td>0.8</td>
<td>1/123</td>
</tr>
<tr>
<td>Pain requiring catheter removal(^{(58, 76, 77, 80, 87, 88)})</td>
<td>0.6</td>
<td>3/486</td>
</tr>
</tbody>
</table>

Experience with IPC suggests that they are also associated with different potential complications from standard chest tubes, related primarily to their long-term use. Symptomatic loculation (i.e. loculation of the pleural space resulting in inability to completely evacuate the pleural fluid with worsening dyspnoea) occurs in some
patients with IPCs\(^{(58, 76, 87-92)}\). There is no robust evidence to determine optimal treatment of loculations but some physicians advocate a therapeutic trial of intrapleural fibrinolytics to try to improve pleural drainage\(^{(93)}\). Furthermore, IPC blockage may occur in about 5% of patients\(^{(58, 73, 77, 80, 88, 90-92, 94, 95)}\). Fibrinolytics have also been instilled to try to restore patency in a blocked catheter.

IPC present an ongoing theoretical risk of infection whilst the catheter remains in situ. Similar to long-term urinary catheters, some IPC are likely to become colonised with bacteria. However, little quality evidence exists on the extent and severity of the problem. Currently available data are limited to small case series that are potentially influenced by selection biases, small cohorts, variable expertise in individual centres and the patient cohort of the specific studies. Despite such colonisation, clinically-relevant pleural infection develops infrequently in only a small percentage of patients\(^{(58, 73, 76, 77, 80, 87, 88, 90-92, 94-99)}\). Soft tissue infection can also occur in small published series\(^{(58, 73, 76, 77, 80, 87, 88, 90-92, 94, 96, 99)}\). Given the relative infrequency of IPC-related infection and its wide variability in the initial reports a large, multinational study was required to assess the true impact of this complication and the possible treatments available.

Catheter tract metastases have been associated with IPC use but many of the patients were asymptomatic\(^{(58, 76, 77, 87, 91, 92, 95, 99, 100)}\). The impact on the patients and the effectiveness of symptom control with analgesia and radiotherapy was not studied and needed addressing. Fracture of the IPC at the time of removal was also noted in some of the patients with IPC and this previously unreported complication also required further study.
These complications required further examination in a systematic fashion. They were inadequately evaluated by the initial studies and their potential to cause significant harm in the longer term demanded further study. The goal of Part II of this thesis was to address this lack of real-world safety data.

**PART III of this thesis aims to discover Predictors of Need for Definitive Therapy:**

MPE cause considerable morbidity and many patients require invasive procedures to drain the fluid and alleviate associated breathlessness and other symptoms. Fluid re-accumulation may occur, necessitating ongoing drainage procedures or treatments to prevent ongoing fluid recurrence, such as pleurodesis. As discussed above, the rate of recurrence of MPE is very variable, from never requiring further procedures, to needing to drain several litres of fluid per week for the rest of the patient’s life.

The risk of complications from pleural drainage procedures is not insignificant for the patient with MPE, so the number and frequency of these interventions need to be minimized, while still maintaining adequate symptom control and quality of life. There are no predictors currently of MPE recurrence rate or need for definitive fluid control, such as talc pleurodesis or IPC insertion. Delay in definitive therapy (IPC or pleurodesis) can expose the patient with recurrent MPE to prolonged symptoms, extra drainage procedures and cumulative complication risks, while a strategy of early
definitive therapy in all patients will mean treating many patients whose MPE would not have recurred.

An algorithm that could predict the likelihood of need for treatment to control the recurrence of MPE and associated symptoms at an early stage in the disease course would improve the care of patients with MPE. It would enable clinicians to effectively counsel their patients on the risk that their symptoms would worsen or recur. Those patients that were less likely to require ongoing pleural procedures could be reassured, while a thorough discussion of the pros and cons of treatment could begin with those that were more likely to recur. It could then provide an opportunity to accelerate the provision of definitive therapy for those who stood to gain the most from early intervention. Part III of this thesis aims to provide the basis for the development of such an algorithm in the future.
Part I

Pleurodesis or Indwelling Pleural Catheter as First Line Treatment for MPE?
**Foreword**

Over 12,500 patients worldwide are diagnosed with a malignant pleural effusion everyday and a decision has to be made as to how to best manage their distressing symptoms. Pleurodesis has been the main technique for control of effusions for decades, but it does have significant shortcomings as described in the Introduction. The introduction of indwelling pleural catheters (IPC) has given clinicians and patients a choice between two effective strategies to control their effusion and their symptoms. However, there remains a lack of evidence to effectively guide this treatment choice.

Part I section 1 describes our study that aimed to address this lack of evidence, especially focusing on the need to maximize independence from hospitals while ensuring optimal symptom control (Published article number 1)(101). It hypothesized that IPC could be as effective as talc pleurodesis in maintaining freedom from hospital and controlling breathlessness. The second section describes our multicenter randomized clinical trial, designed to further verify our findings, with the same hypothesis as the first study. The published protocol is included (Published article number 2)(102). The third section reports our study that hypothesized that mesothelioma, being a primary pleural malignancy, may have different success rates when it comes to pleurodesis. The study revealed suboptimal pleurodesis success rates in patients with mesothelioma, which highlights the need for further treatment advances (Published article number 3)(103).
Section 1:

Indwelling Pleural Catheters Reduce Inpatient Days over Pleurodesis for Malignant Pleural Effusion.
Indwelling Pleural Catheters Reduce Inpatient Days Over Pleurodesis for Malignant Pleural Effusion

Edward T. H. Fysh, MBBS; Grant W. Waterer, PhD; Peter A. Kendall, MBBS; Peter R. Bremner, MBChB; Sharifa Dina, RN; Elizabeth Geelhoed, PhD; Kate McCarney, RN; Sue Morey, NP; Michael Millward, MA; A. W. (Bill) Musk, MD, FCCP; and Y. C. Gary Lee, PhD, FCCP

Background: Patients with malignant pleural effusion (MPE) have limited prognoses. They require long-lasting symptom relief with minimal hospitalization. Indwelling pleural catheters (IPCs) and talc pleurodesis are approved treatments for MPE. Establishing the implications of IPC and talc pleurodesis on subsequent hospital stay will influence patient choice of treatment. Therefore, our objective was to compare patients with MPE treated with IPC vs pleurodesis in terms of hospital bed days (from procedure to death or end of follow-up) and safety.

Methods: In this prospective, 12-month, multicenter study, patients with MPE were treated with IPC or talc pleurodesis, based on patient choice. Key end points were hospital bed days from procedure to death (total and effusion-related). Complications, including infection and protein depletion, were monitored longitudinally.

Results: One hundred sixty patients with MPE were recruited, and 65 required definitive fluid control; 34 chose IPCs and 31 pleurodesis. Total hospital bed days (from any causes) were significantly fewer in patients with IPCs (median, 6.5 days; interquartile range [IQR] = 3.75-13.0 vs pleurodesis, mean, 18.0; IQR, 8.0-26.0; P = .002). Effusion-related hospital bed days were significantly fewer with IPCs (median, 3.0 days; IQR, 1.8-8.3 vs pleurodesis, median, 10.0 days; IQR, 6.0-18.0; P < .001). Patients with IPCs spent significantly fewer of their remaining days of life in hospital (8.0% vs 11.2%, P < .001, χ² = 28.25). Fewer patients with IPCs required further pleural procedures (13.5% vs 32.3% in pleurodesis group). There was no difference in rates of pleural infection (P = .68) and protein (P = .65) or albumin loss (P = .22). More patients treated with IPC reported immediate (within 7 days) improvements in quality of life and dyspnea.

Conclusions: Patients treated with IPCs required significantly fewer days in hospital and fewer additional pleural procedures than those who received pleurodesis. Safety profiles and symptom control were comparable.

Abbreviations: IPC = indwelling pleural catheter; IQR = interquartile range; MID = minimally important difference; MPE = malignant pleural effusion; QoL = quality of life

Malignant pleural effusion (MPE) affects 660 patients per million population each year. The resultant breathlessness is often disabling and impairs quality of life (QoL). Pleurodesis, the conventional management for MPEs, requires either lengthy hospital admission and/or considerable surgical resources. It is not suitable for patients with trapped lung wherein the visceral and parietal pleural layers are apart and not able to be fused. Even in selected patients, the largest clinical trial of talc pleurodesis had a success rate of about 75% at 1 month and <50% by 6 months as well as considerable complications.

Indwelling pleural catheters (IPCs) are an increasingly popular alternative to pleurodesis. More than 39,000 units are sold in the United States each year for management of pleural or peritoneal effusions. IPCs can be inserted as an outpatient procedure and offer rapid relief of dyspnea through ambulatory drainage of effusions. This avoids admission to hospital associated with pleurodesis and the potential side effects from pleurodesing agents.
because of trapped lung). The use of IPC as first-line treatment of MPE remains controversial, and concerns about complications (eg, infection and protein depletion) deter its use. Studies directly comparing first-line therapy with IPCs and talc pleurodesis in a pragmatic setting based on patient/clinician choice are lacking.

The State Health Research Advisory Council study of the Western Australian Health Department was a pilot, prospective, observational study comparing IPC vs pleurodesis in patients with an MPE. The study was nonrandomized but governed by the choice of patients and their attending clinicians. The hypotheses were that (1) patients treated with IPC would spend fewer days in hospital and (2) use of IPCs was safe. The key end point was the number of hospital bed days due to admissions of any cause. Other end points included hospital bed days due to pleural effusion-related admissions, QoL, and symptom measures and major complications.

**Materials and Methods**

This study forms part of the analyses of the Western Australian study of Malignant Pleural Effusion, approved by the Human Research Ethics Committees of the Sir Charles Gairdner, Fremantle, and Royal Perth Hospitals in Western Australia, and the University of Western Australia (approval number 2009-104). All patients provided written, informed consent.

Patients with MPE from the three major public teaching hospitals in Perth, Western Australia (population about 1.7 million) were recruited over 12 months from October 1, 2009, and followed up December 31, 2010, or death. The diagnosis of MPE was confirmed histologically. Patients’ demographic, clinical, radiologic, biochemical (blood and pleural fluid) and histologic information were recorded and followed up longitudinally.

All patients who warranted definitive treatment (by IPC or pleurodesis) had histocytologically confirmed pleural malignancies and demonstrated symptomatic improvement with fluid drainage. No consensus exists for the use of IPC or pleurodesis as first-line therapy for MPE. A realistic, patient-centered approach was, therefore, taken, whereby the choice between IPC and pleurodesis was made by patients and their attending clinicians. The pros and cons of each modality of treatment were discussed with the patient, as per our published reviews.13-14 Pleurodesis and IPC were both offered to patients provided there were no contraindications, which included short predicted survival (either treatment), trapped lung (for pleurodesis), or inability to manage the device (for IPC). In the absence of effective means to predict survival, the subjective assessments of prognosis by the treating physicians were used. These were based on performance status and other clinical factors.15 Pleurodesis or IPC therapy was only undertaken if the clinician felt the treatment was likely to save the patient three or more drainage procedures in the patient’s remaining life span. As trapped lung was regarded as a contraindication to pleurodesis, the IPC group predictably had a higher proportion of these patients (Table 1).

**Indwelling Pleural Catheter**

IPC s (Rocket Medical) were inserted with imaging guidance, usually as a day-case. Patients were reviewed within 10 days after insertion to assess healing, then fortnightly for the first month and monthly thereafter. Additional visits were arranged if clinically indicated. Patients were advised to perform drainage when symptomatic. Patients with IPCs could receive other therapies (including chemotherapy) as clinically appropriate. Removal of the IPC was considered if no fluid could be drained for >1 month or if the patient no longer derived symptomatic benefit from catheter drainage.

Blood and pleural fluid samples were taken at the monthly review or more frequently if indicated. Complete blood picture, electrolytes, liver function tests, and C-reactive protein level were measured from peripheral blood. Pleural fluid was assessed for pH, protein, lactate dehydrogenase, and glucose and subjected to bacterial culture. Empyema was defined as positive pleural fluid cultures or presence of pus with systemic signs of infection. No patients received prophylactic radiotherapy to pleural puncture sites.

**Pleurodesis**

Pleurodesis was performed using graded talc (Novatech) either as bedside talc slurry or thoracoscopic poudrage, as preferred by the clinician in charge, since randomized studies showed no superiority of either method.15-16 All pleurodesis procedures were performed in hospital. Generally, small-bore (12F-15F) tubes inserted by Seldinger technique were used for bedside pleurodesis, whereas large-bore (24F-32F) tubes were placed after thoracoscopy. Timing of talc insertion and chest tube removal were decided by the treating physicians according to local protocols. In general, talc slurry was administered when the lung was fully re-expanded and drainage volume reduced. In the absence of any other reasons for inpatient care, patients were discharged as soon as a satisfactory posterostral chest radiograph was obtained. Failure of pleurodesis was defined as the need for another ipsilateral pleural procedure at any time.

**Determining Length of Hospital Stay and Relation to the Pleural Effusion**

Hospital admissions from any cause were recorded, using a statewide clinical data program available in all recruiting hospitals and using discharge summary data from private hospital admissions. Day case interventional procedures (including IPC insertion)
symptomatic and, in most cases, recurrent effusions

Baseline Demographics

Comparisons were performed, where appropriate, by the

Statistics

Above his/her own baseline, and if no other postprocedure score

difference (MID) is defined. The minimally important difference

the presence or recurrence of the effusion being studied, or a complication of a

prior pleural procedure was found or treated. If none of the criteria explained here was met, the admission was labeled "unrelated to

pleural effusion." For admissions up to and including 7 days, the entire

admission was judged as effusion-related if a pleural procedure

as explained here was met, the admission was labeled "unrelated to

pleural effusion." For admissions up to and including 7 days, the entire

admission was judged as effusion-related if a pleural procedure

as explained here was met, the admission was labeled "unrelated to

pleural effusion." For admissions up to and including 7 days, the entire

admission was judged as effusion-related if a pleural procedure

as explained here was met, the admission was labeled "unrelated to

procedures started from time of inser-

tion of chest tube or thoracoscopy. Presentations to day-stay che-

symptomatic and, in most cases, recurrent effusions

that required definitive treatment. Thirty-four patients
elected to be treated with an IPC and 31 with talc
pleurodesis. The two groups were similar in their baseline characteristics (Table 1).

IPCs were inserted by the respiratory (n = 30), radiology (n = 3), and cardiothoracic (n = 1) services. As

expected, more patients in the IPC group had incomplete lung re-expansion after initial drainage, suggesting

trapped lung (16 of 34 as opposed to one of 31 in the pleurodesis group). The median time IPCs

remained in situ was 53.5 days (interquartile range [IQR], 24-116; range, 1-350). All patients with IPC

except one were followed up at a central service based at Sir Charles Gairdner Hospital, supervised by two investigators (E. T. H. F. and Y. C. G. L.). The median follow-up time in the IPC and pleurodesis groups were 93 days (IQR, 28-172) and 134 days (IQR, 51-215), respectively (P = .18). Fourteen patients (41.2%) who were treated with IPC developed spontaneous pleurodesis after 50.5 days (median; IQR, 55-104) permitting catheter removal. This included four of the 16 patients (25%) whose lung did not re-expand fully after initial drainage.

Pleurodeses were performed as talc slurry (n = 24), pleuroscopic poudrage (n = 1), or video-assisted thoracoscopic surgery (n = 6). Three patients in the pleurodesis group subsequently required an IPC due to fluid reaccumulation. One patient treated with an IPC later underwent pleurectomy.

Chief End Point

Days in Hospital: Patients treated with IPC spent significantly fewer days in hospital (median, 6.5 days; IQR, 3.75-13.0) compared with those who chose pleurodesis (median, 18.0 days; IQR, 8.0-26.0) (P = .002) (Fig 1). The benefits were consistent both in patients with metastatic malignancy (IPC, 5.5 days [median; IQR, 3.0-12.0] vs pleurodesis 18.0 days [IQR, 8.0-32.0], P = .012) and those with mesothelioma (IPC, 9.0 days [IQR, 5.0-13.0] vs pleurodesis 15.5 days [IQR, 8.5-22.0], P = .06).

The differences in pleural effusion-related hospital

bed days were even more pronounced: IPC group median 3.0 days (IQR, 1.75-8.25) vs pleurodesis group 10.0 days (IQR 6.0-18.0), P < .001 (Fig 2). There was no significant difference in the number of episodes of hospital admissions (1) from any cause between the IPC and pleurodesis groups: median 2 (IQR, 1.0-3.0) vs 2 (IQR, 1.0-4.0), respectively; or (2) from effusion-related admissions: 1 (IQR, 1.0-2.0) and 1 (IQR, 1.0-3.0) respectively.

To adjust for shorter follow-up times in the IPC

group, the total number of hospital bed days were compared as a proportion of the total follow-up time for each group. The IPC group incurred 341 hospital bed

Table 1—Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>IPC (n = 34)</th>
<th>Pleurodesis (n = 31)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR), y</td>
<td>69 (65-78)</td>
<td>73 (66-82)</td>
<td>.32</td>
</tr>
<tr>
<td>Male sex</td>
<td>25 (73.5)</td>
<td>19 (61.3)</td>
<td>.58</td>
</tr>
<tr>
<td>Right-sided effusion</td>
<td>21 (61.8)</td>
<td>16 (51.6)</td>
<td>.57</td>
</tr>
<tr>
<td>Trapped lung</td>
<td>16 (47.1)</td>
<td>1 (3.2)</td>
<td>.001</td>
</tr>
<tr>
<td>Malignancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>18 (52.9)</td>
<td>12 (38.7)</td>
<td>.37</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>13 (38.2)</td>
<td>17 (54.8)</td>
<td>.28</td>
</tr>
<tr>
<td>Lung</td>
<td>7</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>4</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Ovarian</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Endometriual</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Esophageal</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>3 (8.7)</td>
<td>2 (6.4)</td>
<td>...</td>
</tr>
</tbody>
</table>

Data are presented as No. or No. (%) unless otherwise noted. No difference was found between the groups in their baseline demographic data, except for trapped lung, as expected. IPC = indwelling pleural catheter; IQR = interquartile range.

counted as 1 day in hospital. Counts of hospital bed days incurred during the pleurodesis procedure started from time of inser-
tion of chest tube or thoracoscopy. Presentations to day-stay che-

Chief End Point

Days in Hospital: Patients treated with IPC spent significantly fewer days in hospital (median, 6.5 days; IQR, 3.75-13.0) compared with those who chose pleurodesis (median, 18.0 days; IQR, 8.0-26.0) (P = .002) (Fig 1). The benefits were consistent both in patients with metastatic malignancy (IPC, 5.5 days [median; IQR, 3.0-12.0] vs pleurodesis 18.0 days [IQR, 8.0-32.0], P = .012) and those with mesothelioma (IPC, 9.0 days [IQR, 5.0-13.0] vs pleurodesis 15.5 days [IQR, 8.5-22.0], P = .06).

The differences in pleural effusion-related hospital

bed days were even more pronounced: IPC group median 3.0 days (IQR, 1.75-8.25) vs pleurodesis group 10.0 days (IQR 6.0-18.0), P < .001 (Fig 2). There was no significant difference in the number of episodes of hospital admissions (1) from any cause between the IPC and pleurodesis groups: median 2 (IQR, 1.0-3.0) vs 2 (IQR, 1.0-4.0), respectively; or (2) from effusion-related admissions: 1 (IQR, 1.0-2.0) and 1 (IQR, 1.0-3.0) respectively.

To adjust for shorter follow-up times in the IPC

group, the total number of hospital bed days were compared as a proportion of the total follow-up time for each group. The IPC group incurred 341 hospital bed
although this did not reach statistical significance (Table 2). The MID for QoL was 12.9 and 10.4 and for dyspnea 9.6 and 10.3 for the IPC and pleurodesis groups, respectively, and comparable to other studies using the same instruments.16-18

Safety: Both procedures were relatively safe (Table 3). One death was directly related to video-assisted thoracoscopic surgery pleurodesis due to postoperative recurrent bleeding and sepsis. The incidence of empyema was comparable in both groups (10.8% IPC, 6.4% pleurodesis group, \( P = .68 \)). All empyemas associated with IPC were successfully treated with drainage via the catheter and antibiotics. None required early removal of the catheter. Two patients spontaneously pleurodesed and the catheters were removed after resolution of the infection.

No significant albumin or protein depletion was seen in either group from initiation of therapy to death or 3-month follow-up; the median change in serum albumin level was \(-1.0 \text{ g/L} (\text{IQR, } -4.5 \text{ to } 1.5)\) in the IPC group and \(+1.0 \text{ g/L} (\text{IQR, } -3.0 \text{ to } 6.0; \ P = .22)\) in the pleurodesis group. Median protein changes were \(-1.7 \text{ g/L} (\text{IQR, } -6.5 \text{ to } 1.0)\) and \(+3.5 \text{ g/L} (\text{IQR, } -10.5 \text{ to } 8.0; \ P = .65)\), respectively (Fig 3). Mean serum albumin levels at death or 3 months were 37.2 (5.6) g/L in the IPC group and 37.8 (5.4) g/L in

![Bed Days (All Causes)](image)

*Figure 1. Total number of days in hospital throughout the follow-up period from any cause of admission. Patients treated with IPCs spent significantly fewer days in hospital. IPC = indwelling pleural catheter; IQR = interquartile range.*

days out of 4,282 days of follow-up (8.0%) as opposed to 600 out of 5,347 days in the pleurodesis group (11.2%) \( (\chi^2 = 28.3; \text{degrees of freedom, } 1; \ P < .001) \).

**Other End Points**

*Control of Effusion:* IPC offered effective fluid control in most patients (86.5%) compared with pleurodesis (67.7%), \( P = .12 \). Failure of pleurodesis requiring subsequent drainage procedures occurred in 10 patients (32.3%) after a median time of 51.5 days (IQR, 22-116). Failure of IPC drainage from symptomatic loculation occurred in five patients (13.5%). All were treated with intrapleural fibrinolytic therapy (\( n = 2 \) urokinase, \( n = 3 \) with tissue plasminogen activator) via the IPC, with success (improvement of symptoms and effusion size radiographically) in four patients, although symptomatic loculations recurred in three.

*Short-term QoL and Dyspnea:* More patients treated with IPCs reported improved QoL scores (\( P = .02 \)). Fourteen patients (93.3%) in the IPC group recorded a significant improvement in QoL, one (6.7%) reported no change, and none (0%) deteriorated (vs 50.0%, 41.7%, and 8.3%, respectively, in the pleurodesis group). Likewise, more patients in the IPC group recorded an improvement in dyspnea than in the pleurodesis group (93.3% vs 78.6%, respectively), although this did not reach statistical significance (Table 2). The MID for QoL was 12.9 and 10.4 and for dyspnea 9.6 and 10.3 for the IPC and pleurodesis groups, respectively, and comparable to other studies using the same instruments.16-18
Table 2—Short-term QoL and Dyspnea Scores

<table>
<thead>
<tr>
<th>Score Type</th>
<th>Significantly Improved</th>
<th>Unchanged or Deteriorated</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>QoL scores</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPC (n = 15)</td>
<td>14 (93.3)</td>
<td>1 (6.7)</td>
<td>.02</td>
</tr>
<tr>
<td>Pleurodesis (n = 12)</td>
<td>6 (50)</td>
<td>6 (50)</td>
<td></td>
</tr>
<tr>
<td>Dyspnea scores</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPC (n = 15)</td>
<td>14 (93.3)</td>
<td>1 (6.7)</td>
<td>.33</td>
</tr>
<tr>
<td>Pleurodesis (n = 14)</td>
<td>7 (53.8)</td>
<td>6 (46.2)</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as No. (%). The QoL and dyspnea scores were recorded immediately before and daily for the first 7 days after IPC insertion or pleurodesis. Complete QoL assessments were received from 15 of 34 (44.1%) and 12 of 31 (38.7%) patients of the IPC and pleurodesis groups, respectively, and completed dyspnea assessments from 15 of 34 (44.1%) and 14 of 31 (45.2%), respectively. QoL = quality of life. See Table 1 legend for expansion of other abbreviation.

Table 3—Complication Rates During Study Period (Minimum 3 mo)

<table>
<thead>
<tr>
<th>Complication</th>
<th>IPC (n = 37)</th>
<th>Pleurodesis (n = 31)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain postprocedure</td>
<td>2 (5.4)</td>
<td>4 (12.9)</td>
<td>.40</td>
</tr>
<tr>
<td>Symptomatic loculation/failed pleurodesis</td>
<td>5 (13.5)</td>
<td>10 (32.3)</td>
<td>.12</td>
</tr>
<tr>
<td>Empyema</td>
<td>4 (10.8)</td>
<td>2 (6.4)</td>
<td>.68</td>
</tr>
<tr>
<td>Hemothorax</td>
<td>1 (2.7)</td>
<td>2 (6.5)</td>
<td>.59</td>
</tr>
<tr>
<td>Dislodgement of catheter</td>
<td>1 (2.7)</td>
<td>3 (9.7)</td>
<td>.32</td>
</tr>
<tr>
<td>No. of patients experienced a complication</td>
<td>7 (18.9)</td>
<td>14 (45.2)</td>
<td>.04</td>
</tr>
</tbody>
</table>

Data are presented as No. (%). See Table 1 legend for expansion of abbreviation.

the pleurodesis group (P = .73), and mean protein levels at this time were 69.5 (7.0) and 70.1 (8.6) g/L, respectively (P = .81).

Discussion

This study confirmed in a prospective, pragmatic, patient-choice setting that the use of IPC significantly reduced the number of hospital bed days for patients with an MPE that required definitive treatment. The nonrandomized, patient-centered design whereby patients and clinicians were allowed to tailor therapy to individual circumstances replicated real-life settings. A median reduction of 11.5 hospital bed days is significant for these patients with limited life spans and can represent substantial health-care savings. The use of IPC also helped avoid further invasive pleural drainage procedures compared with pleurodesis. In this study, IPC had a comparable safety profile and provided equivalent, if not superior, symptom control compared with talc pleurodesis.

MPE can complicate most cancers, and its incidence is rising. Patients with MPE have a median survival of about 3 to 4 months for metastatic pleural disease21,22 and about 9 to 12 months for mesothelioma.23,24 The key aims of management are to provide ambulatory symptom relief without necessitating hospitalization.25

Patients who chose IPC spent 64% less time, or 11.5 (median) fewer days in hospital beds than those who underwent pleurodesis. It would appear that these findings are consistent for both metastatic malignancies and for mesothelioma, although in the latter group the results fell just short of statistical significance. Conventional therapy with pleurodesis requires admission of 4 to 8 days in most published studies, including a randomized trial of an accelerated discharge protocol,24 and in our local data (6.5 days, Western Australia Health Department). In the largest randomized study of talc pleurodesis, the success rate was only about 75% at 1 month, but the failure rate rose to 50% in patients who survived 6 months.5 Our data echoed these findings and found that 32% of pleurodesis patients needed further fluid drainage before death. In comparison, 86% of the patients treated with IPC avoided further invasive drainage, and spontaneous pleurodesis developed in 41% after a median time of 50.5 days, an increasingly reported benefit.9,13 The additional drainage procedures in the pleurodesis group contributed to the significant differences in hospital bed days seen in our study.

The reduction in hospital bed days was for admissions from any cause—a robust measure that is meaningful to patients and health-care providers. There was no difference in the number of admissions to hospital between the groups, suggesting that therapy with an IPC is more effective at reducing the length of the admissions both at initiation of therapy and at readmission.

The management of MPE represents an increasing health-care expenditure. In Western Australia, the inpatient care cost for MPE management doubled between 2003 and 2008 ($5.4 to $11.7 million) and the number of hospital admissions rose from 1,522 to 2,293 per year. Although further analysis is needed to include costs attributable to the increase in outpatient visits incurred by the IPC group, the annual inpatient health-care savings of IPC implicated from our study would exceed $8.4 million per million population (based on 660 patients millionaire population, a difference in mean bed days of 9.4 and $1,353/d of inpatient cost), if the findings are extrapolated to all patients with MPE.

The uptake of IPC use has been variable worldwide, in part due to the paucity of direct comparisons of its safety with talc pleurodesis. Our study adds support to recent reports25,26 that complication rates were comparable, if not in favor of IPC management. Complications in this study (as found previously) were generally mild and easily manageable. A significantly higher proportion of this IPC group reported an
improvement in QoL, and there were trends toward better dyspnea relief. These findings may be explained in part by the pain and fever from talc pleurodesis and the fact that these patients stayed in hospital with a chest tube in situ for several days.

Common concerns of IPC-related infection and protein depletion did not appear to be a major issue in our study. No significant difference in infection risks was observed, and IPC-related empyema responded promptly to antibiotics with no significant long-term sequelae and did not necessitate IPC removal. We also found no significant protein depletion despite frequent effusion drainage via IPC.

There are several limitations to this study. First, it was designed to mimic real-life practice, in which no data exist that define whether IPC or pleurodesis should be the preferred therapy. Patients were not randomized but were allowed to choose, in consultation with the attending physician, between IPC and pleurodesis. Although not randomized, the baseline characteristics of the two groups of patients were similar (Table 1). Nevertheless, the benefits seen in this selected IPC group need to be followed up with a randomized trial. Second, although a significant difference was found in QoL scores between the groups (Table 2), the return rate of questionnaires was < 50%, which is often encountered in other studies of these terminally ill patients. Third, there was a nonsignificant (P = .18) trend toward a shorter follow-up time in the IPC group. This probably reflects the common clinical practice that (1) all patients with advanced disease and trapped lung were treated with IPC as pleurodesis was contraindicated, and (2) clinicians following conventional literature would only recommend pleurodesis to patients with a predicted survival of ≥ 3 months. Analysis of total hospital bed days as a proportion of follow-up time remained highly significant, suggesting that the result is likely to be robust, although a randomized study is still needed to definitively confirm this finding.

This study has shown that IPC treatment is safe and significantly avoids additional pleural procedures for fluid management. Patients with MPE (either from metastatic carcinoma or mesothelioma) who chose IPC management spent significantly less time in hospital compared with those who received pleurodesis. Randomized studies are now needed to compare IPC use as definitive first-line therapy to the traditional use of talc pleurodesis for recurrent symptomatic malignant effusions. These should confirm and define the magnitude of the benefits of IPC treatment and identify subgroups in whom the benefits may be most significant.

ACKNOWLEDGMENTS

Author contributions: Dr Lee is guarantor of the study. Dr Fysh: contributed to study conception and design, data collection and patient care, manuscript drafting and revision, and final approval of the manuscript. Dr Waterer: contributed to study conception and design, manuscript drafting and revision, and final approval of the manuscript. Dr Kendall: contributed to study conception and design, manuscript drafting and revision, and final approval of the manuscript. Dr Bremner: contributed to data collection and patient care, manuscript drafting and revision, and final approval of the manuscript. Ms Dina: contributed to data collection and patient care, manuscript drafting and revision, and final approval of the manuscript. Ms McCarney: contributed to data collection and patient care, manuscript drafting and revision, and final approval of the manuscript. Ms Morey: contributed to study conception and design, data collection and patient care, manuscript drafting and revision, and final approval of the manuscript. Mr Millward: contributed to study conception and design, data collection and patient care, manuscript drafting and revision, and final approval of the manuscript. Dr Musk: contributed to study conception and design, data collection and patient care, manuscript drafting and revision, and final approval of the manuscript. Dr Lee: contributed to study conception and design, data collection and patient care, manuscript drafting and revision, and final approval of the manuscript. Financial/nonfinancial disclosures: The authors have reported to CHEST the following conflicts of interest: Dr Lee was a coinvestigator of the British Lung Foundation Therapeutic Intervention of Malignant Effusion-2 trial, for which catheters used were provided by Rocket Medical plc without charge. He received an honorarium from CareFusion Corporation as an advisory board member. Drs Fysh, Waterer, Kendall, Bremner, Geelhoed, and Musk; Ms Dina, McCarney, and Morey; and Mr Millward have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article. Role of sponsors: The sponsors had no role in the design of the study, the collection and analysis of the data, or in the preparation of the manuscript.
REFERENCES


Section 2

Protocol of the Australasian Malignant Pleural Effusion (AMPLE) Trial- A Multicentre, Randomized Study Comparing Indwelling Pleural Catheter with Talc Pleurodesis
Protocol of the Australasian Malignant Pleural Effusion (AMPLE) trial: a multicentre randomised study comparing indwelling pleural catheter versus talc pleurodesis

Edward T H Fysh,1,2,3 Rajesh Thomas,1,2,3 Catherine A Read,3 Ben C H Lam,4,5 Elaine Yap,6 Fiona C Horwood,6 Pyng Lee,7 Francesco Piccolo,8 Ranjan Shrestha,9 Luke A Garske,10 David C L Lam,11 Andrew Rosenstengel,12,13 Michael Bint,14 Kevin Murray,15 Nicola A Smith,16 Y C Gary Lee1,2,3

ABSTRACT

Introduction: Malignant pleural effusion can complicate most cancers. It causes breathlessness and requires hospitalisation for invasive pleural drainages. Malignant effusions often herald advanced cancers and limited prognosis. Minimising time spent in hospital is of high priority to patients and their families. Various treatment strategies exist for the management of malignant effusions, though there is no consensus governing the best choice. Talc pleurodesis is the conventional management but requires hospitalisation (and substantial healthcare resources), can cause significant side effects, and has a suboptimal success rate. Indwelling pleural catheters (IPCs) allow ambulatory fluid drainage without hospitalisation, and are increasingly employed for management of malignant effusions. Previous studies have only investigated the length of hospital care immediately related to IPC insertion. Whether IPC management reduces time spent in hospital in the patients' remaining lifespan is unknown. A strategy of malignant effusion management that reduces hospital admission days will allow patients to spend more time outside hospital, reduce costs and save healthcare resources.

Methods and analysis: The Australasian Malignant Pleural Effusion (AMPLE) trial is a multicentre, randomised trial designed to compare IPC with talc pleurodesis in pragmatic, ‘real life’, clinical environments. Patients with a malignant pleural effusion are a diverse group with a wide range of underlying cancers, demographics, comorbidity and prognosis.

Strengths and limitations of this study

- Multicentre, randomised trial of indwelling pleural catheter versus talc pleurodesis in malignant pleural effusion.
- The study compares the effects of intervention on total days patients spent in hospital, from any causes, until death or end of study follow-up—a meaningful and important end point for patients with advanced cancers, which has not been studied before.
- The study includes centres from Australia, New Zealand, Singapore and Hong Kong.
- Patients with a malignant pleural effusion are a diverse group with a wide range of underlying cancers, demographics, comorbidity and prognosis.

Malignant pleural effusion is common and can complicate most cancers, including one-third of patients with lung and breast carcinomas1, 2 and most (>90%) patients with malignant pleural mesothelioma.3 Malignant pleural effusions cause breathlessness and frequently require hospitalisation for invasive pleural drainage procedures. In Western Australia (population 1.8 million) alone, inpatient care cost for malignant pleural effusions is estimated to exceed US$12 million per year.
Malignant effusions often herald advanced cancers and limited prognosis. The average life expectancy for patients with this condition is 5 (for metastatic carcinomas) to 9 months (for mesothelioma). Minimising days spent in hospital to maximise time spent at home and/or with family is a high priority to patients. The ideal treatment approach should include effective long-term symptom relief (especially dyspnoea), minimal hospitalisation and have the least adverse effects. Conventional management involves inpatient talc pleurodesis, which requires hospitalisation, often of 4–6 days in reported series.

Talc pleurodesis also has a high failure rate, which necessitates further pleural interventions/drainages and hospital care. A randomised trial of 482 patients with malignant pleural effusions showed that talc pleurodesis, irrespective of whether delivered by thoracoscopic poudrage or talc slurry via tube thoracostomy, successfully controlled fluid recurrence in only ~75% of patients at 1 month, and 50% by 6 months. Our recent study of pleurodesis in patients with mesothelioma also showed that 71% had fluid recurrence, and 32% required further pleural interventions.

Talc pleurodesis is known also to have significant side effects. Pain and fever are common, and transient hypoxaemia in the several days following pleurodesis days has been reported. It is now recognised that pleurodesis with non-graded talc (still the only type of talc preparation available in many countries) can result in acute respiratory distress syndrome. In the study of Dresler et al. 5.5% of 419 evaluable patients developed respiratory failure with a mortality rate of 2%.

Indwelling pleural catheters (IPCs) allow ambulatory fluid drainage and are free from side effects, the need for hospitalisation and costs of pleurodesis. IPC is increasingly employed for the management of malignant effusions. To date, two randomised studies have compared IPC with talc pleurodesis and another with doxycycline pleurodesis. Davies et al. randomised 106 patients with malignant effusions and showed that IPC offered equally good symptom relief (dyspnoea and quality-of-life scores were the key end points) compared with talc pleurodesis. Putnam et al. randomised 144 patients and also found similar symptomatic benefits between IPC and doxycycline pleurodesis. Patients undergoing pleurodesis spend longer times in hospital for the initial procedure (median 4 vs 0 days as reported by Davies et al. and 6.5 vs 1.0 days by Putnam et al.).

Whether the use of IPC or pleurodesis impacts on the subsequent need for hospitalisation in the patient’s remaining lifespan has not been defined. Four comparisons of pleurodesis and IPC all found that patients undergoing pleurodesis were more likely to need subsequent pleural drainage procedures with a pooled failure rate of 22.1% (36/163), compared with 8.9% in IPC patients (21/236). On the other hand, IPC requires ongoing care and is known to have a different set of complications (e.g., infection, blockage, symptomatic loculations, catheter track metastases, etc) which could trigger hospital care.

In a pilot, non-randomised patient-choice study, we found in 65 patients with malignant effusions that those who elected to have IPC management spent fewer days in hospital in their remaining lifespan in pleural-related as well as all-cause hospital stay compared with those treated with talc pleurodesis. The pleurodesis group spent 11.2% of their remaining life in hospital as opposed to 8.0% for the group with IPC (p<0.001). The AMPLE (Australasian Malignant Pleural Effusion) trial is designed to further evaluate the findings in a multicentred and randomised setting.

**METHODS AND ANALYSIS**

The AMPLE trial is a multicentred, prospective, randomised trial designed to compare IPC with talc pleurodesis for the management of malignant pleural effusion. The trial is registered on the Australian New Zealand Clinical Trial Registry (ACTRN12611000567921). The study is also registered on the West Australian Health Research Management System (ID: 2019). The trial will be conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP) and the National Statement.

The primary end point is the total number of days spent in hospital (for any cause of admission) from treatment procedure to death or end of study follow-up. The secondary research end points include:

- Admissions (days and number of episodes) for pleural effusion-associated causes. This includes admissions for management of pleural effusion, associated symptoms, related procedures and/or their complications.
- Survival and adverse events from enrolment to death or end of follow-up.
- Breathlessness score and self-reported quality-of-life scores recorded at regular intervals from enrolment to death or end of follow-up.
- Health cost assessment.
- Need for further pleural interventions.

**Setting**

The study will recruit 146 patients with a malignant pleural effusion (see below for the inclusion criteria) requiring effusion management from the participating centres (see online supplementary appendix 1). Patients will be randomised to receive either IPC or pleurodesis (figure 1).

**Power calculation**

In our pilot non-randomised study, those who chose to have IPC (n=34) for management of their malignant effusion spent a median of 6.5 days (IQR 3.75–13.0) in hospital compared with 18.0 days (IQR 8.0–26.0; p=0.002) in the talc group (n=31). The primary response data are likely to be highly skewed, and hence...
a non-parametric test would be more appropriate. To examine the potential benefit of reduction in hospital stay using IPC, we estimate 65 patients in each group are needed. The study will be able (with 80% power and $\alpha=0.05$) to detect a difference of 5 or more days spent in hospital, based on preliminary estimates of 18 days in the pleurodesis group (from the pilot study) and a SD of 9.3. Allowing for a lost-to-follow-up rate of 12%, 73 patients per group will be needed, to make a total recruitment target of 146. This is a conservative estimate as no patient was lost to follow-up in the pilot study.

**Statistical plan—missing data**

In common with many clinical studies, missing data may exist either in the form of total non-response (eg, attrition due to death or patient withdrawal) or item non-response (when some but not all the required information is collected from the patients). We will attempt to minimise the missing data due to item non-response. Throughout the duration of the trial, participants will have regular contact with the respiratory department, as well as with the research team. The patient will be asked to complete the forms while at clinic. This will maximise proper and complete data collection. The research team will document as accurately as possible the reasons for any non-completion or missing data, thereby minimising truly absent data. The expected dropout from patient death has been factored into the power calculation and is based on survival figures. The detail of the statistical analysis will be set out in the Statistical Analysis Plan.

**Participant screening and selection**

Potential participants will be recruited from the respiratory and/or oncology clinics of the participating centres. Patients with a known or likely malignant pleural effusion that requires management to control symptoms will be identified by the clinicians. The potential patient will be approached about the possibility of taking part in the study if they are at the point of requiring intervention for the management of their malignant pleural effusion.
They will be given an explanation of the study by the doctor and then given the participant information and consent form (PICF) to read through and ask questions of the doctor. An informed consent will be obtained before study enrolment. As both treatment options are well established and approved therapies, one or the other would be employed irrespective of whether the patient decided to be enrolled in the study.

Individual centres will maintain a screening log of patients including those who did not enter the study.

Inclusion criteria
1. Patients must have a symptomatic malignant pleural effusion requiring intervention. The diagnosis may be established by:
   A. Histocytologically proven pleural malignancy or
   B. Recurrent large exudative pleural effusion with histologically proven cancer outside the thorax and no alternative cause
2. Written informed consent

Exclusion criteria
1. Age under 18 years
2. Effusion smaller than 2 cm at maximum depth
3. Expected survival less than 3 months
4. Chylothorax
5. Previous lobectomy or pneumonectomy on the side of the effusion
6. Previous attempted pleurodesis
7. Pleural infection
8. Total blood white cell count less than 1.0×10⁹/L
9. Hypercapnic ventilatory failure
10. Patients who are pregnant or lactating
11. Irreversible bleeding diathesis
12. Irreversible visual impairment
13. Inability to give informed consent or comply with the protocol

Informed consent
A doctor will confirm patient eligibility prior to consent being taken. Patients will be given the opportunity to consider the PICF and time to ask questions prior to written, informed consent being taken by the study doctor.

Randomisation
Patients will be randomly assigned (1:1) to either an indwelling ambulatory pleural catheter or talc pleurodesis for their malignant pleural effusion. Randomisation will include minimisation for:
1. Australasian centres versus centres outside Australasia (Singapore and Hong Kong). This is because of potential differences in patient ethnicity and distribution of cancer types;
2. Mesothelioma versus non-mesothelioma. This is because median survival is significantly longer in mesothelioma compared with metastatic pleural cancers. Also, the risk of catheter-associated subcutaneous tumour invasion may be higher with mesothelioma;
3. The presence versus absence of known trapped lung. The presence of a trapped lung is likely to reduce the likelihood of a successful pleurodesis.

To maintain allocation concealment, randomisation is performed in real time by a web interface (Filemaker Server Advanced, Filemaker Inc, Santa Clara, California, USA). Initially, a minimisation programme was used so that patients within Australia and New Zealand (Australasia) were allocated with a probability of 0.5–0.7 favouring the treatment that would minimise differences between groups on two key prognostic factors (mesothelioma and trapped lung). When Singapore was added as a site in early 2014, stratification by region (Australasia vs Singapore/Hong Kong) was added to account for any potential differences in baseline characteristics between patient and disease cohorts. The probability favouring the treatment that would minimise bias was increased to 0.8 accordingly to compensate for this added variable.

Standard care
All patients will receive usual standard care, for example, chemotherapy and radiotherapy, as recommended by their attending clinicians. Patients requiring assistance from other services, for example, the surgeons, palliative care team or hospice will be referred when needed by the clinical team. Co-enrolment in other clinical trials will be discussed on an individual basis, but will be considered provided compliance with both protocols is possible.

Interventions
Talc slurry pleurodesis
Bedside talc pleurodesis is a commonly used treatment worldwide. Talc is delivered as a suspension in saline via a chest tube, which is clamped for a short time (usually 1–4 h). There are variations among most centres worldwide in the precise details as there is no evidence-based guideline to define the best administration protocols.

As a pragmatic real-life study, the AMPLE trial allows each centre to perform the talc pleurodesis as per their usual practice, including the choice of the size of chest drain used, timing of talc instillation and chest drain removal.

Indwelling pleural catheter
IPC has been approved by the Food and Drug Administration (USA) since the initial safety trials in the late 1990s. The catheter remains in situ as long as it is needed, but can be removed if fluid production stops, or if otherwise clinically indicated. All patients are given an information sheet with detailed instructions and contact details for support. Patients with IPCs have the support and care of the experienced community respiratory nurse and the attending clinical team, as per standard care. The attending clinician will decide on the details of aftercare most suitable for individual patients, including
drainage frequencies, personnel performing the drainage, etc, as well as management of any complications.

**Data collection and management**

Clinical data will be collected at the randomisation visit. Patients will be asked to complete two quality-of-life questionnaires (modified EQ-5D and visual analogue scale (VAS) scores) at the baseline. Following the study intervention, patients will be asked to complete a daily VAS score for their breathlessness and one for quality-of-life every day for the following 14 days. A modified EQ-5D will also be completed by the patient on day 8 after the intervention. Follow-up visits will be undertaken at 10–14 days, and then every 2 weeks for 8 weeks, monthly for 6 months and every 3–12 months thereafter, provided it is feasible. Data will be collected on hospital admissions, details of any chemotherapy received and any adverse events. A clinical review will be conducted by the clinician in-charge. When patients are not, or cannot be, seen in clinic, they will receive a phone call from a study doctor or research nurse to enquire about symptoms at the intervention site. They will also complete the above questionnaires.

**Primary outcome**

The number of days spent in hospital (bed days) for any cause for all hospital admissions following intervention, until death or the end of the study follow-up. The primary end point is chosen as it is the most meaningful outcome for patients with cancer and their clinicians. Hospital admissions will be further categorised and the days of admissions directly attributable to the pleural effusion and/or its treatment will be recorded as ‘effusion-related’ (a secondary end point).

Given the impossibility of blinding, hospital admissions will be decided by the independent treating physicians, not by the investigators, wherever possible. The reason(s) for admission must be documented and satisfy at least one of the following criteria:

- A procedure is required that cannot be performed in the outpatient setting because of the need for >2 h of close nursing or medical attention.
- A coexisting or new medical problem requires inpatient therapy.
- Cancer or effusion-related symptoms cannot be adequately controlled at home with community nursing, general practitioner and outpatient clinic support.

The number of days spent in hospital is defined as the number of nights the patient is an inpatient at midnight. Any hospital admission involving one or more days will be counted towards the primary outcome. Therefore day-case procedures including chemotherapy administration will not be included.

An independent assessor, not related to the clinical trial, will assess the validity of the hospital admissions for its justification and duration. Time-to-event analysis will be used to assess length of hospital stay (measured as time from the study intervention until discharge) using a competing risk model, where death is the competing risk.

**Secondary outcomes**

- Admissions (days and number of episodes) for pleural effusion-associated causes. This includes admissions for management of pleural effusion, associated symptoms, related procedures and/or their complications.
- Survival and adverse events from enrolment to death or end of follow-up.
- Breathlessness (visual analogue) and self-reported quality-of-life scores at regular intervals from enrolment to death or end of follow-up.
- Health cost assessment: direct clinical costs from local department coding data and other estimated community-based costs will be captured from patient data.

**Figure 2** Statistical analysis plan (IPC, indwelling pleural catheter).
Statistical analysis plan
All outcomes will be analysed for superiority. Superiority analyses will be two-sided and considered statistically significant at the 5% level (figure 2). Unless otherwise stated, all analyses will be adjusted for the minimisation variables described above. Mean imputation will be used during analyses to adjust for missing values of baseline variables.

All analyses will be conducted on an intention-to-treat and also per-protocol basis. The primary end point, that is, total bed days for all hospital admissions will be analysed initially using a Mann-Whitney non-parametric test to compare the two treatment arms. Subsequent support analyses will be carried out using a negative binomial model with adjustments made for actual length of follow-up (accounting for death and withdrawals) and important covariates. The total effusion-related bed days for hospital admissions will be analysed similarly to the primary outcome variable. Cox proportional hazards models will be used to analyse time to death, serious adverse events and further pleural intervention. Summaries and frequencies of serious adverse events will be compared between the intervention groups using Fisher’s exact tests. VAS scores will be analysed using linear mixed effects models, including fixed effects of time and time dependent covariates as appropriate and random effects of individual.

Changes to the protocol after the start of the trial
The trial details documented here are consistent with AMPLE trial protocol V.4 (date: 05/05/2014). A summary of the trial amendments can be found in online supplementary appendix 2.

ETHICS AND DISSEMINATION
The trial has been favourably reviewed by the following committees:
- Sir Charles Gairdner Group Human Research Ethics Committee (HREC) for WA Health hospitals (SCGG 2012-005);
- St John of God Health Care Ethics Committee for Bunbury Hospital, WA (Ref: 670);
- St Vincent’s Health and Aged Care HREC for Holy Spirit, Northside Hospital, Queensland (HREC #13/01);
- South Eastern Sydney Local Health District HREC for eastern state hospitals (HREC/13/POWH/110);
- Health and Disability Ethics Committee for New Zealand hospitals (CEN/11/06/031/AM04);
- National Healthcare Group Domain Specific Review Board Approval for National University Hospital, Singapore (2013/00826);
- Institutional Review Board of the University Hong Kong/Hospital Authority Hong Kong West Cluster for Queen Mary Hospital, Hong Kong (UW14-191).

Should a protocol amendment become necessary, the patient consent form and patient information form may need to be revised to reflect the changes to the protocol. It is the responsibility of the investigator to ensure that an amended consent form is reviewed and has received approval/favourable opinion from the ethics committee and other regulatory authorities, as required by ICH GCP and by local laws and regulations, and that it is signed by all patients subsequently entered in the study and those currently in the study, if affected by the amendment (see online supplementary appendix 2).

Monitoring
Data monitoring will be completed by study staff from the lead site. No interim analysis is planned.

Safety reporting
Data will be collected at each trial visit regarding any adverse events and serious adverse events (as defined by ICH GCP). All serious adverse events causally related to treatment procedures will be reported to the relevant HREC, the lead site and the Data and Safety Monitoring Committee (DSMC).

Data safety
Prior to patient participation in the study, written informed consent must be obtained from each patient (or the patient’s legally accepted representative) according to ICH GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient information form retained by the investigator as part of the study records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient’s legally accepted representative.

The patient must be informed that his/her personal study-related data will be used by the principal investigator in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by authorised monitors or clinical auditors appointed by appropriate ethics committee members, and by inspectors from regulatory authorities.

Trial monitoring and oversight
The Trial Steering Committee (TSC) will be responsible for overseeing the progress of the trial and will meet at regular intervals. The TSC includes an independent chairperson, independent member, the chief investigator and the trial coordinators. It will review recommendations from the DSMC through their monitoring of adverse events and therefore determine whether or not there is a need for early trial cessation. The committee has a Standard Operating Procedure that defines the terms and conditions of the group. This is to be sent out to all named committee members.

The DSMC will ensure the safety of study participants through the monitoring of the trial procedure, adverse
events, serious adverse events and impact on the trial from any relevant new literature. The committee has a Standard Operating Procedure which defines the terms and conditions of the group. This is to be sent out to all named committee members.

Author affiliations
1Department of Respiratory Medicine, Sir Charles Gairdner Hospital, Perth, Western Australia, Australia
2School of Medicine & Pharmacology, University of Western Australia, Perth, Western Australia, Australia
3Lung Institute of Western Australia, Perth, Western Australia, Australia
4Department of Respiratory and Sleep Medicine, The Sutherland Hospital, Sydney, New South Wales, Australia
5Department of Respiratory Medicine, St George Hospital, Sydney, Australia
6Department of Respiratory Medicine, Middlemore Hospital, Auckland, New Zealand
7Division of Respiratory & Critical Care Medicine, Department of Medicine, Yong Loo Lin Medical School, National University Hospital, National University of Singapore, Singapore
8Department of Internal Medicine, Swan District Hospital, Perth, Australia
9Department of Respiratory Medicine, Fremantle Hospital, Fremantle, Australia
10Department of Respiratory and Sleep Medicine, Princess Alexandria Hospital, Brisbane, Queensland, Australia
11Department of Medicine, University of Hong Kong. Kong SAR, China
12School of Medicine, University of Queensland, Brisbane, Queensland, Australia
13Holy Spirit Northside Hospital, Brisbane, Queensland, Australia
14Department of Respiratory Medicine, Nambour General Hospital, Sunshine Coast, Queensland, Australia
15Centre for Applied Statistics, University of Western Australia, Perth, Western Australia, Australia
16Medical Research Institute of New Zealand, Wellington Hospital, Wellington, New Zealand

Contributors YCGL and ETHF conceived the initial trial concept and conducted the pilot study. CAR is the trial manager and oversees the data collection and running of the trial. RT is the trial coordinator. ETHF, RT, CAR, NAS, EY, FCH, PL, BCHL, FP, RS, LAG, DCLL, AR, MB and YCGL developed the trial design and protocol. RT, YCGL and KM wrote the statistical analysis plan. YCGL is the chief investigator and takes overall responsibility for all aspects of trial design, the protocol and trial conduct. All authors read and approved the final manuscript.

Funding This project has received funding support from the Cancer Council of Western Australia and the Dust Disease Board of New South Wales. YCGL has also received other research grant support from the Sir Charles Gairdner Research Advisory Council, National Health and Medical Research Council (NH&MRC), Lung Institute of Western Australia (LIWA) and Westcare. ETHF and RT received research scholarship support from NH&MRC; and RT from Western Australia Cancer and Palliative Care Network (WACPCN) and LIWA, Australia. NS has received funding support from the Health Research Council of New Zealand. PL has received funding through a Health Services Research grant from the Ministry of Health, Singapore.

Competing interests YCGL was a co-investigator of the TIME-2 trial for which Rocket Ltd provided the indwelling catheters and supplies without charge. YCGL is an advisory board member for CareFusion and Sequana Medical Ltd. PL has received an honorarium/travel subsidy to attend Carefusion board meetings.

Ethics approval Sir Charles Gairdner Group Human Research Ethics Committee (lead site).

Provenance and peer review Not commissioned; externally peer reviewed.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

REFERENCES
Correction

Fysh ETH, Thomas R, Read CA, et al. Protocol of the Australasian Malignant Pleural Effusion (AMPLE) trial: a multicentre randomised study comparing indwelling pleural catheter versus talc pleurodesis. *BMJ Open* 2014;4:e006757. The name of the fourth author of this paper was published incorrectly; Ben C H Lam should be Ben C H Kwan.

*BMJ Open* 2015;0:e006757corr1. doi:10.1136/bmjopen-2014-006757corr1
Section 3

Pleurodesis Failure Rates in
Malignant Pleural Mesothelioma
Pleurodesis outcome in malignant pleural mesothelioma

Edward Thomas Hamilton Fysh,¹,² Sze Khei Tan,¹,³ Catherine Ann Read,¹
Felicity Lee,¹ Kate McKenzie,¹ Nola Olsen,⁴ Indunil Weerasena,¹ Timothy Threlfall,⁵
Nicholas de Klerk,⁴ A William Musk,¹,⁴ Y C Gary Lee¹,²

ABSTRACT
Few data exist on the pleurodesis outcome in patients with malignant pleural mesothelioma (MPM). A retrospective review of the Western Australian Mesothelioma Registry over 5 years revealed 390 evaluable patients. Only a subset of patients (42.3%) underwent pleurodesis, surgically (n=78) or by bedside instillation of sclerosants (n=87). Surgical pleurodesis showed no advantages over bedside pleurodesis in efficacy (32% vs 31% failures requiring further drainage, p=0.98), patient survival (p=0.52) or total time spent in hospital from procedure till death (p=0.36). No clinical, biochemical or radiographic parameters tested adequately predict pleurodesis outcome.

INTRODUCTION
Malignant pleural mesothelioma (MPM) kills one patient every 4 h in the UK. Pleural effusion affects 85.4%, p<0.001 and 61% vs 74%, p=0.012).

Current clinical practices for MPM effusions are derived from ‘generic’ studies of malignant pleural effusions based predominantly on patients with metastatic (lung, breast, gynaecological and gastrointestinal) carcinomas. Pleurodesis is the conventional recommended treatment. MPMs differ from metastatic effusions based predominantly on patients with malignant pleural mesothelioma (MPM). A retrospective review of the Western Australian Mesothelioma Registry over 5 years revealed 390 evaluable patients. Only a subset of patients (42.3%) underwent pleurodesis, surgically (n=78) or by bedside instillation of sclerosants (n=87). Surgical pleurodesis showed no advantages over bedside pleurodesis in efficacy (32% vs 31% failures requiring further drainage, p=0.98), patient survival (p=0.52) or total time spent in hospital from procedure till death (p=0.36). No clinical, biochemical or radiographic parameters tested adequately predict pleurodesis outcome.

Studies on pleurodesis in MPM have been retrospective, underpowered and employed differing pleurodesis methods and definitions of success. Reports of surgical pleurodesis for MPM were small (n=4–12) and with limited follow-up (≤30 days). Two audits of pleuroscopic talc pleurodesis for malignant effusions included subgroups of 88 and 66 patients with MPM, and both showed a lower pleurodesis success rate for MPM compared with other metastatic effusions (74.1% vs 85.4%, p<0.001 and 61% vs 74%, p=0.012).

We present the largest study on the outcome of MPM effusions to determine (1) the percentage and characteristics of patients with MPM who required pleurodesis for effusion control; (2) the success rate of surgical and bedside pleurodesis; and (3) the need for further interventions in patients who failed pleurodesis.

METHODS
The Western Australia Mesothelioma Registry, which includes all patients with mesothelioma in Western Australia (population ~2.0 million), was interrogated over a 5-year period from 1 August 2004. The medical records of patients who attended the major teaching hospitals in Western Australia were reviewed. The primary outcome was success or failure of pleurodesis. Pleurodeses were defined as a complete success (no further fluid accumulation detected), a partial success (fluid returned but no further intervention required) or a failure (further fluid drainage needed) following the American Thoracic Society/European Respiratory Society consensus. Survival was calculated from the date of diagnosis until death or the end of the study (1 May 2012). Analyses were performed on SigmaPlot v.12. P Values <0.05 were considered significant.

RESULTS
Of the 494 cases of mesothelioma recorded, 478 patients had proven MPM. Of these, 390 (86%) were men, mean (SD) age 70 (10.4) years had accessible medical records from a teaching hospital (see online supplement) and were analysed. Patients with epithelioid MPM had better survival (406 days, IQR 201–778) than those with biphasic (285 days, IQR 151–492) or sarcomatoid disease (149 days, IQR 73–293) (p<0.05).

Incidence of pleurodesis
Pleurodesis was attempted in 165 patients (42.3%), either by surgery (n=78) or bedside instillation of talc (n=86) or bleomycin (n=1). Surgical pleurodesis was performed during video-assisted thoracoscopic surgery (VATS) (n=64), pleuroscopy (n=3) or thoracotomy (n=11); all surgical pleurodesis procedures included talc poudrage and, in addition, 12 had pleurectomy. No differences in age, gender or mesothelioma histological subtypes were found between the groups in whom pleurodesis was and was not performed (see online supplement).

Median survival was significantly longer in the group that underwent pleurodesis: 443 (IQR 197–746) vs 318 (128–574) days (p=0.002). Thirty-three patients (23 in the pleurodesis group) were alive at the end of follow-up. Patients who underwent pleurodesis spent more time in hospital than those in the non-pleurodesis group (median 20 days [IQR 12–31] vs 14 days [IQR 5–25], p<0.001; 5.1% [IQR 2.1–11.1%] vs 4.4% [IQR 1.3–10.0%] of individual patients’ remaining life-span, respectively, p=0.15).
**Pleurodesis outcome**

Complete success was achieved in 29.7% and partial success in 38.8% of patients treated with pleurodesis. Pleurodesis failed in 31.5% of patients, necessitating further drainages (table 1).

Patients undergoing surgical pleurodesis were significantly younger than those treated with bedside pleurodesis: mean (SD) age 67.1 (10.4) years vs 72.3 (10.5) years (p<0.01). The surgical group underwent pleurodesis earlier, often at the same time as diagnostic surgery (median 0.0 days (IQR 0.0–29.5) after diagnosis vs 54.0 days (IQR 18.0–110.0) in the bedside pleurodesis group, p<0.01).

Success rates did not differ between surgical and bedside pleurodesis (table 1). No differences were found in the survival and episodes or days of hospitalisation between the surgical and bedside pleurodesis groups (table 1). The size of the effusion on x-rays, pleural fluid biochemistry (protein, lactate dehydrogenase, pH and glucose levels) and mesothelioma histological subtypes did not predict the outcome of pleurodesis.

The total days of hospitalisation (from any cause) was shortest in the complete success group, followed by the partial success and the failure groups (median 16, 19 and 25 days, respectively, p=0.07). Patients in whom pleurodesis failed and who required further pleural interventions spent more days in hospital than those who had complete or partial success (median 25.0 vs 18.0 days, p=0.03; 6.1% vs 4.8% of individual patients’ remaining lifespan, respectively, p=0.08).

The median survival times from diagnosis to death were 323, 461 and 409 days in the complete success, partial success and failure groups, respectively (p=0.11). The median survival times from the time of pleurodesis among the three groups were 275, 428 and 230 days, respectively (p=0.19).

Four patients died within 14 days of attempted pleurodesis (range 5–13), none related to the procedure. Empyema complicated pleurodesis in five (3.0%) patients (four surgical and one bedside) and one patient developed a chest wall abscess.

Ninety-two further pleural procedures (including 38 thoracotomies, 26 thoracenteses and 21 surgical interventions) were performed on the 52 patients in whom pleurodesis failed (median 1.0 procedure per patient (IQR 1.0–2.0); see online supplement). The median time from pleurodesis to failure (needing further drainage) was 30 days in the surgical pleurodesis group and 71 days in the bedside pleurodesis group (p=0.34).

**DISCUSSION**

In this largest study of pleurodesis outcomes in patients with MPM, 42% of patients underwent pleurodesis. Pleurodesis success rates were suboptimal: <30% of patients achieved complete lifelong control of their effusion and 32% required further pleural drainages. Surgical pleurodesis provided no advantages over bedside pleurodesis in success rate, survival or duration of hospitalisation. None of the clinical, biochemical or radiological parameters studied adequately predicted pleurodesis failure. These results provide, for the first time, MPM-specific data to inform clinicians/patients on the efficacy of pleurodesis and may influence clinical care.

MPM remains incurable and symptom palliation for breathlessness is paramount. Conventional teaching suggests that malignant effusions should be drained and pleurodesis considered in symptomatic patients. However, MPM differs from metastatic pleural carcinomas in their pathobiology, which may explain the lower success rate of pleurodesis. First, pleurodesis failure increases progressively the longer the patient survives. In the Cancer and Leukemia Group B study of malignant effusions (n=454), adequate fluid control was achieved in approximately 75% of patients at 1 month but in only 50% at 6 months. Since the median survival for MPM is significantly longer than metastatic pleural carcinomas (12 vs 3 months), pleurodesis is less likely to provide lifelong fluid control in MPM. Second, MPMs usually involve large areas of the pleural surfaces. Blockade of the parietal stomata and lymphatic drainage system can contribute to rapid fluid accumulation, thus hindering pleurodesis. Visceral pleural disease often causes trapped lung, impairing pleurodesis. Third, some researchers believe that pleurodesis is less successful in the presence of a larger pleural tumour load, as is often found in MPM.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics of patients and outcomes of pleurodesis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pleurodesis outcome</strong></td>
<td>Overall (n=165)</td>
</tr>
<tr>
<td>Complete success</td>
<td>29.7%</td>
</tr>
<tr>
<td>Partial success</td>
<td>38.8%</td>
</tr>
<tr>
<td>Failure</td>
<td>31.5%</td>
</tr>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) age</td>
<td>69.9 (10.5)</td>
</tr>
<tr>
<td>Male</td>
<td>86.7%</td>
</tr>
<tr>
<td>Survival in days (diagnosis to death)</td>
<td>443 (197–743)</td>
</tr>
<tr>
<td>Days from diagnosis to pleurodesis</td>
<td>17 (0.0–63.0)</td>
</tr>
<tr>
<td><strong>Subtype</strong></td>
<td></td>
</tr>
<tr>
<td>Epithelioid</td>
<td>86</td>
</tr>
<tr>
<td>Sarcomatoid</td>
<td>9</td>
</tr>
<tr>
<td>Biphasic</td>
<td>30</td>
</tr>
<tr>
<td>Unclassified*</td>
<td>40</td>
</tr>
<tr>
<td>Hospital admissions (episodes)</td>
<td>6.0 (2.0–9.0)</td>
</tr>
<tr>
<td>Hospital admissions (total days from diagnosis)</td>
<td>20.0 (12.0–31.0)</td>
</tr>
<tr>
<td>Hospital admissions (total days expressed as % of remaining lifespan spent)</td>
<td>5.1% (2.1–10.9%)</td>
</tr>
</tbody>
</table>

*Patients with no histological subtypes defined (usually diagnosed by pleural fluid cytology).
Only 42% of patients with MPM underwent pleurodesis. Whether pleurodesis is underused, unnecessary or contraindicated in the remainder of patients deserves future investigation.

Surgical pleurodesis showed no advantage over bedside talc pleurodesis. This result is consistent with four randomised trials that have found no benefit of VATS talc poudrage over bedside pleurodesis using talc slurry or iodopovidone. Many believe that pleurodesis is more likely to be successful if performed early. In our study, surgical pleurodesis was often performed as early as the same time of the diagnostic thoracoscopy and in younger patients. Despite these biases, surgical pleurodesis showed no superiority over bedside pleurodesis.

This study was retrospective so clinical management and surgical approaches were not standardised. However, the use of a comprehensive statewide database over a significant period offered an unbiased view of current practice. Although not randomised, the comparison groups (eg, surgical vs bedside pleurodesis) were remarkably similar in their baseline demographics. As the largest study on MPM effusions, the results provide a platform to guide future prospective studies.

One recent study in which patients with MPM accounted for 47% of the cohort confirmed that indwelling pleural catheters (IPC) are comparable to pleurodesis in improving dyspnoea and quality of life, and patients managed with IPC spent significantly fewer days in hospital. The role of IPC in the management of MPM effusions needs exploration.

**Contributors**

Guarantor: YCGL. Conception and design: ETHF, YCGL, AWM, SKT and TT. Data collection: ETHF, SKT, TT, CAR, NO, FL, KM and IW. Statistical support: NdeK. Manuscript drafting and revision and final approval: all authors.

**Funding**

YCGL and ETHF have received research grant support from the Sir Charles Gairdner Research Foundation, Cancer Council of Western Australia, Westcare (Western Australia) and the Dust Disease Board of New South Wales. YCGL is a recipient of a National Health and Medical Research Council (NH&MRC) Career Development Fellowship. AWM is a recipient of a NH&MRC Practitioner Fellowship.

**Competing interests**

YCGL was a co-investigator of the British Lung Foundation Therapeutic Intervention of Malignant Effusion-2 trial for which indwelling pleural catheters were provided by Rocket Medical Ltd without charge. He has received an honorarium from CareFusion Ltd as an advisory board member.

**Ethics approval**

Ethical approval was obtained from the Western Australia Department of Health.

**Provenance and peer review**

Not commissioned; internally peer reviewed.

**REFERENCES**

## DATA FOR ONLINE SUPPLEMENT

### Online Table A: Characteristics of patient groups:

<table>
<thead>
<tr>
<th></th>
<th>Overall (n=390)</th>
<th>Pleurodesed (n=165)</th>
<th>Non-Pleurodesed (n=225)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age: mean (SD)</strong></td>
<td>70.0 (10.4)</td>
<td>69.9 (10.8)</td>
<td>70.8 (10.1)</td>
<td>p=0.77</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>85.9%</td>
<td>86.7%</td>
<td>85.3%</td>
<td>p=0.97</td>
</tr>
<tr>
<td><strong>Subtype:</strong></td>
<td></td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Epithelioid</td>
<td>195</td>
<td>87</td>
<td>108</td>
<td></td>
</tr>
<tr>
<td>Sarcomatoid</td>
<td>39</td>
<td>9</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Biphasic</td>
<td>68</td>
<td>30</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Unclassified</td>
<td>88</td>
<td>39</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td><strong>Survival</strong></td>
<td></td>
<td></td>
<td></td>
<td>p=0.002</td>
</tr>
<tr>
<td>(days from diagnosis)</td>
<td>351 (166 - 643)</td>
<td>443 (197 - 746)</td>
<td>318 (128 to 574)</td>
<td></td>
</tr>
<tr>
<td><strong>No. of hospital admissions</strong></td>
<td>5.0 (2.0 - 9.0)</td>
<td>5.0 (2.0 - 9.0)</td>
<td>4.0 (1.0 - 9.0)</td>
<td>p=0.08</td>
</tr>
<tr>
<td><strong>Total inpatient days in hospital from diagnosis</strong></td>
<td>17.0 (8.0 - 28.3)</td>
<td>20.0 (12.0 - 31.3)</td>
<td>14.0 (5.0 - 25.0)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td><strong>% of remaining lifespan spent as hospital inpatient</strong></td>
<td>4.9% (1.6 - 10.3)</td>
<td>5.1% (2.1 - 11.1)</td>
<td>4.4% (1.3 - 10.0)</td>
<td>p=0.15</td>
</tr>
</tbody>
</table>
Online Table B: Comparison of patients by pleurodesis outcome:

<table>
<thead>
<tr>
<th></th>
<th>Successful Pleurodeses (n=49)</th>
<th>Partial Success (n=64)</th>
<th>Failed Pleurodeses (n=52)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age: mean (SD)</strong></td>
<td>73.1 (9.7)</td>
<td>68.7 (11.3)</td>
<td>68.2 (10.6)</td>
<td>p=0.04</td>
</tr>
<tr>
<td><strong>Time in Days</strong> (from diagnosis to pleurodesis)</td>
<td>16.0 (0.0 to 49.5)</td>
<td>30.5 (0.0 - 83.5)</td>
<td>5.5 (0.0 - 61.0)</td>
<td>p=0.19</td>
</tr>
<tr>
<td><strong>Survival after Pleurodesis (days)</strong></td>
<td>275 (138 - 746)</td>
<td>428 (239 - 838)</td>
<td>300 (153 - 681)</td>
<td>p=0.21</td>
</tr>
<tr>
<td><strong>Survival in Days</strong> (from diagnosis to death)</td>
<td>323.0 (142.5 to 742.5)</td>
<td>460.5 (314.3 to 946.5)</td>
<td>409.0 (197.5 to 719.0)</td>
<td>p=0.11</td>
</tr>
<tr>
<td><strong>No. of hospital admissions</strong></td>
<td>4.0 (1.0 to 6.8)</td>
<td>7.0 (2.0 to 9.0)</td>
<td>7.0 (3.0 to 10.0)</td>
<td>p=0.02</td>
</tr>
<tr>
<td><strong>Total days in hospital from diagnosis</strong></td>
<td>16.0 (10.0 - 28.0)</td>
<td>19.0 (11.5 - 32.8)</td>
<td>25.0 (16.3 - 31.8)</td>
<td>p=0.07</td>
</tr>
<tr>
<td><strong>% of survival time</strong> (from diagnosis to death) spent in hospital</td>
<td>5.1% (1.8 to 13.0)</td>
<td>4.4% (1.8 to 8.2)</td>
<td>6.1% (3.0 to 13.5)</td>
<td>p=0.09</td>
</tr>
<tr>
<td><strong>Effusion Size</strong> (% hemithorax)</td>
<td>50% (25 – 75%) (n=43)</td>
<td>50% (25 – 75%) (n=57)</td>
<td>50% (25 – 75%) (n=49)</td>
<td>p=0.67</td>
</tr>
<tr>
<td><strong>pleural fluid pH</strong></td>
<td>7.37 (7.30 - 7.54) (n=14)</td>
<td>7.37 (7.25 - 7.60) (n=19)</td>
<td>7.30 (7.21 - 7.37) (n=21)</td>
<td>p=0.09</td>
</tr>
<tr>
<td><strong>pleural fluid glucose (mmol/L)</strong></td>
<td>4.3 (2.5 - 5.3) (n=26)</td>
<td>5.1 (3.7 - 5.9) (n=16)</td>
<td>3.9 (3.3 - 5.4) (n=26)</td>
<td>p=0.27</td>
</tr>
<tr>
<td><strong>pleural fluid Lactate dehydrogenase (LDH) (IU/L)</strong></td>
<td>428 (342 - 669) (n=17)</td>
<td>361 (235 to 655) (n=18)</td>
<td>505 (233 to 961) (n=34)</td>
<td>p=0.48</td>
</tr>
<tr>
<td><strong>pleural fluid Protein (g/L) Mean (SD)</strong></td>
<td>44.9 (8.3) (n=28)</td>
<td>46.2 (8.7) (n=34)</td>
<td>44.8 (10.7) (n=36)</td>
<td>p=0.80</td>
</tr>
<tr>
<td><strong>Histological Subtype</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epithelioid</td>
<td>25</td>
<td>37</td>
<td>25</td>
<td>p=0.70</td>
</tr>
<tr>
<td>Sarcomatoid</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Biphasic</td>
<td>7</td>
<td>11</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Unclassified</td>
<td>15</td>
<td>13</td>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>
**Online Fig A:** Chart showing the number of procedures undergone by patients whose pleurodesis failed

**No. of Procedures in Patients who Failed Pleurodesis**

![Bar chart showing the number of procedures undergone by patients whose pleurodesis failed](chart1.png)

**Fig B:** Type and number of pleural procedures undertaken in patients with failed pleurodesis

**Type and no. of Procedures**

![Bar chart showing the type and number of procedures](chart2.png)
Part II

Further Examination of Complications of IPC
Foreword

Part II addresses three important complications of treatment with IPC for malignant pleural effusion. The first section focuses on the rate, treatments for and outcomes of IPC-related pleural infection in 11 centres from around the world (published article no.4). The hypothesis of this study was that infection rates with IPC are low enough not to preclude their use in patients with MPE and that when infection does occur it can usually be successfully managed. Pleural infection complicating IPC use remains a feared complication and this concern still prevents referral of appropriate patients for this effective treatment(104).

One of the major concerns about indwelling pleural catheters during their introduction was the potential for catheter track metastasis (CTM), however we observed that this was relatively uncommon. The second section in Part II (published article number 5) aimed to document our experience with this complication and its outcome in our patients (105).

The third section aimed to report the incidence and outcomes of fracture of IPCs (published original articles no. 6 and 7) (106). This is a rare complication but we showed that when it does occur aggressive treatment is unnecessary and outcomes were reassuring for clinicians. In the response letter to Dr Grosu (included) we clarified that while 9.8% of removal procedures reported in the series of complicated removals resulted in fracture, of the total population treated with an IPC, only 2.4% actually fractured.
Section 1

Indwelling Pleural Catheter Related Infection
Tunnelled indwelling pleural catheters (IPCs) are increasingly used worldwide for management of malignant pleural effusions (MPEs). A rapidly growing body of literature confirms that IPC is an effective alternative to pleurodesis in improving symptoms and quality of life and that it can reduce the need for additional pleural procedures and length of hospital stay.1-4

Although observational series5-7 and literature reviews8,9 have shown that serious adverse events are uncommon with the use of IPCs, few published reports exist on the clinical course or outcome of IPC-related complications.10,11 Fear of infection associated with a long-term indwelling device is a significant concern to clinicians and patients.12 Pleural infection, even in the general population, is a serious illness with significant mortality (as high as 20%) and morbidity.13 Given that IPCs are usually used in elderly patients with advanced malignancies who may also receive chemotherapy,14 concerns over IPC-related pleural infection often deter the use of IPCs. Reported cases of IPC-related infection in all published series have been small and often with no details on outcome of
individual patients. This lack of data on IPC-related pleural infection further contributes to clinicians’ anxiety in the use of IPCs.

Bacterial pleural infection is associated with a significant inflammatory pleuritis, which underlies the extensive loculation/septations in empyema and can result in pleural symphysis. Attenuated bacteria (eg, Corynebacterium parvum) or bacterial toxins (eg, OK432 and staphylococcal endotoxin) are used clinically as pleurodesing agents in some countries. Whether IPC-related pleural infection can lead to pleural symphysis, and if so how often, is unknown.

This study combines data from 11 international centers experienced in the use of IPC to provide the largest report on IPC-related pleural infections to date and describes the estimated incidence, clinical outcome, and microbiology of IPC-related pleural infection. The results provide much-needed data to guide everyday clinical care.

Materials and Methods

All individual centers secured prospective local ethics committee approval to report the outcomes and complications of IPC therapy (e-Appendix 1). The Sir Charles Gairdner Group Human Research Ethics Committee of Western Australia approved the collation and storage of the deidentified data used in this study (Trial No. 2011-109).

All patients included in this study had a histologically confirmed MPE. Pleural infection was defined as follows: (1) the presence of positive microscopy or culture of pleural fluid, or pleural pus, with (2) clinical signs and symptoms consistent with pleural infection, and (3) the need for antibiotic therapy.

Data were collected concerning the (1) premorbid state of the patient and their pleural effusion; (2) conditions of the insertion of the IPC and its aftercare; (3) infection and its treatment; and (4) patient outcomes, including the mortality, duration of infection and frequency of postinfection pleurodesis. Demographic data, presence of trapped (nonexpandable) lung, recent chemotherapy, and specifics of IPC drainage patterns were also recorded.

Eleven centers from Australia (n = 4), England (n = 3), the United States (n = 2), Canada (n = 1), and The Netherlands (n = 1) contributed data on a combined total of 1,021 patients who had IPCs inserted. The four Australian centers joined after an e-mail was distributed by the Thoracic Society of Australia and New Zealand to invite its members to participate in the study. Seven other pulmonology centers known to have expertise in the use of IPCs were also invited (and all agreed) to take part. The dates of insertion of IPCs included in this study spanned 11 years, from August 2001 to July 2012. Individual centers had different audit times depending on availability of local records (e-Table 1). Some of the patients have been included in previously published studies of IPC efficacy.

Analysis of Data

All statistical analyses were performed using SigmaPlot, version 12 (Systat Software). Significance was defined as P < .05.

IPC-Related Infection Rates and Outcomes: The overall incidence rates of pleural infections were calculated using the total reported number of IPC insertions from all centers at the time of the last infection as the denominator. The outcomes of infection were classified as complete resolution (treatment able to be ceased with no further infection), chronic infection (the need for antibiotics continuing until death), or death attributable to infection.

Microbiology and Treatments: The species of bacteria isolated were reported. Clinical outcomes of IPC-related pleural infection from different infective agents were compared. The different treatment strategies of interest were as follows: (1) immediate removal of IPC vs not, (2) duration of antibiotic therapy and its route of delivery, (3) hospital admission vs outpatient-based treatment, (4) use of intrapleural therapies, and (5) need of further interventions (thoracostomy or surgery).

Results

IPC-Related Infection Rates and Outcomes

Baseline characteristics of pleural infection cases are shown in Table 1. IPC-related pleural infection affected 50 of the 1,021 patients (4.9%). The median time from IPC insertion to death or last follow-up was 267 days (interquartile range [IQR], 159-456).

Pleural infection occurred at a median of 62 days (IQR, 39-177) after IPC insertion and 216 days (IQR 74-321) after diagnosis of MPE. The median time of follow-up (including until death) was 161 days (IQR, 50-362) after the infection.

IPC-related pleural infection was generally easy to control. All patients received antibiotics, which successfully controlled the infection in 94% (n = 47) of the patients. In 38 patients, the infection completely resolved with no relapse after cessation of antibiotic therapy (complete resolution), whereas nine were still
pus but no organism was cultured (Fig 1). *Staphylococcus aureus* was cultured in 48.0% of cases. In all but one case the *S aureus* was methicillin sensitive. Gram-negative organisms were associated with higher rates of death or chronic infection than gram-positive organisms and mixed infections (60.0% vs 15.2% vs 25.0%, respectively; \( P = .02 \), degrees of freedom = 2, \( \chi^2 = 8.12 \)).

**Management of IPC-Related Infection**

The median duration of antimicrobial therapy was 24 days (IQR, 14-42); 38% of patients were treated solely with oral antibiotics, and the remainder received at least one IV dose. No differences in complete resolution rate were found between those treated with IV or oral antibiotics (\( P = .84 \)).

Many (74%, \( n = 37 \)), but not all, of the patients were admitted to hospital. Three of the remaining 13 patients received IV antibiotics in an outpatient setting.

Table 1—Baseline Demographics of Cases of Pleural Infection

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Pleural Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>65.6 (12.5)</td>
</tr>
<tr>
<td>Sex, male</td>
<td>70.0</td>
</tr>
<tr>
<td>Side, right</td>
<td>68.0</td>
</tr>
<tr>
<td>Cancer type</td>
<td></td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>34.0</td>
</tr>
<tr>
<td>Lung carcinoma</td>
<td>20.0</td>
</tr>
<tr>
<td>Breast carcinoma</td>
<td>18.0</td>
</tr>
<tr>
<td>Adenocarcinoma of unknown origin</td>
<td>8.0</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>4.0</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>4.0</td>
</tr>
<tr>
<td>Colorectal carcinoma</td>
<td>2.0</td>
</tr>
<tr>
<td>Esophageal carcinoma</td>
<td>2.0</td>
</tr>
<tr>
<td>Melanoma</td>
<td>2.0</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>2.0</td>
</tr>
<tr>
<td>Thyroid carcinoma</td>
<td>2.0</td>
</tr>
<tr>
<td>Ovarian carcinoma</td>
<td>2.0</td>
</tr>
<tr>
<td>Nonexpandable lung (n = 49)</td>
<td>46.9</td>
</tr>
<tr>
<td>Chemotherapy in the preceding month (n = 49)</td>
<td>20.0</td>
</tr>
<tr>
<td>Person performing drainages (n = 47)</td>
<td></td>
</tr>
<tr>
<td>Patient and caretaker</td>
<td>51.1</td>
</tr>
<tr>
<td>Community nurses</td>
<td>38.3</td>
</tr>
<tr>
<td>Clinic staff</td>
<td>8.5</td>
</tr>
<tr>
<td>Ward staff</td>
<td>2.1</td>
</tr>
<tr>
<td>Frequency of drainages (n = 39)</td>
<td></td>
</tr>
<tr>
<td>24-48 h</td>
<td>48.7</td>
</tr>
<tr>
<td>Twice weekly</td>
<td>23.7</td>
</tr>
<tr>
<td>Weekly</td>
<td>10.5</td>
</tr>
<tr>
<td>fortnightly</td>
<td>15.8</td>
</tr>
</tbody>
</table>

Data are presented as % unless otherwise specified.

on antibiotics for pleural infection at the time of death (chronic infection). No patient needed surgery for treatment of pleural infection.

The mortality risk from pleural infection in the overall IPC patient cohort was 0.29% (three of 1,021 patients) and 6% (three of 50) in those who developed an IPC-related pleural infection. One patient had sepsis with empyema, and the infection contributed to the death.

In two patients, progression of advanced cancer was considered by the attending team as the principle cause of death, although the infection could not be excluded as a possible contributing factor. We adopted a conservative approach and included these two patients in the calculation of mortality risks.

Nonexpandable lung was present at IPC insertion in 46.9% (23 of 49 patients with available data) of the pleural infection cases (Table 1). A total of 40.8% (20 of 49 patients) had received chemotherapy within 1 month prior to the IPC-related pleural infection. About one-half of the patients (51.1%, \( n = 24 \)) with infection performed IPC drainages at home with the help of a relative, and 48.7% drained every 24 to 48 h.

**Microbiology**

Pleural fluid from 41 patients grew a single organism, seven patients had multiple organisms, and two had

FIGURE 1. Microbiology of indwelling pleural catheter-related pleural infection. -ve = negative; +ve = positive.
The majority of pleural infections (54.0%, n = 27) were successfully managed without removing their IPCs. Of the 23 IPCs removed in an attempt to assist infection control, 11 (47.8%) required another IPC or other form of chest tube drainage of recurrent malignant effusion.

Intrapleural fibrinolytics were administered via IPC in 13 patients (26.0%): Six received combination therapy of tissue plasminogen activator (tPA) and deoxyribonuclease (DNase), four had streptokinase, two had tPA alone, and one had urokinase. Eleven out of these 13 patients (84.6%) had complete resolution of their infection, and the remaining two patients (one with tPA and one tPA plus DNase) had chronic infections requiring ongoing antibiotics. Eleven of the 13 patients treated with intrapleural fibrinolytics went on to auto-pleurodese and have their IPC removed, including one of the patients with chronic infection. Both patients who did not have their IPC removed received tPA and DNase.

Postinfection Pleurodesis

Postinfection pleurodesis was reported in 31 patients (62%) whose fluid drainage ceased after the onset of the infection, allowing the removal of the IPC. Pleurodesis was more common following infections with than those without staphylococci (78.6% vs 45.0%, P = .04). The incidences were similar in patients with primary (mesothelioma) and metastatic pleural malignancies (64.7% vs 72.4%, P = 0.13).

Discussion

This international survey summated the experiences of 1,021 patients treated with IPC at 11 centers worldwide and presented data on the largest cohort of IPC-related pleural infection to our knowledge. The results showed that IPC-related pleural infection is generally mild, often caused by S. aureus, and, in most cases, treatable with antibiotics with a very low mortality.

The introduction of IPC has added greatly to the armamentarium of physicians treating patients with MPE. An estimated 39,000 units of indwelling catheters are sold a year in the United States alone. Although the benefits of IPCs are well established, data on management of IPC complications, especially pleural infections, are inadequate. IPC-related pleural infection remains a major concern deterring the wider uptake of IPCs. The existing literature describing the clinical course of IPC-related pleural infection is inadequate, with only a handful of cases thoroughly reported. This adds further to clinicians’ anxiety when these infections arise.

Our study provides reassurance that IPC-related pleural infection is relatively indolent in the majority of cases. The mortality of about one in 350 patients treated with IPC should be considered very acceptable to most clinicians and patients (especially in view of their often significant comorbidity). Pleural infection developed in <5% of patients and, even when it occurred, was easily managed with antibiotics. In more than one-fourth of cases, the patients did not require hospitalization. These data should help significantly alleviate much of the concern associated with IPC-related pleural infection.

The mortality of 6% in IPC-related pleural infection is indeed significantly lower than reported figures (usually 15%-20%) in large clinical studies of pleural infection in patients without cancer without an IPC. Prompt evacuation of the pleural cavity is the key principle of management of pleural infection, and delayed pleural drainage has been associated with higher morbidity. Patients with an IPC perform regular drainages, which may play an important role to reduce bacterial burden and hence disease severity. IPC-related infection was defined as pleural infection that developed in the setting of current or recent IPC use. It was not possible to be certain of the exact route of entry of bacteria into the pleural space, but it appeared in all cases that entry through or around the catheter was the most likely source. Whether this portal of entry to the pleural space also influences the outcome of pleural infection in comparison with standard empyema remains to be seen.

S. aureus was the most common causative organism, although our series showed that IPC-related pleural infection could arise from a wide range of microbes. This highlights the need for initial broad-spectrum antibiotic cover in management of these patients. Gram-negative infections were associated with worse outcomes in this study, an observation consistent with empyema outcome in patients without an IPC. Pleural infections occurred most commonly at around 2 months after insertion. This would suggest that the majority of infections were not acquired at insertion but later in the disease course and highlights the need for appropriate patient/caregiver education regarding care of the IPC.

IPC-related pleural infections were managed in very diverse manners in our study, reflecting the lack of data and, thus, guidelines for the optimal treatment of this condition. Some centers advocate removal of the IPC, and others do not. Although pleural infection is generally considered a serious illness, a sizeable portion of the patients were successfully managed with oral antibiotics and as an outpatient. This suggested that management should be tailored to the severity, microbiology, and comorbidity of the infection in individual patients. A routine policy for hospital admission, removal of IPC, and a long course of IV antibiotics appeared unnecessary in many patients.
Bacterial infection of the pleural space can induce pleural symphysis (pleurodesis), thus, allowing removal of the catheter in a considerable number of patients. This unexpected benefit from IPC-related pleural infection is not surprising, as many bacteria or related products have been used before as pleurodesing agents around the world. New bacterial toxins are continually being tested and advocated for inducing pleurodesis.16,17,24

Our study was retrospective and has the associated shortcomings. The majority of centers included have an established IPC care program, which may underrepresent the infection risks in nonspecialist centers. The risk factors underlying the development of pleural infection were unable to be rigorously studied. The rarity of IPC-related infection meant there were insufficient numbers to perform a rigorous multivariate analysis. Such analyses would ideally include patient factors (eg, underlying tumor, chemotherapy, and immune status), IPC factors (eg, drainage frequencies, volume, and carer education; manufacturers; duration of IPC in situ), and clinician factors (experience of operator in insertion and aftercare, surveillance program, and so forth).

The separation of pleural infection and colonization is notoriously difficult in patients with IPCs. We adopted stringent criteria for inclusion to ensure that all cases were due to infection rather than colonization—all patients had to have clinical evidence of infection and require antibiotics. It was not possible to be confident in the incidence of colonization, which will require a prospective study with preplanned regular sampling of the fluid. Such data, however, may shed light on early identification of infection risks. Our study, therefore, cannot estimate the incidence of bacterial colonization (without active infection). Likewise, it is difficult to be accurate in determining the contribution of pleural infection to the demise of patients with IPCs who usually have advanced cancers and multiple comorbidities. In addition, this audit cannot provide data on the best management of IPC-related pleural infection, which will require prospective, large, multicenter collaborative efforts.

Withstanding all the limitations previously mentioned, this is, to our knowledge, the largest cohort of IPC-related pleural infections collected in a multicenter collaboration. It provides for the first time, to our knowledge, data on the clinical outcomes of patients with IPC-related pleural infection. Importantly, it reveals that this specific type of pleural infection is relatively uncommon in patients with an IPC, and the infection is generally mild and mortality is low. This study should help reassure clinicians and patients in the safety of the use of IPCs in the management of MPEs.

ACKNOWLEDGMENTS

Author contributions: Prof Lee is guarantor of the article.

Dr Fysh: contributed to study conception and design, data collection and patient care, manuscript drafting and revision, and final approval of the article.

Dr Tremblay: contributed to study conception and design, data collection and patient care, manuscript drafting and revision, and final approval of the article.

Dr Fellow-Kopman: contributed to data collection and patient care, manuscript drafting and revision, and final approval of the article.

Dr Mishra: contributed to data collection and patient care, manuscript drafting and revision, and final approval of the article.

Dr Slade: contributed to study conception and design, data collection and patient care, manuscript drafting and revision, and final approval of the article.

Dr Garske: contributed to study conception and design, data collection and patient care, manuscript drafting and revision, and final approval of the article.

Dr Clive: contributed to data collection and patient care, manuscript drafting and revision, and final approval of the article.

Dr Lamb: contributed to data collection and patient care, manuscript drafting and revision, and final approval of the article.

Dr Boshuizen: contributed to data collection and patient care, manuscript drafting and revision, and final approval of the article.

Dr Ng: contributed to data collection and patient care, manuscript drafting and revision, and final approval of the article.

Dr Rosenstengel: contributed to data collection and patient care, manuscript drafting and revision, and final approval of the article.

Dr Yarmus: contributed to data collection and patient care, manuscript drafting and revision, and final approval of the article.

Dr Rahman: contributed to data collection and patient care, manuscript drafting and revision, and final approval of the article.

Dr Maskell: contributed to study conception and design, data collection and patient care, manuscript drafting and revision, and final approval of the article.

Prof Lee: contributed to study conception and design, data collection and patient care, manuscript drafting and revision, and final approval of the article.

Financial/nonfinancial disclosures: The authors have reported to CHEST the following conflicts of interest: Dr Tremblay holds patents regarding methods of treating pleural effusions, which have been licensed to CareFusion Corporation. Drs Tremblay, Fellow-Kopman, and Maskell and Prof Lee received honoraria from CareFusion Corporation as advisory board members. Dr Maskell and Prof Lee received honoraria from Sequana Medical AG as advisory board members. Drs Mishra and Rahman and Prof Lee were coinvestigators of the British Lung Foundation Therapeutic Intervention of Malignant Effusion-2 trial, for which indwelling catheters were provided by Rocket Medical plc without charge. Drs Fysh, Slade, Garske, Clive, Lamb, Boshuizen, Ng, Rosenstengel, and Yarmus have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Role of sponsors: The sponsors had no role in the design of the study, analysis of the data, or writing of the manuscript.

Additional information: The e-Appendix and e-Table can be found in the “Supplemental Materials” area of the online article.

REFERENCES


Section 2

Catheter Tract Metastasis Associated With

Indwelling Pleural Catheters
Catheter Tract Metastasis Associated With Indwelling Pleural Catheters

Rajesh Thomas, MBBS; Charley A. Budgeon, BSc (Hons); Yi Jin Kuok, MBBS; Catherine Read, BSc (Hons); Edward T. H. Fysh, MBBS; Sean Bydder, MBChB; and Y. C. Gary Lee, PhD, FCCP

BACKGROUND: Indwelling pleural catheters (IPCs) are commonly used to manage malignant effusions. Tumor spread along the catheter tract remains a clinical concern for which limited data exist. We report the largest series of IPC-related catheter tract metastases (CTMs) to date, to our knowledge.

METHODS: This is a single-center, retrospective review of IPCs inserted over a 44-month period. CTM was defined as a new, solid chest wall lesion over the IPC insertion site and/or the tunneled subcutaneous tract that was clinically compatible with a malignant tract metastasis.

RESULTS: One hundred ten IPCs were placed in 107 patients (76.6% men; 60% with mesothelioma). CTM developed in 11 cases (10%): nine with malignant pleural mesothelioma and two with metastatic adenocarcinoma. CTM often developed late (median, 280 days; range, 56-693) post-IPC insertion. Seven cases had chest wall pain, and six received palliative radiotherapy to the CTM. Radiotherapy was well tolerated, with no major complications and causing no damage to the catheters. Longer interval after IPC insertion was the sole significant risk factor for development of CTM (OR, 2.495; 95% CI, 1.247-4.993; P = .0098) in the multivariate analyses.

CONCLUSIONS: IPC-related CTM is uncommon but can complicate both mesothelioma and metastatic carcinomas. The duration of interval after IPC insertion is the key risk factor identified for development of CTM. Symptoms are generally mild and respond well to radiotherapy, which can be administered safely without removal of the catheter.

CHEST 2014; 146(3):557-562
Malignant pleural effusion (MPE) is a common cause of morbidity worldwide, and its management often requires multiple pleural interventions. Needle tract metastasis (NTM) occurs in up to 40% of patients with mesothelioma following pleural interventions (eg, tube thoracostomy and thoracoscopy) and has been reported, although rarely, with malignancies other than mesothelioma.

An indwelling pleural catheter (IPC) is increasingly used in the management of MPE worldwide, especially when pleurodesis fails or is contraindicated (eg, with trapped lung). The use of IPCs can potentially induce a higher risk of subcutaneous tract metastasis posing an ongoing risk of tumor seeding along the catheter tract. Limited literature exists on the incidence and nature of catheter tract metastasis (CTM) related to IPCs, with the largest case series to date consisting of four cases. This retrospective review provides the largest study on CTM to our knowledge and describes its clinical presentation and outcome.

Materials and Methods

All patients who had IPC insertion for MPE in our service were entered prospectively into a database, which was interrogated for the period of July 31, 2009, to February 28, 2013. All IPCs were inserted using standard procedures involving a modified Seldinger approach and subcutaneous tunneling. In our center, patients were instructed to perform pleural drainage via the IPC whenever they became symptomatic. CTM cases were captured through review of individual medical records and available imaging up to May 10, 2013. Patient demographics, relevant risk factors, and survival data were recorded. Follow-up period was defined as the interval between the date of IPC insertion and last clinic follow-up or death. The Sir Charles Gairdner Group human research ethics committee, approval number 2009-104, approved the study.

Results

During the study period, 107 patients underwent insertion of 110 IPCs (Rocket Medical plc) for MPE management (Table 1). One patient had IPCs inserted bilaterally, another had two IPCs inserted into separate collections on the same side, and one had IPCs inserted sequentially on the same side. For the purpose of data analysis, individual IPC insertions (n = 110) rather than individual patients were used. Mesothelioma was the commonest underlying malignancy (60%). No patient received prophylactic radiotherapy following IPC insertion, as per our institutional practice.

Eleven patients developed a CTM, constituting an incidence rate of 10% (Tables 1, 2). The median age was 63 years (range, 53–83 years). Nine of the patients with CTMs (81.8%) had mesothelioma, one had breast adenocarcinoma, and one had ovarian adenocarcinoma. All patients had undergone pleural interventions (mostly between three and five) prior to IPC insertion. Of all patients with CTM, 63.6% were men and 63.6% had left-sided IPCs.

CTM was diagnosed after a median of 280 days (range 56–693 days) post-IPC insertion. In five of the patients who developed CTM, the IPC was removed because of cessation of fluid production; in four of those, CTM was diagnosed after IPC removal. Six patients (four with malignant pleural mesothelioma and two with adenocarcinomas) received chemotherapy prior to CTM diagnosis.

Clinical Presentation

All patients with CTM presented with new chest wall lesions overlying the IPC tract. Seven patients had chest wall pain; most were satisfactorily controlled with oral (usually narcotic) analgesics. One patient had severe CTM-associated pain that necessitated hospitalization for pain control.

Imaging

Radiologic findings were compatible with CTM in all patients (n = 7) in whom CT imaging was performed. CTM occurred around the IPC tract, usually in the lateral or posterolateral chest wall (Figs 1A, 1B). Typically, CT scan appearance was that of linear soft tissue opacity adjacent to the catheter or, in cases where the catheter had been removed, along the old tract. In the early stages, this soft tissue opacity was often interpreted as scarring and in later stages developed nodularity. The
TABLE 1  Demographics Characteristics of Participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total IPCs (N = 110)</th>
<th>Yes (n = 11) (10%)</th>
<th>No (n = 99) (90%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>Mesothelioma</td>
<td>66 (60.0)</td>
<td>9 (13.6)</td>
</tr>
<tr>
<td></td>
<td>Othersa</td>
<td>44 (40.0)</td>
<td>2 (4.6)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>84 (76.4)</td>
<td>7 (8.3)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>26 (23.6)</td>
<td>4 (15.4)</td>
</tr>
<tr>
<td>Side of IPC</td>
<td>Right</td>
<td>67 (60.9)</td>
<td>4 (6.0)</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>43 (39.1)</td>
<td>7 (16.3)</td>
</tr>
<tr>
<td>Status at date of censor</td>
<td>Alive</td>
<td>35 (31.8)</td>
<td>6 (17.1)</td>
</tr>
<tr>
<td></td>
<td>Dead</td>
<td>75 (68.2)</td>
<td>5 (6.7)</td>
</tr>
</tbody>
</table>

Data are presented as No. (%). CTM = catheter tract metastasis; IPC = indwelling pleural catheter.

aA total of 110 IPCs were inserted in 107 patients (one patient had one IPC on both sides, one patient had separate IPCs on the same side simultaneously, and one patient had separate IPCs inserted sequentially on the same side). For the purpose of data modeling and analysis, individual IPC insertions (n = 110) rather than individual patients (n = 107) were used.

bLung cancer (adenocarcinoma): 18 (14); breast carcinoma: 8; ovarian carcinoma: 3; others: 13.

enlarging lesions tended to displace or invade the adjacent muscle and subcutaneous tissue and were infrequently associated with cortical erosion of the adjacent rib. CTMs exhibited mild, late contrast enhancement similar to that seen in the pleura in malignant mesothelioma.

Radiation Therapy

Ten patients were referred for radiotherapy: Six completed therapy, two declined, and two died before treatment started. Five were treated with CT scan-planned 6 MV photons using opposed fields (three with bolus); the most common regimen was 30 Gy in 10 fractions (n = 4) or 20 Gy in five fractions (n = 1). One patient was treated with 12 MeV electrons and received 21 Gy (three fractions) followed 5 months later by 20 Gy (five fractions).

Radiotherapy was tolerated well, with no significant complications. Four of the six patients were judged to have a clinical response. Four patients had IPC in situ during their radiotherapy course; none reported catheter damage or malfunction.

Cumulative incidence of CTM reached a plateau at 2 years after IPC insertion (Fig 2). Univariately, CTM developed more commonly with mesothelioma (13.6%) than with metastatic pleural carcinomas (4.6%) but did not reach statistical significance because of small sample sizes. Age, sex, IPC side, and time from cancer diagnosis to IPC insertion were also not significantly associated with CTM development. Multivariate analyses showed that a longer interval post-IPC insertion was the only significant variable predicting higher risk for developing CTM (OR, 2.495; 95% CI, 1.247-4.993; P = .0098). In the survival analyses, cases with CTM (multivariate HR, 2.692; 95% CI, 1.070-6.774; P = .0354) and mesothelioma (multivariate HR, 2.054; 95% CI, 1.288-3.275; P = .0025) had longer survival post-IPC insertion.

Discussion

This is the largest reported series of IPC-related catheter tract metastases to our knowledge. We showed that CTM could occur particularly, but not exclusively, in patients with mesothelioma, and often causes pain. Radiotherapy is effective and can be delivered safely with the catheter in situ. Our study showed that the duration after IPC placement is the most significant and sole predictor for development of CTM.

IPCs are increasingly used in the management of MPEs worldwide, and their benefits are well established.6,9,10 Adverse events are uncommon, but there is a paucity of studies focusing on IPC complications and their management. NTM is a well-recognized complication of pleural procedures, especially in mesothelioma. Tract metastases associated with IPC are therefore an important clinical concern.

Reports of CTM complicating IPCs are limited in the literature.4,7,11 The largest published series described four cases of CTM in 45 patients with IPC.7 A pooled review of 1,093 patients from 10 studies cited a lower frequency of 0.8%.12 The incidence of 10% in our study is the highest reported and most likely reflects the high incidence of mesothelioma in our cohort and our center’s practice of regular surveillance of patients with IPC for potential complications.

It is noteworthy that CTM can develop in patients with malignancies other than mesothelioma. Our study adds two cases of CTM secondary to metastatic adenocarcinoma to the literature, which consists of only three previous reported cases.7,13,14

Regression Analyses

A pooled review of 1,093 patients from 10 studies cited a lower frequency of 0.8%.12 The incidence of 10% in our study is the highest reported and most likely reflects the high incidence of mesothelioma in our cohort and our center’s practice of regular surveillance of patients with IPC for potential complications.
TABLE 2  | Details of the 11 Patients With CTM

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Malignancy Type</th>
<th>Trapped Lung</th>
<th>Time From IPC Insertion to CTM, d</th>
<th>Radiotherapy</th>
<th>Radiotherapy Dose-Fractionation, Gy/Fractions</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mesothelioma&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>No</td>
<td>693</td>
<td>Yes</td>
<td>30/10</td>
<td>Dead</td>
</tr>
<tr>
<td>2</td>
<td>Mesothelioma&lt;sup&gt;c&lt;/sup&gt;</td>
<td>No</td>
<td>56</td>
<td>Yes</td>
<td>30/10</td>
<td>Alive</td>
</tr>
<tr>
<td>3</td>
<td>Mesothelioma&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Yes</td>
<td>280</td>
<td>Yes</td>
<td>30/10</td>
<td>Alive</td>
</tr>
<tr>
<td>4</td>
<td>Mesothelioma&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Yes</td>
<td>334</td>
<td>Yes</td>
<td>20/5&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Alive</td>
</tr>
<tr>
<td>5</td>
<td>Mesothelioma&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>No</td>
<td>369</td>
<td>No</td>
<td>NA</td>
<td>Alive</td>
</tr>
<tr>
<td>6</td>
<td>Mesothelioma&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>No</td>
<td>390</td>
<td>Yes</td>
<td>30/10</td>
<td>Dead</td>
</tr>
<tr>
<td>7</td>
<td>Mesothelioma&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>No</td>
<td>634</td>
<td>No</td>
<td>NA</td>
<td>Alive</td>
</tr>
<tr>
<td>8</td>
<td>Mesothelioma&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>Yes</td>
<td>100</td>
<td>Yes</td>
<td>21/3, then 20/5&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Dead</td>
</tr>
<tr>
<td>9</td>
<td>Mesothelioma&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>No</td>
<td>112</td>
<td>No</td>
<td>NA</td>
<td>Dead</td>
</tr>
<tr>
<td>10</td>
<td>Adenocarcinoma (ovary)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>No</td>
<td>90</td>
<td>No</td>
<td>NA</td>
<td>Alive</td>
</tr>
<tr>
<td>11</td>
<td>Adenocarcinoma (breast)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>No</td>
<td>203</td>
<td>No</td>
<td>NA</td>
<td>Dead</td>
</tr>
</tbody>
</table>

NA = not applicable. See Table 1 legend for expansion of other abbreviations.

<sup>a</sup> Epithelioid mesothelioma.
<sup>b</sup> Histopathologically proven malignancy: 4 of 11.
<sup>c</sup> Cytology-proven malignancy: 7 of 11.
<sup>d</sup> Modified radiotherapy regimen was used in these patients who lived remotely from the treatment center.

The mechanism of CTM remains unclear. The conventional belief is that cancer cells directly spread from puncture points at the parietal pleura to adjacent subcutaneous tissue. Fluid leak from the pleural cavity to the subcutaneous tissue along the subcutaneous tunnel is another potential source of malignant seeding. The risk of IPC-related CTM may be higher, as IPCs are often placed for the remaining duration of the patients’ lives and may, therefore, pose ongoing risk of tumor seeding, which is different from needle tract spread from one-off procedures.

Prophylactic radiation for NTM remains controversial, with conflicting results from three small randomized trials.<sup>3,15,16</sup> Although prophylactic radiotherapy has not been tested in patients with IPCs, concerns exist about whether it would provide any benefits. First, IPC presents a continual threat of CTM and is less likely to be

Figure 1  – A, CT scan (coronal view) of thorax showing catheter tract metastasis (CTM) surrounding the indwelling pleural catheter (IPC) (white round structure) at its entry site (arrow) and exit site (arrowhead). B, PET scan (axial view) showing CTM (arrowhead) overlying the IPC (arrow).
controlled using prophylactic radiotherapy immediately after insertion. The median time of CTM development in our series was 280 days after IPC insertion, which favored that malignant spread occurred after, rather than at the time of, catheter placement. Second, the incidence of CTM was only 10%, even in an endemic area of mesothelioma (eg, our practice). Third, our study suggests that most patients with CTM had only mild to moderate symptoms responsive to analgesics and radiotherapy. It would be difficult to justify subjecting all patients with IPC to routine prophylactic radiotherapy. Most of the CTMs reported to date and in this study were in patients with mesothelioma. Mesothelioma is known for its higher propensity to metastasize along pleural puncture tracts. The higher incidence of CTM in these patients should not deter the use of IPC in mesothelioma. The best practice to prevent tract metastases is to minimize the number of pleural procedures performed. IPC has been shown to significantly reduce the number of pleural interventions in patients with MPE. For every CTM that developed, there would be several tract metastases saved, if the alternatives of repeated thoracentesis or surgical pleurodesis were performed.

We found that CTM often developed late after IPC insertion (median, 280 days). In our multivariate analyses, the longer the patient survival after IPC insertion, the higher the risk of CTM. Patients with mesothelioma have a significantly longer median survival (12 months) than those with metastatic carcinomas (3-4 months). Mesothelioma per se was not an independent risk factor after adjusting for survival.

The best treatment of CTM is unclear. There is little information on the palliative benefit of radiotherapy, although it is widely practiced. In our cohort, palliative radiotherapy was safe and effective, with no reported damage to the IPC.

Our study has limitations. Although this series is the largest for CTM, the total number remained small, given its low incidence, and data were retrospectively collected. Large cohorts from multicenter collaboration will be required to confirm our findings. Similar to all prior studies, diagnoses of tumor tract metastases were made on clinical and radiologic grounds, and histologic confirmation was only pursued if mimics of CTM were suspected. Finally, Western Australia has one of the highest incidences of mesothelioma; hence, our incidence of CTM is skewed.

Conclusions
In summary, clinicians using IPC should be aware of CTM, especially as a late complication, in patients with mesothelioma and metastatic malignancies. Patients should be educated to report early lesions. Radiotherapy appears effective, and removal of IPC is unnecessary.
Acknowledgments

Author contributions: Y. C. G. L. is guarantor of the study. R. T. and Y. C. G. L. contributed to conception and design of the study, pleural data collection, and drafting, revision, and final approval of the manuscript; C. A. B. contributed to statistical analyses and drafting, revision, and final approval of the manuscript; Y. J. K. contributed to imaging analyses and drafting, revision, and final approval of the manuscript; C. R. and E. T. H. F. contributed to pleural data collection and drafting, revision, and final approval of the manuscript; and S. B. contributed to radiotherapy data collection and drafting, revision, and final approval of the manuscript.

Financial/nonfinancial disclosures: The authors have reported to CHEST the following conflicts of interest: Dr Lee was a coinvestigator of the TIME-2 trial, for which Rocket Medical plc provided the indwelling catheters and supplies without charge. He has served on the advisory board of CareFusion Corporation and Sequana Medical. Drs Thomas, Kuok, Fysh, and Bydder, and Ms Budgeon and Read have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Role of sponsors: The sponsors had no role in the design of the study, the collection and analysis of the data, or in the preparation of the manuscript.

References

Section 3

Fractured Indwelling Pleural Catheters
Indwelling pleural catheters (IPCs) are increasingly used in the management of malignant pleural effusions. IPCs are designed to be secured in situ indefinitely; however, in selected patients, IPCs can be removed when drainage ceases. This case series reports complications of removal of IPCs that resulted in fractured catheters or necessitated deliberate severing of the catheters. From the combined data of two pleural centers, 61 of 170 IPCs inserted (35.9%) were removed. In six cases (9.8%), the removals were complicated, leading to fracture or iatrogenic severing of the IPC. Although four patients had catheter fragments retained within the pleural space, none developed any complications (eg, pain or infection) (median follow-up, 459 days; range, 113-1,119 days), despite two patients undergoing subsequent chemotherapy. Clinicians should be aware that IPC removal can be problematic, but retained fragments are safe, and aggressive retrieval is unnecessary.

**Abbreviations:** IPC = indwelling pleural catheter

Manuscript received March 23, 2011; revision accepted July 1, 2011.

**Affiliations:** From the Centre for Asthma, Allergy, and Respiratory Research (Drs Fysh and Lee), School of Medicine and Pharmacology, University of Western Australia, and Department of Respiratory Medicine (Drs Fysh and Lee), Sir Charles Gairdner Hospital, Perth, WA, Australia; and Oxford Centre for Respiratory Medicine (Drs Wrightson and Rahman), Churchill Hospital, and Oxford NIHR Biomedical Research Centre (Drs Wrightson and Rahman), University of Oxford, Oxford, England.

**Funding/Support:** The authors received research funding from the State Health Research Advisory Council of the Western Australian Health Department (to Dr Lee), the Sir Charles Gairdner Hospital project grants (to Drs Lee and Fysh), the Raine Foundation (to Dr Lee), the National Health Medical Research Council (to Drs Lee and Fysh), the University Postgraduate Award of the University of Western Australia (to Dr Fysh), the Oxford NIHR Biomedical Research Centre (to Drs Wrightson and Rahman), and the UK Medical Research Council (to Dr Rahman).

**Correspondence to:** Y. C. Gary Lee, MBChB, PhD, FCCP, University Department of Medicine, G Block, 4/F, Sir Charles Gairdner Hospital, Perth, WA 6009, Australia; e-mail: gary.lee@uwa.edu.au

**© 2012 American College of Chest Physicians.** Reproduction of this article is prohibited without written permission from the American College of Chest Physicians (http://www.chestpubs.org/site/misc/reprints.xhtml).

**DOI:** 10.1378/chest.11-0724

**Figure 1.** An indwelling pleural catheter. The arrow indicates the polyester cuff that is positioned in the subcutaneous tunnel, promoting fibrosis.
the catheter or by the need for deliberate severing following failed removal attempts. The patients reported are part of a larger series of 170 IPC placements of which 61 underwent removal. We discuss the long-term clinical outcome of retention of residual fractured fragments of IPCs.

**Materials and Methods**

The pleural units at the Churchill Hospital, Oxford, England, and Sir Charles Gairdner Hospital in Perth, Western Australia, are specialist pleural centers active in using IPCs in pleural effusion management. Both units prospectively record in their clinical databases all patients who received an IPC, their complications, and their outcomes as approved by the local ethics committees.

Of the 170 IPCs inserted in the Oxford (n = 122 in 58 months) and Perth (n = 48 in 18 months) units, 61 were removed. Removal of six IPCs (Rocket Medical plc) were complicated, with four fractured during removal and two requiring deliberate severing after failed attempts at removal. Four patients had a portion of the catheter left in situ for a median duration of 459 days (range, 113-1,119 days); none developed any complications associated with the residual in situ catheter fragment.

**Clinical Cases**

**Case 1**

An 81-year-old man with a history of multiple malignancies, including squamous cell carcinoma of the left lung treated with radical radiotherapy 2 years before and previous colorectal, prostate, and bladder cancers, was referred for management of left-sided pleural effusion. He had a trapped lung and recurrent exudative cytology-negative effusions requiring frequent thoracenteses for symptomatic relief. In view of his age and comorbidity, the patient declined further investigations of the effusion and chose IPC for symptomatic management. After 5 weeks, fluid drainage through the IPC ceased, and no fluid reaccumulation was detected radiologically.

An elective removal of the IPC was performed. The catheter was withdrawn from the pleural cavity after dividing the fibrous adhesions around the cuff. Although no excessive force was used, when the IPC was withdrawn, it appeared to have fractured 6 cm proximal to the cuff. The remainder of the catheter remained in situ (Fig 2). The skin incision was closed, and the patient remains well at follow-up after 10 months. There were no adverse events, in particular, associated infection or discomfort.

**Case 2**

A 74-year-old man with mesothelioma had an IPC inserted for recurrent right-sided malignant effusion. The IPC functioned well for 8 months, after which pleural loculations developed and impaired drainage (Fig 3A). The IPC was removed 10 months after insertion. The cuff of the catheter was freed with some difficulties; but the section of the IPC distal to the cuff was strongly adherent to the chest wall.

![Figure 2](http://journal.publications.chestnet.org/)

**Figure 2.** Case 1. Arrow shows retained fragment of indwelling pleural catheter.

![Figure 3](http://journal.publications.chestnet.org/)

**Figure 3.** Case 2. A, Chest radiograph showing the course of the indwelling pleural catheter through loculated fluid (arrow). B, Chest radiograph after attempted removal. Arrows show retained portion of tube, including portion in subcutaneous tissues.
The catheter could not be loosened despite attempts to directly dissect away the visible fibrotic tissue. A break in the catheter developed next to the cuff, and a decision was made to cut the catheter close to the chest wall, and the internal portion was left in situ (Fig 3B). The patient was given a week of oral flucloxacillin because of inflammation around the incision sites. The patient survived a further 21 months, during which he underwent a trial of bortezomib chemotherapy, with no adverse effects from the fractured catheter segment.

Case 3

A 78-year-old man with adenocarcinoma of the right lung developed a malignant pleural effusion and trapped lung. An IPC was inserted for ambulatory management of dyspnea from the effusion. Four weeks after insertion, the effusion drainage from the IPC decreased progressively, and significant loculations of the effusion were confirmed on CT scan (Fig 4). A trial of intrapleural urokinase produced only temporary benefit. The patient’s underlying disease continued to progress, and therapeutic aspiration of residual effusion failed to improve symptoms.

Removal of the IPC was performed 72 days post-insertion. During the procedure, multiple adhesions were dissected away from the cuff and the catheter shaft, and a segment of the catheter proximal to the cuff began to stretch asymmetrically. Learning from prior experience, artery forceps were attached distal to the friable segment. On further traction, the catheter broke, but the artery forceps prevented the retained segment from retracting into the pleural cavity, which allowed complete removal of the catheter. The patient continued to deteriorate rapidly from his underlying disease and died 15 days later.

Case 4

A 67-year-old man with right pleural mesothelioma elected to have an IPC as first line therapy for effusion, which provided excellent symptom relief. He underwent eight cycles of chemotherapy (cisplatin, pemetrexed, and

Figure 4. Case 3. Sagittal CT image showing loculations (top two arrows) separate from the catheter (bottom arrow).

Figure 5. Case 4. Fracture at the junction between the cuff and the inner portion of the indwelling pleural catheter.

Figure 6. Case 5. A, Multiple locules separate from the catheter (arrow) in a contracted hemithorax. B, Severed fragment of the indwelling pleural catheter now recoiled into the pleural space (arrow).
cyclophosphamide), and the effusion drainage continued to reduce and eventually stopped 8 months after the IPC insertion.

During the removal of the IPC, a 2-cm incision was made over the cuff, and blunt dissection of the thick fibrous subcutaneous tissues was performed until the cuff became visible. It was noticed that the catheter had fractured at the junction between the cuff and the proximal section of the catheter (Fig 5). No preceding trauma or other causes could be identified. Careful extraction allowed removal of the entire catheter.

**Case 5**

A 76-year-old woman with metastatic endometrial sarcoma had an IPC inserted for management of malignant pleural effusion. After 6 weeks, she developed dense loculation, impairing drainage (Fig 6A), and an elective removal of the IPC was performed. During the procedure, the cuff was dissected free of fibrous adhesions, but the inner portion of the tube could not be withdrawn. A bedside decision was made to pull the IPC taut and then cut the catheter at the level of the skin. The inner portion recoiled into the pleural space (Fig 6B). She died 4 months later from disease progression. She underwent a course of liposomal doxorubicin in the weeks after removal and had no complications from the retained IPC fragment.

**Case 6**

An 83-year-old patient with mesothelioma had an IPC inserted. It was complicated by an empyema 2 months later that resolved with IV antibiotics. The rate of fluid accumulation significantly decreased postinfection, and an attempt was made to remove the catheter. Despite freeing the subcutaneous segment of the catheter, the intrapleural portion remained fixed. The catheter was, therefore, clipped as close to the chest wall as possible (Fig 7). The patient remains alive for >3 years, with no symptoms from the retained fragment.

**DISCUSSION**

We report on six cases in which IPC removal was complicated by fracture of the catheter, by the need to sever it after failed attempts to remove the IPC en bloc, or both (Table 1). Although a relatively new device, IPC has been adopted rapidly in the clinical management of malignant pleural effusions. New insights into its practical management are gained as the clinical experience of the use of IPCs increases. This series illustrates that removal of IPCs either can be complicated by fracture of the device or can be infeasible, in which case deliberate severing of the IPC is an option. Importantly, our experience suggests that retained fragments of IPC do not cause complications (eg, infection). Clinicians should be aware of this potential difficulty in IPC removal; modification of techniques (as described in case 3) to avoid losing fragmented portions of an IPC into the pleural cavity may be helpful.

IPC removal is indicated in patients who develop spontaneous pleurodesis or when drainage fails (eg, if loculation develops). IPCs are designed to be left permanently in situ for the remainder of the patient's lives. It is logical that removal of IPC can be difficult. Tight adhesions often develop around the cuff securing the IPC, or it can be encased by parietal or chest wall tumors. Infiltration by tumor tissues also may weaken the IPC.

In our combined two-center experience, 35.9% of patients underwent removal of the catheter at a median time after insertion of 95 days (range, 61-149.5 days). The majority of removals were performed without significant difficulties.

![Figure 7. Case 6. Residual fragment of the indwelling pleural catheter (arrow) left in pleural space.](http://journal.publications.chestnet.org/)

**Table 1—A Summary of the Cases**

<table>
<thead>
<tr>
<th>Case</th>
<th>Time Since IPC Insertion, d</th>
<th>Follow-up Time Since Fractured IPC Left In Situ, d</th>
<th>Complications</th>
<th>Chemotherapy While Residual Fragment In Situ</th>
<th>Prophylactic Antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>39</td>
<td>303</td>
<td>None</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Case 2</td>
<td>319</td>
<td>615</td>
<td>None</td>
<td>Bortezomib</td>
<td>1 wk of flucloxacillin</td>
</tr>
<tr>
<td>Case 3</td>
<td>72</td>
<td>…*</td>
<td>None</td>
<td>N/A</td>
<td>No</td>
</tr>
<tr>
<td>Case 4</td>
<td>245</td>
<td>…*</td>
<td>None</td>
<td>N/A</td>
<td>No</td>
</tr>
<tr>
<td>Case 5</td>
<td>84</td>
<td>113</td>
<td>None</td>
<td>Liposomal doxorubicin</td>
<td>1 stat dose of vancomycin</td>
</tr>
<tr>
<td>Case 6</td>
<td>133</td>
<td>1,119</td>
<td>None</td>
<td>None</td>
<td>5 d of coamoxiclav</td>
</tr>
</tbody>
</table>

*No fragments left in situ.

IPC = indwelling pleural catheter; N/A = not applicable.

Downloaded From: http://journal.publications.chestnet.org/ by a Sir Charles Gairdner Hospital User on 06/12/2016
9.8% of removals were complicated as described here. All removals were performed by suitably experienced personnel, and difficulties were not more likely to be encountered earlier or later in their experience. There was no significant difference in the duration IPCs were in situ between the complicated and the uncomplicated removals (108.5 vs 95.0 days, $P = .63$ by Mann-Whitney rank sum test). In half the cases (2, 3, and 4) the fracture occurred close to the inner portion of the cuff.

In four cases (1, 2, 5, and 6), the catheter could not be removed en bloc, and a fragment of the IPC was retained. Importantly, none of the patients experienced any adverse effects from the retained fragments. There were no cases of infection, including in the two patients who underwent chemotherapy with IPC fragments in situ. Three of these patients received prophylactic antibiotics; however, the necessity for antimicrobial cover has not been defined.

Clinicians should be made aware that IPCs can fracture during catheter removal. If fracture occurs, clinicians can be reassured that adverse consequences are unlikely and that aggressive retrieval measures (e.g., thoracoscopy) are unnecessary.

**ACKNOWLEDGEMENTS**

Financial/nonfinancial disclosures: The authors have reported to CHEST the following conflicts of interest: Drs Lee and Rahman are investigators for the TIME-2 study funded by the British Lung Foundation. The IPCs used in the study were provided without charge by Rocket Medical plc. None of the investigators received personal benefits from the study. Dr Lee has received an honorarium from CareFusion Corporation. Dr Rahman has provided consultancy services for Rocket Medical plc. Drs Fysh and Wrightson have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Role of sponsors: The sponsors had no role in the design of the study, the collection and analysis of the data, or in the preparation of the manuscript.

**REFERENCES**


**A Pleural Effusion of Multiple Causes**

Edward T. H. Fysh, MBBS; Ranjan L. Shrestha, MBBS; Benjamin A. Wood, MBBS; and Y. C. Gary Lee, PhD, FCCP

Multiple medical disorders can lead to the development of pleural effusions. Most effusions are given a single diagnosis in clinical practice. However, the cause of the effusion can change during the disease course, and concomitant yet distinct causes are often underrecognized. We highlight this point by reporting a complex case of recurrent pleural effusions with different predominant causes during the disease course. Five causes for the pleural effusion were diagnosed, namely malignant pleural effusion, empyema, chylothorax, transudative pleural effusion secondary to hypoalbuminemia, and esophagopleural fistula. This case serves as a reminder to clinicians that recurrent pleural effusion, even within the same pleural space, can arise from different causes and, whenever clinically appropriate, reinvestigation of the pleural effusion may be needed.

**CHEST 2012; 141(4):1094–1097**

**Abbreviations:** IPC = indwelling pleural catheter

More than 60 diseases can lead to the development of pleural effusions. In clinical practice, however, pleural effusions are often considered to be from a single cause. Establishing the predominant cause of the effusion does not exclude other concurrent causes. Also, the cause of the effusion can change with time. We describe a case of recurrent pleural effusion with different predominant causes at
Complications of Removal of Indwelling Pleural Catheters

To the Editor:

We read with interest the article published by Fysh et al in CHEST (April 2012) describing a high incidence (10%) of fractured, indwelling, pleural catheters (IPCs) and would like to comment on the much lower incidence of this complication as it is reported in the literature and in our experience with IPCs. Our review of seven publications on the subject, including a systemic review by Van Meter et al comprising almost 2,000 IPCs, described only one case of a fractured IPC in a patient with mesothelioma and trapped lung. In a review of our institutional database, we identified only two fractured catheters out of 1,790 IPCs that we placed since 1998. While the cause of this significant discrepancy in the rate of catheter fracture between the authors’ experience and ours is unclear, we would like to highlight several factors that could contribute to the variance:

1. Placement of the polyester cuff within 1 cm of the tunnel entry site is crucial to facilitate catheter removal. More distant placement of the catheter cuff within the tunnel leads to difficulties in dissecting the fibrous adhesions from the cuff and increases the risk of severing or weakening the catheter.

2. The length of the subcutaneous tract ideally should be kept at 5 cm. Longer subcutaneous tracts may result in catheter fenestrations located outside the pleural cavity, within the chest wall or subcutaneous tissue, permitting tissue ingrowth and impeding removal.

3. Catheter tract metastasis associated with IPC and mesothelioma that may lead to catheter damage or tumor ingrowth in the catheter has been reported. Fifty percent of patients with fractured catheters in this article had mesothelioma. Even though the number is too small to draw any conclusions, further research may be warranted.

4. Changes in the manufacturing process can cause structural failure of the catheters.

We had an experience related to defective polyester cuffs (PleurX catheter; CareFusion Corp), which caused a high number of IPC complications. Once the company was notified, changes were made, and subsequently we were able to demonstrate a reduction in the complication rates.

Horiana B. Grosu, MD
Georgie A. Eapen, MD, FCCP
Rodolfo C. Morice, MD, FCCP
David Ost, MD
Lara Bashoura, MD, FCCP
Saadia Faiz, MD, FCCP
Carlos A. Jimenez, MD, FCCP
Houston, TX

Affiliations: From the Department of Pulmonary Medicine, The University of Texas MD Anderson Cancer Center.

Financial/nonfinancial disclosures: Dr Eapen provides consulting services to Olympus Corp and PENTAX Medical Co. Dr Jimenez is investigator for the Intralpleural Catheter Daily Versus Three Times a Week Drainage Study (NCT00761618) funded by CareFusion Corp.

Correspondence to: Carlos A. Jimenez, MD, FCCP, 1400 Hermann Pressler Dr, Unit 1462, Houston, TX 77030-4008; e-mail: cajimenez@mdanderson.org

© 2012 American College of Chest Physicians. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians. See online for more details.

DOI: 10.1378/chest.12-1078

REFERENCES


Response

To the Editor:

We thank Dr Grosu and colleagues for their comments on and interest in our study in CHEST. We would like to clarify some important points.

1. Fractures occurred in four of 61 attempted removals of catheters (6.6%) from our series of 170 patients in total. The incidence of fracture of the overall cohort was, therefore, 2.4%.

2. The incidence of 2.4% would naturally include a degree of selection bias as only centers with experience in the reported complication were included in these statistics.

3. The key message of our article was not to report the incidence of this complication. Rather, it was to show that when this rare complication does occur there is no need to undertake aggressive methods of retrieving the retained portion. Some of the patients even safely proceeded with chemotherapy with the retained portion of the catheter in situ.

Use of the indwelling pleural catheter continues to grow rapidly. Better understanding of the potential complications and...
Role of TB Spirometry in Bronchial Asthma

To the Editor:

In an issue of CHEST (May 2012), Gershon et al1 raised an important but often forgotten issue of spirometry for the diagnosis of bronchial asthma. Spirometry undoubtedly is the cornerstone for the diagnosis of bronchial asthma, and it is equally true that for whatever reason it remains underused throughout most of the world. There are several reasons for its underuse, which vary with country and area. In developing countries, along with the expected reasons of scarcity of physicians and technicians, nonavailability of spirometry, and other basic issues, there is one more important, but expected, factor: TB.

In developing countries like India and China, a sizeable population has past or present TB. Prevalence of TB infection is as high as 40% in India.2 Moreover TB may mimic bronchial asthma (eg, endobronchial TB may present with dyspnea and wheezing). In areas with high TB prevalence, physicians usually rule out TB in almost all patients presenting in chest clinics with any chest symptom. If spirometry is done in a case of pulmonary TB, it may infect the apparatus and spread the infection.3 Thus, as a silent policy it is considered unsafe to use spirometry without having a chest radiograph of the patient. If the radiograph findings suggest TB, which is not a rare scenario, sputum microscopy is required to rule out present active TB. This prolonged diagnostic protocol means more hospital visits and a delay in diagnosis and treatment. This delay is unacceptable when the patient is visibly in discomfort, which often is the case because patients present late in the course of disease. Understandably, physicians feel safer and more comfortable with starting treatment without spirometry than in taking a risk of the spread of infection. There is a need to develop a consensus statement regarding the use of spirometry in countries with a high TB prevalence.

Naveen Dutt, MD
Khanpur, India

REFERENCES


Response

To the Editor:

We thank Dr Dutt for his interest in our study and insightful comments. In Ontario, Canada, the incidence and prevalence of TB is relatively low, and, therefore, it was not examined as a factor associated with pulmonary function testing in our study.2 We

For the diagnosis of bronchial asthma, and it is equally true that for whatever reason it remains underused throughout most of the world. There are several reasons for its underuse, which vary with country and area. In developing countries, along with the expected reasons of scarcity of physicians and technicians, nonavailability of spirometry, and other basic issues, there is one more important, but expected, factor: TB.

In developing countries like India and China, a sizeable population has past or present TB. Prevalence of TB infection is as high as 40% in India. Moreover TB may mimic bronchial asthma (eg, endobronchial TB may present with dyspnea and wheezing). In areas with high TB prevalence, physicians usually rule out TB in almost all patients presenting in chest clinics with any chest symptom. If spirometry is done in a case of pulmonary TB, it may infect the apparatus and spread the infection. Thus, as a silent policy it is considered unsafe to use spirometry without having a chest radiograph of the patient. If the radiograph findings suggest TB, which is not a rare scenario, sputum microscopy is required to rule out present active TB. This prolonged diagnostic protocol means more hospital visits and a delay in diagnosis and treatment. This delay is unacceptable when the patient is visibly in discomfort, which often is the case because patients present late in the course of disease. Understandably, physicians feel safer and more comfortable with starting treatment without spirometry than in taking a risk of the spread of infection. There is a need to develop a consensus statement regarding the use of spirometry in countries with a high TB prevalence.

Naveen Dutt, MD
Khanpur, India

REFERENCES


Response

To the Editor:

We thank Dr Dutt for his interest in our study and insightful comments. In Ontario, Canada, the incidence and prevalence of TB is relatively low, and, therefore, it was not examined as a factor associated with pulmonary function testing in our study.2 We

For the diagnosis of bronchial asthma, and it is equally true that for whatever reason it remains underused throughout most of the world. There are several reasons for its underuse, which vary with country and area. In developing countries, along with the expected reasons of scarcity of physicians and technicians, nonavailability of spirometry, and other basic issues, there is one more important, but expected, factor: TB.

In developing countries like India and China, a sizeable population has past or present TB. Prevalence of TB infection is as high as 40% in India. Moreover TB may mimic bronchial asthma (eg, endobronchial TB may present with dyspnea and wheezing). In areas with high TB prevalence, physicians usually rule out TB in almost all patients presenting in chest clinics with any chest symptom. If spirometry is done in a case of pulmonary TB, it may infect the apparatus and spread the infection. Thus, as a silent policy it is considered unsafe to use spirometry without having a chest radiograph of the patient. If the radiograph findings suggest TB, which is not a rare scenario, sputum microscopy is required to rule out present active TB. This prolonged diagnostic protocol means more hospital visits and a delay in diagnosis and treatment. This delay is unacceptable when the patient is visibly in discomfort, which often is the case because patients present late in the course of disease. Understandably, physicians feel safer and more comfortable with starting treatment without spirometry than in taking a risk of the spread of infection. There is a need to develop a consensus statement regarding the use of spirometry in countries with a high TB prevalence.

Naveen Dutt, MD
Khanpur, India

REFERENCES

Part III

Predicting Need for Definitive Therapy
**Foreword**

Patients with malignant pleural effusion follow very different disease courses, from effusions that reaccumulate rapidly and need invasive drainage procedures every few days, to never recurring again after the first diagnostic thoracentesis. This broad heterogeneity between patients makes it very difficult to prognosticate and plan treatment strategies. This leads to a great deal of anxiety for patients and is a great hindrance to planning effective treatment. Part III describes the largest international study to date that has prospectively collected clinical, radiological and pathological data to generate a multivariate analysis of potential predictors of need for definitive procedures (IPC or pleurodesis) to control recurrent MPE ([published article no. 8](#)). Our hypothesis for this study was that clinical, radiological and biochemical factors could predict which patients were most likely to need definitive treatment of their MPE. This was the primary goal of the Western Australian Malignant Pleural Effusion database, but in order to increase patient numbers, and ensure external validity, a large, prospective database from a collaborating centre in Lleida, Spain was included. This database was also used to provide a test cohort for the development of the LENT score for prognostication of MPE ([published article no.17, see Appendix](#))(39).
Predictors of Clinical Use of Pleurodesis and/or Indwelling Pleural Catheter Therapy for Malignant Pleural Effusion

Edward T. H. Fysh, MBBS; Silvia Bielsa, MD; Charley A. Budgeon, BSc (Hons); Catherine A. Read, RGN, BSc (Hons); Jose M. Porcel, MD, FCCP; Nick A. Maskell, DM, FCCP; and Y. C. Gary Lee, MBChB, PhD, FCCP

BACKGROUND: The clinical course of patients with malignant pleural effusions (MPEs) varies. The decision to undertake “definitive therapy” (pleurodesis, indwelling pleural catheter [IPC], or both) for MPEs is decided on a case-by-case basis. Identifying factors that predict definitive therapy may help guide early initiation of treatment. The aim of the study was to identify clinical, laboratory, and radiologic predictors associated with clinicians’ prescription of definitive therapy for patients with MPE.

METHODS: A multicenter, observational study was conducted over 55 months involving tertiary centers in Perth, Western Australia, Australia, and Lleida, Spain. Demographic, clinical, radiologic, biochemical, and histologic data and the treatments received were recorded. Logistic regression was performed to determine the variables useful for predicting definitive therapy.

RESULTS: Data of 540 patients (365 from Perth and 184 from Lleida) were analyzed; 537 fulfilled the criteria of an MPE. Definitive therapy was used in 288 patients (53.6%): 199 received a pleurodesis and 89 an IPC. Univariate analysis of the combined cohort revealed that definitive therapy was more likely if the effusion has low pH, either as a continuous variable (OR, 30.30; P < .01) or with a pH cutoff of < 7.2 (OR, 2.09; P = .03); was large (> 50% of hemithorax) (OR, 2.75; P < .01); or was associated with mesothelioma (OR, 1.83; P < .01). Following multivariate analysis, low pleural pH (OR, 37.04; P < .01), large effusions (OR, 3.31; P < .01), and increasing age (OR, 1.02, P = .01) were associated with the use of definitive therapy.

CONCLUSIONS: Patients with MPE with an effusion of low pleural fluid pH and large size on radiographs at first presentation are more likely to be treated with pleurodesis and/or IPC.

CHEST 2015; 147(6):1629-1634

FUNDING/SUPPORT: Dr Lee 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 (DDB), Sir Charles Gairdner Research Advisory Committee, Lung Institute of Western Australia (LIWA) Westcare grants, and the Cancer Council Western Australia. Dr Fysh received postgraduate scholarships from the NHMRC and LIWA to undertake this work and project funding from the DDB and Cancer Council Western Australia.

CORRESPONDENCE TO: Y. C. Gary Lee, MBChB, PhD, FCCP, School of Medicine, The University of Western Australia, 533 Harry Perkins Bldg, QE II Medical Centre, Perth, WA 6009, Australia; e-mail: gary.lee@uwa.edu.au

© 2015 AMERICAN COLLEGE OF CHEST PHYSICIANS. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians. See online for more details.

DOI: 10.1378/chest.14-1701
Malignant pleural effusions (MPEs) are common and affect as many as 15% of patients with cancer. MPEs cause considerable symptoms, especially breathlessness, and morbidity. Many patients require inpatient and/or outpatient procedures for fluid evacuation for symptom relief, with significant associated health-care costs.

The rate of recurrence of MPE is very variable, with some patients never requiring any fluid removal, to those needing frequent (even daily) drainages. For patients whose effusion recurs slowly or whose life expectancy is limited, simple thoracentesis is recommended. However, “definitive therapy” is recommended for those who would otherwise require frequent pleural drainages to control their symptoms.

Pleurodesis (usually using talc) and placement of a tunneled indwelling pleural catheter (IPC) are the most commonly used definitive therapy for MPE. The principles of both treatments are the same: to minimize pleural interventions and the associated costs, discomfort, and risks of procedural complications in patients with MPE who often have a limited lifespan. Pleurodesis is the conventional method to obliterate the pleural cavity and prevent fluid accumulation. IPCs facilitate fluid drainage and provide symptom control in an ambulatory setting. Both pleurodesis and IPCs offer comparable improvement in symptom and quality-of-life measurements when used as first-line management of MPE. Nonetheless, pleurodesis and IPCs carry their own costs and risks, and should only be used in patients whose effusions recur and cause symptoms.

At the time of diagnosis, identifying which of the patients with MPE will need definitive therapy and distinguishing them from those in whom observation and/or simple thoracentesis would suffice is notoriously difficult. Delay in definitive therapy can expose the patient with recurrent MPEs to prolonged symptoms, extra drainage interventions, and cumulative procedural complication risks. On the other hand, a blanket strategy of early definitive therapy at diagnosis for all patients with MPE will mean subjecting many to unnecessary interventions.

No studies have specifically examined predictors of need for definitive therapy at the time of diagnosis to guide clinical care. As such, physicians often treat patients on a case-by-case basis. In this study, we interrogated databases of patients with MPE to identify those offered definitive therapy by their attending clinicians. We aim to identify predictors that are associated with the eventual need of definitive therapy. This can potentially allow early selection of suitable patients and avoid repeated pleural procedures. Examining the identified predictors may also provide insight into the biology of the clinical course of MPE.

Materials and Methods

Data from the MPE databases at Sir Charles Gairdner Hospital (which also include patients from Fremantle and Royal Perth Hospitals, Perth, Western Australia, Australia) and at University Hospital Arnaud de Villanova (Lleida, Spain) were interrogated. Respective local ethics committees have approved longitudinal studies on the clinical outcomes of MPE; all patients gave informed consent. Data of patients presenting with an MPE were prospectively collected.

Clinical, pathologic, radiologic, and biochemical variables of interest in predicting the need for intervention in patients with MPE were determined a priori (Table 1). These data were recorded in each local database at the time of diagnosis of MPE from August 2009 to July 2013 in Western Australia and between December 2007 and April 2012 for the Spain cohort. Size of effusion was graded on the initial preprocedure chest radiograph using a previously described system: grade 0 referred to no radiographic evidence of pleural fluid; grade 1 = blunting of the costophrenic angle; grade 2 to 5 referred to fluid occupying <25%, 25% to 50%, 51% to 75%, and ≥75% of the hemithorax, respectively.

Patients were diagnosed as having an MPE if they had (1) histologic or cytologic confirmation or both of malignant cells from pleural tissue biopsy or pleural fluid cytology or (2) an exudative pleural effusion by Light’s criteria in the setting of histocytopathologically proven extrapleural malignancy with no obvious alternative diagnosis of their effusion. The latter mainly referred to individuals who were too frail for or declined further invasive testing.

Patients were followed until death (n = 426, 78.9%) or for a minimum of 6 months. Pleural interventions were recorded prospectively.

Comorbidity was recorded. Pleural effusion was considered loculated if there was evidence of septations on ultrasonography or if drainage was incomplete and the remaining fluid did not collect as expected according to gravity on postprocedure radiography. Nonexpansible lung referred to radiographic evidence that the lung had not fully reexpanded following evacuation of the pleural effusion. Renal failure was defined as an estimated glomerular filtration rate of <30 mL/min. Significant ischemic heart disease was defined by prior myocardial infarction, coronary artery intervention (balloon angioplasty, stent placement, and/or bypass surgery), or both. Left ventricular failure was defined by echocardiographic findings of moderate or severe left ventricular failure. Patient’s home location was classed as metropolitan if they lived within a defined metropolitan area according to the local government definition. COPD and asthma were defined according to the World Health Organization (WHO) definition of these diseases, and patients had to be currently receiving inhaled or other therapy for these conditions.

Predefined variables from the data of Western Australia and Lleida were analyzed separately using univariate and multivariate logistic regression. Then, a combined analysis of all variables with data that were >90% complete and the pleural pH was performed. Pleural pH was included despite being only 74% complete because of its very strong statistical significance in all the univariate analyses compared with the other variables as well as its clinical and biologic importance. Univariate and multivariate binary logistic regressions were conducted on the combined cohort. Two multivariate analyses were performed; the first included pleural pH as a continuous variable and the second used a pH cutoff of 7.2. Variables that were significant at a 5% significance level were retained in the final models. Adjusted ORs and 95% CIs were calculated for the final models. Data were analyzed using R, a language and environment for statistical computing.
Results

Demographics
The 540 patients with MPE recruited included 356 (65.9%) from Western Australia and 184 from Lleida: 407 (75.8%) had histocytologic confirmation of an MPE, and 130 had known metastatic cancer with an exudative pleural effusion without other discernible cause(s). Three patients were excluded: All had metastatic malignancies but without histocytologic confirmation of an MPE—one had a chylous effusion and two had large bilateral effusions.

The baseline characteristics were largely similar between the Western Australia and Lleida cohorts (Table 2). However, Western Australia is known to have one of the highest incidences of malignant mesothelioma in the world. Hence, the Western Australia cohort consisted of more patients with mesothelioma and, accordingly, had a male predominance (66% vs 51%, respectively) and was younger (median age, 69 years vs 74 years, respectively) than the Lleida patients.

Definitive therapy was used in 53.6% (n = 288) of the overall cohort. Of those who received definitive therapy, 199 (69.1%) had a pleurodesis and 89 had an IPC. The other 249 patients (46.4%) received no more aggressive treatment than thoracentesis, either because of poor prognosis, lack of symptomatic relief, or patient choice (Fig 1).

Univariate Analyses
Definitive therapy was more commonly used in the Western Australia subgroup (57.8% vs 45.7%). Univariate analyses were performed first by country and then combined, which revealed very similar predictors. The Western Australia data revealed that the lower the pH the more likely the patient would eventually receive definitive therapy (OR, 10.64; P < .01). A diagnosis of mesothelioma (OR, 1.69; P = .02), a large effusion >50% of hemithorax on radiographs (OR, 1.59; P = .04), and higher pleural fluid protein level (OR, 1.03; P < .05) were also associated with the likelihood of receiving definitive therapy.

Univariate analysis of the Lleida cohort showed strikingly similar results compared with the Western Australia data. Decreasing pleural fluid pH (OR, 33.3; P < .01), a large effusion (OR, 11.81; P < .01), and higher pleural protein levels (OR, 1.91; P < .01) were associated with the use of definitive therapy.

The presence of COPD (OR, 0.37; P = .01) or renal failure (OR, 0.16; P = .02) was associated with a lower likelihood of receiving definitive therapy in the Western Australia but not the Lleida subgroup. Conversely, age was marginally significant (OR, 1.03; P = .01) in the Lleida but not the Western Australia cohort. Patients on diuretic therapy showed a lower likelihood of receiving definitive therapy, although this did not achieve significance (OR, 0.46; P = .07).

Both cohorts were then combined and univariate analyses performed. Decreasing pleural fluid pH (OR, 30.30; P < .01), a large effusion (OR, 2.75; P < .01), and underlying mesothelioma (OR, 1.83; P < .01) were significantly associated with the prescription of definitive therapy for MPE management.

Multivariate Analyses
Multivariate analyses were performed on the separate cohorts and then the combined cohort (Table 3). In the Western Australia cohort, decreasing pleural
fluid pH (OR, 13.70; P < .01), and effusions larger than 50% of the hemithorax size (OR, 1.59; P < .04) were again significantly associated with increased rates of definitive therapy. Patients on diuretic treatment were less likely to receive definitive therapy (OR, 0.27; P = .01). Multivariate analysis of the Lleida cohort also confirmed that low pleural fluid pH (OR, 41.67; P = .02) and larger effusions (OR, 14.95; P < .01) were significant predictors of definitive therapy.

Multivariate analysis of the combined cohort reiterated an association between decreasing pleural pH (continuous variable: OR, 37.04; P < .01), larger effusions (OR, 3.31; P < .01), and use of definitive therapy. Increasing age was also statistically significant, although with a marginal OR of 1.02 (P = .01). If the pH was analyzed as a dichotomized variable at a cutoff of 7.2, the pH was no longer significant; instead, mesothelioma was related to increased rates of definitive therapy (OR, 2.05; P < .01), echoing the findings of the univariate results.

Discussion
To our knowledge, this is the first study of predictors of the likelihood of receiving pleurodesis or IPC in patients diagnosed with MPE. Patients with effusions of lower pleural fluid pH and large sizes were significantly more likely to receive definitive therapy, as confirmed in two separate cohorts.

Our prospective data showed that only 53.6% of patients with MPE received definitive therapy. This is in contrast to the common belief that most MPEs will recur and all patients should be offered early definitive therapy. The latter approach would have seen almost one-half of the patients in our cohort be subjected to unnecessary invasive procedures (and the associated risks and costs). Serious adverse events, including puncture of vital organs and death, complicates about 1% of chest drain insertions, which can amount to a significant number of patients given the high prevalence of MPEs worldwide. Finding predictors that identify the appropriate about 50% of patients will allow clinicians to initiate definitive therapy early and avoid repeated/unnecessary thoracenteses before embarking on pleurodesis or IPC placement. Our study specifically only included patients presenting for the first pleural procedure to avoid selection bias, as patients referred to tertiary centers after failing initial drainages are more likely to require definitive therapy. This may in part explain the higher percentage of patients (46.4%) who did not require definitive therapy.

This pragmatic study examined the real-life prescription behavior of clinicians regarding definitive therapy. It could not establish whether the decisions were “appropriate,” in part as there are no universally accepted rules for these decisions. The factors uncovered are those associated with a higher likelihood that pleurodesis or IPC placement was eventually used, based on clinical judgment.

Lower pleural pH strongly predicted subsequent need for definitive therapy in both the Australian and the Spanish populations, when analyzed separately or

### TABLE 2 Baseline Demographics and Distribution of Most Common Malignancies for Each Country

<table>
<thead>
<tr>
<th>Variable</th>
<th>Western Australia (n = 353)</th>
<th>Lleida, Spain (n = 184)</th>
<th>Combined (N = 537)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), y</td>
<td>69.0 (21-93)</td>
<td>74.0 (15-96)</td>
<td>70.0 (15-96)</td>
<td>P &lt; .01</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>66.0</td>
<td>50.5</td>
<td>60.7</td>
<td>P &lt; .01</td>
</tr>
<tr>
<td>Right side, %</td>
<td>59.5</td>
<td>54.4</td>
<td>56.0</td>
<td>P &lt; .01</td>
</tr>
<tr>
<td>Lung cancer, %</td>
<td>28.0</td>
<td>38.6</td>
<td>31.7</td>
<td>P &lt; .02</td>
</tr>
<tr>
<td>Breast cancer, %</td>
<td>11.3</td>
<td>11.4</td>
<td>11.4</td>
<td>P &lt; .91</td>
</tr>
<tr>
<td>Mesothelioma, %</td>
<td>40.2</td>
<td>2.7</td>
<td>27.4</td>
<td>P &lt; .01</td>
</tr>
<tr>
<td>Ovarian cancer, %</td>
<td>5.4</td>
<td>6.5</td>
<td>5.8</td>
<td>P &lt; .73</td>
</tr>
</tbody>
</table>

The χ² test was used to analyze for all variables except age, which was analyzed by Mann-Whitney rank sum test.
together. Several investigators have suggested that low pleural pH signifies greater disease burden and metabolic activities in the pleural space which may determine the likelihood and rapidity of reaccumulation of malignant effusions.12,13 This may explain why low pH was strongly and independently associated with definitive procedures in our study. Previous research has shown that lower pleural pH was associated with poorer prognosis14-16 and higher failure rate of pleurodesis.17-21 However, the largest study concluded that low pH could not be used as a contraindication for pleurodesis as 68% of patients with pH below 7.3 still had “successful” pleurodesis.18 Further prospective studies are needed to establish whether using pleural pH as part of a treatment decision algorithm can improve patient selection and, if so, what is the best cutoff value for decision-making. These studies need to assess the outcomes of pleurodesis as well as the impact on symptoms, quality of life, and hospital admissions.

The finding that larger effusions were more likely to be treated with definitive procedures is not surprising. These patients are more likely to have significant symptoms, and a large effusion likely represents a faster rate of fluid synthesis and recurrence of the pleural effusion, hence the employment of definitive therapy. Clinicians may perceive that larger effusions present lower risks of procedural complications as well.

MPEs occur in a highly heterogeneous group of patients with varying underlying malignancies, comorbidities, available chemotherapy regimes, and prognoses. The Australian cohort consisted of significantly more patients with mesothelioma (40.2% vs 2.7% in the Spanish subgroup) who have a relatively better median survival (about 12 months) compared with metastatic lung

**TABLE 3** | Univariate and Multivariate Results of the Combined Cohorts Are Presented

<table>
<thead>
<tr>
<th>Variable</th>
<th>Categories</th>
<th>Univariate OR (95% CI)</th>
<th>Multivariate 1 OR (95% CI)</th>
<th>Multivariate 2 OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>P Value</td>
<td>P Value</td>
<td>P Value</td>
</tr>
<tr>
<td>Age</td>
<td>Continuous</td>
<td>1.01 (0.99, 1.02)</td>
<td>1.02 (1.00, 1.04)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P = .40</td>
<td>P = .01</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Male vs female</td>
<td>1.08 (0.76, 1.55)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P = .66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td>Rural vs metropolitan</td>
<td>1.32 (0.93, 1.87)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P = .11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>Yes vs no</td>
<td>1.83 (1.23, 2.72)</td>
<td>NS</td>
<td>2.05 (1.23, 3.40)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P &lt; .01</td>
<td></td>
<td>P &lt; .01</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>Yes vs no</td>
<td>0.65 (0.44, 0.94)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P = .02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side</td>
<td>Left vs right</td>
<td>0.87 (0.61, 1.23)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P = .42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effusion size</td>
<td>&gt; 50% vs ≤ 50%</td>
<td>2.75 (1.91, 3.96)</td>
<td>3.31 (2.11, 5.19)</td>
<td>3.41 (2.20, 5.27)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P &lt; .01</td>
<td>P &lt; .01</td>
<td>P &lt; .01</td>
</tr>
<tr>
<td>COPD</td>
<td>Yes vs no</td>
<td>0.62 (0.35, 1.12)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P = .12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>Yes vs no</td>
<td>0.66 (0.40, 1.10)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P = .11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>Yes vs no</td>
<td>0.84 (0.53, 1.35)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P = .48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleural pH</td>
<td>Continuous (– decreasing pH)</td>
<td>30.3 (6.9, 125.0)</td>
<td>37.0 (7.8, 166.7)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P &lt; .01</td>
<td>P &lt; .01</td>
<td></td>
</tr>
<tr>
<td>Pleural pH</td>
<td>&lt; 7.2 vs ≥ 7.2</td>
<td>2.09 (1.07, 4.08)</td>
<td>NA</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P = .03</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pleural fluid pH was analyzed as a continuous variable in multivariate analysis 1 and as a dichotomized variable (cutoff at 7.20) in multivariate analysis 2. NA = excluded from analysis; NS = not significant.
cancer and thus a higher risk of recurrence of the effusion during their lifetime. It may explain the higher need, and thus rates, of definitive therapy (57.8% vs 45.7%) used in the Australian subgroup. Mesothelioma and pH appeared to be confounding. Mesothelioma was significantly associated with the use of definitive therapy when a binary cutoff pH value of 7.2 was used. Low pleural pH levels are well recognized in mesothelioma, and likely reflect a high local tumor burden and metabolic rate.22

There are limitations of this study. As a longitudinal observation study, there were missing data not recorded by referring physicians, and this precluded the inclusion of other potential predictors, for example, trapped lung. Nonetheless, to our knowledge, our data provided for the first time important variables that warrant validation in future large prospective studies. Heterogeneity exists between the two centers. However, the involvement of more than one cohort offered a higher level of confidence in our findings. The fact that decreasing pleural pH was highly significant in all univariate and multivariate analyses performed in both cohorts, separately or together, confirmed that it is a robust predictor despite the limitations. In conclusion, patients with low pleural pH and large effusions at first presentation after an initial diagnosis of MPE are more likely to be treated with pleurodesis or IPC placement subsequently.

Acknowledgments
Author contributions: Y. C. G. L. is the guarantor. E. T. H. F., J. M. P., N. A. M., and Y. C. G. L. contributed to study conception and design; E. T. H. F., S. B., and C. A. R. were center coordinators and contributed to data collection; C. A. B. performed statistical analyses; E. T. H. F. and Y. C. G. L. contributed to the drafting of the manuscript; and all authors contributed to manuscript revision and final approval.

Financial/nonfinancial disclosures: The authors have reported to CHEST the following conflicts of interest: Drs Maskell and Lee are on the advisory boards of CareFusion Corporation and Sequana Medical. They are co-investigators of the TIME-2 trial in which the indwelling catheters were provided without charge by Rocket Medical plc. Drs Fysh, Bielsa, and Porcel and Mos Badgeron and Read have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Role of sponsors: The sponsors had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

References
Comments on Predictors of Clinical Use of Pleurodesis and/or Indwelling Pleural Catheter Therapy for Malignant Pleural Effusion

To the Editor:

With great interest we read the study by Fysh et al1 in this issue of CHEST (see page 1629). Using both patient and fluid characteristics, they have been able to select patients who are likely to undergo definitive pleural therapy. The authors claim that this knowledge allows early selection of patients, avoiding repeated pleural procedures.

As Fysh and colleagues1 commented, these results are “the real-life prescription behavior of clinicians regarding definitive therapy.” Decisions to undertake definitive therapy are made by the physician together with the patient.

We question the use of a treatment modality as primary end point, as it is influenced by the physician him or herself. Decisions whether to perform pleurodesis or to insert an indwelling pleural catheter or not are not solely based on pH, large-size pleural effusion, mesothelioma, or age. For instance, we demonstrated prospectively that changes in patient-reported dyspnea scores after therapeutic thoracentesis were related to the need for reintervention, too.2 Thus, these predictors can be used together with the objective need for definitive pleural therapy.

We prospectively collected a database from patients with pleural effusions. More than 500 patients with pleural effusions were included. As is expected from a comprehensive cancer center, the majority of patients suffered from malignant pleural effusion. After excluding nonmalignant effusions, 381 patients were enrolled for this analysis. In this cohort, the majority of patients were women (232 of 381). Median age of patients was 61 years. Pleural effusion was predominantly right-sided (213 of 381). In contrast to the population described by Fysh and colleagues,1 our database consisted of more patients suffering from breast cancer (103 of 381), as previously reported.3 At the time of analysis, 42 patients were still alive without either pleurodesis or indwelling pleural catheter insertion, 170 patients (45%) underwent definitive treatment of recurrent malignant pleural effusion, and 169 patients died without a definitive treatment of pleural effusion. No data were available on recurrent thoracenteses.

Inspired by the referred study, univariate analysis of our data showed also a significant correlation with age (OR, 0.979; P = .17). Patients with higher protein levels were more likely to undergo definitive treatment of pleural effusion at some stage during their disease (OR, 1.021; P = .48). No information was available on pleural fluid pH.

We identified one other variable. Patients with bilateral pleural effusion (52 of 381) were more prone to have definitive pleural treatment than patients with unilateral pleural effusion. (OR, 3.884; P < .0001).

Aware of all potential predictive factors, clinicians may be able to inform patients in more detail on future therapies.

Rogier C. Boshuizen, MD
Jacobus A. Burgers, MD, PhD
Michel M. van den Heuvel, MD, PhD
Amsterdam, The Netherlands

AFFILIATIONS: From the Department of Thoracic Oncology, The Netherlands Cancer Institute.

FINANCIAL/NONFINANCIAL DISCLOSURES: The authors have reported to CHEST that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

CORRESPONDENCE TO: Rogier C. Boshuizen, MD, Department of Thoracic Oncology, The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands; e-mail: r.boshuizen@nk.nl

© 2015 AMERICAN COLLEGE OF CHEST PHYSICIANS. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians. See online for more details.

DOI: 10.1378/chest.15-0253

References


Response

To the Editor:

Malignant pleural effusion (MPE) is a significant health-care burden. However, the care needs of individual patients vary. Some patients have rapid recurring MPEs with significant symptoms requiring definitive therapy (including pleurodesis or indwelling pleural catheter placement); in others, the effusion may recur slowly or not at all. The ability to identify early those patients who need definitive therapy can potentially allow more efficient care. Our study in this issue of CHEST found pleural fluid pH, large effusions, age, and mesothelioma to be associated with a greater likelihood of the patient receiving definitive therapy (defined as pleurodesis or indwelling pleural catheter treatment).

We thank Dr Boshuizen and colleagues for sharing their data and are glad to read that they had similar findings in their cohort. Importantly, they also found that only about one-half (45% in their study and 54% in ours) of the patients with MPE underwent definitive treatment, further highlighting the usefulness of a predictive tool. Dr Boshuizen and colleagues also found a higher pleural fluid protein level to be a predictor, similar to our finding on univariate analysis (OR, 1.03; \(P<.05\)). Both studies also identified age as a (weak) predictor. Our study identified pleural fluid pH as the most important predictor. Unfortunately, pH was not captured in the study of Dr Boshuizen and colleagues.

Our study did not intend to determine if the decision for definitive treatment was correct, but rather to identify trends in clinical practice that may then help guide physicians in the early initiation of treatment. We agree with Dr Boshuizen and colleagues that improvement in dyspnea following pleural fluid drainage is and should be the main factor influencing the decision to proceed with definitive therapy. Large prospective multinational databases registries are essential to help answer important management questions in MPE.

Maree Azzopardi, MBBS
Edward T. H. Fysh, MBBS
Y. C. Gary Lee, MBCchB, PhD, FCCP
Perth, Australia

AFFILIATIONS: From Respiratory Medicine, Sir Charles Gairdner Hospital, Western Australia; and Centre for Asthma, Allergy and Respiratory Research and School of Medicine and Pharmacology, The University of Western Australia.

FINANCIAL/NONFINANCIAL DISCLOSURES: The authors have reported to CHEST the following conflicts of interest: Dr Fysh received postgraduate scholarships from the National Health and Medical Research Council (NHMRC) and Lung Institute of Western Australia (LIWA) to undertake this work and project funding from the New South Wales Dust Disease Board (DDB) and Cancer Council Western Australia. Dr Lee is a NHMRC Career Development Fellow and receives project grant funding from the NHMRC, DDB, Sir Charles Gairdner Research Advisory Committee, LIWA Westcare grants, and the Cancer Council Western Australia. Dr Lee is on the advisory board of CareFusion and Sequana Medical and was a coinvestigator of the TIME-2 trial in which the indwelling catheters were provided without charge by Rocket Medical plc. Dr Azzopardi has reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

CORRESPONDENCE TO: Y. C. Gary Lee, MBChB, PhD, FCCP, School of Medicine, The University of Western Australia, 533 Harry Perkins Bldg, QE II Medical Centre, Perth, WA 6009, Australia; e-mail: gary.lee@uwa.edu.au

© 2015 AMERICAN COLLEGE OF CHEST PHYSICIANS. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians. See online for more details.

DOI: 10.1378/chest.15-0558

References

Thesis Summary and Conclusions:
Importance of Malignant Pleural Effusion Research:

The number of cancer patients is increasing dramatically in Australia and worldwide\(^\text{(107-111)}\). MPE develop in fifteen percent of cancer sufferers and so MPE incidence has increased in parallel. MPE causes significant morbidity and has devastating effects on quality of life. Prognosis remains poor in the majority of patients, so rapid, effective palliation of symptoms is the primary objective. Treatment choices must therefore focus on minimizing suffering and maximizing quality of life.

Many patients suffering with MPE will be offered talc pleurodesis (TP), a treatment that has not been significantly improved since its description in the 1930’s\(^\text{(75)}\). TP remains the mainstay of therapy in many centres worldwide and has the potential to permanently seal the pleural space and relieve patients from MPE. However, the efficacy and safety of TP have recently come under scrutiny. As discussed above, pleurodesis success rates are suboptimal at ~75% of MPE patients at one month and ~50% by six months in the largest randomized trial to date\(^\text{(45)}\). Adding the fact that many patients are unsuitable for pleurodesis (e.g. with trapped lungs), TP benefits only a subset of all MPE patients. Randomized trials have also shown that talc induces lung and systemic inflammation\(^\text{(112)}\), and 2.3% of patients in a CALGB study died as a result of talc-induced respiratory failure\(^\text{(113)}\). Although this acute lung injury can be mostly avoided by using large particle size talc preparations\(^\text{(84)}\), such products are unavailable in many countries, including the USA.

Malignant pleural mesothelioma is an example that highlights the inadequacy of current treatments. The benefits of chemotherapy in mesothelioma are marginal at
best with an average improvement in survival of less than 3 months with first line pemetrexed/cisplatin therapy\(^{(114)}\). Our study in Thorax looked at failure rates of pleurodesis in the setting of mesothelioma, a previously poorly studied phenomenon\(^{(115-117)}\). In the largest study of pleurodesis success rates for mesothelioma to date, we found that pleurodesis has a significant failure rate of 31.5\% (n=165) \(^{(103)}\).

Surgical (thoracoscopic) pleurodesis was compared against bedside instillation of talc slurry, and there were no findings in favour of the more invasive procedure despite selection of younger patients and earlier therapy.

Surgical pleurectomy was for years touted by some as the optimal treatment in mesothelioma and radical extrapleural pneumonectomy with chemoradiotherapy was thought by many to be the greatest hope for cure. The results of the Mesothelioma and Radical Surgery (MARS) trial were therefore highly anticipated\(^{(118-120)}\). Patients were randomized to extrapleural pneumonectomy (EPP) or no EPP in the setting of trimodal therapy. It found that patients who underwent EPP had a higher risk of death (adjusted HR 2.75, \(p=0.016\)) and in the few patients that returned quality of life questionnaires from the EPP group quality of life scores were lower.

In comparison with other aspects of cancer treatment, these examples show that MPE treatment lags embarrassingly behind and innovation and research is desperately needed. The data above have provoked intense debate and compelled the pleural community to revisit the principles of MPE care. The fundamental aim in MPE management is to improve dyspnea and quality-of-life (QoL), with minimal intervention and hospitalization. The timely introduction of IPCs which allow fluid evacuation from a single minimally-invasive procedure serves exactly this purpose.
and explains its rapid rise in popularity (over 39,000 units sold in the USA per year)(121).

IPC represents a paradigm shift in therapy for MPE and clinicians are still adapting to the changes needed to realize the full potential of this device. Studies to date have highlighted important questions regarding the role of IPC in MPE management. IPC is generally accepted for treatment of MPE patients in whom pleurodesis has failed or is contraindicated (especially trapped lungs)(85). Many specialist centers now offer IPC as the first-choice therapy in place of TP, amid growing recognition of its limitations. Prior to the work presented in this thesis (and contemporary studies from other groups), however, there were few head-on comparisons between these two strategies.

The aims of this thesis were: first to develop a better understanding of the role of IPC as first line treatment for patients with MPE in comparison with TP; second to study the frequency and management of complications of IPC use; and third to discern which patients may benefit most from this promising new therapy.

**IPC as first line treatment compared with TP:**

The first study in this thesis to address the choice between IPC and TP as first line therapy was our real-world, observational comparison of pleurodesis with IPC (Part I-1)(101). The key outcomes evaluated were: efficacy of the treatment in dealing with the effusion (determined by the later need for further pleural drainage procedures); length of stay in hospital from diagnosis to death or the end of the study for only effusion-
related and then all causes; immediate impacts on quality of life and shortness of breath; and rates of other complications such as infection.

The key findings of this study were first that patients treated with IPC spent three times fewer days in hospital over the rest of their life than did patients with attempts at pleurodesis (6.5 days vs. 18.0, \( p=0.02 \); or, as a percentage of lifespan, 8.0% vs. 11.2%, \( p<0.001 \)). Second, treatment with IPC was more effective in controlling fluid reaccumulation with a median of just 3.0 days in hospital related to the pleural effusion as opposed to 10.0 days in the pleurodesis group over the rest of their lives, and 86.5% never requiring another pleural procedure as opposed to 67.7% in the pleurodesis arm. Third, there were significantly more patient reports of improved quality of life in the first week after treatment. Finally, there was no significant difference in the rates of infection or of protein depletion between the two interventions. This study can reassure physicians that IPC can be safely used as first line treatment in patients with MPE and that they can be at least as effective as TP.

In order to fully compare IPC and TP treatment, and to change current practice around the world, randomized studies are required. The TIME-2 study by Davies et al. has gone some way towards answering this, although it raises several more questions as well\(^{81}\). 106 patients were randomized 1:1 to IPC or talc pleurodesis and the primary endpoint was control of dyspnea measured on a visual analogue scale (VAS) over 42 days. Patients from both groups had significant improvements in dyspnea and there was no difference between the treatment groups in the magnitude of this improvement. At the secondary endpoint of VAS at 6 months there was a statistically significant benefit in the IPC group. Quality of life was not different between the
groups. While initial hospital stay for the trial procedure was shorter for the IPC group, this study did not examine hospital stay for the rest of the trial period. It also was unclear as to the adverse event rates as it would appear that they did not include pleurodesis treatment failure and repeat pleural drainage as an adverse event, reporting it separately. In the light of this, further randomized trials are warranted. The AMPLE study described in Part I-2 will hopefully add significantly to the literature in respect to hospitalization and adverse event rates but also in terms of the specific question of mesothelioma – a stratification subgroup that will be analysed independently.

One further avenue of interest for the future is the potential combination of IPC and pleurodesis in the one procedure. The advantage of this is that if TP fails, the IPC can be used for ongoing drainage without the need for further interventions. Moreover the IPC may also offer a good chance of spontaneous pleurodesis over the subsequent weeks. One study has looked at inserting an IPC at the same time as undertaking thoracoscopic poudrage and others are attempting to design an IPC that is coated with silver nitrate – another effective pleurodesing agent \(^{[61, 122]}\). A potential downside of this maybe that the pleurodesis agent may fail in generating full pleurodesis, but may leave multiple locules of fluid that are still large enough to cause symptoms. The IPC may not be fully effective in this circumstance. Nevertheless larger trials of these therapeutic options are eagerly awaited.

**The safety profile and management of IPC complications:**

The second aim of this thesis was to explore the complications of these treatments in further depth. Part II of this thesis reported three complications that were previously
very poorly documented. The first complication was that of pleural infection related to the use of IPC. This has been an important concern of referring oncologists and all physicians involved in caring for these patients who are often immunosuppressed. Raised CRP and other inflammatory markers have long been recognized as signs of non-infective as well as infective deterioration in patients with lung and other cancers\(^\text{(123-126)}\), and this has further complicated the management of patients with foreign devices such as IPC. Further evidence was sorely needed to help to clarify the true risks of this complication and to guide clinicians in the best management of infection when it does occur\(^\text{(127)}\).

Our study on IPC-related pleural infection was the largest study to date\(^\text{(104)}\). In this study we collated data from 11 centers across 3 continents providing a combined experience of over one thousand patients with IPC for MPE. The incidence of pleural infection was 4.7\%, which was in keeping with previous case series and systematic reviews\(^\text{(86, 128)}\). Most pleural infections could be controlled with antibiotics and drainage of fluid through the IPC or through a new chest tube. The IPC did not have to be removed to secure a favourable outcome and this finding is supported in another recent study\(^\text{(129)}\). The most common organism implicated was \textit{S. aureus} and patients with gram positive organisms had more favourable outcomes compared with gram negative or mixed organisms (85\% vs. 40\% vs. 75\%, respectively). Death with uncontrolled pleural infection occurred in only 0.29\% of patients treated with IPC. Other studies have shown that concerns regarding chemotherapy increasing infection rates in IPC patients are unfounded\(^\text{(130, 131)}\). These results can reassure clinicians that IPC-related pleural infection is uncommon and when it does occur it can almost always be successfully treated with prompt antibiotics and fluid drainage.
Another interesting finding of this study that should stimulate further research is that those patients with pleural infection had higher rates of IPC-related pleurodesis (in comparison to uninfected cohorts published previously), allowing the catheter to be removed. Staphylococcal infections appeared to be the most effective in inducing this effect. This finding appears to be consistent with a separate research group’s results, which suggest that Staphylococcal superantigen can stimulate pleurodesis and potentially increase survival in a cohort of patients with NSCLC and MPE\(^{132,133}\). It is known that Staphylococci have a profound effect on mesothelial physiology and disrupt the barrier formed by mesothelial cell monolayers\(^{134}\). This may be as a result of an ability to induce apoptosis of the pleural mesothelial cells\(^{135}\). Further studies are being planned to clarify the potential benefits of IPC therapy combined with instillation of bacterial products or even attenuated organisms in the future.

The second complication of MPE therapy that was further investigated in detail (Part II-2) was that of fracture of the IPC. Although previously undescribed, this complication arose during 9.8% of removals of the IPC after spontaneous pleurodesis in our combined British and Australian cohort\(^{106}\). In four cases the catheter had to be severed and a portion left within the pleural space. None of these patients suffered any complication and specifically there were no related infections, even in the two patients who underwent further chemotherapy. This study serves to warn physicians that catheter fracture can occur during IPC removal but to reassure clinicians that there is no need to undertake invasive measures to remove retained fragments.
The third and final complication addressed (Part II-3) was catheter track metastasis (CTM). This study found an incidence rate of only 10% despite a high prevalence of mesothelioma, which is generally known as the cancer most associated with needle track metastasis, in the Western Australian population\(^{136, 137}\). The only significant risk factor for CTM was increasing time since IPC insertion. While the CTM was painful in seven of the eleven patients, all but one responded well to oral analgesia. Six patients received radiotherapy, with four having a good clinical response. This study should reassure clinicians that while CTM can occur, it can usually be symptomatically controlled with oral analgesia and radiotherapy can be delivered safely and effectively.

**Predicting IPC or TP use at diagnosis of MPE:**

The third aim of this thesis was to improve the prediction of which patients are most likely to go on to require invasive but potentially definitive treatment with either pleurodesis or IPC, thereby reducing the time taken and the number of procedures undertaken between diagnosis and initiation of these therapies. While the work presented in Part III has limitations, it used a multinational study design with a large population to provide the first practical evidence to guide choice of patients for definitive therapy. It showed that patients with low pleural pH and large effusions at first presentation after an initial diagnosis of MPE are more likely to be treated with pleurodesis or IPC placement. Patients with mesothelioma may also be more likely to require definitive therapy, showing significance when a dichotomized variable of pH less than or greater than 7.2 was used.
This work can be used in the future to design an algorithm to guide patient selection for pleurodesis or IPC, although this will need to be prospectively studied in a validation cohort. The database used for this study is still open for recruitment and has led to further publications including one that may be used to guide prognostication for patients with MPE (12). These studies may help the selection of treatments for patients in the future and achieve the goal of maximizing time free of symptoms and hospital for these patients with limited prognoses.

**Future Directions:**

As well as defining an algorithm that may guide patient selection it will be necessary to further optimize the use of IPC. Dissemination of existing data will help to reassure clinicians of their safety and efficacy, but their use can be improved on with further studies to provide a better evidence base on which to guide therapy. Questions remain about the frequency of drainages – does daily drainage improve outcome over symptom guided drainage? Also the combination of IPC and pleurodesis together, using talc or silver nitrate, may be possible. These questions are already the subject of clinical trials which will hopefully provide answers that further improve the symptoms and quality of life of patients with MPE.

In summary, this PhD thesis has explored the relative benefits of IPC as opposed to TP in those patients that require treatment. It has shown that IPC can be used effectively as first-line therapy. My thesis has then furthered knowledge of the complications of IPC treatment, and studied current strategies to manage these complications reassuring clinicians of the safety of this novel treatment strategy. It has also further defined those subgroups of MPE patients that are more likely to receive definitive therapy, laying the groundwork for a future algorithm to aid decision making in the treatment of MPE. As a result of this work it is hoped that patients...
with MPE and their treating physicians may have a better evidence base to inform treatment decisions.
References (please also see references in printed publications):


