Optimising the Use of Indwelling Pleural Catheter in the Management of Malignant Pleural Effusion

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School of Medicine

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For Aaron and Anjali
Our finest works
If you can dream—and not make dreams your master;
If you can think—and not make thoughts your aim;
If you can meet with Triumph and Disaster
And treat those two impostors just the same;

If you can fill the unforgiving minute
With sixty seconds’ worth of distance run,
Yours is the Earth and everything that’s in it,
And—which is more—you’ll be a Man, my son!

— Rudyard Kipling
ABSTRACT

Introduction

Malignant pleural effusion (MPE) is a common clinical problem. The presence of an MPE usually implies an advanced incurable disease. Treatment is aimed at symptom palliation. Indwelling pleural catheter (IPC) is an effective palliative therapy for MPEs. However, knowledge gaps about the precise benefits and safety of IPC remain.

Aims

1. To define the benefits of IPC treatment on hospitalisation compared to talc slurry pleurodesis (chapters 3 and 4). It was hypothesised that IPC treatment in MPE will provide significant savings in hospital admission days;
2. To define important IPC-related complications, particularly IPC-related symptomatic loculation, catheter tract metastasis (CTM) and catheter interactions in the pleural milieu, and their treatments (chapters 5-7);
3. To understand MPE pathobiology by studying longitudinal changes in the composition of malignant pleural fluid collected during IPC drainage (chapter 8)

Results

1. The Australasian Malignant Pleural Effusion (AMPLE) randomised controlled trial compared the effects of IPC vs. talc pleurodesis on hospitalisation in 146 MPE patients (chapters 3 and 4). The most important finding was that IPC patients spent 3.6 fewer days in hospital (all-cause admission) compared to those who had talc pleurodesis (median 10 vs. 12 days, p=0.026). IPC patients also spent fewer hospital days from effusion-related causes and required fewer
pleural procedures. Both treatments improved breathlessness and quality of life that was sustained for up to 12 months.

2. The observational study of intra-pleural fibrinolytic therapy for IPC-related symptomatic loculation describes the clinical outcomes in 66 patients from four centres (chapter 5). Intra-pleural fibrinolytics improved fluid drainage, dyspnoea, and effusion area on chest radiograph, but carried a small risk of pleural bleeding.

3. Eleven cases of CTM were identified in 110 IPCs inserted over a 44-month period in a single centre (chapter 6). Duration after IPC placement was the sole predictor for development of CTM. It often caused pain however radiotherapy could be delivered safely with the catheter in situ and was effective.

4. The histopathological examination of 41 IPCs removed from MPE patients (chapter 7) showed no evidence of direct tumour invasion or cancer growth in the IPC lumen, thus providing reassuring evidence of the safety of IPC against promotion of tumour growth in the pleural cavity and against tumour invasion of the catheter.

5. The study of longitudinal changes in 638 MPE samples showed that pleural fluid protein (by 8g/L/100 days) and pH (by 0.04/100 days) decreased significantly with cancer progression (chapter 8). The concentration of monocyte chemo-attractant protein (MCP)-1, but not of other cytokines, in mesothelioma MPE increased, suggesting a patho-biologic role for MCP-1 in MPE.

Conclusion

The results of this thesis provide novel information about the benefits and safety of IPC therapy that will inform clinical decisions and will reassure clinicians that IPCs can be used effectively and safely as first-line therapy in MPE.
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Chapter 4  Impact of Indwelling Pleural Catheter Versus Talc Pleurodesis Management for Malignant Pleural Effusions on Time Spent in Hospital in Patients’ Remaining Lives: The Australasian Malignant Pleural Effusion (AMPLE) Randomised Controlled Trial

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DECLARATION

I hereby declare that this submission is my own work and that, to the best of my knowledge, it contains no material that to any substantial extent has been accepted for the award of a degree or diploma from any university. I also declare that the intellectual content of this thesis is the product of my own work. All co-authors of my publications are aware that these studies constitute part of my PhD thesis, and have consented to their use for this thesis.

Most of this thesis is my work including study design, ethics and governance, patient recruitment, trial coordination, data collection, statistical analyses, and manuscript writing. I have clearly stated the individual contribution of other authors in all the studies in the thesis.
PUBLICATIONS ARISING FROM THIS THESIS
INVITED REVIEWS AND BOOK CHAPTERS

INVITED REVIEWS

1. Complications of indwelling pleural catheter use and their management.

2. Physiology of breathlessness and pleural effusions.
Thomas R, Jenkins S, Eastwood P, Lee YCG, Singh B. Curr Opin Pulm Med

3. Interventional therapies for malignant pleural effusions: the present and the future.


5. Advantages of indwelling pleural catheters for management of malignant pleural effusions.

BOOK CHAPTER

1. Effusion from malignant causes.
Thomas R, Kalomenidis I, Jett J, Lee YCG. Textbook of Pleural Diseases, 3rd ed
2016;278-294.
Chapter 3 - Protocol of the Australasian Malignant Pleural Effusion (AMPLE) trial: a multicentre randomised study comparing indwelling pleural catheter versus talc pleurodesis.


* Joint first author

Chapter 4 - Impact of Indwelling Pleural Catheter versus Talc Pleurodesis Management for Malignant Pleural Effusions on Time Spent in Hospital in Patients’ Remaining Lives: The Australasian Malignant Pleural Effusion (AMPLE) Randomised Controlled Trial.


Chapter 5 - Intrapleural fibrinolysis for the treatment of indwelling pleural catheter-related symptomatic loculations - A multi-center observational study.

Chapter 6 - Catheter tract metastasis associated with indwelling pleural catheters.

Chapter 7 - Histopathology of removed indwelling pleural catheters from patients with malignant pleural diseases.

Chapter 8 - Longitudinal measurement of pleural fluid biochemistry and cytokines in malignant pleural effusions.
STATEMENT OF CANDIDATE CONTRIBUTION

Chapter 3: Protocol of the Australasian Malignant Pleural Effusion (AMPLE) trial: a multicentre randomised study comparing indwelling pleural catheter versus talc pleurodesis.

Trial conception and design – 40%
Development of protocol – 50%
Development of Statistical Analysis Plan – 60%
Manuscript writing – 70%

Chapter 4: Impact of indwelling pleural catheter versus talc pleurodesis management for malignant pleural effusions on time spent in hospital in patients’ remaining lives: *The Australasian Malignant PLeural Effusion (AMPLE) Randomised Controlled Trial.*

Trial conception and design – 40%
Development of protocol – 50%
Patient recruitment and data collection – 50%
Trial coordination – 80%
Statistical analysis – 40%
Manuscript writing – 70%


Study conception and design – 100%
Data collection – 70%
Imaging analyses – 80%
Statistical analyses – 80%
Manuscript writing – 80%

**Chapter 6:** Catheter tract metastasis associated with indwelling pleural catheters.

Study conception and design – 100%
Data collection – 100%
Imaging analyses – 100%
Statistical analyses – 80%
Manuscript writing – 80%

**Chapter 7:** Histopathology of removed indwelling pleural catheters from patients with malignant pleural diseases.

Study conception and design – 50%
Data collection – 50%
Statistical analyses – 60%
Histopathology analysis – 0% (100% by pathologists Chai and Segal)
Manuscript writing – 70%

**Chapter 8:** Longitudinal measurement of pleural fluid biochemistry and cytokines in malignant pleural effusions.

Study conception and design – 100%
Data collection – 100%
Statistical analyses – 40%
Manuscript writing – 80%
### ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>AMPLE</td>
<td>Australasian Malignant PLeural Effusion</td>
</tr>
<tr>
<td>CHF</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>CPB</td>
<td>Closed pleural biopsy</td>
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<tr>
<td>CT</td>
<td>Computed tomography</td>
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<tr>
<td>IL</td>
<td>Interleukin</td>
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<tr>
<td>IPC</td>
<td>Indwelling pleural catheter</td>
</tr>
<tr>
<td>LDH</td>
<td>Lactate dehydrogenase</td>
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<tr>
<td>MCP-1</td>
<td>Monocyte chemo-attractant protein-1</td>
</tr>
<tr>
<td>MPE</td>
<td>Malignant pleural effusion</td>
</tr>
<tr>
<td>PPS</td>
<td>Pleuro-peritoneal shunt</td>
</tr>
<tr>
<td>PROM</td>
<td>Patient-reported outcome measures</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of life</td>
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<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
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<tr>
<td>TGF-β</td>
<td>Transforming growth factor-β</td>
</tr>
<tr>
<td>TIME</td>
<td>Therapeutic Intervention of Malignant Effusion</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual analogue scale</td>
</tr>
<tr>
<td>VEGF</td>
<td>Vascular endothelial growth factor</td>
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<tr>
<td>VATS</td>
<td>Video-assisted thoracoscopic surgery</td>
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Chapter 1  Introduction

1.1 PLEURAL EFFUSION

Pleural effusion, an abnormal collection of fluid surrounding the lung within the chest cavity, is a common cause of morbidity worldwide. An estimated one million patients suffer from a pleural effusion annually in the United States alone (1). Pleural effusions may arise from diseases of the pleura or from extra-pleural, particularly cardio-pulmonary, disorders.

1.1.1 Pathophysiology of Pleural Effusion Formation

The normal ‘physiological’ pleural fluid is a transudate with an estimated volume of 0.1-0.2 mL/kg body weight (2). Excessive accumulation of pleural fluid develops when the rate of fluid formation exceeds its drainage capacity. This can result from increased pleural fluid formation or decreased fluid absorption, or often both (3).

Pleural fluid may broadly be classified into a transudate or an exudate; the underlying pathophysiology of fluid formation and the differential diagnoses are different, as is often the management. Transudates arise from an imbalance between the hydrostatic and/or oncotic pressures which result in fluid extravasation and accumulation in the pleural cavity (4). The underlying pleura and the vascular permeability to proteins is not affected. In contrast, most exudative effusions develop as a result of vascular hyper-permeability and plasma leak, usually a manifestation of malignant or inflammatory disorders. The underlying disease(s) may also impair fluid drainage via the stomata on the parietal pleura and/or the downstream lymphatic channels.
Light’s criteria are commonly used to distinguish between transudative and exudative pleural effusions (5). It can identify an exudative effusion with a sensitivity of 98% and specificity of 74% (6), and are better than other parameters proposed to date. An exudative pleural effusion is one that fulfils one or more of the three criteria below whereas a transudate is one that meets none (5):

1) Pleural fluid: Serum protein ratio >0.5
2) Pleural fluid: Serum lactate dehydrogenase (LDH) ratio >0.6, and
3) Pleural fluid LDH >2/3 the upper limit of normal for serum LDH

Defining a pleural effusion as a transudate or exudate remains helpful in directing investigations in the majority of cases. Generally speaking, extensive investigations or pleural drainage procedures are unnecessary in case of transudative effusions; management is primarily directed at treating the systemic disease, e.g. congestive heart failure (CHF). An exudate often demands a more extensive diagnostic evaluation to identify the underlying cause; management is directed towards control of the effusion in addition to treatment of the underlying pathology (7).

1.1.2 Causes of Pleural Effusion

Pleural effusions may be caused by a benign or malignant process. Benign effusions are at least twice as common as malignant effusions in most epidemiological series. The incidence and aetiology of pleural effusions may vary depending on the population studied. Over 90% of all effusions in developed countries are caused by CHF, malignancy, pneumonia and pulmonary embolism (8). Tuberculosis is a common cause of pleural effusions in endemic regions.


1.1.3  Benign Pleural Effusion

Over 60 benign causes have been described (9). CHF and hepatic hydrothorax are the commonest causes for a transudative effusion. The commonest benign causes for an exudative effusion are para-pneumonic effusion and empyema that usually complicate bacterial pneumonia. Over 1 million patients are hospitalised for community-acquired pneumonia annually in the United States (10); almost 50% of these patients will develop a pleural effusion (11). In endemic countries, pleuritis complicates >25% of patients with tuberculosis and is one of the commonest causes exudative pleural effusions (12). Other causes include pulmonary embolism, drugs, systemic autoimmune diseases, chylothorax, post-surgical effusion and benign asbestos pleural effusion.

1.2  MALIGNANT PLEURAL EFFUSION

Malignant pleural effusion (MPE) is a common clinical problem, affecting 150,000 patients in the United States each year (13). Post-mortem examination of patients who died from cancers showed that MPE occurred in 15% of cases (14). MPE accounts for ~22% of all pleural effusions (and 42% of exudates) in epidemiologic studies (8).

1.2.1  Aetiology of Malignant Pleural Effusion

MPE can arise from a primary pleural malignancy, e.g. mesothelioma, or following metastatic pleural spread of extra-pleural malignancies. More than 90% of patients with mesothelioma will develop a MPE, often at the time of presentation (15). Virtually all malignancies can metastasise to the pleura. Lung cancer is the commonest origin of metastatic MPE with a reported incidence of 25 to 52% (16, 17). Breast cancer and lymphoma/leukaemia are the next commonest causes, especially in females and in the young respectively (18, 19). As many as 15% of lung cancer patients have an MPE on initial presentation and up to 50% of disseminated lung and breast cancers will develop
an MPE during the disease course (18, 20).

Histologically, most metastatic cancers to the pleura are carcinomas (~75%), especially adenocarcinomas (~47%). Large cell undifferentiated carcinomas account for 14.3% of cases and lymphoma/leukaemia 15.0% (19). No primary site is found in ~10% cases (19).

1.2.2 Mechanism of Pleural Metastasis
Post-mortem studies have shown that patients with MPE have visceral, but not necessarily parietal, pleural involvement (14). Pleural metastases develop when tumours embolise to the peripheral lung and invade the visceral pleura. The parietal pleura is secondarily affected. Other mechanisms for malignant pleural involvement include direct pleural invasion from adjacent tumours in the lung, breast or chest wall, and haematogenous and lymphatic spread to the parietal pleura. It is currently believed that a combination of increased fluid extravasation from hyper-permeable (pleural and/or tumour) vessels and impaired lymphatic out-flow underlie the development of MPEs. Pleural fluid over-production is dictated by complex tumour-host interplay, which induces pleural inflammation, tumour angiogenesis and vascular hyper-permeability (21). Tumour invasion of the lymphatics reduces lymphatic drainage of pleural fluid via stomata of the parietal pleura, contributing to MPE formation.

1.2.3 Clinical Presentation of Malignant Pleural Effusion
Dyspnoea, pain and cough are the most common symptoms associated with MPE. Most patients experience dyspnoea, though it is often multi-factorial and does not always correlate with the size of the effusion. The underlying mechanism(s) of dyspnoea is complex and poorly understood. Over half of the patients experience chest pain, which
is usually dull rather than pleuritic (22). The presence of chest pain usually implies malignant infiltration of the parietal pleura/chest wall, as the visceral pleura is devoid of pain fibres. Constitutional symptoms, e.g. anorexia, weight loss or tumour fever, from the underlying cancer are common. Symptoms related to the patient’s specific primary malignancy, e.g. cough from bronchogenic carcinoma, are common and can be difficult to separate from the effect of the MPE.

### 1.2.4 Radiographic Appearance of Malignant Pleural Effusion

Most patients, particularly if symptomatic, will have a moderate to large effusion on chest radiograph. A massive pleural effusion is found in ~10% of MPE patients at presentation, and ~70% of massive effusions are malignant (23). Parenchymal and mediastinal abnormalities may be difficult to appreciate on chest radiographs until the fluid is removed. Thoracic ultrasound is useful in detecting pleural effusion and guiding drainage. Ultrasonography can also help localise pleural tumours and guide transthoracic biopsy. A computed tomography (CT) scan of the thorax provides better visualization of the mediastinum to determine if there is any involvement of the chest wall, lymph nodes and/or the presence of extra-pulmonary metastasis. Presence of pleural nodularity, irregularity, mediastinal pleural thickening and pleural thickness >1 cm are highly suggestive of malignant pleural disease (24). Findings of pleural plaques may raise the suspicion of mesothelioma. Positron emission tomography can, in selected cases, guide imaging-guided biopsies of the pleura or other metastatic sites when first-line pleural fluid investigations are unsuccessful.

### 1.2.5 Diagnosis of Malignant Pleural Effusion

Demonstration of malignant cells through cytological analysis of the pleural fluid or histological examination of pleural tissue remains the gold standard for diagnosing MPE.
1.2.5.1 Thoracentesis

A diagnostic thoracentesis is the simplest definitive investigation to confirm MPE. The pleural fluid is usually exudative but a transudative state may be seen in ~5% of MPE patients (25). 50% of MPE is sero-haemorrhagic (26, 27) and 11% is bloody (28). White cell differential count usually is predominantly lymphocytes and mononuclear cells (26, 27). Reduced pleural fluid glucose (< 60mg/dl) and pH (< 7.2) are often seen in MPEs, reflecting higher pleural tumour burden and may indicate a poorer prognosis (29).

1.2.5.2 Pleural Fluid Cytology

Pleural fluid cytological examination has a variable yield (range 62-90%) (16), in part depending on the type of malignancy and expertise of the cytologist. Separating normal, reactive and malignant mesothelial cells is difficult; as is lymphocytes from lymphoma cells or small cell carcinoma (30). Adenocarcinoma and mesothelioma cells can be morphologically similar; their separation often requires a panel of immune-histochemical markers, which may also shed light on the primary site of metastatic carcinomas. If the initial fluid cytology is not diagnostic, a second fluid aspiration for cytology provides a diagnosis in another 27% of cases but further aspirations are unlikely to improve the yield (31).

1.2.5.3 Closed Pleural Biopsy

The diagnostic yield of closed pleural biopsy (CPB) is operator-dependent and is limited by the often-patchy parietal pleural involvement in malignant pleural diseases. CPB offers marginal additional diagnostic yield (7%) over pleural fluid cytology (32), but is associated with a higher risk of complications, e.g. pneumothorax and haemothorax.
1.2.5.4 Image-Guided Closed Pleural Biopsy

Ultrasound-guided pleural biopsy has a diagnostic yield of up to 77-84% for malignancy with a higher yield in the presence of pleural nodularity or thickening on ultrasound examination. The diagnostic yield for malignancy with CT-guided pleural biopsy is as high as 88% if pleural thickening (>10mm) is present (33).

1.2.5.5 Medical Thoracoscopy

Medical thoracoscopy/pleuroscopy provides a higher diagnostic yield over conventional CPB or cytology in the evaluation of MPE (34), and is recommended in most guidelines if the initial pleural fluid cytology is inconclusive. Thoracoscopic biopsy has a false negative rate in ~10% cases.

1.2.5.6 Surgical Pleural Biopsy

In a small number of patients, thoracoscopy may not be feasible or fails. Surgical biopsy by video-assisted thoracoscopic surgery (VATS) or open thoracotomy can be considered if the risks are acceptable.

1.3 MANAGEMENT OF MALIGNANT PLEURAL EFFUSION

The presence of an MPE, whether of primary or metastatic origin, usually implies an advanced incurable disease with a poor prognosis and a median survival of 4-6 months. Among the common cancers, survival is the shortest for those with an MPE from lung cancer and longest (9-12 months) if due to mesothelioma (35).

Treatment is therefore directed at palliation of the symptoms associated with the malignant pleural disease as well as the underlying malignancy. If the underlying cancer is likely to respond to treatment, the associated effusion can resolve/remain stable. Lung
cancer with epidermal growth-factor receptor mutations, small cell lung carcinoma and lymphoma, for example, may respond well to chemotherapy; measures to prevent fluid recurrence may not be necessary in these patients.

Currently available treatment approaches to control malignant effusion include therapeutic thoracentesis, surgery, pleuro-peritoneal shunt, pleurodesis and indwelling pleural catheter.

1.3.1 Therapeutic Thoracentesis

Therapeutic thoracentesis is a simple, effective outpatient-based procedure (36) though its benefits may only be temporary. This is suitable for symptomatic patients who require short-term measures, particularly those with a short expected survival and/or a poor performance status. A therapeutic thoracentesis to relieve immediate symptoms while awaiting treatment response is also justifiable in patients whose underlying malignancy may respond to targeted therapy or systemic chemotherapy.

More definitive treatments to minimise multiple invasive procedures should be considered in other cases of recurrent symptomatic MPEs.

1.3.2 Pleurodesis

Pleurodesis, the iatrogenic induction of a pleural symphysis, has remained the mainstay of treatment of recurrent MPEs for several decades. Creation of a pleurodesis depends on symphysis of the visceral and parietal pleura generated by either chemical or mechanical means. The exact mechanism underlying development of pleurodesis is poorly understood but is believed to occur after induction of an acute pleural inflammatory response from the sclerosants that results in mesothelial cell denudement.
Subsequent chronic inflammation and pleural fibrosis obliterates the pleural space and prevents fluid re-accumulation (37, 38).

Many methods of creating pleurodesis have been used; but no consensus exists on the ideal approach. Intrapleural instillation of a sclerosant (chemical pleurodesis) is the most widely used pleurodesis method. Talc is the most commonly used agent worldwide (39). Tetracycline derivatives, cytotoxic agents such as bleomycin, OK432 (a preparation of Streptococcus pyogenes type A3) (40)) and quinacrine (an anti-malarial agent) (41)) are some of the alternative agents. Talc has been shown to be more effective in comparative trials with bleomycin (42-45), tetracycline derivatives (46, 47) and over no sclerosant controls (48). A Cochrane meta-analysis supported use of talc as the sclerosant of choice (49).

Talc can be administered as a dry powder (poudrage), usually during thoracoscopy or as slurry via a chest tube. Talc poudrage was first described in 1935 (50) and allows distribution of the insufflated talc over the entire pleural surface. It was conventionally believed that talc poudrage is more effective than slurry. This belief has now been refuted by all three randomised trials comparing talc poudrage and slurry pleurodesis (51-53). The largest randomised trial in MPE (51) showed in 482 patients that the success rate of fluid control at 30 days was not significantly different between surgical thoracoscopic talc poudrage and chest-tube talc slurry pleurodesis (78% vs. 71% respectively). Two smaller randomised studies also reported no significant difference in patient outcomes (52, 53). There were no differences in quality of life (QoL), hospitalisation or pleurodesis success rates when compared to talc slurry.

Pleurodesis failure and adverse effects: The largest randomised trial to date showed
that talc pleurodesis provided adequate fluid control in only 72% patients at 30 days and
~50% by 6 months (51). Another study showed that pleurodesis failed in one third of
patients with MPE secondary to mesothelioma necessitating further pleural
interventions (54). This potentially becomes a major problem as the longer the patient
lives, it is more likely that the effusion will recur.

Fever and pain are common after pleurodesis. Complications associated with talc
pleurodesis include acute pneumonitis, ARDS, hypoxia, respiratory failure, and death
(51, 55). Graded talc preparations with larger particle size are safer than products with a
small particle size. Inflammation provoked by systemic absorption of small-sized talc
particles (56) can cause respiratory failure, ARDS (in up to 10% of patients), and death
in 2% as shown by Dressler et al (51).

1.3.3 Surgery
Surgical pleurodesis can be performed through mechanical abrasion or parietal
pleurectomy via either thoracotomy or VATS (57). These procedures are invasive and
have a higher morbidity. Peri-operative mortality can be as high as 12.5% and
prolonged air leak can occur (10-20%). These procedures are generally only applied to
highly selected patients with acceptable operative/anaesthesia risks who have no
alternative options (58). The effectiveness of different surgical pleurodesis techniques
(except for poudrage alone) has not been directly compared with the bedside instillation
of pleurodesing agents. In principle, the more aggressive the surgical techniques
employed, the more likely it will create a successful pleurodesis; however, this needs to
be balanced against the risks of general anaesthesia with the associated greater
possibility of adverse events and higher costs.
1.3.4 Pleuro-Peritoneal Shunt

The pleuro-peritoneal shunt (PPS) is a device with two catheters placed within the pleural and peritoneal cavities and connected by a one-way valve pump chamber. The pump, when compressed, draws fluid from the pleural space into the peritoneal cavity. PPS can be used as an alternative to pleurodesis in patients with trapped lung or following failed pleurodesis (59). PPSs provide effective palliation in up to 95% of patients but the incidence of complications (especially occlusion) is high (~25%), often requiring shunt revision, removal and/or replacement (60).

1.4 THE CHANGE IN DIRECTIONS

The past couple of decades have seen significant changes in the views and, thus approaches, to MPE management. MPE researchers historically focused on stopping the pleural fluid re-accumulation with aggressive measures (e.g. pleurectomy) to obliterate the pleural space. Many (if not most) clinical studies were directed to comparing sclerosing agents. ‘Absence of radiographic evidence of fluid recurrence’, usually in the first month, was the commonest endpoint in these clinical trials - even though it means little to patients with pleural malignancies (61).

Clinicians have since come to recognise that the key goals of MPE management are to achieve complete fluid control, improve patient-reported outcome measures (PROMs) with the least invasive means, preferably out of hospital, and in the most cost effective way. The recently published Therapeutic Intervention of Malignant Effusion (TIME)-2 (62) study was amongst the first randomised trials in this field to use PROMs (breathlessness, chest pain and QoL scores) as its key endpoints.
MPE continues to grow as a global healthcare burden; future therapies must be cost efficient/effective. Reducing hospital-based interventions will be an important direction of research. Other patient-relevant outcomes, e.g. days in hospital, number of pleural procedures endured, are also important. These changes will have profound implications on the directions of clinical care and research into MPE management in the years to come.

1.5 INDWELLING PLEURAL CATHETER

Use of indwelling pleural catheters (IPC) represents a major step towards the new directions of MPE care. IPC is a 15.5-16F silicone catheter and approximately 65cm in length, with a fenestrated proximal end and a ‘capped’ one-way valve at the distal end. The tube is placed in the pleural cavity, tunneled subcutaneously, and brought out through an exit site on the skin. The catheters are designed to remain in situ indefinitely for the remaining lifespan of the patient.

Insertion of the catheter is a minor intervention usually only requiring local anaesthesia or conscious sedation. It can be performed as an outpatient day procedure and the patient is ambulant promptly afterwards. Two incisions are made between which the polyester cuff is tunneled into the subcutaneous tissue. The polyester cuff in the tunneled portion of the catheter promotes tissue fibrosis and avoids inadvertent catheter dislodgement. Tunnelling of the catheter is believed to reduce infection risks though this has not been formally tested. The fenestrated part is inserted into the pleural space using Seldinger’s technique.

The one-way valve at the distal end of the catheter permits ambulatory drainage of pleural fluid: the catheter can be ‘opened’ and connected to drainage devices when
needed; at other times the patient can continue usual daily activities with the catheter capped off. A trained carer or health care worker can perform drainage, removing the need for repeated invasive pleural drainage procedures and the associated risks. The frequency of drainage can be determined by the patient depending on the rate of fluid re-accumulation and severity of symptoms, mainly dyspnoea. It thus provides greater control and flexibility to the patients in managing their condition.

The use of IPCs in the management of MPEs has grown exponentially after the Food and Drug Administration approved their use in 1997. Commonly used commercially available devices include PleurX® catheter (CareFusion, USA) and Rocket® IPC (Rocket Medical, England) which have similar designs. Leading guidelines advocate the use of IPC as the preferred management for use in patients with symptomatic MPE (63-65), particularly those who fail pleurodesis or are unsuitable for pleurodesis (e.g. with trapped lung). It is therefore logical to examine if IPC can be used as the frontline treatment in place of pleurodesis, rather than only when the latter is contraindicated or fails.

1.5.1 Advantages of Indwelling Pleural Catheter

Several key studies (62, 66, 67) have now established that IPC has at least an equivalent benefit in several parameters when compared with pleurodesis, thus challenging the conventional treatment paradigm (68). This is since the first randomised controlled trial (RCT) comparing IPC with (doxycycline) pleurodesis was published in 1999 (67).

1.5.1.1 Effective Drainage

IPCs function as a continuous port of access to the pleural cavity through which pleural fluid can be drained without the need for repeated invasive procedures. A wealth of
literature has testified to the effectiveness of IPCs in pleural fluid drainage. In most studies, over 90% of patients treated with an IPC do not require any further effusion-related pleural intervention (62, 69, 70).

Two schools of thought exist in the clinical application of IPC. In many centres it is advocated as an alternative to pleurodesis with a strong focus of the drainage regime on keeping the pleural cavity dry e.g. via daily or alternate day fluid drainages (71-74). Others believe that the goal of MPE management is symptom palliation, and evacuation of fluid should only need to be performed as guided by patients’ symptoms (75, 76). Often, complex drainage schedules are described (67, 70, 77-79).

1.5.1.2 Improved Dyspnoea and Quality of Life

The primary goal of MPE management is palliation and thus, breathlessness and QoL are essential measurements in assessing any therapy for MPE. Despite the limitations of the study tools and the variations in various trial protocols reported in the literature, the overall picture that has emerged from the published data would support the idea that an IPC is at least as efficient as (talc) pleurodesis in relieving dyspnoea and/or improving QoL.

Two non-randomised observational studies (82 and 66 IPCs each) reported significant improvements in dyspnoea and QoL in patients after IPC insertion (69, 80). In 1999, Putnam and colleagues showed in an RCT with 144 patients (45 pleurodesis: 99 IPC) that at 30 days the modified Borg scale dyspnoea scores were significantly improved in the IPC group compared to those who received doxycycline pleurodesis (67). A smaller randomised trial of 57 patients (29 pleurodesis: 28 IPC) also showed that patients randomised for IPC treatment had better dyspnoea scores than those who were
pleurodesed (66). There was no difference in QoL scores. A recent randomised study of 106 MPE patients (54 pleurodesis: 52 IPC) showed that IPC provided equivalent improvement in dyspnoea measured by the Visual Analog Scale (VAS) compared with pleurodesis at six weeks after randomization (62). Dyspnoea control at 6 months after randomization was superior in the IPC group. There was no difference in the measured QoL at any time point between the two treatment arms.

1.5.1.3 Spontaneous Pleurodesis

Spontaneous pleurodesis, if it occurs, is an added advantage as it allows removal of the catheter, thus negating the associated risks of IPC-related complications, inconvenience and costs. Rates of spontaneous pleurodesis range from 26% to 76% in most large series (62, 69, 70, 81, 82), and the median time to pleurodesis varies from one to three months (67, 70, 82). Spontaneous pleurodesis is seen, though less frequently, even in the presence of trapped lung (73, 74, 83, 84). Requirement for further pleural intervention after catheter removal due to recurrence of effusion is low (<8%) (85).

The mechanism underlying spontaneous pleurodesis is unknown. Numerous factors may confound the incidence of pleurodesis, including degree of lung re-expansion after fluid removal (81) and the incidence of trapped lung in the study cohort, duration of patient survival, underlying types of malignancy, positive pleural fluid cytology, and if pleurodesis has been attempted before (70).

1.5.1.4 Reducing Hospitalisation

Putnam and co-workers retrospectively reviewed hospital durations for patients with an inpatient chest drain (n=68), as well as inpatient (n=40) and outpatient (n=60) IPC. The
latter group had significantly shorter hospitalisation time (median 0 vs 7 days) for the initial procedure (72).

In the patient choice study described previously (69), patients who chose to receive an IPC spent significantly fewer days in hospital for admissions due to effusion-related reasons or overall hospital days from procedure till death (median 3 vs 10 days; p<0.001 and 6.5 vs 18 days; p=0.002, respectively), compared with the bedside pleurodesis group. In the TIME-2 study patients randomised to the IPC group spent a median of 1 day in hospital (vs 4.5 days in the pleurodesis group, p<0.001) for drainage or drain-related complications after 12 months (62). A recent pilot study also suggests that the insertion of an IPC immediately following thoracoscopic poudrage would decrease the hospital days significantly (78).

1.5.2 Complications of Indwelling Pleural Catheter Use

Clinicians must be adequately equipped to handle common complications associated with IPC use, which is reported to occur in 10-20% of patients (82, 86, 87). The overall safety of IPC use has been confirmed in many observation series as well as randomised and non-randomised trials. Wrightson et al summarised the reported complication rates in published literature (88) and showed that common reported adverse events are mild and easily controlled.

Complications include those associated with small bore catheter insertion using Seldinger technique but not specific to IPCs, e.g. wound infection or cellulitis, bleeding, organ injury, pneumothorax, dislodgement, etc (88). Post-insertion pain is the most commonly reported side effect, affecting about one-third of patients, but is transient (<72 hours) and usually only requires simple analgesia.
In addition, there are several important, albeit uncommon complications that are peculiar to IPC use. The current evidence on the occurrence, risk factors and management of these IPC-related complications is herein reviewed.

1.5.2.1 Indwelling Pleural Catheter-Related Pleural Infection

The incidence of IPC-related pleural infection in reported series (usually small) range from 0 to 12%. Morel and colleagues showed that 7 out of 82 IPCs developed a pleural infection (89). A large multi-centre review characterised 1021 patients with IPC from 11 centres in Europe, North America and Australasia and found an infection rate of 4.8% only (90). In the TIME-2 randomised study of 106 patients, five had a significant pleural infection of which only one had received chemotherapy (62).

Cutaneous flora including Staphylococcus species (especially S. aureus), accounts for most of the reported cases, followed by Pseudomonas aeruginosa and Enterobacteriaceae (90). IPC-related pleural infections are generally mild. Most cases resolved with antibiotic treatment. None of the 50 cases in the aforementioned series required surgery (90). Removal of IPC is not necessary unless the infection fails to respond. The overall mortality from pleural infection was only 0.29% in all IPC-treated patients (90). Pleurodesis is common after IPC-related pleural infection and allowed removal of the catheter in 62% of patients (80% in those with S. aureus empyema) (90).

Reassuring data of IPC use in immune-compromised patients is mounting. A recent series of patients with underlying haematological malignancies treated with IPCs reported infection and mortality rates of 7% and 2% respectively, despite the high background risks of ongoing chemotherapy and cytopenia (91). Studies from the Mayo
clinic, USA and from Oxford, UK also found no significant increase in risks of IPC-related pleural infection comparing patients with or without ongoing chemotherapy (89, 92).

1.5.2.2 Nutrition and Cell Loss

There have been concerns that long-term intermittent drainage potentiates nutrient loss and immunological impairment, especially for exudative effusion or chylothorax. Currently, data reporting the effect of IPC drainage on nutrition and immunology are scanty. Most case series of benign and malignant effusions managed by IPC drainage have found no significant changes in nutrition, body weight, blood cell counts or rates of protein depletion (69, 93). However the small sample size, missing data and absence of a control group in most of these studies preclude the drawing of any firm conclusions (93, 94).

1.5.2.3 Fracture of Indwelling Pleural Catheters on Removal

IPC may be removed following cessation of drainage, development of spontaneous pleurodesis, or due to serious complications such as empyema or severe pain (95). Fracture of the catheters during removal, though rare, can occur especially when traction force is applied. This should not raise concerns and aggressive attempts to remove the retained fragments are unnecessary. The IPC is intended to remain in situ for the remaining lifespan of the patient and retained segments have not been shown to increase morbidity (96). In a two-centre series of 61 IPC removals, 10% (6 cases) was complicated by fracture of the catheters or required iatrogenic severing because of difficulty in removal (96). On subsequent follow up, none of the patients suffered from any complications as a result of the retained IPC, including two cases that received chemotherapy.
1.5.2.4 Indwelling Pleural Catheter Blockage

Mechanical faults of the IPC drainage system arise infrequently and most can be corrected without the removal of the catheter. The formation of dense fibrinous tissue around and within the IPC can occasionally lead to blockage of some lumen but complete occlusion of all lumen by clogged materials is uncommon, with an incidence of <5% (88). Saline flush and manipulation along the catheter or instillation of fibrinolytics have been successfully used to re-establish patency of blocked catheters. Rarely, mechanical defects (e.g. incompetent one-way valve) can occur but most can easily be replaced (97).

1.5.2.5 Chest Pain

Mild pain during or immediately after IPC insertion is common (36%), and can be relieved with the use of longer-acting local anaesthetics and intravenous sedation (88). During intermittent drainage under suction, negative pressure may develop inside the pleural cavity with or without entrapment of the pleural tissues resulting in pain. Slowing or stopping the drainage can alleviate this. Severe pain requiring catheter removal is rare (0.6%) (88).
CHAPTER 2

HYPOTHESES
Chapter 2    Hypotheses

Part 1 - Define Advantages of Indwelling Pleural Catheter

Minimizing the total time spent in hospital is an important and meaningful patient-related outcome measure for cancer patients, who have a limited life expectancy (16, 98), and their carers. It is hypothesised that IPC treatment will provide significant hospital days' savings compared to talc pleurodesis. The Australasian Malignant Pleural Effusion (AMPLE) RCT tests this hypothesis.

Part 2 - Define Indwelling Pleural Catheter-Related Complications

Despite their clinical significance, limited data exist on the clinical course or best management of important IPC-related complications, particularly IPC-related symptomatic loculation, catheter tract metastasis (CTM) and catheter interactions in the pleural milieu (95). It is hypothesised that these IPC-related complications are mild and treatable.

Part 3 - Understanding Pathobiology of Malignant Pleural Effusions Through Novel Use of Indwelling Pleural Catheters

It was not possible earlier to collect malignant pleural fluid serially and study changes in the pleural milieu during the disease course. It is hypothesised that serially collected pleural fluid using IPC will demonstrate longitudinal changes in pleural fluid biochemistry and key cytokines level in patients with an MPE.
PART 1 – DEFINE ADVANTAGES OF INDWELLING PLEURAL CATHETER
Hospitalisation Days

The evidence to date suggests that IPCs provide equivalent benefits in breathlessness and QoL compared to talc pleurodesis, and with a shorter initial hospital stay. MPE patients frequently require hospitalisation for invasive pleural drainage procedures to relieve their breathlessness. Allowing patients to remain ambulatory outside hospital is one of the main goals in palliative care. Defining the treatment that minimises hospitalisation in the patients’ remaining lifespan will help guide choice of therapy.

The Australasian Malignant Pleural Effusion (AMPLE) protocol (Chapter 3) and AMPLE randomised controlled trial (Chapter 4) directly compares the effects of IPC versus chest tube and talc slurry pleurodesis on total all-cause hospitalisation in patients with MPE.
CHAPTER 3

PROTOCOL OF THE AUSTRALASIAN MALIGNANT PLEURAL EFFUSION (AMPLE) TRIAL: A MULTICENTRE RANDOMISED STUDY COMPARING INDWELLING PLEURAL CATHETER VERSUS TALC PLEURODESI S
Protocol of the Australasian Malignant Pleural Effusion (AMPLE) trial: a multicentre randomised study comparing indwelling pleural catheter versus talc pleurodesis

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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 multicentred, randomised trial designed to compare IPC with talc pleurodesis for the management of malignant pleural effusion. This study will randomise 146 adults with malignant pleural effusions (1:1) to IPC management or talc slurry pleurodesis. The primary end point is the total number of days spent in hospital (for any admissions) from treatment procedure to death or end of study follow-up. Secondary end points include hospital days specific to pleural effusion management, adverse events, self-reported symptom and quality-of-life scores.

Ethics and dissemination: The Sir Charles Gairdner Group Human Research Ethics Committee has approved the study as have the ethics boards of all the participating hospitals. The trial results will be published in peer-reviewed journals and presented at scientific conferences.

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 carcinomas and most (>90%) patients with malignant pleural mesothelioma. 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 symptoms relief (especially dyspnoea), minimal hospitalisation and have the least adverse effects. Conventional management involves inpatient tcalc 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 (eg, 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 AMPLEx study is designed to further evaluate the findings in a multicentre and randomised setting.

### METHODS AND ANALYSIS

The AMPLEx 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 Trials 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\(^\text{17}\)) 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 bouncing diathesis
12. Irreversible visual impairment
13. Inability to give informed consent or comply with 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 supportive 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.

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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.

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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.

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REFERENCES
CHAPTER 4

IMPACT OF INDWELLING PLEURAL CATHETER
VERSUS TALC PLEURODESIS MANAGEMENT FOR
MALIGNANT PLEURAL EFFUSIONS ON TIME SPENT
IN HOSPITAL IN PATIENTS’ REMAINING LIVES:
THE AUSTRALASIAN MALIGNANT PLEURAL EFFUSION
(AMPLE)
RANDOMISED CONTROLLED TRIAL
Impact of Indwelling Pleural Catheter versus Talc Pleurodesis Management for Malignant Pleural Effusions on Time Spent in Hospital in Patients’ Remaining Lives: The Australasian Malignant Pleural Effusion (AMPLE) Randomized Controlled Trial

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**Conflict of Interest:** YCGL, RT, BCHK, EY, DCCL, LAG and RS are investigators of the AMPLE-2 trial for which Rocket Ltd provided the drainage supplies without charge. YCGL has served on the advisory board of CareFusion Ltd and Sequana Medical and has received an unrestricted educational grant from Rocket Ltd. CK has served on the advisory board of Teva Pharmaceutical Australia and has received travel grants and speakers fees from UCB UK. EF, PL, FP, CAR and KM have no conflicts of interest to declare.
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Short Title: IPC vs Pleurodesis for Malignant Effusion: Total hospital time in patients’ lifespan
Key Points

**Question:** Is management of malignant pleural effusion (MPE) with indwelling pleural catheter (IPC) more effective than talc pleurodesis in minimizing hospitalization in patients’ remaining lifetime?

**Findings:** This randomized clinical trial of 146 MPE patients showed that IPC treatment reduced lifetime hospitalization compared with talc pleurodesis (12.7 vs 16.3 days respectively), a significant difference. Significantly fewer patients in the IPC group required further pleural drainages (4.1% compared with 22.5% of those in pleurodesis group).

**Meaning:** Patients should consider the advantages IPC management offers in reducing hospitalization and further pleural interventions when choosing therapeutic options for their MPEs.
ABSTRACT

Importance: Malignant pleural effusions (MPEs) affect more than a million people worldwide each year. Talc pleurodesis and indwelling pleural catheter (IPC) are established treatments. Available data showed that both treatments offered similar quality-of-life benefits, resulting in equipoise. MPEs herald limited prognoses; freedom from hospitalization and further interventions are important goals of management.

Objective: To determine whether IPCs are more effective than talc pleurodesis in reducing total hospitalization days in the remaining lifespan of MPE patients.

Design: Open-labeled, randomized controlled trial.

Setting: Participants were recruited from nine centers in Australia, New Zealand, Singapore and Hong Kong between July 2012 and October 2014, and were followed up for 12 months.

Participants: 146 patients with symptomatic MPE who had not undergone IPC or pleurodesis treatment.

Interventions: Participants were randomized (1:1) to IPC or talc pleurodesis, minimized by region (Australasia vs Asia), malignancy (mesothelioma vs others), and trapped lung (vs not).
**Main Outcomes and Measures:** The primary endpoint is the total number of days spent in hospital from treatment to death, or to 12 months from trial intervention. Secondary outcomes included further pleural interventions, patient-reported breathlessness scores, quality-of-life measures, and adverse events.

**Results:** The IPC group spent significantly fewer days in hospital than the Pleurodesis group: median (IQR) 10.0 (14) vs 12.0 (14) days, p=0.026, which represented 6.2 (13.8)% vs 11.1 (33.7)% of their remaining lifespan in hospital respectively, p=0.01. Mean reduction in hospitalization days was 3.6 days per patient: 12.7 (IPC) vs 16.3 (Pleurodesis) days. The reduction was mainly in effusion-related hospitalizations: median 1.0 (IPC) vs 4.0 (Pleurodesis) days, p<0.001, though fewer non-effusion related hospitalization days were observed with IPC treatment. Fewer IPC-treated patients required further invasive pleural drainages (4.1% vs 22.5%, 95% CI 7.7-29.2%). Both treatments provided significant improvement in breathlessness and quality-of-life, and had comparable rates of adverse events.

**Conclusions and Relevance:** IPC management reduces the total number of days MPE patients spent in hospital before death and minimizes the need for further invasive pleural interventions, while providing equivalent symptomatic improvement, when compared with conventional talc pleurodesis. These findings can inform patients with MPE in their choice of management.

**Registration:** ACTRN12611000567921
INTRODUCTION

Malignant pleural effusion (MPE) affects over a million people worldwide each year, and can complicate most cancers, especially lung, breast cancers and mesothelioma (1, 2). The resultant breathlessness is often distressing and impairs quality-of-life (QoL). Drainage of the effusion can relieve symptoms but requires presentation to hospital and invasive pleural procedures.

MPEs herald advanced cancers and often limited life expectancies, eg 3-4 months for patients with metastatic lung cancer (3). The aims of MPE management are to provide effective symptom relief with minimal interventions and hospital stay. Freedom from hospital admissions is an important goal for patients with MPE and their families (4).

Talc pleurodesis and drainage with an indwelling pleural catheter (IPC) are two established management approaches for recurrent MPEs (5). No studies have directly compared their impact on the total time MPE patients spent in hospital in their remaining lifespan – a significant endpoint to patients and to the healthcare system.

Talc pleurodesis remains the most commonly employed treatment worldwide since its description in 1935 (6). It requires an initial hospitalization of several days. Two randomized controlled trials (RCTs) both found that talc pleurodesis failed in ~30% of patients within three months, irrespective if talc was administered by poudrage or slurry (7), and via large or small drains (8). Similarly, the largest series of MPE from mesothelioma found that ~30% of patients failed talc pleurodesis and necessitated further pleural drainages (9).
IPC has gained popularity rapidly as an alternative to talc pleurodesis, principally for its ease of insertion as a short-stay procedure and subsequent ambulatory drainage (10). IPC provided equivalent improvement in breathlessness and QoL when compared with talc or doxycycline pleurodesis (11, 12). However, IPC treatment requires ongoing care, and has its own unique range of complications that trigger hospital care e.g. pleural infection, blockage, symptomatic loculation, and catheter track metastasis (13-15).

Our pilot, non-randomized, patient-choice study (n=65) suggested that MPE patients who opted for IPC treatment spent less time in hospital (8% vs 11.2% of their remaining lifespan) before death than those who chose talc pleurodesis (16).

The Australasian Malignant Pleural Effusion (AMPLE) trial was a multi-centered, randomized, open-labeled study designed to compare the effects of IPC and talc slurry pleurodesis on the total number of days MPE patients spent in hospital in their remaining lifespan (17). Secondary endpoints assessed the need for further pleural interventions, effects on hospitalization directly related with pleural effusions, symptom improvements, survival and adverse events.

**METHODS**

The AMPLE trial protocol has been published (17). Ethics and governance approvals were obtained from the human research ethics committee at all sites, the primary site being the Sir Charles Gairdner Group Human Research and Ethics Committee (SCGG 2012-005). The AMPLE trial was conducted from nine centers: Sir Charles Gairdner, Fiona Stanley,
Swan District, Princess Alexandra and St George and Sutherland Hospitals in Australia; Wellington and Middlemore hospitals in New Zealand; National University Hospital Singapore; and Queen Mary Hospital Hong Kong.

All patients enrolled were adults with MPEs with histo-cytological confirmation of pleural malignancy, or recurrent exudative pleural effusions with no alternative cause in the setting of histo-cytologically proven extra-pleural cancer. Exclusion criteria included age <18 years, effusion <2cm at maximum depth on imaging, expected survival <3 months, chylothorax, previous lobectomy or pneumonectomy on the side of effusion, previous attempted pleurodesis, pleural infection, hypercapnic ventilatory failure, blood leukocyte count <1.0x10⁹/l, pregnant or lactating females, irreversible bleeding diathesis, and visual impairment.

**Randomization:** Participants were randomized 1:1 to either IPC or talc slurry pleurodesis in real time by a web interface (Filemaker Server Advanced, Filemaker Inc., Santa Clara, USA) after minimization of 80% to reduce bias from between-group differences in important variables. Randomization was minimized according to centers (Australia/New Zealand vs. Singapore/Hong Kong), mesothelioma (vs. non-mesothelioma), and trapped lung (vs. not) to account for potential differences in ethnicity, median survival of different cancer types, and pleurodesis failure rate respectively (2, 18).

**Interventions:** Patients randomized to the IPC arm had the catheter inserted as per the modified Seldinger technique with tunneling, followed by fluid removal, as a same-day or overnight-stay procedure unless there were other medical reasons necessitating continual
hospitalization. Ambulatory fluid drainages were performed by carers or nurses tailored to patients’ symptoms. IPCs were removed if fluid drainage ceased. Participants randomized to talc pleurodesis underwent thoracostomy (12-18F), followed by instillation of talc slurry as per routine practice of the recruiting hospital. All participants received usual standard care including chemotherapy, radiotherapy, and palliative care as recommended by their attending clinicians.

**Outcomes:** The primary outcome was the total number of days spent in hospital from trial intervention to death, or up to the 12-month follow-up visit. Any hospital, including hospice, admission involving ≥1 day was included. One ‘day’ referred to a hospital stay crossing a midnight. Day-case procedures (eg chemotherapy) were excluded. The duration of hospital admissions were decided independently by the treating physicians. Data on all hospital admissions were collected from participants (during follow-up visits), carers, general practitioners, electronic databases and case records. An independent assessor (CK) reviewed the validity (justification and duration) of each hospital admission based on the discharge summary, and full hospital record (if needed).

**Secondary Outcomes:**

i. Total number of days and episodes of hospitalization from pleural effusion-related causes, including admissions for management of pleural effusion, associated symptoms, related procedures and/or their complications.

ii. Need for further pleural drainage procedures.

iii. Breathlessness as measured using a Visual Analogue Scale (VAS) validated for MPE patients (19). The VAS was a 100mm line anchored with ‘no breathlessness’ at
100mm, and ‘worst imaginable breathlessness’ at 0mm. Participants recorded their VAS scores daily in the initial 14 days, and at follow-up visits at 1, 3, 6, 9 and 12 months. If patients were unable to attend follow-up, a research nurse (CAR) would record the patient’s reported score by telephone.

iv. QoL as quantified by a) a modified EQ5D questionnaire score (20) for QoL and b) a 100mm VAS and recorded at baseline, 8 and 14 days (for EQ5D) or daily for 14 days (for VAS), and 1, 3, 6, 9 and 12 months.

v. Survival.

vii. Adverse and serious adverse events.

Statistical Analyses: The study was powered to detect a difference of 5 days or more spent in hospital between the groups (80% power; \( \alpha=0.05 \)). An estimated 65 participants were needed per group, based on a total stay of 18 days and a SD of 9.3 days in the pleurodesis group from the pilot study (16). The recruitment target of 146 allowed for a lost-to-follow-up rate of 12%.

Two-sided superiority analyses were conducted on an intention-to-treat basis for all outcomes. The primary endpoint was analyzed initially using a Mann Whitney test. Subsequent supporting analyses were carried out using a negative binomial model with adjustments for actual length of follow-up (accounting for death and withdrawals) and minimization variables. The total effusion-related and non-effusion related hospital bed days were analyzed similarly. VAS and EQ5D scores were analyzed using linear mixed effects models, including fixed effects of treatment, time and time-dependent covariates as appropriate and random effects of individual. Cox proportional hazards models were used
to analyze time-to-death. Frequencies of serious adverse events and further pleural intervention were analyzed using chi-squared or Fisher’s exact tests.

**RESULTS**

146 MPE participants were recruited between July 2012 and October 2014 (Fig 1). Both groups were well matched in their demographics, ratio of primary vs secondary pleural malignancies, effusion sizes, baseline symptom scores and ECOG status (Table 1). One patient from each group withdrew before presenting for the randomized intervention; they were excluded from all analyses.

Hence, 144 patients – 73 in the IPC and 71 the pleurodesis arm – informed the intention-to-treat (ITT) analyses. Per-protocol analyses (PPA) were performed in 134 patients, after excluding 12 patients (3 from IPC and 9 from pleurodesis arms) who withdrew and/or did not receive their full allocated treatment (mostly for technical reasons).

**Total Days Spent in Hospital** (Fig 2A): Overall, patients with MPE spent a significant number of days in hospital: median 10.0 (IQR 15.5) days; mean 14.5 (SD 14.4) days. This represented a substantial part of their remaining lifespan: median 7.1 (IQR 26.4) %; mean 21.0 (SD 29.0) %.

Treatment with IPC significantly reduced the total days spent in hospital, compared with talc pleurodesis: median 10 (IQR 14) vs 12 (14) days respectively, \( p=0.026 \). The mean (SD) reduction in hospitalization was 3.6 days per patient: 12.7 (13.4) in the IPC vs 16.3 (15.2) in the Pleurodesis group. Adjusted for individual survival, patients randomized to IPC
treatment spent significantly less of their remaining lifespan in hospital: median 6.2 (IQR 13.8) % in the IPC group vs 11.1 (33.7) % in the Pleurodesis group, \( p=0.01 \).

The above findings remained consistent in Per-Protocol Analysis (PPA) which confirmed a significant reduction in total days spent in hospital using IPC: median (IQR) 10 (14) vs 13 (15) days in Pleurodesis group, \( p=0.015 \). The mean (SD) reduction in hospitalization from PPA was 4.5 days/patient: 12.6 (13.4) in IPC vs 17.1 (15.8) in the Pleurodesis group. Median time spent in hospital represented 5.6 (13.9) % of the patients’ remaining lifespan in the IPC group and 11.1 (33.7) % in the Pleurodesis group, \( p=0.012 \).

The differences in total hospitalization days remained consistent after adjustment for minimization variables and days in trial during ITT and Per-Protocol analyses (Table 2A). Subgroup analysis confirmed the benefits for MPE patients (n=106) with metastatic cancers, reducing days spent in hospital to median 10.0 (IQR 12.0), vs. talc pleurodesis 14.0 (15.0), \( p=0.026 \). A similar, although statistically non-significant, reduction was also seen with the smaller subgroup of mesothelioma patients (n=38).

**Other Endpoints**

*Days Spent in Hospital for Pleural Effusion-related Causes:* IPC significantly reduced the number of total hospitalization days for causes directly related to pleural effusion and treatment complications: median (IQR) 1 (2) day vs 4 (3) days in Pleurodesis group, \( p<0.001 \), and remained significant when adjusted for minimization variables and days in trial \( p<0.001 \). The maximum benefit was seen during the initial hospital admission; median 1 day (IPC) versus 3 days for Pleurodesis group \( (P<0.001) \). The reduction in
effusion-related hospitalization days from IPC treatment over pleurodesis were significant for both metastatic carcinoma patients, median (IQR): 2 (2) vs 4 (3) days respectively, \( p<0.001 \) and for mesothelioma patients: 1 (2) vs 3 (2) days \( (p=0.008) \). A trend of reduction was also seen with non-effusion related hospitalization days.

**Need for Further Pleural Drainage Procedures:** Significantly fewer patients in the IPC group \( (n=3, 4.1\%) \) required further pleural interventions for fluid drainage after the initial procedure \( (n=16 \text{ in the pleurodesis group}, 22.5\%) \), \( \text{RR}=0.18 \ (95\% \text{ CI, 0.06-0.60; } p=0.001) \), Fig 2B.

Talc pleurodesis failed in 16 patients (22.5\%), and required further drainage interventions. after a median of 26.5 (IQR 61.5) days. Most patients with pleurodesis failure \( (n=10) \) were subsequently managed successfully with IPC. Others received repeated therapeutic drainages \( (n=3) \), and repeat talc slurry pleurodesis \( (n=2) \); the latter failed again in one patient who then had VATS with talc poudrage. One underwent thoracotomy with partial pleurectomy and a pericardial window to control recurrent pleural and pericardial fluid.

Three patients in the IPC group required further pleural punctures. One had loculated effusion that prevented IPC insertion and was managed with blunt dissection, large-bore chest drain insertion, followed by successful pleurodesis. One developed a pneumothorax with subcutaneous emphysema that required chest tube placement. The third patient had recurrence of effusion after successful removal of the initial IPC, treated with a second IPC.
IPC was removed in 25/83 (30.1%) patients including those randomized to IPC treatment (21/73 patients) and those who underwent IPC insertion after failed pleurodesis (4/10).

**Breathlessness Scores:** Baseline VAS scores showed that the patients were breathless: IPC group 48mm (SD 27); Pleurodesis group 50.2mm (SD 26). The symptoms were significantly improved by day 1 post-procedure with improvements in VAS score of 14.9mm (95% CI 9.8-20.0) for the IPC group and 17.7mm (95% CI 12.5-22.9) for the Pleurodesis group. The improvements were maintained in subsequent visits up to 12 months. No significant differences were found in the magnitude of symptom benefits derived from IPC treatment or pleurodesis (Fig 3A).

**QoL:** QoL measures quantified by VAS and by modified EQ5D both revealed a pattern similar to that of the breathlessness scores. The groups were balanced at their baseline QoL scores, which significantly increased from initial treatment with IPC or pleurodesis. The improvement was maintained throughout the study follow-up in both groups. No significant differences were found in the magnitude of QoL improvement derived from IPC treatment or pleurodesis (Fig 3B-C).

**Survival:** Within the follow-up period (median 204 days), 60% (44/73) of the patients in the IPC group and 72% (51/71) in the Pleurodesis group died, \( p=0.125 \) (log rank) and \( p=0.085 \) (Cox proportional hazards model adjusting for minimization variables).

**Adverse events** (Table 2B): One patient (1%) in the IPC group vs 3 (4%) in the pleurodesis group experienced serious adverse events (RR 0.32; 95% CI, 0.03-3.04; \( p=0.36 \)). Any
adverse event occurred (n=30) in 22 patients (30%) in the IPC group whereas 13 patients (18%) in the talc group experienced 18 adverse events (RR 1.65; 95% CI, 0.90-3.01; \( p=0.12 \)). Worsening breathlessness and procedure-related pain were the most common adverse events in both groups. The catheter was dislodged in one IPC and four pleurodesis patients. Pleural infection (n=2), cellulitis (n=3), symptomatic fluid loculation (n=1) and catheter blockage (n=3) were reported with IPC management.

**DISCUSSION**

Patients with MPE have limited prognosis; the management goals are to relieve symptoms with minimal intervention and maximize time outside hospital. The AMPLE trial is the first to measure total days spent in hospital in patients’ remaining lifespan as a principle outcome in MPE management. Our data proved superiority of IPC management over talc pleurodesis in reducing i) lifetime all-cause hospital stay, ii) hospital days related to pleural effusion management and iii) further invasive MPE drainages. IPC provided significant improvements in breathlessness and QoL, without increasing adverse events or mortality. Our findings will inform patients and clinicians in deciding management.

Use of IPC significantly minimized the amount of patients’ remaining lifespan spent in hospital (median 6.2% vs 11.1%) over conventional pleurodesis. Reducing an average 3.6 days in hospital per patient will free up substantial hospital beds and resources, considering 150,000 patients have a MPE in USA alone each year (1).

IPC and pleurodesis are two strategies with separate advantages and disadvantages (21); existing literature suggests equipoise (10). In two RCTs comparing IPC with pleurodesis,
by talc (n=106) or doxycycline (n=144), both treatments provided comparable symptomatic benefits; none was found superior (11, 12). Our trial confirmed these findings but provided new data showing a clear advantage of IPC in reducing hospitalization time, and supports IPC as the first choice therapy.

IPC provides several advantages over talc pleurodesis that would have contributed to the reduction in the total hospitalization days before death. First, patients randomized to IPC treatment have shorter initial hospital admissions (p<0.001), as IPCs are placed as day-case or overnight procedures whereas pleurodesis requires chest tube insertion, complete evacuation of fluid, talc instillation, and hospitalization until fluid drainage ceases. Second, talc pleurodesis failed and necessitated further drainage interventions in 23% of patients in our trial, most of whom required admissions for further interventions. This failure rate is in keeping with other trials (7, 22). Conversely, only 4% of IPC-treated patients required further pleural drainages. This explains why total hospitalization days after the initial admission remained lower in the IPC group (median 4 vs 6 days). The lower re-intervention rate with IPC is an important consideration and benefit for patients with advanced cancer. Our data also showed that IPC-specific complications (e.g. empyema) are relatively uncommon, consistent with our other longitudinal studies (23-25), and did not increase the median hospitalization days.

Further studies are underway to optimize the benefits of IPC use. The AMPLE-2 trial is a RCT comparing aggressive (daily) IPC drainages with symptom-guided ‘as required’ approach for dyspnea relief and likelihood of spontaneous pleurodesis (26). Whether talc instillation via an IPC can improve pleurodesis rate is the subject of the ongoing IPC-PLUS
IPC coated with a sclerosant (silver nitrate) has shown promise in animal studies and in a pilot clinical study (28).

Talc can be administered as slurry via a chest tube or as dry powder via thoracoscopic poudrage. Previous randomized studies showed that talc slurry and poudrage have similar failure rates (7, 8); whether the different delivery methods impact on lifetime all-cause hospitalization has yet been studied. Australia has one of the world’s highest incidences of mesothelioma (29). Our study therefore included more mesothelioma patients than would otherwise be expected in many countries. Our study randomization did stratify patients by mesothelioma (vs other cancers) and subgroup analyses showed similar benefits in reducing hospitalization days. Subgroup analysis of individual metastatic cancers with MPE with different survivals e.g. lung and breast cancer were not performed due to small numbers however results remained consistent even after adjustment for 'time in trial'.

Our study has limitations. First, variations are common on talc pleurodesis protocols and no proven ‘gold standard’ exists. In this pragmatic study we allowed treating clinicians to perform talc pleurodesis following their center’s routine practice (including drain size). A recent study suggested that pleurodesis via a 24 Fr chest drain can improve the failure rate over 12 Fr drains (24% vs 30% respectively) (8). However, the margin of improvement was relatively small and unlikely to impact on total hospitalization days. Second, no health economic analyses were planned. This decision was taken a priori as the costs of hospital days, IPC equipment and drainage kits, pleurodesis costs etc vary vastly worldwide (30, 31), including among our participating centers. Clinicians need to translate the reduction of hospital days into local cost currencies to establish the healthcare savings in individual
health systems.

Future studies should address the impact of newer cancer therapies e.g. tyrosine kinase inhibitors for EGFR-positive lung cancers on hospitalization days. Third, VAS and EQ5D QoL scores are not designed to capture the inconvenience and discomfort associated with IPC treatment. However, the significant improvements in QoL with IPC treatment suggests that the associated inconvenience and discomfort is not significant enough to negate the overall benefits.

We conducted the first RCT employing total hospitalization days in patients’ remaining lifespan as the principle endpoint for MPE. We established that IPC minimizes time spent in hospital and invasive pleural re-interventions for MPE patients in their palliative journey.
Table 1 - Baseline Demographic Data for 146 randomized patients with MPE

<table>
<thead>
<tr>
<th></th>
<th>Indwelling Pleural Catheter</th>
<th>Talc Pleurodesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, No.</td>
<td>74</td>
<td>72</td>
</tr>
<tr>
<td>Age, median (range), years</td>
<td>71.0 (38-92)</td>
<td>70.5 (43-90)</td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>39 (53)</td>
<td>43 (60)</td>
</tr>
<tr>
<td>Right side, No. (%)</td>
<td>44 (59)</td>
<td>38 (53)</td>
</tr>
<tr>
<td>Type of primary malignancy, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>20 (27)</td>
<td>18 (25)</td>
</tr>
<tr>
<td>Non-mesothelioma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>19 (26)</td>
<td>29 (40)</td>
</tr>
<tr>
<td>Breast</td>
<td>14 (19)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Others</td>
<td>21 (28)</td>
<td>21 (29)</td>
</tr>
<tr>
<td>Known trapped lung, before randomization, No. (%)</td>
<td>2 (3)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>ECOG, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>53 (72)</td>
<td>53 (74)</td>
</tr>
<tr>
<td>3-4</td>
<td>19 (26)</td>
<td>14 (19)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (3)</td>
<td>5 (17)</td>
</tr>
<tr>
<td>Effusion size*, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small (0-1)</td>
<td>0 (0)</td>
<td>0(0)</td>
</tr>
<tr>
<td>Moderate (2-3)</td>
<td>38 (51)</td>
<td>38 (53)</td>
</tr>
<tr>
<td>Large (4-5)</td>
<td>36 (49)</td>
<td>34 (47)</td>
</tr>
<tr>
<td>VAS dyspnoea score, mean (SD), mm</td>
<td>48.4 (27)</td>
<td>50.2 (26)</td>
</tr>
<tr>
<td>VAS QOL score, mean (SD), mm</td>
<td>51.6 (26.1)</td>
<td>55.9 (25.1)</td>
</tr>
<tr>
<td>EQ-5D QOL score, mean (SD)</td>
<td>31.3 (10.5)</td>
<td>32.6 (9.7)</td>
</tr>
</tbody>
</table>

* Baseline effusion size was graded on chest radiograph immediately prior to trial intervention, using a validated grading system whereby 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[32]. This scale has previously been used to predict pleurodesis and indwelling pleural catheter use in patients with MPE[33].
Table 2A - Summary of primary and secondary outcomes by ITT analysis.

<table>
<thead>
<tr>
<th></th>
<th>Indwelling Pleural Catheter (n=73)</th>
<th>Talc Pleurodesis (n=71)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total all-cause hospital stay</td>
<td>Median (Range)</td>
<td>10 (0-83)</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)*</td>
<td>12.7 (13.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Secondary Outcomes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effusion-related hospital stay</td>
<td>Median (Range)</td>
<td>1 (0-25)</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)*</td>
<td>3.1 (4.3)</td>
</tr>
<tr>
<td>Non-Effusion-related hospital</td>
<td>Median (Range)</td>
<td>5 (0-82)</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)*</td>
<td>9.6 (12.7)</td>
</tr>
<tr>
<td></td>
<td>VAS dyspnoea scores, mean (SD), mm</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>48.0 (27)</td>
<td>50.2 (26)</td>
</tr>
<tr>
<td>Day 1 post-procedure</td>
<td>65.1 (23.6)</td>
<td>69.7 (23.6)</td>
</tr>
<tr>
<td>30 days</td>
<td>69.7 (23.5)</td>
<td>71.7 (23.7)</td>
</tr>
<tr>
<td>6 months</td>
<td>76.2 (19.7)</td>
<td>76.4 (22.7)</td>
</tr>
<tr>
<td>12 months</td>
<td>77.5 (22.2)</td>
<td>65.8 (28.9)</td>
</tr>
<tr>
<td></td>
<td>VAS QoL scores, mean (SD), mm</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>51.6 (26.3)</td>
<td>55.9 (25.1)</td>
</tr>
<tr>
<td>Day 2 post-procedure</td>
<td>61.0 (20.3)</td>
<td>59.7 (22.4)</td>
</tr>
<tr>
<td>30 days post-procedure</td>
<td>62.7 (24.4)</td>
<td>67.2 (23.2)</td>
</tr>
<tr>
<td>6 months post-procedure</td>
<td>74.9 (18.1)</td>
<td>70.9 (24.1)</td>
</tr>
<tr>
<td>12 months post-procedure</td>
<td>71.3 (21)</td>
<td>62.0 (30.1)</td>
</tr>
<tr>
<td></td>
<td>EQ5D QoL scores</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>31.2 (10.5)</td>
<td>32.6 (9.7)</td>
</tr>
<tr>
<td>Day 8 post-procedure</td>
<td>35.3 (11.1)</td>
<td>36.7 (9.8)</td>
</tr>
<tr>
<td>30 days post-procedure</td>
<td>37.3 (12.8)</td>
<td>35.6 (10.5)</td>
</tr>
<tr>
<td>6 months post-procedure</td>
<td>39 (7.9)</td>
<td>37.2 (12.2)</td>
</tr>
<tr>
<td>12 months post-procedure</td>
<td>38.1 (8.1)</td>
<td>36.3 (10.9)</td>
</tr>
<tr>
<td></td>
<td>Survival</td>
<td></td>
</tr>
<tr>
<td>Deaths at 12 months, number (%)</td>
<td>44 (60)</td>
<td>51 (72)</td>
</tr>
<tr>
<td>Complications: number of patients (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>1 (1)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Non serious adverse events</td>
<td>21 (29)</td>
<td>12 (17)</td>
</tr>
<tr>
<td>Total adverse events</td>
<td>22 (30)</td>
<td>13 (18)</td>
</tr>
<tr>
<td>Further pleural procedures</td>
<td>3 (4)</td>
<td>16 (22)</td>
</tr>
</tbody>
</table>

*Data not normally distributed but mean (SD) included for calculations in savings of days in population cohorts.
Table 2B - Summary of serious adverse events and adverse events by ITT analysis

<table>
<thead>
<tr>
<th>Type of adverse event</th>
<th>Indwelling Pleural Catheter n=73</th>
<th>Talc Pleurodesis  n=71</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse events (SAE)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients affected, No. (%)</td>
<td>1 (1)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Total SAE, No.</td>
<td>1*</td>
<td>3**</td>
</tr>
<tr>
<td>Adverse events (AE)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleural infection</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Symptomatic loculation</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Catheter blockage</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pain related to procedure</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Worsening breathlessness</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Tube dislodgement</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Others</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Total AE, No.</td>
<td>29</td>
<td>20</td>
</tr>
<tr>
<td>Total SAE + AE, No.</td>
<td>30</td>
<td>23</td>
</tr>
<tr>
<td>Patients affected by any adverse event, No. (%)</td>
<td>22 (30)</td>
<td>13 (18)</td>
</tr>
</tbody>
</table>

* One patient suffered a Pulseless Electrical Activity cardiac arrest following IPC insertion due to underlying cardiac disease, but was successfully resuscitated without sequelae.

** One patient died during surgery for a femoral fracture after a fall; one developed submassive pulmonary emboli; one developed severe chest pain requiring hospital admission.

The between-group differences in the number of patients suffering SAEs (n=1 vs 3, RR 0.32; 95% CI 0.03-3.04; Fischer’s exact p=0.36) or total AEs (22 vs 13, RR 1.65; 95% CI 0.90-3.01; p=0.12) did not reach statistical significance.
Fig 1 - Consort diagram.

226 MPE patients screened

- Excluded (n = 80)
  - Did not fulfill criteria (n = 25)
  - Declined (n = 38)
  - Other reasons (n = 17)

146 randomized

2 patients (1 from each group) withdrew before any intervention was attempted

144 patients for Intention-to-Treat analysis

IPC arm n = 73
- Withdrew (n = 1)
- Did not receive IPC
  - severe loculation (n = 1)

Pleurodesis arm n = 71
- Withdrew (n = 1)
- Did not receive talc
  - catheter fell out (n = 4)
  - trapped lung (n = 2)
  - severe loculation (n = 1)
Fig 2 - Advantages of IPC management over talc pleurodesis.

Fig 2A) The total days patients spent in hospital until death, or 12 month follow-up, are presented in the *left* panel, as absolute days and in the *right* panel, as a percentage of the patients' remaining lifespans. n=73 in the IPC group; n=71 in the talc pleurodesis group. Box plots show median, interquartile range and 10-90 percentile whiskers. Each dot represents one patient.
Fig 2B) The percentage of patients in each group that required further invasive pleural fluid drainage interventions. IPC (n=3, 4.1%, 2.32SD) and Pleurodesis (n=16, 22.5%, 4.96SD).
Fig 3 - Comparison of IPC vs Pleurodesis in Fig 3A) Breathlessness Score (measured in 100mm VAS); Fig 3B) QoL Score as measured in a 100mm VAS; and Fig 3C) QoL as measured by a modified EQ5D instrument.

**Fig 3A)**

![Graph showing comparison of IPC vs Pleurodesis](image)

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>IPC Mean</th>
<th>IPC Std Dev</th>
<th>IPC N</th>
<th>Pleurodesis Mean</th>
<th>Pleurodesis Std Dev</th>
<th>Pleurodesis N</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>48.0</td>
<td>27.0</td>
<td>64</td>
<td>26.0</td>
<td>26.0</td>
<td>64</td>
</tr>
<tr>
<td>3</td>
<td>70.0</td>
<td>22.1</td>
<td>47</td>
<td>23.0</td>
<td>24.8</td>
<td>44</td>
</tr>
<tr>
<td>6</td>
<td>69.7</td>
<td>23.5</td>
<td>44</td>
<td>23.7</td>
<td>23.7</td>
<td>44</td>
</tr>
<tr>
<td>9</td>
<td>67.6</td>
<td>22.4</td>
<td>43</td>
<td>25.0</td>
<td>25.0</td>
<td>42</td>
</tr>
<tr>
<td>12</td>
<td>74.2</td>
<td>21.8</td>
<td>42</td>
<td>25.9</td>
<td>25.9</td>
<td>42</td>
</tr>
</tbody>
</table>
Fig 3B)

<table>
<thead>
<tr>
<th></th>
<th>IPC</th>
<th>Pleurodesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>51.6</td>
<td>55.0</td>
</tr>
<tr>
<td>Std Dev</td>
<td>26.3</td>
<td>25.1</td>
</tr>
<tr>
<td>N</td>
<td>66</td>
<td>63</td>
</tr>
</tbody>
</table>

Visual Analogue Scale (VAS) Quality of Life (QoL) Score

Time (months)

- IPC
- Pleurodesis
Fig 3C)
REFERENCES


PART 2 – DEFINE INDWELLING PLEURAL CATHETER-RELATED COMPLICATIONS
CHAPTER 5

INTRAPLEURAL FIBRINOLYSIS FOR THE TREATMENT OF INDWELLING PLEURAL CATHETER-RELATED SYMPTOMATIC LOCULATIONS - A MULTI-CENTRE OBSERVATIONAL STUDY
IPCs improve patient symptoms, particularly breathlessness, by allowing ambulatory drainage of recurring pleural fluid. The development of pleural loculations can lead to failure of effective drainage, resulting in fluid re-accumulation and recurrence of breathlessness. This negates the symptomatic benefits of effective IPC drainage and makes the primary goal to palliate symptoms of breathlessness more difficult.

IPC-related symptomatic loculation is defined by residual pleural effusion that fails to evacuate through a patent IPC, breathlessness related to the effusion and absence of evidence of pleural infection. IPC-related symptomatic loculation is common with a reported incidence of 5-14%, and typically occurs at about 2 months after IPC insertion (62, 69, 82, 99, 100). Despite its clinical significance and frequent occurrence, IPC-related symptomatic loculation has seldom been described; only two studies have reported, albeit briefly, on the clinical course and management of IPC-related symptomatic loculation (95). The largest published series by Tremblay et al (82) reported an incidence of 8.4% (n=21) in 250 IPC patients while Fysh et al (69) reported an incidence of 13.5% (n=5) in 34 patients.

Therapeutic options for IPC-related symptomatic loculations are often limited to further invasive procedures e.g. repeated pleural aspirations, insertion of a second IPC, removal of the ineffective IPC and/or replacement by another IPC or chest drain to target the residual locules, surgical breakdown of the loculations, and pharmacological palliation of dyspnoea. These strategies necessitate invasive procedures with inherent risks and need for hospitalisation, and the feasibility depends on the locations and sizes of the residual locules (100).
These can be avoided if pleural fluid drainage could be successfully re-established by breaking down septations pharmacologically. The underlying mechanism for the development of pleural septations and loculations in MPE is excessive fibrin formation due to the increased inflammatory response between the pleural surfaces, increased procoagulant effects and decreased fibrinolytic activity associated with MPEs (101). It has been hypothesised that the IPC may also stimulate fibrin formation and deposition within the pleural cavity. Intrapleural fibrinolytic therapy has been shown to be effective and safe in breaking down pleural septations in loculated MPE (102, 103) and pleural infection (104-106).

Extrapolating this experience, intra-pleural fibrinolytic therapy has been used for IPC-related symptomatic loculations in many centres. However, there is no published literature on its efficacy or safety. Chapter 5 describes a multi-centre, multi-national cohort study that combines the experience of four leading IPC centres in the world in the use of intra-pleural fibrinolytic therapy for IPC-related symptomatic loculations. This study provides novel data to guide clinical decision-making and a platform for future examination of intra-pleural instillation of fibrinolytics in IPC patients.
Intrapleural Fibrinolysis for the Treatment of Indwelling Pleural Catheter-Related Symptomatic Loculations
A Multicenter Observational Study

Rajesh Thomas, MBBS; Francesco Piccolo, MBBS; Daniel Miller, MD; Paul R. MacEachern, MD, FCCP; Alex C. Chee, MD, FCCP; Taha Huseini, MBBS; Lonny Yarmus, DO, FCCP; Rahul Bhatnagar, MBChB; Hans J. Lee, MD, FCCP; David Feller-Kopman, MD, FCCP; Nick A. Maskell, DM, FCCP; Alain Tremblay, MDCM, FCCP; and Y. C. Gary Lee, PhD, FCCP

BACKGROUND: Indwelling pleural catheters (IPCs) are an effective option in the management of malignant pleural effusion. Up to 14% of patients with IPCs develop symptomatic pleural loculations causing ineffective fluid drainage and breathlessness. To our knowledge, this is the first study to describe intrapleural fibrinolytic therapy for IPC-related symptomatic loculations.

METHODS: All patients who received intrapleural fibrinolytic therapy for symptomatic loculations between January 1, 2002, and June 30, 2014, in four established IPC centers were retrospectively included. Patient outcomes, treatment effectiveness, and adverse events were recorded.

RESULTS: Sixty-six patients (mean age, 64.7 ± 14.2 years; 52% women) were included. Lung cancer (31.3%) and malignant pleural mesothelioma (20.3%) were the most common malignancies. Fibrinolytic instillation was performed in outpatient (61%) and inpatient settings. Tissue-plasminogen activator (n = 52), urokinase (n = 12), and streptokinase (n = 2) were used. The majority (69.7%) received only one fibrinolytic dose (range, one to six). Pleural fluid drainage increased in 93% of patients, and dyspnea improved in 83% following therapy. The median cumulative pleural fluid volume drained at 24 h posttreatment was 500 mL (interquartile range 300-1,034 mL). The area of opacity caused by pleural effusion on chest radiograph decreased from (mean, SD) 52% (14%) to 31% (21%) of the hemithorax (n = 13; P = .001). There were two cases of nonfatal pleural bleed (3%).

CONCLUSIONS: Intrapleural fibrinolytic therapy can improve pleural fluid drainage and symptoms in selected patients with IPC and symptomatic loculation, but it carries a small risk of pleural bleeding. There is significant heterogeneity in its use currently, and further studies are needed to determine patient selection and optimal dosing regimen and to define its safety profile.

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References:

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ABBREVIATIONS: CXR = chest radiograph; DNase = deoxyribonuclease; IPC = indwelling pleural catheter; IQR = interquartile range; JHH = Johns Hopkins Hospital; MPE = malignant pleural effusion; SCGH = Sir Charles Gairdner Hospital; SMH = Southmead Hospital; tPA = tissue-plasminogen activator

AFFILIATIONS: From the Department of Respiratory Medicine (Drs Thomas, Huseini, and Y. C. G. Lee), Sir Charles Gairdner Hospital, Perth, WA, Australia; the School of Medicine and Pharmacology (Drs Thomas and Y. C. G. Lee), University of Western Australia, Perth, WA, Australia; the Lung Institute of Western Australia (Drs Thomas and Y. C. G. Lee), Perth, WA, Australia; the Department of Internal Medicine (Dr Piccolo), Swan District Hospital, Perth, WA, Australia; the Division of Respiratory Medicine and Southern Alberta Cancer Research Institute (Drs Miller, MacEachern, Chee, and Tremblay), University of Calgary, Calgary, AB, Canada; the Division of Pulmonary and Critical Care Medicine (Drs Yarmus, H. J. Lee, and Feller-Kopman), Johns Hopkins University, Baltimore, MD, USA; and the School of Medicine (Drs Miller, MacEachern, Chee, and Tremblay), University of Calgary, Calgary, AB, Canada.
Malignant pleural effusion (MPE) continues to be a major cause of morbidity worldwide. Treatment with indwelling pleural catheter (IPC) allows ambulatory drainage of recurrent pleural fluid and is effective for the management of symptomatic MPES. Serious adverse events related to IPC use are uncommon; however, the development of fibrinous loculations within the pleural cavity can impair effective fluid evacuation via an IPC, leading to fluid accumulation and breathlessness.

IPC-related symptomatic loculations develop in up to 14% of patients. Despite its clinical significance and frequent occurrence, IPC-related symptomatic loculation has seldom been described; limited data exist on its clinical course or best management. Intrapleural fibrinolytic therapy has been shown to be effective and safe in the treatment of loculated MPE and, together with deoxyribonuclease (DNase), of pleural infection. Extrapolating from these experiences, intrapleural instillation of fibrinolytics via the catheter has been used increasingly to treat IPC-related symptomatic pleural localizations. There is, however, no published literature on the efficacy or safety of intrapleural fibrinolytic therapy in this setting.

This multinational retrospective study combines the experience of four established IPC centers in the use of intrapleural fibrinolytic therapy for IPC-related symptomatic loculations. The data could provide a platform for future examination of intrapleural instillation of fibrinolytics in patients with IPCs.

Materials and Methods

Data were collected from four respiratory centers in four countries, namely Sir Charles Gairdner Hospital (SCGH) (Perth, Western Australia, Australia), University of Calgary (Calgary, Alberta, Canada), Southmead Hospital (SMH) (Bristol, England), and Johns Hopkins Hospital (JHH) (Baltimore, Maryland). The institutional ethics review boards of each center approved the study (Table 1). All patients who underwent IPC insertion were entered prospectively into local databases at SCGH, SMH, and JHH. Patients who received intrapleural fibrinolytic therapy for symptomatic loculation between January 1, 2002, and June 30, 2014, were captured retrospectively by interrogation of the MPE, cancer, and pharmacy electronic databases at each center. Individual centers audited different time periods depending on the availability of records and the duration of local IPC practice (Table 1).

Relevant data about each case were extracted from the individual patient medical records.

Symptomatic loculation was defined as the presence of (1) radiograph evidence of residual pleural effusion that failed to evacuate through a patent IPC; (2) breathlessness that was clinically judged to be secondary to the residual effusion; and (3) no clinical, biochemical, or microbiologic evidence of active pleural infection (eg, fever, leukocytosis, raised serum C-reactive protein, and/or pleural fluid that was purulent or cultured positive for bacteria).

All patients with an IPC who developed symptomatic loculation and received at least one dose of a fibrinolytic agent to treat the loculation were included in the study. The attending physician of individual patients determined the indication and suitability for fibrinolytic instillation according to local protocol. All patients were followed up regularly in each center until IPC removal or death.

Patient demographics, treatment details, and outcomes were captured. Clinical outcome data collected included the following:

1. Treatment response following fibrinolysis:
   - Cumulative volume of pleural fluid drainage at 24 and 72 h after the first dose of fibrinolytic instillation
   - Subjective response in breathlessness as reported by the patient in his/her medical file
   - Recurrence of symptomatic loculation
   - Need for further pleural or surgical interventions, including further fibrinolytic therapy

2. Other outcomes:
   - Length of the hospital stay from the day of first dose of fibrinolytic instillation to hospital discharge or death
   - Adverse events including significant pleural bleeding (defined as drop in hematocrit requiring blood transfusion)

Radiologic response was assessed for patients (n = 13) treated at SCGH who had had pre- and posttreatment chest radiographs (CXRs) performed (within 72 h of initiation of fibrinolysis). A posttreatment CXR was not performed routinely in other centers. Two independent investigators quantified changes on digital CXRs using a previously validated method. The area of pleural opacity caused by pleural effusion, expressed as a percentage of the ipsilateral hemithorax, was measured on the pretreatment and posttreatment CXRs.

Statistical analyses were performed using computer software (SigmaPlot 11.0; Systat Software). The data were tested for normality using the Shapiro-Wilk test. Results were expressed as mean (SD) if normally distributed and as median (interquartile range [IQR]) if not. The Mann-Whitney rank sum test was used to compare pleural fluid drainage before and after fibrinolytic treatment. The CXR effusion size before and after treatment was compared using a paired t test. Statistical significance was defined as P < .05.
Results

Demographics

One hundred sixty-five patients at SCGH, 105 at SMH, 220 at JHH, and an estimated 1,200 patients at the University of Calgary underwent IPC insertion for the management of recurrent pleural effusions during the study period. A total of 66 patients (52% women) with a mean age of 64.7 (14.2) years fulfilled the inclusion criteria. Most patients (n = 64) had an MPE: 13 (20.3%) from malignant pleural mesothelioma, 20 (31%) from lung carcinoma, and the remainder from pleural metastases of extrathoracic malignancies. Most patients (79%) had received prior chemotherapy, and 37% had radiotherapy. Nonexpandable lung was present on prior chest imaging in 32 of the 62 patients (52%). Of the 51 patients who had previous pleural fluid cultures performed, nine (18%) had bacterial colonization (eight grew coagulase-negative Staphylococcus); none had clinical evidence of active pleural infection.

Setting of Intervention

The median time from IPC insertion to first fibrinolytic treatment dose was 58 days (IQR, 28-100 days; range, 0-600 days). A fibrinolytic agent was administered in 40 patients (61%) in an outpatient setting at two centers (SMH and Calgary). These patients received a single instillation of the fibrinolytic agent via IPC in the outpatient clinic and were discharged home after a brief period of observation. Subsequent IPC drainage was performed either in clinic or in the community. Fibrinolysis was performed solely as inpatient therapy in the remaining centers (SCGH and JHH). In the inpatient group, the median time of hospitalization from day of first fibrinolytic dose to discharge was 2 days (IQR, 1-4 days; range 0-11 days).

Fibrinolytic Agent Used

There was significant variability, both within and among individual centers, in the selection of fibrinolytic agents and the dose regimen used. The agents used included tissue-plasminogen activator (tPA) at empirical doses ranging from 4 to 10 mg (n = 52), urokinase 100,000 International Units (n = 12), and streptokinase 250,000 International Units (n = 2). The majority of cases (69.7%) received only a single dose of the fibrinolytic agent (range, one to six doses).

Treatment Outcomes

Drainage: Intrapleural instillation of fibrinolytics increased the volume of pleural fluid drained in most patients (56 of 60; 93.3%). The cumulative pleural fluid volume drained increased from a median of 0 mL (IQR, 0-50 mL) at baseline to 500 mL (300-1,034 mL) at 24 h (n = 56) (P < .001) and to 900 mL (600-1,825 mL) at 72 h (n = 44) (Fig 1).

Symptomatic Improvement: Of the 48 patients with a recorded symptomatic response, 40 (83%) had

<table>
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<th>Approval Number</th>
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<td>January 1, 2010-June 30, 2014</td>
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Figure 1 – Pleural fluid drained after fibrinolytic therapy. IQR = inter-quartile range.
improvement in breathlessness following therapy. No patient reported worsening of breathlessness following therapy.

**Radiographic Change:** In patients with available pre- and postfibrinolytic therapy CXRs (n = 13), the area of pleural opacity caused by effusion (expressed as a percentage of the hemithorax) improved significantly from a mean 52% (SD, 14) at baseline to 31% (SD, 21) within 72 h (\(P = .001\)) (Fig 2).

**Adverse Events:** There were no episodes of extrathoracic bleeding or other systemic reactions. There were two cases (3%) of significant, but nonfatal, pleural bleeding. Neither patient appeared to have medical comorbidities or was receiving drugs that could have increased their bleeding risks; they had normal coagulation profiles and platelet levels. Case 1 patient had solid pleural metastases from renal cell carcinoma and developed a symptomatic hemoglobin drop (of 48 g/L) 2 days after fibrinolytic treatment. Case 2 patient had metastatic breast carcinoma and developed a significant fall in hemoglobin (of 60 g/L) 3 days after therapy. Both remained hemodynamically stable and responded to supportive management and packed RBC transfusions (6 units over 4 days for case 1 patient; 4 units for case 2 patient). Neither case required invasive radiologic or surgical interventions.

**Recurrence of Symptomatic Loculations:** Symptomatic loculations recurred in 27 patients (40.9%) at a median of 13 days (range, 2-69 days) following therapy. Of these, 10 received repeat fibrinolytic therapy and three had a second IPC inserted. Only one patient had a sustained improvement in drainage and symptoms following the second dose of fibrinolytic therapy.

**Mortality:** Mortality at 30 and 90 days after fibrinolytic therapy was 20% and 54.5%, respectively. All deaths were attributed to progression of underlying malignancy. No death was attributed directly to fibrinolytic therapy.

**Discussion**

Symptomatic pleural loculation is increasingly recognized as a relatively frequent complication of IPC use.\(^3,5\) Fibrinolytic agents have been used in many centers to break down pleural loculations in the hope of reestablishing IPC fluid drainage, without the support of quality evidence or clear guidelines. To our knowledge, this multicenter observational study from four established IPC centers is the first to describe the clinical outcome of intrapleural fibrinolytics for IPC-related symptomatic loculations. It confirms significant heterogeneity in current practice (eg, choice of agent, timing, and dose), reveals potential benefits and harm, and highlights the need for quality research on the use of intrapleural fibrinolytics for this indication.

The increased use of IPCs worldwide has enabled the assessment of long-term safety and potential complications, with recent studies focusing on IPC-associated pleural infection\(^14\) and catheter tract metastases.\(^6\) Symptomatic loculation, another well-recognized complication,\(^3,5\) may develop as a result of the increased procoagulant and decreased fibrinolytic activity in malignant pleural diseases that leads to excessive fibrin formation and pleural septations.\(^13\) Repetitive pleural irritation by the indwelling catheter may also act as a local trigger for fibrin deposition. One of the largest published series, by Tremblay and Michaud,\(^5\) reported an incidence of 8.4% (n = 21) in 250 patients with IPCs, whereas a smaller series reported an incidence of 13.5% (n = 5) in 34 patients with IPCs.\(^3\)

When symptomatic loculations develop despite a patent IPC, the primary aim of palliating breathlessness becomes difficult. Often, these patients have limited options. Many have to undergo further invasive procedures (pleural aspirations or removal of the ineffective IPC and/or replacement by another IPC or chest drain) or are restricted to pharmacologic palliation of their breathlessness. The related hospitalizations, as well as the increased risks and costs of additional procedures,
could be reduced if pleural drainage via the IPC could be reestablished successfully by breaking down the pleural loculations.

Fibrinolytic agents have been used to break down pleural loculations primarily in the setting of pleural infection. However, several small series (involving six to 24 cases) have also described the use of intrapleural fibrinolysis for the management of loculated malignant effusions (although not in the setting of IPCs). Most of these studies reported that fibrinolytics increased fluid drainage and improved radiologic appearance. Intrapleural fibrinolytics have, therefore, been used empirically to treat IPC-related loculations. Intrapleural DNase, when combined with tPA, has been shown to provide additional benefits in pleural infection. The role of combination intrapleural tPA-DNase instilled through small-bore chest drains for patients with loculated MPEs is the subject of an upcoming clinical trial.

The various study sites involved in this series used different fibrinolytic agents, at different dosages, with variable instillation frequency, in both inpatient and outpatient settings, and without consistent predefined patient selection criteria. This heterogeneity reflects the lack of data, paucity of experience, and absence of specific guidelines regarding the use of fibrinolytics for this particular indication.

Data from our series suggested that fibrinolytics may play a role in IPC-related symptomatic loculations. It provided subjective improvement in symptoms, paralleled by an objective increase in the pleural fluid drainage and significant reductions in the radiographic pleural opacity in the majority of patients. However, the duration of benefits varied; in 40% of patients, fibrinolytics provided only short-term relief before the loculations recurred. The reasons for early failure in some patients remain unclear but may be related to host factors (eg, malignancy type), IPC (eg, inflammatory reaction to IPC material), or therapy (eg, dose or frequency of fibrinolytic instillation). It is currently unknown if the presence of a trapped lung predisposes to the development of loculations.

Despite recurrence of loculations in some patients, the short-term benefits from fibrinolytics may be considered worthwhile in the setting of advanced cancers and short expected survival, because palliation of symptoms is the primary aim. Fibrinolytic therapy can also be repeated for recurrent symptomatic loculation; however, the efficacy of this approach needs further evaluation.

Avoiding recurrent or prolonged hospitalizations is an important outcome in patients with malignancy and is considered one of the major benefits of an IPC. In this study, the majority of patients (61%) received therapy as outpatients. Even those who were treated as inpatients mostly required only brief admissions (median, 2 days).

Previous studies have attempted to assess the risk of bleeding following intrapleural fibrinolytic instillation. Intrapleural streptokinase has been shown not to activate systemic fibrinolysis in patients with empyema. Large clinical studies of fibrinolytic therapy for pleural infection have shown a low incidence of major bleeding. In the Multi-Center Intra-pleural Sepsis Trial (MIST)-1 study, seven of 208 patients who were given intrapleural streptokinase developed systemic or pleural bleeding, whereas in the MIST-2 study, tPA, when used in combination with DNase, caused bleeding in three of 52 cases. The risk of systemic absorption of fibrinolytics may be further reduced in patients with a pleural malignancy because of their abnormal pleural surfaces and reduced lymphatic drainage.

Pleural bleeding requiring blood transfusions occurred in two patients in our study. No additional invasive intervention was required in either case, and both made a full recovery. Nonetheless, there are no easily identifiable features to predict pleural bleeding; hence, caution is needed until the risk factors of hemorrhage, and its best management, are defined.

This study has provided useful information to add to the literature. However, it must be interpreted with its many limitations. In our series, fibrinolytic therapy was performed in approximately 4% of all patients with IPCs (66 of a total estimated 1,690 IPC cases), much less than the reported incidence of IPC-related symptomatic loculation (up to 14%). This could reflect underreporting of true cases because of the retrospective nature of the study, selection bias from the likely exclusion of patients with contraindications to intrapleural fibrinolytics, or both. The risks of development of symptomatic loculation and factors that predict response to fibrinolytic therapy could also not be evaluated. The four centers have significant experience in pleural medicine, including IPC management. Whether the finding can be extrapolated to other centers requires validation. Nevertheless, we believe this study remains the first to describe the use of and response to intrapleural fibrinolysis in IPC-related symptomatic loculation.
Conclusions
Intrapleural fibrinolytic therapy can improve pleural drainage and symptoms in selected patients with IPC and symptomatic loculation but it carries a small risk of pleural bleeding. There is significant heterogeneity in how intrapleural fibrinolytics are currently used for IPC-related symptomatic loculation. This therapeutic option needs to be explored further to aid patient selection, determine the optimal dosing regimen, and define its safety profile.

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

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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
CHAPTER 6

CATHETER TRACT METASTASIS ASSOCIATED WITH
INDWELLING PLEURAL CATHETERS
The use of IPCs can potentially induce a higher risk of subcutaneous tract metastasis posing an ongoing risk of tumour seeding along the catheter tract (107). Limited literature exists on the incidence and nature of catheter tract metastasis (CTM) related to IPCs with the largest case series to date consisted of only four cases (107). The reported incidence of CTM in the literature has varied widely with an average figure of less than 5% in earlier studies (88). CTM was only reported in 1 of the 52 IPC-treated patients in a randomised study (62); a pooled review of 1093 patients from 10 studies cited a lower frequency of 0.8% (85%). The variations in incidence in different studies could be related to the difference among primary malignancies in the studies (proportion of mesothelioma versus metastatic cancers), definition of CTM (diagnosis based on clinical, radiological or histopathological factors), and/or a difference in awareness of CTM over the years.

One of the major findings of chapter 6 is the high incidence of CTM in the patients with mesothelioma compared to those with metastatic MPE (13% vs. 4%). The overall incidence of CTM in this study is the highest reported at 10%. This high incidence is likely because ~60% of patients in this cohort had mesothelioma and all patients had regular surveillance for potential complications throughout the study period. Mesothelioma is well known for its higher propensity to spread along pleural puncture tracks; the reported incidence of needle tract metastasis, similar in pathobiology to CTM, is up to 25% following pleural procedures. The risk of IPC-related CTM may be higher due to continuous tumour seeding, different from needle tract spread from one-off procedures, and the larger diameter of the IPC.

The exact reason for the greater incidence of tract metastasis associated with mesothelioma is unclear however is likely to be related to its unique pathobiology and
survival differences compared to metastatic cancers. Mesothelioma is a locally advancing cancer that aggressively spreads along the pleura and surrounding tissues initially; distant metastasis is a late feature. Non-mesothelioma MPEs develop following metastatic spread via blood or lymphatic routes; local infiltration is not a common feature. In mesothelioma, it is believed that cancer cells directly spread from puncture points at the parietal pleura to adjacent subcutaneous tissue and through fluid leak from the pleural cavity to the subcutaneous tissue through the needle tract or subcutaneous tunnel. Patients with mesothelioma survive longer (median survival of 9-12 months compared to 4-6 months for metastatic carcinomas) and therefore, are likely to have the IPC in-situ for a longer period. The multi-regression analysis results reported in this chapter support this theory. A longer interval post-IPC insertion was the only significant variable on multi-variate analysis that predicted a higher risk for developing CTM. Mesothelioma *per se*, was not an independent risk factor after adjusting for survival.

Chapter 6 describes the largest study of CTM performed till now, and describes its incidence, clinical presentation, and outcomes that could help clinicians understand and manage this condition better.
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.

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ABBREVIATIONS: CTM = catheter tract metastasis; IPC = indwelling pleural catheter; MPE = malignant pleural effusion; NTM = needle tract metastasis

AFFILIATIONS: From the Department of Respiratory Medicine (Drs Thomas and Lee), the Department of Research (Ms Budgeon), the Department of Radiography (Dr Kuok), and the Department of Radiation Oncology (Dr Bydder), Sir Charles Gairdner Hospital; the School of Medicine and Pharmacology (Drs Thomas, Fysh, and Lee), and the Centre for Applied Statistics (Ms Budgeon), University of Western Australia; and the Lung Institute of Western Australia (Drs Thomas, Fysh, and Lee and Ms Read), Perth, WA, Australia.

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DOI: 10.1378/chest.13-3057
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

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<th>Variable</th>
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<th>CTM Yes (n = 11) (10%)</th>
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<td>75 (68.2)</td>
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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.

Regression Analyses

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. 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. The largest published series described four cases of CTM in 45 patients with IPC. A pooled review of 1,093 patients from 10 studies cited a lower frequency of 0.8%. 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.
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(^a,b)</td>
<td>No</td>
<td>693</td>
<td>Yes</td>
<td>30/10</td>
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<tr>
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<tr>
<td>3</td>
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<td>280</td>
<td>Yes</td>
<td>NA</td>
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<tr>
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<td>334</td>
<td>Yes</td>
<td>20/5(^d)</td>
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<tr>
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<td>Yes</td>
<td>21/3, then 20/5(^d)</td>
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<tr>
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<td>11</td>
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<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.

\(^a\)Epithelioid mesothelioma.
\(^b\)Histopathologically proven malignancy: 4 of 11.
\(^c\)Cytology-proven malignancy: 7 of 11.
\(^d\)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.\(^3,15,16\) 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.

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, Fyh, 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

CHAPTER 7

HISTOPATHOLOGY OF REMOVED INDWELLING PLEURAL CATHETERS FROM PATIENTS WITH MALIGNANT PLEURAL DISEASES
An IPC is often placed in situ for many months until fluid evacuation is no longer necessary. Placement of a foreign body within a body cavity can have effects on the foreign body itself and locally/systemically. Previous studies of indwelling medical devices involved benign conditions e.g. indwelling urinary catheters and peritoneal dialysis catheters. Chronic inflammation, microbial colonisation, and infections are described in foreign bodies placed for benign aetiologies.

However, there are important differences with an IPC placed in the pleural cavity to treat MPE from invasive cancers including, i. different physical and chemical properties of the catheter material, and its interactions with the surroundings, ii. the local pleural environment that has unique histopathological, biochemical and physiological characteristics compared to other serous cavities, and iii. the surrounding invasive malignant process that may result in direct and indirect effects on the catheter. There is a great concern of the potential risk of seeding of cancer through the tract formed by these catheters (CTM described in chapter 6), and of direct invasion of the catheter tubing itself by cancer. It is also unknown whether the catheter surface supports tumour cell growth within the pleura milieu.

No previous studies have explored these unique aspects of IPC treatment or the interaction of the IPC, as a device, with the local pleural environment, in the setting of invasive malignancy. In particular, little is known about whether the catheter surface supports or promotes tumour growth and/or local inflammation, and whether cancers can invade the catheter material.

Chapter 7 provides the first histological analysis of removed IPCs from patients with underlying pleural malignancy. This is the first study to assess the direct physical effect
of tumours on the IPC and the interaction of the IPC with the local pleural malignant milieu. The findings that there was no direct tumour growth or invasion of the catheters despite the presence of malignant cells in the IPC lumen in a third of cases are reassuring for clinicians and provide further safety data for its long-term use in invasive cancers.
ABSTRACT

Background and objective: Indwelling pleural catheters (IPC), used for management of malignant pleural effusions, are often left in situ for a long duration. This study reports for the first time the histological findings of IPCs removed from patients with underlying pleural malignancy.

Methods: Forty-one IPCs (in situ for median 126 days, interquartile range 43–226) that were removed over a 54-month period from a single centre were examined.

Results: Mesothelioma (n = 18) was the predominant underlying malignancy followed by breast, tubo-ovarian and lung carcinomas. The catheter tubing was fully intact macroscopically in all IPCs. There was no evidence of direct tumour invasion or cancer cell growth on the catheter surfaces in none of the 29 IPCs that were histologically examined. Malignant cells were seen within organizing fibrinous tissues in the lumen of 11 IPCs (27%). A foreign body giant cell reaction was present at the cuff site in all the 29 IPC in which the subcutaneous cuff was examined. Acute (n = 10) and/or chronic inflammatory changes were seen in the luminal contents in all 41 IPCs.

Conclusion: Our study provides reassuring evidence that the IPC material does not support direct tumour growth or invasion even in the setting of high mesothelioma prevalence.

Key words: cytology, histology, mesothelioma, pleural disease.

Abbreviations: HPF, high-powered field; IPCs, Indwelling pleural catheter.

INTRODUCTION

Indwelling pleural catheter (IPC) is now frequently used worldwide for management of malignant pleural effusions. These flexible silicone catheters are tunnelled subcutaneously and allow ambulatory, patient-directed drainage of the pleural space for the patients’ remaining lifespan. The IPC can be removed in 40–50% of patients when fluid formation ceases or spontaneous pleurodesis occurs, and rarely in cases of uncontrolled IPC-related pleural infection or catheter malfunction. Indwelling pleural catheter is often placed in situ for many months, or longer, until fluid evacuation is no longer necessary. The interaction of the IPC, as a device, with the local pleural malignant environment has never been studied. In particular, little is known about whether the catheter surface supports or promotes tumour growth and/or local inflammation and whether cancers can invade the catheter material. This study provides the first histological analysis of removed IPC from patients with underlying pleural malignancy.

METHODS

Forty-one IPCs (Rocket, UK) were removed over a 54-month period from February 2011 and examined by a specialist pleural pathologist (S.M.C. or A.S.). Patient demographics, the underlying tumour type, timing and duration of IPC placement and reason for IPC removal were recorded. The Sir Charles Gairdner Group Human Research Ethics Committee approved the study (2009-104 and 2012-005).

In the first 12 cases, only catheter contents (obtained by washing out all cellular debris inside the IPC lumen) were examined. In the subsequent 29 cases, IPCs were examined in their entirety for (i) the presence of malignant or inflammatory cells within the catheter lumen.

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or at the subcutaneous cuff site and (ii) whether the catheter tubing was intact or had been invaded by tumour. In the latter cases, the whole catheter, including the cuff, was initially inspected for macroscopic defects. Representative sections of the catheter (Fig. 1) with its luminal contents and any identified defects were then sampled; the remaining material within the lumen was also removed for histological examination. Transverse sections of the cuff were taken. Up to five histology blocks were obtained for each case. The samples were formalin fixed and paraffin embedded. Representative 4-μm sections were cut from each block and stained with HE for microscopic analysis. Malignant cells, if present, were further characterized by immuno-histochemistry. The maximum number of inflammatory cells in one high-powered field within the area of densest inflammation and the predominant inflammatory cell type were documented.

RESULTS

Patient demographics
Of the 41 patients who underwent IPC removal, mesothelioma was the predominant underlying malignancy (n=18), followed by breast (n=9), tubo-ovarian (n=5) and lung (n=4) carcinomas. The IPC had been in situ for a median of 126 days (interquartile range 43–226) before removal. The reasons for IPC removal included cessation of fluid formation/spontaneous pleurodesis (n=39), persistent bacteria empyema (n=1) and fungal infection (n=1). No patient received prophylactic tract radiotherapy in line with standard practice at our institution, and none had catheter tract metastases prior to IPC removal.

Macroscopic examination
In 40 cases, the IPC was removed intact; in the remaining patient, the catheter fractured during removal and only the extra-pleural portion of catheter could be studied. No macroscopic tumour invasion or breach of the catheter was seen in any of the IPCs studied. Tissue materials were commonly found within the lumen of the IPCs and frequently occluded some/all of the fenestrations (Fig. 2).

Histopathological analysis
Organized fibrin clots were found within the lumen of all IPCs, often occluding the entire lumen, and accounted for the tissue material observed macroscopically. The catheter tubing was fully intact microscopically in all 29 IPCs examined histologically, with no evidence of direct tumour invasion.

No cancer cells were found directly attached to, or growing on, the internal lumen of the 29 IPCs studied. However, organizing fibrinous tissue in the lumen that may provide a matrix for the cancer cells to anchor upon was noted. Colonies of malignant cells, including mesothelioma (n=7) (Fig. 3a), tubo-ovarian (n=3) (Fig. 3b) and lung carcinomas (n=1), were seen located within the lumen of 11 of the 41 IPCs (27%). In a patient with fungal lung parenchymal and pleural infection, fungal elements were found in the luminal fibrinous tissue (Fig. 3c).

A foreign body giant cell reaction was present at the cuff site in all the 29 IPCs in which the subcutaneous cuff was examined (Fig. 4). Atypical mesothelial cell proliferation was seen within the tissue adherent to the cuff in one case only; in a patient who had underlying mesothelioma but no evidence of concurrent tumour cells within the catheter lumen.

The cellular composition of the luminal contents showed inflammatory changes in all 41 IPCs studied. Acute inflammation (either alone or on a background
of chronic inflammation) was found in 10 IPCs (24%) (Fig. 3d) and were neutrophil predominant in eight cases. The maximum number of inflammatory cells per high-powered field (HPF) in each case was recorded and showed 316 (median, range 60 to over 500) cells/HPF. Inflammation characterized by lymphocytic predominance was observed in 30 cases; the highest density of inflammatory cells in each patient was 50/HPF (median, range 2 to 300).

**DISCUSSION**

This study reports for the first time the histological findings of IPCs placed in patients with pleural malignancy. It is reassuring that no direct tumour growth on the IPC surface or invasion of the IPC material, either macroscopically or histologically, was seen in this cohort. However, cancer cells and inflammatory changes were common within the organizing fibrinous tissue in the catheter lumen.

There are no previous published studies examining the histopathological characteristics of IPCs placed in patients. The catheters frequently remain in situ for long periods of time within the pleural cavity, and directly adjacent to, or in close proximity of, pleural cancers. The effects of the tumour on the catheter, and vice versa, have not been investigated. This is the first attempt to look for any direct physical effect of tumours on the IPC.

Our data showed no evidence that pleural cancers interrupt or invade the IPC material itself. Among all the 29 IPCs that were removed and histologically examined, the IPC tubing was intact and there were no microscopic suggestions of tumour breaching the catheter surface. Malignant cells were present within the organizing fibrin in the lumen of the IPC in some (27%) cases even though the malignant cells did not invade the catheter material. Our findings show that cancer cells from malignant effusions can be trapped within these ‘fibrin clots’, which in turn provide a matrix for cancer cell to anchor. The clinical relevance of this finding is uncertain.

Western Australia has the world’s highest incidence in malignant pleural mesothelioma and explains the high percentage of mesothelioma patients in our cohort. Mesothelioma is notorious for its predilection to invade pleural puncture sites, and needle tract metastases are recognized complications even after one-off pleural interventions. IPC represents a constant risk, as it remains in situ. This is in addition to the fact that patients with mesothelioma have a significantly longer median survival, and therefore, the IPC can remain in situ for longer (median 126 days in this cohort), compared with those with metastatic carcinomas. As a result IPCs in mesothelioma patients presented a higher risk (approximating 14%) of catheter tract...
metastases in our recent published series. It is not known whether tumour invading the catheter tract will also invade the catheter tubing. In this study we found no catheter invasion in any of the removed IPCs despite the high mesothelioma prevalence. This provides further reassurance about the safety of IPC against tumour invasion.

The luminal contents of the IPCs showed varying degrees of inflammation in all cases. The majority of removed catheters showed evidence of mild to moderate chronic lymphocytic inflammation. A small number (n = 4) of patients showed acute inflammatory cells only; three of them were known to have had recent or past pleural infection including one with fungal infection (Fig. 3c). It is intriguing that significant numbers of neutrophils were found several weeks after successful treatment of the infection. In the fourth patient, \textit{Staph lugdunensis} was cultured in the pleural fluid of the patient previously, but there were no clinical signs of pleural infection (and was therefore not treated).

Our results provide for the first time reassuring evidence that there were no tumour cell growth on the IPC material or tumour interruption of the IPC in our cohort with its high mesothelioma prevalence.

**Disclosure statement**

Y.C.G.L. has served on the advisory boards of CareFusion and Sequana Medical. He leads the AMPLE-2 trial for which Rocket Medical provides the drainage equipment without charge and an unrestricted education grant. He is a National Health & Medical Research Council (NH&MRC) Career Development Fellow and receives research project grant funding from the NH&MRC, New South Wales Dust Disease Board, Sir Charles Gairdner Research Advisory Committee, Westcare and the Cancer Council of Western Australia. R.T. has received research scholarship support from NH&MRC, WA Cancer & Palliative Care Network and Institute for Respiratory Health, Australia.

**REFERENCES**

PART 3 – UNDERSTANDING PATHOBIOLOGY OF MALIGNANT PLEURAL EFFUSIONS THROUGH NOVEL USE OF INDWELLING PLEURAL CATHETERS
CHAPTER 8

LONGITUDINAL MEASUREMENT OF PLEURAL FLUID BIOCHEMISTRY AND CYTOKINES IN MALIGNANT PLEURAL EFFUSIONS
The pathobiology of MPE formation is not well understood but is believed to involve plasma extravasation from leaky vasculature in the visceral and parietal pleura, and impaired lymphatic resorption. The malignant fluid is usually an exudate due to higher pleural fluid concentrations of protein and LDH, markers of vascular permeability and pleural inflammation respectively. Pleural fluid pH, glucose and LDH levels can reflect the pleural tumour burden and its metabolic activity. A low pleural fluid pH is associated with poorer survival, predicts MPE recurrence and the clinical need for pleurodesis or IPC placement for MPE management.

MPE was conventionally considered as an inert by-product of cancer growth however has recently been shown to be a rich source of secretory products, with potent biological activities, including growth factors, e.g. vascular endothelial growth factor (VEGF) (108-111), epidermal growth factor (112) and transforming growth factor-β (TGF-β) (113), as well as cytokines/chemokines that promote tumour proliferation, e.g. interleukin (IL)-6 (114), IL-8 (115), monocyte chemoattractant protein-1 (MCP-1) (116, 117) that promote tumour proliferation. Many of these proteins are predictors of patient survival or disease severity. Studies have also shown that MPE fluid has the capacity to increase vascular permeability, thus perpetuating further effusion formation (112). MCP-1 has been shown to play a crucial role in exudative and malignant effusion formation.

The tumour cells are bathed in this malignant fluid containing molecules capable of promoting proliferation and migration. These molecules are present in significantly higher concentrations in the MPE than in corresponding sera, implying their local pleural synthesis. These proteins are involved in a complex interplay between the host and tumour cells to induce pleural inflammation, vascular hyper-permeability and
tumour angiogenesis. Charting the changes in pleural fluid biochemistry and of these molecules during disease progression may provide clues to pleural tumour pathobiology, and may explore their potential as biomarkers of patient survival or disease activity.

A major limitation in malignant pleural research to date is that bio-specimens available for investigations, *e.g.* pleural fluid for biochemical and immunological profiling, are restricted to single cross-sectional samples. The pleural milieu will almost certainly change throughout the disease course, like changes seen in blood/urine, and be influenced by the type, stage, progression (and treatment response) of the underlying cancer as well as host comorbidity etc. Other factors *e.g.* chemotherapy or pleural microbial colonization/infection could also directly alter the pleural milieu. Existing literature on the longitudinal changes in malignant pleural fluid analyses is limited to one pilot study (*n*=9) (118). This demonstrated that pleural fluid (TGF-β) concentration in MPE increased significantly 2 weeks after IPC insertion compared to the level at time of IPC insertion. Plasminogen activator inhibitor-1 and VEGF levels did not show a significant increase.

Till now there was no means to monitor any longitudinal PF changes without subjecting patients to repeated invasive thoracentesis procedures. Repeated sampling (*e.g.* biopsies or thoracentesis) of the pleural space for research is neither practical nor ethical. However, the advent of IPC now offers a unique opportunity, not previously possible, to access the pleural space continuously and obtain serial pleural fluid during the disease course without subjecting patients to repeated pleural interventions This is an exciting opportunity to longitudinally study pleural cancer biology within and between individuals.
Chapter 8 describes the longitudinal changes in pleural fluid biochemistry and key cytokines level in patients with an MPE, and is the first paper to describe these findings. Charting the changes of these molecules during disease progression may provide hints on the key drivers of the fluid formation process and new information about pleural tumour pathobiology, and may help explore their potential as biomarkers of patient survival or disease activity.
Longitudinal Measurement of Pleural Fluid Biochemistry and Cytokines in Malignant Pleural Effusions

Rajesh Thomas, MBBS; Hui Min Cheah, BSc; Jenette Creaney, PhD; Berwin A. Turlach, PhD; and Y. C. Gary Lee, MBChB, PhD, FCCP

BACKGROUND: Malignant pleural effusion (MPE) is common. Existing literature on pleural fluid compositions is restricted to cross-sectional sampling with little information on longitudinal changes of fluid biochemistry and cytokines with disease progression. Indwelling pleural catheters provide the unique opportunity for repeated sampling and longitudinal evaluation of MPE, which may provide insight into tumor pathobiology.

METHODS: We collected 638 MPE samples from 103 patients managed with indwelling pleural catheters over 95 days (median, range 0-735 days) and analyzed them for protein, pH, lactate dehydrogenase, and glucose levels. Peripheral blood was quantified for hematocrit, platelets, leukocytes, protein, and albumin. Cytokine levels (monocyte chemotactic protein [MCP]-1; vascular endothelial growth factor; interleukin-6, -8, and -10; tumor necrosis factor-α; and interferon-gamma) were determined in 298 samples from 35 patients with mesothelioma. Longitudinal changes of all parameters were analyzed using a linear mixed model.

RESULTS: Significant decreases were observed over time in pleural fluid protein by 8 g/L per 100 days (SE, 1.32; P < .0001) and pH (0.04/100 days; SE, 0.02; P = .0203), accompanied by a nonsignificant rise in lactate dehydrogenase. The ratio of pleural fluid to serum protein decreased by 0.06/100 days (SE, 0.02; P = .04). MPEs from mesothelioma (n = 63) had lower pleural fluid glucose (P = .0104) at baseline and a faster rate of decline in glucose (P = .0423) when compared with non-mesothelioma effusions (n = 38). A progressive rise in mesothelioma pleural fluid concentration of \( \log \) MCP-1 (\( \log \) 0.37 pg/mL per 100 days; SE, 0.13; P = .0046), but not of other cytokines, was observed.

CONCLUSIONS: MPE fluids become less exudative and more acidic over the disease course. The rise in MCP-1 levels suggests a pathobiological role in MPE.

KEY WORDS: cytokines; glucose; lactate dehydrogenase; malignant pleural effusion; mesothelioma; monocyte chemotactic protein-1; pH; pleural fluid; protein

ABBREVIATIONS: CRP = C-reactive protein; INF-γ = interferon-gamma; IPC = indwelling pleural catheter; LDH = lactate dehydrogenase; MCP-1 = monocyte chemotactic protein-1; MPE = malignant pleural effusion; TNF-α = tumor necrosis factor-α; VEGF = vascular endothelial growth factor

AFFILIATIONS: From the Department of Respiratory Medicine (Drs Thomas and Lee), Sir Charles Gairdner Hospital; School of Medicine and Pharmacology (Drs Thomas, Creaney, and Lee; and Ms Cheah); Pleural Medicine Unit (Drs Thomas and Lee; and Ms Cheah), Institute of Respiratory Health; National Centre for Asbestos Related Diseases (Dr Creaney); and Centre for Applied Statistics and School of Mathematics and Statistics (Dr Turlach), University of Western Australia, Perth, Australia.

Dr Thomas and Ms Cheah contributed equally to this article.

FUNDING/SUPPORT: Dr Lee is a National Health and Medical Research Council (NH&MRC) Career Development Fellow and receives research project grant funding from the NH&MRC, New South Wales Dust Diseases Board, Sir Charles Gairdner Research Advisory Committee, Westcare and the Cancer Council of Western Australia. Dr Thomas has received research scholarship support from NH&MRC, WA Cancer and Palliative Care Network and the Institute of Respiratory Health. Ms Cheah has received postgraduate research scholarships from the University of Western Australia and the Institute of Respiratory Health. Dr Creaney receives research project grant funding from the NH&MRC, New South Wales Dust Diseases Board, Sir Charles Gairdner Research Advisory Committee and the Cancer Council of Western Australia.
Malignant pleural effusion (MPE) is one of the leading causes of pleural effusions and a common cause of morbidity worldwide. MPE can complicate most cancers, including extrapleural malignancies, especially lung and breast carcinomas, including primary pleural mesothelioma.

The pathophysiology of MPE remains unclear but is believed to involve increased plasma extravasation from hyperpermeable tumor and/or pleural vasculature and impaired lymphatic resorption. However, no biochemical profile of pleural fluid is pathognomonic for MPEs. Pleural fluid concentrations of protein and lactate dehydrogenase (LDH), markers of vascular permeability and pleural inflammation, respectively, are usually in the exudative range by Light’s criteria. Pleural fluid pH, glucose, and LDH levels can reflect the pleural tumor burden and its metabolic activity. Low pleural fluid pH and high levels of LDH have been associated with poorer survival. Lower pleural fluid pH also predicts MPE recurrence and clinical need for pleurodesis or indwelling pleural catheter (IPC) placement for MPE management.

Several inflammatory cytokines and growth factors act as markers of proliferation, migration, invasion, angiogenesis, and inflammation in malignancy. Monocyte chemotactic protein (MCP)-1 has a pivotal role in pleural fluid formation and mesothelial tissue repair in pleural injury in mouse models. Vascular endothelial growth factor (VEGF) moderates angiogenesis, tumor growth, and MPE formation in cancers including mesothelioma. IL-8 regulates mesothelioma cell growth and IL-6 contributes to the formation of MPE. Tumor necrosis factor-α (TNF-α) is important for cell apoptosis, proliferation, and migration in cancer whereas interferon-gamma (IFN-γ) has both protumorigenic and antitumorigenic effects.

MPE fluid bathes the pleural tumors and is a rich source of these secretory products. The molecules are present in significantly higher concentrations in the MPE than in corresponding sera, which implies their local pleural synthesis. These proteins have potent biological effects and are involved in a complex interplay between the host and tumor cells to execute proinflammatory and proangiogenic transcriptional programs that induce pleural inflammation, vascular hyperpermeability, and tumor angiogenesis. Charting the changes of these molecules during disease progression may provide clues to pleural tumor pathobiology and may explore their potential as biomarkers of patient survival or disease activity.

A major limitation in pleural research to date is that biospecimens available for investigations, such as pleural fluid for biochemical and immunological profiling, are restricted to single cross-sectional samples. Repeated sampling (eg, biopsies or thoracentesis) is not practical or ethical. Heterogeneity from interindividual differences (eg, genetics, cancer stages) poses major hurdles to researchers. The pleural milieu will almost certainly change throughout the disease course and be influenced by the type, stage, progression, and treatment response of the underlying cancer as well as host comorbidity, and so on.

The existing literature on longitudinal changes in malignant pleural fluid analyses is limited to one pilot study (n = 9). IPC is now an established treatment for MPE and has been shown to provide comparable symptomatic benefits as talc pleurodesis with shorter hospitalization. The advent of IPC offers a unique opportunity not previously possible to provide serial pleural fluid during patients’ disease course. It is an exciting chance to study pleural cancer biology longitudinally within and between individuals.

This study aimed to describe longitudinal changes in pleural fluid biochemistry and levels of key cytokines and chemokines in patients with MPE.

Materials and Methods

From July 1, 2009 through February 28, 2013, 107 patients in our pleural service underwent insertion of 110 IPCs (Rocket Medical) for management of MPE. It is our routine practice that patients are instructed to drain the effusion via the IPC when they are symptomatic; the frequency of drainage varied from daily to every 2 weeks. Most patients were monitored in the pleural service until the IPC was removed, or until death.

At each outpatient visit, pleural fluid samples were collected and sent for standard biochemical tests (pH, protein, LDH, and glucose) and bacterial cultures. Additional fluids were centrifuged at 1020 g for 10 min at room temperature and supernatants were stored at –80°C until assay.

All longitudinally collected pleural fluid samples were included. Most patients (n = 87) had more than or equal to three fluid samples for longitudinal analysis of pleural fluid biochemistry; four patients cases...
had one and 12 patient cases had two fluid samples. In two patients with bilateral pleural effusions, fluid samples from each side were considered to be separate cases. Cytokine level quantifications were performed on samples from a subset of 35 patients with mesothelioma from this cohort who had three or more samples available from the pleural fluid biobank.

Results of serum biochemistry (protein, albumin, LDH, and C-reactive protein [CRP]) and hematologic (hemoglobin, total WBC, lymphocyte, neutrophil, and platelet counts), performed for any reason and closest to and within 14 days of pleural fluid sampling, were obtained from the hospital pathology service database.

Biochemistry and Hematology Measurement Methods
Protein, albumin, LDH, glucose and CRP levels in blood and/or pleural fluid were measured by spectrophotometry using an Abbott Architect c16000 analyzer. Pleural fluid pH was measured using a Radiometer ABL 800 blood-gas analyzer. Hemoglobin, total WBCs, neutrophils, lymphocytes, and platelets were quantified with the Beckman Coulter DxH800 analyzer, following standard manufacturer’s instructions. All of the measurements were performed at our hospital National Association of Testing Authorities-accredited laboratory.

Cytokine Measurement Method
Enzyme-linked immunosorbent assays were used to measure concentrations of VEGF, IL-6 and IL-8 (R&D), and MCP-1, IL-10, IFN-γ, and TNF-α (eBiosciences). Serial samples of each patient were assayed in duplicate in the same enzyme-linked immunosorbent assay run. The colorimetric assay was quantified by a spectrophotometer and adjusted for background.

Statistical Analyses
We analyzed longitudinal changes in pleural fluid biochemistry and cytokines, serum biochemistry, and blood counts using linear mixed models; specifically, we employed a straight-line model with varying intercepts and varying slopes for each individual. The response at the population level was modeled either on the original scale or on a log scale, via mixed-effects linear regression using time since first pleural fluid collection as the sole regressor. The intercepts and slopes of individuals were assumed to vary randomly about these population parameters, with this variation modeled by a bivariate normal distribution. Results reported are for the population parameters of this model.

Mathematical Details
In mathematical notation, the models fitted are as follows: Let $y_{ij}$ be the response variable measured on individual $i$ at time point $t_j$, $i = 1, \ldots, n_i$, $j = 1, \ldots, n_i$.

The following linear mixed model was fitted to these data:

$$y_{ij} = \beta_0 + \beta_1 t_j + \epsilon_{ij}$$

where $\beta_0$ and $\beta_1$ denote the population intercept and slope, respectively.

The random effects $b_{0i}$ and $b_{1i}$ allow the intercept and slope of the line fitted to individual $i$ to vary about the population parameters. The joint distribution of these random effects is modeled as being a bivariate normal distribution with mean vector 0 and a general variance covariance matrix. The error term, $\epsilon_{ij}$ is assumed to be normally distributed and independent of the random effects.

We obtained consent from subjects to use pleural fluid and blood results for the study. The Sir Charles Gairdner Group Human Research Ethics Committee approved the study (Human Research Ethics Committee study numbers 2009-104/2020, 2011-109/2125, 2012-005/2019, 2012-038/2092, and 2012-156/2121).

Results

Demographics
A total of 107 patients with MPE underwent IPC fluid insertions during the study period; of these, pleural fluid biochemistry was analyzed in 103 (82% were male and 62% had mesothelioma) (Table 1). Longitudinal pleural fluid biochemistry was analyzed in 638 pleural fluid samples (from 103 patients) for protein, 627 for glucose (102 patients), 624 for LDH (103 patients) and 570 for pH (101 patients). Median duration between the first and final pleural fluid sampling was 95 days (range, 0-735 days).

Longitudinal pleural fluid cytokine testing from 35 patients was performed for MCP-1 (298 samples), VEGF (282), IL-6 (286), and IL-8 (261). IL-10, IFN-γ, and TNF-α were tested in 39 samples (five patients) only as we found that their values were below the detection limit of the assay (2 pg/mL IL-10, 4 pg/mL IFN-γ, and 4 pg/mL TNF-α). Median duration between the first and final pleural fluid sampling for this group was 148 days (range, 15-623 days).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Whole Cohort (N = 103)</th>
<th>Cytokine Subset (N = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, No. (%)</td>
<td>82 (80%)</td>
<td>32 (91%)</td>
</tr>
<tr>
<td>Age, median (range), y</td>
<td>63 (53-83)</td>
<td>69 (52-89)</td>
</tr>
<tr>
<td>Cancer type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>63 (61%)</td>
<td>35 (100%)</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>16 (16%)</td>
<td>…</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>6 (5%)</td>
<td>…</td>
</tr>
<tr>
<td>Others</td>
<td>18 (18%)</td>
<td>…</td>
</tr>
<tr>
<td>Patients’ fluid samples, No.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>4</td>
<td>…</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>…</td>
</tr>
<tr>
<td>3-5</td>
<td>41</td>
<td>12</td>
</tr>
<tr>
<td>6-10</td>
<td>31</td>
<td>12</td>
</tr>
<tr>
<td>&gt;10</td>
<td>15</td>
<td>11</td>
</tr>
</tbody>
</table>
Pleural Fluid and Serum Biochemistry Analysis

Pleural fluid protein, pH, and glucose decreased whereas LDH increased over time: Pleural fluid protein (intercept, 40.97 g/L; n = 638) decreased by 8 g/L per 100 days (SE, 1.32; \( P < .0001 \)) (Fig 1). Pleural fluid pH (intercept, 7.34; n = 570) decreased by 0.04 per 100 days (SE, 0.02; \( P = .0203 \)) (Fig 2), whereas pleural fluid glucose (intercept, 3.84 mmol/L; n = 627) showed a nonsignificant decrease by 0.07 mmol/L per 100 days (SE, 0.12; \( P = .4855 \)). On the other hand, pleural fluid LDH [log] values (intercept, 6.29 [log]U/L; n = 624) increased by 0.08 [log]U/L per 100 days (SE, 0.05; \( P = .0787 \)). The final pleural fluid protein to serum protein ratio measured more than 0.5 in 53% of the cases. The final pleural fluid LDH value was greater than two-thirds of the upper limit of normal pleural fluid LDH in 93% of the cases.

Serum albumin significantly decreased with time. Serum protein decreased less than the corresponding pleural fluid protein reduction: Both serum protein (intercept, 70.58 g/L; SE, 0.75; n = 364) and albumin (intercept, 38.35 g/L; n = 384) decreased over time by 0.75 g/L per 100 days (SE, 0.47; \( P = .1068 \)) and 3 g/L per 100 days (SE, 0.51; \( P < .0001 \)), respectively.

Subgroup analysis of 364 samples from 88 cases in which both pleural fluid and corresponding serum protein results were available showed that reduction of protein was greater in the pleural fluid compared with its corresponding serum level. The pleural fluid protein (intercept, 39.85 g/L) and serum protein (intercept, 70.58 g/L) decreased by 5 g/L per 100 days (SE, 1.22; \( P < .0001 \)) and 0.75 g/L per 100 days (SE, 0.47; \( P = .1068 \)), respectively; the ratio of pleural fluid to serum protein (intercept, 0.56; SE, 0.02) decreased by 0.06 per 100 days (SE, 0.02; \( P = .04 \)). Serum CRP levels did not change significantly.

MPEs from patients with mesothelioma vs those without mesothelioma: MPEs from patients with mesothelioma had significantly lower baseline pleural fluid glucose (\( P = .0104 \); n = 63) compared with those from patients without mesothelioma (n = 38). A positive difference in slopes was seen for these two groups of patients (\( P = .0423 \)) with pleural fluid glucose, but not others, which suggested that the reduction in glucose was more in the group without mesothelioma. The significance of this finding is not clear.

Pleural Fluid Cytokine Analysis

Pleural fluid MCP-1, but not of the other tested cytokines, increased significantly over time: Pleural fluid [log]MCP-1 (intercept, [log]6.72 pg/mL; n = 298) increased by [log]0.37 pg/mL per 100 days (SE, 0.13; \( P = .0046 \)) (Fig 3). Levels of [log]VEGF (intercept, [log]6.29 pg/mL; n = 282) increased by [log]0.11 pg/mL per 100 days (SE, 0.05; \( P = .0203 \) for both).
Pleural fluid log (MCP-1) (pg/mL) vs 100 Days

<table>
<thead>
<tr>
<th>Value</th>
<th>SE</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>6.72</td>
<td>0.26</td>
</tr>
<tr>
<td>Δ/100 Days</td>
<td>0.37</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Figure 3 – Shows longitudinal changes in pleural fluid MCP-1 analyzed using linear mixed model. Pleural fluid log (MCP-1) (intercept, 6.72 pg/mL; n = 298) increased by 0.37 pg/mL per 100 days (SE, 0.13; P = .0046). MCP-1 = monocyte chemotactic protein-1.

per 100 days (SE, 0.07; P = .14), [log]IL-6 (intercept, [log]6.52 pg/mL; n = 286) decreased by [log]0.05 pg/mL per 100 days (SE, 0.10; P = .64), and [log]IL-8 (intercept, [log]5.61 pg/mL; n = 261) decreased by [log]0.07 pg/mL per 100 days (SE, 0.09; P = .42).

**Blood Hematology Analysis**

Hemoglobin and lymphocyte counts decreased significantly; platelets increased significantly:

Hemoglobin (intercept, 133.78g/L) decreased by 13 g/L per 100 days (SE, 2.11; P < .0001) in the 480 samples tested. Lymphocytes count (intercept, 1.28 × 10^9/L; n = 457) decreased by 0.07 × 10^9/L per 100 days (SE, 0.02; P = .0012). Platelets (intercept, 299 × 10^9/L) increased significantly by 26 × 10^9/L per 100 days (SE, 6.32; P < .0001). No significant increase in leukocyte and neutrophil counts was observed.

**Discussion**

Pleural fluid bathes the pleura and its importance in providing diagnostic clues (eg, Light’s criteria, fluid cytology) is well-recognized. Previous studies on pleural fluids mainly contain cross-sectional data. The advent of IPC provides a unique opportunity for us to report longitudinal changes in pleural fluid composition and cytokines in a sizeable cohort of MPEs. Our data show that pleural fluid pH decreased significantly over time whereas LDH trended upward. The protein levels remained stable in the blood but decreased in the MPE. The pleural fluid concentration of MCP-1, a cytokine recently shown to have an important role in exudative effusion formation, rose significantly with advanced stage tumor.

The longitudinal reduction in pleural fluid pH and a corresponding rise in LDH were in keeping with increased metabolic activity within the pleural cavity. Low pleural fluid pH is known to reflect greater pleural tumor burden and has been associated with a poorer prognosis and shorter survival in MPE patients.20–22 Our finding that pleural fluid pH continued to decrease with the progression of pleural malignancy over time further supports a relationship between the effusion pH and the cancer load in the pleura.

Pleural fluid glucose, like pH, has been associated with advanced pleural cancers. However, the glucose level in pleural fluid is strongly influenced by its corresponding blood concentration, which in turn can be affected by concurrent diabetes and other illnesses causing hyperglycemia. This may explain the absence of a consistent trend in pleural fluid glucose levels over time.

The protein concentrations in the pleural fluid decreased over time whereas its levels remained stable in the serum. Repeated removal of exudative malignant fluid via IPC drainage did not result in a noticeable reduction in systemic protein levels, a concern that has been raised regarding IPC use. Pleural fluid protein is generally regarded as a marker of plasma leakage from vascular hyperpermeability in the pleura.16 Pleural fluid protein level in the exudative range can be found in more than 50 diseases and is a key mechanism underlying malignant effusion formation. Plasma leakage in MPE is believed to be driven by mechanisms induced by local pleural tumor and substances released by it.

No data exist on longitudinal measurements of effusion protein, but it would be expected to rise with progression of pleural malignancy; our data showed otherwise. The final pleural fluid protein level did not fulfill the exudate criteria in approximately half of the cases (47%); the final pleural fluid LDH level fulfilled the exudate criteria in most (93%). Serum albumin, but not protein level, showed a significant decline.

We hypothesize that a reduction in the pleural fluid protein level results from concurrent driving forces of formation of low-protein pleural fluid, such as heart failure, the presence of trapped lung, and hypoalbuminemia from cancer-associated malnutrition.

The pathobiology of exudative pleural effusion formation (including MPE) is poorly understood. Many cytokines...
and biological mediators are no doubt involved in pleural inflammation and vascular hyperpermeability processes that underlie plasma extravasation. Detailing their longitudinal changes may provide hints about the key drivers of the fluid formation process.

A pilot study of six patients demonstrated that pleural fluid transforming growth factor-β1 concentration in MPE increased significantly 2 weeks after IPC insertion compared with the level at the time of IPC insertion. Plasminogen activator inhibitor-1 and VEGF levels did not show a significant increase. Of the large range of mediators that we tested, MCP-1 rose with time (and tumor progression) in MPE. MCP-1 was the only cytokine to demonstrate a consistent trend. This finding is timely as recent preclinical studies point to MCP-1 having a crucial role in exudative and malignant effusion formation.

MCP-1 was highly expressed by lung cancer cells in a mouse model, and induced vascular permeability and fluid leak. Antagonists of MCP-1 significantly reduced MPE formation in mice with lung cancers. This finding was corroborated in a separate study on the effects of intrapleural fibrinolytics (especially tissue plasminogen activator), which consistently induced the accumulation of a large volume of pleural exudative fluid. Lansley et al also found that MCP-1 levels correlated with fluid volume and strategies to antagonize MCP-1 (eg, using soluble antibodies and receptor antagonists) all significantly reduced exudate formation. Our study lends important human data to support these preclinical studies showing that MCP-1 may be a critical target in future therapy for MPE control.

Our study has limitations. First, it was a retrospective analysis, although most patients included had complete pleural fluid data. Second, there was a relatively high proportion of mesothelioma in this cohort owing to the high prevalence of mesothelioma in Western Australia. Patients with mesothelioma also had a higher number of longitudinal samples as they were more likely to survive and have IPC in situ longer compared with metastatic carcinomas. Third, we accepted data from corresponding blood drawn within 14 days of pleural fluid sampling. However, most paired samples were collected within 3 days of each other (49% on the same day and 70% within 3 days). Fourth, in the mathematical modeling, the use of log-transformation was based mainly on the range of that response variable and the amount of skewness visible in the (marginal) histograms of these variables. Log-transformation can vary the interpretation of the regression parameters. Finally, our linear mixed model assumed an independent and identically distributed residual error structure.

This sizable longitudinal study describes changes in pleural fluid compositions over time; it found that the pleural fluid protein and pH decreased whereas the MCP-1 level increased. Serum protein does not reduce significantly even when the malignant effusion is drained regularly. These data provide an important platform for future studies in the field.
Acknowledgments

Author contributions: Y. C. G. L. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects. R. T. and Y. C. G. L. contributed to the conception and design. R. T. contributed to the clinical data collection. H. M. C. and J. C. conducted the biobanking and sample processing. H. M. C. performed cytokine measurements. R. T., B. A. T., and Y. C. G. L. conducted statistical analyses. All authors drafted, revised and approved the final version of manuscript.

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References

CHAPTER 9

DISCUSSION
Chapter 9  Discussion

9.1.   THESIS OVERVIEW

9.1.1  Summary

The thesis had 3 aims - 1) To define the advantage of IPC treatment versus talc slurry pleurodesis with regards to benefits on hospitalisation 2) To define important IPC-related complications and 3) To define changes in the pathobiology of MPEs using pleural fluid collected longitudinally during IPC drainage

1) To define the advantage of IPC treatment versus talc slurry pleurodesis with regards to benefits on hospitalisation – It was hypothesised that IPC treatment will provide significant savings in hospital admission days. The AMPLE randomised trial (chapters 3 & 4) explored this by directly comparing the effect of IPC versus chest tube and talc slurry pleurodesis on hospital admission days in patients with MPE. The study involved 146 adult MPE patients from 9 centres in Australia, New Zealand, Singapore and Hong Kong; patients were randomised (1:1) to IPC or talc slurry pleurodesis.

The primary outcome was total hospitalisation days (from any cause) from treatment procedure to death or completion of follow-up (12 months). The most important study finding was that IPC patients spent 3.6 fewer days of their remaining life span in hospital (from any cause of admission) compared to those who underwent talc slurry pleurodesis (median 10 vs. 12 days, p=0.026). IPC patients also spent significantly fewer days in hospital from effusion-related causes (median 1 vs. 4 days, p<0.0001). Significantly less number of patients who received IPC treatment required further pleural procedures (6 vs. 17 patients, p=0.01). Both treatments improved breathlessness
and QoL; the improvements were sustained for up to 12 months. Adverse events and mortality rates were similar with both treatments.

2) To define important IPC-related complications - namely, i) symptomatic loculation (and the treatment with intra-pleural fibrinolytics) ii) catheter tract metastasis and iii) catheter interactions in the pleural milieu.

Symptomatic pleural loculation is a well-recognised complication of IPC use. Fibrinolytic agents were used in this setting to re-establish fluid drainage and improve symptoms; this practice was however empirical and not previously well studied. Chapter 5 reports an international, multi-centre observational study and is the first to describe the outcomes of intra-pleural fibrinolytic treatment of IPC-related symptomatic loculation. Clinical outcomes, treatment effectiveness and adverse events in 66 patients from four leading IPC centres who received intra-pleural fibrinolytic therapy for symptomatic loculations are reported.

Intra-pleural fibrinolytic therapy improved pleural fluid drainage (in 93% of patients), dyspnoea (in 83% of patients), and the area of effusion on the chest radiograph (reduced from 52% to 31% of hemi-thorax). There was a small risk of pleural bleeding; two cases developed a non-fatal bleed. There was significant heterogeneity in practice between different centres, particularly with regards to the choice of agent, dose and timing.

IPC-related CTM is an area of great clinical concern with limited information in the literature. Chapter 6 describes the largest series of CTM to date. This single centre study of 110 IPCs inserted over a 44-month period identified eleven cases of CTM (9 with underlying mesothelioma and 2 with metastatic adenocarcinoma). Duration after IPC
placement was the sole predictor for development of CTM (median 280 days). CTMs often caused pain however radiotherapy was usually effective and could be delivered safely with the catheter in situ.

IPCs are often left in situ for a long duration however, the interactions between the catheter and intra-pleural cancer milieu were unknown. Chapter 7 reports for the first time the histological findings of forty-one IPCs (in situ for a median 126 days) that were removed from patients with pleural malignancy, mainly mesothelioma and breast, ovary, and lung carcinomas. This showed that the catheter tubing remained fully intact in all cases without evidence of direct tumour invasion or cancer growth in the IPC lumen. Chronic inflammatory changes were seen in the luminal contents of most IPCs.

3) To study longitudinal changes in MPE pathobiology - Previous pleural fluid studies mostly contained cross-sectional data. Chapter 8 reports the longitudinal changes in the biochemistry of 638 malignant pleural fluid samples (from 103 patients) managed with an IPC. Cytokines levels in 298 pleural fluid samples (from 35 patients) with mesothelioma were also assessed.

The study showed that MPEs become less exudative and more acidic over the disease course. Pleural fluid protein (by 8g/L/100 days) and pH (by 0.04/100 days) decreased significantly; it was accompanied by a non-significant rise in LDH. Concentration of chemo-attractant protein (MCP)-1, but not of other cytokines in mesothelioma effusions increased, suggesting a patho-biologic role for MCP-1 in MPE.
9.1.2 Discussion

Finding a cure for the underlying pleural malignancy, or at least to prevent/control the formation of malignant pleural fluid, remains the holy grail of MPE management. Till then treatments targeting the mechanistic effects of effusion for palliative symptom control are necessary. Despite its many limitations, pleurodesis has remained the mainstay of practice in the past.

For the first time in several decades, patients and clinicians have a genuinely new treatment alternative to pleurodesis. IPC treatment can achieve long-term fluid control and symptom relief without the need for pleural symphysis, and avoids multiple pleural interventions. There is a growing recognition that IPC is an effective palliative therapy for MPEs and worldwide, it is increasingly being used as first line therapy rather than as a second choice following failed pleurodesis.

However, knowledge gaps about other benefits, particularly hospital admissions, and complications unique to IPC use persist. The complex interactions of leaving a permanent foreign body within the malignant pleural environment remain poorly understood. Developing ‘best practice’ guidelines for the optimal choice/applications of IPC procedures has been challenging due to lack of quality evidence, resulting in wide variations in IPC practice worldwide.

This thesis is an early, comprehensive attempt to fill in this evidence gap, and assessed the major benefits and complications of IPCs in a systematic manner. Its results provide new knowledge that will inform clinical decision-making and raises many questions for future research.
The AMPLE study provided new data demonstrating a clear advantage of IPC in reducing hospitalisation time and pleural interventions. It also confirmed findings of previous studies that IPC improve symptoms of breathlessness and QoL. It illustrates how the key goals of MPE management of optimal fluid removal and improved PROMs can be successfully achieved without creation of pleural symphysis (and its associated complications). The primary outcome of hospitalisation days in the AMPLE study is unique and highly meaningful to terminally ill patients facing a short life span. Its successful application highlights the need for researchers to concentrate on clinically relevant, objective and patient-focussed outcomes.

The AMPLE trial is only an early step, and several questions remain about the precise benefits of IPC treatment, especially its cost-effectiveness. The total cost of treatment is highly relevant to the individual patients who have to pay for their treatments in many countries; it also holds great importance to many healthcare systems struggling to reduce the considerable burden of MPE management. Whether savings in hospital bed days ultimately translates into overall cost savings, and its magnitude, needs to be explored through well-designed prospective studies tailored to different health care system scenarios.

The AMPLE study was a pragmatic study that reflected ‘real world’ practice. Participating centres followed their individual, often complex, regimes for IPC drainage and pleurodesis. Most centres prescribed symptom-guided drainage, aimed at optimal palliation of symptoms, for evacuation of fluid. The next step forward is to identify the ideal drainage method that can be tailored to the individual patient to yield maximal benefits and lowest costs.
The AMPLE study utilised validated questionnaires to assess breathlessness and QoL although these are difficult in the MPE patient population as the patients’ sense of discomfort or well-being are often influenced by numerous factors not directly related to the MPE. Causes for breathlessness in patients with end-stage cancer are broad and not always directly related to MPE alone. The confounding comorbidity from the underlying cancer and/or its treatment, as well as psychological issues related to uncertainty about prognosis, produce significant study ‘noise’ that hinders reliable assessment of the impact of IPC treatment in QoL. Besides, these tools are not designed to capture the inconvenience and discomfort specifically associated with IPC treatment. Notwithstanding these limitations, this is an important attempt to decipher the benefits of IPC management in QoL and symptom control. The consistent improvements in overall QoL with IPC treatment suggest that any degree of discomfort that may arise from IPC use is not large enough to negate its benefits.

MPE is an ‘umbrella term’ encompassing a diverse patient population of different prognoses, aetiology and predicted clinical course. Patients are likely to respond differently to various therapies; the relative benefits of IPC treatment in various cancer subtypes are unknown. Subgroup analysis of individual metastatic cancers with MPE e.g. lung and breast cancer were not performed due to the relatively small numbers in each group; this requires further exploration. It is likely that different subsets of patients may benefit from using IPC or pleurodesis as first line of management for their MPE. Patient preference may be important and should be incorporated into the decision-making process on clinical management. Future studies are needed to help identify criteria to guide the choice of therapy in individual patients.

The novel results on the outcomes of common IPC-related complications and their
treatment will reassure patients and clinicians on the safety and efficacy of IPC treatment. However, the studies also reveal great differences in practice exist among different centres, which highlight the lack of robust evidence in guiding a more united approach to the prevention and management of IPC-related complications.

The study on the efficacy and safety profile of intra-pleural fibrinolytic therapy demonstrated encouraging results supporting its use in this setting. It however did not explore the underlying pathobiology or identify the risk factors for development of symptomatic loculations. It also did not explore the ideal fibrinolytic drug, dose or regimen for the treatment of symptomatic loculation. A better understanding of pathobiology and risk factors is crucial to help prevent its development, to optimise treatment, and improve outcomes. The heterogeneity in fibrinolytic treatment practice across centres highlights the need for clinical trials to guide patient selection, optimise the delivery regimen of fibrinolytics, and to define its safety profile.

The CTM study demonstrated that patients with mesothelioma have a higher incidence of CTM however despite this higher incidence, this study builds a strong case to support IPC treatment in mesothelioma. ~90% of patients avoid this complication even in a mesothelioma endemic region, and when it develops, CTM usually causes mild symptoms that responds well to treatment with analgesics and radiotherapy. Patients often benefit from IPC treatment for several months as the CTM develops usually late during the illness. There are no better alternatives with a lower risk of CTM as the best method to prevent tract metastases is to minimize the number of pleural procedures performed; IPC treatment significantly reduces the number of pleural interventions in MPE patients (4% versus 22% with talc pleurodesis in the AMPLE
trial, chapter 4). Several tract metastases from alternative treatments e.g. repeated thoracentesis or surgical pleurodesis could be potentially prevented for every CTM that develops with IPC.

The study did not explore the precise pathobiological mechanism(s) by which a CTM develops. This information may be useful, particularly in mesothelioma associated with the higher incidence and longer survival. Ability to identify patients at the highest risk of developing CTM e.g. by developing reliable predictors of survival, may allow targeted prevention through better patient selection. The results of the most recent randomised study of prophylactic radiotherapy in mesothelioma following pleural intervention shows it is ineffective in preventing symptomatic NTM (119); these results may also be relevant to IPC treatment and CTM, particularly as radiotherapy was shown to be an effective treatment in our study, and could be safely performed without damaging the catheter. The low risk of invasion of the catheter by cancer means that the catheter can be left in situ without damage for as long as is clinically necessary.

We have shown that IPC is a powerful research tool by demonstrating the use of serial pleural fluid samples collected during IPC drainage to study longitudinal changes. This opens exciting possibilities for future research into understanding the pathobiology of pleural effusions of different causes, and the changes in the pleural environment to various stimuli. The continuous access to the pleural space via IPC may allow future therapeutic trials involving direct intra-pleural instillation of drugs e.g. antibiotics and chemotherapy.

There is increasing realisation of the need to evaluate IPC treatment in proper scientific
trials to ensure patient safety and delivery of best patient care. There are more interests now in optimizing IPC therapies and more IPC trials currently than ever before. The successful collaborative efforts involving the research projects in this thesis highlight the benefits and the need for large multi-centre studies in this area. It is vital that future research should continue to focus on optimising IPC treatment that will yield the best results for individual patients. A collaborative approach underpinned by a strong international collaborative trials network will be a powerful tool to produce more high quality research in the future. In turn this will promote the greater uptake and wider application of IPC for the benefit of more MPE patients.

The novel information about IPC therapy resulting from the thesis research will challenge the traditional concepts, and change the paradigm of MPE management in many ways. It has implications not only for MPE patients’ choice of treatment but also on the future directions of clinical care and research. The thesis findings will reassure clinicians that IPCs can be used effectively and safely as first-line therapy in MPE. Patients and physicians will now have more evidence to inform their clinical decisions for MPE treatment. It provides a solid platform for future research into key aspects of MPE care, and ultimately, its cure.
9.2. LIMITATIONS

This thesis has several limitations.

The AMPLE study compared IPC drainage with talc slurry pleurodesis. It is important to acknowledge however that there are wide variations in how each therapy is practised around the world.

Whilst there is a consensus that talc is the best available sclerosant currently available for pleurodesis, there is no agreement on whether talc slurry pleurodesis or surgical talc poudrage is superior over the other. Recent RCTs (51-53) comparing the two techniques have found no major differences in rates of successful pleurodesis yet talc poudrage continues to have strong advocates and remains widely used. The effectiveness of different surgical pleurodesis techniques (other than poudrage alone) has not been directly compared with talc slurry pleurodesis. Even with talc slurry pleurodesis itself there is no agreement on several aspects of its care e.g. optimal timing for sclerosant instillation, ideal timing for chest tube clamping following sclerosant instillation, utility of applying suction pre- and post-instillation of sclerosant to assist apposition of the pleural membranes, etc.

Similarly, drainage practice varies widely in IPC therapy e.g. daily or alternate day drainage regimes are common in North America whilst less aggressive symptom-guide drainage (usually weekly) is more commonly practiced in Australasia and thus, in AMPLE too. Whether aggressive drainage provides significant benefits over symptom-guided drainage is unknown. However, the variations in drainage approaches can impact on patient care and healthcare resource use. Directly comparing two treatment regimens that have not yet been proven to be the 'gold standard' in their own category leaves it open to criticism. However, this study in itself is major step forward and sets the standard for future studies aimed at optimizing IPC (and MPE) care.
The studies on IPC-related complications were retrospective and involved a small number of patients; there was also significant heterogeneity in IPC practices between centres, which highlights the need for quality research. Similar to prior studies, diagnoses of tumour tract metastases and symptomatic loculation were mostly made on clinical and radiologic grounds. These may have resulted in selection bias and/or underreporting of true cases even though most included patients had complete data available. In addition, the risks of development of CTM and symptomatic loculation, and factors predicting response to therapy, could not be evaluated. Nonetheless, the cohorts are the largest of their kind reported so far and the study findings provide useful information that will enhance clinical care and guide future research.

Western Australia has one of the highest incidences of mesothelioma in the world; hence the cohorts in this thesis had a relatively high proportion of mesothelioma cases compared to other studies in the literature. This may have implications for the generalisability of the results as patients with mesothelioma have a different prognosis and clinical course; they are also more likely to survive and have an IPC in situ longer compared with metastatic carcinomas. This could have skewed some results e.g. the incidence of CTM. On the other hand, the high mesothelioma incidence helped contribute to generating the large cohort of cases to study tract metastasis and cancer growth (or lack of) on the catheter.

The results of the other studies are unlikely to have been affected by the high mesothelioma incidence in WA as the studies were multi-centre studies and the majority of cases were metastatic carcinomas, not mesothelioma. In addition, randomization for the AMPLE study was stratified based on cancer type (mesothelioma vs non-
mesothelioma), and analyses after minimization for cancer type were similar to the primary analyses.

Finally, this thesis research involved collaboration with leading pleural centres with considerable experience and expertise in pleural medicine, including IPC management. MPEs are common and usually managed in a 'non-specialised' setting in many hospitals. Whether the findings of the thesis can be extrapolated to or reproduced in other centres requires further validation.

9.3. FUTURE DIRECTIONS

There is growing high-quality evidence, including the information in this thesis, that IPC is an effective and safe palliative therapy for MPEs. This means that the use of IPC as the default treatment for MPE is bound to gain further momentum.

Having established the advantages and safety profile of IPC therapy, the next step is to move beyond simply comparing it with conventional MPE treatments and instead, to focus on further optimization and standardization of IPC therapy. Several trials are already underway in this direction. At least two randomised studies are comparing aggressive (daily) vs. standard (three times a week) drainage regimens with IPC to determine the optimal drainage method that can best produce spontaneous pleurodesis. The second AMPLE study is now halfway through recruitment; AMPLE-2 compares daily vs. symptom-guided (usually weekly) drainage regimens with IPC to determine the drainage method that can best provide improvement in breathlessness and QoL.

There is now considerable research interest on combining the benefits of IPC and pleurodesis to maximise the advantages of both procedures and simultaneously
minimise the adverse effects of long-term IPC use. Placement of IPC at the time of thoracoscopic talc poudrage to provide a ‘safety net’ if pleurodesis fails has been shown feasible in a pilot study. The IPC-PLUS trial investigates a slightly different concept - MPE patients are fitted with an IPC initially; intra-pleural talc instillation is performed subsequently in those without significant trapped lungs to enhance the chances of pleurodesis. Another innovative concept being explored is the use of IPCs with sclerosant coating. Silver nitrate-coated IPC has been shown to be effective in promoting pleurodesis in sheep and rabbit models, and is being tested in humans (120).

Although there is now a wealth of literature on the short-term outcomes of IPC use, reliable data on longer-term outcomes is still sparse. The AMPLE study has provided the longest prospective follow-up data (up to 12 months) till now of IPC use in MPE, and showed that improvements in dyspnoea and QoL with IPC therapy are sustained for up to 12 months. Future studies should focus on identifying long-term complications and its risk factors. Long-term outcomes will become more important as the indications for IPC use expand beyond MPE to include symptomatic, chronic or recurrent benign effusions e.g. chronic heart failure-related effusions.

The full cost of IPC treatment remains to be established as most cost-analysis studies were retrospective and used indirect comparisons with conventional treatments. There is no simple answer as a range of factors that may vary widely in the individual patients can affect the overall cost. In general, the cost of IPC treatment will increase the longer the IPC remains in situ, as the associated requirements for drainage consumables and nursing resources, and risks of complications increase. A well-designed prospective study incorporating a rigorous economic analysis is urgently needed to answer this question.
There are no studies that have directly compared the costs of different drainage regimens either. The AMPLEx-2 randomised trial may provide an answer; it will collect detailed economic data prospectively including direct costs of different drainage regimes (e.g. consumables, nursing care) and indirect costs (e.g. inpatient/outpatient management of complications including treatments e.g. antibiotics, radiotherapy, diagnostic imaging and interventions related to the adverse events).

There is now an increasing realization of the magnitude of the health-care burden imposed by MPE; reducing the cost of its treatment is imperative. The economic burden of MPE treatment will continue to increase in future, primarily due to the escalating cost of hospital admission(s) for inpatient treatment. Therefore, an effective and safe treatment that reduces hospitalisation will reduce costs and be highly attractive to patients and health-care administrators. It is also foreseeable that increased competition between device companies and further refinements in drainage modalities are likely to drive down the costs of IPCs and drainage consumables.

IPCIs offer a practical, safe and continuous access to the pleural space and allow intra-pleural delivery of drugs without the need for repeated invasive procedures. It also permits repeated and non-invasive pleural fluid sampling to monitor tumour response/progress and other changes in the pleural milieu. In the future, this simple unassuming device may well become the choice for intra-pleural delivery of chemotherapy, immune-modulators and gene therapy that are subjects of cutting edge research today.

Drug-eluting catheters for pleurodesis have already been tested; extending this concept
to catheters eluting tumoricidal drugs could also potentially revolutionise MPE treatment. The study of IPC histology allays concerns about breakdown of the catheter that has remained in situ for long periods. Developing the technology to make IPCs able to withstand the effects of drug-elution would be the next step in this direction.

The thesis confirms that IPC treatment is an ideal choice for fluid control, one of the main goals of MPE management. However, it is important to recognise that patients are likely to respond differently to various therapies; this may be an IPC or pleurodesis or some other intervention. Personalised medicine where each MPE patient receives tailored therapy based on the individual’s tumour type, host factors, and effusion characteristics must become the ultimate treatment goal.

Studies of MPE management in the past focused on endpoints such as radiological recurrence of fluid rather than on outcomes important to the patient; however, this is slowly changing. Although it is still early days, patient-recorded scores of breathlessness e.g. VAS scores, QoL questionnaires, e.g. EQ5D, length of hospital stay, and the number of repeated pleural interventions are increasingly used in MPE trials; the AMPLE study is the most recent and arguably the best example. This is a major step forward. There will be a greater emphasis in future to use validated and meaningful PROMs to assess patients and to record clinical trial end-points.

Another exciting development in this direction is using tri-axial accelerometers to measure functional capacity. Accelerometers are validated tools for accurate measurement of physical activity, and have been used in cancer research. Its ease of use, portability and wide availability makes it a very attractive choice in this setting. The AMPLE-2 study is collecting exploratory accelerometry data to determine its feasibility
and utility in MPE research and clinical care. Accelerometry has the potential to become a validated and ideal tool for objective functional assessment and treatment planning in MPE.

Until a systemic cure for metastatic cancer is developed the ultimate aim of MPE treatment must be local eradication, or at least control, of the pleural malignancy. This requires a greater understanding of the complex interplay of host, tumour, and local pleural factors that lead to malignant effusions. Research targeting angiogenesis, vascular hyper-permeability and pleural fluid production are underway, and may offer novel approaches in the future. Translational research will be crucial in the development of novel therapeutic options to achieve the goal of eventually curing MPE.
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