Multidisciplinary approaches to the management of malignant pleural effusions: a guide for the clinician

Abstract:

Malignant pleural effusion (MPE) is a complication of advanced cancer, associated with significant mortality and morbidity. This entity is commonly treated by respiratory physicians, oncologists and thoracic surgeons. There have been various randomised clinical trials assessing chest drain pleurodesis, indwelling pleural catheters, treatment of septated MPEs, use of thoracoscopy and pleurodesis and pleurodesis through IPCs in the past decade which have addressed some key points for management of MPEs with a significant focus on patient related outcomes. In this review we examine and review the literature for management strategies for MPEs and discuss future directions.

Introduction:

Malignant pleural effusion (MPE) is seen in around 15 % of all cancers.(1) A retrospective analysis using the Healthcare Cost and Utilization Project National Inpatient Sample database showed that in the United States, MPE accounted for more than 125 000 admissions with an estimated expense of more than 5 billion dollars per year for inpatient stay with an inpatient mortality of around 12% in 2012.(2) Evidence has shown life expectancy to range from 3 to 12 months following a diagnosis of MPE depending on the primary tumour.(3) This in addition to increased mortality and morbidity due to MPEs is also associated with significant financial burden to the health care system.

The majority of MPEs are caused by lung cancer in males and breast cancer in females, these two cancers account for 50-60% of all MPEs.(4) Malignant effusions develop in about 30% of patients with lung cancer and in around 7-10% patients with breast cancer.(5, 6) Mesothelioma is the most common primary pleural tumour and is associated with MPE in 90% of cases.(7) It has been shown that in patients with lymphoma, presence of MPE on diagnosis is associated with higher chance of disease recurrence post chemotherapy.(8) Just the presence of pleural effusion in patients with lung cancer, even in the absence of proven malignant nature of the effusion, confers a survival disadvantage when compared with those without the effusion (7.49 vs 12.65 months).(9)

With 1 in 8 men and 1 in 10 women developing cancer globally, overall cancer incidence and mortality has increased partly due to aging and growth of population and also due to change in prevalence and distribution of risk factors for cancer. In the UK cancer mortality and incidence is predicted to increase until 2035.(10, 11) Hence it can only be assumed that burden of MPE will also rise in the coming years.

Various theories have been hypothesized for pleural fluid formation in MPE including direct tumour invasion from adjacent structures, haematogenous spread to the pleura, tumour emboli and infiltration of lymphatic drainage with upregulation of angiogenic growth factors by tumour cells which leads to further fluid formation.(12, 13)

Since the presence of a MPE is associated with advanced and incurable cancer with limited survival, treatment options historically have looked at symptom control and are largely palliative in nature.

Management Options

The first randomised control trial for MPE was carried out in 1977.(14) Traditionally studies at that time looked at measures to obliterate pleural space and prevent fluid recurrence in the form of invasive procedures such as pleurectomy or instilling pleurodesis agents and hence most clinical trials were based on finding the optimum pleurodesis agent. The primary outcome in these trials was radiological resolution rather than patient centred outcomes.(15) However, treatment for MPEs has seen a huge change in the past decade with the advent of clinical trials looking at newer devices such as indwelling pleural catheters (IPC) for fluid control, increased focus on patient centred outcomes such as breathlessness and largely shifting treatment strategy towards outpatient management.

Symptom based approach

Whilst most patients with MPE display symptoms of breathlessness, a small proportion of them may be asymptomatic. (7) BTS guidelines in 2010 and recently published ATS guidelines suggest observation for patients who are asymptomatic with MPEs.(7, 16) Although the evidence is weak, based on two retrospective lung cancer cohorts there is currently no justification to intervene in asymptomatic patients with proven metastatic cancer since it would only subject them to a small risk of the procedure without conferring any clinical benefit.(9, 16, 17) A multicentre observational study of 537 patients with MPEs showed that definitive interventions (i.e. pleurodesis, IPC, or both) were required in 54% of cases; patients with low pleural fluid pH (odds ratio (OR) 37.04), effusions occupying >50% of the hemithorax (OR 3.31) and increasing age (OR 1.02) were associated with use of definitive treatment options.(18)

Thoracentesis

Thoracentesis is the first step in management for MPEs in most treatment guidelines. (7, 16) It is a percutaneous procedure in which pleural fluid is drained through the chest wall using a small bore catheter. It serves two important purposes – confirming symptomatic benefit in patients and assessment for the presence of non-expandable or trapped lung which would aid in further management. If the patient has no symptomatic benefit, then other causes for dyspnoea (e.g. pulmonary lymphangitis, pulmonary embolism, endobronchial obstruction, heart failure) should be looked for. Furthermore large volume thoracentesis can help predict rate of re-accumulation of pleural fluid. Recent retrospective data shows that 55% patients will need a repeat aspiration within 14 days.(19) MPEs associated with highly chemosensitive cancers such as lymphoma and small cell lung cancer may only require a single aspiration which temporarily relieves breathlessness till systemic oncological treatment takes effect. According to BTS guidelines, aspiration should be limited to 1.5 litres on a single occasion to prevent re-expansion pulmonary oedema (<0.5% in large series).(20) Most centres undertake large volume aspirations in a controlled manner with stoppage of drainage if the patient experiences symptoms such as chest pain or coughing. Although the BTS guidelines published in 2010 recommended repeated therapeutic aspirations as the treatment of choice for MPE management in patients with life expectancy less than 1 month, this is likely to change in future guidelines with the availability of other treatment options such as indwelling pleural catheters. Furthermore repeated pleural aspirations cumulatively increase the risk of procedure related bleeds, infection and formation of pleural septations and adhesions.(7)

Role of pleural manometry and trapped lung

Trapped lung or non-expandable lung (NEL) is defined as inability of the lung to expand to the chest wall preventing visceral and parietal pleura apposition due to either pleural

disease, endobronchial obstruction or chronic atelectasis.(21) NEL is seen in approximately 30% of patients with MPE.(22) There are no robust tools available to identify NEL and although NEL is commonly seen in chest radiographs, there exists significant inter observer variability.(23) NEL is thought to be associated with pleurodesis failure and hence its identification is important since it will guide clinicians to use IPCs as the treatment of choice in these patients. Pleural manometry is a simple medical procedure that helps to follow pleural pressure changes during therapeutic aspiration.(24) A recent RCT assessed the utility of pleural manometry for symptom guided aspiration in 128 patients and found no difference in patient reported outcomes (i.e. chest pain during aspiration) between the two groups. Based on this RCT, there is currently no role for pleural manometry in routine therapeutic aspiration.(25) However, pleural manometry is useful to measure pleural elastance defined as change in intrapleural pressure divided by change in pleural cavity volume (equal to volume of pleural fluid aspirated) following aspiration.(26) It is hypothesized that elevated pleural elastance is a strong predictor of NEL and a study in which patients are directed for either IPC or chest drain-pleurodesis based on pleural fluid elastance values is currently under recruitment (NCT03319186). (27, 28) Unfortunately there are no methods to detect the presence of a trapped lung prior to pleural aspiration and this study may help in deciding definitive intervention either in the form of IPC or chest drain at the time of pleural aspiration itself, thus, saving an additional procedure and shortening the treatment pathway.

Pleurodesis

Pleurodesis is defined as parietal- visceral pleural adhesion with obliteration of the pleural space. It can be achieved chemically by instillation of a pleurodesis agent or mechanically by surgical abrasion or pleurectomy. This creates a profound inflammatory reaction eventually leading to fibrin accumulation and pleural fibrosis. Pleurodesis can cause significant chest pain and fever as a result of pleural inflammation which is believed to directly correlate with the success of pleurodesis.(29) Various chemical agents (talc, tetracycline, bleomycin and others), bacterial products (Corynebacterium parvum, Streptococcus pyogenes) and autologous blood patch have been used for decades to achieve pleurodesis. In a Cochrane review and meta-analysis for different pleurodesis strategies by Clive et al which included 41 studies evaluating 16 pleurodesis methods and included 2,345 participants, although there was no evidence to support any difference among agents for pleurodesis, in the network analysis the estimated rank of talc poudrage was second, ahead of bleomycin and tetracycline. (30) In another head to head RCT comparing talc versus bleomycin, talc was superior as compared to bleomycin in achieving successful pleurodesis.(31) Hence talc is the most widely used agent and is considered to be the most effective pleurodesis agent. Talc can be administered as a slurry where talc mixed with sterile fluid is administered through a chest tube at the bed side or as a poudrage which is conducted during medical or surgical thoracoscopy where talc is blown in the pleural cavity as a powder.

Medical thoracoscopy is a procedure commonly performed by respiratory physicians to inspect and drain pleural space under conscious sedation and local anaesthesia. It provides the advantage of taking pleural biopsies and inserting a pleurodesis agent at the same time with insertion of chest drain or IPC. In a large RCT 482 patients were randomised to either talc poudrage through surgical thoracoscopy or talc slurry through a chest drain and there was no difference in pleurodesis success at 1 month. (22) In a recently published multicentre study in UK, 330 patients were randomised to poudrage via medical thoracoscopy or slurry through chest drain and pleurodesis success at 3 months was determined. There was no significant difference in rate of pleurodesis failure between the two groups (22% in talc poudrage versus 24% in talc slurry). There was no difference in the secondary outcomes

which included patient reported pain and dyspnoea at 30, 90 and 180 days, overall mortality and health related quality of life between the two groups. (32)

The TIME-1 trial helped gather evidence on two important aspects of pleurodesis via chest tube thoracostomy – chest drain size and use of NSAIDS. This 2 X 2 factorial, phase-3, multicentre RCT randomised 330 patients to either small bore (12Fr) or large bore (24Fr) chest drain along with either opioids or NSAIDS for pain control. NSAIDS were shown to be non-inferior to opioids in terms of pleurodesis success at 3 months. The small bore drains were associated with higher fall out rates, fewer patients receiving talc and higher complication rate for insertion. The pleurodesis failure rates were 30 % versus 24% in the small bore versus large bore drains suggesting a larger bore drain may increase the chances of pleurodesis success. (33) However, a recent meta-analysis found no difference in pleurodesis success between large and small bore chest drains.(34) Further studies that are powered to address the optimum size for chest drain for pleurodesis are needed.

In a recent observational study, successful pleurodesis was also associated with survival benefit.(35) According to the American Thoracic Society, pleurodesis is defined as complete success (absence of fluid re-accumulation until death), partial success (partial re-accumulation of fluid, but no further therapeutic thoracenteses required for the remainder of the patient's life), and failure (lack of success as defined above).(1) In the settings of clinical trials, pleurodesis success is defined as lack of pleural interventions either at one or 3 months. Pleurodesis success with talc, (either slurry or poudrage) has been around 70-80% in different clinical trials, however, this may probably be lower in day to day practice.(22, 32, 33, 36). Dresler et al. showed pleurodesis success rates of around 75% at 1 month which dropped to around 50% at 6 months irrespective of the method of delivery of talc i.e. either slurry or poudrage. (22)However, a recent study by Bhatnagar et al. showed a constant pleurodesis failure rates of about 20-30% at 30 days and 6 months in both groups (poudrage and slurry).(32)

The most common side effects of talc pleurodesis include chest pain (26%) and fever (30%) according to a Cochrane review.(37) Serious complications can include acute respiratory distress syndrome (0.28%) which is rare and is hypothesized due to systemic absorption of small particle size talc (< 15-20) causing systemic inflammation especially after pleural abrasion or multiple pleural biopsies.(38, 39) Historically chest drain pleurodesis requires hospitalization, and has been reported to have a median length of 4 days in clinical trials.(36, 40)

Although pleurodesis through chest drain has shown to be an effective management option for patients with MPE, little is known about timing of pleurodesis and drain removal post pleurodesis. Thoracic ultrasound to look for absence of lung sliding (i.e. movement between parietal and visceral pleural with respiration) can be used to decide timing of pleurodesis and determine which patients have achieved pleurodesis thereby facilitating early removal of drains and shortening hospital stay. A study looking at these factors has recently completed recruitment in UK. (ISRCTN 16441661).

Indwelling pleural catheters

An IPC is a silicone catheter placed in the pleural cavity which is tunnelled subcutaneously. Its distal end has a cuff which over time forms fibrous tissue in the subcutaneous tissue, holding the IPC in place. The IPC is drained via drainage bottles with a one way valve using negative suction and flow and volume can be monitored. IPC offers the advantage for ambulatory management of MPEs and has gained tremendous popularity in the last decade since they minimise hospital admissions. (29, 41) A meta-analysis of 1348 patients with MPE

managed with IPCs showed that 95.6% had symptomatic improvement in dyspnoea and 45.6% achieved spontaneous pleurodesis after a median of 52 days.(42) Given its ease of insertion and management, they have become a dominant management option in many centres worldwide.

There have been various head to head trials comparing IPCs versus chest drain plus pleurodesis for management of MPEs. Putnam et al conducted one of the first randomised trials which showed that in 144 patients with MPE, there was no difference between pleurodesis with doxycycline through a chest tube and IPCs in terms of improvement in dyspnoea and quality of life.(43) The TIME-2 study compared IPCs versus chest drain pleurodesis with talc and the study found that both interventions improved dyspnoea with no difference in the mean visual analogue scale (VAS) dyspnoea at 30 or 42 days after intervention. At 6 months, the VAS between the two groups favoured IPC (mean difference of -14 mm). Hospital stay (median 0 versus 4 days) and number of pleural procedures required was significantly lesser in the IPC arm. (36) These findings were confirmed in the AMPLE study where the primary outcome was mean days spent in hospital. Of the 146 patients randomised, IPC arm had a shorter stay in hospital with the difference in median length of stay being 2.92 days between the two arms.(40) A recent systematic review comparing five RCTs found no difference in survival or measures of dyspnoea between the two groups with the IPC group being associated with a shorter hospital stay and fewer pleural procedures, however, a higher risk of cellulitis.(44)

IPCs are the treatment of choice in patients with NEL. Although there are no dedicated prospective trials to assess the utility of IPCs in trapped lung, a single systematic review including 5 IPC studies for management of MPEs concluded that IPCs are indicated in trapped lung.(44)

IPCs are associated with higher rates of complications. The strongest concern is for pleural infection especially in patients receiving chemotherapy. In a large multicentre review of 1021 patients with IPC, 50 patients (4.9%) developed pleural infection and 94% of these were controlled with antibiotics and pleural infection related mortality was less than 0.3%.(45) There are currently no treatment guidelines for IPC related pleural infection. At our centre, treatment is based on a case by case approach assessing site of infection (tract vs pleural fluid or both) based on ultrasound findings and pleural fluid biochemistry and cultures. Treatment then involves prolonged antibiotics for 4-6 weeks guided by antimicrobial sensitivities, regular IPC drainage and removal of IPC once pleural infection is under control. As suggested by a retrospective observational study, patients with an IPC related pleural infection appear to have higher rates of autopleurodesis and better survival.(46) Pain is frequently seen following IPC insertion, however, there is no difference when compared with chest drain and pleurodesis.(36) Other complications include cellulitis around IPC tract, IPC related symptomatic loculation formation, fracture of IPC on removal (i.e. incomplete removal of IPC) and catheter blockage.(47) Other subjective limitations of IPCs not frequently captured in clinical trials is the restriction in patients' lifestyle due to the presence of a plastic tube adhered to the chest wall and intrusion of personal space with frequent district nurses visits for drainage which are essential factors to consider whilst decision making.(48)

Although IPCs are shown to shorten hospital stay, whether there is cost benefit to the health care system is debatable. Cost analysis of patients in TIME-2 showed no difference in costs between patients treated with chest drain-pleurodesis ($4581) versus patients treated with IPCs ($4993).(49) IPCs are more cost effective than pleurodesis in patients with a limited (6-12 week) survival as direct (drainage bottles, healthcare resources needed for drainage) and indirect costs (associated with management of complications) increase with time. (50)

IPC can be drained by two approaches – symptom based drainage (usually 2-3 times/week) or aggressive with daily drainage. Wahidi et al published the ASAP trial in 2017 which compared aggressive daily drainage with conventional alternate day drainage. Autopleurodesis was achieved in 47% of patients as compared to 24 % in the control arm at 12 weeks (p=0.003), although many patients dropped out or died in both groups before the primary end point was reached. Furthermore the median time to achieve pleurodesis was reduced from 90 days to 54 days. However, this study did not show any difference in quality of life or patient satisfaction between the two groups.(51) The AMPLE-2 study looked at aggressive versus conventional IPC drainage with dyspnoea as their primary outcome. Although there was no difference in dyspnoea between the two groups at 60 days there was higher autopleurodesis rates in the aggressive drainage group (37% vs 11%). This was the first study to show better patient related quality of life in the aggressive drainage group. (52)

Silver nitrate has been used for pleurodesis and has shown success rates of around 90-95%.(53) A recent study by Bhatnagar et al has demonstrated the safety of a drug eluting IPC, using silver nitrate as a slow release coating for achieving pleurodesis. Silver nitrate coated IPC (SNCIPC) was inserted in 10 patients with MPE. Of the 9 patients with expandable lung, 89% achieved pleurodesis after a median of four days. 15 of the 17 IPC related side effects were mild indicating acceptable tolerability and safety profile. Pleurodesis using SNCIPC was far more superior to expected pleurodesis rates by aggressive drainage or talc pleurodesis through the IPC.(54)

The BTS guidelines published in 2010 recommended IPCs as a second line treatment in patients with recurrent effusions or who had failed pleurodesis or with a non-expandable lung. However, given the robust data on the efficacy of IPCs in management of dyspnoea in patients with MPE in the past decade, it is making its place as a first line treatment option in patients with MPE. This has already been incorporated in the ATS and ERS/EACTS guidelines for MPE management published recently.(16, 55)

Combined approaches

Few observational studies have been published which have looked at a combination of various therapeutic interventions for management of MPE. This mainly involves thoracoscopic pleurodesis and IPC. In an observational, feasibility study, Reddy et al performed medical thoracoscopy with talc poudrage followed by IPC insertion in 30 patients. Median duration in hospital was 1.79 days and pleurodesis success was seen in 92% patients, with the IPC being removed in a median of 7.54 days. Dyspnoea and quality of life improved in all patients.(56) IPC PLUS was the first study published which aimed at achieving pleurodesis through an IPC using a sclerosing agent. In this single blind multicentre RCT, 154 patients were randomised to either receive 4 g of talc slurry or placebo at day 10 through the IPC. At day 35, 43% patients in the talc group had successful pleurodesis as compared to 23% in the placebo group.(57)

Surgical options

Surgical options for MPE include pleurectomy and abrasion pleurodesis. Although few case series suggest partial and total pleurectomy are effective treatment options for MPE, several RCTs comparing surgical and medical pleurodesis have found no difference in pleurodesis success rates.(58, 59) In a large RCT, 196 patients with mesothelioma were subjected to either VATS pleurectomy or talc pleurodesis using slurry or poudrage. There was no significant difference in the primary outcome of survival at 1 year (52% in VATS group versus 59% in talc pleurodesis group). VATS group was associated with increased rates of

complications, longer hospital stay and higher expenses.(60) Based on the findings of these studies there is currently no role for surgery in the treatment of MPEs.

Septated and loculated MPE

Loculated effusions are defined as effusions with multiple loci i.e. the effusion is divided into separate pockets of effusion. Septated effusion is defined as the presence of fibrinous strands in the effusion due to excessive fibrin formation. The proportion of MPEs with septations is not clearly known.(61) In a retrospective analysis of 540 patients who underwent medical thoracoscopy for MPE, Bielsa et al. found some degree of septations in 332 (60%) patients which obstructed two thirds or more of the view on thoracoscopy in 84 (15%) patients. The extent of septations correlated with a greater tumor burden and decreased survival (median survival of 9 months in patients without adhesions versus 4.8 months in patients with dense adhesions).(62)

In the TIME3 trial, 71 patients with non-draining MPE due to septations received either urokinase (100000 U, three doses over 36 h) or placebo, followed by talc slurry pleurodesis after 24 h. There was no difference in visual analogue dyspnoea scores over the first month or pleurodesis failure rates at 1 year between the two groups. However, urokinase performed better than placebo for secondary outcome measures, including an 18% greater reduction in pleural opacification on chest radiography 2 days post-randomisation, shorter length of hospital stay (6.2 versus 8.7 days) and improved survival (69 versus 48 days; all $p<0.05$). Moreover, 48% of the study population died within 1 month of randomisation, which highlights the poor prognosis of patients with septated MPEs.(63)

Although intrapleural fibrinolytics increase volume of pleural fluid drained and improve radiological appearances, they have no effect on patient related outcomes such as dyspnoea or survival. Currently treatment options for this cohort are highly limited.

Intrapleural targeted therapies

Treatment options that have been discussed for MPE so far are merely methods to control pleural fluid to provide relief of breathlessness. None of these interventions deal with managing the primary tumor. There have been two phase II trials that have looked into efficacy of intrapleural bevacizumab in patients with MPE secondary to non-small cell lung cancer (NSCLC). In the first study, 24 patients were randomised to either receive intrapleural paclitaxel with intrapleural bevacizumab or isolated intrapleural paclitaxel. The combination therapy significantly reduced pleural fluid level and improved dyspnoea in 78.6% patients as compared to 50% treated with intrapleural paclitaxel alone ($p < 0.005$). Moreover, 1 year survival was better in patients treated with combination therapy (45.8% versus 20.8%; $p < 0.005$). (64) Another phase II study compared intrapleural cisplatin with or without bevacizumab in 70 patients with non squamous NSCLC related MPE. The addition of bevacizumab lead to better MPE response rates (85.7% versus 56.6%). However, a recent review by Sabang et al. concludes that these studies were not adequately powered and lack of placebo controlled trials interferes with determining the actual efficacy of bevacizumab in fluid control.(65)

Bevacizumab acts by inhibiting VEGF thereby decreasing pleural fluid formation and promoting pleural apposition which may enhance efficacy of chemical pleurodesis. However, experimental studies have failed to support this hypothesis and using a rabbit model, intravenous administration of anti-VEGF antibody reduced degree of pleurodesis on post mortem examination.(66)

Hence currently no conclusions can be drawn on the efficacy of antitumor treatment in MPE.

Utility of prognostic scores

It is essential to predict survival in patients with MPE as it will help in triaging patients with better survival prediction to more aggressive pleural interventions and oncology treatment, and patients with a poor survival prediction to a less invasive strategy with higher focus on symptom control. Historically massive effusion has been associated with a poor survival, although there was significant difference in the definition of massive effusion in the studies.(67, 68)

Since 2014, two prognostication tools have been developed and validated in MPE. The LENT score – based on pleural fluid Lactate dehydrogenase, Eastern Cooperative Oncology Group (ECOG) performance score, Neutrophil-to-lymphocyte ratio, and Tumour type (LENT) was developed using data from 789 patients with MPE across three international centres. Based on these variables, patients were separated into low, moderate and high risk groups with median survival of 319, 130 and 44 days respectively. In the validation cohort, the LENT score was significantly better than ECOG performance score in predicting survival at 3 months and 6 months.(3)

The PROMISE study developed a clinical and biological prognostic score for patients with MPE based on ECOG performance score, previous chemo therapy and radiotherapy, cancer type, white blood cell count, C-reactive protein, haemoglobin and tissue inhibitor of metalloproteinases 1 (TIMP 1) levels for the biological score. Based on the score patients are divided into four categories with median survival ranging from < 25% to > 75% at 3 months.(69)

In patients with mesothelioma, the Brims decision tree derived from 482 sequential mesothelioma patients and validated in an independent cohort is the most clinically useful prognostication tool. It is based on symptoms such as weight loss, performance status, haemoglobin, albumin and mesothelioma histology. The decision tree separates patients into four groups with survival falling from 34 months in group 1 to 17.7, 12 and 7.4 months in subsequent groups.(70)

Although all these prognostic markers are validated tools, their complexity and wide range of survival reduced their value in day to day practise and further studies are needed to determine their utility in clinical pathway.

Expert Commentary:

In the current era, there are various interventions available for management of MPEs. While therapeutic large volume aspiration remains the initial intervention choice, it is no longer recommended as a definitive management strategy even for patients with a survival less than one month. Chest drain with pleurodesis and IPC have shown to be highly effective treatment options in patients with MPE. However, neither is perfect. Each has its own set of advantages and disadvantages. While chest drain pleurodesis confers a success rate of around 70% in the setting of clinical trials albeit lower in clinical practise, it is associated with a prolonged hospital stay of 3-5 days adding further morbidity. Although IPCs are attractive as day case options with reduced hospital stay and decreased ‘pleural procedures’ perhaps for the physician, IPC drainage in the communities although not equivalent to aspiration or chest drain insertion should be possibly sought as procedures for the patients. There is no ‘one-fit-all’ treatment option available and decision regarding either procedure should be made on an individual case by case scenario taking into account patient preference and social support, performance status, predicted responsiveness to antitumor therapy, expected survival, effusion characteristics such as trapped lung or septated effusion and resource and

expertise availability. There are various patient centred tools available to ease decision making.(71) IPCs remain the treatment of choice in patients with NEL.

Although health economic analyses have shown that therapeutic aspiration is the most cost effective intervention, it is the least effective in terms of quality of life. IPCs have shown to be the most cost effective strategy particularly when patient survival is predicted to be less than 6 months and further trial designs need incorporation from health care economics to determine the most effective strategy taking into account patient outcomes and cost effectiveness for any health system.

Given the short average life expectancy with MPEs, it would be crucial to target therapies to achieve fluid control and pleurodesis at the earliest to minimise the effect of effusion on quality of life. Whether using ultrasound guidance to determine timing of pleurodesis through chest drain to increase pleurodesis success rates and shorten hospital stay or aggressive drainage through IPCs combined with talc pleurodesis, these strategies will be the way forward. Silver nitrate as a pleurodesis agent has shown to be extremely potent and larger studies investigating its efficacy are needed.

All measures for management of MPEs at the moment are largely for symptom control and an effort to improve quality of life with prevention of fluid recurrence. Whether any of the interventions provide a survival benefit would be an important factor for decision making in the future and may change management pathways for more aggressive strategies for fluid control. There have been observational studies to show successful pleurodesis confers a survival benefit. Further studies are needed to explore this.

The ultimate aim for management of MPEs would be to stop pleural fluid formation. Identification of pleural fluid biomarkers will play an important role in management of MPEs as it will individualise patient treatment and will focus of fluid formation than fluid control and the advent of IPCs makes it an optimum tool to access pleural space long term and administer intrapleural therapy.

Future directions:

Although there is a large body of evidence available for MPE management, there are still many unanswered questions – what is the optimum patient centred outcome? Most trials so far have focussed on patient symptoms such as pain and dyspnea with a few focussing on quality of life. How can we predict rate of pleural fluid recurrence, how to identify patients who will have maximum benefit with interventions and how to predict survival with various interventions? Further clinical trials will perhaps aim to provide answers to many of these questions.

Currently robust evidence is available for fluid control management strategies for MPE although much more evidence is needed for management of trapped lung, septated MPEs in the outpatient setting. Future trials will be aimed at studying pleural markers and developing intrapleural drugs to prevent fluid formation. Recent studies have shown discordance between pleural metastases' tumour microenvironment and primary carcinoma and heterogeneity exists even within pleural tumour cells within the same patient, possibly suggesting MPE formation is an independent entity.(72) Hence, patients with MPEs from different primary tumours should be stratified separately in clinical trials to account for variability in pathogenesis and prognosis. Clearly, better understanding of MPE pathophysiology is needed to facilitate intrapleural specific treatments.

Pleurapump which is a novel pump system allowing pleural fluid to move from the pleural space to the urinary bladder has been recently used in the management of recurrent MPEs.

It offers advantages over IPCs as it does not require frequent drainages which can be intrusive and painful for patients. This has been used in two patients and phase 3 studies are needed to demonstrate the efficacy and utility of this system for management of MPE.(73)

Conclusion:

MPE treatment has progressed tremendously in the past decade. Various treatment options are available and management currently largely depends on patient preferences along with availability of expertise which may be significantly restricted in countries with limited resources. Prediction scores in clinical practice can aid with prognosis and guide choice of therapy as risks, complications and setting of procedures widely varies. A number of unanswered questions remain, and ongoing research will help clinicians enhance care for this patient group.

Key issues:

1. Management of MPE has changed drastically in the past decade with the presence of various high quality randomised controlled trials.
2. MPE management is currently focussed on symptom control with the aim of reaching early and successful pleural symphysis.
3. Chest drain pleurodesis is as effective as IPC in management of dyspnoea and should be offered as first line treatment in patients with MPE with a fully expandable lung.
4. Talc is the most effective agent available for pleurodesis and can be performed as a slurry or poudrage with equal efficacy.
5. IPCs are the management of choice for patients with trapped lung and previous failed pleurodesis. Aggressive IPC drainage and outpatient talc through the IPC increase chances of pleurodesis.
6. Further management strategies in the future would be a combination of different therapeutic interventions.
7. Research is needed to identify pleural fluid biomarkers and prevent pleural fluid formation.

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