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Current best practice in the evaluation and management of malignant pleural effusions

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Abstract: Malignant pleural effusions (MPEs) are an important cause of cancer-related mortality and morbidity. It is a heterogeneous group of conditions, which leads to debilitating symptoms and confers a poor prognosis. Recent well-designed randomized trials have provided a broader evidence base for an expanding range of treatment options. Together, with new prognostic scoring systems and a greater understanding of how different patient phenotypes respond to treatment, this allows greater personalization of management. This article will discuss the current evidence on evaluation and management of MPEs.

Keywords: indwelling pleural catheter, malignant, mesothelioma, pleural effusion, pleural disease, pleurodesis

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Introduction

Malignant pleural effusions (MPEs) represent a significant health burden and are an important cause of cancer-related mortality and morbidity. They are common, affecting 15% of all patients with cancer [Clive *et al.* 2016a]. There are 150,000 new diagnoses of MPE in the USA each year [American Thoracic Society, 2000], and 50,000 in the UK [Rahman *et al.* 2010a]. It is anticipated that incidence will increase as survival rates for cancer improve and the population ages.

The majority of patients with MPE are symptomatic, with breathlessness the predominant symptom [Roberts *et al.* 2010]. Importantly the severity of symptoms does not always correlate to the size of the effusion. Other factors, including the speed of fluid accumulation and the presence of any respiratory comorbidities, contribute to the degree of breathlessness experienced. Patients with MPE may also report chest pain, a dry cough or indigestion and early satiety due to pressure effects on the stomach.

MPE is a marker of poor prognosis, and median survival varies from 3 months to 12 months depending on underlying tumour type [Lui *et al.* 2016a; Roberts *et al.* 2010]. Since management of MPE is invariably palliative, interventions should focus on relieving symptoms whilst minimalizing hospitalization [Thomas *et al.* 2014]. It is worth noting that some patients do not experience any improvement in symptoms following fluid removal, and for these patients a conservative approach is acceptable.

The heterogeneity of MPE with regards to fluid production and response to treatment means that management should be personalized [Bhatnagar and Maskell, 2014]. Clinicians should take into account patient factors, such as individual preference and the presence of comorbidities, MPE factors, including the rate of recurrence, presence of septations or trapped lung, and tumour characteristics, for example, cancer type, disease stage and predicted prognosis [Lui *et al.* 2016a]. Diagnostic and therapeutic interventions undertaken during the patient's initial investigations can help to determine whether symptoms improve after aspiration of fluid, and consequently can inform future management.

Investigations

Imaging

A posterior-anterior chest radiograph is the first-line investigation for suspected MPE. A fluid level will be visible if over 200 ml of pleural fluid is present [Hooper *et al.* 2010]. Other radiological signs of MPE include lobulated pleural

thickening, crowding of ribs, elevation of the hemidiaphragm and mediastinal shift, either towards the affected side due to volume loss from an obstructing tumour, or away from the lesion due to pressure effects from fluid [Heffner and Klein, 2008]. A massive effusion, with mediastinal shift and diaphragmatic inversion, is associated with an increased probability of malignancy [Heffner and Klein, 2008].

Thoracic ultrasound (TUS) is useful to confirm the presence of pleural fluid and to differentiate between pleural fluid, pleural thickening and consolidation [Porcel and Light, 2013]. It can also suggest a malignant aetiology with certain features (e.g. presence of pleural thickening $>$ 1 cm, diaphragmatic nodularity or thickening $>$ 7 mm, visceral pleural thickening and pleural nodularity/irregularity) highly suggestive of malignancy [Porcel and Light, 2013]. TUS has a sensitivity of 73% and specificity of 100% in identifying malignancy and is more sensitive than computed tomography (CT) scans in demonstrating visceral pleural disease and diaphragmatic nodularity [Qureshi *et al.* 2009]. TUS also has a role in MPE management; its use alongside thoracentesis is associated with a 16% reduction in pneumothorax and 39% reduction in haemorrhage [Patel *et al.* 2012].

Contrast-enhanced CT of the thorax is undertaken in most patients with suspected MPE, as it is considered the gold standard of imaging in pleural malignancy. There are four main features on CT that are useful in differentiating malignant from benign disease [Leung *et al.* 1990]: (a) circumferential pleural thickening (specificity 100%, sensitivity 41%); (b) nodular pleural thickening (specificity 94%, sensitivity 51%); (c) parietal pleural thickening greater than 1 cm (specificity 94%, sensitivity 36%); (d) mediastinal pleural involvement (specificity 88%, sensitivity 56%).

In general, CT features have high specificity but poor sensitivity for differentiating malignant from benign disease. In addition CT cannot reliably differentiate malignant pleural mesothelioma from pleural metastases [Leung *et al.* 1990].

Metabolic imaging using 18-fluorodeoxyglucose (FDG) positron emission tomography (PET) scanning is often used to stage primary lung cancer and other malignancies, however, its use in malignant pleural disease is not well defined. A meta-analysis of 14 studies examining the use of FDG PET found a sensitivity of 81% and specificity of 74% for pleural malignancy [Porcel *et al.* 2015]. False negatives can occur in the presence of early or indolent disease, and false positives are possible in the context of inflammatory pleuritis, rheumatoid disease and previous pleurodesis. For this reason PET-CT is not used in routine diagnostic practice.

PET-CT may have a role in determining the optimal sites for image-guided biopsy by identifying the area of highest metabolic activity. This hypothesis is currently under investigation in the TARGET trial (www.isrctn.com ISRCTN14024829), a multicentre, parallel group randomized control trial comparing PET-CT-guided biopsy with CT-guided biopsy in patients who have had previous negative biopsies.

Magnetic resonance imaging (MRI) can be used to evaluate malignant pleural disease. It provides better imaging of soft tissue than CT, can detect invasion into the chest wall and diaphragm, and has higher sensitivity for small effusions [Lorigan and Libshitz, 1989]. It has been shown to have higher inter-observer agreement in assessing pleural thickening, pleural effusion and extra pleural fat when compared with CT [Weber *et al.* 2004]. However, it is not as effective as CT for imaging lung parenchyma.

MRI can also provide functional information *via* the use of diffusion-weighted imaging or dynamic contrast enhancement. Combining this information with standard imaging provides sensitivity and specificity rates of over 90% for differentiating malignant from benign pleural disease [Coolen *et al.* 2012]. However, uncertainty over the optimal protocol for MRI scanning alongside limited access in some centres means that MRI is not currently part of the standard investigatory pathway for MPE.

Pathological diagnosis

Pleural fluid sampling and cytological examination should be undertaken in all patients with a suspected MPE, and will provide a diagnosis in up to 60% of patients [Hooper *et al.* 2010]. Certain tumour types, for example, mesothelioma, sarcoma and squamous cell carcinoma have a much lower diagnostic sensitivity [Porcel and Light, 2013].

In terms of the optimum volume of pleural fluid to maximize the likelihood of achieving a cytological diagnosis, 60 ml appears to be superior to 10 ml [Swiderek *et al.* 2010]. However, another study found no statistically meaningful difference in the detection rate of malignant cells between 25 ml, 50 ml and 150 ml samples (82%, 89% and 93%, respectively) [Khosla *et al.* 2016]. The British Thoracic Society (BTS) guidelines advise that 20–40 ml should be enough, unless more fluid is being taken off for therapeutic purposes [Hooper *et al.* 2010]. Since patients often undergo a therapeutic aspiration, with up to 1.5 L removed at the same time, larger samples may be sent for cytology, but the diagnostic benefit of this is unclear.

There does not appear to be any cumulative diagnostic benefit from sending repeat samples for cytology if the initial sample was negative [Jenkinson and Murphy, 2007]. However, if suspicious cells are seen on the original aspirate, but were insufficient to provide a definitive diagnosis, a repeat, large-volume sample should be considered [Hooper *et al.* 2010]. If cytology does not yield the diagnosis, then histological diagnosis should be obtained *via* pleural biopsy. Historically percutaneous biopsies were performed blind, using a closed (Abrams) needle. However, the low sensitivity (57%) and high complication rate of this procedure has led to a decrease in its use [Bibby and Maskell, 2016; Tomlinson and Sahn, 1987]. Percutaneous biopsies are now usually undertaken under image-guidance, using CT or TUS. This allows the focal area of abnormal pleura to be targeted under direct vision, with consequent higher diagnostic sensitivity and lower complication rates [Metintas *et al.* 2010]. The superiority of CT-guided biopsy over the Abrams technique has been demonstrated in a randomized controlled trial, which revealed a sensitivity of 87% and specificity of 100% for the former method [Maskell *et al.* 2003]. TUS-guided pleural biopsies have a similar diagnostic yield to CT-guided biopsy and offer the additional benefit of no ionizing radiation [Qureshi and Gleeson, 2006; Sconfienza *et al.* 2013]. TUS-guided pleural biopsies can be undertaken by respiratory physicians with a 94% diagnostic yield [Hallifax *et al.* 2014; Metintas *et al.* 2012]

Percutaneous biopsies are not possible in all patients with MPE, for instance if there is minimal pleural thickening or disease is poorly accessible due to the presence of other thoracic organs. In these patients, thoracoscopy is the preferred method for obtaining biopsies. Thoracoscopy can be undertaken under local anaesthetic (LAT) as a physician-operated procedure, or as video-assisted thoracoscopy (VATS) performed by thoracic surgeons under general anaesthetic. Thoracoscopy allows direct visualization of the pleural surface and targeted biopsies of areas of disease. In addition, because pleural effusions are drained to dryness during thoracoscopy, the procedure offers therapeutic benefit as well as diagnostic information. Furthermore, if the pleura appears to be obviously infiltrated with malignant disease, and the lung is not trapped, pleurodesis can be undertaken, thus providing a definitive fluid management option at the same time.

LAT is a safe option with low mortality (0.3%) and major complications rates (1.8%) [Rahman *et al.* 2010a]. It has a diagnostic sensitivity of over 90%, which is comparable to image-guided percutaneous biopsy [Metintas *et al.* 2010].

In order to be suitable for LAT patients need to be able to lie in the lateral decubitus position for at least 30 min and to maintain reasonable oxygenation with conscious sedation. The effusion must be of sufficient size to allow the introducer port to be safely inserted. In patients with small effusions a pneumothorax can be induced with a Boutin needle immediately prior to thoracoscopy. A case series has demonstrated success rates of 87% with this method [Corcoran *et al.* 2015]. Patients with a tethered lung or heavily loculated effusions may not be suitable for LAT as the lung will not collapse away from the chest wall once the introducer port is inserted. These patients should be considered for a surgical VATS instead.

The diagnostic sensitivity of VATS is similar to LAT, at 95%, although no trial has directly compared the two methods [Hooper *et al.* 2010]. As well as being suitable for patients with complex effusions, VATS also offers the potential for therapeutic procedures, such as lung resection or tumour debulking, to be performed during the same procedure. Complications rates from a retrospective audit of 86 patients undergoing VATS in the UK demonstrated no mortalities and a 1.2% major complication rate [Medford *et al.* 2008]. However, due to the invasive nature of VATS and the need for general anaesthetic it is unsuitable for frail patients and those with certain comorbidities.

Tumour markers

Various biomarkers have been proposed as noninvasive tests to help distinguish between benign and malignant pleural disease, and to give information on prognosis or treatment outcomes [Psallidas *et al.* 2016]. Multiple serum and pleural biomarkers such as mesothelin, osteopontin and fibulin-3 have been investigated in MPE [Creaney *et al.* 2014; Pass *et al.* 2005, 2012; Porcel, 2013; Porcel *et al.* 2004]. In general these biomarkers have demonstrated poor specificity and sensitivity and results have not been validated in subsequent studies [Psallidas *et al.* 2016; Sriram *et al.* 2011]. The use of established biomarkers, including carcinoembryonic antigen and cancer antigens (CAs) 15-3 and 125, has limited diagnostic value in determining the aetiology of MPE [Porcel *et al.* 2004]

The most promising biomarker to date is mesothelin, a cell-surface glycoprotein that is overexpressed in mesothelioma [Chang *et al.* 1992]. Mesothelin can be measured in both pleural fluid and serum, with similar diagnostic performances [Cui *et al.* 2014]. A meta-analysis of 4491 individual patients with mesothelioma reported serum mesothelin had a sensitivity of 32% with a specificity of 95% [Hollevoet *et al.* 2012]. Consequently a high pleural mesothelin serum level should prompt further investigations, but a negative test is of limited value. Mesothelin may be more useful in monitoring mesothelioma disease progression and response to treatment rather than as a diagnostic tool, but the assay is not widely available outside the research setting and there are limited data in this area.

Management

The management of MPE should include ongoing monitoring and symptomatic treatment with oxygen and opioids as required. In terms of interventions for MPE, the options include recurrent therapeutic thoracentesis, chest drainage and pleurodesis, insertion of an indwelling pleural catheter (IPC) or surgical intervention. Management should be personalized, and decisions made based on clinical factors and individual patient preference.

Clinical factors that influence management include the predicted rate of pleural effusion recurrence, based on underlying tumour type and rapidity of re-accumulation after previous therapeutic interventions. The patient's prognosis should also be considered. This may be influenced by performance status [Burrows *et al.* 2000], tumour characteristics [Heffner *et al.* 2000], extent of disease [Wu *et al.* 2013], comorbidities and effusion biochemistry [Bielsa *et al.* 2008; Heffner *et al.* 2000; Kao *et al.* 2010]. The LENT score can be used to predict survival in patients presenting with a first episode of MPE [Clive *et al.* 2014]. It is summarized in Table 1, and can be used to stratify patients into low-, moderate- or high-risk groups. Median survival of patients with a high-risk LENT score was 44 days, and 6-month survival was just 3% [Clive *et al.* 2014].

Other clinical factors that may influence MPE management include response to previous therapeutic aspirations, the presence of trapped lung or septated effusion and whether any oncological treatment is planned.

Therapeutic thoracentesis

Most patients will undergo therapeutic thoracentesis at some point in their clinical pathway. This can provide useful information as to whether they derive symptomatic benefit from the removal of pleural fluid. This is important, as breathlessness may be multifactorial in people with MPE, and other pathologies such as bronchial obstruction, carcinomatous lymphangitis, pulmonary embolism or chronic obstructive pulmonary disease may co-exist. If a patient does not experience an improvement in breathlessness following a therapeutic aspiration, then a conservative 'watch and wait' policy might be appropriate.

Unfortunately most MPEs will recur after initial therapeutic aspiration, and a definitive procedure to control the fluid is usually required [Fysh *et al.* 2015]. Undertaking repeated therapeutic thoracentesis will expose the patient to discomfort and an increased risk of complications with each repeated procedure. Consequently this approach is not suitable for most patients. However, if the patient has a limited life expectancy, a slowly re-accumulating effusion or does not wish to have a more invasive procedure, then repeated thoracentesis may be an option.

Table 1. The LENT prognostic score calculation.

Variable		Score
L (LDH in pleural fluid level)		
	< 1500	0
	> 1500	1
E (ECOG PS)		
	0	0
	1	1
	3	2
	3–4	3
N (NLR)		
	< 9	0
	> 9	1
T (Tumour type)		
	Lowest risk tumour types	0
	Mesothelioma	
	Haematological malignancy	
	Moderate risk tumour types	1
	Breast cancer	
	Gynaecological cancer	
	Renal cell carcinoma	
	Highest risk tumour types	2
	Lung cancer	
	Other tumour types	
Risk categories	Total score	
Low risk	0–1	
Moderate risk	2–4	
High risk	5–7	

Reproduced with permission from Clive *et al.* [2014]. ECOG PS, Eastern Cooperative Oncology Group performance score; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio.

Chest drainage and pleurodesis

One method of achieving definitive control of MPE is complete chest drainage followed by chemical pleurodesis. The aim of pleurodesis is to induce pleural inflammation and subsequent adhesion of the visceral and parietal pleura, thus preventing fluid re-accumulation. This can be achieved by instilling a sclerosing agent *via* a chest drain (slurry) or by insufflation during medical thoracoscopy (poudrage). Various agents have been evaluated, including antibiotics (tetracycline, doxycycline, bleomycin), bacterial agents (*Corynebacterium parvum*, OK432) and irritants (talc). A recent Cochrane review of pleurodesis agents reported significant clinical and statistical heterogeneity in trials of pleurodesis agents, but concluded that talc was one of the most effective interventions [Clive *et al.* 2016a].

The success rates of talc pleurodesis are reported as 60–75%, whether delivered *via* a chest drain or at thoracoscopy [Lui *et al.* 2016a]. The TIME-1 trial suggested that wide-bore drains may be superior to small bore in achieving pleurodesis [Rahman *et al.* 2015]. However, smaller chest tubes (12F) are more comfortable for patients [Rahman *et al.* 2010b, 2015]. In the authors' opinion, further data are required before recommending using large-bore chest tubes for all patients. Our unit currently avoids using chest tubes less than 12 F and ensures these are both sutured in well and flushed regularly, ensuring patency is maintained. Rotation of the patient to maximize talc distribution has been advocated in the past, however, subsequent studies using radio-labelled talc have shown that rotation does not affect dispersal, and so it is no longer performed [Dryzer *et al.* 1993; Mager *et al.* 2002]

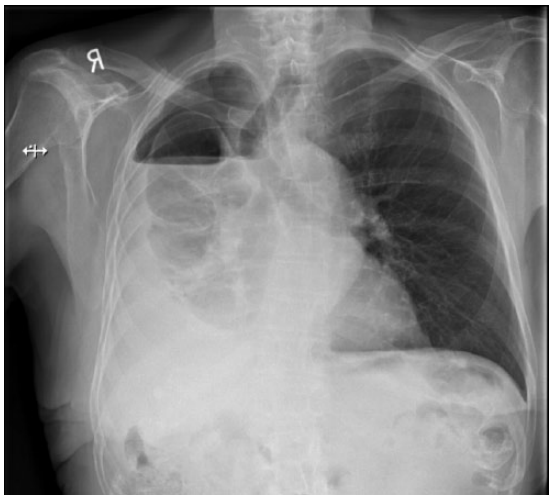

Figure 1. Pleural effusion with trapped lung.

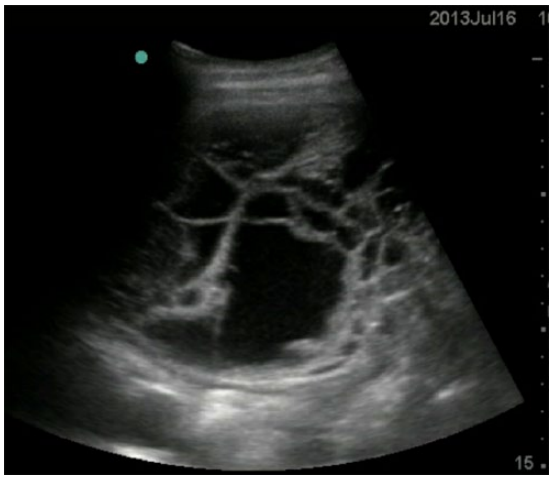

Figure 2. Septated pleural effusion.

Chest drainage and pleurodesis requires an inpatient hospital stay of between 4 days and 7 days [Davies *et al.* 2012]. This may not be appropriate for patients with a limited life expectancy, who wish to spend as much time at home as possible. In addition many patients will experience pain, a fever or both after pleurodesis [Rahman *et al.* 2015]. These factors should be discussed with the patient when management decisions are being made.

Patients with trapped lung (Figure 1) or multiple pleural septations (Figure 2) are unlikely to achieve successful pleurodesis. With trapped lung, there is little or no pleural apposition, and therefore pleurodesis will be futile. An IPC should be offered preferentially in these people [Bhatnagar *et al.* 2016]. Heavily septated pleural effusions are unlikely to drain fully, and consequently pleurodesis will be impaired. There were encouraging results initially from an observational trial investigating the use of fibrinolytics to dissolve septations in loculated MPEs [Thomas *et al.* 2015]. However, a subsequent randomized control trial demonstrated that intrapleural urokinase does not improve dyspnoea or pleurodesis success compared with placebo in patients with non-draining MPEs, and therefore urokinase has no routine role in managing this subgroup of patients with MPE [Mishra *et al.* 2016].

Insertion of an indwelling pleural catheter

Insertion of a tunnelled IPC to allow ambulatory fluid drainage is another definitive method for managing MPE. IPC insertion can be performed as a day case under LAT. Drainages are undertaken at home using sterile vacuum bottles by district nurses or family members. The TIME 2 study showed that IPC insertion was equally effective at relieving dyspnoea as chest drainage and talc slurry [Davies *et al.* 2012]. The Australasian Malignant Pleural Effusion (AMPLE) trial replicated this result, and showed that patients managed with IPCs require significantly fewer days in hospital [Lee *et al.* 2016]. This makes IPC insertion a very attractive option for patients who wish to avoid a hospital stay, and it is important to solicit individual patient's opinions on this when deciding on MPE management [Maskell, 2012].

IPCs can be used in patients who have previously failed pleurodesis, or who are not suitable for pleurodesis due to trapped lung or heavily loculated fluid. Interestingly, in patients whose lungs are not trapped, spontaneous pleurodesis has been reported in 45% of patients with IPCs [Van Meter *et al.* 2011]. If pleurodesis occurs, the IPC can be removed.

Complications of IPC insertion include infection, which is usually quoted as a rate of 4–5% [Fysh *et al.* 2013]. IPC-related infections appear to have a low overall mortality (0.29%), and can usually be treated with oral antibiotics, without the need for IPC removal [Fysh *et al.* 2013]. The risk of infection does not seem to be higher if chemotherapy is given [Fysh *et al.* 2013; Hak *et al.* 2016; Mekhaiel *et al.* 2013], however it does increase over time.

Another potential complication of IPC insertion is the development of catheter tract metastases (CTM). These present as a painful subcutaneous mass near the IPC insertion site or tract. The average incidence is below 5%, but may be influenced by tumour type and duration of IPC placement [Lui *et al.* 2016b]. Patients with CTM can be treated with analgesia and external beam radiotherapy, without the need for IPC removal [Lui *et al.* 2016b]. The use of prophylactic radiotherapy to prevent symptomatic CTM developing was recently shown not to be beneficial, and consequently should not be routinely performed [Clive *et al.* 2016b].

The increasing expertise in IPC usage has allowed novel uses and applications to be investigated. Talc has been instilled *via* IPCs in case studies [Tremblay *et al.* 2007], and is being investigated in a multicentre randomized control trial [Bhatnagar *et al.* 2015] (IPC PLUS www.isrctn.com ISRCTN 73255764). IPCs also offer the opportunity to deliver therapies directly into the pleural space, an approach that is particularly attractive for targeted biological agents and immunotherapy [Islam and Takita, 2012; Sterman *et al.* 2007, 2010]. The opportunity to obtain multiple samples of pleural fluid from IPCs is an exciting prospect and may lead to greater understanding of the pathophysiology of MPE, and the potential to monitor physiological responses to treatments.

Surgery

Surgery has a limited role in the management of MPE, and benefits are often outweighed by perioperative mortality and reduced quality of life [Rintoul *et al.* 2014; Roberts *et al.* 2010]. A small case series reporting VATS partial pleurectomy in patients with MPE secondary to mesothelioma reported high rates of pleural fluid control [Waller *et al.* 1995]. However, a subsequent randomized trial comparing VATS partial pleurectomy with chest drainage and talc pleurodesis reported no difference in pleurodesis rates between the groups at 3 months and 12 months [Rintoul *et al.* 2014]. In addition there was no difference in survival between the groups, and there were significantly more complications in the surgical group [Rintoul *et al.* 2014]. The authors conclude that VATS pleurectomy cannot be recommended in this context. The 2010 BTS pleural guidelines reiterate this, advocating IPC insertion or chest drainage with chemical pleurodesis preferentially [Roberts *et al.* 2010]. At present, patients with MPE should only be considered for surgery in the context of a clinical trial, and only once patients have been fully informed about alternative options and the relative advantages and disadvantages of each method.

Conclusion

MPEs are of source of significant morbidity in patients who have a limited life expectancy. Investigations should focus on achieving a diagnosis *via* the least invasive method, in a timely fashion. Procedures undertaken for investigative purposes can also help to determine future management decisions (e.g. response to therapeutic thoracentesis) and some diagnostic procedures offer simultaneous therapeutic opportunities (e.g. thoracoscopy). In the past decade, a number of well-designed randomized trials have provided a robust evidence base for the investigation and management of MPE, and there is a range of treatment options that can be offered to people with MPE.

MPE is a heterogeneous condition, with multiple underlying aetiologies, variable prognosis and unpredictable responses to treatment. Consequently each patient requires a personalized management approach in which the pros and cons of each therapeutic option are considered and discussed. Patient preference should be prioritized.

Further trials are underway that will hopefully inform and enhance MPE management in the future. Studies aiming to predict more accurately symptomatic response and individual prognosis will enable a more personalized approach in the next few years.

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