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6 Current Trends in Treating Malignant Pleural Effusion: Evidence, Guidelines, and Best Practice Recommendations

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ABSTRACT

Malignant pleural effusion (MPE) is common in individuals with cancer and typically reflects advanced disease. Most cases are symptomatic, with dyspnea and pain having a severe effect on the patient's quality of life (QOL). The management of MPE aims to relieve symptoms, improve QOL, prevent repeated pleural interventions, and minimize hospital admissions. Common treatments for MPE that provide symptomatic relief include thoracentesis, chemical (talc) pleurodesis, or indwelling pleural catheters (IPCs). Talc pleurodesis and IPCs are the mainstay of treatment but represent very different treatment strategies: talc pleurodesis is an inpatient procedure, whereas IPCs are an ambulatory strategy. Given their similar efficacy, treatment decisions in MPE are often determined by other factors, such as the patient's clinical characteristics, individual treatment goals, and preferences for hospital-based or home-based care. We provide a summary of the evidence for different interventions for treating MPE and compare recommendations from the major American, European, British, and Spanish guidelines regarding when to consider each treatment. We highlight specific challenging treatment scenarios and key clinical considerations that may influence treatment decisions for different patients. There are barriers to accessing and receiving evidence-based care. Patients with symptomatic MPE would benefit from early referral from oncology teams to pleural services. We provide best practice recommendations for optimal referral and coordination of care to ensure that patients receive maximum benefits from their interventions.

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INTRODUCTION

Malignant pleural effusion (MPE) affects up to 15% of patients with cancer, and its incidence and prevalence are increasing.¹⁻⁴ Most cases are symptomatic; the most common symptoms are dyspnea due to compression of the lung parenchyma, impaired chest wall movement, and, particularly, diaphragmatic dysfunction.^{3,5-8} MPE usually represents advanced or metastatic disease, with a median survival of 3-12 months depending on the primary cancer site and other prognostic factors.³

The most common treatments for MPE that provide symptomatic relief are therapeutic thoracentesis, chemical pleurodesis (talc slurry), or insertion of an indwelling pleural catheter (IPC) at bedside.⁹ Chemical pleurodesis (eg, talc poudrage, tetracycline, doxycycline, or bleomycin) or mechanical pleurodesis can also be performed during surgery. Pleurectomy or abrasion pleurodesis is still performed in rare cases. Therapeutic thoracentesis involves ultrasound-guided insertion of a catheter-over-needle into the pleural space to extract as much pleural fluid as possible. Following thoracentesis, fluid reaccumulates in more than 50% of patients, necessitating multiple

thoracentesis procedures.³ Therefore, thoracentesis is not considered a long-term treatment option.³ In contrast, talc pleurodesis and IPCs are considered definitive therapies. Talc pleurodesis is typically conducted as an inpatient procedure and involves the delivery of graded talc into the pleural cavity via thoracoscopy (poudrage) or chest tube (slurry) following complete drainage of the MPE and lung re-expansion.^{3,10} Talc pleurodesis is successful in 70%-75% of cases,¹¹ and slurry and poudrage appear to be equally effective.^{12,13}

Installation of an IPC is usually an ambulatory procedure and involves the insertion of a tube attached to a one-way valve into the pleural space, allowing fluid to be drained from the pleural cavity as needed. Community nurses and caregivers are typically assigned to undertake regular fluid drainage at the patient's home. Approximately 50% of patients achieve autopleurodesis after 3 months of treatment with daily drainage using an IPC.^{14,15}

Surgical interventions have similar efficacy to talc pleurodesis but are much more invasive.¹⁶ Therefore, surgery is typically reserved for unusual cases in which talc pleurodesis or IPC placement is not possible.

The management of MPE aims to relieve symptoms, improve quality of life (QOL), prevent repeated pleural interventions, and minimize hospital admissions.⁵ There are no differences in the mean efficacy between talc pleurodesis and IPCs in reducing breathlessness. In the TIME2 trial, Davies et al¹⁷ randomly assigned patients to receive IPC or inpatient talc slurry pleurodesis, and found no significant difference in the primary outcome of dyspnea scores at 6 weeks. Similarly, the AMPLE randomized controlled trial found that IPC or talc slurry resulted in sustained improvements in breathlessness and QOL scores, with no difference between the two treatment arms.² Furthermore, the OPTIMUM trial found no significant differences in patient-reported global health status (measured by the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-C30) at 1 month between IPC and talc slurry pleurodesis.¹⁸ Since neither talc pleurodesis nor IPCs are clearly more efficacious for symptom control, treatment choices are made on a patient-by-patient basis based on the preferences, characteristics, and specific clinical challenges of each patient.¹⁹

This review aims to support clinicians in making individual treatment decisions for MPE. We summarize the current treatment guidelines, provide guidance on specific difficult treatment scenarios, outline key clinical considerations for treatment choice, and recommend best practices to support optimal referral and coordination of care.

REVIEW OF GUIDELINES

Asymptomatic MPE

In asymptomatic patients with known or suspected MPE, the general consensus is that therapeutic pleural interventions should not be performed.^{20,21}

Symptomatic MPE With Nonexpandable Lung

Approximately 30% of patients with symptomatic MPE exhibit nonexpandable lungs, which is defined as an inability to occupy over 75% of the chest cavity after drainage.²² The American Thoracic Society (ATS) advises against chemical (talc) pleurodesis in the setting of known nonexpandable lungs, highlighting its rare effectiveness, and instead recommends IPCs as the treatment of choice.²⁰ For nonexpandable lung cases with a predicted very short survival, ATS recommends palliative care for dyspnea, involving repeat thoracentesis, oxygen, and morphine.²⁰ Similarly, the European Respiratory Society (ERS), European Association for Cardio-Thoracic Surgery (EACTS), and Spanish Society of Pulmonology and Thoracic Surgery (SECT) advocate for IPCs in MPE cases with nonexpandable lung.^{3,21}

In contrast, the British Thoracic Society (BTS) 2023 guidelines propose stratified treatment on the basis of the extent of lung re-expansion.²² For patients with radiologically significant (>25%) nonexpandable lungs, IPCs are favored over talc pleurodesis, whereas those with <25% nonexpandable

lungs may obtain QOL benefits from talc slurry pleurodesis or IPC.²² Surgical intervention is generally not recommended, although in highly selected patients with trapped lungs, where expandable lungs are a key priority, decortication can be considered. Although BTS acknowledges thoracentesis as an option, it recommends discussing alternatives with the patient due to the need for multiple procedures.²²

Symptomatic MPE With Known or Likely Expandable Lung

The guidance is more nuanced for cases of MPE with known or likely expandable lungs. ATS recommends IPCs or talc (slurry or poudrage) pleurodesis when no previous definitive therapy has been administered.²⁰ As a second-line treatment for patients with failed pleurodesis, ATS recommends IPCs over talc pleurodesis. Combined treatment with IPCs and talc slurry pleurodesis may also be considered. Patients with good performance status and a low LENT score (a score of 0–1 based on criteria including pleural fluid lactate dehydrogenase, Eastern Cooperative Oncology Group [ECOG] performance status, neutrophil-to-lymphocyte ratio, and tumor type) indicative of a relatively good survival prognosis in MPE may be considered for minimally invasive decortication.^{20,23} Any decision to use IPCs should be based on patient-specific considerations and the support network available for IPC drainage.²⁰ ERS and EACTS consider both talc pleurodesis (slurry or poudrage) and IPCs to be highly effective but make no recommendations for combined treatment.³ In the United Kingdom, BTS advises offering patients with known or likely expandable lung a choice between IPCs, talc pleurodesis, or combined treatment as a first-line intervention.²² The guideline explicitly states that relative risks and benefits should be discussed with patients to choose an optimal treatment strategy, taking into account inpatient versus ambulatory management and the need for further interventions. Patients preferring inpatient strategies are offered talc pleurodesis, whereas those favoring ambulatory approaches are offered IPCs with or without talc pleurodesis.²² Where IPC removal and pleurodesis are priorities, BTS recommends daily drainage and instillation of talc via IPC.²² Patients not expected to benefit from definitive interventions (chemical pleurodesis, IPC, or surgery), for example, due to short life expectancy, should be offered best supportive care, likely including repeated thoracentesis.²²

Spanish guidelines systematically consider the ECOG performance status in treatment decisions.²¹ For patients with severe impairment (ECOG 3–4), IPCs are recommended as a first-line option with or without talc slurry pleurodesis. If IPC placement is not feasible, therapeutic thoracentesis is recommended. For patients with mild to moderate impairment (ECOG 0–2), talc slurry pleurodesis (provided that the lung is expandable) or IPC is recommended as the first-line treatment.²¹ If talc slurry pleurodesis fails, IPC is advised instead of repeated pleurodesis.²¹ When IPC placement is not feasible, talc poudrage pleurodesis is recommended.²¹

All four guidelines mention that performance status can be helpful in planning treatment. Although Spanish guidelines systematically apply performance status to guide decisions, in other regions it is considered as additional information to assess patient prognosis. Under all four guidelines, if a patient has a very poor performance status and therefore poor prognosis, they will likely not benefit from definitive treatments (chemical pleurodesis, IPC, or surgery) and will be offered best supportive care, including thoracentesis.^{3,20-22}

Shared Decision Making

Patient involvement in the decision-making process is crucial to ensure the best treatment option for a particular person. Patients should be provided with clear information in their preferred format (eg, spoken, written, via a translator, website links) about each treatment so that they can make informed choices on the basis of their own preferences, treatment goals, and the risk-benefit profile of the treatments.

Having regular conversations with patients and their caregivers about their treatment thoughts and concerns will help identify and rectify any treatment issues early, enabling patients to obtain maximum benefit from their treatment.

CHALLENGING SCENARIOS

Septated MPE

Septated MPE describes the presence of fibrinous strands within the effusion, often due to inflammatory-mediated changes in procoagulant and fibrinolytic activity.²⁴ Septations are common. In a retrospective analysis of 540 consecutive patients undergoing medical thoracoscopy, septations were observed in 60% of the cases and obstructed two thirds or more of the view in 15% of the cases, correlating with a greater pleural tumor burden and shorter median survival.²⁵ Septations do not necessarily prevent drainage of the effusion, and usual care can be applied.³ However, nondraining septated fluids are more challenging owing to a lack of treatment options in this group and require a personalized approach on the basis of the patient's clinical characteristics.

Treatment strategies for symptomatic septated MPE vary among guidelines, reflecting the limited evidence for any single intervention. The ATS guidelines offer no specific recommendations,²⁰ whereas the ERS guidelines suggest breaking septations during thoracoscopy.³ The British guidelines propose intrapleural fibrinolytics such as urokinase through an IPC for draining septated MPE if initially flushing the IPC with normal or heparinized saline does not improve drainage. Fibrinolytics may be considered in nondraining cases, reserving surgery for very select patients with significantly septated symptomatic MPE with a favorable prognosis and performance status.²² In contrast, the Spanish guidelines and ERS/EACTS task force highlight that, although intrapleural fibrinolytics may improve radiological

appearance and shorten hospital stay, they have limited effect on dyspnea or pleurodesis success.^{3,21,26}

Loculated MPE

Loculated MPE involves multiple fluid collections in separate pockets,³ often requiring a chest tube in each pocket to obtain successful drainage. Loculations can prevent complete drainage of the pleural space and limit lung re-expansion, often contraindicating talc pleurodesis or resulting in insufficient symptomatic relief from IPCs.^{3,27} Loculations and septations may coexist. Up to 14% of patients with MPE develop symptomatic loculations, and septated effusions may progress to loculated forms.^{3,20}

The guidelines differ in terms of loculated MPE treatment recommendations. ATS recommends IPC over talc pleurodesis because IPC may enable further drainage of fluid, alleviation of symptoms, avoidance of admission, and fewer subsequent procedures. The guideline also emphasizes the heterogeneity within the loculated effusion group, such that patients with few loculations may still benefit from talc pleurodesis. Minimally invasive decortication may be considered in patients with a good performance status and low LENT score.^{20,23}

The ERS/EATC and SECT guidelines lack strong recommendations, noting that a nonexpandable lung contraindicates pleurodesis and that IPCs may fail to completely drain the pleural space, limiting symptom improvement.^{3,21} Both guidelines suggest intrapleural fibrinolytics, acknowledging their limited effects on dyspnea or pleurodesis success.^{3,21} The ERS/EATC guideline adds that thoracic surgery may be needed for multiple loculations, particularly near the mediastinum, with limited options for surgically ineligible patients.³ BTS guidelines provide no specific recommendations for loculated MPE, except for referral to the pleural team.²²

In our experience, therapeutic thoracentesis can be initially performed in loculated cases, as in nonloculated effusions, to observe the effect on dyspnea and pulmonary expansibility. This procedure can aid in differentiating loculated effusions from atelectasis or consolidation, and facilitates pleural fluid analysis if not previously conducted. An exception to this would be if the decision had been taken to treat the loculated MPE with an IPC, in which case the IPC could be inserted without previous therapeutic thoracentesis.

CLINICAL CONSIDERATIONS

Intervention During Pleural Biopsy

Pleural biopsy may be required to confirm the diagnosis of unilateral pleural effusion with pleural malignancy.^{21,22} The BTS guidelines recommend that patients with MPE undergoing thoroscopic biopsy should receive talc poudrage during the biopsy procedure.²² The Spanish guidelines also highlight (though do not explicitly recommend) that

pleurodesis or IPC insertion can be performed during video thoroscopic biopsy.²¹ Given the difficulties in distinguishing between MPE and pleural tuberculosis on thoracoscopy in areas with high tuberculosis prevalence, we recommend initiation of treatment for MPE only after definitive confirmation of the diagnosis.

Treatment Goals

Life expectancy guides treatment goals: for patients with a very short prognosis, treatment goals may shift from long-term control to palliative care. ATS emphasizes that predicting the prognosis of a patient is challenging for clinicians. Consequently, life expectancy serves only as a rough guide, and care should be individualized on a case-by-case basis.²⁰

In most cases, treatment choice is driven by patient preference and suitability for an ambulatory home-based strategy (IPC) or a shorter, more intensive inpatient strategy (talc pleurodesis). In the AMPLE trial, participants randomly assigned to IPC spent fewer days in hospital than those randomly assigned to talc slurry pleurodesis (median, 10.0 v 12.0 days; $P = .03$), and fewer patients in the IPC group required further invasive pleural drainage (4.1% v 22.5%).² A 2020 meta-analysis of randomized controlled trials reached the same conclusion. However, across trials, successful pleurodesis was more likely with talc pleurodesis (relative risk, 1.56 [95% CI, 1.26 to 1.92]) than with IPC.²⁸

Some patients prefer IPCs over talc pleurodesis because of reduced hospital visits, fewer pleural interventions, and flexible at-home drainage. In contrast, talc pleurodesis may suit patients who prioritize a shorter, intensive regimen or pursue pleurodesis as an important treatment goal. IPC drainage frequency can be symptom-guided or fixed and adapted depending on the treatment goal. The ASAP, AM-
PLE2, and OPTIMUM trials demonstrated that daily drainage schedules are tolerated by many patients and enhance pleurodesis rates compared with symptom-guided or every-other-day drainage.^{15,18,29}

There is alternatively the middle-ground option of combined IPC-talc pleurodesis treatment via instillation of talc slurry through the IPC. Combined approaches may maximize the advantages of both treatments, thereby minimizing the time required to achieve pleurodesis.¹² Another major driver of treatment choice is the potential effect of treatment on QOL. In a randomized controlled trial, in which patients were allowed to choose their preferred management strategy for MPE, those who selected IPCs were significantly more likely to report improvements in QOL than those who chose talc pleurodesis.³⁰ However, no significant differences in QOL outcomes were found in the large TIME2 and AMPLE randomized controlled trials comparing IPCs and talc pleurodesis.^{2,17} Similar findings were observed in the OPTIMUM trial, with no significant difference reported in self-reported overall QOL after 30 days. However, QOL scores improved significantly in both groups.¹⁸

The effect of each treatment on QOL varies from patient to patient. For some patients, fewer hospital visits or pleural interventions may have a substantial positive effect on QOL. Others may find that some aspects of IPCs negatively affect their QOL, such as experiencing psychological discomfort from having a visible catheter or difficulty sleeping.³¹ In some patients, pleurodesis is painful,³ whereas others experience pain from IPCs due to the device itself or during drainage. Patients should therefore be consulted about what aspects of care are important for their QOL and followed up after the initial treatment choice, including discussion of pain, so that adjustments to treatment can be made if necessary.

Adverse Events

Both IPCs and talc pleurodesis entail adverse events. A meta-analysis found no significant overall differences in the frequency of adverse events between treatments²⁸; however, distinct adverse event profiles exist for each.^{28,32} IPCs pose a higher risk of infection due to prolonged foreign body insertion, with skin or pleural fluid infections occurring in approximately 8% of cases.¹⁴ Although IPC-related infections have attracted attention, they typically respond to treatment without IPC removal.^{20,21} Antibiotics, guided by local sensitivities, can be used to manage infections with case-specific escalation (intravenous antibiotics, hospital admission, and IPC removal) if the infection worsens.²⁰ Pleural infections can sometimes result in autopleurodesis. Other minor IPC-related complications include catheter obstruction (approximately 5%) and septa development (<15%).^{14,21}

Adverse events associated with graded talc pleurodesis include pain, dyspnea, infection, postprocedural fever, tube blockage, and tube displacement. These adverse events occur in <10% of patients.^{2,18,33} Acute respiratory distress syndrome is a feared complication due to small talc particles. This complication is avoided by using graded talc.³⁴

Both IPCs and talc pleurodesis necessitate close monitoring and management of adverse events to ensure optimal patient outcomes.

Patient Characteristics

Treatment decisions hinge on clinical factors, such as nonexpandable lungs. With pleurodesis contraindicated in nonexpandable lung cases, IPC is the sole therapeutic option, emphasizing the need for accurate prediction.²¹ Pleural manometry aids in predicting whether the lung will expand on the basis of elastance (change in pleural space pressure in cm H₂O/L of fluid removed). Elastance over 14.5 cm H₂O/L suggests a nonexpandable lung, whereas elastance over 19 cm H₂O/L indicates an increased risk of pleurodesis failure.^{21,35,36} Similarly, thoracic ultrasound is an established noninvasive technique in pleural medicine, and the M-mode measure can assess lung movement. A recent study found that M-mode movement at the lung bases of <0.94 cm was indicative of a nonexpandable lung.³⁷

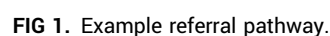
Anticancer Treatment

Some oncologists are concerned that the risk of infection is increased when IPCs are used simultaneously with chemotherapy, whereas others are concerned about unknown interactions between anticancer treatments and IPCs. However, current evidence does not support these concerns. IPCs do not increase the risk of infection in most cases; therefore, chemotherapy should not be withheld from patients with an IPC.⁴⁰ Furthermore, the infection rate is similar in patients with or without neutropenia receiving chemotherapy; therefore, neutropenia should not contraindicate simultaneous treatment with chemotherapy and IPC.⁴¹ Drugs can cause adverse pulmonary effects, including pulmonary damage or pleural effusion,^{42,43} but these are rare and can be monitored for early identification and management. Some clinicians are concerned that chemotherapy can accumulate in undrained effusions, leading to increased toxicity or increased distribution volume^{44,45}; however, these concerns can be addressed by draining the effusions before initiating chemotherapy.³

Cost-effectiveness considerations depend on local and national health authorities. In well-funded areas, such as Europe and the United States, decisions between IPCs and talc pleurodesis prioritize patient suitability and clinical factors. In less affluent regions, cost-effectiveness will be given more consideration.⁴⁶ Both talc pleurodesis and

OPTIMAL REFERRAL AND COORDINATION OF CARE

Ideally, every hospital should have a pleural service or a dedicated MPE unit. For hospitals without such services, the Expert Committee recommends that clinicians map the availability of local specialist units/services to identify gaps in patient care pathways. Specialists can then support the development of new centers to target these gaps. If an oncology department lacks specialized IPC services, we recommend that oncologists refer patients to pulmonology



departments for specialized care rather than managing pleural effusion symptoms independently.

Multidisciplinary teams (MDTs) facilitate the sharing of expertise and resources between departments, whereas regular MDT meetings facilitate clear communication between different services. High-quality care is based on multidisciplinary collaboration with patients at the center. Although some oncology teams may face logistical or organizational constraints to working within an MDT framework, the integration of pleural services with oncology departments can be a beneficial alternative solution.

What Does Optimal Communication Look Like?

Optimal communication involves a clear, written referral from the oncology team to the pleural services/pulmonology team. Referral should encourage two-way communication by including an invitation to contact the referrer if the receiving department has any queries. Proactive collaboration and communication between referring and recipient services is crucial for ensuring that guidelines are followed, and any deviations from the guidelines are appropriate. Subsequent interactions can be via phone, e-mail, or in-person and should focus on addressing treatment issues. The referring clinician must also ensure that the recipient team is adequately trained. Identification of knowledge gaps should prompt clinicians to organize training initiatives that should be led by health care professionals experienced in the treatment of MPE.

The pulmonologist placing the IPC should report the details of the procedure, including the amount of fluid drained, followed by specific recommendations on drainage frequency and volume at home.

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Unanswered Questions

Treatments for MPE have seen little evolution for decades. Talc pleurodesis was first described in 1935 and IPCs were released onto the market in 1997.⁴⁹ In the coming decade, we hope for progress on several key unanswered research questions, which could be transformative for the management of MPE and patient outcomes.

Unanswered questions:

1. Are there biomarkers that may help predict which treatment a patient will benefit the most from?
2. Are there drugs that may suppress pleural fluid production, thus avoiding interventions on the pleural space?
3. Are there any novel oncologic treatments that might be effective for managing MPE?
4. What are patients' and carers' key priorities concerning future MPE management?

In conclusion, the benefits and drawbacks of various treatment options may result in certain patients deriving greater advantages from one particular treatment than from another. It is possible that some patients are not offered optimal treatment, at times due to a reliance on specific local procedures, personal preferences of clinicians, lack of awareness, or misconceptions about specific treatment options. One size does not fit all; treatment choice needs to be made on the basis of the suitability, benefits, and risk profile for each particular patient. A detailed consideration of the patient's clinical characteristics at each step of the treatment pathway will help clinicians and patients to identify the optimal treatment. This can be supported by providing patients with balanced information regarding the benefits and risks of all treatment options. Following treatment choice, effective coordination of care between different teams will help maximize the benefits that each person can obtain from their chosen intervention.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Current Trends in Treating Malignant Pleural Effusion: Evidence, Guidelines and Best Practice Recommendations**

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