AMERICAN THORACIC SOCIETY DOCUMENTS

Management of Malignant Pleural Effusions

An Official ATS/STS/STR Clinical Practice Guideline

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Background: This Guideline, a collaborative effort from the American Thoracic Society, Society of Thoracic Surgeons, and Society of Thoracic Radiology, aims to provide evidence-based recommendations to guide contemporary management of patients with a malignant pleural effusion (MPE).

Methods: A multidisciplinary panel developed seven questions using the PICO (Population, Intervention, Comparator, and Outcomes) format. The GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach and the Evidence to Decision framework was applied to each question. Recommendations were formulated, discussed, and approved by the entire panel.

Results: The panel made weak recommendations in favor of: *1*) using ultrasound to guide pleural interventions; *2*) not performing pleural interventions in asymptomatic patients with MPE; *3*) using either an indwelling pleural catheter (IPC) or chemical pleurodesis in symptomatic patients with MPE and suspected expandable lung; *4*) performing large-volume thoracentesis to assess symptomatic response and lung expansion; *5*) using either talc poudrage or talc slurry for chemical pleurodesis; *6*) using IPC instead of chemical pleurodesis in patients with nonexpandable lung or failed pleurodesis; and *7*) treating IPC-associated infections with antibiotics and not removing the catheter.

Conclusions: These recommendations, based on the best available evidence, can guide management of patients with MPE and improve patient outcomes.

Keywords: pleural effusion; malignant; palliation; pleurodesis; pleural catheter

Contents

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Summary of Recommendations

PICO 1: In patients with known or suspected malignant pleural effusion (MPE), we suggest that ultrasound imaging be used to guide pleural interventions.

PICO 2: In patients with known or suspected MPE who are asymptomatic, we suggest that therapeutic pleural interventions should not be performed.

PICO 3: In patients with symptomatic MPE, we suggest large-volume thoracentesis if it is uncertain whether the patient's symptoms are related to the effusion and/or if the lung is expandable (the latter if pleurodesis is contemplated), to assess lung expansion.

PICO 4: In patients with symptomatic MPE with known (or likely) suspected expandable lung, and no prior definitive therapy, we suggest that either an indwelling pleural catheter (IPC) or chemical pleurodesis be used as first-line definitive pleural intervention for management of dyspnea.

PICO 5: In patients with symptomatic MPE and expandable lung undergoing talc pleurodesis, we suggest the use of either talc poudrage or talc slurry.

PICO 6: In patients with symptomatic malignant pleural effusions with nonexpandable lung, failed pleurodesis, or loculated effusion, we suggest the use of IPCs over chemical pleurodesis.

PICO 7: In patients with IPC-associated infections, treating through the infection without catheter removal is usually adequate. We suggest catheter removal if the infection fails to improve.

Introduction

Malignant pleural effusions (MPEs) are the second leading cause (next to parapneumonic effusions) of exudative effusions, accounting for greater than 125,000 hospital admissions per year in the United States and estimated inpatient charges of greater than $5 billion per year (1). Though some patients are initially asymptomatic, the majority will eventually develop dyspnea at rest. Likewise, as MPE is associated with an average survival of 4–7 months (2), treatment should aim to relieve dyspnea in a minimally invasive manner, and ideally minimize repeated procedures and interaction with the healthcare system (i.e., to provide a definitive pleural intervention) (3). With increasing focus on patient-centered outcomes, many of these techniques, including thoracoscopy and placement of indwelling pleural catheters (IPCs), can be performed in the outpatient setting (4–6). The American Thoracic Society published the first guidelines for management of MPE in 2000 (7), followed by the British Thoracic Society guidelines, published in 2010 (8). Both were based on the consensus of a group of international experts in the field who reviewed the available literature at that time. However, recent data suggest that these guidelines are followed less than 50% of the time (9). Since publication of the British Thoracic Society guidelines, there have been several large, multicenter, randomized trials, as well as other well-conducted studies that have substantially impacted the way patients with MPE are evaluated and treated. A recent survey by the European Society of Thoracic Surgeons found a majority of respondents who were aware of existing guidelines suggested that they are in need of updating/revisions (9).

This document aims to provide practicing clinicians with the synthesis of latest evidence along with recommendations to improve patient centered outcomes. Because the clinical questions surrounding the management of MPEs can be broad and beyond the scope of a single document, this panel opted to narrow the focus of the guidelines to key issues that are of the most relevance to clinicians and patients/caregivers.

Methods

We used the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach (10, 11) to formulate clinical questions in PICO (Patient, Intervention, Comparator, and Outcome) format, summarize relevant evidence, and develop recommendations for clinical practice. To identify the best available evidence, we identified existing systematic reviews and performed additional systematic reviews, including a systematic review for PICO4 that will be published separately. Full methodologic details and tables supporting the recommendations here can be found in the online supplement.

Recommendations for Specific Treatment Questions

PICO 1: In Patients with Known or Suspected MPE, Should Thoracic Ultrasound Be Used to Guide Pleural Interventions?

Background. Pleural interventions (e.g., thoracentesis, pleural drainage catheter insertion) are frequently performed for diagnostic or therapeutic purposes in patients with MPE. These procedures may be performed with or without imaging guidance, in both inpatient and outpatient settings.

Iatrogenic pneumothorax is the most common complication of thoracentesis, and, in a minority of cases, requires chest tube placement, which can necessitate or lengthen hospital stay. Historically, the rate of pneumothorax after thoracentesis for any/all causes of pleural effusions has been reported to be as high as 39% (12), although more recent and larger studies have shown substantially lower rates of pneumothorax in all cases, but especially when ultrasound

guidance is used (13, 14). The use of ultrasound guidance for thoracentesis has also been shown to reduce the rates of "dry taps" and less common complications, such as solid organ puncture or hemothorax (12, 15).

Although the largest studies in the literature have assessed the use of ultrasound for thoracentesis in all types of pleural effusions, this question appraised the evidence for whether ultrasound is superior for guiding pleural interventions specifically for MPE.

Summary of the evidence. The search strategy for this question obtained one retrospective observational study that specifically assessed complication rates for thoracentesis in MPE with or without ultrasound guidance (16). Three retrospective observational studies assessed safety and efficacy for ultrasound guidance of pleural effusions, including, but not limited to, MPE were also included in the initial review (17–19). In addition, two studies comprised of larger patient populations, including a meta-analysis (13) and large retrospective cohort (14) that reviewed complication rates after thoracentesis for all causes of pleural effusion were included to help formulate the recommendation.

The outcomes of pneumothorax, and pneumothorax requiring chest tube placement, were considered critical. No studies assessed other complication rates (i.e., hemothorax, pain at site) or procedural success specifically for malignant effusions.

The use of ultrasound guidance reduced the risk of pneumothorax after thoracentesis for malignant effusions (1.0% vs. 8.9%, relative risk [RR] = 0.10, 95% confidence interval [CI] = 0.03–0.37) (16). There were no chest tubes placed in the ultrasound guidance group compared with three (2.2%) chest tubes in the group without image guidance (95% CI not estimable) (16). The other three observational studies (17–19) assessed safety and success of ultrasound guidance in pleural effusions of all causes, and did not report complication rates specifically for malignant effusions.

Two larger studies assessed the risk of pneumothorax after thoracentesis with or without ultrasound guidance for all causes of pleural effusion. A meta-analysis of 24 studies and 6,605 thoracenteses published in 2010 found that the overall pneumothorax risk after thoracentesis was 6.0%, and that ultrasound guidance was associated with a lower risk of pneumothorax (4.0% vs. 9.3%; odds ratio = 0.3, 95% CI = 0.2–0.7) (13). Moreover, 34.1% of pneumothoraces in this meta-analysis required chest tube placement (13).

A more recent, large, retrospective cohort study published in 2013 that reviewed 62,261 thoracenteses for pleural effusions of all causes reported an overall risk of pneumothorax of 2.7% and found that ultrasound guidance reduced the risk of pneumothorax by 19% (odds ratio = 0.81, 95% CI = 0.74–0.90) (14). The frequency of chest tube placement was not reported for this study, but pneumothorax was associated with a significantly longer length of hospital stay and total patient hospitalization cost (14). Despite the lack of a randomized trial comparing thoracentesis with and without ultrasound specifically in patients with MPE, the panel agrees that ultrasound guidance, which has no significant harms associated with its usage, has an important benefit of reducing pneumothorax rates.

Recommendation. In patients with known or suspected MPE, we suggest that ultrasound imaging be used to guide pleural interventions (conditional recommendation, very low confidence in estimate of effects; *see* Tables E4A and E5A in the online supplement).

Justification and implementation considerations. This recommendation is based not only on the limited observational evidence for ultrasound guidance for management of malignant effusions, but also on the stronger evidence from larger studies in the management of pleural effusions of all types described previously here.

The decision to use ultrasound guidance for pleural interventions in patients with malignant effusions will depend on local expertise, availability, and access to ultrasound machines.

Research priorities. Future studies should further investigate the use of ultrasound in expanded roles for pleural interventions in patients with malignant effusions. For example, ultrasound can be used to identify intercostal vessels, with the goal of decreasing the small, but real, risk of hemorrhagic complications associated with pleural procedures (20). In addition, ultrasound can be used to evaluate for nonexpandable lung before thoracentesis, which may aid in guiding definitive management (21), or to determine if pleurodesis was successful.

PICO 2: In Patients with Known or Suspected MPE Who Are Asymptomatic, Should Pleural Drainage Be Performed?

Background. Asymptomatic MPEs are a commonly encountered scenario for clinicians. All invasive pleural procedures carry a small risk of complications, and, therefore, any intervention must have benefits that outweigh these risks. One potential benefit of early intervention that has been regularly proposed is the possible reduced risk of developing a nonexpandable lung at a later stage in the disease process.

Summary of the evidence. The search revealed two studies pertinent to the clinical question. Improvement in quality of life, breathlessness, and other symptoms (e.g., pain), future need of interventions, and days spent in hospital during the patient's remaining lifespan were considered critical outcomes, and healthcare costs for fluid management in remaining lifespan and walking distance or other exertional activities were considered important outcomes. Tremblay and colleagues (22) undertook a retrospective review of 113 patients presenting to a lung cancer clinic over a 3-month period in Canada with a pleural effusion on chest radiography or computed tomography (CT) thorax. A total of 14 of these were asymptomatic or did not require intervention; 13 patients were then followed up for a median time of 98 days, and none required intervention during this period. The study's conclusions were limited by the small number of patients and its retrospective design. It was also limited to patients with lung cancer, and the follow-up period was relatively short. Porcel and colleagues (2) published a retrospective study of 556 patients with newly diagnosed lung cancer. They found that 40% of patients with lung cancer developed a pleural effusion during the course of their disease, half of which were too small for any sampling or intervention. Of these 112 (20%) cases with small/minimal pleural effusions, none required an interventional procedure during follow up (mean $\pm$ SD = 10 $\pm$ 11 mo). Although these small effusions did not go on to become symptomatic, they did confer a survival disadvantage compared with those without a pleural effusion

(median survival, 7.5 vs. 12.7 mo; $P < 0.001$). This finding was mirrored in a larger Korean series (7.7 mo vs. 17.7 mo; $P < 0.001$) (23).

Recommendation. In patients with known or suspected MPE who are asymptomatic, we suggest that therapeutic pleural interventions not be performed (conditional recommendation, very low confidence in estimate of effects; Tables E4B and E5B).

Justification. Data are insufficient to recommend sampling or draining these asymptomatic effusions. Unless there are clinical indications, such as obtaining fluid to define clinical stage/obtain molecular markers, the drainage of asymptomatic effusions would only subject the patient to the risks of the procedure (albeit a small risk) without providing clinical benefit. Clearly, if pleural fluid is required for diagnostic purposes, fluid and/or tissue sampling would be appropriate.

Research priorities. Published literature on this topic has focused exclusively on MPE in the lung cancer setting. A large prospective study of all MPEs is needed with longer follow up of subjects. A prospective study evaluating whether delay in draining asymptomatic pleural effusions increases the risk of subsequent nonexpandable lung should also be investigated. Likewise, as pleural palliation can still be achieved in patients who develop symptoms even with nonexpandable lung, trials defining the optimal way to palliate effusions from a patient and cost perspective are essential. It is also vital for us to improve our understanding of what biological role an MPE may play in disease progression and why survival is significantly worsened by the development of asymptomatic pleural effusion in patients with known lung cancer.

PICO 3: Should the Management of Patients with Symptomatic Known or Suspected MPE Be Guided by Large-Volume Thoracentesis and Pleural Manometry?

Background. Performing a therapeutic drainage before a definitive pleural intervention in patients with MPE can serve two purposes: confirming symptomatic improvement after fluid drainage and identifying the presence of nonexpandable lung (also referred to as "unexpandable lung" or "lung entrapment" in the literature) (24). Nonexpandable lung occurs in at least 30% of patients with MPEs, and may be a contraindication for pleurodesis (8, 25–27). The absence of lung expansion after fluid evacuation should ideally steer the clinician to avoid futile attempts at pleurodesis and use IPCs as the treatment of choice in these patients.

Measurement of pleural pressures or elastance (change in pressure over volume drained) is one of the most studied approaches to predict if the lung will expand after drainage. Studies to date generally included both malignant and benign effusions, and the majority investigated the "safety" limit of how much fluid can be removed, and prediction of nonexpandable lungs was based on the changes in pressure curves, rather than a post-drainage chest CT (26, 28, 29). Lung expansion can be assessed with positive-pressure ventilation if the patient undergoes thoracoscopy performed under general anesthesia (30). Post-procedure imaging after draining all/most-all of the pleural fluid can also assess lung expansion. Another benefit of a large-volume drainage procedure lies in confirming that the patient's dyspnea is due to the effusion. This may not be apparent if only a small-volume diagnostic thoracentesis is performed (31). If the patient does not receive benefit from the thoracentesis, the clinician needs to investigate other causes of dyspnea (i.e., pulmonary embolism, pericardial effusion, etc.), and further attempts at pleural palliation are not required. Likewise, a large-volume thoracentesis may offer further insight into the speed of pleural fluid reaccumulation after drainage. Recent data suggest that up to 60% of patients will require another procedure within 9 days after initial drainage (3).

Summary of the evidence. Studies of drainage/manometry are limited by variation in how manometry was performed, cut-off values selected, exact parameter(s) captured, heterogeneity of patient populations enrolled, and lack of long-term follow up. Only one study has examined the use of manometry in predicting "longer-term" outcomes. Lan and colleagues (32) reported results of 55 patients with MPE who underwent bleomycin pleurodesis. An elastance of less than 19 cm H_2O measured after draining 500 ml of fluid predicted a 98% chance of success, defined as pleural fluid control at 1 month. All 11 patients with an elastance of 19 cm H_2O or greater did not achieve pleurodesis. The small cohort size, lack of a validation group, and longer-term follow-up preclude a more definitive conclusion. Likewise, there are no studies that demonstrate the benefits of a therapeutic thoracentesis to guide definitive pleural intervention. Despite the sparse evidence, the panel agreed that the potential benefits of large-volume thoracentesis, including identification of lung entrapment and nonresolution of dyspnea, outweighed the harms.

Recommendation. In patients with symptomatic MPE, we suggest large-volume thoracentesis if it is uncertain whether the patient's symptoms are related to the effusion and/or if the lung is expandable (the latter if pleurodesis is contemplated) to assess lung expansion (conditional recommendation, very low confidence in estimate of effects; Tables E4C and E5C).

Justification. There is limited evidence defining the benefits on clinical outcomes in patients with MPEs to support the routine use of pleural pressure measurements or therapeutic thoracentesis to guide definitive pleural palliation. Despite the sparse evidence, the panel agreed that the potential benefits of large-volume thoracentesis, including identification of nonexpandable lung entrapment and nonresolution of dyspnea, outweighed the harms. It is also noteworthy (see the subsequent PICOs) that IPC is an option suitable for both patients with expandable and nonexpandable lung, and is now considered an adequate alternative to pleurodesis in patients who have expandable lung. As such, if the plan is to manage the MPE with an IPC, a large-volume thoracentesis to assess lung expansion, regardless of whether the lung expands an additional procedure (therapeutic thoracentesis), may not be required.

Research priorities. Research is needed to establish better means to predict symptomatic response from MPE drainage, and also to predict lung expansion to guide individualized treatment. Future studies of manometry should first focus on standardizing measurement parameters, and then applying it to the algorithm of MPE management to assess its role (if any) on long-term clinical outcomes. In addition, prospective studies investigating the utility of performing a therapeutic thoracentesis before definitive therapy, especially focusing on patient-centered outcomes, are needed. Advanced ultrasound methods are also being investigated to identify nonexpandable lung before thoracentesis (21).

PICO 4: In Patients with Symptomatic MPE with Known or Suspected Expandable Lung and No Prior Definitive Therapy, Should IPCs or Chemical Pleurodesis Be Used as First-Line Definitive Pleural Intervention for Management of Dyspnea?

Background. Historically, the treatment of choice for patients with MPE has been pleurodesis, with talc being the recommended agent of choice (8, 33). To achieve pleurodesis, it is necessary to have the visceral and parietal pleura in apposition. Given that at least 30% of patients with MPE have nonexpandable lung (25), and the fact that dyspnea in patients with pleural effusion relates more to diaphragmatic inefficiency than lung expansion (34), IPCs have become the treatment of choice for patients with known nonexpandable lung (8). There are currently no recommendations as to whether IPCs or pleurodesis should be used in patients with known or suspected expandable lung.

Summary of the evidence. The search strategy for this question yielded 10 studies, including 1,279 participants. Studies included pleurodesis via surgical or medical thoracoscopy with talc poudrage, chest tube with talc slurry, repeat thoracentesis, or no treatment. Of the studies included, five were randomized controlled trials (Putnam and colleagues [35], NVALT [Dutch Society of Pulmonologists]-14 [36], TIME [Therapeutic Intervention in Malignant Effusion]-2 [37], CALGB [Cancer and Leukemia Group B] 30102 [38], and AMPLE [Australian Malignant Pleural Effusion] [39]), four were retrospective observational studies (40–43), and one was a prospective observational study (44). The critical outcomes included improvement in dyspnea, survival, mortality, hospital length of stay (LOS), and treatment failure, as measured by the need for additional interventions. Empyema, bleeding requiring intervention, and cellulitis were considered important.

Both interventions resulted in improved dyspnea scores from baseline, but no differences were found between interventions at 30 days (39, 42) or 42 days (36, 37). In the TIME-2 trial, the improvement in the Visual Analog Score between the groups at 6 months favored IPCs (mean difference of −14.0 mm, 95% CI = −25.2 to −2.8; $P = 0.01$) (37).

There was no significant difference in survival between the two interventions, although no study examined survival as a primary outcome. Two studies reporting 3-month mortality showed no difference between IPC and pleurodesis (RR = 1.25, 95% CI = 0.45–3.45) (25, 37).

For hospital LOS, IPCs were favored in all studies that reported this outcome. In the AMPLE study, the difference in median LOS was 2.92 days (95% CI = 0.43–5.84) (30). NVALT-14 also reported fewer median hospital days for patients who underwent IPC compared with chemical pleurodesis (2 d vs. 7 d, respectively; $P < 0.001$) (27), whereas the TIME-2 reported a median of 3.5 fewer hospital days (95% CI = −4.8 to −1.5) (36, 37).

For treatment failure as assessed by the need for additional ipsilateral interventions, pooled results from four studies favored IPCs over chemical pleurodesis (RR = 0.32, 95% CI = 0.18–0.55) (36, 37, 39, 42). Infectious complications were reported more frequently with IPCs. Pooled results from four randomized controlled trials (RCTs) showed a fivefold-increased risk of cellulitis with IPCs when compared with chemical pleurodesis (RR = 5.83, 95% CI = 1.56–21.87) (36, 37, 39, 42); there was a similar trend for increased rates of pleural infection with IPCs (RR = 3.32, 95% CI = 0.82–13.44).

No RCTs reported bleeding complications requiring intervention. Pooled results from 174 patients in two retrospective studies showed no difference between treatment arms (IPC 2.2% vs. chemical pleurodesis 3.7%) (41, 43).

Recommendation. In patients with MPE with known (or likely) suspected expandable lung and no prior definitive therapy, and whose symptoms are attributable to the effusion, we suggest that either IPCs or chemical pleurodesis be used as first-line definitive intervention for management of dyspnea (conditional recommendation, low confidence in estimate of effects; Tables E4D and E5D).

Justification. The available data favored IPCs in terms of fewer days spent in the hospital in patients' remaining life and less risk of treatment failure. On the other hand, data were in favor of chemical pleurodesis with respect to the risk of cellulitis. We prioritized hospital days and treatment failure as critical, patient-centered outcomes; cellulitis, although ranked below the critical outcomes, was so strongly associated with IPCs as to result in a neutral recommendation for either option for relief of dyspnea. Clearly, when performed as an inpatient, chemical pleurodesis will have an increased initial hospital stay compared with an outpatient IPC placement. When choosing one option over the other, care providers should factor in the specific patient's values and preferences by taking into consideration that IPCs reduce time in hospital, but are associated with an increased risk of cellulitis. A recently published RCT, the IPC-Plus study (6), showed that the combination of IPC and talc slurry resulted in higher pleurodesis rates and improved quality of life in the IPC-talc group as compared with the IPC-saline group. Our recommendation is an important advance in the management of MPE, as previous guidelines had recommended IPCs as a treatment option only for patients with nonexpandable lungs, and some physicians had refrained from placing IPCs in patients with expandable lungs.

Research priorities. Additional studies should be conducted to validate the findings of the aforementioned studies and further assess whether IPCs may be superior to pleurodesis for outcomes, such as total days spent in the hospital, patient-reported quality of life, and other patient-centered measures. Other factors that should be addressed in future studies include patients' preference, cost implications, and variation in practice and resources in different regions of the world. Studies combining IPCs with chemical pleurodesis are being conducted, and the results from these trials may provide additional options that can be beneficial to the patients.

PICO 5: In Patients with Symptomatic MPE Undergoing Talc Pleurodesis, Should Talc Poudrage or Talc Slurry Be Used?

Background. More than 50% of malignant effusions will reaccumulate after initial drainage (3), and therefore definitive pleural intervention (i.e., an intervention to prevent recurrent presentation with breathlessness and minimize symptoms/repeated procedures) is a

priority. Guidelines recommend the use of a "definitive" pleural procedure after recurrence of pleural fluid after an initial thoracentesis; however, a recent large retrospective study of 23,431 patients with MPE demonstrated that only 24% underwent a definitive pleural procedure (as opposed to repeat thoracentesis) after rapid reaccumulation of fluid (3). Those undergoing definitive pleural procedures experienced fewer additional pleural procedures, fewer procedures performed in the emergency department, and fewer complications than those undergoing repeat thoracentesis, underlining the importance of definitive pleural intervention at the appropriate time in the treatment process.

Pleurodesis involves the administration of a drug or material in the pleural space to cause adhesions between the parietal and visceral pleura, and prevention of fluid reaccumulation. Talc is the most widely used pleurodesis agent, and has been shown in previous meta-analysis (33) and a head-to-head RCT (45) to be the most effective pleurodesis agent. There are two delivery methods: talc poudrage (also known as insufflation), which is conducted during either surgical or medical thoracoscopy, when talc is blown in as a dry powder; or talc slurry, when talc mixed with sterile fluid is injected through a chest tube at the bedside.

Summary of the evidence. The search strategy for this question found three randomized trials (25, 46, 47), two prospective observational studies (48, 49), four meta-analyses (50–53), and a network meta-analysis (33). Studies included both general anesthetic and local anesthetic thoracoscopic talc poudrage under either general or local anesthesia, and poudrage conducted either by pulmnologists or surgeons. Data from the published meta-analyses were not used for evidence synthesis, as they were outdated, included unpublished data, or reported outcomes that were poorly defined. For example, Mummadi and colleagues (52) pooled all respiratory complications as one outcome, whereas Tan and colleagues (51) did not define the outcome of effusion recurrence. In our review, the outcomes of mortality, respiratory failure, and treatment success (defined as no further ipsilateral pleural intervention) were considered critical, and the outcomes of complications (empyema, bleeding, pneumonia) were considered important. Other complications (cellulitis and fever) were considered not important for this outcome.

Of the randomized trials, the largest one compared surgical thoracoscopic talc poudrage to talc slurry pleurodesis in 482 patients, assessing only those with greater than 90% expansion of the lung on chest radiograph (25). No difference was found between pleurodesis success at 1 month (78% for poudrage vs. 72% for slurry). Yim and colleagues (46) randomized 57 patients with expandable lung and good performance status to talc poudrage or slurry pleurodesis, with no difference between groups in terms of pleurodesis success or hospital stay. Terra and colleagues (47) randomized 60 patients to surgical poudrage or talc slurry pleurodesis and demonstrated a higher rate of immediate lung expansion (>90% on CT) in the surgical group, but no difference in any other outcome over 6 months.

Collating all the evidence, there were inconclusive findings for mortality in the randomized trials (RR = 0.70, 95% CI = 0.33–1.12). There was a larger and statistically significant effect seen in the observational studies (RR = 0.22, 95% CI = 0.06–0.80) favoring talc poudrage, but it is likely that selection bias seriously affects this result (as fitter patients will be selected for talc poudrage over slurry in observational studies).

Findings were also inconclusive, with no significant differences between treatment arms for respiratory failure (RR = 1.74, 95% CI = 0.81–3.74) or for treatment failure in either the randomized trials (RR = 1.02, 95% CI = 0.31–3.31) or the observational studies (RR = 0.74, 95% CI = 0.51–1.06).

There were no significant differences in complications between poudrage and slurry (see evidence table), with the exception of an increase in pneumonia favoring talc slurry, but this was imprecisely estimated (RR = 2.18, 95% CI = 1.02–4.64).

In a *post hoc* subgroup analysis, the largest study to date (25) reported results that favored poudrage compared with slurry in patients with expandable lung, and MPE due to either lung cancer or breast cancer (82% vs. 67% pleurodesis success at 1 mo in those alive to be assessed; $P = 0.022$). However, care should be taken in interpretation of this finding in isolation and as a *post hoc* subgroup analysis.

There were no extractable data for important outcomes, such as breathlessness and time in hospital.

A published network meta-analysis (33) assessed optimal management for prevention of malignant effusion recurrence, and included 62 randomized studies of all pleurodesis agents, including talc and IPCs. This analysis rated talc pleurodesis as highly effective for prevention of fluid recurrence. Both talc poudrage and slurry were ranked highly, but one method was not significantly better than the other, consistent with our findings described previously here.

Recommendation. In patients with symptomatic MPE and expandable lung undergoing talc pleurodesis, we suggest the use of either talc poudrage or talc slurry (conditional recommendation, low confidence in estimate of effects; Tables E4E and E5E).

Justification and implementation considerations. Given the low confidence estimates for critical outcomes, the panel could not recommend one approach over the other. The decision to use poudrage or slurry should depend on several factors, including local expertise (i.e., availability of thoracoscopy), whether additional tissue is needed for molecular-marker analysis (would favor thoracoscopy), as well as patient-related factors (i.e., if a chest tube is already in place).

Research priorities. A prospective, randomized study of patients with expandable lung comparing talc poudrage via medical thoracoscopy and slurry via "small bore" (<14F) chest tubes is ongoing (54). There are a number of important research areas that require further evidence. These should focus on patient-centered outcome measures of breathlessness/quality of life, if patients undergoing talc pleurodesis (via either poudrage or slurry) require hospital admission and if aggressive pleural drainage schedules can lead to lower total catheter days in patients treated with both IPC and talc than the more conservative schedule used in the IPC-plus study (6).

PICO 6: In Patients with Symptomatic MPE with Nonexpandable Lung, Failed Pleurodesis, or Loculated Effusion, Should an IPC or Chemical Pleurodesis Be Used?

Background. At least 30% of patients with MPE will have nonexpandable lung (25).

Likewise, pleurodesis is unsuccessful in up to 30% of patients (25), and as many as 14% of patients with MPE develop symptomatic loculations after prior treatment (8, 44). The use of an IPC in these patient groups may enable further drainage of fluid, alleviation of symptoms, and avoidance of admission and multiple subsequent procedures.

Summary of the evidence. The search strategy for this question yielded five noncomparative case series (55–59) and a single prospective, comparative observational study (60). The outcomes of mortality and reduced hospital stay (LOS of 2 d or less) were considered critical, and the outcomes of complications (i.e., empyema) were considered important.

No difference was demonstrated in mortality in the single comparative study (60). There appeared to be a large effect of reduced hospital stay using IPCs in the single comparative study, with 19 of 34 patients with IPC (56%) staying in the hospital less than 2 days compared with 0 of 7 patients receiving talc pleurodesis (60).

There were no comparative data on complications, but the pooled risk of complications across case series for IPCs used in patients with nonexpandable lung or failed pleurodesis was relatively low for both empyema (2.4%) and cellulitis (3.8%) (55, 56, 58, 59).

No studies reported breathlessness or treatment failure as an outcome.

Recommendation. In patients with symptomatic MPEs with nonexpandable lung, failed pleurodesis, or loculated effusion, we suggest the use of IPCs over chemical pleurodesis (conditional recommendation, very low confidence in estimate of effects; Tables E4F and E5F).

Justification. This recommendation is based primarily on the reduced LOS and low observed incidence of complications associated with IPCs, as well as abundant clinical experience that chemical pleurodesis is rarely effective in the setting of nonexpandable lung. None of the studies examined the success rate (resolution of symptoms or need for additional pleural procedures) of talc pleurodesis in patients who either had prior unsuccessful attempts at pleurodesis or developed symptomatic loculations after either pleurodesis or IPC placement.

Research priorities. Given the paucity of robust clinical data, there is a clear need for studies to directly compare IPC and pleurodesis for alleviating breathlessness in patients with partially expandable lung, loculated effusion, and failed talc pleurodesis. Thomas and colleagues (61) have shown significant increases in pleural drainage and improvement in symptoms in selected patients with IPC-related symptomatic loculations with the use of fibrinolytics; however, there was a small (3%) risk of nonfatal hemorrhagic complications. A recent RCT, however, suggested no benefit of intrapleural urokinase (given via a chest tube) in patients with loculated MPE (62). Additional prospective studies are required to define the role that fibrinolytics have in the treatment of symptomatic loculations, including dose, dwell time, and clinical setting (inpatient vs. outpatient). It should also be noted that "loculated effusion" can represent a very heterogenous group, and that patients with a few loculations may still benefit from pleurodesis. Likewise, in a patient with a good performance status and low LENT (pleural fluid lactate dehydrogenase, Eastern Cooperative Oncology Group performance score, neutrophil-to-lymphocyte ratio, and tumor type) score (a marker of expected relatively good survival in MPE) (63), it may not be unreasonable to offer minimally invasive (video-assisted thoracoscopic surgery or robotic assisted) decortication.

PICO 7: In Patients with IPC-associated Infection (Cellulitis, Tunnel Infection, or Pleural Infection), Should Medical Therapy Alone or Medical Therapy and Catheter Removal Be Used?

Background. IPCs have become the treatment of choice for many patients with MPE (8, 38, 40, 64–66). Though the incidence of IPC-related infection is low, catheter-related infection remains a concern, as well as a potential barrier to their use. Aggregated data from three RCTs show IPC-related rates of cellulitis and pleural space infection of 7.3% and 4.6%, respectively (35, 37, 44). Unfortunately, there are few data regarding the management of IPC-related infection.

Summary of the evidence. The search strategy for this question yielded six noncomparative observational studies (44, 64, 67–70) and one nested case series within an RCT (37) that reported clinical outcomes of IPC-associated infection among 107 patients. One case series comprising nearly half of the pooled patient population did not comment on whether infected IPCs were removed (67). In the remaining case series, 41 of 57 patients (72%) were managed without removing the infected IPC (44, 64, 68–70). Although no comparative data were reported between the two groups, the pooled mortality attributed to the IPC infection among these 57 patients was 12.3%. When examining all case series with 107 patients, the pooled mortality attributed to IPC infection was 9.3%.

There are no data suggesting that catheter removal is superior or inferior to keeping the catheter in place.

Recommendation. In patients with IPC-associated infections, treating through the infection without catheter removal is usually adequate. We suggest catheter removal if the infection fails to improve (conditional recommendation, very low confidence in estimate of effects; Tables E4G and E5G).

Justification. Given the lack of strong data supporting one method of treatment over another, clinical experience suggests that patients can be treated in a variety of ways, including oral or intravenous antibiotics, as well as keeping the catheter in place, or removing the catheter. Treatment decisions should be made on an individual basis. Considerations should be made based on the clinical status of the patient, including signs/symptoms of pleural sepsis (i.e., fever, leukocytosis, failure to thrive), as well as the type of infection (pleural space vs. tunnel infection vs. cellulitis) and the risks of symptomatic fluid reaccumulation should the catheter be removed. Considerations as to resources available to provide home intravenous antibiotic therapy, the proximity of the patient to the care team, as well as the patient's local support network should be taken into account. Patients with IPC-related pleural infection require close monitoring to assure clinical improvement with the implemented treatment plan. Should there be any worsening of the patient's clinical status (i.e., development of pleural sepsis), it would be appropriate to escalate intervention (i.e., switch from oral to intravenous antibiotics, consider catheter removal, rediscuss the patient's course with a multidisciplinary team).

Research priorities. Future studies should investigate the best treatment for IPC-related pleural infection, including the need for catheter removal, the initial use of oral versus intravenous antibiotics, inpatient versus outpatient therapy, and the use of rTPA-DNase through the IPC. Outcomes should include mortality, resource utilization, and need for escalation of care. Confounders in future studies include colonization versus true infection, as well as distinguishing cellulitis versus tunnel infection versus empyema.

Discussion

These recommendations (Figure 1) focus on patient-centered outcomes, such as dyspnea, and the need for recurrent procedures and hospitalizations. Clearly, as with the PICO 3 recommendations that

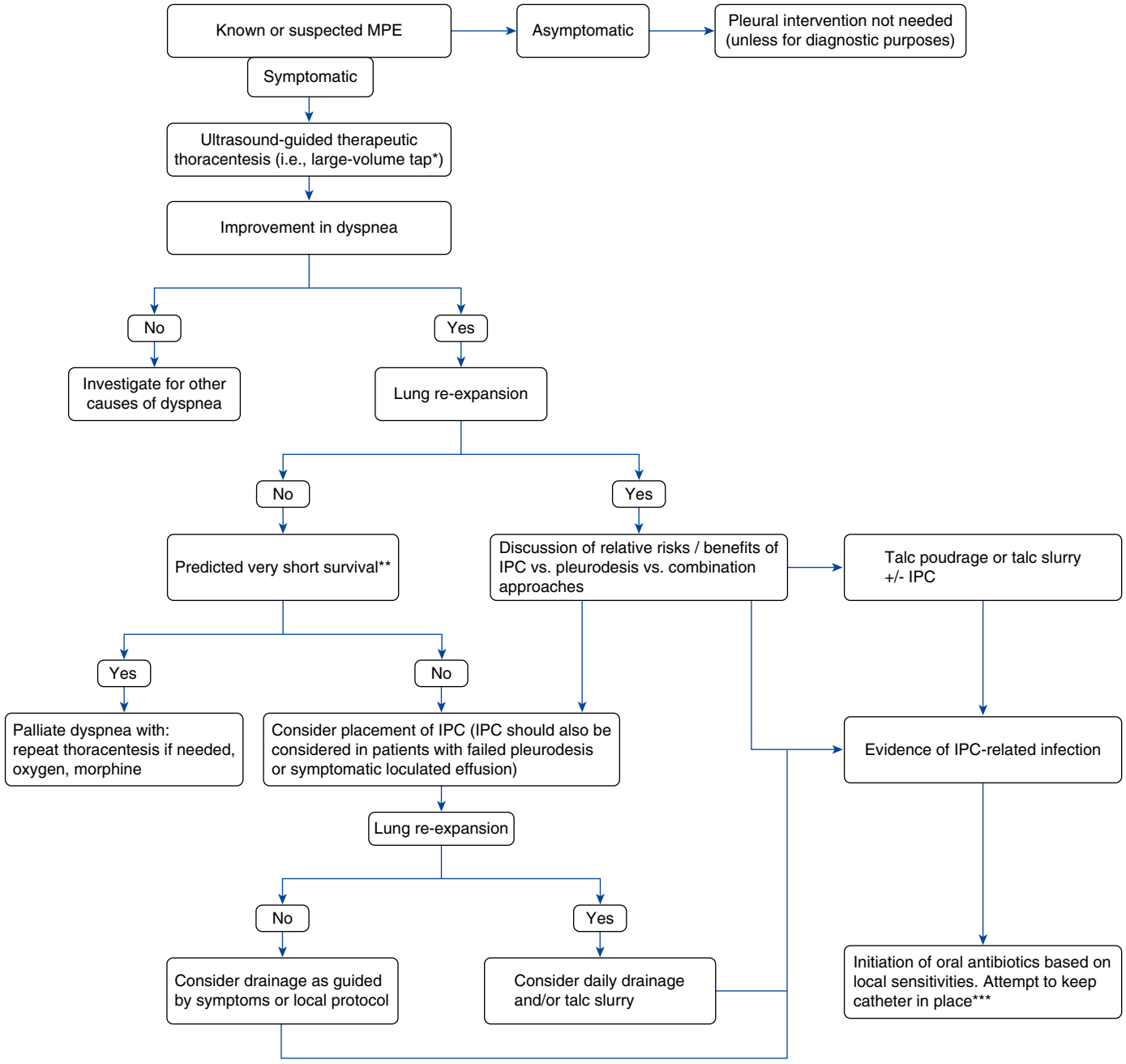

Figure 1. Management of patients with known or suspected malignant pleural effusion (MPE). *With goals of assessing lung expansion and relief of dyspnea. This step may not be necessary if the patient's dyspnea is known to be attributable to the MPE. **Physicians are not great predictors of prognosis. As such, the recommendation of "Predicted very short survival" should be used as a rough guideline and individualized on a case-by-case basis. ***Note: there is a low likelihood (2–4%) of indwelling pleural catheter (IPC)–related infection. Escalation of care (intravenous antibiotics, hospital admission, removal of catheter) should be made on a case-by-case basis and is recommended if there are any signs/symptoms of worsening infection.

IPCs or chemical pleurodesis can be used for patients with MPE and expandable lung, the specific risks and benefits of each procedure should be discussed in detail with the patient/caregiver, and decisions should be made on an individual basis. Factors influencing this specific decision can include the availability of a support network to help with IPC drainage, and the patient's desire to avoid hospitalization. Likewise, small studies have suggested that we may be able to achieve the "best of both worlds" in the future, with approaches combining IPCs with pleurodesis agents (6, 71).

As our understanding of the molecular mechanisms of pleural fluid formation/resorption and pleurodesis evolve (72, 73), future trials can focus on "turning off" production, increasing resorption, or creating pleurodesis with minimally invasive techniques. In addition, the role of gene therapy and immunotherapy may significantly alter our approach to these patients (74). Patient-reported outcome measures should be prioritized over secondary endpoints, such as radiographic improvement (31). Given the "critical mass" of interested researchers and collaboration between the traditionally siloed disciplines of surgery, medicine, and radiology, we anticipate significant progress in the field of MPE in the forthcoming years and the need to re-evaluate our practice on a regular basis. ■

This official guideline was developed by an *ad hoc* subcommittee of the ATS, STS, and STR.

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