AABIP Evidence-informed Guidelines and Expert Panel Report for the Management of Indwelling Pleural Catheters

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Background: **While the efficacy of Indwelling pleural catheters for palliation of malignant pleural effusions is supported by relatively robust evidence, there is less clarity surrounding the postinsertion management.**

Methods: **The Trustworthy Consensus-Based Statement approach was utilized to develop unbiased, scientifically valid guidance for the management of patients with malignant effusions treated with indwelling pleural catheters. A comprehensive electronic database search of PubMed was performed based on a priori crafted PICO questions (Population/Intervention/Comparator/Outcomes paradigm). Manual searches of the literature were performed to identify additional relevant**

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literature. Dual screenings at the title, abstract, and full-text levels were performed. Identified studies were then assessed for quality based on a combination of validated tools. Appropriateness for data pooling and formation of evidence-based recommendations was assessed using predetermined criteria. All panel members participated in development of the final recommendations utilizing the modified Delphi technique.

Results: **A total of 7 studies were identified for formal quality assessment, all of which were deemed to have a high risk of bias. There was insufficient evidence to allow for data pooling and formation of any evidence-based recommendations. Panel consensus resulted in 11 ungraded consensus-based recommendations.**

Conclusion: **This manuscript was developed to provide clinicians with guidance on the management of patients with indwelling pleural catheters placed for palliation of malignant pleural effusions. Through a systematic and rigorous process, management suggestions were developed based on the best available evidence with augmentation by expert opinion when necessary. In addition, these guidelines highlight important gaps in knowledge which require further study.**

Key Words: indwelling pleural catheter, pleural effusion, malignant, palliation, guidelines

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Malignant pleural effusion (MPE) is a substantial health care burden. It signifies advanced disease, usually results in symptomatic patient morbidity, and is associated with a poor overall prognosis. Consequently, MPE leads to >125,000 hospitalizations annually in the United States and contributes to over $5 billion in health care costs.[1] Therefore, efficient management of the condition is of utmost importance to optimizing health care resource utilization and enhancing the quality of a patient's remaining lifespan.

There is no single best approach to definitively manage recurrent MPE. Two of the most widely used methods are chemical pleurodesis, achieved via either bedside or thoracoscopic means, and insertion of an indwelling pleural catheter (IPC). The relative advantages and disadvantages of each, along with supporting literature, are presented and discussed in a recent expert clinical practice guideline published on behalf of the American Thoracic Society (ATS), the Society of Thoracic Surgeons (STS), and Society of Thoracic Radiology (STR).[2] These guidelines reinforce the multiple approaches available, which vary based on factors including underlying disease characteristics, prognosis, clinician expertise, and patient-related considerations such as social situation and personal preference.

Nevertheless, due to the efficacy, practicality, and safety profile, IPCs have emerged as a preferred tool for many clinicians aiming to efficiently palliate MPEs. IPC placement is relatively straightforward, usually performed in an outpatient setting under minimal or no sedation, and decreases the need for future palliative interventions.[3] This offers an attractive and minimally invasive option for patients seeking to enhance quality of life (QoL) and limit time spent in the hospital.

Accordingly, insertion of IPCs has expanded considerably in the last decade. While the aforementioned ATS/STS/STR document advises the clinician on the potential approach to a patient with MPE, similar recommendations do not exist for managing an IPC once placed. Our objective was to evaluate the existing literature and provide recommendations for various aspects of IPC utilization postinsertion including drainage frequency, management of catheter dysfunction and associated infection, and follow-up care.

METHODOLOGY

There are limitations in developing evidence-based guidelines with newer medical devices due to gaps in the evidence base, small sample sizes, a paucity of methodologically rigorous randomized controlled trials (RCTs), and variation in usage and techniques, limiting the feasibility of quantitative analyses. Under these constraints, it is important to provide physicians, other health care providers, and patients with trusted advice.[4–6] The American Association for Bronchoscopy and Interventional Pulmonology (AABIP) selected to employ the Trustworthy Consensus-Based Statement (TCBS) approach,[7] already utilized by several medical professional societies.[8] The TCBS approach results in unbiased, scientifically valid, standards-compliant, and trustworthy guidance based on both the available evidence, identified in a systematic approach to reduce biases, and expert clinical advice.

The TCBS approach brings thoroughness and transparency to the consensus of experts during the guideline development process.[6] This approach is based on 5 important pillars:

- Confidence in the panel composition and screening.
- Systematic and comprehensive evidence searches.
- Formal methods for consensus achievement.
- Transparency of data and methods throughout.
- Rigorous review of both methods and content by internal and external stakeholders.

Panel Composition and Screening

Panel selection for physicians was based on previous publication record in pleural diseases and willingness to participate, while advanced-practice providers were selected based on reputation and willingness to participate. A minimum procedural volume and/or number of publications related to the management of MPEs and IPCs was not used in determining eligibility for panel inclusion. The panel was composed of 14 interventional pulmonologists (including 1 chairman and 1 co-chairman), and 2 advanced-practice providers. All panel members participated equally without differentiations such as "expert" or "writing committee." Conflicts of interest were disclosed and vetted by the Panel Chair(s). All panelists received training on the TCBS process. The Panel Chairs oversight included adherence to methods, assurance of transparency, and project management.

PICO Question Development

The panel chair and co-chair developed the initial broad categories of IPC management for the development of PICO (Population/Intervention/Comparator/Outcomes paradigm) questions:

Category 1: Routine management of IPC patients, such as QoL, drainage schedules, and patient monitoring.

Category 2: Mechanical complications of IPCs such as catheter obstruction.

Category 3: Infectious complications of IPCs including identification, treatment, and prevention.

A subgroup of panel members was assigned to each category and tasked with developing a draft of PICO questions for topics within the category. After draft PICO questions were developed all panel members were allowed to suggest additional PICO questions regardless of category assignment. All members then participated in open discussions (via email and phone conferences) to discuss the merits of the individual PICO questions and to suggest modifications. The chair and co-chair then decided on the final set of PICO questions based on the input of panel members.

Systematic and Comprehensive Literature Review

The evidence-informed recommendations (called suggestions for transparency's sake) were supported by a comprehensive and systematic search of PubMed for relevant scientific literature. Additional relevant literature was identified through manual searches performed by the panel membership. The search strategies were developed based on a priori crafted PICO questions and applied from January 2000 to January 2019. Details of search strategies are included in the online supplement (Appendix 1, Supplemental Digital Content 1, http://links.lww.com/LBR/A205). Studies were included if they met the following criteria: (1) publications in English, (2) IPC only utilized for MPE or suspected MPE, (3) clinical trials, well conducted retrospective studies, meta-analyses, or systematic reviews. The following studies were excluded: (1) expert reviews, (2) case reports, (3) retrospective studies or case series with <50 patients. The search yield was then screened for studies with primary or secondary outcomes addressing the PICO or sub-PICO question. Dual screenings at the title and abstract level, followed by dual screening of the full texts were performed. Third-party adjudication was utilized when disagreements occurred. The studies were assessed for quality based on a combination of the validated tools, determined in advance for use based on study design. The RoB2[9] assessment tool was used to assess randomized studies, the ROBINS-I[10] was used for nonrandomized intervention studies, and the Specialist Unit for Review Evidence (SURE) checklist[11] was used for evaluation of case series.

The decision to utilize data pooling to form an evidence-based recommendation was based on the criteria utilized by the *CHEST* guideline oversight committee.[7] This threshold requires identifying a minimum of 2 studies (RCT or observational) of at least fair quality which meet inclusion criteria and evaluate comparable outcomes or interventions. When this threshold is not met, a consensus-based approach guided by lower quality evidence and expert opinion is utilized.

Formal Method for Consensus Achievement

The Delphi technique is a widely used and well-accepted process for soliciting feedback and achieving consensus.[12] Although there are several variations,[13–16] the modified Delphi approach for guideline recommendations allows consideration of the evidence base as well as expert opinion, while suppressing the introduction of group interaction bias. Panel chairs drafted the initial suggestions for the first survey informed by the evidence and expert clinical judgment. All initial suggestions were drafted recommending the most invasive potential strategies regardless of the chair's interpretation of evidence, personal clinical judgment, or expected panel responses to avoid biasing the membership. All members, except for the chair, co-chair and methodologist electronically voted on agreement with each drafted suggestion using a 5-point Likert

scale with options ranging between strongly agree and strongly disagree. Panelists were not permitted to discuss the drafted recommendations other than in the open comments field during the anonymous voting to avoid the occurrence or perception of group interaction bias. The chair and co-chair abstained from voting as they had access to the membership's comments before deidentification. Up to 3 rounds of anonymous online surveys were performed with interim revisions by the Panel Chairs based on voters' feedback. Verbatim anonymous comments, from the previous round of voting, were provided to the panel members along with the interim revisions. A priori rules defined consensus as $\geq 80\%$ of respondents either strongly agreeing or agreeing with the recommendation, with a minimal response rate of 75%. Panel members who disagreed with the final consensus recommendation were given the opportunity to include a "minority report" accompanying the recommendation in the final manuscript. Final survey tallies indicating the voting percentages are included in the online supplement (Appendix 2, E-Figs. 2a–2k, Supplemental Digital Content 2, http://links.lww.com/LBR/A206).

Transparency and Reviews

In the TCBS process, full transparency means recommendations are called suggestions and are not graded but marked as consensus-based. Final suggestions, once consensus was achieved, can no longer be changed. Remarks that accompany the suggestions should be considered part of the suggestion. *The AABIP advises that as suggestions are uploaded into digital platforms, incorporated into separate lists, or otherwise removed from this full guideline publication, the remarks should always be kept with the rest of the suggestion as a single unit.* Manuscripts were drafted and revised by the Panel Chairs. Initial review of the revised manuscript was performed by a core group of the 5 most senior and experienced members, modifications were made until the group agreed with content. The full panel then reviewed the manuscript and was given an opportunity to comment before final submission. In addition to many iterations by the chairs and panelists, reviews of the manuscripts and processes were conducted by leaders in the AABIP. The AABIP leadership review was solely for the purpose of oversight and societal endorsement. The AABIP did not participate in guideline or manuscript development. Patients and health care professionals can trust the methods and rely on the final suggestions to guide clinical practice decisions.

Diversions From the Process

No diversions from the TCBS process occurred.

Future Updates

As the evidence base evolves in this relatively new area, the AABIP will maintain the currency of these recommendations employing methodologically rigorous techniques with updated literature searches and quantitative analyses.

Funding

The sole source of funding for these guidelines was the American Association for Bronchoscopy and Interventional Pulmonology.

RESULTS

Following dual screening at the title, abstract and full-text levels, a total of 7 studies[17–23] were identified which met criteria for quality assessment. The overall search results are highlighted as a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram (Fig. 1) and individual PRISMA diagrams for each PICO question are included in the online supplement (Appendix 1, E-Figs. 1a–1u, Supplemental Digital Content 1, http://links.lww.com/LBR/A205). Two RCTs[21,22] were evaluated with the RoB2,[9] 3 nonrandomized intervention studies[18–20] with ROBINS-I,[10] and 2 case series[17,23] required the Specialist Unit for Review Evidence (SURE) checklist.[11] All the assessments revealed high/serious risks of bias. Detailed results are available upon request and the evidence table (E-Table 1, Supplemental Digital Content 3, http://links.lww.com/LBR/A207) is included in the online supplement. Additional literature monitoring took place in December 2019 confirming that there were no additional studies published that met the inclusion criteria. The threshold to form an evidence-based recommendation, based on the criteria utilized by the *CHEST* guideline oversight committee[7] were not met for any of the PICO questions. Therefore, no formal data extractions were conducted, and all suggestions were based on the TCBS approach.

Recommendation 1:

In patients with IPCs for the management of known or suspected MPEs without evidence of trapped lung, we suggest daily drainage of the IPC when, in addition to symptom control, achieving pleurodesis and catheter removal is an important patient-centered goal. When pleurodesis and catheter removal is unlikely or not

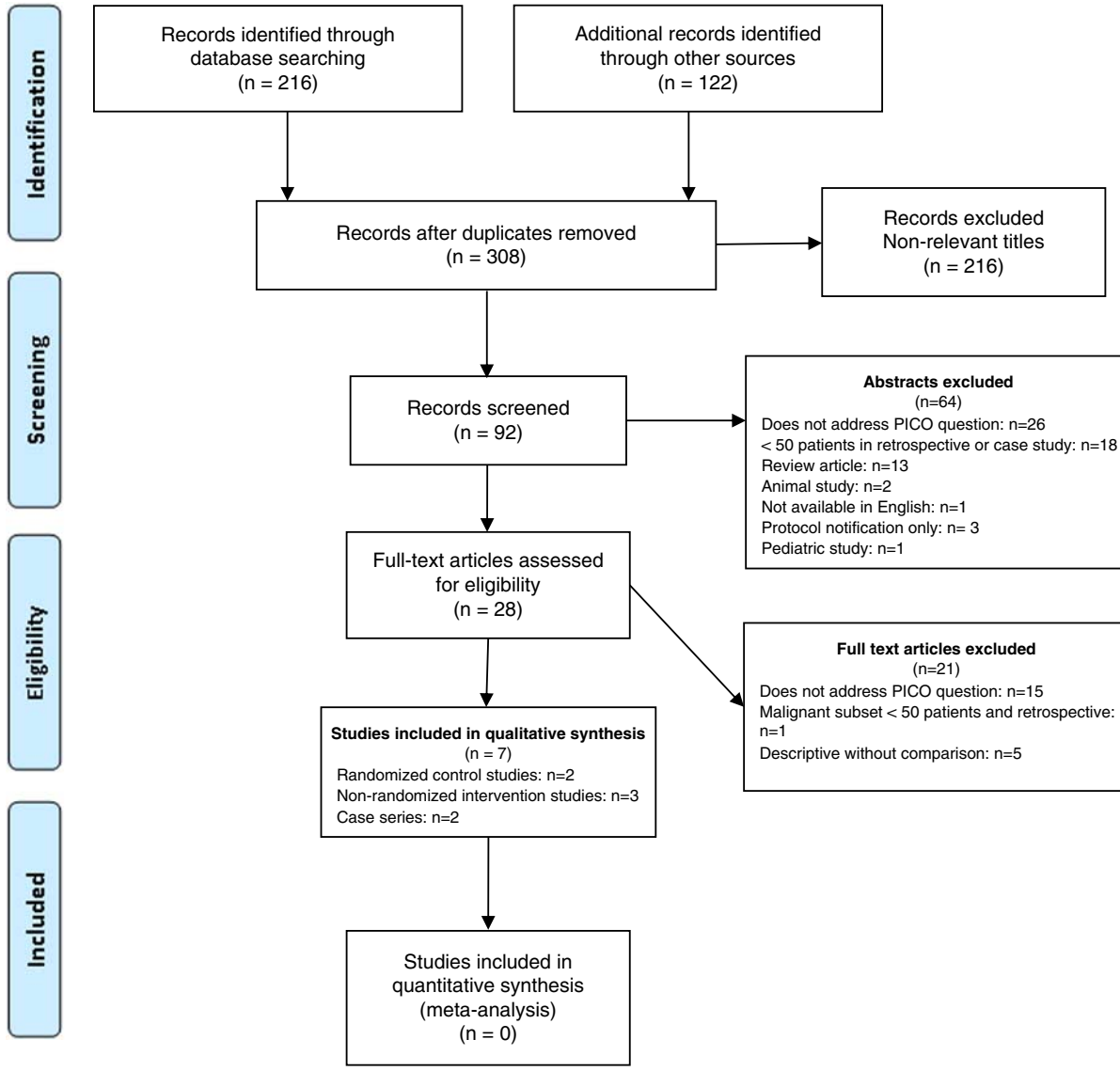

FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study selection. *a+*

considered important, less frequent drainage schedules or symptom-based drainage is appropriate (Ungraded Consensus-Based Statement).

Background

Defining and balancing the goals of IPC therapy for patients with MPEs is important when deciding on a drainage schedule. The primary intent of IPCs in these patients is symptom palliation that enhances QoL and minimizes additional interventions and health care visits. The literature consistently supports the efficacy of IPCs in achieving these goals.[3,24,25] Therefore, draining the pleural space as needed to accomplish the desired effect may be enough. However, achieving spontaneous pleurodesis that allows catheter removal is also an important outcome which may be influenced by drainage frequency. The likelihood of achieving spontaneous pleurodesis, the expected lifespan of the patient and their personal preferences all need to be considered when deciding on an ideal drainage schedule.

Summary of Evidence

(1) Effect of drainage schedule on QoL: When catheter removal is not considered an important outcome there is very little data supporting aggressive drainage regimens improve QoL or dyspnea. The AMPLE-2 trial compared daily to symptom-guided drainage over the first 60 days after catheter

placement.[22] In the symptom-based group, drainages were performed at a median frequency of every 5.45 days. Difference in breathlessness between the groups was measured using the Visual Analog Scale (VAS) breathlessness score. Broader differences in QoL were measured with the VAS-QoL score and the EuroQoL-5 Dimensions-5 Levels (EQ-5D-5L) QoL assessment. While the primary outcome of VAS breathlessness score was similar between groups, there was a statistically and clinically significant improvement in the EQ-5D-5L score, as well as a nonsignificant trend toward improvement in VAS-QoL scores in the aggressive daily drainage group. No between-group differences were found in pain scores, complications, inpatient hospital days, or mortality.

The ASAP trial was designed to evaluate rates of autopleurodesis between daily drainage and every-other-day drainage, but included secondary outcomes of QoL using the Karnofsky performance scale and the SF-36 score at baseline, 2 weeks postinsertion, and 12 weeks postinsertion.[21] It found no differences in these measures between the 2 groups. Overall patient satisfaction scores and frequency of adverse events were also similar.

(2) Effect of drainage schedule on pleurodesis: The majority of currently available data guiding optimal drainage schedules for purposes of achieving pleurodesis also comes from the ASAP and AMPLE-2 trials. In the ASAP trial, the primary outcome of autopleurodesis was achieved at a higher rate in the daily drainage group than the every-other-day drainage group (47% vs. 24%) at the end of the 12-week study period. However, substantial subject losses to follow-up as well as early deaths in the latter arm introduces uncertainty in this conclusion. Although not the primary outcome, the AMPLE-2 trial found that a daily drainage schedule was superior to the symptom-based protocol at achieving pleurodesis at 60 days (37.3% vs. 11.4%). This advantage persisted at 6 months (44.2% vs. 15.9%).

Justification for Recommendation

We recognize that spontaneous pleurodesis and subsequent catheter removal are important and realistic outcomes in selected patients, such as those with expandable lung and in whom persistence of the catheter represents a practical burden. For these patients, the committee suggests a daily drainage schedule based on the results of the ASAP and AMPLE-2 trials.

If catheter removal is not an important patient-centered outcome, the committee cannot recommend aggressive drainage schedules. While there was a small improvement in secondary QoL scores for patients in the aggressive drainage arm of the AMPLE-2 trial, there has been no convincing evidence to date to support aggressive drainage for the purpose of improving breathlessness or QoL. The committee is also unable to endorse an aggressive drainage protocol in patients with limited life-expectancy (eg, ≤ 3 mo) as even if pleurodesis is achieved before death, the remaining time without the catheter will be short.

Recommendation 2

In patients with IPCs for the management of known or suspected MPEs with suspected trapped lung, we suggest that the ideal drainage schedule is unknown and should be decided on an individual case basis. Daily drainage of the IPC might be considered when, in addition to symptom control, achieving pleurodesis and catheter removal is considered an important goal, as pleurodesis might still be possible. Conversely, aggressive drainage may result in increased chest discomfort in some individuals, and if present should lead to less frequent or symptomatic driven drainage schedules (Ungraded Consensus-Based Statement).

Background

In the presence of a nonexpandable lung, pleurodesis procedures are unlikely to be successful[26] and IPCs are generally considered the standard of care for symptom management.[27] Nonexpandable lung is often not reversible when associated with a fibrous noncompliant visceral pleura caused by chronic inflammation. However, late reexpansion can occasionally occur in the setting of more active pleural processes. Available bedside methods for assessing the pleura and pleural elastance, such as pleural manometry and ultrasound, have not been shown to predict late lung reexpansion.[28,29]

Summary of Evidence

Although, by definition, pleurodesis is not possible with a truly nonexpandable lung, patients presumptively diagnosed with nonexpandable lung might still be able to achieve pleurodesis. In a post hoc analysis of AMPLE-2 trial, which compared daily pleural drainage to symptom-based drainage, there was a small subgroup of 28 patients categorized with trapped lung in which 4 (14.3%) were able to achieve pleurodesis at 60 days and 8 (28.6%) were able to achieve pleurodesis at 6 months.[22] The majority of successful pleurodesis occurred in patients undergoing daily drainage. At 6 months,

7 of 14 patients (50%) in the daily drainage group achieved pleurodesis compared with 1 of 14 patients (7.1%) in the symptom-driven group.

Justification for Recommendation

While, in the AMPLE-2 trial, late lung reexpansion was more common in the aggressive drainage group, the data is based on a post hoc analysis of only 28 total patients. In addition, daily drainage is not without its risks in patients with nonexpandable lung as drainage can result in significant pain which can be quite distressing to the patient.[30] These symptoms often limit drainage volume, which likely further reduces the chances of obtaining pleurodesis. While it is not unreasonable to attempt daily drainage in patients who do not develop pain or other symptoms related to drainage, there is likely little benefit to aggressive drainage schedules in those who do develop symptoms with drainage. In this subset either less frequent scheduled drainage or symptom-based drainage are likely more appropriate.

Recommendation 3

In patients with IPCs for the management of known or suspected MPEs, we suggest that, even in the absence of catheter-related concerns, regular clinical follow-up with a provider experienced in the management of IPCs should be offered, with the frequency decided on an individual basis (Ungraded Consensus-Based Statement).

Background

As with any ongoing therapy that involves indwelling material, availability of experienced providers to answer questions regarding maintenance and evaluate for potential complications is considered standard of care. In the absence of active catheter-related concerns, there are several factors, such as availability of home health nurses, reliability of caregivers and patient preferences, that should be considered when deciding on need and frequency of follow-up.

Summary of Evidence

The value of routine clinical follow-up in patients with IPCs for the management of pleural effusions has not been explored in the literature, and therefore the committee makes this recommendation based solely on expert opinion.

Justification for Recommendation

It seems reasonable that regular follow-up care could proactively identify problems or concerns which the patient and/or caregiver might not otherwise recognize. However, the potential benefit of such regular visits should be balanced against their potential practical and financial burden of excessive office visits. More frequent visits are likely beneficial in patients with less reliable caregivers and those who fail to demonstrate a strong understanding of potential complications and troubleshooting techniques despite attempts at training. In contrast, regular clinical follow-up can likely be limited to an as-needed schedule when catheters are managed by a hospice team, experienced home health nurses, or by a reliable and medically competent family caregiver. At minimum, the committee recommends some form of clinical follow-up be offered to the patient, either by phone or in person, and shared decision-making used to guide subsequent visits. The effect of regular clinical follow-up on QoL and complications remains unknown and future research is necessary to help clarify this important question.

Recommendation 4

In patients with IPCs for the management of known or suspected MPEs and symptomatic pleural fluid reaccumulation due to a nondraining pleural catheter, we suggest saline flushing of the catheter to relieve any obstruction. If saline is unsuccessful at relieving the obstruction, and there are no contraindications, instillation of fibrinolytics via the catheter should be attempted to restore flow (Ungraded Consensus-Based Statement).

Background

Reduced drainage from an IPC can indicate successful pleurodesis or a poorly draining pleural space. Worsening dyspnea and increasing effusion on chest imaging suggests the latter scenario. Nondraining IPCs in the setting of symptomatic pleural fluid reaccumulation have been reported to occur in 5% to 14% of patients.[3,24,31–34] A sudden cessation of previously large-volume drainage suggests malfunction of the catheter, which is most commonly caused by fibrin occlusion. Catheter fracture and migration out of the pleural space have also been reported.[32,35] However, when reduction in drainage is more gradual in the setting of a persistent or enlarging effusion, it is likely related to increased pleural fluid viscosity, poor communication of the fluid with the catheter due to loculations, or partial obstruction of the catheter.[31] In the currently available literature, studies do not always differentiate between these potential causes. Terminology such as "catheter obstruction" and "symptomatic loculations" are sometimes used interchangeably to describe cessation or reduction

of drainage in the setting of a persistent and symptomatic effusion.

Summary of Evidence

Wilshire et al[36] retrospectively reviewed the charts of 172 patients with IPCs over a 5-year period in a single center. Thirty-seven IPCs were identified as nondraining of which 29 were placed for malignant or paramalignant effusions. Restoration of drainage occurred in all IPCs following instillation of intrapleural alteplase. After successful drainage, the 18 patients who did not die or undergo successful pleurodesis eventually required repeat alteplase, all of which were deemed successful. No complications were observed in the study. A major limitation was the use of a conservative drainage volume of 10 mL to define therapy success. This is not typically considered a clinically meaningful volume and 22% of those deemed successful produced <150 mL of fluid posttreatment. The 10 mL threshold was based on the internal capacity of the catheter and the assumption that in the presence of residual fluid a nondraining catheter was only due to an obstruction within the catheter, rather than a poorly draining pleural space, for example due to loculations. A small increase of fluid output would not indicate adequate treatment of an organized pleural space. While the clinical relevance of this study is limited, it does demonstrate the safety of intrapleural alteplase at doses of 2 to 5 mg.

Thomas et al[33] evaluated the use of fibrinolytics for the purpose of restoring flow to a nondraining catheter in a multi-institutional retrospective review. This study used the term "symptomatic loculations" to describe a nondraining catheter in the setting of radiographic evidence of residual pleural fluid, with effusion-related breathlessness and absence of evidence of pleural infection. In total, 66 patients were analyzed. After pleural instillation of fibrinolytics, drainage volume increased in 93% of patients, to a median of 500 mL at 24 hours and 900 mL at 72 hours. In addition, 83% of patients had an improvement of breathlessness and there was a 21% decrease of the size of effusion on chest radiography at 2 hours. However, 41% of catheters developed recurrent obstruction at a median of 13 days postintervention. Ten of these patients received a second fibrinolytic treatment while the remaining had the catheter replaced. Of those who were retreated, only 1 had sustained effect, possibly suggesting the difficulty in managing a pleural space prone to organization. The only observed complication was significant nonfatal pleural bleeding which occurred in 2 of 66 patients.

As the study was a multicenter retrospective review, the protocols used between institutions varied resulting in a heterogenous dataset. The choice of both fibrinolytic agent and dose varied among the 4 centers. While most patients (79%) received alteplase, both streptokinase and urokinase were used as well. Of those who received alteplase, individual doses ranged from 4 to 10 mg and up to 6 doses were given to individual patients per treatment. Dose-dependent and agent-dependent variations in outcomes and complications were not reported. In addition, as some institutions did not collect the necessary data to report all outcomes, some of the findings were based on a very limited dataset.

Finally, in 2016 the largest and most clinically relevant study to date of the effect of fibrinolytics on a nondraining IPC was performed by Vial et al.[17] The advantage of this study is that it incorporated a standardized, multistep algorithmic pathway in managing a poorly draining pleural space. In this retrospective review, patients with abrupt cessation of fluid drainage or with reduction in drainage to <150 mL on 3 consecutive occasions on an every-other-day schedule would receive a chest radiograph. If the effusion occupied >20% of the hemithorax, the catheter would be flushed with 20 mL of saline. If drainage postsaline flushing remained under 150 mL, then 4 mg of alteplase was instilled into the IPC followed by a second dose if initial dose was unsuccessful. If drainage remained poor, the IPC was removed and other palliative options, to include catheter replacement, were considered.

As this was a retrospective review, and only patients who received alteplase were captured, the success of saline flushing alone to restore flow was not reported. A single dose of alteplase was able to restore flow to >150 mL in 85% (83/97) of patients. However, as in the aforementioned studies, reocclusion was common, occurring in 32% (27/83). A second treatment after reocclusion was successful in 72% of patients, and unlike the Thomas study, the majority (87.5%) of patients had a sustained response and did not require a third treatment. Of the 45 patients who had a baseline Borg score of at least 1 and successful drainage, symptomatic benefit was only seen in 53% of patients. As in the previously discussed studies, complications were infrequent, occurring in 4% of instillations (5/121) with 2 cases of nonfatal hemothorax, and 3 infectious complications.

Justification for Recommendation

While none of the studies specifically evaluated the efficacy of saline flushes to restore IPC patency, the committee feels this is an important first step before attempting fibrinolytic therapy. The efficacy of saline flushing to maintain patency of small bore chest tubes has been demonstrated to be effective and safe.[37] In addition, while not directly evaluated in the literature, clinical experience suggests saline flushing may be successful at restoring flow to many nondraining IPCs. It also provides an easy, cost-effective initial assessment in potentially differentiating an occluded catheter from an organized pleural space that may require more intensive treatment. Further study of the efficacy of saline flushing compared with fibrinolytics is warranted.

Alteplase, at a dose range between 2 and 10 mg, is the most frequently used fibrinolytic agent in the previously mentioned trials.[17,33,36] However, fibrinolytic choice and dosing varied and data to guide specific protocols are limited. Therefore, the committee does not recommend a specific fibrinolytic agent or dosage when attempting to restore patency to a nondraining catheter, and future study is necessary. Contraindications to fibrinolytics are also unclear. The most commonly encountered complication to intrapleural fibrinolytics is pleural bleeding.[38] While a coagulopathy likely increases the bleeding risk, the degree of coagulopathy associated with an unacceptable bleeding risk is unknown. Therefore, at this point we suggest clinical judgment be used when considering fibrinolytic therapy in patients with elevated bleeding risk.

Recommendation 5

In patients with IPCs for the management of known or suspected MPEs and suspected catheter-related pleural space infections, we suggest obtaining pleural fluid for microbiological studies to guide antibiotic therapy. The optimal method of obtaining pleural fluid (eg, either by thoracentesis or directly from the IPC) is unclear and warrants further study (Ungraded Consensus-Based Statement).

Background

In patients with tunneled pleural catheters, who develop symptoms of pleural space infections, cultures can be useful in guiding antibiotic treatment. As there are several potential pathogens, initial treatment often requires broad coverage and identification of a particular organism will allow for expeditious tailoring of therapy. This is especially important in patients with limited life-expectancy related to malignancy, as more rapid narrowing of antibiotics may hasten time to discharge and reduce the risk of complications, such as gastrointestinal *Clostridium difficile* infections.[39]

Summary of Evidence

The method of obtaining cultures in the setting of IPC-related infections has not been evaluated in the literature. The recommendations are therefore based on a combination of indirect evidence and expert opinion.

Justification for Recommendation

While we feel there is benefit to obtaining cultures for the aforementioned reasons, the most appropriate method of obtaining pleural fluid for culture is unknown. The rate of IPC bacterial colonization has not been studied. However, extrapolating from indirect data one can assume that colonization does occur, as with other long-term drainage devices such as urinary catheters. In a 2010 study of nontunneled pleural drains placed after lung resection, 83% of patients developed bacterial colonization within their chest tubes within 4 days of placement.[40] Consequently, positive cultures obtained from a catheter in the absence of clinical features to support infection should be interpreted with caution. Due to the risk of obtaining false-positive and/or nonrepresentative organisms when pleural fluid is collected directly from the IPC, some clinicians favor thoracentesis to directly obtain fluid for cultures. Others believe cultures obtained from the IPC are sufficient in a clinical context suggestive of pleural infection, as studies of other common indwelling catheters suggest bacteria which produce biofilms are often the precipitating organism in infections.[41,42] Without further study we cannot conclude which method of obtaining fluid for cultures is superior at this time.

Recommendation 6

In patients with IPCs for known or suspected MPEs and catheter-associated cellulitis or exit-site infections, we suggest a trial of oral antibiotics with coverage for typical skin pathogens is appropriate, and catheter removal is only necessary in the setting of antibiotic failure (Ungraded Consensus-Based Statement).

Background

Currently, there are no universally accepted definitions characterizing soft tissue infection associated with IPCs and many of the definitions

used in the literature are extrapolated from the peritoneal dialysis literature. Cellulitis is usually characterized by redness, warmth, edema, and mild pain of the skin and immediate subcutaneous tissue. However, clinical judgment is needed to differentiate IPC-related cellulitis from noninfectious skin findings. These may include localized erythema associated with the catheter (especially in the immediate period following placement) or a localized reaction related to frequent dressing changes. Exit-site infections can be defined as purulent drainage at the catheter-epidermal interface, which can be associated with induration and erythema of the catheter tract, localized within 2 m of the exit site. In contrast, tunnel tract infections can be defined as presence of erythema, edema, induration and tenderness along the catheter tract, >2 cm proximal from the exit site.[42–44] Some also advocate for using ultrasound imaging to demonstrate a fluid collection along the catheter tract surrounding the cuff as additional criteria supporting the diagnosis.[43] While tunnel tract infections are often associated with exit-site infections they may also occur alone.

Summary of Evidence

The appropriate management of IPC-related soft tissue infections has not been studied. The recommendations are therefore based on a combination of indirect evidence and expert opinion.

Justification for Recommendation

While we acknowledge that research analyzing peritoneal dialysis catheters (PDCs) does not directly translate to IPCs, the committee believes the extracavitary components of IPCs and PDCs are similar enough that, when addressing the diagnosis and management of catheter-related skin soft tissue infections, extrapolation is reasonable. While the microbiology of cutaneous infections associated with IPCs has not been well characterized, within the PDC literature the most common organisms associated with these infections are skin colonizers, such as *Corynebacterium* species and coagulase-negative *Staphylococcus*, as well as more virulent organisms such as *Pseudomonas aeruginosa* and *Staphylococcus aureus*.[45] In PDC patients, oral antibiotics which cover *S. aureus* species are typically sufficient to treat these infections, while patients with a history of pseudomonas infections or methicillin-resistant *S. aureus* might require antibiotics with more broad coverage.[45] While antibiotics alone are typically sufficient, progression of disease does occasionally warrant catheter removal. In a recent review of 448 IPCs placed for the management of MPEs at a single center, 14 patients were diagnosed with localized skin infections of which only 2 required catheter removal.[46]

Recommendation 7

In patients with IPCs for the management of known or suspected MPEs who develop a catheter-related pleural space infection without a concomitant tunnel tract infection, we suggest attempting continuous fluid drainage through the IPC over catheter removal (Ungraded Consensus-Based Statement).

Background

Pleural space infections are generally reported to occur with <5% of IPCs.[23,32,44,47,48] While various definitions have been used, we suggest an IPC-related pleural space infection exists when any of the following are present: (1) obvious pus drained from the catheter; (2) presence of clinical symptoms consistent with infection with positive pleural fluid gram stain or cultures; (3) presence of clinical symptoms consistent with infection along with pleural fluid biochemical analysis supportive of infection, such as elevated lactate dehydrogenase, low glucose or low pH.[44,49] As already discussed, catheter colonization is not infrequent and positive cultures alone should not define a pleural space infection.

Summary of Evidence

In 2013, Fysh et al[23] retrospectively analyzed 1021 patients with IPCs treated at 11 international centers of which 50 patients with IPC-related pleural infections were identified. In this trial all patients were initially treated with antibiotics and catheter drainage. Of the IPC-infected patients, 74% were treated as inpatients, 3/50 died before infection resolution, with a 94% overall rate of infection control. Catheter removal was performed in 46% of patients. In those who required IPC removal, reinsertion of a chest tube or IPC was required in 48% of patients and no surgical interventions were necessary for infection control.

The Fysh study, was the largest cohort of IPC-related pleural space infections, with the next 3 largest cohorts of MPE related IPC pleural space infections included 25, 19, and 13 IPCs respectively.[23] Bibby et al[50] retrospectively analyzed 672 patients with IPC for MPEs of which 25 IPC-related pleural infections were identified. Of the IPC-infected patients, 60% were treated as inpatients, 3/25 died within 30 days of infection

diagnosis, and the overall infection control rate was 88%. Catheter removal was performed in 12% of patients. In those who required IPC removal, none required reinsertion of a chest tube or IPC or surgical interventions for infection control. Porcel et al[49] retrospectively analyzed 279 IPCs placed for MPEs of which 19 IPC-related pleural infections were identified. Of the IPC-infected patients, 23% were treated as inpatients; death was not reported specifically among this group. Catheter removal was not required in any of patients and no surgical interventions were required for infection control. Gilbert et al[51] used a prospective database of 225 patients with IPC for MPEs of which 13 IPC-related pleural infections were identified. Of the IPC-infected patients, there were no deaths attributed to infectious complications with a 100% overall rate of infection control. Catheter removal was required in 69% of patients. In those who required IPC removal, reinsertion of a chest tube or IPC was required in 33% of patients and surgical intervention was required in 22% of patients for infection control.

Justification for Recommendation

In complicated pleural space infections, the primary principles of management include antimicrobial treatment and source control with complete drainage, regardless of the source and cause.[52] Despite variable rates of catheter removal, deaths from IPC-related pleural space infections is rare. The lowest rate of catheter removal in the recently published Porcel study is likely a result of knowledge gained from the other reviews. Given the extremely low rate of IPC infection-related deaths, immediate removal of an IPC is not recommended. In addition, chest tube placement or IPC reinsertion after IPC removal is not required in the absence of pleural fluid accumulation, as infection-related pleural inflammation causing pleurodesis is frequently encountered.

While the literature does not specifically address the role of continuous drainage over intermittent drainage for IPC-related pleural space infections, guidelines for managing complicated parapneumonic effusions recommend continuous drainage via chest tube over serial drainage with thoracentesis, albeit based on limited data.[53] The ease of noncontinuous IPC drainage might lead some to ponder use of a frequent intermittent drainage strategy, however, this has not been studied and the committee suggest following the principle of continuous drainage applied to parapneumonic effusions.

While many patients will require hospital admission, continuous drainage can be performed in the outpatient setting using portable continuous chest tube drainage systems, digital suction drainage systems, or even a simple leg bag.[54–56] The decision regarding inpatient or outpatient management should be made on a case-by-case basis.

Recommendation 8

In patients with IPCs for the management of known or suspected MPEs who develop a catheter-related pleural space infection which cannot be adequately drained despite continuous drainage, we suggest instillation of fibrinolytics and DNase via the catheter to aid in catheter drainage and clearance of infection (Ungraded Consensus-Based Statement).

Background

Inadequate drainage of an infected and organized pleural space can lead to poor infection control, further reduced pleural compliance, and worsening symptoms and outcome.[57] While surgery is often an effective means of sterilizing the pleural space, patients with MPE being treated with IPCs are often poor surgical candidates with limited lifespans.[58] Therefore, non-surgical interventions that reduce morbidity and length of hospitalization, should be given preferential consideration in the management of IPC-related pleural space infections.

Summary of Evidence

Currently there is a paucity of data regarding the efficacy of combined fibrinolytics and DNase in the management of IPC-related pleural space infections. In a retrospective report on IPC-related pleural space infections, Fysh et al[23] reviewed 50 patients, 13 of whom received some form of fibrinolytic therapy. Of these patients, 85% achieved complete resolution of the infection without the need for surgical intervention. However, only 6 of these patients received combination alteplase and DNase. In addition, the rationale for single agent versus combination therapy was not provided. There were no complications reported with this regimen. The efficacy of intrapleural alteplase combined with DNase in the management of parapneumonic pleural space infections to reduce need for surgical intervention and duration of hospital stay was demonstrated in the MIST II trial.[59] The applicability of the MIST II data in the

management of IPC-related pleural space infections thus far is unknown.

Justification for Recommendation

As the direct data was limited to a group of only 6 patents within a retrospective review, to guide the suggestion we relied solely on the indirect data extrapolated from the MIST II trial[59] and clinical experience. We acknowledge that the differences in biology between infected MPEs and primary pleural space infections might result in differences in both efficacy and bleeding risk. The committee, however, believes that based on clinical experience combined intrapleural therapy for treating IPC-related pleural space infections, in patients who do not have contradictions, is reasonable. There are no high-quality data supporting single agent fibrinolytics or DNase in treating pleural space infections. Furthermore, the use of DNase as monotherapy in the MIST II trial resulted in worsening systemic inflammatory response and more frequent surgical referral.[59] As such, the committee suggests avoiding DNase monotherapy in pleural space infections but cannot recommend for or against fibrinolytic monotherapy in this setting. A larger series examining the use of alteplase and DNase in the management of IPC-related pleural space infections is underway which may contribute to answering this question.[60]

Recommendation 9

In patients with IPCs for the management of known or suspected MPEs who develop a catheter-related pleural space infection, we suggest catheter removal and drainage of the pleural space with a new chest tube should be considered if any of the following are present: a tunnel tract infection, poor catheter drainage despite the use of fibrinolytics and DNase, or persistent sepsis despite antibiotics and drainage through the original IPC (Ungraded Consensus-Based Statement).

Background

While it appears that many patients with IPC-related pleural space infections can be treated successfully without removing the catheter, patients may require removal in situations when infection control is difficult or failing. As such, identification of indications for catheter removal and replacement is an important part of the management of patients with IPCs for malignant disease.

Summary of Evidence

The indications for IPC removal in the setting of pleural space infections has not been adequately evaluated in the literature. The recommendations are therefore based on a combination of epidemiological data discussed in recommendation 7, indirect evidence, and expert opinion.

Justification for Recommendation

Typically, treatment of tunnel tract infections is similar to that of exit-site infections but usually require longer antibiotic courses.[42] However, a simultaneous tunnel and visceral space infection may predict a poorer outcome. In this scenario, the PDC literature predicts a low likelihood of eradication of infection without catheter removal.[61–63] One exception is the presence of coagulase-negative staphylococcal infection, for which high rates of catheter salvage have been reported.[62] While the indirect evidence favors removal in the presence of virulent organisms, there is no direct evidence to support this strategy in IPC patients. Given the lack of direct evidence and the overall low mortality associated with IPC-related pleural space infections, one might consider a trial of antibiotics without IPC removal, with the understanding that in the setting of virulent organisms failure rates are likely high.

While there is no evidence to guide decisions regarding catheter removal, the committee believes that failure to respond to treatment, suggested by either poor clinical response or inadequate IPC drainage, should prompt catheter removal. Placement of a new chest tube for continued drainage is also suggested in the setting of persistent fluid after IPC removal.

Recommendation 10

In patients with IPCs for the management of known or suspected MPEs who develop a catheter-related pleural space infection, we suggest empiric antibiotics with broad coverage for catheter-related organisms including *S. aureus* and gram-negative organisms, while awaiting results of microbiological testing (Ungraded Consensus-Based Statement).

Background

While most patients with IPC-related pleural space infections eventually grow a causative organism from culture, prompt empiric antimicrobial coverage is a critical part of management. The choice of empiric antimicrobial agents depends on the local epidemiology of the potential culprit organisms, which in turn depends on source. It is important to recognize that cultures

may ultimately be unrevealing or only grow contaminant organisms. In the absence of frank pus, it is problematic to rely solely on pleural space biomarkers associated with infection (low glucose, low pH, high lactate dehydrogenase) since this profile can also be seen in noninfected MPEs.[64] Our recommendation and the following discussion assume a high suspicion for IPC-related pleural space infection.

Summary of Evidence

The evidence analyzing the microbiology of IPC pleural space infections is limited and based on small retrospective reviews. Pleural fluid cultures typically identify an organism in IPC-related pleural space infections.[50,65] In Fysh et al's[23] retrospective review of 50 IPC-related pleural space infections, pleural fluid sampling identified an organism in 48 patients. In total, 17 different organisms were identified of which 6 patients had multiple organisms. The predominant organism was *S. aureus* which was isolated in 48% of cases, followed by gram-negative bacteria at 18%. *P. aeruginosa* was the most common of this latter group (10% of all cases). Gram-positive organisms other than *S. aureus* were found in 14% of patients, while anaerobic organisms were isolated in only 6%. The median antibiotic duration was 24 days; however, the authors did not report any specific criteria for selecting duration of therapy. In addition, 38% of patients received only oral antibiotics and the authors did not identify differences in response rate compared with intravenous agents.

Justification for Recommendation

Since the efficacy of specific antimicrobial agents has not been evaluated in the literature, the committee can only suggest coverage directed by identified pathogenic organisms. On the basis of the Fysh trial, empiric therapy should include treatment for *S. aureus* (including methicillin-resistant *S. aureus*) and *P. aeruginosa*, while broader coverage should be considered, as 15 other pathogens were identified in the 29 remaining patients with positive cultures.[23] Empiric coverage for resistant organisms should be based on both local susceptibility rates and resistance patterns from known colonization or previous infections.

The committee recognizes the lack of evidence supporting empiric anaerobic coverage. However, including empiric anaerobic coverage may be reasonable for 2 reasons. First, while anaerobic organisms might be infrequent causes of IPC-related pleural space infections, they are commonly isolated in parapneumonic infections.[66] Sometimes it is difficult to distinguish the source of a pleural space infection in the setting of an IPC, and the clinician should make every effort to recognize a coexisting pneumonia when deciding on empiric regimen. Second, while anaerobes were only found in 3/50 cases in the Fysh trial, this may have been an underrepresentation as the use of inoculated anaerobic blood culture bottles has been shown to significantly increase detection of anaerobic organisms.[67] While the manuscript did not specifically address culture method, at the time of the study (2001-2012) this was not yet standard practice.

As with complicated parapneumonic effusions, the appropriate length of therapy is unknown and likely should be based on severity of illness, systemic response, drainage adequacy. Whether repeat cultures have any role in guiding therapy duration is also unknown. Decisions regarding route of delivery and narrowing of coverage should likely be based on a combination of severity of illness, response to initial therapy, patient preferences regarding hospitalization, and suspicion for presence of resistant organisms. There is no data regarding the use of intrapleural antimicrobials, however, with the IPC as an easy method of access to the pleural space this is an intriguing question that is worth evaluating further in clinical studies.

Recommendation 11

In patients with IPCs for the management of known or suspected MPEs who are receiving chemotherapy, we suggest against removing the catheter for the purpose of reducing infection risk (Ungraded Consensus-Based Statement).

Background

The concern over IPC infection in immunocompromised patients receiving chemotherapy is reasonable as the indwelling catheter serves as a potential portal of entry for infectious organisms. However, given the palliative benefit of IPCs and their positive impact on functional status, in anticipation of chemotherapy a risk-benefit analysis is warranted before deciding on IPC removal or placement.

Summary of Evidence

In a single center, 6-year retrospective review, Mekhaiel et al[19] compared infection rate in MPE patients with IPCs who were receiving chemotherapy to those who were not. A total of 262 IPCs in 243 patients were included, of which 173 IPCs

(66%) were in the chemotherapy group. Both IPC-related pleural space infections and soft tissue infections were analyzed. The authors defined active chemotherapy as patients having received chemotherapeutic agents within 6 weeks of IPC placement or at any timepoint during which the IPC was in situ. Overall infection rate was 6.1% of which 3.8% were IPC-related pleural space infections and 2.3% were soft tissue infections. The overall infection rate in the chemotherapy arm was 5.2% compared with 7.9% in the nonchemotherapy arm, a statistically insignificant difference ($P = 0.4$).

A similar study by Hak et al[18] analyzed 104 IPC patients with MPE, of which 43 (41%) were receiving chemotherapy. The rate of infection within 6 months of IPC insertion was 9.3% in the chemotherapy arm versus 4.9% in the nonchemotherapy arm which was also not statistically different ($P = 0.311$). The 6-month mortality was significantly higher in those not receiving chemotherapy, which can be explained by severity of illness precluding chemotherapy.

Mitchell et al[20] retrospectively reviewed a 10-year cohort of patients with IPCs placed for MPEs associated with breast cancer. In this study the effect of chemotherapy on IPC removal was the primary outcome, while development of infections was secondarily evaluated. A total of 207 patients were included of which 104 (48.2%) received chemotherapy with IPC in situ. Both infection rates and overall rate of IPC removal were similar between the 2 groups.

In patients with hematologic malignancies, who often receive cytotoxic chemotherapy resulting in significant neutropenia, there also does not appear to be an increased infection risk. Gilbert et al[65] evaluated 91 such patients with IPCs and found an 8% overall rate of infection with a mean catheter duration of 90 days. While there was no comparison group, the infection rate was similar to those found in other reviews of IPC infections in malignant disease.[31] Only 43% of patients were receiving active chemotherapy and the specific frequency of infections in this subgroup was not reported. Overall mortality related to infection was 2%. However, of the 7 patients who did develop IPC-related infections, 2 died from the infection (29%). Four of the patients who survived had IPCs removed, while 2 of the 3 patients whose IPCs were retained died.

Faiz et al[44] reviewed the rates of IPC-related infections in hematologic malignancies over a 14-year period at a single large-volume cancer center. A total of 172 patients with 208 IPCs were analyzed. Nine patients (5.2%) developed infectious complications. Of these, 5 (2.9%) were pleural space infections, 3 (1.7%) were tunnel tract infections and 1 (0.6%) was an exit-site infection. Again, these rates are similar to those discussed previously.[31,32,68,69]

Justification for Recommendation

The risk of IPC-related infections in patients receiving chemotherapy appears to be low across several subgroups of cancer patients. While there are no prospective, randomized trials assessing this question, multiple robust retrospective reviews are consistent in demonstrating these findings, with reported infection rates similar to those with IPCs not undergoing chemotherapy.[18–20,44] The committee finds these results, combined with the palliative benefit of IPCs, compelling justification for its recommendation.

CONCLUSIONS

To the best of our knowledge this is the first guideline devoted to the postinsertion management of IPCs in patients with MPEs. Our goal was to provide a framework based on the best available evidence and where data was lacking expert opinion. In developing our document, we utilized the TCBS approach,[7] which results in unbiased, scientifically valid, standards-compliant, and trustworthy guidance. However, despite what we considered a rigorous methodological process for synthesizing and reporting the evidence, we acknowledge limitations to our recommendations.

All chosen topics for evaluation were felt to be clinically important and potentially actionable. We do recognize that certain topics were not addressed. Some of these topics were intentionally avoided due to inability to define best practices or unclear relevance and applicability to general practice. Examples include the use of serial examinations of pleural cytology or biomarkers to guide interventions, and the role of maintaining a daily drainage log.

A major limitation of our document is the lack of quality clinical trials to support decision-making. Most of the available evidence is confined to retrospective reviews. Consequently, despite our methods, we were unable to provide any guidance with strength exceeding that of suggestions. As such, it is important to emphasize that a lack of strict adherence to these guidelines should not be considered a deviation from standard of care. Nevertheless, we feel our document uses the appropriate guidance

and transparency for the reader to decide the relative value of each recommendation.

We also concede several methodological limitations. In this project, searches were not peer-reviewed by objective medical librarians, and quality assessments were made by only 1 methodologist and not confirmed by dual critiques. However, the authors believe that the risk of missing relevant manuscripts by not including a librarian in the literature search is low since the body of literature dedicated to the management of IPCs for the management of MPEs is relatively small. Also, through a combination of the PubMed search developed by the authors and the manual searches performed by the panel membership (who are very familiar with the existing literature within the field), the authors feel confident that the literature review was sufficiently comprehensive. While dual quality assessments by 2 methodologists is ideal, the decision was made to limit to a single methodologist due to cost restraints. Given the small number of articles which underwent methodological assessment, all of which clearly had high/serious risks of bias, the authors do not believe that this altered the final conclusions.

The composition of the panel membership is another potential limitation. The voting membership included only interventional pulmonologists and mid-level providers who practice under the supervision of interventional pulmonologists. There are multiple other provider specialties which are involved in the placement of IPCs for MPEs as well as patient monitoring and management of complication, such as thoracic surgeons, interventional radiologists, oncologists, and infectious disease specialists. Consensus opinions might have differed depending on the distribution of disciplines represented but this is unknown.

Finally, the panel did not include a consumer representative, which in this case would have been a patient with MPE managed with an IPC. This is recommended as part of the TCBS development protocol.[7] However, such an inclusion was deemed impractical based on the timeline developed for the guidelines which exceeded the average life-expectancy of such patients. In future updates, which the authors expect to be less time-intensive, aggressive attempts will be made to include a consumer representative.

Our process identified several areas in need of more rigorous investigation. Since IPC patients with MPEs typically have a limited lifespan, require frequent hospitalizations and palliative interventions, and may have an increased risk for complications such as infection, focusing on these aspects is paramount. Some specific targets for further clinical investigation could include the feasibility and efficacy of outpatient management of IPC-related pleural space infections; better methods of identifying factors predicting successful spontaneous pleurodesis; the value of combining IPC and pleurodesis approaches for minimizing time to and enhancing rate of catheter removal; or more precise methods of diagnosing IPC-related pleural infections. We also encourage reexamination of areas that have already been addressed, such as various outcomes related to aggressive IPC drainage schedules. These additional trials may help either solidify existing evidence or raise further questions by refuting it.

In conclusion, these guidelines were developed to provide practical and useful assistance to clinicians caring for patients with IPCs and MPEs. The authors hope that this document not only provides a valuable data summary and expert-based opinion for the reader but will stimulate future study and allow for more robust and evidence-based guidelines in the future.

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