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Title: Management of Indwelling Tunneled Pleural Catheters: A Modified Delphi Consensus Statement

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Abbreviations List

MPE – malignant pleural effusion
IPC – indwelling tunneled pleural catheter
QOL – quality of life

Keywords

- Malignant pleural effusion
- Indwelling tunneled pleural catheter
- Pleurodesis
- Pleural catheter infection
- Pleural catheter management

Abstract

Background: The management of recurrent pleural effusions remains a challenging issue for clinicians. Advances in management have led to increased use of indwelling tunneled pleural catheters (IPC) due to their effectiveness and ease of outpatient placement. However, with the increase in IPC placement there have also been increasing reports of complications, including infections. Currently there is minimal guidance in IPC related management issues after placement. Our objective was to formulate consensus clinical recommendations related to perioperative and long-term IPC catheter management based on a modified Delphi process from experts in pleural disease management.

Methods: Expert panel members utilized a modified Delphi process to reach consensus on common perioperative and long-term management options related to IPC use. Members were identified from multiple countries, specialties, and practice settings. A series of meetings and anonymous online surveys were completed. Responses were utilized to formulate consensus statements among panel experts using a modified Delphi process. Consensus was defined *a priori* as greater than 80% agreement among panel constituents.

Results: A total of twenty-five physicians participated in this project. The following topics were addressed during the process: definition of an IPC infection, management of IPC related infectious complications, interventions to prevent IPC infections, IPC related obstruction/malfunction management, assessment of IPC removal, and instructions regarding IPC management by patients and caregivers. Consensus was obtained on thirty-three statements. No consensus was obtained on twenty-nine statements.

Conclusion: The management of recurrent pleural disease with IPC remains complex and challenging. This statement offers clinical recommendations for care in numerous areas related to indwelling tunneled pleural catheter management based on expert consensus, as well as identifying areas that lack consensus. Further studies related to long-term management of IPC are likely warranted.

Manuscript

Introduction

The management of recurrent pleural effusions and malignant pleural effusions (MPE) remains a challenging and perplexing clinical problem. Interventions must balance invasiveness, procedural risks, and quality of life improvement. Numerous interventions for MPE have been proposed over the years, often focused at obliteration of the pleural space (pleurodesis) to prevent fluid recurrence. Some of these interventions described more than half a century ago are no longer utilized, such as radioactive gold[1], however other interventions have stood the test of time and are still performed today for the palliation of MPE, including thoracentesis[2-4] and chemical pleurodesis[5,6]. Within the last few decades there has been renewed interest in the study and management of pleural disease. The introduction of the indwelling pleural catheter (IPC)[7-9] has helped transition MPE management from the inpatient (chemical pleurodesis) to the outpatient (IPC) setting, potentially allowing patients to spend a significant percentage of their remaining lifespan out of the hospital and decreasing the cost of care.

Recommendations from leading respiratory societies suggest IPC as the treatment of choice for patients with MPE that also have evidence of an entrapped lung[10-12]. For those with expandable lung, the evidence for IPC use is less clear, however additional study remains ongoing. Evidence suggests that IPC use has been increasing over time[13], regardless of the underlying pleural physiology and/or potential chance of successful chemical pleurodesis. Additionally, studies in hepatic hydrothorax[14,15] congestive heart failure[16] or other disorders causing recurrent pleural disease (i.e., chylothorax, renal disease, etc.)[17] have demonstrated the feasibility of utilizing IPCs in non-malignant diseases.

While guidelines regarding patient selection and indications for IPC placement have been proposed, little guidance is currently available on optimal IPC management once they are *in situ*. The recent American Thoracic Society guidelines on IPC offer some insight into IPC management, related to IPC related infections[12] - suggesting that infections should be attempted to be treated with the catheter *in situ.* However, with widespread use of IPCs there are increasingly frequent reports of infectious and non-infectious complications, and a paucity of literature to guide clinicians. Given the existing gaps within the medical literature and in an attempt to assist clinicians with an evidence-based IPC recommendations, members of the Interventional Pulmonology Working Group, a Section of the Thoracic Oncology Assembly of the American Thoracic Society, assembled an expert panel to develop a statement on the management of IPCs.

Methods

During the working session meeting of the Interventional Pulmonology Working Group at the 2018 American Thoracic Society international conference, members participated in a panel discussion on IPC management and controversies, expressing concern about current lack of evidence and wide practice variation in topic areas such as complication management, evaluation of catheter removal, and patient teaching. An executive committee was subsequently convened (CRG, MW, FM, ML, LBY) to be responsible for reviewing the existing evidence and in the absence of evidence, formulate topics for Delphi consensus review as a modified Delphi method was planned for use to establish areas of consensus and non-consensus.

The executive committee invited additional experts to ensure that relevant specialties and stakeholders were represented. Panelists were identified based on their expertise relative to the potential topic areas, previous publication history in pleural disease, practice location, and willingness to participate within the process. All panelists were reviewed for potential conflicts of interest. An overall depiction of the process is given in Figure 1. In order to proceed with a modified Delphi process, a total of twenty-six physicians were invited to participate. One physician ultimately declined the invitation to participate, providing a final number of 25 participants. Within this group, participants self-identified as the following specialties - Interventional Pulmonology - 17, Pulmonology - 5, Thoracic Surgery - 2, Infectious Disease - 1.

After identification of the expert panel an in-person meeting was convened, facilitated by three leaders (CRG, MW, LBY). The following topics/domains related to IPC management were considered of most clinical importance/relevance to clinicians in practice, and therefore were the focus of the project:

- Definition of IPC related infection
- Management of IPC related infectious complications
- Interventions to prevent IPC infections
- IPC related obstruction/malfunction management
- Assessment of IPC removal
- Instructions/Management of IPC by patients/caregivers

A series of three anonymous online surveys (Qualtics Survey Solutions, Qualtics XM) were distributed via an email link to self-provided email addresses. Each survey consisted of a series of questions addressing the focused facets of IPC management discussed above. The first round consisted of open-ended questions to help identify particular trends related to these management issues. The second and third round consisted of questions and/or case scenarios in which the participants had to rank their agreement/ disagreement on a 5-point Likert scale (strongly disagree, somewhat disagree, neither agree nor disagree, somewhat agree, strongly agree). These responses were then scored Agree (strongly agree, somewhat agree), Neutral (I neither agree or disagree), or Disagree (strongly disagree, somewhat disagree) for presentation purposes. Questions that reached consensus during the second round were considered completed and not re-presented. After the second round, results and feedback were reviewed, with the areas of non-consensus re-presented with different arrangement of wording and/or available options in an attempt to achieve consensus. After the third round was completed, no additional surveys were distributed. During each round, a total of three reminders were sent to participants.

All data were collected prospectively using the Qualtics Survey software, which was exported into Microsoft Excel (Microsoft, Redmond, WA) for analysis. Basic descriptive statistics were utilized for analysis. Consensus was defined *a priori* as greater than or equal to 80% agreement response to a question.

Results

The first survey, containing 33 open-ended questions, was sent out on November 13, 2018 and completed surveys were returned by December 31, 2018. Survey completion was 92% (23/25). The second survey, containing 65 multiple choice questions, was sent out on April 12, 2019 and completed surveys were returned by May 28, 2019. Survey completion was 100% (25/25). The third survey, containing 34 multiple choice questions, was sent out on June 12,

2019 and completed surveys were returned by July 15, 2019. Survey completion was 100% (25/25).

As the initial section of the survey, we established criterion that would provide clinical utility in a real world setting to define IPC-related infectious complications (Table 1), of which consensus was achieved. Subsequent sections evaluated IPC management and are summarized here and in Table 2. In patients with localized IPC site infections, the following statements reached consensus. They should be managed as outpatients unless additional need dictates hospital admission (clinically unstable, unable to follow-up, failure of outpatient management, etc). Antibiotics should be directed at typical gram-positive organisms, duration should be 7-10 days, and IPC should remain in place during initial management. Most agreed (but did not reach consensus) that IPC removal is indicated when initial management with antibiotics and drainage does not result in clinical improvement. In patients with deep space pleural infections, the following statements reached consensus. During initial management, the IPC should remain in place, drained more frequently (continuous as an inpatient, at least daily as an outpatient, etc), and surgical decortication was not favored as first-line therapy. Additional therapy including intrapleural fibrinolytic therapy, followed by additional chest tubes and surgical interventions may be performed in the setting of undrained fluid collections and/or lack of clinical improvement. Initial antibiotic regimen should be directed at a wider empirical regimen including consideration of gram-positive, gram-negative, and anaerobic coverage, allowing pleural fluid culture results to help dictate subsequent therapy. The duration of antibiotics was not agreed upon, however most disagreed with treating for only 1 week (79%). The highest amount of agreement for antibiotic duration occurred at 4 weeks of treatment (64%). While most suggested patients can managed as outpatients, this did not reach consensus (79% agree on outpatient initial management).

Attempts to prevent IPC related infections include the use of full body draping and performance of IPC placement in a dedicated environment. The use of pre-operative antibiotics was not favored (60%), however did not reach consensus. Family and/or caregivers should be taught how to sterilely access and care for the IPC.

IPC function and patency should be tested at time of placement, and the presence of decreased pleural fluid output from a previously draining IPC should prompt imaging, preferably with pleural ultrasound as a first step. In the setting of decreased pleural fluid output, recurrent symptoms, and evidence of recurrent fluid within the pleural space, management can include attempts at flushing the IPC to reestablish patency (with saline and/or alteplase) or removal of the current IPC and placement of another IPC. IPC removal in the setting of decreased pleural fluid and the lack of symptom and radiographic recurrence fluid should occur with less than 50 cc of fluid on three consecutive drainages.

Overall, we were able to obtain consensus on 36 statements regarding IPC management and unable to obtain consensus on 29 statements. Additional information on the Delphi methodology outcomes for consensus and non-consensus statements are provided in the data supplement (Supplemental Table 1 & 2).

Discussion

The management of recurrent pleural effusions often confronts physicians with a challenging decision-making processes, both in regards to IPC placement as well as its longer-

term management. This study presents the first report of expert consensus opinions for the management of IPC after placement.

Conclusions from Delphi Process

The management of IPC-related infections appears generally feasible in the outpatient setting, as long as the patient appears clinically appropriate for outpatient management (able to take medications by mouth, able to follow-up with appropriate outpatient support, no clear evidence of sepsis/shock, etc.) and there is no need for additional procedures to provide optimal management at the time of initial presentation. We were able to reach consensus on this topic in regard to localized IPC site infections, but not in the case of deep pleural space infections. It appears that some experts routinely admit all pleural space infections to the hospital, although this is likely be influenced by local practices patterns and available support. We were able to reach consensus on antibiotic duration for localized site infections (7-10 days) but were unable to do so for deep space pleural infections. Most experts disagree that one week of antibiotic therapy is adequate, with more agreement appearing within the 4+ week range for adequate duration. It remains unclear as to why were unable to obtain consensus. Each antibiotic range was offered as a separate question as opposed to one question that would allow one answer. While perhaps this type of questioning led to the inability to obtain consensus, this same type of questioning was utilized for localized IPC site infections and we were able to obtain consensus. This would suggest that there still remains debate/uncertainty in the antibiotic treatment regimen for deep space pleural infections. In the case of an IPC related infected pleural space infection, most attempt to continue with the pleural catheter in place which remains in line with the practice guidelines [12] as well as increased drainage frequency and "step-up" therapy in aggressiveness depending on clinical course.

Interventions to prevent IPC infections include the use of full body draping, use of sterile gowns, performance of IPC placement within a sterile environment, and family/caregiver education on IPC access and sterile technique during the draining process. Prior study has suggested a benefit with pre-operative antibiotics, sterile precautions and limitation of IPC placement to one location[18]. The majority (60%) of clinicians however do not routinely use pre-operative antibiotics and additional prospective studies are needed to determine the true benefit.

The evaluation of IPCs that are no longer draining raised some interesting questions and responses from the group. Initially it was discovered that many physicians had numerous comments and disagreements about the phenomenon that is commonly labeled as "autopleurodesis" or "spontaneous pleurodesis". This is commonly reported in the setting of a previously draining IPC, that is no longer draining, without symptom or radiographic recurrence[7,19,20]. For the purpose of the Delphi survey it was agreed that this type of terminology/definition was avoided due to the concern and disagreement, therefore we attempted to focus on specific situations regarding decreased pleural fluid output from the IPC, and in certain situations referred to this as a non-draining IPC. The management of a non-draining IPC is often related to the other associated signs and/or symptoms at the time. In the setting of a non-draining IPC and recurrent symptoms (dyspnea, chest pressure, cough, etc) chest imaging should be performed, often with the use of pleural ultrasound. Attempts at salvaging the current IPC with flushing of saline and/or alteplase should be undertaken if pleural fluid recurrence is confirmed on imaging. However, in the setting of a non-draining IPC and no evidence of symptom or radiographic recurrence, IPC removal should be considered after fluid drainage of less than 50 mL occurs on three consecutive attempts.

While most clinicians suggested that a particular drainage schedule should be prescribed to patients with IPCs, the scheduled regimen was not agreed upon. The most commonly agreed upon schedules were daily or every other day, however both only reached 50% agreement. The current data suggests that everyday drainage for patients with adequate lung re-expansion leads to faster pleurodesis rates[19], however the role of everyday drainage in patients with a non-expandable lung remains unclear. Despite a recent trial suggesting that symptom driven IPC drainage (minimum drainage at once every two weeks) is equivalent to daily drainage for controlling breathlessness[21], few appear to be utilizing this approach. It is also acknowledged that some of this practice variation may be related to the underlying intent of IPC placement. If the overall goals are for pleurodesis, perhaps the use of daily drainage may be offered to patients, whereas if the intent is symptom relief, then less aggressive drainage schedules may be recommended.

Most clinicians also offer advice on IPC drainage and symptoms that occur during drainage. Most suggested terminating fluid drainage when there was no additional fluid or when chest discomfort/pain developed. If pain occurs during drainage many suggest slowing down the speed of drainage or utilizing pain medication approximately 30-60 minutes prior to drainage.

The Delphi Method and Limitations

The Delphi method has generally been used to obtain "pooled intelligence" and appears helpful in healthcare situations where there is a lack of data available, as the use of expert opinion may be helpful to fill knowledge gaps[22]. The use of anonymity during the Delphi process allows for the avoidance of more vocal persons to influence the remaining responders[23,24], perhaps an advantage in some expert panel situations. This method has proven informative in numerous other guideline formulations in the past as well[25-27]. The Delphi method also allows for easy and repeated engagement of experts in various geographic and practice/hospital locations. We believe the expert recommendations we present are strengthened by the use of a modified Delphi method during their attainment as well as the high participation rate of experts.

A limitations of the Delphi method include the formation of the "expert" panel as its consistency may bias the panel responses. We sought out participants that would be interested in participating in such a process and have an interest in pleural disease, as defined by prior publication or presentation at national meetings. We also sought out a multidisciplinary panel that included interventional pulmonology, pulmonology, thoracic surgery, and infectious disease. The majority of participants were self-identified as interventional pulmonology, providing a potential bias, however also sought the opinion of thoracic surgery (one whom was also on the executive committee).

Additional limitation of our Delphi method includes the inability to identify "why" certain answers were chosen, as respondents were polled anonymously. Another limitation is the lack of the ability to account for patient input during the decision-making process for many of these situations. MPE and IPC placement/management is often targeted at quality of life decisions, many of which require patient input and vary dramatically from patient to patient. We attempted to ask questions that would generally occur within daily practice of IPC management but did not want present so many situations/questions that would lead to question answering fatigue. We are certain that situations will arise not covered by the statements provided heretofore, but hope this document can provide a framework for clinicians to utilize in their decision making process. Additionally there is limited data available on certain aspects, such as how often patients should drain their catheter, however a study identifying the "best approach"

likely does not exist. Currently available are two prospective, randomized trials, ASAP[19] and AMPLE-2[21]that evaluated IPC drainage schedules, however the drainage schedules and primary endpoints of the studies differed dramatically, likely impacting clinical decision-making. The ASAP trial concluded that daily IPC drainage leads to faster removal, however the AMPLE-2 trial concluded that symptom driven drainage leads to equivalent breathlessness scores – therefore the goal of IPC placement (early removal vs relief of symptoms) may influence clinicians recommendations to patients, a question we did not specifically explore. This available data likely allows for individual variability in response both based on physician interpretation of the data, as well as the application to an individual patient. Therefore, in a question such as – how often do you suggest patients drain their IPC – a high degree of variability is to be expected, however it appears that the majority still recommend to drain every day or every other day. Despite this potential limitation we hope the results of this survey will provide clinicians with guidance on how experts may be managing many of their patients. We believe that our consensus answers represent what each member of the expert panel would suggest in the ideal situation, and similar to interpreting and applying data from any clinical trial, patient considerations and clinical situations may still dictate management options.

Final Comments

In conclusion, the use of IPCs in the management of recurrent pleural effusions remains an effective and popular treatment strategy. As IPC use continues to gain popularity, important questions such as how to manage the everyday use of IPCs remain important, as do the management of complications related to catheter use. The current literature base remains sparse, and it is difficult to provide robust evidence-based guidelines for such care. This manuscript offers recommendations for care in numerous and clinically relevant areas of IPC related management as currently being utilized by experts in pleural disease. However, the significant limitations of expert-based opinion must be acknowledged within the context of providing recommendations for care. Further studies are now warranted in various aspects of MPE management, including the numerous questions and complications that can arise after IPC insertion.

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Figure Legends

Figure 1. Schematic representation of the Modified Delphi Process. This figure represents a summary of the overall process, flow, and steps involved during this process.