

2022

## Indwelling pleural catheterization maximizes functionality and quality of life in management of recurrent malignant pleural effusions

Avinash Ramkissoon  
*Wayne State University*, [gt2165@wayne.edu](mailto:gt2165@wayne.edu)

Follow this and additional works at: <https://digitalcommons.wayne.edu/crp>



Part of the [Medical Education Commons](#), [Neoplasms Commons](#), [Oncology Commons](#), [Pulmonology Commons](#), [Respiratory Tract Diseases Commons](#), [Therapeutics Commons](#), and the [Translational Medical Research Commons](#)

---

### Recommended Citation

RAMKISSOON A. Indwelling pleural catheterization maximizes functionality and quality of life in management of recurrent malignant pleural effusions. *Clin Res Prac*. Dec 6 2022;8(2):eP2831. <https://doi.org/10.22237/crp/1667260980>

This Clinical Decision Report is brought to you for free and open access by the Open Access Journals at DigitalCommons@WayneState. It has been accepted for inclusion in Clinical Research in Practice: The Journal of Team Hippocrates by an authorized editor of DigitalCommons@WayneState.

# Indwelling pleural catheterization maximizes functionality and quality of life in management of recurrent malignant pleural effusions

AVINASH RAMKISSOON, HBSC, MPH, Wayne State University School of Medicine, [gt2165@wayne.edu](mailto:gt2165@wayne.edu)

**ABSTRACT** A clinical decision report using:

Davies HE, Mishra EK, Kahan BC, et al. Effect of an indwelling pleural catheter vs chest tube and talc pleurodesis for relieving dyspnea in patients with malignant pleural effusion: The TIME2 randomized controlled trial. *J Am Med Assoc.* 2012;307(22):2383-2389. <https://doi.org/10.1001/jama.2012.5535>

for the management of recurrent malignant pleural effusions in a patient with metastatic renal cell carcinoma.

**Keywords:** *pleural effusion, indwelling pleural catheterization, pleurodesis, cancer, quality of life*

## Clinical-Social Context

Ms. Erin Mills (pseudonym) is a middle-aged woman with a history of type I diabetes, pulmonary embolism for which she underwent a thrombectomy, and right-sided clear cell renal cell carcinoma with local invasion of the inferior vena cava and extensive metastases to her lungs and liver. She presented to the Emergency Department for progressive exertional dyspnea, and initial chest X-ray demonstrated a new, moderate-sized right-sided pleural effusion. In the initial interview, she told the care team, "I can hardly walk up the stairs to my bedroom anymore, and I need to take a seat on the steps halfway. It's even exhausting to stand at the sink to do the dishes". Thoracentesis demonstrated a lymphocyte-predominant exudative effusion, consistent with progression of Ms. Mills' malignancy. During her stay at the hospital, the effusion would quickly reaccumulate, and required multiple thoracentesis for symptomatic relief. One of the members of her care team described the cyclic changes as the effusion would be drained and then reaccumulate, "The afternoon after she'd go to interventional radiology, she seemed like a whole new person. She would be walking down the hallways, chatting with other patients and the staff. Over the next few days, she'd slow down, spend more time sitting in her chair, and eventually she'd wind up in bed for the better part of the day again."

Prior to this admission, Ms. Mills was able to perform her activities of daily living without assistance, and it was crucial that she maintained that level of independence despite this new complication of her disease. Ms. Mills lives in a three-story house with her husband, and her dyspnea made it progressively more difficult to navigate through her home. Mr. Mills (pseudonym) provides significant home support in addition to working a full-time job; Ms. Mills was adamant about not placing additional burden on her husband.

AVINASH RAMKISSOON, HBSc, MPH, is a medical student at the Wayne State University School of Medicine.



ISSN: 2379-4550

<http://digitalcommons.wayne.edu/crp>, © 2022 The Author(s)

Licensed under [Creative Commons Attribution 4.0 International \(CC-BY-4.0\)](https://creativecommons.org/licenses/by/4.0/)

The Clinical Practice Guidelines from the American Thoracic Society provides recommendations to guide therapeutic options for patients with malignant pleural effusions (MPEs).<sup>1</sup> For patients with symptomatic MPEs with expandable lungs and no prior definitive therapy, the recommendation is either indwelling pleural catheterization (IPC) or chemical pleurodesis as first-line intervention for management of dyspnea.<sup>1</sup> IPC placement is a semi-permanent solution that allows intermittent external drainage of the pleural space to relieve respiratory symptoms associated with a pleural effusion. Chemical pleurodesis involves obliteration of the pleural space, often with dry talc powder or a talc slurry, which prevents further accumulation of an effusion when performed successfully.

In discussion of these two management options with our patient, Ms. Mills had questions about the level of maintenance that would be required for each intervention, possible complications, and how it would impact her ability to carry out her usual daily functions. Between pleurodesis and catheterization, there was not a clear best option for her situation, and we turned to the literature to guide our clinical decision.

## Clinical Question

For the management of recurrent malignant pleural effusions, which therapeutic option, IPC or pleurodesis, would maximize a patient's functional status and quality of life?

## Research Article

Davies HE, Mishra EK, Kahan BC, et al. Effect of an indwelling pleural catheter vs chest tube and talc pleurodesis for relieving dyspnea in patients with malignant pleural effusion: The TIME2 randomized controlled trial. *J Am Med Assoc*. 2012;307(22):2383-2389. <https://doi.org/10.1001/jama.2012.5535><sup>2</sup>

## Description of Related Literature

A literature review initiated on PubMed with the following search terms: (pleural effusion) AND ((indwelling pleural catheter) OR (pleurodesis)) yields 1684 results. The results were narrowed down to only include malignant pleural effusions: (malignant pleural effusion) AND ((indwelling pleural catheter) OR (pleurodesis)), yielding 1089 results. The search strategy was further adjusted to include results that report on both treatment options: (malignant pleural effusion) AND ((indwelling pleural catheter) AND (pleurodesis)), yielding 215 results. Filtering these 215 results by clinical trials and randomized controlled trials (RCTs) yields 27 results. There are also 6 meta-analyses, 12 systematic reviews, and 74 review articles published on this topic. Review of the Medical Subject Headings (MeSH) terms of the RCTs demonstrates the search strategy generates appropriate results. Related articles associated with the 27 results were reviewed for other relevant studies, which yielded 12 additional studies, of which two were RCTs that were relevant to the study question. In total, 29 clinical trials were identified. Finally, the search strategy was repeated in Google Scholar, and no additional RCTs relevant to the study question were identified. The article of interest was located in Google Scholar, and the "Related Articles" function yields 101 results. These results were reviewed, and no additional clinical trials were identified.

Of these 29 clinical trial results, several relevant studies emerged, including the AMPLE RCT, which compares the cumulative duration of hospitalization between patients with MPEs treated with IPC compared to pleurodesis.<sup>3</sup> The AMPLE study concluded that patients treated with IPC (n = 73) compared to pleurodesis (n = 71) had a statistically significant decrease in the days of hospitalization from initial treatment to death (p = 0.03); however, this difference may not be clinically significant.<sup>3</sup>

The TIME2 RCT examines the clinical question from a different angle than the AMPLE RCT, and investigates the effectiveness of pleurodesis and IPCs at relieving dyspnea in addition to a variety of secondary measures.<sup>2</sup> Over the first 6 weeks, there was improvement in dyspnea for both groups, but the between-group difference was non-significant (p = 0.96). Secondary outcomes included longer follow-up; the between-group difference in dyspnea after 6 months was significant, favoring IPC (p = 0.01) and shorter hospital length of stay (p < 0.001), compared to the pleurodesis group.<sup>2</sup> However, there was a higher risk of adverse events, such as infection or pleural space loculation, occurring in the IPC group compared to pleurodesis group (OR = 4.7, p = 0.02).<sup>2</sup>



The AMPLE-2 and ASAP trials examine the optimal frequency of drainage of MPE among patients with IPCs.<sup>4,5</sup> The AMPLE-2 and ASAP trials do not address the above clinical question directly but can still provide some insights for patient education. There are other studies related to the cost-effectiveness of each option, but do not comment on the therapeutic benefit to the patient.<sup>6,7</sup>

UpToDate's article Management of malignant pleural effusions outlines therapeutic options based on the frequency of recurrence and lung expandability. For those with rapid MPE accumulation like Ms. Mills, the optimal therapy is unclear, but article's author states their preferred initial intervention is IPC placement, citing the AMPLE and TIME2 RCTs, and two other studies related to quality-of-life changes post-IPC therapy. One of these studies concluded that global health status, quality-of-life, and dyspnea were improved after 2 weeks of IPC treatment compared to baseline status, while the other (NVALT-14 RCT) found that IPC was non-superior to talc pleurodesis for relief of dyspnea, which is consistent with the findings of the AMPLE and TIME2 trials.<sup>8,9</sup>

There were 3 meta-analyses in the literature search that addressed the clinical question, and they all reached similar conclusions – Both IPC and pleurodesis are effective in management of recurrent MPEs; however IPC results in shorter hospital length of stay.<sup>10-12</sup> These findings are consistent with the conclusions of the AMPLE, TIME2 and NVALT-14 trials.

The AMPLE and TIME2 trials are the closest to answering the clinical question outlined above and both were cited in the American Thoracic Society guidelines and UpToDate. Ms. Mills' primary concern was for her ability to maintain independence in her activities of daily living; to that end, symptomatic management is essential to maximizing her functional status and quality-of-life. Additionally, Ms. Mills fits the inclusion and exclusion criteria of the TIME2 study, making it quite applicable to this clinical decision. Thus, the TIME2 study was selected for further critical appraisal.

There are consistent findings in the form of more than two systematic reviews of RCTs with meta-analyses, leading to a level A SORT Strength of Recommendation.<sup>13</sup>

## Critical Appraisal

The TIME2 trial was an open-label multi-center randomized controlled trial in the UK. It was funded by the British Lung Foundation and Robert Luff Foundation, and was sponsored by the University of Oxford. The sponsors did not participate in the design nor the execution of the study. Participants were randomized in a 1:1 manner to each treatment arm of the trial (IPC or pleurodesis) with minimization of between-group differences. The nature of the intervention precluded blinding of the patients and investigators; however, the statistical analysis was conducted in a blinded manner. Baseline characteristics of the two groups did not differ significantly at the time of randomization. Demographics included sex and age only; other social factors like socioeconomic status and ethnicity were not reported. Self-reported dyspnea levels were not significantly different at baseline. However, the site of primary malignancy did vary slightly between groups; breast cancers were proportionally higher in the IPC group, and lung cancers in the pleurodesis group.

After randomization, participants either had an IPC placed as an outpatient procedure (unless currently hospitalized) or talc slurry pleurodesis as an inpatient procedure. Additionally, all patients received standard of care treatment for their primary malignancy. The intervention appears to favor the IPC group, since that procedure is performed in an outpatient manner, whereas pleurodesis necessitated hospitalization. Besides the intervention, both groups received equivalent care and follow-up. Participants were followed for 12 months after randomization. Patients completed daily 100 mm visual analog scale (VAS) scores for dyspnea and chest pain for the first 6 weeks, and at various points up to 12 months. Additionally, a standardized cancer quality of life questionnaire was administered at similar points up to 12 months. The primary outcome was a comparison of mean daily VAS dyspnea scores over the first 6 weeks between the groups on an intention to treat basis, which provides better support for using this trial to guide clinical decision-making. The authors also explored several secondary measures, including reductions in dyspnea and chest pain, total duration of hospitalizations, all-cause mortality, self-reported quality of life, and frequency of adverse effects.

Criteria for inclusion were diagnosis of symptomatic MPE among patients with a pleural malignancy, or recurrent MPE in a non-pleural malignancy. Participants were excluded if they were younger than 18 years of age, had an expected survival less than 3 months, prior attempted treatment for the MPE, pleural infection, leukocytopenia (WBC < 1000/uL), hypercapnic ventilatory failure, pregnancy, lactating mothers, irreversible hypocoagulability, and irreversible visual impairment. Overall, the eligibility criteria were broad and allow generalizability to most patients suffering from recurrent MPEs, including Ms. Mills. The study does not outline how

patients were enrolled into the study; only that they were screened for eligibility based on the inclusion criteria. The setting (inpatient, emergency department, or outpatient) was not disclosed, nor was it clear who conducted the recruitment.

54 patients were randomized into the talc pleurodesis group and 47 were included in the analysis. 52 patients were randomized into the IPC group, and 49 were included in the analysis. With 106 total participants, there was sufficient power (>90%) to conduct the analysis at a 5% significance level. Less than 10% of participants were lost to follow-up. The authors had a predetermined threshold of a 10 mm difference in VAS score to be deemed clinically significant. The authors comprehensively reported the results of their analysis, including precision estimates, sensitivity analysis, and survival analysis between the treatment groups. In summary, they found that dyspnea improved from baseline measurements in both groups, but the difference in mean dyspnea between groups was non-significant in the first 6 weeks (0.16 mm, 95% CI: (-6.82 – 7.15);  $p = 0.96$ ). At 6 months, the difference in dyspnea became statistically significant, favoring IPC (8.9 mm, 95% CI: (2.8 – 25.2);  $p = 0.01$ ); however, this falls below the predetermined threshold of 10 mm to be clinically significant. Notably, 54 out of the 106 (51%) enrolled patients survived to 6 months. Among the IPC group, 42 out of 49 (86%) had a clinically significant improvement in dyspnea compared to 35 out of 47 (74%) in the pleurodesis group. Once again, the difference was not statistically significant (OR = 0.90, 95% CI: (0.18 – 4.43);  $p = 0.90$ ). Secondary measures were explored, including quality of life, repeat hospitalizations, and 1-year survival, all of which were not significantly different between the IPC and pleurodesis groups. However, adverse events, such as infection, were more common in the IPC group (OR = 4.70, 95% CI: (1.75 – 12.60);  $p = 0.002$ ) and repeat pleural interventions were less common in the IPC group (OR = 0.21, 95% CI: (0.04 – 0.86);  $p = 0.03$ ).

A major limitation to this study is the lack of patient and investigator blinding due to the nature of the interventions, and the primary outcome measure was a subjective score. As such, there is the possibility of bias in the self-reported dyspnea measurements. However, the management of MPEs is inherently palliative, so using a patient-oriented subjective scale is appropriate in this setting.

This trial does not meet the SORT criteria for a high-quality RCT, and thus falls under Evidence Level = 2.<sup>13</sup>

## Clinical Application

The TIME2 trial demonstrates that both IPC and pleurodesis are effective at relieving dyspnea in patients with MPEs and both improve quality of life compared to baseline, and that one intervention is not superior to the other. There may be some clinical considerations favoring the use of IPC, including the shorter duration of hospital stay and less frequent repeat pleural interventions. The downside is that IPC is associated with an increased rate of pleural and skin infection.

Ms. Mills fits all eligibility criteria and would have been a candidate for this study, meaning that the results are likely applicable to her situation. Returning to the clinical question, this study suggests that neither option is better than the other as it relates to functional status and quality of life, but there are other tangible benefits to IPC over pleurodesis. Based on the appraisal of the TIME2 study, it would be appropriate for Ms. Mills to undergo IPC for management of her recurrent MPEs. Other benefits that were not discussed in the TIME2 trial are that spontaneous pleurodesis can be achieved in 46 – 51% of patients after IPC, and it does not preclude the use of talc slurry pleurodesis in the future if IPC treatment is unsuccessful.<sup>5</sup> It would be beneficial to explore other patient-centered measures, such as patient preferences, patient education on home IPC use, and long-term cost implications, which may help guide the decision on MPE intervention.

Ultimately, Ms. Mills decided on IPC placement, and her symptoms have been well-managed since the procedure. She has since been discharged, and upon follow-up contact, she reports that “my breathing is so much better now that I have control over my effusion. I can remove the fluid every morning, and my breathing difficulties are almost entirely gone”. In terms of affecting her quality of life, she states, “it’s become part of my routine, and doesn’t interfere with my daily life at all. I know the drain has to stay clean and dry, and my husband helps me a lot with that”. Although the TIME2 study did not address the impact of other comorbidities, patients with diabetes, like Ms. Mills, are at higher risk for infection, which is a concern with IPCs.<sup>14</sup> She will continue to monitor the catheter site for signs of local and systemic infection and check for spontaneous pleurodesis, in which case the catheter can be removed.



## New Knowledge Related to Clinical Decision Science

This case highlights the importance of patient-oriented decision-making. When given two treatment options with similar efficacy, it can often be difficult for patients and clinicians to choose one over the other. Returning to the clinical decision at hand – deciding which treatment option is more effective – no clear answer is provided in the literature.

The development of recurrent MPEs reflects advanced disease and is associated with poor prognosis; it is therefore important to respect the patient's goals of care and other factors that may not be easily quantified through a clinical study. In patients where hospice care is considered, patients may not survive beyond 6 months, when IPC has an observed benefit over talc pleurodesis. Additionally, in patients where hospice care is under consideration, it would be ideal to minimize the number of drains and lines to maximize patient comfort. In such a situation, talc pleurodesis may be the preferred option.

Ms. Mills was not approaching end of life care, and she wanted to maintain her independence and functionality, rather than seeking the most comfortable or convenient option. With those goals and her clinical picture in mind, IPC is certainly the preferred treatment option.

## Conflict Of Interest Statement

The author declares no conflicts of interest.

## References

1. Feller-Kopman DJ, Reddy CB, Gould MK, et al. Management of malignant pleural effusions: An official ATS/STS/STR clinical practice guideline. *Am J Respir Crit Care Med*. 2018;198(7):839-849. <https://doi.org/10.1164/rccm.201807-1415ST>
2. Davies HE, Mishra EK, Kahan BC, et al. Effect of an indwelling pleural catheter vs chest tube and talc pleurodesis for relieving dyspnea in patients with malignant pleural effusion: The TIME2 randomized controlled trial. *JAMA - J Am Med Assoc*. 2012;307(22):2383-2389. <https://doi.org/10.1001/jama.2012.5535>
3. Thomas R, Fysh ETH, Smith NA, et al. Effect of an indwelling pleural catheter vs talc pleurodesis on hospitalization days in patients with malignant pleural effusion: The AMPLE randomized clinical trial. *JAMA - J Am Med Assoc*. 2017;318(19):1903-1912. <https://doi.org/10.1001/jama.2017.17426>
4. Muruganandan S, Azzopardi M, Fitzgerald DB, et al. Aggressive versus symptom-guided drainage of malignant pleural effusion via indwelling pleural catheters (AMPLE-2): an open-label randomised trial. *Lancet Respir Med*. 2018;6(9):671-680. [https://doi.org/10.1016/S2213-2600\(18\)30288-1](https://doi.org/10.1016/S2213-2600(18)30288-1)
5. Wahidi MM, Reddy C, Yarmus L, et al. Randomized trial of pleural fluid drainage frequency in patients with malignant pleural effusions the ASAP trial. *Am J Respir Crit Care Med*. 2017;195(8):1050-1057. <https://doi.org/10.1164/rccm.201607-1404OC>
6. Penz ED, Mishra EK, Davies HE, Manns BJ, Miller RF, Rahman NM. Comparing cost of indwelling pleural catheter vs talc pleurodesis for malignant pleural effusion. *Chest*. 2014;146(4):991-1000. <https://doi.org/10.1378/chest.13-2481>
7. Olfert JAP, Penz ED, Manns BJ, et al. Cost-effectiveness of indwelling pleural catheter compared with talc in malignant pleural effusion. *Respirology*. 2017;22(4):764-770. <https://doi.org/10.1111/resp.12962>
8. Boshuizen RC, vd Noort V, Burgers JA, et al. A randomized controlled trial comparing indwelling pleural catheters with talc pleurodesis (NVALT-14). *Lung Cancer*. 2017;108(2017):9-14. <https://doi.org/10.1016/j.lungcan.2017.01.019>
9. Sabur NF, Chee A, Stather DR, et al. The impact of tunneled pleural catheters on the quality of life of patients with malignant pleural effusions. *Respiration*. 2012;85(1):36-42. <https://doi.org/10.1159/000342343>
10. Iyer NP, Reddy CB, Wahidi MM, et al. Indwelling pleural catheter versus pleurodesis for malignant pleural effusions a systematic review and meta-analysis. *Ann Am Thorac Soc*. 2019;16(1):124-131. <https://doi.org/10.1513/AnnalsATS.201807-495OC>
11. Yeung M, Loh EW, Tiong TY, Tam KW. Indwelling pleural catheter versus talc pleurodesis for malignant pleural effusion: a meta-analysis. *Clin Exp Metastasis*. 2020;37(4):541-549. <https://doi.org/10.1007/s10585-020-10042-2>
12. Wang L, Deng H, Chen X, et al. Talc pleurodesis versus indwelling pleural catheter among patients with malignant pleural effusion: A meta-analysis of randomized controlled trials. *World J Surg Oncol*. 2020;18(1):1-9. <https://doi.org/10.1186/s12957-020-01940-6>



13. Ebell MH, Siwek J, Weiss BD, et al. Strength of Recommendation Taxonomy (SORT): A patient-centered approach to grading evidence in the medical literature. *J Am Board Fam Pract*. 2004;17(1):59-67. <https://doi.org/10.3122/jabfm.17.1.59>
14. Carey IM, Critchley JA, Dewilde S, Harris T, Hosking FJ, Cook DG. Risk of infection in type 1 and type 2 diabetes compared with the general population: A matched cohort study. *Diabetes Care*. 2018;41(3):513-521. <https://doi.org/10.2337/dc17-2131>

