Indwelling Pleural Catheter versus Pleurodesis for Malignant Pleural Effusions

A Systematic Review and Meta-Analysis

Narayan P. Iyer[1], Chakravarthy B. Reddy[2], Momen M. Wahidi[3], Sandra Z. Lewis[4], Rebecca L. Diekemper[4], David Feller-Kopman[5], Michael K. Gould[6], and Alex A. Balekian[7]

[1]Children's Hospital Los Angeles, Keck School of Medicine of the University of Southern California, Los Angeles, California; [2]Huntsman Cancer Institute, University of Utah, Salt Lake City, Utah; [3]Department of Medicine, Duke University School of Medicine, Durham, North Carolina; [4]Doctor Evidence, Santa Monica, California; [5]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland; [6]Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, California; and [7]Department of Medicine, Keck School of Medicine at the University of Southern California, Los Angeles, California

ORCID ID: 0000-0002-1664-9942 (A.A.B.).

Abstract

Rationale: Several randomized trials have compared the efficacy of an indwelling pleural catheter (IPC) versus the more traditional chemical pleurodesis in the management of malignant pleural effusion (MPE).

Objectives: As part of the American Thoracic Society's guidelines for management of MPE, we performed a systematic review and a meta-analysis to compare patient-centered outcomes with the use of a tunneled pleural catheter versus chemical pleurodesis for the first-line treatment of malignant pleural effusions.

Methods: We performed literature searches in MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials. We included randomized controlled trials comparing IPC and pleurodesis in adult patients with symptomatic MPE. Risk of bias was assessed with the Cochrane Risk of Bias tool recommended by the Cochrane Methods Bias Group. The meta-analysis was performed with Review Manager software, using a random effects model. We used risk ratios (RRs) with 95% confidence interval (CI) as the effect measure for dichotomous outcomes and mean differences for continuous outcomes.

Results: We identified five randomized trials, involving 545 patients, that compared IPC and pleurodesis. Lack of blinding and the inevitable attrition of patients due to death resulted in an overall high risk of bias among the studies. No differences in survival or measures of dyspnea were observed in any of the studies. Total hospital length of stay was shorter, and repeat pleural interventions were less common in the IPC group (RR, 0.32; 95% CI, 0.18–0.55). However, the risk of cellulitis was higher with IPC (RR, 5.83; 95% CI, 1.56–21.8). No differences were noted in other adverse events.

Conclusions: Compared with chemical pleurodesis, IPC results in shorter hospital length of stay and fewer repeat pleural procedures but carries a higher risk of cellulitis. Careful assessment of individual patient preferences and costs should be considered when choosing between IPC and pleurodesis.

Keywords: indwelling pleural catheter; malignant pleural effusion; meta-analysis; pleurodesis; systematic review

(Received in original form July 25, 2018; accepted in final form September 28, 2018)

Author Contributions: C.B.R. and D.F.-K. contributed to study design. C.B.R. and M.M.W. contributed to data collection. N.P.I., S.Z.L., R.L.D., M.K.G., and A.A.B. contributed to statistical analysis and data interpretation. All authors contributed equally to manuscript preparation.

Correspondence and requests for reprints should be addressed to Alex A. Balekian, M.D., M.S.H.S., Keck School of Medicine of USC, 2020 Zonal Avenue, IRD 723, Los Angeles, CA 90033. E-mail: alex.balekian@med.usc.edu.

Ann Am Thorac Soc Vol 16, No 1, pp 124–131, Jan 2019

DOI: 10.1513/AnnalsATS.201807-495OC
Internet address: www.atsjournals.org

Malignant pleural effusions (MPEs) affect a significant proportion of patients with cancer (1). The annual incidence of MPE in the United States is estimated to be greater than 150,000, and MPE accounts for 42–77% of all exudative effusions in adults (2). Symptoms of MPE include often debilitating breathlessness, chest pain, and constitutional symptoms such as anorexia and weight loss. Generally considered a manifestation of terminal malignancy, the main goal of treatment is to palliate and provide symptom relief (3). This has often been interpreted to support the use of the least intrusive intervention that is both

effective and has minimal adverse effects. For several decades, management has focused on chemical pleurodesis using various agents such as doxycycline, talc, and bleomycin (1). However, pleurodesis fails within a few months in a substantial proportion of patients (4, 5). Pleurodesis generally requires inpatient hospitalization and when done using thoracoscopy, often necessitates the use of general anesthesia. Indwelling pleural catheters (IPCs) have been successfully used for ongoing control of MPE, especially when survival of months to a few years is expected. The publication of several randomized controlled trials (RCTs) comparing IPC with chemical pleurodesis has mandated a reassessment of existing evidence. As part of the American Thoracic Society (ATS) clinical practice guidelines for malignant pleural effusions, we performed a systematic review and meta-analysis to examine the patient-centered outcomes with the use of tunneled pleural catheter versus chemical pleurodesis as the first-line treatment of MPE (6).

Methods

We synthesized the best available evidence for the following Population, Intervention, Comparator, and Outcome (PICO) question:

1. Patients: Symptomatic MPE
2. Intervention: IPC
3. Comparator: Chemical pleurodesis
4. Outcomes: Improvement in dyspnea, survival, mortality, hospital length of stay (LOS); treatment failure as measured by the need for additional pleural interventions (preferred) or radiologic/clinical criteria; and adverse events such as cellulitis, pleural infection, and bleeding requiring intervention. Selection of outcomes was done by a panel of experts who were part of the ATS guideline committee for the management of MPE

Electronic literature searches and data extractions were conducted by Doctor Evidence, a medical evidence software and services company, using their proprietary software platform (Doctor Evidence, 2018: DOC Library, DOC Data, version 2.0; Doctor Evidence, LLC). Standard methodology for conducting systematic reviews as per guidelines provided by the *Cochrane Handbook for Systematic Reviews of Interventions* were followed (7). Search results were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (8).

Study Identification and Eligibility

Study identification and eligibility criteria were developed and documented in a search strategy (Table 1) using the PICO framework as described in the Cochrane handbook (7) In addition, where relevant, the review took into account criteria associated with timing, setting, and study design.

The literature searches were performed in MEDLINE (via PubMed), Embase (via OvidSP), and the Cochrane Central Register of Controlled Trials (CENTRAL) (via Wiley) for citations from January 1, 1974 to December 31, 2017, by using a range of Medical Subject Headings (MeSH), Emtree, and free-text terms based on the search protocol. All search strategies were peer-reviewed by a senior Doctor Evidence librarian.

In addition to bibliographic databases, a manual search was performed on the reference lists of identified eligible studies, previously published systematic literature reviews on the same topic, and conference proceedings and registries, including the U.S. National Library of Medicine's ClinicalTrials.gov (https://clinicaltrials.gov) and the World Health Organization International Clinical Trials Registry (http://apps.who.int/trialsearch/).

Study Screening and Ascertainment of Eligibility

Eligibility criteria were developed by the project team and checked by a senior methodologist. Before screening began, duplicate studies and those that did not meet language or date restrictions were excluded.

The screening procedure was conducted on the basis of a two-step process: *1*) title/abstract screening and *2*) full-text screening. At both stages, the reasons for exclusion were documented. Title/abstract screening was conducted by a single screener and checked by a second person. Full-text screening was conducted by two independent reviewers (M.M.W. and C.B.R.). Discrepancies between reviewers were identified and resolved by an independent third reviewer (A.A.B.).

We included RCTs of any follow-up duration that were reported as full text and enrolled adults more than 18 years of age with pleural effusion in the presence of a known malignancy involving the pleura or outside the pleural space. Studies that were included compared IPC (any make or brand) and chemical pleurodesis (with any chemical agent) delivered with bedside chest tube placement. For randomized trials, we chose only studies with direct comparison of the two interventions.

For each trial, study, patient, and treatment characteristics, and efficacy/effectiveness/safety outcomes, were extracted. In particular for continuous variables, the appropriate estimate measures and dispersion (mean, median, SD, and range) were extracted. For dichotomous and categorical variables, the number and/or proportion of patients were extracted. Because most studies had patient attrition, we included all patients who received at least some aspect of the intervention. We did not include patients who died before any intervention was provided or who had the wrong intervention provided to them.

Risk of Bias Assessment

Risk of bias (study quality) of included studies was assessed with the tool recommended by the Cochrane Statistical Methods Group and the Cochrane Methods Bias Group (7). In brief, this tool includes sequence generation (allocation bias), allocation sequence concealment (allocation bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other potential sources of bias. Each category was graded as high, low, or unclear risk of bias by two authors reviewing independently. The risk of bias is reported pictorially as a graph as there is no summary score for an overall risk of bias.

Quantitative synthesis was performed with Review Manager (RevMan) software, version 5.3 (Nordic Cochrane Centre, Cochrane Collaboration, 2014). We did not pool RCT data with data from observational studies. In this way, the results may differ from other previously published meta-analyses that used different inclusion criteria or mixed RCT and non-RCT study data. For continuous measures where the SD was not reported in an included study, these were imputed using the methodology recommended by the Cochrane handbook (7). We used random effects modeling for

Table 1. Prespecified search strategy and study selection criteria for use of indwelling pleural catheter versus chemical pleurodesis as first-line management of malignant pleural effusions: MEDLINE (PubMed) search strategy to identify evidence

Step	Concept	Search Term	Result*
1	Malignant pleural effusions	"Pleural Effusion, Malignant/therapy"[Mesh]	1,230
2	Pleural catheter	(pleural catheter [tiab] OR pleural catheter [ot] OR pleural catheters [tiab] OR pleural catheters [ot])	293
3	Pleural drain	Pleurx [tiab] OR pleurx [ot] OR "Pleural port" [tiab] OR "pleural ports" [tiab] OR "pleural port" [ot] OR "pleural ports" [ot] OR "indwelling tunneled catheter" [tiab] OR "indwelling tunneled catheters" [tiab] OR "indwelling tunneled catheter" [ot] OR "indwelling tunneled catheters" [ot] OR Pleural drain [tiab] OR pleural drains [tiab] OR Pleural drain [ot] OR pleural drains [ot]	155
4	Pigtail catheter	((pigtail catheter [tiab] OR pigtail catheters [tiab] OR pig-tail catheter [tiab] OR pig-tail catheters [tiab] OR pigtail catheter [ot] OR pigtail catheters [ot] OR pig-tail catheter [ot] OR pig-tail catheters [ot]) AND (pleura [tiab] OR pleural [tiab] OR pleura [ot] OR pleural [ot] OR effusion [tiab] OR effusions [tiab] OR effusion [ot] OR effusions [ot] OR chylothorax [tiab] OR chylothorax [ot]))	97
5	Indwelling pleural catheter	("Catheters, Indwelling"[Mesh] AND (pleura [tiab] OR pleural [tiab] OR pleura [ot] OR pleural [ot] OR effusion [tiab] OR effusions [tiab] OR effusion [ot] OR effusions [ot] OR chylothorax [tiab] OR chylothorax [ot]))	333
6	Malignant pleural effusion catheter	(Catheters, Indwelling [Mesh]) AND (Pleural Effusion, Malignant [Mesh])	130
7	Pleural drainage	("Drainage/instrumentation"[Mesh] AND (pleura [tiab] OR pleural [tiab] OR pleura [ot] OR pleural [ot] OR effusion [tiab] OR effusions [tiab] OR effusion [ot] OR effusions [ot] OR chylothorax [tiab] OR chylothorax [ot]))	470
8	Small-bore catheter†	(small-bore catheter [tiab] AND (pleura [tiab] OR pleural [tiab] OR pleura [ot] OR pleural [ot] OR effusion [tiab] OR effusions [tiab] OR effusion [ot] OR effusions [ot] OR chylothorax [tiab] OR chylothorax [ot]))	40
9		#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	2,008

Definition of abbreviations: tiab = title/abstract; ot = other term.
Study selection criteria: Studies were selected if they *1*) enrolled patients with known or suspected malignant pleural effusion without nonexpandable lung or prior intervention, *2*) compared patients who underwent indwelling pleural catheter placement versus chemical pleurodesis, and *3*) measured patient-important outcomes. We initially sought published systematic reviews that included trials that met these selection criteria, with the plan to search step-wise for randomized trials and then observational studies if no suitable systematic reviews were identified. If such systematic reviews were identified, we planned to combine the systematic review with relevant studies published after the systematic review. Studies identified in this fashion were to be supplemented with unsystematic observations from the committee members.
*Although the individual searches total 2,748 results, there were 2,008 unique results for step 9.
†The same search terms were adapted to strategies to search Embase, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews.

the meta-analysis. Randomized trials in MPE included small to medium-sized studies (50–200 patients per study) with no single large study and with significant but varying attrition of patients during follow-up. We, therefore, used the random effects model because it weights smaller studies more equally (7). Dichotomous outcomes were reported as relative risk (RR) with 95% confidence interval (CI), and continuous outcomes were reported as mean differences unless otherwise specified. We performed subgroup analysis if an *a priori* subgroup stratification was described in individual studies. We measured heterogeneity using the I^2 statistic. When substantial heterogeneity was identified, we explored possible causes and performed subgroup analysis where possible. Sensitivity analysis was performed when outcomes were not clearly reported in individual studies (e.g., the outcome "infection" could be interpreted as pleural infection or cellulitis).

Results

Study Characteristics

The number of studies identified and screened at each step is documented in Figure 1. The search strategy for the PICO question yielded 10 studies including 1,279 participants. Of the studies identified, five were RCTs (9–13), four were retrospective observational studies (14–17), and one was a prospective observational study (18). The five RCTs enrolling 545 patients were included in the quantitative synthesis. One RCT compared IPC with doxycycline pleurodesis, and four RCTs compared IPC with talc pleurodesis. A summary of characteristics of the randomized and nonrandomized studies is provided in Tables 2 and 3, respectively. Among the randomized studies, two each used PleurX (10, 12) and Rocket (9, 11) brand IPCs, whereas the fifth study did not specify the type of device (13). All trials were small, with the largest sample size being 144 patients. Patients had known malignant or highly suspicious exudative pleural effusions associated with an underlying cancer, most commonly breast or lung cancer, although mesothelioma comprised one-fourth of cases in one study (13). Investigators did not attempt to enroll patients with failed prior pleurodesis or known trapped lung, although some patients were found to have trapped lung after randomization and large-volume drainage. Improvement in dyspnea was the primary outcome in two studies (9, 11), and total hospital days were examined as the primary outcome in two other studies (12, 13). The last study examined recurrence of the pleural effusion, but this outcome was fairly subjective. Because a network meta-analysis showed no differences in the outcome of malignant pleural effusions managed with different chemical agents, we combined results for both talc and doxycycline for the meta-analysis (19).

Study Quality

The risk of bias across studies is shown in Figure 2. Overall, the risk of bias was high,

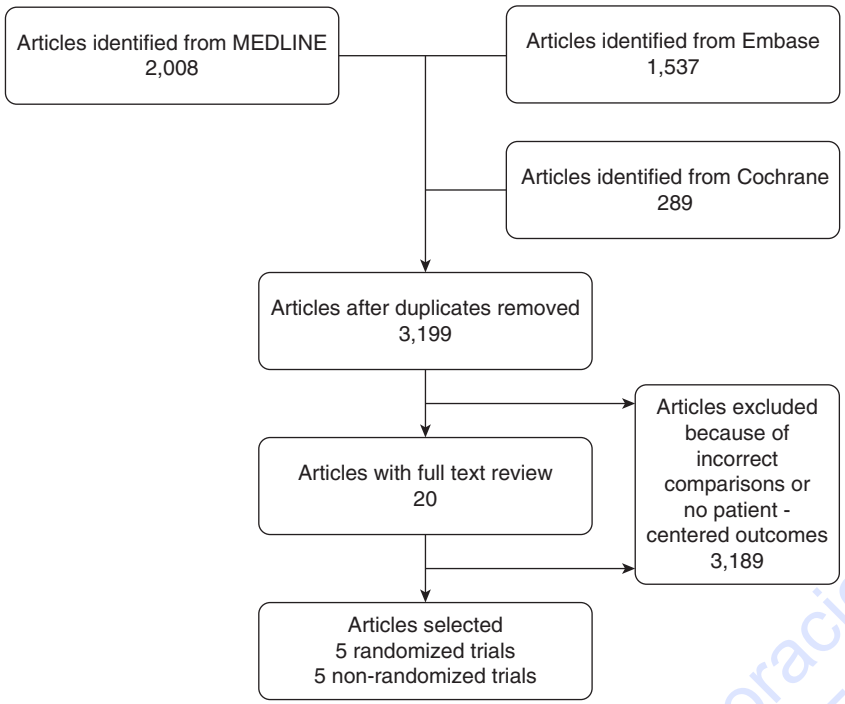

Figure 1. Flow of information through a systematic review examining the use of indwelling pleural catheters versus chemical pleurodesis for the first-line management of malignant pleural effusions.

mainly because of lack of blinding. Attrition of patients due to death also commonly occurred in these studies. Although both the attrition and lack of blinding are not avoidable in this context, they nevertheless lead to increased risk of bias. Because only five RCTs were included in the review, we were not able to use funnel plots to explore possible publication bias.

Dyspnea

Two studies examined dyspnea as a primary outcome. Using a modified Borg score, Boshuizen and colleagues reported improved scores after the initial treatment, but no difference between treatment groups either after the initial treatment or during subsequent follow-up (9). Davies and colleagues reported no difference in visual analog scale scores between groups at 6 weeks (24.7 mm in IPC vs. 24.4 mm in chemical pleurodesis; $P = 0.96$), but there was a significant difference between groups favoring IPC at 6 months (−14.0 mm; 95% CI, −25.2 to −2.8 mm; $P = 0.01$) (11). However, less than one-half of enrolled patients survived to report symptoms at 6 months.

Three studies reported dyspnea as secondary outcomes. The AMPLE study reported visual analog scale scores, whereas Putnam and colleagues reported Borg scores at rest and during exercise; both studies similarly reported improvement in symptoms within groups after the initial treatment, but no significant difference between groups during the follow-up period (12, 13). One article reported Condensed Memorial Symptom Assessment Scale scores and noted differences in scores favoring IPC only after *post hoc* adjustment of covariates (10).

Pooled data for improvement in Borg score did not show any difference between treatment groups at rest or during exercise. The results for this outcome need to be interpreted with caution as the SDs for data from Boshuizen and colleagues were not originally reported and these have been imputed from the *P* values and sample sizes (9). Patient attrition, small sample sizes, and imputation of the SD possibly account for the heterogeneity in these outcomes.

Survival

Median follow-up time varied from 71 to 204 days. Pooled results from two studies did not show any difference in mortality between IPC and pleurodesis groups at 3 months (10, 11). Individually, no study noted a difference between treatment groups in short-term or long-term mortality. Boshuizen and colleagues reported the composite outcome of survival and lack of repeat interventions and found a statistically significant difference at 6 weeks favoring the IPC group (88.7%; 95% CI, 78.8–99.8%) compared with the pleurodesis group (66.2%; 95% CI, 53–82.7%) (9). Demmy and colleagues reported a statistically significant difference in the composite outcome of survival and nonrecurrence of effusion (radiologic) at 1 month favoring the IPC group over the pleurodesis group (82% vs. 52%; $P = 0.02$) (10).

Hospital Length of Stay

Hospital length of stay (LOS) was reported in four studies (9, 11–13), but only one of these studies (13) reported the data in terms of mean (SD) and we were therefore not able to pool results. Two studies examined LOS for the initial therapy as a primary outcome. Thomas and colleagues reported a lower median LOS favoring IPC (difference of 2.92 d; 95% CI, 0.43–5.84), while Putnam also reported a similar difference favoring IPC (median LOS, 1.0 vs. 6.5 d; no range reported) (12, 13).

Two additional studies reported hospital LOS as a secondary outcome. The NVALT-14 study reported fewer median hospital days for patients who underwent IPC compared with chemical pleurodesis (2 vs. 7 d, respectively; $P < 0.001$) (9). The TIME2 authors reported median LOS for initial therapy favoring IPC, with a difference of 3.5 fewer days compared with chemical pleurodesis (95% CI, −4.8 to −1.5), and IPC also resulted in fewer complication-related hospital days up to 1 year (1 vs. 4.5 d; $P < 0.001$) (11).

Need for Further Pleural Interventions

All studies reported a lower frequency of recurrent pleural effusion or need for reintervention in the IPC group. Because the clinical importance of radiologic recurrence of effusion can be variable, we chose to pool data on repeat pleural procedures as a measure of recurrence. Four studies reported the number of repeat ipsilateral pleural procedures performed during follow-up (9, 11–13), and the IPC group required

Table 2. Characteristics of randomized controlled trials included in meta-analysis

Author, Year (Ref.)	Study Acronym	Country	Sample Size		Cancer Types	Chemical Used	Primary Outcome
			IPC	Pleurodesis			
Putnam, 1999 (12)	—	U.S.A.	94	43	Breast, 27% Lung, 40% Other, 33% *Mesothelioma not specified*	Doxycycline	Hospital LOS, dyspnea, quality of life
Davies, 2012 (11)	TIME2	UK	51	52	Breast, 26% Lung, 24% Mesothelioma, 10%; other, 40%	Talc	Dyspnea
Demmy, 2012 (10)	CALGB-30102	U.S.A.	28	29	Breast, 12% Lung, 63% Mesothelioma, 0%; other, 25%	Talc	Reexpansion of lung
Thomas, 2017 (13)	AMPLE	Multinational	73	71	Breast, 12% Lung, 33% Mesothelioma, 26%; other, 29%	Talc	Hospital LOS
Boshuizen, 2017 (9)	NVALT-14	Netherlands	46	48	Breast, 21% Lung, 33% Other, 46% *Mesothelioma not specified*	Talc	Dyspnea

Definition of abbreviations: AMPLE = Australasian Malignant Pleural Effusion; CALGB = Cancer and Leukemia Group B; IPC = indwelling pleural catheter; LOS = length of stay; NVALT-14 = Randomized Trial Comparing Longstanding Indwelling Pleural Catheters with Pleurodesis as a Frontline Treatment for Malignant Pleural Effusion; TIME2 = Second Therapeutic Intervention in Malignant Effusion Trial.

one-third of the repeat procedures compared with the pleurodesis group (RR, 0.32; 95% CI, 0.18–0.55; $P < 0.01$) (Figure 3).

Cellulitis

Four studies examined cellulitis at the tube insertion site. These studies reported a consistently higher risk of skin infection at the insertion site for patients in the IPC group (4, 11–13). Pooled results showed a higher risk of cellulitis with IPC than with chemical pleurodesis (6.9% vs. 0.5%; RR, 5.83; 95% CI, 1.56–21.87), with no evidence of heterogeneity across studies (Figure 3).

One study (NVALT-14) reported adverse events simply as "infection," without specifying either cellulitis or pleural infection. After adding these results, there was no change in the association between IPC and skin infection.

Pleural Infection

Four studies reported pleural infection for patients in both arms (10–13). Pooled results among 369 patients in three of the studies were inconclusive (RR, 3.32; 95% CI, 0.82–13.44). Because the RevMan software calculates weighted relative risks after excluding studies with no events in both arms, we employed an alternative random effects method to that of Mantel-Haenszel to calculate a weighted relative risk for pleural infection, using all four studies (20). With this method, the relative risk of pleural space infection for IPC was not markedly different (RR, 4.87; 95% CI, 0.71–33.52).

Results from NVALT-14 were not included because it reported adverse events simply as "infection," without specifying either cellulitis or pleural infection. After adding these results, there was no change in the association between IPC and pleural infection.

Other outcomes including serious adverse events (grade 3 or 4), chest pain, reexpansion pulmonary edema, and hydro/pneumothorax were not different between the groups. We did not perform subgroup analysis based on type of cancer because none of the studies reported results on the basis of these subgroups.

Discussion

This systematic review and meta-analysis compared the safety and effectiveness of indwelling pleural catheters versus chemical pleurodesis via tube thoracostomy for the initial management of malignant pleural effusions. Pooled data from more than 500 patients across five different studies showed that IPCs were associated with shorter length of procedure-related hospital stay and lower risks of ipsilateral pleural interventions when compared with chemical pleurodesis; conversely, IPCs were associated with a higher risk of cellulitis. There were no differences in dyspnea or survival between the two therapies.

MPE is generally considered to be a manifestation of a malignancy in its preterminal stage. The main goal of care is palliation of symptoms. In our meta-analysis, improvement of dyspnea was noted with both IPC and pleurodesis, and there was no difference between the two interventions for this outcome. However, there were fewer repeat pleural procedures with IPC than pleurodesis. Studies with longer follow-up (12 mo) showed a more marked difference in the need for repeat pleural procedures compared with studies with shorter follow-up (6 wk). In addition, spontaneous

Table 3. Characteristics of nonrandomized trials identified from systematic review

Author, Year (Ref.)	Country	Sample Size		Cancer Types	Chemical Used	Primary Outcome
		IPC	Pleurodesis			
Putnam, 2000 (16)	U.S.A.	100	68	Breast, 23% Lung, 36% Lymphoma, 7% Other, 34% *Mesothelioma not specified*	Doxycycline	Survival, complications, hospital LOS, health care charges
Hunt, 2012 (15)	U.S.A.	59	50	Breast, 14% Lung, 39% Mesothelioma, 18%; other, 29%	Talc poudrage	Fluid accumulation, repeat procedures, hospital LOS
Fysh, 2012 (18)	Australia	34	31	Breast, 17% Lung, 18% Mesothelioma, 46%; other, 19%	Talc	Hospital LOS
Freeman, 2013 (14)	U.S.A.	30	30	Breast, 21% Lung, 33% Mesothelioma, 0%; ovarian, 15%	Talc poudrage	Repeat procedures, performance score
Srour, 2013 (17)	Canada	193	167	Breast, 24% Lung, 43% Mesothelioma, 4%; other, 29%	Talc	Control of effusion

Definition of abbreviations: IPC = indwelling pleural catheter; LOS = length of stay.

pleurodesis was seen in 30–68% of patients in the IPC group. This clear benefit in reduced need for repeat pleural procedures needs to be balanced against the statistically significant increase in cellulitis and an accompanying trend toward an increased risk of pleural infection with the IPC. These data should inform the risk-versus-benefit calculation of IPC as the first-line treatment of MPE.

The RCTs included patients with MPE who likely represent typical patients with MPE, for whom clinicians need guidance regarding management. All cancer types were included and four of the five studies had at least some plan to balance the randomized groups on the basis of cancer type and performance status. The interventions tested in the randomized trials were well defined, and there was not much difference in the type of interventions between studies. Although for some individual outcomes the overall risk of bias was considered "low risk," it is possible that the lack of blinding affected outcomes that relied on patient self-report or physician judgment. Data regarding the decreased need for further pleural interventions need to be taken with caution because of the unblinded nature of the studies. In many institutions, the same clinicians place both IPCs and tube thoracostomies; the investigators may have had a lower threshold of intervening in the chemical pleurodesis

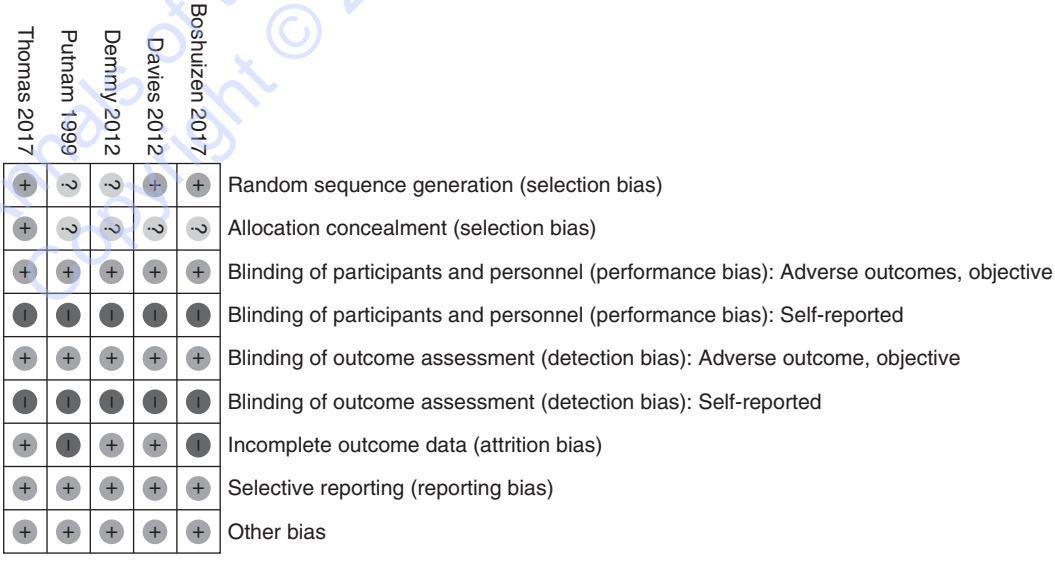

Figure 2. Risk of bias assessment for randomized controlled trials included in the meta-analysis.

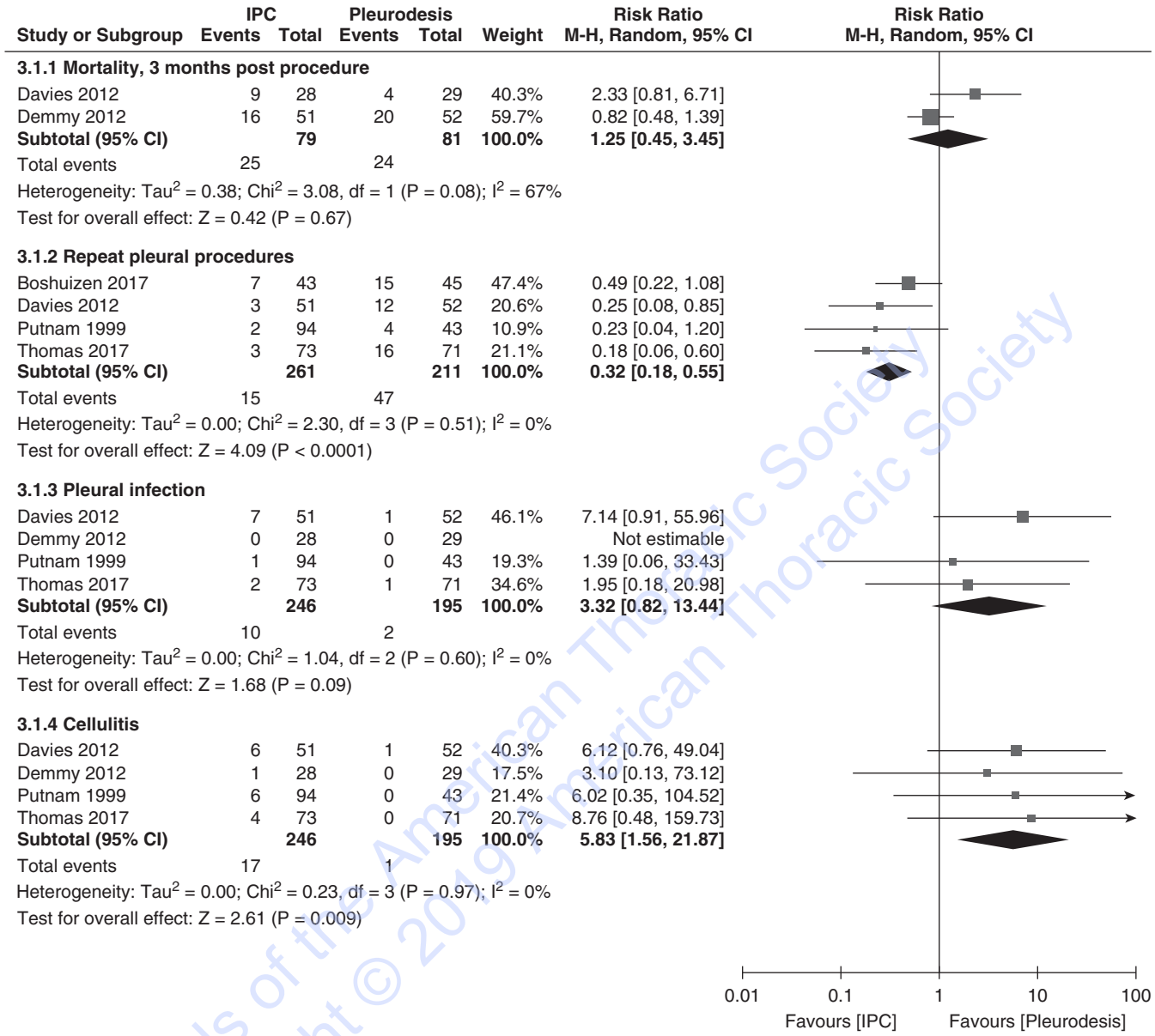

Figure 3. Forest plots and assessments of heterogeneity for select clinical outcomes among randomized controlled trials included in the meta-analysis. CI = confidence interval; IPC = indwelling pleural catheter; M-H = Mantel-Haenszel.

group, especially because several chemical pleurodesis patients underwent IPC placement as a form of further pleural intervention. Alternatively, investigators may have had a higher threshold for performing additional pleural interventions in patients who underwent IPC placement; rather than performing an additional pleural drainage, one study's authors reported readjusting the indwelling IPC in some patients (12). However, proponents of IPCs cite this ability to readjust in lieu of replacing the catheter as one of its advantages over tube thoracostomy.

The results of the meta-analysis may be impacted by future, larger randomized trials. Most outcomes were reported in fewer than 300 patients. With attrition due to early death, longer term outcomes were reported in even fewer patients. Further, outcomes such as hospital LOS and need for repeat procedures are often influenced by local practices and resources. These outcomes are difficult to standardize and subsequently pool in a meta-analysis. Similarly, the clinical importance of outcomes such as cellulitis and pleural infection (requiring administration of intravenous antibiotics on an outpatient basis) are likely to be different in different contexts. Patient preferences and the economic impact of the treatment options also need to be considered when choosing between IPC and pleurodesis. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

References

1 Roberts ME, Neville E, Berrisford RG, Antunes G, Ali NJ; BTS Pleural Disease Guideline Group. Management of a malignant pleural effusion: British Thoracic Society pleural disease guideline 2010. *Thorax* 2010;65:ii32–ii40.

2 American Thoracic Society. Management of malignant pleural effusions. *Am J Respir Crit Care Med* 2000;162:1987–2001.

3 Antony VB, Loddenkemper R, Astoul P, Boutin C, Goldstraw P, Hott J, *et al*. Management of malignant pleural effusions. *Eur Respir J* 2001; 18:402–419.

4 Dresler CM, Olak J, Herndon JE II, Richards WG, Scalzetti E, Fleishman SB, *et al*.; Cooperative Groups Cancer and Leukemia Group B; Eastern Cooperative Oncology Group; North Central Cooperative Oncology Group; Radiation Therapy Oncology Group. Phase III intergroup study of talc poudrage vs talc slurry sclerosis for malignant pleural effusion. *Chest* 2005;127:909–915.

5 Rahman NM, Pepperell J, Rehal S, Saba T, Tang A, Ali N, *et al*. Effect of opioids vs NSAIDs and larger vs smaller chest tube size on pain control and pleurodesis efficacy among patients with malignant pleural effusion: the TIME1 randomized clinical trial. *JAMA* 2015;314:2641–2653.

6 Feller-Kopman DJ, Reddy CB, DeCamp MM, Diekemper RL, Gould MK, Henry T, *et al*. Management of malignant pleural effusions: an official American Thoracic Society/Society of Thoracic Surgeons/Society of Thoracic Radiology clinical practice guideline. *Am J Respir Crit Care Med* 2018;198:839–849.

7 Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions, version 5.1.0 [updated 2011 March; accessed 2018 Oct 27]. The Cochrane Collaboration; 2011. Available from: https://training.cochrane.org/handbook.

8 Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA statement. *J Clin Epidemiol* 2009;62:1006–1012.

9 Boshuizen RC, van der Noort V, Burgers JA, Herder GJM, Hashemi SMS, Hiltermann TJN, *et al*. A randomized controlled trial comparing indwelling pleural catheters with talc pleurodesis (NVALT-14). *Lung Cancer* 2017;108:9–14.

10 Demmy TL, Gu L, Burkhalter JE, Toloza EM, D'Amico TA, Sutherland S, *et al*.; Cancer and Leukemia Group B. Optimal management of malignant pleural effusions (results of CALGB 30102). *J Natl Compr Canc Netw* 2012;10:975–982.

11 Davies HE, Mishra EK, Kahan BC, Wrightson JM, Stanton AE, Guhan A, *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* 2012;307: 2383–2389.

12 Putnam JB Jr, Light RW, Rodriguez RM, Ponn R, Olak J, Pollak JS, *et al*. A randomized comparison of indwelling pleural catheter and doxycycline pleurodesis in the management of malignant pleural effusions. *Cancer* 1999;86:1992–1999.

13 Thomas R, Fysh ETH, Smith NA, Lee P, Kwan BCH, Yap E, *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* 2017;318:1903–1912.

14 Freeman RK, Ascioti AJ, Mahidhara RS. A propensity-matched comparison of pleurodesis or tunneled pleural catheter in patients undergoing diagnostic thoracoscopy for malignancy. *Ann Thorac Surg* 2013;96:259–263; discussion 263–264.

15 Hunt BM, Farivar AS, Vallières E, Louie BE, Aye RW, Flores EE, *et al*. Thoracoscopic talc versus tunneled pleural catheters for palliation of malignant pleural effusions. *Ann Thorac Surg* 2012;94:1053–1057; discussion 1057–1059.

16 Putnam JB Jr, Walsh GL, Swisher SG, Roth JA, Suell DM, Vaporciyan AA, *et al*. Outpatient management of malignant pleural effusion by a chronic indwelling pleural catheter. *Ann Thorac Surg* 2000;69: 369–375.

17 Srour N, Amjadi K, Forster A, Aaron S. Management of malignant pleural effusions with indwelling pleural catheters or talc pleurodesis. *Can Respir J* 2013;20:106–110.

18 Fysh ETH, Waterer GW, Kendall PA, Bremner PR, Dina S, Geelhoed E, *et al*. Indwelling pleural catheters reduce inpatient days over pleurodesis for malignant pleural effusion. *Chest* 2012;142:394–400.

19 Clive AO, Jones HE, Bhatnagar R, Preston NJ, Maskell N. Interventions for the management of malignant pleural effusions: a network meta-analysis. *Cochrane Database Syst Rev* 2016;5:CD010529.

20 Shuster JJ, Guo JD, Skyler JS. Meta-analysis of safety for low event-rate binomial trials. *Res Synth Methods* 2012;3:30–50.