RESEARCH AND GUIDELINE UPDATE

# Cochrane corner: interventions for the management of malignant pleural effusions

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## ABSTRACT

Optimal management of symptomatic malignant pleural effusions remains an important issue as it affects a significant number of patients each year internationally. The overall survival remains poor, necessitating an evidence based treatment strategy that provides the best outcomes for individual patients. This paper summarises the results of the recently published Cochrane review on interventions in malignant pleural effusions.


## INTRODUCTION

Malignant pleural effusion (MPE) is a common clinical problem, affecting around 15% of those with cancer,[1] equating to at least 250 000 people each year in the UK and US combined.[2] The resultant breathlessness it causes can impact on the quality of life of those with advanced malignancy and necessitate repeated invasive procedures to manage their symptoms. The growing number of potential management strategies, including indwelling pleural catheters (IPC), pleurodesis via a chest drain, thoracoscopic delivery of sclerosant and an increasing number of potential pleurodesis agents, has led clinicians to question what the optimal treatment is for this condition.

We performed a multiple interventions systematic review, meta-analyses and network meta-analyses (NMA) to compare alternative management strategies. NMA provides estimates of the relative effects of each pair of interventions in a connected network, including those that have not been directly compared.

## METHODS

Full details of the methods are reported in the original Cochrane publication.[3] Briefly, we systematically reviewed the literature up to May 2015 to identify randomised controlled trials (RCTs) comparing the use of two or more interventions (types of sclerosant, mode of administration or IPC use) in adults with symptomatic MPE. Our primary outcome was pleurodesis failure rate. We also assessed differences in patient-reported outcomes and adverse effects. Two reviewers independently extracted data from the eligible RCTs and completed the Cochrane Risk of Bias Tool.

When two or more studies provided direct evidence on a particular comparison, we pooled across these using pairwise meta-analysis of ORs. Since clinical heterogeneity across studies was anticipated, we used random effects models. Where NMA was assessed to be appropriate, this was performed within a Bayesian statistical framework, and incorporated random effects. In addition to providing OR estimates for all possible pairwise comparisons, the NMA also provides estimates of the rank of each intervention, with 95% credible intervals (Cr-I) reflecting uncertainty about these. Statistical heterogeneity across the network was quantified using the estimated between-studies SD in relative effect estimates. For our primary outcome, we performed a range of sensitivity analyses to assess the robustness of results and whether heterogeneity could be reduced by excluding trials with particular characteristics, such as those at higher risk of bias.

## RESULTS

### Included studies

Our search identified 1888 records, from which 62 eligible RCTs were identified for inclusion in this review. These trials included 3428 patients in total, randomised between 1977 and 2015. Most were small (only five trials presenting data for >100 patients). The majority (39/62) compared alternative sclerosants. The most studied agent was talc, followed by bleomycin and tetracycline. Some studies compared different methods to obtain a pleurodesis (chest drain/thoracoscopy/IPC), while others compared specific aspects of pleurodesis technique, such as chest drain size, duration of drainage or dose of sclerosant. Several methodological differences between studies were identified; for example, pleurodesis failure was measured in a variety of ways (eg, need for repeat intervention vs radiological appearances) or at different follow-up time points.

All studies were assessed to be at high or unclear risk of bias for at least one domain of the Cochrane risk of bias tool. In particular, blinding of participants or personnel was often not possible. A total of 37/62 RCTs included in the study were high risk of bias for two or more of the seven risk of bias domains.

### Main effects of the intervention

Direct evidence on pleurodesis failure rates was available from two or more RCTs for eight pairwise comparisons, and one RCT for 24 comparisons. There was statistical evidence for several differences in pleurodesis effectiveness (see the original Cochrane publication). Heterogeneity between studies making the same comparison was generally low.

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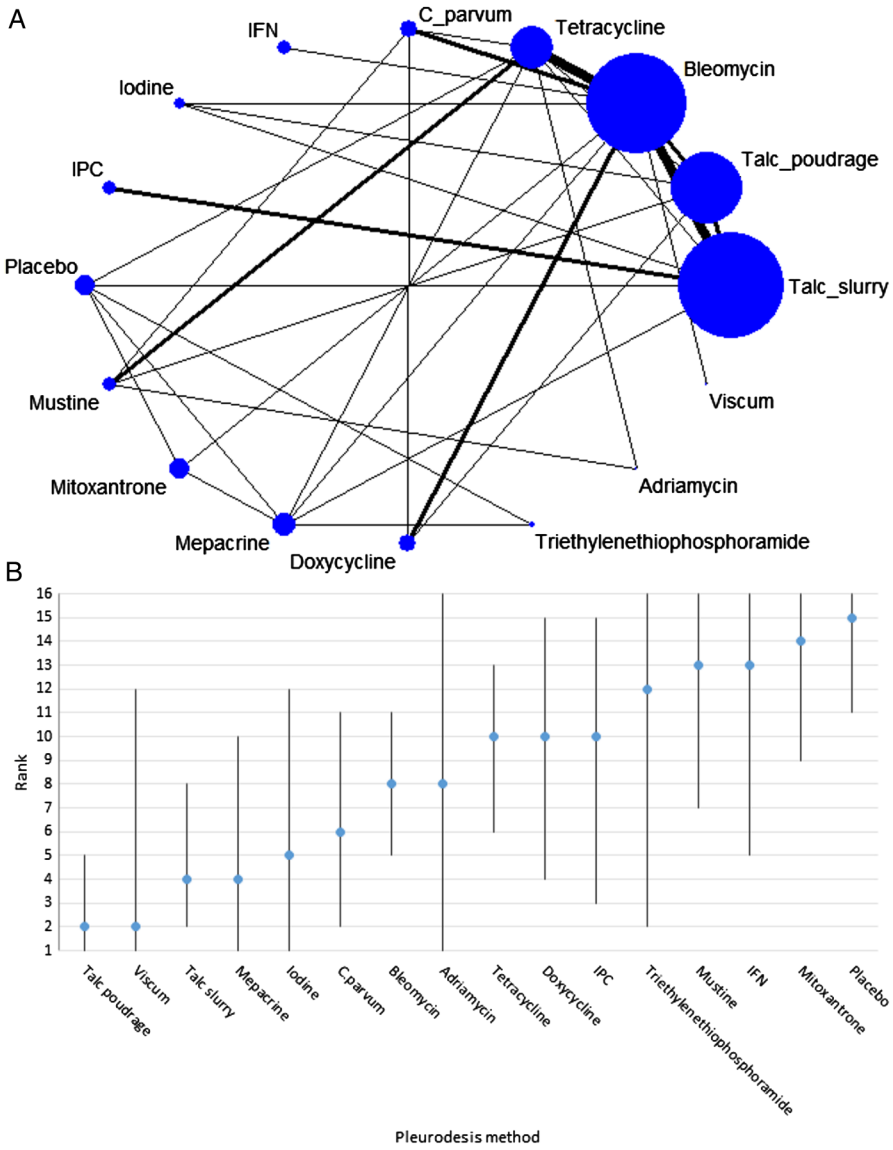


**Figure 1** (A) Network plot of the pleurodesis efficacy network. The nodes are weighted according to the number of patients randomised to the intervention. The edges (line thicknesses) are weighted according to the number of studies included in each comparison. (B) Estimated ranks with 95% Cr-Is for each of the pleurodesis methods.

Figure 1A shows the connected network of evidence on pleurodesis failure. Forty-one RCTs examining 16 interventions were included in the NMA. Estimated ORs for each of the 120 pairwise comparisons are shown in the online supplementary appendix. The estimated ranks in figure 1B provide a summary of this more detailed information. The wide Cr-Is indicate considerable uncertainty about relative ranks. However, talc poudrage appeared to perform relatively well, with an estimated rank of second of 16 (95% Cr-I 1st to 5th), and statistically strong evidence to support it being more effective than bleomycin, tetracycline, interferon, IPC, placebo, mustine, mitoxantrone and doxycycline (see online supplementary appendix).

There was also good evidence that talc slurry (ranked 4th of 16 (95% Cr-I 2 to 8)) was more effective than tetracycline, placebo, mustine and mitoxantrone, and some evidence of it being superior to bleomycin. Talc poudrage was estimated to be more successful than talc slurry, but the evidence was inconclusive (OR for pleurodesis failure=0.42, 95% Cr-I 0.13 to 1.19).

Although *Viscum* might be noted to have a higher estimated rank than talc slurry, the Cr-I for this was too wide to be meaningful (rank 2, 95% Cr-I 1 to 12), which is a consequence of extremely sparse evidence regarding its use. There was evidence that placebo (ranked 15th of 16, 95% Cr-I 11 to 16), mitoxantrone (14th, 95% Cr-I 9 to 16) and, to a lesser extent, mustine (13th, 95% Cr-I 7 to 16) performed relatively poorly.

There was considerable statistical heterogeneity across the network, with a between-studies SD of 0.88 (95% Cr-I 0.42 to 1.48). This estimate was reduced in a sensitivity analysis in which studies assessed to be at high risk of bias for two or more domains were excluded, although the Cr-Is overlapped, indicating uncertainty about this.

We also performed an NMA for pain (17 RCTs, 9 treatments), fever (23 RCTs, 11 treatments) and mortality (20 RCTs, 12 treatments). The pain and mortality networks were sparse, leading to imprecise results and little statistical evidence for any differences between interventions. Analysis suggested that *Corynebacterium parvum* (rank=11th of 11, 95% Cr-I 7 to 11) and mepacrine (rank=10th, 95% Cr-I 6 to 11) might lead to relatively more fever than other treatments, and placebo the least (rank=1st, 95% Cr-I 1 to 7). However, there was again considerable heterogeneity in this network.

For other important patient-centred outcomes, such as breathlessness, quality of life, length of hospital stay and patient acceptability, there was insufficient data to perform NMA. These outcomes were inconsistently reported and measured using a variety of tools.

Full results are available in the original Cochrane review.[3]

## DISCUSSION

This is the largest systematic review to date of evidence for interventions in MPE, and the first to include NMA.

We found that talc poudrage performed relatively well in terms of pleurodesis success rate and was better than a number of alternatives, such as bleomycin and tetracycline. However, the evidence was less conclusive when comparing it with other commonly used methods, such as talc slurry or doxycycline. There was a large amount of uncertainty about the performance of several other interventions due to a sparsity of evidence. Both statistical and clinical heterogeneity across studies was also large. Results were relatively robust to exclusion of sets of studies such as those at higher risk of bias, but it was not feasible to explore the impact of some other variables, such as dose. Other potential reasons for heterogeneity might include varying tumour subtypes, differing definitions of pleurodesis failure and the high risk of bias of many of the studies.

A key assumption of NMA is the consistency of direct and indirect evidence for each comparison. We used approaches described by Dias *et al*[4] to test this assumption. Although there was no evidence of 'global' (overall) inconsistency across the network, we found evidence of inconsistencies in some specific parts of the network: the talc slurry versus bleomycin versus talc poudrage and talc slurry versus bleomycin versus mepacrine loops. We were unable to explain these inconsistencies using reported study characteristics, although our attempts to do so were limited by the small number of studies per direct comparison.

The available data for many other clinically important outcomes, such as quality of life, length of hospital stay and symptom control, were lacking in many of the included studies, precluding formal statistical analysis.

It is important to note that pleurodesis efficacy is only one factor used in the clinical decision making in this patient group and there is an increasing understanding that a variety of factors should be considered when selecting the best treatment for MPE for an individual. A 'one size fits all' approach is somewhat outdated and our hunt for the 'best' pleurodesis technique was likely an oversimplification; different techniques are known to have unique advantages and disadvantages and may thus be suited to different cohorts of patients. Improved understanding of prognostication will help identify appropriate management strategies for an individual, and the potential to combine treatment techniques, and hence benefits, of the varying methods may shape the management of this condition in the future.

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**Contributors** The protocol for the Cochrane review was written collaboratively by all authors. The searches were performed by Jane Hayes and Joanne Abbott. AOC screened the titles and abstracts and obtained the full text papers. AOC and NAM assessed the full text articles for inclusion. AOC, NJP, RB and NAM performed the data extractions. AOC performed data entry and undertook pair-wise comparisons. HEJ performed the network meta-analysis and provided statistical support. AOC drafted the final Cochrane report, which was reviewed and amended by all the authors. The current manuscript has been approved by all the authors.

**Competing interests** AOC was involved in co-ordinating and recruiting to the TIME-3 trial. RB has been the trial co-ordinator for the TAPPS and IPC-Plus studies since 2012 (IPC-Plus; TAPPS) but did not perform the data extractions for these studies for the purposes of this review. NAM is a member of the trial steering committee for TIME-1 and TIME-3 trials. NAM is a co-author for one of the included studies, however, he did not perform the data extractions for this study for the purposes of this review. North Bristol NHS Trust received unrestricted research funding from CareFusion, to run the IPC-Plus trial (IPC-Plus) (2013–2016) for which NM was the chief investigator. NAM also received honoraria from CareFusion for medical advisory board meetings (2013–2015).

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