

# Online Appendix D5      **BTS Guideline for Pleural Disease**

## **Section D              Pleural malignancy**

### **Question D5            Evidence Review and Protocol**

**D5      For adults with malignant pleural effusion (MPE) is thoracoscopy and talc poudrage pleurodesis better than chest drain and talc slurry pleurodesis at improving clinical outcomes?**

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## Question Evidence Review

### D5 For adults with malignant pleural effusion (MPE) is thoracoscopy and talc poudrage pleurodesis better than chest drain and talc slurry pleurodesis at improving clinical outcomes?

#### Background

In adults with malignant pleural effusion (MPE), talc pleurodesis is commonly used to provide long term control of fluid. However, there is debate as to the best way to administer talc. This can either be talc slurry (emulsification of talc in normal saline which is then injected via a chest drain) or poudrage (administration of talc powder as an aerosol during thoracoscopy). Both techniques enable effective delivery of talc to the pleural space, but it has been theorised that talc poudrage may allow better coverage of the pleural space as the talc is directly visualised and may be associated with shorter length of stay as talc is delivered at the same procedure as fluid drainage. However, thoracoscopy is a more invasive procedure.

#### Outcomes

Quality of life, length of hospital stay, need for re-intervention, symptoms (breathlessness, chest pain), complications and pleurodesis rates

#### Evidence Review

From 47 studies identified as potentially relevant in the literature review, five were identified as relevant to the question. Three of these were randomised control trials<sup>1-3</sup> and two were prospective cohort studies<sup>4,5</sup>. It should be noted that talc poudrage was performed under general anaesthetic or conscious sedation as part of video-assisted thoracoscopy surgery (VATS) or medical thoracoscopy, which could also include division of adhesions and pleural biopsies, and talc slurry was given following chest tube insertion and pleural fluid drainage, therefore, differences identified in the outcomes may not be due to the mode of talc administration alone.

#### Quality of life

Quality of life was reported in two studies. Bhatnagar et al used the EuroQoL-5 dimensions-5 levels questionnaire (EQ-5D-5L)<sup>1</sup> and Walker et al used the Function Assessment of Chronic Illness Therapy-Palliative (FACIT-Pal) questionnaire<sup>5</sup>. Data are summarised in [Table D5a](#) and no significance was found between the groups in both studies. Dresler et al used the European Organization for Research and Treatment of Cancer QLQ-C30, but only reported significant subscales.<sup>2</sup>

Table D5a: Quality of life comparison between talc slurry pleurodesis and talc poudrage

Study	QoL tool	Talc Slurry	Talc Poudrage	Significance
		Mean ± SD		
Bhatnagar 2019 <sup>1</sup>	EQ-5D-5L	0.60 ± 0.27	0.60 ± 0.26	NS
		Median (CIs)		
Walker 2016 <sup>5</sup>	FACIT-Pal	0.32 (0.09, 0.54)	0.36 (0.06, 0.66)	NS

EQ-5D-5L – EuroQoL-5 dimensions-5 levels; FACIT-PAL – Functional Assessment of Chronic Illness Therapy – Palliative Care; QoL – quality of life

#### Length of hospital stay

Three studies reported on length of hospital stay. Yim et al and Walker et al reported length of stay following the procedure<sup>3,5</sup> and Bhatnagar reported total number of nights spent in hospital within 90 days<sup>1</sup>. No studies showed a significant difference in length of hospital stay between the two procedures and data are summarised in [Table D5b](#).

Table D5b: Comparison of talc slurry pleurodesis versus talc poudrage on length of hospital stay

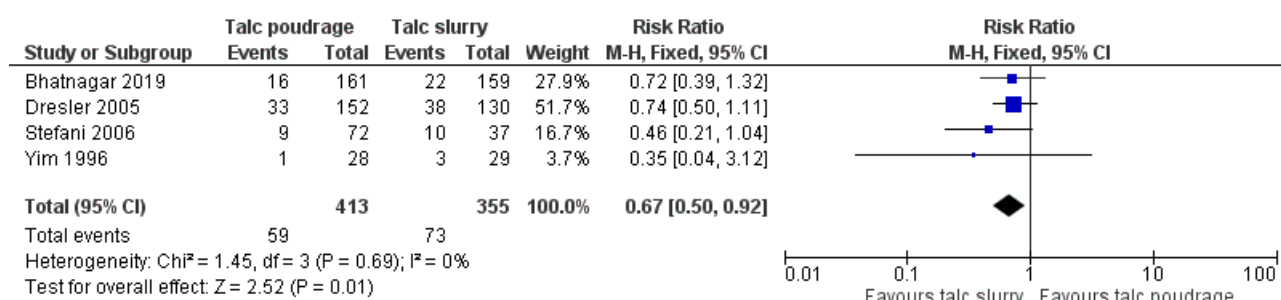
Study	Length of stay (days)		Significance
	Talc Slurry	Talc Poudrage	
	Mean ± SD		
Bhatnagar 2019 <sup>1</sup>	10.8 ± 10.0	12.1 ± 13.0	NS
Yim 1996 <sup>3</sup>	5.8 ± 3.1	7.6 ± 2.8	NS
	Median (range)		
Walker 2016 <sup>5</sup>	10 (5-58)	6 (2-22)	NS

NS – not significant

#### Need for re-intervention and pleurodesis rates

The need for re-intervention and pleurodesis rates data were usually combined. Four studies reported on pleurodesis rate, but different definitions were used between studies. Dresler et al and Stefani et al reported pleurodesis rate as 30 days freedom from radiographic malignant pleural effusion (MPE) recurrence<sup>2,4</sup>, Yim et al reported it as time to failure<sup>3</sup> and Bhatnagar et al reported it as no need for another pleural procedure in the first 30, 90 and 180 days<sup>1</sup>. Meta-analysis of the pleurodesis failure rate at day 30 showed that pleurodesis failure was higher in the talc slurry group ([206 per 1000](#)) than the talc poudrage group ([138 per 1000 \(103 to 189\)](#)) ([Figure D5a](#)).

Figure D5a: Need for re-intervention and pleurodesis rates (talc poudrage versus talc slurry pleurodesis)



#### Symptoms (breathlessness, chest pain)

##### Breathlessness

Two studies also reported on breathlessness. Walker et al used the London Chest Activity of Daily Living scale and reported that both treatments (talc slurry and talc poudrage) suggested a decreasing trend in daily living scale total scores post-treatment, but neither reached significance ( $p = 0.13$  and  $0.06$  respectively) and there was no significant difference between the treatment groups.<sup>5</sup> Bhatnagar et al reported breathlessness using change VAS dyspnoea score from baseline at 7, 30, 90 and 180 days post-treatment, Both groups showed a clinically and statistically important decrease in breathlessness at all time points, with no significant differences between the two treatment groups.<sup>1</sup>

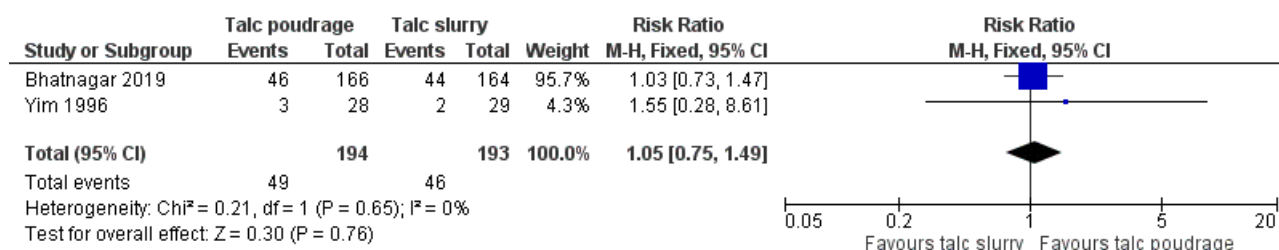
##### Chest pain

Two studies reported on chest pain. Bhatnagar et al reported change in visual analogue scale (VAS) thoracic pain from baseline at days 7, 30, 90, and 180 post-treatment and showed no significant differences between the treatment groups (talc slurry and talc poudrage) at any of the post-treatment time points.<sup>1</sup> In contrast, Dresler et al narratively reported that 10% of talc slurry study arm patients (20/196) experienced chest pain toxicity of at least GRADE 3 (according to National Cancer Institute common toxicity criteria<sup>6</sup>), but only 5% of patients experienced at least the same level of toxicity in the talc poudrage study arm (11/223). Talc poudrage was also perceived to provide more comfort ( $p = 0.019$ ) and a pain control ( $p = 0.07$ ) when compared to talc slurry, but, overall, the incidence of pain did not differ between the two study arms.<sup>2</sup>

## Complications

Complications were reported by Bhatnagar et al, Dresler et al, Stefani et al and Yim et al.<sup>1-4</sup> Only two studies reported on the number of patients who had experienced one, or more complications and meta-analysis of the results showed no difference in the number of patients who are likely to experience one, or more complications between the two treatment groups ([238 per 1000](#) for the talc slurry group and [250 per 1000 \(179 to 355\)](#) for the talc poudrage group).<sup>1,3</sup> ([Figure D5b](#))

Figure D5b: Complications (talc poudrage versus talc slurry pleurodesis)



All studies reported on the total number of complications per treatment group and a summary of the results is shown in [Table D5c](#). Although the meta-analysis suggests that the likelihood of experiencing complications following talc slurry or talc poudrage are very similar, the number of complications per patient appears to be higher in the talc poudrage group.<sup>1-4</sup>

Table D5c: Comparison of number of complications per talc slurry and talc poudrage treatment groups

Study	Talc poudrage		Talc slurry	
	No. complications	No. patients	No. complications	No. patients
Bhatnagar 2019 <sup>1</sup>	143	166	122	164
Dresler 2005 <sup>2</sup>	171	223	118	196
Stefani 2006 <sup>4</sup>	35	72	15	72
Yim 1996 <sup>3</sup>	3	28	2	29
<b>Total across studies</b>	<b>352</b>	<b>489</b>	<b>257</b>	<b>461</b>

Complications associated with chest pain and breathlessness have been excluded

## Evidence statements

There appears to be no difference in health-related quality of life, length of hospital stay, chest pain or breathlessness in adults with malignant pleural effusion (MPE) treated with chest drain and talc slurry or thoracoscopy and talc poudrage (**Ungraded**)

Pleurodesis failure rate appears to be lower in adults who have thoracoscopy and talc poudrage for the treatment of MPE when compared to chest drain and talc slurry (**Low**)

There appears to be no difference in the occurrence of one, or more complications following treatment with chest drain and talc slurry or thoracoscopy and talc poudrage in adults with MPE (**Very low**), but thoracoscopy and talc poudrage may cause an increased number of complications per patient (**Ungraded**)

## Recommendation

- Talc slurry or talc poudrage may be offered to patients with MPE to control fluid and reduce the need or repeated procedures (**Conditional**)

## Good Practice Point

- ✓ Where a diagnostic procedure is being conducted at thoracoscopy (pleural biopsies), if talc pleurodesis is reasonable, this should be conducted during the same procedure via poudrage

## Research Recommendation

- Further research is needed into comparing the clinical outcomes of thoracoscopy (local anaesthetic or VATS) with talc poudrage pleurodesis and chest drain with talc slurry pleurodesis in treating patients with malignant pleural effusion

## Risk of bias summary

	Selection bias	Performance bias	Detection bias	Attrition bias	Publication bias
Bhatnagar 2019	+	?	?	+	+
Dresler 2005	?	?	?	+	+
Stefani 2006	?	?	?	-	+
Walker 2016	?	?	?	?	+
Yim 1996	?	?	?	-	+

## GRADE analyses

**For adults with malignant pleural effusion, is thoracoscopy (local anaesthetic or VATS) and talc poudrage pleurodesis better than chest drain and talc slurry pleurodesis at improving clinical outcomes?**

Population: Adults aged 18+ with malignant pleural effusion

Intervention: Thoracoscopy and talc poudrage

Comparator: Chest drain and talc slurry pleurodesis

Outcome	Number of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects		Quality of the Evidence (GRADE)
			Talc slurry	Talc poudrage	
<b>Pleurodesis rate</b>	768 (4 studies)	RR 0.67 (0.5 to 0.92)	<b>206 per 1000</b>	<b>138 per 1000</b> (103 to 189)	⊕⊕○○ <b>LOW</b> <sup>a,b</sup>
<b>Complications</b>	387 (2 studies)	RR 1.05 (0.79 to 1.34)	<b>238 per 1000</b>	<b>250 per 1000</b> (179 to 355)	⊕○○○ <b>VERY LOW</b> <sup>a,c,d</sup>

CI: Confidence interval

### Explanations

- Non-blinded studies
- Some imprecision, wide CIs, CIs crosses one MID
- Some inconsistency across studies
- Serious imprecision, wide CIs, CIs cross both MIDs

## Recommendation Table

### Question Details

<b>POPULATION:</b>	Adults aged 18+ with malignant pleural effusion
<b>INTERVENTION:</b>	Thoracoscopy and talc poudrage
<b>COMPARISON:</b>	Chest drain and talc slurry pleurodesis
<b>OUTCOMES:</b>	Quality of life; length of hospital stay; need for re-intervention; symptoms (breathlessness, chest pain); complications; pleurodesis rates

### SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	<b>Probably no</b>	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	<b>Small</b>	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	<b>Small</b>	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	<b>Low</b>	Moderate	High			No included studies
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	<b>Does not favour the intervention or the comparison</b>	Probably favours the intervention	Favours the intervention	Varies	Don't know

### TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	<b>Conditional recommendation for either the intervention or the comparison</b>	Conditional recommendation for the intervention	Strong recommendation for the intervention
<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

## CONCLUSIONS

### Recommendation

Talc slurry or talc poudrage may be offered to patients with MPE to control fluid and reduce the need or repeated procedures

### Justification

There appears to be no difference in health-related quality of life, length of hospital stay, chest pain or breathlessness in adults with malignant pleural effusion (MPE) treated with chest drain and talc slurry or thoracoscopy and talc poudrage (**Ungraded**)

Pleurodesis failure rate appears to be lower in adults who have thoracoscopy and talc poudrage for the treatment of MPE when compared to chest drain and talc slurry (**Low**)

There appears to be no difference in the occurrence of one, or more complications following treatment with chest drain and talc slurry or thoracoscopy and talc poudrage in adults with MPE (**Very low**), but thoracoscopy and talc poudrage may cause an increased number of complications per patient (**Ungraded**)

### Subgroup considerations

There was not enough evidence for subgroup consideration (trapped lung, non-trapped lung, unknown)

### Research priorities

Further research is needed into comparing the clinical outcomes of thoracoscopy (local anaesthetic or VATS) with talc poudrage pleurodesis and chest drain with talc slurry pleurodesis in treating patients with malignant pleural effusion

## References

1. Bhatnagar R, Piotrowska HEG, Laskawiec-Szkonter M, et al. Effect of thoracoscopic talc poudrage vs talc slurry via chest tube on pleurodesis failure rate among patients with malignant pleural effusions: a randomized clinical trial. *Jama*. 2019.
2. Dresler CM, Olak J, Herndon JE, 2nd, et al. Phase III intergroup study of talc poudrage vs talc slurry sclerosis for malignant pleural effusion. *Chest*. 2005;127(3):909-915.
3. Yim AP, Chan AT, Lee TW, Wan IY, Ho JK. Thoracoscopic talc insufflation versus talc slurry for symptomatic malignant pleural effusion. *Annals of Thoracic Surgery*. 1996;62(6):1655-1658.
4. Stefani A, Natali P, Casali C, Morandi U. Talc poudrage versus talc slurry in the treatment of malignant pleural effusion. A prospective comparative study. *European Journal of Cardio-Thoracic Surgery*. 2006;30(6):827-832.
5. Walker S, Zubrinic M, Massey C, Shargall Y, Bedard E, Darling G. A prospective study of patient-centred outcomes in the management of malignant pleural effusions. *Int J Palliat Nurs*. 2016;22(7):351-358.
6. *Common toxicity criteria, version 2.0*. Bethesda, MD: National Cancer Institute 1999.

## Question Protocol

Field	Content
Review Question	For adults with malignant pleural effusion, is talc poudrage pleurodesis better than talc slurry pleurodesis at improving clinical outcomes?
Type of review question	Intervention review
Objective of the review	One of a series of questions comparing the standard of care (chest tube and talc slurry) with another intervention. Is medical thoracoscopy and talc poudrage superior?
Eligibility criteria – population / disease / condition / issue / domain	Adults (18+) with malignant pleural effusion
Eligibility criteria – intervention(s)	Talc poudrage pleurodesis
Eligibility criteria – comparators(s)	Talc slurry pleurodesis
Outcomes and prioritisation	Quality of life Length of hospital stay Need for re-intervention Symptoms (breathlessness, chest pain) Complications Pleurodesis rates
Eligibility criteria – study design	RCTs Prospective comparative studies Case series of >100 patients
Other inclusion /exclusion criteria	Non-English language excluded unless full English translation Conference abstracts, Cochrane reviews, systematic reviews, reviews Cochrane reviews and systematic reviews can be referenced in the text, but <b>DO NOT</b> use in a meta-analysis



Proposed sensitivity / subgroup analysis, or meta-regression	Trapped lung Non-trapped lung Unknown
Selection process – duplicate screening / selection / analysis	Agreement should be reached between Guideline members who are working on the question. If no agreement can be reached, a decision should be made by the Guideline co-chairs. If there is still no decision, the matter should be brought to the Guideline group and a decision will be made by consensus
Data management (software)	RevMan5      Pairwise meta-analyses Evidence review/considered judgement. Storing Guideline text, tables, figures, etc.  Gradeprofiler      Quality of evidence assessment Gradepro      Recommendations
Information sources – databases and dates	MEDLINE, Embase, PubMed, Central Register of Controlled Trials and Cochrane Database of Systematic Reviews  1966 - present
Methods for assessing bias at outcome / study level	RevMan5 intervention review template and NICE risk of bias checklist (follow instructions in ' <i>BTS Guideline Process Handbook – Intervention Review</i> ')
Methods for quantitative analysis – combining studies and exploring (in)consistency	If 3 or more relevant studies: RevMan5 for meta-analysis, heterogeneity testing and forest plots (follow instructions in ' <i>BTS Guideline Process Handbook – Intervention Review</i> ')
Meta-bias assessment – publication bias, selective reporting bias	GRADEprofiler      Intervention review quality of evidence assessment for each outcome  (follow instructions in ' <i>BTS Guideline Process Handbook – Intervention Review</i> ')
Rationale / context – what is known	Talc slurry through an intercostal tube remains the standard of care. What is the evidence that informs this practice?