Online Appendix D7 BTS Guideline for Pleural Disease

Section D Pleural malignancy

Question D7 Evidence Review and Protocol

D7 For adults with malignant pleural effusion and non-expandable lung, is pleural aspiration, talc slurry pleurodesis, talc poudrage pleurodesis or decortication surgery better than using an indwelling pleural catheter at improving clinical outcomes?

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Question Evidence Review

D7 For adults with malignant pleural effusion and non-expandable lung, is pleural aspiration, talc slurry pleurodesis, talc poudrage pleurodesis or decortication surgery better than using an indwelling pleural catheter at improving clinical outcomes?

Background

Management of non-expandable lung (NEL) patients can be challenging. Indwelling pleural catheters (IPCs) have become the preferred management technique for these patients, and this review addresses the usefulness of using alternative techniques (pleural aspiration, talc slurry pleurodesis, talc poudrage pleurodesis and decortication surgery) to manage non-expandable lung in malignant pleural disease. There is no well-defined objective definition of what constitutes "non-expandable lung", but for the purposes of this guideline, NEL has been defined on expert group consensus as radiologically significant (with more than 25% of the lung not apposed to the chest wall) based upon chest x-ray appearances. It should be noted that there is significant inter-observer variation in chest radiograph interpretation of the presence of NEL and NEL may be associated with worse prognosis in MPE.[1] NEL may occur because:

i) The visceral pleural is thickened limiting re-expansion, or
ii) There is endobronchial obstruction preventing re-expansion.

Outcomes

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

Evidence Review

1. Pleural aspiration

From 13 studies identified in the literature search, none compared pleural aspiration against indwelling pleural catheter (IPC) to treat malignant pleural effusion in adult patients with non-expandable lung (NEL), but three retrospective case series were deemed relevant to the review.[2-4]

Quality of life

Efthymiou et al retrospectively identified 116 patients undergoing indwelling pleural catheter insertion for non-expandable lung diagnosed intra-operatively during video-assisted thoracoscopic surgery (VATS). Of 48/116 patients able to complete a questionnaire following IPC insertion, 65% were moderately or very satisfied in the improvement in mobility post-procedure.[2]

Length of hospital stay

There was no information available on the effect of pleural aspiration, or IPC at improving length of hospital stay in adult patients with malignant pleural effusion and non-expandable lung.

Need for re-intervention

No study reported on the need for re-intervention.

Symptoms (breathlessness, chest pain)

The questionnaire completed by 48/116 patients in the Efthymiou et al study, following VATS IPC placement for the treatment of non-expandable lung, reported a 'moderate', or 'very satisfied' improvement in breathlessness in 48% of these patients.[2]

Complications

Warren et al retrospectively reviewed 231 IPC procedures, including 28 patients with non-expandable lung, and found that the presence of non-expandable lung was associated with a significantly higher chance of

the IPC being *in situ* for >100 days. The rate of pleural infection was 4.9% and 94% of infections could be controlled with antibiotics (62% by intravenous route).[3]

Pleurodesis rates

Qureshi et al undertook a retrospective review of 52 patients undergoing IPC insertion for trapped lung. Spontaneous pleurodesis occurred in 48% and the average length of time the IPC was *in situ* was 94 days (range 30-255). 94% of patients reported a symptomatic improvement.[4]

2. Talc slurry pleurodesis

The initial literature search identified 37 papers, but no studies directly compared talc slurry pleurodesis against using an IPC. One study compared the administration of sodium chloride (placebo) or talc slurry via an IPC. 14/76 (18%) patients in the sodium chloride group and 16/78 (21%) in the talc group had <25% lung entrapment, but pleurodesis success in the subgroup of patients with NEL was not included.[5]

3. Talc poudrage pleurodesis

The initial literature search identified 35 papers, but no studies directly compared talc poudrage pleurodesis with IPC to treat malignant pleural effusion patients with non-expandable lung.

4. Decortication surgery

The initial literature search identified 18 papers, but no study specifically investigated whether surgical decortication was better at improving clinical outcomes than IPC. However, one retrospective study compared decortication surgery for NEL with no decortication surgery.[6]

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

No data were reported on quality of life, length of hospital stay, need for re-intervention, symptoms (breathlessness, chest pain) or complications.

Pleurodesis rates

Cardillo et al reported 29 patients who underwent decortication surgery, prior to talc pleurodesis, for NEL and had a pleurodesis success rate of 97%. In contrast, a further 15 patients with NEL who did not undergo decortication had a pleurodesis success rate of 13%.[6]

Evidence Statements

Indwelling pleural catheters (IPC) may improve quality of life and breathlessness in malignant pleural effusion patients with non-expandable lung, but may result in the IPC remaining *in situ* for a prolonged period (>100 days). IPC carries a small risk of pleural infection in malignant pleural effusion patients with non-expandable lung (**Ungraded**)

There is no direct evidence to support the use of talc slurry pleurodesis over IPC, but talc slurry pleurodesis may improve quality of life, symptoms and pleurodesis rate in MPE patients with less than 25% lung non-expandable lung (**Ungraded**)

There is no direct evidence to support the use of talc poudrage pleurodesis over IPC in MPE patients with non-expandable lung (**Ungraded**)

Pleurodesis failure rates may increase in MPE patients with non-expandable lung if thoracoscopic decortication is not performed (**Ungraded**)

Recommendations

No recommendations can be made on the use of pleural aspiration, talc slurry pleurodesis, talc poudrage pleurodesis or decortication surgery versus an indwelling pleural catheter to control symptoms in patients with malignant pleural effusion and non-expanded lung.

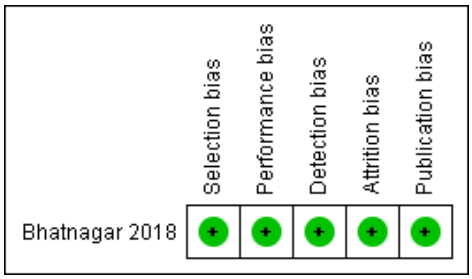
Good Practice Points

- ✓ Decisions on treatment modality for malignant pleural effusion and non-expanded lung should be based on patient choice, with the relative risks and benefits of each modality discussed with the patient, but patients should be made aware of the limited evidence base regarding treatment options for non-expandable lung
- ✓ Indwelling pleural catheters are effective at controlling symptoms in non-expanded lung and should be considered, but it may be appropriate to undertake pleural aspiration first to assess symptomatic response
- ✓ Pleural aspiration may result in a need for multiple procedures so alternatives should be discussed with the patient
- ✓ In patients with radiologically significant (>25%) non-expandable lung requiring intervention for a symptomatic malignant pleural effusion, current evidence suggests the use of an indwelling pleural catheter rather than talc pleurodesis
- ✓ In malignant pleural effusion patients with less than 25% non-expandable lung, talc slurry pleurodesis may improve quality of life, chest pain, breathlessness and pleurodesis rates
- ✓ Decortication surgery may improve pleurodesis success in selected malignant pleural effusion patients with non-expanded lung, but the risks and benefits of IPC and surgical treatment should be discussed with patients, and treatment individualised according to circumstances (for example, fitness to undergo thoracic surgery)

Research Recommendations

- Research is needed into the optimum management pathways for non-expanded lung
- Research is needed on the optimum definition of non-expandable lung, including how radiological abnormalities relate to symptoms and outcomes.
- Research is needed on the impact of talc slurry pleurodesis on patient reported outcome measures in patients with minimal non-expandable lung (e.g. <25%)
- Research is required as to a non-invasive method (other than pleural aspiration and a subsequent chest x-ray) for identifying non-expandable lung prior to intervention

Risk of bias summary



References

1. Martin GA, Kidd AC, Tsim S, et al. Inter-observer variation in image interpretation and the prognostic importance of non-expansile lung in malignant pleural effusion. *Respirology.* 2020;25(3):298-304.
2. Efthymiou CA, Masudi T, Thorpe JA, Papagiannopoulos K. Malignant pleural effusion in the presence of trapped lung. Five-year experience of PleurX tunnelled catheters. *Interact Cardiovasc Thorac Surg.* 2009;9(6):961-964.
3. Warren WH, Kim AW, Liptay MJ. Identification of clinical factors predicting Pleurx catheter removal in patients treated for malignant pleural effusion. *Eur J Cardiothorac Surg.* 2008;33(1):89-94.
4. Qureshi RA, Collinson SL, Powell RJ, Froeschle PO, Berrisford RG. Management of malignant pleural effusion associated with trapped lung syndrome. *Asian Cardiovasc Thorac Ann.* 2008;16(2):120-123.
5. Bhatnagar R, Keenan EK, Morley AJ, et al. Outpatient talc administration by indwelling pleural catheter for malignant effusion. *N Engl J Med.* 2018;378(14):1313-1322.
6. Cardillo G, Facciolo F, Carbone L, et al. Long-term follow-up of video-assisted talc pleurodesis in malignant recurrent pleural effusions. *Eur J Cardiothorac Surg.* 2002;21(2):302-305; discussion 305-306.

Question Protocols

1. Pleural aspiration versus indwelling pleural catheter (IPC)

Field	Content
Review Question	For adults with malignant pleural effusion and non-expandable lung, is pleural aspiration better than using an indwelling pleural catheter at improving clinical outcomes?
Type of review question	Intervention review
Objective of the review	For patients who are known to have non-expandable lung, is it better to insert an indwelling pleural catheter, or repeatedly aspirate?
Eligibility criteria – population / disease / condition / issue / domain	Adults (18+) with malignant pleural effusion and non-expandable lung
Eligibility criteria – intervention(s)	Pleural aspiration
Eligibility criteria – comparators(s)	Indwelling pleural catheter (IPC)
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 **DO NOT** use in a meta-analysis

Proposed sensitivity / subgroup analysis, or meta-regression	None
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 '*BTS Guideline Process Handbook – Intervention Review'*)
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 '*BTS Guideline Process Handbook – Intervention Review'*)
Meta-bias assessment – publication bias, selective reporting bias	GRADEprofiler — Intervention review quality of evidence assessment for each outcome (follow instructions in '*BTS Guideline Process Handbook – Intervention Review'*)
Rationale / context – what is known	Indwelling catheters are often used in the presence of non-expandable lung. Is there any evidence for this use?

2. Talc slurry pleurodesis versus IPC

Field	Content
Review Question	For adults with malignant pleural effusion and non-expandable lung, is talc slurry pleurodesis better than using an indwelling pleural catheter at improving clinical outcomes?
Type of review question	Intervention review
Objective of the review	For patients with MPE who are known to have non-expandable lung, is it better to have a talc slurry pleurodesis rather than an indwelling pleural catheter?
Eligibility criteria – population / disease / condition / issue / domain	Adults (18+) with malignant pleural effusion and non-expandable lung
Eligibility criteria – intervention(s)	Talc slurry pleurodesis
Eligibility criteria – comparators(s)	Indwelling pleural catheter (IPC)
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 **DO NOT** use in a meta-analysis

Proposed sensitivity / subgroup analysis, or meta-regression	None
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
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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 '*BTS Guideline Process Handbook – Intervention Review'*)
Meta-bias assessment – publication bias, selective reporting bias	GRADEprofiler — Intervention review quality of evidence assessment for each outcome (follow instructions in '*BTS Guideline Process Handbook – Intervention Review'*)
Rationale / context – what is known	Indwelling catheters are often used in the presence of non-expandable lung but occasionally if the lung is not completely trapped talc slurry may be used. Is there any evidence for this use?

3. Talc poudrage pleurodesis versus IPC

Field	Content
Review Question	For adults with malignant pleural effusion and non-expandable lung, is talc poudrage pleurodesis better than using an indwelling pleural catheter at improving clinical outcomes?
Type of review question	Intervention review
Objective of the review	For patients with MPE who are known to have non-expandable lung, is it better to have a talc poudrage pleurodesis rather than an indwelling pleural catheter?
Eligibility criteria – population / disease / condition / issue / domain	Adults (18+) with malignant pleural effusion and non-expandable lung
Eligibility criteria – intervention(s)	Talc poudrage pleurodesis
Eligibility criteria – comparators(s)	Indwelling pleural catheter (IPC)
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 **DO NOT** use in a meta-analysis
Proposed sensitivity / subgroup analysis, or meta-regression	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
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 '*BTS Guideline Process Handbook – Intervention Review'*)
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 '*BTS Guideline Process Handbook – Intervention Review'*)
Meta-bias assessment – publication bias, selective reporting bias	GRADEprofiler — Intervention review quality of evidence assessment for each outcome (follow instructions in '*BTS Guideline Process Handbook – Intervention Review'*)
Rationale / context – what is known	Indwelling catheters are often used in the presence of non-expandable lung but occasionally if the lung is not completely trapped talc poudrage may be used. Is there any evidence for this use?

4. Decortication surgery versus IPC

Field	Content
Review Question	For adults with malignant pleural effusion and non-expandable lung, is decortication surgery better than using an indwelling pleural catheter at improving clinical outcomes?
Type of review question	Intervention review
Objective of the review	Indwelling catheters are often used in the presence of non-expandable lung but occasionally decortication surgery is offered. Is there any evidence for this use?
Eligibility criteria – population / disease / condition / issue / domain	Adults (18+) with malignant pleural effusion and non-expandable lung
Eligibility criteria – intervention(s)	Surgery (decortication)
Eligibility criteria – comparators(s)	Indwelling pleural catheter (IPC)
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 **DO NOT** use in a meta-analysis

Proposed sensitivity / subgroup analysis, or meta-regression	Mesothelioma patients Non mesothelioma malignancy
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 '*BTS Guideline Process Handbook – Intervention Review'*)
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 '*BTS Guideline Process Handbook – Intervention Review'*)
Meta-bias assessment – publication bias, selective reporting bias	GRADEprofiler — Intervention review quality of evidence assessment for each outcome (follow instructions in '*BTS Guideline Process Handbook – Intervention Review'*)
Rationale / context – what is known	Indwelling catheters and decortication have been used as treatments for symptomatic non-expandable lung in MPE, but is there any evidence that one is better than the other?