Online Appendix B2 BTS Guideline for Pleural Disease

Section B Investigation of the undiagnosed pleural effusion

Question B2 Evidence Review and Protocol

B2 For adults with suspected unilateral pleural effusion, is image-guided intervention better than non-image-guided intervention at improving clinical outcomes?

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Question Evidence Review

B2 For adults with suspected unilateral pleural effusion, is image-guided intervention better than non-image-guided intervention at improving clinical outcomes?

Background

Thoracentesis (pleural aspiration) is a key intervention for both diagnostic and therapeutic purposes in the investigation and management of the patient with a unilateral pleural effusion. The use of thoracic ultrasound immediately prior to pleural intervention for suspected fluid has been strongly advocated as a means of improving patient safety by reducing the frequency of iatrogenic complications and improving diagnostic yield. This is different to the temporally and geographically remote use of thoracic ultrasound prior to pleural intervention, also known as the "X marks the spot" technique. The aim of this review was to assess whether image-guided (i.e. ultrasound assisted techniques where the anatomy is confirmed on ultrasound and an intervention is immediately conducted and "real time" or ultrasound guided where needles are watched under ultrasound in to the pleural space) intervention had better clinical outcomes when compared to non-image-guided intervention in adult patients with suspected unilateral pleural effusion.

Outcomes

Complications (bleeding/pneumothorax), success of obtaining pleural fluid, need for another procedure, time in hospital and mortality

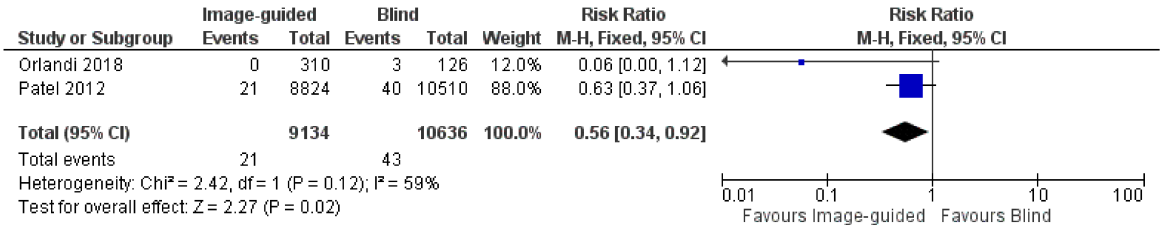
Evidence Review

The initial literature search identified 31 papers of which seven were deemed relevant. These included two randomised controlled trials[1,2] and five retrospective cohort studies[3-7]. All seven papers used ultrasound as the imaging modality to guide subsequent thoracentesis.

Complications – bleeding

Two papers reported rates of iatrogenic haemorrhage (bleeding) when comparing image-guided thoracentesis against non-image guided thoracentesis. Meta-analysis revealed there was a reduced risk of bleeding with an image-guided intervention (2 per 1000 patients (1 to 4)) compared to a non-image-guided intervention (4 per 1000 patients) (Figure B2a).[3,4]

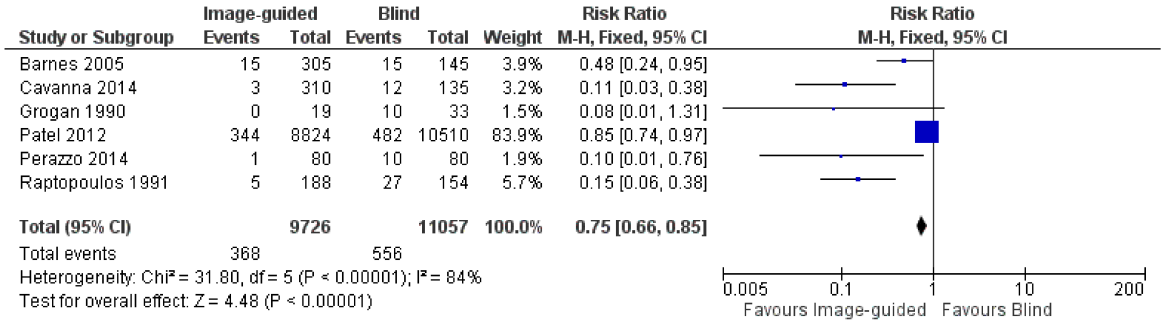
Figure B2a: Complications – bleeding (image-guided intervention versus non-image-guided intervention)



Complications – pneumothorax

All relevant papers reported rates of iatrogenic pneumothorax, but one paper was excluded[3] as the results were taken from the same population studied in another paper (Cavanna *et al.*, 2014) already included in the analysis[6]. Meta-analysis of the remaining studies revealed less risk of pneumothorax with an image-guided intervention (38 per 1000 patients (33 to 43) than with a non-image-guided intervention (50 per 1000 patients) (Figure B2b).[1,4-8]

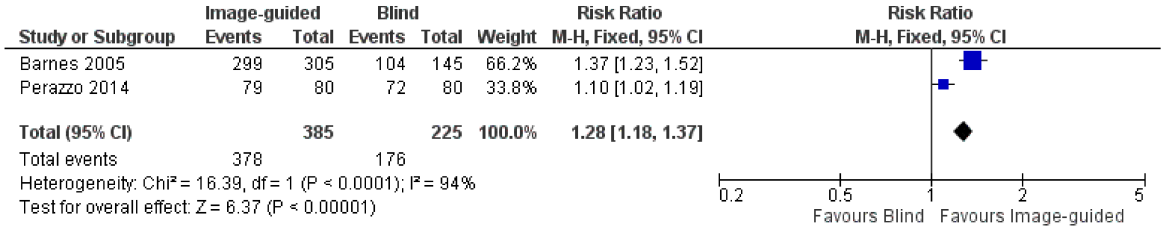
Figure B2b: Complications – pneumothorax (image-guided intervention versus non-image-guided intervention)



Success of obtaining pleural fluid

Two studies reported on the success of obtaining pleural fluid and meta-analysis of the results revealed that those undergoing image-guided thoracentesis were more likely to have successful pleural fluid removal (1000 per 1000 patients (923 to 1000)) compared with 782 patients per 1000 undergoing non-image guided thoracentesis (Figure B2c).[1,5]

Figure B2c: Success of obtaining pleural fluid (image-guided intervention versus non-image-guided intervention)



Need for another procedure

No studies reported on the need for another procedure.

Time in hospital

Patel et al. reported on the length of hospital stay with and without ultrasound. Data were presented as unadjusted and adjusted (using a multivariate linear regression model to adjust for demographic and hospital variables). Although the adjusted data were significantly different, the difference in length of stay between the two procedures was not clinically relevant. The data are summarised in Table B2a.[4]

Table B2a: Comparison of hospital stay for image-guided and non-image-guided thoracentesis

	Length of hospital stay (mean ± SD days)		
	Image-guided	**Non-image guided**	***p***
Unadjusted	7.3 ± 5.8	7.7 ± 6.3	NS
Adjusted	7.5 ± 2.6	7.6 ± 2.7	<0.0001

NS – not significant

Mortality

No studies reported on mortality.

Additional Information

Two publications relating to complications arising from thoracentesis were expected but did not appear in the literature search for this review.[9,10] Further inspection revealed that both papers had been indexed under the MeSH term “pneumothorax” rather than “pleural effusion”. It is noted that both publications would have supported the evidence statements and recommendations in this review.

Evidence statements

The use of ultrasound guidance immediately prior to thoracentesis reduces the risk of pneumothorax when compared to non-image guided thoracentesis (**Very low**)

Image-guided thoracentesis reduces the risk of pneumothorax when compared to non-image guided thoracentesis (**Very low**)

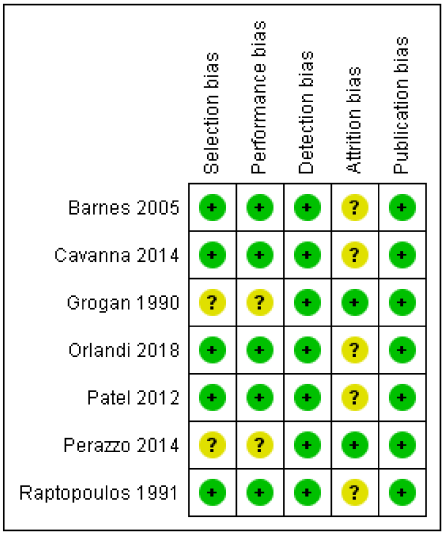
Image-guided thoracentesis improves the rate of successful fluid sampling when compared to non-image guided thoracentesis (**Very low**)

Length of hospital stay is not reduced if choosing image-guided thoracentesis over non-image guided thoracentesis (**Ungraded**)

Recommendation

- Image-guided thoracentesis should always be used to reduce the risk of complications (**Strong** – by consensus)

Risk of bias summary



GRADE analyses

For adults with suspected unilateral pleural effusion, is image-guided intervention better than non-image-guided intervention at improving clinical outcomes?

Population: Adults with unilateral pleural effusion, 18+

Intervention: Image-guided intervention

Comparator: Non-image-guided intervention

Outcome	Number of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects		Quality of the Evidence (GRADE)
			Blind	Image-guided	
Pneumothorax	20783 (6 studies)	RR 0.25 (0.10 to 0.63)	**50 per 1000**	**13 per 1000** (5 to 32)	⨁◯◯◯ **VERY LOW** [a,b]
Haemorrhage	19770 (2 studies)	RR 0.56 (0.34 to 0.92)	**4 per 1000**	**2 per 1000** (1 to 4)	⨁◯◯◯ **VERY LOW** [b,c]
Success of obtaining pleural fluid	610 (2 studies)	RR 1.28 (1.18 to 1.37)	**782 per 1000**	**1000 per 1000** (923 to 1000)	⨁◯◯◯ **VERY LOW** [b]

CI: Confidence interval

Explanations

a. Serious inconsistency, I_2=84%
b. Some imprecision, CIs cross one MID
c. Some inconsistency, I_2=59%

References

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3. Orlandi E, Citterio C, Seghini P, Di Nunzio C, Mordenti P, Cavanna L. Thoracentesis in advanced cancer patients with severe thrombocytopenia: Ultrasound guide improves safety and reduces bleeding risk. *Clinical Respiratory Journal.* 2018;12(4):1747-1752.
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6. Cavanna L, Mordenti P, Berte R, et al. Ultrasound guidance reduces pneumothorax rate and improves safety of thoracentesis in malignant pleural effusion: report on 445 consecutive patients with advanced cancer. *World Journal of Surgical Oncology.* 2014;12:139.
7. Raptopoulos V, Davis LM, Lee G, Umali C, Lew RI, rwin RS. Factors affecting the development of pneumothorax associated with thoracentesis. *AJR Am J Roentgenol.* 1991;156(5):917-920.
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9. Mercaldi CJ, Lanes SF. Ultrasound guidance decreases complications and improves the cost of care among patients undergoing thoracentesis and paracentesis. *Chest.* 2013;143(2):532-538.
10. Gordon CE, Feller-Kopman D, Balk EM, Smetana GW. Pneumothorax following thoracentesis: a systematic review and meta-analysis. *Arch Intern Med.* 2010;170(4):332-339.

Question Protocol

Field	Content
Review Question	For adults with suspected unilateral pleural effusion, is image guided intervention better than non-image guided intervention at improving clinical outcomes?
Type of review question	Intervention review
Objective of the review	To assess the data addressing the safety and accuracy of image guided (ultrasound, CT intervention (aspiration, biopsy) compared with non-image guided intervention
Eligibility criteria – population / disease / condition / issue / domain	Adults with unilateral pleural effusion, 18+
Eligibility criteria – intervention(s)	Image guided (CT or ultrasound)
Eligibility criteria – comparators(s)	Blind (not image guided)
Outcomes and prioritisation	Complications (bleeding /pneumothorax) Success of obtaining pleural fluid Need for another procedure Time in hospital Mortality
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	Ultrasound increases safety and procedure accuracy for pleural effusion. CT guided biopsy increases yield compared with blind pleural biopsy. Little evidence in last BTS guidelines – any new good quality data?