Online Appendix C3 BTS Guideline for Pleural Disease

Section C Pleural infection

Question C3 Evidence Review and Protocol

C3 For adults with established pleural infection, what initial drainage strategy provides the best clinical outcomes?

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Question Evidence Review

C3 For adults with established pleural infection, what initial drainage strategy provides the best clinical outcomes?

Background

The adequate drainage of infected fluid and material from the pleural space in order to achieve source control is a cornerstone of the initial management of pleural infection. There are a number of means by which the infected pleural fluid may be removed, ranging from simple percutaneous aspiration or drainage via chest tube to more invasive surgical measures. Hence this review assesses which approach to drainage of the infected pleural space is the most successful at improving clinical outcomes.

Outcomes

Mortality, need for repeat intervention, surgery, quality of life, patient symptoms, length of hospital stay and complications

Evidence review

The initial literature search identified 41 papers for review, but closer inspection revealed substantial heterogeneity in the studies meaning that meta-analysis would not be possible. A pragmatic approach was therefore adopted, taking a narrative approach to answer key questions with the data available.

Six relevant studies included one post-hoc randomised controlled trail (RCT)[1], two assumed prospective studies (no *a priori* power calculation or agreement on outcome interpretation provided)[2,3] and three retrospective cohorts[4-6]. These studies compared small bore (≤14F) chest tube drainage versus large bore (>14F) chest tube drainage[1], chest tube drainage versus drainage under video-assisted thoracoscopic surgery (VATS)[2,4], chest tube drainage versus drainage under VATS or drainage under open thoracotomy[5], chest tube drainage (with or without streptokinase) versus drainage under VATS or drainage under open thoracotomy[6] and large bore (36F) chest tube drainage plus intrapleural streptokinase versus drainage under VATS[3].

Limitations to the presented data

When interpreting the data it should be noted that Metin et al focused on class V empyema per Light's classification[7], and hence may not have included all patients presenting with pleural infection over the study period, and that 16/114 (14.0%) patients included in the study had tuberculous empyema[4]. Similarly, 28/104 (26.9%) patients in the Wozniak et al study presented with either post-surgical or post-traumatic empyema or 15/104 (14.4%) appeared to have simple parapneumonic effusions (described as free flowing with pleural fluid pH >7.3) as opposed to true pleural infection.[6] Finally, in the Semenkovich et al study, the population of patients initially managed with chest tube drainage were significantly older with a higher frequency of co-morbidities than the surgical population and hence there is a risk of treatment selection bias with a more conservative approach taken in patients not thought to be well enough for surgery and therefore already likely to have a worse outcome from their pleural infection.[5]

No studies compared medical thoracoscopic drainage against either simple chest tube or surgical (VATS or open thoracotomy) drainage. However, Bilgin et al performed 29/35 (82.9%) VATS procedures under analgo-sedation rather than a general anaesthetic, although these remained procedures led by a thoracic surgeon as opposed to a physician.[2]

Mortality

Five studies reported on mortality across different drainage strategies, and a summary of the results is shown in Table C3a.[1-5]

Table C3a: Comparison of mortality rate following different drainage strategy protocols for the treatment of pleural infection in adults

Study	**Mortality rate** (no. patients)				p
	Chest tube drainage, bore size comparison				
	<10F	*10-14F*	*15-20F*	*>20F*	
Rahman 2010[1]	17% (10/58)	22% (46/208)	25% (18/70)	25% (17/69)	0.67
	Chest tube drainage		*Surgical drainage*		
			VATS	*Thoracotomy*	
Bilgin 2006[2]	3% (1/35)		0% (0/35)	-	NR
Semenkovich 2018[5]	21% (322/1563)		6% (83/1313)	4% (47/1219)	<0.001
	- Streptokinase	*+ Streptokinase*			
Metin 2010[4]	4% (2/47)	0% (0/23)	0% (0/44)	-	NA
Wait 1997[3]	-	11% (1/9)	9% (1/11)	-	NR

NA – not applicable; NR – not reported; VATS – video-assisted thoracoscopic surgery

Need for repeat intervention

Three studies reported on the need for repeat intervention. Two studies compared the need for repeat intervention following chest tube drainage or surgical drainage (thoracotomy and/or VATS)[5,6] and the third study compared the need for repeat intervention following chest tube drainage, with or without streptokinase fibrinolytic therapy, versus VATS surgical drainage[4] (Table C3b).

Table C3b: Comparison of the need for repeat intervention following different drainage strategy protocols for the treatment of pleural infection in adults

Study	**Rate of need for repeat intervention** (no. patients)				p
	Chest tube drainage		*Surgical drainage*		
			VATS	*Thoracotomy*	
Wozniak 2009[6]	56% (28/50)		13% (7/54)	-	<0.001
Semenkovich 2018[5]	9% (113/1563)		3% (37/1313)	4% (45/1219)	<0.001
	- Streptokinase	*+ Streptokinase*			
Metin 2010[4]	36% (17/47)	0% (0/23)	0% (0/44)	-	<0.001

VATS – video-assisted thoracoscopic surgery

Surgery

Four studies also reported on the need for thoracic surgery following chest tube drainage or surgical drainage and the results are summarised in Table C3c.[1-3,5]

Quality of life and patient symptoms

No studies reported on quality of life or patient symptoms.

Table C3c: Comparison of the need for thoracic surgery following different drainage strategy protocols for the treatment of pleural infection in adults

Study	**Rate of need for thoracic surgery** (no. patients)				***p***
	Chest tube drainage, bore size comparison				
	<10F	*10-14F*	*15-20F*	*>20F*	
Rahman 2010[1]	19% (11/58)	17% (35/208)	19% (13/70)	19% (13/69)	0.97
	Chest tube drainage		*Surgical drainage*		
			VATS	*Thoracotomy*	
Bilgin 2006[2]	37% (13/35)		17% (6/35)	-	<0.05
Semenkovich 2018[5]	48% (1342/2780)		40% (300/758)	4% (47/1219)	NR
	- Streptokinase	*+ Streptokinase*			
Wait 1997[3]	-	56% (5/9)	0% (0/11)	-	0.05

NR – not reported; VATS – video-assisted thoracoscopic surgery

Length of hospital stay

Length of hospital stay following chest tube drainage or surgical drainage was reported in five studies and a summary of the results is shown in Table C3d.[1-5]

Table C3d: Comparison of length of hospital stay following different drainage strategy protocols for the treatment of pleural infection in adults

Study	**Length of hospital stay** (days) (mean ± SD, median [range] or mean [range]†)				***p***
	Chest tube drainage, bore size comparison				
	<10F	*10-14F*	*15-20F*	*>20F*	
Rahman 2010[1]	26 ± 29	24 ± 32	31 ± 39	28 ± 23	0.37
	Chest tube drainage		*Surgical drainage*		
			VATS	*Thoracotomy*	
Bilgin 2006[2]	12.8 [12-18] †		8.3 [7-11] †	-	<0.05
Semenkovich 2018[5]	14 [9-22]		12 [9-19]	15 [10-21]	<0.001
	- Streptokinase	*+ Streptokinase*			
Metin 2010[4]	13 ± 4	11 ± 3	3 ± 1	-	<0.001*
Wait 1997[3]	-	12.8 ± 1.1	8.7 ± 0.9	-	0.009

* Chest tube drainage with streptokinase or chest tube drainage without streptokinase versus surgical drainage under VATS, chest tube drainage with streptokinase versus chest tube drainage without streptokinase, p = 0.209

† Bilgin 2006 data presented as mean [range]

VATS – video-assisted thoracoscopic surgery

Complications

Finally, four studies reported on post-treatment complications following chest tube drainage or surgical drainage[1-4] and complications included bronchopleural fistula[2], air space, air leak >5 days, atelectasis, bleeding, air-fluid level, wound infection[4] and pain[1]. A summary of the data is shown in Table C3e.

Table C3e: Comparison post-treatment complications following different drainage strategy protocols for the treatment of pleural infection in adults

Study	Complications				*p*
	Chest tube drainage, bore size comparison (median pain score [range]}				
	<10F	*10-14F*	*15-20F*	*>20F*	
Rahman 2010[1]	6 [4-7]	5 [4-6]	6 [5-7]	6 [6-8]	0.008
	Chest tube drainage		*Surgical drainage*		
			VATS	*Thoracotomy*	
Bilgin 2006[2]	0% (0/35)*		3% (1/35)*	-	NR
	- Streptokinase	*+ Streptokinase*			
Metin 2010[4]	23 (47)†	9 (23)†	3 (44)†	-	<0.001
Wait 1997[3]	-	11% (1/9)*	0% (0/11)*	-	NR

* Rate of patients experiencing one or more complications (no. patients)

† Number of complications reported (no. patients)

NR – not reported; VATS – video-assisted thoracoscopic surgery

Evidence statements

Based on the limited evidence, which may include selection bias:

Chest tube bore size appears to have no effect on mortality rate, the need for post-treatment thoracic surgery, or the length of hospital stay following chest tube drainage to treat pleural infection in adults, but bore size >14F may increase post-treatment pain (**Ungraded**)

Drainage under video-assisted thoracoscopic surgery (VATS) or open thoracotomy appears to reduce mortality, the need for repeat intervention, and the length of hospital stay when compared with standard chest tube drainage for the treatment of pleural infection in adults (**Ungraded**)

Recommendation

➢ Initial drainage of pleural infection should be undertaken using a small bore chest tube (14F or smaller) (**Conditional** - by consensus)

Good Practice Points

✓ Due to the lack of supporting evidence, early surgical drainage under VATS or thoracotomy should not be considered over chest tube ("medical") drainage for the initial treatment of pleural infection

✓ Due to lack of supporting evidence, medical thoracoscopy should not be considered as initial treatment for pleural infection

Research Recommendations

- Further research, using robust methodology with a prospective, randomised study design, is needed into determining whether initial chest tube drainage or surgical drainage is better for the treatment of pleural infection in adults
- Further research is needed into the feasibility and role of medical thoracoscopic drainage for pleural infection

Risk of bias summary

	Selection bias	Performance bias	Detection bias	Attrition bias	Publication bias
Bilgin 2006	+	?	?	+	+
Metin 2010	–	?	?	–	+
Rahman 2010	+	+	+	+	+
Semenkovich 2018	+	?	?	?	+
Wait 1997	?	?	?	+	+
Wozniak 2009	?	?	?	+	+

References

1. Rahman NM, Maskell NA, Davies CW, et al. The relationship between chest tube size and clinical outcome in pleural infection. *Chest.* 2010;137(3):536-543.
2. Bilgin M, Akcali Y, Oguzkaya F. Benefits of early aggressive management of empyema thoracis. *ANZ Journal of Surgery.* 2006;76(3):120-122.
3. Wait MA, Sharma S, Hohn J, Dal Nogare A. A randomized trial of empyema therapy. *Chest.* 1997;111(6):1548-1551.
4. Metin M, Yeginsu A, Sayar A, et al. Treatment of multiloculated empyema thoracis using minimally invasive methods. *Singapore Medical Journal.* 2010;51(3):242-246.
5. Semenkovich TR, Olsen MA, Puri V, Meyers BF, Kozower BD. Current state of empyema management. *Annals of Thoracic Surgery.* 2018;105(6):1589-1596.
6. Wozniak CJ, Paull DE, Moezzi JE, et al. Choice of first intervention is related to outcomes in the management of empyema. *Annals of Thoracic Surgery.* 2009;87(5):1525-1530; discussion 1530-1521.
7. Light RW. A new classification of parapneumonic effusions and empyema. *Chest.* 1995;108(2):299-301.

Question Protocol

Field	Content
Review Question	For adults with established pleural infection, what initial drainage strategy provides the best clinical outcomes?
Type of review question	Intervention review
Objective of the review	In patients with infected pleural fluid that require drainage, what is the optimal initial drainage strategy of infected material, comparing standard of care (small bore chest drains <14F) with no drainage, pleural aspiration, large bore chest drain (>14F), medical thoracoscopy and surgical treatments.
Eligibility criteria – population / disease / condition / issue / domain	Adults (18+) with established pleural infection
Eligibility criteria – intervention(s)	Small bore chest drain (≤ 14F)
Eligibility criteria – comparators(s)	No drainage Pleural aspiration Large bore chest drain (>14F) Medical thoracoscopy Surgery (VATS / thoracotomy)
Outcomes and prioritisation	Mortality Need for repeat intervention Surgery Quality of life Patient symptoms Length of hospital stay Complications
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	Small bore chest drains for pleural infection remain the standard of care for initial treatment of pleural infection. What is the evidence that informs this practice?