

**Section D              Pleural malignancy**

**Question D9           Evidence Review and Protocol**

**D9      For adults with malignant pleural effusion treated with indwelling pleural catheters, does symptom-based / conservative drainage have better clinical outcomes than daily drainage?**

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## Question Evidence Review

### D9 For adults with malignant pleural effusion treated with indwelling pleural catheters, does symptom-based / conservative drainage have better clinical outcomes than daily drainage?

#### Background

Indwelling pleural catheters (IPCs) offer an ambulatory management pathway in patients with refractory malignant pleural effusion (MPE). The original studies (TIME2<sup>1</sup> and AMPLE<sup>2</sup>) used regimes of alternate day drainages and this has been incorporated in routine practice. There has been interest on the optimal drainage regime, whether a once-daily drainage regime would offer better clinical outcomes than the less frequent standard alternate days or whether it would be better to offer drainage when patients are symptomatic (symptom-based / conservative drainage regimes).

#### Outcomes

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

#### Evidence Review

The initial literature search identified seven papers, of which two randomised controlled trials were deemed relevant, but the studies used different strategies for the symptom-based / conservative arm. One study used a 'symptom-guided' strategy, where patients carried out drainages in response to effusion-related symptoms,<sup>3</sup> and the other used an alternate day drainage strategy.<sup>4</sup>

#### Quality of life

Both studies examined quality of life, but meta-analysis was not possible because of the heterogeneity in the methods chosen to measure quality of life. Wahidi et al (ASAP trial) reported that quality of life and patient satisfaction were similar in both groups, with both arms showing high overall satisfaction with the IPC.<sup>4</sup> In contrast, the AMPLE-2 trial reported that patient reported quality of life (QoL) measures were better in the aggressive daily drainage group than the symptoms-guided drainage group.<sup>3</sup> A summary of the data is shown in [Table D9a](#).

Table D9a: Comparison of quality of life for patients with malignant pleural effusion treated with an daily drainages versus symptom-guided/alternate daily drainages

Study	QoL tool	Timepoints	Symptom-based	Daily	p
<b>QoL score (mean ± SE)</b>					
Wahidi 2017 <sup>4</sup>	KPS	Pre-insertion	63.5 ± 1.8	65.9 ± 1.8	0.33
		2 weeks	65.0 ± 2.4	70.0 ± 2.4	0.15
		12 weeks	71.8 ± 5.2	80.4 ± 4.8	0.24
<b>Estimated means [95% CIs]</b>					
Muruganandan 2018 <sup>3</sup>	EQ-5D-5L	Baseline	0.60 [0.54–0.67]	0.71 [0.65–0.78]	0.0174
		2 weeks			
		4 weeks			
		Monthly until 6 months			

EQ-5D-5L – EuroQoL-5 dimensions-5 levels; KPS – Karnofsky performance score; QoL – quality of life

#### Length of hospital stay

Only one study examined length of hospital stay, examining total number of episodes and duration of hospital stay for any cause (excluding elective admission for any cause) for the 6-month study period. Hospital

admissions were sub-divided into pleural-related and non-pleural-related hospital days. There were no reported differences in total episodes of hospital admission, total days in hospital or effusion-related bed days between the 'symptom-guided' drainage and daily drainage groups.<sup>3</sup>

#### Need for re-intervention

No study reported on the need for re-intervention.

#### Symptoms (breathlessness, chest pain)

Both studies reported on pain<sup>3,4</sup> and one study reported on breathlessness<sup>3</sup>. Although both studies reported pain measurements, one used visual analogue scale (VAS) scores, while the other looked at pain as part of the RAND MOS SF-36 Survey (1 part of a 9-part score). A summary of the results is shown in [Table D9b](#) and no study demonstrated significant benefit of one treatment over the other.

Table D9b: Comparison of breathlessness and pain symptom scores with malignant pleural effusion treated with an daily drainages versus symptom-guided/alternate daily drainages

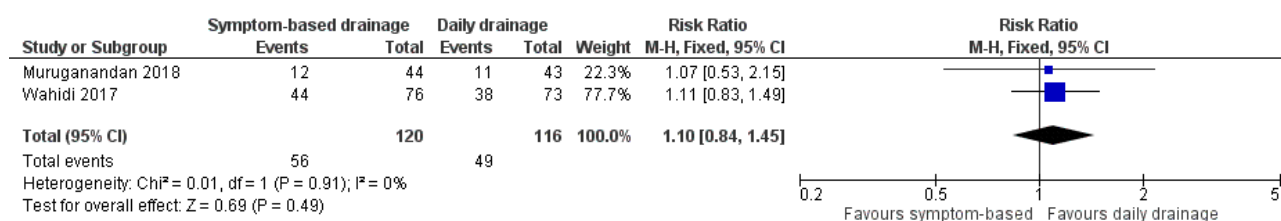
Outcome	Study	Drainage strategy		p
		Symptom-based	Daily	
<i>Breathlessness</i>				
VAS (mean daily score [95% CIs])	Muruganandan 2018 <sup>3</sup>	17.3 [13.0-22.0]	13.1 [9.8-17.4]	NS
<i>Pain</i>				
SF-36 (no. of subjects)	Wahidi 2017 <sup>4</sup>	25/34	44/58	NS
VAS (mean ± SD, days 1-60)	Muruganandan 2018 <sup>3</sup>	16.31 ± 16.58	10.74 ± 12.80	NS

NS – not significant; RCT – random controlled trial SF-36 – RAND medical outcome study 36-item short form health survey; VAS – visual analogue scale

#### Complications

Adverse events were similar in both treatment groups, with meta-analysis revealing complications in [422 per 1000](#) patients in the daily drainage group compared to [465 per 1000 \(355 to 612\)](#) in the symptom-based drainage group ([Figure D9a](#)).<sup>3,4</sup>

Figure D9a: Complications (symptom-based / conservative drainage versus daily drainage)

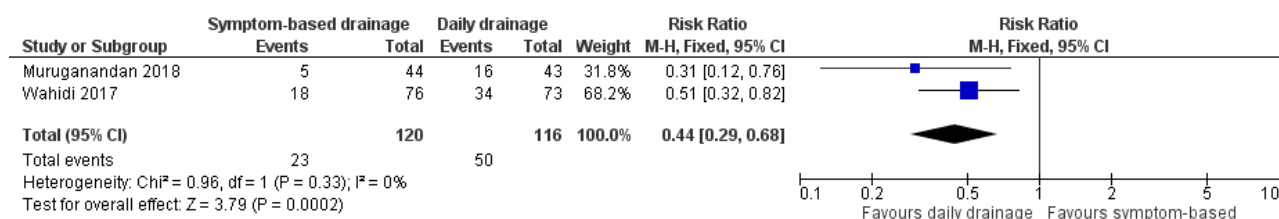


#### Pleurodesis rates

Pleurodesis rates were reported in both studies and meta-analysis revealed that spontaneous pleurodesis by 60 days (AMPLE-2) or autopleurodesis by 12 weeks (ASAP) was less frequent in the symptom-based drainage group ([190 patients per 1000 \(125 to 293\)](#) compared with [431 per 1000](#) in the daily drainage group) ([Figure D9b](#)).<sup>3,4</sup>

The ASAP trial measured the median time to pleurodesis, with a shorter median time in the daily drainage group (54 days [34-83] compared with 90 days [70 to non-estimable], median [95% CIs], p = 0.005).<sup>4</sup>

Figure D9b: Pleurodesis rate (symptom-based / conservative drainage versus daily drainage)



## Evidence statements

Symptoms (breathlessness and chest pain), complications and length of hospital stay appear to be the same for daily drainage, symptom guided drainage or alternate daily drainage (**Ungraded**)

There appear to be no differences in the occurrence of complications between daily drainage and symptom-based/conservative drainage regimes (**Low**)

Daily drainage appears to increase pleurodesis rates when compared to alternate drainage or symptom-based drainage regimes (**Low**)

Daily drainage may improve quality of life when compared to a symptom-based/conservative drainage approach, but there is no current evidence that daily drainage improves quality of life when compared to alternate daily drainages (**Ungraded**)

## Recommendations

- Where indwelling pleural catheter (IPC) removal is a priority, daily IPC drainages are recommended to offer increased rates of pleurodesis when compared with less frequent drainages of symptom-guided or alternate drainage regimes (**Conditional**)
- Patients should be advised that they do not require daily drainage to control symptoms of breathlessness and chest pain if they wish to opt for a less intensive regime (**Strong** – by consensus)

## Good Practice Points

- ✓ Decisions on the optimal drainage frequency should be based on patient choice
- ✓ Informed decision making should include the explanation of the effect of drainage regimes on the patient-centre outcomes such as breathlessness and the possibility of auto-pleurodesis during the disease course
- ✓ Although daily drainage may result in earlier removal of IPCs, there may be an associated cost associated with the increased number of drainage events (both to the healthcare system, and to the patient). This has been addressed in a modelling study<sup>5</sup> and should be considered

## Research Recommendation

- Further research is needed comparing the risks and benefits of indwelling pleural catheter daily drainage and symptom-based drainage for managing adult patients with malignant pleural effusion

## Risk of bias summary

	Selection bias	Performance bias	Detection bias	Attrition bias	Publication bias
Muruganandan 2018	+	?	+	+	+
Wahidi 2017	?	?	+	?	+

## GRADE analyses

**For adults with malignant pleural effusion treated with indwelling pleural catheters, does symptom-based drainage have better clinical outcomes than daily drainage?**

**Population:** Adults aged 18+ with malignant pleural effusion and treated with an indwelling pleural catheter

**Intervention:** Symptom-based drainage

**Comparator:** Daily drainage

Outcome	Number of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects Daily drainage	Anticipated absolute effects Symptom-based drainage	Quality of the Evidence (GRADE)
<b>Complications</b>	236 (2 studies)	RR 1.10 (0.84 to 1.45)	<b>422 per 1000</b>	<b>465 per 1000</b> (355 to 612)	⊕⊕○○ <b>LOW</b> <sup>a,b</sup>
<b>Pleurodesis rate</b>	236 (2 studies)	RR 0.44 (0.29 to 0.68)	<b>431 per 1000</b>	<b>190 per 1000</b> (125 to 293)	⊕⊕○○ <b>LOW</b> <sup>a,b</sup>

CI: Confidence interval

### Explanations

- a. Some risk of bias across both studies
- b. Some imprecision, CIs cross one MID

## Recommendation Table

### Question Details

<b>POPULATION:</b>	Adults aged 18+ with malignant pleural effusion and treated with an indwelling pleural catheter
<b>INTERVENTION:</b>	Symptom-based drainage
<b>COMPARISON:</b>	Daily drainage
<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	Probably no	<b>Probably yes</b>	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	<b>Moderate</b>	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	<b>Probably favours the comparison</b>	Does not favour the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	Don't know

### TYPE OF RECOMMENDATION

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

## CONCLUSIONS

### Recommendation

Where indwelling pleural catheter (IPC) removal is a priority, daily IPC drainages are recommended to offer increased rates of pleurodesis when compared with less frequent drainages of symptom-guided or alternate drainage regimes

Patients should be advised that they do not require daily drainage to control symptoms of breathlessness and chest pain if they wish to opt for a less intensive regime

### Justification

Symptoms (breathlessness and chest pain), complications and length of hospital stay appear to be the same for daily drainage, symptom guided drainage or alternate daily drainage (**Ungraded**)

There appear to be no differences in the occurrence of complications between daily drainage and symptom-based/conservative drainage regimes (**Low**)

Daily drainage increases pleurodesis rates when compared to alternate drainage or symptom-based drainage regimes (**Low**)

Daily drainage may improve quality of life when compared to a symptom-based/conservative drainage approach, but there is no current evidence that daily drainage improves quality of life when compared to alternate daily drainages (**Ungraded**)

### Subgroup considerations

There was not enough evidence for subgroup consideration (high volume producing tumours, low volume producing tumours, trapped lung, non-trapped lung)

### Research priorities

Further research is needed comparing the risks and benefits of indwelling pleural catheter daily drainage and symptom-based drainage for managing adult patients with malignant pleural effusion

## References

1. Davies H, Mishra EK, Wrightson JM, et al. The second therapeutic intervention in malignant effusion trial (TIME2): a randomised controlled trial to assess the efficacy and safety of patient controlled malignant pleural effusion drainage by indwelling pleural catheter compared to chest tube and talc slurry pleurodesis. *American journal of respiratory and critical care medicine*. 2012;185.
2. Lee YG, Fysh ETH, Thomas R, Smith NA, Lee P, Kwan BCH. Australasian malignant pleural effusion (AMPLE) Trial: a multicentre randomised study comparing indwelling pleural catheter versus talc pleurodesis. *American journal of respiratory and critical care medicine*. 2016;193:A7812.
3. Muruganandan S, Azzopardi M, Fitzgerald DB, et al. Aggressive versus symptom-guided drainage of malignant pleural effusion via indwelling pleural catheters (AMPLE-2): an open-label randomised trial. *The Lancet Respiratory Medicine*. 2018;6(9):671-680.
4. Wahidi MM, Reddy C, Yarmus L, et al. Randomized trial of pleural fluid drainage frequency in patients with malignant pleural effusions. The ASAP trial. *American Journal of Respiratory & Critical Care Medicine*. 2017;195(8):1050-1057.
5. Shafiq M, Simkovich S, Hossen S, Feller-Kopman DJ. Indwelling pleural catheter drainage strategy for malignant effusion: a cost-effectiveness analysis. *Annals of the American Thoracic Society*. 2020;17(6):746-753.



## Question Protocol

Field	Content
Review Question	For adults with malignant pleural effusion treated with indwelling pleural catheters, does symptom-based drainage have better clinical outcomes than daily drainage?
Type of review question	Intervention review
Objective of the review	Indwelling pleural catheters are increasingly used in the management of MPE. This question explores the best drainage method in terms of frequency of drainage
Eligibility criteria – population / disease / condition / issue / domain	Adults (18+) with malignant pleural effusion treated with indwelling pleural catheters
Eligibility criteria – intervention(s)	Symptom based drainage
Eligibility criteria – comparators(s)	Daily drainage
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	High volume producing tumours (e.g. Lymphoma, small cell cancer, melanoma) Low volume producing tumours Trapped lung Non-trapped lung
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	This question addresses the optimal drainage regime of IPC's in patients with MPE. This is important as regular drainages could increase infection rates and inconvenience but may lead to quicker pleurodesis and drain removal