



## RANDOMIZED TRIAL OF INDWELLING PLEURAL CATHETERS FOR REFRACTORY TRANSUDATIVE PLEURAL EFFUSIONS - REDUCE STUDY



### THE CLINICAL QUESTION

In refractory transudative effusions, do indwelling pleural catheters (IPC) offer superior control of breathlessness compared to the standard approach of as needed therapeutic thoracentesis (TT)?

### STUDY CONCLUSION

IPCs do not offer superior symptomatic benefit compared to as needed TT for refractory transudative effusions.



### STUDY BACKGROUND



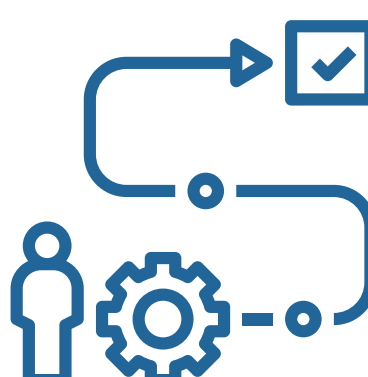
Transudative pleural effusions are common. Their initial management typically aims to optimize volume status using diuretics or by using dialysis in renal failure. However, a significant proportion of transudative effusions are refractory to medical management and require procedural intervention.

In refractory transudative effusions, the standard next step in management is TT, which carries risk.

Interestingly, observational data suggest IPCs reduce breathlessness with a low risk of complications in non-malignant effusions. Management of transudates using IPCs has been extrapolated from data on malignant pleural effusions. There have been no randomized controlled trials (RCT) exploring efficacy of IPCs in refractory transudative effusions. Despite the paucity of data specific to transudates, IPCs are approved by the U.S. Food and Drug Administration to treat non-malignant effusions.

### CURRENT PRACTICE

There is currently no gold standard method or guideline to manage symptomatic non-malignant pleural effusions, so this study endeavors to provide clarity in such an approach.



# STUDY DESIGN



## Type of trial:

Open-label, multicenter, non-blinded RCT. Randomization occurred with 1:1 allocation to each group and was performed using minimization factors of effusion etiology (heart or renal failure vs. liver failure) and effusion size ( $\geq\frac{1}{2}$  hemithorax vs.  $<\frac{1}{2}$  hemithorax). N: 68 patients randomized, intention-to-treat analysis

## Study groups:

- 1)IPC arm (n=33 patients)
- 2)TT arm (n=35 patients)

## Settings:

13 secondary and tertiary care centers in the United Kingdom

Enrollment: April 2015 – December 2019

Follow up: 4, 8, and 12 weeks post-randomization

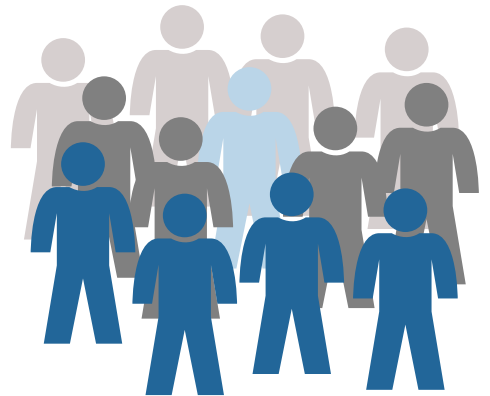
## Primary outcome:

Mean daily breathlessness score at follow-up over the 12-week study period as measured using visual analog scale (VAS) scores spanning from “not breathless at all” to “worst possible breathlessness”.

# POPULATION

## Inclusion criteria

- Patients with persistent symptomatic pleural effusions due to either heart, renal, or liver failure despite optimized medical therapy.
- Assessment by cardiologist, hepatologist, or nephrologist to determine presence of respective disease states.
- At least one prior aspiration of pleural fluid with characteristics as follows:
  - Transudative by Light’s criteria
  - Exudative, but confident exclusion of infection or malignancy and with primary cause thought secondary to cardiac, renal, or liver failure



## Exclusion criteria

- Age <18 years
- Life expectancy <3 months
- Pregnant, lactating, or intention to become pregnant
- Known pleural malignancy
- Pleural fluid pH <7.2
- Prior IPC in hemithorax of interest or current IPC in contralateral hemithorax
- Absolute contraindication to IPC insertion such as skin infection over the insertion site or uncorrectable coagulopathy
- Inability to give consent
- No access to telephone

## Baseline characteristics

There were no apparent differences between groups in regard to age, etiology of effusion, size of initial effusion, duration of symptoms, baseline albumin, anticoagulation use, diuretic use, and need for dialysis.

# INTERVENTIONS



1. Patients in the IPC arm underwent IPC placement and effusion drainage followed by home drainage 3x/week for two weeks with subsequent drainage on an as needed basis.
2. Patients in the TT arm underwent an initial thoracentesis, removing up to 1.5L, with subsequent as needed thoracenteses.

# OUTCOMES

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## Primary outcomes

- There was no significant difference in the mean breathlessness score (VAS) over the 12-week study period between the IPC group (39.7 mm, SD 29.4) and the TT group (45.0 mm, SD 26.1) (mean difference -2.9mm, 95% CI -16.1 to 10.3; p=0.67).
- There was also no difference in the primary outcome when differentiated by specific disease state (heart & renal vs. liver) or by the size of the initial effusion ( $\geq\frac{1}{2}$  hemithorax vs.  $<\frac{1}{2}$  hemithorax).

## Secondary outcomes

- Post hoc analysis showed a gradual, but non-significant, improvement in breathlessness in the IPC arm and stable mean breathlessness scores in the TT arm over time.
- More volume was drained in the IPC group than the TT group, mean 17,412 ml (SD 17,936) vs. 2,901 ml (SD 2,416) (difference 13,892 ml; 95% CI 7669 to 20,116; p<0.001), respectively.
- Serum albumin was lower in the IPC group than the TT group at 12 weeks, 27.0 g/L (SD 7.5) vs. 32.5 g/L (SD 5.1) (p-value <0.001), respectively.
- TT group failed their initially randomized treatment more often than the IPC group:
  - 17% (6/35) of TT patients required chest drains, talc pleurodesis, subsequent IPC, or thoracoscopy.
  - One patient (1/33) in the IPC group required an additional invasive pleural procedure to replace a malfunctioning catheter.
- TT group required 1.3 (SD 1.4) additional drains and the IPC group required no additional thoracenteses during the study period.

There were no differences between groups in the following:

- All-cause mortality within the 12-week randomization period using available data;
  - 6% in the TT group (2/35) and 16% in the IPC group (5/31)(3.8; 95% CI 0.65 to 22.15; p=0.14)
- Breathlessness over the first 7 or first 28 days
- Healthcare-related quality of life at baseline or at subsequent follow-ups as measured by EQ-5D-5L
- Number of bed days or hospital visits
- Pleurodesis success rates

## Adverse events

There were significantly more adverse events in the IPC group compared to the TT group, although there was no significant difference in all-cause mortality between groups.

- At least one adverse event was seen in 59% (19/32) of patients in the IPC group vs. 37% (13/35) in the TT group (OR 3.13 (1.07, 9.13), p = 0.04).
- There were 39 adverse events in the IPC arm and 24 in the TT arm.
- There were 12 serious adverse events in the IPC group (medical outcomes that resulted in death, were life threatening, required prolonged hospitalization, or resulted in significant disability or incapacity) and 7 serious adverse events in the TT group.
- Pleural or site-related infection rates differed between groups (2/33 in IPC group vs. 0/35 in TT group), with one site infection that progressed to pleural space infection and death.

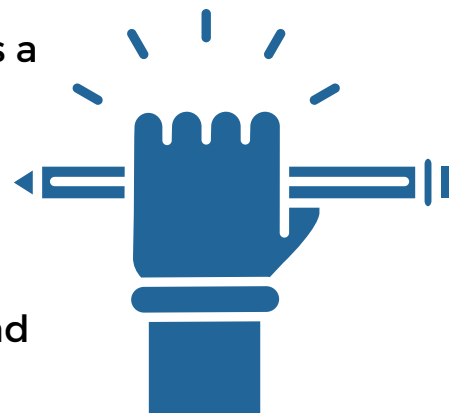
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## STUDY STRENGTHS

This is the first RCT assessing whether there is a benefit to IPCs over recurrent TTs in patients with transudative effusions. The secondary analysis was thorough with multiple interesting endpoints that shed light on the safety profile of IPCs, such as infection rate and all-cause mortality, which is an often-cited concern when considering their placement.



## STUDY LIMITATIONS

This study had a rather small N with 12% attrition in the IPC group compared to no attrition in the TT group. Several measures signaled an effect between groups but were not significant. One signal was especially apparent in the study's graphical representation of mean change in VAS score over the treatment period between the IPC and TT groups. When comparing mean breathlessness over time, perhaps a larger N would power the study to identify meaningful differences more robustly. Baseline characteristics seem reasonably matched between groups.

There were incidents of missing values which were statistically managed using the mean imputation model and missing-at-random model and might introduce bias. Some of these missing values were in the assessment of baseline breathlessness, which might be rather variable between patients. The estimation of these missing values could have blunted actual differences between groups, especially if the number of missing values is more common in one group (i.e., the IPC group).

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## RESEARCH QUESTION

In future higher-powered studies, will a difference in symptomatic control over time between the IPC and TT groups become significant? Furthermore, are there additional significant benefits to IPC over TT, such as factors of convenience or specific measures of safety?



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## TAKE HOME MESSAGE



In the first randomized trial exploring refractory transudative pleural effusions, indwelling pleural catheters (IPCs) did not offer superior symptomatic control compared to as needed therapeutic thoracentesis (TT). Patients in the TT group failed their initial randomized treatment more often and required additional procedures. In the context of this small study, there were also more adverse events and a lower albumin level of uncertain clinical significance in the IPC group. Notably, there was no difference in all cause-mortality between groups.

Although the results of this study do not support use of IPC over TT and suggest more adverse events with IPCs, the safety outcomes in this study do not preclude their use. Thus, the discussion regarding whether IPCs for transudates are more appropriate in certain patient populations from a convenience or safety perspective remains open.

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## FUNDING

BD CareFusion (New Jersey, USA)



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## SUGGESTED READING



1. Davies HE, Mishra EK, Kahan BC, Wrightson JM, Stanton AE, Guhan A, et al. Effect of an indwelling pleural catheter vs chest tube and talc pleurodesis for relieving dyspnoea in patients with malignant pleural effusion: the TIME2 randomised controlled trial. JAMA. 2012; 307(22):2383-9.

2. Thomas R, Fysh ET, Smith NA, Lee P, Kwan BC, Yap E, et al. Effect of an indwelling pleural catheter vs talc pleurodesis on hospitalization days in patients with malignant pleural effusion: The AMPLE randomised clinical trial. JAMA. 2017; 318(19):1903-12.

3. Patil M, Dhillon SS, Attwood K, Saoud M, Alraiyes AH, Harris K. Management of Benign Pleural Effusions Using Indwelling Pleural Catheters: A Systematic Review and Meta-analysis. Chest. 2017; 151(3):626-35.

4. Walker SP, Morley AJ, Staddon L, De Fonseka D, Arnold DT, Medford AR, Maskell NA. Non-Malignant Pleural Effusions (NMPE): a prospective study of 356 consecutive unselected patients. Chest. 2017; 151(5):1099-105.

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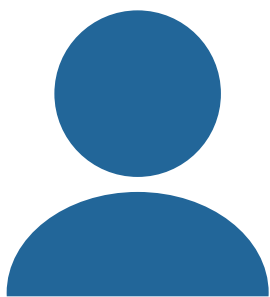
## ARTICLE CITATION

Walker SP, Bintcliffe O, Keenan E, et al. Randomised trial of indwelling pleural catheters for refractory transudative pleural effusions. Eur Respir J 2021; in press (<https://doi.org/10.1183/13993003.01362-2021>).



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