Pleurodesis and drains are painful\(^1\):  
- 60% report moderate pain despite analgesia\(^4\)

**Current analgesia use:**  
- Majority of physicians use opiates\(^4\)


**The best analgesia...**

**NSAIDS in MPE**  
Do NSAIDs impair pleurodesis?  
- No human data  
- Three animal studies\(^1-3\)  
- Histological reduction in pleurodesis score

\(^3\) Teixeira LR et al, Chest 2005;128:4041-5.

**Drain Size for Pleurodesis**  
**Observational, non-comparative series:**  
- Small drains effective and comfortable

**Direct comparison:**  
- Only one randomised study  
  - Clementsen et al (n=18)  
  - Underpowered:  
    - 95% CI for pleurodesis rate = \(20-80\%\)

**T.I.M.E. 1**
MPE requiring pleurodesis

**Randomisation**
- Large drain + NSAID
- Small drain + NSAID
- Large Drain + Opiate
- Small Drain + Opiate

Pleurodesis using standardised protocol of analgesia and sedation

Average pain score over drain in situ time
Pleurodesis success at 4 weeks + 3 months

**Interventions**

**Analgesic Regimens:**
- NSAID = Ibuprofen 800mg tds
- Opiate = Oramorph 5-10mg qds

**Chest drains:**
- Large = 24F (blunt dissection)
- Small = 12F (guide-wire)

**TIME1 Primary Outcomes**

**Outcome assessment**
- Pain - superiority
- Pleurodesis – non-inferiority

**Assumptions...**

1. NSAIDs reduce pleurodesis
2. Chest tube size makes no difference to pleurodesis
3. Larger tubes are more painful and associated with more complications
Pain while tube in situ to 5 days (superiority)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>No. of patients analysed</th>
<th>Outcome</th>
<th>Treatment effect</th>
<th>Confidence Interval (%)</th>
<th>Significance (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain while tube in situ to 5 days (superiority)</td>
<td>Mean Pain Score, mm (SD)</td>
<td>Difference (mm)</td>
<td>-6.0</td>
<td>-11.7 to -0.2 (95% CI)</td>
<td>0.04</td>
</tr>
<tr>
<td>24F</td>
<td>50</td>
<td>26.8 (16.9)</td>
<td>-6.0</td>
<td>-11.7 to -0.2 (95% CI)</td>
<td>0.04</td>
</tr>
<tr>
<td>12F</td>
<td>54</td>
<td>22.0 (16.6)</td>
<td>-6.0</td>
<td>-11.7 to -0.2 (95% CI)</td>
<td>0.04</td>
</tr>
<tr>
<td>Opiate</td>
<td>155</td>
<td>23.8 (15.8)</td>
<td>-1.5</td>
<td>-5.0 to 2.0 (95% CI)</td>
<td>0.40</td>
</tr>
<tr>
<td>NSAID</td>
<td>153</td>
<td>22.1 (16.9)</td>
<td>-1.5</td>
<td>-5.0 to 2.0 (95% CI)</td>
<td>0.40</td>
</tr>
</tbody>
</table>
Pleurodesis

Primary Outcome – Pleurodesis (15% non-inferiority margin)

<table>
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<tbody>
<tr>
<td>Pleurodesis Failure at three months (non-inferiority, ITT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opiate</td>
<td>150</td>
<td>30 (20)</td>
<td>-3</td>
<td>-12% to 8% (95% CI)</td>
<td>0.004</td>
</tr>
<tr>
<td>NSAID</td>
<td>144</td>
<td>33 (23)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24F</td>
<td>244</td>
<td>48 (20)</td>
<td>10%</td>
<td>-21% to 6% (95% CI)</td>
<td>0.24</td>
</tr>
<tr>
<td>12F</td>
<td>50</td>
<td>15 (30)</td>
<td></td>
<td></td>
<td></td>
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</table>

Complications on Tube Insertion

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<tr>
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<th>Treatment effect</th>
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<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>24F (n=56)</td>
<td>56</td>
<td>8 (14)</td>
<td>1.9</td>
<td>0.7 to 5.1</td>
<td>0.20</td>
</tr>
<tr>
<td>12F (n=55)</td>
<td>55</td>
<td>13 (24)</td>
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Complications on Tube Insertion

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Proportion Receiving Talc

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>No. of patients analysed</th>
<th>Outcome</th>
<th>Treatment effect</th>
<th>Odds Ratio</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>24F (n=56)</td>
<td>56</td>
<td>52 (93)</td>
<td>3.3</td>
<td>3.3; 3.9</td>
<td>0.048</td>
</tr>
<tr>
<td>12F (n=55)</td>
<td>55</td>
<td>44 (80)</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>
### Current optimal pleurodesis?

**What is the ADVANTAGE of a smaller drain?**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Outcome (versus 24F drain)</th>
</tr>
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<tbody>
<tr>
<td>Pain</td>
<td>Lower (clinically not significant)</td>
</tr>
<tr>
<td>Safety</td>
<td>More complications</td>
</tr>
<tr>
<td>Inability to give talc</td>
<td>Higher</td>
</tr>
<tr>
<td>Fall out rate</td>
<td>Higher</td>
</tr>
</tbody>
</table>

### What have we learnt from TIME1?

1. **NSAIDs do not reduce pleurodesis efficacy**
2. Smaller drains are less painful:
   - Not clinically significant (6.0mm, MCID 14mm)
3. **12F fail to meet non-inferiority vs 24F for pleurodesis**
4. **12F have**
   - Increased complications
   - Higher fall out
   - Less ability to give talc
Pleural Infection Outcomes

High morbidity:
- Mean hospital stay 10-14 days
- Surgical rate up to 35%

>20% one year mortality:
- Unchanged over last 20 years
- 7% in MI
- 8% in hospitalised pneumonia

Baigent et al [BMJ; 316:1337-43]
Neill et al [Thorax; 51: 1010-16]

Pleural Infection Rx

1. Accurate diagnosis
2. Control sepsis:
   - Suitable antibiotic therapy
3. Drainage of infected material:
   - Intercostal tube drainage
   - Intrapleural adjunctive therapies
   - Surgery

Assumptions...

1. Draining infected fluid is the priority
2. Disrupting septations is key to adequate drainage
Microbiology

Fluid microbiological yield is poor:
- 40% microbiologically negative
- Due to:
  - Prior antibiotic use
  - Brisk intrapleural immune reaction

Pleural Infection microbiology

Are we looking in the right place?

Advanced Ultrasound in Diagnosis of Pleural Infection

Psallidas et al, Chest 2018
Optimal Drainage
Intrapleural Fibrinolytics

4 small RCTs
- Davies et al 1997
- Bouros et al 1997
- Bouros et al 1999
- Tuncozgur et al 2001

- Total 104 adults
- Surrogate outcomes (CRP / fever / fluid output)

MIST1
Purulent pleural fluid
Acidic, pH<7.2
Bacteria positive

Co-primary outcomes:
Surgical Intervention
Mortality

RANDOMISATION
Placebo
Streptokinase

Maskell et al NEJM, 352: 865-874
Streptokinase is ineffective in pleural infection

NEJM; 352: 865-874

1. Viscosity

V

SK

SK/DNase

DNase

Lung 2000; 178:13-8

Chest 2000; 117: 1728-33

2. Biofilm

Intrapleural Use of Tissue Plasminogen Activator and DNase in Pleural Infection

Nash M., Rahman, D.R.H., Nicholas A., Marshall, D.M., Alex West, M.R.C.P.,
David Pechère, M.B., Chris W.H., Davies, M.D., Nabil Al, M.D.,
William Kimac, M.D., Andrew Bartlett, M.D., Brennan C., Fakan, M.Sc.,
John M., Wightman, M.R.C.P., Helen E., Davies, M.R.C.P.,
Claire E., Hooper, M.R.C.P., Y.C. Gary Lee, Ph.D., Emma L., Huddle,
Nicky Crosthwaite, F.C.N., Louise Chou, M.Sc., Emma J., Helm, F.R.C.R.
Fergus Y., Gravoton, M.D., Andrew J., Nunn, M.Sc., and Robert J.D., Davies, M.D.®
MIST2
Purulent pleural fluid
Acidic, pH<7.2
Bacteria positive

Radiograph outcome
Surgical Rate / Mortality

Primary Outcome

Day 1
Day 7

Absolute change = (day 7 – day 1) = 8.0 - 38.9 = -30.9%
Relative change = (day 7 – day 1) / day 1 = -30.9/38.9 = -79.4%

Primary Result

tPA + Dnase:
- Improves radiographic drainage
- Individual agents do not have any effect

Does this translate to other clinical benefit?
Secondary Outcomes

**MIST2**

Should tPA + DNase be standard care?

- Definitive evidence of chest radiograph improvement
- Strong suggestion of improving other parameters
- NOT YET enough data to use in every patient

**Use now?**

- Where no other treatment options are available
- While waiting for surgical intervention
- As part of a clinical trial

Fibrinolytics alone in Pleural infection

- Two large scale RCTs demonstrate no efficacy above placebo
- Why is there still a strong clinical feeling that they work?
Explaining MIST1+2

**Original Research**

Tissue Plasminogen Activator Potently Stimulates Pleural Effusion via a Monocyte Chemotactic Protein-1-Dependent Mechanism

Sally M. Linstead, Fatimah M. Al-Sherick, Julie P. Venn, Vincent Linshe, Azeez Olayemi, and Y. C. Gary Lee

1. Bacteria in pleural infection preferentially occupy the parietal pleural surface
2. Disrupting septations alone is insufficient to resolve infection
3. Removing fluid and reducing viscosity/stripping the biofilm appear to be important

---

**Pleural infection – what have we learnt**

1. Bacteria in pleural infection preferentially occupy the parietal pleural surface
2. Disrupting septations alone is insufficient to resolve infection
3. Removing fluid and reducing viscosity/stripping the biofilm appear to be important

---

**MIST3**

Purulent pleural fluid
Acidic, pH<7.2
Bacteria positive

**Randomisation**

- Early VATS 25
- Standard Care 25
- DNase & TPA 26

**Outcomes:**
1. Feasibility of recruitment
2. Acceptance of randomisation
3. Feasibility of data collection

---

**Pleural Trials**

Outcomes:

- Feasibility of recruitment
- Acceptance of randomisation
- Feasibility of data collection
Overall Conclusions

- Large number of high quality studies ongoing and being published in pleural disease
- The pleura is no longer an evidence free space
- Collaborative pleural research is feasible

2536 patients randomised to interventional studies pleural studies in 7 years

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