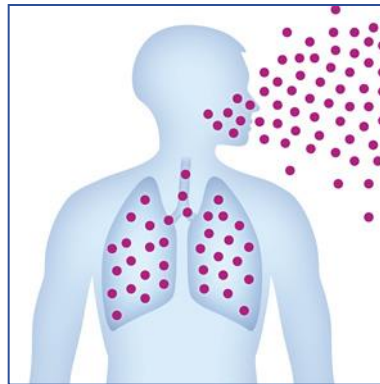


# Pneumo Update Europe 2018

15 - 16 June, Budapest

## Pleural Disease



**Julius Janssen, Netherlands**

# Subtopics

- Non-specific pleuritis
- Spontaneous pneumothorax
- Malignant pleural effusion
- Thoracoscopy

# **Subtopic**

## **Non specific pleuritis**

# State of the Art

- Non-specific pleuritis (NSP) is pleuritis of indeterminate cause.
- Diagnosis is established on pleural biopsy after thoracoscopy.
- False negative cases of NSP occur in 5-19%, most due to mesothelioma
- Pleural effusion in patients with active malignancy is considered a bad prognostic sign

***Non-specific pleuritis*** (Janssen JP et al., Clin Resp J, in press)

# State of the Art

| Author             | Year | No of cases | Non-specific pleuritis (NSP) | No of malignancy during follow-up | Follow-up period |
|--------------------|------|-------------|------------------------------|-----------------------------------|------------------|
| Janssen            | 2004 | 709         | 208 (29%)                    | 31 (15%)                          | 2 years          |
| Venekamp           | 2005 | -           | 60                           | 5 (8%)                            | 3 years          |
| Davies             | 2010 | 142         | 44 (31%)                     | 5 (12%)                           | 21 months        |
| Metintas           | 2012 | 287         | 101(35%)                     | 19 (19%)                          | 2 years          |
| DePew <sup>1</sup> | 2014 | 413         | 64 (15%)                     | 3 (5%)                            | 5 years          |
| Yang               | 2017 | 833         | 52 (6%)                      | 8 (15%)                           | 35 months        |
| Vakil <sup>2</sup> | 2018 | 199         | 90 (52%)                     | 3 (3%)                            | 23 months        |

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# Non-specific pleuritis (NSP) in patients with active malignancy

- Thoracoscopy in 172 patients with pleural effusion and active malignancy
- 52% non-specific pleuritis
- 42% malignant pleural effusion
- 5% eosinophilic pleuritis

*(Vakil et al., Respirology, 2018, 23: 213-218)*

# Non-specific pleuritis (NSP) in patients with active malignancy

- 52% (90/172) non-specific pleuritis
  - Chemotherapy induced 24 (27%)
  - Radiation induced 27 (30%)
  - Paramalignant effusion 11 (12%)
  - Idiopathic pleuritis 31 (35%)
- At follow-up (23 mth) malignant PE in 3

*(Vakil et al., Respiriology, 2018, 23: 213-218)*



# Take-Home Message

- Pleural effusion in patients with active malignancy is malignant in minority of cases.
- If non-specific pleuritis is found in this group, this is a true diagnosis in 97% of cases
- In case of pleural effusion in otherwise resectable (lung) cancer, patients should not be refused for surgery, but have a thoracoscopy to exclude malignant pleural metastasis

# Spontaneous Pneumothorax

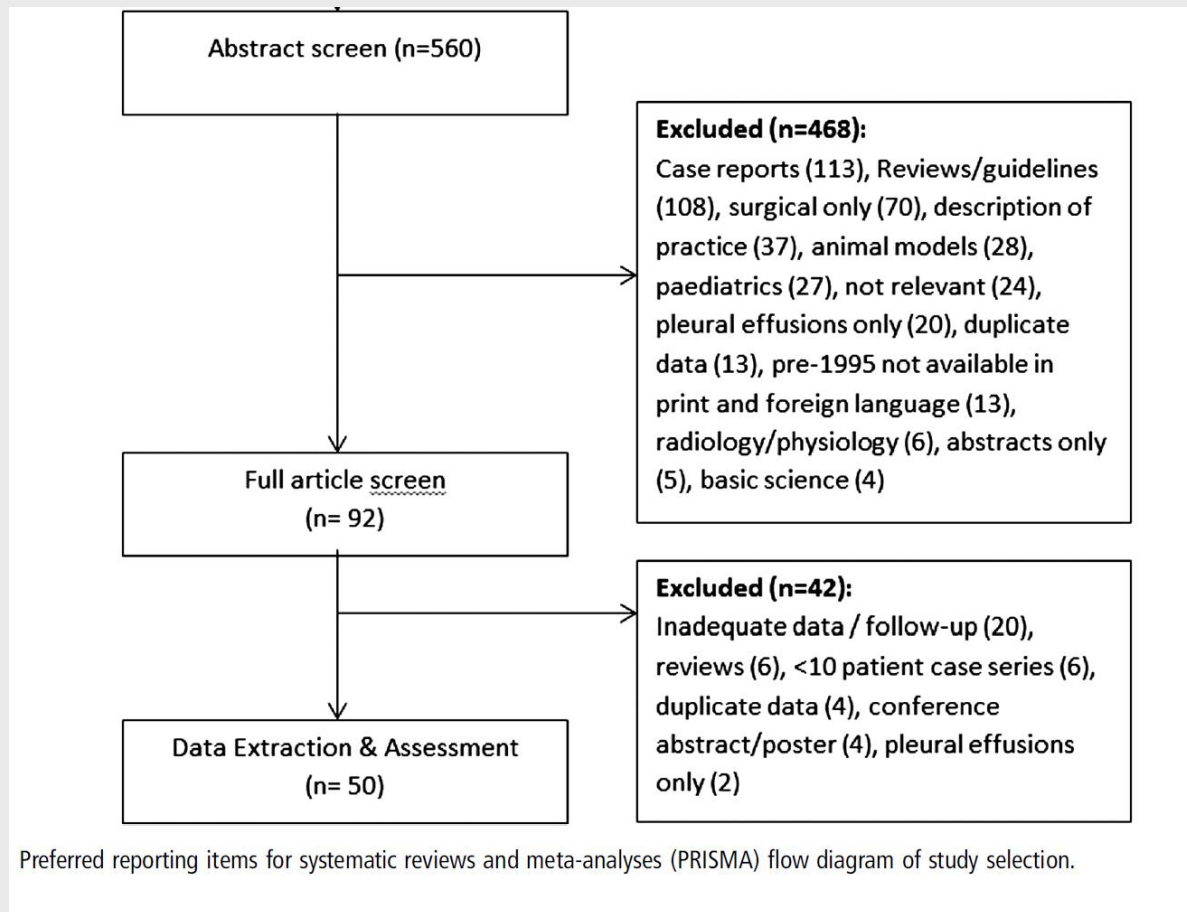
# State of the Art: treatment of spontaneous pneumothorax

Many opinions, little evidence for:

- Surgical or non-surgical treatment
- Surgical treatment: bleb resection or not
- Non-surgical treatment: Chest tube or manual aspiration, observation
- In- or out of hospital treatment
- Different or same treatment for primary spontaneous pneumothorax (PSP) or secondary spontaneous pneumothorax (SSP)

***Pneumothorax; improve the evidence*** (Maskell et al., Thorax 2017,72: 1065)

# Effectiveness of chemical pleurodesis in Sp PTX recurrence prevention: a systematic review



*(Hallifax et al., Thorax, 2017, 72: 1121-31)*

# Effectiveness of chemical pleurodesis in Sp PTX recurrence prevention: a systematic review

- Recurrence rate of pneumothorax:
  - Chest tube only: 26-50%
  - Chest tube plus tetracyclin: 13-33%
  - Thoracoscopic talc poudrage: 2-10%
  - VATS plus talc poudrage: 0-3%

*(Hallifax et al., Thorax, 2017, 72: 1121-31)*

# Effectiveness of chemical pleurodesis in Sp PTX recurrence prevention: a systematic review

- Patients unfit for surgery
  - Without persisting airleak: talc slurry; recurrence rate 13-30%
  - With persisting air leak: autologous blood patch; recurrence rate 15-16%

*(Hallifax et al., Thorax, 2017, 72: 1121-31)*

# Manual aspiration (MA) vs. Intercostal tube drainage (CTD) for primary spontaneous pneumothorax



Manual Aspiration (MA)  
outpatient procedure



Chest Tube Drainage (CTD)  
invasive, inpatient procedure

# Manual aspiration (MA) vs. Intercostal tube drainage (CTD) for primary spontaneous pneumothorax

6 RCT's, of 435 participants

- Immediate success: favours CTD (RR 0.78)
- Duration of hospitalisation: favours MA (-1.7day)
- Adverse events: favours MA
- No difference: one year success rate

*(Carson-Chahoud et al., Cochrane database of systematic reviews 2017)*



# Manual aspiration (MA) vs. Intercostal tube drainage (CTD) for primary spontaneous pneumothorax

| Outcomes   | Illustrative comparative risks (95% CI) |                            | Relative effect (95% CI) | No. of participants (studies) | Quality of the ev (GRADE)      |
|--|---|----------------------------|--------------------------|-------------------------------|--------------------------------|
|  | Intercostal drainage                    | tube Simple aspiration     |                          |                               |                                |
| Immediate success rate<br>Follow-up: 3 days to 24 months | 714 per 1000                            | 557 per 1000 (493 to 635)  | RR 0.78 (0.69 to 0.89)   | 435 (6 studies)               | ⊕⊕⊕○ moderate <sup>a</sup>     |
| One-year success rate<br>Follow-up: 12 to 24 months      | 766 per 1000                            | 820 per 1000 (735 to 904)  | RR 1.07 (0.96 to 1.18)   | 318 (4 studies)               | ⊕⊕⊕○ moderate <sup>a</sup>     |
| Hospitalization rate<br>Follow-up: 3 days to 24 months   | 862 per 1000                            | 517 per 1000 (215 to 1000) | RR 0.60 (0.25 to 1.47)   | 245 (3 studies)               | ⊕○○○ very low <sup>a,b,c</sup> |

*(Carson-Chahoud et al., Cochrane database of systematic reviews 2017)*

# Randomised comparison of manual aspiration (MA) and chest tube drainage (CTD) in spontaneous pneumothorax

Not included in Cochrane review

What makes this study interesting:

- Randomised Multicenter study, including pulmonary and surgery departments in all 3 hospitals
- Inclusion of both PSP (69) and SSP (48) cases
- Procedures by junior physicians (real life study)

*(Thelle et al., Eur Respir J, 2017, 49: 1601296)*

# Randomised comparison of manual aspiration (MA) and chest tube drainage (CTD) in spontaneous pneumothorax

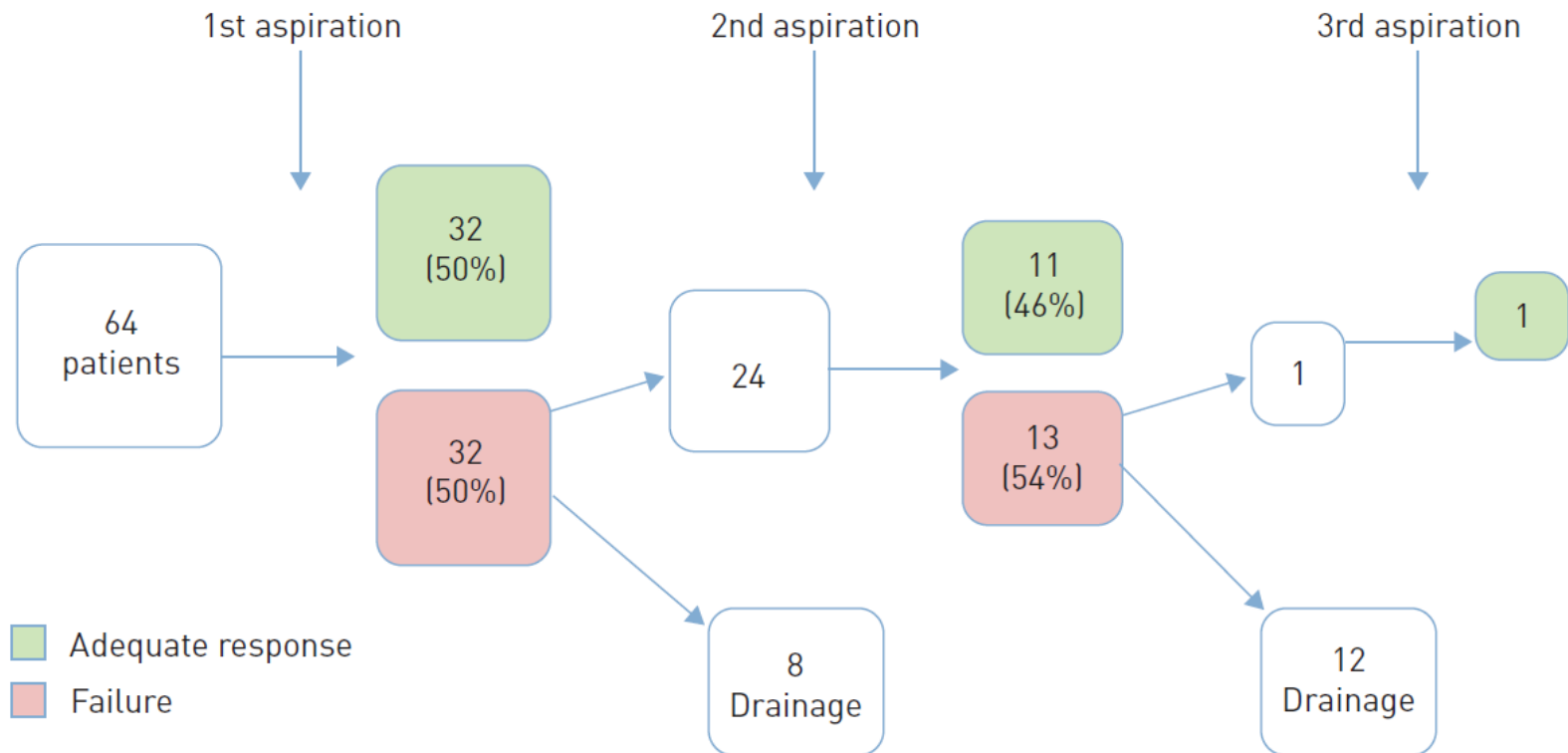


FIGURE 1 Flow of patients in the needle aspiration group.

*(Thelle et al., Eur Respir J, 2017, 49: 1601296)*

# Randomised comparison of manual aspiration (MA) and chest tube drainage (CTD) in spontaneous pneumothorax

- 63 patients underwent CTD, 64 MA (24 twice)
- Primary endpoint: duration of hospital stay
- Hospital stay:
  - MA: 2.4 days, CTD 4.6 Days ( $p < 0.001$ )
  - Subgroup SSP; MA: 2.5 days, CTD 5.5 days ( $p = 0.049$ )

*(Thelle et al., Eur Respir J, 2017, 49: 1601296)*

# Randomised comparison of manual aspiration (MA) and chest tube drainage (CTD) in spontaneous pneumothorax

- Secondary endpoints:
  - immediate- and 1-week success,
  - complications.
- Immediate success MA 69%, CTD 32%  
( $p < 0.001$ )  
also for SSP cases!
- No significant difference in 1-week success rates

*(Thelle et al., Eur Respir J, 2017, 49: 1601296)*

# Randomised comparison of manual aspiration (MA) and chest tube drainage (CTD) in spontaneous pneumothorax

## Secondary endpoint

- Complications:
  - MA: none
  - CTD:
    - wound infection=4,
    - bleeding=2,
    - subcutaneous emphysema=7,
    - pneumonia=1,
    - empyema=1(fatal),
    - replacement of drain necessary=16.

*(Thelle et al., Eur Respir J, 2017, 49: 1601296)*

# Editorial Comment

## Spontaneous pneumothorax: stop chest tube as first-line therapy

Jean-Marie Tschopp<sup>1</sup> and Charles-Hugo Marquette<sup>2</sup>

**Affiliations:** <sup>1</sup>Centre Valaisan de Pneumologie, Montana, Switzerland. <sup>2</sup>Université Côte d'Azur, CHU de Nice, FHU Oncoage, Service de Pneumologie, Nice, France.

Chest tube drainage: painful, may cause complications, unnecessary in-hospital immobilisation.

We need to focus on ambulatory management

*(Thelle et al., Eur Respir J, 2017, 49: 1601296)*

*(Tschopp JM, Eur Resp J, 2017, 49:1700306)*

# **Take-Home Message; Pneumothorax 1**

- For chemical pleurodesis, talc powder is most effective
- If not fit for surgery and no air leak, talc slurry is a good option
- In case of persisting airleak in non-operable patients autologous blood patch is a good alternative



# Take-Home Message;

## Pneumothorax 2

- Manual aspiration has the same success rate as chest tube drainage
- This is also true for secondary pneumothorax
- Manual aspiration has the advantage of
  - Shorter hospital stay
  - Ambulatory treatment of pneumothorax
  - No complication, compared to significant complications in chest tube drainage
  - Safe procedure performed by trained junior doctors

# **Malignant pleural effusion (MPE)**

# Malignant Pleural Effusion

## state of the art

- Halt fluid accumulation:
  - Therapeutic thoracocentesis
  - Indwelling pleural catheter (IPC)
- Pleurodesis
  - Thoracoscopy / talc powder
  - Chest tube / talc slurry
- Successful pleurodesis: lack of recurrence of pleural fluid



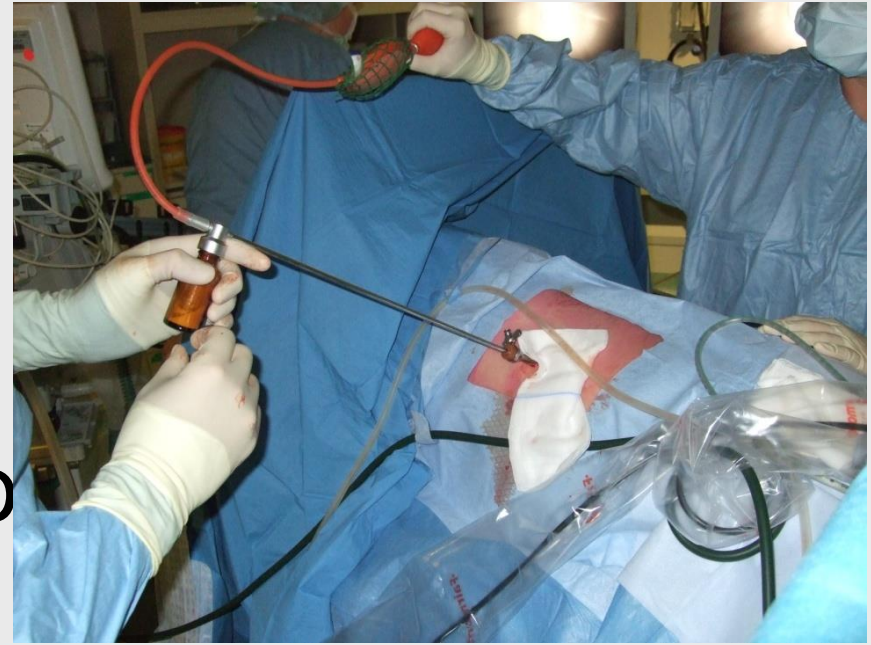
# **Changed attitude: What does your patient want?**

- Reduction of dyspnea and discomfort
- Limited number of interventions
- Limited time spent in hospital
- No intervention with little symptom reduction
- No intervention when life expectancy is limited
  
- Modern aim of MPE treatment:
- Reduction of symptoms
- Outpatient management

# Malignant pleural effusion: IPC or talc pleurodesis?



**Indwelling Pleural Catheter (IPC)**



**Thoracoscopy / talc pleurodesis**

# Malignant pleural effusion: IPC or talc pleurodesis?

## Indwelling Pleural Catheter (IPC)

- Day case placement
- Permanent chest tube
- Frequent drainage of pleural fluid at home
- Spontaneous pleurodesis in 45% after > 50 days
- Infection rate up to 5%

## Thoracoscopy / talc pleurodesis

- In hospital procedure
- Includes tissue-diagnosis
- Pleurodesis rate 70%
- No need for home care

# Urokinase vs placebo for nondraining MPE

- Multicentre study, 12 UK centres
- 71 patients nondraining MPE  
randomized: 36 urokinase, 35 placebo
- Result: no difference in:
  - Dyspnea
  - Pleurodesis failure rate

*(Mishra et al., AJRCCM 2018, 197: 502-8)*

# ASAP trial: randomized trial of pleural fluid drainage frequency of IPC

- In MPE patients with IPC, does daily drainage lead to higher rate of autopleurodesis?
- 149 patients with IPC randomized:
  - 73 daily drainage
  - 76 every other day drainage (control group)

**ASAP trial** (Wahidi et al., AJRCCM 2017, 195: 1050-57)



# ASAP trial: randomized trial of pleural fluid drainage frequency of IPC

- In MPE patients with IPC, does daily drainage lead to higher rate of autopleurodesis?
- Autopleurodesis and IPC removal:
- 47% daily dr. group vs. 24% control group
- Median time to autopleurodesis:
- 54 days daily dr. group vs. 90 days contr. gr.

**ASAP trial** (*Wahidi et al., AJRCCM 2017, 195: 1050-57*)

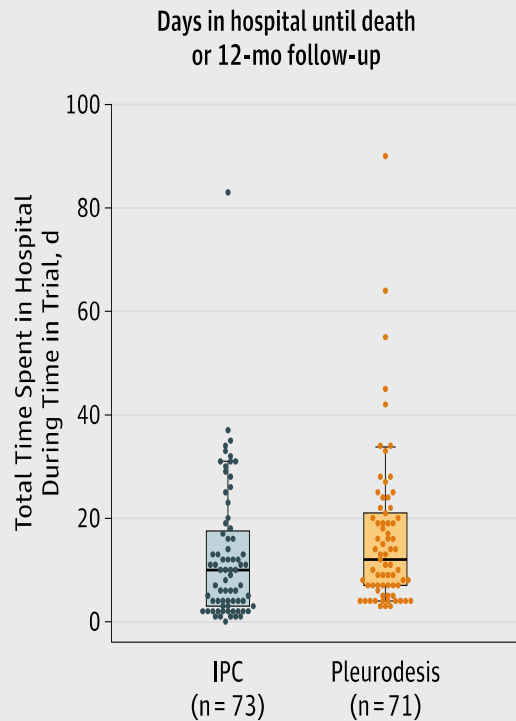
# Effect of IPC vs. Talc pleurodesis on hospitalisation days

- Randomized study 9 ctrs. Austr/Asia
- IPC (n=74) vs. Talc pleurodesis (n=72)
- Primary endpoint: days spent in hospital
- Secondary endpoints: further interventions, Breathlessness, QoL, Adverse events

**AMPLE study** (Thomas et al., JAMA, 2017, 318: 1903-12)

# Effect of IPC vs. Talc pleurodesis on hospitalisation days

Figure 2. Time in Hospital Until Death or 12-Month Follow-up

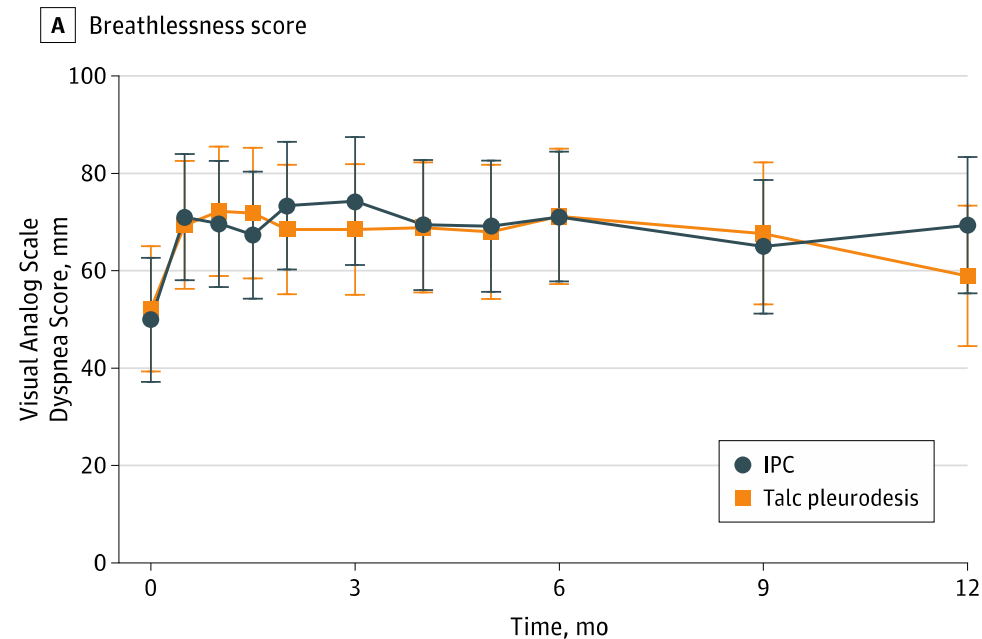


- Hospital days :
  - IPC: 12.7 days
  - Talc: 16.3 days
- Further interventions:
  - IPC: 3 (4.1%)
  - Talc: 16 (22.5%)
- Pleurodesis:
  - IPC: 28.8%
  - Talc: 77.5%

**AMPLE study** (Thomas et al., JAMA, 2017, 318: 1903-12)

# Effect of IPC vs. Talc pleurodesis on hospitalisation days

Figure 3. Comparison of Patient-Reported Outcomes Between Those Randomized to Receive an Indwelling Pleural Catheter (IPC) and Those Randomized to Receive Talc Pleurodesis



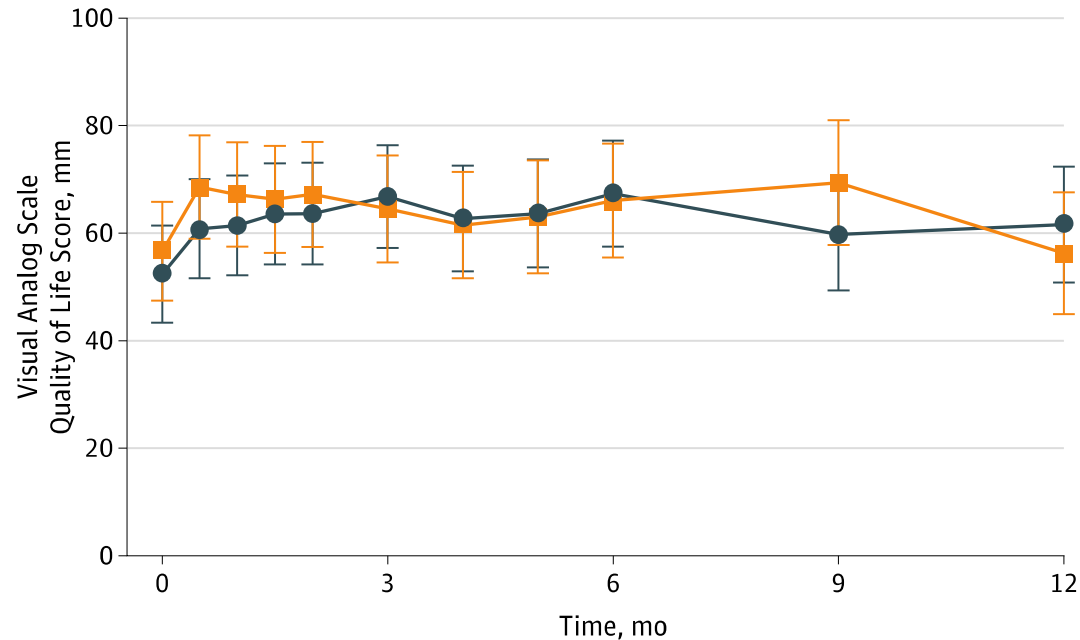
**AMPLE study** (Thomas et al., JAMA, 2017, 318: 1903-12)

# Effect of IPC vs. Talc pleurodesis on hospitalisation days

Group, No.

|             |    |    |    |    |    |    |    |    |    |    |    |
|-------------|----|----|----|----|----|----|----|----|----|----|----|
| IPC         | 66 | 56 | 53 | 49 | 47 | 44 | 37 | 33 | 37 | 27 | 23 |
| Pleurodesis | 64 | 47 | 44 | 38 | 42 | 38 | 39 | 28 | 27 | 18 | 20 |

**B** Quality of life



**AMPLE study** (Thomas et al., JAMA, 2017, 318: 1903-12)

# Outpatient talc administration by indwelling pleural catheter (IPC) for malignant effusion

- Multicentre (18, UK) randomized study
  - IPC in 154 patients.
  - If no lung entrapment at day 10, randomisation 4G talc slurry or placebo
- 70 placebo group, 69 talc group

*(Bhatnagar et al., NEJM 2018, 378: 1313-22)*

# Outpatient talc administration by indwelling pleural catheter (IPC) for malignant effusion

- 70 placebo group, 69 talc group
- Pleurodesis at day 35:
  - 30/69 (43%) in the talc group
  - 16/70 (23%) in the placebo group ( $p=0.008$ )
- No adverse events in both groups
- Conclusion: combination of IPC and talc > significantly more pleurodesis

*(Bhatnagar et al., NEJM 2018, 378: 1313-22)*

# IPC plus pleurodesis: Drug Eluting IPC

- IPC with slow-release coating of silver nitrate (100 mg)
- 10 patients, mean age 70.
- 4 anti-cancer therapy
- 69 AE, 17 device related: one SAE : chest pain requiring removal
- Pleurodesis 89% (8/9)
- Time to pleurodesis 4 days, maintained at day 60.

***SEAL-MPE study*** (Bhatnagar R., AJRCCM 2018,197:136-7)



# Take Home Message

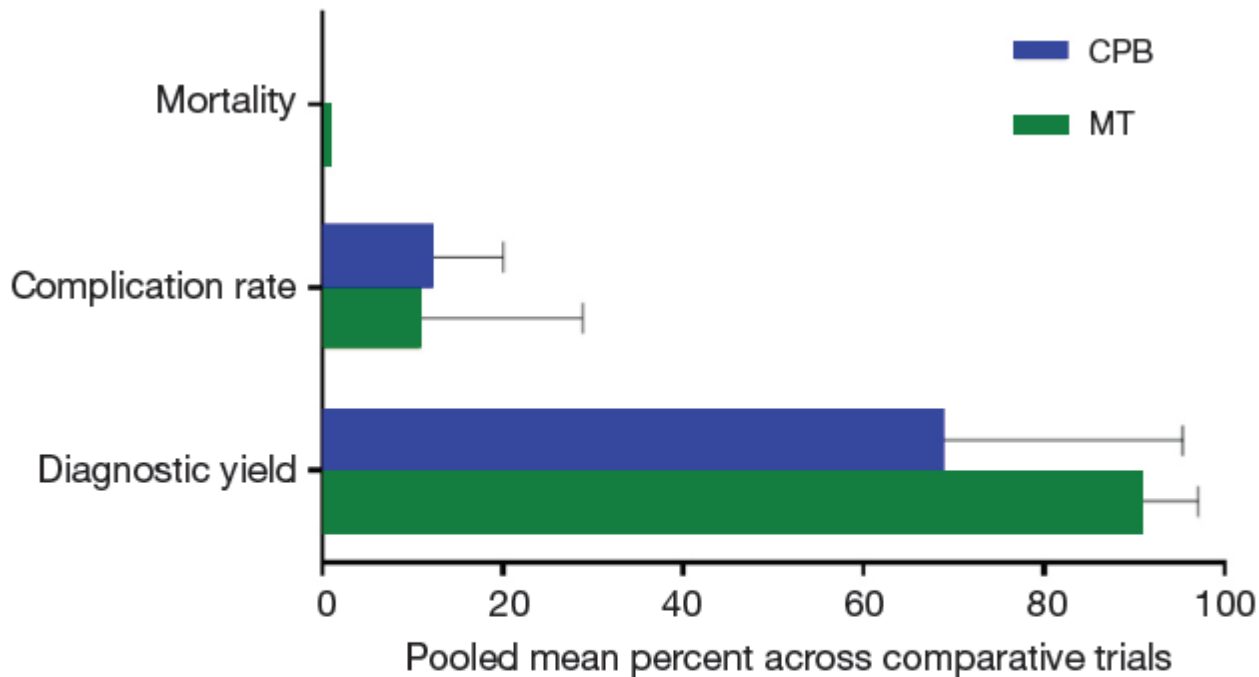
- Future:
  - better selection of patients who will benefit from:
    - Talc (poudrage or talc slurry (TAPPS trial))
    - Indwelling Pleural Catheter
- Combination of pleurodesis and IPC:
  - IPC removal in 43% within 35 days
  - Drug eluting IPC
- ERS task force statement malignant pleural effusion is on the way

# Thoracoscopy

# State of the Art

- Thoracoscopy is the gold standard as diagnostic and therapeutic procedure in pleural disease
  - In hospital procedure
  - Day case procedure?
  - Role of Closed Pleural Biopsy (CPB)?

# Evolving role of thoracoscopy in the diagnosis and treatment of pleural disease



**Figure 1** Pooled analysis (mean and SD) of trials directly comparing CPB and medical thoracoscopy (6,12-15). CPB, closed pleural biopsy.

(Murthy et al., *J Thorac Dis*, 2017, 9: S1011-21)

# Provision of Day-Case Local Anesthetic Thoracoscopy

- Multicentre review of practice
- 5 centres: 4 UK, one USA
- 202 day-case thoracoscopies
- 98% without complications
- Diagnostic yield 97%

*(Psallidas et al., Chest, 2017, 151: 511)*

# Take-Home Message

- Thoracoscopy is the gold standard as diagnostic and therapeutic procedure in pleural disease
- Diagnostic yield and complication rate better than closed pleural biopsy
- Day-case thoracoscopy is a convenient alternative to the traditional inpatient approach with excellent diagnostic yield and safety profile

# The future: clinical trials

- PLEASE: factors of effusion-related dyspnea
  - TAPPS: Talc slurry vs. Thoracoscopic talc poudrage
  - OPTIMUM: QoL outpatient IPC vs. talc slurry
  - SWIFT: IPC +/- Silver nitrate
- 
- ERS task force statement malignant pleural effusion is on the way

# List of References

1. Janssen JP et al., Clin Resp J, in press
2. Vakil et al., Respirology, 2018, 23: 213-218
3. Maskell et al., Thorax 2017,72: 1065
4. Hallifax et al., Thorax, 2017, 72: 1121-31
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11. Thomas et al., JAMA, 2017, 318: 1903-12
12. Bhatnagar R., AJRCCM 2018,197:136-7
13. Murthy et al.,J Thorac Dis, 2017, 9: S1011-21
14. Psallidas et al.,Chest, 2017, 151: 511



# List of Abbreviations

- NSP = Non specific pleuritis
- PSP = primary spontaneous pneumothorax
- SSP = secondary spontaneous pneumothorax
- Sp PTX = spontaneous pneumothorax
- MA = manual aspiration
- CTD = chest tube drainage
- MPE = Malignant pleural effusion
- IPC = Indwelling pleural catheter
- QoL = Quality of life
- CPB = Closed pleural biopsy