Management of Malignant Pleural Effusions
An update

Lung Cancer and Mesothelioma
MPE

• Common
  – 15% all cancers
  – Increasing
  – Represents advanced or metastatic disease
  – Poor survival

• Lots of high quality trials in recent years
  – Bit confusing

• ERS Statement: *Eur Respir J* 2018; 52: 1800349
• Optimal management of symptomatic MPE
• Prognostic factors
• Role of oncological treatments
• Is histology required?
• Management of trapped lung
• Management of loculated MPE
• **Optimal management of symptomatic MPE**
• Prognostic factors
• Role of oncological treatments
• Is histology required?
• Management of trapped lung
• Management of loculated MPE
• MPE usually associated with significant symptoms

• Majority experience fluid re-accumulation after aspiration

• Need a definitive intervention to provide long term relief from symptoms

• NOT serial aspirations
Chemical Pleurodesis

- 3 systematic reviews
  - Silver nitrate pleurodesis rates of 89-96%
  - Talc slurry 84%
- Good evidence for silver nitrate when talc fails
- Talc better than Bleomycin / Doxycycline
- Large particle (graded) talc NOT mixed
- Lack of patient reported outcomes
Talc: Poudrage vs Slurry

• Poudrage (at VATS or MT) better than slurry
  – Higher pleurodesis success rates
  – Shorter drain duration
  – Longer effusion-free survival

• BUT poudrage *may* have higher risk of complications
  – Appears to only be related to non-graded talc
Does size matter?

• 2 previous studies found no difference in pleurodesis rates between 10F and 24F drains
  – Underpowered; not designed as non-inferiority

• Oxford group **TIME1 JAMA 2015**
  – 2x2 RCT: opiates vs NSAIDs and 12F vs 24F drains
  – 320 patients
  – Small bore tubes failed to meet non-inferiority margin (30% vs 24% pleurodesis failure)
Other issues with pleurodesis

• Pain
  – NSAIDs traditionally avoided – no need

• Effect on survival??
  – Talc poudrage associated with longer survival compared to repeated aspirations in 1 study
  – Poor PS and previous chemo/radiotherapy associated with poorer survival post talc poudrage
Surgical options

• Pleurectomy / abrasions are effective
• 4 RCTs comparing surgery with ‘medical’ pleurodesis
• No significant difference (but shorter stay in surgical group)

• Rintoul et al (J Thorac Oncol 2013;8:s2-s3)
  – 196 Mesothelioma patients
  – VATS pleurectomy vs Talc pleurodesis (poudrage or slurry)
  – No difference in pleurodesis rates
  – VATS associated with higher expense and adverse events
Indwelling Pleural Catheters
Indwelling Pleural Catheters (IPCs)

• Alternative to pleurodesis (?)
• Long term symptom control via regular home drainage
• Multiple case series (1533 patients) reporting improved breathlessness and QOL
• Systematic review of 19 case series (1370 patients) reported symptomatic improvement in 96% with removal due to complications required in 8.5%
IPC

- 4 RCTs comparing IPC with chemical pleurodesis:
  - TIME 2 *(JAMA 2012; 307: 2383-2389)*
  - AMPLE *(JAMA 2017; 318: 1903-1912)*
  - Demmy et al *(CALGB J Natl Compr Canc Netw 2012; 10: 975-982)*
IPC

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TIME2

- IPC vs in-patient talc slurry via 12F drain
- Primary outcome = patient reported breathlessness
- No significant difference in dyspnoea scores
- Small difference favouring IPC at 6 months
- IPC reduced time in hospital (0 vs 4 days)
- IPC reduced need for further procedures
AMPLE

- 146 MPE patients IPC vs talc via chest drain
- IPC shorter hospital stay
- Fewer subsequent pleural interventions
- Both groups reported sustained improvements in SOB, QOL – no difference between 2 arms
- Complications higher in IPC group (but only 1x SAE)
IPC drainage regimens

  - 11 centres
  - Symptomatic MPE
  - Daily vs symptom guided drainage over 60 days
  - 6 month FU
  - SOB / spontaneous pleurodesis (SP) / QOL
  - No difference in breathlessness control
  - Earlier SP in aggressive group with some effect on QOL
Combined procedures
**Trial flowchart**

**Pleural effusion**

**Inclusion criteria**
1. Symptomatic malignant pleural effusion, agreed at appropriate local/regional level to require IPC defined as pleural fluid in the context of:
   - Histologically proven pleural malignancy OR
   - Otherwise unexplained pleural effusion in the context of clinically proven cancer elsewhere OR
   - Radiologically proven pleural malignancy as diagnosed in normal clinical practice on thoracic CT in the absence of histological proof
2. Expected survival greater than 2 months and WHO/EORTC PS 0 or 1. Patients with a PS of 3 may be included if in the view that removal of pleural fluid would improve their performance status to 2 or better
3. Written informed consent to trial participation

**Exclusion criteria**
1. Age > 80 years
2. Females who are pregnant or lactating
3. Patient unable to provide informed consent
4. Previous attempt of pleurodesis within the last 56 days on same side as effusion requiring management
5. Previously documented adverse reaction to talc or tetracycline
6. Community services unable to drain indwelling pleural catheter at least twice per week
7. Evidence of active lung entrapment on CXR or CT, or significant fluid collection on ultrasound, to a level which would normally be a contraindication to attempted talc pleurodesis or IPC insertion
8. Other contraindication to indwelling pleural catheter insertion
9. Patient has no access to a telephone

**Baseline assessment**

**Insertion of indwelling pleural catheter as day case**

**No significant lung entrapment at Day 10 post IPC insertion**

**RANDOMISATION**

Randomisation by volume of fluid drained in first 10 days (≤1000mls or >1000mls), presence of trapped lung (present, but must randomisation criteria or none), and type of underlying malignancy (metastatic breast and ovarian cancer only)

**TALC ARM**
4g sterile talc slurry via IPC. Patients blind.

**PLACEBO ARM**
30ml 0.9% saline via IPC. Patients blind.

**10 week follow-up period**

Standard care = community drainage of IPC (must be done by healthcare professional for first 28 days post randomisation), minimum frequency of twice per week, volumes to be documented.

Daily self-assessed VAS for thoracic pain and S00.

Assessments at 2 weekly intervals at trial centre (Visits Day 42 and Day 56 may be done via telephone)

Each assessment performed at trial centre to be preceded by IPC drainage and chest x-ray, then to include VAS chest, performance status, quality of life questionnaires, and documentation of cumulative drainage volumes and previous 2 weeks' VAS scores.

Successful pleurodesis = 50mls or less of fluid drained on 3 consecutive occasions, confirmed on chest x-ray and USS.

**Primary endpoint:** number of patients with successful pleurodesis at 5 weeks
IPC-plus

• 18 UK centres, 4 years, 154 patients (584)
• 43% Pleurodesis in talc vs 23% placebo
• No difference in effusion size, complexity, in-patient days, mortality or AE’s

• In patients without lung entrapment, OP talc via IPC results in significantly higher chance of successful pleurodesis (at 35 days) without deleterious effects
Summary

• Talc most effective agent for chemical pleurodesis
• Poudrage at VATS or MT may be slightly more effective than slurry (TAPPS trial will hopefully clarify)
• Surgical procedures are no more effective than talc, especially in mesothelioma
• Large bore tubes are associated with higher successful pleurodesis rate
• NSAIDs do not lower pleurodesis rates
• IPCs are as effective as talc but with advantage of reduced IP stay
• Combined IPC with talc is associated with significantly higher rate of pleurodesis
Questions?