

Management of malignant pleural effusions in a Palliative Care/Oncology setting

This CPG was devised from a targeted literature review, rather than a more formal rigorous and very time consuming 'systematic literature review process' as defined by the 'Cochrane collaborative process'. The Cochrane database has been searched and referred to frequently for up to date information.¹ Recent articles were particularly looked for (since 1996), with an emphasis on finding and reading systematic literature reviews identified via Medline, CINAHL, Cochrane and the Journal of Palliative Medicine. The CPG derived has been peer reviewed locally for implementation and has been trialled in our hospital unit over the last six months and refined.

Major references used were:

- Antunes g et al 2003 *BTS guidelines for the management of malignant pleural effusions Thorax 2003;58 (Suppl II):ii29-ii38*
- Shaw P et al 2004 *Pleurodesis for malignant pleural effusions (Cochrane Review) Cochrane Library, Issue 2, 2004*
- American Thoracic Society 2000 *Management of Malignant Pleural Effusions Am J Respir Crit Care Med Vol162,pp1987-2001, 2000*
- Lee G et al 2004 *Management of malignant pleural effusions Respirology 9,148-156, 2004*
- West S et al *Pleurodesis for malignant pleural effusions: current controversies and variations in practices Curr Opin in Pulm Med 10:305-310, 2004*
- Davies C, et al (1999) *Intrapleural streptokinase in the management of malignant multiloculated pleural effusions Chest 1999; 115:729-733*
- Spiegler P, et al (2003) *Rapid pleurodesis for malignant pleural effusions Chest 2003; 123:1895-1898*

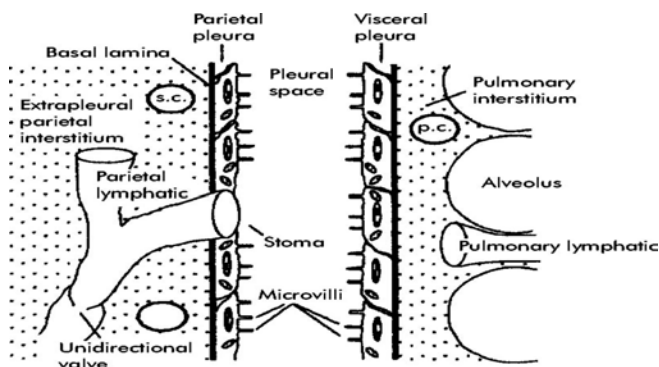
The British Thoracic Society has provided a clear system for grading evidence and derived recommendations. This was published in *Thorax 2003; 58(Suppl II)* and summary tables, from the introduction, appear below:

Grading the evidence	Grading the recommendations
Ia Meta-analysis of randomised trials Ib Randomised controlled trial	A (Supported by paper(s) of levels Ia or Ib) Requires at least one randomised trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation B (Supported by paper(s) of levels IIa, IIb or III) Requires the availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation (or poor/inadequate randomised trials not supported by sufficient other literature to achieve grade A) C (supported by level IV evidence) Requires evidence from expert committee reports or opinions &/or clinical experience of respected authorities.
IIa Well designed controlled study without randomisation	
IIb Another type of well designed quasi-experimental study	
III Well designed non-experimental descriptive Studies such as comparative studies, Correlation studies & case control studies	
IV Opinion of expert committee reports or opinions and/or clinical experience of respected authorities	

Etiology, some stats. & Demographics:

- Aust. & NZ estimates are of 13,000 patients per annum with malignant pleural effusions
- Up to 50% of pleural effusions referred to respiratory units per year are found to be malignant
- 13% of patients with cancer present with a pleural effusion
- Lung, Breast, Lymphoma, Ovary account for >80%
- CUP & GIT account for approx. 18%

Pathophysiology:



Mechanisms:

- Involvement/obstruction of lymphatic drainage parietal pleura (affecting normal pleural fluid circulation & drainage) or mediastinal LN disruption of lymphatic flow
- Direct Ca. invasion of visceral or parietal pleura – exudate production
- Local inflammatory changes: may be related to VEGF (a potent inducer of vascular permeability)

Paramalignant causes:

- Post obstructive pneumonia
- obstruction of thoracic duct
- P.E.
- Atelectasis
- Low oncotic pressure due to low albumin secondary to cachexia
- Iatrogenic: XRT & ChemoRx
- Co-morbidities: CCF etc.
- SVC obstruction – transudate due to increased systemic pressure

Practices specific to our unit:

- Hardly any pleurodeses at start of project, little collaboration with respiratory physicians, patients are either dealt with by respiratory team or oncology team
- Up to one litre of pleural fluid drained at a time, no use of Streptokinase to either overcome loculations or effect complete drainage
- Use of large bore ICCs (>22G) to drain pleural effusions, if pleurodesis contemplated

Common reasons to drain MPE's

- Dyspnoea
- Orthopnoea
- Cough
- Pain – especially associated with effusions related to mesotheliomas and parietal pleura invasion (visceral pleura has no pain fibres)
- Mediastinal shift: cardiac compromise or haemodynamic instability

Relative Contraindications to Thoracentesis

- Little fluid as increases risk of pneumothorax etc.
Increased risk of haemorrhage:
- PT or APTT >2X normal
- INR > 1.5
- Moderate to severe renal failure
- Plt <50,000

Costs of Equipment used

- Cannula + connectors etc. \$15
- Thoracentesis kit (metal) \$40
- Pig-tail drain sealed \$80
- Intercostal catheter + u/water \$65
- Safe-T-Centesis with pig-tail \$116

Management Options: (main)

- Observation if asymptomatic
- Therapeutic pleural aspiration, although ~100% recurrence by 1 month
- Caution if draining >1.5 litres as increased risk of re-expansion pulmonary oedema (RPO)
- Complete drainage and chemical pleurodesis early (>60% success rate, should be reflected in referral patterns especially if symptomatic relief with thoracentesis and good performance status & prognosis >3/12)

Management Options: (less common)

- Long term indwelling catheter – increased infection risk
- Pleuroperitoneal shunt – suitable for intractable effusions and trapped lung (good performance status required to manage shunt, not recommended for mesothelioma due to risk of peritoneal spread, also 25% occlusion risk)
- Pleurectomy – significant morbidity and mortality (10-13% mortality: with open Sx, less with VATS)

Notes on Repeated Therapeutic Pleural Aspiration:

- Some evidence that repeated thoracentesis increases the likelihood of multiloculation by inducing the local release of proinflammatory cytokines such as TNF- α , IL-8 & PAI-1 which subsequently leads to increased fibrin formation
- Although there seems to be a small but significant non-fibrinous group that also do not have great success rates with pleurodesis (60% vs >90%) who do not have induced increase in fibrin

Complete drainage and chemical pleurodesis early (>60% success rate)

- Insert small bore ICC (~14F)
- Controlled drainage of pleural fluid to avoid RPO (no more than 1.5L in 24hrs & <500mls/hr) +/- suction (high vol./low pressure: max -20cm H₂O) & Cease steroids
- Confirm full re-expansion on CXR
- Administer premed (e.g. Fent/Midaz), Instill Lignocaine intrapleural (3mg/kg max 250mg)
- Instill Talc Slurry (>15micro.m particle size) & clamp for upto 4 hours (no need for rotation)
- Reconfirm full re-expansion and remove ICC

Effecting complete drainage:

- No evidence that use of intrapleural streptokinase (IPSK) or urokinase (IPUK) (more expensive) is contra-indicated in Malignant Pleural Effusions: so far several small studies 1999-2001 showing great benefit of these agents in effecting complete drainage and allowing subsequent successful pleurodesis.
- IPSK 250,000 amps. 1-6X allows complete drainage in multiloculated effusions, but not in trapped lung situations.

Talc Controversies:

- Talc pleurodesis can be followed by systemic (rise in CRP) & pulmonary inflammation (ARDS - 40 cases worldwide):
- ? Related to particle size < 15micro.m (mixed/small talc USA vs France larger graded talc: ARDS rarer), (smaller particles found in lung, liver, spleen, kidney & brain)
- ? Related to dose >5g Talc
- Induced inflammatory IL8 by mesothelial cells and fibroblasts needed for pleurodesis may be systemically absorbed

Cochrane 2004:Pleurodesis review

- 30 Day success rate for Talc is >90% (complete ~50% & ~40% partial (comparable rates are not seen for any other substances)
- Bleomycin 60-70% (total)
- Others used are Doxycycline, OK432 (Japan), Quinacrine (Scandinavia), iodoprovidone, silver nitrate at best approach 65% (total)

Novel Agents being tested

- TGF - β transforming growth factor beta, a unique cytokine that upregulates collagen production without increasing IL-8 from mesothelial cells, hence may increase success of pleurodesis whilst decreasing side effects of pain & fever
- OK432 & other anti VEGF path factors

ⁱ Shaw P, et al (2004) *Pleurodesis for malignant pleural effusions (Cochrane Review)* **Cochrane Library**, Issue 2, 2004