# INTRAPLEURAL AGENTS FOR PLEURODESIS AND FIBRINOLYSIS

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# 1. PLEURODESIS AGENTS

# CONTENTS

# DEFINITION

- Pleurodesis is a procedure to achieve symphysis between the two layers of pleura aimed at preventing accumulation of either air or fluid in the pleural space
- Methods:
  - Chemical pleurodesis : achieved by either a chemical agent
  - Mechanical pleurodesis : by physical abrasion of the pleural surfaces during thoracotomy or thoracoscopy
- Abrasion or the sclerosant stimulates an inflammatory reaction within the pleural cavity, which results in fusion of the visceral and parietal pleura

Agarwal R et al. Indian J med Res. 2012 Mar; 135(3): 297–304

# METHODS USED FOR CHEMICAL PLEURODESIS

- Intercostal chest tube drain ( Bedside or slurry pleurodesis)
  - Chest tube drainage of the pleural fluid followed by sclerosant instilled into the pleural space via the drain to induce inflammation
- Thoracoscopy
  - Medical thoracoscopy – performed under conscious sedation
  - Surgical thoracoscopy (VATS)– performed under general anaesthesia
  - Here, pleural cavity is visualized using a fibre optic camera and pleurodesis agent is instilled using insufflation (poudrage)

*ATS 2018 guidelines*

# INDICATIONS FOR PLEURODESIS

A. Malignant pleural effusions
B. Pneumothorax
1. Secondary spontaneous pneumothorax
2. Primary spontaneous pneumothorax with any one of the following:
   - Second episode of PSP
   - Persisting air leak >3–5 days
   - Haemopneumothorax
   - Bilateral pneumothorax
   - Professions at risk (aircraft personnel, divers)

C. Benign pleural effusions (Recurrent and undiagnosed)

Tschopp JM et al. Eur Respir J. 2015 Aug;46(2):321-35
BTS GUIDELINES 2010

# INDICATIONS FOR PLEURODESIS

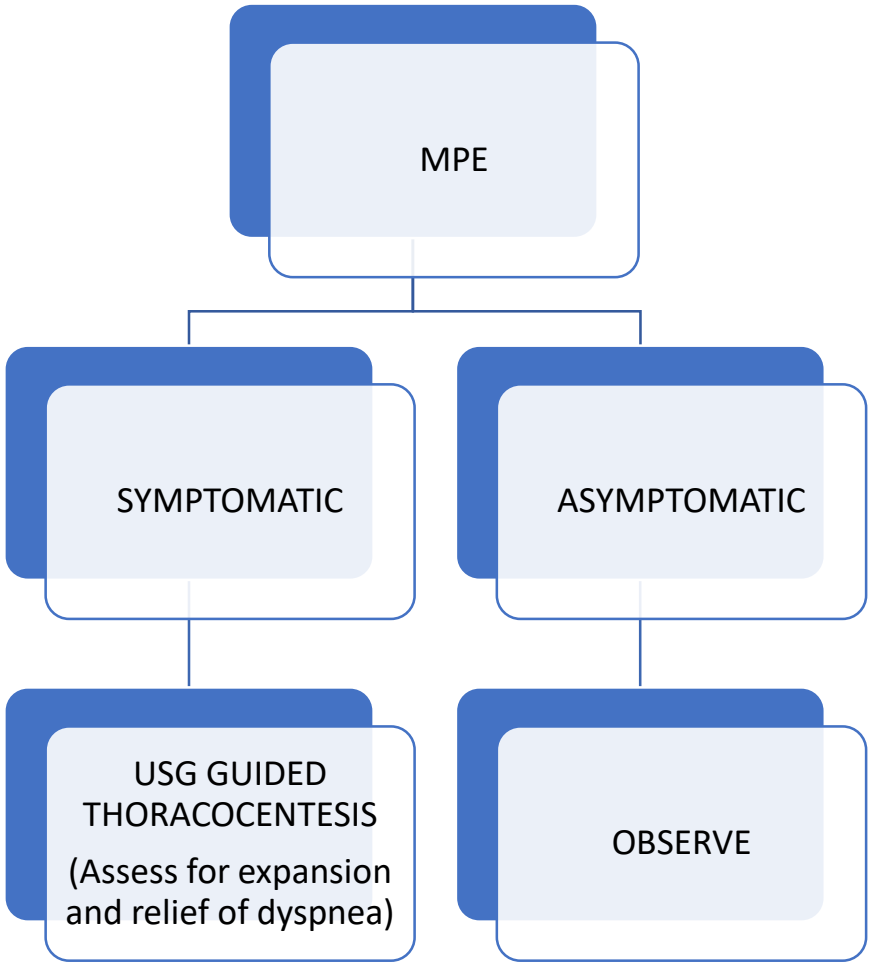
C. Benign pleural effusions
   1. Peritoneal dialysis
   2. Chylous effusion
   3. Catamenial effusion/pneumothorax
   4. Systemic lupus erythematosus
   5. Hepatic hydrothorax

# CONTRAINDICATIONS

- No absolute contraindications
- Lung transplantation – not a contraindication but some centres advice against pleurodesis
- Severely debilitated patients

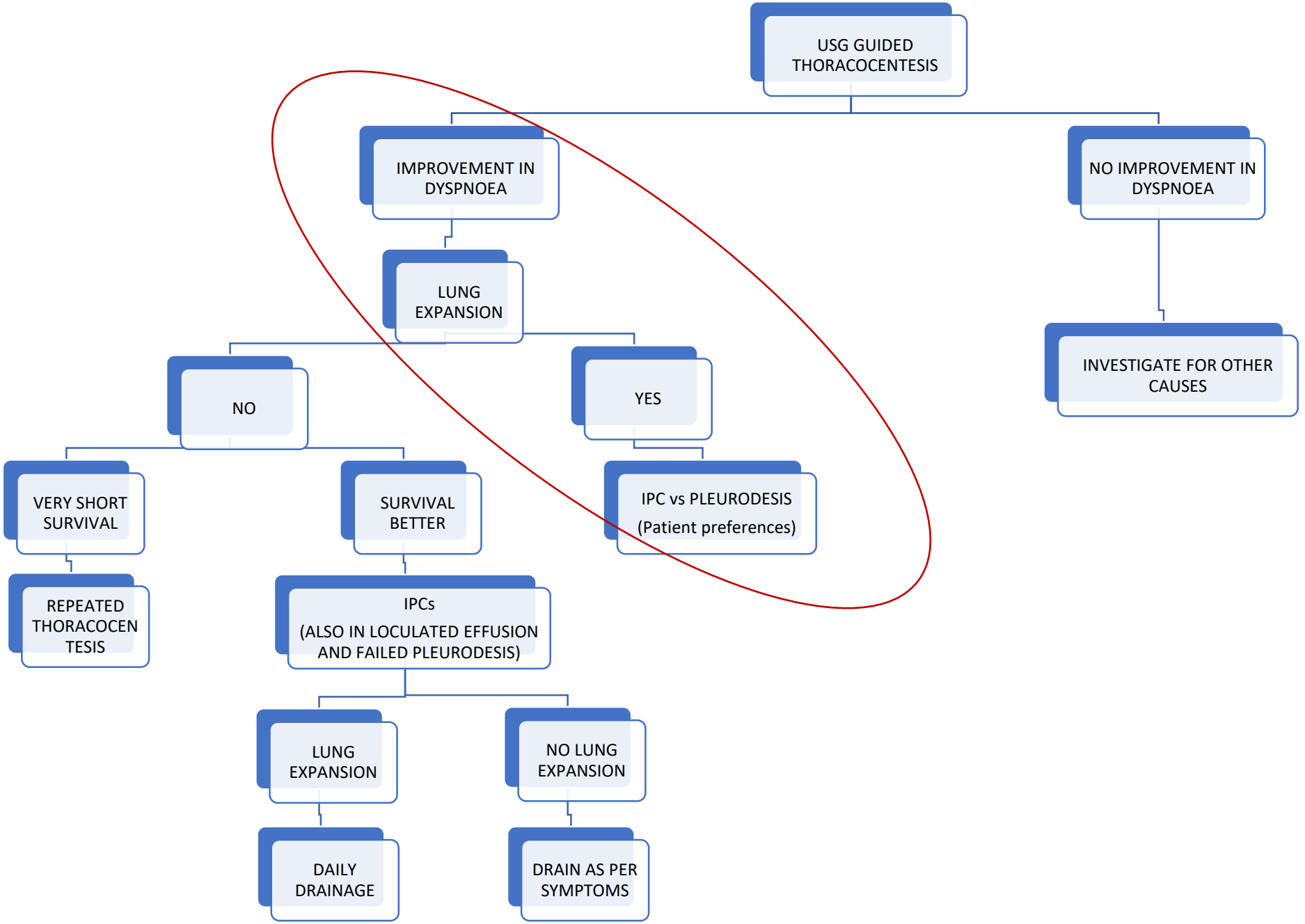
Mercer RM. Expert Rev Respir Med. 2018 Apr;12(4):323-4

# WHEN TO DO PLEURODESIS IN MALIGNANT PLEURAL EFFUSION?




IPCs - Indwelling Pleural Catheters
MPE – Malignant Pleural Effusion

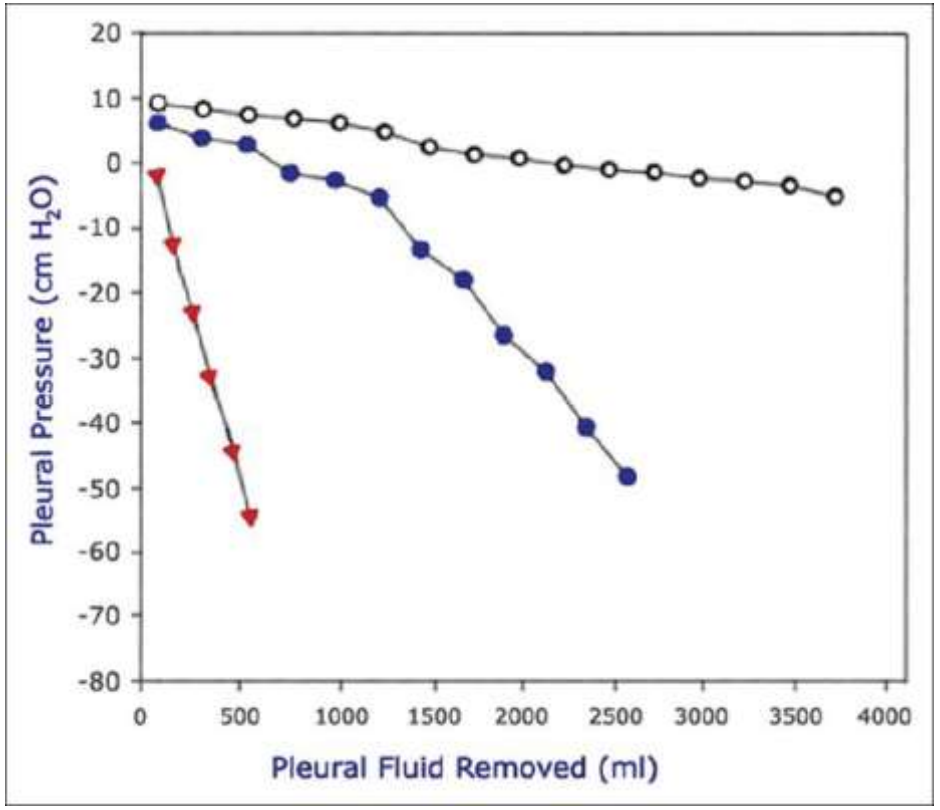
*ATS 2018 guidelines*




*ATS 2018 guidelines*

# HOW TO IDENTIFY EXPANDABLE LUNG?

## Pleural Manometer




- Expandable lung - Gradual fall from Positive pressure to negative pressure
- Entrapped lung - Already negative pressure and there is an abrupt fall after pleural tapping

(i) Open circles – plain hydrothorax
(ii) blue-closed circles – entrapped lung
(iii) red-closed triangles – pleural fibrosis

Chawla et al. Lung India. 2016 Jul-Aug; 33(4): 468–70

# CAN PLEURAL PRESSURES PREDICT SUCCESSFUL PLEURODESIS ?

| **Study** | Prospective cohort study |
|---|---|
| Subjects | 65 patients with symptomatic malignant pleural effusion |
| Intervention | Chest tube insertion and pleurodesis with bleomycin |
| Measurement | Fall in pleural pressure after draining 500 ml fluid |
| Outcome | Elastance of $\geq$ 19 cmH2O – higher failure rates of pleurodesis |

*Elastance – Fall in pleural pressure*

Lan Rs et al. Ann Intern Med. 1997 May 15;126(10):768-74

# IPCs vs PLEURODESIS IN EXPANDABLE MPE

| STUDY | SUBJECTS | INTERVENTION | Dyspnoea score improvement | Duration of Hospitalisation |
|---|---|---|---|---|
| Putnam JB Jr et al[1] | 144 | 2:1 (IPCs vs Doxycycline pleurodesis) | Similar | **IPCs < Doxycycline pleurodesis** |
| NVALT 14 trial[2] | 94 | 1:1 (IPCs vs Talc pleurodesis) | Similar | **IPCs < TP** |
| TIME2[3] | 106 | 1:1 (IPCs vs Talc pleurodesis) | Similar | **IPCs < TP** |
| AMPLE[4] | 146 | 1:1 (IPCs vs Talc pleurodesis) | Similar | **IPCs < TP** |

TP- Talc pleurodesis
IPCs – Indwelling pleural catheters

[1]Putnam JB Jr et al. Cancer. 1999 Nov 15;86(10):1992-9
[2]Boshuizen RC et al. Lung Cancer. 2017 Jun;108:9-14
[3]Davies HE et al. JAMA. 2012 Jun 13;307(22):2383-9
[4]Thomas R et al. JAMA. 2017 Nov 21;318(19):1903-12

# CHEMICAL VS MECHANICAL PLEURODESIS IN MALIGNANT PLEURAL EFFUSION

Pleural abrasion is not currently used in the control of recurrent neoplastic pleural effusions due to its lesser efficacy, as well as due to the high risk of bleeding in the regions involved and to the possibility of tumor dissemination

Vaz MC et al. J Bras Pneumol. 2006;32(4):347-56

# CHEMICAL VS MECHANICAL PLEURODESIS IN PRIMARY SPONTANEOUS PNEUMOTHORAX

| Study | Year | Patients | Mean follow up (months) | Recurrence rate % |
|---|---|---|---|---|
| **Simple talc poudrage under medical thoracoscopy** | | | | |
| TSCHOPP | 2002 | 59 | 60 | 5 |
| BOUTIN | 1991 | 505 | 42 | 7 |
| EL KHAWAND | 1995 | 142 | 39 | 6 |
| GYÖRIK | 2007 | 56 | 118 | 5 |
| **Talc poudrage with VATS and surgical treatment of lung lesions** | | | | |
| CARDILLO | 2006 | 861 | 52.5 | 1.73 |
| CARDILLO | 2000 | 279 | 38 | 1.27 |
| **Mechanical abrasion** | | | | |
| GOSSOT | 2004 | 111 | 36.5 | 3.6 |
| LANG-LAZDUNSKI | 2003 | 167 | 93 | 3 |
| **Pleurectomy** | | | | 2 |
| AYED | 2003 | 100 | 48 | |

Tschopp JM et al. Eur Respir J. 2015 Aug;46(2):321-35

# ROLE OF PLEURODESIS IN PNEUMOTHORAX

- The rate of recurrence following surgical pleurodesis via thoracotomy or VATS is far less than following simple medical pleurodesis with chemical agents

- *Chemical pleurodesis can control difficult or recurrent pneumothoraces but, since surgical options are more effective, it should only be used if a patient is either unwilling or unable to undergo surgery*

BTS GUIDELINES 2010

# IDEAL SCLEROSANT

- A high molecular weight and chemical polarity
- Low regional clearance
- Rapid systemic clearance
- Steep dose-response curve
- Minimal or no side effects
- Easily available
- Easy to administer
- Inexpensive

Agarwal R et al. Indian J med Res. 2012 Mar; 135(3): 297–304

# PLEURODESIS AGENTS

- CHEMICAL AGENTS
  - Talc
  - Iodopovidone
  - Antimicrobials:
    - Tetracyclines: (Tetracycline, minocycline, doxycycline, tigecycline )
    - Quinacrine
  - Cytotoxic drugs (bleomycin, mitoxantrone, mitomycin, carboplatin)
  - Bevacizumab
  - Silver nitrate
  - Sodium hydroxide
  - 50% glucose

Mercer RM. Expert Rev Respir Med. 2018 Apr;12(4):323-4

# PLEURODESIS AGENTS

- BIOLOGICAL
  - Corynebacterium parvum
  - OK 432
  - Staphylococcal superantigen
  - Viscum album (mistletoe)
  - Recombinant tumor necrosis factor
  - Platelet-rich plasma and fibrin glue
  - Blood patch

Mercer RM. Expert Rev Respir Med. 2018 Apr;12(4):323-4

# TALC

- Talc ($Mg_3Si_4O_{10}(OH)_2$) is a trilayered magnesium silicate sheet that is inert and was first used as a sclerosing agent in 1935
- Administered in two ways :
  - Talc poudrage - at thoracoscopy using an atomiser (or)
  - Talc slurry - via an intercostal tube in the form of a suspension
- Success rates range from 81-100% in malignant effusions and around 91% success rates in pneumothorax
- Both methods are equally efficacious in malignant effusion
- Most common side effects : Pleuritic pain, fever

BTS GUIDELINES 2010

# PROCEDURE – TALC SLURRY PLEURODESIS

- Insert small-bore intercostal tube (10F to 14 F)
- Controlled evacuation of pleural fluid
- Confirm full lung re-expansion and position of intercostal tube with chest x-ray
- Administer premedication prior to pleurodesis (no recommendation)
- Instill lidocaine solution (3 mg/kg; maximum 250 mg) into pleural space followed by 4-5 g sterile graded talc in 50 ml 0.9% saline
- Clamp tube for 1-2 hours
- Remove intercostal tube within 24-48 hours

BTS GUIDELINES 2010

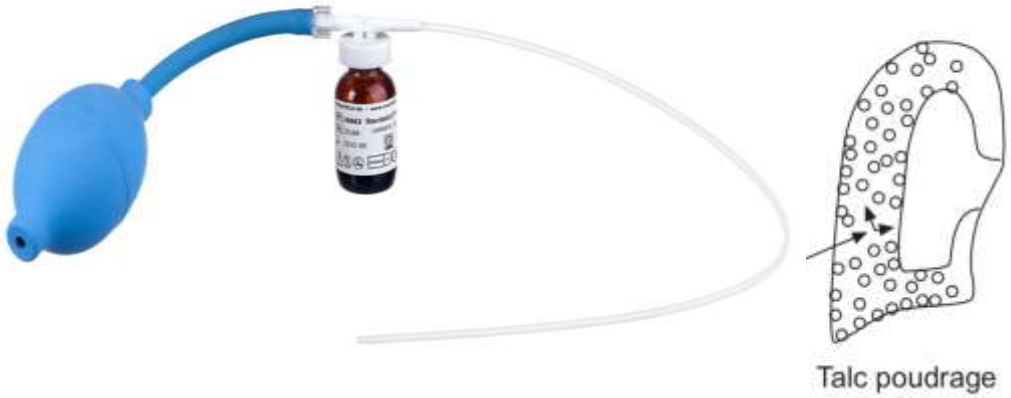
# PROCEDURE – TALC SLURRY PLEURODESIS

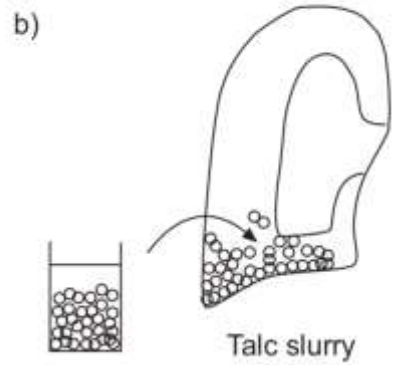
- Large pleural effusions should be drained in a controlled fashion to reduce the risk of re-expansion pulmonary oedema (1.5L)
- Only partial pleural apposition can be achieved - chemical pleurodesis may still be attempted
- Lung expansion is more important than the amount of drain fluid (< 150ml/day)
- Suction - generally avoided (Avoid pleural pressure < -20cmH2O)

BTS GUIDELINES 2010

# TALC POUDRAGE

- Talc is not water-soluble and, when applied in suspension as a slurry, does not distribute evenly in the pleural cavity
- Talc poudrage can be performed under local anaesthesia with conscious sedation or general anaesthesia





Rodriguez P et al. Eur Respir J 2006; 28: 409–421

# WHY SLURRY PREFERRED OVER POUDRAGE IN MALIGNANT EFFUSION?

- Better studied
- Simple bedside technique
- Can be performed in patients who are very sick, with poor performance status, or in those with contralateral pleural involvement

Rodriguez P et al. Eur Respir J 2006; 28: 409–421

# TALC PLEURODESIS – EFFICACY/SAFETY

| STUDY | Meta analysis |
|---|---|
| SUBJECTS | 20 trials, 1525 MPE patients |
| METHOD | Talc slurry/poudrage pleurodesis vs controls |
| OBJECTIVE | Efficacy and safety |
| RESULTS | **Success rates significantly higher with talc pleurodesis**<br>(Relative risk, 1.21; 95% confidence interval, 1.01–1.45; p = 0.035)<br>Adverse events:<br>**Fever** : No significant difference (RR, 1.15; 95% CI, 0.69–1.94; p = 0.589)<br>**Pain** : No significant difference (RR, 0.74; 95% CI, 0.40–1.40; p = 0.360)<br>**Emphysema** : No significant difference (RR, 1.35; 95% CI, 0.45–4.08; p = 0.596)<br>**Wound Infection** : No significant difference (RR, 2.18; 95% CI, 0.85–5.58; p = 0.106) |

Xia H et al. PLoS One. 2014 Jan 27;9(1):e87060

# TALC SLURRY PLEURODESIS(TSP) VS POUDRAGE (TTP) IN PNEUMOTHORAX

17 elderly patients with persistent air leak who received talc pleurodesis for secondary pneumothorax from April 2013 to March 2017

**Table 2** Results of talc pleurodesis

| Variable | TTP under general anesthesia (n=11) | TSP via a chest tube under local anesthesia (n=6) | P value |
|---|---|---|---|
| Drainage period after pleurodesis (days) | | | |
| Median [range] | 6 [2–11] | 12 [8–45] | 0.005 |
| Length of hospital stay (days) | | | |
| Median [range] | 23 [14–46] | 37.5 [20–60] | 0.154 |
| Complications: total (%) | 1 (9.1) | 4 (66.7) | 0.028 |
| Atrial fibrillation | 1 (9.1) | 0 | 1.000 |
| Chest pain | 0 | 2 (33.3) | 0.110 |
| Bronchial asthma attack | 0 | 1 (16.7) | 0.353 |
| Pneumonia | 0 | 1 (16.7) | 0.353 |
| Mortality | 0 | 1 (16.7) | 0.353 |

TTP, thoracoscopic talc poudrage; TSP, talc slurry pleurodesis.

TTP better than slurry in pneumothorax

Watanabe T et al. J Thorac Dis. 2019 Jan;11(1):171-6

# TALC PNEUMONITIS/ARDS

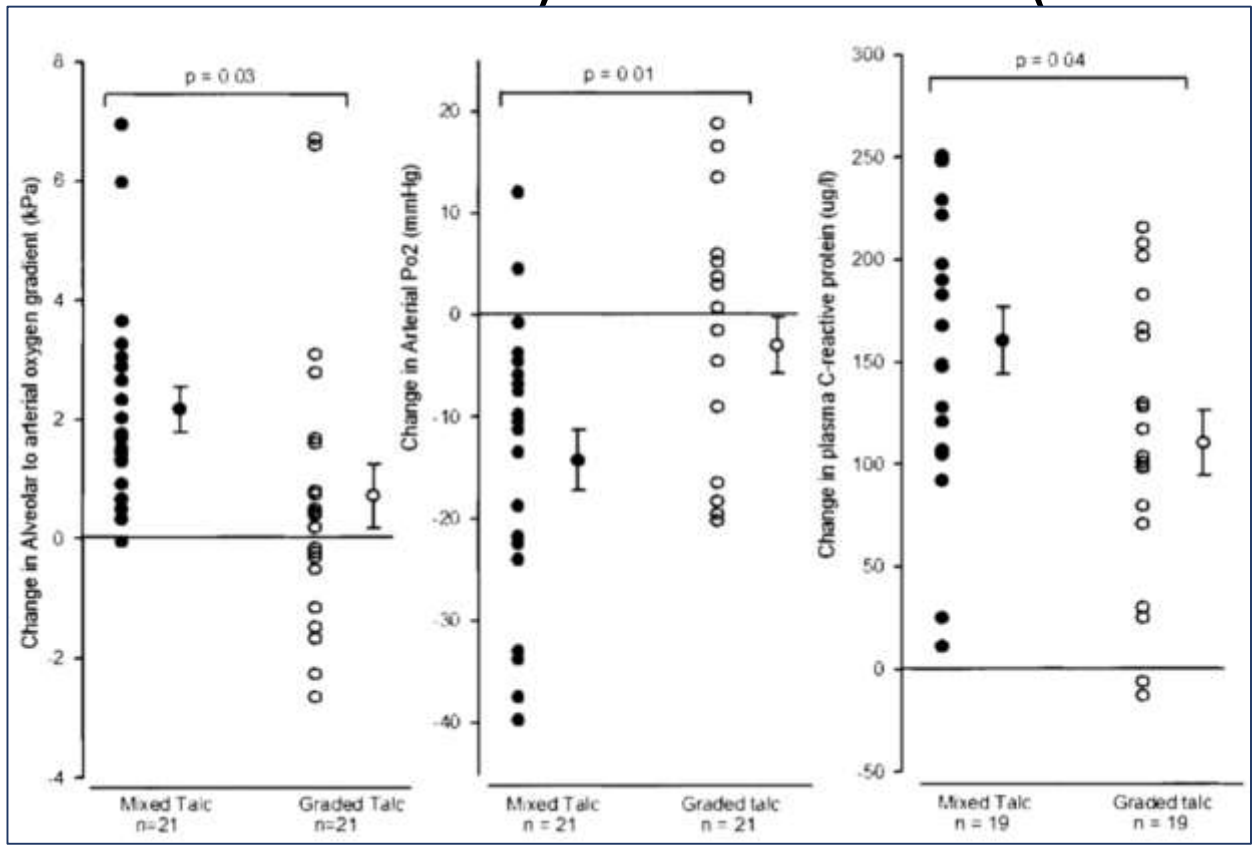
- The most severe adverse effect
- The mechanism of acute talc pneumonitis is unclear
- Hypothesis : Escape of very small talc particles from the pleural space through the parietal pleural pores
- Reported with both talc poudrage and slurry
- Commercially available Talc has 2 types:
  - Mixed Talc  (Thornton and Ross, Huddersfield, UK)
  - Graded Talc (Novatech, Grasse, France)
- This complication is related to the grade of talc used

Maskell NA et al. Am J Respir Crit Care Med. 2004 Aug 15;170(4):377-82

# TALC PNEUMONITIS

- 52 malignant pleural effusion patients randomized to pleurodesis with Mixed Talc (50% particles < 15 microns) vs Graded Talc ( 50% > 25 microns)
- Implication :

  Routine use of graded talc for pleurodesis would reduce the morbidity of this procedure




Maskell NA et al. Am J Respir Crit Care Med. 2004 Aug 15;170(4):377-82

# POVIDONE IODINE

- Mode of action: Unclear, likely related to low pH, oxidative and cytotoxic properties
- Inexpensive and easily available
- Used in both pneumothorax and malignant pleural effusion
- **Recommended dose** : 20 ml of 10% iodopovidone with 80 ml of 0.9 per cent saline administered intra pleurally either through tube thoracostomy or during thoracoscopy

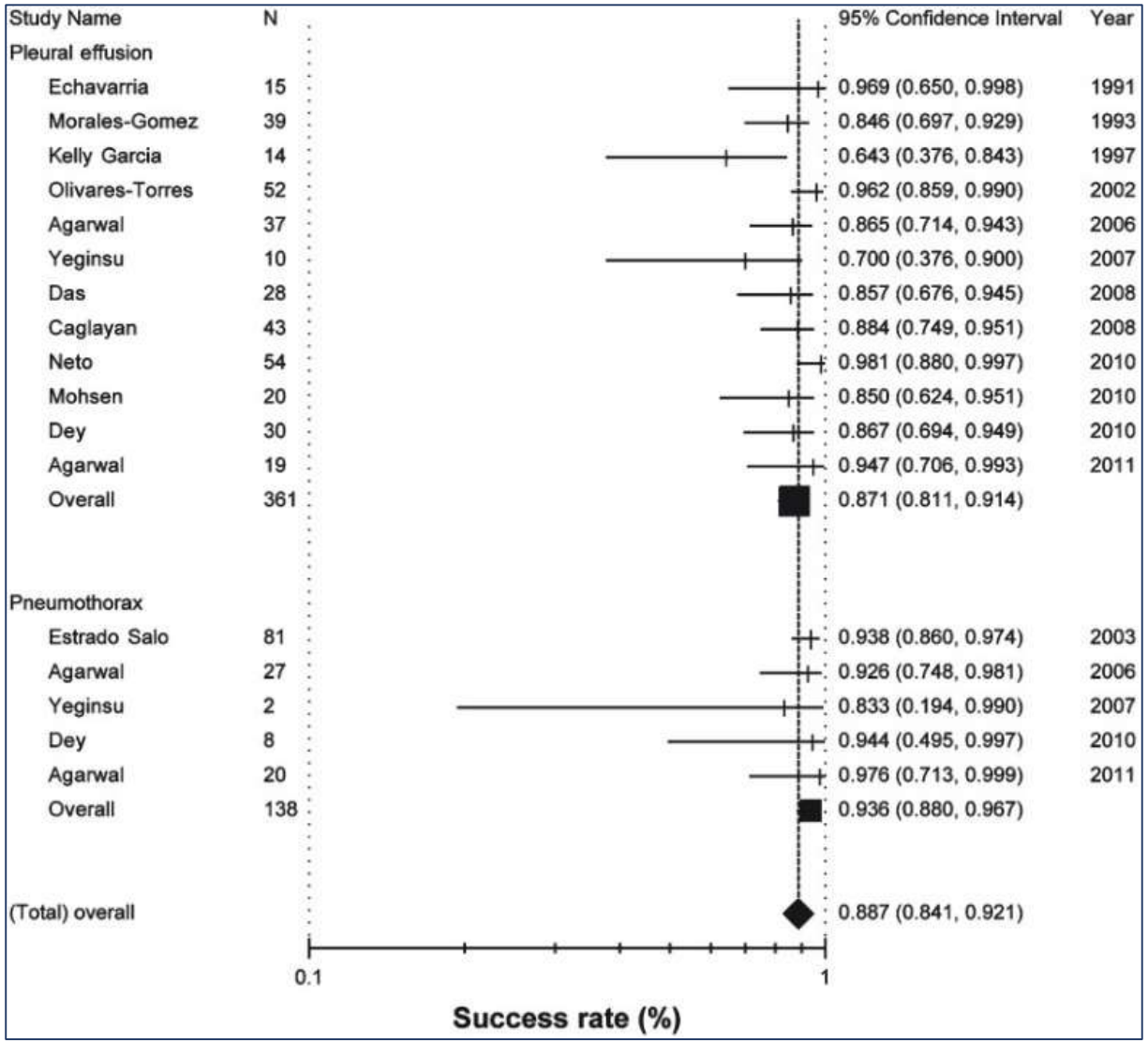
Agarwal R et al. Indian J med Res. 2012 Mar; 135(3): 297–304

# POVIDONE IODINE

| STUDY | SYSTEMIC REVIEW AND METAANALYSIS |
|---|---|
| SUBJECTS | 13 studies with 499 patients with recurrent pleural effusion and pneumothorax |
| OBJECTIVE | Efficacy and safety of povidone iodine pleurodesis |
| RESULTS | Pooled success rate being 88.7 per cent (95% CI, 84.1 to 92.1)<br>Tube thoracostomy vs Thoracoscopy (89.6 vs. 94.2%)<br>Pleural effusion vs pneumothorax (89.2 vs. 94.9%) |
| ADVERSE EFFECTS | **Only significant complication : Chest pain**<br>Hypotension – 2 studies, likely vasovagal secondary to pain<br>ARDS or deaths - 0 |

Agarwal R et al. Indian J med Res. 2012 Mar; 135(3): 297–304

# POVIDONE IODINE PLEURODESIS




COMMENTS:

- Povidone iodine is as efficacious as talc and is easily available at a low cost
- Also devoid of major adverse events

Agarwal R et al. Indian J med Res. 2012 Mar; 135(3): 297–304

# TETRACYCLINE

- Not used nowadays and less efficacious than Talc pleurodesis
- Studied in both malignant pleural effusions and pneumothorax
- Dose used in MPE : 35 mg/kg ( powder from capsules ) – success rates 77% and intravenous formulations (1.5g or 20mg/kg) - 50-92%

| STUDY | RCT |
|---|---|
| SUBJECTS | 96, spontaneous pneumothorax |
| INTERVENTION | Chest drain (n=34) vs Chest drain+ Talc slurry(n=29) vs Chest drain + tetracycline pleurodesis(n=33) |
| RESULTS | Recurrence rates :<br>Chest drain : 36%<br>Chest drain + Talc slurry pleurodesis : 8%<br>**Chest drain + Tetracycline pleurodesis :13%** |
| COMMENT | **Tetracycline inferior to Talc pleurodesis** |

Tettey M et al. Ghana Med J. 2005 Dec; 39(4): 128–31
Almind M et al. Thorax. 1989;44:627-630

# MINOCYCLINE

- Derivative of tetracycline and has been studied in both pneumothorax and malignant pleural effusions

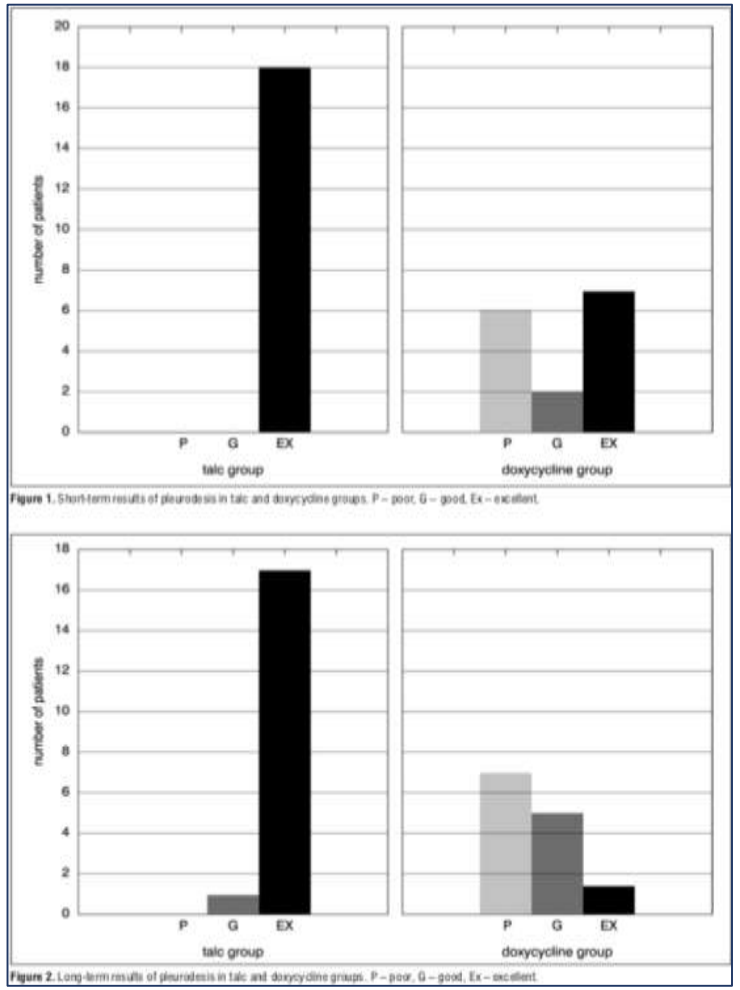
| STUDY | RCT |
|---|---|
| SUBJECTS | N=214, primary spontaneous pneumothorax |
| INTERVENTION | Chest drainage (108) vs Chest drainage + Minocycline 300 mg (106) |
| RESULT | **Pain**:<br>Minocycline group – (72 of 106), **67.9%** vs Chest drain group -(21 of 108), 19.4%<br>**Recurrence rate** :<br>Significantly lower in the minocycline group (31 patients, **29.2%)** than in the control group (**53 patients, 49.1%)** |
| COMMENT | **Pain and lower efficacy – Not the preferred agent** |

Chen et al. Current Opinion in Pulmonary Medicine. 2014. 20(4), 371–6.

# DOXYCYCLINE

- Derivative of tetracycline, inhibit Matrix metalloproteinase[1]
- Has been tried in pleurodesis of Malignant pleural effusion and sometimes in pneumothorax
- Dose used – 500mg -1000 mg
- Success rates[3] – short term 67% and long term 81%

| STUDY[2] | RCT |
|---|---|
| SUBJECTS | Malignant pleural effusions, n=33 |
| INTERVENTION | Talc pleurodesis by poudrage (10g), n=18<br>Doxycycline pleurodesis (500mg), n=15 |
| OUTCOME | Doxycycline pleurodesis less efficacious than Talc poudrage |




[1]Read CA et al. Chest.1994 Mar;105(3):823-5
[2]Kuzdzal J et al. Med Sci Monit. 2003 Jun;9(6):PI54-9
[3]Heffner JE et al. Chest. 1994. June.;105(6): 1743-7

# AUTOLOGOUS BLOOD PATCH PLEURODESIS

- The technique was first described by Robinson in 1987
- **Indication**:

  Spontaneous/Post operative pneumothorax with prolonged air leak (5-7 days) – unable to undergo surgery
- Simple, painless, inexpensive
- **Mechanism**: "Patch effect"- coagulated blood seals the site of the air leak
- Recurrence rates : 0-29%

Andrade et al. Lung India. 2018 Jul-Aug; 35(4): 341–2
Rinaldi et al. Thorax 2009;64:258-260

# AUTOLOGOUS BLOOD PATCH PROCEDURE

1. Add an extension tube to the chest drain
2. Under aseptic precautions inject 100 ml (2ml/kg) of patients own blood into the chest drain
3. Loop the drainage tube over the drip stand and clamp the tube for 1 hour(if no air leak)
4. Don’t clamp if air leak persists
5. Avoid patient rotation
6. After 4 hours drainage tube should be replaced to the original position and leave overnight
7. If no air leak and lung expanded, chest drain can be removed
8. If unsuccessful the procedure can be repeated upto a total of 3 times

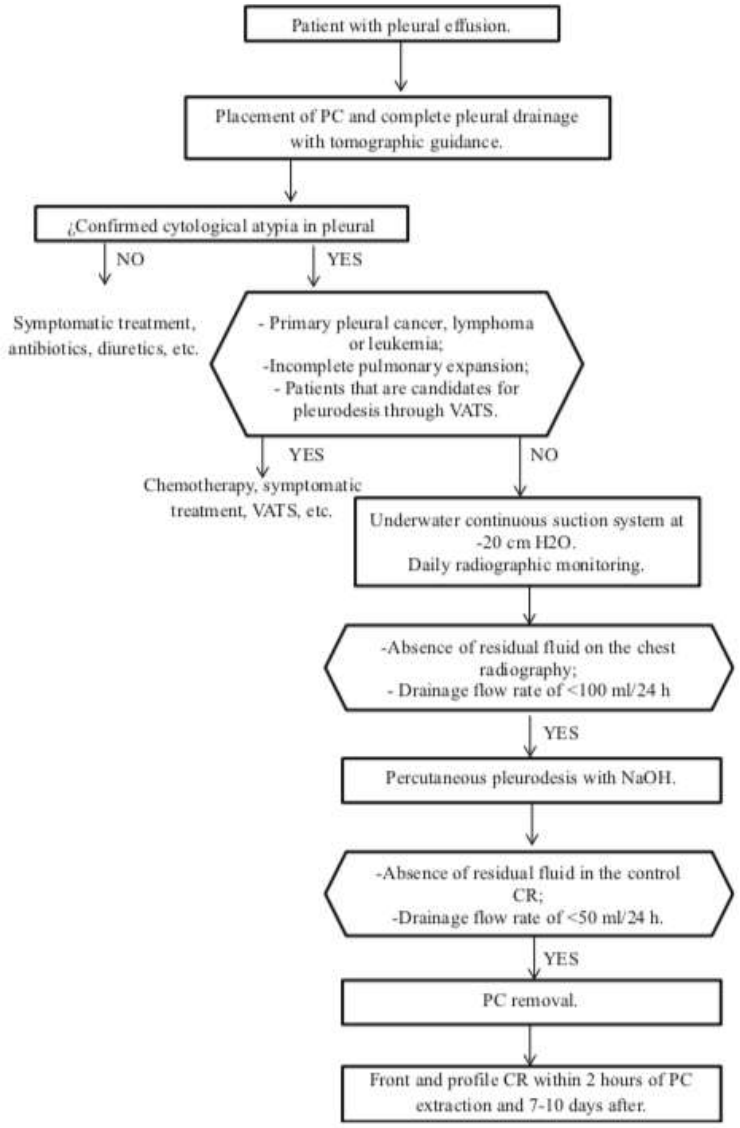
Andrade et al. Lung India. 2018 Jul-Aug; 35(4): 341–2
Rinaldi et al. Thorax 2009;64:258-260

# AUTOLOGOUS BLOOD PATCH PROCEDURE

- **Complications**: Empyema and tension pneumothorax can occur
- **Precautions** : Saline flush should be ready, avoid narrow bore chest tube
- **Advantages** : Less incidence of systemic inflammatory response and pain and no need for analgesia or anaesthesia

Andrade et al. Lung India. 2018 Jul-Aug; 35(4): 341–2
Rinaldi et al. Thorax 2009;64:258-260

# SODIUM HYDROXIDE




Extremely basic solution (pH 13) - alters the volume of pleural fluid by reducing its production, destroying the layer of mesothelial cells and obliterating the pleural capillaries

60 patients with symptomatic neoplastic pleural effusion

1. 20 ml of 2% lidocaine was instilled through the pleural catheter 15 min prior
2. 200 ml of sterile 0.5% NaOH solution
3. Clamped for 6 hours

Success rate - 75%

Raices M et al. Updates Surg. 2018 Dec;70(4):535-544

# ERYTHROMYCIN

| STUDY | RCT |
|---|---|
| SUBJECTS | Refractory (recurrent or persistent) spontaneous pneumothorax , n=57 |
| INTERVENTION | Erythromycin poudrage (30) vs Erythromycin slurry (27) , Dose used – 1 gram |
| OUTCOME | Success rate : **80% vs 59.26%,** Similar side effects – fever and chest pain |
| COMMENT | Alternate pleurodesis agent for PSP |

NEEDS RCTs TO COMPARE EFFICACY WITH OTHER AGENTS

Zhai CC et al. J Thorac Dis. 2018 Feb;10(2):757-765

# SILVER NITRATE

## Is silver nitrate an effective means of pleurodesis?

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### Abstract

A best evidence topic was written according to a structured protocol. The question addressed was whether silver nitrate (SN) is an effective means of pleurodesis. A total of 42 papers were identified using the reported search, of which 8 represented the best evidence to address the clinical question. The authors, journal, date and country of publication, patient group studied, study type, relevant outcomes and results of these papers are tabulated. Three studies assessed the efficacy of SN in inducing pleurodesis in patients with malignant pleural effusion (MPE). Using intrapleural injections of SN in concentrations of 0.5–1%, they reported success rates of 89–96% at 30 days. One of these studies compared SN with talc slurry and found equally effective pleurodesis at monthly intervals up to 4 months ($P = 0.349$–1). Another two studies retrospectively reviewed the efficacy of thoracosopic SN instillation (1 or 10%) in patients with primary spontaneous pneumothorax (PSP). Recurrence rates were 0–1.1% during long-term follow-up. One of these compared SN with simple drainage and reported a therapeutic gain of 45 ± 30% (95% CI) with SN, at the cost of increased analgesia consumption, chest drainage and hospital stay. Finally, three studies reported the results of the comparison of intrapleural injections of SN, talc or tetracycline in inducing pleurodesis in rabbits. SN was equally effective with tetracycline and superior to talc at producing pleurodesis, with lower concentrations of SN (0.1%) resulting in significantly attenuated systemic inflammatory response when compared with either higher SN concentrations (0.5%) or talc. Although not commonly used, available evidence suggests that SN is an effective agent in inducing pleurodesis in patients with either MPE or PSP. Compared with universally employed talc, it seems to result in at least similar short-term recurrence rates for MPE, with a demonstrably good side-effect profile; the longer-term efficacy is, as yet, undetermined. In cases of PSP, evidence suggests that thoracoscopic SN instillation is at least as effective as talc, with potentially fewer systemic side effects.

Bucknor A et al. Interact Cardiovasc Thorac Surg. 2015 Oct;21(4):521-5

# OK-432 (Picibanil)

- Lyophilized mixture of a low virulence strain (Su) of Streptococcus pyogenes incubated with benzyl penicillin
- Studied in both pneumothorax and malignant pleural effusion

| STUDY(2011-2016) | Retrospective analysis |
|---|---|
| SUBJECTS | 64 – malignant pleural effusion (33- lung cancer ) |
| INTERVENTION | 52 – Picobanil vs<br>12 –Talc pleurodesis |
| RESULTS | **Success rate : (p-0.72).**<br>• Picobanil-75%<br>• Talc - 83.3%<br>**Duration of drain : (p-0.52)**<br>• Picobanil-2.4 days<br>• Talc-2.5 days<br>**Relapse** : **(p-0.34)**<br>• Picobanil-40.4%<br>• Talc-58.3%<br>**Side effects** : Fever, pain – similar<br>ILD – 2 patients with Talc pleurodesis |

Ishii K et al. Am J Respir Crit Care Med. 2017;195:A3529

# ANTI CANCER DRUGS IN PLEURODESIS

- Various chemical agents have been used in an attempt to produce pleurodesis
- The complete success rate with fibrosing agents (non anticancer agents) was 75%, compared with a complete success rate of only 44% for anticancer agents

| Study | Prospective |
|---|---|
| Subjects | • N=20, proven malignant pleural effusion secondary to lung cancer<br>• Progressed after chemoradiotherapy |
| Intervention | Intrapleural OK-432 10 KE + Doxorubicin 30 mg (after thoracocentesis) and OK-432 can be repeated every 3 days |
| Outcome | **Objective response 90%** |

Kishi K et al. Eur Respir J. 2004 Aug;24(2):263-6

# BLEOMYCIN

- Chemical sclerosant
- Although 45% of the administered bleomycin is absorbed systemically, it has been shown to cause minimal or no myelosuppression
- Success rates **58% to 85% and less efficacious** than talc in MPE
- Side effects : Fever, chest pain and cough
- Dose recommended : 60,000 units with normal saline
- **Expensive**
- **Animal studies showed ineffective pleurodesis in pneumothorax – hence not indicated for non-malignant conditions**

CH How et al. Journal of the Formosan Medical Association. 2013. 112(12). 749-55
BTS GUIDELINES 2010

# SERICIN

Sociedad Española de Neumología y Cirugía Torácica SEPAR

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Original article

## Does Sericin, as a Novel Pleurodesis Agent, Have Higher Effectiveness Compared to Talcum Powder, Doxycycline, and Silver Nitrate Pleurodesis?☆

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ABSTRACT

*Introduction:* The usefulness of sericin as pleurodesis agent has previously been described. Present study aims to compare sericin pleurodesis regarding success, effectiveness, tolerability, and side-effects.
*Methods:* Adult, 12-week-old Wistar-albino rats ($n = 60$), divided to five groups as sericin, talcum-powder, doxycycline, silver-nitrate and control. Agents were administrated through left thoracotomy, rats sacrificed twelve-days after.
*Results:* Highest ratio of collagen fibers was observed in sericin group, and the intensity was higher than talcum-powder group ($p < 0.05$). Compared to silver nitrate, sericin group displayed better mesothelial reaction, and multi-layer mesothelium was also better ($p < 0.05$). Foreign body reaction and emphysema were less frequent in sericin group ($p < 0.05$). The presence of biological tissue in parenchyma was less prominent in sericin group ($p < 0.05$). Foreign body reaction on thoracic wall was less common in sericin group ($p < 0.05$). Presence of biological tissue glue in thoracic wall was less prominent in sericin group ($p < 0.05$).
Glomerular degeneration was lower in sericin group compared to the silver nitrate group ($p < 0.05$), and tubular degeneration was less common in sericin group than talcum group ($p < 0.05$). Pericarditis was less common in sericin group compared to the other groups ($p < 0.05$).
*Conclusion:* As an intrinsic, natural glue protein, sericin protects the lung parenchyma and tissues, and its glue-like characteristics enable pleurodesis. The success of sericin in pleurodesis was demonstrated in the present study based on investigations of the pleurae. Being cost-effective and better tolerated agent associated with a low potential of side effects, sericin is more effective, less expensive and provides more lung parenchyma protection.

Yazicioglu et al. luArchivos de Bronconeumología. 2019; 55(7): 357-67

# VEGF INHIBITORS

- VEGF: Over expressed in many solid tumours causing excessive angiogenesis and vascular permeability thereby leading to malignant pleural effusion
- Bevacizumab is a recombinant humanized monoclonal antibody that selectively binds to VEGF and interferes with its receptor interactions
- Endostatin is another endogenous VEGF inhibitor being studied in controlling malignant pleural effusion

Sabang RL et al. Expert Rev Respir Med. 2018 Feb;12(2):87-94

# BEVACIZUMAB AS PLEURODESIS AGENT?

| Author | Study design (phase) | N | Regimen | Comparator | MPE control rate | *P*-value |
|---|---|---|---|---|---|---|
| **INTRAVENOUS BEVACIZUMAB** | | | | | | |
| Kitamura et al. | R | 13 | Bevacizumab + Carboplatin based chemotherapies | None | 12/13 (92.3%)[a] | N/A |
| Masago et al. | R | 21 | Bevacizumab + Carboplatin-based chemotherapies | None | 15/21 (71.4%)[b] | N/A |
| Jiang et al. | R | 86 | Bevacizumab + EGFR-TKI therapies | Bevacizumab + standard chemotherapies | 42/47 (89.4%) vs. 25/39 (64.1%)[b] | $p = 0.005$ |
| Tamiya et al. | P (II) | 23 | Bevacizumab + Carboplatin + Paclitaxel | None | 21/23 (91.3%)[a] | N/A |
| Usui et al. | P (II) | 28 | Bevacizumab + Carboplatin + Pemetrexed | None | 26/28 (92.9%)[c] | N/A |
| **INTRAPLEURAL BEVACIZUMAB** | | | | | | |
| Chen et al. | R | 300 | Bevacizumab | IP Chemotherapy | 41/50 (82%) vs. 191/250(76.4%)[d] | $p < 0.01$ |
| Jiang et al. | R | 43 | Bevacizumab + Cisplatin | IP Cisplatin | 16/20 (80.0%) vs. 11/23 (47.8%)[b] | $p = 0.03$ |
| Du et al. | P | 72 | Bevacizumab + Cisplatin | IP Cisplatin | 30/36 (83.3%) vs. 17/34 (50.0%)[b] | $p < 0.05$ |
| Qi et al. | P | 24 | Bevacizumab + Paclitaxel | IP Paclitaxel | 11/14 (78.6%) vs. 5/10 (50.0%)[d] | $p < 0.05$ |

N: total study population; MPE: malignant pleural effusion; R: retrospective; P: prospective; IP: intrapleural/intracavitary; EGFR-TKI: epidermal growth factor receptor-tyrosine kinase inhibitor.
[a]MPE control defined as no reaccumulation of MPE for ≥8 weeks after the start of treatment.
[b]MPE control defined as complete response (CR) + partial response (PR); CR – defined as complete disappearance of pleural effusion at 4weeks; PR – defined as ≥50% reduction of pleural effusion at 4weeks.
[c]MPE control defined as not needing pleurodesis at 8 weeks of treatment
[d]MPE control defined as PR + CR; CR – effusion and symptoms disappeared and patient was stable for ≥8weeks; PR – size of effusion was reduced by ≥50% with improvement of symptoms for ≥8 weeks.

Sabang RL et al. Expert Rev Respir Med. 2018 Feb;12(2):87-94

# VISCUM

- Abnobaviscum F is an extract of *V. album* (European mistletoe), which grows on trees of the genus Fraxinus
- Mechanism: Stimulation of antitumor immunity
- Used in the pleurodesis of malignant effusions and also recently shown to be effective in pneumothorax with persistent air leaks

| Study | Phase 3 trial |
|---|---|
| Subjects | 62 MPE |
| Intervention | 1. Remove pleural fluid<br>2. Viscum pleurodesis (5 ampoules of 20 mg with 0.9% normal saline)<br>3. Repeated at a dosing interval of 3-7 days till adequate response |
| Outcome | Efficacy : 96.77%<br>Most common side effect : Fever |

Cho JS et al. Ann Thorac Cardiovasc Surg. 2016; 22(1): 20–26
Song KS et al. Korean J Thorac Cardiovasc Surg. 2017 Aug; 50(4): 281–6.

# OTHER PLEURODESIS AGENTS STUDIED IN MALIGNANT PLEURAL EFFUSION

- MEPACRINE - Anti malarial drug, acts as a sclerosant
- MITOXANTRONE - synthetic anthracenedione (Doxorubicin analogue), acts via inflammatory and anti-neoplastic mechanism
- CORNYBACTERIUM PARVUM – Immunological agent
- MUSTINE – Cytotoxic agent

# NETWORK META ANALYSIS COMPARING DIFFERENT AGENTS IN MALIGNANT PLEURAL EFFUSION

## Inclusion criteria:

- 62 studies - 3248 patients
- Symptomatic MPE

## Exclusion criteria:

- Studies recruiting both malignant and non-malignant effusions
- Other than intrapleural route
- Studies including participants with effusions in other body cavities

Clive AO et al. Cochrane Database Syst Rev. 2016 May 8;(5):CD010529

# PLEURODESIS EFFICACY – NETWORK METAANALYSIS RESULTS

| | Talc slurry | Talc poudrag | Bleomy | Tetra-cy-cline | *C. parvum* | Inter-feron | Io-dine | In-dwellin pleu-ral catheter | Placebo | Mus-tine | Mi-tox-antrone | Mepacr | Doxy-cyline | Tri-ethylen phos-pho-ramide | vis-cum |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Talc poudra | 0. 42 (0. 13, 1. 19) | NA | - | - | - | - | - | - | - | - | - | - | - | - | - |
| Bleomy | **2. 56 (1. 05, 6. 67)** | **6. 03 (2. 19, 20. 46)** | NA | - | - | - | - | - | - | - | - | - | - | - | - |
| Tetra-cy-cline | **3. 71 (1. 22, 11. 67)** | **8. 77 (2. 74, 33. 01)** | 1. 45 (0. 59, 3. 46) | NA | - | - | - | - | - | - | - | - | - | - | - |

Clive AO et al. Cochrane Database Syst Rev. 2016 May 8;(5):CD010529

| | Talc slurry | Talc poudrag | Bleomy | Tetra-cy-cline | *C. parvum* | Inter-feron | Io-dine | In-dwelling pleu-ral catheter | Placebo | Mus-tine | Mi-tox-antrone | Mepacr | Doxy-cyline | Tri-ethylen phos-pho-ramide | vis-cum |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *C. parvum* | 1. 48 (0. 34, 6. 57) | 3.49 (0.79, 17. 64) | 0. 58 (0. 16, 1. 95) | 0. 40 (0. 10, 1. 52) | NA | - | - | - | - | - | - | - | - | - | - |
| Inter-feron | 8.49 (0.94, 82. 98) | **19. 96 (2. 22, 229. 60)** | 3.33 (0.43, 25. 66) | 2.29 (0.26, 21. 65) | 5.75 (0.55, 64. 16) | NA | - | - | - | - | - | - | - | - | - |
| Io-dine | 1. 25 (0. 22, 6. 77) | 2.97 (0.55, 17. 21) | 0. 49 (0. 09, 2. 49) | 0. 34 (0. 05, 2. 04) | 0. 85 (0. 11, 6. 35) | 0. 15 (0. 01, 1. 90) | NA | - | - | - | - | - | - | - | - |
| In-dwellin pleu-ral cathete | 3.47 (0.75, 16. 46) | **8. 19 (1. 32, 59. 02)** | 1. 36 (0. 22, 8. 01) | 0. 94 (0. 14, 6. 27) | 2.36 (0.28, 19. 88) | 0. 41 (0. 03, 5. 96) | 2.76 (0.29, 28. 48) | NA | - | - | - | - | - | - | - |
| Placebo | **19. 50 (3. 73, 128. 50)** | **46. 51 (7. 86, 375. 90)** | **7. 64 (1. 55, 44. 22)** | **5. 29 (1. 04, 31. 95)** | **13. 28 (1. 91, 110. 80)** | 2.29 (0.18, 34. 14) | **15. 63 (1. 72, 179. 10)** | 5.61 (0.59, 65. 18) | NA | - | - | - | - | - | - |
| Mus-tine | **7. 50 (1. 35, 43. 86)** | **17. 75 (3. 59, 105. 70)** | 2.94 (0.58, 14. 84) | 2. 02 (0. 43, 9. 79) | 5.07 (0.91, 29. 81) | 0.88 (0.06, 11. 71) | 5.98 (0.68, 58. 17) | 2.16 (0.22, 22. 76) | 0. 38 (0. 04, 3. 32) | NA | - | - | - | - | - |
| Mi-tox-antrone | **12. 87 (2. 36, 89. 02)** | **30. 53 (5. 11, 259. 50)** | **5. 04 (1. 04, 28. 67)** | 3.48 (0.64, 22. 72) | **8. 76 (1. 24, 73. 66)** | 1.51 (0.12, 22. 89) | **10. 28 (1. 12, 119. 70)** | 3.71 (0.38, 44. 85) | 0. 66 (0. 13, 3. 52) | 1.73 (0.19, 17.80 | NA | - | - | - | - |
| Mepacr | 0. 98 (0. 22, 4. 15) | 2.32 (0.45, 12. 99) | 0. 38 (0. 09, 1. 52) | 0. 27 (0. 05, 1. 17) | 0. 67 (0. 10, 4. 06) | 0. 12 (0. 01, 1. 31) | 0. 78 (0. 09, 6. 55) | 0. 28 (0. 03, 2. 32) | **0. 05 (0. 01, 0. 28)** | 0. 13 (0. 02, 0. 99) | **0. 08 (0. 01, 0. 47)** | NA | - | - | - |
| Doxy-cy-cline | 3.49 (0.68, 19. 56) | **8. 23 (1. 70, 50. 18)** | 1. 37 (0. 31, 6. 09) | 0. 94 (0. 18, 5. 09) | 2.36 (0.46, 13. 09) | 0. 41 (0. 03, 5. 14) | 2.78 (0.33, 26. 50) | 1.00 (0.11, 10. 23) | 0. 18 (0. 02, 1. 53) | 0. 47 (0. 06, 3. 77) | 0. 27 (0. 03, 2. 31) | 3.56 (0.50, 28. 59) | NA | - | - |

Clive AO et al. Cochrane Database Syst Rev. 2016 May 8;(5):CD010529

# PLEURODESIS EFFICACY (VIA CHEST DRAIN)

| | Talc slurry | Doxy-cycline | Bleomycin | Tetra-cycline | *C. parvum* | Inter-feron |
|---|---|---|---|---|---|---|
| Doxy-cycline | 1.10 (0.13, 8.65) | NA | - | - | - | - |
| Bleomycin | 1.56 (0.53, 4.88) | 1.41 (0.25, 9.11) | NA | - | - | - |
| Tetra-cycline | 2.28 (0.58, 9.13) | 2.06 (0.30, 15.92) | 1.46 (0.53, 3.90) | NA | - | - |
| *C. parvum* | 0.82 (0.15, 4.60) | 0.75 (0.11, 5.33) | 0.53 (0.13, 2.00) | 0.36 (0.08, 1.57) | NA | - |
| Inter-feron | 5.18 (0.43, 68.49) | 4.72 (0.28, 92.65) | 3.33 (0.34, 32.42) | 2.28 (0.19, 28.27) | 6.31 (0.47, 93.70) | NA |
| Iodine | 1.13 (0.12, 9.77) | 1.02 (0.06, 16.19) | 0.72 (0.08, 5.65) | 0.50 (0.05, 4.77) | 1.37 (0.11, 16.45) | 0.22 (0.01, 4.46) |

| | Talc slurry | Doxy-cycline | Bleomycin | Tetra-cycline | *C. parvum* | Inter-feron | Iodine | Adri-amycin | Placebo | Mus-tine | Mitox-antrone | Mepacrine |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Adri-amycin | 1.48 (0.02, 114.80) | 1.36 (0.01, 130.60) | 0.95 (0.01, 65.87) | 0.65 (0.01, 41.36) | 1.80 (0.02, 139.40) | 0.28 (0.00, 33.67) | 1.33 (0.01, 143.20) | NA | - | - | - | - |
| Placebo | 9.24 (0.91, 109.90) | 8.42 (0.56, 156.30) | 5.96 (0.69, 55.43) | 4.06 (0.50, 37.88) | 11.26 (0.99, 149.50) | 1.77 (0.08, 44.50) | 8.24 (0.44, 188.50) | 6.31 (0.06, 765.80) | NA | - | - | - |
| Mus-tine | 3.89 (0.63, 62.33) | 5.36 (0.43, 81.82) | 3.78 (0.50, 31.32) | 2.59 (0.39, 19.27) | 7.17 (0.95, 62.55) | 1.14 (0.05, 25.58) | 5.26 (0.30, 109.10) | 3.99 (0.06, 354.40) | 0.64 (0.04, 11.13) | NA | - | - |
| Mitox-antrone | 7.23 (0.97, 69.79) | 6.57 (0.57, 104.40) | 4.63 (0.79, 33.87) | 3.18 (0.49, 26.67) | **8.81 (1.01, 98.38)** | 1.39 (0.08, 29.47) | 6.46 (0.44, 125.50) | 4.99 (0.05, 570.00) | 0.79 (0.12, 5.83) | 1.23 (0.09, 19.34) | NA | - |
| Mepacrin | 0.71 (0.12, 3.65) | 0.64 (0.06, 7.05) | 0.46 (0.08, 2.15) | 0.31 (0.05, 1.69) | 0.86 (0.10, 6.55) | 0.14 (0.01, 2.06) | 0.63 (0.05, 8.48) | 0.48 (0.01, 45.93) | **0.08 (0.00, 0.91)** | 0.12 (0.01, 1.40) | **0.10 (0.01, 0.82)** | NA |
| Viscum | 0.23 (0.01, 6.09) | 0.21 (0.01, 7.69) | 0.15 (0.01, 3.19) | 0.10 (0.00, 2.60) | 0.28 (0.01, 8.17) | 0.04 (0.00, 1.99) | 0.20 (0.00, 8.98) | 0.15 (0.00, 32.36) | 0.02 (0.00, 1.05) | 0.04 (0.00, 1.54) | 0.03 (0.00, 1.09) | 0.33 (0.01, 11.30) |

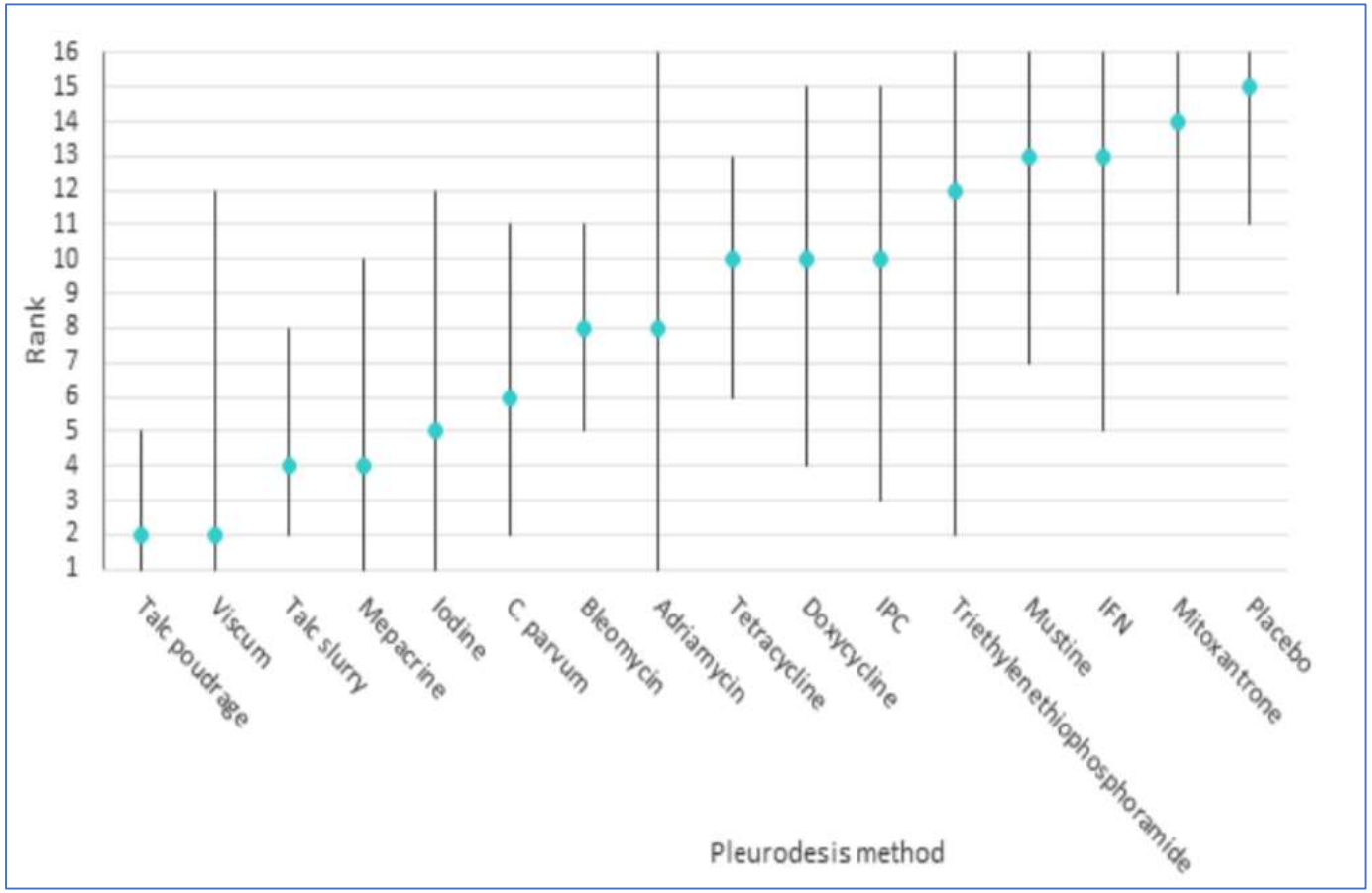
Clive AO et al. Cochrane Database Syst Rev. 2016 May 8;(5):CD010529

# PLEURODESIS – TECHNICAL CONSIDERATIONS

| TYPE OF METHOD | STUDY | INTERVENTION 1 | FAILURE RATE 1 | INTERVENTION 2 | FAILURE RATE 2 | ODDS RATIO |
|---|---|---|---|---|---|---|
| Chest tube size | CLEMENTSEN 1998 | Small bore chest tube | 2/9 | Large bore chest tube | 3/9 | 0.57 (0.07, 4.64) |
| Patient rotation | Mager 2002 | Rotation after talc instillation | 2/10 | No rotation | 1/10 | 2.25 (0.17, 29.77) |
| Duration of drainage after administration of sclerosant | Goodman 2006 | Drain removed 24 hours after pleurodesis | 2/16 | Drain removed 72 hours later | 4/19 | 0.54 (0.08, 3.40) |
| | Villanueva 1994 | Drain removed the day after | 2/9 | Removed when output < 150ml/day | 3/15 | 1.14 (0.15,8.59) |
| Duration of drainage prior to administration of sclerosant | Ozkul 2014 | Early instillation of talc slurry after drain insertion | 5/40 | Instillation of talc slurry when daily drainage < 300ml/day | 6/39 | 0.79 (0.22, 2.82) |

Clive AO et al. Cochrane Database Syst Rev. 2016 May 8;(5):CD010529

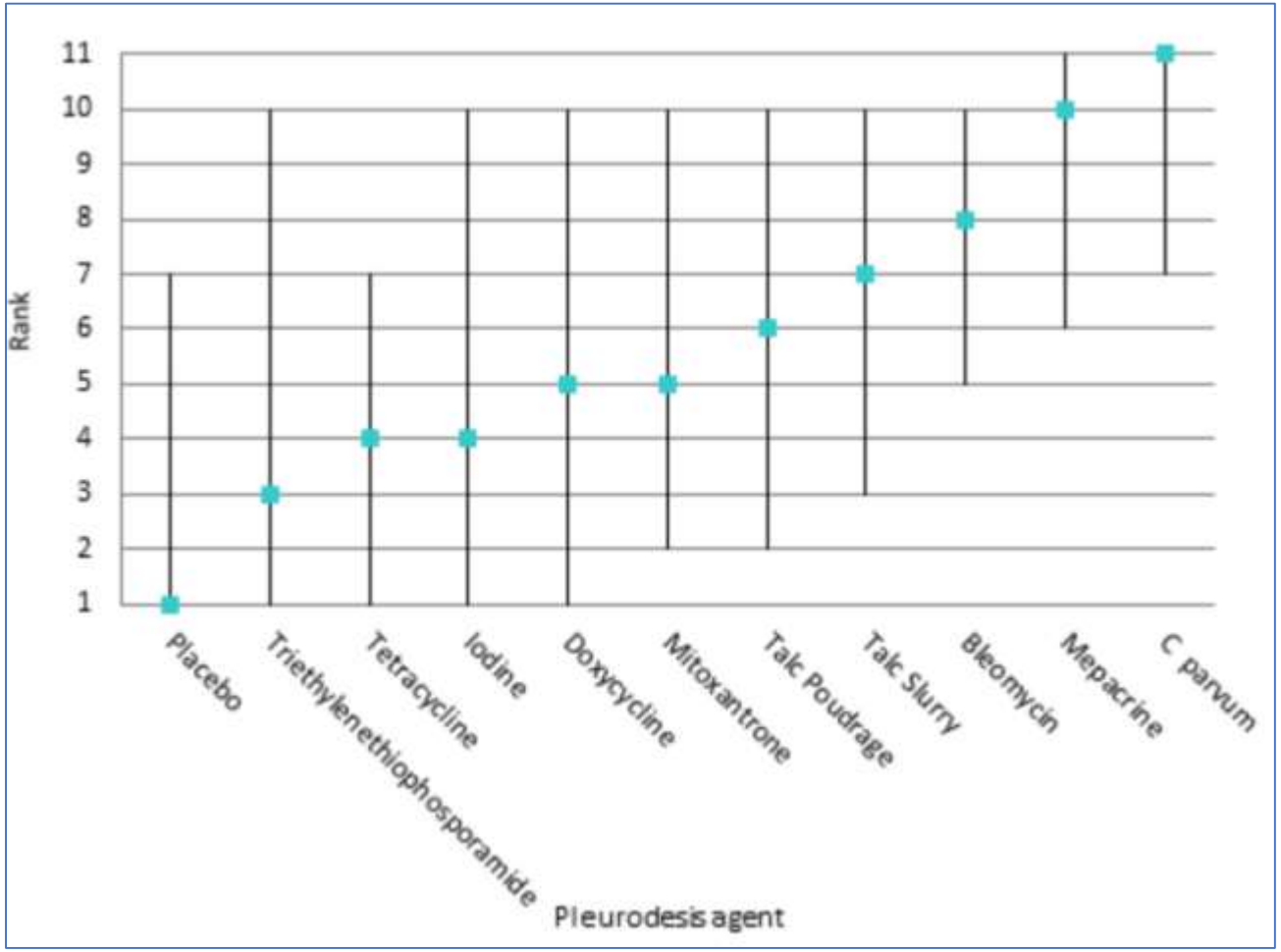
# PLEURODESIS EFFICACY – ESTIMATED RANK




TALC POUDRAGE > TALC SLURRY > IODINE > DOXYCYCLINE

Clive AO et al. Cochrane Database Syst Rev. 2016 May 8;(5):CD010529

# ADVERSE EFFECTS - FEVER




TALC SLURRY > TALC POUDRAGE > DOXYCYCLINE > IODINE

Clive AO et al. Cochrane Database Syst Rev. 2016 May 8;(5):CD010529

# ADVERSE EFFECTS - PAIN

| Pleurodesis agent | Estimated rank (95% CI) |
|---|---|
| Talc poudrage | 1 (1,8) |
| Talc slurry | 2 (1,7) |
| Doxycycline | 3 (1,8) |
| Bleomycin | 4 (2,6) |
| Tetracycline | 5 (2,8) |
| Triethylenetriophosphoramide | 6 (1,9) |
| C. parvum | 7 (4,9) |
| Mitoxantrone | 7 (1,9) |
| Mepacrine | 8 (4,9) |

TALC POUDRAGE < TALC SLURRY < DOXYCYCLINE

Clive AO et al. Cochrane Database Syst Rev. 2016 May 8;(5):CD010529

# CHEST TUBE SIZE AND ANALGESIA

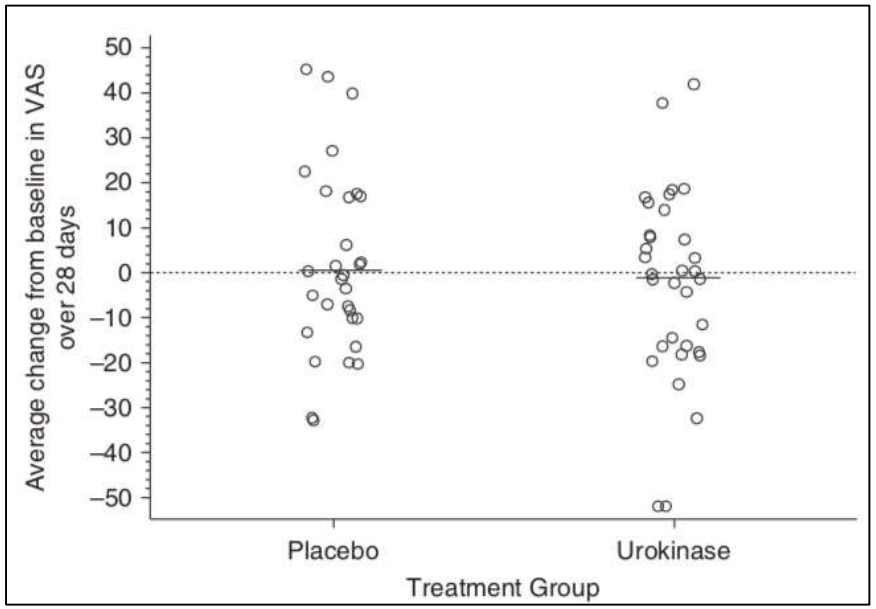
| STUDY | TIME1 trial - RCT |
|---|---|
| SUBJECTS | Malignant pleural effusion, n=320 |
| INTERVENTION | n=206, thoracoscopy, 24 F tube, (103 – NSAID vs 103 Opiods)<br>n=114, 4 groups (24F +NSAID, 24F+Opiod, 12F+NSAID,12F+Opiod) |
| OUTCOME | • NSAID non-inferior to Opiod in analgesia and had similar pleurodesis failure rates<br>• 12F drain had higher failure pleurodesis rates than 24F drain (30% vs 24%) although it had significantly better analgesia (mean VAS score : 22 vs 28) |
| COMMENT | **Large bore chest drain preferred for pleurodesis in malignant effusions with either NSAID/Opiod analgesia** |

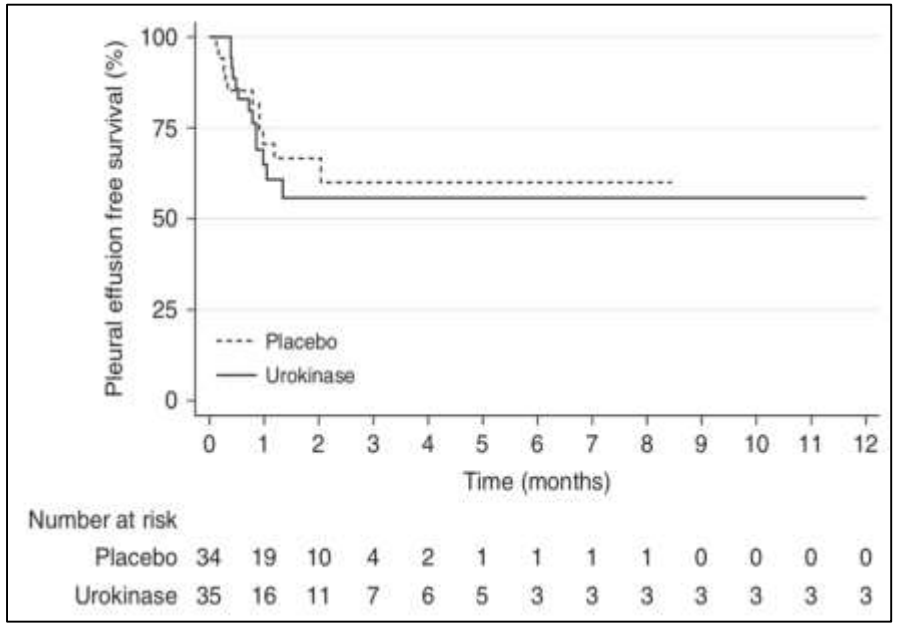
Rahman NM et al. JAMA. 2015;314(24):2641-2653

# SEPTATED MALIGNANT PLEURAL EFFUSIONS
## FIBRINOLYSIS f/b PLEURODESIS

Non draining pleural effusion
N=71

1:1 ( Intrapleural urokinase : placebo)
1,00,000 IU 3 doses 12 hourly f/b
Talc slurry pleurodesis




**VAS Dyspnoea score** at day 28 (mean difference, 3.8 mm; 95% confidence interval [CI], 212 to 4.4 mm; **P = 0.36**) **similar**

**Pleurodesis failure rates** - (urokinase, 13 of 35 [37%]; placebo, 11 of 34 [32%]; adjusted hazard ratio, 1.2; **P = 0.65) similar**

Mishra EK et al. Am J Respir Crit Care Med. 2018 Feb 15;197(4):502-8

# SEPTATED MALIGNANT PLEURAL EFFUSIONS ROLE OF FIBRINOLYTICS BEFORE PLEURODESIS?

| STUDY | SUBJECTS | INTERVENTION |
|---|---|---|
| Okur E et al[1] | 47, Non expanding MPE | 1:1 (STK 2.5 lakh units 3 cycles vs placebo) f/b Talc slurry pleurodesis |

| Variable | Fibrinolytic Group | Control Group | *p* Value |
|---|---|---|---|
| Drainage in first 24 h (mL) | 1,783 ± 157 | 1,654 ± 191 | 0.570 |
| Drainage in 24–48 h (mL) | 423 ± 102 | 523 ± 92 | 0.070 |
| Drainage in 48–72 h (mL) | 793 ± 59 | 271 ± 84 | < 0.001 |
| Total drainage (mL) | 3611 ± 278 | 2536 ± 345 | 0.010 |
| Lung expansion (yes/no) | 23/1 | 17/6 | 0.035 |
| Success of pleurodesis | 14/19 (74%) | 9/16 (56%) | 0.280 |

| STUDY | SUBJECTS | INTERVENTION |
|---|---|---|
| Saydam et al[2] | 40, Multiloculated MPE | 1:1 ( STK vs placebo f/b Talc slurry pleurodesis) |

| | Fibrinolytic group | Control group | *P* value |
|---|---|---|---|
| Mean age | 57.3 | 58.3 | 0.65 |
| Mean drainage at 24–48 h | 493 cc | 248 cc | <0.001 |
| Mean drainage at 48–72 h | 446 cc | 198 cc | <0.001 |
| Mean drainage at 24–72 h | 939 cc | 446 cc | <0.001 |
| CT score (3/2/1) | 11/6/3 | 2/5/13 | 0.001 |
| Dyspneic patients | 2 (10 %) | 9 (45 %) | 0.03 |
| Recurrence rate | 11 % | 45 % | 0.07 |

MPE – Malignant pleural Effusion

[1]Okur E et al. Asian Cardiovasc Thorac Ann. 2011 Jun;19(3-4):238-43

[2]Saydam et al. Med Oncol (2015) 32:179

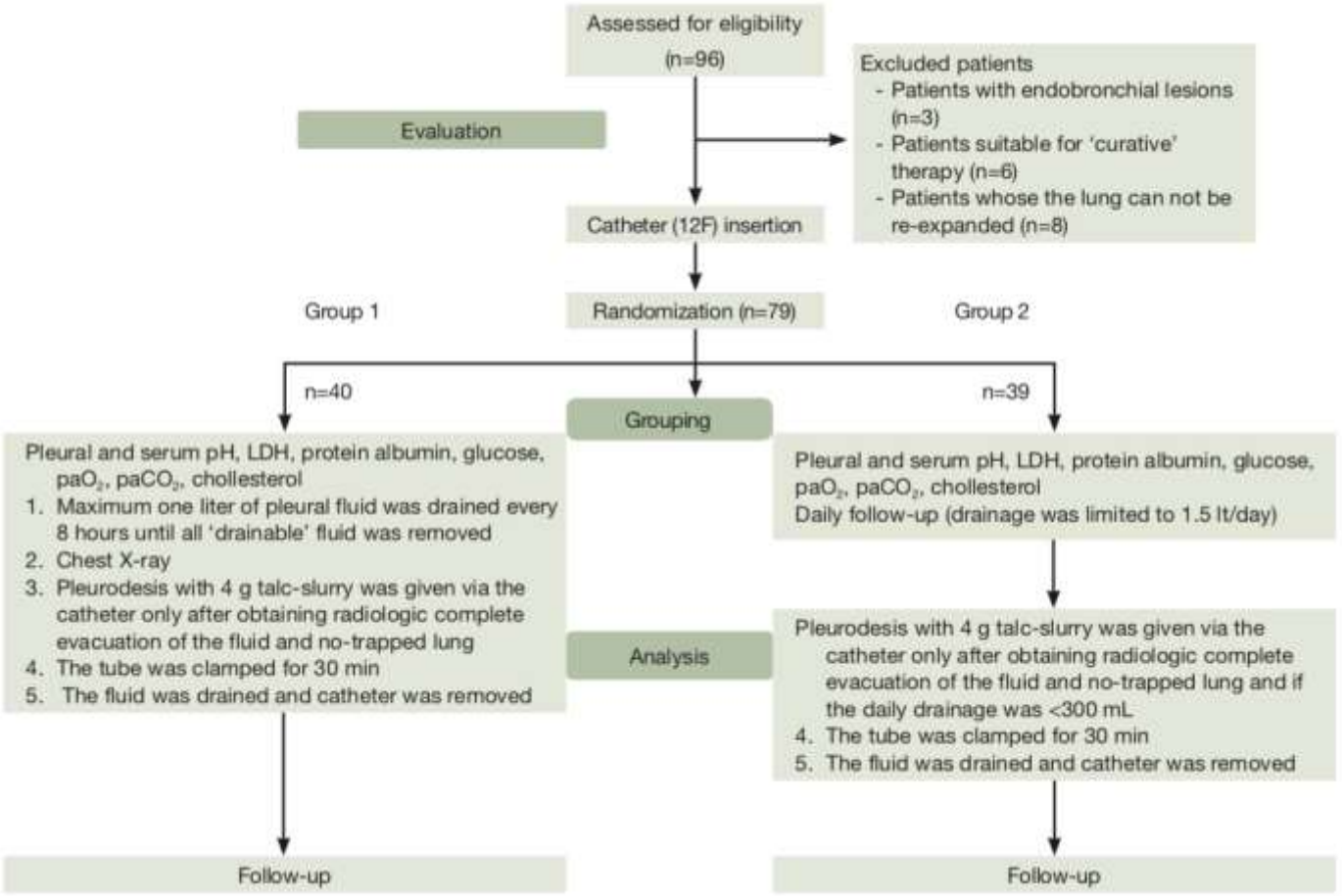
# SEPTATED MALIGNANT PLEURAL EFFUSIONS ROLE OF FIBRINOLYTICS BEFORE PLEURODESIS?

## CONCLUSION

1. Using fibrinolytics before pleurodesis in MPE increases drain output and improves lung expansion
2. But this is not translated into improvement in dyspnoea and pleurodesis success rates probably due to small sample sizes in the studies evaluating these approaches

# RAPID PLEURODESIS IN MALIGNANT PLEURAL EFFUSION

- A prospective randomized ‘non-inferiority’ trial was conducted in 96 patients with malignant pleural effusion (MPE)




Ozkul et al. J Thorac Dis 2014;6(12):1731-5

- Complete or partial response - 35 (87.5%) vs 33 (84.6%) (P=0.670)
- **The mean total drainage** -2,703 mL vs 4,329 mL (P=0.016)
- **The mean drainage time**- 40.7 hours vs 165.2 hours (P<0.001)
- **The mean length of stay** -2.2 days vs 9.0 days (P<0.001)
- ***Comment***:

Prolonged drainage and hospitalization seems unnecessary if the fluid is completely drained and the lung is re-expanded

Ozkul et al. J Thorac Dis 2014;6(12):1731-5

# GUIDELINES – PLEURODESIS IN MPE

- Talc is the most effective sclerosant available for pleurodesis
- Graded talc should always be used in preference to ungraded talc as it reduces the risk of arterial hypoxemia complicating talc pleurodesis
- Talc pleurodesis is equally effective when administered as a slurry or by insufflation
- Large bore $\geq$ 24F chest tube preferred
- Intrapleural instillation of fibrinolytic drugs is recommended for the relief of distressing dyspnoea due to multiloculated malignant effusion resistant to simple drainage
- Patient rotation is not necessary after intrapleural instillation of sclerosant

BTS GUIDELINES 2010
ERS/EACTS STATEMENT ON MPE 2018

# PLEURODESIS IN PNEUMOTHORAX – SYSTEMATIC REVIEW

| STUDY | METAANALYSIS |
|---|---|
| SUBJECTS | 50 studies with spontaneous pneumothorax |
| OBJECTIVE | Chemical pleurodesis efficacy |
| RESULTS | **Recurrence rates:**<br>ICTD drainage alone : 26.1% - 40.1%<br>Thoracoscopic Talc poudrage : 2.5% - 10.2%<br>VATS f/b Talc : 0.0% - 3.2%<br>VATS f/b minocycline : 0.0% - 2.9%<br>ICTD + tetracycline : 13% - 33.3%<br>Autologous blood patch pleurodesis : 15.6% - 18.2% |

Hallifax RJ et al. Thorax. 2017 Dec;72(12):1121-1131

# BTS GUIDELINES – PLEURODESIS IN PNEUMOTHORAX

- Surgical chemical pleurodesis is best achieved by using 5 g sterile graded talc
- VATS preferred over thoracotomy in view of lesser perioperative morbidity and shorter hospital stay
- Medical pleurodesis may be appropriate for inoperable and unwilling patients
- **ERS statement** : Talc slurry is not used in patients with PSP as these patients are able to tolerate pleurodesis with poudrage, which is more effective

# PLEURODESIS IN BENIGN PLEURAL EFFUSIONS ?

| STUDY | Retrospective/prospective (1992-1997) |
|---|---|
| SUBJECTS | Non malignant pleural effusions, n=16, CHF -6, Liver failure -4 Yellow Nail syndrome – 1, Chylothorax – 1, SLE -1, Undiagnosed - 3 |
| INTERVENTION | Talc slurry pleurodesis |
| OUTCOME | Pleurodesis success rate -94%, No significant complications |
| COMMENT | **Pleurodesis can be used in recurrent benign and undiagnosed pleural effusions** |

Glazer M et al. Chest. 2000 May;117(5):1404-9

# 2. FIBRINOLYTIC AGENTS

# CONTENTS

- Fibrinolytic agents
- Mechanism
- Role of fibrinolytics in parapneumonic effusion
- Surgery vs fibrinolytics
- Streptokinase (MIST 1 trial)
- Urokinase and Alteplase
- Meta analysis of fibrinolytic agents
- DNase
- Saline irrigation
- Protocol to follow
- Take home message

# FIBRINOLYTIC AGENTS

| DRUG | FIBRIN SELECTIVITY | SYSTEMIC LYTIC STATE | ALLERGIC REACTIONS | HALF LIFE |
|---|---|---|---|---|
| **STREPTOKINASE** | NO | YES | YES | 30 minutes |
| ANISTREPLASE | NO | YES | YES | 88-112 minutes |
| **UROKINASE** | NO | YES | NO | 20 minutes |
| **ALTEPLASE** | YES | NO | NO | 3-5 minutes |
| **TENECTEPLASE** | YES | NO | NO | 20-24 minutes |
| RETEPLASE | YES | NO | NO | 13-16 minutes |

# MECHANISM OF FIBRINOLYTICS

- Dissolve the fibrin membranes that are responsible for the loculation and facilitate drainage of the effusion
- Uncontrolled studies have shown that intrapleural fibrinolytics increased the drainage of loculated effusions

Light RW et al. Chest. 1995 Aug;108(2):299-301

| | | | |
|---|---|---|---|
| **Class 1** | **Non significant Parapneumonic effusion** | Small , <10mm thick on decubitus x ray | **No thoracentesis indicated** |
| Class 2 | Typical parapneumonic effusion | >10mm thick,<br>Glucose >40 mg/dL, pH>7.20, Gram stain and culture negative | Antibiotics alone |
| Class 3 | Borderline complicated Parapneumonic effusion | 7.0<pH<7.20 and/or LDH>1,000 and glucose>40 mg/dL,<br>Gram stain and culture negative | Antibiotics plus serial thoracentesis |
| Class 4 | Simple complicated Parapneumonic effusion | pH<7.00 and/or glucose < 40 mg/dL and/or Gram stain or culture positive<br>Not loculated, not frank pus | Tube thoracostomy plus antibiotics |
| Class 5 | Complex complicated parapneumonic effusion | pH<7.00 and/or glucose < 40 mg/dL and/or Gram stain or culture positive<br>Multiloculated | Tube thoracostomy plus thrombolytics(Rarely require thoracoscopy or decortication) |
| Class 6 | Simple empyema | Frank pus present<br>Single locule or free flowing | Tube thoracostomy± decortication |
| Class 7 | Complex empyema | Frank pus present<br>Multiple locules | Tube thoracostomy + thrombolytics<br>Often require thoracoscopy or decortication |

Light RW et al. Chest. 1995 Aug;108(2):299-301

# SURGERY VS NON-SURGICAL MANAGAMENT


**Surgical versus non-surgical management for pleural empyema (Review)**

Redden MD, Chin TY, van Driel ML

# RESULTS

**VATS compared to thoracostomy drainage for pleural empyema**

**Patient or population:** children and adults with pleural empyema
**Intervention:** VATS
**Comparison:** thoracostomy drainage

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Quality of the evidence (GRADE) |
|---|---|---|---|---|---|
| | Thoracostomy drainage | VATS | | | |
| **Mortality** | Risk in study population | | **OR 0.80** (0.04 to 14.89) | 361 (7 RCTs) | ⊕⊕◯◯ LOW[1] |
| | **6 per 1000** | **5 per 1000** (0 to 78) | | | |
| **Mortality: children** | Risk in study population | | Not estimable | 271 (5 RCTs) | ⊕⊕⊕◯ MODERATE [2] |
| | Not pooled | Not pooled | | | |
| **Mortality: adults** Follow-up: not reported | Risk in study population | | **OR 0.80** (0.04 to 14.89) | 90 (2 RCTs) | ⊕⊕⊕◯ MODERATE [3] |
| | **23 per 1000** | **18 per 1000** (1 to 257) | | | |
| **Length of hospital stay (days)** Follow-up: 1 year in Cobanoglu 2011 and 3 months in Marhuenda 2014 | Control group | The mean length of hospital stay in the intervention group was **2.52 days fewer** (4.26 fewer to 0.77 fewer). | | 231 (5 RCTs) | ⊕⊕⊕◯ MODERATE[4] |

VATS and thoracotomy clearly better than thoracostomy drainage in terms of hospital stay and duration of tube drainage

Redden MD et al. Cochrane Database Syst Rev. 2017 Mar

# MIST 1 (STK) TRIAL

- 454 patients with pleural infection (defined by the presence of purulent pleural fluid or pleural fluid with a pH below 7.2 with signs of infection or by proven bacterial invasion of the pleural space) were randomised
- Intrapleural streptokinase (250,000 IU twice daily for three days) or placebo

Maskell NA et al. N Engl J Med 2005;352:865-74

# MIST -1 (STK) TRIAL PATIENT CHARACTERISTICS

**Table 1. Baseline Characteristics of the Patients, According to Study Group.***

| Variable | Streptokinase (N=208) | Placebo (N=222) |
|---|---|---|
| **Demographic and clinical characteristics** | | |
| Sex — no. | | |
| Male | 139 | 160 |
| Female | 69 | 62 |
| Age — yr | 60±18 | 61±18 |
| Side with empyema — no. (%) | | |
| Right | 105 (60) | 109 (55) |
| Left | 71 (40) | 88 (45) |
| Duration of symptoms before randomization — days | | |
| Median | 14 | 15 |
| Interquartile range | 8–28 | 8–28 |
| Concurrent heparin or warfarin therapy at randomization — no. (%) | 20 (10) | 23 (10) |
| Portion of hemithorax opacified by pleural effusion on chest radiograph — % | | |
| Median | 40 | 35 |
| Interquartile range | 20–60 | 20–60 |
| Chest-tube bore at randomization — French | | |
| Median | 12 | 12 |
| Interquartile range | 12–20 | 12–16 |
| Coexisting illness — no. (%)† | 135 (65) | 159 (72) |
| Cardiac disease | 49 (24) | 67 (30) |
| Respiratory disease | 30 (14) | 52 (23) |
| Diabetes mellitus | 22 (11) | 22 (10) |
| Excess alcohol intake | 22 (11) | 19 (9) |
| Joint disease | 17 (8) | 23 (10) |
| Gastroesophageal disease | 12 (6) | 22 (10) |
| Neurologic disease | 18 (9) | 15 (7) |
| Kidney disease | 13 (6) | 7 (3) |
| Liver disease | 8 (4) | 10 (5) |
| Other | 37 (18) | 31 (14) |
| Thoracic-surgery facilities on site at the patient's hospital — no. (%) | 109 (52) | 112 (50) |
| **Pleural-fluid characteristics** | | |
| Visibly purulent — no. (%) | 170 (82) | 185 (83) |
| Gram-positive for bacteria — no. (%) | 43 (21) | 45 (20) |
| Culture-positive for bacteria — no. (%) | 34 (16) | 30 (14) |
| pH in patients without frankly purulent fluid | 6.8±0.4 | 6.8±0.5 |
| Lactate dehydrogenase — IU/liter | | |
| Median | 7609 | 4439 |
| Interquartile range | 1862–23,010 | 1044–14,458 |

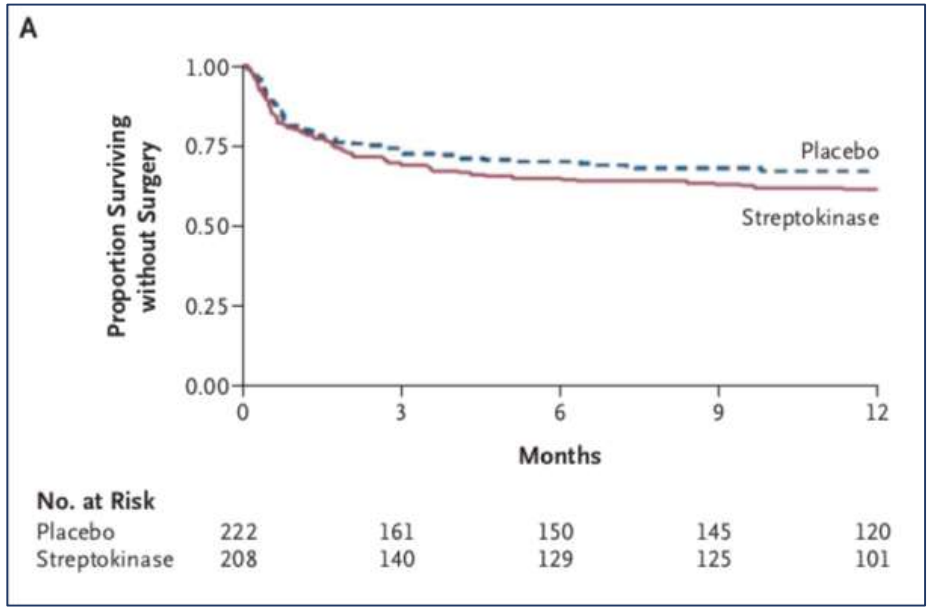
Maskell NA et al. N Engl J Med 2005;352:865-74

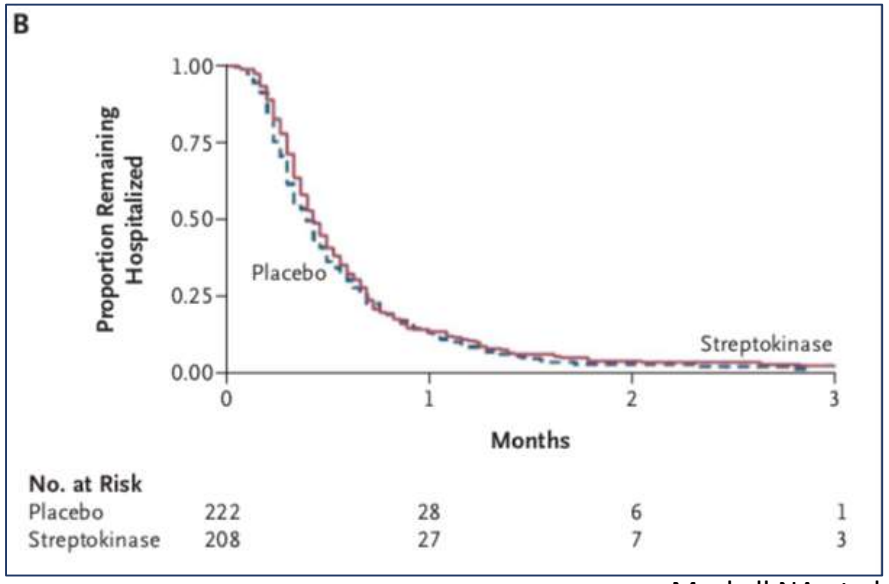
# MIST-1 TRIAL OUTCOMES

- No significant difference - Need for surgery or death at 3 months

  (with streptokinase: 64 of 206 patients [31 percent]; with placebo: 60 of 221 [27 percent]; relative risk, 1.14 [95 percent confidence interval, 0.85 to 1.54; P=0.43)

- No benefit to streptokinase in terms of mortality, rate of surgery, radiographic outcomes, or length of the hospital stay




Maskell NA et al. N Engl J Med 2005;352:865-74

# MIST 1 –TRIAL OUTCOMES

**Table 3. Outcomes on Chest Radiography at Three Months.***

| Outcome | Streptokinase | Placebo | Difference between Groups (95% CI) | P Value |
|---|---|---|---|---|
| Residual pleural thickening at lateral chest wall — mm† | 12±14 | 15±19 | 3 (−1 to 7) | 0.20 |
| Vertical height of thorax on affected side — mm† | 209±30 | 221±33 | 12 (4 to 19) | 0.003 |
| Improvement in the area of pleural-fluid opacity in patients not requiring surgery — no. (%)‡ | | | | 0.30§ |
| No. of patients | 102 | 133 | | |
| 0–25% | 7 (7) | 12 (9) | | |
| 26–75% | 6 (6) | 12 (9) | | |
| 76–90% | 12 (12) | 24 (18) | | |
| >90% | 77 (75) | 85 (64) | | |

- No significant radiological resolution seen
- Subgroup analysis done for loculated effusion, frank pus, chest tube size - all failed to show any benefit in primary outcome

Maskell NA et al. N Engl J Med 2005;352:865-74

# MIST -1 TRIAL ADVERSE EVENTS

**Table 2. Adverse Events Possibly Attributable to Study Treatment, According to Severity and Type.**

| Variable | Streptokinase (N=208) | Placebo (N=222) | Relative Risk (95% CI)* | P Value |
|---|---|---|---|---|
| | *no. (%)* | | | |
| **Severity** | | | | |
| Serious | 14 (7) | 6 (3) | 2.49 (0.98–6.36) | 0.08 |
| Other | 8 (4) | 8 (4) | 1.07 (0.41–2.81) | 0.91 |
| Total | 22 (11) | 14 (6) | 1.68 (0.88–3.19) | 0.15 |
| **Type** | | | | |
| Hemorrhage (local pleural or systemic) | 7 (3) | 6 (3) | | |
| Chest pain | 4 (2) | 1 (<1) | | |
| Fever, rash, and allergy | 5 (2) | 1 (<1) | | |
| Other | 6 (3) | 6 (3) | | |

**CONCLUSION**:

- Streptokinase failed to show any benefit in empyema or complicated parapneumonic effusion
- On the contrary it had shown adverse events

Maskell NA et al. N Engl J Med 2005;352:865-74

# OTHER FIBRINOLYTICS

| STUDY | RCT (Tuncozgur et al) | Cross over RCT (Thommi et al) | RCT (Refaat et al) |
|---|---|---|---|
| NUMBER OF SUBJECTS | 49 | 108 | 94 |
| DRUGS COMPARED | **Urokinase** vs placebo | **Alteplase** vs placebo | **Tenecteplase** vs placebo |
| DOSE USED | 1,00,000 units OD – 3 days | 25mg OD – 3 days | 15 mg OD (upto 5 doses) |
| OUTCOME | **Reduced need for surgery**<br>No mortality benefit | **Reduced need for surgery**<br>95% vs 12% | **Reduced need for surgery** |
| BLEEDING | No significant increase | No significant increase | No significant increase |

# UROKINASE VS ALTEPLASE

| STUDY | RCT |
|---|---|
| SUBJECTS | CPPE/empyema, n= 99 |
| INTERVENTION | 51 received alteplase 20mg/10 mg OD - 6 days<br>48 received- urokinase 1,00,000 units OD- 6 days |
| OUTCOMES | 1. Success rates for urokinase and alteplase at 3 and 6 days were not significantly different **(91.6% vs 78.4%)**<br>**2. CPPE subgroup- Urokinase better**<br>3. There were no differences in mortality or surgical need or duration of hospital stay |
| ADVERSE EVENTS | Alteplase 20 mg – 28% bleeding, 10mg – 20 % bleeding<br>Urokinase - no bleeding |

UROKINASE BETTER THAN ALTEPLASE ESPECIALLY IN CPPE (only in radiological and clinical improvement)

Aleman C et al. Lung. 2015 Dec;193(6):993-1000

# Efficacy of intrapleural instillation of fibrinolytics for treating pleural empyema and parapneumonic effusion: a meta-analysis of randomized control trials

- Ten trials with a total of 977 patients were included

| Reference | Year | Enrolled no. | | Male, % | | Age (means ± SD, year) | | Fibrinolytics | Treatment dose per day | Duration (day) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | TG | CG | TG | CG | TG | CG | | | |
| Davies *et al*. (31) | 1997 | 12 | 12 | 75 | 67 | 62 (23) | 60 (23) | Streptokinase | 250 000 IU | 3 |
| Bouros *et al*. (30) | 1999 | 15 | 16 | 73 | 81 | 54* | 57* | Urokinase | 100 000 IU | 3 |
| Tuncozgur *et al*. (29) | 2001 | 24 | 25 | 83 | 72 | 34 (14) | 33 (16) | Urokinase | 100 000 IU | 5 |
| Thomson *et al*. (32) | 2002 | 29 | 29 | – | – | 3.6 | 3.0 | Urokinase | 80 000 IU | 3 |
| Singh *et al*. (27) | 2004 | 19 | 21 | 53 | 52 | 6.4 (2.8) | 6.8 (3.1) | Streptokinase | 15 000 IU/kg | 3 |
| Diacon *et al*. (28) | 2004 | 22 | 22 | 82 | 68 | 40 (13) | 40 (14) | Streptokinase | 250 000 IU | up to 7 |
| Misthos *et al*. (17) | 2005 | 57 | 70 | 39 | 51 | 45* | 46* | Streptokinase | 250 000 IU | 3 |
| Maskell *et al*. (8) | 2005 | 208 | 222 | 67 | 72 | 60 (18) | 61 (18) | Streptokinase | 500 000 IU | 3 |
| Rahman *et al*. (24) | 2011 | 52 | 55 | 75 | 71 | 60 (17) | 58 (19) | t-PA | 20 mg | 3 |
| Thommi *et al*. (25) | 2012 | 35 | 32 | – | – | – | – | t-PA | 25 mg | 3 |

Nie W et al. Clin Respir J. 2014 Jul;8(3):281-91

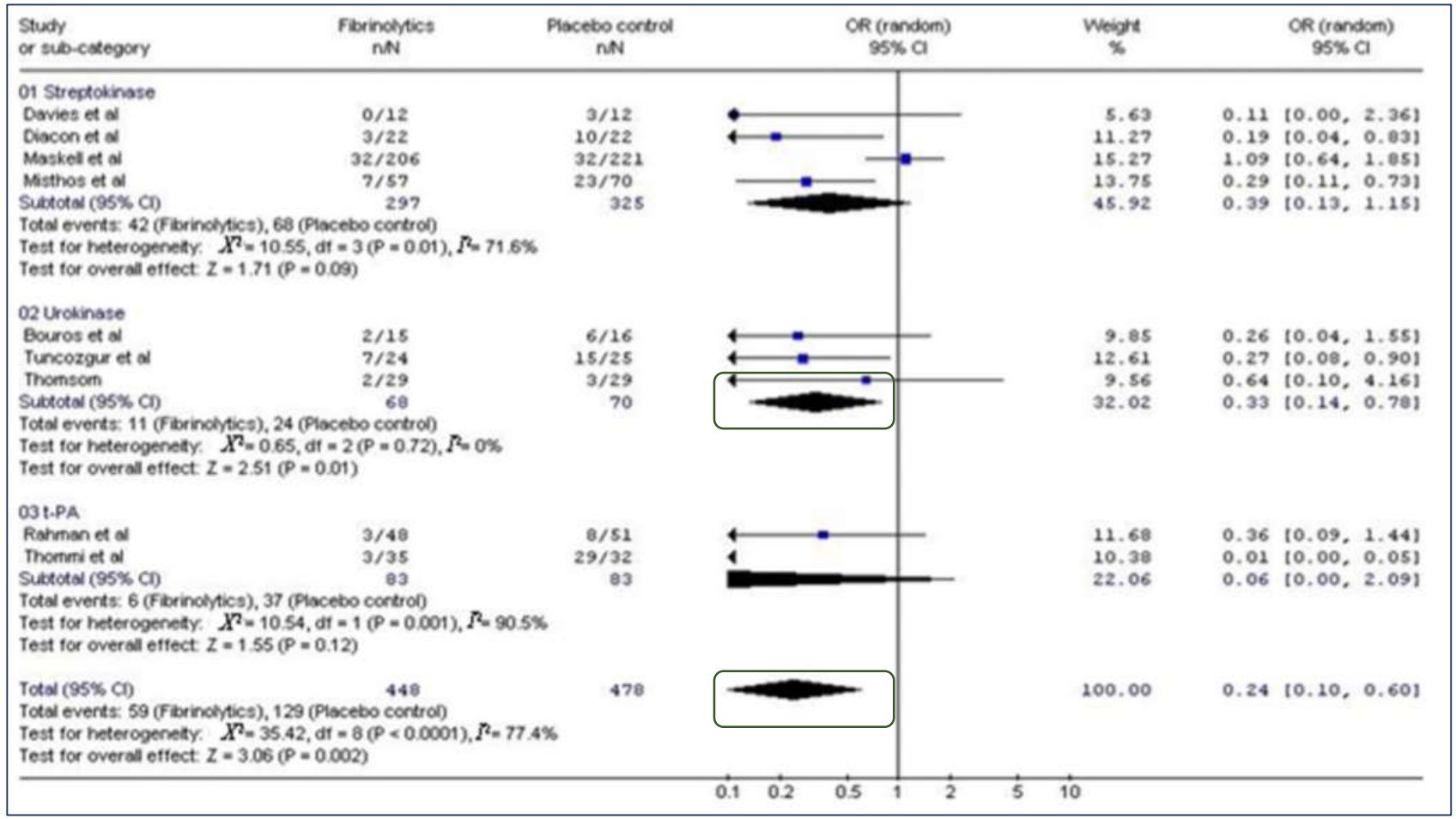
# OUTCOMES

| | Surgery or death (*n*) | | Surgery (*n*) | | Death (*n*) | | Duration of hospital stay (means ± SD, days) | | Severe side effects (*n*) | |
|---|---|---|---|---|---|---|---|---|---|---|
| Reference | Fibrinolysis | Placebo | Fibrinolysis | Placebo | Fibrinolysis | Placebo | Fibrinolysis | Placebo | Fibrinolysis | Placebo |
| Davies *et al.* (31) | 0/12 | 3/12 | 0/12 | 3/12 | 0/12 | 0/12 | 16 (13) | 13 (8) | 0/12 | 0/12 |
| Bouros *et al.* (30) | 2/15 | 6/16 | 2/15 | 6/16 | 0/15 | 0/16 | 13 (4) | 18 (5) | 0/15 | 0/16 |
| Tuncozgur *et al.* (29) | 7/24 | 15/25 | 7/24 | 15/25 | 0/24 | 0/25 | 14 (4) | 21 (4) | 0/24 | 0/25 |
| Thomson *et al.* (32) | 2/29 | 3/29 | 2/29 | 3/29 | 0/29 | 0/29 | 6.8 | 8.8 | 1/29 | 0/29 |
| Singh *et al.* (27) | 0/19 | 0/21 | – | – | 0/19 | 0/21 | – | – | 0/19 | 0/21 |
| Diacon *et al.* (28) | 4/22 | 11/22 | 3/22 | 10/22 | 1/22 | 1/22 | 10.5 (10.6)* | 9 (7.7)* | – | – |
| Misthos *et al.* (17) | 7/57 | 25/70 | 7/57 | 23/70 | 1/57 | 3/70 | 7 (1.7) | 15.5 (4) | 0/57 | 0/70 |
| Maskell *et al.* (8) | 64/206 | 60/221 | 32/206 | 32/221 | 32/206 | 30/221 | 13* | 12* | 14/208 | 6/222 |
| Rahman *et al.* (24) | – | – | 3/48 | 8/51 | 4/48 | 2/50 | 16.5 (22.8) | 24.8 (56.1) | 0/52 | 1/55 |
| Thommi *et al.* (25) | 3/35 | 29/32 | 3/35 | 29/32 | 0/35 | 0/32 | – | – | 2/35 | 2/32 |

Intrapleural fibrinolytic therapy **decreased the OR for surgical intervention** [OR = 0.24; 95% confidence interval (CI): 0.10–0.60] and **the length of hospital stay** (weighted mean difference=−6.47; 95% CI: −8.87, −4.08)

Nie W et al. Clin Respir J. 2014 Jul;8(3):281-91

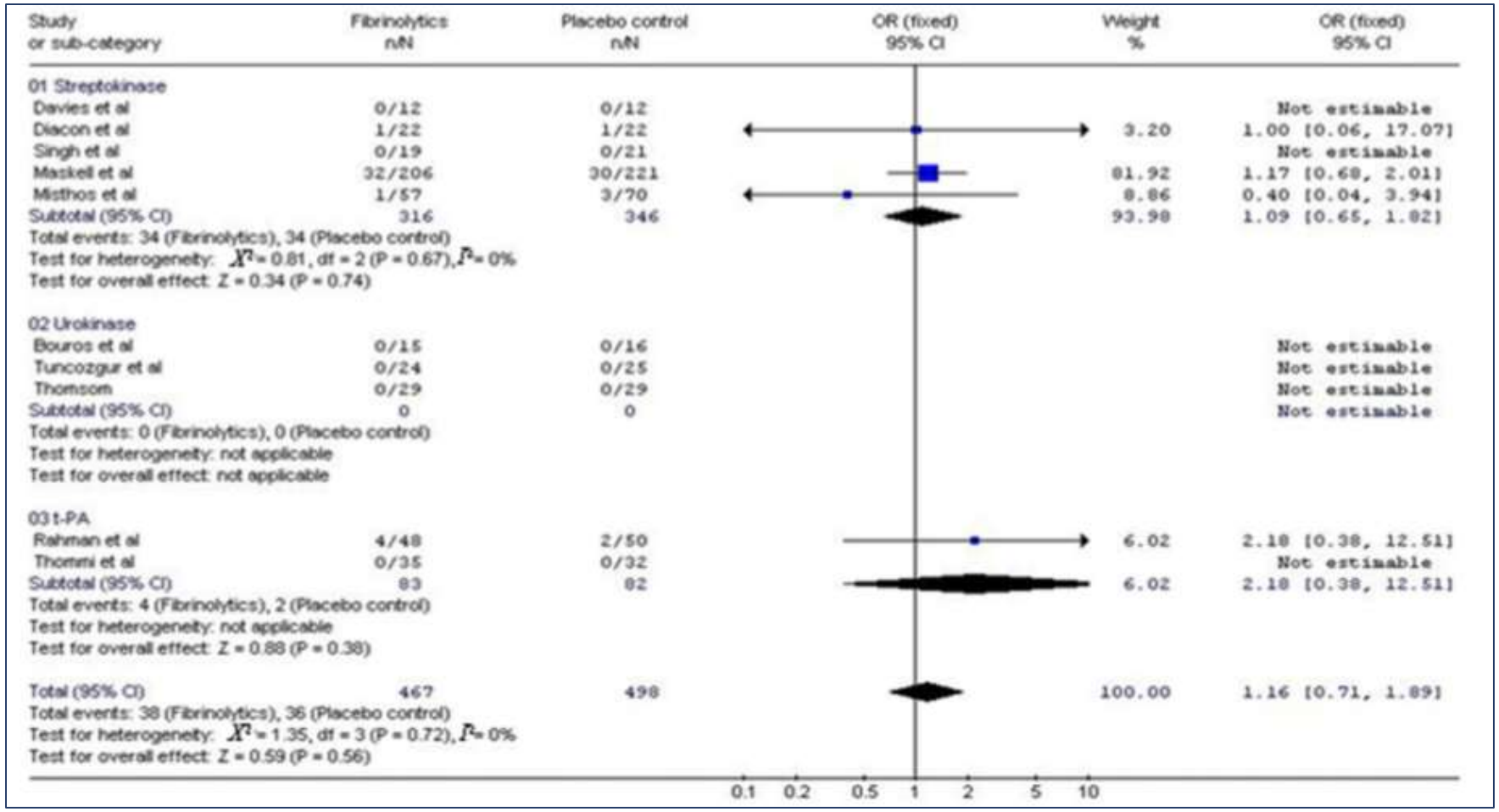
# OUTCOMES – REQUIREMENT FOR SURGERY




Subgroup analyses indicated that urokinase had marked positive effects on reducing surgical intervention (OR = 0.33; 95% CI: 0.14–0.78), but neither streptokinase nor alteplase did

Nie W et al. Clin Respir J. 2014 Jul;8(3):281-91

# OUTCOMES - MORTALITY




Intrapleural fibrinolysis was associated with a non-significant reduction in mortality rate (OR = 1.16; 95% CI: 0.71–1.89)
ADVERSE EFFECTS – No significant increase

Nie W et al. Clin Respir J. 2014 Jul;8(3):281-91

# DORNASE ALFA (PULMOZYME)

- Recombinant human deoxyribonuclease I (rhDNase) - an enzyme which selectively cleaves DNA
- The protein is produced by genetically engineered Chinese Hamster Ovary (CHO) cells containing DNA encoding for the native human protein, deoxyribonuclease I (DNase)
- Extremely safe and effective when it is administered by nebulisation in the treatment of cystic fibrosis – FDA Approved
- Its role in pleural effusion is under evaluation

# MIST 2 TRIAL

210 patients with empyema/complicated parapneumonic effusion were randomised to any of the following:

1. Double placebo
2. Intrapleural tissue plasminogen activator (t-PA) and DNase
3. t-PA and placebo
4. DNase and placebo

Rahman NM et al. N Engl J Med. 2011 Aug 11;365(6):518-26

# MIST 2 TRIAL

**Dosing and schedule**:

- tPA (Actilyse, Boehringer Ingelheim) 10 mg
- DNase (Pulmozyme, Roche) 5 mg
- The test drugs were given twice daily along with 30ml Normal saline and sterile water for 3 days
- tPA administrated first and 2 hours later Dnase administrated
- Tube clamped for 1 hour post administration

# MIST 2 TRIAL – STUDY POPULATION

**Table 1. Baseline Characteristics of the Patients, According to Study Group.***

| Characteristic | t-PA (N=52) | DNase (N=51) | t-PA–DNase (N=52) | Placebo (N=55) |
|---|---|---|---|---|
| Age — yr | 60±17 | 57±18 | 60±19 | 58±19 |
| Male sex — no. (%) | 39 (75) | 42 (82) | 31 (60) | 39 (71) |
| Percent of hemithorax occupied with pleural fluid | 39.8±22.6 | 41.9±22.9 | 44.2±24.9 | 36.3±23.3 |
| Duration of symptoms before randomization — days | | | | |
| Median | 14 | 14 | 13 | 13 |
| Interquartile range | 7–30 | 7–30 | 7–22 | 7–21 |
| Small-bore tube, <15 French — no. (%)† | 41 (80) | 44 (88) | 48 (94) | 49 (91) |
| Community-acquired infection — no. (%) | 44 (85) | 44 (86) | 45 (87) | 49 (89) |
| Radiographic evidence of loculation — no. (%)‡ | 49 (94) | 47 (92) | 49 (94) | 47 (85) |
| Purulent pleural fluid — no. (%) | 24 (46) | 25 (49) | 27 (52) | 26 (47) |
| Positive Gram's stain or culture of pleural fluid — no. (%) | 5 (10) | 5 (10) | 4 (8) | 7 (13) |
| Pleural-fluid pH | | | | |
| Median | 6.9 | 7.0 | 6.9 | 6.9 |
| Interquartile range | 6.8–7.1 | 6.8–7.1 | 6.8–7.1 | 6.8–7.1 |
| Lactate dehydrogenase in pleural fluid — IU/liter | | | | |
| Median | 2935 | 3077 | 3418 | 3337 |
| Interquartile range | 871–9908 | 365–7903 | 1321–7328 | 1034–8943 |

Rahman NM et al. N Engl J Med. 2011 Aug 11;365(6):518-26

# MIST -2 TRIAL OUTCOMES

**Table 2. Primary and Major Secondary Outcomes, According to Study Group.***

| Outcome | t-PA | DNase | t-PA–DNase | Placebo |
|---|---|---|---|---|
| Change from baseline in hemithorax area occupied by effusion (primary outcome) — % | −17.2±24.3 | −14.7±16.3 | −29.5±23.3 | −17.2±19.6 |
| Percent difference vs. placebo (95% CI) | 2.0 (−4.6 to 8.6) | 4.5 (−1.5 to 10.5) | −7.9 (−13.4 to −2.4) | NA |
| P value | 0.55 | 0.14 | 0.005 | NA |
| Surgical referral — no. referred/total no. (%) | 3/48 (6) | 18/46 (39) | 2/48 (4) | 8/51 (16) |
| Odds ratio vs. placebo (95% CI) | 0.29 (0.07 to 1.25) | 3.56 (1.30 to 9.75) | 0.17 (0.03 to 0.87) | NA |
| P value | 0.10 | 0.01 | 0.03 | NA |
| Hospital stay — no. of days | 16.5±22.8 | 28.2±61.4 | 11.8±9.4 | 24.8±56.1 |
| Percent difference vs. placebo (95% CI) | −8.6 (−40.8 to 3.3) | 3.6 (−19.0 to 30.8) | −14.8 (−53.7 to −4.6) | NA |
| P value | 0.21 | 0.73 | <0.001 | NA |

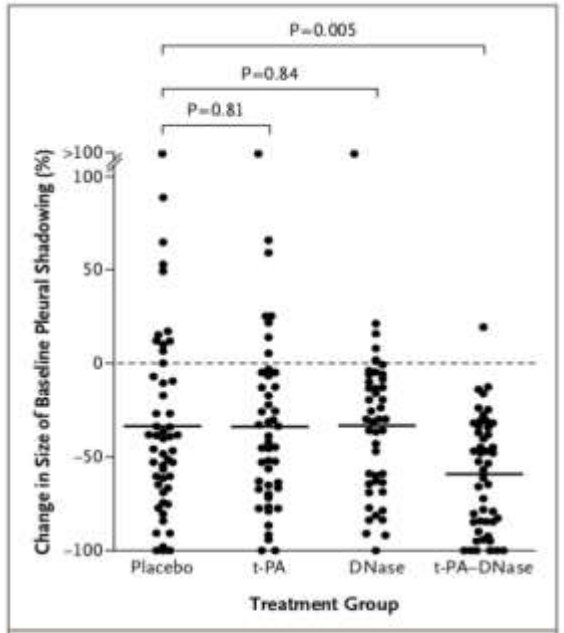


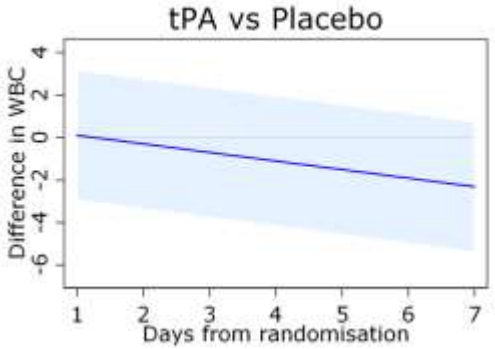

**Figure 2. Change in Area of Pleural Fluid on Chest Radiography on Day 7 versus Day 1, According to Study Group.**
Each circle represents an individual patient, and mean changes are indicated by the horizontal bars.

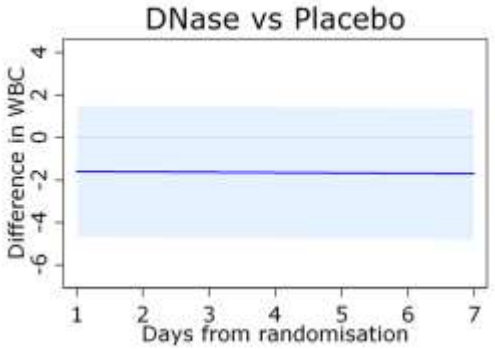
SUBGROUP ANALYSES: purulent versus non purulent pleural fluid, use of large-bore versus small-bore chest tube, and radiographic evidence of loculation versus no evidence of loculation.

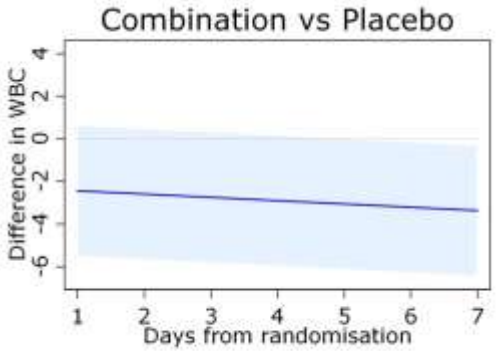
Rahman NM et al. N Engl J Med. 2011 Aug 11;365(6):518-26

# MIST-2 TRIAL OUTCOMES

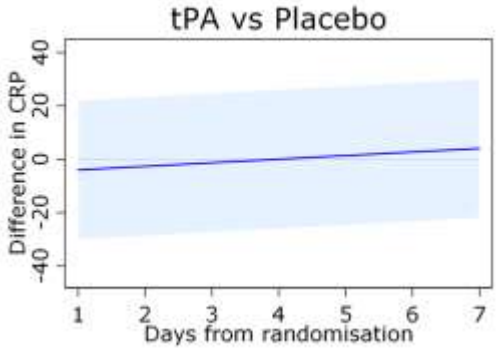
- Mortality benefit – Not seen both at 3 months and at 12 months
- Inflammatory markers

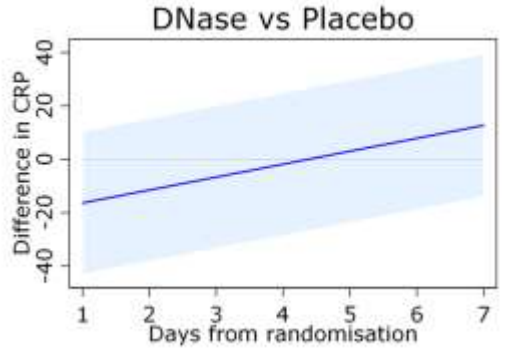


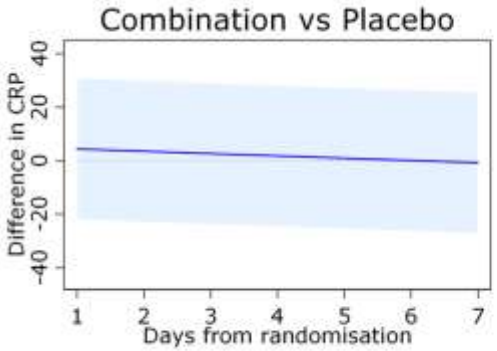




WBC COUNT




CRP LEVELS

Rahman NM et al. N Engl J Med. 2011 Aug 11;365(6):518-26

# MIST -2 TRIAL – ADVERSE EVENTS

- Intrapleural haemorrhage – 2 cases (tPA + Dnase)
- Hemoptysis – 1 case (tPA + Dnase)
- P value 0.22

Rahman NM et al. N Engl J Med. 2011 Aug 11;365(6):518-26

# MIST-2 TRIAL

**Conflicting result with MIST 1 trial** :

Use of a different fibrinolytic agent (i.e., t-PA rather than streptokinase) and the additional cleavage of uncoiled DNA by DNase may have allowed fibrinolytic treatment to work

**DNase alone** :

- Ineffective in improving pleural drainage and was associated with an increase in surgical referrals by a factor of 3
- *Hypothesis* : Systemic absorption of bacterial or inflammatory components after DNase-mediated biofilm disruption in a pleural space with ineffective drainage due to undisrupted fibrinous septations

Rahman NM et al. N Engl J Med. 2011 Aug 11;365(6):518-26

# COST – IS IT AFFORDABLE ??

Dnase (Pulmozyme)- 1 ampoule (2.5mg/2.5 ml)- 48.10 dollars

14000 rupees/day

tPA (Actilyse)- 1 ampoule (20mg)

19800 rupees/day

**Total – 1,01,400 rupees for total 3 days course**

# tPA + DNase – OPTIMUM SCHEDULE ?

| STUDY | SUBJECTS | DOSE (tPA + Dnase) | Mean time before administration | Administration | Clamping time | ICTD Manipulations/day | Total Doses | Efficacy | Bleeding |
|---|---|---|---|---|---|---|---|---|---|
| MIST 2[1] | 52 | 10mg BD/5mg BD (6 doses) | Immediate post ICTD | Sequential (2 hours) | 1 hour | 4 | 6 | 96% | 5.7% |
| Piccolo et al[2] | 107 | Same (upto 6 doses) | > 24 hours (Rescue therapy) | Sequential (1 hour) | 1 hour | 4 | 6 | 92.3% | 1.8% |
| Majid A et al[3] | 73 | Same (upto 6 doses) | Less than 24 hours (71.2%) | Concurrent | 2 hours | 2 | 2 (Median) | 90.4% | 5.4% |
| Popowicz et al (ADAPT 1)[4] | 61 | 5mg BD+5mgBD ( 6 doses) 11.5% needed dose escalation | > 24 hours (Rescue therapy) | Sequential (1 hour) | 1 hour | 6 | 6 | 89% without dose escalation | 4.9% |
| Hugh Ip et al ADAPT 2[5] | 21 | 2.5mg BD + 5mg BD (6 doses) | NA | NA | NA | NA | 90% needed 3 doses or less | 71% without dose escalation | 0% |

*ADAPT - Alteplase Dose Assessment for Pleural infection Therapy*


[1]Rahman NM et al. N Engl J Med. 2011 Aug 11;365(6):518-26
[2]Piccolo et al. Ann Am Thorac Soc. 2014 Nov;11(9):1419-25
[3]Majid A et al. Ann Am Thorac Soc. 2016 Sep;13(9):1512-8
[4]Popowicz et al. Ann Am Thorac Soc. 2017 Jun;14(6):929-936
[5]Hugh Ip et al. European Respiratory Journal 2018 52: Suppl. 62, PA4712

# DNase ALONE – CAN IT BE TRIED?

- MIST-2 trial has reported lack of improvement with DNase if used alone and infact it increased the need for surgery

| STUDY | SUBJECTS | NUMBER | DOSE USED | INTERVENTION (POST ICTD) | NEGATIVE SUCTION | CLAMPING | OUTCOME |
|---|---|---|---|---|---|---|---|
| Retrospective[1] | Empyema | 10 | 2.5 mg Once (SOS) | After drain output decreases ($4^{th}$ day or $6^{th}$ day – in this study) | **APPLIED** | **4 hours** | 50% success |
| MIST 2 (RCT) | CPE/Empyema | 51 | 5 mg BD | Immediate | **NOT APPLIED** | **1 hour** | No benefit |

[1]Bobek V et al. Int J Clin Exp Med. 2015; 8(11): 22011-5

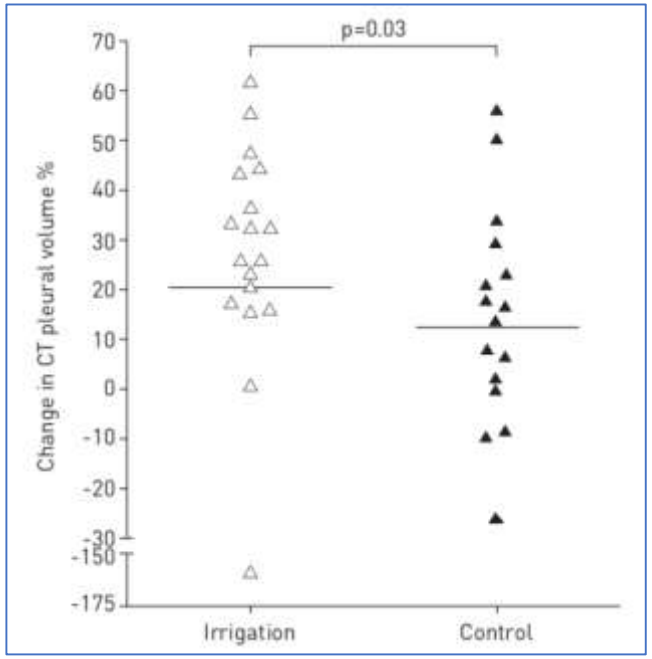
# DOES SALINE IRRIGATION HELP?- PIT TRIAL

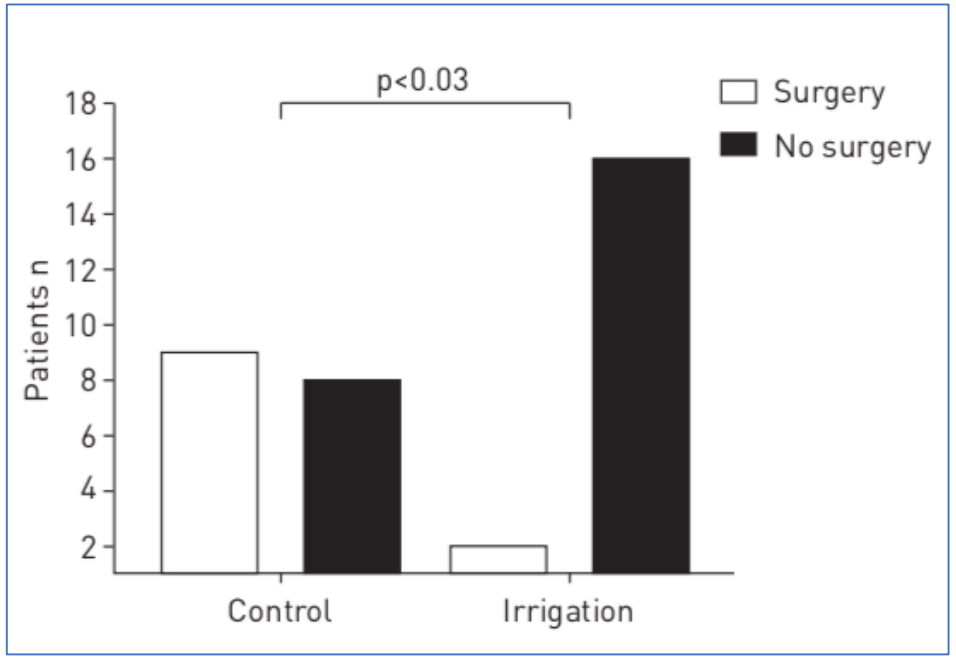
- 30 patients with pleural infection
- ICTD placed and CT scan done 12 hours later
- Those with residual effusion were randomized to saline irrigation vs saline flush
- Study group:
  - 250 ml 0.9% saline infused using gravity over 1 hour and allowed to drain freely
  - Repeated 3 times/ day for 3 days
- Control group:
  - 30 ml 0.9% saline flushed 3 times/day for 3 days
- Both groups- Negative suction -20cmH2O applied

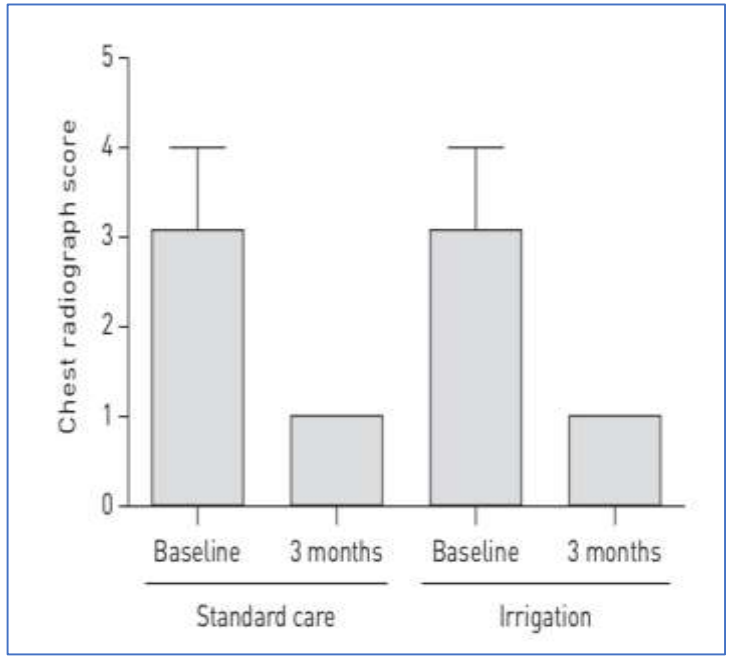
Hooper CE et al. Eur Respir J. 2015 Aug;46(2):456-63

# PIT TRIAL

## SHORT TERM RESULTS– HOSPITAL DURATION



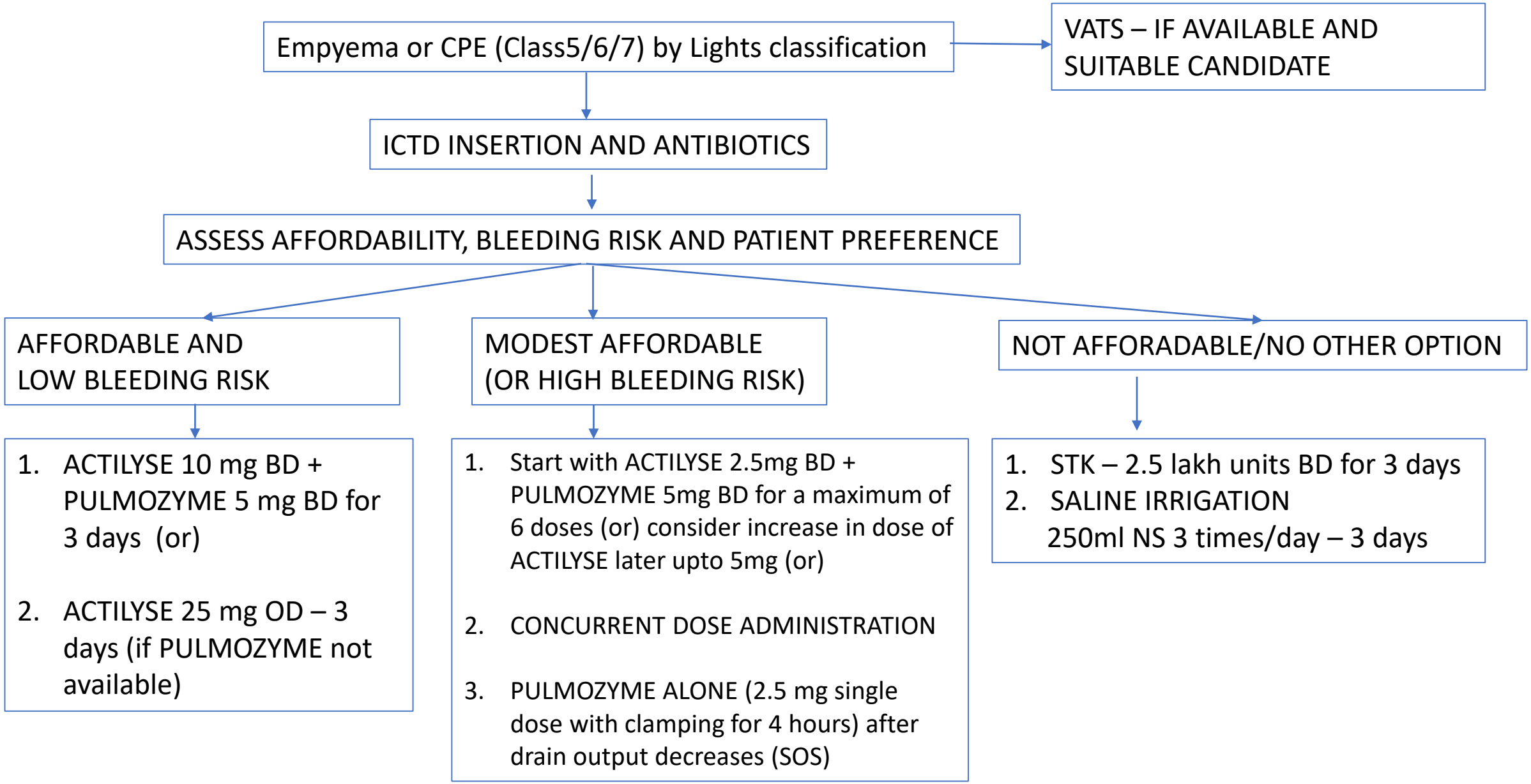




Comment : 3 months radiological resolution, lung function tests and mortality similar between the groups

Hooper CE et al. Eur Respir J. 2015 Aug;46(2):456-63

# PROTOCOL TO FOLLOW?



# PROTOCOL TO FOLLOW?

- Eligible:
    1. Gross pus (or) Gram stain (or) culture positive (or) pH<7.2
    2. Patients fit for thoracic surgery but transfer delayed, and interim measures needed
    3. Patients not fit for thoracic surgery and medical management agreed
- Ineligible:
    1. Previous treatment with intrapleural fibrinolytic agents, dornase, or both for empyema
    2. Coincidental stroke
    3. Major haemorrhage or major trauma
    4. Major surgery in the preceding 5 days
    5. Previous pneumonectomy on the infected side
    6. Pregnancy or lactation

# HOW TO ADMINISTER ?

1. Reconstitute Alteplase 20mg vial with 20mL water for injection

2. This can be retained for 24 hours at 2-8 degree celsius and can be used for 2 doses

3. For a single dose, 10mg should be withdrawn and further diluted with 30mL sodium chloride 0.9%

4. Instill diluted alteplase first into the chest drain, clamp the drain for 1 hour and then unclamp and allow drainage for 1 hour

5. After 1 hour drainage repeat with dornase alfa (2x2.5mg ampoules diluted with 30mL water for injection) and clamp for 1 hour

6. Repeat upto 6 doses, 12 hours apart

# TAKE HOME MESSAGE

- Talc is still the most efficacious pleurodesis agent
- However severe adverse effects prompt using alternate pleurodesis agents
- Povidone iodine and Doxycycline appear to be promising alternatives
- Povidone iodine appears the agent of choice in view of relatively less side effects
- Newer agents are under evaluation
- Fibrinolytics are to be used in empyema only when VATS not applicable
- Streptokinase to be used only if no other option
- tPA along with DNase appear promising agents but without any mortality benefit

# THANK YOU