



TIME1 - rationale



Pleurodesis and drains are painful¹⁻³:

- 60% report moderate pain despite analgesia⁴

Current analgesia use:

- Majority of physicians use opiates⁴

1. Luketich JD et al. *Clin J Pain* 1998;14:152-4.
3. Owen S et al *J Clin Nurs*. 1997;6:215-25.

2. Fox V et al, *J Clin Nurs*. 1999;8:684-92.
4. Lee YC et al *Chest* 2003;124:2229-36.



The best analgesia...



Analgesic	Number of patients in comparison	Percent with at least 50% pain relief	NNT	Lower confidence interval	Higher confidence interval
Ibuprofen 600	76	100	1.5	1.3	2.2
Paracetamol 50	69	97	1.5	1.4	2.3
Kalbitor 60 (intramuscular)	116	96	1.8	1.5	2.3
Diclofenac 100	411	67	1.5	1.6	2.2
Proxicam 40	30	80	1.9	1.2	4.3
Paracetamol 1000 + Codeine 60	197	97	2.2	1.7	2.9
Oxycodone 8.5 + Paracetamol 600	150	80	2.2	1.7	3.2
Bromfenac 25	370	51	2.2	1.9	2.6
Rofecoxib 50	675	54	2.3	2.0	2.6
Diclofenac 50	738	63	2.3	2.0	2.7
Naproxen 440	257	50	2.3	2.0	2.9
Oxycodone IR 15	60	73	2.3	1.5	4.9
Ibuprofen 600	203	79	2.4	2.0	4.2
Ibuprofen 400	4703	56	2.4	2.3	2.6
Aspirin 1200	279	61	2.4	1.9	3.2
Bromfenac 50	247	53	2.4	2.0	3.3
Bromfenac 100	95	62	2.6	1.8	4.8
Oxycodone IR 10 + Paracetamol 650	315	66	2.6	2.0	3.5
Kalbitor 10	790	50	2.6	2.3	3.1
Ibuprofen 200	1414	46	2.7	2.5	3.1
Oxycodone IR 10+Paracetamol 1000	83	87	2.7	1.7	5.8
Proxicam 25	280	63	2.7	2.1	3.8
Diclofenac 25	204	54	2.8	2.1	4.3
Dextropropoxyphene 130	50	40	2.8	1.8	6.5
Bromfenac 10	223	39	2.8	2.3	4.0
Flurbiprofen 100 (intramuscular)	364	54	2.9	2.3	3.9
Flurbiprofen 100 (intramuscular)	456	55	2.9	2.4	3.6
Morphine 10 (intramuscular)	945	50	2.9	2.6	3.6
Morphine 100	426	42	3.2	2.5	4.2



NSAIDs in MPE



Do NSAIDs impair pleurodesis?

- No human data
- Three animal studies¹⁻³
- Histological reduction in pleurodesis score

1 = Lardinois D et al. *Eur.J Cardiothorac.Surg.* 2004;25:865-71.

2 = Ors KS et al. *J.Investig.Med.* 2005;53:267-70.

3 = Teixeira LR et al. *Chest* 2005;128:4041-5.



Drain Size for Pleurodesis

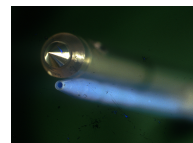


Observational, non-comparative series:

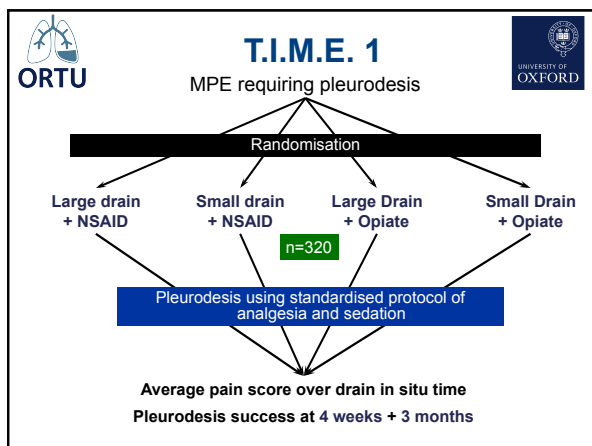
- Small drains effective and comfortable

Direct comparison:

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



Clementsen P et al. *Respir.Med.* 1998;92:593-6.



- ### Assumptions...
1. NSAIDs reduce pleurodesis
 2. Chest tube size makes no difference to pleurodesis
 3. Larger tubes are more painful and associated with more complications

Interventions

Analgesic Regimens:

- NSAID = Ibuprofen 800mg tds
- Opiate = Oramorph 5-10mg qds

Chest drains:

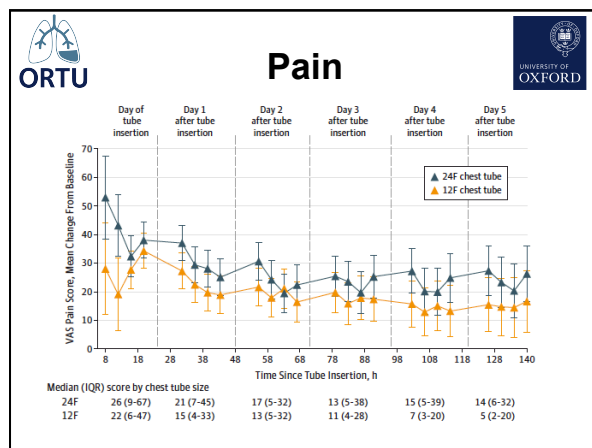
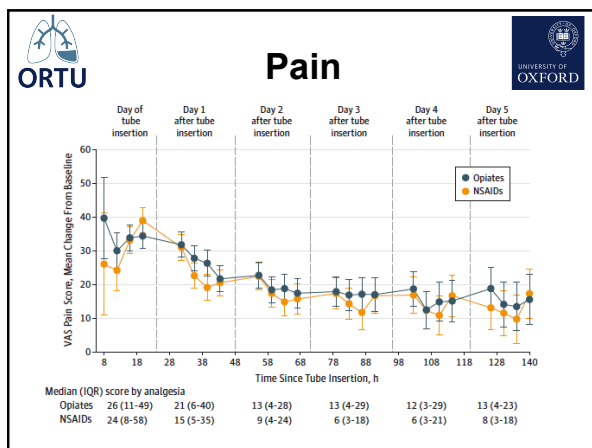
- Large = 24F (blunt dissection)
- Small = 12F (guide-wire)

TIME1 Primary Outcomes

Outcome assessment

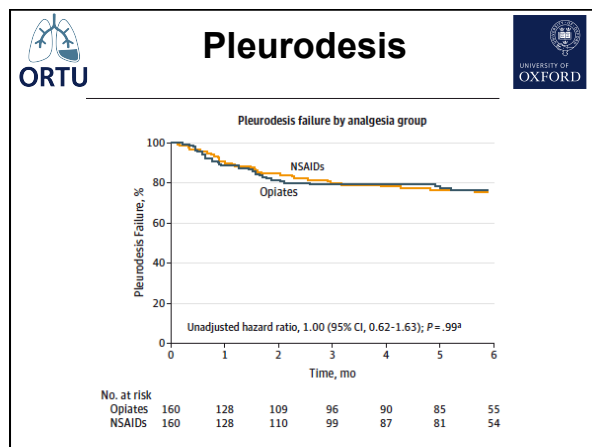
- Pain - superiority
- Pleurodesis – non-inferiority

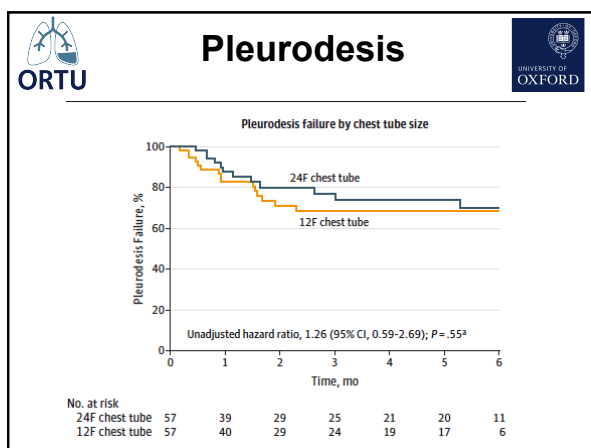
No pain 0mm | 100mm Maximum pain



Primary Outcome - Pain

Treatment group	No. of patients analysed	Outcome	Treatment effect	Confidence Interval (%)	Significance (P value)
Pain while tube in situ to 5 days (superiority)					
		Mean Pain Score, mm (SD)	Difference (mm)		
24F	56	26.8 (16.9)	-6.0	-11.7 to -0.2 (95% CI)	0.04
12F	54	22.0 (16.6)			
Opiate	155	23.8 (15.8)	-1.5	-5.0 to 2.0 (95% CI)	0.40
NSAID	153	22.1 (16.9)			







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

Treatment group	No. of patients analysed	Outcome	Treatment effect	Confidence Interval (%)	Significance (P value)
Pleurodesis Failure at three months (non-inferiority, ITT)					
		No. pleurodesis failures (%)	Difference (%)		
Opiate	150	30 (20)	-3	-12% to ∞** (95% CI)	0.004
NSAID	144	33 (23)			
24F	244	48 (20)	10%	-21% to ∞* (90% CI)	0.24
12F	50	15 (30)			



Adverse Events

Treatment group	No. of patients analysed	Outcome	Treatment effect	95% CI	Significance
Complications on Tube Insertion					
24F (n=56)	56	n (%) 8 (14)	Odds Ratio 1.9	0.7 to 5.1	0.20
12F (n=55)	55	13 (24)			

Adverse Events

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Complications on Tube Insertion					
24F (n=56)	56	n (%) 8 (14)	Odds Ratio 1.9	0.7 to 5.1	0.20
12F (n=55)	55	13 (24)			
Proportion Receiving Talc					
24F (n=56)	56	n (%) 52 (93)	Odds Ratio 3.3	3df, 3.9	0.048
12F (n=55)	55	44 (80)			

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Proportion Receiving Talc					
24F (n=56)	56	n (%) 52 (93)	Odds Ratio 3.3	3df, 3.9	0.048
12F (n=55)	55	44 (80)			
Drain Fall Out Rate					
24F (n=263)	263	n (%) 74 (28)	Odds Ratio 1.9	3df, 4.3	0.038
12F (n=57)	57	24 (42)			

What have we learnt from TIME1?

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

Current optimal pleurodesis?

What is the ADVANTAGE of a smaller drain?

Parameter	Outcome (versus 24F drain)
Pain	Lower (clinically not significant)
Safety	More complications
Inability to give talc	Higher
Fall out rate	Higher

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Pleural Infection



Pleural Infection Outcomes

High morbidity:

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

>20% one year mortality:

- Unchanged over last 20 years
- 7% in MI Baigent *et al* BMJ; 316:1337-43
- 8% in hospitalised pneumonia Neill *et al* Thorax; 51: 1010-16

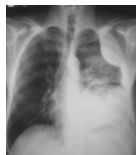


Pleural Infection Rx

1. Accurate diagnosis

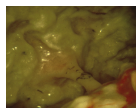
2. Control sepsis:

- Suitable antibiotic therapy



3. Drainage of infected material:

- Intercostal tube drainage
- Intrapleural adjunctive therapies
- Surgery



Assumptions...

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



Microbiology



Fluid microbiological yield is poor:

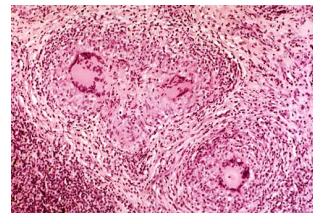
- **40%** microbiologically negative
- Due to:
 - Prior antibiotic use
 - Brisk intrapleural immune reaction



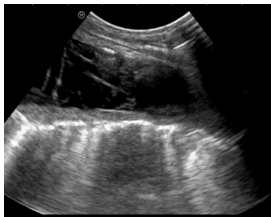
Pleural Infection microbiology



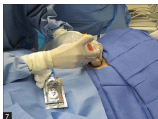
Are we looking in the right place?



AUDIO



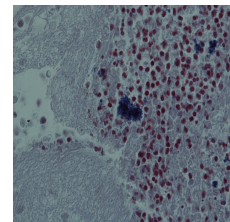
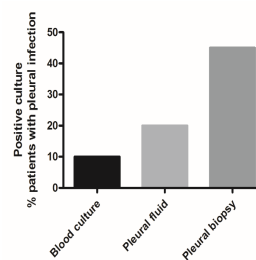
Advanced Ultrasound in Diagnosis of Pleural Infection



Psallidas et al, Chest 2018



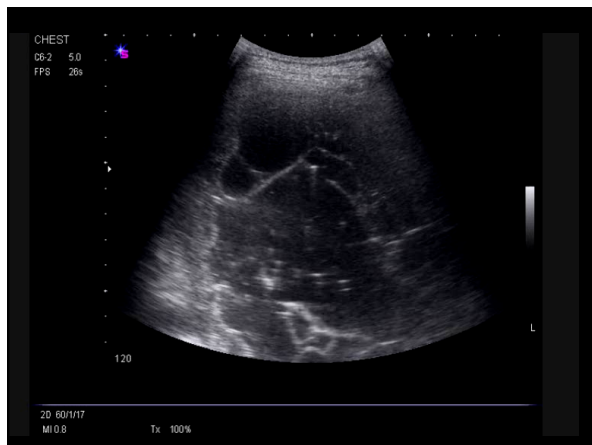
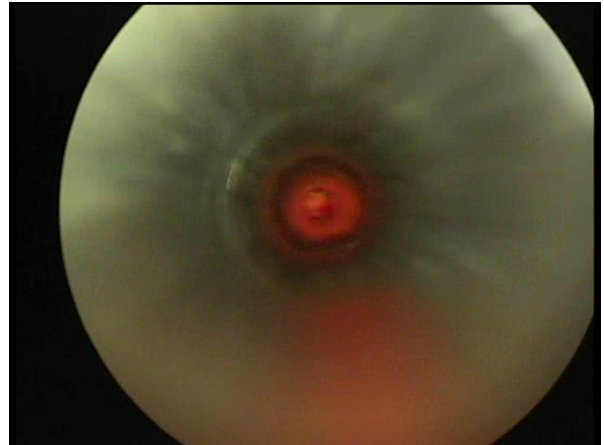
AUDIO

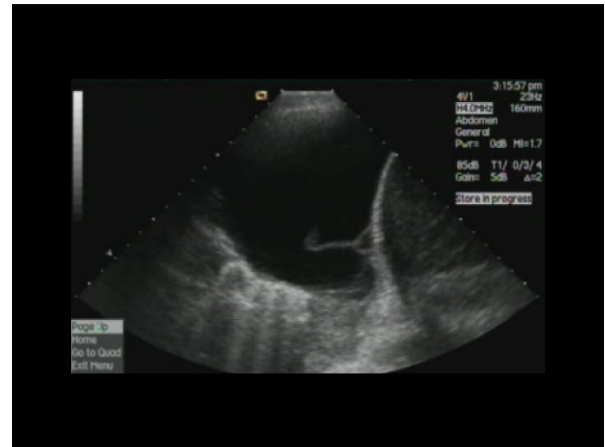
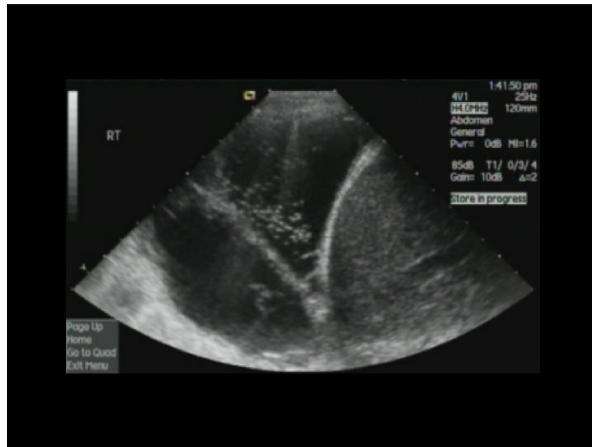



Psallidas et al, Chest 2018



Optimal Drainage








Intrapleural Fibrinolytics

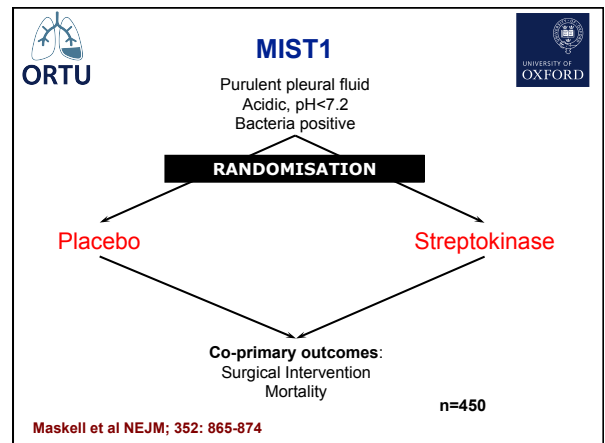
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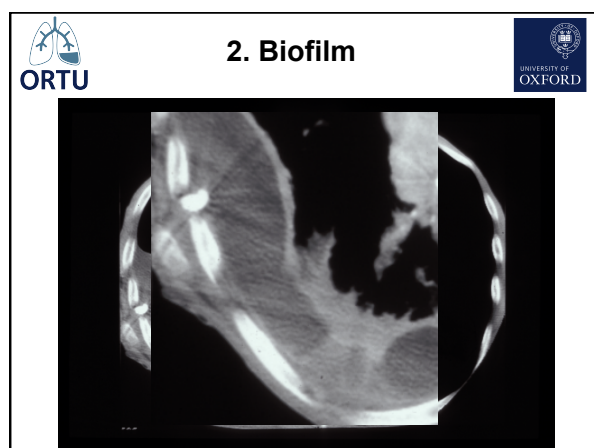
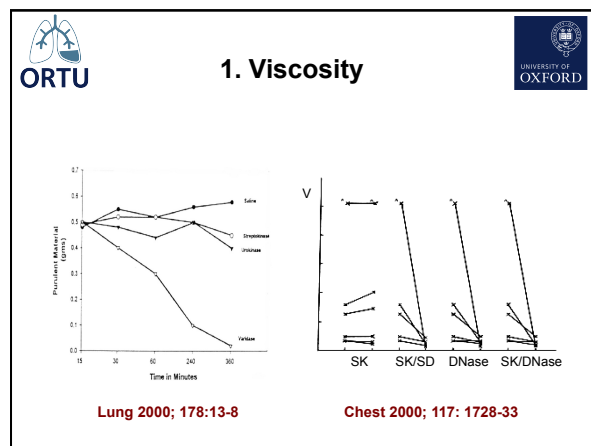
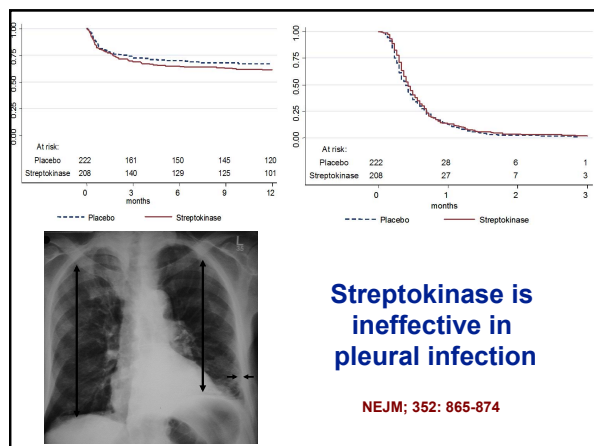


4 small RCTs

- Davies et al 1997
- Bouros et al 1997
- Bouros et al 1999
- Tuncozgun et al 2001

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





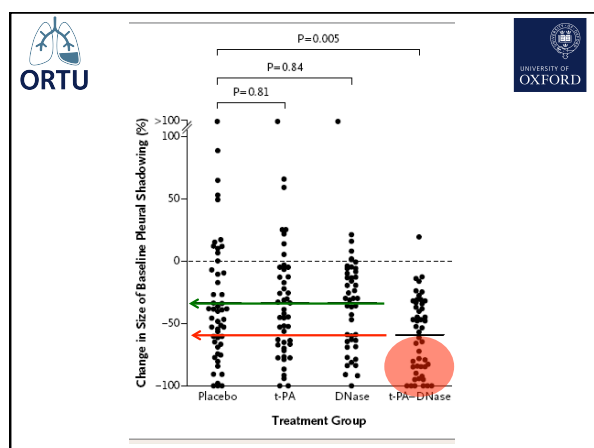
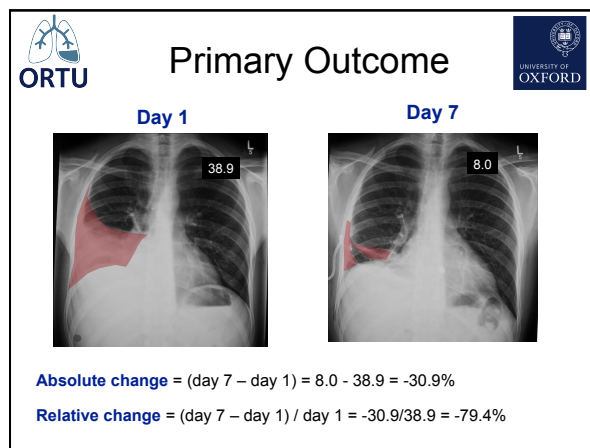
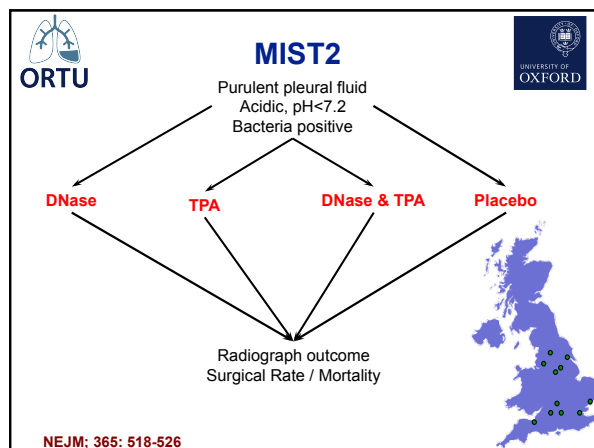
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2. Biofilm

ORIGINAL ARTICLE

Intrapleural Use of Tissue Plasminogen Activator and DNase in Pleural Infection

Najib M. Rahman, D.Phil., Nicholas A. Maskell, D.M., Alex West, M.R.C.P., Richard Teoh, M.R.C.P., Anthony Arnold, M.R.C.P., Carolyn Mackinlay, M.R.C.P., Daniel Peckham, M.D., Chris W.H. Davies, M.D., Nabeel Ali, M.D., William Kinnear, M.D., Andrew Bentley, M.D., Brennan C. Kahan, M.Sc., John M. Wrightson, M.R.C.P., Helen E. Davies, M.R.C.P., Clare E. Hooper, M.R.C.P., Y.C. Gary Lee, Ph.D., Emma L. Hedley, Nicky Crosthwaite, R.G.N., Louise Choo, M.Sc., Emma J. Helm, F.R.C.R., Fergus V. Gleeson, M.D., Andrew J. Nunn, M.Sc., and Robert J.O. Davies, M.D.*



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Primary Result

tPA + Dnase:

- Improves radiographic drainage
- Individual agents do not have any effect

Does this translate to other clinical benefit?



Secondary Outcomes



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

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)	0.37 (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



MIST2



Should tPA + DNase be standard care?

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

Use now?

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



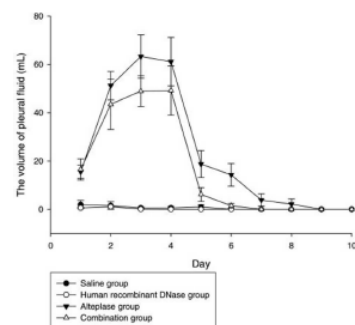
Fibrinolytics alone in Pleural infection



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



Explaining MIST1+2

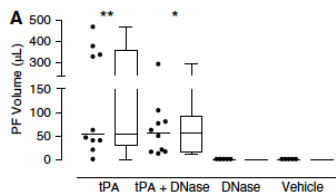


Explaining MIST1+2

ORIGINAL RESEARCH

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

Sally M. Lansley¹, Hui Min Cheah^{1,2}, Julius F. Varano della Vergiliana¹, Aron Chakera^{2,3}, and Y. C. Gary Lee^{1,2,4}



Pleural infection – what have we learnt

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

Surgery is therefore the best treatment?

MIST3

Purulent pleural fluid
Acidic, pH < 7.2
Bacteria positive

RANDOMISATION

Early VATS
25

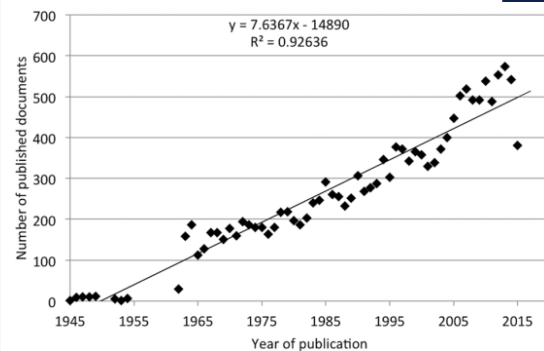
Standard Care
25

DNase & TPA
25

Outcomes:

1. Feasibility of recruitment
2. Acceptance of randomisation
3. Feasibility of data collection

Pleural Trials





Overall Conclusions



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

2536 patients randomised to interventional studies
pleural studies in 7 years



Acknowledgments



INVESTIGATORS

J. Pepperell
T. Saba
A. Tang
N. Ali
A. West
G. Hettiarachchi
D. Mukerjee
J. Samuel
A. Bentley
L. Dowson
J. Miles
F. Ryan
K. Yoneda
M. Al-Aloul
M. Evison
A. Guhan
R. Sathyamurthy

A. Chauhan
A. Leonard
S. Fowler
A. Ionescu
J. Kastelik
H. Davies
A. Stanton
C. Davies
A. Guhan
J. Grayez
R. Harrison
A. Prasad
A. Clive
A. Hart-Thomas
R. Harrison
M. Callister
N. Maskell

ORTU

E. Mishra
J. Wrightson
E. Hedley
N. Crosthwaite
B. McFadyen
M. Laskawiec-Szkonte
R. Shaw
M. Dobson
M. Chapman
J. Quaddy
J. Corcoran
R. Halifax
H. Davies
RJO Davies
I. Psallidas

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J. Pepperell
N.A. Maskell
Y.C.G. Lee
A. West
A.J. Nunn
S. Rehal
E. Hedley
R. Shaw
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