



What have we learnt from recent RCTs in Pleural Disease?

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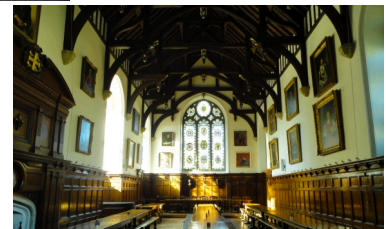
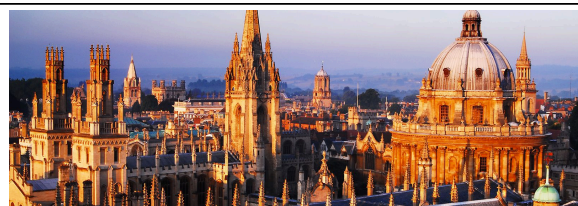
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Financial disclosures

- Drugs and matched placebos for clinical trials:
 - Roche / Genentech / Boehringer / Lunamed / Syner-Med
- Technical equipment for trials:
 - Rocket Medical UK/ GE Medical
- Trials unit funding:
 - Roche / Syner-Med / GSK
- Clinical advice consultancy:
 - Rocket Medical
- IP:
 - Lipoteichoic acid for pleurodesis
- Research funding:
 - NIHR / HTA trials / MRC / UKCRN / CRUK / BLF / UKNRCI / NIHR BRC





Overview



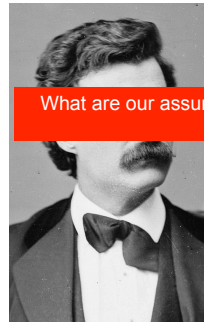
Trials in Malignant Effusion Mx

Trials in Pleural Infection Mx

Outcomes and assumptions



What have we learnt?



“What gets us in to trouble is not what we don’t know, but what we think we know.”
What are our assumptions in the treatment of MPE?

“It’s what we know for sure that just ain’t so”

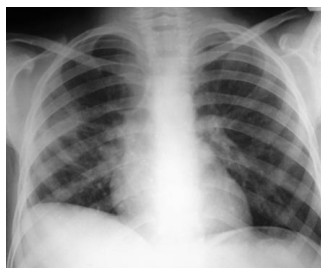


Assumptions



1. CXR is the best outcome in MPE

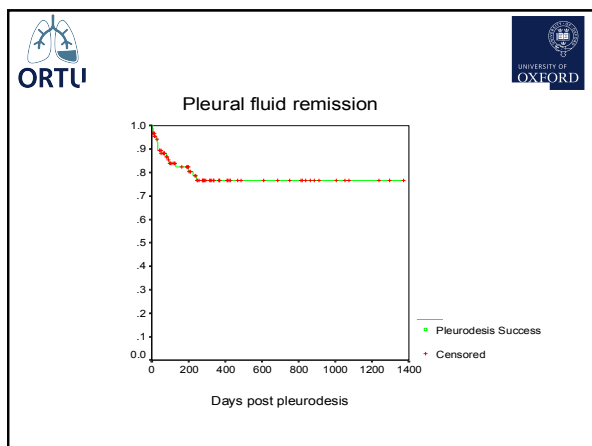
2. Pleurodesis success rate is ~90%



ies, such as trastuzumab.¹³ Overall, in 18 of 71 (26%) patients we obtained an alteration of therapy by using systematically intraoperative pleural biopsies.

One month after surgery, 71 (100%) patients showed an effective pleurodesis with a total or subtotal disappearance of the pleural effusion. Eight (11%) patients had a recurrence 6 months after surgery; of these, one patient relapsed at 1 year. After a mean follow-up of 22 months (range, 2–81 mos), the overall success rate was 89% (Fig. 3). The overall survival time was 17 months (range, 2–80 mos) (Fig. 1).

Of all prognostic factors evaluated, the only factor which negatively affected survival was the number of



The TIME trials

Therapeutic Interventions in Malignant Pleural Effusion

Purpose

- Answer clinically meaningful question in MPE management
- Randomised controlled trials with real life comparators

The TIME2 randomised controlled trial

ORIGINAL CONTRIBUTION

ONLINE FIRST

Effect of an Indwelling Pleural Catheter vs Chest Tube and Talc Pleurodesis for Relieving Dyspnea in Patients With Malignant Pleural Effusion

The TIME2 Randomized Controlled Trial

Davies et al, JAMA 2012 Jun 13;307(22):2383-9

TIME2 - rationale

What's wrong with talc?

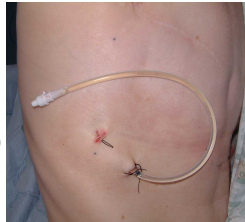
- 30-40% failure rate
- Median hospital stay 5 days
- 15% with trapped lung
- Side effects – systemic and local

IPCs in MPE treatment

Advantages:

- Day case insertion
- Domiciliary drainage
- “Single” procedure
- Patient in control
- Spontaneous pleurodesis (46%)
- No “failure rate”

Disadvantages....

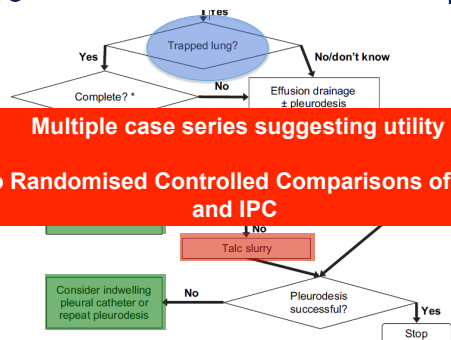


IPC complications

Complication	Frequency
Failed/displaced insertion	4.0%
Symptomatic loculation	8.4%
Asymptomatic loculation	4.0%
Empyema	3.2%
Air in pleural space	2.4%
Infection	1.6%
Dislodged	1.2%
Bleeding	0.8%
Tumour seeding	0.4%
Pain requiring removal	0.4%

Tremblay and Michaud *et al.* Chest 2006; 129: 362-8

BTS Guidelines 2010



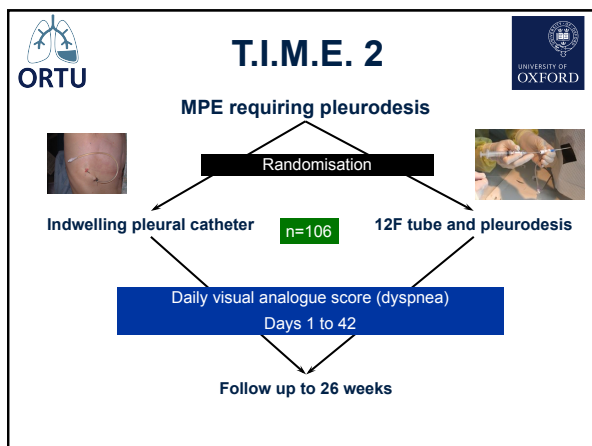
Multiple case series suggesting utility

No Randomised Controlled Comparisons of talc and IPC

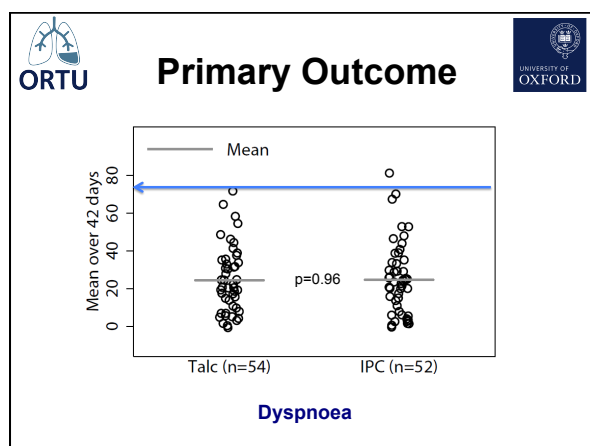
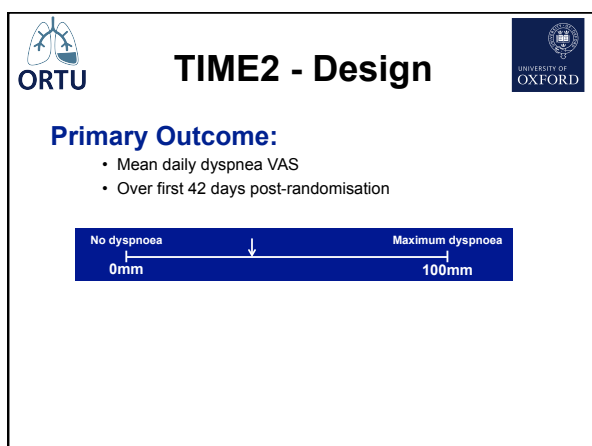
What outcomes?

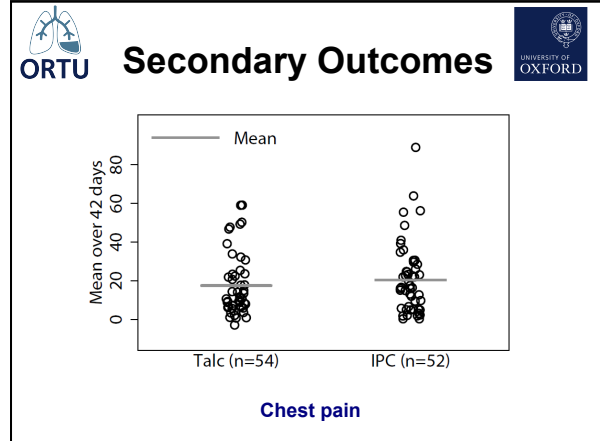
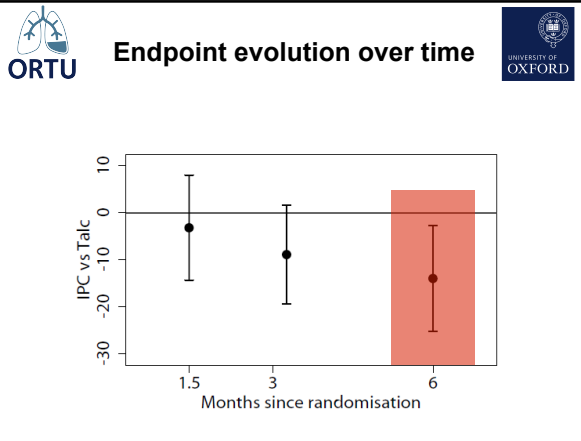
What is the purpose of Rx?


- CXR improvement?
- “Failed pleurodesis”?
- Survival?
- **Improve quality of life:**
 - Breathlessness
 - Time in Hospital
 - Need for further invasive procedures



- Assumptions...**
1. IPCs are “better”
 2. Talc is much more painful than an IPC
 3. IPCs will get patients out of hospital earlier and improve quality of life






ORTU **Secondary Outcomes** 

Comparison (IPC versus Talc)	Comparator	Statistical Significance
Hospital stay (days)	-3.5 days	p<0.001 95% CI -4.8 to -1.5
Days in hospital over 12 months	-3.5 days	p<0.001
Requirement for further pleural procedures	OR 0.21	p=0.03 95% CI 0.04 to 0.86
Adverse Events	OR 4.70	p=0.002 95% CI 1.75 to 12.60

No significant difference in quality of life

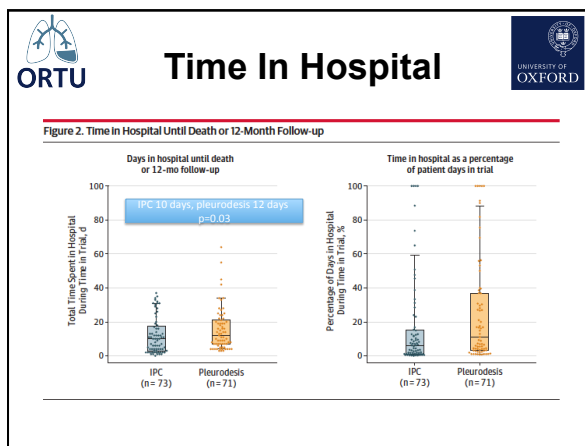
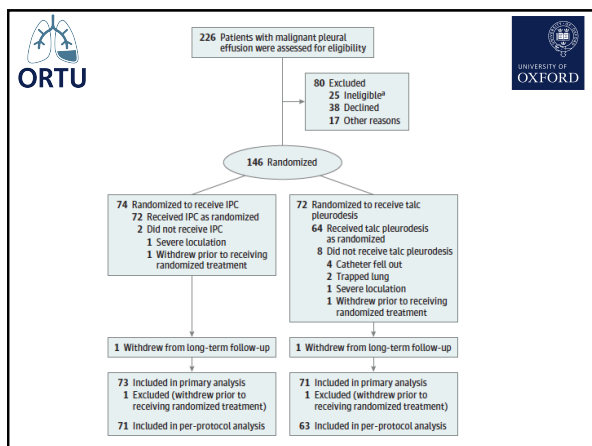
ORTU **AMPLE1** 


Research

JAMA | Original Investigation

Effect of an Indwelling Pleural Catheter vs Talc Pleurodesis on Hospitalization Days in Patients With Malignant Pleural Effusion: The AMPLE Randomized Clinical Trial


Rajesh Thomas, MBBS, PhD, FRACP; Edward T. H. Fyfe, MBBS, PhD, FRACP; Nicola A. Smith, MBChB, FRACP; Pyng Lee, MBBS, PhD, FRCP; Benjamin C. H. Kwan, MBBS, FRACP; Elaine Yap, MBChB, FRACP; Fiona C. Horwood, MBChB, FRACP; Francesco Piccolo, MBBS, BMedSci, FRACP; David C. L. Lam, MBBS, MRCP, FHKCP, FHKAM, PhD, FRCP; Luke A. Garske, MBBS, FRACP; Ranjan Shrestha, MBBS, FRACP; Christopher Kosky, MBBS, FRCP, FRACP; Catherine A. Read, RGN, BSc; Kevin Murray, PhD; Y. C. Gary Lee, MBChB, PhD, FRCP, FRACP



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What have we learnt?

1. IPCs are **not superior** to talc pleurodesis in relieving breathlessness
2. **Both IPCs and talc:**
 - Improve breathlessness
 - Improve quality of life
 - Reduce chest pain
3. **IPCs associated with:**
 - Reduced hospital stay (2 days)
 - Reduced further pleural procedures
 - Increased adverse events

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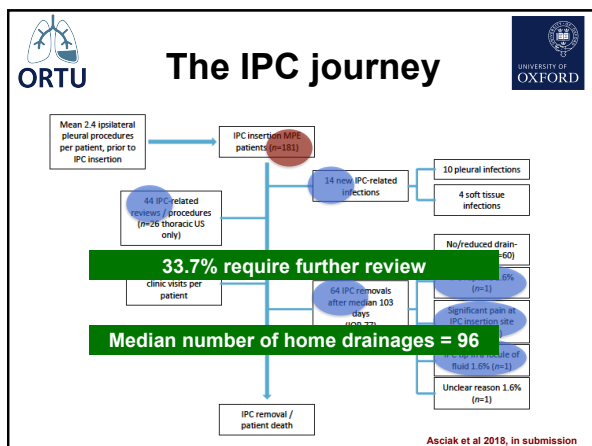
Do IPCs truly “reduce pleural procedures”?

“Number of further procedures required”

- TIME2 OR=0.21, $p=0.03$
- AMPLE1 OR=0.18, $p=0.009$

IPCs are therefore clearly better...

- Is this the correct outcome?



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Where next for IPC vs Talc?

Studies to address

- Patient priorities
- Disease specific quality of life

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The TIME1 randomised controlled trial

Research

Original Investigation

Effect of Opioids vs NSAIDs and Larger vs Smaller Chest Tube Size on Pain Control and Pleurodesis Efficacy Among Patients With Malignant Pleural Effusion

The TIME1 Randomized Clinical Trial

Najib M. Rahman, PhD, Alex West, MRCP, Jonathan Miles, MD, John M. Wrightson, MD, Douglas Seaton, MD, Nick A. Maskell, DM, Andrew J. Nunn, MSc, Robert F. Miller, FRCP

What constitutes optimal (best outcome, least pain) pleurodesis in MPE?