JOURNAL CLUB

Presented by : Sqn Ldr Pillai Jayakrishnan S, Resident Medicine

Moderated by: Lt Col S K Singh, Prof (Medicine)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Intrapleural Use of Tissue Plasminogen Activator and DNase in Pleural Infection

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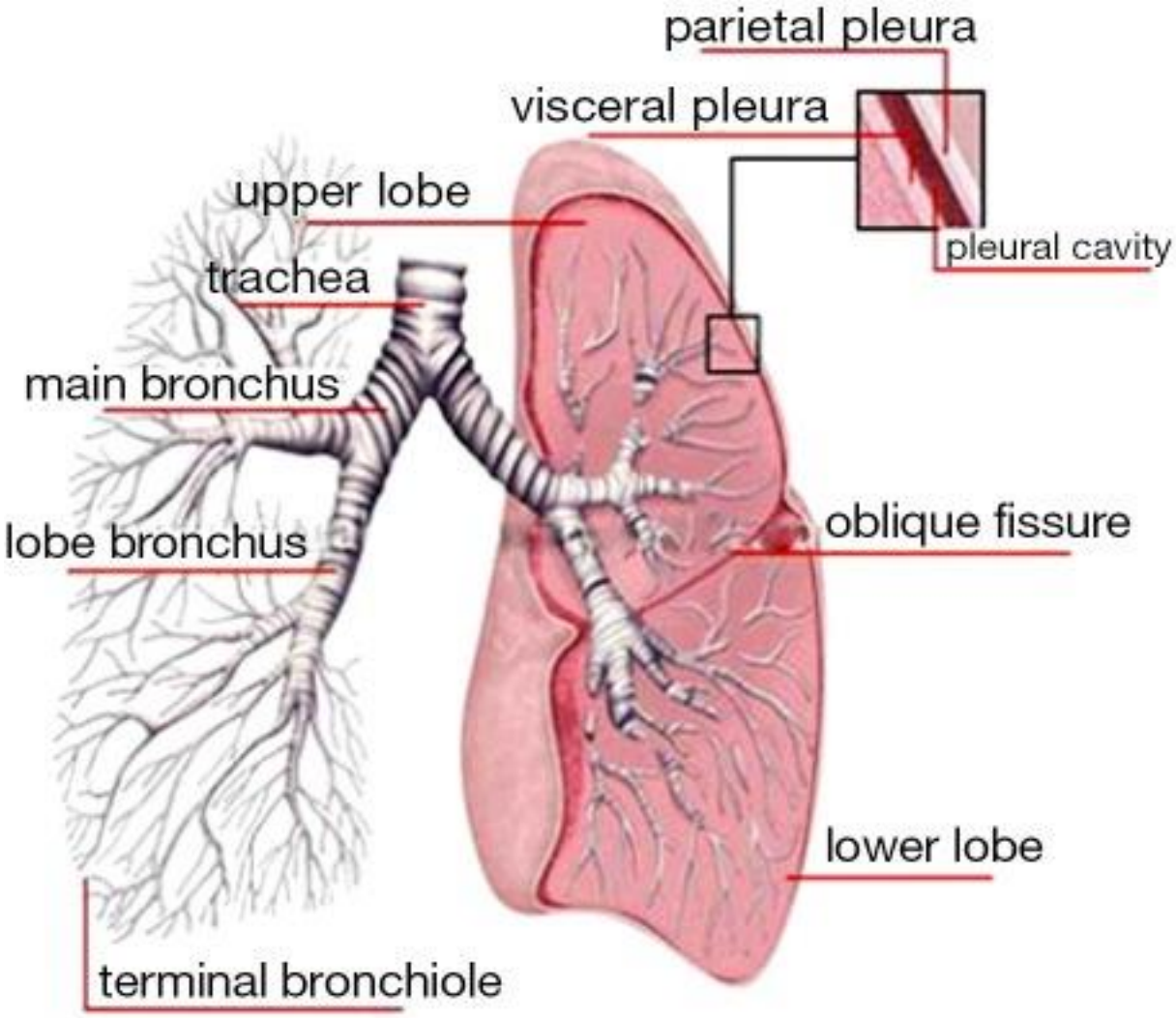
The pleural cavity



Pleural Infection

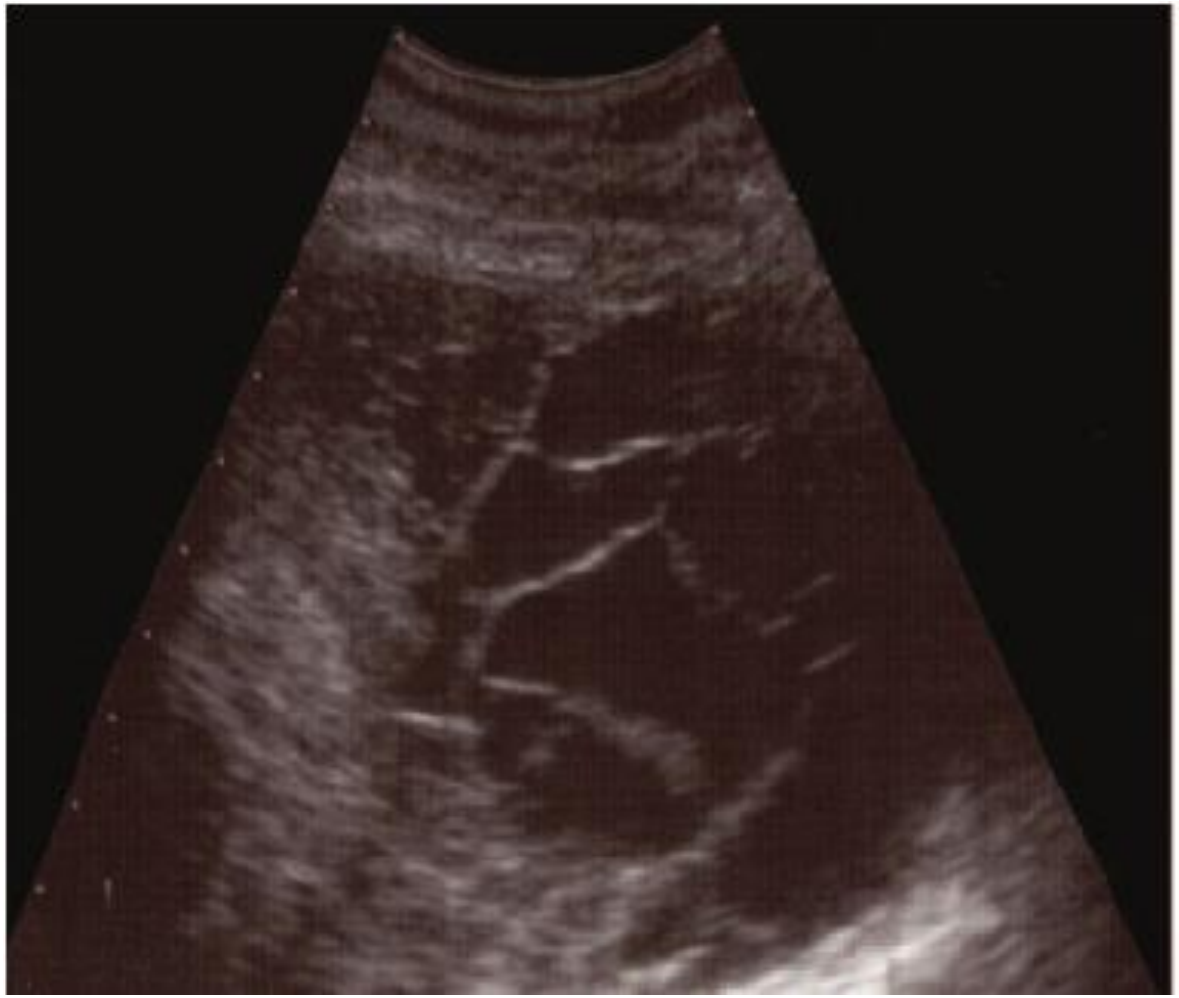
- Pleural Infection is a major complication of pneumonia where infected fluid collects around the lung
- 30% of patients with this problem either die or require major surgery for recovery
- Aim of treatment: Drain the infected fluid from the chest via a tube
- Challenge: Thick fluid and divided into pockets

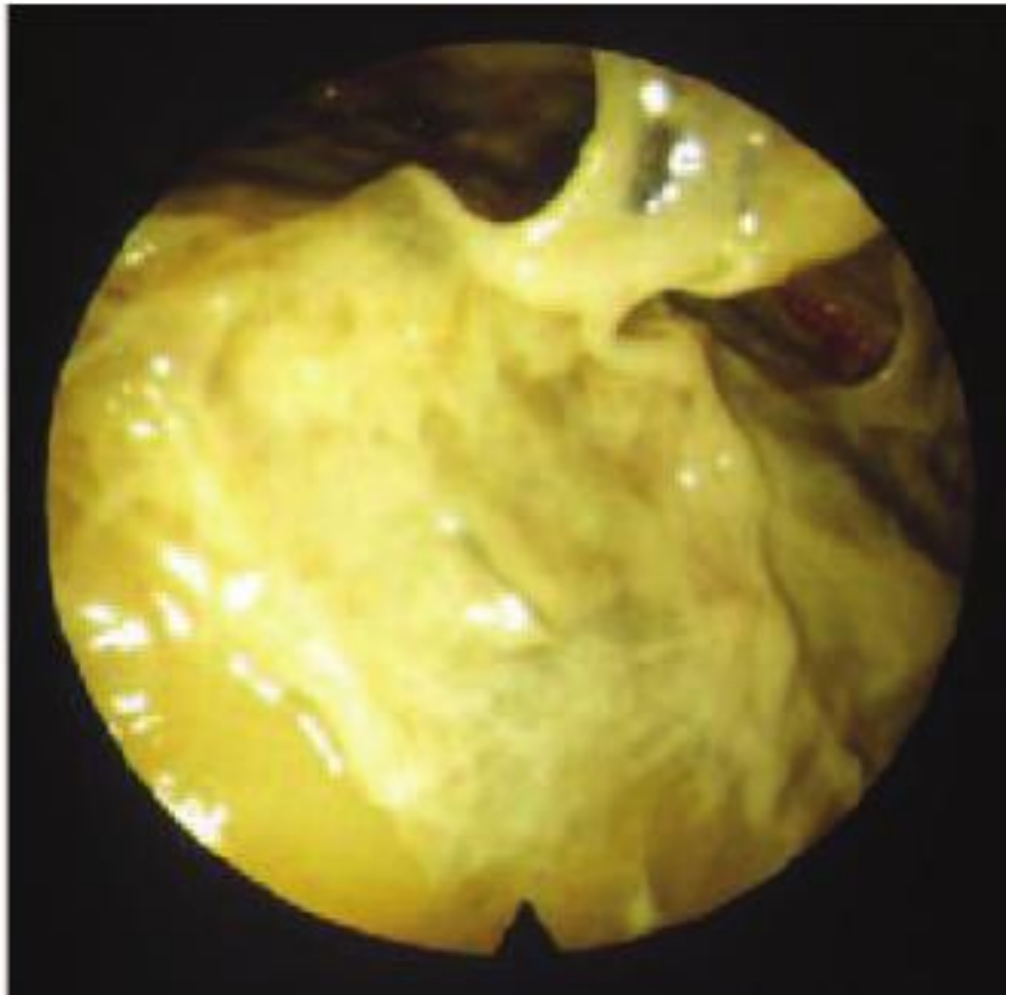
Parapneumonic effusion & Empyema

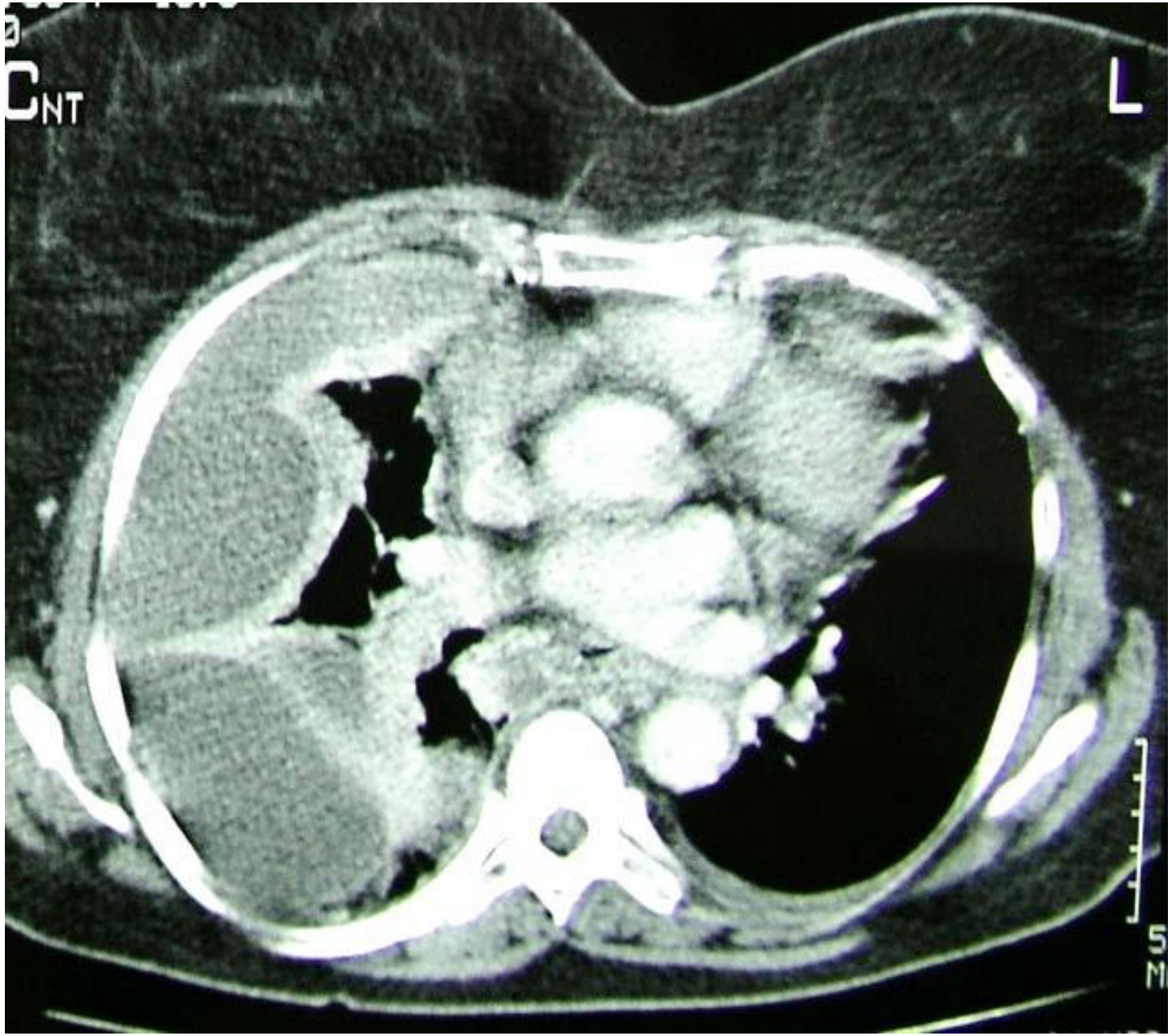
Terminology	Definition
Parapneumonic effusion	Fluid in the pleural space in the setting of an adjacent pneumonia
Simple parapneumonic effusion	Free flowing effusion that is sterile
Complicated parapneumonic effusion	Effusion infected with bacteria or other micro organisms or having biochemical properties of recent infection
Empyema	Pus in the pleural space (from pneumonia or other source)
Complex effusion	Effusion with internal loculations (septae)
Uniloculated effusion	Effusion that is without internal septae (free flowing or fixed)

Ref: UpToDate

Loculated empyema



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What's in the Trial?

- Trial assesses whether 2 drugs assist fluid drainage

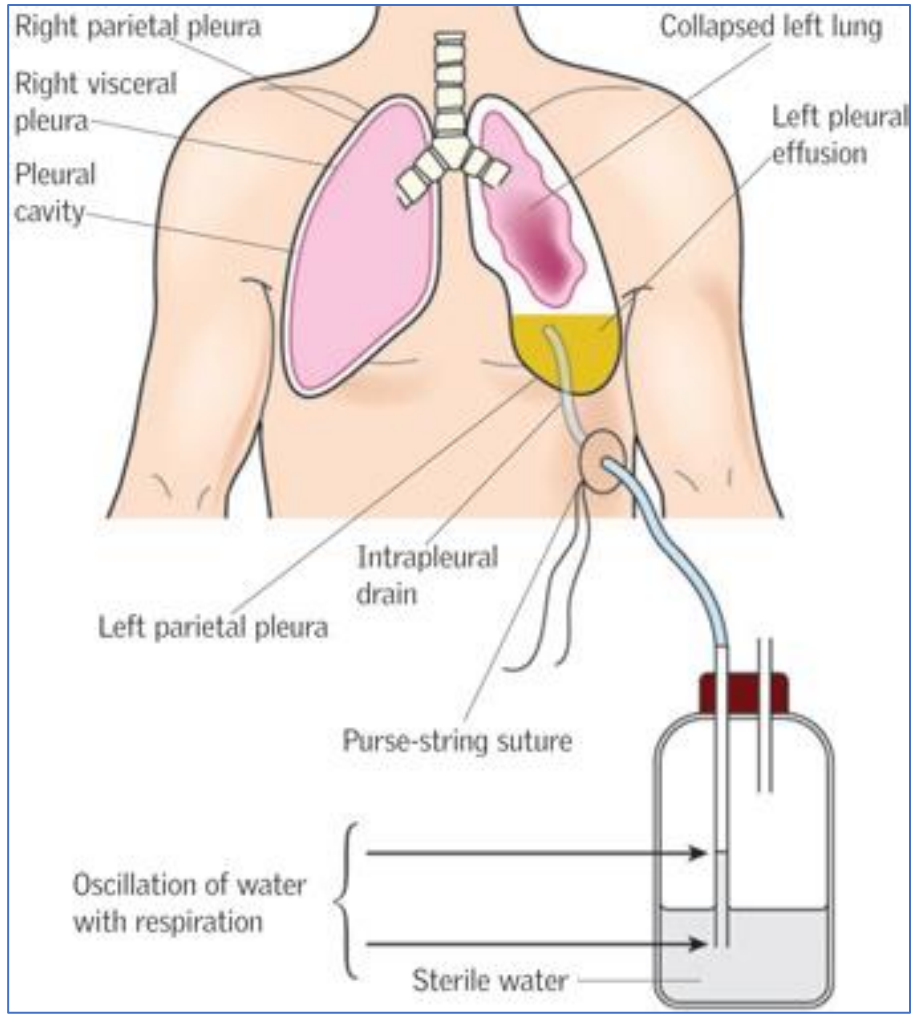
    1. DNase - known to thin infected fluids

    2. Alteplase – capable of uniting separate pockets of infected fluid

- Assess effectiveness?

    - Serial Chest X rays

Non trial treatment



- All patients should receive chest tube drainage of infected pleural fluid. (minimum bore 12 Fr)
- All patients to receive antibiotics at least 3 weeks based on blood and pleural fluid culture and analysis (if any) else as below
- CA - empyema: Cefuroxime and Metronidazole parenterally followed by co-amoxiclav orally
- HA - Empyema: Vancomycin and Meropenem

Tissue Plasminogen Activator

Streptokinase in MIST 1 v/s Alteplase in MIST 2, Why?

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U.K. Controlled Trial of Intrapleural Streptokinase for Pleural Infection

Nicholas A. Maskell, M.R.C.P., Christopher W.H. Davies, M.D., Andrew J. Nunn, M.Sc., Emma L. Hedley, Fergus V. Gleeson, F.R.C.P., Robert Miller, F.R.C.P., Rhian Gabe, M.Phil., Glyn L. Rees, Timothy E.A. Peto, F.R.C.P., Mark A. Woodhead, F.R.C.P., Donald J. Lane, F.R.C.P., Janet H. Darbyshire, M.B., Ch.B., and Robert J.O. Davies, D.M., for the First Multicenter Intrapleural Sepsis Trial (MIST1) Group*

MIST 1 Trial

- First Multicentre Intrapleural Sepsis Trial (MIST 1) showed no benefit of intrapleural streptokinase

- What we learnt?
  - Safety of intrapleural use of fibrinolytics
  - Mono agent fibrinolytic (Streptokinase) alone is not sufficient
  - Formed basis for calculation of sample size in MIST2

DNase

- Deoxyribonuclease is a good candidate for pus thinning agent to act synergistically with a fibrinolytic

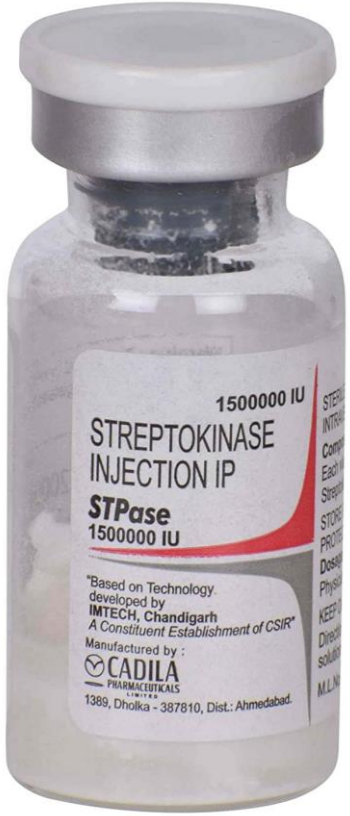
- Evidence: 2 studies describe in vitro effect of DNase on viscosity of the pus, so pharmacological action – evident.
  1. Light *et al*: Urokinase/ Streptokinase/ Varidase (DNase +) on pus from empyema
  2. Simpson *et al*: DNase liquefies pus from human empyema and extra-thoracic abscesses and that saline and fibrinolytic agents alone have no effect

- In-vivo?
  - MIST2

t-PA + DNase

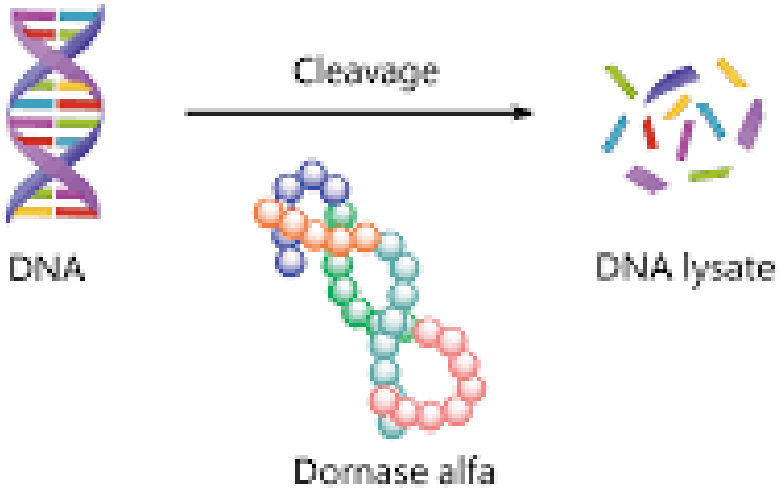
- Pus thinning + Fibrinolysis
- DNase cause pus thinning and t-PA cause fibrinolysis
- Synergism?
- Fibrinolytic disrupt the fibrinous septations dividing the infected collection, allowing DNase access to the thick pus
- DNase may allow the fibrinolytic effective access to the septations by thinning the fluid allowing effective drainage and better distribution of both agents

Can you combine the two ?

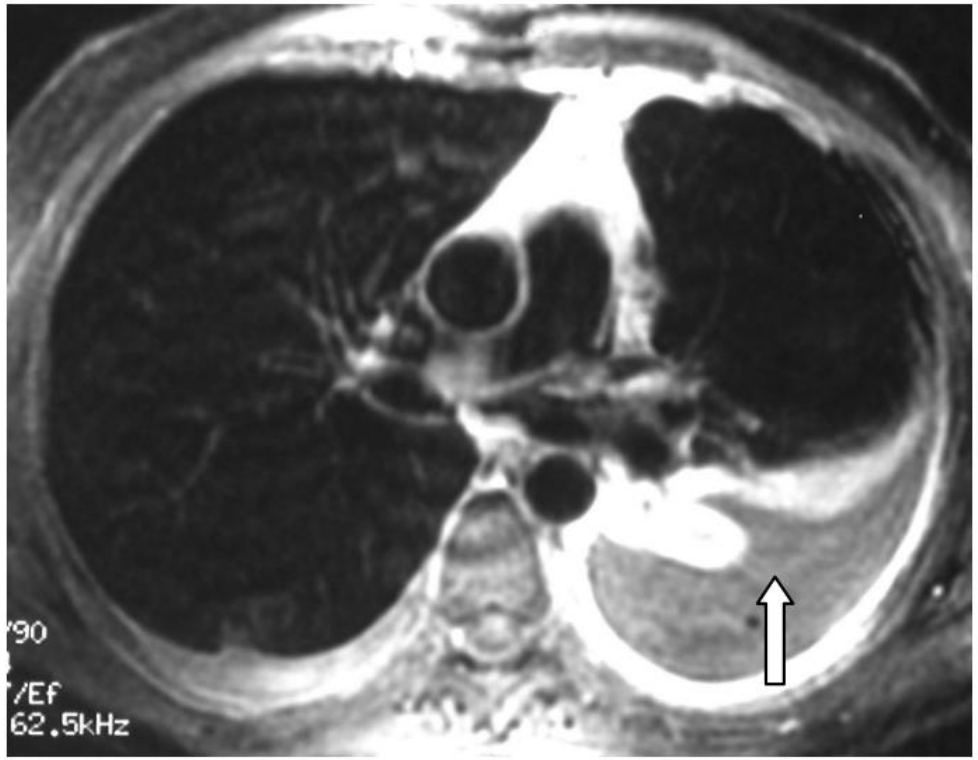


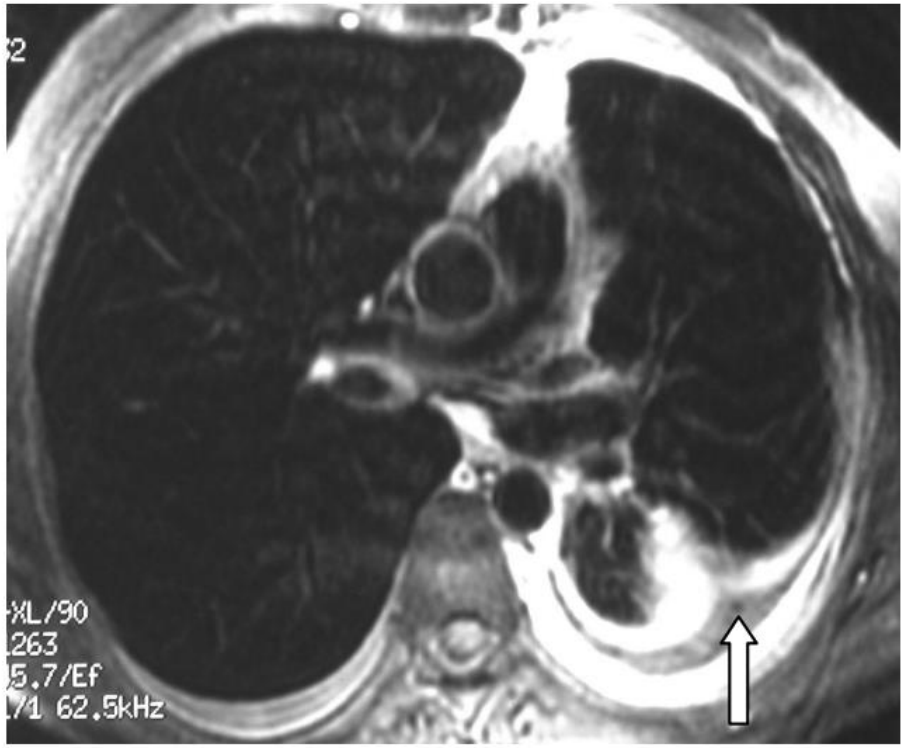
DNase in vivo

- One case report Intrapleural DNase – rescue therapy in pleural infection unresponsive to standard therapy
- Oxford 4 documented cases, of which 3 showed clear clinical and radiological improvement, no need for surgery and no adverse events
- MIST 2 Trial



Is it possible?





Residual empyema collection after Streptokinase

Resolution of the collection after 3 days DNase

Figure showing the effective drainage of a thoracic empyema with DNase following failed drainage with prior Streptokinase.

MIST 2 Trial

- Second Multicentre Intrapleural Sepsis Trial (MIST2)
- Why Alteplase?

Why was Alteplase chosen?

STREPTOKINASE	ALTEPLASE
Mechanism involves generation of plasminogen streptokinase activator complex which causes low residual plasminogen in empyema to convert to active fibrinolytic	Mechanism is direct and doesn't involve generation of an activator complex
Indirect Plasminogen Activator	Direct Plasminogen Activator
Safe in Intrapleural use (MIST1)	MIST1 safety success encouraged its use in MIST2
6.8% serious adverse events Immunological side effects	2.7% serious adverse side effects Lower tendency to produce immunological reactions
Bacterial origin	Recombinant human proteins

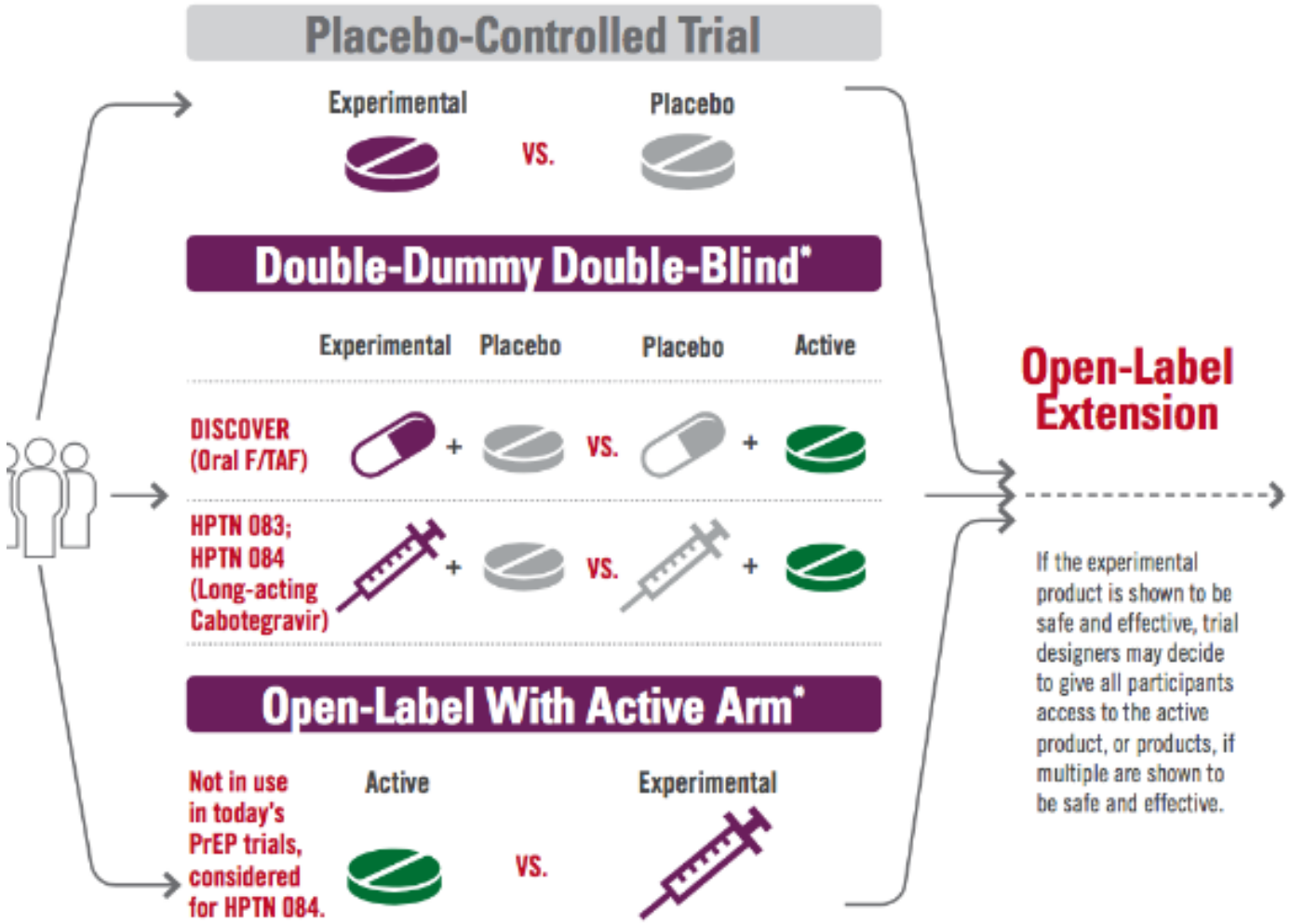
Aim and Objective

- To assess whether intrapleural DNase and Alteplase are safe and improve pleural drainage quantified from chest radiograph in patients with pleural infection

Study Design

- Randomisation (Trial Entry)
- Double blinded, double dummy
- Placebo controlled
- Factorial trial
- Multicentre (11 centers in UK)

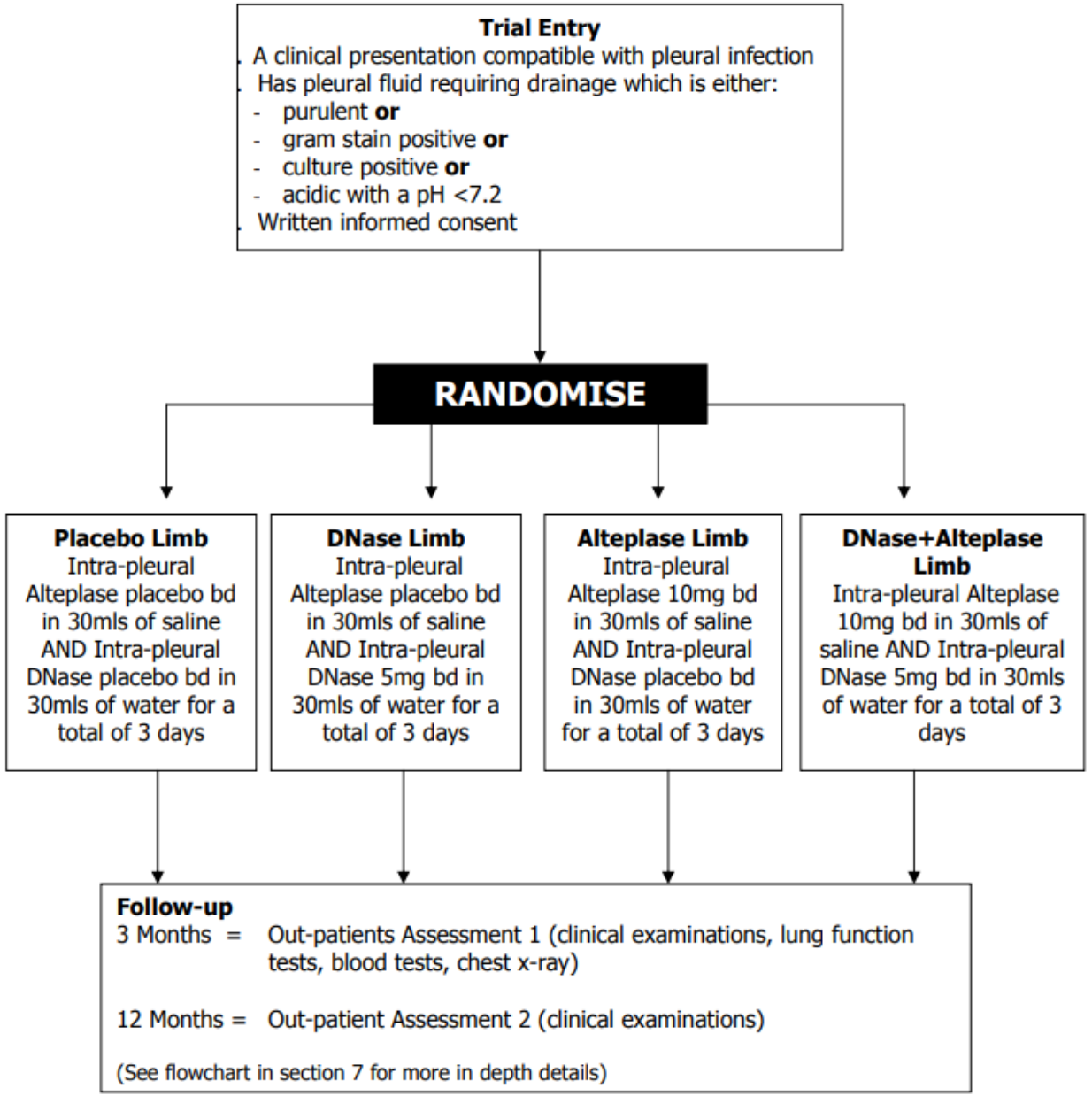
Double dummy, double blinded trial



Detail about the study

Parameter	Answer
Duration of study	December 2005 to November 2008
Sponsor	University of Oxford
Grant	Unrestricted from Roche UK
Source of drugs	Roche UK and Boehringer Ingelheim UK
Dose of Dnase	Pulmozyme, Roche 5 mg BD X 3 days
Dose of TPA	Actilyse, Boehringer Ingelheim 10 mg BD X 3 days
Adminstration of drug	Intrapleural
Duration of clamp	1 hour after each administration

Methodology



Sample size calculation

- Results of MIST1 trial
- Power: 80%
- α: 0.05
- Loss of follow up: 5%
- Sample size 210

Inclusion Criteria

- Clinical presentation compatible with pleural infection
- Has pleural fluid requiring drainage which is either:
  - Purulent or
  - Gram Stain positive or
  - Culture positive or
  - Acidic with a pH <7.2
- Written informed consent

Exclusion Criteria

- Age < 18 years
- Has previously received intra-pleural fibrinolytics and/ or DNase for this empyema
- Has a known sensitivity to DNase or Tissue Plasminogen Activator
- Has had a coincidental stroke, major haemorrhage or major trauma
- Major surgery in the past 5 days
- Has had a previous pneumonectomy on the side of the infection

Exclusion criteria

- Patients who are pregnant or lactating
- Expected survival less than three months from a different pathology to this empyema (e.g; metastatic lung carcinoma)
- Inability to give informed consent

Primary Outcome

- Radiographic improvement in the area of pleural collection (between the area of the pleural collection on the CXR at randomisation and the chest radiograph taken on day 6/ 7)

- In higher centres CT or MRI can be performed at baseline and Day 6/7 to validate the CXR endpoint

- X rays were stored and scored centrally by digitising the area of the pleural opacity on the PA chest radiograph

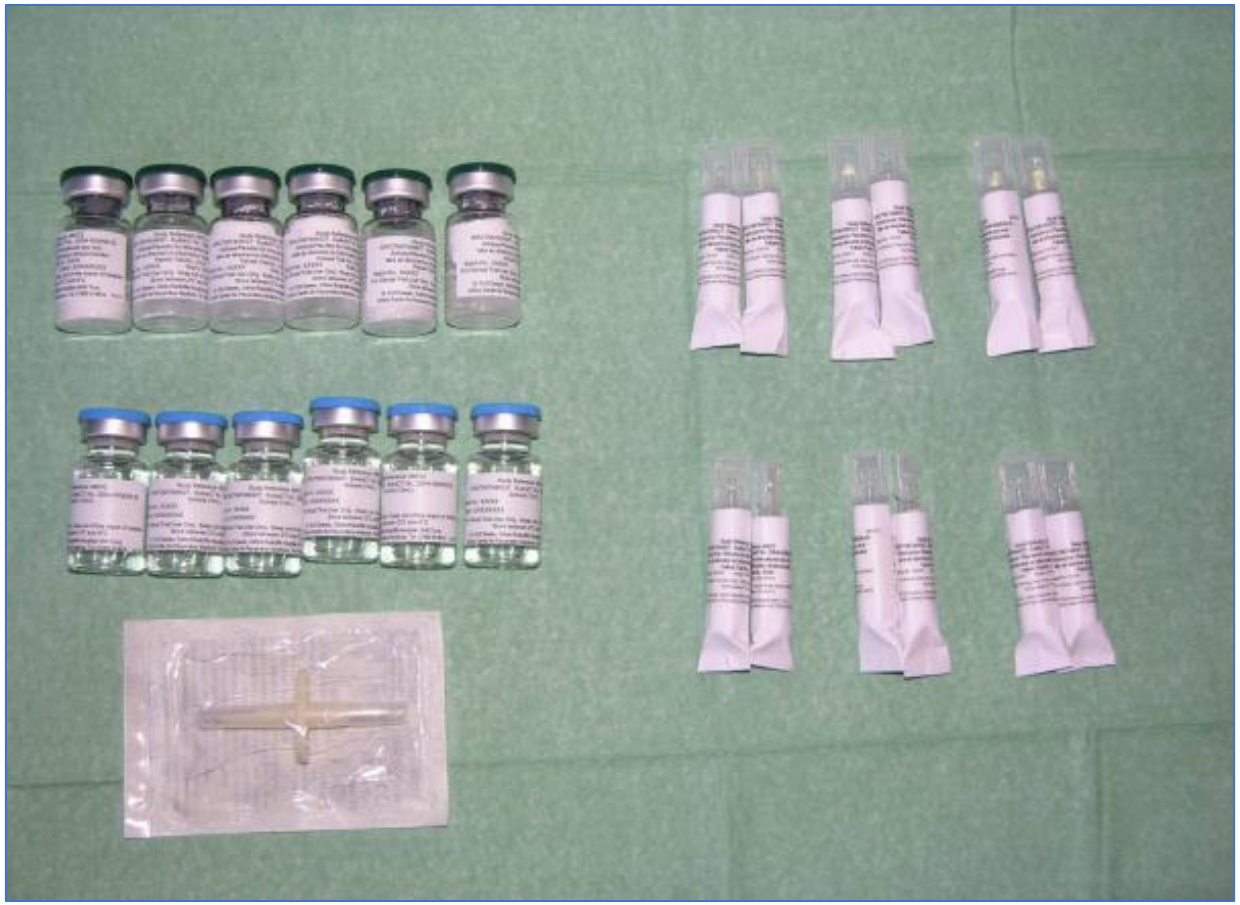
Secondary Outcome

- The fall in the blood C reactive protein level from randomisation to the Day 6/7
- Time from randomisation to remain apyrexal for 36 hours
- Total volume of the pleural fluid drainage
- Blood DNase levels during the intra-pleural Dnase administration and anti DNase Ab at baseline and 14 days post randomisation (or at hospital discharge)

Secondary Outcome

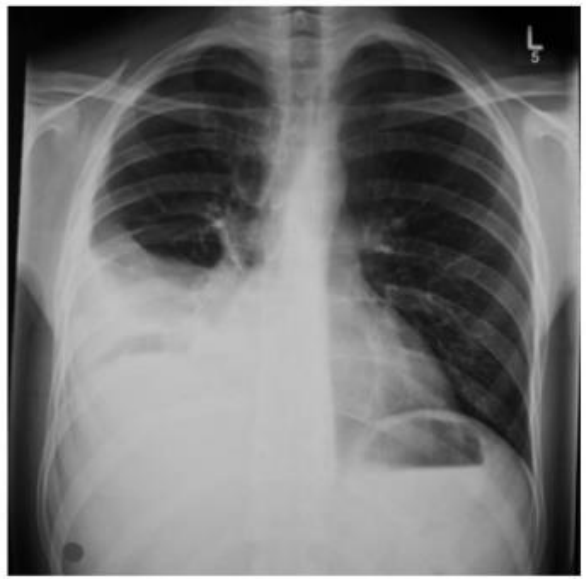
- The duration of hospital stay
- Rate of thoracic surgery and mortality at 3 months post randomisation
- Rate of thoracic surgery and mortality at 12 months post randomisation

Trial medications

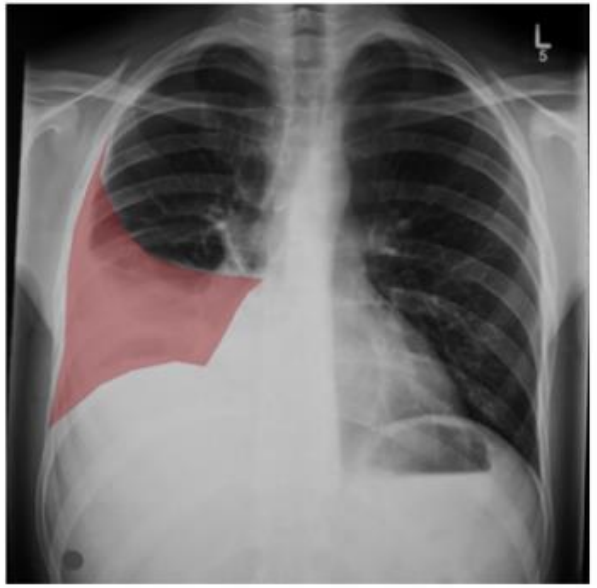


Trial medication showing a mixture of active and placebo trial drug vials to demonstrate that there was no difference in the physical appearance between active and placebo trial drugs.
Trial specific labels are also shown. Green topped vials contain tPA/ placebo (powder 10 mg per vial), blue top vial contains diluent with standard supply connector below and plastic vials on the right contains DNAse/ placebo 2.5 mg/vial

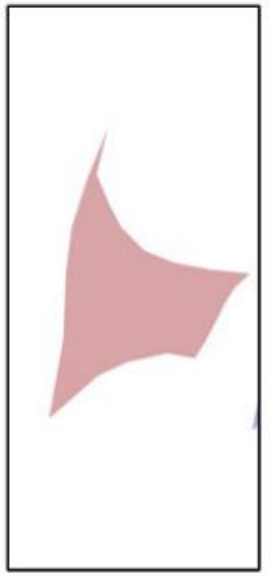
How was the effusion measured?



Original chest radiograph



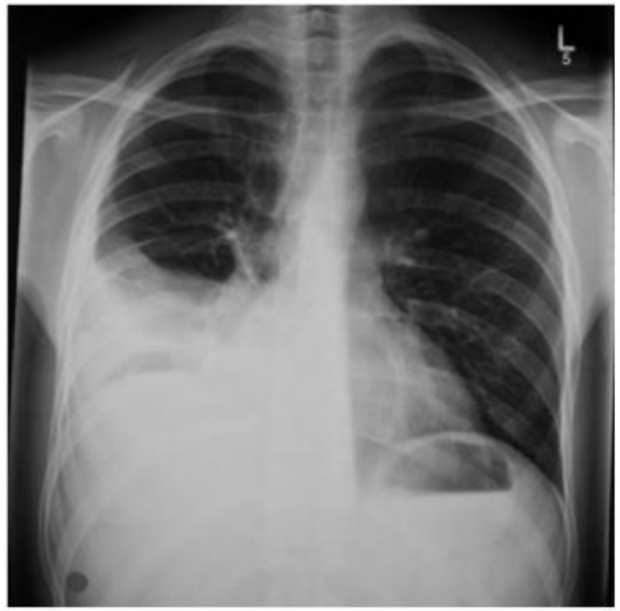
Effusion area measured



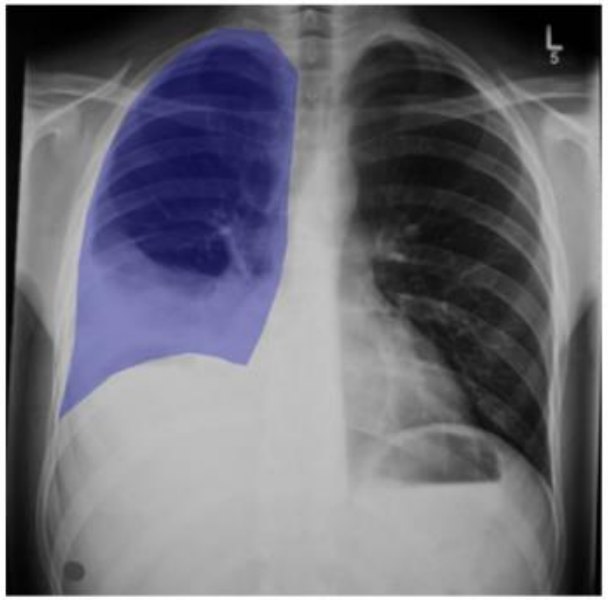
Area of effusion alone preserved for analysis

Digital Measurement strategy of effusion area

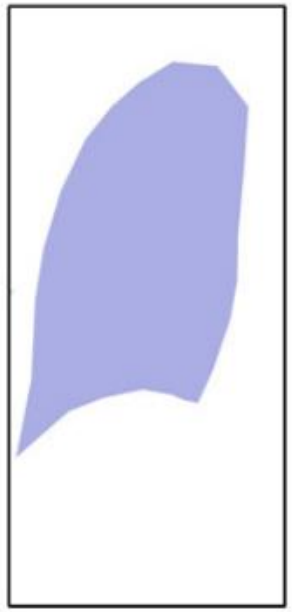
Measure hemithorax area



Original chest radiograph



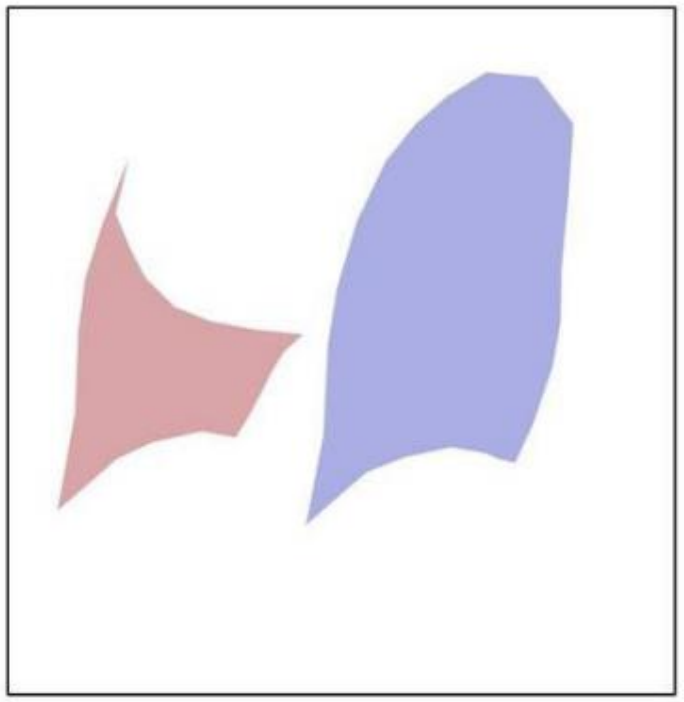
Hemithorax area measured



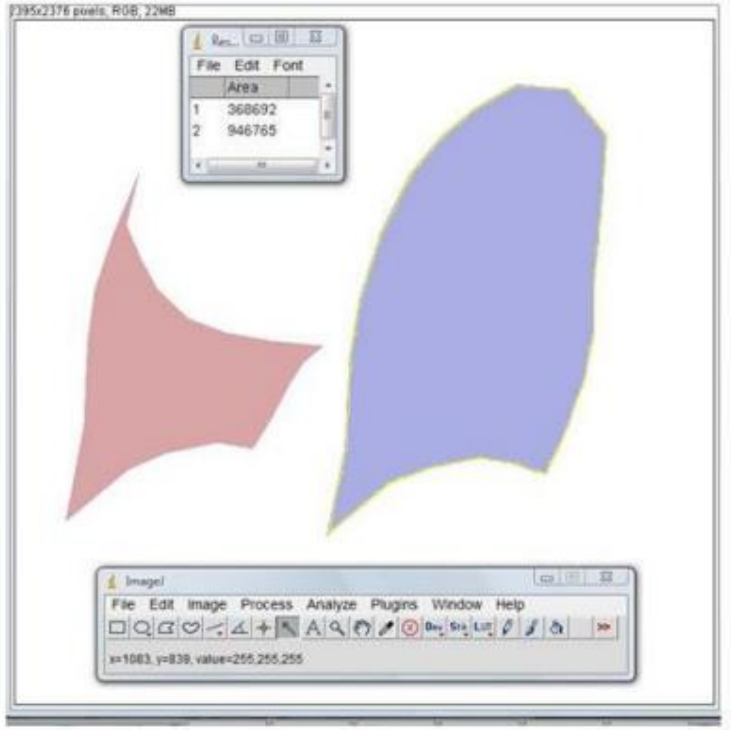
Area of hemithorax alone preserved for analysis

Digital measurement strategy of the hemithorax area

Using the Image J software



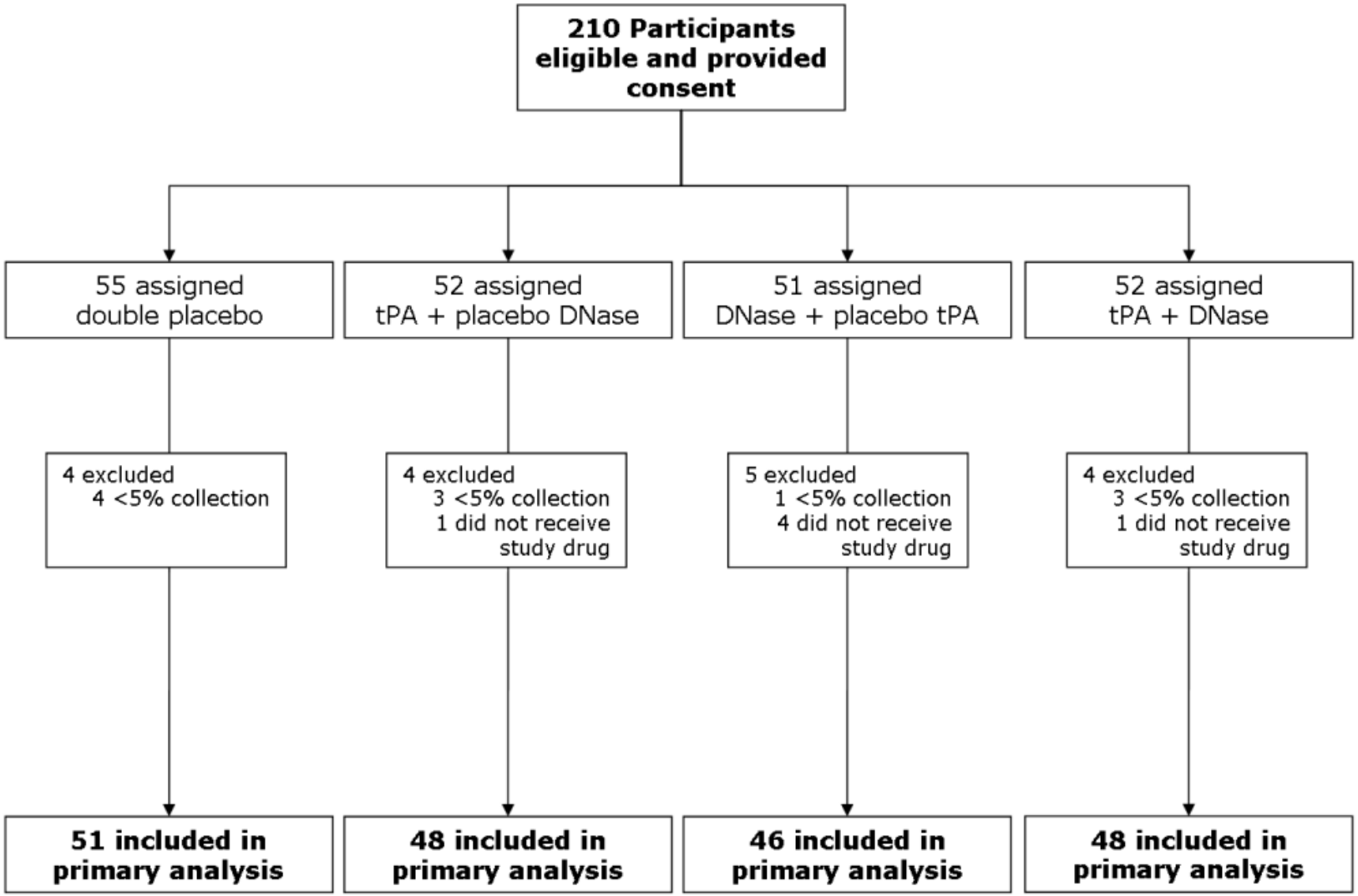
Polyhedron areas separated from chest radiograph



Areas measured using ImageJ software

Area measurement using the Image J software

Assignment to intervention



Baseline characteristics of patients

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

Primary and Secondary Outcomes

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

Statistical analysis

Critical appraisal

Title and Abstract

Title	
Is it interesting ?	Yes

Abstract	
Will the conclusions (if valid) likely to be useful to you, in your area of clinical practice of research?	Yes
Whether the settings in the material methods are similar to our own settings?	Yes

Research question

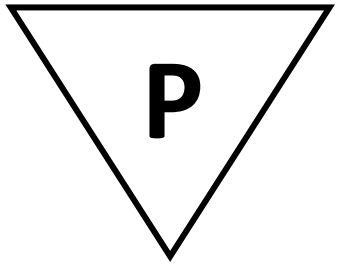
Research Question	
Is there a clear cut/ specific research question?	Yes
Was it feasible for the authors to study this question, given that there are technical expertise and available facilities?	Yes
Does the research question have some element of novelty?	Yes

Validity

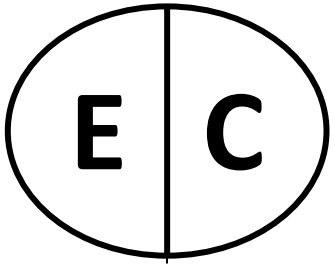
Validity	
Have the authors made a mention of Actual/ Study Population ?	No
Is the method of sampling been described ?	Yes
Whether a mention of all the potential confounding factors been made ?	No
Any Selection or information bias could have occurred ?	Yes

Gate Frame Assessment : PECOT

PARTICIPANTS : 210

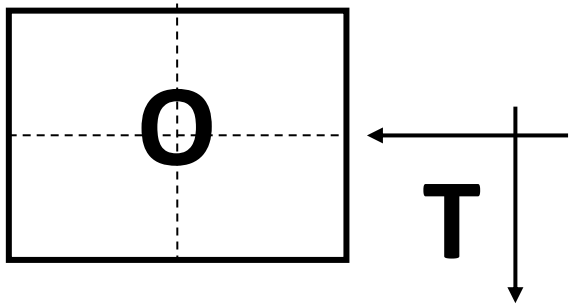


EXPOSURE GROUP : 52



COMPARISON GROUP: 158

OUTCOME:
Radiographic improvement in the area of pleural collection



DURATION:
DEC 2005 TO NOV 2008

Assessing study bias: The RAMMbo acronym

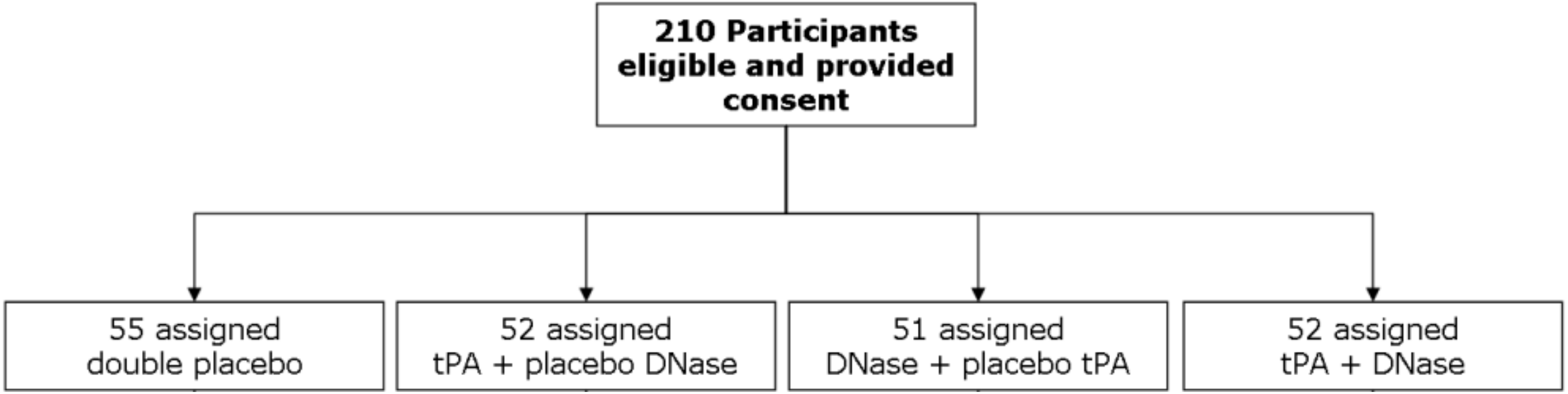
Assessing Study Bias

	R	Recruitment
	A	Allocation
	M	Maintenance
M	**B**	Blind
	O	Objective measurement

Recruitment

Recruitment	
Study setting and eligibility criteria well described	Yes No
Participants representative of eligible?	Yes
Prognostic/ risk profile appropriate to study question?	Yes
Randomisation process described adequately	Yes

Allocation


210 Participants eligible and provided consent
55 assigned double placebo
52 assigned tPA + placebo DNase
51 assigned DNase + placebo tPA
52 assigned tPA + DNase

Maintenance

Maintenance	
Good maintenance	Yes
Did most of the participants remain in the allocated groups?	Yes
Participants and/ or investigators blind to exposure (and comparison exposure)	Yes
Compliance high and similar in EG and CG	Yes
Completeness of follow up high and similar in EG and CG	Yes

Measurement of Outcomes Blind or Objective

Measurement of outcomes Blind or objectives	
Outcome measurements were	Blind
Authors reviewed all results	Yes

Strengths

- Sample size adequate
- Multicentre study
- Adherence to protocol
- Relevance of topic and has become the basis to define standard of care in management
- High compliance with the study drugs ensured

Limitations

- All participants are only from UK
- Minimisation induces some level of selection bias due to deterministic allotment
- No allocation concealment

Conclusion

Group	Observation	Results
TPA + DNase	Improved drainage of infected fluid in patients with pleural infection	30% reduction of ipsilateral hemithorax volume and 60% reduction in pleural collection. No excess adverse events
	Reduced referrals to thoracic surgery, reduction in hospital stay	Need larger study (Power) Encouraged in cases where standard medical management fails
TPA alone	No drainage benefit	Discouraged
DNase alone	No drainage benefit Increase in surgical referral	Discouraged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Thank you