Medical Management of Pleural Infections

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SpR Respiratory Wessex.

Pleural Infection - Definition

Pleural insult
No effuion

Simple effusion
pH >7.2

Complicated effusion
pH <7.2, fibrin +

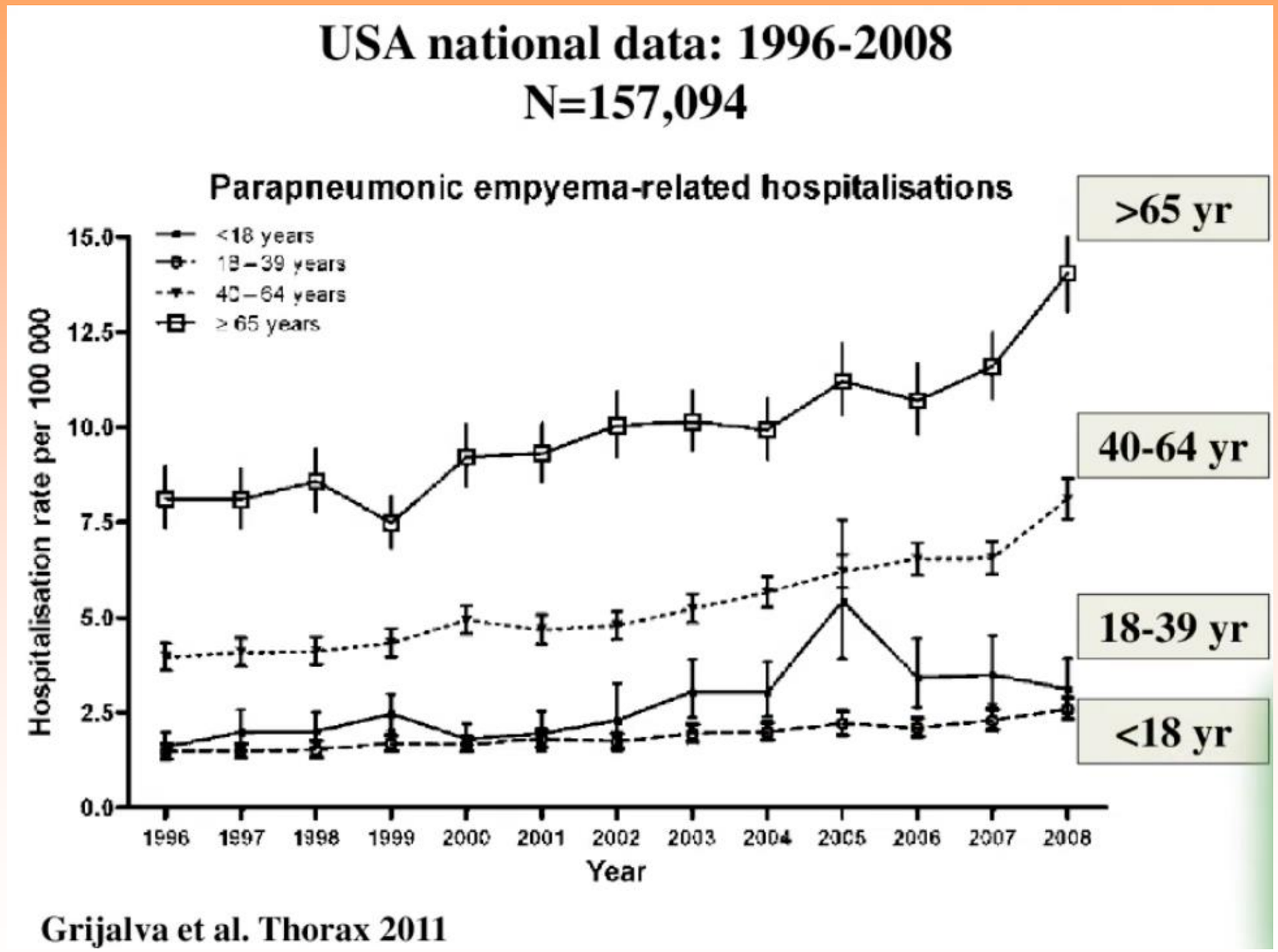
Empyema
Pus: fibrin ++

Sundaralingam, A., Banka, R. & Rahman, N.M. Management of Pleural Infection. *Pulm Ther* (2020).

Pleural Infection

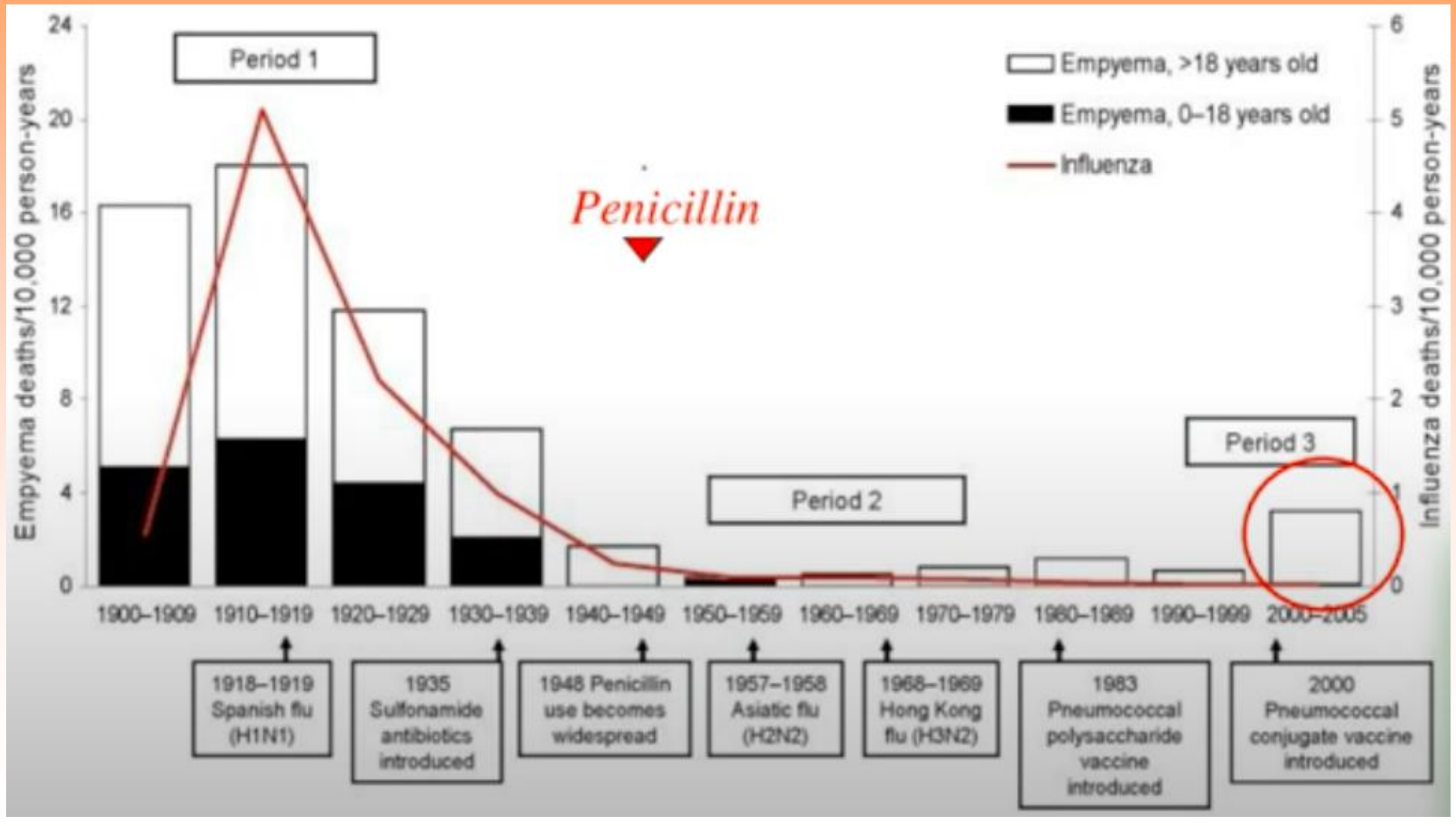
		Pleural fluid characteristics	Radiological features
Stage 1	Simple exudate Uncomplicated parapneumonic effusion	pH >7.3 Glue > 60mg/dL	Free-flowing effusion
Stage 2	Fibrinopurulent Complicated parapneumonic effusion	pH <7.20 Glucose <35mg/dL LDH >10000 IU/L Neutrophilic +ve micro Pus	Echogenic effusion +/- separations & loculations
Stage 3	Organising	pH <7.20 Glucose <35mg/dL LDH >10000 IU/L Neutrophilic +ve micro	Visceral pleural thickening. Trapped lung

Rates of Pleural Infections Increasing



Grijalva et al. Thorax 2011

Mortality - Increasing



Pleural effusion & Pneumonia - Poor prognostic sign

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Chest. 2016 Jun; 149(6): 1509–1515. PMCID: PMC6026265
Published online 2016 Jan 16. PMID: 26836918
doi: 10.1016/j.chest.2015.12.027

Pleural Effusions at First ED Encounter Predict Worse Clinical Outcomes in Patients With Pneumonia

Nathan C. Dean, MD, FCCP,[a,b,*] Paula P. Griffith, MD,[c]
Jeffrey S. Sorensen, MStat,[a] Lindsay McCauley, DO,[a,b]
Barbara E. Jones, MD,[b,d] and Y.C. Gary Lee, PhD, FCCP[e]

eCURB with Pleural Effusions

	WITHOUT Effusion N = 4081	WITH Effusion N=690
Predicted Mortality	4.7%	7.0%
Actual Mortality	5.0%	14.0%

P = 0.001

Prognostic Score of Mortality

Adults ~ 20% mortality by 3 months.

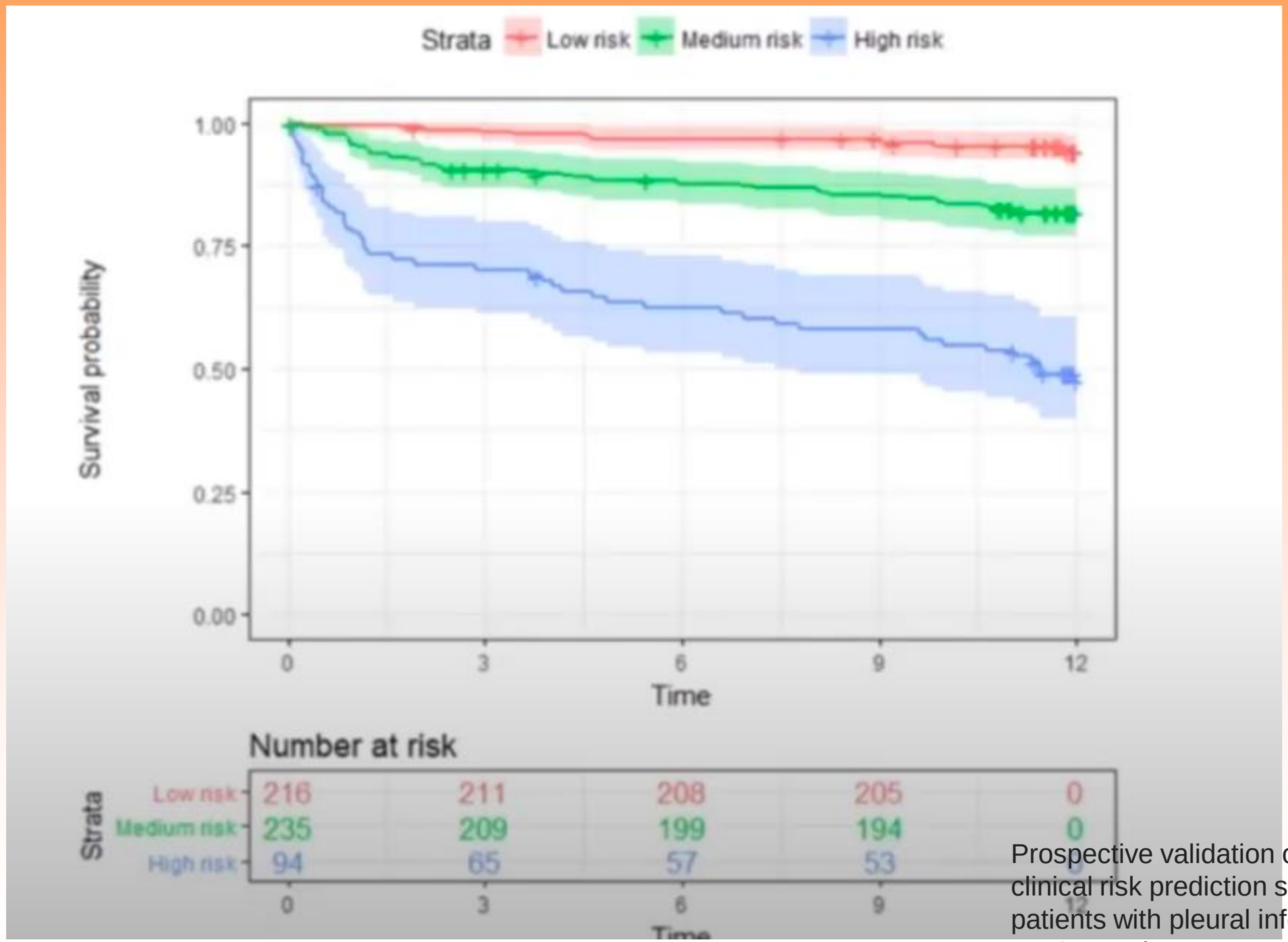
RAPID SCORE ~ a validated prognostic guide developed:
MIST-1 (n = 454); validated; MIST-2 (n=196)

Outcome prediction in pleural infection
RAPID score

Parameter	Measure		Score
Renal	Urea	<5mmol/L 5-8 mmol/L >8 mmol/L	0 1 2
Age	Age	<50 years 50-70 years >70 years	0 1 2
Purulence of fluid	Purulent Non-purulent		0 1
Infection Source	Community acquired Hospital acquired		0 1
Dietary Factors	Albumin	> or = 27mmol/L <27mmol/L	0 1
Risk categories	**Score 0-2** **Score 2-4** **Score 5-7**		**Low risk** **Medium-Risk** **High Risk**

August 11, 2011
N Engl J Med 2011; 365:518-526
DOI: 10.1056/NEJMoa1012740

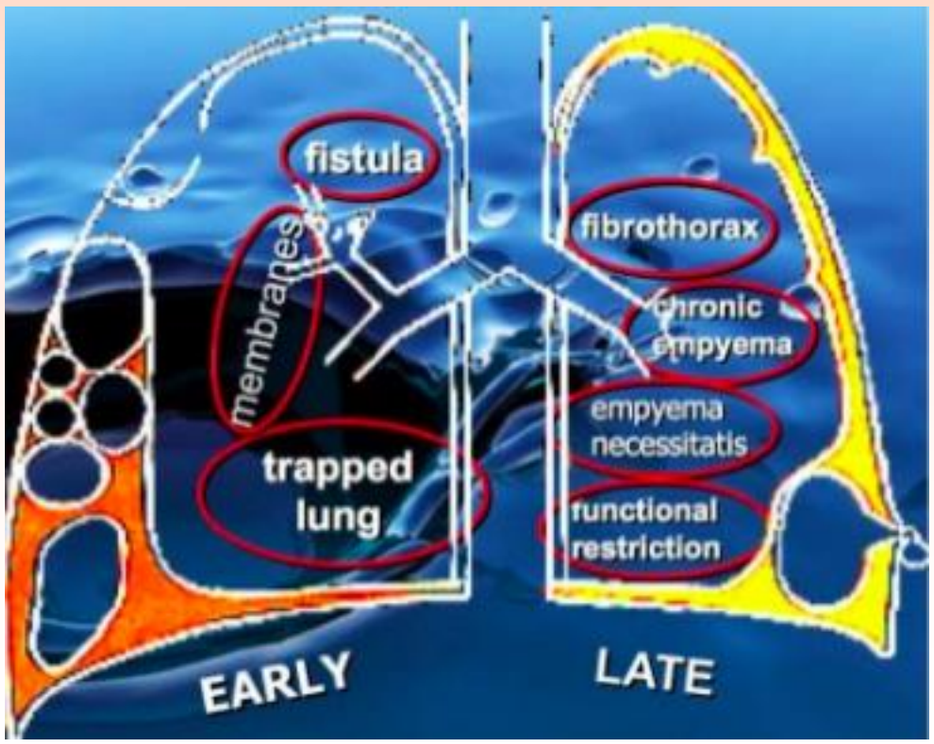
The PILOT study



Prospective validation of the RAPID clinical risk prediction score in adult patients with pleural infection: the PILOT study. Eur Respir J. 2020 Nov 26;56(5):2000130.

Treatment

- Antibiotics - which/ when/ where
- Drainage of infected material - which/ when
- Intrapleural adjuvants
- Steroids???
- Surgery



Antimicrobials

- Guided by the specific pathogen
- Bacterial aetiology of pleural infection

CMI CLINICAL MICROBIOLOGY AND INFECTION

ORIGINAL ARTICLE | VOLUME 25, ISSUE 8, P981-986, AUGUST 01, 2019

The bacterial aetiology of pleural empyema. A descriptive and comparative metagenomic study

R. Dyrhovden • R.M. Nygaard • R. Patel • E. Ulvestad • Ø. Kommedal

Open Access • Published: December 20, 2018 • DOI: https://doi.org/10.1016/j.cmi.2018.11.030

Sundaralingam, A., Banka, R. & Rahman, N.M. Management of Pleural Infection. *Pulm Ther* (2020).

Antimicrobials

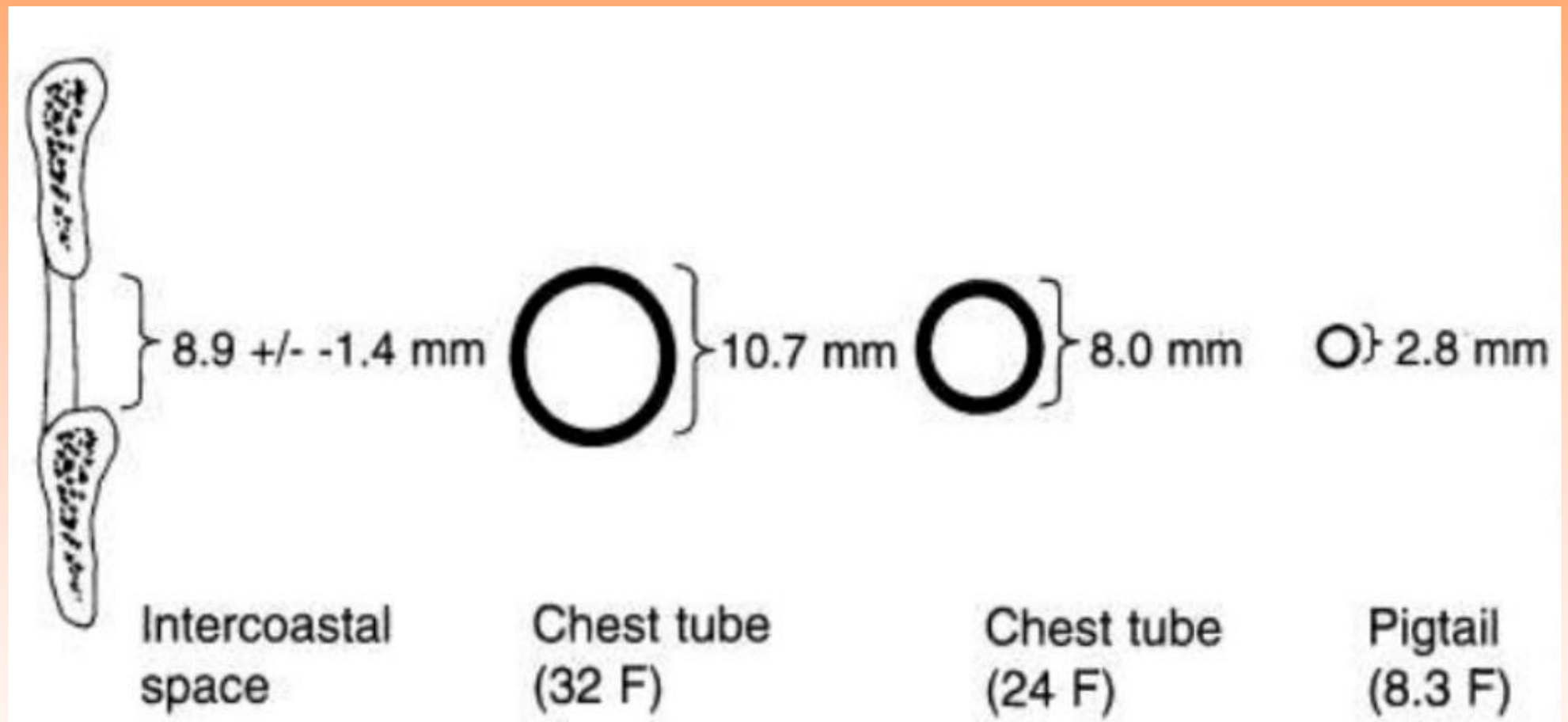
- Pleural fluid cultures +ve - 30-40% of cases
- Increase Pleural fluid cultures yield - blood culture bottles
- Anaerobic cover
- Good pleural space penetration - Penicillins/ beta-lactamase inhibitors, cephalosporins
- AVOID aminoglycosides
- Empirical hospital acquired - MRSA cover and anaerobic cover.
- Duration……

Community Acquired	Hospital Acquired
Viridans Strep	Staph Aureus (MRSA)
Strep Pneumoniae	Enterobacteriaceae
Staph Aureus (MSSA)	Enterococci
Enterobacteriaceae	Viridans Strep
Klebsiella	Pseudomonas
Pseudomonas	Klebsiella

Chest Tube Placement

Control group Tx with chest drain + abx	Succesful Tx rate
MIST 1 NEJM 2005	73%
MIST 2 NEJM 2011	84%

Chest Tube Placement



Medical Management of Pleural Infections

Despite optimal antibiotics and drainage ~ 20-30% will fail treatment

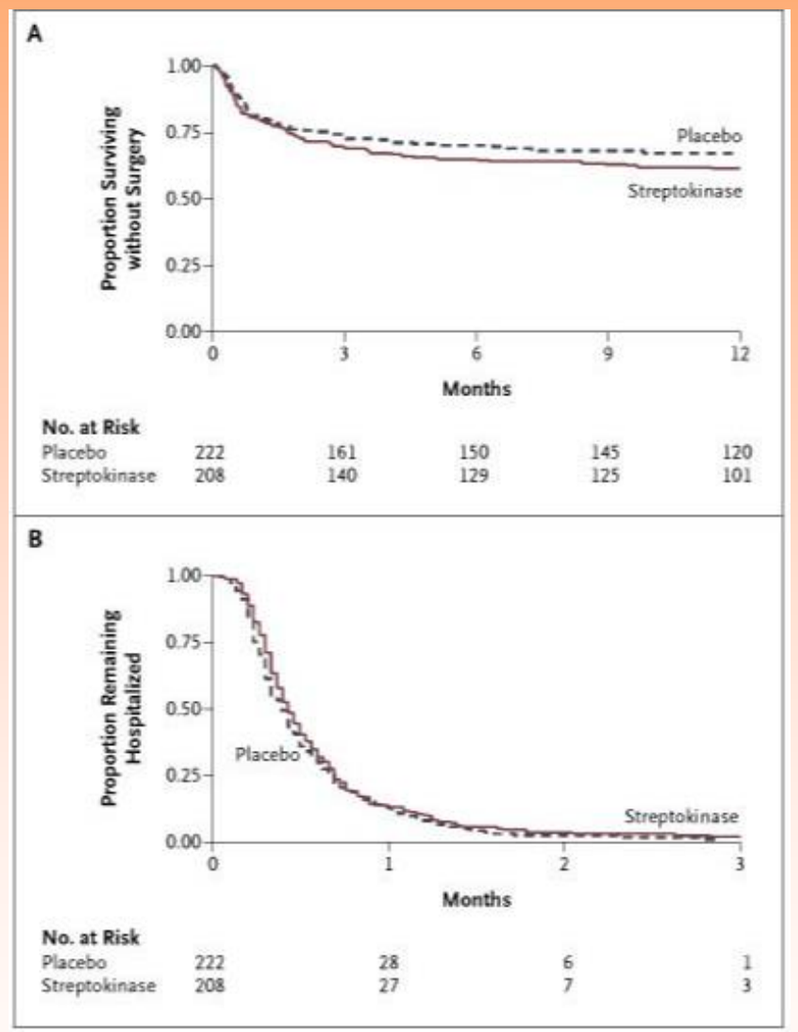
What next????

- Surgery
- Intrapleural enzyme therapy

Adjunct Therapy for Drainage of Empyema

- Breakdown loculations help drainage volume but..

- 2x RCT: *no mortality/ surgical benefit of streptokinase alone vs Saline*
  - Maskel et al. NEJM. 2005
  - Diacon et al. AJRCCM 2004



March 3, 2005
N Engl J Med 2005; 352:865-874
DOI: 10.1056/NEJMoa042473

Mechanism of action of tPA and DNase

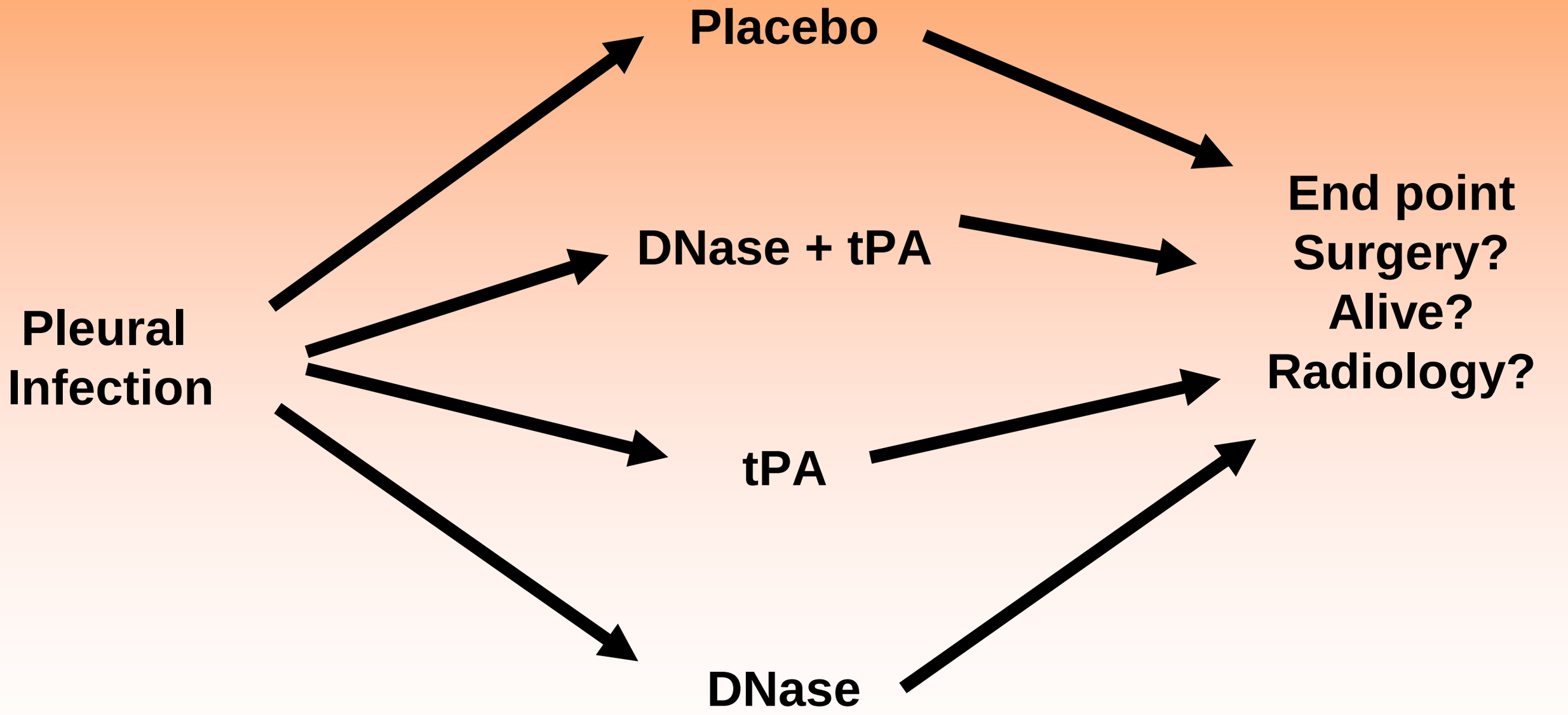
tPA
Lysis of pleural adhesions
?increase pleural fluid production

DNase
Decrease viscosity
Disrupt biofilms

Synergistic effect
Improved pleural drainage

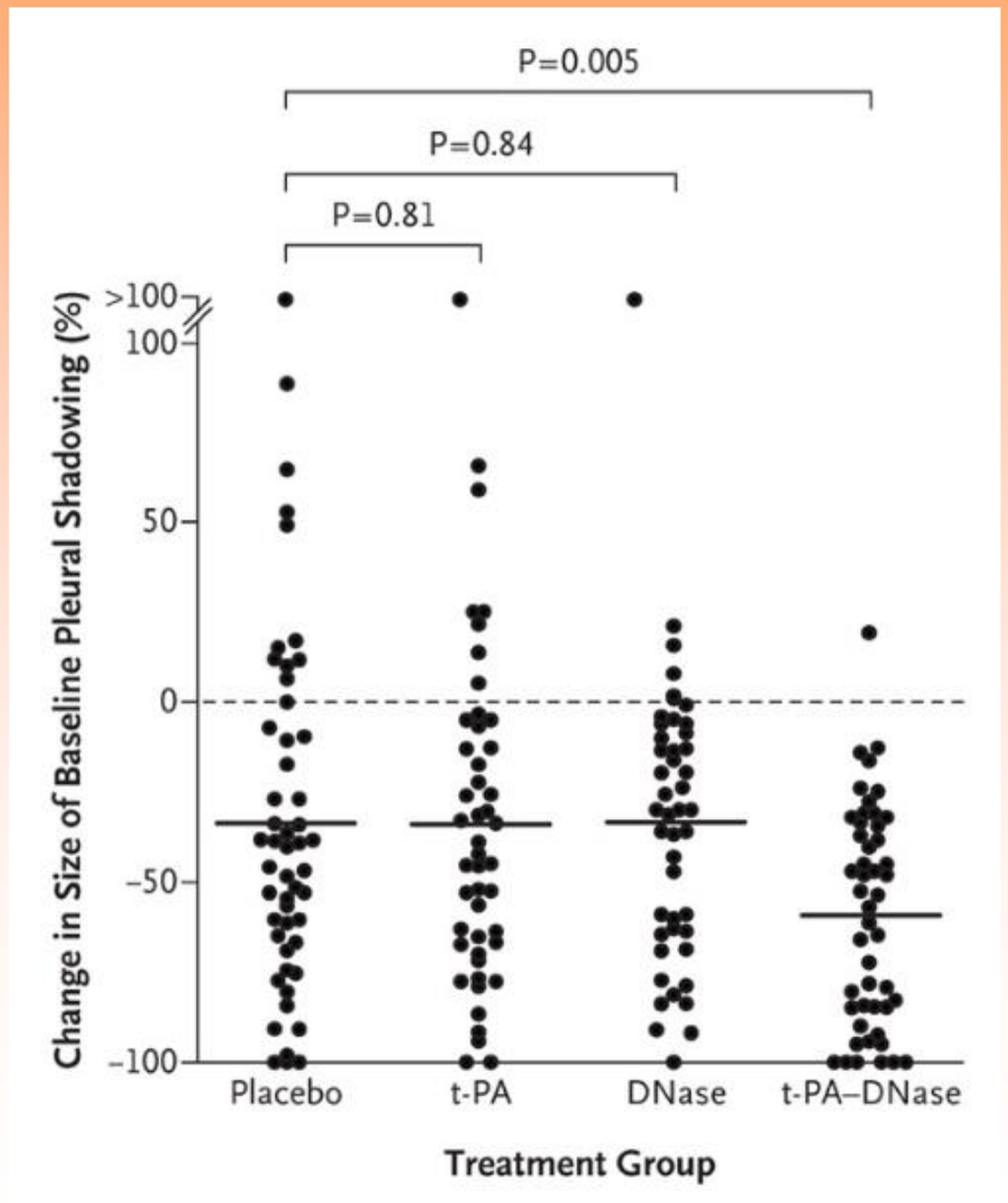
Zhu Z, et.al Chest. 2006 Jun; 129(6):1577-83. doi: 10.1378/chest.129.6.1577. PMID: 16778278.

Multi-Centre Intrapleural Sepsis Trial-2



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

MIST-2 Radiological improvement



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

MIST-2 Surgical Referral

	Requiring surgery	Odds Ratio	95% CI	
Placebo	15.7%	n/a	n/a	n/a
tPA	6.2%	0.30	0.07 - 1.25	P = 0.10
DNase	39.1%	3.56	1.30 - 9.75	P = 0.01
tPA + DNase	4.2%	**0.17**	0.03- 0.87	**P = 0.03**

Significant reduction in length of hospital stay

No difference in Mortality

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

MIST-2

Primary End-point

- Combination intrapleural tPa and DNase significantly improves CXR
- tPa and DNase alone are less effective

Secondary end points

- Combination may:
  - Reduce hospital stay
  - Reduce sepsis
  - Reduce need for surgery

MIST-2 in Clinical Practice

- tPA + DNase used for all patients in that arm **AT DIAGNOSIS**
- tPA + DNase - only 48 patients
- 84% successful treated in the Abx and chest drain. (placebo group)

So when she we use tPA+DNase

- As rescue therapy?
- Guided by RAPID score?

MIST2 Conclusions

Should this be standard care?

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

When to use?

- Where clinically it is vital to decompress the hemithorax
- Where no other treatment options are available
- Where difficult to accurately assess/select patients for surgery (often elderly with co-morbidities)

Open label use of tPA+DNase

ORIGINAL RESEARCH

Intrapleural Tissue Plasminogen Activator and Deoxyribonuclease for Pleural Infection

An Effective and Safe Alternative to Surgery

Francesco Piccolo[1], Nicholas Pitman[2], Rahul Bhatnagar[3], Natalia Popowicz[4], Nicola A. Smith[5], Ben Brockway[6], Robert Nickels[7], Andrew J. Burke[8], Conroy A. Wong[9], Ruth McCartney[10], Brian Choo-Kang[11], Kevin G. Blyth[12], Nick A. Maskell[3], and Y. C. Gary Lee[4,13]

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Abstract

Rationale: Intrapleural tissue plasminogen activator (tPA)/deoxyribonuclease (DNase) therapy for pleural infection given at the time of diagnosis has been shown to significantly improve radiological outcomes. Published cases are limited to only a single randomized controlled trial and a few case reports.

Objectives: Multinational observation series to evaluate the pragmatic "real-life" application of tPA/DNase treatment for pleural infection in a large cohort of unselected patients.

Methods: All patients from eight centers who received intrapleural tPA/DNase for pleural infection between January 2010 and September 2013 were included. Measured outcomes included treatment success at 30 days, volume of pleural fluid drained, improvement in radiographic pleural opacity and inflammatory markers, need for surgery, and adverse events.

Measurements and Main Results: Of 107 patients treated, the majority (92.3%) were successfully managed without the need for surgical intervention. No patients died as a result of pleural infection. Most patients (84%) received tPA/DNase more than 24 hours after failing to respond to initial conservative management with antibiotics and thoracostomy. tPA/DNase increased fluid drained from a median of 250 ml (interquartile range [IQR], 100–654) in the 24 hours preceding commencement of intrapleural therapy to 2,475 ml (IQR 1,800–3,585) in the 72 hours following treatment initiation ($P < 0.05$). We observed a corresponding clearance of pleural opacity on chest radiographs from a median of 35% (IQR 25–31) to 14% (7–28) of the hemithorax ($P < 0.001$), as well as significant reduction in C-reactive protein ($P < 0.05$). Pain necessitating escalation of analgesia occurred in 19.6% patients, and nonfatal bleeding occurred in 1.8%.

Conclusions: This large series of patients who received intrapleural tPA/DNase therapy provides important evidence that the treatment is effective and safe, especially as a "rescue therapy" in patients who do not initially respond to antibiotics and thoracostomy drainage.

Keywords: deoxyribonuclease; empyema; fibrinolytic; infection; pleural; tissue plasminogen activator

Outcome

93% successful Tx with tPA+DNase

Did not require surgery

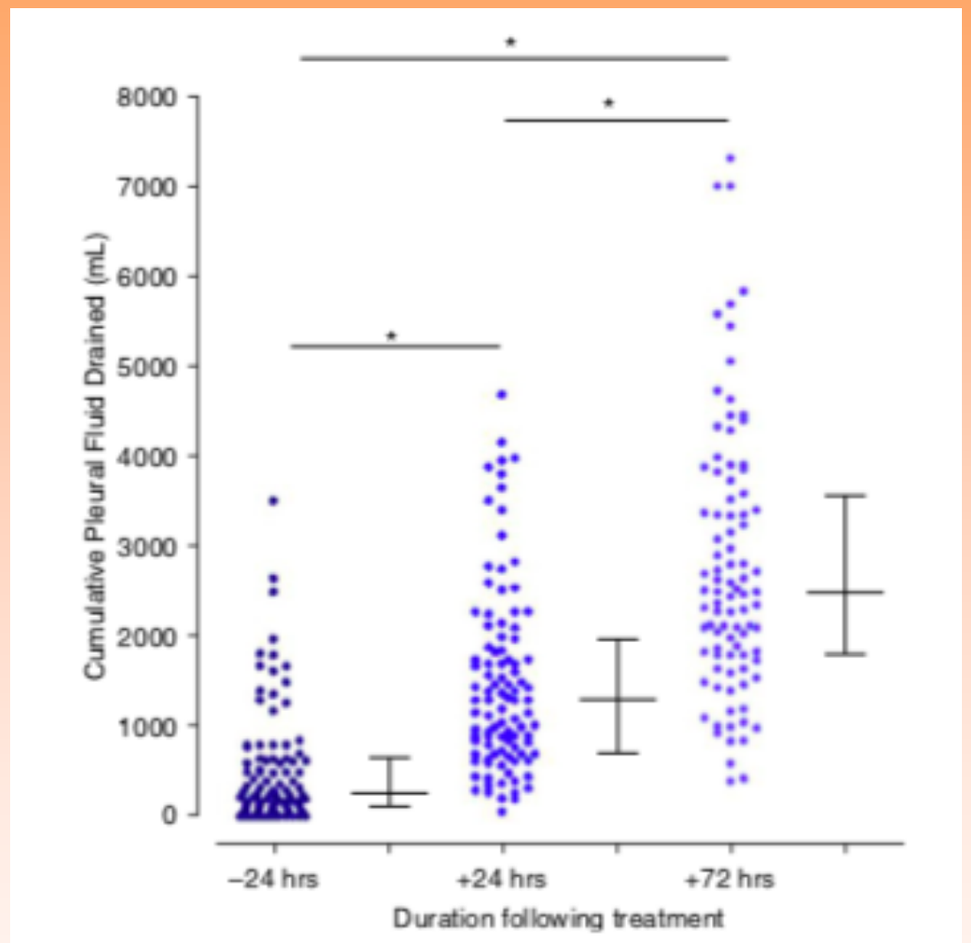
Decrease in radiological effusion

Resolution of clinical and inflammatory marker infection

Discharged (median 10 days from 1st dose

Piccolo F, et al. Ann Am Thorac Soc. 2014 Nov;11(9):1419-25.

Open label use of tPA+DNase



	24hrs pre	24hrs post	72 hr post
Median (mL)	250	1300	2475
IQR	100-645	735-1980	1800-3585

Outcome

93% successful Tx with tPA+DNase

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Decrease in radiological effusion

Resolution of clinical and inflammatory marker infection

Discharged (median 10 days from 1st dose

Piccolo F, et al. Ann Am Thorac Soc. 2014 Nov;11(9):1419-25.

Safety profile of tPA+DNase

- Large volume of haemorrhagic exudative pleural fluid
  - Stops when tPA stopped
  - Rarely causes haemodynamic collapse.

- Slow drop in Hb —> may need Blood Transfusion

	N =	Fatal bleed	Pleural Bleed	Systemic Bleed
Piccolo Ann Am Thor Soc 2015	107	0	2	0
Rahman NEJM 2011	48	0	2	3
Majid Ann Am Thor Soc 2016	73	0	4	0
Mehta Respiratory 2016	55	0	0	0
Popwicz Ann Am Thor Soc 2017	61	0	3	0
TOTAL		0/344 0%	11/344 3.2%	3/344 0.8%

G Lee 2021
Management of Complicated Pleural Infections.

When to consider IPFT?

- Clinician may consider that standard medical treatment has failed in the following circumstances:
  - persistent adverse clinical features (raised temperature, tachycardia, hypotension)
  - non-responsive biochemical markers (WBC, Neutrophils, CRP)
  - non-draining residual pleural collection (defined on imaging by one or more of chest radiograph, thoracic CT scan or thoracic ultrasound)

When to consider IPFT?

- Standard medical treatment (intercostal drainage and antibiotics) has failed to achieve satisfactory clearance of the pleural space after 12-24 hours, and
- Surgical intervention is considered clinically inappropriate or will be significantly delayed potentially leading to a negative impact on patient outcome.
  - But what about Covid, long transfer waits etc?

Contraindications to IPFT

Contraindications

Absolute

Less than 18 years of age
Known sensitivity or allergy to intra-pleural fibrinolytic agents
Coincidental stroke
Coincidental major haemorrhage or trauma (including thoracic haemorhage or trauma)
Major surgery in the previous week
Irreversible bleeding diathesis or platelet count <50 $x10^9$/L
Previous pneumonectomy on the affected side
Pregnant or breastfeeding

Relative

Concurrent anticoagulation with Warfarin, treatment dose LMWH or Direct Oral Anticoagulant (DOAC) or concurrent use of Clopidogrel.

Severe hepatic and renal failure – these patients are often at higher risk of bleeding and a careful consideration of risk:benefit ratio will need to be made. It may be appropriate to use a lower dose of Alteplase and/or frequency of administration.

Which fibrinolytic? Which Regime

- tPA - used in 1st study
- Other are currently being made/ studied

	Rahman NEJM 2011
Step 1	tPA (alteplase)10mg intrapleural via chest drain
Step 2	Clamp tube for 45min
Step 3	Reopen drain for 45min on free drainage
Step 4	DNase 5mg intrapleural via chest drain
Step 5	Clamp tube for 45min
Step 6	Reopen drain for 45min on free drainage
	Twice daily installations. *Daily bloods & CXR* *Stop if fluid is clear* *Approx 6 doses*

Further questions?

- What is the optimal regime? — 6 doses?
- When is the optimal time to give intrapleural?
- Can we mix the drugs at installation - currently being tested
- Can we risk stratify patient to treatments? - RAPID score
- Long term safety risk - developed outside of pharmaceutical company
- New Novel intrapleural therapies with longer half-lives?
- MIST 3 - early VATS vs Interpleural enzyme therapy
- MUST HAVE CONSENT FOR TREATMENT.

Surgery

Thank you to the surgeons

Steroids

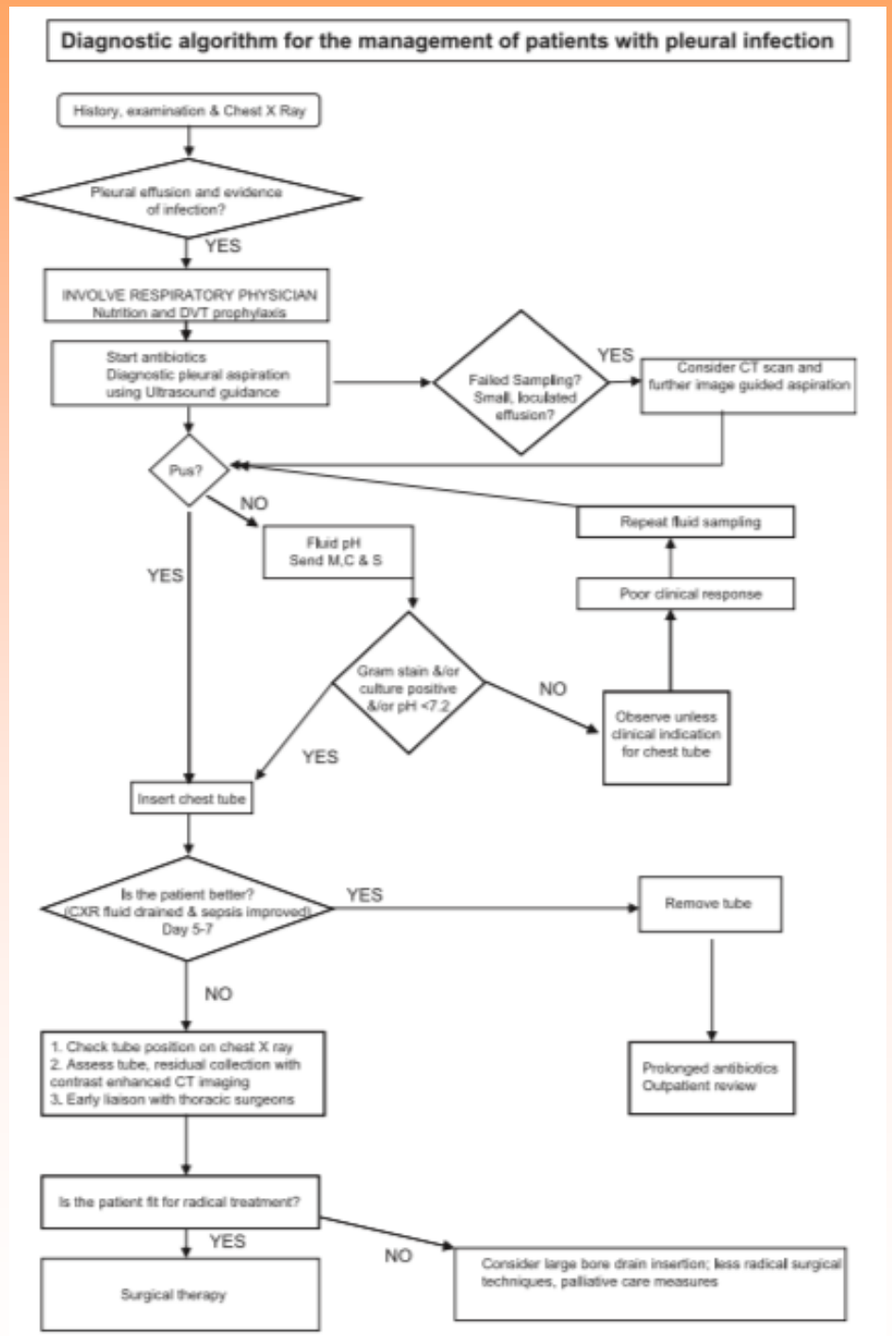
- There is a hypothesis that parapneumonic effusions is due to an erroneous immune response———> steroids

- COPD patients have lower incidences of pleural infection—-> ? Due to inhaled steroids

- STOPPE trail - Steroid therapy and outcomes of parapneumonic pleural effusions

Current BTS guidelines 2010

1. Respiratory specialist involved in care
2. Adequate nutrition
3. VTE prophylaxis
4. Regular monitoring for improvement/ blood cultures
5. Radiographic imagining
6. Pleural fluid testing - pH (or glucose as surrogate if not available



Current BTS guidelines 2010

1. Drainage if; pus/ +ve culture/ pH<7.2/ loculated/ failure to respond

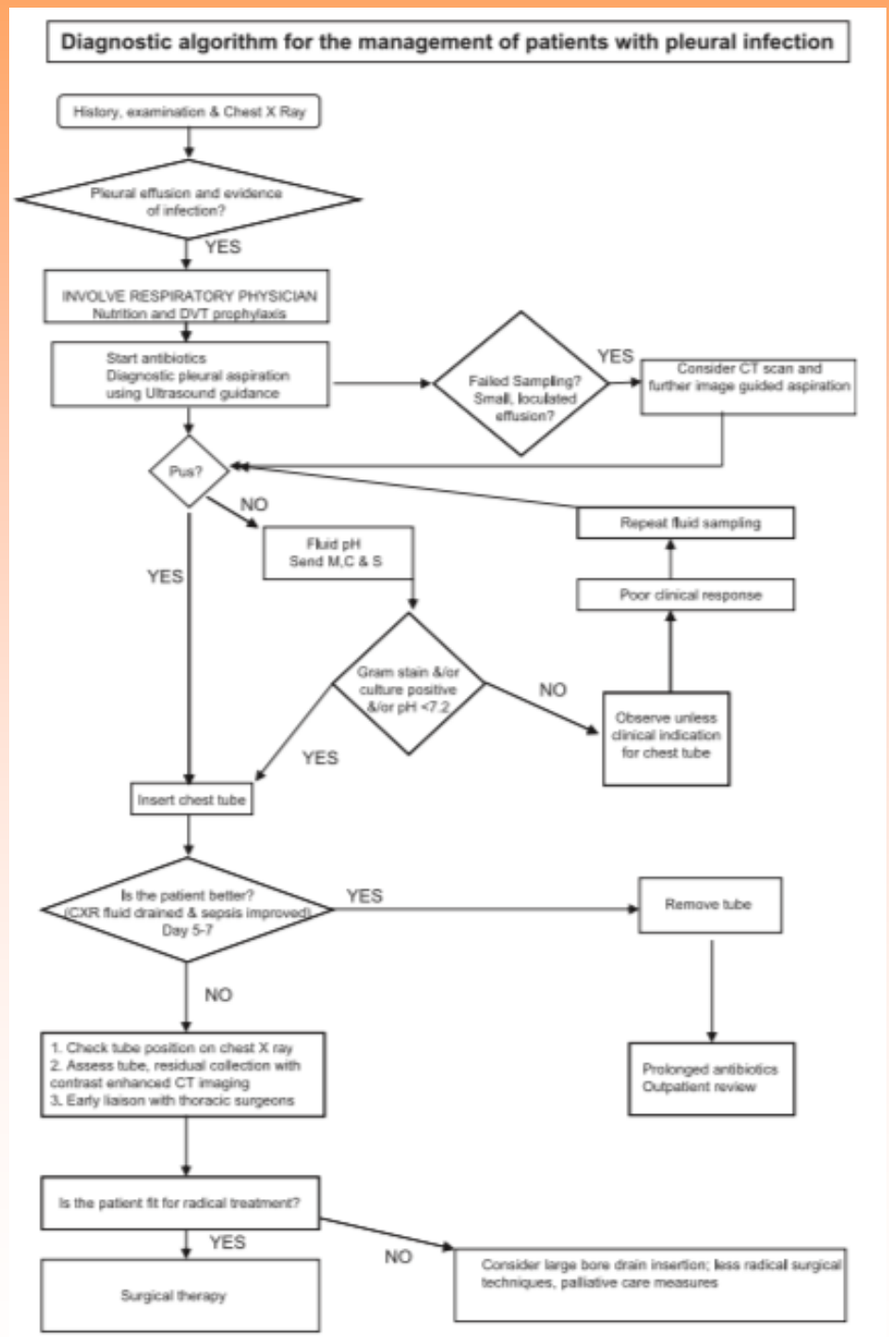
2. No consensus on chest drain size - if small bore —> regular flushes

3. Abx - guided by local policies and resistance pattern. (anaerobic infection should be used in all patients except those with culture proven pneumococcal infection)

4. Avoid aminoglycoside abx

5. Macrolide antibiotics - not indicated unless evidence or high clinical suspicion of ‘atypical’ pathogens.

6. Intrapleural antibiotics are not recommended.



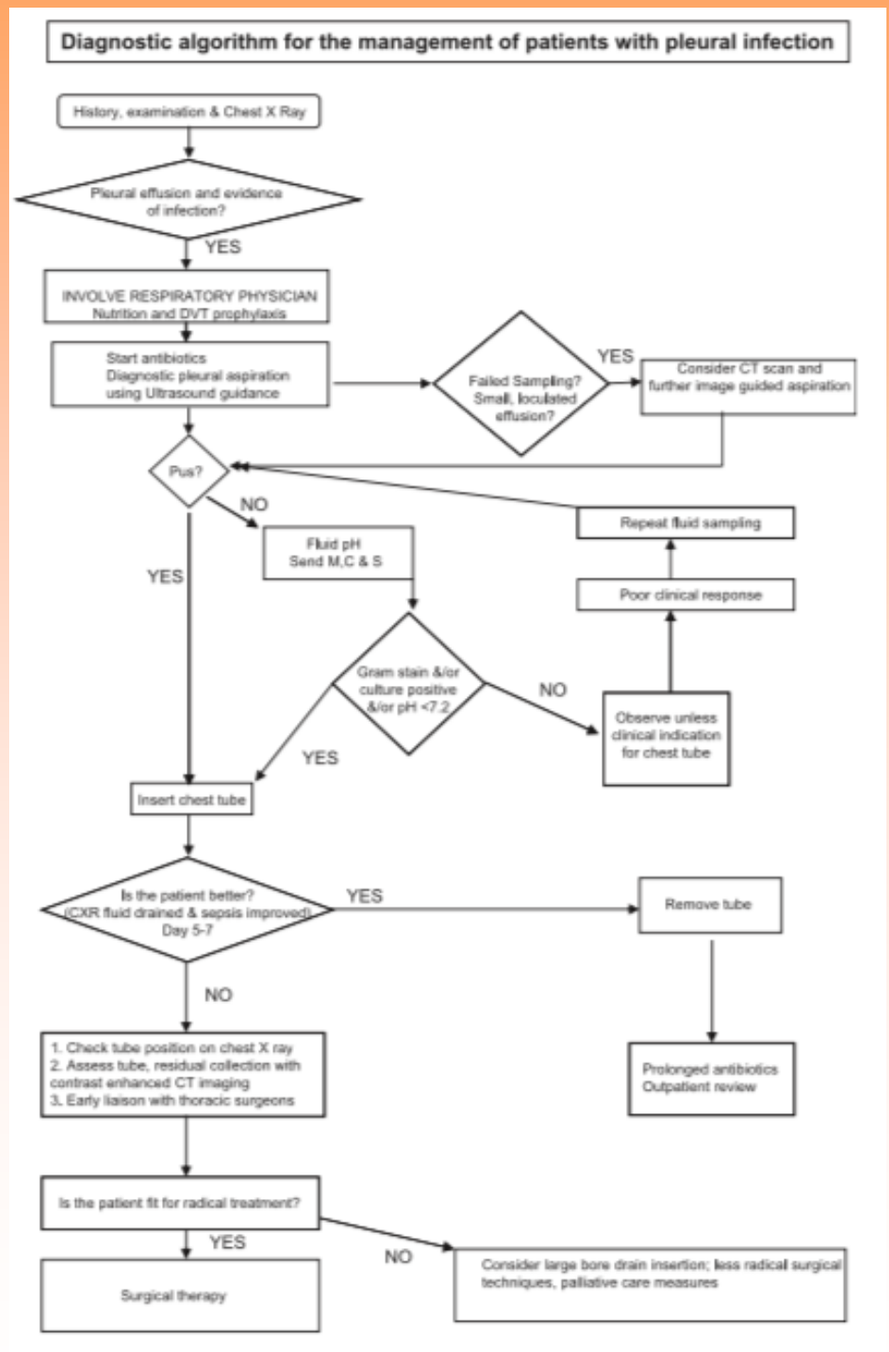
Current BTS guidelines 2010

- **No role for intrapleural fibrinolytic????**

- Persistent sepsis & residual collection —> discuss with thoracic surgeon

- Persistent effusion & sepsis but not fit for surgery - re-imaging / further chest drain/ intrapleural fibrinolytic after discussion with a thoracic surgeon.

- Palliation may be appropriate



Thank you