Pleural Sepsis: 
Current Management Guidelines and 
Current Evidence

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Pleural Infection

Ancient History:
• ‘A diseased wound in the breast’*
• ‘An abscess with prominent head from the breast’ǂ

• Descriptions emphasise the need to ensure drainage of infected fluid

*From the ‘Edwin Smith papyrus’, c1500 BC (trans. Breasted JH, 1930)
ǂAttributed to Egyptian physician Imhotep, c3000 BC

Guillaume Dupuytren
(1777-1835)

‘I would rather die at the hand of God than at the hand of a surgeon’

Sir William Osler
(1849-1919)

‘Empyema needs the cold steel of a surgeon rather than some fool of a physician…’

Died of surgical complications
Management of pleural infection in adults: British Thoracic Society pleural disease guideline 2010

Helen S Davies,1 Robert J O Davies,1 Christopher W H Davies,2 on behalf of the BTS Pleural Disease Guideline Group

Introduction
Pleural effusion is a frequent clinical problem with an approximate annual incidence of up to 08/000 cases in the UK and USA combined. The associated morbidity and mortality is high, in the 15-20% of patients with empyema, and approximately 40% of patients aspirate to contain pleural effusion which will only occur for approximately 3% of pleural infections. The prevalence of Empyema is increasing, and the development of multi-drug resistant bacteria in the 15% increased complications and mortality. Hence, the importance of early recognition of sepsis and empyema.

Overview
- Accurate diagnosis
- Microbiological profile and antibiotics
- Optimal drainage strategy
- Outcome prediction
- Intrapleural therapy

Burden

Pneumonia:
- Combined (UK + USA) ~ 1.5 million cases of pneumonia per year

Related Pleural Effusion:
- Estimated 30-40% develop parapneumonic effusions ~ 600,000 cases per year
- Total number of complicated PPEs / empyemas = 80,000 cases per year
- i.e. around 10% of parapneumonic effusions are complicated or frankly infected

Pleural Infection – Rx principles

1. Accurate diagnosis
2. Control sepsis:
   - Suitable antibiotic therapy
3. Drainage of infected material:
   - Intercostal tube drainage
   - Intrapleural adjunctive therapies
   - Surgery
4. Good nutrition / VTE prophylaxis
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
- 8% in hospitalised pneumonia

Studies:
- Farjah et al, J Thorac Cardiovasc Surg 2007:
  - Annual increase in incidence of 2.8%
- Finley et al, Can Respir J 2008:
  - IRR 1.30 (95% CI 1.20 to 1.41)
- Grijalva et al, Thorax 2011:
  - Two fold increase in incidence
  - Highest in >65 years
  - Robust study design / large national database
  - Streptococcal / staphylococcal empyema increased

Overview

- Accurate diagnosis
- Microbiological profile – where does this infection come from?
- Optimal drainage strategy
- Outcome prediction
- Intrapleural therapy
Pleural fluid pH

Use:
- Highly sensitive measure of poor clinical outcome
- Clinically used as aid to decide which patients to drain
- Not 100% sensitive

When to question pH

1. Not in keeping with clinical picture
2. Multiloculation¹
3. Variants in measurement²:
   - Contaminant
   - Delay
   - Air not excluded from syringe
   - Not blood gas analyser
Overview

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Pleural Infection

Is this just “pneumonia gone bad?”

Empyema with no associated parenchymal consolidation

Empyema with associated parenchymal consolidation + air bronchograms

Empyema with associated cavitating consolidation

Frequency (%) of CT features of empyema
97 patients with confirmed pleural infection
- Triple scored by independent radiologists
- Blind to clinical outcome and treatment

Franklin et al., in submission
Conventional microbiological yield is poor:
- 40% (including frank pus) microbiologically negative
- "Empirical" therapy therefore required in large minority

Community acquired empyema
- Cefuroxime 1.5g tds + Metronidazole 400mg tds
- Clindamycin 300mg qds po + Ciprofloxacin 500mg bd

Hospital acquired empyema
- Vancomycin 1g bd + Meropenem 1g tds
- Teicoplanin 400mg bd for 3 doses then 400mg daily and Meropenem 1g tds
Increasing diagnostic yield:
- Increase yield using Blood Culture Bottle Media?
- Supportive evidence from PD patients

The BCB study:
- Direct comparison
- Usual culture only vs addition of BCB inoculation
- Prospective, powered, control group
- Varied volumes

Use of Bactec system in addition to culture:
- Increases diagnostic yield by 21%
- Directly alters antibiotics in 4%
- No false positives
- All fluid volumes (2 / 5 / 10mls) equivalent
- BCB alone results in some false negatives

Menzies et al, Thorax 2011 66:658

Increasing yield:
- Today:
  - Innoculate pleural fluid in to BCB in addition to standard culture

- Tomorrow?:
  - Molecular microbiological techniques
Pleural Infection microbiology
Are we looking in the right place?
Overview

- Accurate diagnosis
- Microbiological profile – where does this infection come from?
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- Intrapleural therapy
- Role of surgery

Pleural Infection Rx

Intercostal drainage

Bigger is better?

Chest tube size and outcome

- Multiple case series:
  - Radiologically guided small bore chest tubes
  - Good outcomes
- Strongly held clinical belief remains
- Single direct comparison (pediatric)
Chest drain size

- Smaller tubes associated with less discomfort
- No apparent clinical disadvantage

Overview

- Accurate diagnosis
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Outcome prediction in pleural infection

MIST1 + MIST2 cohorts:
- Identical recruitment criteria
- Multivariate modelling
- Identify factors which predict outcome which are:
  - Clinically accessible at baseline
  - Biologically plausible

Radiological prediction?

Chen et al., 2000:
- 163 patients, 83 septated at ultrasound
- Comparing septated to non-septated:
  - Longer hospital stay
  - Higher rate of fibrinolysis
  - Increased surgical rate

Chen et al., 2009:
- 141 small bore catheters, patients, 81 septated at ultrasound
- Comparing septated to non-septated:
  - Success rate lower
  - Higher ICU admission
  - Increased mortality

Problems:
- High tube failure rate
- Retrospective design
- Unblinded design
- Significant bias

Outcome prediction in pleural infection

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<tr>
<td>Renal</td>
<td>Urea</td>
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<tr>
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<tr>
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Risk categories:
- Score 0-2  Low risk
- Score 2-4  Medium-Risk
- Score 5-7  High Risk
Kaplan-Meier Survival Estimates by RAPID score

Rahman et al, Chest 2015 145(4) 848

Outcome prediction - conclusions

- Prospective validation of RAPID score required
- No current reliable way of predicting management failure
- Treatment trial of “medical therapy” is reasonable in all cases

The PILOT Study

The Pleural Infection Longitudinal Outcome Study

Rationale:
- Protocolised management
- Identical data sets
- Biological samples
- Recruited 535/550 (97%) from
  - 25 UK centres
  - 5 international centres

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- Role of surgery
Intrapleural Fibrinolytics

- 4 small RCTs
  - Davies et al 1997
  - Bouros et al 1997
  - Bouros et al 1999
  - Tuncozgur et al 2001

Total of 104 adults

Surrogate outcomes

- Purulent pleural fluid
- Acidal pH<7.2
- Bacteria positive

Co-primary outcomes:
- Surgical Intervention
- Mortality

Streptokinase is ineffective in pleural infection

No differential effect by subgroups

Streptokinase is ineffective in pleural infection

NEJM 352: 865-874

MIST1

Purulent pleural fluid
Acidic pH<7.2
Bacteria positive

RANDOMISATION

Placebo
Streptokinase

Co-primary outcomes:
- Surgical Intervention
- Mortality

n=450

Cancer
Excluded
Purulent only

Short clinical history

NEJM 352: 865-874
Where from MIST1?

Explaining the result:
1. Wrong fibrinolytic
2. Fibrinolytic alone is not enough
   - Viscosity
   - Biofilms

Wrong Strategy: Viscosity

Wrong Strategy: Biofilms

Biofilms:
- Matrix of fibrin/uncoiled DNA + bacteria
- Bacteria resistant to antibiotics >100x MIC
  - Metabolically inactive bacteria
- Late clinical relapse
Biofilm forming empyema pathogens

- Staphylococci 11%
- Pneumoniae 13%
- Strep Milleri group 32%
- Enterobacteriacea 7%
- Proteus 2%
- Anaerobes 16%
- Hemophilus Influenza 3%
- Other 8%
- Other 8%
- Proteus 2%
- Enterobacteriacea 7%
- Anaerobes 16%
- Hemophilus Influenza 3%
- Other 8%

Community Acquired Pleural infection

Intrapeural Use of Tissue Plasminogen Activator and DNase in Pleural Infection

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John M. Wrightson, M.R.C.P., Helen E. Davies, M.R.C.P.,
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Nicki Cordwellis, R.G.N., Louis Chiu, M.Sc., Emma J. Holm, F.R.C.R.,
Fergur V. Gleeson, M.D., Andrew J. Nunn, M.Sc., and Robert D. Davies, M.D. 8

MIST2

- Purulent pleural fluid
- Acidic, pH<7.2
- Bacteria positive

Radiograph outcome
- Surgical Rate / Mortality

TPA
- DNase & TPA
- Placebo

Rahman et al, NEJM; 365: 518-526
Primary Outcome

Day 1

Day 7

Absolute change = (day 7 - day 1) = 8.0 - 38.9 = -30.9%
Relative change = (day 7 - day 1) / day 1 = -30.9/38.9 = -79.4%

Primary Result

tPA + DNase:
- Clear improvement in drainage
- Apparently safe
- Individual agents do not have any effect compared to placebo

Does this translate to other clinical benefit?

Secondary Outcomes
**Odds of fever**

- **tPA vs Placebo**
- **DNase vs Placebo**
- **Combination vs Placebo**

**MIST2 - Conclusions**

**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?:**
- Surgery remains the first line treatment (in my view)
- Where no other treatment options are available
- As part of a clinical trial

**Current use**

- Picolo et al, Ann Am Thor Soc 2014
  - 8 centres, n=107
  - All “failing medical therapy”
  - All given MIST2 regimen
  - 92.3% “success rate”

- Conclude
  - “Safe and effective as rescue therapy”

**Conclusions**

- Pleural infection is increasing
- Microbiology is complex – knowledge of likely microbiology essential in nearly half of cases
- Less pain from smaller drains and they seem to work
- RAPID - potential prediction algorithm (requires validation)
- tPA + DNase improves CXR (and maybe more)
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