Empyema in Australia
(and related Soapbox topics)
Adam Jaffe
Introduction

• Relatively rare
• < 1% pneumonias → empyema

Definitions

• Pleuritis
  – inflammatory process

• Exudative (Stage I) (simple parapneumonic)
  – ongoing inflammation
  – fluid clear
  – low WBCs
  – normal pH, LDH <1000 (NB Adults)

Hamm and Light ERJ 1997:10;1150
Stages of Empyema

• **Fibropurulent (Stage II)** (complicated parapneumonic)
  – Fibrin clots and membranes
  – accompanied by bacterial invasion
  – Increased WBCs and frank pus (empyema)
  – pH< 7.2, LDH >1000

• **Organisational (Stage III)**
  – fibroblast formation
  – peel formation and trapped lung
• Pleural space contains 0.3 ml/kg of fluid

• Pleural fluid circulation- lymphatics deal with several 100 mLs of extra fluid/ 24 hrs
empyema = pus within
Epidemiology

EMPYEMA IN CHILDREN
A Twenty-Five-Year Study
Basil Lionakis, M.D., Stephen W. Gray, Ph.D., John E. Skandalakis, M.D., and W. A. Hopkins, M.D.
Atlanta, Ga.

FIG. 1.—Incidence and mortality of empyema, 1932-1956. The bars represent the number of cases; the solid portions represent the number of deaths. The line indicates the probable trend of the incidence.
Epidemiology

It seems probable that this study covers the period of the practical extinction of empyema as an important thoracic disease.

Unless new, resistant bacterial strains develop faster than do the new antibiotics, 1947 should mark the essential closing of this chapter of the history of thoracic surgery.
Epidemiology

- England & Scotland

Roxburgh et al. Arch Dis Child 2008
Epidemiology

- USA

Epidemiology

- Australia

* Number of hospitalizations per million (10^6) person-years. There were 31,846,901 person-years in the period from July 1998 to June 2004 and 27,713,068 person-years in the period from July 2005 to June 2010.

# Bacterial Causes

**Empyema in Children**

*J of Peds 1938*

**A Twenty-five-Year Study**

Basil Lionakis, M.D., Stephen W. Gray, Ph.D., John E. Skandalakis, M.D.,

and W. A. Hopkins, M.D.

Atlanta, Ga.

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## Table V. Incidence of Infective Organism

<table>
<thead>
<tr>
<th>Organism</th>
<th>Under 2 Years of Age</th>
<th>Over 2 Years of Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus only</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Streptococcus only</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Pneumococcus only</td>
<td>11</td>
<td>51</td>
</tr>
<tr>
<td>Pneumococcus and staphylococcus</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Pneumococcus and streptococcus</td>
<td>2</td>
<td>19</td>
</tr>
<tr>
<td>Other mixed infections</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Sterile</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>8</td>
</tr>
</tbody>
</table>
Australian Research Network in Empyema

March 2007, 2 years

All blood and pleural fluid cultured

Pleural fluid was tested using polymerase chain reaction to identify the S. Pneumoniae autolysin gene (lytA)

- Serotypes identified by multiplex PCR reverse line blot assay (mPCR/RLB)
- PCR also for SA, MRSA and HI

Strachan et al EID 2011;17:10
<table>
<thead>
<tr>
<th>Organism</th>
<th>Blood culture, n = 152</th>
<th>Pleural fluid, n = 150</th>
<th>Pleural fluid, n = 145</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%) positive samples</td>
<td>Culture, No.</td>
<td>PCR, No.</td>
</tr>
<tr>
<td><strong>Streptococcus pneumoniae</strong></td>
<td>19 (12.5)</td>
<td>12 (7.5)</td>
<td>74 (51)</td>
</tr>
<tr>
<td>S. pyogenes</td>
<td>3 (2.0)</td>
<td>14 (8.8)</td>
<td>NA</td>
</tr>
<tr>
<td>S. milleri</td>
<td>NA</td>
<td>4 (2.5)</td>
<td>NA</td>
</tr>
<tr>
<td>MSSA</td>
<td>1 (0.7)</td>
<td>11 (6.8)</td>
<td>6 (4.1)</td>
</tr>
<tr>
<td>MRSA</td>
<td>1 (0.7)</td>
<td>6 (3.8)</td>
<td>7 (4.8)</td>
</tr>
<tr>
<td>Coagulase-negative staphylococci</td>
<td>4 (2.6)</td>
<td>2 (1.3)</td>
<td>NA</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>1 (0.7)</td>
<td>NA</td>
<td>4 (2.8)</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis</td>
<td>NA</td>
<td>1 (0.6)</td>
<td>NA</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>NA</td>
<td>1 (0.6)</td>
<td>NA</td>
</tr>
<tr>
<td>Mycoplasma pneumoniae</td>
<td>NA</td>
<td>NA</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Chlamydia pneumoniae</td>
<td>NA</td>
<td>NA</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Other†</td>
<td>4 (2.6)</td>
<td>4 (2.5)</td>
<td>NA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>7vPCV/7vPCV serotypes</th>
<th>13vPCV/13vPCV serotypes</th>
<th>Non-13vPCV/Non-7vPCV serotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotype</td>
<td>7vPCV 13vPCV Non-13vPCV</td>
<td>Non-7vPCV Non-13vPCV</td>
</tr>
<tr>
<td>Number</td>
<td>9V/14</td>
<td>1 3 7F/A 19A 6C 15F 21 22F/A</td>
</tr>
<tr>
<td>(%)</td>
<td>1.80 1.80</td>
<td>14.50 32.70 3.60 36.40 1.80 1.80 1.80 3.60</td>
</tr>
</tbody>
</table>
Figure 1 Comparison of proportions of vaccine-related serotypes identified among pleural fluid specimen (n = 29; typed by mPCR/RLB) and sterile site isolates (n = 331; typed by Quellung reaction) reported in national surveillance data (pneumococcal conjugate vaccine (PCV) serotypes are: PCV-7: 4, 6B, 9V, 14, 18C, 19F, 23F; PCV-10: as for PCV-7 plus 1, 5 and 7F; PCV-13: as for PCV-10 plus 3, 6A and 19A).
Empyema Post-7vPCV

- USA

Epidemiology

- Australia

Epidemiology

• Australia

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- Introduction of the PCV7 in Australia for all children less than 2 years old in January 2005

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*Number of hospitalizations per million (10^6) person–years. There were 31846 901 person–years in the period from July 1998 to June 2004 and 27713 068 person–years in the period from July 2005 to June 2010.*

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*Strachan et al Bull World Health Org 2013;91:167-173*
Vaccine effectiveness of 13vPCV

Early Impact of 13-Valent Pneumococcal Conjugate Vaccine on Community-Acquired Pneumonia in Children

Clinical Infectious Diseases 2014;58(7):918–24

- France PCV13 in June 2010
- 8 centres from June 2009-May 2012, n=5645
- CAP with pleural effusion n=365
- Pneumococcal CAP n=136

Angoulvant et al CID 2013;58:918-24
Vaccine effectiveness of 13vPCV

- CAP decreased by 16% (pre v post)
- Pleural effusions decreased by 53% (167 to 79)
- Pneumococcal CAP decreased 63% (64 to 24)
- Number of additional PCV13 serotypes decreased 74% (27 to 7)
- ST 1 decreased 27 to 5 (still present in older children)
- Younger children benefitted most

Angoulvant et al CID 2013;58:918-24
Targeted Enhanced Surveillance To Observe Vaccine impact against Pneumococcus
Objectives

1. Determine contribution of SP to complicated and uncomplicated pneumonia in 13vPCV era.
2. Assess serotype replacement by comparing serotypes with those obtained in ARNiE.
3. Determine VE of PCV for SP-confirmed and all-cause pneumonia.
4. Assess contribution of non-SP bacteria to complicated childhood pneumonia.
Definitions

Radiographic pneumonia confirmed by blinded assessors according to WHO criteria

Empyema (complicated pneumonia) defined by the confirmation of microscopic purulence

Pneumonia with raised inflammatory markers (PwiRIM) radiographic pneumonia + total WCC ≥ 20x10⁹ cells/L or CRP ≥ 20U/mL

Pneumonia without raised inflammatory markers (PwoRIM) radiographic pneumonia with a WCC < 20x10⁹ cells/L, and without a CRP ≥ 20U/mL.
Radiological pneumonia and FBE taken

Consent

Basic demo/clinical/lab data

De-identified CXR
200uL blood for PCR
NPA or nasal swab for culture
+/− 10mL of pleural fluid

ACIR

Enter data into web-based database
Xray assessment

- De-identified CXR assigned random number
- Issued to two blinded assessors
- Assessed according to WHO criteria
- Tie-breaker expert assessor if discrepancy
Pneumococcal confirmation

Pneumococcus positive on culture/PCR of blood or pleural fluid

Serotyping by Quellung reaction or multiplex PCR reverse line assay

= serotype attributable pneumococcal pneumonia

Pneumo autolysin (lytA) gene positive on blood

NPA/ nasal swab cultured on enhanced growth medium

Serotyping by Quellung reaction

= serotype attributable pneumococcal pneumonia
Vaccine effectiveness

Pneumococcal confirmed pneumonia case

DOB matched anonymous controls from de-identified ACIR database

‘Inverse matching’ of controls up to case DOB +/- 7 days

OR of PCV vaccination of case cf matched controls using CLR
### Recruitment target

<table>
<thead>
<tr>
<th>End-point</th>
<th>Recruitment sites</th>
<th>% SP-confirmed</th>
<th>No. SP-confirmed</th>
<th>Target</th>
<th>Av. target per site</th>
<th>Minimum detectable VE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empyema</td>
<td>All ARNiE sites</td>
<td>30%</td>
<td>60</td>
<td>200</td>
<td>15 (13)</td>
<td>71% vs SP+</td>
</tr>
<tr>
<td>PwiRIM</td>
<td>7 sites (each jurisdiction)</td>
<td>20%</td>
<td>200</td>
<td>1000</td>
<td>154 (7)</td>
<td>51% vs SP+</td>
</tr>
<tr>
<td>PwoRIM</td>
<td>7 sites (each jurisdiction)</td>
<td>10%</td>
<td>100</td>
<td>1000</td>
<td>154 (7)</td>
<td>63% vs SP+</td>
</tr>
<tr>
<td>Pooled</td>
<td>All ARNiE sites</td>
<td>16%</td>
<td>360</td>
<td>2200</td>
<td></td>
<td>52% vs all SP+</td>
</tr>
</tbody>
</table>

Projected hospitalisations for pneumonia across Australia over 36 months: 21,770
Why do some children get empyema?

- N=72 children <5 yrs with CAP +/- PPE
- SP bacterial load quantified using RT-PCR targeting lytA
- More children in PPE group had higher bacterial load (>265 DNA copies/ML)
- ST 19A significantly associated with higher bacterial load and PPE

Investigate role of transcription factor nuclear factor (NF)-kB in host response to pneumococcus

Genotyped 62 SNPs in inhibitors of NF-kB (IkB)

– NFKBIA, NFKBIB, NFKBIE

N=1060 adults IPD (not just chest) and controls

N=632 adults with thoracic empyema and controls

• 2 SNPS in *NFKBIA* promoter region conferred protection to IPD and pneumococcal empyema

• 1 *NFKBIE* SNP associated with IPD but not pneumococcal empyema

• Genetic variation in inhibitor of NF-kB may cause a rare immunodeficiency and predispose to IPD and empyema

Management

- French Academy of Medicine produced guidelines 1840s
- Trousseau 1843: Thoracocentesis is standard Rx
- Boston critic: ‘I would sooner send a bullet into the chest than plunge in a trocar’
- Have we made much progress?
Management

BTS guidelines for the management of pleural infection in children

I M Balfour-Lynn, E Abrahamson, G Cohen, J Hartley, S King, D Parikh, D Spencer, A H Thomson, D Urquhart, on behalf of the Paediatric Pleural Diseases Subcommittee of the BTS Standards of Care Committee

Recommendations for managing paediatric empyema thoracis

Summary of a position statement from the Thoracic Society of Australia and New Zealand*

Roxanne E Strachan, † BN, Research Nurse
Adam Jaffé, † MB BS, MD, FRACP, Respiratory Paediatrician and Head
Department of Respiratory Medicine, Sydney Children’s Hospital, Sydney, NSW.
Management

• Aims of treatment:
  – Sterilise pleural cavity
  – Drain fluid
  – Expand the lung

  – Ultimate aim is normal lung function
Investigations - CXR

- Not always possible to differentiate fluid from solid lung
- Cannot differentiate parapneumonic effusion from empyema
- No need for lateral
- May show scoliosis
Investigations - Ultrasound

- Fluid from solid lung
- Useful to stage disease
  - (not in adults where gold standard is Light’s criteria)
- Estimates size
- Demonstrates loculations
- Marks spot
Investigations - CT

- Not good for loculations
- Not good for differentiating simple parapneumonic effusions from empyema
- Road map for surgeons
- Excludes underlying abscess/tumour
- Malignancy risk
- Routine use controversial
Role of routine CT scans

• Aim
  – To investigate the role of routine CT scans in children with empyema

• Methods
  – As part of VATS/Urokinase study
  – 3 year prospective study
  – All children had USS, CXR, CT
  – CT scans in Urokinase group not used for placement of drains

Jaffe et al Thorax 2008;63:897-902
Methods- Pleural Collections

- Scoring system developed for US and CT scans for
  - Pleural effusions
  - Parenchyma

Jaffe et al Thorax 2008;63:897-902
Results

- 60 recruited
  - 46 USS available
  - 36 CT available
    - Exclusions:
      - local hospital n=14
      - no contrast enhancement n=2
      - drain in situ n=3
      - unavailable n=5
  - 31 CXR/CT/USS available
CTs more sensitive for parenchyma

No abnormality detected on CT which changed management e.g. abscess

Neither USS =/- CT were able to predict outcome

No need for routine pre-drain insertion CT

Table 5: Parenchymal changes detected on CT scan and chest radiograph (CXR)

<table>
<thead>
<tr>
<th>CT findings</th>
<th>Simple</th>
<th>Cavitation</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple</td>
<td>14</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>Pneumatoceles</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Necrotising pneumonia</td>
<td>7</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Cavitary necrosis</td>
<td>3</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Abscess</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>6</td>
<td>31</td>
</tr>
</tbody>
</table>

Jaffe et al Thorax 2008;63:897-902
Controversies in Management

- Antibiotics alone
- + recurrent thoracocentesis
- + chest drain
- + chest drain + fibrinolytics
- Open decortication
- VATS
Controversies in Management

• Antibiotics alone
  • + recurrent thoracocentesis
  • + chest drain
  • + chest drain + fibrinolytics
• Open decortication
• VATS
• Retrospective n=182
• Practice of 48hrs IV abs → pleural drainage if no improvement
• 95 (52%) antibiotics alone
• 87 (45%) drainage
  – 21 chest drain alone
  – 57 VATS/thoracotomy
  – 8 chest drain followed by VATS/thoracotomy
Size is important

- Strongest predictors requiring drainage
  - ICU admission
  - Large effusion >1/2 thorax
  - Younger age

- Pleural fluid loculation NOT a predictor

- No patient with small effusion <10 mm or <1/4 thorax filled) required drainage

- May help with decision making process

Carter et al Ped Pulm 2010;45:475-480
Dupuytren
(Napoleon’s surgeon) 1835

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

He lived 12 days
Overall Summary

- Empyema is increasing ?serotype replacement
- Serotypes 1,3 and 19A most prevalent
- PCR increases detection of bacteria
- No need for routine CT scan
- Need for appropriate vaccines
- Enhanced surveillance needed to monitor vaccine introduction
‘empyema needs a surgeon and three inches of cold steel, instead of a fool of a physician’

-Sir William Osler c1900
9 years later developed empyema and died at the hands of a surgeon following a rib resection.
Acknowledgements

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NHMRC