The Changing Face of Complicated Pneumonia in the Era of Pneumococcal Conjugated Vaccine

Philadelphia   ATS   2020

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Director, Division of Pediatric Pulmonology
Pneumonia  
(lower respiratory infection - LRI)

• A highly prevalent entity in childhood
• The largest single cause of morbidity and mortality worldwide in children <5 years outside the neonatal period
• Statistics from the western world suggest an annual incidence of 3-4% of the pediatric population below age 5, a substantially higher incidence than in adults
• It is important to acknowledge that the review today may not be reflective of large low-income parts of the world
<table>
<thead>
<tr>
<th>Complications</th>
<th>Pulmonary Complications</th>
<th>Metastatic Complications</th>
<th>Systemic Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural effusion or empyema</td>
<td>Pneumothorax</td>
<td>Meningitis</td>
<td>Systemic inflammatory response syndrome or sepsis</td>
</tr>
<tr>
<td>Lung abscess</td>
<td>Bronchopleural fistula</td>
<td>Central nervous system abscess</td>
<td>Hemolytic uremic syndrome</td>
</tr>
<tr>
<td>Necrotizing pneumonia</td>
<td>Acute respiratory failure</td>
<td>Pericarditis</td>
<td></td>
</tr>
</tbody>
</table>
Community-Acquired Pneumonia Hospitalization - U.S. Children

Darker shading - only the single pathogen was detected
Lighter shading – pathogen in combination with at least one other pathogen

From Jain, NEJM, 2015
Pleural effusion in Children

Empyema

literally means
“purulent appearing” = “it looks like pus”

It is loosely used as
“predictor of complicated outcome”
Ultrasound for pleural effusion

Complex septated pleural effusion
Timing is crucial
Intervention should occur before
the effusion is organized

The Sun Should Never Set on a
Parapneumonic Effusion

It has been documented that pleural effusions are
frequently associated with pneumonia, whether it
be pneumococcal, staphylococcal, Gram-negative aer-
obic, or anaerobic.\cite{1,2} The most common cause of an
empyema or complicated parapneumonic effusion to-
day is anaerobic pulmonary infection.\cite{3} This is largely
related to the pathogenesis of anaerobic pulmonary
infection, since the disease frequently occurs in the
alcoholic patient or in those with impaired conscious-

Sahn and Light, Chest, 1989
Stages Of Parapneumonic Exudate

- **exudative** phase
  free flow, low cellularity

- **fibropurulent** phase
  fibrin accumulation, abundant PMN - loculation occurs

- **organizing** phase
  fibroblastic activity, “peel” formation
Predictors Of Complicated Outcome Of Pleural Effusion

The hierarchy that emerges from the literature as to the relative efficacy of individual pleural fluid parameters to predict complicated outcome of pleural effusion:

- pH
- Glucose
- LDH
- Cell count
Pleural effusion

- Pleural effusions are a frequent complication of childhood pneumonia
- Opinions regarding diagnosis and treatment of pleural effusion vary widely

- **ABX therapy/delay pleural tap**
  (Epaud 2006, Carter 2010)
- **Thrombolysis w pigtail drain**
- **Early video-assisted thoracoscopy**
  (Schultz 2004)
- **Repeated U/S-guided needle thoracocentesis**
  (Shoseyov 2002)
Urokinase vs. VATS for Childhood Empyema

flow diagram

Enrollment
- Empyema referrals = 80
- Excluded = 20
  - Not meeting inclusion criteria = 13
  - Refused to participate = 4
  - Other reasons = 3
- Randomized = 60

Allocation
- Allocated to VATS = 30
  - Received VATS only = 25
  - VATS + mini thoracotomy = 4
  - VATS × 2 = 1
- Allocated to intrapleural urokinase = 30
  - Received urokinase = 28
  - Received VATS = 2
  - Urokinase failed → VATS/open surgery = 5

Sonnappa, ARJCCM, 2006
Urokinase vs. VATS for Childhood Empyema
Primary End Point

No clinically significant difference in hospital stay between the two groups
(p = 0.311, 95% CI of the median difference, -2 to 1).

Median post-intervention hospital stay
VATS 6 d (range, 3–16 d)
Urokinase 6 d (range, 4–25 d)

Sonnappa, ARJCCM, 2006
Pathway for evaluation and management of parapneumonic effusion in children

Improvement is assessed clinically (child feels better, becomes more active, temperature and inflammatory markers fall)

- Laboratory evaluation
  (Acute reactants, blood culture, PCR)
  + Imaging
  (CXR, lung US, occasionally chest CT)

  Mediastinal shift
  Respiratory distress
  Loculations

  Small effusion
  No respiratory distress

  iv antibiotics
  Pleural fluid analysis
  (Cytology, biochemistry, culture, PCR)
  iv empirical antibiotics

  VATS*
  No response
  Response
  Complications
  Consider major surgery

Legenda: PCR: Polymerase Chain Reaction; CXR: chest radiography; US: ultrasound; CT: computed tomography; VATS: video assisted thoracoscopic surgery; * "Primary" VATS may be considered in a very advanced organizing stage
Empyema hospitalizations increased in US Children despite pneumococcal conjugated vaccine

Empyema-associated hospitalization rates / 100,000 children

Li & Tancredi, Pediatrics, 2010
Necrotizing Pneumonia

(Massive Pulmonary Gangrene)
First description of 4 cases of necrotizing pneumonia in childhood

Ages ranged 1 – 7.5 years

Presentation with bacteremic pneumococcal pneumonia
Pulmonary parenchymal liquefaction and necrosis was determined by CT scan.

The clinical course was prolonged with fever lasting up to 20 days and hospitalization up to 26 days.

Contrary to adults, complete recovery was noted and no invasive investigation required.
National Hospitalization Trends for Pediatric Pneumonia and Associated Complications

Grace E. Lee, Scott A. Lorch, Seth Sheffler-Collins, Matthew P. Kronman and Samir S. Shah
## Rates of CAP

### TABLE 3  Rates of CAP in 1997–2006, Stratified According to Age

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>Rate, Estimate (95% CI), Cases per 100 000</td>
<td>n (%)</td>
<td>Rate, Estimate (95% CI), Cases per 100 000</td>
<td>n (%)</td>
</tr>
<tr>
<td>&lt;1 y</td>
<td>43 851 (30)</td>
<td>1169.0 (1158.2–1179.9)</td>
<td>44 691 (28)</td>
<td>1159.1 (1148.4–1169.8)</td>
<td>37 798 (24)</td>
</tr>
<tr>
<td>1–5 y</td>
<td>75 033 (50)</td>
<td>383.1 (380.3–385.8)</td>
<td>76 775 (48)</td>
<td>397.7 (394.9–400.5)</td>
<td>77 530 (49)</td>
</tr>
<tr>
<td>6–12 y</td>
<td>19 372 (13)</td>
<td>69.3 (68.3–70.2)</td>
<td>21 531 (14)</td>
<td>74.1 (73.1–75.1)</td>
<td>23 126 (15)</td>
</tr>
<tr>
<td>13–18 y</td>
<td>10 446 (7)</td>
<td>44.7 (43.8–45.5)</td>
<td>15 663 (10)</td>
<td>64.7 (63.6–65.7)</td>
<td>19 289 (12)</td>
</tr>
</tbody>
</table>

Rates are reported as cases per 100,000 age-specific US population.
Rates of CAP – associated complications: Overall

**TABLE 2** Rates of CAP and Associated Complications in 1997–2006

<table>
<thead>
<tr>
<th>Complication</th>
<th>1997 (95% CI)</th>
<th>2000 (95% CI)</th>
<th>2003 (95% CI)</th>
<th>2006 (95% CI)</th>
<th>Change (1997 vs 2006)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any complication</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate, cases per 100,000</td>
<td>11.8 (11.6–12.1)</td>
<td>14.6 (14.3–14.8)</td>
<td>15.8 (15.3–15.8)</td>
<td>15.1 (14.8–15.3)</td>
<td>28.0</td>
</tr>
<tr>
<td>Proportion of CAP cases (%)</td>
<td>5.9</td>
<td>7.0</td>
<td>7.7</td>
<td>7.5</td>
<td></td>
</tr>
<tr>
<td><strong>Local complications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate, cases per 100,000</td>
<td>5.4 (5.2–5.6)</td>
<td>7.4 (7.2–7.6)</td>
<td>8.9 (8.6–9.0)</td>
<td>9.6 (9.4–9.9)</td>
<td>77.8</td>
</tr>
<tr>
<td>Proportion of CAP cases (%)</td>
<td>2.7</td>
<td>3.6</td>
<td>4.4</td>
<td>4.8</td>
<td></td>
</tr>
<tr>
<td><strong>Systemic complications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate, cases per 100,000</td>
<td>6.8 (6.6–7.0)</td>
<td>7.7 (7.5–7.9)</td>
<td>7.5 (7.3–7.7)</td>
<td>6.2 (6.0–6.3)</td>
<td>−8.8</td>
</tr>
<tr>
<td>Proportion of CAP cases (%)</td>
<td>3.4</td>
<td>3.7</td>
<td>3.7</td>
<td>3.1</td>
<td></td>
</tr>
</tbody>
</table>

Rates are reported as cases per 100,000 age-specific US population.

Local – empyema, lung abscess, necrotizing pneumonia, or bronchopulmonary fistula

Systemic – acute resp. failure, sepsis, ECMO, or HUS
Rates of CAP – associated complications: By age

A. Age <1
-25.5%
-35.5%
+67.2%

B. Age 1-5
+31.5%
+79.3%

C. Age 6-12
+44.4%
+71.4%

D. Age 13-18
+67.2%
+88.1%
Following the introduction of PCV7 in 2000

- **Rates of CAP:**
  - Decreased for infants <1 yo
  - Increased for children >5 yo

- **Systemic complications:**
  - Decreased for infants <1 yo

- **Local complications:**
  - Increased for all age groups
NECROTIZING PNEUMONIA

Unknown organism assumed

S. pneumoniae
• 3 year and 9 month old girl admitted with fever, cough, respiratory distress

• Five days of nasal congestion, cough, fever to $39^0\text{C}$ and worsening dyspnea

• Refused to get out of bed for 2 days

• Was not seen by MD, parents considered this to be URI. Received no oral antibiotics
• Ultrasound of the chest to determine effusion revealed minimal amount, not tapped

• Assumed most likely
  *Strep. pneumoniae*, possibly
  *Staph. aureus*.

  Started on high dose intravenous ampicillin - sulbactam
December 28
(Day IV)
December 28
(Day IV)

CT with contrast
December 31
(Day VI)
December 31
(Day VI)

Note the rapid transition from necrosis to cavitation
January 3
(Day IX)
January 3
(Day IX)

CT with contrast
May 9

4 months later
Necrotising pneumonia is an increasingly detected complication of pneumonia in children

Eur Resp J, 2008

G.S. Sawicki*, F.L. Lu*, C. Valim#, R.H. Cleveland‡ and A.A. Colin*

The largest study of necrotizing pneumonia published to date
Necrotizing Pneumonia
Children’s Hospital Boston (1990-2005)

• The electronic database of the Department of Radiology was reviewed for 1/1990-2/2005
• All CT scans with the term ”necrotizing” in the full radiologic report
• All reports were inspected to identify misleading terms such as “no evidence of necrotizing pneumonia”
• The senior Radiology author (RHC) then screened each individual scan to determine whether there was imaging evidence of necrotizing pneumonia present
We identified a total of 80 cases of community acquired necrotizing pneumonia during the study period from January 1, 1990 through February 28, 2005.

No identified cases between 1990-1993.

The median age was 3.6 years (range 0.25-19).

53% were male.
Necrotizing Pneumonia
Children’s Hospital Boston (1990-2005)
Clinical features

• Ninety-six percent of patients reported an initial symptom of high fever
• 84% reported cough
• 91% were seen by a doctor prior to admission
• 53% required oxygen supplementation for at least one hospital day
• mean duration of fever 6 d (range 5-27)
• Mean length of stay 15 d (range 3-84)
• Mean duration of antibiotics 13 d (range 3-95)
NP Cases Per Year

- Zero cases were detected between 1990-1993

Sawicki, Lu et al, Eur Resp J, 2008
Newcastle upon Tyne
Cavitatory disease per year

Children’s Hospital Boston
1990-2004

Zero cases were detected between 1990-1993

Ramphul, Ped Pulmonol, 2006

Sawicki, Lu et al, Eur Resp J, 2008

Hôpital Robert-Debre

Lemaitre, Pediatr Infectious Dis J, 2013
Queensland, Australia, 2017

Masters et al. Pneumonia (2017) 9:11
DOI 10.1186/s41479-017-0035-0

Pneumonia

Necrotizing pneumonia: an emerging problem in children?

I. Brent Masters¹, Alan F. Isles¹ and Keith Grimwood²,³*

This study estimated NP to complicate up to 7% of pediatric CAP admission
Necrotizing Pneumonia – Underlying mechanisms

- Extensive inflammation and necrosis
- Fibrinous microthrombi
- Fragmented red cells

Kidney

Fibrinous microthrombi

Hsieh, Pediatr Pulmonol, 2006
Is this a vasculopathy?

Blue = Effusion  Gray = necrotic lung
Pink = consolidated or atelectatic (non-necrotic) intact lung
Necrotizing Pneumonia
Conclusions

Incidense and course

• We think that necrotizing pneumonia is a more common condition than appreciated
• CT scan is required to establish the diagnosis with confidence
• Similar to previous reports, our study reveals that the clinical course is typically prolonged and often complicated
Microbiology

No causative organism was identified in 42/80 cases

Sawicki, Lu et al, Eur Resp J, 2008
• Positive cultures were obtained in 38/80 (48%) cases

• Pleural fluid culture had the highest yield

• *Pneumococcus* was isolated in 18/80 (23%) cases

![Graph showing number of cases for different years and negative cultures vs. Pneumococcus](image_url)

Sawicki, Lu et al, Eur Resp J, 2008
Microbiology

Sawicki, Lu et al, Eur Resp J, 2008
NECROTIZING PNEUMONIA

4-month-old

Organism

Methicillin Resistant S. aureus (MRSA)
Gabriella M
Gabriella M
Staph aureus and PVL in NP

• S. aureus has many virulence factors
• Of these, Panton-Valentine leukocidin (PVL) is most notable in our context
• PVL is a pore-forming exotoxin, activates and then destroys immune cells, such as neutrophils, with release of damaging proteases into lung milieu
• Often with MRSA

Multicenter French study, NP with PVL
• mixed child-adult (median age was 14.5 years (interquartile range 1.8-36 yrs)
• The overall mortality rate was 56%, and the median survival was 10 days Gillet, Clin Infect Dis, 2007
No causative organism was identified in 42/80 cases.
Novel technologies to overcome low yield of cultures

- Molecular diagnostic tests, based on amplification of DNA and detection of specific genes, have been a major advance in the diagnosis of respiratory infections.
- PCR is less affected by antimicrobial therapy than culture techniques; it also offers the advantage of providing results and serotyping within a few hours.
- Several studies have shown that PCR of blood and pleural fluid is significantly more sensitive than culture in identifying pathogens in pediatric empyema especially in the context of preceding antibiotic treatment.

de Benedictis, Lancet, 2020
Taiwan

- 5 cases of necrotizing pneumonia
- Ages ranging 3 - 14 years of age
- All with pleural effusion
- All tested positive for *Mycoplasma pneumoniae*

**Sequela:**
- 3 full resolution
- 1 persistent atelectasis
- 1 persistent pneumatocele at 180 days follow-up

Wang, Pediatr Infect Dis J 2004
Mycoplasma pneumoniae-associated necrotizing pneumonitis (China)

Lung abscess vs necrotizing pneumonia
Lung abscess vs necrotizing pneumonia
Complicated pneumonia - Treatment

• Treatment is with a prolonged course of intravenous followed by oral antibiotics

• The initial choice is guided by local microbiological knowledge followed by subsequent positive cultures and molecular testing, importantly on pleural fluid when available

• Duration of therapy is conventionally prolonged, but no data are available for comparisons

de Benedictis, Lancet, 2020
Pneumococcal Conjugate Vaccine

- PCV7 was designed to protect against the most common serotypes (4, 6B, 9V, 14, 18C, 19F, 23F) that cause invasive pneumococcal disease in children
  - Meningitis
  - Bacteremia
  - Pneumonia
By the end of 2007, estimated coverage with 3 - 4 doses of PCV7 among U.S. children aged 19-35 months was 90% and 76% respectively.
In a large multicenter study on admission with *S. pneumoniae*

The prevailing serotypes causing disease were 1, 6, 14, 19 which were NOT covered by the pneumococcal conjugated vaccine

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**Uncomplicated Pneumonia**

- 19: 14.5%
- 14: 33%
- 23: 6.3%
- Other: 5.4%
- 3: 2.7%
- 4: 6%
- 5: 1.8%
- 9: 7.7%
- 6: 19%

**Complicated Pneumonia**

- 19: 9%
- 23: 3.4%
- Other: 5.5%
- 1: 24.4%
- 14: 29.1%
- 9: 5%
- 6: 8.4%
- 5: 3.4%
- 4: 3.4%

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Tan, Pediatrics, 2002
Necrotizing pneumonia - an increasing complication of community acquired pneumonia in childhood

Andrew Colin, M.D.
Boston Children’s Hospital
Harvard Medical School
Necrotising pneumonia is an increasingly detected complication of pneumonia in children

Eur Resp J, 2008

G.S. Sawicki*, F.L. Lu*, C. Valim#, R.H. Cleveland† and A.A. Colin*
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Pneumonia

REVIEW

Necrotizing pneumonia: an emerging problem in children?

I. Brent Masters¹, Alan F. Isles¹ and Keith Grimwood²,³*
Increase of necrotizing pneumonia after PCV-7

• Retrospective analysis 1/97 – 3/06 for all pneumococcal pneumonias <18 yo in a tertiary center
• 124 children identified
• 33 (27%) of these had radiographic evidence of NP
  • 1997–2000, 5/39 (13%) had PNP
  • 2001–2006, 28/85 (33%) had NP
    (OR, 3.34; 95% CI, 1.11–12.03)

Bender, Clin Infect Dis, 2008
Increase of necrotizing pneumonia after PCV-7

- Non–PCV-7 serotypes:
  - 1997–2000 - 49%
  - 2001–2006 - 88%
    (OR, 7.89; 95% CI, 2.91–21.90)

- **Serotype 3** most often associated with NP
  - 11/14 (79%) cases of serotype 3–associated pneumonia were associated with PNP
  - Compared with all other serotypes, serotype 3 was strongly associated with NP
    (OR, 14.67; 95% CI, 3.39–86.25)

Bender, Clin Infect Dis, 2008
Serotype replacement in disease after pneumococcal vaccination

Daniel M Weinberger
Richard Malley
Marc Lipsitch
Epidemiology of post PCV7 vaccination

*Serotype replacement*

- There is strong evidence that colonization with Non-vaccine types (NVTs) increases in vaccinated populations.
- Non-vaccine types (NVTs) have increased among asymptomatic carriers in a process dubbed “serotype replacement”.
- To a lesser extent, NVTs have increased as causes of invasive pneumococcal disease (IPD).
Enter PCV 13

- Starting 2010
- 6 capsular antigens of serotypes 1, 3, 5, 6A, 7F, and 19A were added to those included in PCV7

4, 6B, 9V, 14, 18C, 19F and 23F

With very effective reduction of Invasive Pulmonary Diseases (IPD) in children in the US

Moore, Lancet Respir Med, 2016
Rates of invasive pneumococcal disease
Children <5 years of age, 1998–2015

CDC - Manual for the Surveillance of Vaccine-Preventable Diseases, 2016
Annual trends in Invasive Pulmonary Diseases (IPD) children < 5 yrs
2006-13

Moore, CDC Report, 2014
Cumulative cases of PCV5-type IPD Children <5 yrs (2006-2013)

“PCV5” types include those in PCV13 but not in PCV7.

Moore, CDC Report, 2013
National Cases & Deaths of IPD Prevented following PCV13 Introduction 2010 - 2013

~ 30,000 cases prevented

~ 3,000 deaths prevented

Moore, CDC Report, 2014; Moore, Lancet Infect Dis 2015
Annual 7VT, 13VT and non-13VT serotype IPD rates in Israeli children <5years

Ben Shimol, Vaccine 2014
Annual serotype-specific IPD rates in children <5 years, Israel 2004-2013

Ben Shimol, Vaccine, 2014
Necrotizing Pneumonia
Pleural complications

- Children with necrotizing pneumonia mostly present as complicated pleuropneumonia
- Pleural effusion is the initial therapeutic challenge in this complex disease
- The recognition that a necrotizing pneumonia complicates the disease comes late in the course, when the treatment for the pleural disease is ongoing but symptoms persist
- It is the pleural element that typically extends the course
In our study 5 of 9 children with necrotizing pneumonia developed bronchopleural fistulae following chest tube placement. None with abscess developed such complication.

We concluded that the placement of chest tubes probably increases the risk of fistula formation in the presence of necrotizing pneumonia, and may extend the duration of the disease.
Necrotizing Pneumonia
Children’s Hospital Boston (1990-2005)
Pleural complications/Surgery

- 83% of the patients had pleural effusion
- 76% had pleural drainage
- Median duration of drainage 6 d (range 1-52)
- 15% had surgical intervention

- 10 patients (12.5%) developed bronchopleural fistula during the course of treatment
- All these patients had pleural drainage greater than 7 days
- One patient had a partial lobectomy

Sawicki, Lu et al, Eur Resp J, 2008
Necrotizing Pneumonia
Pleura - Conclusions
The necrotizing pneumonia – empyema conundrum

• Given that 83% of the cases in our series had a pleural effusion, a serious conundrum emerges, namely, whether the severe morbidity conventionally attributed to empyema may in reality reflect necrotizing pneumonia

• No study ever attempted to uncouple coexisting pleural effusion and necrotizing pneumonia
Necrotizing Pneumonia

Pleura - Conclusions

Length of treatment of pleural effusion

• The treatment or pleural effusion in the face of NP may require a more cautious approach; attempting to minimize drainage time because of risk of bronchopleural fistulae

• We think that the incidence of bronchopleural fistulae has decreased since we have become more conservative in the use of pleural drains
Necrotizing Pneumonia
Conclusions
NP vs. Lung abscess

- It is an enormous error to view necrotizing pneumonia as a lung abscess
- In particular if this will lead to manipulation and attempted drainage of the “abscess”
- This is almost guaranteed to lead to bronchopleural fistula and complicate the care and outcome
Necrotizing Pneumonia
Late pleural complications

On the Nature of Pleural Involvement in Necrotizing Pneumonia: A Report of Two Cases of Life Threatening Late Complications

Nadir Demirel, MD,1* Annabelle Quizon, MD,1 Edgar Leonel Belteton De Leon, MD,2 Joel Reiter, MD,1 and Andrew A. Colin, MD1
DT – 1 year old  11/3
DT – 1 year old  11/8
DT – 1 year old  11/17
DT – 1 year old  11/17
DT – 1 year old    11/17
DT – 1 year old

- Discharged on 11/24 to complete a total of 4 weeks of antibiotics with follow up by Pediatric Pulmonology
- She was not seen because of insurance issues
- She returned on 12/28 to the Pedi ER for fever, cough, and increased WOB for 1 day
- Completed antibiotics 3 weeks prior
DT – 1 year old   1/8/11
DT – 1 year old 1/8/11
Necrotizing Pneumonia
Conclusions
The residual cavity – pneumatocele vs. pneumothorax conundrum

- Many patients are discharged with residual cavities after admission with NP
- These cavities are referred to as pneumatoceles and are viewed as risk free
- Many of these cavities may in reality represent loculated pneumothoraces and as such may have late complications
- Should discharge orders for parents be modified accordingly?