

UNIVERSITY OF MIAMI MILLER SCHOOL of MEDICINE



The Changing Face of Complicated Pneumonia in the Era of Pneumococcal Conjugated Vaccine Philadelphia ATS 2020

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# 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 2. Complications Associated With Community-Acquired Pneumonia

Pulmonary	
Pleural effusion or empyer	na
- Pneumothorax	
Lung abscess	
Bronchopleural fistula	
Necrotizing pneumonia	
Acute respiratory failure	
Metastatic	
Meningitis	
Central nervous system ab	scess
Pericarditis	
Endocarditis	
Osteomyelitis	
Septic arthritis	
Systemic	
Systemic inflammatory res	ponse syndrome or sepsis
Hemolytic uremic syndrom	ne -

#### Bradley JS. Clin infect Dis, 2011

# Community-Acquired Pneumonia Hospitalization - U.S. Children



#### 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 aerobic, or anaerobic.<sup>1+1</sup> The most common cause of an empyema or complicated parapneumonic effusion today is anaerobic pulmonary infection.<sup>5</sup> 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

48-72 hours

- 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



# **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

(Thomson 2001, Balfour-Lynn 2005)

- Early video-assisted thoracoscopy
- (Schultz 2004)
   Repeated U/S-guided needle thoracocentesis (Shoseyov 2002)

# Urokinase vs. VATS for Childhood Empyema flow diagram



#### 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)



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

#### de Benedictis, Lancet, 2020

# Empyema hospitalizations increased in US Children despite penumococcal conjugated vaccine

![](_page_15_Figure_1.jpeg)

Empyema- associated hospitalization rates / 100,000 children

Li & Tancredi, Pediatrics, 2010

#### Necrotizing or Cavitating Pneumonia Due to Streptococcus pneumoniae: Medicine, 1980 REPORT OF FOUR CASES AND REVIEW OF THE LITERATURE

BIENVENIDO G. YANGCO, M.D., M.P.H. AND STANLEY C. DERESINSKI, M.D.<sup>1</sup>

## Necrotizing Pneumonia

(Massive Pulmonary Gangrene)

![](_page_16_Picture_4.jpeg)

#### Bacteremic Necrotizing Pneumococcal Pneumonia in Children

#### AM J RESP CRIT CARE MED, 1994

EITAN KEREM, YAACOV BAR ZIV, BERNARD RUDENSKI, SHMUEL KATZ, DAVID KLEID, and DAVID BRANSKI

Departments of Pediatrics, Pulmonary and Cystic Fibrosis Clinic, and Clinical Microbiology, Shaare Zedek Medical Center, and Departments of Radiology and Pediatric Surgery, Hadassah Medical Center, Jerusalem, Israel

- First description of 4 cases of necrotizing pneumonia in childhood
- Ages ranged 1 7.5 years
- Presentation with bacteremic pneumococcal pneumonia

#### Bacteremic Necrotizing Pneumococcal Pneumonia in Children

EITAN KEREM, YAACOV BAR ZIV, BERNARD RUDENSKI, SHMUEL KATZ, DAVID KLEID, and DAVID BRANSKI

- 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

Pediatrics 2010

# Rates of CAP

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

Age	1997		2000		2003		2006		Change,
	n (%)	Rate, Estimate (95% CI), Cases per 100 000	n (%)	Rate, Estimate (95% CI), Cases per 100 000	n (%)	Rate, Estimate (95% Cl), Cases per 100 000	n (%)	Rate, Estimate (95% CI), Cases per 100 000	1997 vs 2006, %
<1 y	43 851 (30)	1169.0 (1158.2–1179.9)	44 691 (28)	1159.1 (1148.4–1169.8)	37 798 (24)	937.6 (928.2–947.0)	37 705 (24)	912.9 (903.8–922.1)	-21.9
1–5 y	75 033 (50)	383.1 (380.3–385.8)	76 775 (48)	397.7 (394.9-400.5)	77 530 (49)	395.6 (392.8–398.4)	79 519 (51)	390.4 (387.7–393.2)	1.9
6—12 y	19 372 (13)	69.3 (68.3-70.2)	21 531 (14)	74.1 (73.1–75.1)	23 126 (15)	80.9 (79.9-82.0)	23 494 (15)	84.5 (83.4-85.6)	21.9
13–18 y	10 446 (7)	44.7 (43.8–45.5)	15 663 (10)	64.7 (63.6–65.7)	19 289 (12)	77.1 (76.1–78.2)	16 092 (10)	62.8 (61.9–63.8)	40.5

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										
	1997	2000	2003	2006	Change, 1997 vs 2006, %					
CAP discharges, estimate (95% CI), cases per 100 000	199.1 (198.1–200.1)	207.6 (206.6–208.6)	204.3 (203.1–205.3)	201.2 (200.2–202.2)	1.1					
Any complication										
Rate, estimate (95% Cl), cases per 100 000	11.8 (11.6–12.1)	14.6 (14.3–14.8)	15.8 (15.3–15.8)	15.1 (14.8–15.3)	28.0					
Proportion of CAP cases, %	5.9	7.0	7.7	7.5						
Local complications >97% emp	•									
Rate, estimate (95% Cl), cases per 100 000	5.4 (5.2–5.6)	7.4 (7.2–7.6)	8.9 (8.6–9.0)	9.6 (9.4–9.9)	77.8					
Proportion of CAP cases, %	2.7	3.6	4.4	4.8						
Systemic complications										
Rate, estimate (95% Cl), cases per 100 000	6.8 (6.6-7.0)	7.7 (7.5–7.9)	7.5 (7.3–7.7)	6.2 (6.0-6.3)	-8.8					
Proportion of CAP cases, %	3.4	3.7	3.7	3.1						

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

![](_page_22_Figure_1.jpeg)

# Following the introduction of PCV7 in 2000

- Rates of CAP:
  - Decreased for infants <1yo</li>
  - Increased for children >5 yo
- Systemic complications:
   Decreased for infants <1yo</li>
- 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°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

#### December 25

![](_page_26_Picture_1.jpeg)

- 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

![](_page_28_Picture_0.jpeg)

## December 28 (Day IV)

#### **CT with contrast**

![](_page_29_Picture_2.jpeg)

![](_page_30_Picture_0.jpeg)

### December 31 (Day VI)

### Large irregular pneumatocele

No wall

![](_page_31_Picture_3.jpeg)

### Note the rapid transition from necrosis to cavitation

January 3 (Day IX)

![](_page_32_Picture_1.jpeg)

## January 3 (Day IX)

#### **CT** with contrast

![](_page_33_Picture_2.jpeg)

## January 19 (Day XXV)

![](_page_34_Picture_1.jpeg)

![](_page_35_Picture_0.jpeg)

## May 9 4 months later

![](_page_35_Picture_2.jpeg)
### September 7



#### January 3

#### September 7



Necrotising pneumonia is an increasingly detected complication of pneumonia in children Eur Resp J, 2008

G.S. Sawicki\*<sup>,+</sup>, F.L. Lu<sup>\*,+</sup>, C. Valim<sup>#</sup>, R.H. Cleveland<sup>¶</sup> and A.A. Colin<sup>\*</sup>

The largest study of necrotizing pneumonia published to date



Children's Hospital Boston Harvard Medical School



# 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

Necrotizing Pneumonia Children's Hospital Boston (1990-2005) Demographics

- 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



#### Newcastle upon Tyne Cavitatory disease per year



### **Children's Hospital Boston** 1990-2004

#### Zero cases were detected between 1990-1993

28



Sawicki, Lu et al, Eur Resp J, 2008

Ramphul, Ped Pulmonol, 2006

### Necrotizing Pneumonia in Children: Report of 41 Cases Between 2006 and 2011 French Tertiary Care Center



#### Lemaitre, Pediatr Infectious Dis J, 2013

### Queensland, Australia, 2017

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

#### REVIEW



**Open Access** 

# Necrotizing pneumonia: an emerging problem in children?

I. Brent Masters<sup>1</sup>, Alan F. Isles<sup>1</sup> and Keith Grimwood<sup>2,3\*</sup>

This study estimated NP to complicate up to 7% of pediatric CAP admission

### Necrotizing Pneumonia – Underlying mechanisms









Hsieh, Pediatr Pulmonol, 2006

## Is this a vasculopathy?



#### Lai, PLoS ONE, 2015

### Kamran M



#### Kamran M



Full

5mm/div

### Blue= Effusion Gray= necrotic lung

Pink= consolidated or atelectatic (non-necrotic) intact lung



Necrotizing Pneumonia Conclusions Incidence 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

42 (52%) **Negative Cultures** 25 20 <del>၂</del> Number of Cases 10 S 0 1993-94 1995-96 1997-98 2001-02 2003-04 1999-00 (N = 1)(N = 11)(N = 11)(N = 17)(N = 12)(N = 28)

No causative organism was identified in 42/80 cases

- Positive cultures were obtained in 38/80 (48%) cases
- Pleural fluid culture had the highest yield
- Pneumococcus was isolated in 18/80 (23%) cases



# Microbiology



### **NECROTIZING PNEUMONIA**

### 4-month-old

Organism Methicillin Resistant *S. aureus* (MRSA)





















## 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

# Microbiology

**Negative Cultures** 42 (52%) 25 20 15 Number of Cases 10 S 0 1993-94 1995-96 1997-98 1999-00 2001-02 2003-04 (N = 1)(N = 11)(N = 11)(N = 12)(N = 17)(N = 28)

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

# Taiwan

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

Mycoplasma pneumoniae

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

Wang, Pediatr Infect Dis J 2004



### (China)









#### Wang, Pediatrics International, 2012

### 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
## 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

Centers for Disease Control and Prevention The National Center for Health Statistics The National Immunization Survey 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



#### 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\*<sup>,+</sup>, F.L. Lu<sup>\*,+</sup>, C. Valim<sup>#</sup>, R.H. Cleveland<sup>¶</sup> and A.A. Colin<sup>\*</sup>



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#### REVIEW

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# Necrotizing pneumonia: an emerging problem in children?

I. Brent Masters<sup>1</sup>, Alan F. Isles<sup>1</sup> and Keith Grimwood<sup>2,3\*</sup>

# 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

Lancet 2011; 378: 1962-73

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)



Moore, CDC Report, 2013

#### National Cases & Deaths of IPD Prevented following PCV13 Introduction 2010 - 2013



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

Fredric A. Hoffer David A. Bloom Andrew A. Colin Steven J. Fishman Lung abscess versus necrotizing pneumonia: implications for interventional therapy

- 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



#### **CT with contrast**



#### JR 13 months



### CM 6-11-05



### 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, мр,<sup>1</sup>\* Annabelle Quizon, мр,<sup>1</sup> Edgar Leonel Beltetón De Leon, мр,<sup>2</sup> Joel Reiter, мр,<sup>1</sup> and Andrew A. Colin, мр<sup>1</sup>

Pediatric Pulmonology, 2014














### 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 12/28



#### DT – 1 year old 12/29



### DT – 1 year old 1/8/11



# DT - 1 year old 1/8/11



# 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?