Pneumococcal disease in children—Epidemiology and evolution

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Overview

- History of *Streptococcus pneumoniae* - microbiological studies
- Pathogenesis and diseases associated with pneumococcus
- Vaccine development and efficacy
- Seroepidemiology - US and worldwide
- Disease in the pre- and post- PCV-7 era
- Antibiotic susceptibility patterns of *Streptococcus pneumoniae*

Case #1 - Emma

- Jan 2001
- 2 y/o F, previously well
  - Full-term, no previous hospitalizations
  - 2-3 episodes AOM
- Developed fever to 102.2, decreased activity, emesis
- Following day fussy, refused PO, minimally active, temp 104.2
- Left tympanic membrane opaque, erythematous, mildly volume-depleted. Otherwise non-focal exam.
- Evaluated and hospitalized for IVF administration, IV ceftriaxone (emesis, PO refusal)

- CBC 45,3>12.9/37/6<479
- 57segs 17 bands 2 lymphs, 14 monos 9 atypical lymphocytes (initially reported as blasts)
- Blood culture positive at 16 hours:
  - Vancomycin added
  - *Streptococcus pneumoniae*
    - Sensitive to Penicillin, clindamycin, cefotaxime, vancomycin

- Repeat blood cultures negative
- CT scan of head with fluid in L mastoid air cells
- LP – 0 WBC
- Developed L ear proptosis, erythema over mastoid (subsequently resolved)
- Required tympanostomy for persistent fever after 4 days of fever
- Full recovery
**Streptococcus pneumoniae**

- Worldwide - estimated to cause >1 million annual pediatric deaths
  - #1 cause of vaccine-preventable deaths in children
- Developed countries
  - Remains leading bacterial cause of pneumonia, meningitis, and otitis media

1881- first description by Sternberg “Micrococcus pasteuri and Pasteur “Microbe septic antique du salive”
Later renamed *Diplococcus pneumoniae* in 1920, then *Streptococcus pneumoniae* in 1974
Gram reported lancet-shaped diplococci retaining the stain of gentian violet - from lung tissue of pneumonia cases

**The Organism**

- Alpha-hemolytic streptococcus
- Catalase -negative
- Elongated pairs on gram stain, short chains in liquid media,
- Relatively fastidious growth
- Optochin-sensitive, bile-solubility

**Disease Entities**

- Respiratory pathogen - #1 bacterial cause
  - Upper (Otitis media, Sinusitis)
  - Pneumonia – young children and older adults
- Meningitis
- Bacteremia
  - Occult
  - Fulminant sepsis
- Less commonly: osteoarticular infections, soft-tissue infections, primary peritonitis
- Rarely – neonatal infections, endocarditis/pericarditis
- Invasive Pneumococcal Disease (IPD) – defined by isolation from normally sterile site

**High risk for IPD**

- Children <5 (highest from 3-23 months)
- Older adults >65 years
- Immunodeficient patients
- Functional or anatomic asplenia
- Cranial defects, basilar skull fractures, cochlear implants
- Chronic illness (heart, lung, diabetes)
- Certain ethnic or racial groups (Native Americans esp Alaskan, Aboriginal Australian)
- Nephrotic syndrome
Colonization

- 5-10% of healthy adults
- 20-30% of healthy children
- Up to 60+% in daycare attendees
- Colonizing isolates induce some type-specific immunity

Occult Bacteremia

- Children 3-36 months with fever ≥ 40°C or > 39.5°C with WBC > 15 x 10^9/liter and no focus of infection
- N = 519
- 60 positive cultures

Bacterial Meningitis

- Prior to conjugate vaccine licensure in 1987 H influenzae type B outnumbered
- Surveillance for bacterial meningitis in 1995 demonstrated shift

Polysaccharide Capsule

- 1890s – early serostudies demonstrating immunity conferred by injecting rabbit serum from previously infected rabbits
- Strain specific
- Non-bactericidal, but promoted phagocytosis
- Earliest demonstration of protective effect of serum
- 1902 – Neufeld identified quellung reaction of capsule
- Serotype-specific
- 1910-1923 – series of experiments describing 3 specific serotypes and a heterogeneous “group 4”, and capsular polysaccharide determined type specificity
- Today > 90 serotypes have been identified, varying in frequency and pathogenicity
- Unencapsulated forms non-pathogenic

Shift in Serotypes

- “Epidemic” serotypes 1,2,3,5
  - Disease in military recruits, hospitalized patients
- Outbreaks of pneumonia in South African gold miners – whole killed pneumococcal vaccine partially protective
- 1926-1930’s definitive evidence that polysaccharide conferred immunity – experimental vaccines with 2 or 3 serotypes able to reduce rates in outbreak
Earliest Vaccines

- 1940’s: continued identification of new serotypes
  - 6-valent vaccine licensed after WWII.
  - No widespread use, and withdrawn due to efficacy of new antimicrobial agents
- Mortality of pneumococcal pneumonia in adults was 20-30% - reduced to 5-8% with penicillin therapy
  - Vaccine research and interest in serotyping nearly abandoned

Vaccines

- 1960’s- Austrian – surveillance studies
- Noted 80% of IPD occurred with 14 serotypes
  - Licensure of 14-valent vaccine in 1977
- 1983 – replaced with 23-valent (still in use today) – covered 87% of reported bacteremia serogroup/types

Polysaccharide vaccines

- Primarily a T-independent immune response
  - Limits on duration of protection:
    - Meningococcal, typhoid, pneumococcal
- Poorly immunogenic in infants
  - Immature development of splenic marginal zone?
  - Generally not considered protective for children <2 years of age, unlike inactivated or toxoids (age 2+ months) or live-virus (age 1+ years)
  - No reduction in nasopharyngeal carriage (limited induction of mucosal immunity)

Protein Conjugate Pneumococcal Vaccines

- T-cell dependent response enacted by linking pneumococcal capsular polysaccharide to a protein carrier
  - Linked to diphtheria toxin cross-reactive material (CRM197) carrier protein
- Prevnar (Wyeth) licensed in the US
  - 2000 – FDA approval of PCV-7
  - 7 most common serotypes associated with invasive disease in children in Western Populations:
    - 4, 6B, 9V, 14, 18C, 19F, 23F
  - Also confers some immunity to related strains
  - No cross-reactive immunity between 19F and 19A
- 2010-PCV13 (Wyeth/Pfizer)
  - Addition of serotypes 1, 3, 5, 6A, 7F, 19A

Recommendation for Use

- Infants 2, 4, 6, 12-15 months
- Catch-up schedule if >6 months
Epidemiology (Post PCV-7)

Pre-vaccine – approximately 65,000 cases of IPD reported annually (25% in children < 5 years).
80% of disease in young children caused by PCV-7 serotypes.

Influence on Invasive Disease in Older Children and Adults

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Basal Rate ('95-'00)</th>
<th>Prevnar ('00-'02)</th>
<th>% Reduction (p value)</th>
<th>Prevnar ('02-'03)</th>
<th>% Reduction (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-19</td>
<td>2.60</td>
<td>2.13</td>
<td>18</td>
<td>1.57</td>
<td>39</td>
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<tr>
<td>20-39</td>
<td>5.72</td>
<td>2.41</td>
<td>58 (0.001)</td>
<td>2.72</td>
<td>52 (0.001)</td>
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<tr>
<td>40-59</td>
<td>10.2</td>
<td>8.70</td>
<td>15</td>
<td>8.60</td>
<td>16</td>
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<tr>
<td>60+</td>
<td>35.59</td>
<td>30.34</td>
<td>14 (0.03)</td>
<td>25.65</td>
<td>27 (0.0006)</td>
</tr>
<tr>
<td>All &gt; 5</td>
<td>11.37</td>
<td>9.27</td>
<td>18 (0.0001)</td>
<td>8.54</td>
<td>25 (0.0001)</td>
</tr>
</tbody>
</table>

Reduction in IPD

Impact of the Pneumococcal Conjugate Vaccine on Otitis Media

- Objective: Examine the impact of PCV on the incidence of otitis media, frequent otitis media and tympanostomy tube placement.
- Measured: Visits for Otitis, frequent visits for otitis, and tympanostomy tube procedures.

Efficacy of a Pneumococcal Conjugate Vaccine Against Acute Otitis Media

- Randomized double-blind study on efficacy vs. acute otitis media
- Reduction in all episodes - 6% (CI: -4% to 16%)
- Reduction in culture-confirmed pneumococcal episodes by 34% (CI: 21-45%)
- Reduction in vaccine serotypes by 57% (CI: 44-67%)
  - Other serotypes increased by 33%

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Pediatr Infect Dis J 2004; 23:485-489

Pediatr Infect Dis J 2003; 22:10-16

NEJM 2001; 403-409
Impact of the pneumococcal conjugate vaccine on otitis media

- % Reduction OM by Age
  - < 1 y/o - 8.2%
  - 1-2 y/o - 8.7%
  - > 2 y/o - 3.7%

- % Reduction in tympanostomy tube placement
  - ITT - 23.2%
  - Protocol - 24.2%

Effect on recurrent acute otitis media: a randomized study

- Randomized patients 1-7 years of age who had 2 episodes of OM in the previous year
- Children received 7-valent or 23-valent pneumococcal vaccine
- No reduction of AOM episodes by vaccination

Changes in Frequency and Pathogens Causing Acute Otitis Media in 1995-2003

- 2001-2003 - Changes noted in the etiologic agents causing acute otitis media
  - Attributed to increase Pneumococcal conjugate vaccine and high-dose amoxicillin
  - 24% decline of persistent AOM and AOM treatment failures
  - Statistically significant increase in H. flu (57%) and decrease in pneumococcus (31%) isolates
  - Decrease in penicillin resistant pneumococcus

Vaccination with the Heptavalent Pneumococcal Conjugate Significantly Alters the Microbiology of Acute Otitis Media

- Isolates from severe or refractory AOM were compared pre- and post- Prevnar
  - Pneumococcus decreased from 48% to 31%
  - H. flu increased from 41% to 56%
  - Decrease in Penicillin-Resistant Pneumococcus
  - Gram (-) accounted for 2/3 and B-lactamase producers 1/2 of all isolates post-vaccination

Epidemiology of Acute Otitis Media Caused by Streptococcus pneumoniae Before and After Licensure of the 7-Valent Pneumococcal Protein Conjugate Vaccine

- Percent nonvaccine serogroup
  - Two doses of Prevnar - 46.7%
  - No Prevnar - 20.8%
- Proposed mechanism - Capsular switching

Acute otitis media due to penicillin-nonsusceptible Streptococcus pneumoniae before and after

- Determined by myringotomy or PET placement
- Non-Prevnar serotypes increased 12% -32%
- Vaccine-related serotypes increased depending on the number of doses
  - 10% one dose, 19% three doses
- Penicillin-resistance decreased from 73% to 53%
Otitis Media Summary

- Mild reduction in AOM
- Decreased PE tube placement
- More + culture chronic middle ear effusions
- Changes in the microbiology
  - More *H. influenzae*
- Less antibiotic resistance
- Less vaccine serotype specificity

19A increase

![Graph showing the percentage of cases per 100,000 population over years.](image)

Serotype Replacement

![Graph showing serotype replacement in children and adults.](image)

Global Epidemiology: PCV-7 vs PCV-13 serotypes

![Graph showing the percentage of serotypes in different regions.](image)
Global Burden of Disease


Antibiotic Resistance

Drug-resistant *Streptococcus pneumoniae*

- Early resistance – optochin, sulfonamides
- Laboratory isolates with reduced susceptibility to penicillin – 1940’s
- Mid 1960’s – sporadic reports of clinical isolates
- 1970’s-1990’s steady increase in penicillin, then cephalosporin-resistance
  - 1990’s – rates in US increased
  - Risk included daycare, antibiotic use
- Multiply drug-resistant (>3 classes)

Define Resistance

- Original Clinical Laboratory Standards Institute (CLSI) breakpoints
  - Minimal inhibitory concentration (MIC)
  - <=0.06 sensitive, 0.12-1 intermediate, >1 resistant
- 2008: new breakpoints:
  - <=2 sensitive, 4 intermediate, >=8 resistant
  - Old breakpoints apply treatment with oral penicillin therapy
  - Meningitis: <=0.06 sensitive, >0.12 resistant
- Similar revision for 3rd gen cephalosporins occurred in 2003

Reclassification of Nonmeningeal Isolates

MMWR. February 27, 2004 / 53(07);152-154
**Time above MIC**

- 2001-2003 Uruguay
- 33 children with CAP
  - 8 patients with S pneumoniae isolated from blood or pleural fluid (all with penicillin MIC<1) – used MIC of 4 as theoretical pathogen
  - Treated with IV ampicillin or penicillin q4h
  - Serum levels 30min, 3 hrs after dose
  - Pleural fluid levels when available
- Even when serum levels were low/undetectable, calculated time above MIC was >40%, and pleural fluid levels exceeded MIC in almost all.

**Pending IDSA Guidelines**

- Management of community-acquired pneumonia in children
- Recommendations – amoxicillin (not high dose?) or ampicillin IV for inpatients
  - Caveat – incompletely immunized children or areas with “high” levels of penicillin-resistance should receive alternate therapy (3rd generation cephalosporin)

**Percent of Nonsusceptible IPD Isolates**

**Case #2 - Ella**

- November 2010
- 3 y/o F with multiple medical problems
- SOD, hypopituitarism, FTT, single kidney, unrepaired ASD, developmental delay, history of cleft lip/palate repair
- Facial dysmorphism, no specific syndrome
- Complained of fever, headache, nausea/vomiting for one week PTA
- Abdominal pain, GT feed intolerance, watery stools, decreased activity, decreased UOP
- Seen in the ER – azithromycin for “possible” pneumonia
  - ? opacities—c/w viral
- Acute abdominal series in the ER, unremarkable
- Hospitalized for IV hydration/observation

**Reduction in DRSP – 1996-2004**

- Reduction in DRSP – 1996-2004
- Children < 2 years

**Percent of Nonsusceptible IPD Isolates**

Case #2

- 5.7 WBC 13.7/40.2<239
- 57 seg, 12 bands 11 lymphocytes 2 monos
- Blood culture obtained at admission
- GPCs noted at 15 hours
  - Ceftriaxone at 100mg/kg/day
- Rapid decompensation – hypotension, transferred to PICU
- LP obtained
  - CSF – glucose 46 protein 63
  - “Hazy” - WBC 84 (84 PMN 16 mono)

Case #2

- Blood - *S pneumoniae*
  - Penicillin resistant
  - Ceftriaxone >4 (R) vancomycin 0.3 (S) meropenem
    0.75 (I) cefepime 4 (R)
- Subsequent blood culture negative
- CSF +
  - Vanc 0.38 (S) clindamycin (R) Ceftriaxone MIC=3 (R)

Case #2

- Obtunded, intubated
- Subsequent development of hydrocephalus
- Ventriculostomy placement
- Unable to wean from vent, eventual placement of tracheostomy
- Eventual withdrawal of care

Summary

- Occult bacteremia and IPD has dramatically decreased since the introduction of PCV-7
- Serotype replacement
  - 19A
- Drug-resistant disease decreased, but stable amount of drug resistance
- Introduction of PCV-13 should reduce
  - Future shifts in serotypes unknown
- Resurgence of IPD?