What’s Hot in Pediatric Infectious Diseases?

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Objectives

• To highlight a selection of the most important and interesting literature in pediatric infectious diseases and vaccination from the last year

• To provide a global perspective on recent developments
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• To highlight a selection of the most important and interesting literature in pediatric infectious diseases and vaccination from the last year

• To provide a global perspective on recent developments

• (To provide a Canadian perspective on recent developments)
What We Don’t See

Margaret Kendrick Hostetter, M.D.

Child Mortality/1000

~50
~100
~150

Lancet 2007; 370: 1040–54

Broad SOCIAL Intervention (e.g. Sanitation)

Global APPLICATION (e.g. HIV-ART in MTCT)

KNOWLEDGE leads to Prophylaxis (e.g. Smallpox Eradication)
Child Death
< 5 yo

- Neonatal Deaths, 41%
- Preterm birth complications, 12%
- Birth asphyxia, 9%
- Sepsis, 6%
- Other, 5%
- Congenital abnormalities, 3%
- Tetanus, 1%
- Measles, 1%
- Injury, 3%
- Malaria, 8%
- AIDS, 2%
- Pertussis, 2%
- Other infections, 9%
- Other noncommunicable diseases, 4%*
- Pneumonia, 14%
61% of < 5 y.o. deaths due to infections (globally)
Land
Death < 5 yo due to infection
Child Death < 5 yo

- Pneumonia: 14%
- Preterm birth complications: 12%
- Neonatal Deaths: 41%
- Birth asphyxia: 9%
- Other noncommunicable diseases: 4%
- Other infections: 9%
- Meningitis: 2%
- Pertussis: 2%
- AIDS: 2%
- Malaria: 8%
- Injury: 3%
- Measles: 1%
- Diarrhea: 14%
- Other: 5%
- Congenital abnormalities: 3%
- Tetanus: 1%

Sepsis: 6%
Early-onset neonatal sepsis: It is not only group B streptococcus anymore.

Michael Sgro MD FRCPC¹, Mark H Yudin MD MSc FRCSC², Shoo Lee MD FRCPC PhD³, Koravangattu Sankaran MD FRCPC⁴, Dat Tran MD FRCPC MSc⁵, Douglas Campbell MSc MD FRCPC⁶

Paediatr Child Health Vol 16 No 5 May 2011
Changing Face of Neonatal Sepsis

• Predominant pathogen was GAS in 1930-1940 (pre-antibiotic era)
• The “Coliforms” emerged 1940-1960 (E. coli; P. aeruginosa in up to 20%)
• GBS starts rising in 1960s

Resurgence of (now Amp$^R$) E. coli: 1990 onward

### Table 1: Distribution of Organisms Causing EOS in All Infants

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram-positive</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GBS</td>
<td>56</td>
<td>39</td>
<td>44</td>
<td>139</td>
<td></td>
<td>68.1</td>
</tr>
<tr>
<td>Enterococci</td>
<td>3</td>
<td>4</td>
<td>6</td>
<td>13</td>
<td></td>
<td>41.5</td>
</tr>
<tr>
<td>Other streptococci</td>
<td>13</td>
<td>3</td>
<td>23</td>
<td>39</td>
<td></td>
<td>11.6</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>2</td>
<td>5</td>
<td>6</td>
<td>13</td>
<td></td>
<td>3.8</td>
</tr>
<tr>
<td>Coagulase-negative staphylococci</td>
<td>2</td>
<td>2</td>
<td>10</td>
<td>14</td>
<td></td>
<td>4.2</td>
</tr>
<tr>
<td>Listeria</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td></td>
<td>0.6</td>
</tr>
<tr>
<td>Other Gram-positive species</td>
<td>1</td>
<td>0</td>
<td>7</td>
<td>8</td>
<td></td>
<td>2.4</td>
</tr>
<tr>
<td>Ampicillin-resistant, Gram-positive species</td>
<td>5</td>
<td>7</td>
<td>26</td>
<td>38</td>
<td></td>
<td>11.6</td>
</tr>
<tr>
<td><strong>Gram-negative</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>15</td>
<td>16</td>
<td>40</td>
<td>71</td>
<td></td>
<td>20.2</td>
</tr>
<tr>
<td><em>Bacteroides spp</em></td>
<td>1</td>
<td>4</td>
<td>10</td>
<td>15</td>
<td></td>
<td>4.5</td>
</tr>
<tr>
<td><em>Klebsiella spp</em></td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td></td>
<td>1.3</td>
</tr>
<tr>
<td><em>Haemophilus influenza</em></td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td></td>
<td>1.9</td>
</tr>
<tr>
<td>Other Gram-negative species</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td>8</td>
<td></td>
<td>2.6</td>
</tr>
<tr>
<td>Ampicillin-resistant, Gram-negative species</td>
<td>12</td>
<td>12</td>
<td>38</td>
<td>62</td>
<td></td>
<td>18.5</td>
</tr>
<tr>
<td><strong>Fungi</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total ampicillin-resistant species</td>
<td>17</td>
<td>20</td>
<td>66</td>
<td>103</td>
<td></td>
<td>30.7</td>
</tr>
<tr>
<td>Total</td>
<td>96</td>
<td>78</td>
<td>161</td>
<td>335</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>


Slide from Dr. A Wright, UBC
Early-onset neonatal sepsis: rate and organism pattern between 2003 and 2008

M Sagh1,2,5, PS Shah3,4,5, D Campbell1,2, A Tenuta4, S Shivamana4 and SK Lee3,4,5,
The Canadian Neonatal Network

What is not clear in 2012

• Whether the increase in Amp-resistance is due to:
  A. Antepartum or intrapartum antibiotic prophylaxis?
  B. Community changes in resistance?

• Global Strategy to combat neonatal sepsis

Pathogens in neonatal sepsis in the developing world:

- Not GBS!
- *Gram-negatives* predominate

Summary

1. Microbes causing neonatal sepsis are changing. Consider adapting empiric therapy.
Child Death < 5 yo

Diarrhea
Diarrhea: Rotavirus rules!

Globally, rotaviruses (RVs)
- cause of ~40% of all childhood gastroenteritis
- 125 million cases of acute gastroenteritis/yr
- ~ half a million deaths each year

The incidence of RV gastroenteritis is similar both in industrialized and in developing countries.

The outcome is not!
Nearly all children will be infected by RVs before the age of 3-5 years:
- highest incidence rate between 6-24 months of age
- greatest risk for developing severe disease by RV occurs under 12 months of age.

The Journal of Maternal-Fetal and Neonatal Medicine, 2011; 24(S(2)): 48-51
In Canada:
- 36% of children with rotavirus will see a physician
- 15% will be assessed in an emergency room
- 7% will be hospitalized
- societal cost ranges from $8.9 to $18.4 million

Diarrhea: Rotavirus rules!

- Journal of Infection Prevention 2011;
Diarrhea: Rotavirus vaccine rules!

Vaccine efficacy against severe rotavirus gastroenteritis ranges from 85% to 96% during the first rotavirus season and 79% to 86% during the second season.
Diarrhea: Rotavirus vaccine rules!

Efficacy of pentavalent rotavirus vaccine against severe rotavirus gastroenteritis in infants in developing countries in Asia: a randomised, double-blind, placebo-controlled trial


Lancet 2010; 376: 615–23
In 1999 the rhesus tetravalent rotavirus vaccine (RRV, Rotashield, Wyeth) was withdrawn from the market due to a significantly increased risk of intussusception following vaccination.

The largest increased risk (30-fold) of intussusception was observed during the 3 to 7 days following the first dose of the vaccine.

Since then, 2 vaccines to prevent rotavirus infection have been licensed for use in the United States:
- a pentavalent rotavirus vaccine (RV5, RotaTeq, Merck) in 2006
- a monovalent rotavirus vaccine (RV1, Rotarix, GlaxoSmithKline Biologicals) in 2008.
Diarrhea: Rotavirus vaccine rules?

A post-licensure safety study in the United States after 2 years of surveillance (~200,000 doses) did not find evidence for an increased risk of intussusception.

Diarrhea: Rotavirus vaccine rules?

However, 2 international post-licensure evaluations have observed an increased risk of intussusception in the first week after administration of the first dose of rotavirus vaccines:

- An Australian study, found a statistically significant increased risk of nearly 5-fold for intussusception in the week following the first dose of RV5. 
  Vaccine. 2011;29(16):3061-3066.

- A study in Mexico and Brazil, found an approximate 5-fold increased risk of intussusception in the first week following the first dose of RV1 in Mexico but not in Brazil.
Diarrhea: Rotavirus vaccine rules?

Risk of Intussusception Following Administration of a Pentavalent Rotavirus Vaccine in US Infants

- 786,725 total RV5 doses, which included 309,844 first doses
- No statistically significant increased risk of intussusception with in either the 1- to 7-day or 1- to 30-day risk window.
Diarrhea: Rotavirus vaccine rules?

Risk of Intussusception Following Administration of a Pentavalent Rotavirus Vaccine in US Infants

“The benefits of rotavirus vaccination in US infants outweighs the potential risks, even if a risk similar to that seen in Mexico or Australia would exist in the United States.”
Diarrhea: Rotavirus **vaccine** rules!!!

“Rotavirus vaccines are now recommended, and provided free (as of January 1st, 2012), to infants at the routine 2 month and 4 month immunization appointments”.

- Ontario implemented RV1 in August 2011
- QC in November 2011

http://immunizebc.ca/diseases-vaccinations/rotavirus
Diarrhea (all causes)
Global Rotavirus Deaths vs. Vaccination Coverage

Rotavirus deaths in children under 5 (deaths per 100,000):
- > 100
- 20 to 100
- < 20

www.gavi.org
Summary

1. Microbes causing neonatal sepsis are changing. Consider adapting empiric therapy.

2. Rotavirus infant vaccination is safe and effective. Give 2 doses before 8 months of age.
Child Death < 5 yo

- Pneumonia: 41%
- Neonatal deaths: 41%
- Other noncommunicable diseases: 4%*
- Other infections: 9%
- Meningitis: 2%
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- Diarrhea: 14%
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- Preterm birth complications: 12%
- Birth asphyxia: 9%

*Note: This data is from the reference [N Engl J Med 2012;366:1328-34.](#)
PNEUMONIA
THE FORGOTTEN KILLER OF CHILDREN
# Pathogen-Specific Causes of Severe Pneumonia Cases

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Distribution of severe pneumonia cases by cause</th>
<th>Discussion</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptococcus pneumoniae</em> (bacterium)</td>
<td>Leading cause</td>
<td><em>S. pneumoniae</em> is the leading pathogen in almost all studies from around the world. Recent vaccine trial data indicate that in Africa it may be responsible for over 50% of severe pneumonia cases, and probably a higher proportion of fatal cases. This proportion may vary in different parts of the world.</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em> (bacterium)</td>
<td>Major cause</td>
<td>Most disease is caused by type b (Hb). Vaccine studies from Bangladesh, Chile and the Gambia suggest that Hb causes around 20% of severe pneumonia cases, although the proportion may vary in different parts of the world.</td>
</tr>
<tr>
<td>Other important pathogens</td>
<td>Less common</td>
<td>These pathogens include important viruses such as respiratory syncytial virus (RSV) and influenza; other bacteria, such as <em>Staphylococcus aureus</em> and <em>Klebsiella pneumoniae</em>, and the fungus <em>Pneumocystis jiroveci</em> (PCP), which is particularly important in young children with AIDS (see Box 3, page 8).</td>
</tr>
</tbody>
</table>
Figure 11. Rates of Invasive Pneumococcal Infection per 100,000 among Children ≤ 23 Months of Age According to Year and Serotype*

PCV7
(4, 6B, 9V, 14, 18C, 19F and 23F)

• PCV7 infant immunization has led to near eradication of vaccine-serotype invasive pneumococcal disease (IPD) in vaccinated Canadian children as well as in older children and adults, through herd effect.
Strain Replacement?

The graph shows the proportion of PID (pneumococcal disease) caused by various serotypes over different time periods:

- **1997-2001 (n=278)**: The proportion of PID caused by 7vPCV serotypes is high, while non-7vPCV serotypes and 19A serotype are present but at lower proportions.
- **2002-2004 (n=145)**: The proportion of PID caused by 7vPCV serotypes is still high, with a notable rise in non-7vPCV serotypes.
- **2005-2007 (n=59)**: A significant increase in non-7vPCV serotypes is observed, along with a notable proportion of 19A serotype.

Paediatric Respiratory Reviews; in press 2012
Serotype replacement in disease after pneumococcal vaccination

Daniel M Weinberger, Richard Malley, Marc Lipsitch

• Among asymptomatic carriers, the prevalence of non-vaccine types (NVTs) has increased substantially post PCV7

• In many populations, pneumococcal disease caused by NVT has increased

• In most cases this increase has been less than the increase in NVT carriage (except in Alaska)
Strain Replacement?

Niche and Neutral Effects of Acquired Immunity Permit Coexistence of Pneumococcal Serotypes

Sarah Cobey¹* and Marc Lipsitch¹,²

16 MARCH 2012    VOL 335    SCIENCE

• complex interactions of host and pathogen lead to changes in patterns of colonization
• diversity of a pathogen (i.e. strain replacement) can be explained by the interaction of acquired (capsular) specific and nonspecific immunity to pneumococcus

= attention to the details of immune responses needs to be paid to gauge the impact of vaccines
Strain Diversity

North America

Europe

Middle East

Asia Pacific

Latin America

Africa

Paediatric Respiratory Reviews; in press 2012
PCV13
(PCV7 & 1, 3, 5, 6A, 7F and 19A)

• The serotypes in PCV13 are the most common serotypes causing IPD globally, accounting for 75% of IPD in children <5 years of age worldwide.

• PCV13 would prevent 64% of the remaining cases of invasive pneumococcal disease (IPD) in children in, mostly attributed to serotype 19A (42%), including serotype 5, which has recently emerged in Western Canada.

• Pneumococcal empyema would also be better covered, given that only 48% of isolates in Canada were PCV7 serotypes, whereas the remainder were contained with PCV13.
Safety and Immunogenicity of a 13-valent Pneumococcal Conjugate Vaccine in Healthy Infants and Toddlers Given With Routine Pediatric Vaccinations in Canada
• Double-blind RCT
• Children at 2, 4, 6, and 12 months received PCV13 (n= 300) or PCV7 (n= 303) with routine immunizations
• 1 month later responses to Hib, pertussis, menC, and specific pneumococcal serotypes were measured
• Safety and tolerability were assessed daily for 4 days by parents
Vaccine Reports

• No statistically significant differences between the groups in responses to Hib, pertussis, or menC after primary or booster vaccinations.

• >95% of subjects in the PCV13 group had antibody titers correlating with protection (>0.35 mcg/mL) to each pneumococcal serotype 1 month after the third dose, except with serotypes 23F (90%), 3 (80%), and 5 (87%).

• After the fourth dose, 98% to 100% of subjects achieved protective serotype-specific antibody concentrations except for serotype 3 (85%).

• Safety and tolerability did not differ between groups.
Pneumococcal Vaccination

“The Pneumococcal Conjugate vaccine (PCV 13) protects against infection from 13 types of pneumococcal bacteria and is free for children as part of their routine immunizations”.

Similar program for PCV13 in all provinces.
Pneumonia (all causes)
In 2011, - Kenya introduced the PCV10
- Sierra Leone introduced PCV13
Summary

1. Microbes causing neonatal sepsis are changing. Consider adapting empiric therapy.

2. Rotavirus infant vaccination is safe and effective. Give 2 doses before 8 months of age.

3. PCV7 is effective. PCV13 is safe & immunogenic.
Child Death
< 5 yo

- Neonatal deaths, 41%
- Pneumonia, 14%
- Other noncommunicable diseases, 4%*
- Other infections, 9%
- Meningitis, 2%
- Pertussis, 2%
- AIDS, 2%
- Malaria, 8%
- Injury, 3%
- Measles, 1%
- Diarrhea, 14%
- Preterm birth complications, 12%
- Birth asphyxia, 9%
- Sepsis, 6%
- Other congenital abnormalities, 5%
- Tetanus, 3%

61% of deaths < 5 yo due to infection
Helplessness Inquiry Responsibility

Broad SOCIAL Intervention

KNOWLEDGE leads to Prophylaxis

Global APPLICATION

Child Death < 5 yo

- Pneumonia: 41%
- Neonatal Deaths:
- Preterm birth complications: 12%
- Birth asphyxia: 9%
- Sepsis: 6%
- Other, congenital abnormalities: 5%
- Other infections: 9%
- AIDS: 2%
- Pertussis: 2%
- Meningitis: 2%
- Malaria: 8%
- Injury: 3%
- Measles: 1%
- Diarrhea: 14%
- Other, noncommunicable diseases: 4%
Pneumonia (all causes)
2007-2009 Mean Invasive Pneumococcal Rates by Age Gender and Status
(FN = First Nations)

Marcus Lem, MD, MHSc, FRCPC
Health Protection Directorate, First Nations and Inuit Health, Health Canada - BC Region
• Disproportionate burden of respiratory tract infection among First Nations living on-reserve and Inuit children.

(No data for First Nations without status, Métis and urban Aboriginal children.)
Child Death < 5 yo

- Neonatal Deaths, 41%
- Pneumonia, 14%
- Preterm birth complications, 12%
- Birth asphyxia, 9%
- Sepsis, 6%
- Other, 5%
- Congenital abnormalities, 1%
- Tetanus, 1%
- Measles, 1%
- Injury, 3%
- Malaria, 8%
- Pertussis, 2%
- AIDS, 2%
- Other noncommunicable diseases, 4%*
- Diarrhea

*Indicates a high percentage compared to other causes.
Diarrhea (all causes)
Oral rehydration therapy and early refeeding in the management of childhood gastroenteritis

“Prolonged diarrhea and malnutrition are primary causes of morbidity and mortality in Canadian native populations.” (no reference)

• No data on gastroenteritis in the report.
Child Death < 5 yo

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- Preterm birth complications: 12%
- Birth asphyxia: 9%
- Other noncommunicable diseases: 4%
- Other infections: 9%
- Meningitis: 2%
- Pertussis: 2%
- AIDS: 2%
- Malaria: 8%
- Injury: 3%
- Measles: 1%
- Diarrhea: 14%
- Tetanus: 1%
- Congenital abnormalities: 5%
- Sepsis: 6%
Newborn death < 1 week of age (all causes)
• Neonatal mortality among First Nations is nearly twice the rate in the general Canadian population
• Neonatal mortality among Inuit is four times higher than the general Canadian population
• No data (yet) on specific causes of neonatal sepsis in First Nations or Inuit newborns.
“But gradually, the attitude of helplessness changed, first to inquiry and then to responsibility.”
Thank You!

Questions?

tkollm@mac.com