# Changing spectrum of invasive bacterial disease

PIGS course Basel  
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## Overhelming sepsis in previously healthy children

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Girl 3 years of age previously healthy</th>
<th>Boy 2 years of age previously healthy</th>
<th>Boy 6 months of age previously healthy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>vomiting, diarrhea</td>
<td>rhinitis, fever</td>
<td>cough, fever</td>
</tr>
<tr>
<td>Course</td>
<td>9h septical shock (at home)</td>
<td>12h respiratory distress cyanosis (at home)</td>
<td>24h thorax rx: neg. 44h respiratory distress (at home)</td>
</tr>
<tr>
<td>Lab</td>
<td>9.5h resuscitation</td>
<td>14h intubation</td>
<td>51h shock</td>
</tr>
<tr>
<td></td>
<td>10h exitus</td>
<td>18h shock: reanification</td>
<td>52h pleuropneumonia</td>
</tr>
<tr>
<td>Microbio (p.mortem)</td>
<td>S. pneumoniae in blood, lung, spleen</td>
<td>S. pneumoniae in lung</td>
<td>S. pneumoniae in blood, lung</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Pneumococcal sepsis Waterhouse Friederichson</td>
<td>Pneumococcal sepsis circulatory collapse</td>
<td>Pneumococcal sepsis circulatory collapse</td>
</tr>
<tr>
<td></td>
<td>24h thorax rx: neg.</td>
<td>53h exitus</td>
<td></td>
</tr>
</tbody>
</table>
Invasive bacterial infections in children

- High incidence in the first 2(-5) years of life

- Pneumonia
- Sepsis
- Meningitis
- Arthritis

encapsulated bacteria:
*Streptococcus pneumoniae*
*Neisseria meningitidis*
*Haemophilus influenzae* typ b

Pathogenesis: Pneumococcal infection

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Figure 1. Pathogenic routes for *S. pneumoniae* infection. Redrawn from reference 2. Organs infected through the airborne and hematogenic routes are depicted in blue and red, respectively.
Bacterial Meningitis: Epidemiology

After introduction of conjugate vaccines
- *Haemophilus influenzae* type b (1990)
- Pneumococci (2000 PCV7, PCV13 2010)
- (GBS screening in pregnancy?)

- Reduction in incidence of meningitis at all ages except age < 2 months
- Age: median <5 years → 42 years

- Incidence (USA 2006/2007)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Incidence per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2 months</td>
<td>80</td>
</tr>
<tr>
<td>2-11 months</td>
<td>8.5</td>
</tr>
<tr>
<td>2-23 months</td>
<td>6.9</td>
</tr>
<tr>
<td>2-10 years</td>
<td>0.56</td>
</tr>
<tr>
<td>11-17 years</td>
<td>0.43</td>
</tr>
</tbody>
</table>

Trend in the incidence of IPD in the US: comparison of prelicensure years to postlicensure years

Serotype replacement in pneumococcal meningitis

US (1998-2005): overall reduction of cases - 30.1%

England and Wales (2004 - 2009): overall, no significant reduction of cases


Ampofo K et al. Pediatr Infect Dis J 2012;31: 228
Pneumonia with effusion

Predominantly pneumococcal infection:
Serotypes 1, 3, 7F, 19A
and after PCV13?

- Antimicrobial treatment targeted against S. pneumoniae: Amoxicillin
- Conservative management
- Minimize interventions
- Excellent long term follow up

Invasive Pneumococcal Disease according to age in Switzerland 2001-2012

Incidence per 100000 population

Age group: <2, 2-4, >4, >64, total
Incidence: <2, 2-4, >4, >64, total

< 5 y: 8
> 64 y: 35
Total: 11


Swiss Pediatric Sepsis Study
Recruitment: in 2 years

All 8 pediatric A clinics in CH
Children < 18 years of age with
- positive blood culture
- SIRS / sepsis

Start November September 2011

Recruitment: 2 years, mean monthly frequency: 20

CRF Forms | Total
---|---
Eligibility | 510
Infectious data assessment | 495
Outcome | 435
Blood sampling data | 476
Swiss Pediatric Sepsis Study
Pathogens and Severity

CoNS
S. aureus
S. pneumoniae
Group A streptococcus
• 25% required PICU/NICU admission

S. pneumoniae
42 (12%) (3 died)
• 19% mechanical ventilation

Group A streptococcus
30 (9%) (2 died)

Enterococcus
7 (2%) (2 died)

Enterobacter cloacaee
31 (9%)

E. coli
52 (14%) (4 died)

Klebsiella pneumoniae
14 (4%) (1 died)

P. aeruginosa
10 (3%)

N. meningitidis
7 (2%)

H. influenzae
7 (2%)

other gram-negative
23 (6%) (1 died)

other gram-positive
45 (12%) (1 died)

fungi
8 (2%)

Surviving sepsis campaign:
Antimicrobial therapy

Each hour of delay in administering effective antibiotics increases mortality
Goal: administration < 1 hour.

Start empiric treatment with one or more antimicrobials
- effective against the likely pathogens
- reaching adequate concentration in the tissue to be the source of sepsis

Reassess antimicrobial treatment daily
- combination therapy < 3-5 days, duration of treatment 7-10 days
- non-infectious SIRS: stop antimicrobials

Pediatric Sepsis
Sepsis mortality is associated with:
- multiple comorbid illnesses
- multiple organ dysfunction
- greater severity of illness

begin high flow O2
give iv fluid
administer antibiotics <1h
Swiss Pediatric Sepsis Study
Risk groups / acquisition

- Hospitalized prior to sepsis (nosocomial sepsis):
- Neonates
- NICU/PICU prior to sepsis
- Chronic disease
- Immunosuppression
- Surgery
- Primary ID

- Community acquired „no risk“? → GWAS, EUCLIDS…
- Risk: „nosocomial“ and „health-care-associated“

 Acquisition of infection

Hospital admission

- Community-acquired (CAI)

- Health-care-associated (HCAI)

- Nosocomial (NI)
The changing burden of pediatric bloodstream infections in Calgary 2000-2006

BSI incidence: 53 per 100000, highest in neonates, Decreasing incidence of community acquired disease over time

<table>
<thead>
<tr>
<th>Isolate</th>
<th>Nosocomial</th>
<th>Healthcare</th>
<th>Community</th>
<th>Total</th>
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<tbody>
<tr>
<td>Viridans streptococci</td>
<td>36</td>
<td>76</td>
<td>112</td>
<td>224</td>
</tr>
<tr>
<td>group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptococcus pneumonia</td>
<td>5</td>
<td>33</td>
<td>121</td>
<td>159</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>32</td>
<td>21</td>
<td>67</td>
<td>120</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>25</td>
<td>48</td>
<td>46</td>
<td>119</td>
</tr>
<tr>
<td>Coagulase negative</td>
<td>43</td>
<td>5</td>
<td>4</td>
<td>52</td>
</tr>
<tr>
<td>staphylococci</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterococcus species</td>
<td>20</td>
<td>7</td>
<td>4</td>
<td>31</td>
</tr>
<tr>
<td>Group A Streptococcus</td>
<td>4</td>
<td>6</td>
<td>17</td>
<td>27</td>
</tr>
<tr>
<td>Group B Streptococcus</td>
<td>16</td>
<td>9</td>
<td>1</td>
<td>26</td>
</tr>
<tr>
<td>Klebsiella spp</td>
<td>12</td>
<td>10</td>
<td>4</td>
<td>26</td>
</tr>
<tr>
<td>Neisseria spp</td>
<td>5</td>
<td>4</td>
<td>15</td>
<td>24</td>
</tr>
<tr>
<td>Salmonella spp</td>
<td>2</td>
<td>1</td>
<td>20</td>
<td>23</td>
</tr>
<tr>
<td>Enterobacter spp</td>
<td>16</td>
<td>2</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>Candida spp</td>
<td>20</td>
<td>1</td>
<td>1</td>
<td>22</td>
</tr>
<tr>
<td><strong>..</strong></td>
<td></td>
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</tr>
</tbody>
</table>

Laupland KB. et al PIDJ 2009; 28:114

Febrile neutropenia in children treated for cancer

Immediate empirical treatment to prevent invasive infection

Increasing time to antibiotic administration is associated with poor outcomes of FN in children

Shift from Gram- to Gram + infections in the 1980 and 1990

High prevalence of streptococcal infections

CoNS (catheter associated infections)

Antibiotic-resistant Gram negative bacteria

Possible infection

Probable infection

Bacteremia

Sepsis

Risk stratification

De-escalation

Antibiotic stewardship

Fletcher M et al Pediatr Blood Cancer 2013;60:1299

C.Berger, Kinderspital Zürich 2013
Gram-negative bacteremia* in paediatric oncologic patients

Antibiotic resistant (= resistant to ticarcillin-clav + gentamicin)
Gram-negative bacteremia is associated with increased adverse outcomes
- after high-intensity chemotherapy,
- in patients that have been in hospital beyond 48 hours
- in patients with previous AR GN infection or colonization

Incidence of neonatal invasive group B streptococcal (GBS) disease (US)

- Intrapartum prophylaxis reduced GBS early onset sepsis
- the burden of GBS and E. coli disease continues.
Late onset neonatal sepsis nosocomial! can it be prevented?

- SOPs: standardized procedures
  - Accurate diagnosis (CONS)
  - Surveillance
- Hand hygiene!
  - Remove catheters as soon as possible
  - Early enteral feeding
- Remove catheters as soon as possible
- Early enteral feeding
- Restricted vancomycin use
- Careful with H2 blockers
- Fluconazole prophylaxis cave!

Mean age: 2-3 weeks

↑ Sepsis incidence
  - Birth weight ↓
  - CVC days ↑
  - Ventilation days ↑
  - Parenteral hyperalimentation

Antimicrobial resistance

Mortality:
Gram-pos << Gram-neg, fungi

Antimicrobial resistance

Spread of extensively resistant VIM-2-positive ST235 Pseudomonas aeruginosa in Belarus, Kazakhstan, and Russia: a longitudinal epidemiological and clinical study
Mikhail V. Eshchenko, Elena N. Shibanova, Olisensa V. Shevchenko, Jrison W. D. Soares, Dmitriy V. Topolskii, Irina S. Aitov, Marina V. Sukhovolova, Roman A. Pavlovskov, Roman S. Kazakov, Mark A. Telemann, Timothy R. Walsh

Extensively-drug-resistant i.e. metallo-β-lactamase (MBL) positive Pseudomonas aeruginosa were resistant to all antibiotics except colistin

Increases in the use of colistin will probably result in further spread of ST235 P aeruginosa resistant to all drugs

Lancet Infect Dis 2013; 13: 867-76

C. Berger, Kinderspital Zürich 2013
The changing spectrum of invasive bacterial infection

The introduction of conjugate vaccines has reduced the burden and changed the spectrum of community-acquired bacteremia.

Up to half of pediatric sepsis is health-care and hospital acquired.

1. Antibiotic stewardship and infection prevention / hygiene bundles are needed to limit nosocomial infections

2. Children with severe comorbidity account for a larger % of invasive infections. Recognizing those as „health-care-associated infections“ may allow to optimize their needs