Key Aspects of Epidemiology, Prevention, Diagnosis and Clinical Management of Neonatal and Pediatric Sepsis

WHO Sepsis Technical Expert Meeting
16-17 January 2018

Professor Mike Sharland
Tuesday 16th January

St George’s
University of London
Epidemiology - factors

- **Community** setting – ANISA/SATT Afrinest
- Classical pathogens – CAI (E coli, MSSA, GBS) Lower rates of MDR
- **Hospital** Setting
- M/XDR Gram Negs/MSSA
- Underlying disease (prem/HIV/Malnutrition)
- HAI– ESBL/CRO
An estimated 2.9 millions deaths every year (44% of all deaths in children younger than 5 years) worldwide – one quarter of these are due to neonatal sepsis.

Maternal and child mortality has halved worldwide in the past two decades but the number of neonatal deaths has remained unacceptably high – due to infections, prematurity and asphyxia.

NeoAMR BSI Sepsis in 2016

**Gram Negative**
- Blood cultures with growth of Escherichia coli
- Blood cultures with growth of Klebsiella spp.
- Blood cultures with growth of Enterobacter spp.
- Blood cultures with growth of Acinetobacter spp.
- Blood cultures with growth of Pseudomonas spp.

**Gram Positive**
- Blood cultures with growth of Staphylococcus aureus
- How many of these isolates were tested for methicillin resistance (MRSA)?
- Blood cultures with growth of Enterococcus spp.
- Blood cultures with growth of Group B streptococcus
- Blood cultures with growth of Group A streptococcus
1159 infections with pathogen specified

527 Gram positive
632 Gram negative

GARPEC BSI 2016
GARPEC BSI 2016 Neonatal/Pediatric

- Escherichia coli
- Klebsiella spp.
- Staphylococcus aureus
- Streptococcus agalactiae
- Enterococcus faecalis
- Serratia spp.
- Candida spp.
- Enterobacter spp.
- Acinetobacter baumanii
- Enterococcus faecium
- Pseudomonas aeruginosa
- Streptococcus pyogenes
- Enterococcus spp.
- Burkholderia cepacia
- Streptococcus pneumoniae
- Campylobacter
- Haemophilus influenzae
- Proteus spp.
- Salmonella (NTS & typ)

Percentage by age category

[Bar chart showing the percentage of each bacterial species by age category]
Diagnosis

• Clinical signs – validation/prognosis
• Underlying Disease/ High Risk Setting
• Laboratory
• PPV NPV
• Appropriate specimens; BC rate..
• Microbiology
• Empiric prescribing algorithms
Pathogens distribution for studies conducted in Africa and reported after 1995 in children > 2 months (4-16)
Pathogens distribution for studies conducted in Asia and reported after 1995 in children >2months (16-29)
Data obtained from 17,273 children

- HAI prevalence of 4.2% (95%CI 3.7-4.8%)
- Highest prevalence in larger hospitals and in PICU/NICU

Independent risk factors for HAI:
- medical devices
- young age (particularly neonates)
- prolonged length of stay

Substantially different pattern of HAIs in children compared to adults - *sepsis*
Prevention

- Exclusive breast feeding, cord care
- Vaccines - Pneumococcal 15/18, Hib, Men B and C (extending serotypes); Salmonella/Shigella (mortality typhoid)
- GBS (CID SR’s) vaccines/intra partum antibiotics. GAS
- RSV/Influenza
- E coli (O antigen); SA
- Monoclonals
- Emollients/ Lactoferrin/synbiotics (Panigrahi Nature 2017)
Current challenges in the management of sepsis in ICUs in resource-poor settings and suggestions for the future


Recommendations for infection management in patients with sepsis and septic shock in resource-limited settings

C. Louise Thwaites, Ganbold Lundeg, Arjen M. Dondorp and For the sepsis in resource-limited settings—expert consensus recommendations group of the European Society of Intensive Care Medicine (ESICM) and the Mahidol-Oxford Research Unit (MORU) in Bangkok, Thailand
Treatment

• **Early appropriate** antibiotics
• Concordant/discordant – ESBL (1); CRO (2)
• Optimal dosing strategies
• High dose, short durations..MIC/RIC
• More frequent dosing/extended infusions
• Risk based approach to empiric regimens
AWaRe Index - EMLc

- Metric for stewardship
- Track progress in rational use of antibiotics over time
- Quantify optimal use at local, national and global levels
- Set Quality Goals
5. Management of neonatal sepsis

Prophylactic antibiotics for prevention of sepsis

► A neonate with risk factors for infection (i.e. membranes ruptured >18 hours before delivery, mother had fever >38 °C before delivery or during labour, or amniotic fluid was foul smelling or purulent) should be treated with the prophylactic antibiotics ampicillin (Intramuscular – IM – or intravenously, IV) and gentamicin for at least two days. After two days, the neonate should be reassessed and treatment continued only if there are signs of sepsis or a positive blood culture.

*(Weak recommendation, very low quality evidence)*  
*Source*

Empirical antibiotics for suspected neonatal sepsis

► Neonates with signs of sepsis should be treated with ampicillin (or penicillin) and gentamicin as the first line antibiotic treatment for at least 10 days.

*(Strong recommendation, low quality evidence)*  
*Source*

► If a neonate with sepsis is at greater risk of staphylococcus infection (e.g. extensive skin pustules, abscess, or omphalitis in addition to signs of sepsis), they should be given cloxacillin and gentamicin instead of penicillin and gentamicin.

*(Strong recommendation, quality of evidence not graded)*  
*Source*

► Where possible, blood cultures should be obtained before starting antibiotics. If an infant does not improve in two to three days, antibiotic treatment should be changed, or the infant should be referred for further management.

*(Strong recommendation, quality of evidence not graded)*  
*Source*
## NeoAMR Feasibility - Empiric Antibiotics used

<table>
<thead>
<tr>
<th>Country</th>
<th>City/Town</th>
<th>Early Onset Sepsis</th>
<th>Late Onset Sepsis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Antibiotic 1</td>
<td>Antibiotic 2</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>Dhaka</td>
<td>Ceftazidime</td>
<td>Amikacin</td>
</tr>
<tr>
<td>Brazil</td>
<td>Rio De Janeiro</td>
<td>Ampicillin</td>
<td>Gentamicin</td>
</tr>
<tr>
<td>Brazil</td>
<td>São Paulo</td>
<td>Ampicillin</td>
<td>Gentamicin</td>
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<tr>
<td>Cambodia</td>
<td>Siem Reap</td>
<td>Ampicillin</td>
<td>Gentamicin</td>
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<tr>
<td>China</td>
<td>Shenzhen</td>
<td>Ceftazidime</td>
<td>Ceftriaxone</td>
</tr>
<tr>
<td>China</td>
<td>Beijing</td>
<td>Ceftazidime</td>
<td>Amoxicillin +BLI</td>
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<tr>
<td>China</td>
<td>Tianjin</td>
<td>Benzylpenicillin</td>
<td>Ceftriaxone</td>
</tr>
<tr>
<td>China</td>
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<td>Other</td>
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<tr>
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<td>Cefepime</td>
<td>Meropenem</td>
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<td>Gentamicin</td>
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</table>
658 children with sepsis with 984 antibiotic prescriptions

Median 1 prescription per child, range 1-6

165 different treatments regimens (1 or more antibiotic)

Six children (0.9%) received WHO-recommended first-line treatment (ampicillin/gentamicin or penicillin/gentamicin)

85 (12.9%) received WHO-recommended second-line treatment (ceftriaxone):

- 76/314 (24.2%) of those with CAI
- 7/311 (2.3%) of those with HAI
NEW ANTIBIOTICS

Improved Outcomes With Plazomicin Compared With Colistin in Patients With Bloodstream Infections Caused by Carbapenem-resistant Enterobacteriaceae (CRE) Results From the CARE Study

**Figure 2. Mortality-Based Outcomes**

Difference (plazomicin minus colistin) (90% CI)

-39.0 (-65.5 to -9.4)  
-32.9 (-60.1 to -4.0)

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>All-cause mortality at day 28 or significant complications</th>
<th>All-cause mortality at day 28</th>
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<tbody>
<tr>
<td></td>
<td>Plazomicin</td>
<td>Colistin</td>
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<tr>
<td>14.3</td>
<td>2/14</td>
<td>8/15</td>
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<tr>
<td>53.3</td>
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<tr>
<td>7.1</td>
<td>1/14</td>
<td>6/15</td>
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<tr>
<td>40.0</td>
<td></td>
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</tbody>
</table>

Two-sided 90% CI calculated based on the unconditional exact method.

**Figure 3. Survival Through Day 60**

Plazomicin | Colistin
--- | ---
Patients Alive (%)
100 | 100
80 | 80
60 | 60
40 | 40
20 | 20
10 | 10
0 | 0

HR for death through day 60 (plazomicin:colistin) (90% CI)
0.37 (0.15-0.91)

Time to death through day 60 was estimated with the Kaplan–Meier approach and the hazard ratio (HR) was calculated using a Cox proportional hazards regression model.
NeoAMR prospective observational hospital based cohort study of empirical treatment and outcome

**Primary Endpoint**
The mortality at day 28 after start of empiric treatment of infants treated for clinical sepsis

**Trial Design**
Prospective, multinational, multicentre, observational cohort study of the inpatient management of neonatal sepsis in approximately 15-20 sites.

**Sample size**
Recruiting 200 infants per site provides >80% power to detect differences in mortality of 50% in 5% blood culture positives vs 10% in 95% blood culture negatives, as observed in DENIS study, assuming an inflation factor of 15% to allow for lost to follow-up (2 sided alpha =0.05).
DH Ambition - Gram-negative bloodstream infections 50% reduction by end of FY 2020/21
Thank You

Acknowledgment and special thanks to:

All the SGUL team

GARDP