Prevention and management of late-onset sepsis: an update

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Outline

• **Burden of disease:**
  – Incidence, classification, pathogens in LateOnset Sepsis

• **Prevention:**
  – Which strategies for Prevention? The role of Probiotics, Lactoferrin and Nutrients

• **Management:**
  – Stewardship in the use of antibiotics, CVC management
SEPSIS in preterm VLBW Neonates in NICU: causative agents and timing

E. coli
SGB
CONS
H. influenzae

CONS
S. aureus
Candida spp
E. coli

(data from NICHD, 2002-2003)

≤ 72 hrs

Early-Onset 1.5%

Late-Onset 20%

> 3 giorni

> 60 days

Very Late-Onset 1%

Kaufman, Clin Microbiol Rev 2004
Early-Onset vs. Late-Onset Sepsis: which are the differences?

<table>
<thead>
<tr>
<th></th>
<th>Early</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Timing</strong></td>
<td>&lt;72 -96 hrs</td>
<td>&gt;72 -96 hrs</td>
</tr>
<tr>
<td><strong>Causative agents</strong></td>
<td>&gt;Gram neg</td>
<td>&gt;Gram pos</td>
</tr>
<tr>
<td><strong>Origin</strong></td>
<td>&gt;maternal</td>
<td>&gt;hospital / nosocomial</td>
</tr>
<tr>
<td><strong>Diagnostic Markers</strong></td>
<td>Reliability +/-</td>
<td>Reliability ++/-</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>high</td>
<td>medium</td>
</tr>
<tr>
<td><strong>Prevention</strong></td>
<td>maternal</td>
<td>in the hospital/ nursery</td>
</tr>
</tbody>
</table>
Use of antibiotics in preterm VLBW neonates

USA - National Institute of Child Health and Human Development Neonatal Research Network

<table>
<thead>
<tr>
<th></th>
<th>Numbers</th>
<th>Incidence rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis late-onset</td>
<td>1313 of 6215</td>
<td>21%</td>
</tr>
<tr>
<td>Antibiotic treatment</td>
<td>3459 of 6215</td>
<td>56%</td>
</tr>
<tr>
<td>Sepsis early-onset</td>
<td>147 of 7606</td>
<td>1.9%</td>
</tr>
<tr>
<td>Antibiotic treatment</td>
<td>3652 of 7606</td>
<td>48%</td>
</tr>
</tbody>
</table>

Stoll, 2002; Stoll, 1996

Mortality in neonatal sepsis

<table>
<thead>
<tr>
<th></th>
<th>Mortality rates – preterm infants with sepsis</th>
<th>Mortality rates - preterm infants without sepsis</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemming, 1976</td>
<td>33%</td>
<td>14%</td>
<td>0.001</td>
</tr>
<tr>
<td>Stronati, 1990</td>
<td>20.9%</td>
<td>10.8%</td>
<td>0.05</td>
</tr>
<tr>
<td>Auriti, 2003</td>
<td>12.7%</td>
<td>5.8%</td>
<td>0.13</td>
</tr>
<tr>
<td>Aziz, 2005</td>
<td>8.5%</td>
<td>1.3%</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Stronati et a, 1 2008
Outline

• Burden of disease:
  – Incidence, classification, pathogens in LOS

• Prevention:
  – Which strategies for Prevention? The role of Probiotics, Lactoferrin and Nutrients

• Management:
  – Stewardship in the use of antibiotics, CVC management
It is better to prevent than cure: possible preventative strategies

• Neonatal Management:
  • Hygiene measures
  • Breastfeeding
  • Cautious CVC management
  • Enhancing Enteric microbiota composition with use of Probiotics
  • H2-blockers restrictions

• Pharmacological prophylactic interventions:
  • General Anti-infective prophylaxis: bioactive substances, probiotics, lactoferrin
  • Specific Antifungal prophylaxis: fluconazole
  • Specific Anti-RSV prophylaxis: palivizumab
A 24-year-old man was found on routine surveillance cultures to have methicillin-resistant Staphylococcus aureus (MRSA) colonization of his anterior nares.

To assess the potential implications of the patient's MRSA carriage for infection control, an imprint of a health care worker's ungloved hand was obtained for culture after the worker had performed an abdominal examination of the patient, and repeated after the worker washed his hands.
Strategies of reinforced hygiene, surveillance and prevention provide measurable results over years and have a strong clinical impact.
Medical stewardship:
Treatment with Antibiotics+Steroids can promote concomitant Colonization and Dissemination by Fungi (mice model)

<table>
<thead>
<tr>
<th></th>
<th>+/+</th>
<th>-/-</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cecal colonisation (Log 10/g)</td>
<td>7.7</td>
<td>6.7</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Mesenteric Lymphnodes</td>
<td>57%</td>
<td>13%</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Dissemination to kidney</td>
<td>83%</td>
<td>4%</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

## Medical stewardship:
Gastric Acidity Inhibitors (IGA, i.e. H2-blockers and PPI) are associated with Late-Onset Sepsis

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal - Year</th>
<th>Design of the study</th>
<th>Single or Multi Center</th>
<th>RCT</th>
<th>Type of H2B exposure</th>
<th>OR for sepsis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beck-Sague GM</strong></td>
<td>Ped Infect Dis J 1994</td>
<td>Prospective, observational</td>
<td>multi (3)</td>
<td>NO</td>
<td>YES or NO</td>
<td>4.2</td>
</tr>
<tr>
<td><strong>Graham PL</strong></td>
<td>Ped Infect Dis J 2006</td>
<td>Case-control</td>
<td>single</td>
<td>NO</td>
<td>YES or NO</td>
<td>++</td>
</tr>
<tr>
<td><strong>Bianconi S</strong></td>
<td>J Perinat Med.2007</td>
<td>Retrospective 3 years</td>
<td>single</td>
<td>NO</td>
<td>YES or NO</td>
<td>6.99</td>
</tr>
<tr>
<td><strong>Terrin G</strong></td>
<td>Pediatrics 2011</td>
<td>Prospective, observational</td>
<td>multi (4)</td>
<td>NO</td>
<td>Less than 1 week vs more than 1 week</td>
<td>3.2</td>
</tr>
<tr>
<td><strong>More K</strong></td>
<td>Am J Perinatol 2013</td>
<td>Systematic Review</td>
<td>meta-analysis</td>
<td>NO</td>
<td>YES or NO</td>
<td>5.5</td>
</tr>
</tbody>
</table>

**LIMITATIONS:**

- An association between H2B and Infections has been assessed only with a dichotomous approach (i.e., exposure to IGA/H2B : yes vs. no).
- Data on the magnitude of the association (e.g., O.R. for each day of exposure) are lacking.
- The hypothesis of an association between IGA/H2B and neonatal infections has never been tested so far in the context of a prospective, randomized clinical trial design.
### IGA and Infections: data from a new multicenter RCT

<table>
<thead>
<tr>
<th>Neonates WITH or WITHOUT:</th>
<th>Mean days of H2-Blockers in infants WITH the specific outcome</th>
<th>Mean days of H2-Blockers in infants WITHOUT the specific outcome</th>
<th>O.R.</th>
<th>95 C.I.</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>➢ Proven infection (late-onset sepsis LOS)</td>
<td>4.67</td>
<td>2.49</td>
<td>1.037</td>
<td>1.008-1.066</td>
<td>0.011</td>
</tr>
<tr>
<td>➢ Gram-positive infection</td>
<td>2.60</td>
<td>2.75</td>
<td>0.985</td>
<td>0.925-1.055</td>
<td>0.69</td>
</tr>
<tr>
<td>➢ Gram-negative infection</td>
<td>5.83</td>
<td>2.44</td>
<td>1.046</td>
<td>1.019-1.074</td>
<td>0.01</td>
</tr>
<tr>
<td>➢ Fungal infection</td>
<td>7.75</td>
<td>2.56</td>
<td>1.063</td>
<td>1.025-1.102</td>
<td>0.01</td>
</tr>
<tr>
<td>➢ Fungal colonization</td>
<td>5.48</td>
<td>2.27</td>
<td>1.045</td>
<td>1.021-1.070</td>
<td>0.001</td>
</tr>
<tr>
<td>➢ Death prior to discharge</td>
<td>1.90</td>
<td>2.77</td>
<td>0.947</td>
<td>0.872-1.029</td>
<td>0.19</td>
</tr>
<tr>
<td>➢ Severe NEC (surgical stages)</td>
<td>4.01</td>
<td>2.79</td>
<td>1.023</td>
<td>0.966-1.083</td>
<td>0.044</td>
</tr>
</tbody>
</table>

Each additional day of H2B treatment confers an additional 3.7% odd to develop infections.
### Medical stewardship: correct management of CVCs

Sepsis are associated with the duration of CVC maintenance

<table>
<thead>
<tr>
<th>Days of PICC</th>
<th>N° pz</th>
<th>Sepsis</th>
<th>OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3367</td>
<td>13%</td>
<td>1,0</td>
</tr>
<tr>
<td>1-7</td>
<td>381</td>
<td>24%</td>
<td>1,9 (1,4-2,5)</td>
</tr>
<tr>
<td>8-14</td>
<td>733</td>
<td>20%</td>
<td>1,5 (1,2-1,9)</td>
</tr>
<tr>
<td>15-21</td>
<td>592</td>
<td>29%</td>
<td>2,2 (1,8-2,8)</td>
</tr>
<tr>
<td>≥22</td>
<td>1125</td>
<td>42%</td>
<td>3,7 (3,1-4,4) (P=0,01)</td>
</tr>
</tbody>
</table>

Data from 6,215 VLBW neonates

**Stoll B, Pediatrics 2002**

<table>
<thead>
<tr>
<th>Catheters</th>
<th>Sepsis (n=1313)</th>
<th>Non sepsis (n°=4902)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PICC</td>
<td>16,4 ± 0,41 gg</td>
<td>8,5 ± 0,21 gg</td>
<td>&lt;0,001</td>
</tr>
<tr>
<td>UVC</td>
<td>4,0 ± 0,14 gg</td>
<td>2,8 ± 0,07 gg</td>
<td>&lt;0,001</td>
</tr>
</tbody>
</table>
“Proactive” management of percutaneously inserted central catheters results in decreased incidence of infection in the ELBW population: creation of a “dedicated task-Force” for the Unit CVC management

<table>
<thead>
<tr>
<th></th>
<th>Incidence of CVC-related infections</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRE-Not any “CVC specific task-force”</td>
<td>15.8 / 1000 catheters/day</td>
<td></td>
</tr>
<tr>
<td>POST-Specific “task-force” for the management of CVCs</td>
<td>5.1 / 1000 catheters/day</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Golombeck SG, J Perinatol, 2002
## Prophylactic fluconazole is effective in preventing fungal colonisation and infection in preterm neonates

Data from a multicenter, randomised trial in Italy of FLUCONAZOLE (3mg or 6mg every 2nd day) vs. PLACEBO

<table>
<thead>
<tr>
<th></th>
<th>Fluconazole N=216</th>
<th>Placebo n=106</th>
<th>R.R.</th>
<th>95% C.I.</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total invasive fungal infections (IFI; %)</td>
<td>3.2%</td>
<td>13.2%</td>
<td>0.25</td>
<td>0.10-0.59</td>
<td>0.001</td>
</tr>
<tr>
<td>Overall colonisation</td>
<td>8.8%</td>
<td>29.2%</td>
<td>0.30</td>
<td>0.18-0.51</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Overall mortality</td>
<td>8.3%</td>
<td>9.4%</td>
<td></td>
<td></td>
<td>0.83</td>
</tr>
<tr>
<td>Mortality attributable to fungi</td>
<td>0%</td>
<td>1.9%</td>
<td></td>
<td></td>
<td>0.10</td>
</tr>
</tbody>
</table>

Oral Lactoferrin for Prevention of Sepsis in Preterm Infants

- 4 RCTs retrieved (3 BLF, 1 rHLF)
- 648 VLBW infants analysed. No heterogeneity
- R.R. 0.49
- NNT 11
- Current available evidence graded as “moderate quality”
Nutritional stewardship: promoting the use of Human (possibly fresh) Milk

Human milk prevents:
- Infections  (Schanler 2005, Hylander 1998)

The beneficial effects of human fresh milk depend on intake volumes

### TABLE 5. Reduced Logistic Regression Model for Infection in Relation to Confounding Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (wk)</td>
<td>0.80</td>
<td>(0.68–0.95)</td>
<td>.009</td>
</tr>
<tr>
<td>Apgar score at 5 minutes</td>
<td>0.93</td>
<td>(0.77–1.14)</td>
<td>.494</td>
</tr>
<tr>
<td>Days without enteral feedings (NPO)</td>
<td>1.03</td>
<td>(0.99–1.07)</td>
<td>.153</td>
</tr>
<tr>
<td>Mechanical ventilator days</td>
<td>1.01</td>
<td>(0.99–1.03)</td>
<td>.184</td>
</tr>
<tr>
<td>Human milk-fed</td>
<td><strong>0.43</strong></td>
<td>(0.23–0.81)</td>
<td><strong>.010</strong></td>
</tr>
</tbody>
</table>

**Note:** Bold indicates statistical significance.
Maternal milk contains probiotics. An infant fed with 800 ml/day of maternal milk will ingest $10^5$-$10^7$ bacteria every day.

**Bifidobacteria and Lactobacilli content in human milk: urban areas**

**Bifidobacteria and Lactobacilli content in human milk: rural areas**

Martin R 2003; Heikkilä MP 2003; Sinkiewicz G 2006
Probiotics are beneficial in promoting a “good” enteric microbiota in preterm neonates, preventing colonization by many pathogens including the various *Candida spp* (Neu et al, *Pediatr Res* 2010)

**Lactobacilli are the probiotics that are effective in preventing Candida colonization in neonates**

<table>
<thead>
<tr>
<th>RCTs</th>
<th>Probiotic used</th>
<th>Primary outcome</th>
<th>Results in probiotic group</th>
<th>Results in placebo group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manzoni et al, • <em>Clin Infect Dis</em> 2006 • <em>JPGN</em> 2007</td>
<td><strong>Lactobacillus rhamnosus</strong> GG</td>
<td>Candida gut Colonization in &lt;1500g neonates</td>
<td>23.1%</td>
<td>48.8%</td>
<td>0.01</td>
</tr>
<tr>
<td>Romeo et al, • <em>J Perinatol</em> 2011</td>
<td><strong>Lactobacillus Reuterii</strong></td>
<td>Candida gut Colonization in &lt;2500g neonates</td>
<td>7.1%</td>
<td>22.9%</td>
<td>0.01</td>
</tr>
<tr>
<td>Romeo et al, • <em>J Perinatol</em> 2011</td>
<td><strong>Lactobacillus rhamnosus</strong> GG</td>
<td>Candida gut Colonization in &lt;2500g neonates</td>
<td>10.7%</td>
<td>22.9%</td>
<td>0.01</td>
</tr>
</tbody>
</table>
AlFaleh K et al

Updated (2016)
Cochrane Review on
Probiotics feeding in
VLBW infants

Outcome: Sepsis (any pathogen)
The IMpact-RSV Trial: RCT on effectiveness of PALIVIZUMAB on RSV-related Hospitalizations (Pediatrics 1998)

Palivizumab is the current standard of care for selected groups of neonates and infants at high-risk for severe RSV infection
Outline

• Burden of disease:
  – incidence, classification, pathogens of LOS
• Prevention:
  – Which strategies for Prevention? The role of Probiotics, Lactoferrin and Nutrients
• Management:
  – Stewardship in the use of antibiotics, CVC management
Stewardship in Antibiotic use in Neonatal Intensive Care Unit

“….judicious use of antibiotics is an important tool for limiting the emergence of resistant organisms, and appropriate antibiotic policies should be developed in every NICU in order to restrict the use of unnecessary broad spectrum antibiotic therapy….”


General Recommendations:

- Don’t use if not necessary
- If use, withdraw if not/nomore necessary
- Use the narrowest possible spectrum
Don’t use if not necessary: No evidence to support any PROPHYLACTIC use of Antibiotics in the NICU (1)

Prophylactic antibiotics to reduce morbidity and mortality in neonates with umbilical venous catheters (Review)

Inglis GDT, Davies MW

Authors’ conclusions

There is insufficient evidence from randomised trials to support or refute the use of prophylactic antibiotics when UVCs are inserted in newborn infants. There is no evidence to support or refute continuing antibiotics once initial cultures rule out infection in newborn infants with UVCs.
Don’t use if not necessary: No evidence to support any PROPHYLACTIC use of Antibiotics in the NICU (2)

Prophylactic antibiotics to reduce morbidity and mortality in neonates with umbilical artery catheters (Review)

Inglis GDT, Jardine LA, Davies MW

Authors’ conclusions

There is insufficient evidence from randomised trials to support or refute the use of prophylactic antibiotics when umbilical artery catheters are inserted in newborn infants, and no evidence to support or refute continuing antibiotics once initial cultures rule out infection in newborn infants with umbilical artery catheters.
Don’t use if not necessary: No evidence to support any PROPHYLACTIC use of Antibiotics in the NICU (3)

Prophylactic systemic antibiotics to reduce morbidity and mortality in neonates with central venous catheters (Review)

Jardine LA, Inglis GDT, Davies MW

Authors’ conclusions

Prophylactic systemic antibiotics in neonates with a central venous catheter reduces the rate of proven or suspected septicaemia. However, this may not be clinically important in the face of no significant difference in overall mortality and the lack of data on long-term neurodevelopmental outcome. Furthermore, there is a lack of data pertaining to the potentially significant disadvantages of this approach such as the selection of resistant organisms. The routine use of prophylactic antibiotics in infants with central venous catheters in neonatal units cannot currently be recommended.
No evidence to support any PROPHYLACTIC use of Antibiotics in the NICU: the CDC policy statements

Systemic Antibiotic Prophylaxis

Do not administer systemic antimicrobial prophylaxis routinely before insertion or during use of an intravascular catheter to prevent catheter colonization or CRBSI [114].

Category IB

Umbilical Catheters

No recommendation can be made regarding attempts to salvage an umbilical catheter by administering antibiotic treatment through the catheter. Unresolved issue
1. it is appropriate to consider any premature infant with microbiological or clinical evidence of infection as having disseminated disease:

- perform all measures to screen out end-organ involvements
- perform careful follow-up to capture/intercept late NDI sequelae associated with infection
Neurodevelopmental Impairment and Bloodstream Infection in Infants <1000 g: it is mandatory to prevent infections in the NICU, rather than to cure only.

*P ≤ 0.001 vs. no infection

Stoll, JAMA 2004
List of Key points for appropriate management of infections in the NICU (1)

2. Two antibiotic treatment strategies are possible:
   - Targeted therapy

   This last option is the most frequent one, given the rarity of cases in which the causative pathogen is known since the beginning.
The Limits of blood cultures in the diagnosis of infections

- Failure to identify the various species of pathogens (e.g., up to 15% of the microbiological samples can be actually contaminated with Candida spp.).

- Phases of bacteraemia are fleeting, or not protracted, in many cases of systemic infections (and this is true for Candida spp more than for bacterial sepsis).

- The aliquots of drawn blood are usually not suitable → a good blood culture would need at least 3 ml!

- Blood drawn from "peripheral" vs. "central" sites
3. **Rules about the choice of antibiotics when instituting antibiotic treatment:**

- a combination of agents active on both Gram-negative and – positive is strongly recommended
- use narrow-spectrum antibiotics: start antibiotics with the most possible limited spectrum
- Meropenem and Imipenem can select carbapenem-resistant strains
- Broad-spectrum antibiotics are associated with increased risk of systemic fungal infections
- when previous antibiotic exposure is reported, switch to a different antibiotic class
- therapy adjustments based on the microbiology findings need to follow.
Protocols for empiric antibiotic treatment in VLBW infants

**Early-Onset:** Ampicillin + Aminoglycoside

**Late-Onset:** Vancomycin + Aminoglycoside

- **2nd line** Teicoplanin + Piperacillin/Tazobactam
- **3rd line** add Meropenem, consider Micafungin
Surveillance of multidrug-resistant gram-negative bacilli in NICU: prominent role of duration of exposure to Antibiotics

<table>
<thead>
<tr>
<th>Neonates n= 210</th>
<th>Colonized by multi- resistant Bacilli N= 116</th>
<th>Colonized by susceptible Bacteria N= 39</th>
<th>Not colonized N=55</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total time of exposure to antibiotics</td>
<td>8 days</td>
<td>2.3 days</td>
<td>5.5 days</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Mammina et al, AJIC 2007
Can restricting antibiotics effect resistance patterns?

*P. aeruginosa* susceptibilities before and after implementation of antibiotic restrictions

Sunenshine RH et al. CID 1997;25:230-39
4. Microbiology is Pivotal!

- Always perform blood/deep cultures when starting antibiotics
- Even though many episodes of sepsis are caused by a breakthrough, pathogenic microorganism, in many other cases peripheral colonization usually precede systemic infection
- Be guided by local ecology and epidemiology (information from surveillance cultures is useful)
- Treat sepsis, not colonization
- Be aware of maternal infectious diseases
- Consider the central venous catheter status and the possibility/probability that biofilms have formed
- Start Empirical, but switch as soon as you can to targeted
Risk of CVC-related sepsis

Having a CVC is a risk for infections. Many pathogens may form biofilms on prosthetic devices, and hence disseminate through the bloodstream through septic thrombi.

OR = 2.0 (95% CI 1.1-3.9)  
(Avila-Figueroa, 1998)

RR = 3.81 (P < 0.001)  
(Pediatric Prevention Network, 2001)

RR = 5.87 (P = 0.001)  
(Auriti, 2003)

OR = 13.6 (p = 0.01)  
(Rojas, 2005)

Fungal Biofilms
The Timing of Onset of Fungal Colonisation in the Premature Neonate in NICU

Positive rectal cultures expressed as percent of total number of cultures performed at each interval and in each treatment group. Infants of birth weight <1500g with rectal cultures performed from DOR to DOL 28.

5. **Role of laboratory markers:**
   - Limited value in diagnosis
   - Good confirmatory value of diagnosis
   - Good guidance for assessing response to therapy
Issues related to the Timing of the markers

- Interleukins → all have an extremely fleeting "peak"
- PCR → a snapshot with 24-36 hr delay
- PCT → a snapshot with 12-18 hr delay
- The combined use of different markers is reliable only in longitudinal perspective (= serial controls), much less in case of checks "spot"
### Clinical Signs of Sepsis: the most sensitive Indicator

Predictive Values of ANC, I:T Ratio, and Clinical Examination among newborns weighing \( \geq 2000 \) g at birth evaluated for sepsis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>+PV</th>
<th>-PV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of clinical signs</td>
<td>92%</td>
<td>53%</td>
<td>4%</td>
<td>99%</td>
</tr>
<tr>
<td>Baby critically ill</td>
<td>31%</td>
<td>6%</td>
<td>10%</td>
<td>98%</td>
</tr>
<tr>
<td>ANC &lt;10th percentile</td>
<td>48%</td>
<td>73%</td>
<td>4%</td>
<td>98%</td>
</tr>
<tr>
<td>ANC &lt;10th percentile</td>
<td>16%</td>
<td>96%</td>
<td>8%</td>
<td>98%</td>
</tr>
<tr>
<td>Manroe et al</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I:T ratio, ( \geq .25 ) cutoff</td>
<td>45%</td>
<td>84%</td>
<td>6%</td>
<td>98%</td>
</tr>
<tr>
<td>I:T ratio, ( \geq .30 ) cutoff</td>
<td>35%</td>
<td>89%</td>
<td>7%</td>
<td>98%</td>
</tr>
</tbody>
</table>

List of Key points for appropriate management of infections in the NICU (4)

6. **Be ready to withdraw as much as you are ready to institute antibiotics:**
   - discontinue antibiotics as soon as possible if clinical-diagnostics allows
   - There is a general consensus on discontinuation of therapy after 48-72 hours if negativity of blood cultures and in absence of clinical signs suggestive of suspected sepsis
Should Antibiotics be Discontinued at 48 Hours for Negative Late-Onset Sepsis Evaluations in the Neonatal Intensive Care Unit?

Jeffrey R. Kaiser, MD, MA
James E. Cassat, BS
Mary Jo Lewno, MT (ASCP)

98% (97% blood; 100% Urine e CSF)

8 pos >48 hrs

2783 Cultures

283 Pos (10.2%)

“...it is easier to institute than to withdraw antibiotics...”
Bundles of prescription and of discontinuation for use of antibiotics in the NICU

JB Cantey, PS Wozniak, JE Pruszynski, PJ Sánchez
Reducing unnecessary antibiotic use in the neonatal intensive care unit (SCOUT): a prospective interrupted time-series study
Lancet Infect Dis 2016. 16 (10), 1178–1184

- Observational study in the level 3 NICU at Parkland Hospital, Dallas, TX, USA.
- All antibiotic use in infants admitted to the NICU during 9 months was monitored and analysed. Continuation of empirical antibiotic therapy for ruled-out sepsis courses beyond 48 h, pneumonia, and “culture-negative” sepsis were selected as targets for antibiotic stewardship interventions.
During the 9-month intervention period, (1) empirical antibiotic therapy was set to discontinue after 48 h in the electronic medical record and (2) the duration of therapy for pneumonia and culture-negative sepsis was limited to 5 days.

Changes in Antibiotic use, defined as days of therapy per 1000 patient-days, were compared between the baseline and intervention periods (primary outcome).

Antibiotic use declined from 343 days of therapy/1000 patient-days during the baseline period to 252 days of therapy/1000 patient-days in the intervention period (p<0.0001), representing an overall decrease of 27%.

No difference in safety outcomes was observed between the intervention and baseline periods.
7. Which duration of antibiotic treatment?

- At least 2 weeks in bloodstream infections
- At least 3-4 weeks in end-organ localizations
- At least 4 weeks in meningitis:
  - Meningitis due to Gram positive → 2 weeks after sterilization
  - Meningitis due to Gram negative → 3 weeks after sterilization
- In any case, recommended duration is 7-10 days AFTER the first negative blood culture
- A number of studies are currently exploring efficacy of shortened courses of certain ATBs (e.g., Vancomycin), related to updated PK information for certain drugs

Reducing unnecessary antibiotic exposure in preterm neonates: an achievable goal

In summary: the main take-home messages

1. Discontinue ATBs after 48 hrs if sepsis is not confirmed
2. Try shorter duration of courses if sepsis is confirmed
3. Avoid unnecessary prophylactic exposures (i.e., for UVC, CVC, etc)
4. Reinforce prophylaxis to prevent infections and bypass any need for ATBs (e.g., bundles of care, CVC bundles, reinforced hygiene measures, prophylactic fluconazole, lactoferrin, probiotics, fresh human milk, etc)
Thank you for your attention!

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INTERNATIONAL CONFERENCE on
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May 23rd - 26th 2018

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paolomanzoni@hotmail.com
Fluconazole prophylaxis prevents invasive *Candida* infections in preterm infants

- Meta-analysis of 10 studies
  - 7 retrospective, 3 RCTs

Fluconazole prophylaxis reduces:

- The chance of developing IFI in high-risk infants <1000g
  (OR 0.10; 95% CI 0.05-0.22; P<0.0001)
- The chance of developing IFI in all infants <1500g
  (OR 0.15; 95% CI 0.09-0.26; P<0.0001)
- The overall mortality rate (11% vs. 16.3%)
  (OR 0.74; 95% CI 0.58-0.95; P=0.017)
- The *Candida*-related mortality
  (from 25 non-treated infants to 1 fluconazole prophylaxis patient)
- No effect on developmental long-term outcomes assessed
- Ecological safety data available up to 8 years:
  - No shifts towards fluconazole-resistant spp
  - No selection of resistant strains

RSV → leading agent of viral death in neonates and infants

Nosocomial RSV infection is more severe than Community-acquired (CA) RSV infection

Hospitalised Patients (%)

- N-RSV (n=91)
- CA-RSV (n=1,516)

Langley. (PICNIC) Pediatrics 1997