Neonatal sepsis: Management in the NICU

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Fondazione “Crescere insieme al S. Anna-ONLUS”

Clinical Trial Center, OPBG - Roma, Italy
• Burden of disease: incidence, outcomes
• Classification: late-onset sepsis
• EOS $\rightarrow$ GBS
• LOS $\rightarrow$ pathogens, characteristics
• Risk factors
• Diagnosis
• Prevention
• Management: use of antibiotics; CVC management; nutritional 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)

Early-Onset 1.5%
Late-Onset 20%
Very Late-Onset 1%

< 72 hrs
> 3 giorni
> 60 days

Kaufman, Clin Microbiol Rev 2004
Use of antibiotics in USA nei preterm VLBW neonates

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>1313/6215</td>
<td>21%</td>
</tr>
<tr>
<td>Antibiotic treatment</td>
<td>3459/6215</td>
<td>56%</td>
</tr>
<tr>
<td>Sepsis early-onset</td>
<td>147/7606</td>
<td>1.9%</td>
</tr>
<tr>
<td>Antibiotic treatment</td>
<td>3652/7606</td>
<td>48%</td>
</tr>
</tbody>
</table>

Stoll, 2002
Stoll, 1996
Randomized controlled trials of antibiotics for neonatal infections: a systematic review


Many antibiotics used, Poor evidence from RCTs!

### Table 2. Tested antibiotics and context of evaluation in the 35 relevant randomized controlled trials in neonates

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Infection/Disease</th>
<th>Number of RCTs (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamicin</td>
<td>Suspected or proven bacterial sepsis or focal infection</td>
<td>12 (34%)</td>
</tr>
<tr>
<td></td>
<td>Meconium aspiration syndrome</td>
<td>8*</td>
</tr>
<tr>
<td></td>
<td>Type of infection not stated</td>
<td>1</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>Meconium aspiration syndrome</td>
<td>5 (14%)</td>
</tr>
<tr>
<td>+ aminoglycosides</td>
<td>Neonatal pneumoniae (+ gentamicin)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Meconium aspiration syndrome (+ gentamicin/amikacin)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Bacterial infection in high risk infants (+ netilmicin)</td>
<td>1</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Nosocomial coagulase-negative staphylococci infections</td>
<td>4 (11%)</td>
</tr>
<tr>
<td></td>
<td>Necrotising enterocolitis</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Catheter-related bloodstream infections (+ heparin lock)</td>
<td>1</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Chronic lung disease with/without Ureaplasma Urealyticum colonisation</td>
<td>4 (11%)</td>
</tr>
<tr>
<td></td>
<td>Infectious conjunctivitis</td>
<td>3</td>
</tr>
<tr>
<td>Fucidic acid</td>
<td>Catheter-related bloodstream infections (+ heparin lock)</td>
<td>2 (6%)</td>
</tr>
<tr>
<td></td>
<td>Infectious conjunctivitis</td>
<td>1</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>Catheter-related bloodstream infections</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Benzathine penicillin</td>
<td>Congenital syphils</td>
<td>1</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Sepsis due to resistant Gram + bacteria</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>Coagulase-negative staphylococci infections</td>
<td>1</td>
</tr>
<tr>
<td>Amikacin</td>
<td>Suspected or proven bacterial infection</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Chronic lung disease</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Ceftazidim</td>
<td>Suspected or proven sepsis</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Various antibiotics</td>
<td>Suspected or proven sepsis</td>
<td>1</td>
</tr>
</tbody>
</table>

* Antibiotic efficacy was evaluated upon pharmacokinetic parameters
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;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 nursery</td>
</tr>
</tbody>
</table>
Mortality and birth weight

- 32% Mortality <1500
- 38% Mortality <1000
- 47% Mortality <750

NICHD Neonatal Network Data, Sept 1, 1998-Aug 31, 2000
Neurodevelopmental Impairment and Bloodstream Infection in Infants <1000 g

*P ≤ 0.001 vs. no infection

Stoll, JAMA 2004
• Burden of disease: incidence, outcomes
• Classification: Early and late-onset sepsis
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• Diagnosis
• Prevention
• Management: use of antibiotics; CVC management; nutritional management
Prematurity Interrupts Optimal Transfer of Maternal IgG

Adapted from data and formulas as published by Yeung CY, Hobbs, JR. *Lancet.* 1968;7553:1167-70
Factors affecting the Enteric Microflora composition in neonates

- Mode of Delivery (Cesarean or Vaginal)
- Normal Transition or Intensive Care
- Type of Feedings (Human Milk or Formula)
- Antibiotic Exposure
- Gestational Age (Term or Preterm)
Surgical Population in NICU is at highest risk: Complicated Gastrointestinal Disease

Gastroschisis

Omphalocele

Necrotizing Enterocolitis

Focal Bowel Perforation

16.5% Candidemia

44% Candida Peritonitis
Coates, 2005
Risk of CVC-related sepsis

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

- Electron micrograph of biofilm formed by *C. albicans* on catheter material

*Jabra-Rizk MA et al (Baltimore), Emerg Infect Dis 2004;10:14-9*
• Burden of disease: incidence, outcomes
• Classification: Early and late-onset sepsis
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• Diagnosis
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• Management: use of antibiotics; CVC management; nutritional management
The role of Neonatologists

1. timely diagnosis
2. timely treatment

To do this, neonatologists need to have:

- Accurate knowledge of the maternal history with regard to occurrence of infectious diseases and/or colonization
- Careful adherence to the neonatal GBS prevention protocols
- Full knowledge of what you can expect from the laboratory markers and the microbiology -culture evaluations
### Table 3. Sensitivity, specificity, and positive and negative predictive value of some laboratory tests used in the diagnosis of infection in the newborn (Ref. 4)

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood culture</td>
<td>11–38</td>
<td>68–100</td>
<td>90–100</td>
<td>72–100</td>
</tr>
<tr>
<td>WBC &lt;5000 &gt;30,000</td>
<td>17–90</td>
<td>31–100</td>
<td>50–86</td>
<td>60–89</td>
</tr>
<tr>
<td>I/T ratio &gt;0.02</td>
<td>81</td>
<td>45</td>
<td>23</td>
<td>92</td>
</tr>
<tr>
<td>CRP &gt;10 mg/L</td>
<td>37</td>
<td>95</td>
<td>63</td>
<td>87</td>
</tr>
<tr>
<td>IL-8 &gt;70 pg/mL</td>
<td>77</td>
<td>76</td>
<td>42</td>
<td>94</td>
</tr>
<tr>
<td>I/T ratio &gt;0.02 + CRP &gt; 10 mg/L</td>
<td>89</td>
<td>41</td>
<td>24</td>
<td>94</td>
</tr>
<tr>
<td>IL-8 &gt; 70 pg/mL + CRP &gt;10 mg/L</td>
<td>91</td>
<td>74</td>
<td>43</td>
<td>98</td>
</tr>
<tr>
<td>16 S PCR&lt;sup&gt;a&lt;/sup&gt;</td>
<td>96.0</td>
<td>99.4</td>
<td>88.9</td>
<td>99.8</td>
</tr>
</tbody>
</table>

PPV, positive predictive value; NPV, negative predictive value; WBC, white blood cell count; I/T, immature/total neutrophil ratio; CRP, C-reactive protein; IL, interleukin; PCR, polymerase chain reaction.

<sup>a</sup>From Ref. 35. All values are percentages.
The Limits of blood cultures in the diagnosis of infections

- Failure to identify the various species of pathogens (eg., 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 "peripheral" vs. blood "central"
Issues related to the Timing of the sepsis markers
Possible laboratory “markers” that are suggestive for causative pathogens of neonatal infections

- **Hyperglycaemia** *(Manzoni et al, Acta Paediatr 2006)*
- **Glycosuria** *(Bekhof et al, BMC Pediatr 2015)*
- **Thrombocytopenia** *(Guida et al, Pediatrics 2003; Benjamin et al, Pediatrics 2003)*
- **CRP increase** *(Makhoul IR, Pediatrics 2002)*

<table>
<thead>
<tr>
<th>Table 1</th>
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</thead>
<tbody>
<tr>
<td>Summary of hematologic changes in neonatal sepsis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pathogen or Group of Pathogens</th>
<th>RBC Count</th>
<th>WBC Count</th>
<th>Neutrophils Count</th>
<th>Lymphocytes Count</th>
<th>Platelets Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram positives</td>
<td>a</td>
<td>↑ or ↓</td>
<td>a (rarely ↓)</td>
<td>a</td>
<td>↓ ↓</td>
</tr>
<tr>
<td>Gram negatives</td>
<td>a</td>
<td>↑ or ↓</td>
<td>↓</td>
<td>a</td>
<td>↓</td>
</tr>
<tr>
<td>Fungi</td>
<td>a</td>
<td>↑ or ↓</td>
<td>↓ ↓</td>
<td>a</td>
<td>↓ ↓ ↓</td>
</tr>
</tbody>
</table>

### Clinical Signs of Sepsis: 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></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>

• Burden of disease: incidence, outcomes
• Classification: Early and late-onset sepsis
• EOS → GBS
• LOS → pathogens, characteristics
• Risk factors
• Diagnosis
• **Key points for appropriate management**
List of Key points for appropriate management of infections in the NICU (1)

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

2. two antibiotic treatment strategies are possible:
   ✓ targeted therapy
   ✓ empirical/pre-emptive treatment.
      → This last option is the most frequent one, given the rarity of cases in which the causative pathogen is known since the beginning.
List of Key points for appropriate management of infections in the NICU (2)

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.
Antibiotics in Neonatal Intensive Care Unit: need to reinforce stewardship

“...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
Protocols for empiric antibiotic treatment in VLBW infants

Early-Onset: Ampicillin+Aminoglicoside

Late-Onset: Vancomycin + Aminoglicoside

→ 2nd line  Teicoplanin + add Piperacillin tazobactam

→ 3rd line  add Meropenem, consider Micafungin
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 disease
- 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
5. Role of laboratory markers:
   - Limited value in diagnosis
   - Good confirmatory value of diagnosis
   - Good guidance for assessing response to therapy

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%)
Withdraw antibiotics if not – no more necessary

“….Antibiotic should be started empirically whenever a neonatal severe infection is suspected and suspended after 48-72 h, if cultures and clinical signs exclude infection….“

7. **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
How can we prevent Antibiotic resistance?

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

Antibiotics in Neonatal Intensive Care Unit

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.
Why is it necessary to target antibiotic use? Risk for selection of resistances
# Most frequent Gram-positive and Gram-negative resistant organisms in the NICU

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONS</td>
<td>oxacillin/methicillin</td>
</tr>
<tr>
<td>MRSA</td>
<td>oxacillin/methicillin</td>
</tr>
<tr>
<td>Enterococci VRE</td>
<td>vamcomycin</td>
</tr>
<tr>
<td>ESBLs (extended spectrum β lactamase)</td>
<td>piperacillin-tazobactam, ceftazidime, and/or gentamicin, 3(^{rd}) generation cephalosporins, including cefotaxime, ceftriaxone, and ceftazidime</td>
</tr>
<tr>
<td><strong>Klebsiella pneumoniae</strong> carbapenemases producers (KPCs)</td>
<td>imipenem and meropenem</td>
</tr>
</tbody>
</table>
Antibiotic exposure increases the risks of development of resistances

<table>
<thead>
<tr>
<th>Pathogen and Antibiotic Exposure</th>
<th>Increased Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbapenem Resistant Enterobacteriaceae and Carbapenems</td>
<td>15 fold</td>
</tr>
<tr>
<td>ESBL producing organisms and Cephalosporins</td>
<td>6-29 fold</td>
</tr>
</tbody>
</table>

Trend of Ampicillin Susceptibility of *E. coli* from Early-Onset Sepsis Cases Preterm Infants, Selected Counties CA and GA, 1998-2000

![Bar chart showing the trend of Ampicillin Susceptibility over years 1998, 1999, and 2000. The number of sensitive cases and resistant cases are indicated for each year.]

- **1998**:
  - Sensitive: 5
  - Resistant: 2
- **1999**:
  - Sensitive: 2
  - Resistant: 10
- **2000**:
  - Sensitive: 3
  - Resistant: 15

**Additional Information**: N=37, p=0.02, linear trend

*Hyde, Pediatrics, 2001; 110(4):690-95*
Surveillance of multidrug-resistant gram-negative bacilli in NICU: prominent role of cross transmission

<table>
<thead>
<tr>
<th>Neonates n= 210</th>
<th>Colonized ny 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, 2007
“New” Antibiotics:
their use in neonates should always be, at the moment, only “targeted” and “rescue”

1. Linezolid
2. Daptomyin
3. Tygecicline

Mainly active on Gram-pos

1. Colystin
2. Ertapenem
3. Doripenem

Mainly active on Gram-neg
And what about antibiotic management of the Central Line?
Don’t use if not necessary: No evidence to support any PROPHYLACTIC use of Antibiotics in the NICU (1)

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 sepsis. 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.

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
Bacteremia, central catheters and neonates: when to pull the line

<table>
<thead>
<tr>
<th>Early catheter removal</th>
<th>Complicated Sepsis</th>
</tr>
</thead>
<tbody>
<tr>
<td>YES</td>
<td>2/25 (8%)</td>
</tr>
<tr>
<td>NO</td>
<td>59/128 (46%)</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>9.8 (2.2-43.4)</td>
</tr>
</tbody>
</table>

Complications:
- End-organ localization
- Persistent bacteriemia
- Death

Benjamin, Pediatrics 2001
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)

Manzoni P, Dall’Agnola A. Lancet Infect Dis 2016
And what about fungal infections?
Optimal rescue strategy

→ to perform treatment with the most potent antifungal available to minimise the risk that septic foci may escape treatment and disseminate

- Ideal antifungal drugs for neonates must have:
  - significant activity against biofilms
  - significant activity against *C. glabrata*, *C. tropicalis* and *C. krusei* (because they may survive prophylactic fluconazole)
  - ability to be used in mono-therapy
  - good tolerability
  - no pharmacological interactions

HIT FAST, HIT HARD !!
- The Echinocandins are the most appropriate class of antifungal agents to date available to address the specific neonatal needs
- Micafungin is the only antifungal agent to date approved for neonatal use in Europe

<table>
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<tr>
<th></th>
<th>Micafungin(^1)</th>
<th>Caspofungin(^2)</th>
<th>Anidulafungin(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Invasive candidiasis</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Neutropenic patients</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Paediatric patients</strong></td>
<td>Yes</td>
<td>≥ 12 months</td>
<td>No</td>
</tr>
<tr>
<td><strong>Neonates</strong></td>
<td>Yes</td>
<td>Limited data</td>
<td>No</td>
</tr>
<tr>
<td><strong>Prophylaxis in HSCT patients</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>or expected neutropenic patients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Paediatric patients</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Neonates</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Manzoni et al, EHD 2012
Should Central Venous Catheters Be Removed as Soon as Candidemia Is Detected in Neonates?

Conclusions

Failure to remove CVC as soon as candidemia is detected in preterm neonates is associated with significantly increased mortality in *C albicans candidemia* and prolonged duration of candidemia regardless of *Candida spp.*
Thank you!

7th ICCN
INTERNATIONAL CONFERENCE on
CLINICAL NEONATOLOGY

TURIN - ITALY
Centro Congressi Unione Industriale
Via Fanti, 17 - 10128 Torino
May 23rd - 26th 2018
www.iccn2018.eu

CHAIRMAN
Paolo Manzoni

CO-CHAIRMEN
Eduardo Bancalari
Louis Bont
Avroy Fanaroff
Hans van Goudoever

MAIN TOPICS
- Hypothermia in preterms: what’s new?
- Late hypothermia after 6 hrs of life
- Regenerative medicine: stem cells trials in neonates
- Is MRI necessary, or “only” helpful?
- IGF-1, anti-VEGF, surgery to treat severe ROP: where are we now? which is the best choice?
- Early strategies to prevent BPD: budesonide? anything more?
- Is LISA necessary, or “only” helpful, or nothing at all?
- Teamworking in the NICU
- Lactoferrin for premature brain
- EPO and neuroprotection: an update
- ECMO: indications, risks and benefits
- Nutrition of preterm infants
- NIDCAP and family-centered care
- Kidney injury in the preterm infant
- NEC: an update
- “Omics” in neonatology
- Multiresistant organisms: challenges and solutions
- Laboratory at bedside: what’s new in the NICU?
- Less surfactant and less intubation: has this policy improved the neonatal outcomes?
- Morbidity associated with early infection by Respiratory Viruses
- Prematurity and late wheezing: is there a link?
Risk factors for fungal infection in neonates

• **In preterm infants:**
  1. Extreme prematurity: lowest gestational ages
  2. Candida colonisation
  3. Risk for biofilms
  4. Antibiotic and medication practices
  5. Central venous catheter
  6. Prior bacterial bloodstream infection
  7. Lack of enteral feeding
  8. Skin immaturity / burns
  9. Hyperglycaemia
  10. Use of H2-blockers
  11. Duration of mech. ventilation
     (Chronic lung disease ± postnatal steroids)

• **In any gestational age neonate:**
  – Complicated gastrointestinal (GI) disease

Activity of *Candida* spp. in Biofilms (48h)