Invasive Fungal Infections (IFI) in Neonates
– The state of the art –

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Do the data of neonatal IFI accurately reflect the real incidence?
The true burden of *Candida* infections in preterm neonates in NICU is likely higher

- Invasive Fungal infections (IFI) in neonates → 95% are *Candida* spp infections
- IFI in 7% of all preterm, VLBW neonates
- 74% of all IFI occurs in infants <1000g
- Huge variability of reported incidence rates of IFI among Settings: In the USA, in a survey including around 30 third level NICUs, IFI incidence in VLBWs varied from 2% to 25%!

TOTAL estimated, ‘real-life’ incidence → more than 9%

Poor outcomes after Neonatal IFI: higher burden of Neurodevelopmental Impairment after IFI in infants <1000g

*P ≤ 0.001 vs. no infection

57% fungal
44% bacterial
28% no sepsis
Poor outcomes after Neonatal IFI: negative Neurodevelopmental performances at 20 months of age in survivors from neonatal IFI by *Candida* spp

Data from 4,589 ELBW neonates in the US neonatal network

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Candidiasis %</th>
<th>Controls %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bayley MDI &lt; 70</td>
<td>48.4</td>
<td>29.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Bayley PDI &lt; 70</td>
<td>31.5</td>
<td>19.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cerebral Palsy</td>
<td>13.6</td>
<td>5.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>23.5</td>
<td>13.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Blindness</td>
<td>1.9</td>
<td>0.6</td>
<td>.03</td>
</tr>
<tr>
<td>Hearing impairment</td>
<td>10.5</td>
<td>2.9</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Deafness</td>
<td>6.2</td>
<td>1.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mental retardation</td>
<td>57.2</td>
<td>35.8</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Benjamin et al., Pediatrics 2006
Best management → PREVENTION!!
Outline of all possible preventative strategies

**Neonatal management:**
- Breastfeeding – fresh human milk
- Hygiene measures
- Cautious CVC management
- Enhancing enteric microbiota composition with use of probiotics
- H2-blockers, steroids and 3rd generation cephalosporin restrictions

**Pharmacological prophylactic interventions:**
- Bioactive substances (Bovine Lactoferrin)
- Probiotics
- Non-absorbable antifungal agents preventing gut colonisation: Nystatin
- Specific antifungal prophylaxis: **fluconazole**
Update on the management of *Candida* infections in preterm neonates

P Manzoni,¹ M Mostert,² E Castagnola³

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**Box 2 Key issues in the management of systemic fungal infections in neonates: summary**

1. Consider any premature infant with microbiological or clinical evidence of invasive candidiasis as having disseminated disease.
2. Indirect diagnostic tests (eg, 1–3-β-D-glucan) are not yet validated for clinical use in neonatal settings.
3. Two antifungal treatment strategies are possible: targeted therapy or empirical/pre-emptive/diagnostic-driven treatment.
4. Information on local epidemiology and fungal ecology is mandatory and pivotal to guide initial therapeutic choices.
5. Consider penetration of antifungal drugs in sanctuaries and target the CNS and the Candida bio-films.
6. Consider colonisation status.
7. Consider the central venous catheter status and the possibility/probability that bio-films have formed.
8. Assess and rule out possible end-organ localisations.
9. Consider previous exposure to antifungal prophylaxis, if any, and switch to a different antifungal class.
Fluconazole prophylaxis prevents invasive *Candida* infections in preterm infants

- Meta-analysis of 11 studies\(^1\)
  - 7 retrospective, 4 RCTs

**Fluconazole prophylaxis reduces:**\(^1\)

- The chance of developing IFI in high-risk infants <1000g by 91%
  (OR 0.09; 95% CI 0.04 to 0.24; \(p=0.0004\))
- The chance of developing IFI in all infants <1500g by 85%
  (OR 0.15; 95% CI 0.08 to 0.26; \(p<0.0001\)).
- The overall mortality rate by 26% (11% vs. 16.3%)
  (OR 0.74; 95% CI 0.58-0.95; \(P=0.017\))
- The *Candida*-related mortality by 96% (virtually eliminated)
  (OR 0.04; 95% CI 0.01 to 0.31; \(p=0.006\))
- No effect on developmental long-term outcomes assessed\(^2\)
- Ecological safety data available up to 8 years:
  - No shifts towards fluconazole-resistant spp\(^3\)
  - No selection of resistant strains\(^4\)

Summary of pending, unresolved issues with neonatal IFI (1)

- Blood culture may often be negative \(\rightarrow\) need for \textit{empiric treatment}

- Frequent \textit{end-organ localisations} and high risk of CNS involvement \(\rightarrow\) poor NeuroDevelopm outcomes \(\rightarrow\) better to treat with the most potent and wide-spectrum antifungal available (to avoid/limit poor outcomes) : \textit{“Hit fast, Hit hard” strategy}

- Causative fungal agents \(\rightarrow\) 99\% \textit{Candida spp.}, but 5–10\% are inherently resistant to fluconazole \(\rightarrow\) avoid Fluco for treatment

- \textbf{Neonates have a prolonged need for CVC} \(\rightarrow\) high risk of \textit{hub colonisation} + \textit{biofilms} \(\rightarrow\) choose a drug active on biofilms (not Fluco !!)

Hence, \textbf{ideal antifungal drugs for neonates must have}:

- Significant activity against biofilms
- Significant activity against \textit{C. glabrata, C. tropicalis} and \textit{C. krusei} (because they may survive prophylactic fluconazole)
- Ability to be used in mono-therapy, good tolerability, No interactions
Summary of pending, unresolved issues with neonatal IFI (2)

- Fluconazole is widely used for prophylaxis, but not authorized;
  - how can we find a solution?

- RCT of fluco prophylaxis are no more feasible/ethical
  - how can we find a solution?

- Micafungin is authorized, but effective dosages are likely different than those in the label
  - how can we find a solution?

- Studies on “Old” antifungals (e.g., Ampho B, Liposomal Ampho, etc) are not supported by Pharma as they are not rentable in neonatology
  - how can we find a solution?

- Superiority trials for new antifungals are impossible to perform in preterm neonates owing to limited numerosity, but nonetheless new antifungals would be welcome

- The outcome to measure for neonatal trials should be “survival free from NDI at 20 months”, and not “survival”, “clearance of infection”, or similar other indicators
  - how can we find a solution?
Thank you for your attention!

Neonatology and Neonatal Research Foundation
“Crescere insieme al Sant’Anna”
www.fondazionesantanna.org

See you in TORINO 2016

5th INTERNATIONAL NEONATOLOGY CONFERENCE

September 2016

www.iccn2014.eu
Disclosure slide

Conflicts of interest in the last 5 years

- Acted as an advisor or consultant for BIOSYNEXUS Inc., USA, and ASTELLAS US.
- Served as a paid speaker or chairman for ABBVIE, USA and ASTELLAS, UK
KEY ISSUES for TREATMENT of Neonatal IFI: what to do when prophylactic fluconazole is not given, or when it does not work

Consider the specific characteristics of neonatal SFI
- Prolonged need for CVC → high risk of hub colonisation + biofilms
- Blood culture may often be negative → need for empiric treatment
- Frequent end-organ localisations and high risk of CNS involvement
- Causative fungal agents → 99% Candida spp. (Aspergillus spp. very uncommon in neonates), 5–10% inherently resistant to fluconazole

Optimal rescue strategy → “Hit fast, Hit hard”
- Treat with the most potent and wide-spectrum antifungal available (to avoid/limit poor outcomes)

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
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>
<thead>
<tr>
<th></th>
<th>Micafungin&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Caspofungin&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Anidulafungin&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive candidiasis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Neutropenic patients</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Paediatric patients</td>
<td>Yes</td>
<td>≥ 12 months</td>
<td>No</td>
</tr>
<tr>
<td>Neonates</td>
<td>Yes</td>
<td>Limited data</td>
<td>No</td>
</tr>
<tr>
<td>Prophylaxis in HSCT patients or expected neutropenic patients</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>

1. MYCAMINE® (micafungin) powder for solution for infusion SPC. Astellas Pharma Ltd. September 2011
2. CANDICAS® (caspofungin) powder for concentrate for solution for infusion SPC. Merck Sharp & Dohme Limited. September 2011
3. ECALTA® (anidulafungin) powder and solvent for concentrate for solution for infusion SPC. Pfizer Limited. August 2011
Probiotics are beneficial in promoting a ‘good’ enteric microbiota in preterm neonates, preventing colonisation by many pathogens including the various *Candida* spp\(^1\)

**Which probiotic products?**

<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, Clin Infect Dis 2006</td>
<td>Lactobacillus <em>rhamnosus</em> GG</td>
<td><em>Candida</em> gut colonisation in &lt;1500g neonates</td>
<td>23.1%</td>
<td>48.8%</td>
<td>0.01</td>
</tr>
<tr>
<td>Romeo et al, J Perinatol 2011</td>
<td>Lactobacillus <em>reuterii</em></td>
<td><em>Candida</em> gut colonisation in &lt;2500g neonates</td>
<td>7.1%</td>
<td>22.9%</td>
<td>0.01</td>
</tr>
<tr>
<td>Romeo et al, J Perinatol 2011</td>
<td>Lactobacillus <em>rhamnosus</em> GG</td>
<td><em>Candida</em> gut colonisation in &lt;2500g neonates</td>
<td>10.7%</td>
<td>22.9%</td>
<td>0.01</td>
</tr>
</tbody>
</table>

LACTOFERRIN prevents sepsis by all pathogens, including *Candida* spp

<table>
<thead>
<tr>
<th></th>
<th>LF combined N=304</th>
<th>PLACEBO N=168</th>
<th>R.R.</th>
<th>95% C.I.</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late-onset sepsis (all agents)</td>
<td>5.3%</td>
<td>17.3%</td>
<td>0.28</td>
<td>0.16–0.50</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LOS by Gram-positive</td>
<td>1.2%</td>
<td>5.4%</td>
<td>0.21</td>
<td>0.07–0.82</td>
<td>0.02</td>
</tr>
<tr>
<td>LOS by Gram-negative</td>
<td>3.4%</td>
<td>6.5%</td>
<td>0.48</td>
<td>0.35–0.98</td>
<td>0.05</td>
</tr>
<tr>
<td><em>Candida</em> enteric colonisation</td>
<td>17.1%</td>
<td>13.9%</td>
<td></td>
<td></td>
<td>0.43</td>
</tr>
<tr>
<td><em>Candida</em> systemic infection</td>
<td>0.8%</td>
<td>5.4%</td>
<td></td>
<td>0.09–0.77</td>
<td>0.009</td>
</tr>
<tr>
<td>Rate of progression from <em>Candida</em> colonisation to infection</td>
<td>7.8%</td>
<td>41.9%</td>
<td>0.29</td>
<td>0.09–0.89</td>
<td>0.02</td>
</tr>
<tr>
<td>Mortality attributable to <em>Candida</em> spp</td>
<td>0%</td>
<td>1.2%</td>
<td></td>
<td></td>
<td>0.50</td>
</tr>
</tbody>
</table>

Study Design
- Prospective, randomised, double-blind clinical trial over a 30-month period
- 100 preterm ELBW infants (ventilated, or with CVC) randomly assigned to intravenous fluconazole (3 mg/kg every second day) or placebo during the first 6 weeks of life
- Weekly surveillance cultures from all patients

<table>
<thead>
<tr>
<th></th>
<th>Fluconazole</th>
<th>Placebo</th>
<th>95% C.I</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fungal colonisation</td>
<td>22%</td>
<td>60%</td>
<td>0.18–0.56</td>
<td>0.002</td>
</tr>
<tr>
<td>Invasive fungal infection</td>
<td>0%</td>
<td>20%</td>
<td>0.04–0.36</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Conclusions
Patterns of sensitivity to fluconazole of fungal isolates did not change during the study period. No adverse effects of fluconazole treatment were documented.

“Prophylactic IV fluconazole during the first six weeks of life in ELBW infants is effective in preventing fungal colonisation and infection”
**FLUCONAZOLE** either dosage (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><strong>Total invasive fungal infections (IFI; %)</strong></td>
<td>7/216 (3.2%)</td>
<td>14/106 (13.2%)</td>
<td>0.25</td>
<td>0.10-0.59</td>
<td>0.001</td>
</tr>
<tr>
<td>IFI caused by natively fluconazole-resistant <em>Candida</em> spp</td>
<td>1/7</td>
<td>1/14</td>
<td></td>
<td></td>
<td>&gt;0.99</td>
</tr>
<tr>
<td><strong>Overall colonisation</strong></td>
<td>19/216 (8.8%)</td>
<td>31/106 (29.2%)</td>
<td>0.30</td>
<td>0.18-0.51</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Colonisation by natively fluconazole-resistant <em>Candida</em> spp</td>
<td>3/216 (1.4%)</td>
<td>2/106 (1.9%)</td>
<td></td>
<td></td>
<td>0.67</td>
</tr>
<tr>
<td><strong>Overall mortality</strong></td>
<td>18/216 (8.3%)</td>
<td>10/106 (9.4%)</td>
<td></td>
<td></td>
<td>0.83</td>
</tr>
<tr>
<td>Mortality attributable to fungi</td>
<td>0/216 (0%)</td>
<td>2/106 (1.9%)</td>
<td></td>
<td></td>
<td>0.10</td>
</tr>
</tbody>
</table>

Manzoni P, Stolfi I, Pugni L, et al (on behalf of The Italian Task Force for the study and prevention of Neonatal Fungal Infections)

*Prophylactic fluconazole is effective in preventing fungal colonisation and infection in preterm neonates: a multicenter, randomised trial in Italy*

Candida spp distribution in preterm neonates

- C. albicans: 58%
- C. parapsilosis: 34%
- C. tropicalis: 4%
- C. glabrata: 2%
- C. lusitaniae: 2%
- C. krusei: 0.2%

Mortality and fungal species in preterm neonates

<table>
<thead>
<tr>
<th>Organism</th>
<th>Deaths /nr. of isolates</th>
<th>Mortality rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. albicans</td>
<td>63/147</td>
<td>42.9 %</td>
</tr>
<tr>
<td>C. parapsilosis</td>
<td>25/127</td>
<td>19.7 %</td>
</tr>
<tr>
<td>C. tropicalis</td>
<td>0/3</td>
<td>0.0 %</td>
</tr>
<tr>
<td>Other Candida spp</td>
<td>8/25</td>
<td>32.3 %</td>
</tr>
</tbody>
</table>