Preventing neonatal fungal infections

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University of Sydney, Australia
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WSPID 2011
www.kenes.com/wspid
Invasive fungal infection in neonates

- Incidence highest in smallest infants
- Diagnosed late
- High mortality
- Rising incidence
Invasive fungal infection in neonates

CLINICAL FEATURES
Age at culture diagnosis: median 15 days (range 1-90)
Haematological

• Neutropenia common

• Commonest cause of neutropenia is IUGR

• For any septic neutropenic baby, bacterial sepsis more likely than fungal
Risk factors

- Broad spectrum antibiotics
- Prolonged parenteral nutrition
- Central venous catheters
- Prolonged endotracheal intubation
- H2 blockers
- Fungal colonisation (especially heavy)
Broad spectrum antibiotics

• Cotton CM et al, Pediatrics 2006; 118: 717-22

• NICHHD study

• 284 babies with invasive candidiasis

• Third generation cephalosporin exposure: RR 2.2 (95% CI 1.4-3.3)
Early enteral feeding

- Rapid enteral feeds (median <12.5 days) or Slow enteral feeds (median >12.5 days)
- Reduced incidence of late-onset bacterial sepsis in babies fed earlier:
  - 14.0% vs 20.4%  \( P=0.002 \)
- No data on fungal infections
- Fewer central lines
Invasive fungal infection in neonates

INCIDENCE
ASGNI

Prospective, multi-center study of systemic sepsis in Australasian neonates

23 hospitals contributed since 1992

Invasive fungal infection

Positive blood +/- CSF culture (or raised CSF WBC)
Babies <1500g
1993 - 2006

15 hospitals - median 7.5 per year (range 4 - 11)
Invasive fungal infection by birth weight: ASGNI, 1993-2006

![Bar chart showing the number of invasive fungal infections by birth weight. The chart indicates a significant increase in infections among newborns weighing less than 750 grams, with a substantial decrease in infections among those weighing between 750 and 999 grams and a minor decrease among those weighing between 1000 and 1499 grams.]
Incidence of fungal infection

\[ \leq 1500\text{g} \]

118 of 14,788 = 0.82\% (95\% CI 0.66-0.95\%)

\[ \leq 1000\text{g} \]

106 of 5,968 = 2.02\% (95\% CI 1.92-2.12\%)
# International studies

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Definition</th>
<th>Birth weight</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA¹</td>
<td>1998 - 2001</td>
<td>Blood &amp; CSF</td>
<td>&lt;1000g</td>
<td>7.7%</td>
</tr>
<tr>
<td>Italy²</td>
<td>2004 - 2005</td>
<td>Blood &amp; CSF</td>
<td>&lt;1500g</td>
<td>9.4%</td>
</tr>
<tr>
<td>UK³</td>
<td>2003</td>
<td>Blood, CSF, urine + others</td>
<td>&lt;1500g &lt;1000g</td>
<td>1.0% 2.1%</td>
</tr>
<tr>
<td>Australia + NZ⁴</td>
<td>1993 - 2006</td>
<td>Blood &amp; CSF</td>
<td>&lt;1500g &lt;1000g</td>
<td>0.8% 2.0%</td>
</tr>
</tbody>
</table>

Species variation

- C. parapsilosis: 33%
- C. glabrata: 3%
- C. famata: 1%
- C. guilliermondii: 1%
- C. albicans: 62%
Invasive fungal infection in neonates

ANTIFUNGAL PROPHYLAXIS
Which prophylaxis?

- Fluconazole
- Amphotericin
- Oral nystatin
Fluconazole prophylaxis

• Azole antifungal: well absorbed

• Given (oral or IV) for
  – 30 days to babies <1500g
  – 45 days to babies <1000g

• Selective chemoprophylaxis:
  – <1500g if on broad spectrum antibiotics >3days
  – third generation cephalosporin
  – Colonised with Candida
Randomised placebo controlled trials of fluconazole: invasive fungal infection

<table>
<thead>
<tr>
<th></th>
<th>Fluconazole</th>
<th>Placebo</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infected</td>
<td>10 (3.1%)</td>
<td>30 (14.2%)</td>
<td>40</td>
</tr>
<tr>
<td>Not infected</td>
<td>315</td>
<td>181</td>
<td>496</td>
</tr>
<tr>
<td>TOTAL</td>
<td>325</td>
<td>211</td>
<td>536</td>
</tr>
</tbody>
</table>

Relative risk 0.23 (95% CI 0.11, 0.46)
Randomised placebo controlled trials of fluconazole: death from all causes

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<thead>
<tr>
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<th>Fluconazole</th>
<th>Placebo</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died</td>
<td>27 (8.5%)</td>
<td>30 (14.6%)</td>
<td>57</td>
</tr>
<tr>
<td>Survived</td>
<td>292</td>
<td>176</td>
<td>468</td>
</tr>
<tr>
<td>TOTAL</td>
<td>319</td>
<td>206</td>
<td>525</td>
</tr>
</tbody>
</table>

Relative risk 0.61 (95% CI: 0.37, 1.03)
Evidence regarding fluconazole

- Fluconazole prevents fungal infections
- Trend to saving lives
- High incidence: NNT <1500g = 8 (5-20)
- Low incidence: NNT = 125 (or 45 <1000g)
Fluconazole: safety concerns

Hepatotoxic

May induce resistance

Selection of non-albicans Candida
Amphotericin B

• Much more toxic

• Much more expensive
WHAT ARE THE SIDE EFFECTS OF THIS PRESCRIPTION?

PHARMACY

POVERTY
Oral nystatin

- Polyene antifungal
- Not absorbed from GI tract
- Reduces colonisation
- Given orally 1mL 8-hourly until well
Nystatin prophylaxis


• Babies <1250g

• Oral nystatin 100,000U in 1 mL, 8-hourly

33 treated: 4 colonised (12%); 2 sepsis (6%)

34 control: 15 colonised (44%); 11 sepsis (32%)
### ASGNI, 1993-2006

Oral nystatin prophylaxis

[Howell A et al. ADC(F&N) 2009; 94: F429-33. ]

<table>
<thead>
<tr>
<th>Incidence &lt;1500g</th>
<th>Incidence &lt;1000g</th>
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</thead>
<tbody>
<tr>
<td>Yes 0.54%</td>
<td>Yes 1.23%</td>
</tr>
<tr>
<td>No 1.23%</td>
<td>No 2.67%</td>
</tr>
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</table>

P<0.0001
Three hospitals changed policy

<table>
<thead>
<tr>
<th>Incidence &lt;1500g</th>
<th>Incidence &lt;1000g</th>
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</thead>
<tbody>
<tr>
<td>Yes 0.69%</td>
<td>Yes 1.23%</td>
</tr>
<tr>
<td>No 1.13%</td>
<td>No 3.25%</td>
</tr>
<tr>
<td>P&gt;0.05</td>
<td>P&lt;0.005</td>
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</table>
Meta-analysis
Invasive fungal infections <1500g

• Fluconazole (6.6%) vs. placebo (16.6%)
  RR = 0.37 (95% CI 0.24-0.56)

• Oral nystatin (5.3%) vs. placebo (32.9%)
  RR = 0.16 (0.11-0.23)

• Fluconazole (4.1%) vs. oral nystatin (7.3%)
  RR = 0.56 (95% CI 0.20-1.60)
Conclusions

• Reduce broad spectrum antibiotic use

• Reduce third generation cephalosporin use

• Early enteral feeds, catheters out, less TPN

• Antifungal prophylaxis is effective: use it

• Nystatin may be as good as fluconazole

• Use nystatin when incidence low or cost an issue
ACKNOWLEDGEMENTS

ASGNI
