What’s New in Neonatal Candidiasis

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Anatomic
  • Primary barriers to defense in children (mucosa and integument) are fragile and easily colonized

Physiologic
  • Greater ability to tolerate more intensive treatments

Immunologic
  • Functional immaturity of phagocytes and T lymphocytes
  • Congenital immunodeficiencies

Candidiasis: Incidence

Zaoutis T, *PIDJ* 2004
Zaoutis, et al. *CID* 2005
Epidemiology

- 3rd most common cause of late-onset neonatal sepsis – 12.2% of cases
- Incidence/100,000 admissions – 2000 National Data
  - Neonates 150 (95% CI: 130, 160)
  - Older Children 43 (95% CI: 35, 52)
  - Adults 30 (95% CI: 26-34)
- US National Nosocomial Surveillance System Hospitals (NNIS) from 1995 to 2004
  - 128 NICUs (130,523 neonates)
  - 1997 cases of Candidemia
  - Median 7.5% (IQR: 4.6, 13.5%)

Stoll BJ, Pediatrics 2002; Zaoutis TE, CID 2007; Fridkin SK Pediatrics 2006
Neonatal Candidiasis: Incidence and Birth Weight

- >1500 gms: 0.00%
- 1001-1500: 2.00%
- 751-1000: 4.00%
- 401-750: 12.00%

Benjamin DK et al. Pediatrics 2005
Risk Factors

- Gestational age
- Prolonged rupture of membranes
- H$_2$ blockers
- Intubation
- Third-generation cephalosporins
  - Carbapenemems and other broad-spectrum antibiotics
- Hyperalimentation
  - Lack of enteral feeding
- Central venous catheters

Neonatal Candidiasis: Incidence over Time

Neonatal Candidiasis: Incidence over Time by Species

Neurodevelopmental Outcomes and Bloodstream Infection in Infants <1000 g

* * *

57%

* p ≤ 0.001 vs no infection.

## Attributable Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Mortality (95% CI)</th>
<th>LOS (95% CI)</th>
<th>Cost (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal &lt; 1000 g</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12% (5.5, 18.3)</td>
<td>3 (-5, 9)</td>
<td>39,045</td>
<td></td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(1,374 - 76,715)</td>
<td>(1,374 - 76,715)</td>
<td></td>
</tr>
<tr>
<td>Neonatal &gt; 1000 g</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 4% (-9.8, 1.4)</td>
<td>16 (8,24)</td>
<td>122,302</td>
<td></td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td>(80,457 - 164,148)</td>
<td></td>
</tr>
</tbody>
</table>

Clinical Vignette

- 26-week, 620-gram infant
- Extubated to CPAP on day of life (DOL) 2
- Enteral feedings started DOL 3
- DOL 15
  - Apnea
  - Hypotension
  - Platelet count fell from 165,000 to 70,000
- Blood, Urine and CSF sent for culture
  - Broad spectrum antibiotic therapy started
Should Empiric Antifungal Therapy Be Initiated?

- Review of 49 cases with fungal sepsis (Makhoul IR, Pediatrics 2001)
  - No mortality in 35 VLBW infants with fungal sepsis
  - Attributed this outcome to empiric therapy with amB
- Pre-post intervention study (Procianoy RS. Eur J Pediatr)
- <1500 g or “Very Sick NICU patient”
- Clinical signs of infection plus
  - Vancomycin and/or 3rd generation cephalosporin x 7 days
  - And 1 of the following: TPN, Mechanical ventilation, Postnatal steroids, H2 blocker, Candida rash or thrush
- Eliminated Candida-related mortality
  - 11 of 18 (61%) - No empiric therapy
  - 0 of 6 (0%) - Empiric therapy
## Multivariable Analysis of Predictors of Candidemia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Category</th>
<th>OR</th>
<th>95%CI</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age</td>
<td>≥28 wk</td>
<td>Referent</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>25-27 wk</td>
<td>2.02</td>
<td>(1.52-3.05)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&lt;25 wk</td>
<td>4.15</td>
<td>(3.12-6.12)</td>
<td>2</td>
</tr>
<tr>
<td>Thrombocytopenic</td>
<td>Value ≥150</td>
<td>Referent</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Value &lt;150</td>
<td>3.56</td>
<td>(2.68-4.74)</td>
<td></td>
</tr>
<tr>
<td>Cephalosporin or</td>
<td>No</td>
<td>Referent</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>carbapenem</td>
<td>Yes</td>
<td>1.77</td>
<td>(1.33-2.29)</td>
<td></td>
</tr>
</tbody>
</table>

Need for Empiric Antifungal Therapy: Clinical Predictive Model

<table>
<thead>
<tr>
<th>Score</th>
<th>Candidemic</th>
<th>Not Candidemic</th>
<th>Sensitivity</th>
<th>Calculated Specificity</th>
<th>LR(+)</th>
<th>LR(-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4</td>
<td>2882</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>47</td>
<td>6626</td>
<td>99%</td>
<td>14%</td>
<td>1.15</td>
<td>0.08</td>
</tr>
<tr>
<td>2</td>
<td>79</td>
<td>5155</td>
<td>85%</td>
<td>47%</td>
<td>1.62</td>
<td>0.31</td>
</tr>
<tr>
<td>3</td>
<td>77</td>
<td>3112</td>
<td>63%</td>
<td>71%</td>
<td>2.18</td>
<td>0.52</td>
</tr>
<tr>
<td>4</td>
<td>82</td>
<td>2233</td>
<td>41%</td>
<td>85%</td>
<td>2.78</td>
<td>0.70</td>
</tr>
<tr>
<td>5</td>
<td>59</td>
<td>877</td>
<td>17%</td>
<td>96%</td>
<td>4.10</td>
<td>0.87</td>
</tr>
</tbody>
</table>

Selection of Antifungal Agent

- IDSA Guidelines for the Treatment of Neonatal Candidiasis
- AmB deoxycholate 1 mg/kg (A-II)
  - Test dose not required; may contribute to delayed clearance
  - Tolerated well with limited effect on creatinine
- Lipid formulations at 3-5 mg/kg (B-II)
- Fluconazole 12/mg/kg (B-II)
- Echinocandins should be used with caution
  - Caspofungin 25 mg/m^2 once daily similar levels to adult dose of 50 mg/day^4
  - Micafungin 5-7 mg/kg in neonates > 1000 grams similar levels to adults receiving 100 mg and 150 mg

Does removal of the catheter improve outcomes?

- Prompt removal is associated with:
  - Lowered mortality rates
  - Shorter duration of candidemia
  - Reduced end-organ dissemination
- Intravascular catheter removal is strongly recommended (A-II)

Cohort study of 320 infants with candidemia Prompt (<24 h) vs. delayed

- All cases of candidemia
  - Mortality 21% vs. 37% \((P=0.024)\)
  - Combined mortality + neurodevelopmental impairment (NDI) \((P=0.01)\)
  - No difference for NDI alone (45% vs. 63%) \((P=0.08)\)
  - No difference in time to clearance (5 vs 7.3 d)

- **Catheter removal and species**
  - *C albicans*: 35% vs. 48%
  - *C.parapsilosis*: 10% vs. 31%

Does Removal of the Catheter Improve Outcomes?

<table>
<thead>
<tr>
<th>Variable</th>
<th>No.</th>
<th>OR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catheter removal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early (within 1 day)</td>
<td>57</td>
<td></td>
<td>Reference</td>
</tr>
<tr>
<td>Late</td>
<td>132</td>
<td>2.69</td>
<td>1.25-5.79</td>
</tr>
<tr>
<td>Gestational age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 25 weeks</td>
<td>83</td>
<td></td>
<td>Reference</td>
</tr>
<tr>
<td>&lt; 25 weeks</td>
<td>106</td>
<td>3.91</td>
<td>1.85-8.29</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>94</td>
<td></td>
<td>Reference</td>
</tr>
<tr>
<td>Male</td>
<td>95</td>
<td>2.30</td>
<td>1.09-4.84</td>
</tr>
</tbody>
</table>

Benjamin et al Pediatrics 2006
When is the Bloodstream Clear of *Candida*?

- Duration of candidemia often prolonged
- Up to 10% of neonates will have positive blood cultures > 14 days
- 21% of infants with *Candida* BSI will have intermittent negative cultures between positive cultures
- Daily cultures should be performed until 3 or more documented negative cultures
- New central access could be placed >2 days after 3rd culture documenting clearance
- Duration of therapy: 3 weeks

End-Organ Dissemination

- Meta-Analysis
- Prevalence of:
  - Endophtalmitis 3% (IQR: 0-17%)
  - Meningitis 15% (IQR: 3-23%)
  - Brain Abscess or Ventriculitis 4% (IQR: 3-21%)
  - Endocarditis 5% (IQR: 0-13%)
  - Renal Candidiasis
    - By renal ultrasound 5% (IQR: 0-14%)
    - Positive urine culture 61% (IQR: 40-76%)
  - Lumbar puncture and eye exam recommended (B-III)
  - Imaging if persistently positive cultures

Antifungal Prophylaxis (FP) in Preterm Infants

Let’s look at the data.....
Oral Prophylaxis - Nystatin

• One RCT to date
  – 67 intubated infants, birth weight < 1250 g
  – Bloodstream infection
    • 0/33 (0%) vs. 2/34 (6%) placebo, $P= .16$
  – UTI
    • 2/33 (6%) vs. 10/34 (29%) placebo, $P= .01$

• 1988-2006
  – A few retrospective reports of nystatin failure when initiated after colonization was detected

Oral Prophylaxis - Nystatin

• Prospective quasi-randomized study
  – Oral nystatin prophylaxis (NP) reduced the invasive candidiasis in ELBW and VLBW infants ($P=0.004$)
    • Controls 36%
    • In colonized infants 14%
    • NP started at birth 3.6%

Fluconazole Prophylaxis Studies

• Randomized Placebo Controlled studies
  – Kicklighter  2001 (Colonization Study)
  – Kaufman  2001
  – Parikh  2007
  – Manzoni 2007 (Multicenter RCT)

• Randomized Controlled studies
  – Kaufman  2005 (Dosing schedule comparison study)

• Non-randomized with historic retrospective controls
  – Bertini  2005
  – Healy  2005 and 2008
  – Manzoni 2006
  – Uko  2006
  – Aghai  2006
  – Weitkamp  2008
Fluconazole Prophylaxis: Randomized Placebo-Controlled Trials

3 mg/kg with IV access up to 6 weeks

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>FP</th>
<th>Placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaufman 2001</td>
<td>100 &lt;1000 g</td>
<td>0 of 50 (0%)</td>
<td>10 of 50 (20%)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Subanalysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N</th>
<th>FP</th>
<th>Placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subgroup &lt;24 wks</td>
<td>9</td>
<td>0 of 4 (0%)</td>
<td>4 of 5 (80%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Subgroup ≥24 wks</td>
<td>91</td>
<td>0 of 46 (0%)</td>
<td>6 of 45 (13%)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Fluconazole Prophylaxis: Randomized Placebo-Controlled Trials

- Multicenter, randomized, controlled trial
- 1:1:1 randomization
- 3 mg/kg, 6 mg/kg, or placebo

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>FP</th>
<th>Placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manzoni 2007 (NEJM)</td>
<td>322 &lt;1500 g</td>
<td>7 of 216 (3.2%)</td>
<td>14 of 106 (13.2%)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

3 mg/kg and 6 mg/kg BOTH equally effective
*<1000 g (P=.02)
*<27 weeks (P=.007)

Analysis of Randomized Controlled Trials

• Efficacy
  – Cochrane Review 2007
  – Typical relative risk: 0.23; 95% confidence interval, 0.11, 0.46
  – Number needed to treat of 9 (95% confidence interval 6, 17)

## Fluconazole Prophylaxis
### Retrospective Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>N (BIRTH WEIGHT)</th>
<th>FP</th>
<th>Control Group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healy 2005</td>
<td>446 (&lt;1000 g)</td>
<td>3 of 240 (1%)</td>
<td>15 of 206 (7%)</td>
<td>.001</td>
</tr>
<tr>
<td>Manzoni 2006</td>
<td>129 (&lt;1000 g)</td>
<td>1 of 72 (1.4%)</td>
<td>13 of 57 (22.8%)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>336 (1000-1500 g)</td>
<td>3 of 153 (2%)</td>
<td>9 of 183 (4.9%)</td>
<td>.009</td>
</tr>
<tr>
<td>Bertini 2005</td>
<td>255 (&lt;1500 g)</td>
<td>0 of 136 (0%)</td>
<td>9 of 119 (7%)</td>
<td>.003</td>
</tr>
<tr>
<td>Uko 2006</td>
<td>384 (&lt;1500 g)</td>
<td>2 of 178 (1.1%)</td>
<td>13 of 206 (6.3%)</td>
<td>.007</td>
</tr>
<tr>
<td>Aghai 2006</td>
<td>277 (&lt;1000 g)</td>
<td>0 of 140 (0%)</td>
<td>9 of 137 (6.6%)</td>
<td>&lt;.006</td>
</tr>
</tbody>
</table>

Adverse Events

• No increase in other infections
  – Bacteremia
  – Necrotizing enterocolitis

• Long-term outcomes (mean 14 months)
  • No effect on growth
  • No effect on cholestasis or other liver disease
  • No increase in adverse neurodevelopmental outcomes

### Fluconazole Prophylaxis: Cholestasis

#### Retrospective studies:

<table>
<thead>
<tr>
<th>Study</th>
<th>Cholestasis</th>
<th>FP</th>
<th>Control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aghai 2006</td>
<td>db &gt;2</td>
<td>43%</td>
<td>8.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Discharge</td>
<td>6.7%</td>
<td>3.6%</td>
<td>0.54</td>
</tr>
<tr>
<td>Uko 2006</td>
<td>db &gt;5</td>
<td>0.6 (0-19)</td>
<td>0.9 (0-21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>db &gt;5</td>
<td>4%</td>
<td>12%</td>
<td>0.015</td>
</tr>
</tbody>
</table>

#### Randomized placebo controlled trials:

<table>
<thead>
<tr>
<th>Study</th>
<th>FP</th>
<th>Placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaufman 2001</td>
<td>NO DIFFERENCE</td>
<td>0.34</td>
<td></td>
</tr>
<tr>
<td>Manzoni 2007</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Fluconazole Prophylaxis: Resistance

• No significant resistance in 1232 FP treated patients
  – During 4 - 6 week prophylaxis periods for any patient
  – During 24 - 36 month study periods for all patients

• No increase of candidemia due to *C glabrata* or *C krusei*

Colonization and Infection with *C. glabrata* or *C. krusei* Species

Colonization During and After FP

Susceptible-Dose-Dependent and Resistant Isolates

Kaufman DA et al. E-PAS2008:633758.10
Treatment of Invasive Candidiasis in Fluconazole Prophylaxis Studies

• All studies used amphotericin B primarily for treatment of infections
  – Both AmB deoxycholate or lipid preparations
  – This decreases overall unit exposure to fluconazole
  – May have intermittently eliminated less susceptible or resistant fungi
Changes in fluconazole susceptibility over time among bloodstream isolates of *C. parapsilosis*

<table>
<thead>
<tr>
<th>Time Period</th>
<th>No. of Isolates</th>
<th>MIC (mg/liter)</th>
<th>% of isolates at MIC (mg/liter of:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Range</td>
<td>50%</td>
<td>90%</td>
</tr>
<tr>
<td>1990-1994</td>
<td>7</td>
<td>0.5-2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>1999-2000</td>
<td>7</td>
<td>1-16</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>2001-2002</td>
<td>12</td>
<td>2-64</td>
<td>8</td>
<td>64</td>
</tr>
<tr>
<td>TOTAL</td>
<td>26</td>
<td>0.5-64</td>
<td>2</td>
<td>16</td>
</tr>
</tbody>
</table>

* 50%, MIC at which 50% of the isolates are inhibited; 90%, MIC at which 90% of the isolates are inhibited.

Fluconazole Prophylaxis Costs

- Fluconazole prophylaxis is cost effective.
- Uko et al. examined the cost with fluconazole prophylaxis and showed a significant cost benefit of $516,702 over 18 months in their NICU.
- The pharmacy costs of one dose is approximately $18, making the cost of a 4 to 6 week course (8 to 12 doses) between $144 and $216 per patient.

### Impact of Prevalence on Decision to Administer Prophylaxis

#### Incidence < 1000 grams

<table>
<thead>
<tr>
<th>center</th>
<th>incidence</th>
<th>6 weeks</th>
<th>Reduce</th>
<th>Risk Difference</th>
<th>NNT</th>
<th>NNT Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>&gt;250</td>
<td>&gt;750</td>
</tr>
<tr>
<td>Low</td>
<td>1.2%</td>
<td>1.0%</td>
<td>0.2%</td>
<td>0.8%</td>
<td>126</td>
<td>379</td>
</tr>
<tr>
<td>Low</td>
<td>2.1%</td>
<td>1.8%</td>
<td>0.4%</td>
<td>1.4%</td>
<td>69</td>
<td>207</td>
</tr>
<tr>
<td>Moderate</td>
<td>4.4%</td>
<td>3.7%</td>
<td>0.7%</td>
<td>3.0%</td>
<td>33</td>
<td>100</td>
</tr>
<tr>
<td>Moderate</td>
<td>6.7%</td>
<td>5.7%</td>
<td>1.1%</td>
<td>4.5%</td>
<td>22</td>
<td>66</td>
</tr>
<tr>
<td>High</td>
<td>10.7%</td>
<td>9.1%</td>
<td>1.8%</td>
<td>7.3%</td>
<td>14</td>
<td>41</td>
</tr>
<tr>
<td>Danger</td>
<td>17.9%</td>
<td>15.2%</td>
<td>3.0%</td>
<td>12.1%</td>
<td>8</td>
<td>25</td>
</tr>
</tbody>
</table>
Fluconazole Prophylaxis: Who and How?

- In nurseries with high rates of invasive candidiasis, fluconazole prophylaxis may be considered in neonates with birth weights less than 1000 grams (A-I).
- Antifungal drug resistance, drug-related toxicity, and neurodevelopmental outcomes should be observed (A-III).
- 3 mg/kg IV fluconazole
  - Similar efficacy and less risk for resistance compared to higher doses
  - While they require IV access
  - Starting on DOL 1; First 6 weeks of life
  - Twice weekly dosing
- Use of different antifungal for treatment or empiric therapy
- AAP survey 34% of neonatologists used prophylaxis

Pappas P, CID 2009; Burwell L, Pediatrics 2006
Summary

- An important cause of morbidity and mortality
- Empiric therapy and catheter removal improve outcomes
- Amphotericin B is drug of choice for treatment
- Prophylaxis with fluconazole is effective in high-risk neonates
- More studies needed to determine long term impact of fluconazole on developing neonates
International Pediatric Fungal Network

About the International PFN

Dedicated to Understanding Pediatric Fungal Invasive Infections and Antifungals Through Global Collaboration

The incidence of pediatric invasive fungal disease is increasing. Coordinated clinical and laboratory investigative efforts have enhanced our understanding of fungal disease and improved the treatment of adult patients. However, most of these efforts have not incorporated children and neonates. Pediatric exclusion has limited our knowledge of the epidemiology and pathophysiology of pediatric fungal disease and has resulted in a paucity of data regarding the safety and efficacy of pediatric antifungal therapy. Previous pediatric cooperative models in other disciplines, including the Children’s Oncology Group and the Pediatric AIDS Clinical Trials Group, have successfully advanced our understanding and treatments of other childhood diseases.

The multi-center International Pediatric Fungal Network (PFN) was created to gain a complete understanding of the scope and character of pediatric fungal infections in order to improve the care of our patients. The primary mission of the PFN is to increase the knowledge of pediatric invasive fungal infections and discern any undescribed characteristics or outcomes unique to pediatric patients through a coordinated network of scientific investigation. In addition to advancing our understanding of the fundamental epidemiology of pediatric invasive fungal infections, the PFN will serve as an effective vehicle of cohesive investigators and centers to conduct ground-breaking diagnostic and therapeutic clinical trials focused on pediatric fungal infections, diagnostic surrogates, and antifungals. Clinical information on patients is captured through a secure electronic portal to maximize efficiency of data collection and analysis. Investigators are linked through conference calls and meetings to both plan future studies and analyze results.