Pharmacological Choices for the ELBW Infant

Antibiotics, Indomethacin, Caffeine, iNO, Hydrocortisone

What Is The Evidence?
Matthew M. Laughon, MD, MPH
Associate Professor
The University of North Carolina at Chapel Hill

FDA Disclosures
Not approved and off-label uses of iNO, caffeine and hydrocortisone will be discussed.

“All drugs cause harm to at least a small proportion of children who receive them.
Some drugs reduce or cure disease in children, and very few drugs benefit more children than are harmed by their use.”


Clinical Case

24 week male, 652 grams
» Intubated, surfactant in DR
• “Rule out sepsis”
» Ampicillin, gentamicin
• Hypotension
» Dopamine, dobutamine, hydrocortisone
• In preparation for extubation
» Caffeine
• PDA on echocardiogram on postnatal day 8
» Indomethacin

Postnatal day 14: worsening lung disease, r/o sepsis
» Vancomycin, piperacillin-tazobactam
• Postnatal day 22: NEC (medical)
» Ampicillin, gentamicin, metronidazole
» Morphine, lorazepam
• Day 28-60: evolving “BPD”
» Diuretics, dexamethasone x2 (DART), albuterol
» Dopamine, dobutamine, hydrocortisone
• PMA 36 weeks: pulmonary hypertension
» Sildenafil, diuretics, oxygen

Clinical Case

Synthetic vitamin K
kernicterus 1945–1961
• Sulfisoxazole
kernicterus 1953–1956
• Chloramphenicol
“gray baby” 1956–1960
• Novobiocin
jaundice 1957–1962
• Hexachlorophene
brain lesions 1952–1971

Neonatology Medication Mistakes

Epsom salt enemas
Mg intoxication 1964–1965
• Benzyl alcohol
“gasping” syndrome –1982
• E-ferol – 1980s
• Cisapride
prolonged QT – 1990-2000
• 2010s?

From: Robertson AF, Reflections on Errors in Neonatology (Part I,II,III) J Perinatology 2003; Slide courtesy of Reese Clark
Drugs used in ELBW Infants

- Adults
- Children
- Premature infants (including ELBW)
- Rare for neonatal specific drugs
  » Exceptions: surfactant, iNO

Sources of Dosing Information

Medications in ELBW Infants

<table>
<thead>
<tr>
<th>Rank</th>
<th>Medication</th>
<th>Exposure</th>
<th>FDA-approved</th>
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<tbody>
<tr>
<td>1</td>
<td>Gentamicin</td>
<td>896</td>
<td>Yes</td>
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<tr>
<td>2</td>
<td>Ampicillin</td>
<td>881</td>
<td>No</td>
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<tr>
<td>3</td>
<td>Caffeine citrate</td>
<td>704</td>
<td>No</td>
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<tr>
<td>4</td>
<td>Vancomycin</td>
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<tr>
<td>5</td>
<td>Furosemide</td>
<td>495</td>
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<td>6</td>
<td>Dopamine</td>
<td>425</td>
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<td>7</td>
<td>Beractant</td>
<td>339</td>
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<td>8</td>
<td>Iodosmethalin</td>
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<tr>
<td>9</td>
<td>Fentanyl</td>
<td>322</td>
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<tr>
<td>10</td>
<td>Albuterol</td>
<td>241</td>
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</table>

Relative increase in exposure between 2005 and 2010: ELBW

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<tr>
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<td>1</td>
<td>Azithromycin</td>
<td>2050</td>
<td>0.4</td>
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<td>2</td>
<td>Ibuprofen</td>
<td>1340</td>
<td>7.8</td>
<td>112</td>
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<td>3</td>
<td>Sildenafil</td>
<td>1125</td>
<td>1.6</td>
<td>20</td>
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<td>4</td>
<td>Caffeine</td>
<td>733</td>
<td>3.6</td>
<td>30</td>
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<td>5</td>
<td>Ceftiraxone</td>
<td>700</td>
<td>0.2</td>
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<td>6</td>
<td>Minirone</td>
<td>525</td>
<td>1.6</td>
<td>10</td>
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<td>7</td>
<td>Linazolid</td>
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<td>18</td>
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<td>8</td>
<td>Amiodarone</td>
<td>291</td>
<td>1.1</td>
<td>4.3</td>
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<td>9</td>
<td>Losartan</td>
<td>334</td>
<td>1.1</td>
<td>1.1</td>
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<td>10</td>
<td>Cotixin</td>
<td>219</td>
<td>2.7</td>
<td>8.6</td>
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Stages of Drug Development

- Phase 0: Pre-clinical
- Phase 1: Dosing (single or multiple)
- Phase 2: Safety (dosing)
- Phase 3: Efficacy
- Phase 4: Post-marketing

Phase I Trials

- Analysis
  » Pharmacokinetics
    » Dosing
    » Age effects on dosing?
  » Pharmacodynamics (effect)
    » Was the target achieved?
- Safety
  » Adverse events: related, not related, serious?
Phase I Trials

- Reporting/labeling
  - Data submission to FDA
  - Is disease similar to adults?
  - Pediatric dosing included in the label

Phase I Trials

- Are phase I trials important in pediatrics?
- Can't we just divide the adult dose by 70kg?

Organ Function Changes Over Time

Patient studies (phase 2 trials)

- 150-350 ill patients; informed consent
- OBJECTIVES: indication for use; type of patient; severity of disease; dose range, schedule and increment; pharmacokinetic studies in ill people; nature of side effects and severity; effects in special groups.

Phase I Trials: Peds Surprises

<table>
<thead>
<tr>
<th>Drug</th>
<th>Preferred adult dosing (mg/kg/day)</th>
<th>Pediatric or infant dosing (mg/kg/day)</th>
<th>PK data available in infants</th>
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<tbody>
<tr>
<td>Ampicillin</td>
<td>30–50</td>
<td>50</td>
<td>&gt;28 weeks GA</td>
</tr>
<tr>
<td>Piperacillin</td>
<td>250–340</td>
<td>150–300</td>
<td>&gt;28 weeks GA</td>
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<tr>
<td>Ciprofloxacin</td>
<td>10</td>
<td>30</td>
<td>&gt;4 months</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>3–7</td>
<td>3.5–7.5</td>
<td>&gt;28 weeks GA</td>
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<tr>
<td>Daptomycin</td>
<td>4–6</td>
<td>12</td>
<td>No data available</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>30</td>
<td>15</td>
<td>&gt;7 days of life</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>3–6</td>
<td>12</td>
<td>&gt;28 weeks GA</td>
</tr>
<tr>
<td>Micafungin</td>
<td>3</td>
<td>10–15</td>
<td>&gt;28 weeks GA</td>
</tr>
</tbody>
</table>

Patient studies (phase 3 trials)

- 1500-3500 ill patients
- multicenter
- more certain data for the objectives of phase 2 studies
- interactions between drugs start to become measurable in the larger population
- sub-groups start to be established
- special features and problems show up
New Drugs for Neonates

• 28 drugs studied in neonates; 24 related labeling changes
• 11/24 established safety and effectiveness
• 13 were never used in NICUs
• 8 were used in <60 neonates
• Ranitidine was used most often
  » 15,627 neonates, 35 exposures per 1000 admissions

Laughon. JAMA Pediatrics. 2013

Antibiotics

• Dosing
  » “Low hanging fruit”
  » Surrogate PD targets
  » Target adult exposures
  » Extrapolation

Antibiotics

- Dosing
- “Low hanging fruit”
- Surrogate PD targets
- Target adult exposures
- Extrapolation

Broad-spectrum antibiotic use

Meropenem Study Design

• NIH sponsored – BPCA off-patent mechanism
• 20 center, 200 infant, open-label, PK, and safety
• Inclusion Criteria
  » < 91 days of age
  » AND 1 of the following
    • 1) Complicated intra-abdominal infection
    • 2) Possible necrotizing enterocolitis
    • 3) Receiving meropenem per standard of care

Smith, PIDJ, 2011.

Neonatal Drug Development: BPD

<table>
<thead>
<tr>
<th>Drug</th>
<th>Inhaled in RCTs</th>
<th>Inhaled Data</th>
<th>Inhaled RCTs</th>
<th>Surrogate PD targets</th>
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<tbody>
<tr>
<td>Vitamin A</td>
<td>Y</td>
<td>Y</td>
<td>1/2 (50)</td>
<td>0/2</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Y</td>
<td>Y</td>
<td>1/1 (100)</td>
<td>0/1</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Y</td>
<td>N</td>
<td>4/8 (50)</td>
<td>0/8</td>
</tr>
<tr>
<td>Inositol</td>
<td>Y</td>
<td>N</td>
<td>1/1 (100)</td>
<td>0/1</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Y</td>
<td>N</td>
<td>1/1 (100)</td>
<td>0/1</td>
</tr>
<tr>
<td>Surfactant</td>
<td>Y</td>
<td>N</td>
<td>4/8 (50)</td>
<td>0/8</td>
</tr>
<tr>
<td>Inhaled nitric oxide</td>
<td>Y</td>
<td>N</td>
<td>2/7 (28)</td>
<td>0/7</td>
</tr>
<tr>
<td>Selenium</td>
<td>N</td>
<td>N</td>
<td>0/1 (0)</td>
<td>0/1</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>Y</td>
<td>N</td>
<td>0/3 (0)</td>
<td>0/3</td>
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<tr>
<td>N-acetylcysteine</td>
<td>N</td>
<td>N</td>
<td>0/1 (0)</td>
<td>0/1</td>
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<tr>
<td>Inhaled beclomethasone</td>
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<td>N</td>
<td>0/2 (0)</td>
<td>0/2</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Y</td>
<td>N</td>
<td>0/1 (0)</td>
<td>0/1</td>
</tr>
<tr>
<td>Estrogen/progesterone</td>
<td>Y</td>
<td>N</td>
<td>0/1 (0)</td>
<td>0/1</td>
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<tr>
<td>Alpha-1-antitrypsin</td>
<td>N</td>
<td>N</td>
<td>0/1 (0)</td>
<td>0/1</td>
</tr>
<tr>
<td>Inhaled salbutamol</td>
<td>Y</td>
<td>N</td>
<td>0/1 (0)</td>
<td>0/1</td>
</tr>
<tr>
<td>Superoxide dismutase</td>
<td>Y</td>
<td>N</td>
<td>0/1 (0)</td>
<td>0/1</td>
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<tr>
<td>Cromolyn sodium</td>
<td>Y</td>
<td>N</td>
<td>0/1 (0)</td>
<td>0/1</td>
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<tr>
<td>Inhaled fluticasone</td>
<td>Y</td>
<td>N</td>
<td>0/1 (0)</td>
<td>0/1</td>
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<tr>
<td>Thyroxine</td>
<td>N</td>
<td>N</td>
<td>0/1 (0)</td>
<td>0/1</td>
</tr>
</tbody>
</table>

Swan et al, PAS. 2013.

Meropenem Dosing

- GA <32 weeks:
  - < 2 weeks PNA: 20 mg/kg q12
  - ≥ 2 weeks PNA: 20 mg/kg q8

- GA ≥32 weeks:
  - < 2 weeks PNA: 20 mg/kg q8
  - 30 mg/kg q8
  - ≥ 2 weeks PNA: 30 mg/kg q8
  - 40 mg/kg q8

Plasma PD targets

- >2 µg/mL for 75% of the dose interval
  - 92% (173/188) of patients

Piperacillin-tazobactam

- Piperacillin
  - semisynthetic derivative of ampicillin enhanced activity against resistant Gram-negative bacteria.
- FDA approved ≥ 2 months
  - Appendicitis and peritonitis

Piperacillin-tazobactam Study Design

- NIH sponsored study
- 4 center, 32 infant, open-label, PK, and safety study
- Inclusion Criteria
  - < 61 days of age
  - AND ONE OF THE FOLLOWING
  - Suspected systemic infection
  - Receiving piperacillin-tazobactam as standard of care

Fluconazole

- Azole antifungal
- Target AUC for adults is 400 to 800 mg/hr/L
- Target for treatment – (time>MIC) >80%
**Antifungals**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing differences between infants and adults</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adult</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>mg/kg/day</td>
</tr>
<tr>
<td>Micafungin</td>
<td>3-6</td>
</tr>
</tbody>
</table>

**Fluconazole prophylaxis**

![Graph showing cumulative incidence](Alapa_Pediatrics_2014.png)

**Candidiasis - Cumulative Incidence**

![Graph showing cumulative incidence](Alapa_Pediatrics_2014.png)

**Pipeline**

- Rifampin
- Clindamycin
- Ticarclin-clavulanate
- SCAMP
  - Phase II/III safety and preliminary effectiveness trial

**Indomethacin/ibuprofen**

**Indomethacin**

- Cox inhibitors such as indomethacin or ibuprofen close the PDA
- Is closure of the PDA an acceptable outcome?
- What about other outcomes?
Factors influencing the decision of whether or how to treat

- Rate of spontaneous closure
  
  **High rates would discourage therapy**

- Risks associated with persistent patency
  
  **Strong associations with serious morbidity would encourage therapy**

- Benefits and risks of treatments for closure
  
  **Benefits should outweigh risks**

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**Indomethacin vs Ibuprofen**

Data from the Pediatric Clinical Data Warehouse; slide courtesy of Reese Clark

**Center Variation: Treatment**

Pediatric Medical Group

**iNO**

- FDA labeled for use in term and near-term (>34 weeks gestation) neonates with hypoxic respiratory failure
  
  » Improve oxygenation

- Not indicated for prevention of BPD
  
  » 2/3 trials submitted to FDA failed (Kinsella 2006, Mercier 2010); Ballard 2006 was successful

  » Ikaria sponsored trial completed, awaiting public information (NCT00931632)

**iNO Administration (Truog)**

Slide courtesy of William Truog
Changes in Use of iNO in the NICU

- Treatment of pressor-resistant hypotension
  - Use lowest effective dose
- Prevention of BPD <1 week postnatal age
  - Unsuccessful
  - IP (particularly with indomethacin)
- Prevention of BPD > 1 week postnatal age
  - NICHD NRN Trial (among others) ongoing

Hydrocortisone

Blood Pressure

Conclusions

- All drugs have adverse events
- Some drugs' benefits outweigh adverse events
- Good principles of drug development generally result in safe and effective drugs
- Participate in phase I-II trials
- Phase III trials are seductive but not always optimal

Thank You

- Questions?

Extra Slides
Intravenous indomethacin: Mortality
Outcomes following Treatment for Symptomatic PDAs

<table>
<thead>
<tr>
<th>Study Setting</th>
<th>Control</th>
<th>Treated</th>
<th>Total</th>
<th>Risk Ratio</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>Pre-1981</td>
<td>144</td>
<td>150</td>
<td>294</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>post-1990</td>
<td>240</td>
<td>250</td>
<td>490</td>
<td>0.84</td>
<td>0.59-1.21</td>
</tr>
</tbody>
</table>

Invasive Candidiasis

- Mortality – 20%
- Morbidity
  - Poor neurodevelopmental outcome (even in the absence of meningitis)
  - Severe retinopathy of prematurity
  - Chronic lung disease

Candida Meningoencephalitis

- Found in 15% of cases of candidemia
- CSF parameters are often normal
- Complications
  - Obstructive hydrocephalus
  - Calcifications
  - Periventricular leukomalacia

Risk factors for candidiasis

- Prematurity
  - >2500g: 0.3%
  - <1500g: 3%
  - <1000g: 7%
  - 1001-1500 g: 1%
  - 751-1000 g: 3%
  - 500-750 g: 12%
- Abdominal surgery
- Broad spectrum antibiotics
- Central venous catheters
- Endotracheal tubes
- H₂ blockers

Antifungal Use in the Nursery

<table>
<thead>
<tr>
<th>Drug</th>
<th>Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B deoxycholate</td>
<td>42</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>52</td>
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<tr>
<td>Intravenous amphotericin B</td>
<td>74</td>
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<tr>
<td>Amphotericin B lipid complex</td>
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<td>Micafungin</td>
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<tr>
<td>Caspofungin</td>
<td>197</td>
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<tr>
<td>Amphotericin B colloidal dispersion</td>
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<tr>
<td>Anidulafungin</td>
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<tr>
<td>Micafungin</td>
<td>NN</td>
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<tr>
<td>Voriconazole</td>
<td>NN</td>
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</tbody>
</table>

Daptomycin

- Cyclic lipopeptide antibiotic
- FDA approved ≥ 18 years
  - complicated skin and skin structure infections caused by Gram-positive organisms
  - S. aureus bloodstream infections
- Adults dosed at 4 and 6 mg/kg q 24 hours have area under the curve (AUC) of 494 and 632 µg*h/mL, respectively
- Clearance higher in younger children (2-6 years of age) compared with adolescents

Study Design

- Single dose (6 mg/kg), open-label, PK and safety study
- Inclusion Criteria
  - > 48 hours and <120 days of age
  - Suspected systemic infection
- Exclusion Criteria
  - Creatinine >1.0 mg/dL

PK Results – Daptomycin 6 mg/kg

- The median (range) AUC_{24} of daptomycin was 262.4 mg*h/L (166.7, 340.2)
- No relationship between GA, PNA, PMA, or SCR with daptomycin CL was observed.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>GA</th>
<th>PNA</th>
<th>PMA</th>
<th>SCR</th>
<th>Dose</th>
<th>Dosing interval</th>
<th>Infusion</th>
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<td>&lt;14</td>
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<td></td>
<td></td>
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<tr>
<td>≥32</td>
<td>≥14</td>
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<tr>
<td>&gt;36</td>
<td>&gt;7</td>
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