Optimal management of the Patent Ductus Arteriosus in Preterm Infants

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Disclosures

I receive support from the US government for work in neonatal clinical pharmacology, clinical trials, and cohort studies including:

1. FDA R01 FD005101, PI Laughon
2. NHLBI R34 HL124038, PI Laughon
3. NIH Office of the Director ECHO Coordinating Center U2C OD023375, PI Smith, Duke
4. NICHD Pediatric Trials Network Government Contract HHSN267200700051C, PI Benjamin, Duke
5. Satellite site PI for the NICHD Neonatal Research Network NICHD U10 HD040492, PI Cotten, Duke

Industry: Astellas, Cempra, Medipost, Abbvie for DSMBs and consulting
I intend to discuss an unapproved/ investigative use of a commercial product/device in my presentation.
“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.”


COFN AAP 2016 PDA

“Despite a large body of basic science and clinical research and clinical experience with thousands of infants over nearly 6 decades, there is still uncertainty and controversy about the significance, evaluation, and management of patent ductus arteriosus in preterm infants, resulting in substantial heterogeneity in clinical practice.”

COFN AAP Clinical Report Jan 2016
Clinical Case #1

• 24 week male, 652 grams
  » Intubated, surfactant in DR

• Day 4: “bounding” pulses, hyperactive precordium, widened pulse pressure

• Mechanical ventilation, moderate settings, FiO2 0.40

• Echocardiogram: Large PDA with L to R shunt

Management options

• A. Administer indomethacin
• B. Administer ibuprofen
• C. Administer acetaminophen
• D. Ligation (or cardiac catheterization)
• E. “Watchful waiting”
Medical therapies

- Which patients benefit from PDA ligation or from PDA treatment with indomethacin/ibuprofen?

- Cox inhibitors such as indomethacin or ibuprofen close the PDA

- Is closure of the PDA the optimal outcome?

- What about other outcomes?

FDA label

- Used when “usual measures fail”: fluid restriction, diuretics, respiratory support

- IV only

- Indomethacin
  - Close hemodynamically significant PDA, infants 500-1750 g
  - Dose depends on postnatal age, Q12 or Q24
    - First dose dose
  - Renal impairment, bleeding, NEC, CHD

- Ibuprofen
  - Close hemodynamically significant PDA, infants 500-1500 g
  - Dose depends on postnatal age, Q24
  - Renal impairment, bleeding, NEC, CHD, infection
FDA label, Cochrane

• Acetaminophen
  » No indication for PDA closure
• “Black box” warning: hepatotoxicity
• Mild to moderate pain; Fever
  » 12.5 mg/kg q 6, do not exceed 50 mg/kg/day
• Cochrane: 8 studies, 916 infants; similar closure to indomethacin/ibuprofen with less renal impairment
• Dose range
  » 10 mg/kg q6 x 3-7 days
  » 15 mg/kg q6 x 2-3 days
  » 20 mg/kg loading then 7.5 mg/kg q 6 x 4 days

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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“Natural history of persistent ductus arteriosus”

- Infants, children, and adults

- “.the duct having closed in one of these at the age of 34, after 17 years of observation.”

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Campbell, British Medical Journal, 1968
Spontaneous Closure

- "Spontaneous Closure of Patent Ductus Arteriosus in Infants ≤1500 g"
- 2012-2014, echocardiograms every 1-2 weeks
### Outcomes

**TABLE 3** Comparison of the Neonatal Outcomes of All the Infants Eligible for the Study (BW ≤ 1500 g) Including Deaths and Congenital Anomalies to the Vermont-Oxford Network (BW 401–1500 g or GA From 22 Weeks, 0 Days to 29 Weeks, 6 Days)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Eligible Infants (n = 368)</th>
<th>Vermont-Oxford Network 2013 (n = 60562)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality (% Q1, Q3)</td>
<td>9.0</td>
<td>14.6 [9.0, 18.4]</td>
</tr>
<tr>
<td>CLD (%) Q1, Q3</td>
<td>14.6</td>
<td>24.5 [10.5, 30.7]</td>
</tr>
<tr>
<td>Severe IVH (grade III and IV) (% Q1, Q3)</td>
<td>5.0</td>
<td>8.1 [3.5, 10.6]</td>
</tr>
<tr>
<td>PVL (%) Q1, Q3</td>
<td>2.4</td>
<td>2.9 [0.0, 4.1]</td>
</tr>
<tr>
<td>NEC ≥IIb (% Q1, Q3)</td>
<td>3.6</td>
<td>4.6 [0.0, 6.5]</td>
</tr>
<tr>
<td>Severe ROP (stage ≥IIIb) (%) Q1, Q3</td>
<td>2.4</td>
<td>6.2 [0.0, 8.3]</td>
</tr>
</tbody>
</table>

Semberova Pediatrics 2017
Time to Closure (Median, IQR)

<table>
<thead>
<tr>
<th>BW, g</th>
<th>Median (IQR)</th>
<th>GA, weeks</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;751</td>
<td>48 (8, 94)</td>
<td>&lt;26</td>
<td>71 (18, NA)</td>
</tr>
<tr>
<td>751-1000</td>
<td>22 (7, NA)</td>
<td>26-27</td>
<td>13 (6, NA)</td>
</tr>
<tr>
<td>1001-1250</td>
<td>9 (3, 44)</td>
<td>28-29</td>
<td>8 (5, 17)</td>
</tr>
<tr>
<td>1251-1500</td>
<td>8 (3, 12)</td>
<td>&gt;30</td>
<td>9 (2, 11)</td>
</tr>
</tbody>
</table>

Spontaneous Closure, review

- In a center with limited treatment, nearly all PDAs close by one year.
- PDAs remain open longer in infants with lower GA and lower BW.
- Outcomes were similar to those in VON.
Clinical Case, Continued

- Day 5-10: indomethacin, 2 courses (6 doses)
  - NPO, TPN
  - Increase in FiO2, ventilator settings

Management

- A. Ligation
- B. Cardiac catheterization
- C. Indomethacin (round 3!)
- D. Ibuprofen (or acetaminophen)
- E. “Watchful waiting”
Factors influencing the decision of whether or how to treat

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

Risks associated with persistent ductal patency

- **BPD**
  - Left to right shunting results in decreased compliance (↑ lung water) and impairment of oxygenation, increased need for respiratory support, increased oxidative stress and ventilator-induced lung injury, and increased CLD.
- **NEC**
  - Left to right shunting results in a “steal syndrome”, causing decreased intestinal perfusion, decreased oxygen delivery with subsequent intestinal damage, and decreased motility resulting in an increased risk for feeding intolerance and NEC.
BPD: Cohort Studies

- Marshall et al:
  » Prospective, population-based study of 1460 infants in North Carolina
  » CLD associated with PDA (OR 1.9)

- Oh et al:
  » 1382 infants 401-1000 g in NICHD Network
  » CLD associated with PDA (adjusted OR 1.4)

PDA and NEC: Observational Studies

- 6146 VLBW infants in the Israel National database for risk factors of NEC (95-00)
- PDA associated with NEC (adj OR 1.85)
- PDA treated with indo associated with NEC (adj OR 1.53)

Dollberg et al., JPN 40:184, 2005
PDA and morbidities

- **Association vs. Causation**
- **CLD**
  - Biologic plausibility, some support in human studies
  - Strong association
- **NEC and feeding intolerance**
  - Biologic plausibility and some physiologic support in humans
  - Association in observational studies

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*
Benefits and Risks of Treatments for Closure: Problems

- Designed to test the efficacy of therapy in closing a PDA and not the impact of persistent patency of the DA or the benefit of closure.

- All permitted “back-up” treatment of the PDA; no true placebo group.

- Because of features of study design, it is challenging to quantify the benefits and risks of therapies to close the PDA.
Risks

- Oliguria
- Bleeding
- Small bowel perforation/NEC

Intestinal Perforation

- Complication of hydrocortisone when accompanied by indomethacin
- “Spontaneous” perforation:
  - 17/180 (9%) vs 4/188 (2%)
  - 14/17 infants also treated with indomethacin

Watterberg et al. Pediatrics 114:1649, 2005
• What should the clinician do when the benefits and risks of a treatment are unknown?

Center Variation: Treatment

Pediatrrix Medical Group

Laughon. J Perinatol. 2007
Changes over time: Pediatrix

- N=61,520
  - Inborn, discharged from 280 NICUs, and 23-30 weeks gestation at birth

Bixler et al, J Peds. 2017
Trial?
### "Before-After" Cohort Studies

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1999-04</td>
<td>31</td>
<td>30</td>
<td>216</td>
<td>180</td>
</tr>
<tr>
<td>2005-06</td>
<td>26</td>
<td>26</td>
<td>26</td>
<td>27</td>
</tr>
<tr>
<td>2005-07</td>
<td>27</td>
<td>27</td>
<td>27</td>
<td>25</td>
</tr>
<tr>
<td>2008-09</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>25</td>
</tr>
</tbody>
</table>

- **N**: Sample size
- **GA, mean**: Gestational age, mean
- **BW, mean**: Birth weight, mean
- **Indomethacin, %**: Percentage of infants receiving prophylactic indomethacin
- **Ligation, %**: Percentage of infants requiring ligation
- **BPD, %**: Percentage of infants with bronchopulmonary dysplasia
- **Mortality, %**: Percentage of infants who died

*Not reported

1. 100% of infants in this study received prophylactic indomethacin, and 100% with a PDA received indomethacin (27% of cohort in “before” and 28% in “after”)

### “Active treatment” vs. “Expectant Management”

- Infants <27 weeks, n=180
  - Mean 26 wks, 826 g
  - Prophylactic indomethacin
  - Echo 48-72 hours
  - Indo x 3; 6 if needed
  - Ligation if “needed” (31/180 ligated (20%))
  - BPD = 28%
  - Death = 11%

- Infants 23-26 weeks, n=97
  - Mean 24.5 wks, 718 g
  - No prophylaxis
  - No indo, ibuprofen
  - PDA closure = 44 postnatal days (mean)
  - No ligation
  - BPD = 38%
  - Death = 9%

Jhaveri 2010, Sung 2016
NICHD NRN PDA trial

- Active treatment: treatment when infant has sPDA
- Expectant management: treatment when infant has cardiopulmonary compromise
- Primary: Death or BPD (physiologic definition) at 36 weeks PMA
- N=1116 infants

<table>
<thead>
<tr>
<th>No sPDA</th>
<th>sPDA</th>
<th>Cardiopulmonary compromise</th>
</tr>
</thead>
<tbody>
<tr>
<td>No PDA on echocardiogram</td>
<td>Small, moderate, large PDA</td>
<td>Large PDA on echocardiogram AND Severe clinical symptoms</td>
</tr>
<tr>
<td>Asymptomatic clinically</td>
<td>Mild, moderate clinical symptoms</td>
<td></td>
</tr>
</tbody>
</table>
Clinical Case, continued

- Day 12: To OR for PDA ligation
- Day 14: Death from cardiovascular collapse
Clinical Case #2

- 25 week twin girls, 674g and 725g
  » Intubated in DR, surfactant
- DOL 5: bounding pulses, hyperactive precordium, ECHO demonstrates moderate-large PDA
- DOL 6-21: Monitoring; weekend attending has gastritis
- DOL 21-60: “typical” 25 week infant course

- DOL 98 and 103: D/C home with open ducts, room air
- One closed spontaneously within 2 months of discharge; mother refused cardiac cath on the other; closed spontaneously at 22 months adjusted age

Categories of Clinicians

- Treat based on biologic plausibility, anecdote, or personal experience
  » The Empiricists
- Treat based on clinical evidence of benefit
  » The Pragmatists
- Treat only if incontrovertible evidence that benefits greater than the risks
  » The Nihilists
Conclusions

- Indomethacin and ibuprofen are FDA labeled for PDA closure. Acetaminophen likely closes PDA at similar rate; safety is unknown.
- Because of study design, it is challenging to quantify the risks and benefits of active treatment compared to expectant management.
- Depending on type of clinician/site, treatment modalities will vary.
- PDA trial of active treatment comparing active treatment versus expectant management is ongoing in the NICHD NRN.

Thank You

- Questions?
Extra slides
PDA and BPD: Lung Compliance

- Closure of the PDA improved lung mechanics
  - 11 ventilated infants tested before and after indomethacin
  - Compared to 9 infants without PDA
  - $C_{dyn}$ and TV increased 59% and 63% after ductal closure
  - No changes in control group


Benefits and Risks of Treatment for Closure: Trials

Outcomes following Prophylactic Indomethacin

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Indomethacin m/N</th>
<th>Control m/N</th>
<th>Relative Risk (Fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>109/771</td>
<td>132/796</td>
<td>0.52 [0.65, 1.30]</td>
</tr>
<tr>
<td>Chronic lung disease in surviving infants 0-6 weeks</td>
<td>223/916</td>
<td>213/509</td>
<td>1.06 [0.92, 1.22]</td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
<td>84/1187</td>
<td>77/1214</td>
<td>1.09 [0.82, 1.46]</td>
</tr>
<tr>
<td>Symptomatic PDA</td>
<td>204/1093</td>
<td>473/1100</td>
<td>0.44 [0.38, 0.50]</td>
</tr>
<tr>
<td>PDA ligation</td>
<td>49/891</td>
<td>97/900</td>
<td>0.51 [0.37, 0.71]</td>
</tr>
<tr>
<td>IVH Grade 3 and 4</td>
<td>113/1283</td>
<td>177/1303</td>
<td>0.66 [0.53, 0.82]</td>
</tr>
</tbody>
</table>
Benefits and Risks of Treatment for Closure: Trials
Outcomes following Treatment for Symptomatic PDAs

<table>
<thead>
<tr>
<th>n</th>
<th>BW</th>
<th>Therapy</th>
<th>Age</th>
<th>Placebo</th>
<th>Crossover</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cotton 1978 25</td>
<td>794-1361</td>
<td>Ligation</td>
<td>8 days</td>
<td>No</td>
<td>N/A</td>
</tr>
<tr>
<td>Yeh 1981 55</td>
<td>&lt;2040</td>
<td>IV indo</td>
<td>9.9 days</td>
<td>Yes</td>
<td>NR</td>
</tr>
<tr>
<td>Yanagi 1981 39</td>
<td>1340 mean</td>
<td>PO indo</td>
<td>Yes</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Merritt 1981 25</td>
<td>&lt;1350</td>
<td>IV indo</td>
<td>48 hr</td>
<td>No</td>
<td>85%</td>
</tr>
<tr>
<td>Rudd 1983 30</td>
<td>&lt;1500</td>
<td>PO indo</td>
<td>8 days</td>
<td>Yes</td>
<td>73%</td>
</tr>
<tr>
<td>Gersony 1982 405</td>
<td>&lt;1750</td>
<td>IV ligation</td>
<td>Yes</td>
<td>65%</td>
<td></td>
</tr>
</tbody>
</table>


PDA and NEC: Physiological Study

- 19 infants with hemodynamically significant PDA, < 1000 g, treated with surfactant
  - Decrement in splanchnic and renal blood flow velocities measured by ultrasound in the presence of a PDA
- Improved flow after closure

BPD: TIPP trial secondary analysis

Survivors to 36 wks PMA
N = 999

Indo
N = 496

No PDA
N = 391

BPD
43%

Placebo
N = 503

No PDA
N = 257

BPD
30%

Indomethacin associated with increase in \( F_O_2 \) (↑) and decrease weight loss in first postnatal week