Evidence Based Prevention of BPD

Kathleen A. Kennedy MD, MPH

Prevention of BPD – Evidence for Medical Interventions

Kathleen A. Kennedy, MD, MPH

Disclosure Statement

Kathleen Kennedy MD does not have any financial arrangements or affiliations with a commercial entity.

Dr. Kennedy will be discussing the unlabeled use of Vitamin A, Dexamethasone, Hydrocortisone, Caffeine.

What is “Good Evidence”?

- At least one large, preferably multi-center, randomized trial or a systematic review of multiple trials
- Rigorously designed and conducted
- Measured all important outcomes
- Showed benefits (ARDs) that clearly justify the adverse effects and expense.

Range of Possibilities

- High-quality evidence with consistent effects and benefits justify risks
- High-quality evidence but inconsistent effects or risks as well as benefits
- High-quality evidence but uncertain generalizability to current practice or to specific patient groups
- Some good-quality evidence but not enough to be confident about the findings
- High-quality evidence with no benefit or benefit does not justify risks or costs
- Too little evidence – we just don’t know

NIH Workshop Definition of BPD - 2001

<table>
<thead>
<tr>
<th>Gestational Age at Birth</th>
<th>Age at Assessment</th>
<th>Mild BPD</th>
<th>Moderate BPD</th>
<th>Severe BPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 32 weeks</td>
<td>36 weeks postmenstrual age (or discharge if discharged sooner)</td>
<td>Treatment with &gt;21% oxygen for at least 28 days AND Breathing room air at time of assessment</td>
<td>Needing &lt;30% oxygen at time of assessment</td>
<td>Needing &gt;30% oxygen or positive pressure at time of assessment</td>
</tr>
<tr>
<td>≥ 32 weeks</td>
<td>56 days postnatal age (or discharge if discharged sooner)</td>
<td>Treatment with &gt;21% oxygen for at least 28 days AND Breathing room air at time of assessment</td>
<td>Needing &lt;30% oxygen at time of assessment</td>
<td>Needing &gt;30% oxygen or positive pressure at time of assessment</td>
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</tbody>
</table>

Jobe A et al, Am J Respir Crit Care Med 2001

Death as a Competing Outcome

- Doesn’t matter if survival is exactly the same in both groups

Control

<table>
<thead>
<tr>
<th></th>
<th>Deaths</th>
<th>Survive with BPD</th>
<th>Survive without BPD</th>
</tr>
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</table>

Treatment

<table>
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<tr>
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<th>Deaths</th>
<th>Survive with BPD</th>
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- But what if it isn’t?
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Death as a Competing Outcome

- Improvement in survival
- Minimal or no change in proportion of survivors with BPD

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- Is there an effect on BPD?

Timing of Interventions

- At birth or shortly thereafter
  - Prevention lung injury from getting started
  - Promote physiologic lung function and growth
- 1 to 4 weeks after birth
  - Redirect the lung injury process
  - Promote lung healing and prevent further lung damage
- After 4 weeks
  - In addition to above
  - Treat cardiac and other complications of lung injury

Early Fluid Administration

- “Restricted” fluid intake in the first 5 to 30 days of age, as compared to more “liberal” intake
- “Non-significant” reduction in death (5 trials, 582 infants): RR = 0.81 (95% CI 0.54-1.23)
- “Non-significant” reduction in BPD (4 trials, 526 infants): RR = 0.85 (95% CI 0.63-1.14)
- Did not report “death or BPD”

Early Sodium Administration

- 2 trials, 63 infants
- 3-4 mEq/kg/day Na begun on 1 st or 2 nd day of life compared to same amount beginning on 5 th day (Costarino) or after 6% weight loss achieved (Hartnoll)
- Early sodium groups had less negative fluid balance in each of the studies.
- Significant reduction in BPD at 28-30 days (unpublished meta-analysis): RR = 0.49 (95% CI 0.27-0.91)

What to Make of This

- We have some fairly good evidence that early fluid and sodium administration make a difference.
- Different regimens were used.
- All of the studies were done before early use of humidified incubators became common practice.
- Hard to generalize into clear treatment recommendations for current practice

Prophylactic Indomethacin

- 19 trials, 2872 infants
- May have other benefits depending on how you choose to look at the data

Death before Discharge (1567)

PDA (2193)
PDA Ligation (1791)
BPD at 36 wks (999)

RR with 95% CI

0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0 1.1 1.2 1.3

Fowlie P et al. Cochrane Review 2010
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Vitamin A
- 2 trials, 847 infants with 36 week outcomes reported
  - BPD at 36 wks in Survivors (724)
  - Death (847)
  - Death or BPD (847)
  - Sepsis (807)
  - Grade 3/4 ICH (847)
  - PVL (646)

Darlow B et al, Cochrane Review 2011

Inositol
- 3 trials, 355 infants randomized
  - All from low antenatal steroid use era, inconsistent use of surfactant

Howlett A et al, Cochrane Review 2012

Macrolide Antibiotics
- Association between maternal colonization with Ureaplasma and BPD
- Could be used at birth for infants at high risk based on birth weight/gestational age or started later and limited to infants who are colonized with Ureaplasma
- 5 trials, 440 infants enrolled
  - Some heterogeneity (two trials included only Ureaplasma positive; one trial excluded Ureaplasma positive; largest trial included both)
  - Intention-to-treat not followed (382 analyzed for BPD)

Unpublished meta-analysis

Caffeine for Apnea
- Randomized infants believed to warrant methylxanthine treatment (for apnea or pre-extubation) to caffeine vs no caffeine
- 501-1250 g infants, <10 days old, 2006 infants enrolled
- Significant decrease in primary outcome of death or neurologic disability: OR = 0.77 (0.64-0.93); NNT = 17
- OR for BPD (supplemental O2 at 36 wks): 0.63 (0.52-0.76); NNT = 8

Schmidt B et al, NEJM 2006
Schmidt B et al, NEJM 2007

BPD at 36 Weeks (Macrolide vs Control)

Unpublished meta-analysis

Early Postnatal Steroids (<8 days)
- Well-studied (29 trials, 3750 patients)
- Significantly reduced BPD and combined outcome of death or BPD
- Increased intestinal perforation, especially if used with indomethacin
- Increased cerebral palsy (increase not significant for combined outcome of death or cerebral palsy)

Doyle L et al. Cochrane Review 2014
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Meta-Regression of Reviews of Systemic Postnatal Steroids

Absolute risk difference in combined outcome of death or CP according to risk of CLD in the control group

Late Postnatal Steroids (>7 days)

- Almost as well-studied (21 trials, 1424 patients)

Not Well-Studied

- Early or late nutrition practices
- Aggressive vs conservative management of PDA
- Caffeine for infants not close to extubation
- Fluid or sodium restriction after the first week or month
- Diuretics
- Bronchodilators
- Pulmonary vasodilators

Where are we?

- We know more about prevention of BPD than we do about many other areas in neonatology.
- There is a lot more to learn.
- We have almost no high-quality evidence from RCTs to inform the management of infants with established BPD.