Preventive Strategies of Chronic Lung Disease (BPD prevention bundle)

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Disclosure

• I have no conflict to disclose
Objectives

• To understand the background of BPD, its incidence and burden
• To review pathophysiology and risk factors of BPD
• To understand the physiology and rationale behind application of these bundle of strategies to prevent BPD with the current available evidence
The Big 5 Morbidities

- IVH
- ROP
- Infection
- NEC
- BPD
Definition

• Northway et al, 1967
  – first clinical definition of BPD
  – Any infant requiring supplemental oxygen at 28 days of life or 36 wks of corrected gestation.

• Alan Jobe et al 2001
  – Revised definition
<table>
<thead>
<tr>
<th></th>
<th>&lt;32 weeks GA</th>
<th>&gt;32 weeks GA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment with oxygen</td>
<td>&gt;21% for at least 28 days</td>
<td>&gt;21% for at least 28 days</td>
</tr>
<tr>
<td>Time point of assessment</td>
<td>36 weeks PMA or discharge*</td>
<td>&gt;28 days but &lt;56 days postnatal age or discharge*</td>
</tr>
<tr>
<td>Grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>Breathing room air at 36 weeks PMA or discharge*</td>
<td>Breathing room air at 56 days Postnatal age or discharge*</td>
</tr>
<tr>
<td>Moderate</td>
<td>Need for &lt;30% oxygen at 36 weeks PMA or discharge*</td>
<td>Need for &lt;30% oxygen at 56 days Postnatal age or discharge*</td>
</tr>
<tr>
<td>Severe</td>
<td>Need for ≥30% oxygen and/or positive pressure (IMV/CPAP) at 36 weeks PMA or discharge*</td>
<td>Need for ≥30% oxygen and/or positive pressure (IMV/CPAP) at 56 days Postnatal age or discharge*</td>
</tr>
</tbody>
</table>
### CNN Definition of BPD

<table>
<thead>
<tr>
<th>Severity</th>
<th>Respiratory support at time of classification (at 36 weeks’ PMA or at discharge if baby was discharged prior to 36 weeks’ PMA)</th>
<th>Oxygen</th>
<th>Flow rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CLD</td>
<td>None</td>
<td>21%</td>
<td>None</td>
</tr>
<tr>
<td>Mild CLD</td>
<td>Headbox or incubator</td>
<td>&gt;21%</td>
<td>Any amount</td>
</tr>
<tr>
<td></td>
<td>Nasal cannula</td>
<td>100%</td>
<td>&lt;100cc/min</td>
</tr>
<tr>
<td></td>
<td>Nasal cannula blended air/oxygen</td>
<td>21-99%</td>
<td>&lt;1.5L/min</td>
</tr>
<tr>
<td>Moderate CLD</td>
<td>Nasal cannula</td>
<td>100%</td>
<td>&gt;100cc/min</td>
</tr>
<tr>
<td></td>
<td>Nasal cannula blended air/oxygen</td>
<td>21-29%</td>
<td>&gt;1.5L/min</td>
</tr>
<tr>
<td></td>
<td>CPAP, SIPAP, NIPPV, NIHFV</td>
<td>21-29%</td>
<td></td>
</tr>
<tr>
<td>Severe CLD</td>
<td>Nasal cannula blended oxygen</td>
<td>&gt;30%</td>
<td>&gt;1.5L/min</td>
</tr>
<tr>
<td></td>
<td>CPAP, SIPAP, NIPPV, NIHFV</td>
<td>&gt;30%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mechanical ventilation (intubated)</td>
<td>21-100%</td>
<td></td>
</tr>
<tr>
<td>Etiology</td>
<td>Old BPD</td>
<td>New BPD</td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td>---------</td>
<td>----------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>High O2 &amp; mechanical ventilation</td>
<td>Disorder of lung development</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Babies</td>
<td>Originally reported by Northway in 1967, infants with a mean gestational age of 33 weeks and a birth weight of 2,000 g</td>
<td>mean gestational age under 28 weeks and birth weight under 1,000 g.</td>
<td></td>
</tr>
<tr>
<td>Pathology</td>
<td>emphysema, atelectasis and fibrosis, and marked epithelial metaplasia and smooth muscle hypertrophy in the airways and in the pulmonary vasculature.</td>
<td>The major abnormalities are a decrease in alveolar number (referred to as <em>alveolar hypoplasia</em>) and <em>dysregulated microvascular growth</em></td>
<td></td>
</tr>
</tbody>
</table>

(Bhatt et al, 2001; Burri, 1997; Coalson et al, 1999; De Paepe et al, 2006)
CNN Data 2017
EPIQ Data
What can we do to improve?

- Understanding the Pathophysiology
- Identifying the Risk factors
- Knowledge sharing and translation
- QI steps to minimize these risk factors
- Staged implementation
- Knowledge sharing and translation
- PDSA cycle
Pathophysiology
Figure 1. Stages of Lung Development, Potentially Damaging Factors, and Types of Lung Injury. In premature newborns, the lungs are often exposed to several sources of injury, both before and after birth. These exposures, along with genetic susceptibility to problematic lung development, can cause direct airway and parenchymal damage and induce a deviation from the normal developmental path. Depending on the timing and extent of the exposures, lung injury may range from early developmental arrest (new bronchopulmonary dysplasia) to structural damage of a relatively immature lung (old bronchopulmonary dysplasia). Premature infants born at a gestational age of 23 to 30 weeks (shaded region)—during the canicular and saccular stages of lung development—are at the greatest risk for bronchopulmonary dysplasia. From Eugenio Baraldi, M.D.; Marco Filippone, M.D. Chronic Lung Disease after Premature Birth. N. Engl. J. Med. 2007, 357, 1946–1955. Copyright © 2007 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.
Factors Contributing to Lung Injury

Proinflammation

Chronic Chorioamnionitis → Initiation of Ventilation → Ventilatory Support → Oxygen → Sepsis

Fetal Lung → Preterm Lung → BPD

Corticosteroids → Surfactant → Corticosteroids

Anti-Inflammation

Jobe: Neoreviews 2006
Risk factors - overview

• Prematurity- arrest of alveolarization.
• Mechanical ventilation- pressure and volume trauma
• Oxygen toxicity –free oxygen radicles
• Patent ductus arteriosus (PDA) - Fluid overload
• Pre- and postnatal infection & Inflammation - damage lung tissues
• Growth restriction or nutritional deficits- poor lung growth
• Genetic predisposition- hyperreactive lung disease in families
• Excess early intravenous fluid administration- pulmonary edema
Pathogenesis

• The etiology of BPD is clearly multifactorial and involves:
  – derangements in multiple aspects of lung function
    • Surfactant production,
    • Repair from injury (e.g., elastin deposition) and
    • Growth and development (e.g., alveologenesis).
Figure 1 - Pathogenesis of bronchopulmonary dysplasia

- Prematurity
- Mechanical ventilation
- Oxygen
- Ductus arteriosus
- Infection
- Genetics (?)
- Healing
- Emphysema
- Atelectasis
- Edema
- Fibrosis

Bronchopulmonary dysplasia
How can we prevent?
Prevention - overview

- Antenatal steroids
- Early use of surfactants
- Gentle ventilation
- Caffeine therapy
- Vitamin A supplementation
- Judicial use of systemic steroids
- Conservative management of PDA
- Fluid restriction
- Infection control plus treatment of Myco / Ureaplasma
- Nutritional support and family-centered care philosophy.
Preventive Strategies
Chorioamnionitis

• Intrauterine Inflammation Increases the risk of Preterm Birth
• Histopathological evidence of chorioamnionitis is present in 40-70% of preterm births (vs. 4-18% of term deliveries)
• Incidence of infection (positive AF culture) is 32-35% with pPROM and 10-15% (spontaneous onset of preterm labor with intact membranes)
Placentas harboring microorganism (in %)

- Biopsy of the chorion from 1,083 placentas (initiator of delivery: preterm labor, preeclampsia) before the 28th week (Culture/PCR)


<table>
<thead>
<tr>
<th>Week of pregnancy</th>
<th>23</th>
<th>24</th>
<th>25</th>
<th>26</th>
<th>27</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initiator of Delivery</strong></td>
<td><strong>Route</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preterm labor:</td>
<td>CS 56</td>
<td>62</td>
<td>42</td>
<td>46</td>
<td>34</td>
</tr>
<tr>
<td>vaginal</td>
<td>87</td>
<td>74</td>
<td>68</td>
<td>48</td>
<td>58</td>
</tr>
<tr>
<td>Preeclampsia:</td>
<td>CS 33</td>
<td>24</td>
<td>21</td>
<td>28</td>
<td>22</td>
</tr>
</tbody>
</table>
Intrauterine Infection and Preterm Labor

Goldenberg, NEJM: May, 2000
There is a strong relationship between markers of inflammation and BPD

- Amniotic fluid proinflammatory cytokine levels are increased in infants who develop BPD
- Cord blood IL-6 concentration is an independent risk factor for BPD

ELGAN study group:

<table>
<thead>
<tr>
<th></th>
<th>Chorioamnionitis</th>
<th>No chorioamnionitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>RDS</td>
<td>33%</td>
<td>73%</td>
</tr>
<tr>
<td>BPD</td>
<td>63%</td>
<td>27%</td>
</tr>
</tbody>
</table>
Mechanical ventilation

- Mechanical ventilation in experimental animals injures the lung (and affects alveolarization).
- Infants with CLD have persistence of leukocytes in alveolar lavages with high concentrations of inflammatory mediators.
- Over distention of the lung during mechanical ventilation (volutrauma) disrupts structural elements and leads to production of inflammatory mediators.
- Ventilation at low lung volumes (atelectrauma) also causes release of cytokines and influx of white blood cells.
Ventilation Strategies

• “Gentle ventilation,” through the use of permissive hypercapnia with minimal liberalization of pCO2 targets (45-55)
• Use of Volume-targeted ventilation, HFJV, HFOV
• NAVA – (Neurally Adjusted Ventilatory Assist)
• CPAP, SNIPPPV post-extubation, HHHFNC
Oxygen toxicity

• Exposure to supraphysiologic oxygen alone induces a phenotype comparable to that seen with BPD in animal models
• Some evidence of decrease in BPD with restricted use of oxygen or lower saturation targets
• Antioxidant - recombinant superoxide dismutase did not reduce rates of BPD
  – (Ambalavanan et al Physiol. 2016, 311, L924–L927)
Oxygen targeting

• SUPPORT, The Canadian Oxygen Trial (COT), BOOST I and then II found slightly lower rates of BPD (38% vs. 41.7%) low (85-89%) vs high (91-95%) targets

• However the meta-analysis including all five studies still failed to identify a significant difference in rates of oxygen requirement at 36 weeks

• Despite the theoretical concerns for increased risk of oxidative lung injury and pulmonary vascular remodeling, many units now use higher saturation limits of 91%–95% based upon the collective finding of improved survival in these five trials. – Saugstad, O.D.; Aune, D. Optimal oxygenation of extremely low birth weight infants: A meta-analysis and systematic review of the oxygen saturation target studies. Neonatology 2014, 105, 55–63.
Delivery Room Management

- Alan Jobe’s quote, J Peds. 2005
- “There is perhaps nothing more dangerous for the preterm lung than an anxious physician waiting in the delivery room with an endotracheal tube and a bag”
- Non-invasive support
Surfactant

• Although there is not substantial evidence, the use of surfactant has decreased the likelihood of chronic lung disease.

• Rescue therapy, administer earlier in <26+0

• Less invasive surfactant administration (LISA)

• Consider later replacement of surfactant, during a period of secondary surfactant dysfunction (who require mechanical ventilation after the 1st week of life) Merrill et al, 2004
Fluid Therapy & BPD

• All newborn infants exhibit an increase in urine output postnatally (usually in the first day of life).
• In infants with RDS, the diuretic phase is delayed and commonly occurs between 24 & 48 hours of life.
• A delay in the onset of diuresis until 5-7 days is associated with an increased risk of BPD.
• Fluid restriction during the first week of life
Growth restriction

- Preterm infants who are small for their gestational age (SGA) or IUGR are at increased risk of BPD
- Twofold increased risk of both BPD (28% vs. 14%) and neonatal mortality (23% vs. 11%) with SGA
Nutrition

• Nutrition plays an important role in lung development and maturation
• Aggressive parenteral nutrition and early enteral feeding may help decrease the incidence of BPD.
  – Biniwale et al, Semin Perinatol 2006;30:200-8
• Mother's own milk is the preferred form of nutrition
• Infants developing BPD require 20 to 40% more calories than their age-matched healthy controls.
• Their caloric requirement varies from 120 to 150 Kcal/kg/day. (HMF / Fat supplement)
Genetics

• Genome-wide association studies (GWAS) failed to identify genomic loci or pathways that accounted for the previously described heritability for BPD

• A second analysis concluded that the SPOCK2 gene may represent a possible candidate susceptibility gene and a key regulator of alveolarization

Antenatal Steroid

• Antenatal steroids decrease the incidence of BPD
• Recommended to administer at 23 to 34 weeks of gestation who is at high risk for preterm delivery within the next seven days.
• Decreases the neonatal risk of RDS, IVH and mortality.
• Trials have consistently confirmed lesser need for mechanical ventilation and oxygen supplementation, which are the risk factors for BPD.
Postnatal steroids

• Benefits are outweighed by their known short-term and long-term adverse effects, including cerebral palsy,

• Reserve administration of low-dose corticosteroids for preterm infants at high risk for BPD (GA <28 weeks) who remain ventilator-dependent and/or have an oxygen requirement of >50 percent

• Steroid therapy may be used in an infant at two weeks of age who requires extremely high levels of respiratory support to prevent further lung damage from volutrauma

• Low-dose hydrocortisone for the first 10 days prevents BPD but was associated with almost twice risk of late-onset sepsis

• Inhaled corticosteroids, despite reducing BPD, were associated with a higher mortality rate.
Caffeine

• CAP trial, early initiation of caffeine was found to result in lower incidence of BPD
• The specific mechanism remains unclear
• Possibly reduced incidence of apnea of prematurity and extubation failure could play a role
Vitamin A

• Vitamin A deficiency may predispose to chronic lung disease
• As it plays a critical role in maintaining the integrity of respiratory tract epithelium and is a key regulator of normal lung growth
• Recent meta-analysis suggests supplementation of preterm infants with vitamin A results in reduction in the combined outcome of death and BPD, (in infants less than 1000 grams)
• Administration requires intramuscular injections, high cost
• A larger trial of oral vitamin A is ongoing (Neo Vita A Trial )
Nitric oxide

- Numerous studies with inconsistent findings
- Meta-analysis concluded early use of iNO in preterm infants did not improve survival without BPD
- Routine use could not be recommended
Others

• **Azithromycin** - decreases the risk of developing BPD in infants with documented Ureaplasma colonization or infection.

• **Diuretics** - In infants with well-developed BPD, pulmonary edema is a major component of the illness. Diuretics may help by increasing the reabsorption of fluid from the lungs.

• In view of the lack of data, a routine or sustained use of systemic loop diuretics in infants with (or developing) CLD cannot be recommended based on current evidence.
  
  – Cochrane 2003
BPD Prevention strategies

1. The application of surfactant without endotracheal ventilation
2. The use of volume-targeted ventilation in infants who require intubation.
3. Following extubation, synchronized nasal ventilation
4. Commencing caffeine on postnatal day 1 or 2 more effective than a later start.
5. Intramuscular vitamin A for the first 4 weeks reduces BPD but is expensive and painful and thus not widely used, still pending trial with oral formulation.
6. Dexamethasone to infants who still requiring mechanical ventilation around postnatal weeks 2-3
7. Aggressive parenteral and early enteral nutrition - Exclusive breastmilk feeding
8. Fluid restriction during the first week
9. Better prevention of nosocomial infections
10. Identifying infants colonized with ureaplasma and treating those requiring intubation and mechanical ventilation with azithromycin