The Preterm Lung: Past, Present & Future

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Professor, Pediatrics
Case Western Reserve University
Cleveland, Ohio
Advice for an Entry Level Neonatologist in the 1970s

- “A solution for prematurity is at hand”. Implication: this is a risky career move

- “All the respiratory problems have been solved”. Implication: avoid respiratory research
The Preterm Lung

- **Historical successes**
  - Antenatal steroids
  - Postnatal surfactant
  - Ventilatory support

- **Ongoing strategic challenges**
  - Spectrum of neonatal lung disease
  - Novel therapeutic approaches

- **Longer term respiratory outcome**
A CONTROLLED TRIAL OF ANTEPARTUM GLUCOCORTICOID TREATMENT FOR PREVENTION OF THE RESPIRATORY DISTRESS SYNDROME IN PREMATURE INFANTS

Effect of Corticosteroids for Fetal Maturation on Perinatal Outcomes
Antenatal Steroids: Unresolved

- Lower and upper limits of gestational age for administration not uniformly accepted
  - Likely benefit at $\leq 24$ weeks
  - Benefit at $\geq 34$ weeks under study
- No consensus on repetitive doses
  - A second course after 14 days may offer benefit
Relative Contributions to Neonatal Respiratory Distress

Rates of Respiratory Distress

Gestational Age (weeks)

Surfactant deficiency

Inefficient fluid absorption

Helve, Neonatology 2009
Airway Expression of the Epithelial Sodium Channel α-Subunit Correlates With Cortisol in Term Newborns

Janer, Pediatrics 2011
Respiratory Distress after Elective Repeat Cesarean Section

Births Induced at 36-38 Weeks with No Apparent Medical Indication for Early Delivery (by month) 2006-2012

Source: Ohio Department of Health, Vital Statistics
Surface Properties in Relation to Atelectasis and Hyaline Membrane Disease

Mary Ellen Avery, M.D., and Jere Mead, M.D., Boston
Timing of Surfactant Administration

Horbar, Pediatrics 2004
Prophylactic vs Selective Surfactant

“When all studies were evaluated together, the benefits of prophylactic surfactant could no longer be demonstrated.”

_Cochrane Update 2012_

“The day for routine aggressive prophylactic surfactant to all infants at risk of RDS has passed.”

_Roger F. Soll_
Surfactant Therapy: Unresolved

- Role of dosage versus preparation in subtle differences in benefit
- Optimal preparation for selective indications
  - Animal based vs. synthetic
- Role in immune protection (SP-A and SP-D)
- Potential role for later dosing to prevent BPD
Surfactant Therapy: Unresolved

- Possible non-invasive administration
  - Laryngeal mask, aerosol, intratracheal catheter
- Assessment of need via gastric aspirate
  - Microbubble test, lamellar body count
- Surfactant as a vehicle for other drugs, e.g., steroids
ASSISTED VENTILATION
IN TERMINAL HYALINE MEMBRANE DISEASE

BY

MARIA DELIVORIA-PAPADOPOULOS and PAUL R. SWYER

Reprinted from Archives of Disease in Childhood, Vol. 39, No. 207 October 1964
Frequency Spectrum for Assisted Ventilation

Carlo and Martin, 1986
Treatment of the Idiopathic Respiratory-Distress Syndrome with Continuous Positive Airway Pressure

George A. Gregory, M.D., Joseph A. Kitterman, M.D., Roderic H. Phibbs, M.D., William H. Tooley, M.D., and William K. Hamilton, M.D.

Should CPAP/PEEP begin in the delivery room?

Are all CPAP strategies and delivery systems equivalent?

What pH, PCO$_2$, FiO$_2$ constitutes CPAP failure?

Is the incidence of BPD reduced?

Role of other non-invasive techniques

- Bi-level CPAP, nasal IMV, high flow nasal cannula [HFNC]
CPAP or Intubation?

“Good” Infants

Success on CPAP

Marginal Infants

Early Extubation

“Bad” Infants

Require Intubation

Jobe A., Personal Conversation
The Preterm Lung

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- **Longer term respiratory outcome**
PULMONARY DISEASE FOLLOWING RESPIRATOR THERAPY OF
HYALINE-MEMBRANE DISEASE*

Bronchopulmonary Dysplasia

WILLIAM H. NORTHWAY, JR., M.D.,† ROBERT C. ROSAN, M.D.,‡ AND DAVID Y. PORTER, M.D.§

PALO ALTO, CALIFORNIA
Patterns of Progression to BPD

Laughon, Pediatrics 2009
Inspired O₂

Baro/volutrauma

Low Gestation

Genetic Susceptibility

Low Birthweight

BPD/CLD

PDA

Sepsis/inflammation

Nutritional Deficit
The BPD Challenge

- Incidence in ELBW infants approaches 50%
- No clear definition
- Animal models remain a challenge
Interventions for BPD

Early Treatment
- Infants more vulnerable
- Intervention may be unnecessary
- Benefit likely maximized

Late Treatment
- Infants less vulnerable
- Intervention selective
- Benefit probably decreased
“The only treatments that have reduced the incidence of BPD in randomized trials without serious adverse events in premature infants are caffeine and vitamin A”.

Laughon: JAMA Pediatr 2014
Effect of Vitamin A Shortage on Death or BPD

Tolia VN: JAMA Pediatr 2014
Vitamin A & Chronic Lung Disease in Infants: What Happened When There Wasn’t Any? [500-1000 gm infants who survived ≥28 days]

<table>
<thead>
<tr>
<th></th>
<th>Vitamin A [n=74]</th>
<th>No Vitamin A [n=140]</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPD @ 36 wk</td>
<td>37.8</td>
<td>58.6</td>
<td>0.004</td>
</tr>
<tr>
<td>Mortality</td>
<td>1.3</td>
<td>5.7</td>
<td>0.13</td>
</tr>
<tr>
<td>O2 @ 28 days</td>
<td>67.5</td>
<td>75.7</td>
<td>0.26</td>
</tr>
</tbody>
</table>

Paluso AM et al: PAS 2015
Novel Strategies for BPD

- Control of inflammation
- Inositol
- Elastase inhibition
- Antioxidants
- Stem cell therapy
- Enhancement of NO bioactivity
Postnatal Steroids: Unresolved

To Whom?

When?

How much?

Which one?

The More I Think
The More Confused I Get
Postnatal Steroids: Unresolved

- May be indicated in a subpopulation with significant ventilator dependence if BPD risk exceeds about 50%
- Aim for as short a course and as low a dose as possible
- Do not assume there is a safe window for treatment
- Clarification of mechanism in order to identify more specific anti-inflammatory approaches
Ureaplasma has been associated with BPD, however, further studies should be done to confirm a possible benefit of azithromycin in the neonatal population.
Novel Strategies for BPD

- Control of inflammation
- Inositol
- Elastase inhibition
- Antioxidants
- Stem cell therapy
- Enhancement of NO bioactivity
# Inositol Supplementation in Premature Infants with RDS

<table>
<thead>
<tr>
<th></th>
<th>Placebo [n=107]</th>
<th>Inositol [n=114]</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Death during first 28 days</strong></td>
<td>26</td>
<td>13</td>
<td>0.012</td>
</tr>
<tr>
<td><strong>Survival up to 28 days</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>with BPD</td>
<td>26</td>
<td>20</td>
<td>0.022</td>
</tr>
<tr>
<td>without BPD</td>
<td>55</td>
<td>81</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Novel Strategies for BPD

- Control of inflammation
- Inositol
- Elastase inhibition
- Antioxidants
- Stem cell therapy
- Enhancement of NO bioactivity
Risk Factors for the Degradation of Lung Elastic Fibers in the Ventilated Neonate

Implications for Impaired Lung Development in Bronchopulmonary Dysplasia\textsuperscript{1-3}

MARGARET C. BRUCE, MARK SCHUYLER, RICHARD J. MARTIN, BARRY C. STARCHER, JOSEPH F. TOMASHEFSKI, JR., AND KATHY E. WEDIG

Inhibiting Lung Elastase Activity Enables Lung Growth in Mechanically Ventilated Newborn Mice

Anne Hilgendorff\textsuperscript{1,4}, Kakoli Parai\textsuperscript{1}, Robert Ertsey\textsuperscript{1}, Noopur Jain\textsuperscript{1}, Edwin F. Navarro\textsuperscript{1}, Joanna L. Peterson\textsuperscript{1}, Rasa Tamosiuniene\textsuperscript{2}, Mark R. Nicolls\textsuperscript{2}, Barry C. Starcher\textsuperscript{3}, Marlene Rabinovitch\textsuperscript{1}, and Richard D. Bland\textsuperscript{1}

\textsuperscript{1}Department of Pediatrics and \textsuperscript{2}Department of Medicine, Stanford University, Stanford, California; \textsuperscript{3}Department of Biochemistry, University of Texas, Tyler, Texas; and \textsuperscript{4}Department of Pediatrics, University of Munich, Munich, Germany
Novel Strategies for BPD

- Control of inflammation
- Inositol
- Elastase inhibition
- Antioxidants
- Stem cell therapy
- Enhancement of NO bioactivity
Recombinant Human CuZn Superoxide Dismutase and 1 year Pulmonary Outcome

Davis, JM, Pediatrics 2003
Antioxidant Enzyme Activity in Preterm Infant (<28 wk gestation) Cord Blood: Influence of Gender

Days before birth since last dose of antenatal corticosteroid administration.

Vento 2009
Novel Strategies for BPD

- Control of inflammation
- Inositol
- Elastase inhibition
- Antioxidants
- Stem cell therapy
- Enhancement of NO bioactivity
Airway Delivery of BM-derived MSC Prevents Alveolar Injury in O₂-inducted BPD in Newborn Rats

van Haaften: Am J Respir Crit Care Med 2009
Challenges of Mesenchymal Stem Cell Therapy

- Source and route of administration
- Preventive vs therapeutic approach
- Role of cell engraftment vs exposure to stem cell conditioned medium
- Optimization of cell type targeted
- Donor cells both produce growth factors (e.g., VEGF) and induce production by recipient cells
Novel Strategies for BPD

- Control of inflammation
- Inositol
- Elastase inhibition
- Antioxidants
- Stem cell therapy
- Enhancement of NO bioactivity
Proposed Effects of Nitric Oxide on the Development of the Respiratory System

Martin, N Engl J Med 2005
“Available evidence does not support use of iNO in routine care of premature infants who require respiratory support”.

“Future research should seek to understand the gap between benefits on lung development and function suggested by basic research and animal studies, and the results of clinical trials to date”.

*Pediatrics 2011*
NOS and Arginase Compete for the Substrate L-Arginine

L-Arginine

Arginase → Urea

L-ornithine

L-citrulline

NOS → NO

GTP → sGC → cGMP → PDE5 → Smooth muscle relaxation

H2O → NO

L-ornithine → Polyamine → Cell proliferation

Proline → Collagen synthesis
**NOS and Arginase Compete for the Substrate L-Arginine: Effect of Hyperoxia**

- **L-Arginine**
  - H$_2$O
  - Arginase
  - Urea
  - L-ornithine
  - Proline
  - Polyamine
  - Collagen synthesis
  - Cell proliferation

- **NOS**
  - NO
  - GTP
  - sGC
  - cGMP
  - PDE$_5$
  - L-citrulline
  - GDP

- **Other**
  - Polyamine
  - Proline
  - Smooth muscle relaxation
Potential Alternate Approaches to Enhance Endogenous NO Bioactivity

- Arginine supplementation
- Arginase inhibition
- Phosphodiesterase inhibition
  - e.g., Sildenafil
- Complementary antioxidant
- Ethyl nitrite inhalation as a source of nitrosothiols
The Preterm Lung

- **Historical successes**
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- **Ongoing strategic challenges**
  - Spectrum of neonatal lung disease
  - Novel therapeutic approaches

- **Longer term respiratory outcome**
“Most adolescents and young adults who had bronchopulmonary dysplasia in infancy have some degree of pulmonary dysfunction, consisting of airway obstruction, airway hyperreactivity, and hyperinflation. The clinical consequences of this dysfunction are not known.”

W. H. Northway Jr., et al. NEJM 1990
“Although the aetiology and clinical course of BPD have changed during the past four decades, respiratory dysfunction continues to be observed. The largely **obstructive** nature of this dysfunction has long term implications for future lung health”.

*UK EPICure Study data 2010*
Airway Hyperresponsiveness in School Children Born Very Preterm

FEV$_1$%

p<0.0001  p<0.0001

BPD  Non-BPD  Controls

Asthma at School Age in ELBW Infants Born in the 1990’s

<table>
<thead>
<tr>
<th></th>
<th>ELBW (n=219)</th>
<th>TERM CONTROLS (n=176)</th>
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<tbody>
<tr>
<td>OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td></td>
<td>0.001</td>
</tr>
</tbody>
</table>

OR 3.0, 95% CI 1.6-5.6, p=0.001

* need for medication

Hack et al, JAMA 2005
Incidence of Clinically Significant Airflow Reduction in Late Adolescence in VLBW (<1.5kg) Subjects

Percent with FEV₁ < 75%

BPD

No BPD

$p=0.001$

Doyle, Pediatrics 2006
**Infection** (pre/postnatal)  
**Oxygen** (oxidant/antioxidant balance)  
**Ventilation** (baro/volutrauma)  

- Structural Immaturity  
- Inflammatory Response  
- Biochemical Imbalance  

- Alveolar remodeling  
- Altered pulmonary vasculature

**Impaired Airway Structure and Function**
Biologic Contributors to Altered Airway Function in Former Preterm Infants

- Lung parenchymal injury
- Selective contribution from airway smooth muscle
Altered Neonatal Airway Function: Lung Parenchymal Injury

Effect of Neonatal Hyperoxia on Bronchiolar-Alveolar Attachments in 10 Month Old Mice
[65% oxygen from birth to DOL 7]

Control

Hyperoxia

O’Reilly M: Neonatology 105:39, 2014
Effect of 7-Day Oxygen Exposure in Mice on Lung Structure at 3 Weeks

Ctrl  40% O₂  70% O₂

Mild and Severe Hyperoxia Both Impair Subsequent Lung Structure in Mouse Pups

Mild Hyperoxia Markedly Increases Subsequent Airway Hyperreactivity in Mouse Pups

Mild Hyperoxia Markedly Increases Airway Smooth Muscle [ASM] in Mouse Pups
Predisposition to Later “Wheezeing Disorders”

Neonatal hyperoxia

Selective ASM proliferation

Alveolar simplification

Decreased bronchiolar-alveolar attachments

Airway hyperreactivity
Predisposition to Later “Wheezing Disorders”

- Neonatal hyperoxia
  - Selective ASM proliferation
  - Alveolar simplification
    - Decreased bronchiolar-alveolar attachments
  - Airway hyperreactivity
- non-BPD
- BPD
Recommendations: Clinical

- Protect the immature airway against environmental hazards/infectious agents
- Recognize risk of wheezing in the moderately low birth weight/late preterm infant
- Recognize the increased risk of sleep disordered breathing in former preterm infants
Speculation

- Modest therapeutic interventions in the NICU, e.g., sustained low FiO$_2$ and/or CPAP may predispose to selective airway smooth muscle proliferation and resultant symptomatology
Obrigado