Why do former premature wheeze?

Richard J. Martin, M.D.
Drusinsky-Fanaroff Chair in Neonatology
Rainbow Babies & Children’s Hospital
Professor, Pediatrics
Case Western Reserve University
Cleveland, Ohio
“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*
Respiratory Morbidity in Former Preterm Infants

- Preterm birth and low birth weight as risk factors for later morbidity
- How much is attributable to BPD?
- What about the later preterm?
- Proposed biologic mechanisms
- The clinical challenge
Relation of birth weight and childhood respiratory infection to adult lung function and death from chronic obstructive airways disease

D J P Barker, K M Godfrey, C Fall, C Osmond, P D Winter, S O Shaheen

“Intrauterine influences which retard fetal weight gain may irrevocably constrain the growth of the airways”.

BMJ, 1991
Risk Factors for Childhood Asthma Diagnosed before 3 Years: Population Based Study in Finland

### Odds of Recurrent Wheezing [mean age 2 yrs], Chorioamnionitis and Prematurity

<table>
<thead>
<tr>
<th>Chorioamnionitis</th>
<th>Gestation [weeks]</th>
<th>OR [95%CI]</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>&gt;37</td>
<td>1.0</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>33 – 37</td>
<td>1.7 [1.0-2.9]</td>
<td>.03</td>
</tr>
<tr>
<td></td>
<td>&lt;33</td>
<td>2.7 [1.3-5.5]</td>
<td>.005</td>
</tr>
<tr>
<td>Yes</td>
<td>&gt;37</td>
<td>2.0 [1.1-3.8]</td>
<td>.03</td>
</tr>
<tr>
<td></td>
<td>33 – 37</td>
<td>1.3 [0.4-3.6]</td>
<td>.67</td>
</tr>
<tr>
<td></td>
<td>&lt;33</td>
<td>4.0 [2.0-8.0]</td>
<td>.0001</td>
</tr>
</tbody>
</table>

*Boston data: Kumar R: J Allergy Clin Immunol 2008*
Risk for Recurrent Wheezing in Former Preterm Infants

Chorioamnionitis

Prematurity → Recurrent Wheezing
Risk for Recurrent Wheezing in Former Preterm Infants

Choriamnionitis

Prematurity

Recurrent Wheezing

Viral infection [rhinovirus, RSV]
Asthma at School Age in ELBW Infants Born in the 1990’s

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

Hack et al: JAMA 2005

*need for medication
Does the asthma phenotype differ between former preterm and term infants?
Prevalence of Asthma* between Childhood and Adolescence

Subjects with Asthma (%)

<table>
<thead>
<tr>
<th></th>
<th>8 Years</th>
<th>14 Years</th>
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</thead>
<tbody>
<tr>
<td>ELBW</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>NBW</td>
<td>10</td>
<td>18</td>
</tr>
</tbody>
</table>

* need for medication

Hack et al: JAMA 2011
Adult Progression of Bronchial Responsiveness after Term and Extremely Preterm [EP] Birth

Respiratory Morbidity in Former Preterm Infants

- Preterm birth and low birth weight as risk factors for later morbidity
- How much is attributable to BPD?
- What about the later preterm?
- Proposed biologic mechanisms
- The clinical challenge
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
“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
Infection (pre/postnataal)  Oxygen (oxidant/antioxidant balance)  Ventilation (baro/volutrauma)

Structural Immaturity  Inflammatory Response  Biochemical Imbalance

Alveolar remodeling  Altered pulmonary vasculature
Impaired Airway Structure and Function

- Infection (pre/postnatal)
- Oxygen (oxidant/antioxidant balance)
- Ventilation (baro/volutrauma)

- Alveolar remodeling
- Altered pulmonary vasculature

- Structural Immaturity
- Inflammatory Response
- Biochemical Imbalance
Airway Hyperresponsiveness in School Children Born Very Preterm

Respiratory Morbidity in Former Preterm Infants

- Preterm birth and low birth weight as risk factors for later morbidity
- How much is attributable to BPD?
- **What about the late preterm?**
- Proposed biologic mechanisms
- The clinical challenge
Moderately Preterm Children Have More Respiratory Problems during Their First 5 Years of Life Than Children Born Full Term

Elianne J. L. E. Vrijlandt¹,², Jorien M. Kerstjens³, Eric J. Duiverman¹,², Arend F. Bos³, and Sijmen A. Reijneveld⁴
<table>
<thead>
<tr>
<th></th>
<th>Adj OR [95%CI]</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderately preterm</td>
<td>1.49 [1.34-1.66]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>[≥32 wk]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very preterm</td>
<td>2.81 [2.52-3.12]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>[&lt;32 wk]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Been JV et al: PLOS 2014*
Respiratory Morbidity in Former Preterm Infants

Resolved

- Preterm birth is a risk factor for longer term airway hyperreactivity

- Much, but by no means all, of this is attributable to BPD

- The later preterm without significant neonatal lung disease is also at risk
Respiratory Morbidity in Former Preterm Infants

- Preterm birth and low birth weight as risk factors for asthma
- How much is attributable to BPD?
- What about the late preterm?
- **Proposed biologic mechanisms**
- The clinical challenge
Neonatal Contributors to Altered Airway Function

- Modulated neural output
- Parenchymal [alveolar] injury
- Airway dysfunction
Imbalance of Neural Regulation of Airway Caliber

vagus

vagal postganglionic neuron

epithelium

NOS  PG  NOS

Ach  mAchR

airway smooth muscle

Contraction

Relaxation

cAMP/cGMP
Neonatal Contributors to Altered Airway Function

Modulated neural output

Parenchymal [alveolar] injury

Airway dysfunction
Altered Neonatal Airway Function: Lung Parenchymal Injury

Neonatal Contributors to Altered Airway Function

- Modulated neural output
- Parenchymal [alveolar] injury
- Airway dysfunction
Developmental Progression of Airway Vulnerability

- Increased extracellular matrix
- Passive collapse
- Active bronchospasm
- Increased extracellular matrix
Hypothesis

Modest therapeutic interventions, such as low supplemental oxygen and/or CPAP, may elicit longer term airway hyperreactivity in former preterm infants.
Ventilation in Extremely Preterm Infants and Respiratory Function at 8 Years

Lex W. Doyle, M.D., Elizabeth Carse, M.D., Anne-Marie Adams, Ph.D., Sarath Ranganathan, Ph.D., Gillian Opie, M.B., B.S., Jeanie L.Y. Cheong, M.D., for the Victorian Infant Collaborative Study Group

N Engl J Med
Volume 377(4):329-337
July 27, 2017
# Days of Respiratory Support in Extremely Preterm Infants [<28 wk]

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>Endotracheal ventilation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>19</td>
<td>10</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>8–32</td>
<td>2.5–23.5</td>
</tr>
<tr>
<td>Mean</td>
<td>23.1±21.0</td>
<td>19.9±28.6</td>
</tr>
<tr>
<td><strong>Nasal CPAP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>24</td>
<td>31.5§</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>14–36</td>
<td>16.8–42§</td>
</tr>
<tr>
<td>Mean</td>
<td>26.0±15.3</td>
<td>33.3±26.0§</td>
</tr>
<tr>
<td><strong>Supplemental oxygen</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>45</td>
<td>53.5</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>10.5–88</td>
<td>9.8–106</td>
</tr>
<tr>
<td>Mean</td>
<td>65.1±48.0</td>
<td>75.1±68.0</td>
</tr>
</tbody>
</table>

*Doyle LW: NEJM 2017*
**Expiratory Flows at 8 Years of Age in Each Period**

<table>
<thead>
<tr>
<th>Variable</th>
<th>1997 (N=112)</th>
<th>2005 (N=123)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raw value — liters</td>
<td>1.43±0.30</td>
<td>1.25±0.28</td>
</tr>
<tr>
<td>z score</td>
<td>-0.65±1.30</td>
<td>-1.19±1.17↑</td>
</tr>
<tr>
<td>Percent of predicted value</td>
<td>92.0±15.7</td>
<td>85.4±14.4↑</td>
</tr>
</tbody>
</table>

Doyle LW: NEJM 2017
PROS
Very immature
Grows up fast
Survivable
Amenable to genetics
Inexpensive

CONS
Very small
Not a human infant
Airway Reactivity in Mice is Delayed after Neonatal Hyperoxia [day 21]
Effect of Oxygen Exposure on ASM Proliferation and Apoptosis

Rainbow Mouse Pup NICU

Courtesy: PM MacFarlane, Ph.D.
Increased Airway Reactivity in a Neonatal Mouse Model of CPAP: data from male pups at day 7

A. Small airways

B. Large airways

Conclusion

- Mild postnatal oxygen exposure and CPAP both cause airway smooth muscle proliferation and airway hyperreactivity in a neonatal rodent model.

- This may contribute to the increased incidence of wheezing observed in former preterm infants, many of whom may not manifest BPD.
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“...no evidence that salbutamol reduces mortality or CLD at 28 days in preterm infants at risk of developing CLD.”
Effect of Smoking on Age-related Decline in Airway Function

Potential Maturational Parallels?

- OSA
- COPD
- Adverse Outcomes

- Apnea of Prematurity
- BPD
- Adverse Outcomes
Thank you to My Research Lab Collaborators

Catherine Mayer

Peter MacFarlane

YS Prakash

Thomas Raffay

NHLBI, NICHD