They shall beat their swords into plowshares, and their spears into pruninghooks: nation shall not lift up sword against nation, neither shall they learn war any more.

(Bible)
BRONCHOPULMONARY DYSPLASIA

CHRONIC NEONATAL LUNG DISEASE (CLD)

2nd BERLIN NEONATOLOGY SUMMER SCHOOL
September 2014
Mt. Scopus
Ein Kerem
BRONCHOPULMONARY DYSPLASIA

1960: Ventilation of Neonates
1967: Northway describes BPD as “prolonged ventilator dependence after RDS”
1990’s:
- Northway: Abnormal respiratory function and symptoms persist into adolescence and early adulthood
Survival of tiny infants – new form of BPD – milder, more chronic
2000+: Abnormal alveolar development
Ongoing pulmonary disease
Risk for BPD
Odds Ratios & 95% CI

Birth weight/GA
Severe RDS
Infection
PDA
PDA+ Infection

González A et al, J Pediatr 1996
BRONCHOPULMONARY DYSPLASIA

DEFINITION 1

• PATIENTS WHO CONTINUED TO REQUIRE RESPIRATORY SUPPORT (VENTILATION, OXYGEN) BEYOND 28 DAYS OF AGE

• CHARACTERISTIC RADIOGRAPHIC CHANGES IN CHEST X-RAY.
BRONCHOPULMONARY DYSPLASIA

DEFINITION 2

- NEED FOR ADDITIONAL OXYGEN AT 36 WEEKS POSTMENESTRUAL AGE (PMA)

- MORE ACCURATE PREDICTOR OF OUTCOME
BRONCHOPULMONARY DYSPLASIA

Current Definition for Infants at Gestational Ages of Less Than 32 Weeks

Time of assessment 36w PMA or discharge

Treatment with oxygen > 21% for at least 28 days plus –

* **Mild BPD:** Breathing room air at 36 weeks PMA or discharge
* **Moderate BPD:** Need for < 30% oxygen at 36 weeks PMA or discharge
* **Severe PBD:** Need for > 30% oxygen and/or positive pressure at 36 weeks PMA

NICDH Workshop Summary on BPD:
Jobe & Bancalari, Am J Respir Crit Care Med 2001;163:1723
BRONCHOPULMONARY DYSPLASIA

Current Definition for Infants at Gestational Ages of more than 32 Weeks

Time of assessment more than 28 d less than 56 d post natal days or discharge

Treatment with oxygen > 21% for at least 28 days plus –

* **Mild BPD:** Breathing room air at 56 days post natal age or discharge

* **Moderate BPD:** Need for < 30% oxygen at 56 days post natal age or discharge

* **Severe PBD:** Need for > 30% oxygen and/or positive pressure at 56 days post natal age or discharge

NICDH Workshop Summary on BPD:
Jobe & Bancalari, Am J Respir Crit Care Med 2001;163:1723
BRONCHOPULMONARY DYSPLASIA

Physiologic Definition

• Infants with supplemental oxygen less than 30%.

• **Oxygen Reduction Test**
  • Base line – Oxygen saturation 88% and above
  • Fail – Oxygen saturation 80% to 87% for 5 minutes or less than 80% for 1 minute.
  • Pass – Saturation above 96% for 15 minutes Saturations exceed 88% for 60 minutes.

BRONCHOPULMONARY DYSPLASIA

Stages of Lung Development, Potentially Damaging Factors, and Types of Lung Injury

Antenatal Exposures
- Steroids
- Chorioamnionitis
- Intrauterine growth restriction

Genetic susceptibility

Premature delivery

Postnatal Exposures
- Ventilator-induced lung injury
- Oxidative stress
- Infections
- Steroids
- Pulmonary fluid overload
- Nutritional deficits

Stages of lung development
- Canalicular stage: 16 wk
- Saccular stage: 23 wk
- Alveolar stage: 32 wk
- 38 wk

Developmental arrest or delay

New bronchopulmonary dysplasia

Old bronchopulmonary dysplasia

Structural injury
BRONCHOPULMONARY DYSPLASIA

Classic ("old") Versus New BPD

**"Old" classic BPD**

- Larger infants, 34 wks 2.3 Kg
- No prenatal steroids
- Severe RDS (no surfactant)
- Aggressive ventilation
- High $O_2$
- Airway injury, epithelial metaplasia, muscle hypertrophy, fibrosis and emphysema

**New BPD**

- Smaller infants < 28 wks, <1 kg
- Prenatal steroids exposure
- Mild RDS (apnea, poor respiratory efforts)
- Improved ventilation
- Restricted $O_2$ treatment
- Decreased lung alveolar septation and microvascular development
In old BPD, intense inflammation and disruption of normal pulmonary structures lead to a nonhomogeneous airway and parenchymal disease.
The main feature of new BPD is diffusely reduced alveolar development, which is associated with a clinically significant loss of surface area for gas exchange, with airway injury, inflammation, and fibrosis that are usually milder than in old BPD.
BPD OLD VS. NEW

New
Arrest of alveolarization

Old
Inflammation and fibrosis
HISTOLOGY

New

Old
Prenatal events

- Chorioamnionitis - Cytokine exposure of the fetus

Postnatal events

+ Resuscitation
+ Oxygen toxicity
+ Mechanical ventilation
+ Pulmonary and/or systemic infection
+ PDA

Sequential lung injury

Pulmonary inflammatory response

Aberrant wound healing

Inhibition of alveolarization and vascular development

“New” BPD
BRONCOPULMONARY DYSPLASIA

Factors modulating PATHOGENESIS

FETAL INFECTION and INFLAMATION
ANTENATAL STEROIDS
PREMATURITY
OXYGEN AND OXIDANT STRESS
BAROTRAUMA / VOLUTRAUMA (VILI)
POSTNATAL INFECTION and INFLAMATION
NUTRITION
GENETIC FACTORS
ABNORMAL GROWTH-FACTOR SIGNALING

Kinsella JP, Lancet 2006
BRONCHOPULMONARY DYSPLASIA

The bulk of cases of “new” BPD – in infants less than 30 weeks GA and less than 1200 gr BW. It is not clear whether the incidence of BPD is increasing, decreasing or staying constant (Changing epidemiology and definitions).

**INCIDENCE (750 gr - 1500 gr)**

<table>
<thead>
<tr>
<th>Without Surfactant</th>
<th>19%-63%</th>
</tr>
</thead>
<tbody>
<tr>
<td>With Surfactant</td>
<td>11%-57%</td>
</tr>
</tbody>
</table>

**INCIDENCE (500 gr-1500 gr)** — (Fanaroff AA, Am J Obstat Gynecol. 2007)

- 501-750 gr: 42%
- 751-1000 gr: 25%
- 1001-1250 gr: 11%
- 1251-1500 gr: 5%

**MORTALITY 20% - 40%**
Neonatal survival and incidence of BPD defined as ≥ 28 days' duration of oxygen dependency during hospitalization 1995 - 2000 (n = 1266 inborn infants; birthweight, 500 - 1500 g).

Bancalari E et al, Semin Neonatol, 2003
BRONCHOPULMONARY DYSPLASIA

OUTCOME

MORTALITY -
30%- 40% IN THE FIRST YEAR (80% DURING INITIAL HOSPITALIZATION).

PULMONARY FUNCTION -
HIGH RESISTANCE AND REACTIVITY;
LOW COMPLIANCE.
BRONCHOPULMONARY DYSPLASIA

OUTCOME (CONT).

CARDIAC FUNCTION
RIGHT VENTRICULAR HYPERTROPHY
COR PULMONALE

INFECTION
INCREASED SUSCEPTIBILITY - RSV.
BRONCHOPULMONARY DYSPLASIA

OUTCOME (CONT).

GROWTH
INCREASED RISK FOR GROWTH FAILURE.

NEUROLOGIC DEVELOPMENT
Impaired in about 25% SURVIVORS.
Treatment

- Nutrition
  - High calories, low fluid intake
- Diuretics – thiazides, spironolactone, furosemide
- Bronchodilators – salbutamol, terbutaline, methylxanthines
- Steroids – systemic, inhaled
- Infection Control - RSV immunization, Streptococcal immunization

Have patience!!
Most will recover
The **BEST** treatment of BPD is **PREVENTION**

**Prevention of premature birth** is the single most effective preventive measure !!!!
Strategies
how to reduce inflammation in the airways and pulmonary tissue

- Use lower SaO\textsubscript{2}, FiO\textsubscript{2}
- Reduce mechanical ventilation, reduce suctioning damage, extubate early
- Use surfactant as early as possible
- Close PDA: Prolonged PDA and late closure are associated with an increased risk of BPD
Strategies how to reduce inflammation in the airways and pulmonary tissue

- Treat sepsis and pulmonary infections properly
- Early nutrition, early amino acid administration
- Caffeine
- Vitamin A
- Dexamethasone and other glucocorticoids (cannot currently be recommended for prevention of BPD)
- Inhaled NO

Strategies how to reduce inflammation in the airways and pulmonary tissue

More Therapies:

- SOD
- Glutathione
- Cimetidine
- Macrolides
- Inositol
- HFV
- Cell Therapy

BRONCHOPULMONARY DYSPLASIA

Kugelmam A. Pediatric Pulmonology, 2011
Prevention and Treatment – What do we know?

The only **effective** drugs for preventing BPD:

**Caffeine** – can prevent BPD.

**Vitamin A** – effective but improvement was small.

**Prevention and Treatment – What do we know? (cont.)**

**Surfactant** - Evidence is insufficient to support treatment beyond the immediate neonatal period for the prevention of BPD.

**PDA** - Early ductal closure by:
- **Surgery** (Clyman R et al, J Pediatr 2009)
- or
- **Indomethacin** (Fowlie & Davis, ADC-FNE 2003)

Does not reduce the rate of BPD, or may even increase it.
Prevention and Treatment – What do we know? (cont.)

**Steroids (postnatal):**

**Systemic:** Significant reduction in the incidence of BPD but have negative neurodevelopmental consequences.

**Inhaled:** Ineffective in reducing incidence of BPD

**Diuretics:**
Improved lung function in short-term but no decrease in the incidence of BPD.

**Antibiotics:** Treatment of Ureaplasma has not shown a decrease in BPD.

Prevention and Treatment – What do we know? (cont.)

**Inhaled NO:**
No overall reduction in BPD but a trend toward reduction in BPD in selected populations.

**Bronchodilators:**
Insufficient data to evaluate safety and efficacy for prevention or treatment of BPD.

**Antioxidants:**
Protect against inflammation and oxygen toxicity. Have not proven successful in reducing the incidence of BPD

Primary prevention for BPD: Windows of opportunities

Stages of lung development:
- Embryonic
- Pseudoglandular
- Canalicular
- Saccular
- Alveolar

PRETERM BIRTH
- Highest BPD risk
- 2-3 years

Primary BPD Prevention Blocking One or More Factors
- Genetic Makeup
  - Gene mutations
  - Susceptibility genes
  - Pharmacogenetic response to drugs
- Epigenetics
- Fetal Programming
  - Prenatal, perinatal and intergenerational exposures to toxins, stress, smoke, diet
  - IUGR, nutrition, placental function, maternal illness, antenatal steroids
- Predisease State
  - Structurally & biochemically immature lung, infection/inflammation, oxidant injury, volutrauma, apnea, poor nutrition
- Lung Disease
  - Altered alveolar, vascular & airway structure and function; enhanced susceptibility to childhood and adult lung disease

Healthy Newborn Lung
- Lifelong Lung Health

IUGR, nutrition, placental function, maternal illness, antenatal steroids
• Genetics:

• Behind the scope of my presentation but:

• Lavoie et al – Genetics of bronchopulmonary dysplasia in the age of genomics. *Current Opinion in Pediatrics, 2010.*

• Madurga et al – Recent advances in late lung development and the pathogenesis of bronchopulmonary dysplasia. *American Journal of physiology – Lung cell and molecular physiology, 2013.*

• Shaw et al – Progress in understanding the genetics of bronchopulmonary dysplasia. *Seminars in Perinatology, 2013.*

BRONCHOPULMONARY DYSPLASIA

BPD - Chronic Disease but, there is a hope !!!

Groothuis JR, Makari D
Definition and outpatient management of the VLBW infant with BPD

Greenough A
BPD – long term follow up
BRONCHOPULMONARY DYSPLASIA

Discharge planning:

Discharge planning team –

• Neonatologist, pulmonary specialist, neonatal nurses, therapists in nutrition, respiratory, home healthcare, social workers

• Parents or primary caregiver
# BRONCHOPULMONARY DYSPLASIA

## Respiratory System

- Oxygen dependency
- Pneumonia
- RSV
- Reactive airways
- Aspiration
- Exercise intolerance
- Glottic and subglottic damage
- Tracheal and bronchial stenosis
- Tracheobronchomalacia
- ALTE
- SIDS

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BRONCHOPULMONARY DYSPLASIA

Cardiovascular System –

Hypertension

Pulmonary Hypertension

Cor pulmonale

Congestive heart failure

BRONCHOPULMONARY DYSPLASIA

Neurologic system and development -

Impaired motor and cognitive function

Impaired social responsiveness.

BRONCHOPULMONARY DYSPLASIA

GIT, Feeding and Nutrition –

FTT

Mineral deficiencies

Vitamin deficiencies

Feeding intolerance

Food aversion

GERD

BRONCHOPULMONARY DYSPLASIA

Other –

Decreased GFR and Renal blood flow

Renal calcifications

Osteopenia, rickets, fractures

Hearing loss

Medications

BRONCHOPULMONARY DYSPLASIA

RSV Prophylaxis:

- Prematurity 32w + 6d – First year
- Prematurity 33w to 34w + 6d – First 6 months
- BPD + Oxygen - First two years
- BPD + medications in hospital – First year
- Congenital heart disease – CHF, PHT, Cyanotic heart disease – First year
- Below 1 kg – First year
- CLD, severe – First year

November till March – once a month for 5 months
THANKS !!!