RESPIRATORY DISORDERS ASSOCIATED WITH BRONCHOPULMONARY DYSPLASIA

Respiratory 2 Department

CONTENT:

- Introduction
- Respiratory disorders:
  1. Upper airway disease
  2. Central airway disease
  3. Sleep hypoxemia
  4. Pulmonary function
  5. Asthma-like symptoms
  6. Repiratory infection
  7. Pulmonary artery hypertension
- Conclusion

INTRODUCTION

Bronchopulmonary dysplasia is a chronic lung disease in premature infants who required long-term oxygen.

	<32 weeks GA	>32 weeks GA
Treatment with oxygen	>21% for at least 28 days	>21% for at least 28 days
Time point of assessment	36 weeks PMA or discharge*	>28 days but <56 days postnatal age or discharge*
Grade :		
Mild	Breathing room air at 36 weeks PMA or discharge*	Breathing room air at 56 days Postnatal age or discharge*
Moderate	Need for <30% oxygen at 36 weeks PMA or discharge*	Need for <30% oxygen at 56 days Postnatal age or discharge*
Severe	Need for ≥30% oxygen and/or positive pressure (IMV/CPAP) at 36 weeks PMA or discharge*	Need for ≥30% oxygen and/or positive pressure (IMV/CPAP) at 56 days Postnatal age or discharge*

Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med 2001;163:1723-9 Definition of Bronchopulmonary Dysplasia: Diagnostic Criteria. Reprinted with permission of
the American Thoracic Society. Copyright © 2016 American Thoracic Society. Jobe, A.H.; Bancalari, E.Bronchopulmonary Dysplasia. Am. J. Respir. Crit. Care Med. 2001, 163.

INTRODUCTION

- Have advances in perinatal care and a steady decline in mortality rates among very low birth weight infants (<1500g), BPD remains a major complication of premature birth.

- BPD tends to improve with advancing age, it can lead to lifelong consequences.

1. Upper airway disease

- Children born preterm may be more likely to have obstructive sleep apnea compared with term, may persist into adulthood.

- Deficit of intelligence quotient and and possible neuronal injury.

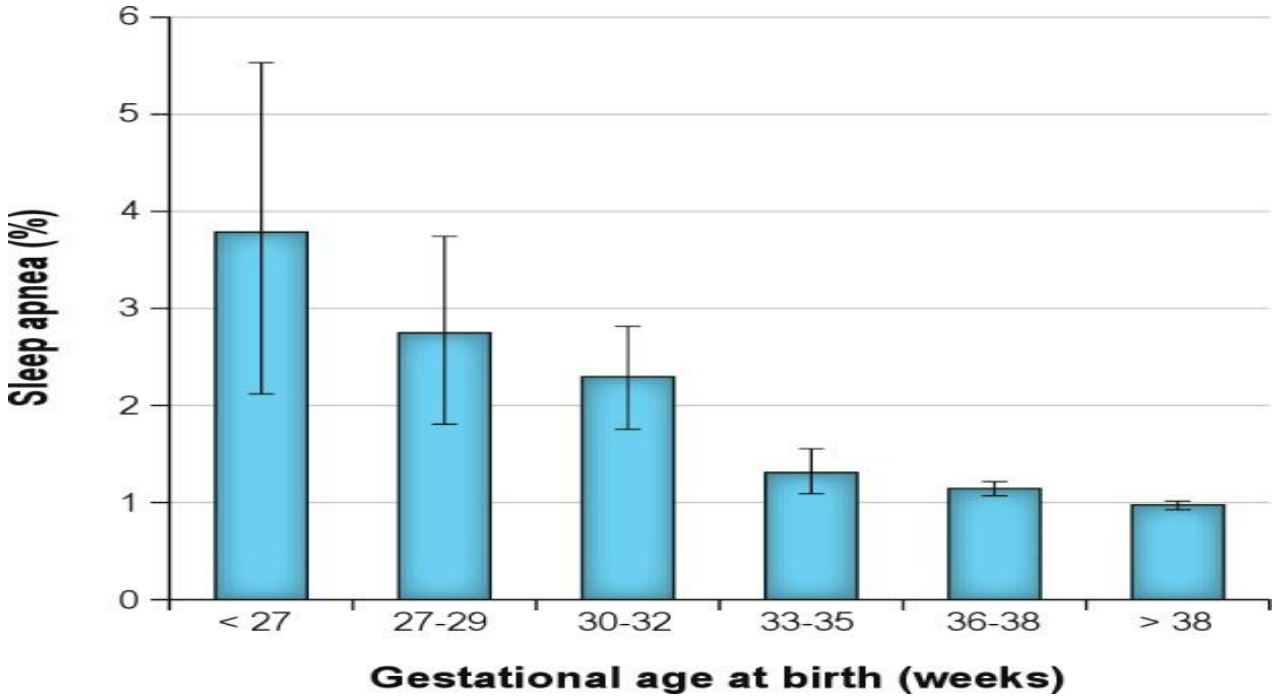
Sleep Apnea in Early Childhood Associated with Preterm Birth but Not Small for Gestational Age: A Population-Based Record Linkage Study

Camille H. Raynes-Greenow, PhD, Ruth M. Hadfield, PhD, Peter A. Cistulli, PhD, Jenny Bowen, PhD, Hugh Allen, MBBS, and Christine L. Roberts, DrPH

Sleep. 2012 Nov 1; 35(11): 1475–1480

PARTICIPANTS: 398,961 children, aged 2.5 to 6 years.

RESULTS:



2- Central airway disease

Children with BPD are at increased risk of developing central airway collapse or obstruction, including:

- *Glottic and subglottic damage*
- *Acquired tracheobronchomalacia*
- *Tracheal & bronchial stenosis and granuloma formation*

a. Glottic and subglottic damage:

- Reported after endotracheal intubation.
- Risk factor: intubated for many weeks, required more intubations, use inappropriatedly large endotracheal tubes.
- Postextubation stridor is common sign of moderate to severe subglottic stenosis. This child may have chronic symptoms or exhibit symptoms only during acute upper respiratory tract infections.

b. Acquired tracheobronchomalacia:

- Common in infant with classic BPD treated with prolonged positive pressure ventilation.
- Associated with barotrauma, chronic or recurrent infection, chronic aspiration, and endotracheal intubation.
- Improve with age, as the tracheal cartilage matures.
- Symptoms: reflex apnea or chronic wheezing (don’t improve or worsen with bronchodilator) ; increase with crying or exertion.

b. Acquired tracheobronchomalacia:

- Infants with classic BPD, tracheomalacia was found in 45% and bronchomalacia was found in 34%.

(Cohn RC, Kercsmar C. *Am J Dis Child*. 1988;142(11):1225)

ATS Journals

Vol. 14, No. 9 | Sep 01, 2017

Tracheobronchomalacia Is Associated with Increased Morbidity in Bronchopulmonary Dysplasia

Erik B. Hysinger [1,2], **Nicholas L. Friedman** [1], **Michael A. Padula** [3], **Russell T. Shinohara** [2], **Huayan Zhang** [3], **Howard B. Panitch** [1], and **Steven M. Kawut** [2,4]; Children's Hospitals Neonatal Consortium

+ Author Affiliations

- Study of 974 neonates with BPD

  Tracheobronchomalacia : 353 (36.2%)

  Without Tracheobronchomalacia : 621 (63.8%)

- **Results:** Neonates with TBM and BPD had more comorbidities, such as gastroesophageal reflux and pneumonia, and more commonly required surgeries, such as tracheostomy and gastrostomy, than those without TBM

c. Tracheal and bronchial stenosis and granuloma formation:

- Result of trauma from artificial airways and suctioning techniques.
- Cause long-term pulmonary problems: acquired lobar emphysema, persistent lobar atelectasis.

3- Sleep Hypoxemia

- Infants with BPD are more experience hypoventilation and hypoxemic episodes during sleep; may be clinically silent.
- Common during rapid eye movement (REM) sleep
- Due to reduction of intercostal and upper airway muscle tone, inadequate autonomic response mechanisms and hypoxemia-induced airway narrowing.
- Hypoxemic episodes during sleep can also affect older children, associated with growth delay.

4- Pulmonary Function

- Decrease FEV_1 and FEV_1/FVC, consistent with airflow limitation and small airway obstruction.

- Airflow limitation may be consequence of dysanaptic growth: length and diameter of the airways grow less rapidly than the lung parenchyma.

Effect of preterm birth on later FEV_1: a systematic review and meta-analysis

Sarah J Kotecha,[1] Martin O Edwards,[1] W John Watkins,[1] A John Henderson,[3] Shantini Paranjothy,[2] Frank D Dunstan,[2] Sailesh Kotecha[1]

Thorax. 2013 Aug;68(8):760-6.

Study characteristics: 59 studies; ages ranged from 5 to 23 years; preterm-born subjects were born between 24 and 36 weeks gestation.

Results:

The mean differences for $\%FEV_1$ compared with term-born controls:

- preterm-born group without BPD : −7.2% (−8.7% to −5.6%)
- preterm-born group with BPD_{28} : −16.2% (−19.9% to −12.4%)
- preterm-born group with BPD_{36} : −18.9% (−21.1% to −16.7%)

Pooled $\%FEV_1$ estimate:

- preterm-born group without BPD : 91.0% (88.8% to 93.1%)
- preterm-born group with BPD_{28} : 83.7% (80.2% to 87.2%)
- preterm-born group with BPD_{36} : 79.1% (76.9% to 81.3%)

BPD_{28} supplemental oxygen dependency at 28 days
BPD_{36} supplemental oxygen dependency 36 weeks postmenstrual age

5- Asthma-like Symptoms:

- Recurrent wheezing episodes: common in children with BPD, beginning in the preschool years and continuing into adulthood .

- "The prevalence of asthma was higher in children and adolescents with a history of prematurity and BPD compared with those who did not develop BPD."

Allergol Immunopathol (Madr). 2017 Jun 28. pii: S0301-0546(17)30062-9.

ATS Journals

Vol. 182, No. 2 | Jul 15, 2010

Lung Function and Respiratory Symptoms at 11 Years in Children Born Extremely Preterm

The EPICure Study

Joseph Fawke [1] *, Sooky Lum [2] *, Jane Kirkby [2], Enid Hennessy [3], Neil Marlow [1,4], Victoria Rowell [1], Sue Thomas [1], and Janet Stocks [2]

- **Results**: Children born EP had significantly more chest deformities and respiratory symptoms than classmates, with twice as many (25% vs. 13%; $P < 0.01$) having a current diagnosis of asthma. 56% of children born EP had abnormal baseline spirometry and 27% had a positive bronchodilator response

Extremely Preterm: born at or less than 25 completed weeks of gestation

5- Asthma-like Symptoms:

- BPD and asthma differ in underlying pathophysiology:

  BPD: fixed obstruction + neutrophilic inflammation

  Asthma: reversible obstruction + eosinophilic inflammation

- If spirometry suggests obstructive lung disease, a trial of standard asthma-management techniques is appropriate

- May respond to bronchodilator and inhaled corticosteroids, but the effect is less consistent than in children with asthma.

METHODS:
44 children with BPD with a mean gestational age of 25.6 weeks measured of lung function V(max)FRC and FRC at 6, 12, and 24 months after initial discharge from the neonatal care unit.

RESULTS:
Response to bronchodilator was significant in approximately 1/3 patients, similar to the findings of Robin et al, who reported 35% of their patients to have significant response to bronchodilator.

Mean FRC was significantly higher in children who were using bronchodilators and inhaled steroids but showed no correlation with clinical symptoms. Bronchodilator response was initially present in 30% of the patients and declined to 20% at the end of the study

Fakhoury KF. Serial Measurements of Lung Function in a Cohort of Young Children With Bronchopulmonary Dysplasia. *Pediatrics* 2010 Jun;125(6):e1441-7

6- Respiratory Infection

- 50% BPD require rehospitalization during the first two years of life due to a respiratory illness.
- Pathogen is usually viruses (RSV, Rhino virus,…)
- Respiratory infections, including RSV, can cause particularly severe illness, can be life-threatening.
- Respiratory Infections may interfere with postnatal lung growth and adversely affect lung function in later life.

6- Respiratory Infection

- BPD hospitalized with an RSV infection within the first 2 years of life have increased health care costs and worse lung function at school age.
- BPD may require additional immunizations and immunoprophylaxis for RSV (Palivizumab).
- Rhinovirus predominately causes upper airway symptoms in healthy individuals, but causes severe lower respiratory tract disease can occur in children with BPD.

7- Pulmonary Artery Hypertension

- An important complication associated with BPD.
- PAH was diagnosed prior to hospital discharge in 18% of ELBW infants.

(Bhat R, Salas AA, Foster C. *Pediatrics*.2012;129(3):e682)

- BPD infants with PAH more require supplemental respiratory support, have longer initial hospitalizations, and higher medical costs.
- Resolves with age and catch-up lung growth
- Mortality rates in BPD infants with PAH: 14% - 38% in retrospective studies

(An HS, Bae EJ, Kim GB. *Korean Circ J*. 2010 Mar;40(3):131-6)

and 12% in one prospective study.

(Bhat R, Salas AA, Foster C. *Pediatrics*.2012;129(3):e682)

Risk factor for PAH:

1. Extremely Low Gestational Age (GA < 28 weeks)
2. Very Low Birth Weight (<1500 g)
3. Small for gestational age birth weight
4. Oligohydramnios
5. Prolonged mechanical ventilation
6. Prolonged oxygen therapy

Pathogenesis for PAH:

- **Abnormal pulmonary vascular bed**: reduce size and complexity of pulmonary vascular bed, and increased reactivity of the arteries.
- **Oxygen toxicity and barotrauma**: interfere with alveolar development, reducing the number of alveoli and intra-acinar arteries →impaired production of nitric oxide and vascular endothelial growth factor (VEGF).
- **Alveolar hypoxia**: cause vasoconstriction and injury endothelial cell, hypertrophy of pulmonary arterial wall.
- **Cardiac dysfunction**: Left ventricular diastolic dysfunction.

Candidates for screening PAH:

1. VLBW (<1500 g) with BPD
2. ELBW (<1000 g) with or without BPD
3. Infants unable to wean from supplemental oxygen and/or positive pressure ventilation by 2 months of age
4. VLBW infants with poor weight gain
5. Infants born small for gestational age

CONCLUSION

- BPD can lead to lifelong consequences:
  - Upper and lower airway disease
  - Altered pulmonary function
  - Pulmonary artery hypertension

- To minimize lung injury:
  - Avoid recurrent respiratory infections
  - Minimize feeding-related aspiration
  - Optimize nutrition

particularly during the first two years of life.

CONCLUSION

- Recurrent wheezing is common in children with BPD, but pathophysiology differs from asthma. If spirometry suggests obstructive lung disease, a trial of standard asthma-management techniques is appropriate.
- Severe BPD may develop PAH. Infants need for supplemental oxygen at the time of hospital discharge should be evaluated for PAH.

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THANK YOU FOR ATTENTION