Bronchopulmonary Dysplasia

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Disclosures

• I have nothing to disclose

Learning Objectives

• Discuss how the diagnosis of BPD has evolved since its first description in 1967
• Recognize the differences between “Old BPD” and “New BPD”
• List the primary risk factors for BPD
• Identify strategies to prevent BPD
• Describe current and potential future management of BPD
What is BPD?

• BPD was first described in 1967 in the NEJM by Stanford Radiologist Northway in preterm infants with severe respiratory distress syndrome (RDS)
• “a new chronic pulmonary syndrome that is associated with the use of intermittent-positive pressure respirators and high oxygen for more than 6 days”


What is BPD?

• Infants required oxygen at 28 days
• Progressive changes on CXR
• Bronchopulmonary dysplasia - airway and lung parenchyma affected


Pathology “Old BPD”

Vascular changes consistent with pulmonary hypertension
Alveolar hyperinflation and atelectasis
Pulmonary inflammation and fibrosis

“Old” BPD

Mortality 59%
Mean gestational age 34 weeks
Mean birthweight 2,234 gm


Old BPD

- Mechanical Ventilation just beginning to be used for preterm infants
- Few extremely low birthweight (ELBW) infants less than 1 kg survived
- The causes of BPD were primarily mechanical ventilation and oxygen exposure of the preterm lung

Jobe AH, NeoReviews. 2006;7:e531-545
Old BPD

- Complication of BPD so worrisome, a conference was held in Paris in 1969 to discuss the dilemma of whether it was appropriate to push forward with assisted ventilation in neonates


OLD BPD

- Improvements in neonatal care in the 1970s and 1980s led to increased survival of preterm infants
  - Thermoregulation
  - Improved ventilation with PEEP/HFOV
  - Improved nutrition/TPN
  - Pulse oximetry

Jobe AH, Am J Respir Crit Care Med. 2001;163(7):1723-1729

OLD BPD

- Despite improvements in neonatal care, the 1980s have been described as an "era of chronic ventilator dependence, with some infants being ventilated for several months. Whereas many were eventually able to be weaned, some were 'pulmonary cripples' and others died of cor pulmonale after several months in the NICU."

Alistair GS, Semin Fetal and Neonatal Med. 2009;14(6):333-338
What is BPD? 1980s

– 1988 - BPD criteria changed from oxygen requirement at 28 days of life to oxygen supplementation at 36 weeks post menstrual age (PMA)
– This definition more accurately predicted abnormal pulmonary outcome at 2 years of age

Jobe AH, Am J Respir Crit Care Med. 2001;163(7):357-368

• Surfactant
• Antenatal Steroids

Surfactant

• 1929 Kurt von Neergaard performed experiments in isolated porcine lung suggesting the presence of pulmonary surfactant and its importance to the newborn’s first breath

Halliday HL, J of Perinatal. 2008;28:547-556
Surfactant

• 1959 Mary Ellen Avery demonstrated that Hyaline Membrane Disease (later known as RDS) was due to a lack of surfactant

Halliday HL, J of Perinatol. 2008;28:S47-S56

Surfactant

• The death of Patrick Kennedy in 1963 from RDS increased public awareness of the disease and stimulated further research into its treatment

Halliday HL, J of Perinatol. 2008;28:S47-S56

Surfactant

• 1960s Initial trials of nebulized synthetic surfactant (protein-free) were unsuccessful
• 1970s natural surfactants (containing proteins) were effective in rabbit model of RDS
• 1980 Fujiwara demonstrated the beneficial effects of a modified bovine surfactant administered to 10 preterm infants

Halliday HL, J of Perinatol. 2008;28:S47-S56
Surfactant

• Many RCTs in 1980s with synthetic and natural surfactants demonstrated reductions in pulmonary air leaks and neonatal mortality
• By 1991 both colfosciril, a synthetic surfactant, and beractant, a bovine-extract surfactant were approved by the FDA for the treatment of RDS
• Natural surfactants have been shown to be superior to protein-free synthetic products

Halliday HL, J of Perinatol. 2008;28:S47-S56

Surfactant

• Reduces both neonatal mortality and pulmonary air leaks by 50%
• 6% reduction in infant mortality in the United States
• Surfactant increases the likelihood of surviving without BPD largely by improving survival rather than the incidence of BPD

Halliday HL, J of Perinatol. 2008;28:S47-S56

Surfactant

• Three natural surfactants are currently available
  – Poractant alfa (porcine lung mince)
  – Calfactant (calf lung lavage)
  – Beractant (bovine lung mince)
• Synthetic surfactant – lucinactant
  – Contains synthetic peptide KL4 that mimics SP-B

Halliday HL, J of Perinatol. 2008;28:S47-S56
Antenatal Steroids

• 1969 – Steroid treatment of pregnant ewes found to accelerate lung development in fetal sheep
  

Antenatal Steroids

• 1972 - Liggins and Howie published landmark double-blind controlled trial of antepartum glucocorticoids for the prevention of RDS
• Mortality decreased from 15% to 3.2%, RDS from 26% to 9%
• (Initially submitted to Nature and Lancet, published in Pediatrics)
  

Antenatal Steroids

• 1990 – Crowely et al published a systematic review of the effectiveness of antenatal corticosteroid administration before preterm birth
• 1994 ACOG best practice guidelines that led to widespread use of antenatal corticosteroids
  
Antenatal Steroids

- Antenatal corticosteroids for fetal lung maturation are one of the most studied perinatal interventions
- Antenatal corticosteroids decrease the risk of RDS, IVH, and neonatal mortality
- Recommended for women between 24 and 34 weeks gestation at risk for delivery within 7 days
- The majority of eligible women with threatened preterm labor now receive antenatal corticosteroids (92-97%)


New BPD

- With advances in neonatal care, antenatal corticosteroids, and surfactant, BPD in more mature infants (Old BPD) is now rare
- Incidence of BPD has not changed significantly due to increased survival of ELBW infants
- Characteristics of the disease have changed (New BPD)

Thebaud B, Neon reviews. 2013;14:e252-258

New BPD

ELBW infant
New BPD

• With prenatal corticosteroids and surfactant, RDS often mild
• Not exposed to aggressive ventilation and higher oxygen
• Other factors must be contributing to development of lung disease

Kair LR, Pediatrics in Review. 2012;33:255-264

New BPD

• 1999 Alan Jobe coined term “new BPD” to describe arrest in lung development found in this new form of disease in ELBW infants
• Persistent oxygen requirement that slowly resolves, less airway reactivity, less pulmonary hypertension
• Minimal cystic emphysema or hyperinflation on CXR – “Hazy lung fields”


New BPD
Pathology New BPD

Normal lung, 5 month old born at term

New BPD - lung section shows enlarged alveolar ducts and few alveoli. Arrest of alveolarization results in the appearance of emphysema.

Jobe AH, NeoReviews 2006;531-545

Pathology New BPD

The new BPD may result primarily from the interference with the generation of respiratory bronchioles and alveolar ducts.

NIH 2000 severity based definition of BPD

- Treatment with oxygen >21% for 28 days and:
  - Mild BPD: RA at 36 wks PMA or discharge
  - Moderate BPD: Need for < 30% oxygen at 36 wks PMA or discharge
  - Severe BPD: Need for > 30% oxygen and or positive pressure at 36 wks PMA or discharge

Physiologic Test for Diagnosis

- Infants at 35 to 37 wks on > 30% oxygen with saturations less than < 96% or on CPAP/mechanical ventilation have BPD
- Infants on < 30% or on > 30% with saturations less than 96% are tested for oxygen need
  - Gradually wean to RA
  - No BPD if saturation is >90 % for 30 min

Walsh MC, Pediatrics. 2004;114:1305-1311

New BPD

- Oxygen > 36 wk PMA definition, 42% of infants with birthweight 401 to 1500 grams and GA 22 to 28 6/7 wks diagnosed with BPD
- Severity based definition:
  - 68% diagnosed with BPD: 27% mild, 23% moderate, 18% severe
- Physiologic definition 40%

Stoll B, Pediatrics. 2010;126(3):443-456

Risk Factors for BPD

- Prematurity – incidence inversely related to birthweight and gestational age

Risk Factors for BPD

• Genetic predisposition
  – Twin studies estimate heritability between 50 and 80%, no gene or gene pathway identified
  – Family history of asthma
  – Severity of BPD associated with male gender
  – Caucasian


Risk Factors for BPD

• Peripartum inflammation/infection
  – Maternal chorioamnionitis?
  – Ureaplasma colonization
  – Anenatal exposure to inflammation likely will not cause BPD but may potentiate postnatal inflammatory events

Risk Factors for BPD

• Fluid overload – high fluid intakes in the first few days of life have been associated with BPD and patent ductus arteriosus (PDA)
• Left to right shunting through a PDA may lead to lung endothelial damage and prolonged need for mechanical ventilation

Kair LR, Pediatrics in Review. 2012;33:255-263
Risk Factors for BPD

• Postnatal Infection/Inflammation
  – Early onset sepsis increased BPD from 35% to 62% in one cohort study
  – Coag negative sepsis, other gram-positive and gram-negative pathogens strongly associated with BPD

Kair LR, Pediatrics in Review. 2012;33:255-263

Risk Factors for BPD

• Mechanical ventilation
  – Volutrauma and barotrauma
  – Seen with old BPD, also plays role in new BPD
  – Even a small number of large volume breaths can create lung injury, especially in surfactant deficient lungs

Kair LR, Pediatrics in Review. 2012;33:255-263

Risk Factors for BPD

• Oxygen Toxicity
  – Hyperoxia can create reactive oxygen species, arrest lung development, and trigger inflammatory cascade
  – Initial resuscitation with 30% vs 90% oxygen, BPD reduced in half in 30% oxygen group

Risk factors for BPD

- Malnutrition
  - Malnutrition has significant adverse effects on pulmonary function and lung growth
  - Specific nutrients such as Vitamin A, Inositol, Vitamin E, Vitamin C, Selenium and Glutamine may play a role in protection of lung parenchyma or healing of injured tissue

Biniwa MA, Semin Perinatol. 2006;30(4):200-208

Prevention/Management

- Antenatal
  - Decrease prematurity
  - Corticosteroids 24 to 34 weeks standard of care
    - Effect on incidence of BPD controversial
    - Animal studies suggest corticosteroids may lead to arrest of alveolarization and microvascular development
    - < 24 weeks

Kair LR, Pediatrics in Review. 2012;33:255-263
Surfactant

• Has not lead to a decrease in the incidence of BPD at 36 weeks
• Surfactant has contributed to the transition from “Old BPD” to “New BPD”

Haliday HL, J of Perinatol. 2008;28:S47-S56

Prevention/Management

• Ventilatory strategies
  – Gentle Ventilation – prevent volutrauma and barotrauma
    • HFOV vs CMV – no difference
    • Optimal PEEP, small TV
    • Lower rates of BPD volume-targeted vs pressure limited
    • Ideal ventilation strategy for ELBW infant unknown
  – Permissive hypercapnia – PaCO2 45-55, pH >7.20
    • Trends toward BPD reduction without adverse effects

Ambalavan N Semin Perinatol 2006;30:192-199

Prevention/Management

• Avoid Mechanical Ventilation
  – NCPAP and NIMV
  – INSURE – Intubation, surfactant, extubation to nasal respiratory support is associated with a lower risk of BPD than later selective surfactant

Stevens TP Cochrane Database Syst Rev. 2007;74(4):CD003063
Prevention/Management

• Oxygen
  – Targeting lower saturations (89-94% vs 95-98%) reduces ROP (20.9 to 9.5%) and BPD (40.8 to 29.7%)


Prevention/Management

• Oxygen
  – SUPPORT trial – 1316 infants 24 to 27 6/7 weeks, increased mortality 19.9 % vs 16.2 % when lower oxygen saturations of 85-89% are targeted vs 91 to 95%
  – relative risk 1.27, CU 1.01 to 1.60; p=0.04


Prevention/Management

• Oxygen saturations
  – Saturations outside limits about 50% of time
  – Auto control 40% of the time in the intended range vs 32% manual

  – Neonatal Oxygenation Prospective Meta-analysis Collaboration (NeoProM) out 2014?

Prevention/Management

• Fluid Restriction
  – Higher fluid intake and less weight loss first 10 DOL associated with increased BPD
  – Infants with BPD tolerate excess fluid poorly and have a tendency to accumulate fluid in their lungs


Prevention/Management

• Nutrition
  – Plays a critical role in the prevention and management of BPD
  – Malnutrition can worsen BPD by compromising lung growth
  – Nutritional management starts 1st day of life

Biniwale MA, Semin Perinatol. 2006;30(4):200-208

Prevention/Management

• Nutrition
  – Increased caloric expenditure- infants with BPD may need 20 to 40% more kcals
  – Early TPN with protein and early enteral feedings may decrease incidence BPD

Biniwale MA, Semin Perinatol. 2006;30(4):200-208
Prevention/Management

• Nutrition
  – High calorie fortified breast milk or concentrated formula often needed if fluid restricted
  – Close discharge follow up of infants with BPD necessary to follow growth

Binisawale MA, Semin Perinatol 2006;30(4):200-208

Prevention/Management

• Vitamin A
  – Involved in the regulation of lung development and injury repair
  – Low levels associated with increased BPD


Prevention/Management

• Vitamin A Supplementation
  – Prophylactic Vitamin A decreases incidence of BPD in ELBW infants
  – 5000 IU Vitamin A IM three times weekly for four weeks
  – 1 infant survived without chronic lung disease for every 14 to 15 infants treated

Prevention/Management

• Caffeine
  – Caffeine for Apnea of Prematurity or CAP trial
  – Caffeine vs placebo first 10 DOL, BPD at 36 wks reduced to 36% from 47%
  – Mechanism unknown


Prevention/Management

• Systemic Corticosteroids
  – High dose, prolonged courses of dexamethasone used to be standard of care
  – Long-term outcome studies revealed that such use leads to cerebral palsy and global neurodevelopmental impairment

Prevention/Management

• Systemic Corticosteroids
  – 2002 Joint policy statement from AAP and Canadian Pediatric Society recommended that use of postnatal systemic steroids in infants with or at risk for BPD be limited to “exceptional clinical circumstances”
  – Many neonatologist stopped using corticosteroids

Barrington KL, CMAJ. 2001;165:33-4
Pediatrics 2002;109:310-8
Meta-Regression Analysis Benefit of systemic corticosteroids may depend on risk of BPD

2010 AAP Policy Statement

- High dose dexamethasone not recommended
- Insufficient evidence for recommendation regarding low-dose dexamethasone
- Hydrocortisone may be beneficial in a specific patient population, however insufficient evidence to recommend its use for all infants at risk of BPD

2010 AAP Policy Statement

- “Because available data are conflicting and inconclusive, clinicians must use their own clinical judgement. This individualized decision should be made in conjunction with the infant’s parents.”

Pediatrics 2010;115:655-61

Pediatrics 2010;126(4):800-808
Systemic Corticosteroids

- Vermont Oxford Network
- 8% of VLBW infants were treated with postnatal steroids in 2009 vs 24% in 2002
- Smallest infants receive steroids at the highest rates

Soll RF Pediatrics 2013;132:222-8

Prevention/Management

- Nitric Oxide
  - Animal models have shown benefit on oxidative stress and lung development
  - 1 multicenter randomized controlled trial suggests that iNO at 20ppm beginning in the 2nd postnatal week may provide a small reduction in the rate of BPD

Kumar P and Committee on Fetus and Newborn, Pediatrics. 2014;133:164-170

Prevention/Management

- Nitric Oxide
  - 2011 NIH Consensus Statement does not support use of NO in routine care of preterm neonates
  - 2014 AAP Committee on Fetus and Newborn “preponderance of evidence does not support treating preterm infants with the purpose of preventing/ameliorating BPD”

Prevention/Management

- Pentoxiphylline
  - Nonspecific phosphodiesterase inhibitor that decreases pulmonary inflammation
  - Nebulized pentoxiphylline decreased BPD risk by 27% in one study
  - Not used routinely

- Azithromycin
  - Decreased incidence of BPD in subset of infants colonized with Ureaplasma


Treatment of Established BPD

- Diuretics
- Inhaled Steroids
- Bronchodilators

Diuretics

- Used to decrease pulmonary interstitial edema and improve lung function
- 86% of infants with BPD received a diuretic

Diuretics
• Furosemide
  – No effect or inconsistent effect infants < 3 weeks
  – Transient improvement in lung mechanics single IV dose infants > 3 weeks
• Thiazides and spironolactone
  – Treatment for 4 weeks improves pulmonary compliance
  – No evidence improves long term outcome
  Brion LP, Cochrane Database Sys Rev. 2002;(1):CD001453
  Brion LP, Cochrane Database Sys Rev. 2002;(1):CD001817

Diuretics – Side Effects
• Electrolyte imbalance
• Ototoxicity
• Nephrocalcinosis
• Osteopenia
  Bavera R, Semin Prinatol. 2006;30:8209-21

Inhaled Steroids
• Inhaled corticosteroids
  – Evidence supporting use mixed
  – Cochrane review no evidence early use decreases incidence of BPD
  – Theoretically less neurodevelopmental risk than systemic steroids
  Shah V, Cochrane Database Syst Rev. 2007;4:CD001969
Bronchodilators

- β adrenergic agonist can aid in short-term improvement in lung function and may be helpful during acute exacerbations
- Not for chronic care


Future Treatment?

- Stem cells
- Mesenchymal Stromal Cell (MSC)
  - Originally isolated from bone marrow
  - Human cord blood derived MSCs

MSCs

- Protect alveolar epithelial cells from oxygen induced apoptosis
- Accelerate wound healing
- Promote lung vascular endothelial network formation
- Attenuate lung inflammation and fibrosis

MSCs

• Rodent studies
  – Human cord blood MSCs preserve alveolar and lung vascular growth, lung function, and prevent pulmonary hypertension in hyperoxic exposed rats
  – Airway delivery 2 weeks after oxygen exposure restores alveolar growth and lung function

Thebaud B, Neoreviews. 2013;14:e252-257
Sdrimas K, Antioxidants and Redox signaling, 2013 online ahead of print

Long-Term Outcome – “New BPD”

• Pulmonary Outcome
  – Pulmonary function tests performed in children with history of VLBW and BPD compared to age matched controls
  – Preterm-born children with history of BPD more likely to have abnormal lung function at school age
  – Mean age 9.5 years
    • 36% vs 8% with respiratory symptoms
    • 21% vs 0% received asthma medications


Long-Term Outcome – “New BPD”

• Pulmonary Outcome
  – Children with history of BPD had significantly lower FEV1, FVC, and FEF50
  – Duration of oxygen supplementation inversely associated with FEV1
  – However, in children with BPD and lung function abnormalities, only 33% reported symptoms
  – 29% of children in non-BPD group had PFT abnormalities and no symptoms
  – Bronchodilator therapy was effective in improving expiratory flow limitations

Long-Term Outcome

- Lung disease can persist into adulthood, including airway obstruction, reactive airways, and emphysema

Cardiovascular Sequelae

- Infants with BPD can develop pulmonary arterial hypertension (PAH), cor pulmonale, and systemic hypertension
- Prevalence of PAH difficult to know, lack of consensus for when and how to screen (25-38%)
- Severity of PAH correlates with severity BPD
- 14-38% who develop PAH condition is fatal

Neurodevelopmental Outcomes

- Poor neurodevelopmental outcome associated with BPD
  - Language delays
  - Fine and gross motor impairment
- Degree of impairment correlates with severity of lung disease
- Strongest predictor of poor neurodevelopmental outcome was need for positive pressure support > 28 days and discharge at > 43 wks PMA

Kair LR, Pediatr in Review. 2012;33:255-264

Outpatient Management

- Experienced multidisciplinary teams
- Home oxygen
- Home mechanical ventilation
- Nutritional support
- RSV prevention
- Routine Immunizations
- Developmental follow-up

Banclari E Early Human Development (2005)81,171-179

Conclusions

- “Old BPD” hallmarked by airway inflammation, fibrosis, and smooth muscle hypertrophy secondary to ventilator induce lung injury has all but disappeared
- “New BPD” is a disease of more premature infants who have multifactorial chronic lung disease characterized by arrested lung development

Conclusions

- Factors contributing to the development of BPD include prematurity, genetic predisposition, infection/inflammation, mechanical ventilation, oxygen toxicity, malnutrition, fluid overload, and PDA
Conclusions

- Vitamin A and caffeine therapy have been shown to reduce the incidence of BPD
- Optimal Nutrition is vital for the prevention and management of BPD
- Strategies that limit endotracheal intubation such as CPAP, NIMV, and ENSURE may reduce incidence of BPD
- The optimal mode of ventilation of ELBW infants is unknown

Conclusions

- Diuretics, inhaled bronchodilators and inhaled corticosteroids are often used to treat BPD, although there is little evidence to support chronic use
- Cell based therapies that promote both lung repair and lung growth may be available for the treatment/prevention of BPD in the not so distant future