Bronchopulmonary Dysplasia: Chronic Lung Disease of Prematurity

Prevention, Management and Long-Term Implications

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OBJECTIVES

To understand the:

- Definitions of RDS/HMD/BPD/CLD
- Natural history and pathogenesis of BPD
- Epidemiology
- Clinical features
- Prevention and management
- Outcome and long-term implications

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Definitions

- Northway (1967) described "classic" BPD characterized by typical clinical progression of severe RDS and CXR findings
- Bancalari modification: persistent O2 requirement beyond 28 days of life (the "new BPD"), includes infants with less severe symptoms initially (post-surfactant era) who go on to develop CLD
- Shennan modification: O2 requirement at 36 weeks PCA more predictive of long term pulmonary (and medical & neurodevelopmental) morbidity
- NICHD classification

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NICHD Criteria (2001)

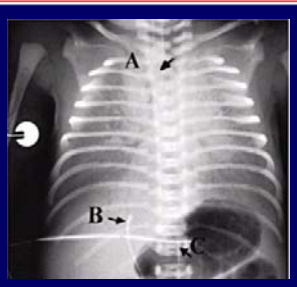
Gestational Age

	<32 weeks	>/= 32 weeks
Time Point of Assessment	36 wks PMA or discharge	>28 days but <56 DOL or discharge

Treatment with oxygen > 21% for at least 28+ days

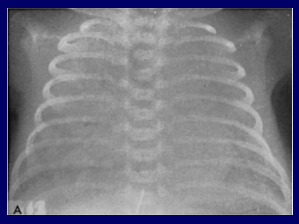
Mild BPD	Breathes RA at 36 wks PMA or discharge	Breathes RA by DOL 56 or discharge
Moderate BPD	Needs <30% FiO2 at 36 wks PMA or discharge	Needs <30% FiO2 at DOL 56 or discharge
Severe BPD	Needs >\= 30% FiO2 or PPV/NCPAP at 36 wks PMA or discharge	Needs >/=30% FiO2 or PPV/NCPAP at 36 wks PMA or discharge

"Classic BPD" Stage I: HMD/ RDS



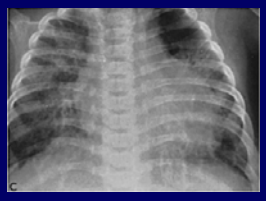
- Day of life 1-3
- Clinical: RDS
- CXR: hazy "groundglass" representing microatelectatic lung fields (surfactant deficiency)
- HMD= histologic dx

Stage 2 – Late HMD



- 4-10 days
- Clinical: increased FiO2/ PIP, end of "honeymoon"
- CXR: diffusely hazy w/more white-out, obscured heart borders

Stage 3 – Evolving BPD



- >10 days
- Continuing ventilator needs
- CXR diffusely bubbly, interstitial pattern

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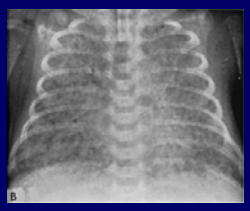
Stage 4 - CLD



- >1 month
- Continuing FiO2 needs
- CXR: fibrotic/ cystic lungs, hyperaeration, focal hyperlucency, alternating areas of opacification

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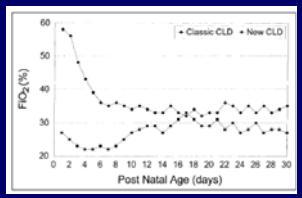
The "New BPD"

- Post antenatal steroid/ surfactant era
- Despite less exposure to high PIP/ FiO2, some infants go on to develop CLD via different / milder clinical course



? Role of different pathogenesis / predominating etiological factors

From Bancalari *NeoReviews* 2000

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BPD - Etiology

- "Classic BPD" – surfactant deficiency + …
- Duration of mechanical ventilation
  - Barotrauma: direct relation to high PIP
  - Volutrauma: in animal studies, as few as 6 breaths with manual PPV resulted in greater histologic lung injury (Bjorkland et al)
- Oxygen toxicity
  - Room air is relatively hyperoxic compared to in utero
  - immature antioxidant enzymes in lungs
- Infection
  - maternal (chorio) & fetal (sepsis)
  - secondary to cytokine release

BPD- Other Risk Factors

- Nutritional deficiency – e.g. Vit A protects epithelial integrity and promote cell differentiation and growth- small but significant improvement in BPD severity with supplementation
- Maternal/ neonatal colonization with *Ureaplasma histolyticum* (Hannaford et al, 1999)
- Initial severe respiratory distress (ECMO, pulmonary hypoplasia, meconium aspiration)- continued cytokine/ inflammatory mediators
- Fluid overload (excess pulmonary water)
- Hemodynamically significant PDA

Multifactorial Etiology, Common Pathogenesis

Multifactorial Lung Injury

↓

Inflammation (activated inflammatory cells, inflammatory mediators, cytokines)

↓

Lung Scarring, fibrosis, decreased alveolarization/ septation

Inflammation

Increased Inflammatory Mediators

↓

Complement activation → Mobilization of Neutrophils in the Interstitial and Alveolar Compartments

↓ ↓

Increased Vascular Permeability | Release of Oxygen Free Radicals, Elastase and Collagenase

↓ ↓

Protein Leakage → Lung Injury/BPD

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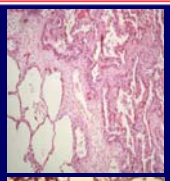
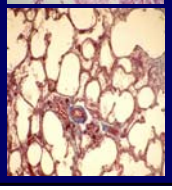
Pathology





"Classic BPD" – severe lung injury, inflammation, parenchymal fibrosis

"New BPD" - Decreased septation and alveoloar hypoplasia → fewer, larger alveoli
Severe cases include fibrosis, bronchial smooth muscle hypertrophy and interstitial edema/ thickening, increased elastic tissue formation

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Epidemiology

- Overall rate 25% for all VLBW (<1500g)
- Varies WIDELY by institution, range 3-43%
- Inversely related to GA/ BW →
- ? Increased incidence, greater severity in males and Caucasian population

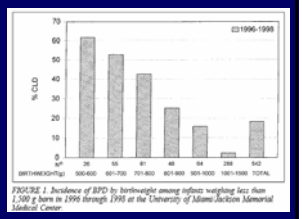

FIGURE 1. Incidence of BPD by birthweight among infants weighing less than 1,500 g born in 1996 through 1998 at the University of Miami/Jackson Memorial Medical Center

From Bancalari *Neoreviews* 2000

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Clinical Aspects

- Tachypnea, retractions, wheezing, rales
- Persistent hypoxia (V/Q mismatch)
- Increased risk of infection (RSV, PNA)
- Delayed growth- tachypnea → higher metabolic expenditures
- Pulmonary hypertension
- Cor pulmonale
- Increased risk for IVH, ROP, death

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Prevention

- Prenatal steroids
- Surfactant: not shown to decrease risk of BPD BUT does increase survival and decrease BPD severity
- Gentile ventilation: permissive hypercapnia, accept pO2 50-60 or SaO2 88-94%
- Optimal nutrition:
  - appropriate fluid goal (avoid overload)
  - may have higher caloric requirements (130+kcal/kg/d, monitor growth)
  - Vitamin A* (more later)
- Prevent (pulmonary toilet) & treat (abx) infections

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Surfactant administration

- Indicated in preterm infants with RDS clinically (FiO2 >30%) and on CXR
- Ideally within 6-8 hrs of life, 2nd dose may be given after 6 hrs if above indications still present
- 2 kinds on formulary at CNMC (if 2nd dose give whatever formulation given at OSH)
  - Survanta: 4 ml/kg
  - Curosurf: 2.5 ml/kg (1st dose), 1.25 ml/kg (2nd dose)

Confirm ET placement
Cut 5Fr feeding tube to length of ET
Use sterile gloves
Instill in 4 aliquots (above), w/ PPV between each quadrant*
*can dose in midline position if unstable

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Vitamin A

- ELBW preemies are deficient
- Vitamin A deficiency associated with impaired lung healing, increased squamous metaplasia, decreased alveolar number, increased susceptibility to infection, loss of cilia
- Supplementation associated with small but significant risk reduction for death or BPD (Tyson et al.)
- ***CONSIDER*** for Infants <1250 gm on O2 > 24 hours
  - 5000 I.U. IM QMWF for the first month of life/or while on prolonged TPN
  - Follow Vitamin A and Retinal Binding Protein levels (run every other Wednesday)
  - D/c when enteral nutrition reaches 60 kcal/kg/day

Other Management Strategies

- To decrease lung water:
  - Fluid restriction (may concentrate formula up to 30 kcal/oz)
  - Diuretics (lasix, aldactazide)
- To decrease airway hyperreactivity: bronchodilators such as albuterol,
  Lev-albuterol (2nd line, only if tachycardia)
- To decrease inflammation: inhaled corticosteriods
- To prevent aspiration, airway inflammation: control GERD

Systemic Steroid Use

High dose steroids may *facilitate extubation* and reduce lung inflammation acutely… BUT they have not been shown to alter outcome and…

They are associated with many deleterious effects:
hyperglycemia, hypertension, intestinal perforation, infection, poor brain & somatic growth, worse neuromotor and developmental outcomes

So, they are used very judiciously (mainly in severe BPD) after discussion with team/ attending *and family*

Other considerations

- If on chronic steroids: remember stress dose for surgery, shock/sepsis etc
- If on chronic lasix: watch for hematuria as sign of nephrocalcinosis
- If severe BPD: consider EKG or ECHO prior to discharge to look for RVH, pulmonary HTN

Discharge Considerations

- Transition to Home O2: no blender so FiO2 100%, $^1/_8$ to ½ L flow)
- Need home monitor, CPR training for parents
- Synagis information
- Pulmonary and development follow-up

RSV Prophylaxis – Synagis®

- Has been shown to decrease the rate of hospitalization by 50%
- For those hospitalized, illness is less severe with decreased length of stay and fewer O2 days
- RSV season – October to March (varies by geographical location)
- Synagis® given monthly during season
- @CNMC given once a week on Thursdays (with few exceptions!)

Synagis® Indications:

- Infants of any GA <2 yrs at start of season with CLD or significant CHD
- Infants <28 wks GA who are <1 yr at start of season
- Infants 29-32 wks GA who are <6 mo at start of season
- Infants 32-35 wks who are <6 mo at start of season and have additional risk factors*

RSV Risk Factors

- Low birth weight (<2500g)
- Siblings
- Day care attendance
- Multiple birth
- Family history of asthma
- Limited availability of hospital care for severe respiratory illness
- Exposure to tobacco smoke and other environmental air pollutants
- Other underlying conditions such as neuromuscular disease and congenital abnormalities of the airways

Outcome - Pulmonary

- 2x risk of wheezing/ asthma, lower respiratory tract infections, rehospitalization in early childhood compared to GA matched controls (up to 50% in some series)
- PFT abnormalities (decreased FVC, FEV, FEF) persist into school age, improve by 7-11 years (remember alveolar lung growth continues until 5 years of age)
- 24% of "classic BPD" infants have respiratory symptoms into young adulthood

Outcome - Cardiovascular

- Increased risk of systemic HTN (6-11%)
- Pulmonary hypertension (smooth muscle hypertrophy and loss of cross sectional area of pulmonary vascular bed) => cor pulmonale
- Higher risk of ALTE (20%) and SIDS (3%)
- Post discharge mortality up to 6% (usually cardiopulmonary complications)

Outcome – Medical/ Long Term

- Delayed catch up growth
- May have renal dysfunction (if nephrocalcinosis persists)
- Independently associated with adverse neurodevelopmental outcome
  - neuromotor/ CP
  - cognitive (academic delay, lower IQ, language problems)