In-person
March 13-16, 2024

Virtual
May – July 31, 2024

45th National Conference on Pediatric Health Care

Bronchopulmonary Dysplasia

NICU and Beyond:
Review of the sequela of chronic lung disease of prematurity

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Speaker Disclosure

- No financial disclosures
- Photo consent has been obtained for all children in this presentation

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Learning Objectives

- Understand the epidemiology of Chronic Lung Disease (CLD) of Prematurity/BPD
- Describe normal fetal lung development and physiology of "New BPD"
- Describe the short term and long-term pulmonary care of premature infants
- Identify the multisystem comorbidities associated with premature infants and BPD
- Create a care plan for the outpatient care of infants and children with BPD

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NICU Course – 24 weeks

- 24 3/7, AGA week premature female
- Birth weight: 677 grams
- Respiratory Course in NICU:
  - Invasive mechanical ventilation: PMA 34 weeks
  - Non-Invasive ventilation support until PMA 38 weeks
  - Weaned to 0.5 L/min for home with steroid course
- Systemic steroid course
  - Prednisone → helped wean to home oxygen

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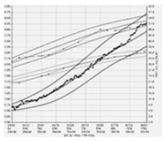
NICU Course: 24 weeks

- CV: Pulmonary Hypertension (PH) - 30 weeks PMA
  - Treated with Inhaled Nitric Oxide (iNO) – potent vasodilator
  - Repeat echocardiograms improved
- Neuro: Intraventricular hemorrhage (IVH) R- grade 1
  - Resolved – no MRI
- GI:
  - Good weight gain through NICU
  - 27kcal formula
  - Speech involvement – increased risk of aspiration with increased WOB



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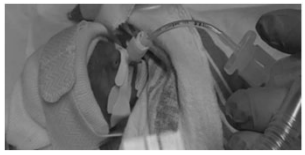
CLD/BPD

- The most common comorbidity associated with prematurity
- 30-40% of infants < 29 weeks gestation
- Up to 50,000 new cases of BPD each year [1]
- Incidence of BPD is increasing
  - Likely related to survival of extremely premature infants



1 Levin, 2023

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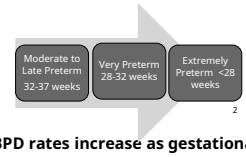
Prematurity

- Prematurity <37 weeks
  - 6-14% of infants depending on the country
- US: 12.4/100 births - preterm [1]



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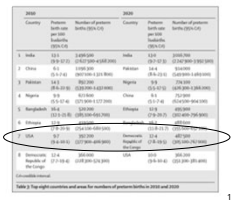

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***BPD rates increase as gestational age and birth weight decrease *** [2]

1. Ohuma, 2023
2. Thébaud, 2019

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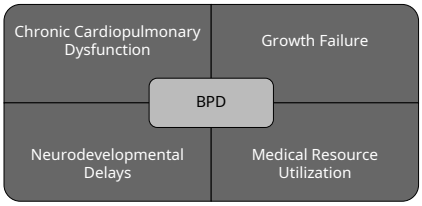
CLD/BPD

BPD is a strong predictor of adverse health outcomes [1]



1 Jensen & Schmidt, 2014

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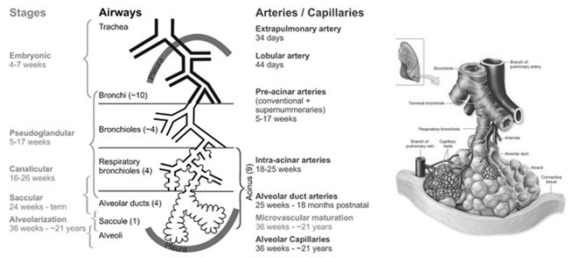
Normal Fetal Lung Growth



Schittny, 2017

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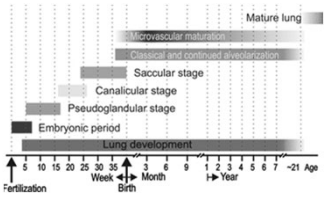
Normal Fetal Lung Growth

- Two phases of alveolarization:
  - classical (or bulk) alveolarization
    - 36 weeks to 2-3 years
  - continued alveolarization
    - 2 years to young adulthood



Schittny, 2017

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Risk Factors for Development of BPD

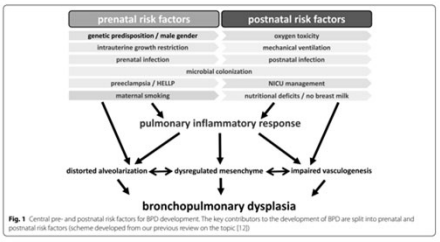

Fig. 1 Central pre- and postnatal risk factors for BPD development. The key contributors to the development of BPD are split into prenatal and postnatal risk factors (scheme developed from our previous review on the topic [12])

Holzfurtner, L, 2022

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Changes in physiology of BPD

- Advances in OBGYN and NICU care have changed the physiology of BPD
  - Antenatal steroids (Betamethasone)
  - Surfactant
  - Changes in ventilator strategy, early extubation, improved nutrition
- Changes in Physiology
  - Old BPD
    - obstructive bronchiolitis and fibrosis of lung parenchyma
  - New BPD
    - abnormalities of central and small airways, impaired alveolar growth leading to diffusely reduced alveolar development and impaired vascular growth

Holzfurtner, 2022

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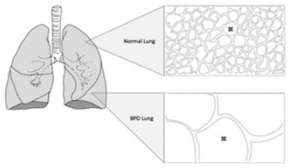
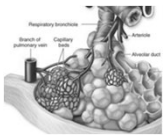
"New" BPD

- Alveoli of infant with "new" BPD:
  - Fewer
  - Larger
  - Less complex
- Microvascular arrest
  - "dysmorphic" microvasculature
  - decreased vessel growth
  - dilated vessels without extensive network organization



https://www.breathingnyc.com/bpd



Abman, 2001

Schittny, 2017

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Classification Systems for BPD

- National Institute of Child Health and Human Development (NICHD)
  - 2001
  - Revised in 2018
- Jensen Criteria[1]
- Infants are classified at 36 weeks PMA

	NICHD 2018	Jensen	
Mild	NC <1 L/min, FiO2 22-70% NC 1-3 L/min, FiO2 22-29% CPAP, NIPPV or NC ≥3 L/min, FiO2 21%	NC ≤2 L/min	Grade 1
Moderate	NC <1 L/min, FiO2 ≥70% NC 1-3 L/min, FiO2 ≥30% CPAP, NIPPV or NC ≥3 L/min, FiO2 22-29% Mechanical ventilation, FiO2 21%	NC >2 L/min CPAP or NIPPV	Grade 2
Severe	CPAP, NIPPV or NC ≥3 L/min, FiO2 ≥30% Mechanical ventilation, FiO2 >21%	Mechanical ventilation	Grade 3

28 week premature infant
36 weeks CGA
NIPPV, FiO2: 45% = _____

Comparison:
similar predictive values in predicting death or severe respiratory morbidity at CGA 18–24 months [2]

1 Kurihara, 2021
2. Wang, 2023

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Outpatient Respiratory Support

- Respiratory Support
  - Oxygen
    - 0.25-0.5L
    - Finer et al, 1996 – calculation to determine percentage of oxygen via low flow cannula
    - Training
      - Pulse oximeter monitoring
      - CPR and oxygen training
    - Weaning
      - Monitor WOB and growth
    - Often require nighttime oxygen longer
    - Pulm Clinic every 4-6 weeks

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Severe BPD- Tracheostomy and Ventilator Dependence

- Tracheostomy to provide ventilator support
  - Decision to place tracheostomy
    - Sustained respiratory distress
    - Cyanotic or brady episodes
    - Intolerance of developmental therapies
    - Poor growth
    - Pulmonary Hypertension
    - Use or need of repeated steroid courses
  - Average vent support – 2 years
- Challenges:
  - Extensive training, 24 caregiver/nurse supervision

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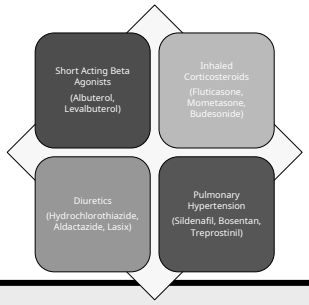
Common Pulmonary Medications at Discharge from NICU



Abman, 2017

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Factors Affecting Pulmonary Dysfunction

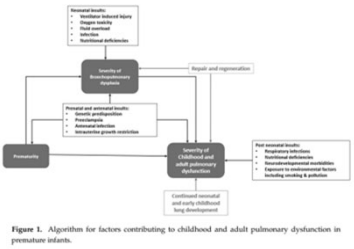

Figure 1. Algorithm for factors contributing to childhood and adult pulmonary dysfunction in premature infants.

**<u>Prematurity alone</u> without the diagnosis of BPD increases risk for pulmonary dysfunction

Jain et al., 2020

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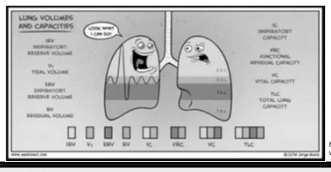
Pulmonary Function Tests

- Spirometry
- Plethysmography
- DLCO (Diffusion capacity of the lungs for CO)
- Bronchoprovocation - Exercise
- CPET – Cardiopulmonary Exercise Testing



https://www.medcomic.com/medcomic/lung-volumes-and-capacities

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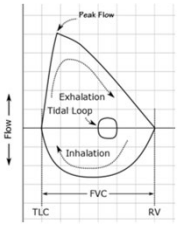
Pulmonary Function Testing

- Spirometry
  - Most common – screening test
  - Available in some primary care offices
  - Operator and effort dependent
  - Comparison to predicted values based on age and height
    - (Global lung Initiatives) predictive values
- Interpretation
  - Assessing the tests for acceptability and repeatability
  - Identifying the spirometry pattern (normal, obstructive, restrictive, or mixed
  - Grading the severity of the pattern identified

Jat, 2013



https://pftforum.com/review/tutorials/spirometry-tutorials/assessing-flow-volume-loops/

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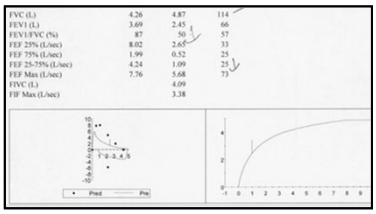
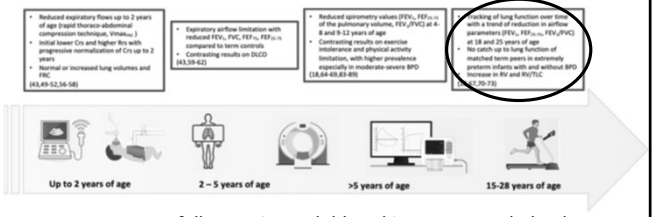
Obstructive Lung disease

- BPD → increased risk of obstructive lung disease

Obstruction Defined As:
Abnormal FVC/FEV1 Ratio < 80%
- Mild: 70-79%
- Moderate 60-69%
- Moderately Severe: 50-59%
- Severe 35-49%
- Very Severe < 35% (Calogero, 2018)



What happens to the lungs?



- Long term follow up into adulthood is recommended to better understand the evolution of pulmonary function
  - preterm-born subjects with and without BPD

Moschino, 2021

Pulmonary Complications

Doyle, 2019
- Young adults<28 weeks, <1,000 g
- PFT at age 8,18 and 25
- Decreased airway function compared to controls
- Increased risk of developing COPD

Ni, 2023
- Birthweight and Asthma Diagnosis
- Retrospective study
- VLBW significantly increases risk of asthma
- Limitations: largely done on parental report of asthma

Pulakka, 2023
- Nationwide register study from Norway and Finland
- COPD at age 30–50 years, the OR was 7.44 for those born at <28 weeks
- Odds of any obstructive airway disease in adulthood for those born at <28 or 28–31 completed weeks were 2–3-fold of those born full term

Landry, 2015
- Cross sectional cohort study
- PFT comparison – age 21
  - healthy term infants
  - BPD
  - Premature infants without BPD
- More airflow obstruction
- More gas trapping
- Decreased diffusion capacity

Cardiovascular Complications

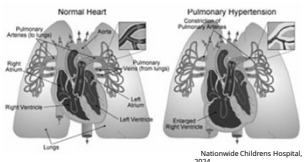
- **Pulmonary Hypertension**
- Pulmonary vein stenosis
- Persistent shunts that cause increased pulmonary blood flow
  - ASD
  - PDA
- Systemic Hypertension

1. Rivera, 2016
2. Kumar, 2019

Pulmonary Hypertension

- Increased blood pressure in pulmonary arteries → right heart failure
  - Abnormal vascular remodeling and vascular growth arrest
  - 25% -30% of infants with moderate to severe BPD develop PH
  - PH that persists beyond the first few months → mortality rates as high as 40–50%

Hansmann et al., 2021



Nationwide Childrens Hospital, 2024

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Pulmonary Hypertension

- Evaluation
  - Echo – indirect measures
    - Minimum 1 x per month while on respiratory support, Once discharged every 1-3 months
  - Biomarkers: BNP, ProBNP
  - Cardiac catherization
- Prevention
  - Limiting hypoxia and hyperoxia
  - Close attention to growth and nutrition. ** remember lung growth continues in the first 2 years of life
  - Early treatment of lung infections
  - Supporting the lungs with chronic mechanical ventilation

1. Rivera, 2016
2. Hansmann, 2021

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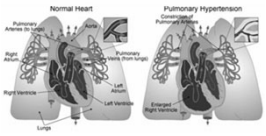
Pulmonary Hypertension Treatment

- Supplemental oxygen
  - Suspected PH: >93%
  - Proven PH >95%
- Inhaled nitric oxide (acute setting)
- Pharmacotherapy
  - Pulmonary vasodilators (off label)
    - PDE5 inhibitors (Sildenafil, Tadalafil)
    - Endothelin receptor antagonist (Bosentan, Ambrisentan)
    - Treprostinil (SQ continuous infusion)



Rivera, 2016

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Developmental Delays

- Infants with BPD have worse neurodevelopmental outcomes
  - Often < 28 weeks
  - Recurrent hypoxemia – neonatal brain injury
  - Longer time in NICU
  - Longer exposure to mechanical ventilation
  - More exposure to sedatives
  - Less stimulation/tolerance of therapies secondary to WOB

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Developmental Delays and BPD

Drummond, 2019
- Eval of 15 year olds -VLBW
- BPD was associated with a higher risk to attend a school for children with special needs
- Higher risk for repeating a grade (p = 0.01)
- Increased number of medical and paramedical consultations, including PT,OT, speech

Gou, 2018
- Meta-analysis
- 11 studies comparing the association of BPD with CP
- BPD is significantly associated with CP
  - Challenges:
    - Small number of studies
    - Inconsistent definitions of BPD and CP

Tréluyer, 2022
- Contemporary group of preterm infants
- ASQ scores were significantly lower in infants with BPD (Jensen criteria) at 36 weeks
- BPD was associated with increased odds of developmental delay at 2 years

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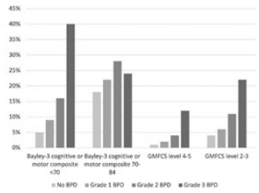
Cognitive and gross motor scores related to severity of BPD

- Bayley scale for infant development
- Gross Motor Function Classification System



Jensen et al, 2019. DeMauro, 2021

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Outpatient Neurodevelopmental Care

- Follow up with Neurodevelopmental Specialist
  - **Early intervention**
  - Automatic qualifier < 1,000 grams
- Hearing loss in 10-20 times higher in premature infants
  - exposure to ototoxic drugs in NICU (Lasix, gentamicin)
  - May require ABR
- Vision deficits
  - ROP

** Follow up with family to ensure they are receiving services **

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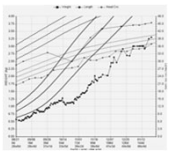
Nutrition and growth - BPD

- Supporting growth can be challenging
  - periods of hypermetabolic states
  - increased work of breathing and increased caloric expenditure
  - growth suppression from chronic stress and inflammation and chronic steroid or diuretic use
- IUGR and SGA
  - high-risk conditions for developing sBPD and may set the stage for persistent abnormal growth patterns in the postnatal period
- Slowest growth velocities → Highest risk for BPD



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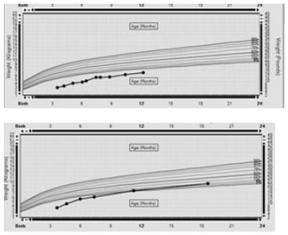
Outpatient Nutrition and Growth Goals

- Goals for growth:
  - Weight for length 50th%
  - Adequate linear growth
  - Catch up growth
    - Continue fortified milk/formula until 10th% weight uncorrected growth chart
  - Advance feeds (solids) according to adjusted age (not chronological age)



GI conditions affecting children with BPD

- Reflux
  - Peaks 4 months
  - Symptoms
    - Feeding refusal
    - Vomiting
    - Poor weight gain
    - Irritability
  - Treatment
    - AR, smaller volume feeds, medications
- Constipation
  - Distended abdomen affect movement of the diaphragm and respiratory muscle compliance
  - Increased risk with higher calorie formula 27kcal/oz and 30kcal/oz
  - Treatment: Lactulose <6 months, Miralax > 6 months, Glycerin PRN [1]

Consider referral to Pediatric GI

1. Vandeplas, 2015

Feeding Difficulties

- Oral motor dysfunction/dysphagia and Aspiration
  - Neurologic impairments: IVH, Hydrocephalus, immaturity
  - Increased work of breathing can affect coordination of suck, swallow/breathe
  - Evaluation
    - Clinical swallow evaluation/ Video swallow study
  - Treatment
    - Thickeners/slow flow nipples
    - Feeding Support with GT
    - Continued active therapy to enhance suck swallow coordination
- Recurrent microaspiration → chronic respiratory symptoms
    - Coughing, wheezing, tachypnea, poor weight gain,
    - Acute aspiration: LRTI often with need for increased respiratory support
- Oral Aversion
  - Refer to feeding specialist

Infection Prevention

- Most admissions in children with BPD → Lower Respiratory Tract Infections (LRTI)
  - RSV, Rhinovirus, Human Metapneumovirus,
- RSV prophylaxis with monoclonal antibody [1]

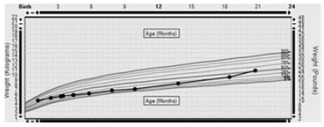
Palivizumab	• FDA approved 1998 • Monthly injection during RSV season • Must have qualifying diagnosis or gestational age
Nirsevimab	• FDA Approved 2023 • One time injection • Includes healthy infants

- Hand hygiene
- Avoiding exposure to sick contacts, large gatherings
- Limiting daycare in infants with severe BPD if able for the first year of life.

Abman, 2017

Post NICU Course:

- Oxygen dependent until 14 months
- Asthma: treated with ICS (fluticasone) and SABA
- Pulmonary Function Testing:
  - Spirometry attempted but not reproducible yet
- Sleep study: age 3
  - Moderate OSA, AHI 6.7
  - s/p, T&A
- GI: slow weight gain from DC
  - 65th% - 10th%
  - Age 5: BMI <10th%
- Development: kindergarten, PT, OT, speech, hyperactive, behavior concerns



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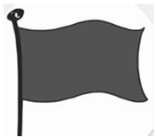
Red flags at follow up



- Respiratory:
  - Change in WOB
  - Desaturations
  - Fatigue/lethargy
  - Wheezing/coughing
  - Repeated hospitalizations
- CV:
  - increased HR (pulse ox monitor), poor growth, desaturations
- GI:
  - Coughing with feeds
  - Oral aversion/poor intake
  - Poor growth
- Social
  - Poor follow up with appointments
  - Parental involvement/support

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Outpatient Follow Up Plan

Gastrointestinal:
follow growth closely
Extra weight checks if needed
Monitor for reflux and constipation
Early referral to GI/feeding specialists

Infection Prevention
Encourage all vaccines
Annual influenza and COVID vaccine
Mononoclonal antibody for RSV

Pulmonary:
Follow with pulmonary specialist
Evaluate and treat asthma
Pulmonary function test >age 6
Encourage continued pulmonary evaluation into adulthood

Neurodevelopmental Care:
-Screening
-Early Intervention Program
- Follow with Neurodevelopmental Specialist

Cardiology:
- Screening for Pulmonary hypertension while on oxygen or ventilator support

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