

Going home with BPD 'preparing for the journey ahead'

Dr Sumesh Thomas MB.BS, DCH, FRCP(Edin), FRCPCH(UK) FRCPC
Neonatologist and Clinical Professor
Department of Pediatrics



UNIVERSITY OF
CALGARY

Objective

- Getting baby and family ready for home
- Challenges, opportunities and uncertainty ahead
- Working together to make the best of the future



Introduction

- Bronchopulmonary dysplasia (BPD) is the most common complication of prematurity and associated with significant short and long-term morbidity

Stenmark et al. Ann Rev Physiol. 2005

- Despite advances in neonatal care including the increase in use of non-invasive respiratory support strategies, the incidence of BPD has remained relatively stagnant
 - ❖ 30-40% in ELBW and 50-70% in ILBW infants

Stoll et al. JAMA. 2015

Historical perspective 'Old / New BPD'

- Multisystem disorder primarily affecting the respiratory system/histological distortion of lung and vasculature
- “old” BPD - extensive inflammatory and fibrotic changes in the airway and lung parenchyma
- “new” BPD - developmental disorder of immature lungs to reach full structural complexity
 - Fewer, larger alveoli with smaller surface for gas exchange
 - Airways relatively spared, inflammation is less prominent

Defining BPD

- Mild <32wks - supplemental oxygen for >28 days and in RA at 36 wks. PMA
- Moderate <32wks - supplemental oxygen for >28 days and <30% FiO₂ at 36wks PMA
- Severe <32wks - supplemental oxygen for >28 days >30% oxygen and or positive pressure support at 36wks PMA

Modified from Jobe and Bancalari Am J Respir Crit Care Med 2001
NIH June 2000 severity-based definition of BPD for infants

- Low-flow (≤ 2 L/min) nasal cannula at 36 wks. PMA (Grade 1)
- High flow (>2 L/min) nasal cannula, NCPAP or NIPPV at 36 wks. PMA (Grade 2)
- Invasive positive pressure ventilation at 36 wks. PMA (Grade 3)

Physiological BPD (PBPD)

Room air challenge @ 36 wk. CGA if requiring

- >30% O₂ with SaO₂ >96%
- <30% O₂ with SaO₂ 90-96%

PBPD was defined as oxygen saturation of <80% for 1 minute
80-87% for 5 min or SaO₂ <90% after 30 min

At risk infants with BPD



< 30% FiO₂ or positive pressure support at 36wk CGA - Moderate
> 30% FiO₂ and or positive pressure support 36wk CGA - Severe

Zakariya Puthattayil, et al. Canadian Neonatal Follow-Up Network. Risk factors for re-hospitalization following neonatal discharge of extremely preterm infants in Canada, Paediatrics & Child Health, Volume 26, Issue 2, April-May 2021

High flow (>2 L/min) nasal cannula, NCPAP or NIPPV at 36 wks. PMA (Grade 2)
Invasive positive pressure ventilation at 36 wks. PMA (Grade 3)

Association of newer definitions of bronchopulmonary dysplasia with pulmonary hypertension and long-term outcomes. Hwang Jae Kyo, et al. Frontiers in Pediatrics. Vol :11 2023

Discharge with BPD: Challenges

- Hospital readmissions
- Growth failure
- Pulmonary and systemic hypertension
- Developmental delay
- Family stress

Magnitude of risk Re-hospitalization with BPD

2014-2018. 354 Babies <32wks. Readmission at ≤ 2 yrs. University Hospitals in Korea – 2023

	<u>>1 readmissions</u>	<u>No readmissions</u>	<u>P-Value</u>
BPD (all)	24% (n-85)	13 % (n-269)	<0.01
Grade 2/3	42%		

Association of newer definitions of bronchopulmonary dysplasia with pulmonary hypertension and long-term outcomes. Hwang Jae Kyoon, et al. Frontiers in Pediatrics. Vol :11 2023

2009-2011 2275 Babies 22-28wks - @18-24 months. CNFUN- 2021

BPD	54.6% (n-456)	39.7% (n-570)	<0.01
Home O ₂	27.2% (n-227)	9.7% (n-139)	<0.01

Canadian Neonatal Follow-Up Network. Risk factors for re-hospitalization following neonatal discharge of extremely preterm infants in Canada, Paediatrics & Child Health, Volume 26, Issue 2, April-May 2021

1995-1999 1597 Babies <33 wks. @ 12 months. Harvard School of Public Health - 2004

BPD	49% (n-118)	23% (n- 309)	<0.001
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Smith VC, Zupancic JA et al. Rehospitalization in the first year of life among infants with bronchopulmonary dysplasia. J Pediatr. 2004

Growth failure

ELBW infants with (BPD) are more likely to develop postnatal growth failure

- Energy expenditure for respiratory needs
- Intercurrent illnesses
- Fluid restriction
- Use of Diuretics and Postnatal steroids

Cooke RJ Arch Dis Child Fetal Neonatal Ed 2004

Faster weight trajectory associated with a decreased probability of having at least one BSID III score <70 for infants with grade 1–2 BPD ($p < 0.0001$)

Munoz, et al. Does faster weight trajectory lead to improved neurodevelopmental outcomes in ELBW infants with bronchopulmonary dysplasia?. J Perinatol 44, 301–306 (2024)

Growth failure

- Inadequate nutritional intake.
- Suboptimal treatment of BPD.
- Evolving pulmonary hypertension.

Study Author, Year	Wt. <10 th % OR (95% CI)	Ht. <10 th % OR (95% CI)	HC. <10 th % OR (95% CI)
Han 2022 (n-2961)	1.50 (1.16-1.94)	1.33 (1.02-1.73)	1.36 (1.04-1.78)

Han, et al. The impact of neonatal morbidities on child growth and developmental outcomes in very low birth weight infants: a nationwide cohort study. Eur J Pediatr 181, 197–205 (2022).

- Other causes – UTI, metabolic acidosis, hyponatremia, hypothyroidism.

Growth failure

- Disproportionate weight-to-length linked to the development of BPD in infants born <26 weeks GA.
- Length is the strongest determinant of lung function throughout infancy.
- Head circumferences were significantly smaller in infants who developed moderate/severe BPD when compared with infants with no/mild BPD.

Nguyen TT et al, Pediatr Pulmonol 2013

- PNGR induces right ventricular and pulmonary vascular remodeling in neonatal rats

Wedgwood S, et al. Postnatal growth restriction augments oxygen-induced pulmonary hypertension in a neonatal rat model of bronchopulmonary dysplasia. Pediatr Res. 2016

Monitoring growth—BPD CPG

- Close assessment of nutritional intake to promote optimal growth.
- Close attention to Weight, **Length** and HC
- Monitoring of bone health* / electrolyte & acid base status
- Monitoring of haematological parameters/reticulocyte response
- Metabolic screening \pm TSH, Free T4 as indicated.

Cause of failure to thrive should be considered / investigations initiated before committing to caloric intake $>140\text{kcal/kg/day}$

Pulmonary Hypertension

- Reduction in cross-sectional area of the pulmonary vasculature.
- Decreased vascular branching - altered distribution within the interstitium, precapillary AV anastomotic vessels.
- Disruption of angiogenesis + impairing alveolarization and septation
- Vascular remodeling with thicker-walled pulmonary arteries

Ambalavanan, et al. "Pulmonary hypertension in bronchopulmonary dysplasia." Birth Defects Research Part A: Clinical and Molecular Teratology 100.3 (2014): 240-246.

- 'Fixed' structural - due to a lack of proliferation of pulmonary arteries.
- Oxygen responsive 'reactive' - through acute vasoconstriction hypoxia, hypercarbia, and acidosis.

Pulmonary hypertension

Echocardiogram at - 36 weeks PMA - further investigations/assessment at the discretion of the cardiologist

Pulmonary hypertension is suggested by any of the following ECHO findings:

- Elevated right ventricular systolic pressure (RVSP) $> 40\text{mmHg}$
- RVSP/systemic systolic pressure ratio > 0.5
- Cardiac shunt with bidirectional or right to left flow
- RV dysfunction/Right ventricular hypertrophy
- Flattening of interventricular septum

Pulmonary Hypertension

Systematic review published 2000-2017 onwards on both BPD with and without PH

Comparisons	Studies (n)	Subjects (n)	Pooled results OR (95% CI)
All BPD (vs. no BPD)	4	838	3.0 [1.2, 7.7]
Mod-Severe BPD (vs. no or mild BPD)	6	1351	8.1 [2.9, 22.6]

Outcomes in BPD+PH vs. BPD only

Outcomes	Studies (n)	Subjects (n)	Pooled results (95% CI)
Mortality prior to discharge	3	384	5.3 [2.1, 13.6]*
Duration of hospital stay (d)	3	422	40.7 [3.8, 77.5]†
Home O ₂ requirement	3	402	3.49 [0.94, 12.93]*

Pulmonary Hypertension - Outcome

- Growth @ Discharge

Study Author, Year	Outcome	BPD+PH	BPD Only
An, 2010 (n-116)	Weight < 3 rd %ile	64% (14/23)	31% (26/86)
Kim, 2012 (n-145)	Weight < 3 rd %ile	65% (13/20)	53% (38/72)

- Mortality and resolution of PH

Study Author, Year	2-year mortality	Resolution @1yr	Resolution @2yr
Arjaans 2020 (n-28) ¹	39%	47%	79%
Arjaans 2018 (n-416) ²	40%	65% (13/20)	53% (38/72)

¹ Arjaans, et al. "Fate of pulmonary hypertension associated with bronchopulmonary dysplasia beyond 36 weeks postmenstrual age." Archives of Disease in Childhood-Fetal and Neonatal Edition (2020).

² Arjaans et al. Identification of gaps in the current knowledge on pulmonary hypertension in extremely preterm infants: a systematic review and meta-analysis. Paediatr Perinat Epidemiol (2018)

Systemic hypertension with BPD

The cause of the systemic hypertension associated with BPD is unclear.
43% incidence in BPD vs 4.5% without BPD

- Intermittent hypoxia - catecholamine release and increased vasomotor tone /arterial chemoreceptors
- Abnormalities in Renin–angiotensin–aldosterone system (RAAS)
- UAC - 95% incidence of asymptomatic arterial thrombosis
- AKI and ? Nephrocalcinosis

Starr, Michelle C., and Amy C. Wilson. "Systemic hypertension in infants with bronchopulmonary dysplasia." Current Hypertension Reports 24.6 (2022): 193-203.

Nephrocalcinosis

- Incidence: 7 to 41% In VLBW infants <32 week
 - NC 12% of neonates born before 32 weeks' gestation
 - NC 26% gestational weeks 28
- Etiology: multifactorial – Prematurity VLBW, family history, mechanical ventilation, oxygen therapy - **BPD**, furosemide, methylxanthine, dexamethasone, gentamicin, TPN, acidosis, hypercalcemia, hypophosphatemia, hypercalciuria

Schell-Feith EA, Kist-van Holthe JE, van der Heijden AJ. Nephrocalcinosis in preterm neonates. *Pediatr Nephrol*. 2010;25(2):221–230

Fayard, J., Pradat, P., Lorthois, S. et al. Nephrocalcinosis in very low birth weight infants: incidence, associated factors, and natural course. *Pediatr Nephrol* 37, 3093–3104 (2022).

Nephrocalcinosis

- Short-term complications -UTI, renal stone, hydronephrosis, hematuria, and colicky pain.
- Long-term implications: Unclear/ ? Systemic hypertension
- Resolution rate was
 - 66% - 15 months
 - 85% - 30 months
 - 90% - 7.5 years

Ho Sung Kim, Korean J Perinatol Mar., 2015

Respiratory care @ 36 weeks CGA

- Chest radiograph / Capillary Blood Gas
- 12–24-hour Oximetry - done during 4 phases
 - wakeful activity
 - sleep
 - feeding
 - handling for routine care

Review - Oxygen therapy, Target saturation

Discharge Planning 1-2 wks.

- Optimize Oxygen therapy
- Assess need for prescription medications or discontinuation with appropriate period of clinical observation in advance of anticipated discharge.
- Review of growth/nutrition /Fortification of feeds/Nutritional supplements
- Eligibility for RSV prophylaxis/Scheduled immunizations
- Health education for parents e.g. avoidance of smoke inhalation/Resuscitation Training/indications to seek medical attention etc.

Criteria for discharge to community

Satisfactory Oxygen Saturation trending

- $\leq 10\%$ of time spent below targeted oxygen saturation range.
- Stable SpO_2 in target range with stable or reducing nasal cannula flow $O_2 < 1.0$ L/min.
- No apnea or bradycardia events requiring stimulation or intervention (exclusive of events associated with feeds, witnessed by care provide during feed) for 5-7 days prior to discharge.

Weaning oxygen

- Infants usually reach their lowest saturations within 40 minutes of discontinuing oxygen.
- SaO₂ of $\geq 90\%$ in AIR predicted readiness for weaning judged by 6 months of follow-up.
- Oxygen flow rate of ≤ 20 mL/kg/min weight most likely to be weaned off within 12 months.

Before removing equipment / Travel

- Child has coped with at least one respiratory tract infection while off oxygen.

Domiciliary oxygen for children.
Balfour-Lynn IM. Pediatr Clin North Am. 2009 Feb

Travel

- $\text{FiO}_2 = 15\text{-}17\%$ at 8000ft.
- If traveling with oxygen, increase by 250ml/Min for duration of flight.
- If off Oxygen in last 3 months, consider giving 250ml/Min for duration of flight.

A rational approach to home oxygen use in infants and children.
MacLean JE, Fitzgerald DA. Paediatr Respir Rev. 2006 Sep

Neurocognitive outcomes

- Volumetric MR of preterm with BPD showed a uniform ↓ in cerebral volumes.
- ↓ in brain volume correlates with functional deficits seen in survivors with BPD

Murphy, Brendan P., et al. "Impaired cerebral cortical gray matter growth after treatment with dexamethasone for neonatal chronic lung disease." *Pediatrics* 107.2 (2001): 217-221.

- 602 infants - 123 infants with BPD. NDI was present in 30.3% and 56.1% at 2 and 5 years CA
- 5-fold increased risk NDI seen from 2 years to 5 years with severe BPD

Katz TA, van Kaam AH, et al. Risk Factors for Neurodevelopmental Impairment at 2- and 5-Years Corrected Age in Preterm Infants with Established Bronchopulmonary Dysplasia. *Neonatology*. 2024;121(1):125-132.

Family support

- NAT more common with Prematurity (24.8% vs 12.7%, $p = 0.0004$) and major comorbidities (25.6% vs 7.2%, $p < 0.0001$)

A. Doud et al. Prematurity and neonatal comorbidities as risk factors for nonaccidental trauma. Journal of Pediatric Surgery. Volume 50, Issue 6, June 2015

- National Maternal and Infant Survey 1988 ($n = 6016$) - parents of very VLBW (<1500 g) infants were twice as likely to have separated or divorced by 2yrs of age than parents of higher birth weight >1500 g infants

Swaminathan, et al. Delivering a very low birth weight infant and the subsequent risk of divorce or separation. Matern. Child Health J. 2006

Recommendations @ 36wk

- Review of growth/nutrition– attention to Length in relation to Wt.
- ECHO to exclude PH
- CXR to evaluate lung parenchyma and exclude old fractures
- HUSS \pm MRI close to term CGA
- Renal USS – Nephrocalcinosis
- Appropriate specialist follow up arrangements
- Psychological support and education for families

Summary

- Multidisciplinary collaboration to facilitate transition to community
- Optimal growth & nutrition/bone health
- Optimal respiratory support
- Screening for pulmonary/systemic hypertension/cardiac shunts/nephrocalcinosis
- Follow up appointments
 - Specialist care: Respiriology \pm Cardiology \pm Nephrology \pm Ophthalmology \pm Others
 - Dietetics: Growth/Nutrition
 - Developmental follow up
 - Pediatrician
 - Family Medicine
- Parental education and support

Long term Uncertainty

Does the definition of BPD as oxygen dependence at 36 weeks add value to neonatal care?

Editorial: *Arch Dis Child Fetal Neonatal Ed* 2014

Using a specific age at which BPD is diagnosed is arbitrary and rather simplistic. A baby weaned off oxygen at 35+6 does not have moderate BPD while one off oxygen at 36+0 has BPD. Neither the first nor the second has normal lungs or likely to be a pulmonary cripple.....

E Bancalari

Take home message

- BPD is a multisystem disorder with consequences beyond the neonatal period
- Close attention to nutrition/growth to optimize outcome
- Evaluate patients with BPD to avoid life threatening complications
- Infants with BPD require long term follow up to understand health and lifestyle implications for the future