Cross Canada Rounds

Short cases on BPD

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BC Children's Hospital

Key questions

1. What is BPD (definition and epidemiology)
2. How has BPD changed over time
3. What treatments can improve or prevent BPD
4. Can we predict who will develop severe BPD
5. How should Pulmonary hypertension in BPD be managed

Case 1

Baby MB

- Day 153 (5 months old)
- Born 24+1, CGA 45 weeks, BW 630g
- Currently – weight 3600g
  - CPAP PEEP 8 with short periods on 0.25L O2 via nasal prongs
  - NG feeds
  - Medications: Spironolactone, Hydroxychlorothiazine, Hydrocortisone
- Examination:
  - Spo2 98% RR 40/min, no increased work of breathing, chest clear, CVS normal, tone normal

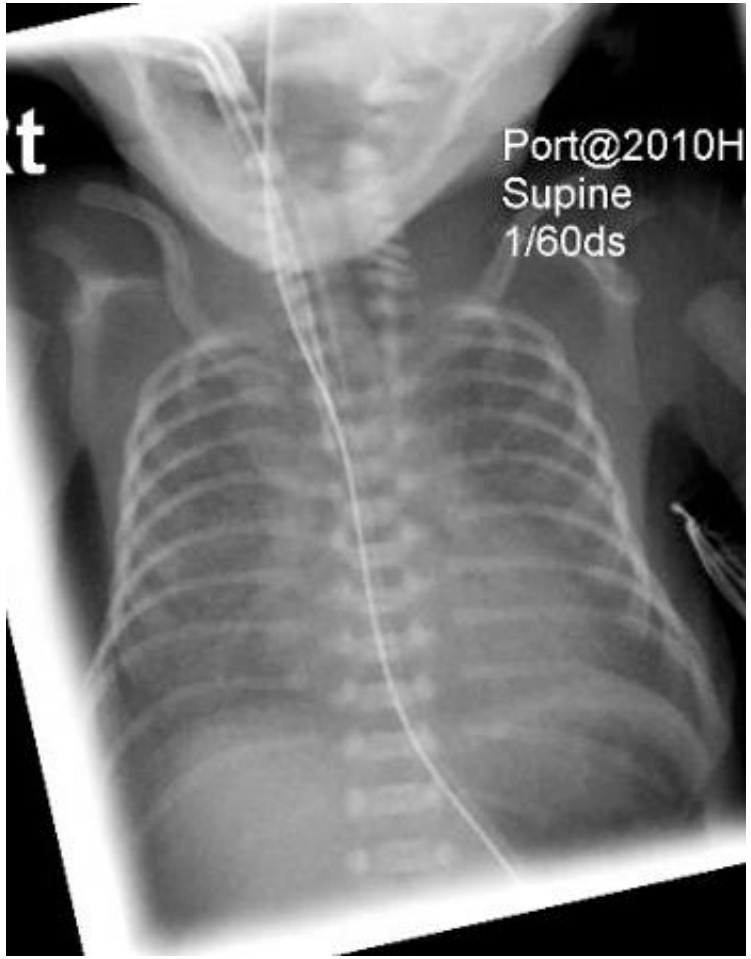
Baby MB – neonatal history

- Emergency C-section: spontaneous labour, breech
- Received antenatal steroids
- Mum – G3 P1 (born 28weeks)
  - well in pregnancy. Screening serology normal, USS normal
  - No smoking, alcohol, medications
- Birth – good condition, commenced on CPAP
- Rising FiO2 within 3 hours - intubated and given surfactant

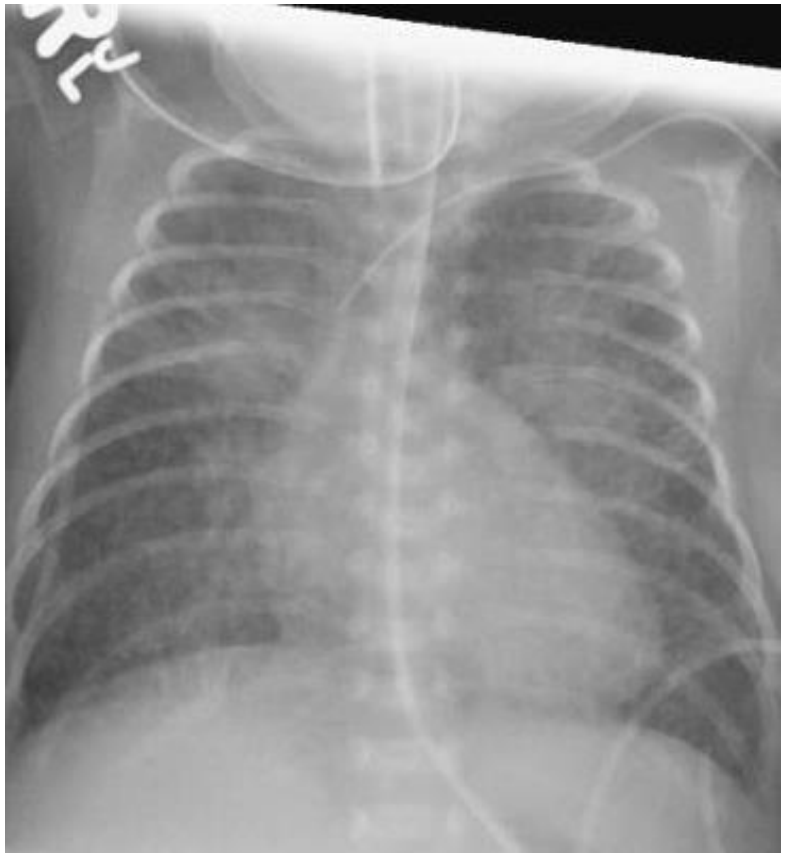
Respiratory course

- Ventilated day 1 – day 52 (HFOV/CMV)
- PDA treated with Indomethacin (day 10)
- X1 episode VAP, x1 episode CONS sepsis
- DART x1 - Extubated Day 52
- BiPAP day 52 to 82
- CPAP day 82 – day 124
- Day 124 to 154 CPAP with x2 2hours low flow O2

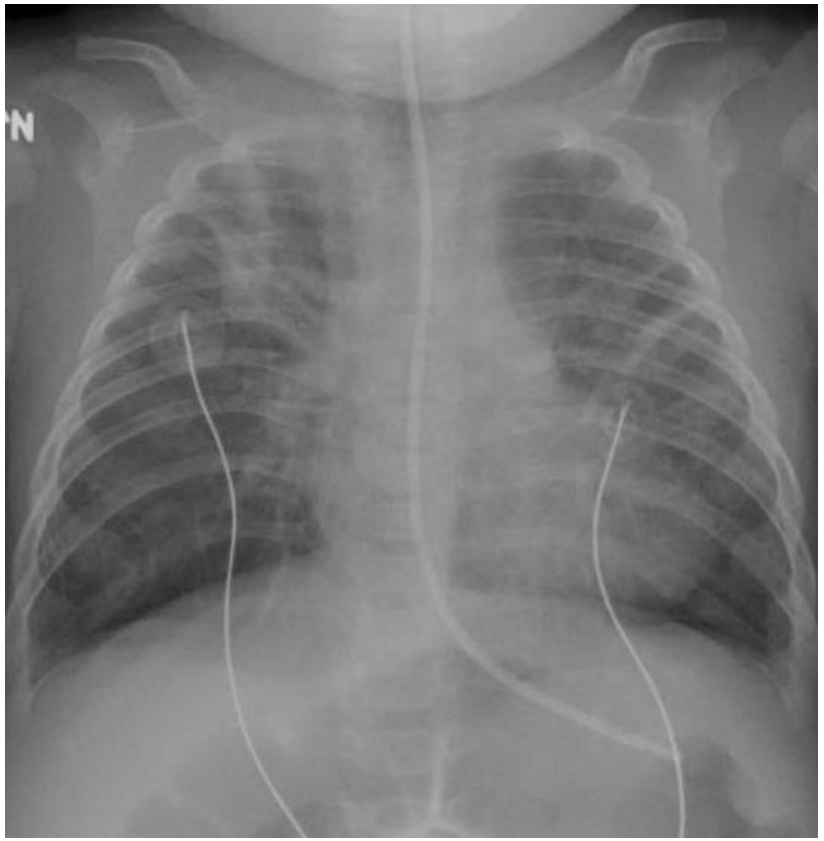
Day 1



Day 28



Term



Case 1 management

- Continued increasing time off CPAP
- Oral feeding assessment satisfactory
- Commenced oral feeds, with gradual decrease of NG volumes
- Discharged on 0.5litres O2 24 hours per day and full oral feeds
- By 9 months off day time O2, on 0.25litres at night

BPD Definition, Epidemiology and pathogenesis

Question

Which one of the following is true

1. BPD is classified radiologically
2. Rates of BPD are falling
3. New BPD is a result of hyperoxic damage
4. None of the above
5. All of the above

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2. Rates of BPD are falling
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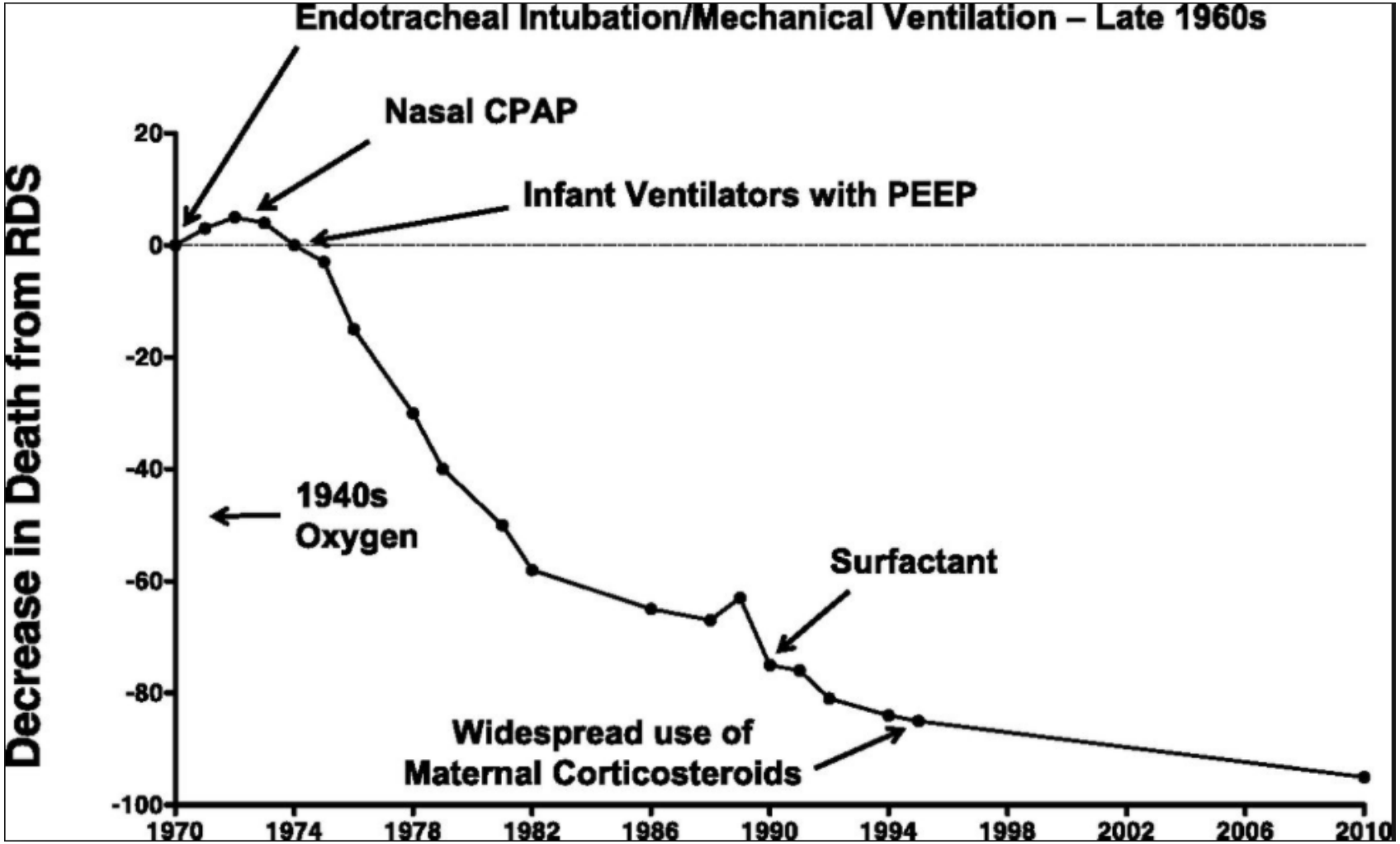
Definition and classification of BPD (NIH)

Table I. BPD definition with severity

BPD severity	Definition (Modified from Jobe and Bancalari[4])	Relative incidence (Data from Ehrenkranz et al[5])	Postdischarge mortality (Data from Ehrenkranzet al[5])
None	O_2 treatment <28 d and breathing room air at 36 wk PMA or discharge home, whichever comes first	23.1%	1.8%
Mild	O_2 treatment at least 28 d and breathing room air at 36 wk PMA or discharge home, whichever comes first	30.3%	1.5%
Moderate	O_2 treatment at least 28 d and receiving <30% O_2 at 36 wk PMA or discharge home, whichever comes first	30.2%	2.0%
Severe (type 1)	O_2 treatment at least 28 d and receiving ≥30% O_2 or nasal CPAP/HFNC at ≥36 wk PMA	16.4%	4.8%
Severe (type 2)	O_2 treatment at least 28 d and receiving mechanical ventilation at ≥36 wk PMA.		

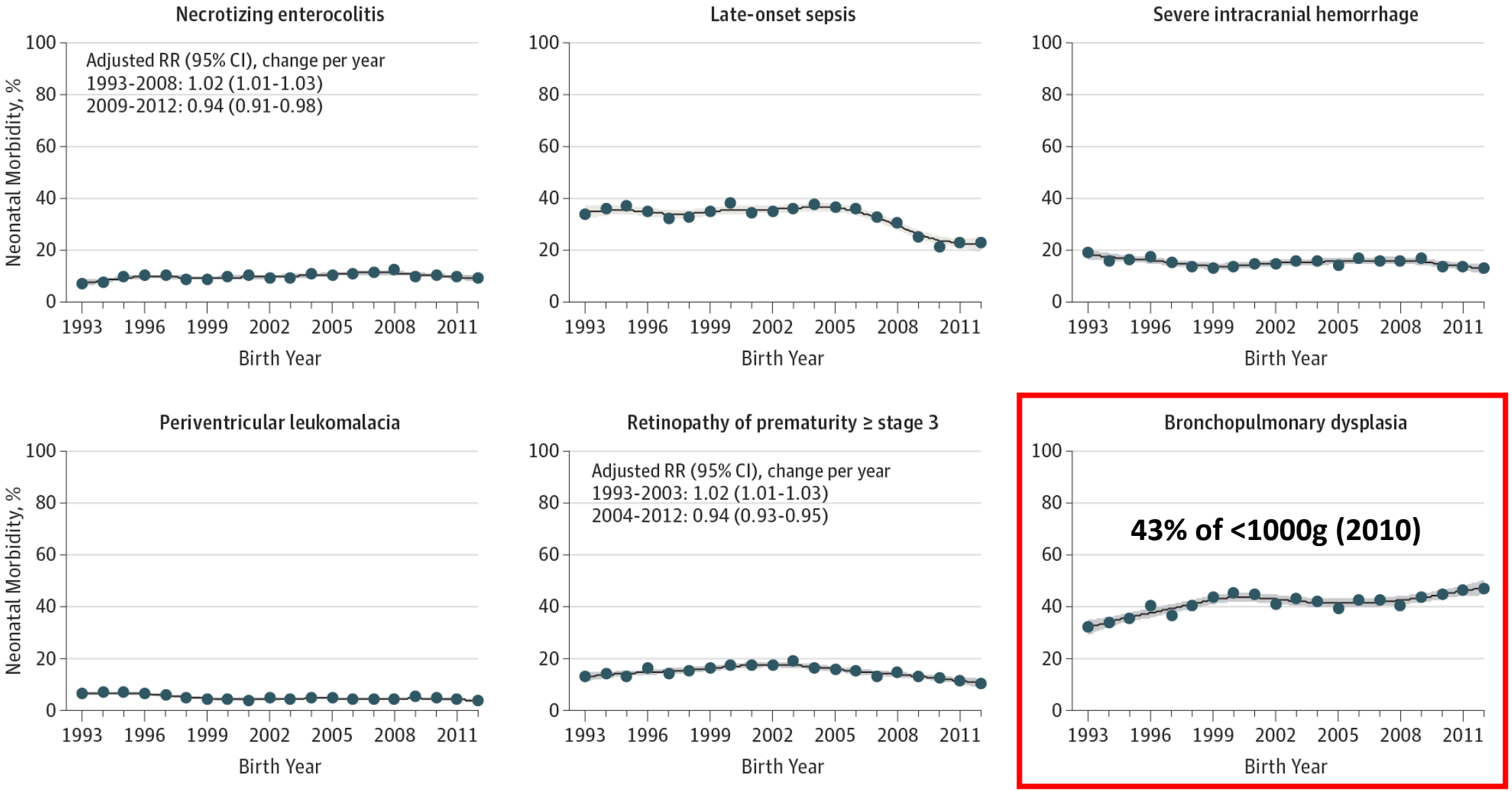
Ehrenkranz RA,Walsh MC, Vohr BR, Jobe AH,Wright LL, Fanaroff AA, et al. Validation of the National Institutes of Health consensus definition of bronchopulmonary dysplasia. Pediatrics 2005;116:1353-60.

Changes in Neonatal care over 50 years



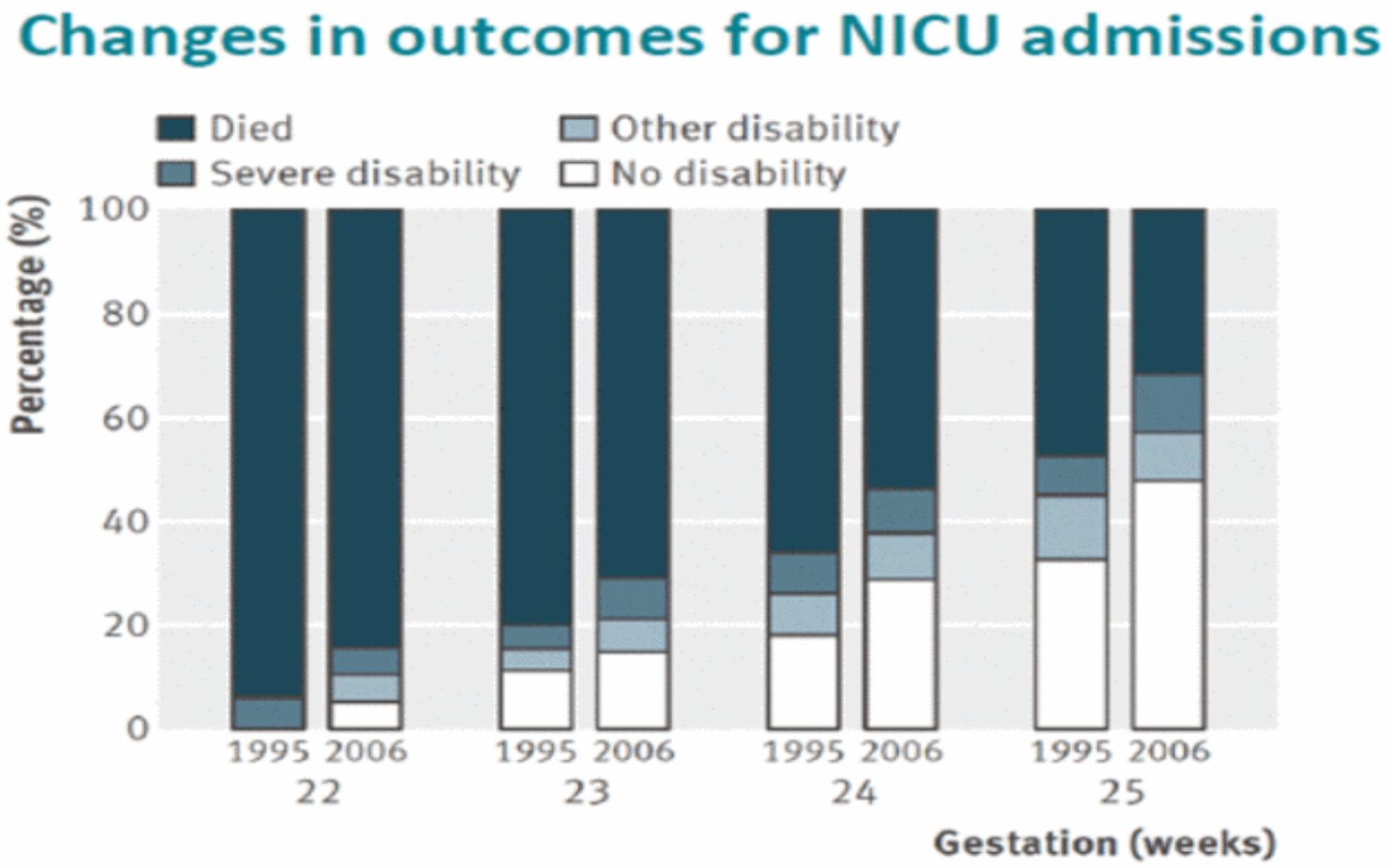
Neonatal Morbidities for Infants Born at Gestational Ages 22 Through 28 Weeks

National Institute of Child Health and Human Development Neonatal Research Network



Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. Pediatrics.2010

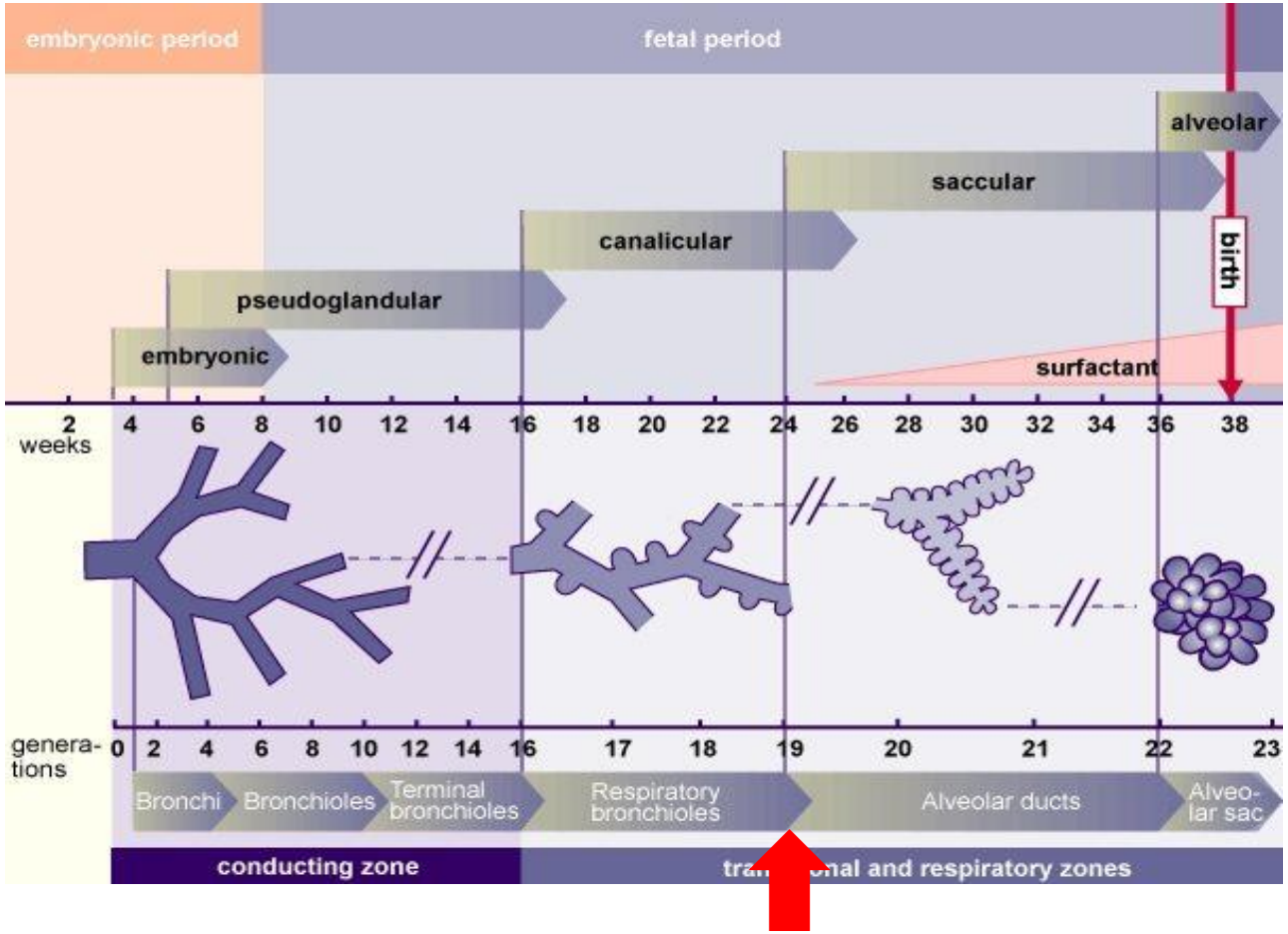
EPIcure preterm survival data



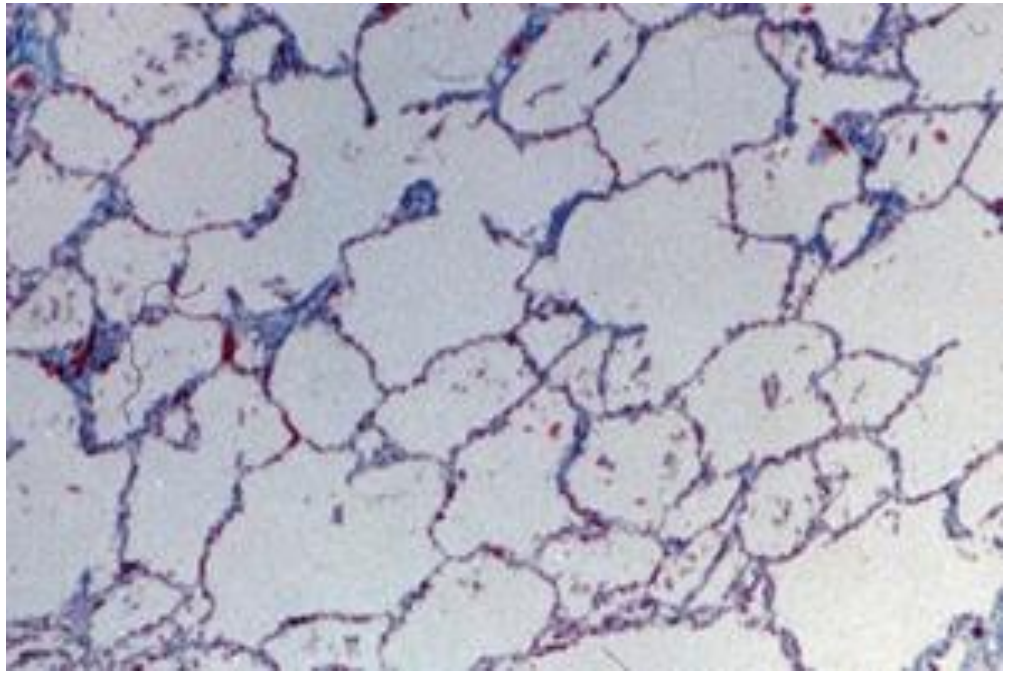
2016
24 week
survival
60-70%

Short term outcomes after extreme preterm birth in England: comparison of two birth cohorts in 1995 and 2006 (the EPICure studies) Kate L Costeloe, Enid M Hennessy, Sadia Haider, Fiona Stacey, Neil Marlow and E S Draper *BMJ: British Medical Journal* Vol. 345, No. 7886 (8 December 2012)

‘New BPD’ is born *Jobe 1999*

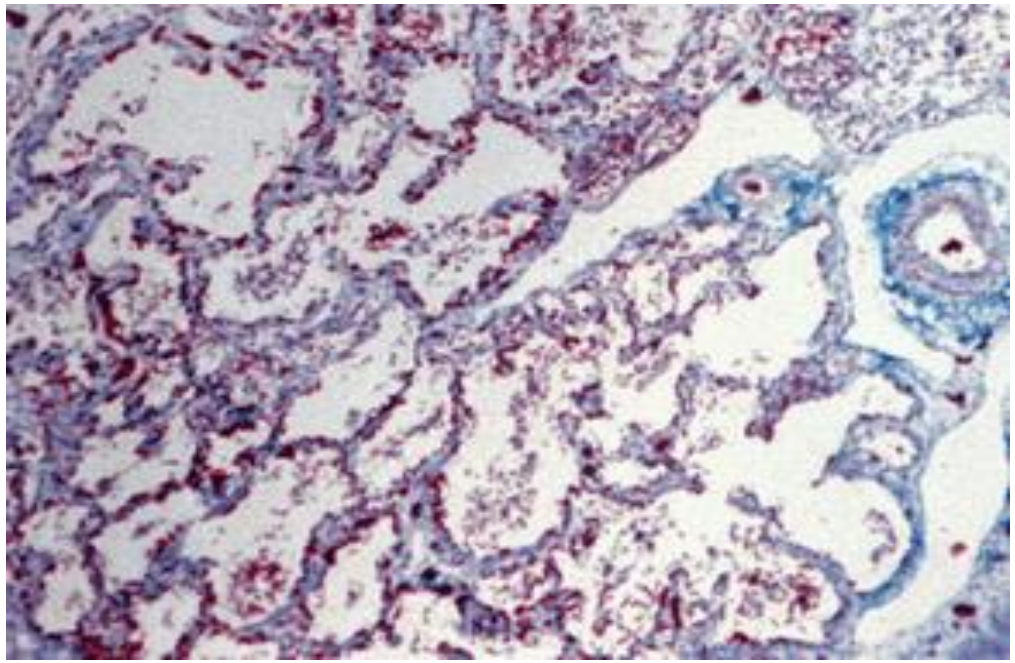


New BPD



- Fewer, larger, simplified aveoli with dysmorphic vasculature
- Due to arrested lung development

Old BPD



- Inflammation and parenchymal fibrosis
- Due to mechanical ventilation and oxygen toxicity

Pathogensis of BPD

- Inflammation
  - External – chorioamnionitis, post natal infection/sepsis
  - Iatrogenic – oxygen, ventilation
  - Host factors – immune responses
- Genetic predisposition suggested by twin studies
- Nearly 30 studies trying to predict BPD from proinflammatory biomarkers in tracheal aspirate, blood, and urine samples
- No definitive biomarker but a lot of evolving information

Targeting inflammation to prevent bronchopulmonary dysplasia: can new insights be translated into therapies? Pediatrics 2011;128:111-126
Lavoie et al.. Heritability of bronchopulmonary dysplasia, defined according to the consensus statement of the national institutes of health. Pediatrics. 2008;122(3):479–485

Predicting which babies will develop BPD

- Large multicentre study identified the relative contributions of risk factors to the prediction of BPD
- Almost 4000 23–30 week gestation born in 17 centres
- 6 predictive factors
  - birth weight, gestational age, male sex, oxygen therapy at 24 hours, mechanical ventilation at 48 hours, and duration of assisted ventilation
  - Web based BPD risk calculator https://neonatal.rti.org/.

Laughon MM, Langer JC, Bose CL, Smith PB, Ambalavanan N, Kennedy KA, et al. Prediction of bronchopulmonary dysplasia by postnatal age in extremely premature infants. Am J Respir Crit Care Med 2011;183:1715-22

Case 2

Case 2 – Baby HB

- Day 154, 5 month old girl
- Born 24 weeks, CGA 46 weeks
- Transferred from DGH for assessment as unable to wean ventilation
- No acute change in clinical status
- Current support BIPAP 22/12, FiO2 1

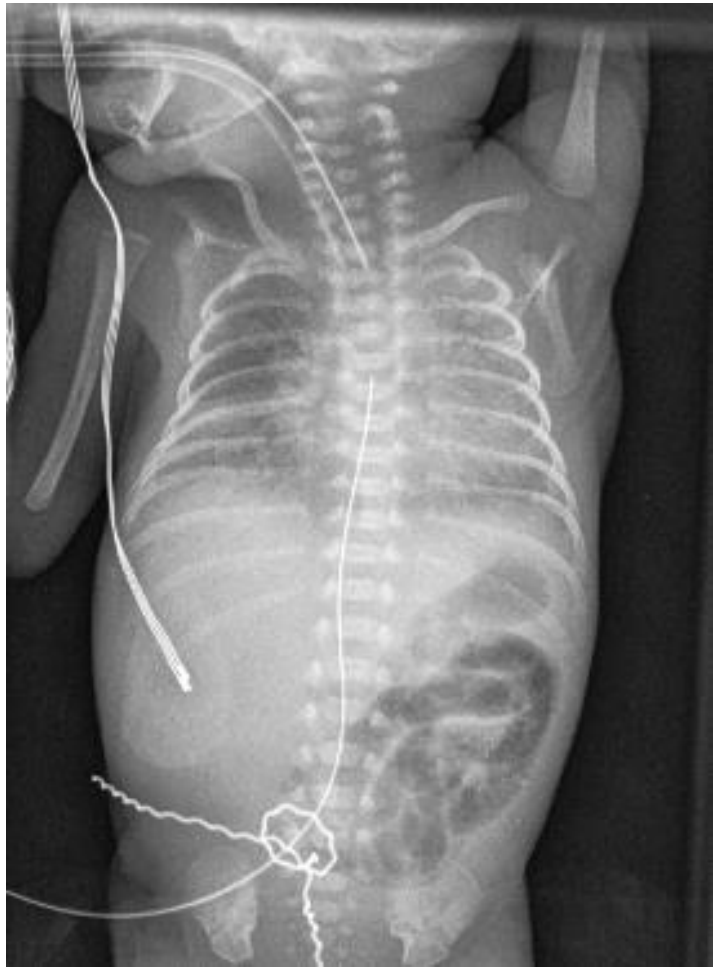
Antenatal and Birth history

- Mum – obesity, hypertension, smoker during pregnancy
- Hypertensive crisis, reversed end diastolic flow
- Emergency C-section 24+2
- Had pre-natal steroid
- Intubated at 3 mins + surfactant
- Birthweight 600g

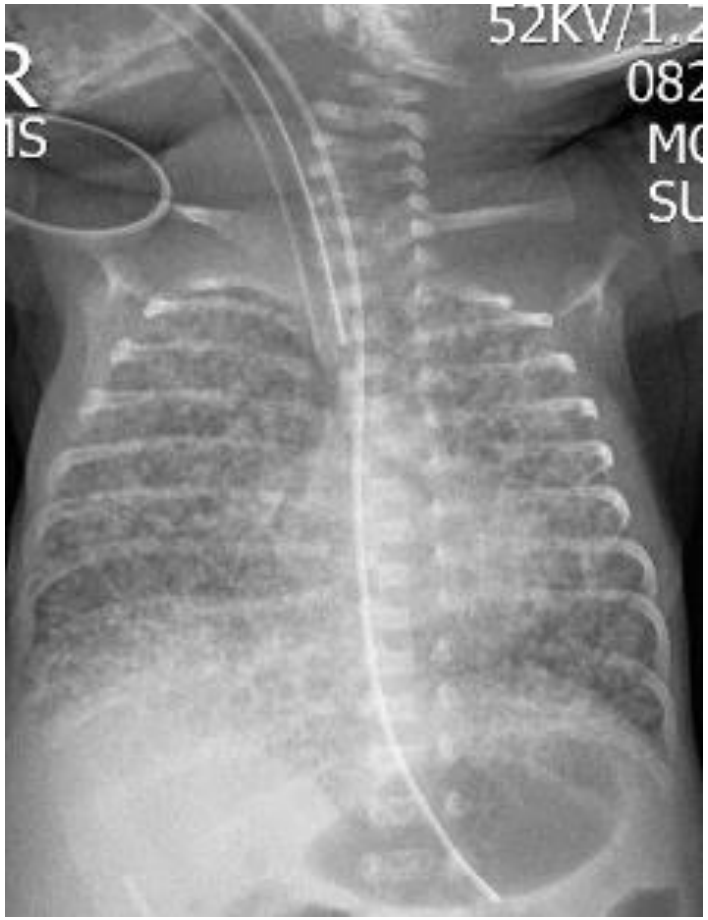
NICU course (day 1 to day 154)

- Surfactant x3
- Large PDA day 7 – Indomethacin
- Suspected sepsis d14, VAP d30
- HFJV/HFOV – 99 days
- INO day 53-105, then Sildenafil
- DART x3 (Day 30, day 40, day 80)
- Extubated day 99 (was still ventilated at 36wks PMA)

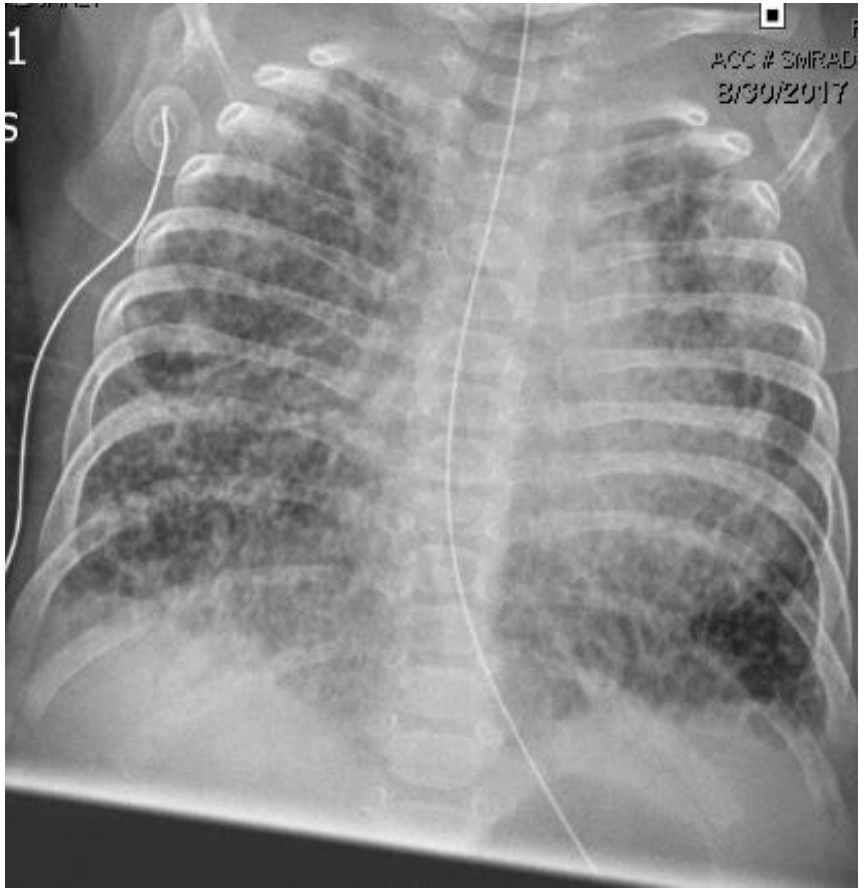
Day 1



Day 28



Day 140 (term)



Current status: Day 154 CGA 46wks

- Ventilation: NIV P 20/10, FiO2 1.0 (not acute)
- Feeds via NG
- Medications: Sildenafil, Furosemide, Budesonide, hydrocortisone
- Examination
  - Growth 10th percentile
  - RR 50-60, SpO2 86-92%,moderate increased work of breathing, weak cry, unsettled/agitated, HS 1+2 (loud P2)

Gases

Day	pH	CO2	Bicarbonate	BE	Mode of ventilation
93	7.46	44	31	7	Intubated and ventilated
114	7.38	66	39	14	BIPAP 16/8
134	7.32	81	42	15	BIPAP 18/10
139	7.33	86	45	20	BIPAP 20/10
143	7.36	74	42	16	BiPAP 22/12, nasal mask. Hydrocortisone
154	7.32	97	39	19	BiPAP 22/12, full face mask

Extubated day 99

Echocardiogram

- ECHO Day 154
  - Structurally normal heart. PFO with L– R flow
  - Insufficient TR jet to estimate RV pressure
  - Interventricular septum mildly flattened
- Previous ECHOs
  - Several. Unable to measure TR

Question

What would you do next?

1. Increase BIPAP pressures 24/12
2. Intubate
3. Tracheostomy
4. Cardiac catheterisation
5. Bronchoscopy to assess airway

Question

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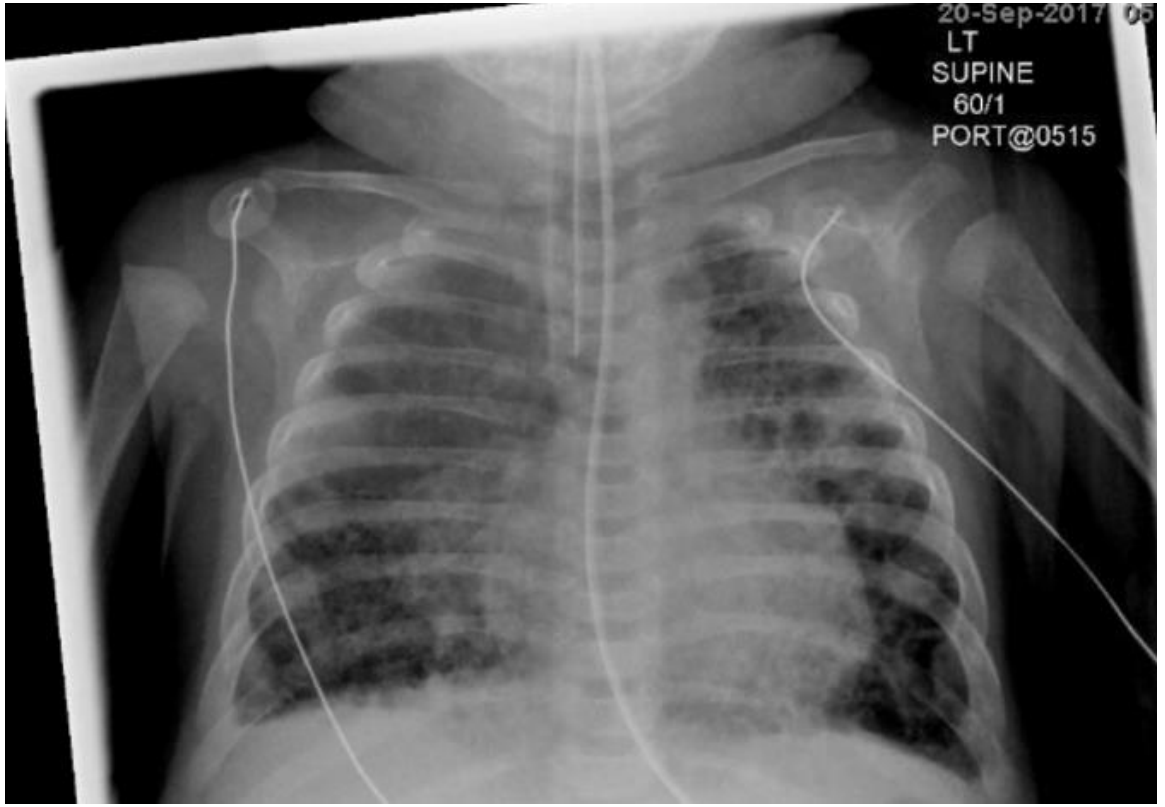
Case 2 management

- Baby intubated and ventilated needing high pressures (31/11)
- Gas ph 7.42, CO2 69, HCO3 37, BE 16
- O2 requirement improved to 60% within 6 hours
- NJ feeds to minimise aspiration
- If fails to stabilise with ventilation – Cath, Bronchoscopy
- Likely require tracheostomy to facilitate long term ventilation



Managing BPD

Managing BPD

- Ventilation strategies
- Nutrition
- Pharmacology
- Investigate and manage co-morbidity in severe BPD
  - Pulmonary hypertension
  - Airway abnormalities
  - Aspiration

Ventilation strategies in BPD

- First days/weeks – lung homogeneity, low compliance, normal airway resistance
    - Strategy to prevent lung injury
    - High rate, low TV, short T1
- As BPD evolves
    - High airway resistance, air trapping, heterogeneous aeration
    - Strategy should optimise gas exchange, reduce atelectasis, decrease dead space
    - High TV, prolonged Ti, Slow rate

Abman et al. Interdisciplinary are in children with severe BPD. Journal of paediatrics 2017

When to consider Tracheostomy in BPD?

- Difficult decision
- Goal to provide long term ventilatory support to reduce respiratory distress and establish clinical stability
- Allow lung growth and repair
- To enhance survival and optimise long term development, neurocognitive outcomes
- Needs consistent support of interdisciplinary team

Nutritional strategies in BPD

- sBPD growth worse than infants with no BPD, mild/mod BPD
- Hypermetabolic states, increased work of breathing, repair, growth
- Growth suppression: chronic stress, inflammation, steroids, diuretics
- Increased risk of aspiration Immature swallow, neurological insults
- Early NJ feeding, low threshold for G/GJ tube

Pharmacology in BPD

Question

Which one of the following has demonstrated improvement in BPD

1. Caffeine
2. Late ‘topup’ surfactant
3. Diuretics
4. Montelukast
5. Inhaled corticosteroid

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Pharmacology in BPD

	Evidence	Sufficient evidence for use in BPD
Caffeine	**CAP trial (2007). Commenced early. BPD 36% vs 47% in supplemental O2 at 36wks**	**Yes**
Vitamin A	**Large RCT 1999 NEJM Tyson et al. BPD 55 vs 62%**	**Yes**
Late surfactant	No evidence that repeat surfactant at 10 days improves BPD outcomes	No
Diuretics	Cochrane review 2011: Cant support loop diuretics in BPD due to lack of current evidence	No
Bronchodilators	One RCT 1998 - 173 ventilated day 10 to receive inhaled salbutamol, placebo via MDI for 28 days. no on BPD, O2 or ventilation	No
Montelukast	RCT 2015 Kim et al No difference in BPD vs placebo	No
Inhaled steroid	Cochrane review – 7 studies, 492 infants, no evidence to support the routine use of ICS in prevention of BPD (2012)	No

ICS in BPD

Largest multicentre European RCT 863 ELBW infants in first 12h to Budesonide vs placebo 2015

Budesonide MDI via mini-Aerochamber: 800mcg for 2 wks then 400mcg until 32 weeks or off all support

Primary Outcome	Placebo	Budesonide	Relative Risk (95% CI)	Relative Risk Adjusted for GA (95% CI)	P Value	Odds Ratio Adjusted for GA, birth weight, caffeine, mech. ventilation (95% CI)
Primary Outcome	194/419 (46.3)	175/437 (40.0)	0.86 (0.74-1.01)	0.86 (0.75-1.00)	0.053	0.71 (0.53-0.97)
Components of primary outcome						
Death at <36 wk of gestational age	57/419 (13.6)	74/437 (16.9)	1.24 (0.91-1.71)	1.24 (0.91-1.69)	0.165	
Survival with BPD	138/363 (38.0)	101/363 (27.8)	0.73 (0.59-0.90)	0.74 (0.60-0.91)	0.004	

Bassler D, Plavka R, Shinwell ES, et al. Early inhaled budesonide for the prevention of bronchopulmonary dysplasia. N Engl J Med 2015;373:1497–506

ADC

Systemic corticosteroids in BPD

- Early corticosteroid before day 8 increases extubation and reduced risk of BPD (Halliday et al. 2014)
  - BUT very significant increase in GI perforation, and CP. Not recommended
- Late corticosteroid after day 8, increases extubation and reduced BPD with less risk death or CP (Halliday et al 2014)
  - Late corticosteroid treatment could be used for infants who are ventilator dependent as a rescue therapy
  - Timing/doses/duration unclear
- Low dose corticosteroid (DART) – higher rate of extubation vs placebo 60% vs 12% within 10 days

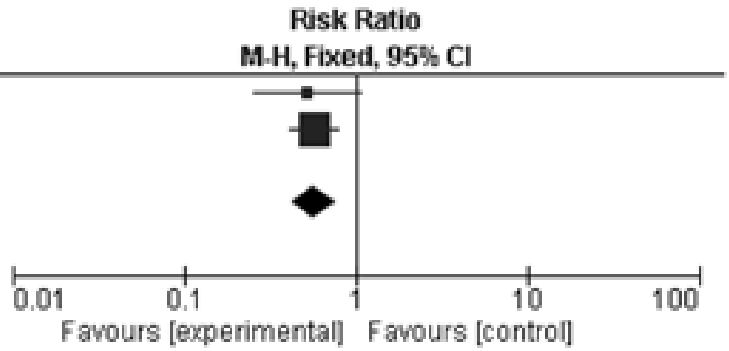
Abman et al. Interdisciplinary are in children with severe BPD. Journal of paediatrics 2017
Doyle et al. Low-dose dexamethasone facilitates extubation among chronically ventilator-dependent infants: a multicenter, international, randomized, controlled trial. Pediatrics 2006

Intratracheal Administration of Budesonide-Surfactant in Prevention of Bronchopulmonary Dysplasia in Very Low Birth Weight Infants: A Systematic Review and Meta-Analysis (2017)

Outcome: **Bronchopulmonary dysplasia (BPD)**

	Budesonide		Control			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Yeh 2008	9	60	16	56	20.0%	0.53 [0.25, 1.09]
Yeh 2016	38	131	67	134	80.0%	0.58 [0.42, 0.80]
Total (95% CI)		**191**		**190**	**100.0%**	**0.57 [0.43, 0.76]**
Total events	47		83			

Heterogeneity: Chi² = 0.06, df = 1 (P = 0.81); I² = 0%
Test for overall effect: Z = 3.78 (P = 0.0002)

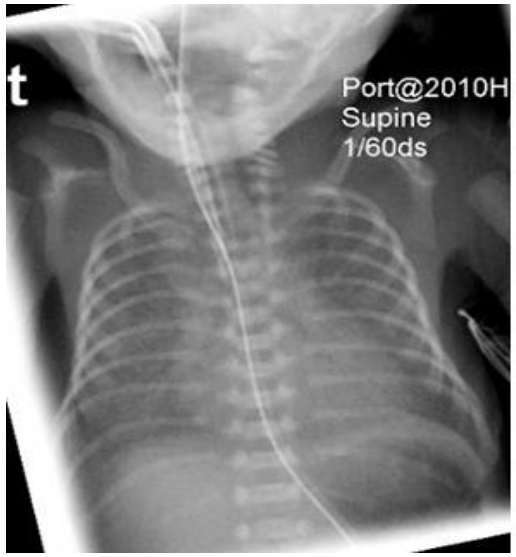


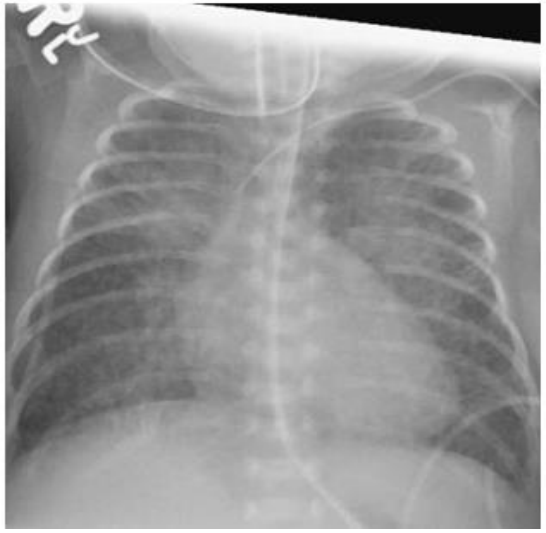
Budesonide-surfactant mixture vs surfactant alone: risk of BPD decreased from 44 to 25% absolute risk reduction of 19% (ARR: 0.191; 95%CI: 0.096-0.281)

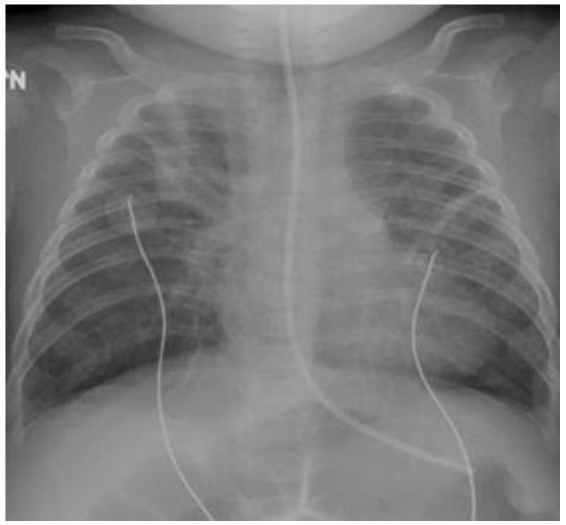
Pediatric Pulmonology Volume 52, Issue 7, pages 968-975, 6 FEB 2017 DOI: 10.1002/ppul.23680

Severe BPD

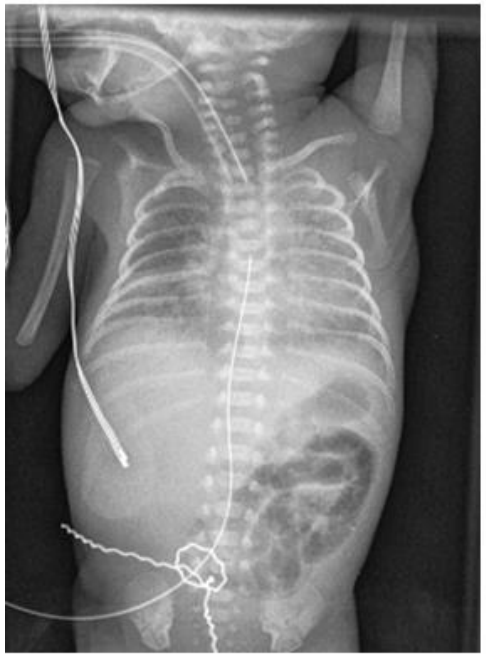
CASE 1

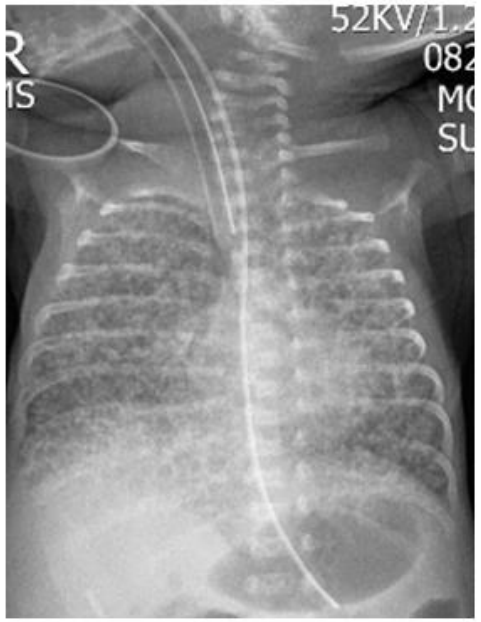


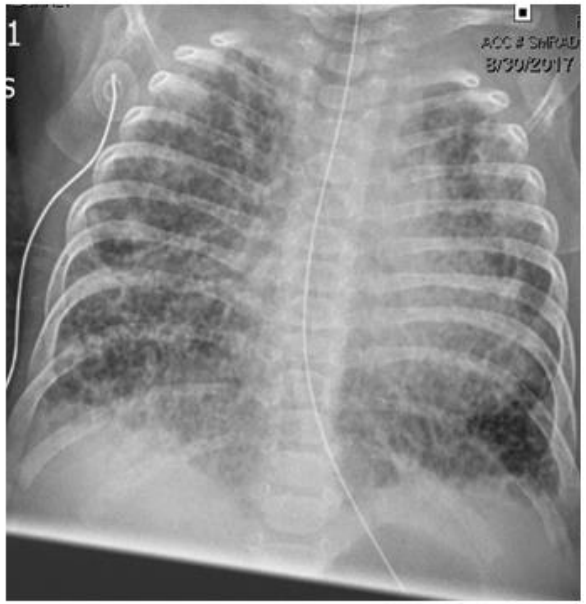




CASE 2







Question

Which one of the following is true regarding severe BPD

1. Is twice as likely in male infants
2. Tracheobronchomalacia occurs in 10%
3. Sildenafil has been demonstrated to be safe and effective for treatment of BPD related PH
4. All of the above
5. None of the above

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5. None of the above

Incidence of severe BPD (sBPD)

- 16% for all infants born at <32 weeks (CHND data US based on 900 sBPD infants)
  - 91% survived to discharge
  - 66% were discharged on supplemental oxygen
  - 4% on mechanical ventilation
  - 5% received tracheostomy

Padula, M.A., et al. "Therapeutic interventions and short-term outcomes for infants with severe bronchopulmonary dysplasia born at < 32 weeks' gestation." *Journal of Perinatology*, vol. 33, no. 11, 2013

Predicting who will develop sBPD

- Male sex, sepsis, NEC strongly associated with the development of sBPD
- Early sepsis - rates of BPD increased from 35% to 62% in a cohort of 5447 very low birth weight infants (Stoll et al)
- PDA
  - Short-term effects on pulmonary oedema and pulmonary mechanics established
  - Lack of data confirming its role in the development of BPD

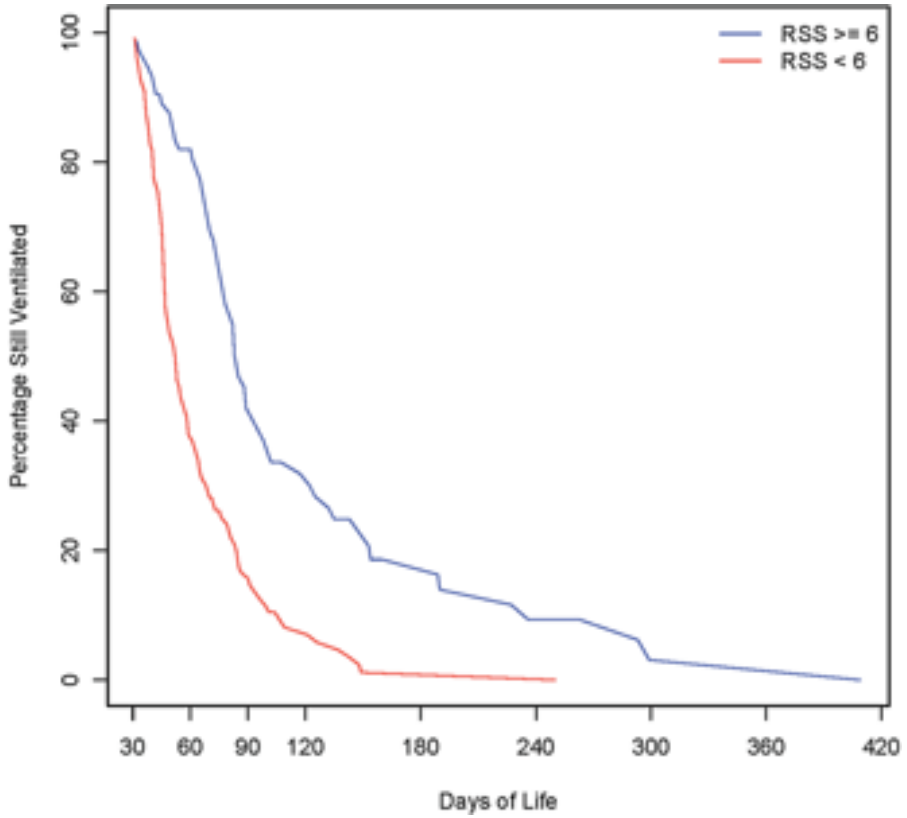
Stoll BJ, Hansen N,Fanaroff AA, et al . Changes in pathogens causing early-onset sepsis in very-low-birth-weight infants. N Engl J Med.2002;347(4):240–247

Benitz WE Patent ductus arteriosus: to treat or not to treat? *Archives of Disease in Childhood - Fetal and Neonatal Edition* 2012;**97:**F80-F82

Predicting sBPD

Respiratory severity score (RSS) on day 30 is predictive of mortality and the length of mechanical ventilation in BPD

RSS = MAP x FiO2



186 infants <1500g

$P < 0.001$ between RSS ≥ 6 and RSS < 6

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Malkar MB. Respiratory severity score on day of life 30 is predictive of mortality and the length of mechanical ventilation in premature infants with protracted ventilationPediatr Pulm 2015

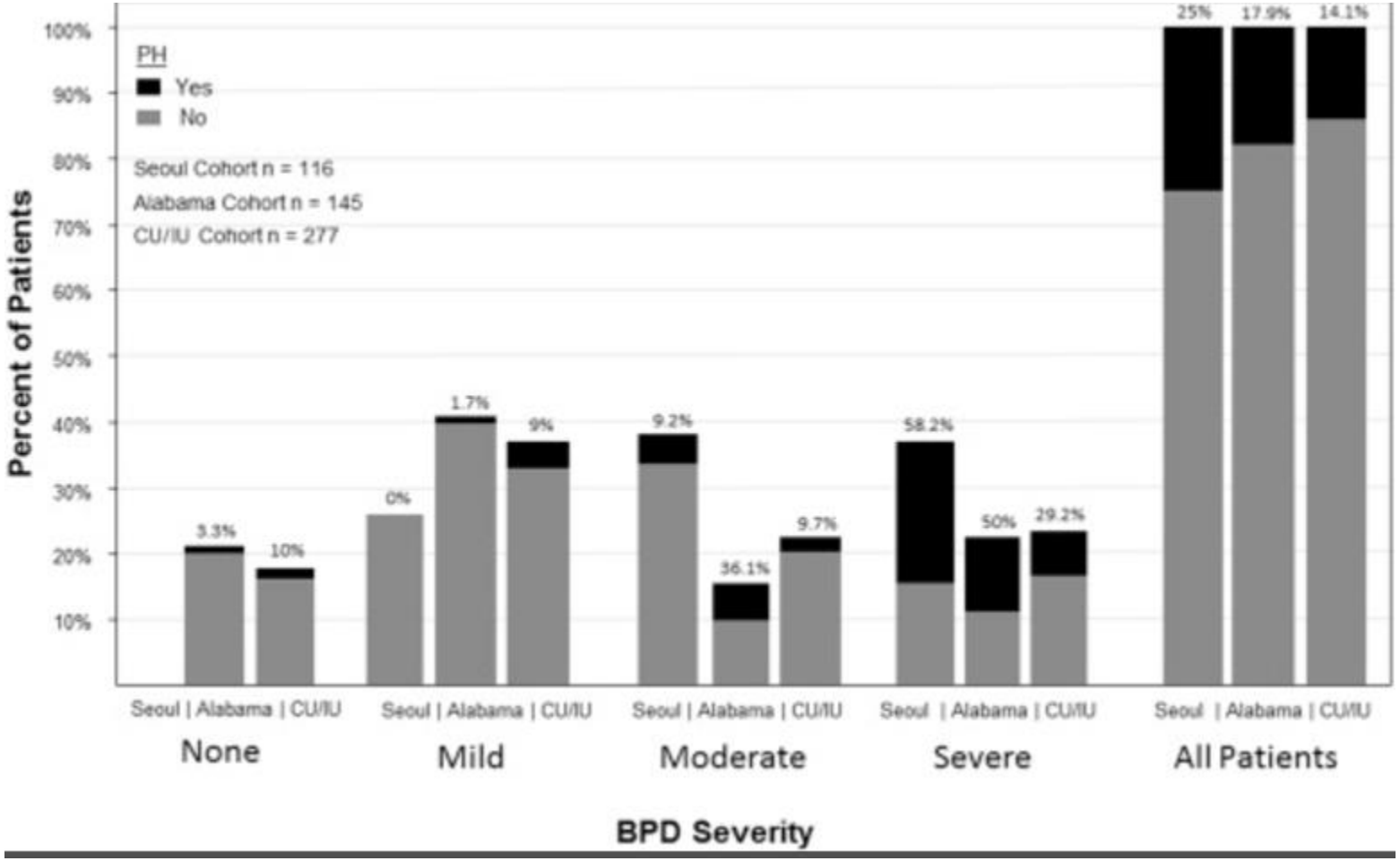
Co-morbidity in sBPD

Surgical procedures and pulmonary hypertension in sBPD on the day of the "snapshot"

Percentage (%) center	*N*	Tracheostomy (% yes)	Gastrostomy (% yes)	Fundoplication (% yes)	Pulmonary hypertension[a] (% yes)
1	30	14%	10%	3%	21%
2	11	27%	27%	0%	18%
3	15	7%	13%	7%	36%
4	6	0%	0%	0%	17%
5	10	0%	0%	0%	20%
6	22	14%	10%	10%	19%
7	18	12%	12%	12%	29%
8	16	13%	31%	19%	19%
Entire sBPD population	128	12% ($n = 125$)	14% ($n = 125$)	7% ($n = 125$)	23% ($n = 114$)

Guaman MC, Collaco JM. Point prevalence, clinical characteristics, and treatment variation for infants with severe bronchopulmonary dysplasia. Am J Perinatol 2015;32:960-7.

Incidence of PH according to BPD severity



Mourani, Abman et al. Pulmonary hyperteniosn and vascular abnormalities in Bronchopulmonary dysplasis. Clinics in Perinatology. 2015

Pulmonary Hypertension

- PH complicates the course in up to 25% of patients with sBPD
- Babies with sBPD with PH on ECHO four times more likely to die compared to sBPD without PH
- Survival rate 53% at 2 years after diagnosis of PH in 42 ELBW babies with BPD

Khemani E., McElhinney D.B., Rhein L., et al: Pulmonary artery hypertension in formerly premature infants with bronchopulmonary dysplasia: clinical features and outcomes in the surfactant era. Pediatrics 2007; 120: pp. 1260-1269

Pulmonary Hypertension - screening

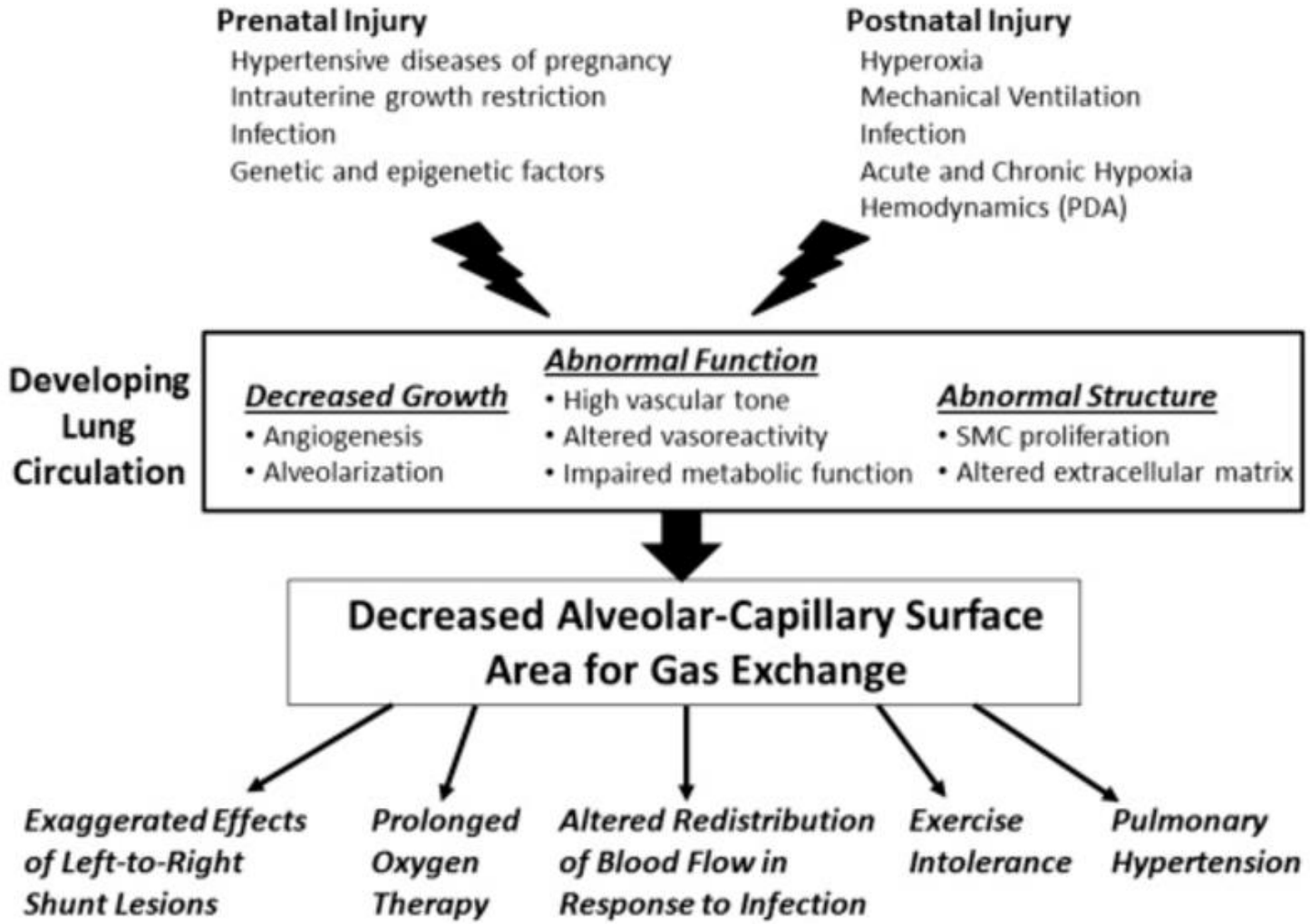
- A 2015 large prospective study screened 172 ELBW babies at 28 days of life for PH. Then serial ECHOs every 4 weeks.
  - 6% of the infants showed evidence for PH at 28 days
  - On serial echo another 12% of the babies developed PH later

- Associated with longer hospitalisation times and higher mortality

Mourani PM, Abman SH. Pulmonary Hypertension and vascular abnormalities in bronchopulmonary dysplasia. Clin Perinatol 2015;42:839

Contributing factors to PVD in BPD and clinical manifestations

Mourani et al. 2015



Management of PH

1. Ensure adequate oxygenation (awake,sleep,feeds)
2. Assess adequacy of ventilation
3. Minimise chronic aspiration
4. Optimise nutrition
5. Consider ICS/Bronchodilators
6. Pulmonary vasodilators ?

Pulmonary vasodilators

- Effects of long term Sildenafil studied by Mourani et al, n=25 (2009)
  - Improvement in PH by 20% in 88% of patients
  - No significant adverse events
  - Time to improvement variable (median 40 days)
- No studies on endothelin receptor antagonists (Bosantan)
- Prostacyclin analogs: Treprostinil may provide additional benefit in BPD and PH that is poorly responsive to other medications

Ferdman DJ, Rosenzweig EB, ZuckermanWA, Krishnan U. Subcutaneous treprostinil for pulmonary hypertension in chronic lung disease of infancy. Pediatrics 2014;134:e274-8.

Airway issues in BPD

- Estimated tracheobronchomalacia of 10% in BPD
- Recent cohort study of extreme preterm infants 2010-2015 who had bronchoscopy at CHOP (111) – for sBPD/airway concerns
  - 40% had TBM
  - Needed longer ventilation, higher MAPs, higher Gtube rate, higher frequency of pneumonia

Tracheobronchomalacia is associated with increased morbidty in BPD. Hysinger et al. Ann Am Thorac Soc 2017

Summary

- Survival of extremely preterm infants has increased over recent years, but BPD remains a major cause of morbidity
- Pathogenesis is complex and inflammation is a key factor as a consequence of various neonatal insults
- Severe BPD requires a structured management approach, but few effective treatments
- PH and TBM are more common in severe BPD and are associated with increased morbidity and mortality and should be considered in difficult cases

Questions?