Respiratory Conference
Adult, Adolescent and Neonatal

Bronchopulmonary Dysplasia Prevention & Treatment

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THE UNIVERSITY OF TENNESSEE HEALTH SCIENCE CENTER | Le Bonheur Children's Hospital

Disclosures

I receive a consultant fee from American Academy of Pediatrics for serving as Associate Editor for *Pediatrics in Review*.

I receive a consultant fee from Abbott for serving on Medical Advisory Board and as speaker for Amplatzer Piccolo™ Occluder.

This presentation does not contain a discussion of an unapproved/ investigative use of a commercial product/device.

Objectives

- Define BPD.
- Identify risk factors and current strategies used to prevent/treat BDP.
- Describe management of BPD.
- Give prognosis/outcomes for the disease.

Bronchopulmonary Dysplasia

TABLE 1. DEFINITION OF BRONCHOPULMONARY DYSPLASIA: DIAGNOSTIC CRITERIA

Gestational Age	< 32 wk	$\geqslant 32$ wk
Time point of assessment	36 wk PMA or discharge to home, whichever comes first	> 28 d but < 56 d postnatal age or discharge to home, whichever comes first
	Treatment with oxygen $> 21\%$ for at least 28 d **plus**	
Mild BPD	Breathing room air at 36 wk PMA or discharge, whichever comes first	Breathing room air by 56 d postnatal age or discharge, whichever comes first
Moderate BPD	Need* for $< 30\%$ oxygen at 36 wk PMA or discharge, whichever comes first	Need* for $< 30\%$ oxygen at 56 d postnatal age or discharge, whichever comes first
Severe BPD	Need* for $\geqslant 30\%$ oxygen and/or positive pressure, (PPV or NCPAP) at 36 wk PMA or discharge, whichever comes first	Need* for $\geqslant 30\%$ oxygen and/or positive pressure (PPV or NCPAP) at 56 d postnatal age or discharge, whichever comes first

Definition of abbreviations: BPD = bronchopulmonary dysplasia; NCPAP = nasal continuous positive airway pressure; PMA = postmenstrual age; PPV = positive-pressure ventilation.

* A physiologic test confirming that the oxygen requirement at the assessment time point remains to be defined. This assessment may include a pulse oximetry saturation range.

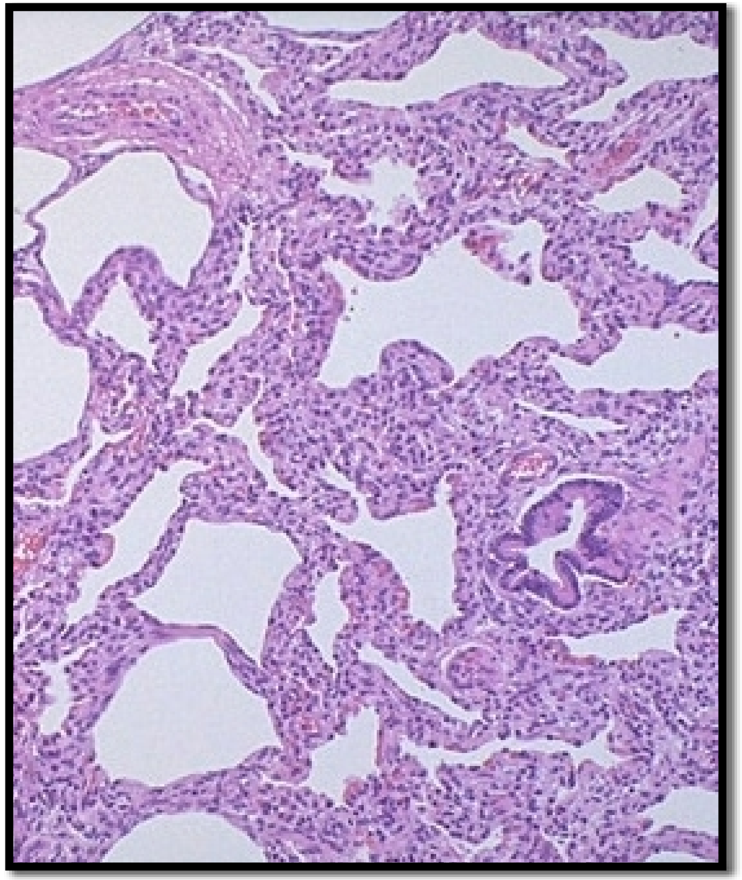
Jobe & Bancalari. *J. Respir. Crit. Care Med.* 2001.

Bronchopulmonary Dysplasia

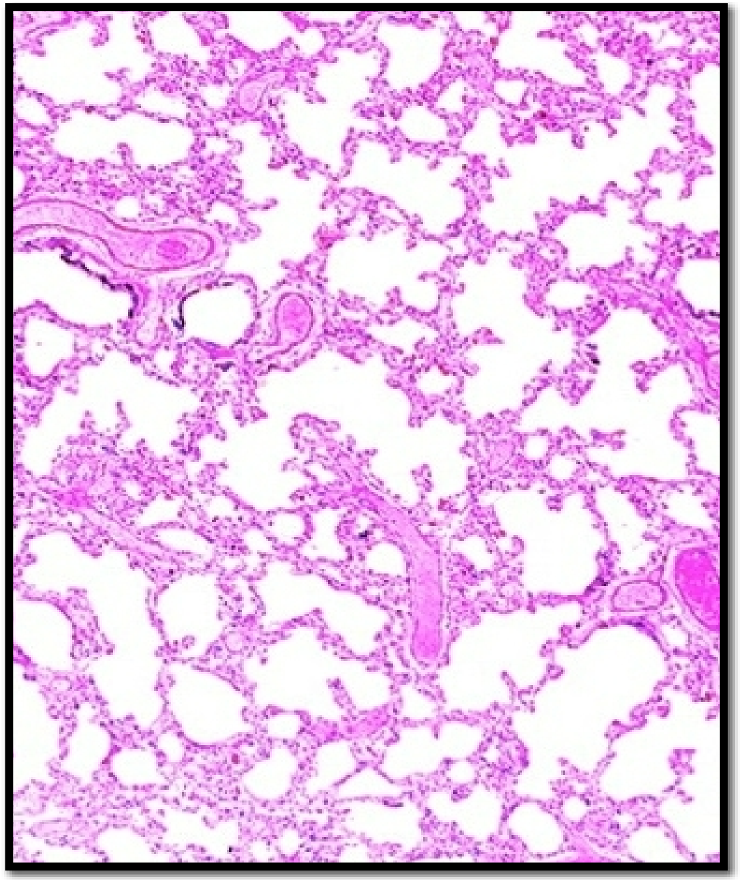
- 1964: Maria Delivoria-Papadopoulos & Paul Swyer described 1st successful mechanical ventilation for a late preterm neonate with RDS (HMD)
  - 17 others in series died
- 1967: Northway, Rosan & Porter described Bronchopulmonary Dysplasia
  - Attributed to mechanical ventilation & high O_2 delivery

Bronchopulmonary Dysplasia

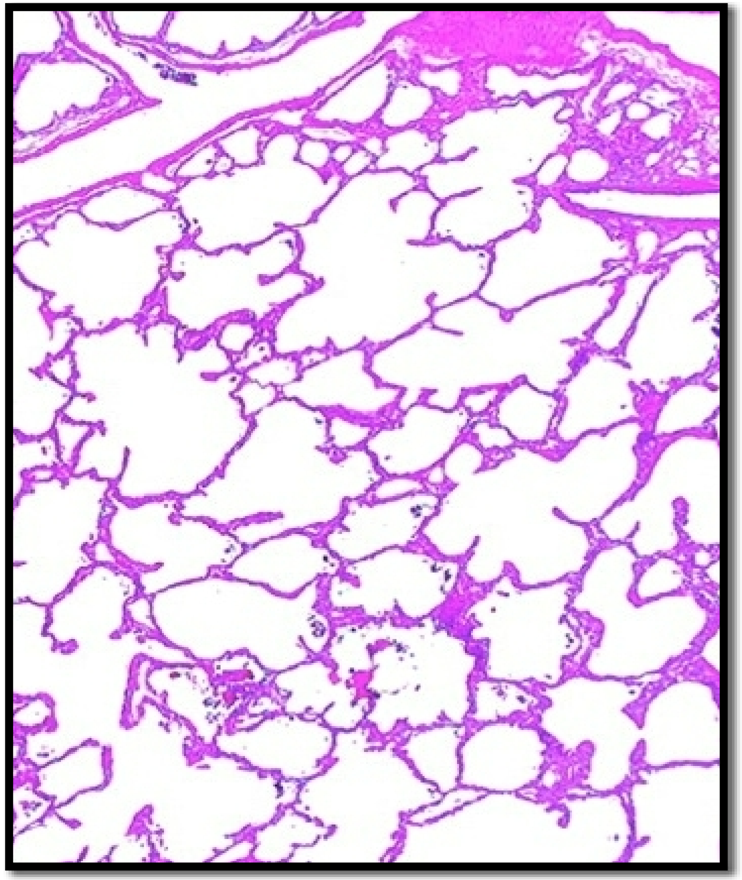
Old BPD



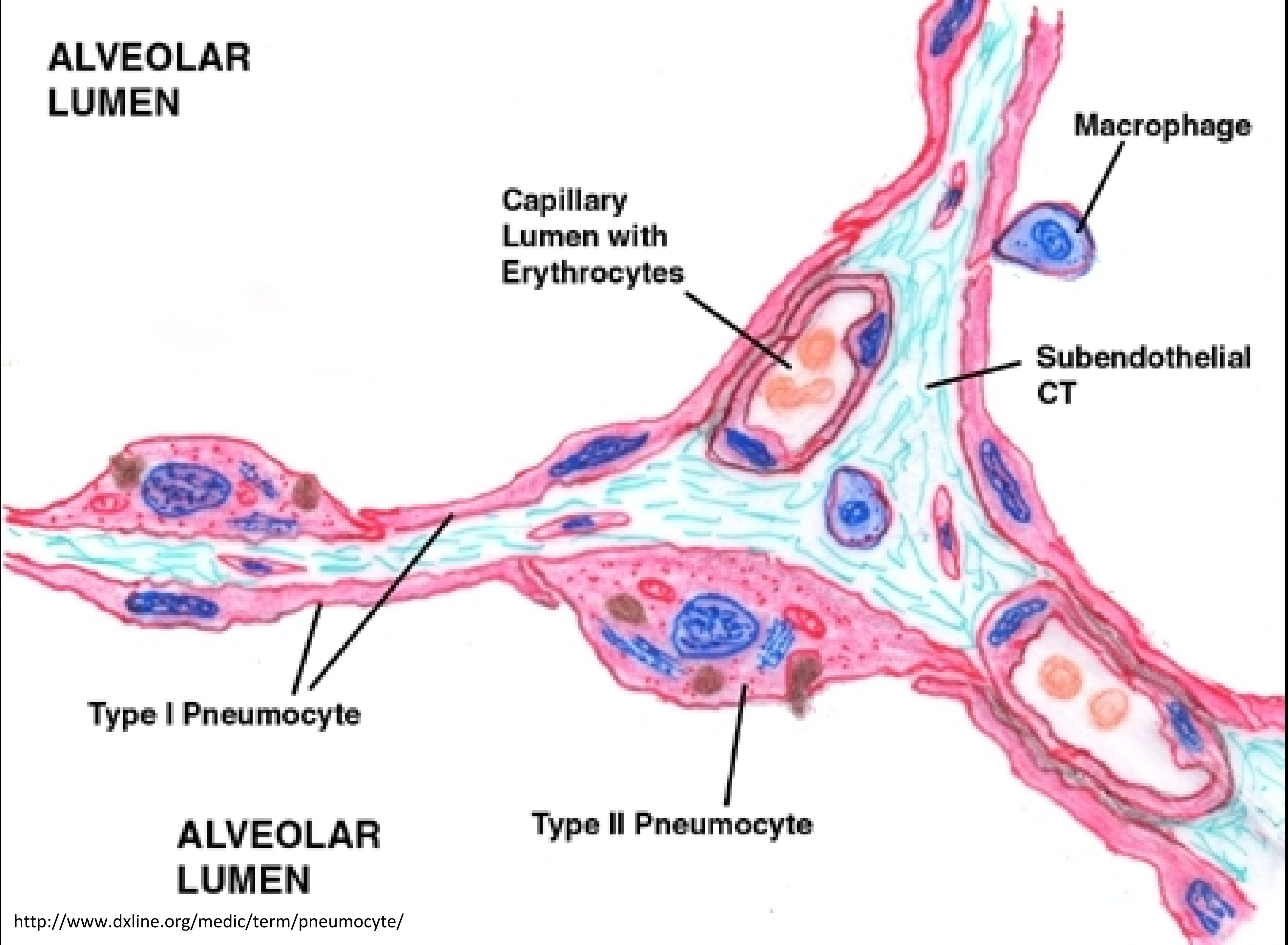
Normal Lung



New BPD

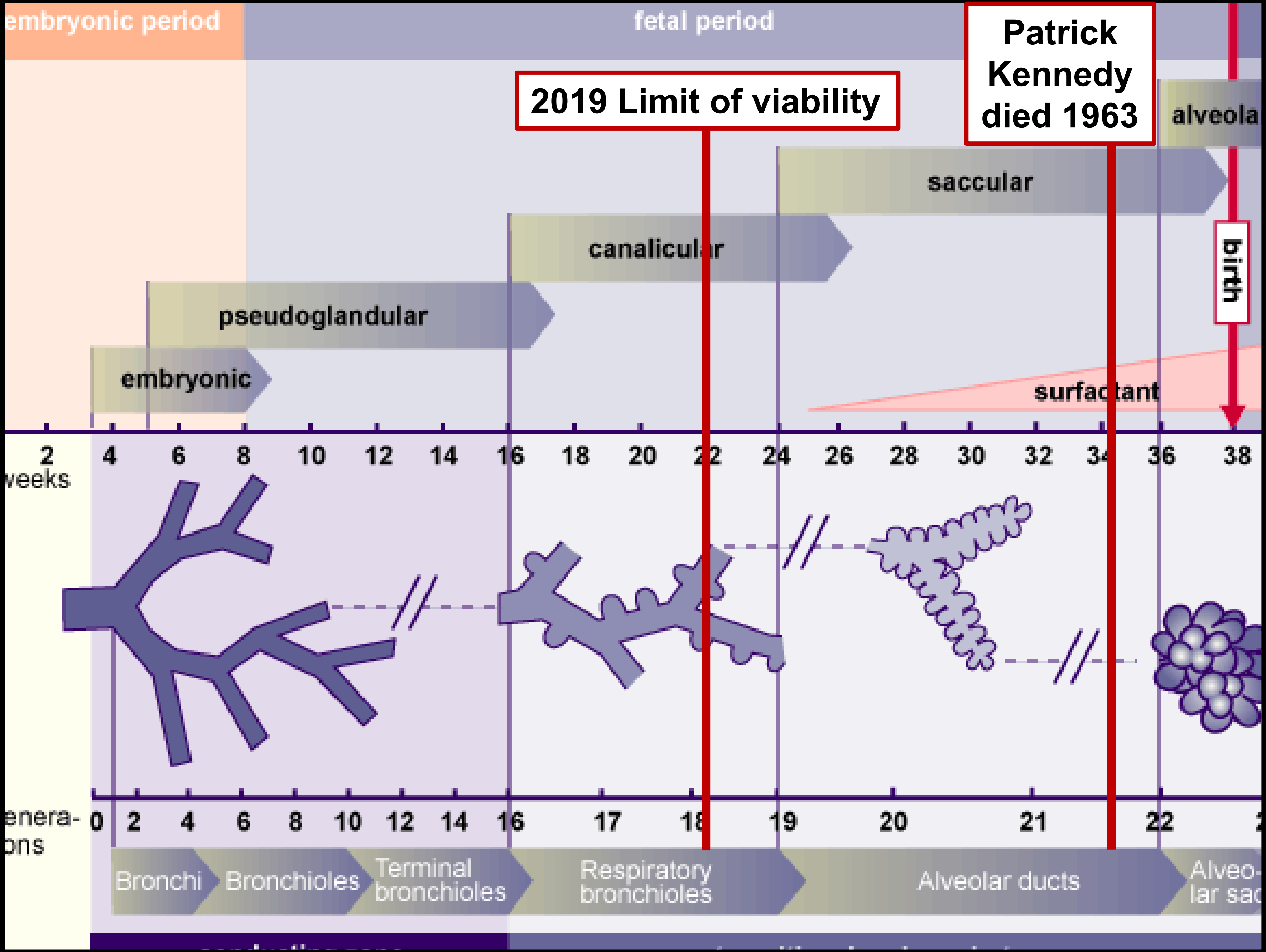


Jobe A, *NeoReviews,* 2006.
http://library.med.utah.edu/WebPath/PEDHTML/PED216.html

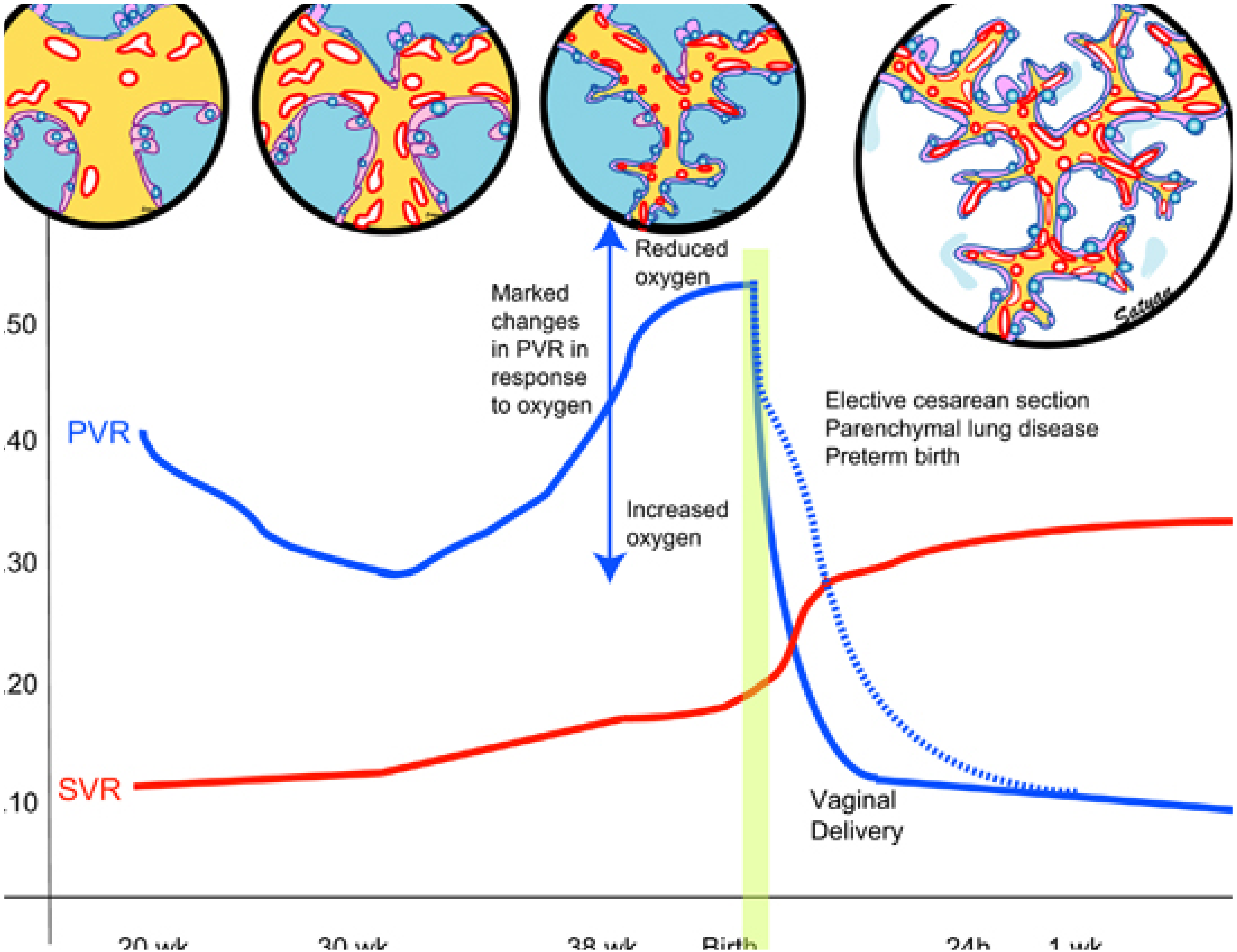


http://www.dxline.org/medic/term/pneumocyte/

http://www.dxline.org/medic/term/pneumocyte/

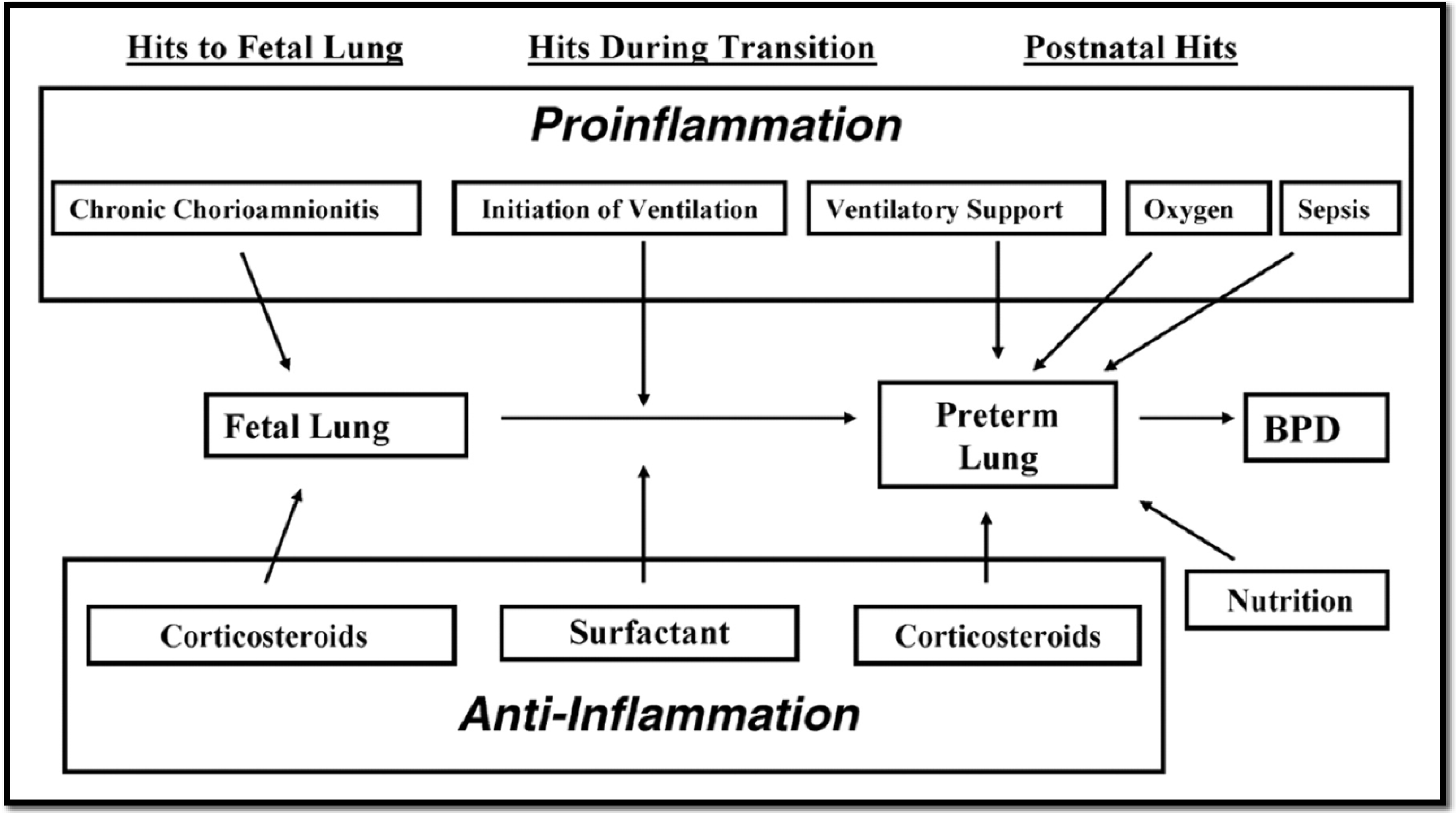


embryonic period
fetal period
2019 Limit of viability
Patrick Kennedy died 1963
alveola
saccular
canalicular
pseudoglandular
embryonic
surfactant
birth
2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38
weeks
0 2 4 6 8 10 12 14 16 17 18 19 20 21 22
Bronchi
Bronchioles
Terminal bronchioles
Respiratory bronchioles
Alveolar ducts



kshminrusimha, S and Saugstad, OD. *J Perinatology* 2016.

BPD Risk Factors



Jobe A. *NeoReviews* 2006.

Antenatal Steroids

Molecular effects

- Upregulates Cholinephosphate cytidyltransferase
- Increases surfactant production
- Mesenchymal thinning of fetal lung

Clinical effects

- Reduced RDS
- Reduced NEC
- Reduced Severe IVH & Death

Antenatal Steroids

NIH Consensus Statement, 2000

- Recommended for anticipated delivery within 7 days for gestational age 24-34 weeks.

ACOG, 2016

- Not recommended before limits of viability.
- Considered for anticipated preterm birth for gestational age 34 $^{0}/_{7}$-36 $^{6}/_{7}$ weeks.

Carlo et al, *JAMA,* 2011

- Benefits infants born in 23-25 weeks.

Surfactant

Decreases surface tension

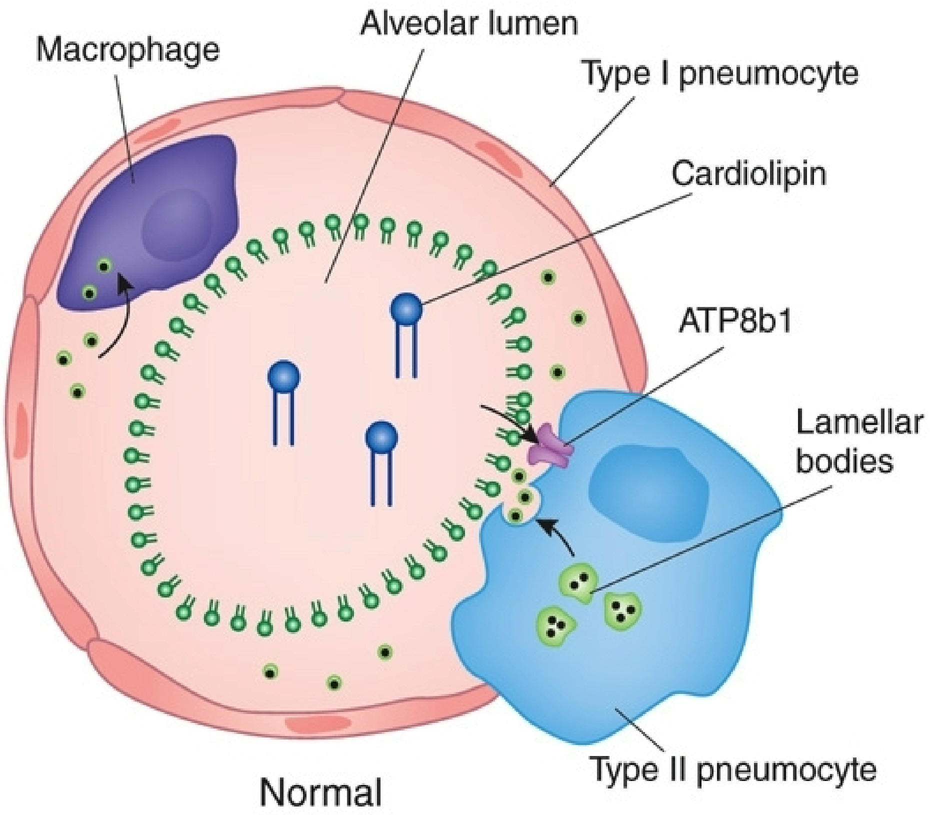
Anti-oxidant

Host defense

Anti-inflammatory

Adult 2-3mg/kg

Term neonate 100mg/kg



Surfactant Administration

- Reduces RDS, air leak, and mortality in preterm infants w/ RDS
- CPAP with early rescue (<2 hours) decreases BPD/death compared to prophylaxis
- Improves oxygenation & reduces need for ECMO in meconium aspiration syndrome
- Does not improve outcomes in CDH

Surfactant Administration

AAP Recommendation, 2014

- Preterm infants <30 weeks on mechanical ventilation
- Consider CPAP with selective administration
- Infants with hypoxic respiratory failure due to surfactant deficiency (meconium, pneumonia)

ROH Protocol

- Prophylaxis <26 weeks
- Rescue for any preterm on mechanical ventilation

INSURE

<u>In</u>tubate

<u>Sur</u>factant

<u>E</u>xtubate

Verder, et al

- 1994: 68 infants on NCPAP, GA 25-35 weeks
  - Rescue INSURE reduced need for MV: 33% vs. 83% (p<0.001)
- 1999: 60 infants with RDS on NCPAP, GA <30 weeks
  - Earlier INSURE improved oxygenation and reduced MV/Death and MV

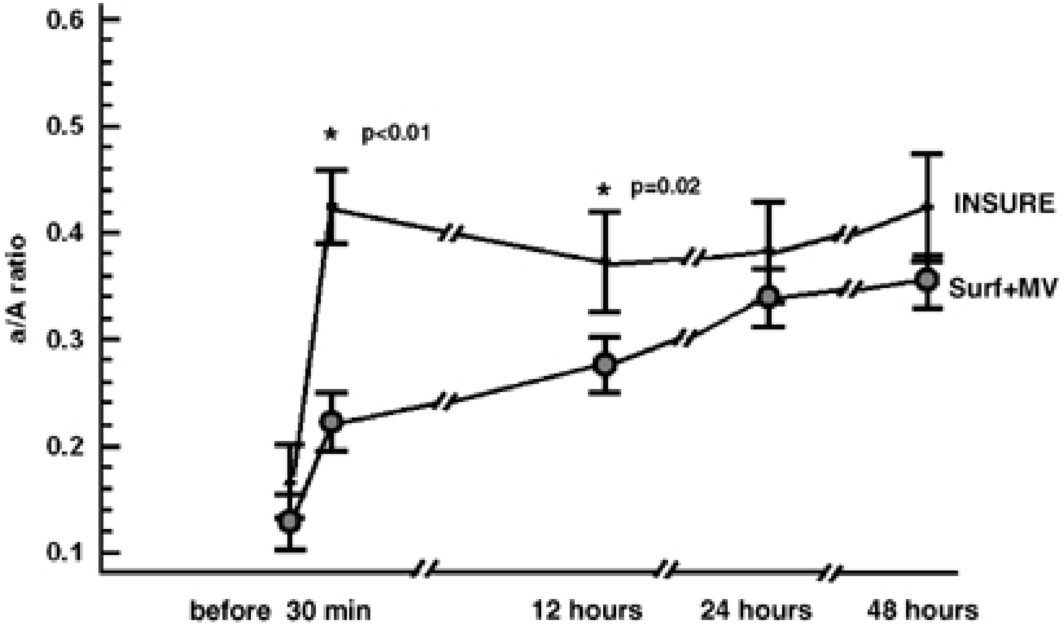
Verder, et al. NEJM, 1994. Verder, et al. *PEDIATRICS,* 1999.

INSURE

Intubate

Surfactant

Extubate

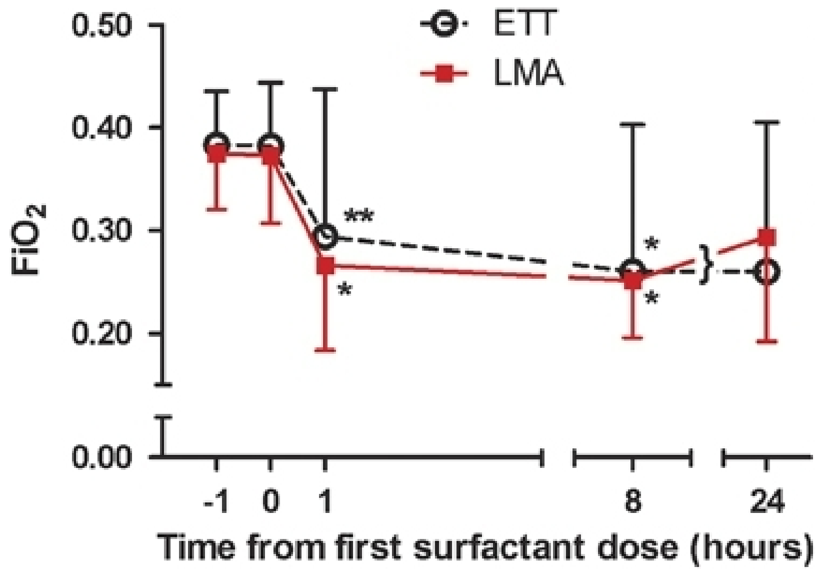


INSURE-treated infants, GA 27-34 weeks, had improved oxygenation from 30 min to 48 hours compared to Surf+MV-treated infants. Implementation of INSURE reduced MV by 50%.

Bohlin, et al. *JPerinatology,* 2007.

ETT vs LMA Surfactant

- Rescue calfactant
  - 60 preterm infants
  - BW 2031g



Intervention Failure	*LMA group*	*ETT group*	*Comparison between groups*
Any failure	9 (30%)	23 (77%)	$P<0.001$
Early failure	1 (3%)	20 (67%)	$P<0.001$
Late failure	8 (27%)	3 (10%)	$P=0.181$
Other failure	2 (7%)	3 (10%)	$P=1.0$

Abbreviations: ETT, endotracheal tube; LMA, laryngeal mask airway.

Pinheiro, *J Perinatology*, 2016.

Corticosteroids

Positive

- Decrease inflammation & pulmonary edema

Negative

- Decrease alveolarization & pulmonary vascularization
- Growth impairment
- Poor neurodevelopmental outcomes

Little evidence to balance risk/benefit in individual patients

NICHD Cochrane Reviews

First week dexamethasone not recommended

- Facilitates extubation
- Decreases BPD & PDA
- Adverse events
  - GI bleeding, SIP, Hyperglycemia, Hypertension, Hypertrophic cardiomyopathy, Growth failure
  - Abnormal neuro exam, Cerebral palsy

First week Hydrocortisone

- No respiratory benefit or harmful effects

NICHD Cochrane Reviews

Corticosteroids starting 7-14 days

- Decreases mortality
- Decreases BPD
- Adverse short-term effects
  - Hypertension, Hyperglycaemia, GI bleeding, Hypertrophic cardiomyopathy and infection

Late steroids >7 days

- Reduced mortality
- Limited long-term safety evidence

NICHD Cochrane Reviews

Inhaled steroids

- Treatment in first 2 weeks does not decrease BPD
- Treatment after 7 days does not decrease BPD
- Not routinely recommended for prevention or treatment of BPD in ventilated infants

Dexamethasone: A Randomized Trial DART

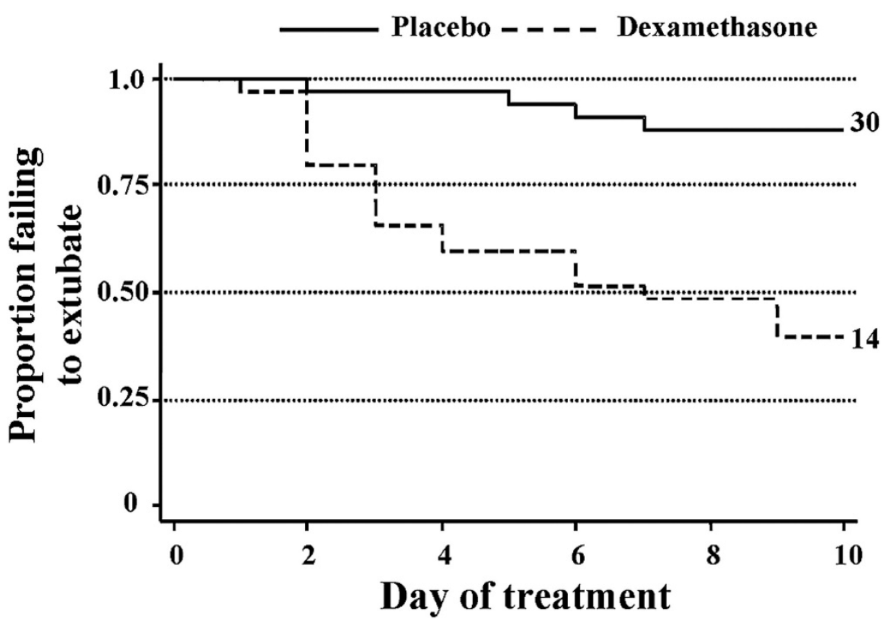
70 infants, BW <1000g, >7 days

Low dose dexamethasone

Facilitates extubation

Shortens duration of mechanical ventilation

No increased morbidity at 2 years



Doyle, *PEDIATRICS*, 2006.
Doyle, *PEDIATRICS*, 2007.

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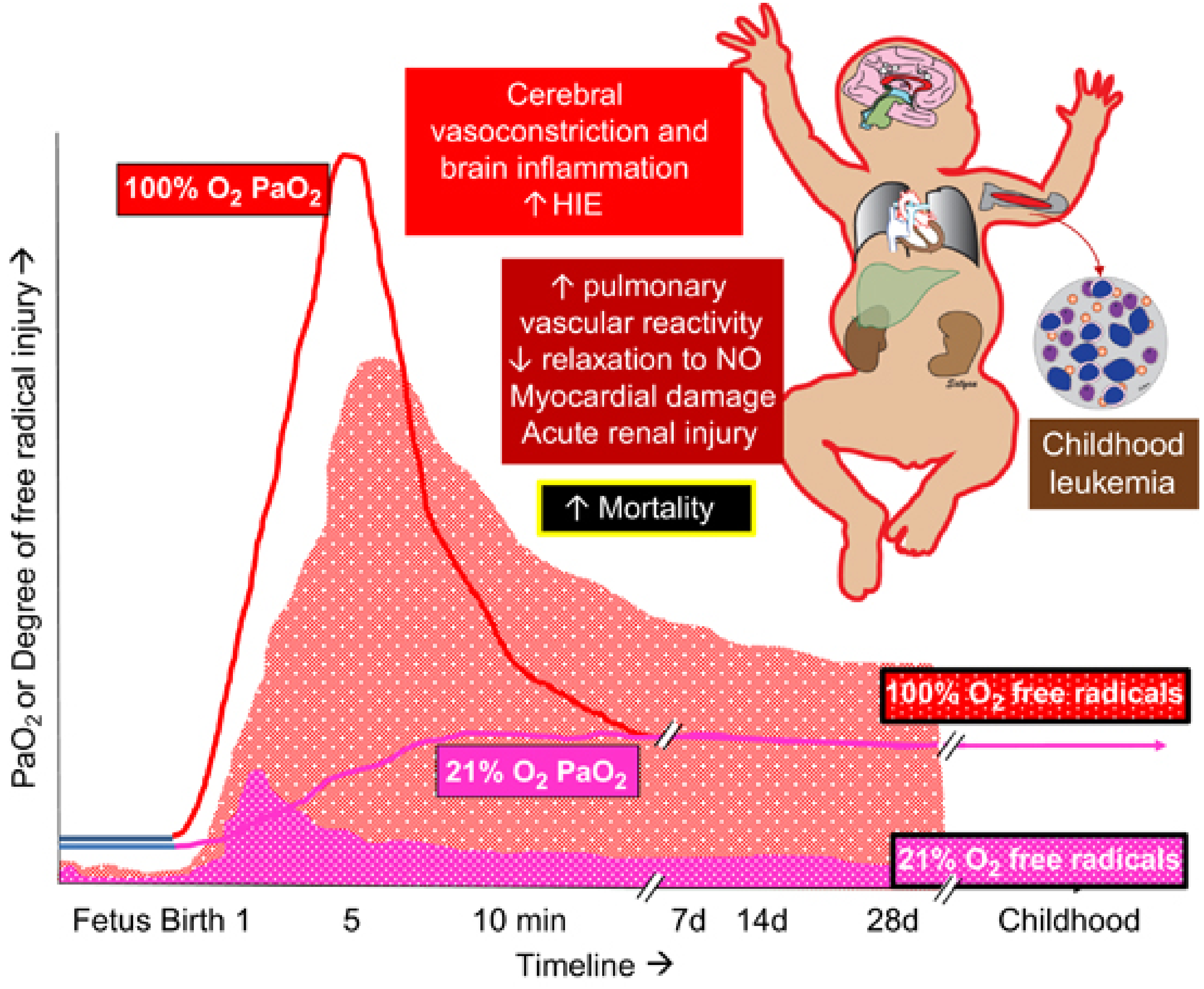
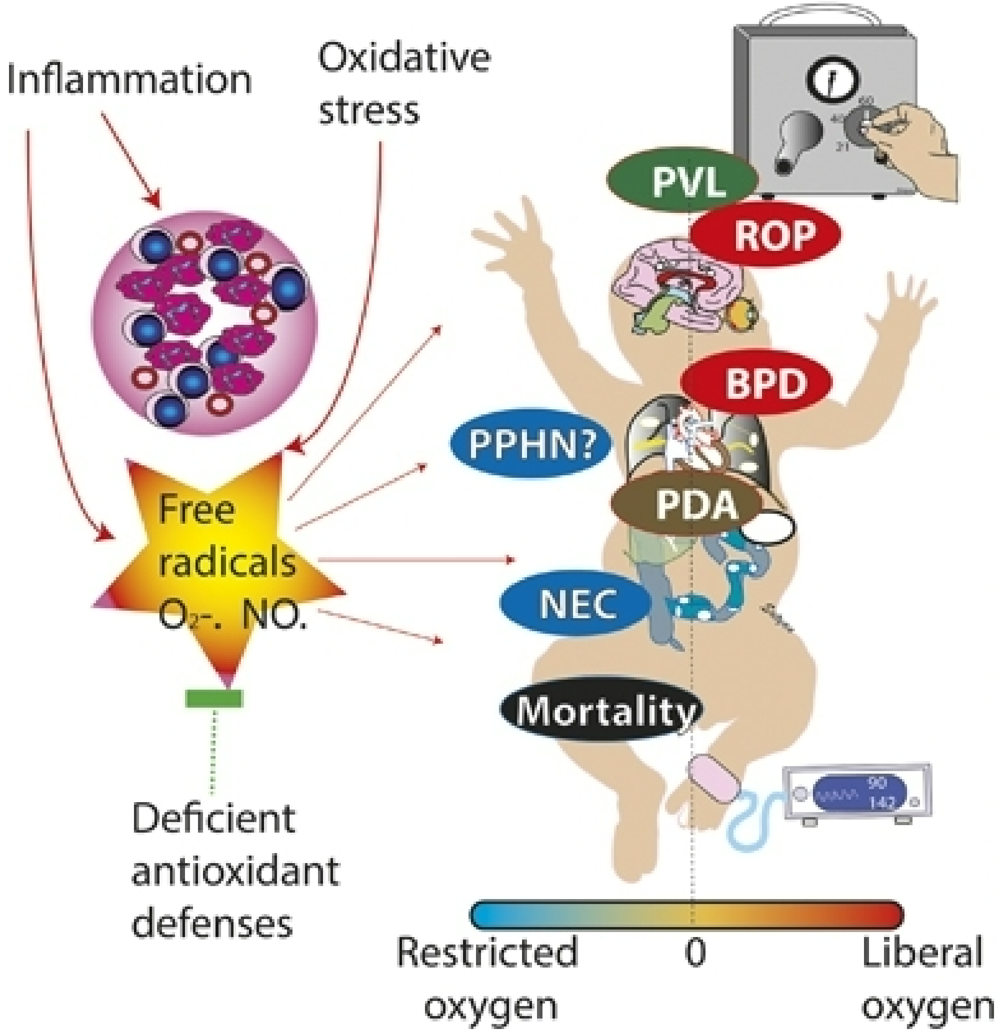
Oxygen



Lakshminrusimha, S and Saugstad, OD. *J Perinatology* 2016.

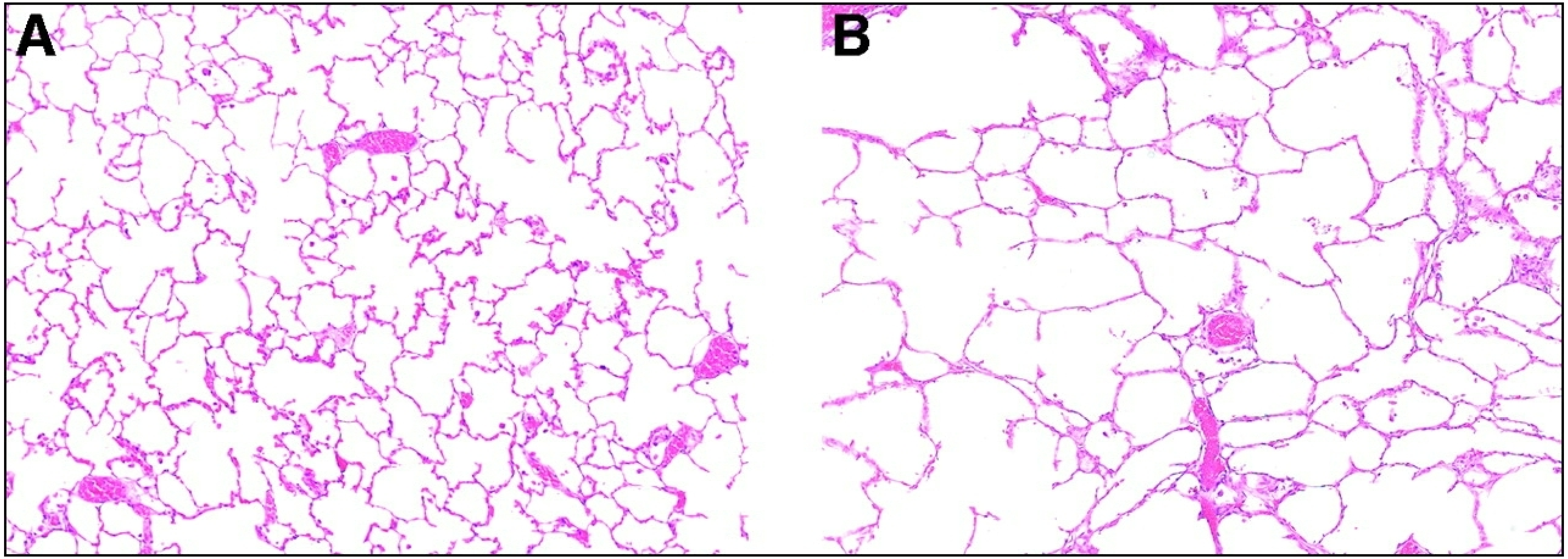
Oxygen



Lakshminrusimha, S and Saugstad, OD. *J Perinatology* 2016.

Oxygen

Ventilation + Normal O_2 — Ventilation + 80-100% O_2

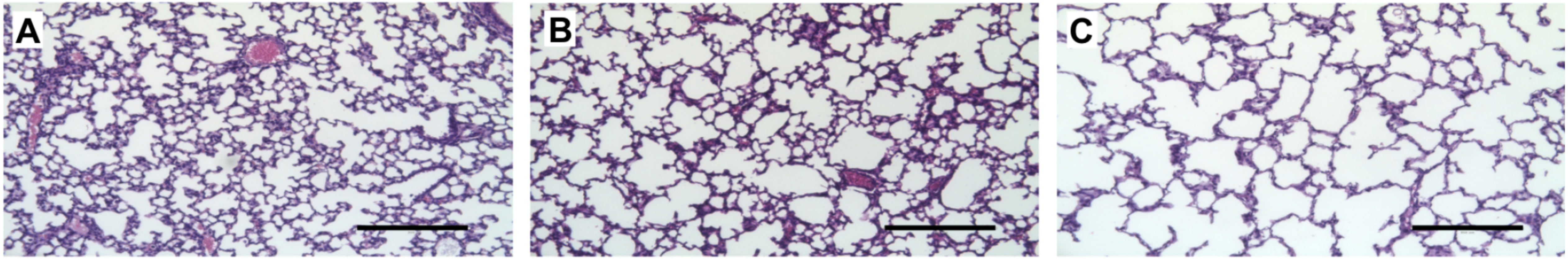


Preterm baboons ventilated x21 days, lung biopsy at 33 weeks

Jobe A. *NeoReviews* 2006.

Oxygen in Preterm Mouse Model

15 Days Oxygen Exposure: 21% 60% 85%



Courtesy of Kent Willis, MD.

ETT Ventilation in 1st Week

Infants ≤30 weeks receiving primarily ETT ventilation were at increased risk for BPD or death compared to those receiving non-invasive respiratory support

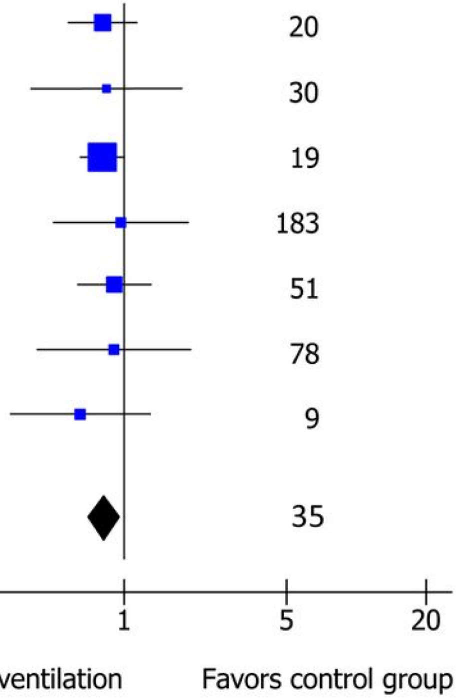
- OR 3.1 (95% CI 1.3-7.8)
- Adjusted for gender, BW, Sepsis, PDA, Race, Surfactant, & Time to regain BW.

Dumpa, et al. *AmJPerinatology*, 2011.

Effect of avoiding eMV on death or BPD

Preterm infants, GA <30 weeks

Study or Subgroup	Avoid ventilation BPD/death	Avoid ventilation Total	Control group BPD/death	Control group Total	Weight, %	Odds Ratio Random effects model (95% CI)	NNT
COIN (2008)	108	307	122	303	19.8	0.81 (0.58–1.12)	20
CNRN (2009)	53	74	54	72	4.0	0.84 (0.40–1.75)	30
SUPPORT (2010)	323	663	353	653	45.5	0.81 (0.65–1.00)	19
CURPAP (2010)	22	103	23	105	4.9	0.97 (0.50–1.87)	183
DRM (2011)	68	223	138	425	17.4	0.91 (0.64–1.29)	51
AMV (2011)	15	108	17	112	3.8	0.90 (0.43–1.91)	78
Take Care (2013)	25	74	30	67	4.6	0.63 (0.32–1.24)	9
Total	614	1552	737	1737	100	0.83 (0.71–0.96)	35



Test for overall effect: $z = 2.55$ ($P = .01$)

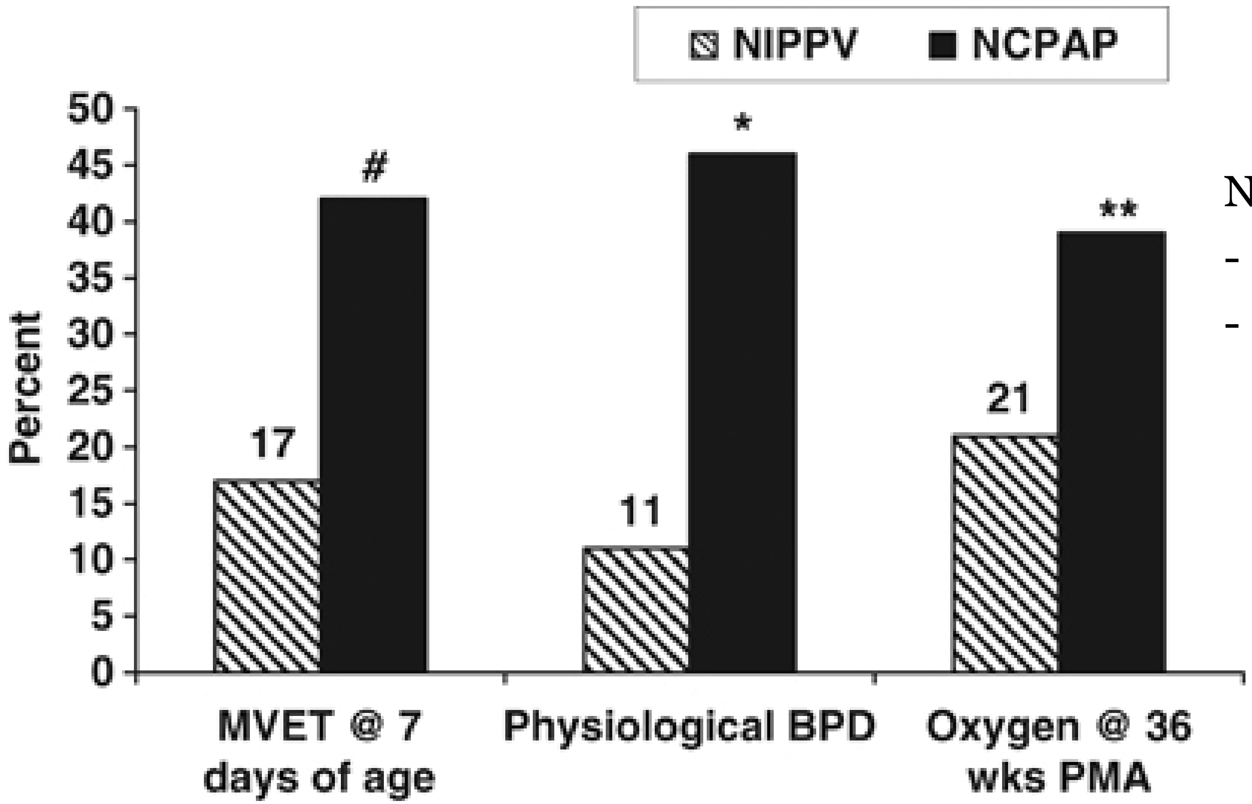
Heterogeneity: $Tau^2 = 0.00$; $\chi^2 = 1.27$; df = 6 ($P = .97$); $I^2 = 0\%$

Hendrik S. Fischer, and Christoph Bührer Pediatrics 2013;132:e1351-e1360

PEDIATRICS®

NIPPV vs. NCPAP

110 Preterm infants
GA 26-29 6/7 weeks



NIPPV Group:

- Fewer extubation failures
- Fewer days with supplemental O2

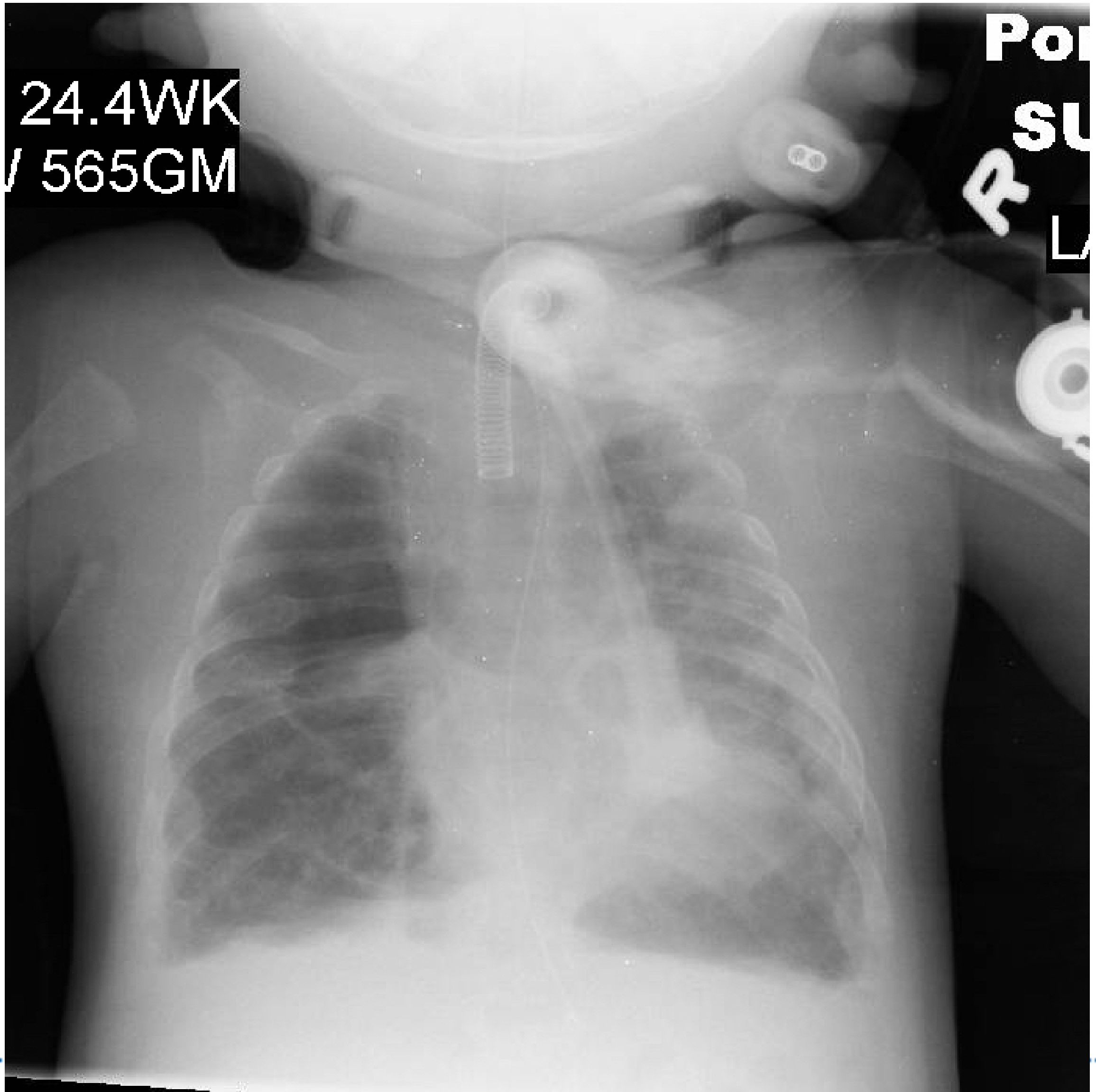
Primary and secondary outcomes. [†]Logistic regression to control for potentially confounding effects of GA, gender, center, antenatal steroid use and multiple births was done; #*P*=0.005, **P*=0.001, ***P*=0.04, MVET, mechanical ventilation via endotracheal tube; BPD, bronchopulmonary dysplasia; PMA, postmenstrual age.

Ramanathan, et al. *J Perinatology,* 2012.

Nutrition

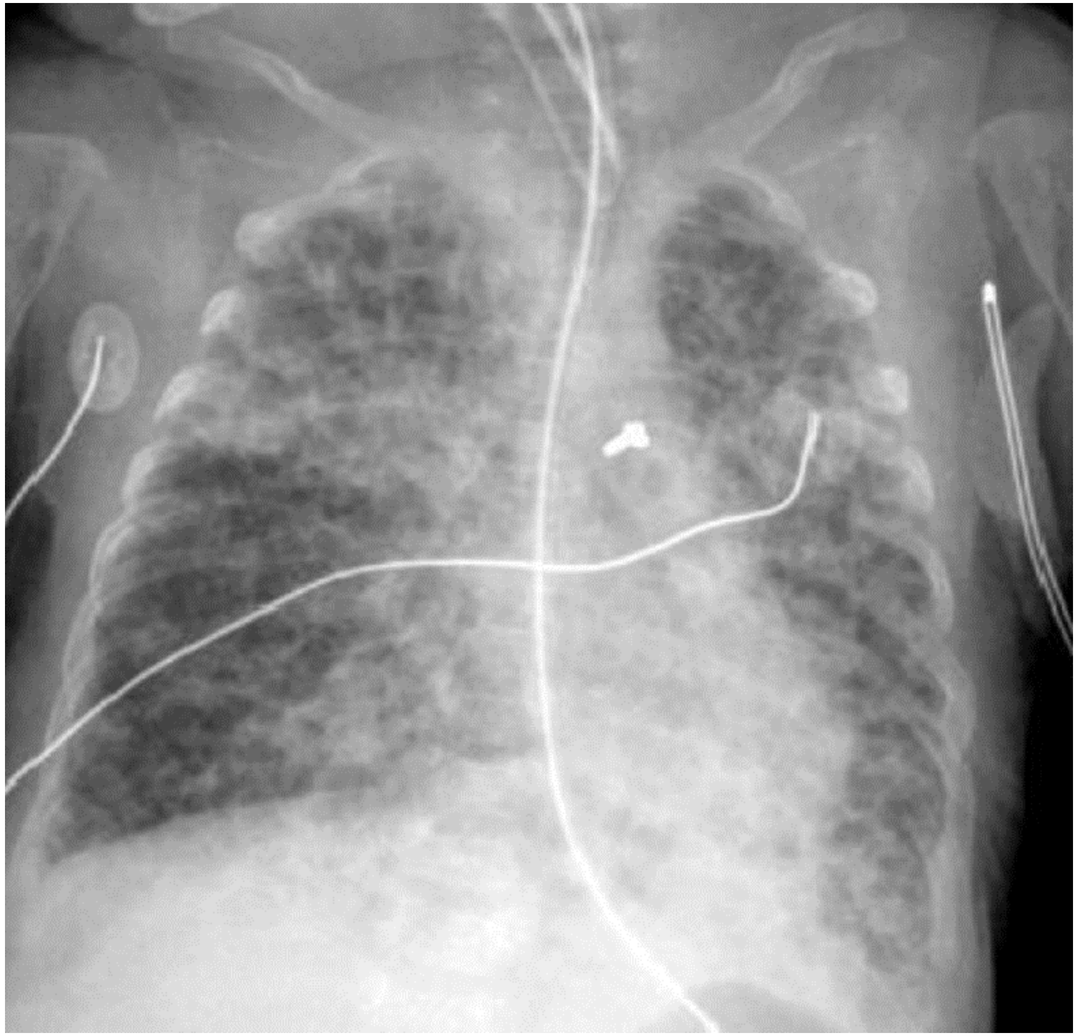
- Other factors that can interfere with lung development are corticosteroids and starvation. Newborn rabbits that are fed less calories have increased sensitivity to oxidant damage, and adult rodents that are starved develop an emphysematous lung, which returns to normal with refeeding. (18) There is no information in newborn humans about the effects of low calorie intake on lung development. However, nutritional status may be an important and underappreciated variable on the pathway to BPD.

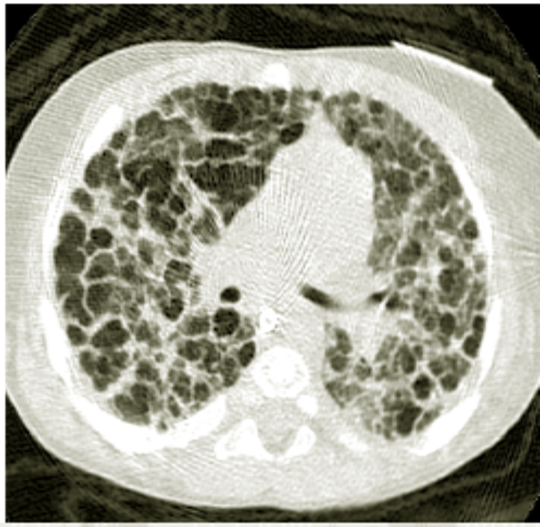
Bronchopulmonary Dysplasia



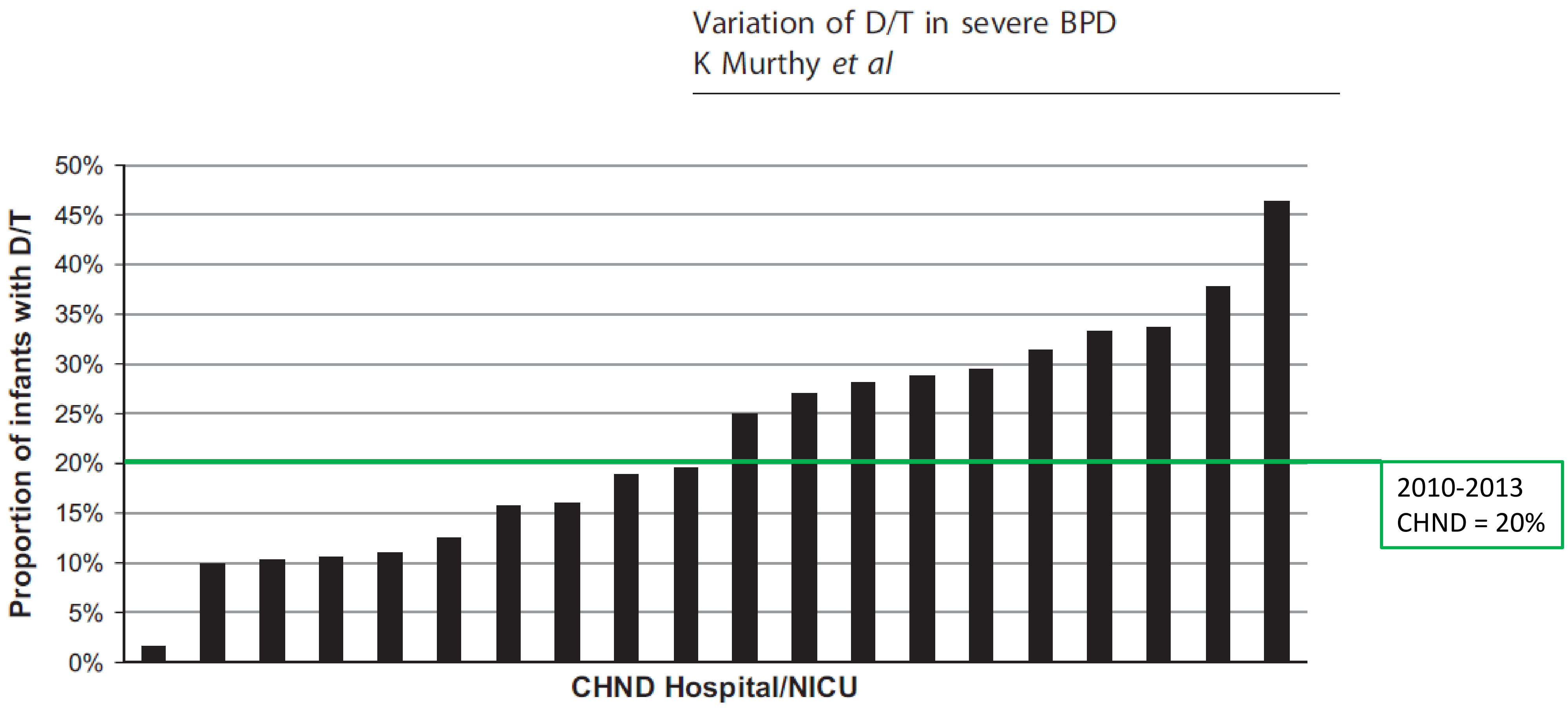
Heterogeneous lung disease
Long time constant
High resistance
High compliance
Impaired hemodynamics
Large tidal volume
Low rate
Extremely long eTime
CMV

Severe BPD





Death or Trach <32 weeks



Unadjusted inter-center variation in death or tracheostomy placement (D/T).

Murthy, et al. Inter-center variation in death or tracheostomy placement in infants with severe bronchopulmonary dysplasia. *J Perinatology*, 2017.

Severe BPD

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.		

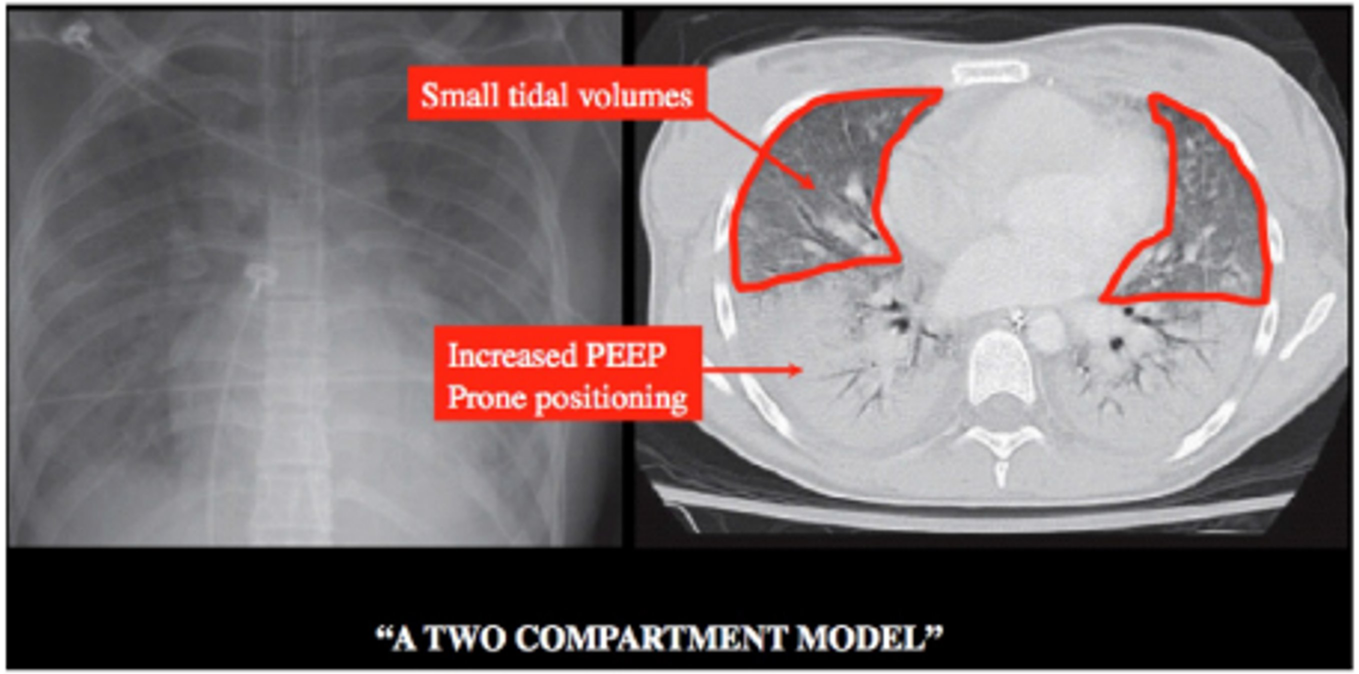
HFNC, high flow nasal cannula; *O_2*, oxygen.

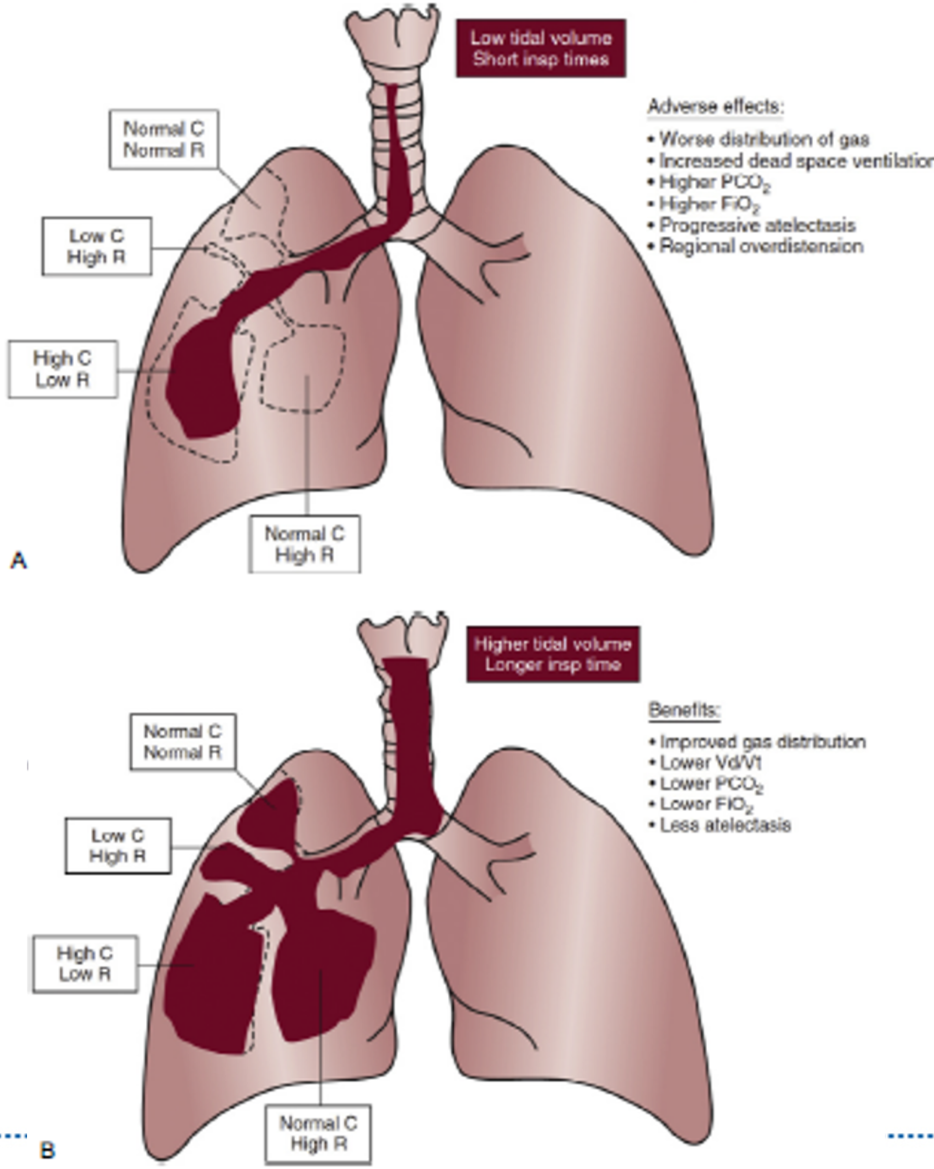
Severe BPD

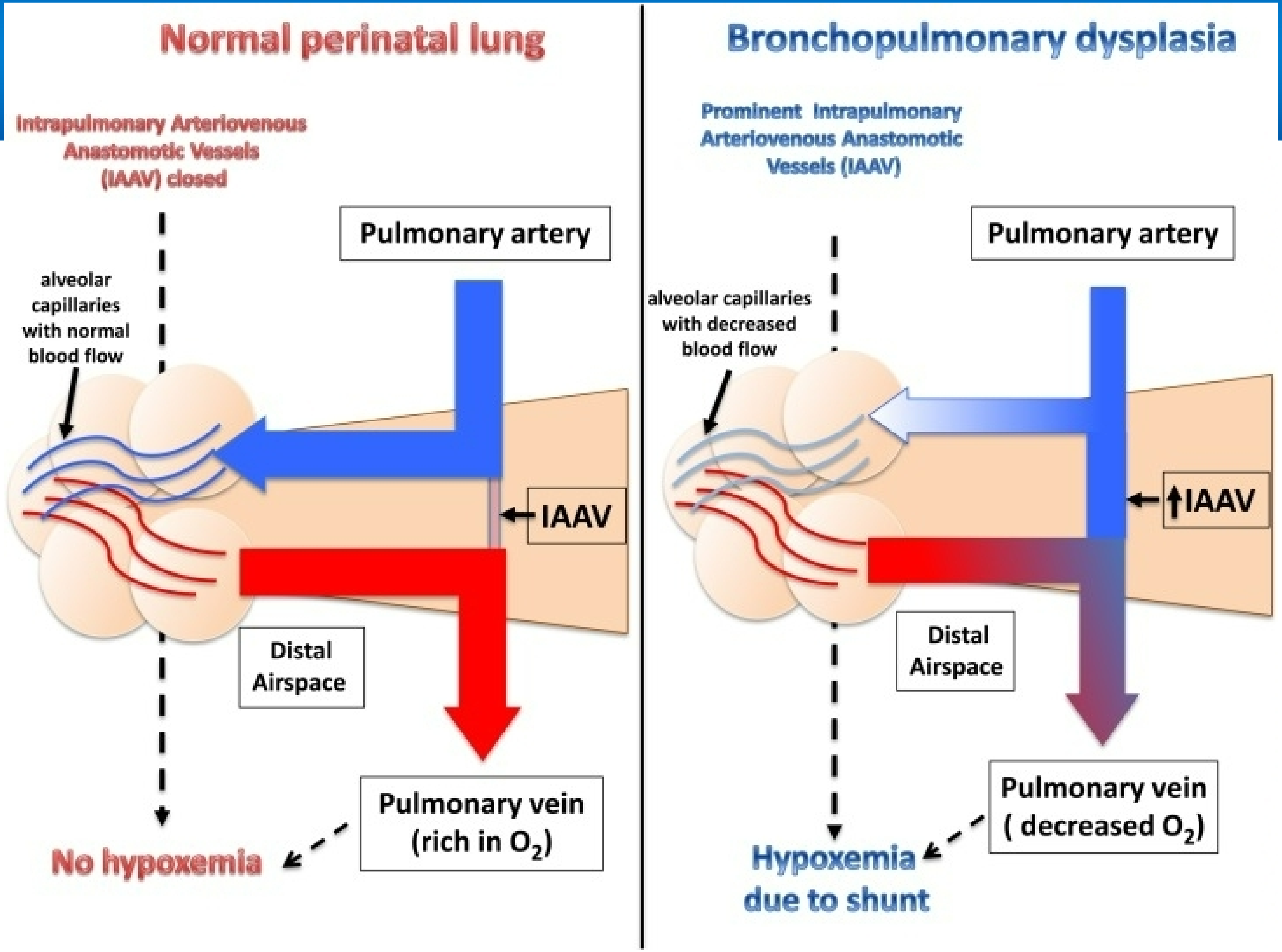
Table III. Comparison of ventilator strategies and goals during progression of early disease to established sBPD (modified from Abman and Nelin[29])

Early (prevention)	Strategies to prevent acute lung injury	Low tidal volumes (3-5 mL/kg) Short inspiratory times (0.2-0.3 seconds) Increased PEEP for lung recruitment without overdistension
	Strategies for gas exchange	Adjust FiO_2 to target SpO_2 (range: 91%-95%) Permissive hypercapnia
Late (established BPD)	Strategies for gas exchange	Marked regional heterogeneity Larger tidal volumes (10-12 mL/kg) Longer inspiratory times (≥0.6 s) Airways obstruction Slower rates allow for better emptying, especially with larger tidal volumes (10-20 bpm) Complex roles for PEEP with dynamic airway collapse Interactive effects of ventilator strategies Changes in rate, tidal volume, inspiratory and expiratory times, and pressure support are highly interdependent Overdistension can increase agitation and paradoxically worsen ventilation
	Strategies for gas exchange	Adjust FiO_2 to target higher SpO_2 (92%-95%) Permissive hypercapnia to facilitate weaning

Severe BPD


Small tidal volumes
Increased PEEP
Prone positioning
"A TWO COMPARTMENT MODEL"


Low tidal volume
Short insp times
Adverse effects:
• Worse distribution of gas
• Increased dead space ventilatio
• Higher PCO_2
• Higher FiO_2
• Progressive atelectasis
• Regional overdistension
Normal C
Normal R
Low C
High R
High C
Low R
Normal C
High R
A
Higher tidal volume
Longer insp time
Benefits:
• Improved gas distribution
• Lower Vd/Vt
• Lower PCO_2
• Lower FiO_2
• Less atelectasis
Normal C
Normal R
Low C
High R
High C
Low R
Normal C
High R
B



Ann Am Thorac Soc. 2013 Oct; 10(5): 474–481.

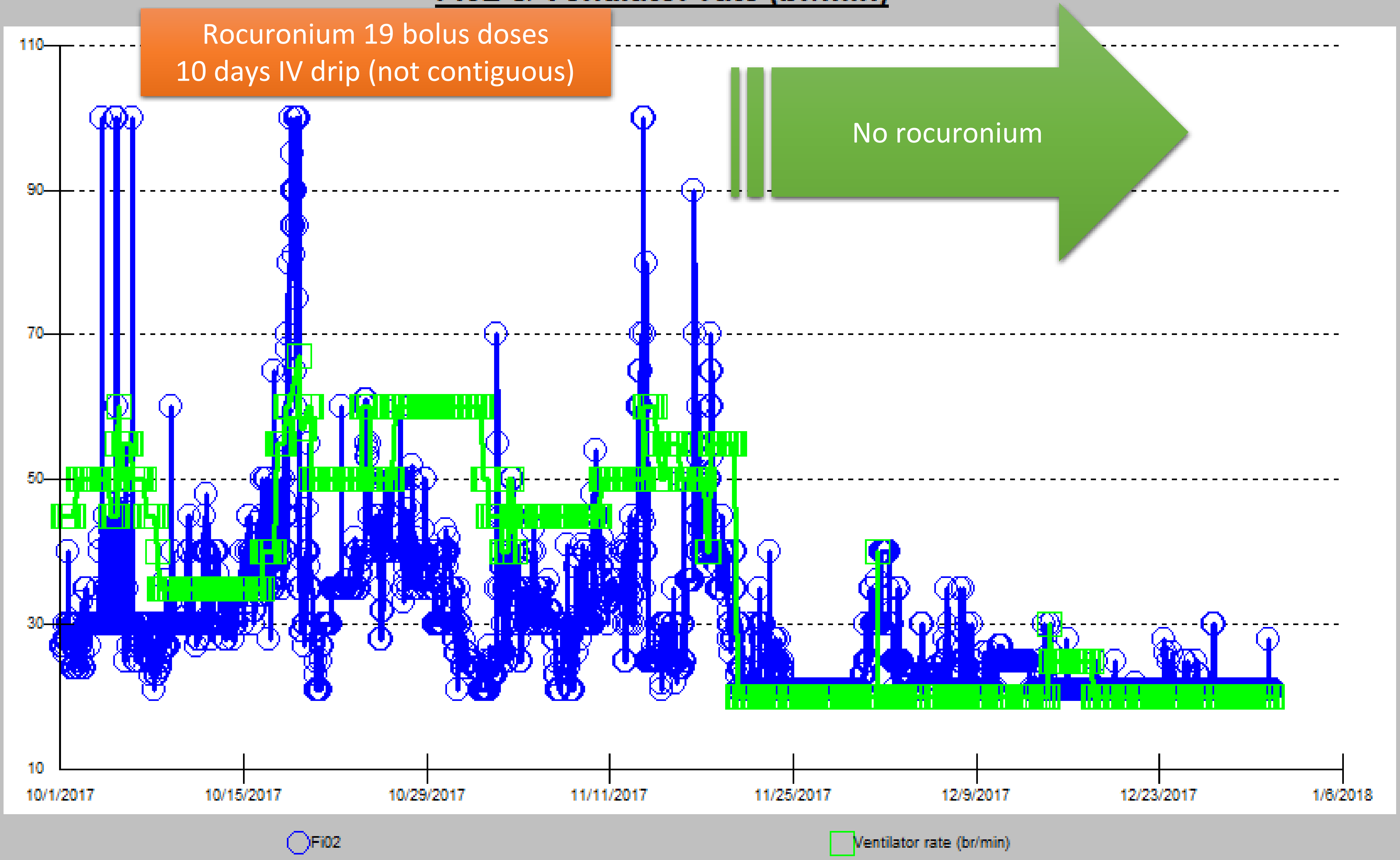
Severe BPD

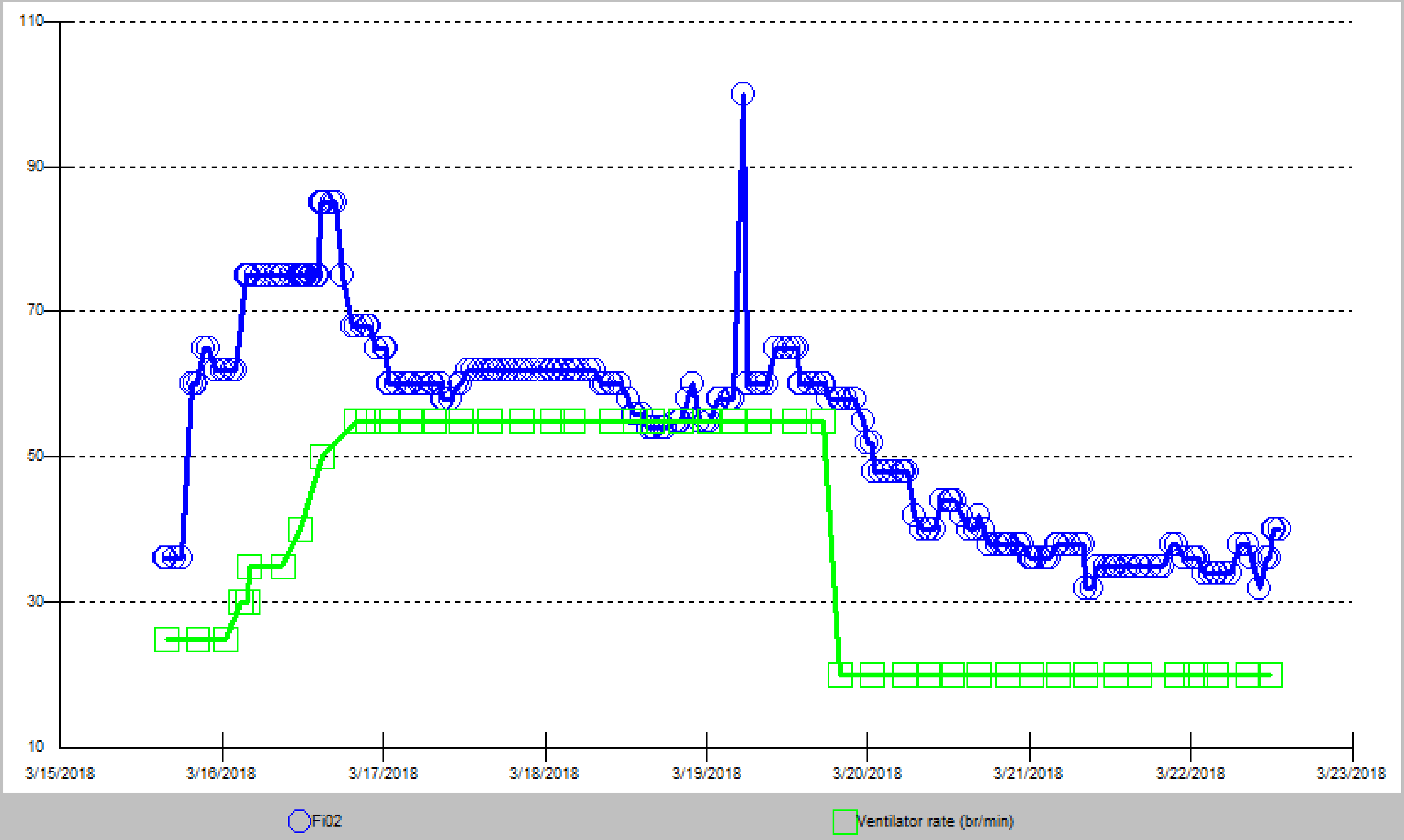
Table V. Pharmacology of sBPD

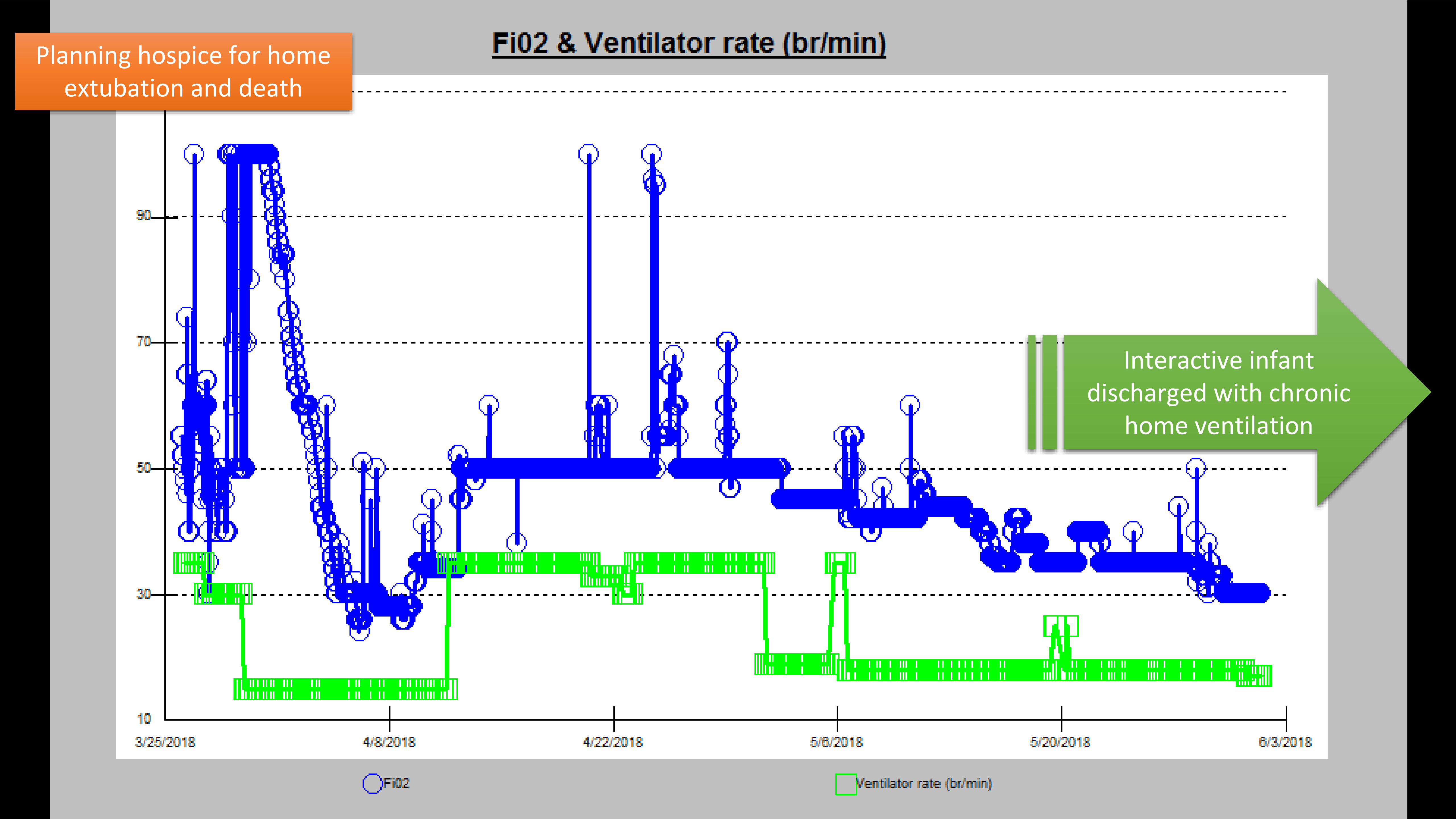
Categories	Medications	Dosing	Comments
Diuretics (Enteral dosing)	Furosemide	1-2 mg/kg/dose q12-24h	Often PRN
	Chlorothiazide	20-40 mg/kg/d divided q12h	
	Spironolactone	2-4 mg/kg/d divided q12-24h	
Bronchodilators	Albuterol	2.5 mg nebulized or 2 puffs q4-12h	Often PRN
	Ipratropium	0.5 mg q6-12h	Often PRN
	Levalbuterol	0.31-1.25 mg or 2 puffs q4-12h	Often PRN
Inhaled corticosteroids	Beclomethasone	2 puffs q12h	40 or 80 mcg MDIs
	Budesonide	1 neb q12-24h	0.25 or 0.5 mg nebs
	Fluticasone	2 puffs q12h	44, 110, 220 mcg MDIs
Pulmonary hypertensive agents	Bosentan	½ tab BID PO	
	Sildenafil	0.25-0.5 mg/kg/dose q 6-8 h	
	Treprostinil	Starting dose: 2 ng/kg/min iv or SQ	
Antireflux agents (enteral dosing)	Erythromycin	2-4 mg/kg/dose q6-8h	
	Lansoprazole	0.5-1.0 mg/kg/dose BID	
	Metoclopramide	0.1-0.2 mg/kg/dose q6-8 h	
	Omeprazole	0.5-1.5 mg/kg/d	
	Ranitidine	2-4 mg/kg/d divided q8-12 h	

MDI, metered dose inhaler; *PRN*, as needed.

Fi02 & Ventilator rate (br/min)




110
90
70
50
30
10
3/15/2018
3/16/2018
3/17/2018
3/18/2018
3/19/2018
3/20/2018
3/21/2018
3/22/2018
3/23/2018
Fi02
Ventilator rate (br/min)



Planning hospice for home extubation and death
Fi02 & Ventilator rate (br/min)
90
70
50
30
10
3/25/2018
4/8/2018
4/22/2018
5/6/2018
5/20/2018
6/3/2018
Interactive infant discharged with chronic home ventilation
Fi02
Ventilator rate (br/min)


TINY