The PCO_2 Conundrum:

Balancing Lung and Brain Protection

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Disclaimer and Disclosure

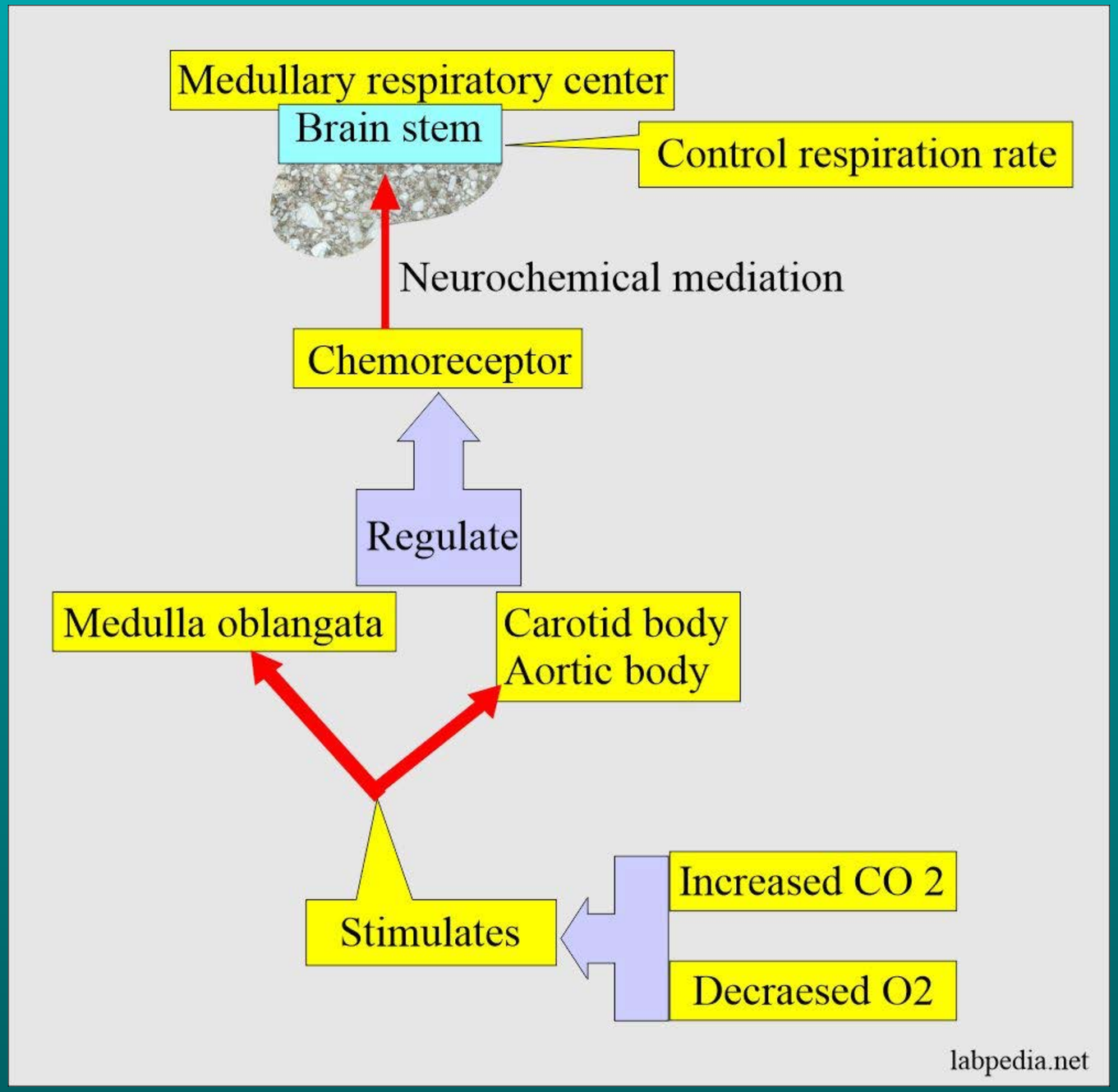
- I spent 28 years as a clinician in the NICU so I suppose I'm very biased and passionate about all things related to caring for our littles!!

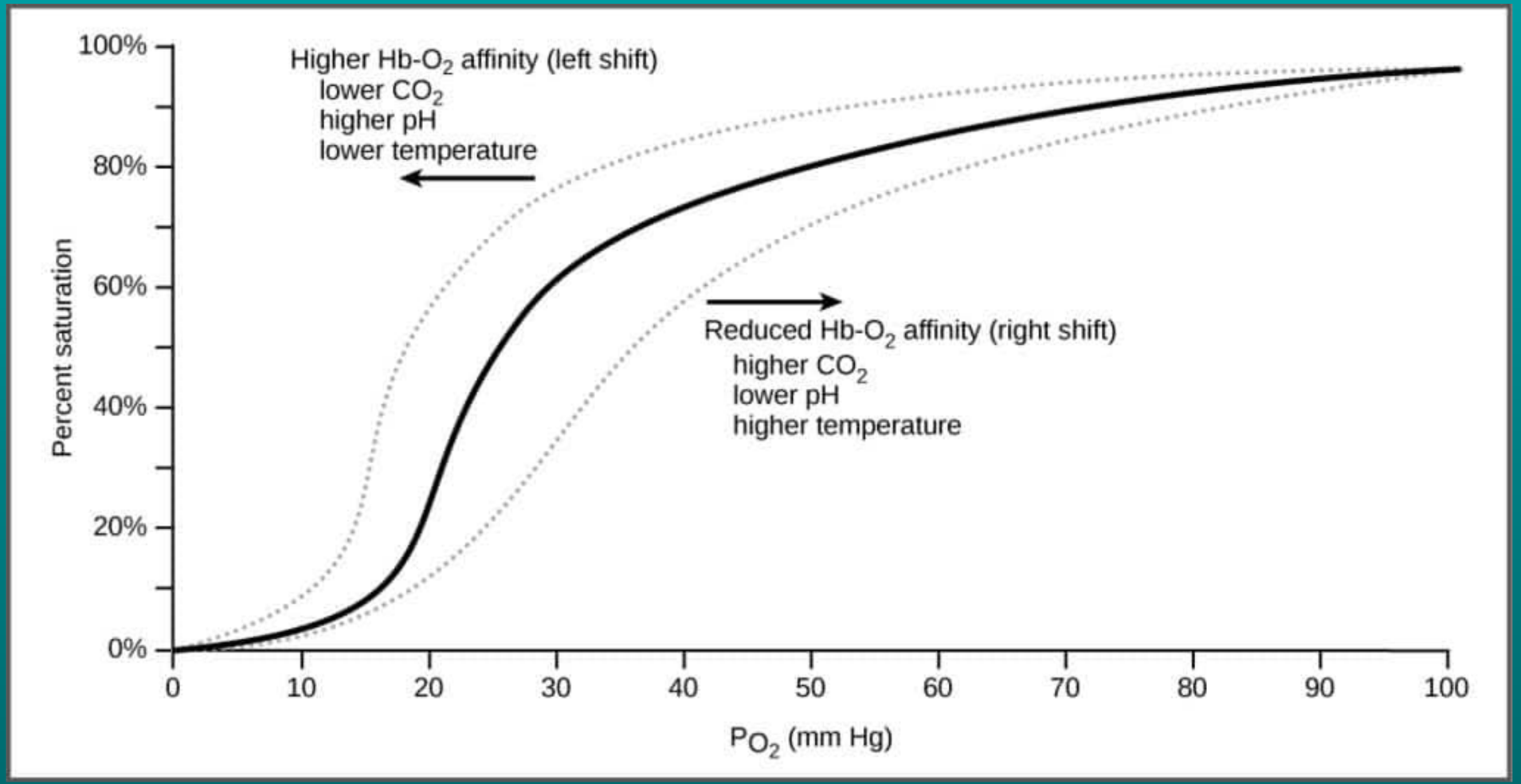
Objectives

- Understand the role of $PaCO_2$ in physiologic acid-base balance
- Understand the definition of BPD and CLD as it relates to overall development of the neonate
- Explain the difference between lung protective and neurologically protective $PaCO_2$ management strategies

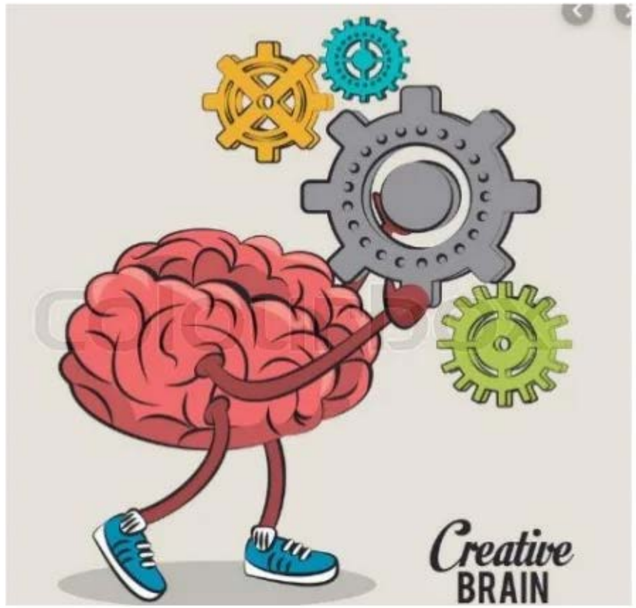
The Basics

- Our body likes to keep things in balance
  - Acid / Base balance - pH, PCO_2
  - PCO_2 and PO_2


Medullary respiratory center
Brain stem
Control respiration rate
Neurochemical mediation
Chemoreceptor
Regulate
Medulla oblangata
Carotid body
Aortic body
Stimulates
Increased CO 2
Decraesed O2
labpedia.net


100%
80%
60%
40%
20%
0%
Percent saturation
Higher Hb-O2 affinity (left shift)
lower CO2
higher pH
lower temperature
Reduced Hb-O2 affinity (right shift)
higher CO2
lower pH
higher temperature
0
10
20
30
40
50
60
70
80
90
100
PO2 (mm Hg)

Metabolism in Brain



Brain- dependent on aerobic metabolism

Receives 25% of the
cardiac output

Uses 20% of total body oxygen
consumption

25% of glucose utilization (Magistretti, 2000)

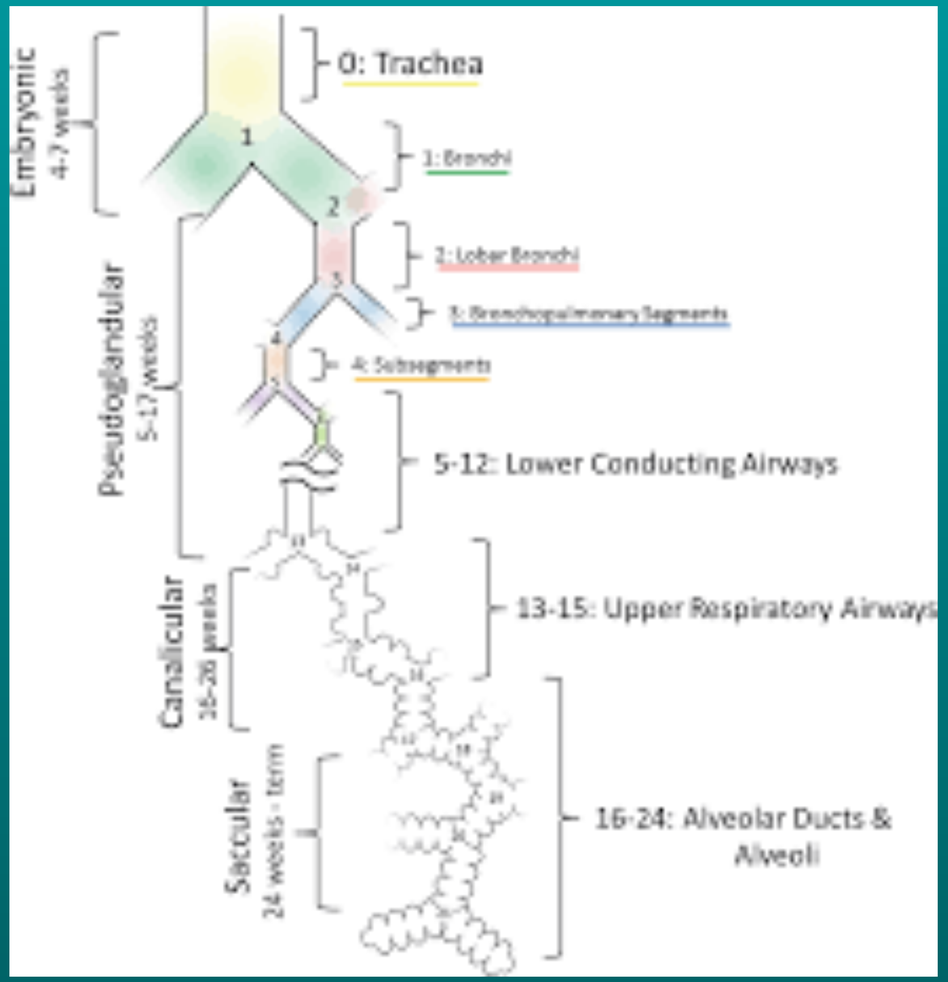
↑CO_2 and the Brain

- Vasodilation- brain's response to increased CO_2 (and decreased O2) levels
  - Linked to the H^+ central chemo-receptors…ie the stimulus to breathe
- Cerebral blood flow increases 3-4% per mmHg of PCO_2, reaching highest level when $PaCO_2$ is 10-20mmHg above normal (Brugniaux et al, 2007)
- Autoregulation becomes ineffective in hypercapnia (Czosnyka et al, 1993)

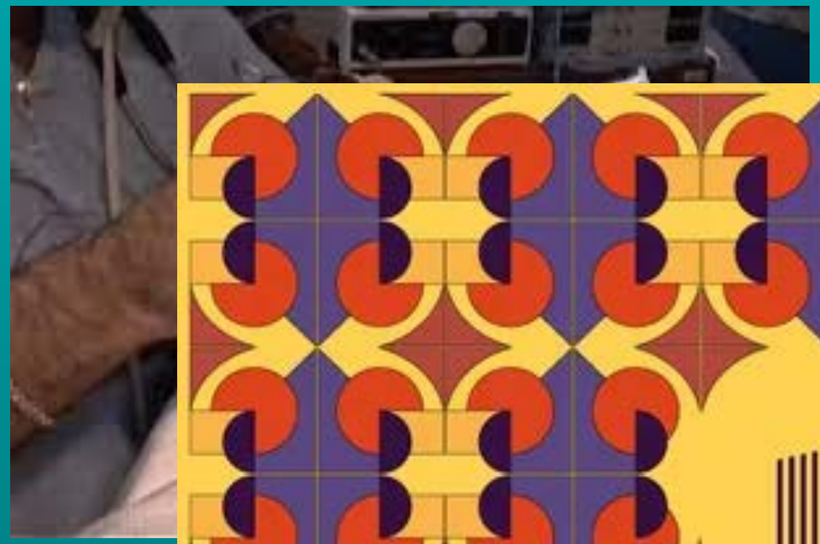
↓CO_2 and the Brain

- Hypocapnia causes cerebral vasoconstriction
  - Less Oxygen delivered to brain
  - Cerebral hypoxia leads to brain cell death

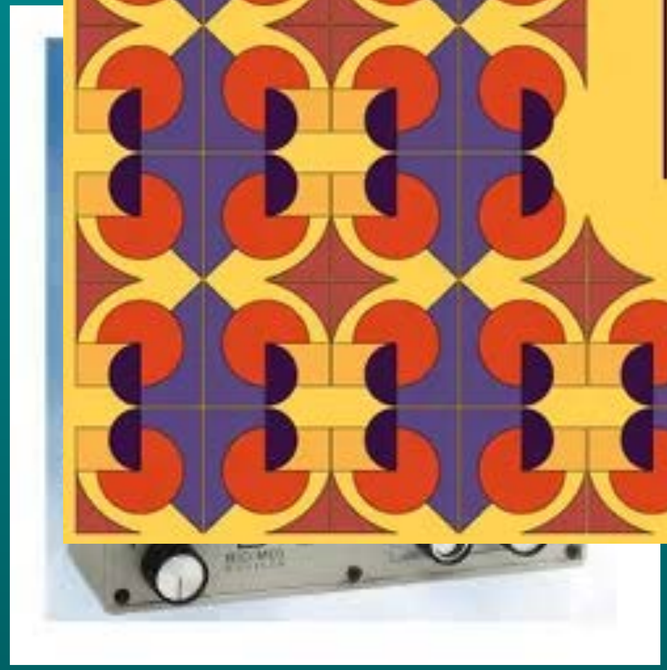
Neonates…

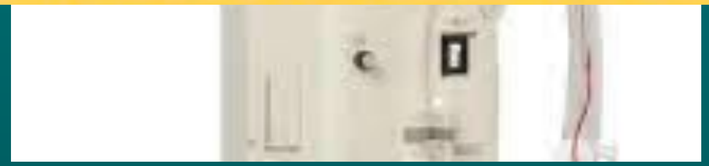


- Lungs…last system to develop and alveolar ducts only beginning to form during the last ‘trimester’



1970s





Working Definition of BPD

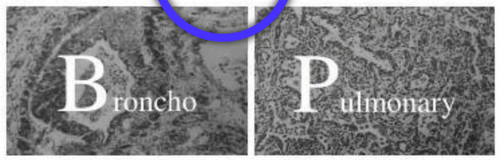
Bronchopulmonary Dysplasia

The New England Journal of Medicine

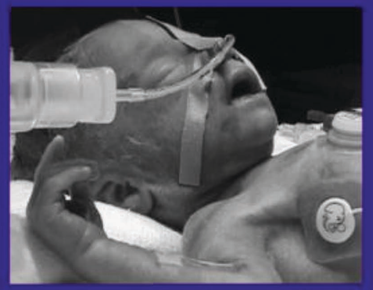
Northway WH Jr, Rosan RC, Porter DY.

Pulmonary disease following respiratory therapy of hyaline membrane disease: Bronchopulmonary Dysplasia.

N Engl J Med 1967;276:357-68



Dysplasia



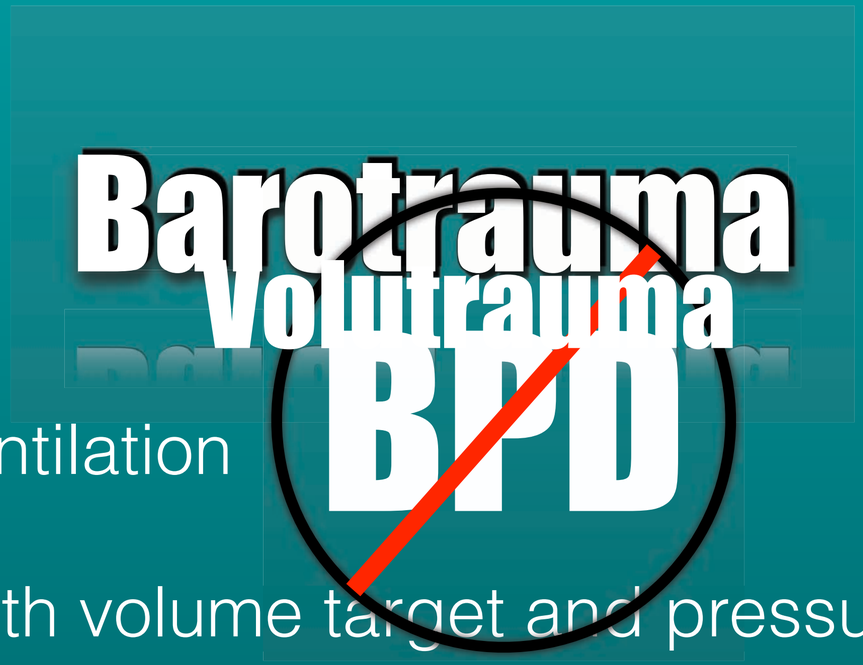
BPD Definition (Northway, 1967)

“Disease progression from acute respiratory failure with diffuse parenchymal lung disease and low lung volumes, then known as hyaline membrane disease or infant respiratory distress syndrome to chronic signs of ‘sponge-like’ or cystic lesions dispersed among heterogeneous infiltrates and areas of severe hyperinflation.”

Long Term Effects BPD / CLD

- BPD affects an estimated 10-15,000 infants each year in the US
- Can lead to:
  - Trouble feeding
  - GERD
  - Pulmonary Hypertension
  - Learning difficulties
  - Infections
  - Delayed speech

The Quest To Improve



- 4-6 ml / kg
- Synchronized ventilation
- Hybrid modes with volume target and pressure limits (Dreyfus, 1993)
- New generation ventilators

NIV

VON Vermont Oxford NETWORK

Permissive HyperCapnia

The Cochrane Results

"The review of the trials found there was not enough evidence to show the effect of permissive hypercapnia compared to routine ventilation for preterm babies. More research is needed."

CV

HFV

PHELBI Trial

362 total patients enrolled

23 weeks to 28 6/7 weeks gestation

400g - 1000g BW

High Target Group:
PCO_2 55-65 torr, days 1-3
PCO_2 60-70 torr, days 4-6
PCO_2 65-75 torr, days 7-14

Control Group:
PCO_2 40-50 torr, days 1-3
PCO_2 45-55 torr, days 4-6
PCO_2 50-60 torr, days 7-14

PHELBI Trial

The rate of bronchopulmonary dysplasia or death in the high target group did not differ significantly from the control group (p=0·18)

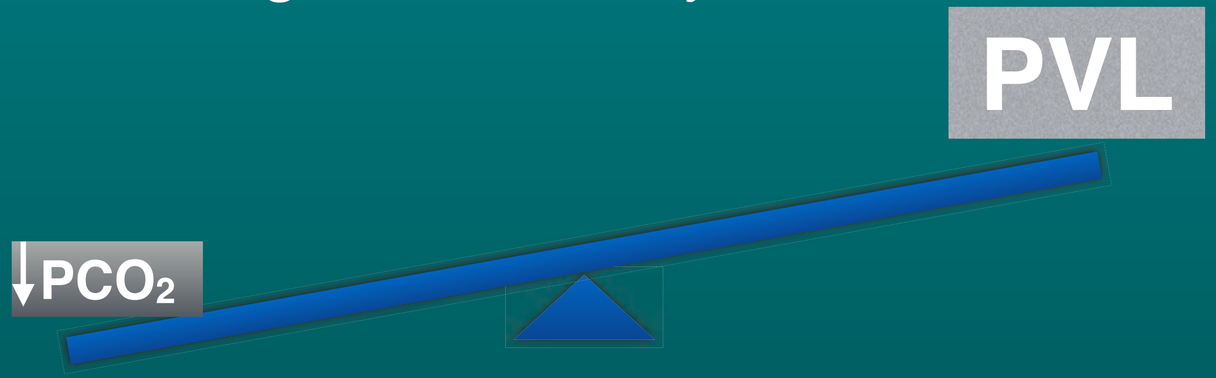
Mortality was 14% in the high target group and 11% (p=0·32) in the control group

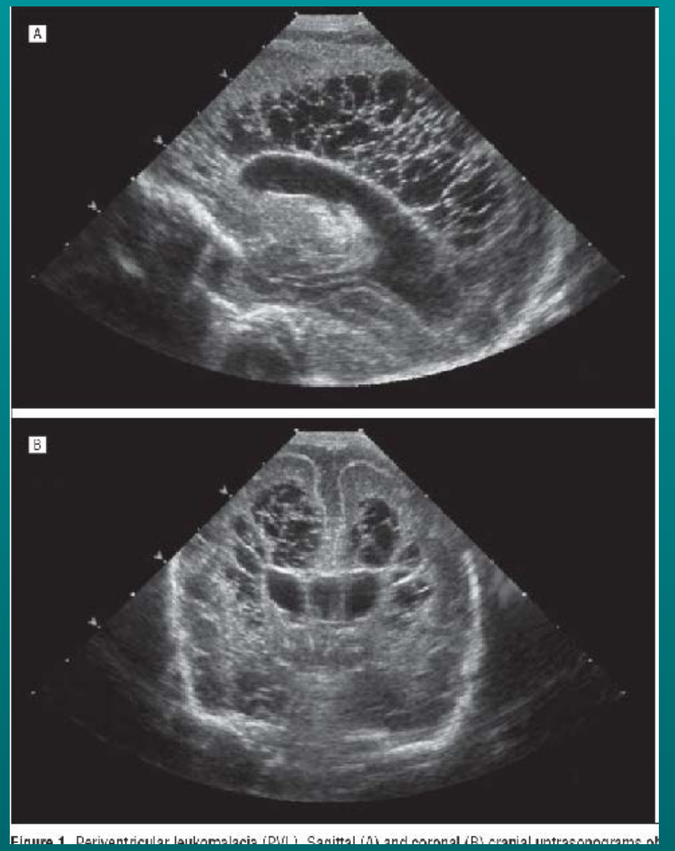
Grade 3-4 intraventricular haemorrhage was 15% and 12% (p=0·30)

Rate of severe retinopathy recorded was 11% and 14% (p=0·36)

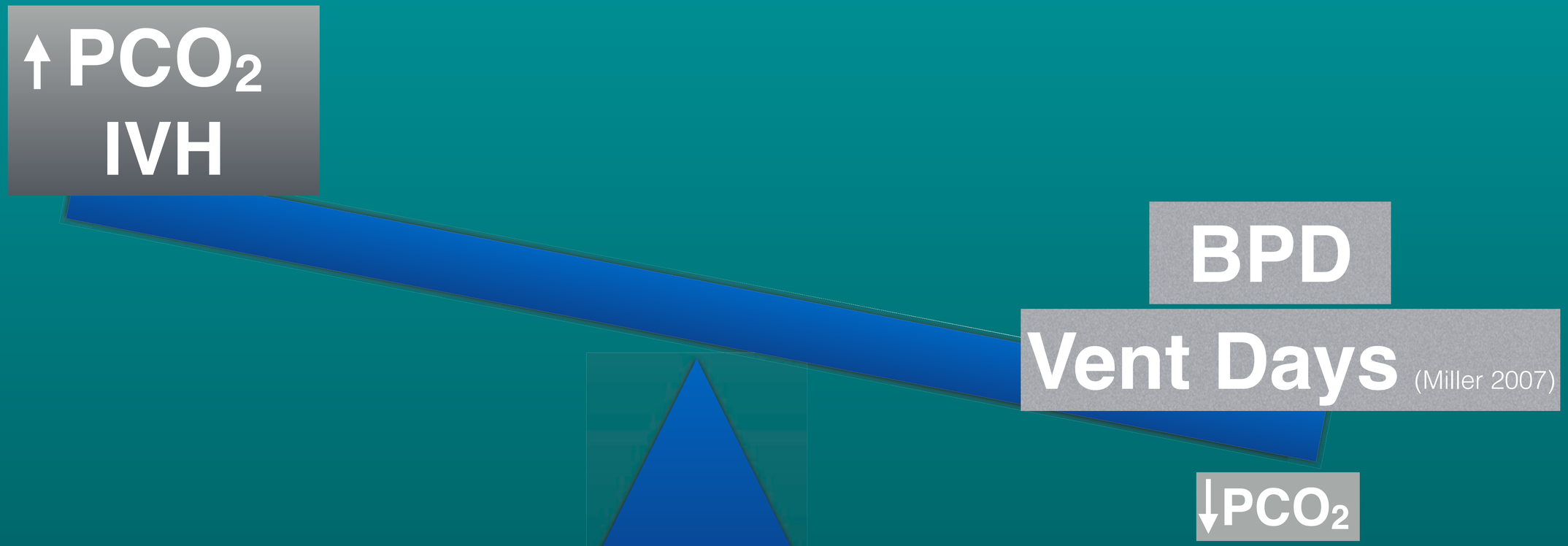
What Did We Learn??

- We became really good at ventilating babies…
- Correlation between low PCO_2 and PVL
  - White matter of the brain softens and dies, leaving fluid-filled cysts

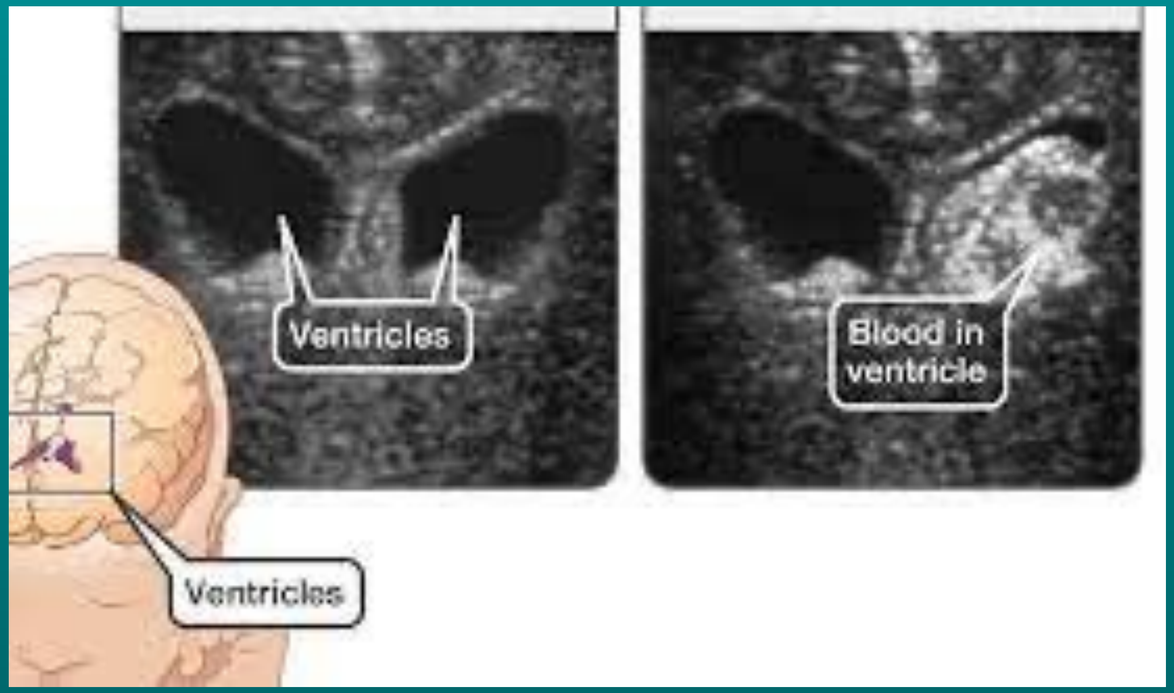


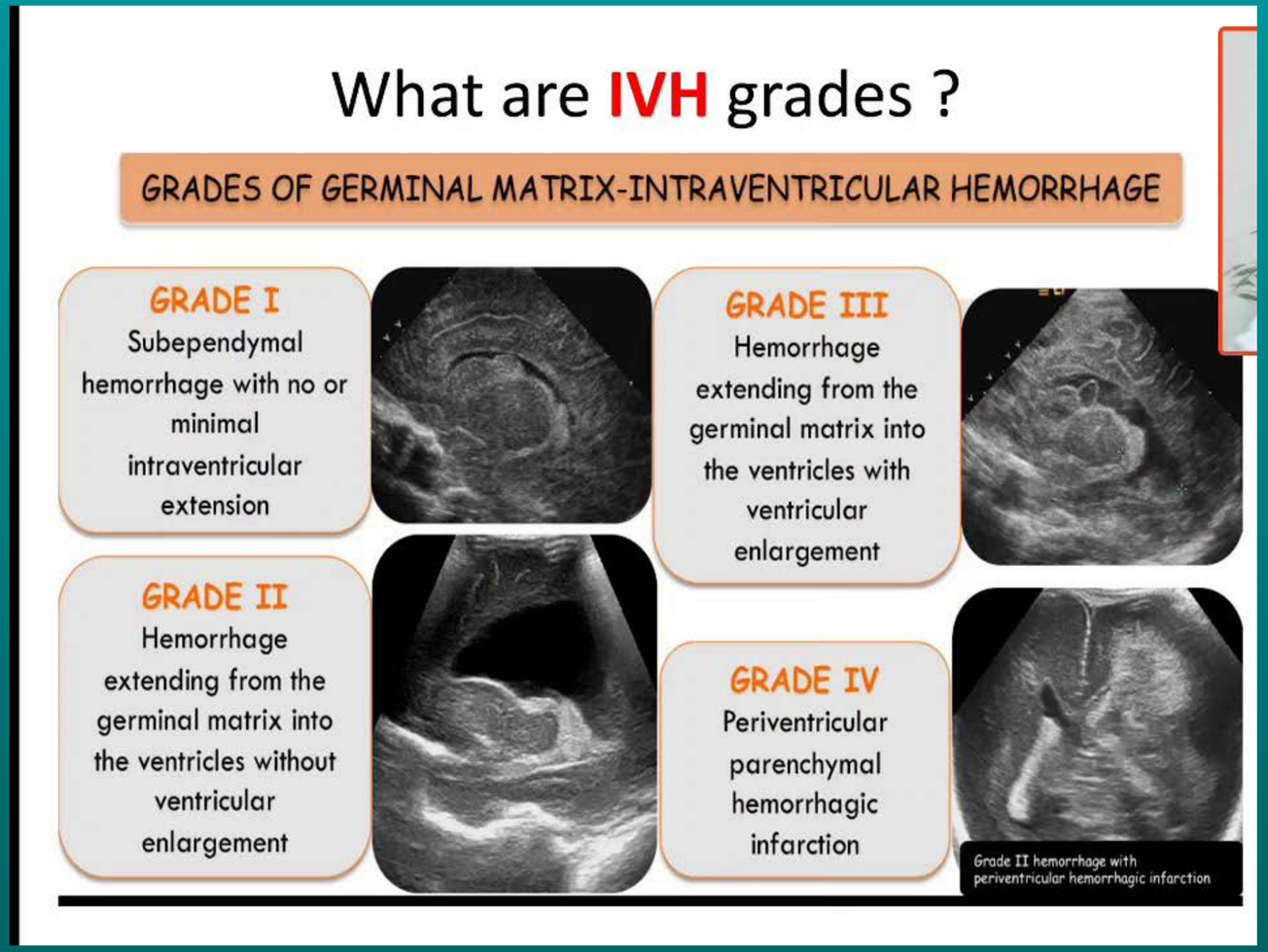


The CO_2 Pendulum



IVH


Ventricles
Blood in ventricle
Ventricles


What are IVH grades ?
GRADES OF GERMINAL MATRIX-INTRAVENTRICULAR HEMORRHAGE
GRADE I
Subependymal hemorrhage with no or minimal intraventricular extension
GRADE II
Hemorrhage extending from the germinal matrix into the ventricles without ventricular enlargement
GRADE III
Hemorrhage extending from the germinal matrix into the ventricles with ventricular enlargement
GRADE IV
Periventricular parenchymal hemorrhagic infarction
Grade II hemorrhage with periventricular hemorrhagic infarction

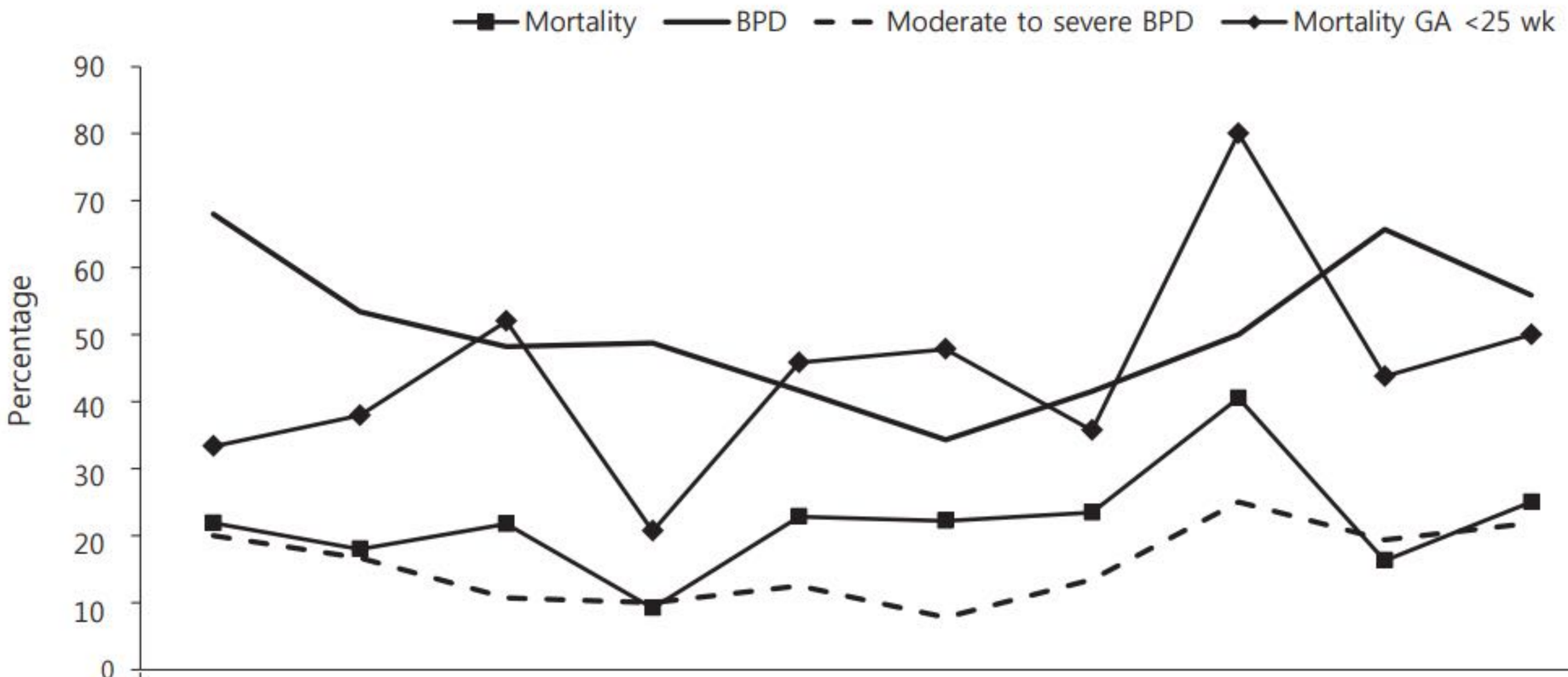
Interesting Findings

- Some research has stated that PHC may be helpful for improving neurologic outcomes simply by protecting against *hypo*-capnia (Thome 2008), thus the risk of PVL
- More widely recongnized that extreme swings in PCO_2 are to be avoided (Fabres et al, 2007 & Tsuji et al, 2000)

CO_2 Management

- Luckily, we have new and better ways to keep track of CO_2 in ‘live’ time…
  - Improvements in sensors so we don’t burn skin
- Better ventilator graphics and monitoring so we can see changes in volumes
  - Hybrid modes that adjust pressure and volume

Modes of Mechanical Ventilation	Types of Breaths	Independent Variable	Dependent Variable	Notes
Volume Assist/Control	Assisted or Controlled	Preset Tidal Volume	PIP & Plateau Pressures	Control tidal volume (lung protective) Control of minute ventilation (RR & Vt)
Pressure Assist/Control	Assisted or Controlled	Preset Pressure	Adequate Tidal Volumes (not too high or low)	Patient comfort (decelerating flow), Control over delivered pressures (avoid barotrauma)
Pressure Support (PS)	Supported	Preset Pressure	Adequate Tidal Volumes (not too high or low)	Patient comfort Allows patient to maintain respiratory work effort
Synchronized Intermittent Mandatory Ventilation (SIMV) + PS	Assisted, Controlled or Supported	PC-SIMV=Preset Pressure VC-SIMV=Preset Tidal Volume	PC-SIMV=Adequate Tidal Volumes (not too high or low) VC-SIMV=PIP & Plateau Pressures	Can get benefits of supported breaths (PS), but still ensure minimum number of mandatory breaths (controlled or assisted)
Pressure Regulated Volume Control (PRVC)	Assisted or Controlled	Preset Tidal Volume	PIP & Plateau Pressures	Control Minute Ventilation Control Vt, Patient comfort (decelerating flow), Can limit high pressures (avoid barotrauma)



	Birth year									
	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Mortality (%)	21.9	18.0	21.7	9.2	22.8	22.2	23.4	40.5	16.3	25.0
BPD (%)	68.0	53.4	48.2	48.8	41.7	34.3	41.5	50.0	65.7	55.9
Moderate to severe BPD(%)	20.0	16.7	10.7	10.0	12.5	7.8	13.5	25.0	19.4	21.9
Mortality GA <25 wk (%)	33.3	37.9	52.0	20.7	45.8	47.8	35.7	80.0	43.8	50.0

The ‘New’ BPD

- “With the improvement in neonatal care and the introduction of gentler ventilation strategies, the use of antenatal steroids and surfactant therapy, the pathophysiology of lung disease in premature infants changed, leading to major differences on the histological level, which in turn changed the management strategies of BPD.” (Ibrahim and Bhandari, 2018)

Redefining BPD

	'Old' BPD	*'New' BPD*
Characteristic	Northway *et al.*[1]	Jobe and Bancalari[5]
Gestational age	32 Weeks of gestation	24–26 Weeks of gestation
Birth weight (average)	1900 g	600 g
Infants at risk	More mature	Extremely low gestational age
Airway injury	Severe	Mild to none
Fibrosis	Severe	Minimal
Alveoli	Well developed in regions without fibrosis	Uniformly arrested development
Causes	Oxygen toxicity, mechanical ventilation	Interference with development

Abbreviation: BPD, bronchopulmonary dysplasia.
Clinical and histological characteristics and probable causes of patients diagnosed with old and new BPD.

Old BPD	New BPD
Larger preterm infants	Extremely premature infants
High ventilation and oxygen needs	Modest ventilation and oxygen needs
Severe large airway injury	Minimal large airway disease
Interstitial and alveolar edema	Arrested alveolarization
Extensive small airway disease with alternating areas of overinflation and fibrosis	Minimal small airway disease with less inflammation and fibrosis
Pulmonary artery muscularization	Fewer and abnormal pulmonary arteries

The ‘New’ BPD…are these babies just sicker?

Through all the advances in Neonatology we have had an increase in the absolute number of survivors with CLD, but the overall incidence has remain unchanged (Varughese et al, 2002)

Some evidence pointing to moderate PHC as beneficial in decreasing morbidity in infants > 1500g

Hypercapnia is associated with greater disease severity which likely contributes to worse outcomes
(Thome et al, 2018)

Infants most vulnerable-

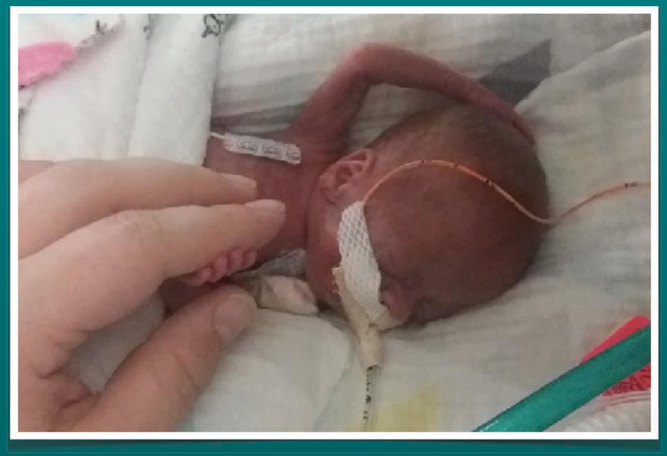
Lowest GA

Male

Post-Natal Steroids

Outcome	Time of initiation of corticosteroid course		
	Early	Moderately early	Delayed
BPD	↓	↓	↓
Death or BPD	↓	↓	↓
Failure to extubate	↓	↓	↓
Mortality at 28 days	No effect	↓	Not applicable
Mortality by discharge	No effect	No effect	No effect
Neurodevelopment	Worse	No different (?)	↑ CP, ↓ mortality

BPD, bronchopulmonary dysplasia; CP, cerebral palsy.
Adapted from Halliday *et al.*[9–11]




hello
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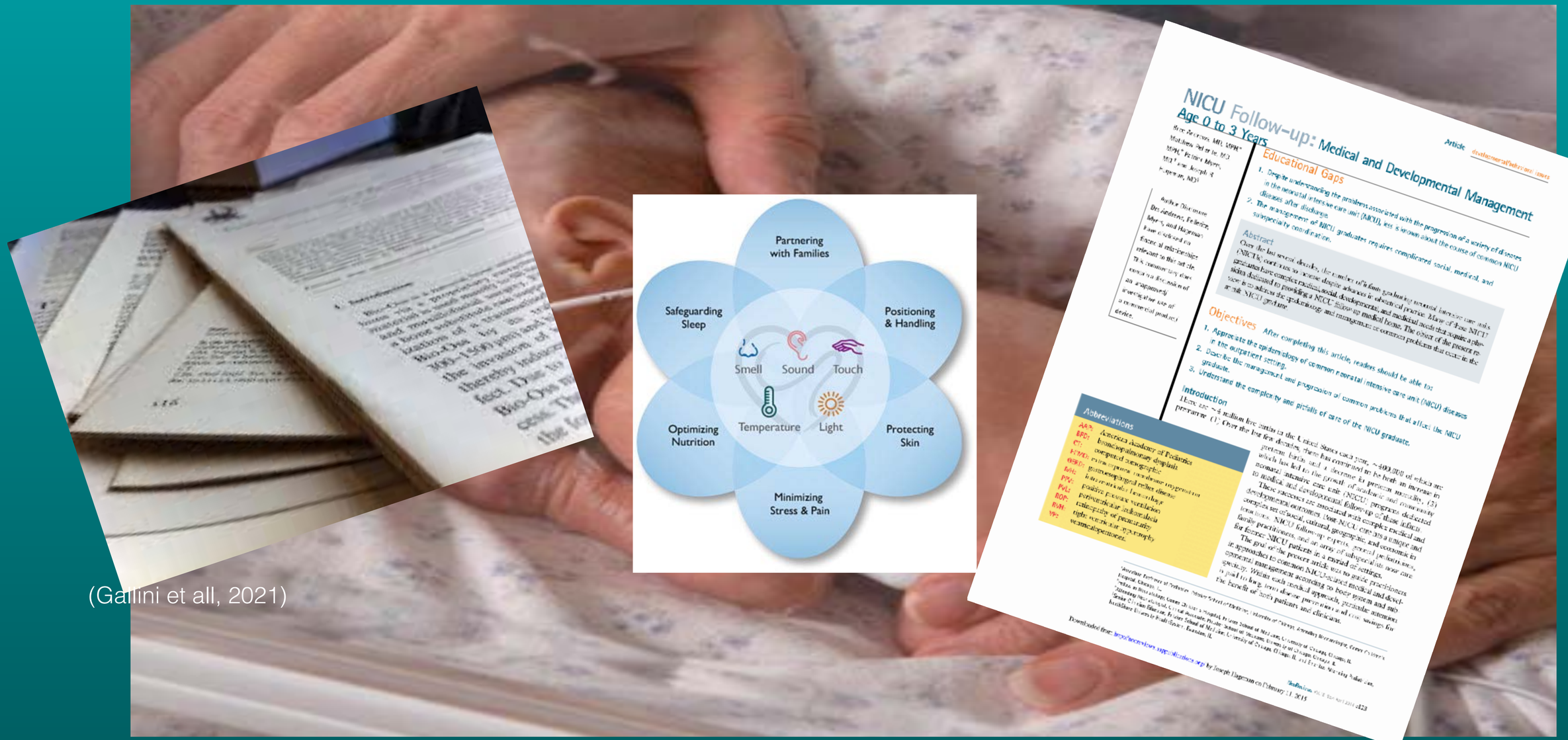
WORLD
RECORDS
2021


nage credit: guinnessworldrecords.com

BPD and Neurological Development



(Gallini et all, 2021)

According to the CDC, raising a child with Cerebral Palsy costs an average of $45,000 per year (CDC, Oct 2020)

Health Care and Societal Costs of Bronchopulmonary Dysplasia

(Lapcharoensap, 2018)

16x

RSV

Study Examines How Premature Babies Develop Brain Injuries

A new report from Stanford sheds light on this issue, which can affect millions of prematurely born babies worldwide.

By Sintia Radu

May 8, 2019, at 5:13 p.m.


stay tuned...
More to Come!

And Other Interesting Findings:

- Published in Pediatric Research in 2010
- Systemic reviews and meta-analyses of long term ND impairment of surviving preterm babies

2.7% moderate or severe

4.4% mild

90% with NO impairment

Conclusions

- Finding the ‘right’ PCO2 is a delicate balance
- There is no overwhelming evidence in support of or against
- Neonatology continues to defy the odds of survival…we must always be congnizant of the ‘cost’ of our efforts

Family

RT

Neonatology

Nutrition

Family

PT / OT

Speech Therapy

Case Mgmt

Nursing


MIRACLE

Thank you!