Could We Decrease The Incidence Of BPD?

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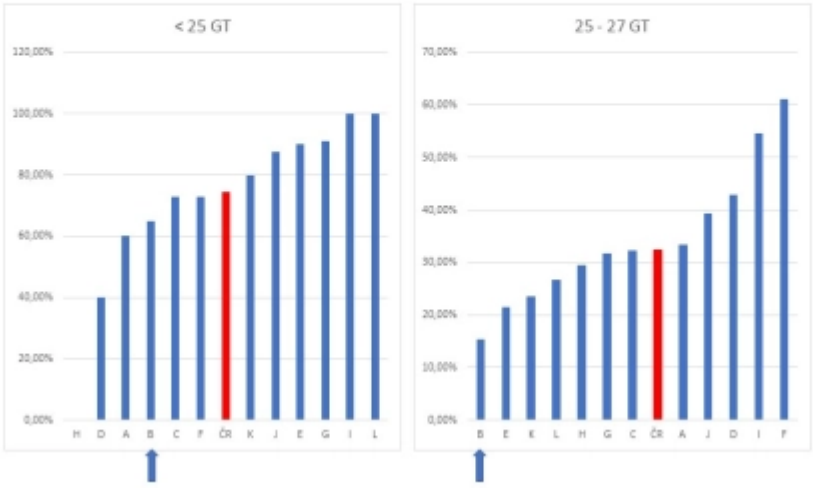
Richard Plavka, MD., Ph.D., Professor

CZECH REPUBLIC
DEVELOPMENT COOPERATION

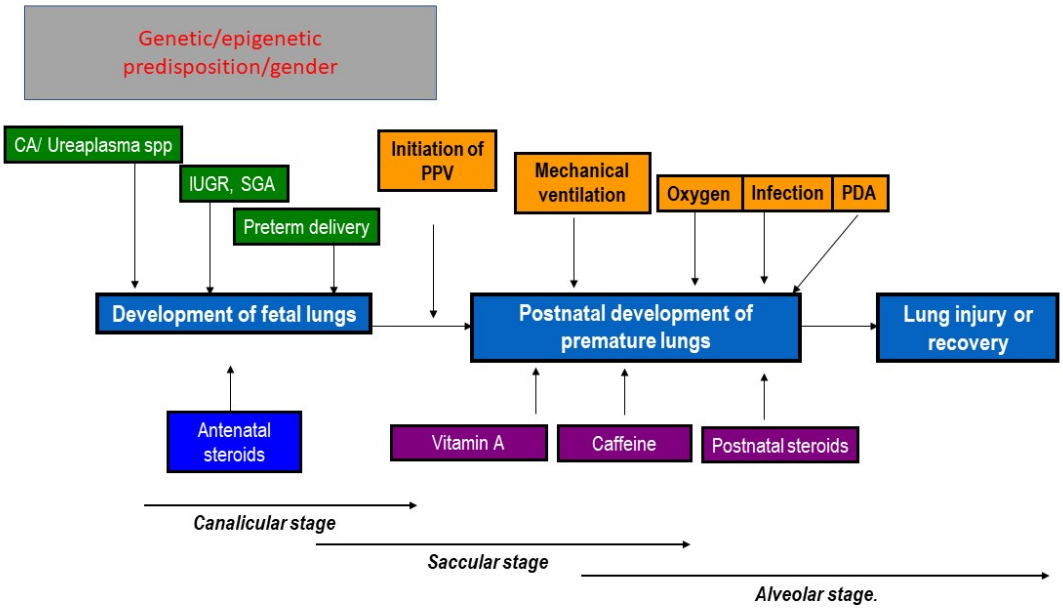
BPD

Czech Neonatal Network

Combined outcome
Moderate and severe BPD/Death
12 PCIP in 2017

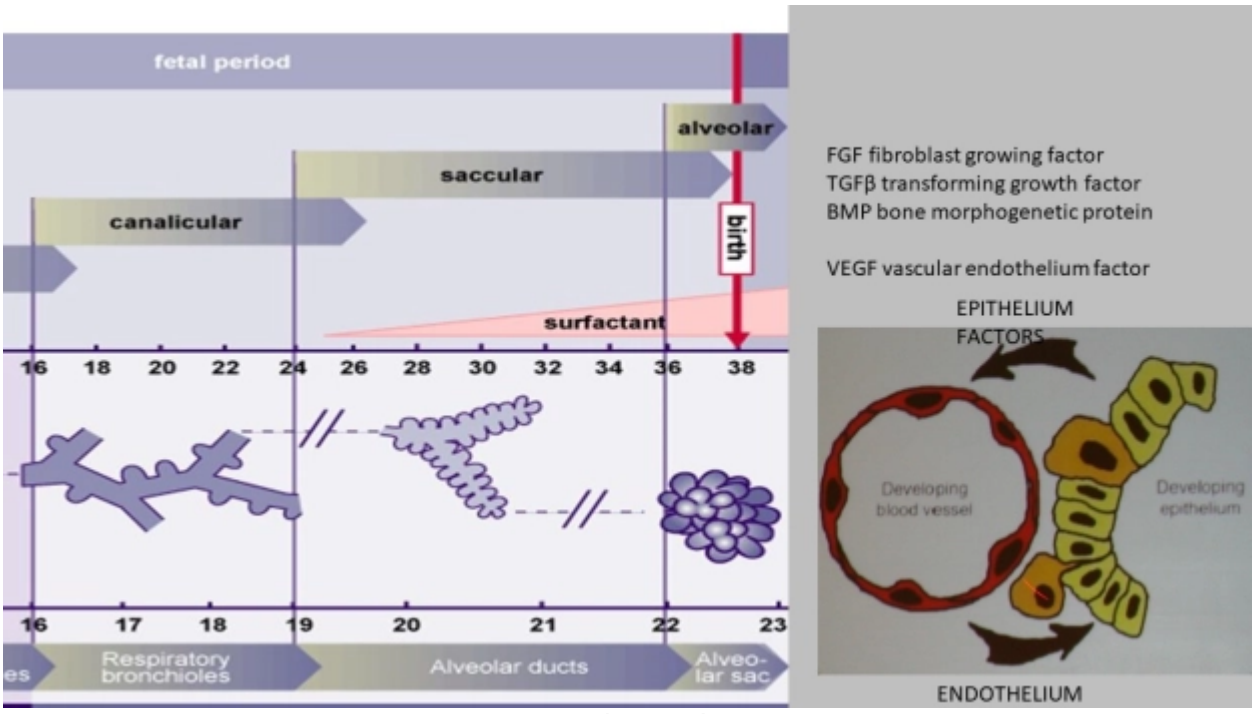


BPD



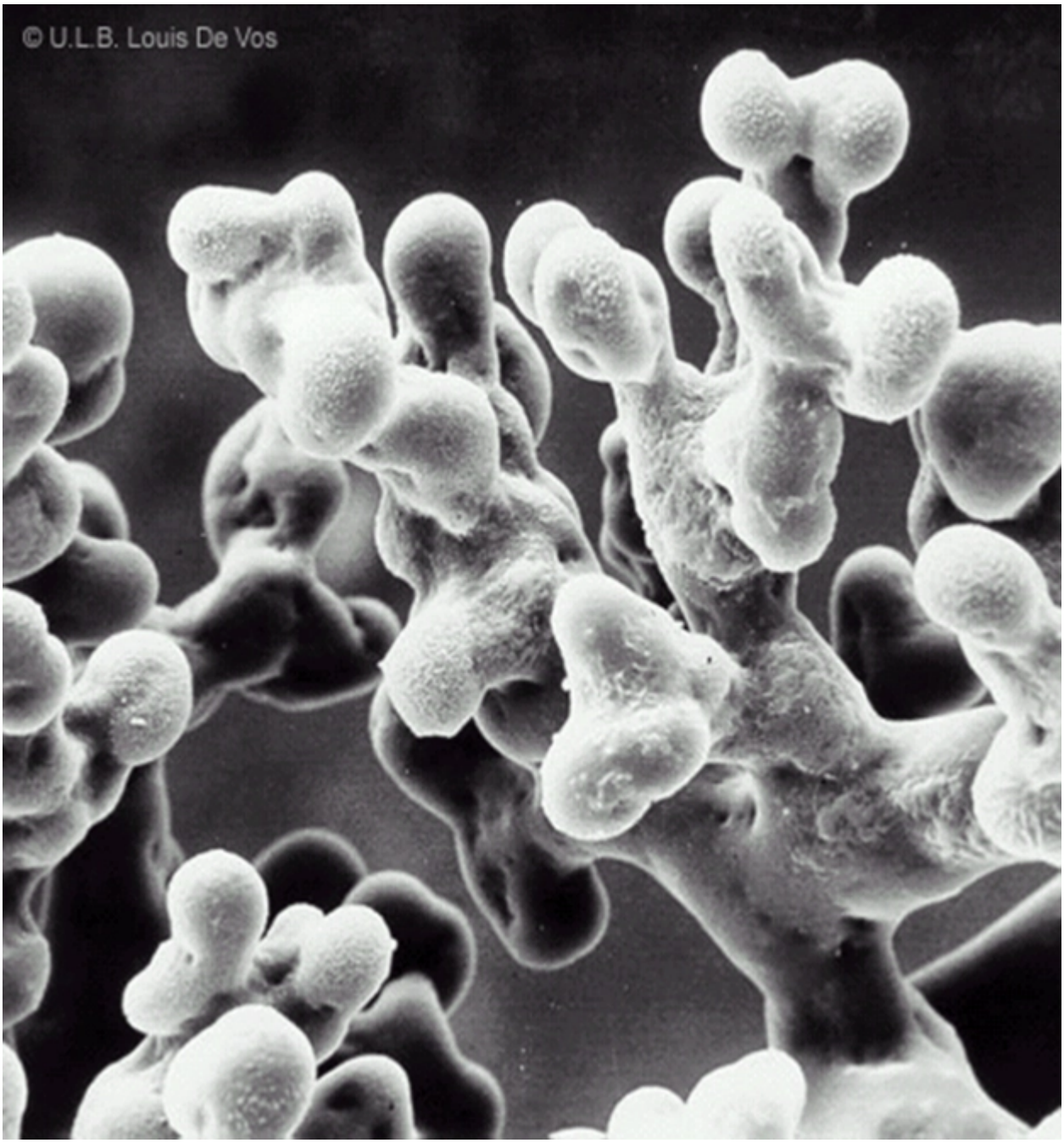
Modified from Jobe A

Genetic



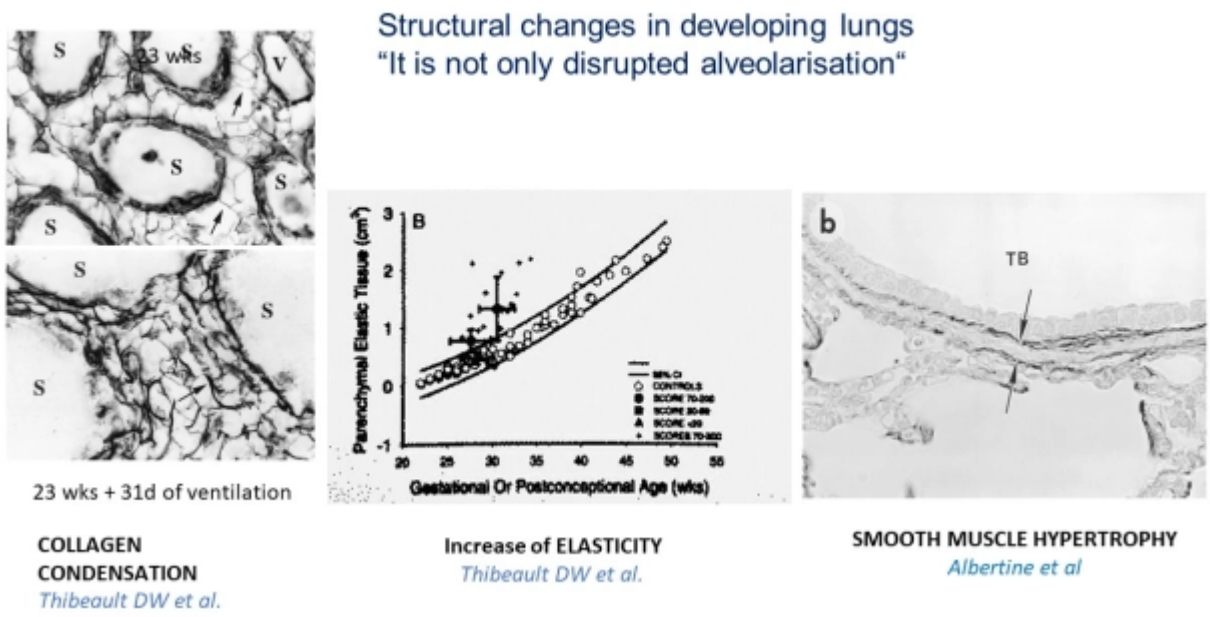
Fetal period

Premature lung in canalicular-saccular stage



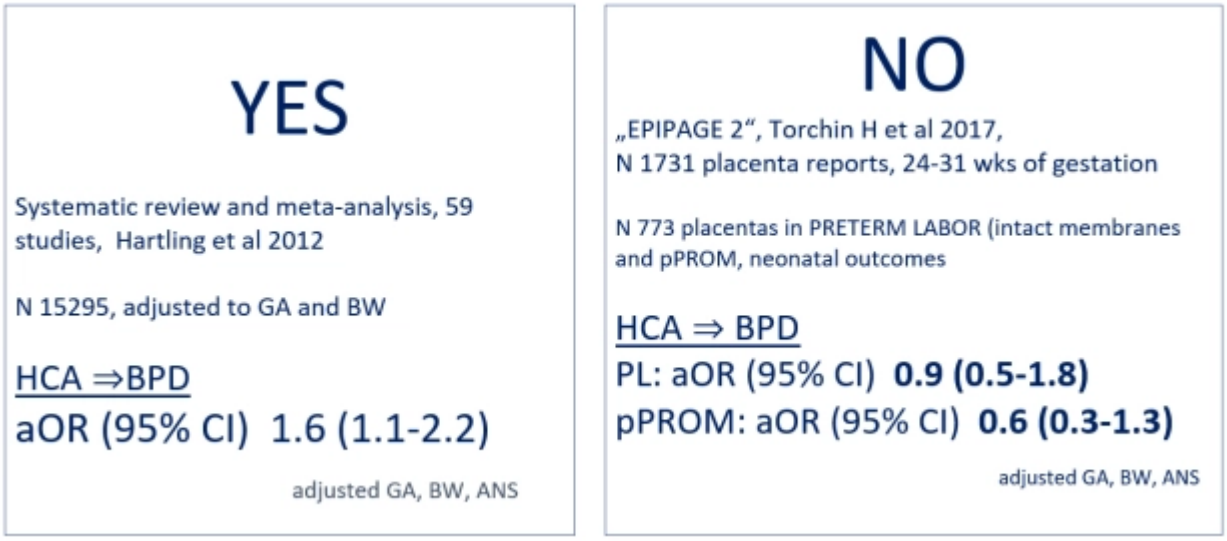
Courtesy of Professor Louis De Vos

http://www.ulb.ac.be/sciences/biodic/index.html



Alveolarisation

Chorioamnionitis (HCA) a BPD



BPD

Chorioamnionitis (HCA) a BPD

NICHD data, van Marter L et al 2003
193 of preterm infants with BW < 1500g , 1:1 matched controls without BPD

HCA OR (95% CI) 0.2 (0.15-0.31)

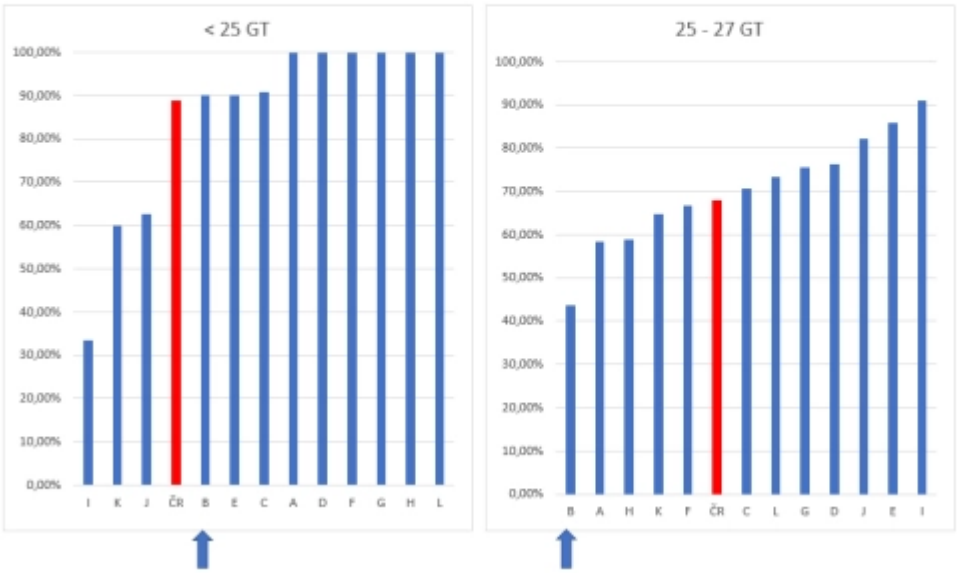
HCA + MV > 7days OR (95% CI) 3.2 (0.9-0.11)

HCA + postnatal sepsis OR (95% CI) 2.9 (1.1-7.4)

HCA

Czech Neonatal Network

Mechanical ventilation
12 PCIP in 2017



Ventilation

JAMA | Original Investigation

Association of Noninvasive Ventilation Strategies With Mortality and Bronchopulmonary Dysplasia Among Preterm Infants
A Systematic Review and Meta-analysis

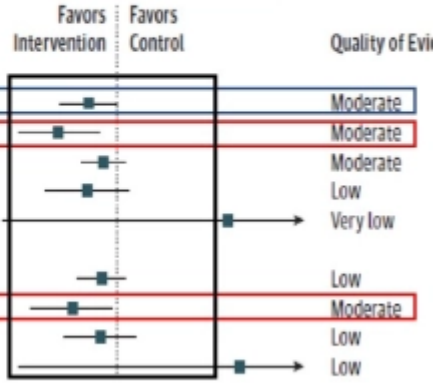
Tetsuya Isayama, MD, MSc; Hiroko Iwami, MD; Sarah McDonald, MD, FRCSC, MSc; Joseph Beyene, PhD

PREVENCE

30 RTC, 5598 infants <33 wks, within 24hrs
Primary outcome: Death or BPD

ÚMRTÍ anebo BRONCHOPULMONÁLNÍ DYSPLASIE

Source	No. of Infants	No. of Trials	Network Absolute RD per 1000 (95% CI)	Network OR (95% CI)	Quality of Evi
MV (control)					
INSURE	419	2	83 Fewer (5 fewer-160 fewer)[a]	0.71 (0.50-0.98)	Moderate
LISA	189	1	164 Fewer (57 fewer-253 fewer)[a]	0.49 (0.30-0.79)	Moderate
Nasal CPAP	2085	3	40 Fewer (24 more-99 fewer)	0.85 (0.66-1.10)	Moderate
NPPV			86 Fewer (30 more-194 fewer)	0.70 (0.42-1.13)	Low
LMA			311 More (280 fewer-539 more)	3.90 (0.25-119.88)	Very low
Nasal CPAP (control)					
INSURE	1186	7	41 Fewer (22 more-96 fewer)	0.83 (0.63-1.10)	Low
LISA			112 Fewer (16 fewer-190 fewer)[a]	0.58 (0.35-0.93)[a]	Moderate
NPPV	775	5	44 Fewer (50 more-127 fewer)	0.82 (0.53-1.24)	Low
LMA			362 More (210 fewer-639 fewer)	4.58 (0.30-141.08)	Low



Ventilation

Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants

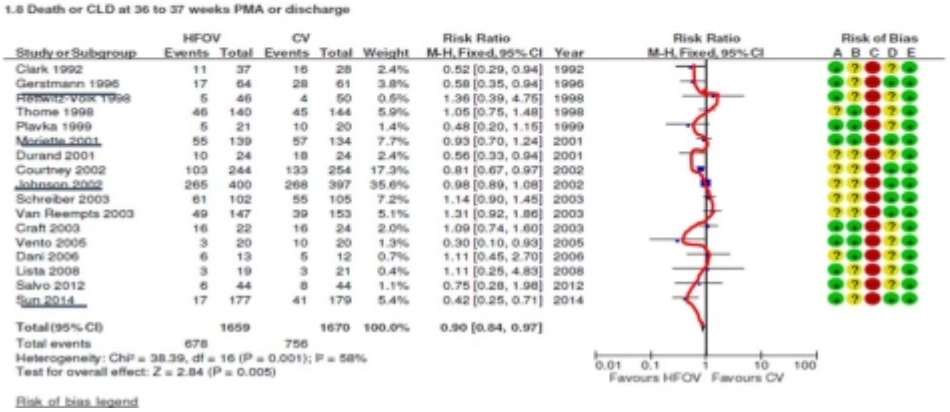
Filip Cools[1], Martin Offringa[2], Lisa M Askie[3]

Cochrane database Syst rev 2015

Decrease the death or BPD, RR 0.90 (0.84; 0.97)

Inconsistent results across studies

Benefits may be attenuated by higher risk of AIR –Leak syndrom



Ventilation

Lung function and neurologic outcomes slightly favouring HFOV against CV-PLV.

PROVO (6-7years)

- **HFOV cohort had a better lung functions**, $p < 0.05$. *Gerstmann D et al 2001*

MRCT in France (2 years)

- **HFOV was associated with a better neurologic outcome** (↓DMO,$p< 0.004$) despite more IVH. *Truffert P et al, PAS 2007*

UKOS (adolescents between 11-14 years)

- HFOV cohort had a better tests evaluating function of small airways (forsed exhalation, FEV, vital capacita of lungs) *Zivanovic S et al NEJM 2014*

Chinese MRCT (18 months)

- HFOV had **less moderate/severe neurologic impairment 18 months** ($p < 0.03$). *Sun H et al Respir Care 2014*

Cochrane Library
Cochrane Database of Systematic Reviews

Volume-targeted versus pressure-limited ventilation in neonates (Review)

Klingenberg C, Wheeler KI, McCallion N, Morley CJ, Davis PG

Cochrane Database of Systematic Reviews 2017

20 RCTs, 16 (977 infants) parallel trials and 4 (88 infants) cross-over trials

	RR	95% CI	NNT
Death or BPD	**0.73**	0.59 – 0.89	8
IVH	**0.53**	0.37 -0.77	11
IVH/cPVL	**0.47**	0.28 – 0.80	11
Hypocarbia	**0.49**	0.33 – 0.72	3
Pneumothorax	**0.52**	0.31 – 0.87	20

Ventilation

Systemic corticosteroids decrease the incidence of BPD

- Timing of administration: ≤ 7 days vs > 7 days
- Choice of drug: Dexamethasone vs Hydrocortison
- Cumulative dose
- When benefits overweight harmfuls

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Early (~ 8 days) systemic postnatal corticosteroids for prevention of bronchopulmonary dysplasia in preterm infants (Review)

32 RCTs, 4395 infants

Doyle LW, Cheong JL, Ehrenkranz RA, Halliday HL
Cochrane Database of Systematic Reviews 2017, Issue 10. Art. No.: CD001146.

Primary outcome				
2 Death or BPD at 36 weeks' postmenstrual age	25	3960	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.83, 0.93]
2.1 Dexamethasone	16	2581	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.80, 0.94]
2.2 Hydrocortisone	9	1379	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.82, 0.99]
11 Cerebral palsy	13	1973	Risk Ratio (IV, Fixed, 95% CI)	1.42 [1.06, 1.91]
11.1 Dexamethasone	7	921	Risk Ratio (IV, Fixed, 95% CI)	1.75 [1.20, 2.55]
11.2 Hydrocortisone	6	1052	Risk Ratio (IV, Fixed, 95% CI)	1.05 [0.66, 1.66]

Early postnatal steroids to prevent BPD do not overweight risk of neurodevelopmental impairments (Dexamethasone). Early administration Hydrocortisone may decrease short-term morbidity without negative effects on neurodevelopment.

Corticosteroids

Effect of early low-dose hydrocortisone on survival without bronchopulmonary dysplasia in extremely preterm infants (PREMILOC): a double-blind, placebo-controlled, multicentre, randomised trial

NNT 12

Olivier Baud, Laure Maury, Florence Lebail, Duksha Ramful, Fatima El Moussawi, Claire Nicaise, Véronique Zupan-Simunek, Anne Coursol, Alain Beuchée, Pascal Bolot, Pierre Andrini, Damir Mohamed, Corinne Alberti, for the PREMILOC trial study group*

Double blind MC RCT, ELGA infants < 28wks, (24-25wks/26-27wks subgroups); **Hydrocortisone 2 x 0.5mg a 12h /7days + 0.5mg a 24hrs/3days; CD 8.5mg/kg**

	Hydrocortison N 255	Placebo N 266		P value
Primary outcome assessed at 36 weeks PMA*				
Survival without BPD	153 (60%)	136 (51%)	1·48 (1·02 to 2·16)	0·04
Secondary outcomes				
Extubated patients on day 10*	152 (60%)	116 (44%)	2·07 (1·42 to 3·02); 0·15 (0·07 to 0·23)	0·0002
Weaning from any ventilatory support at 36 weeks PMA†	170 (67%)	160 (60%)	1·15 (0·92 to 1·45)	0·22
Weaning from any supplemental oxygen at 36 weeks PMA†	139 (55%)	119 (45%)	1·31 (1·02 to 1·68)	0·04
PDA ligation†	37 (15%)	55 (21%)	0·63 (0·42 to 0·97)	0·03
Late Onset Sepsis (Infants 24-25wks)	30(40%)	21(23%)	1.87 (1.1-3.2),	0.02

Hydrocortisone

Corticosteroids for the prevention of bronchopulmonary dysplasia in preterm infants: a network meta-analysis

Zeng L, *et al. Arch Dis Child Fetal Neonatal Ed* 2018;**0**:F1–F6.

47 RCT, 6747 infants

BPD at 36 weeks´ PMA (primary outcome)

~~Dexamethasone (high dose)~~	6/659	0.34 (0.20 to 0.57)
Dexamethasone (low dose)	13/2180	0.66 (0.54 to 0.80)
Hydrocortisone	5/1022	0.80 (0.61 to 1.05)

CEREBRAL PALSY

~~Dexamethasone (high dose)~~	5/307	2.30 (1.22 to 4.36)
Dexamethasone (low dose)	3/245	0.61 (0.28 to 1.34)
Hydrocortisone	3/334	1.09 (0.57 to 2.11)

Dexamethasone is a more effective to decrease the rate of BPD than Hydrocortisone and in a low dose course is still more effective without higher risk of CP.

Corticosteroids

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 15, 2015 VOL. 373 NO. 16

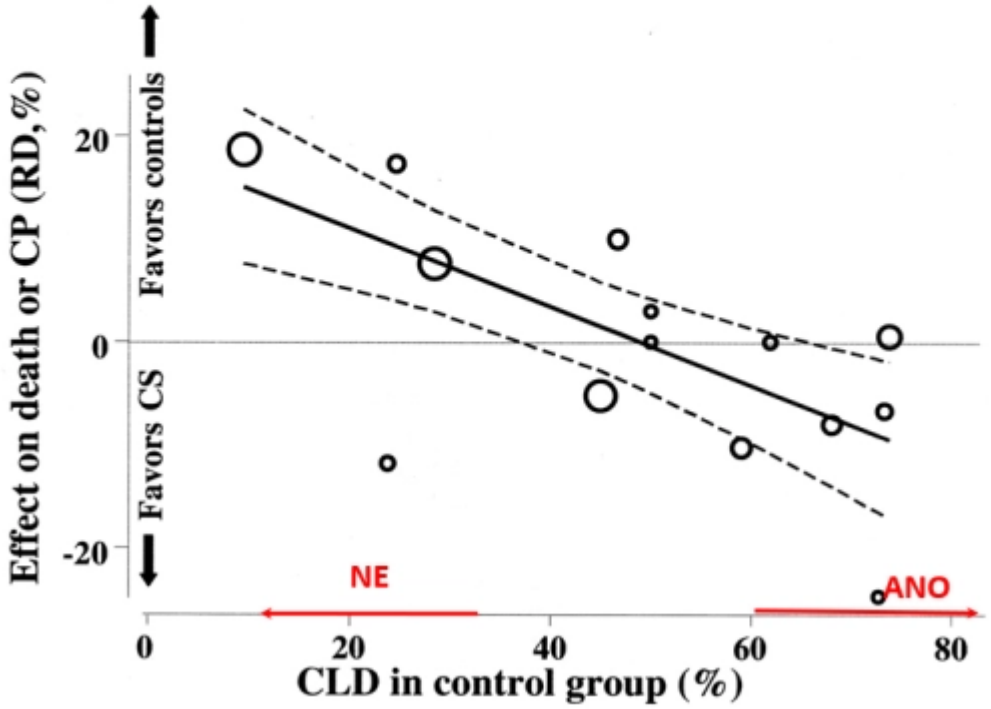
Early Inhaled Budesonide for the Prevention of Bronchopulmonary Dysplasia

Dirk Bassler, M.D., Richard Plavka, M.D., Ph.D., Eric S. Shinwell, M.D., Mikko Hallman, M.D., Ph.D., Pierre-Henri Jarreau, M.D., Ph.D., Virgilio Carnielli, M.D., Johannes N. Van den Anker, M.D., Ph.D., Christoph Meisner, Ph.D., Corinna Engel, Ph.D., Matthias Schwab, M.D., Henry L. Halliday, M.D., and Christian F. Poets, M.D., for the NEUROSIS Trial Group*

Outcome	Budesonide Group no./ total no. (%)	Placebo Group no./total no. (%)	Relative risk	P Value	Odds Ratio** (95% CI)
Primary outcome					
Death at <36 wk of postmenstrual age or BPD* **	**175/437 (40.0)**	**194/419 (46.3)**	**0.86 (0.74–1.00)**	**0.053**	**0.71 (0.53–0.97)**
*Components of primary outcome*risk* (95% CI					
Death at <36 wk of postmenstrual age	74/437 (16.9)	57/419 (13.6)	1.24 (0.90–1.71)	0.17	1.39 (0.89–2.18)
BPD* **	**101/363 (27.8)**	**138****/363 (38.0)**	**0.73 (0.59–0.90)**	**0.004**	**0.61 (0.44–0.85)**

Dysplasia

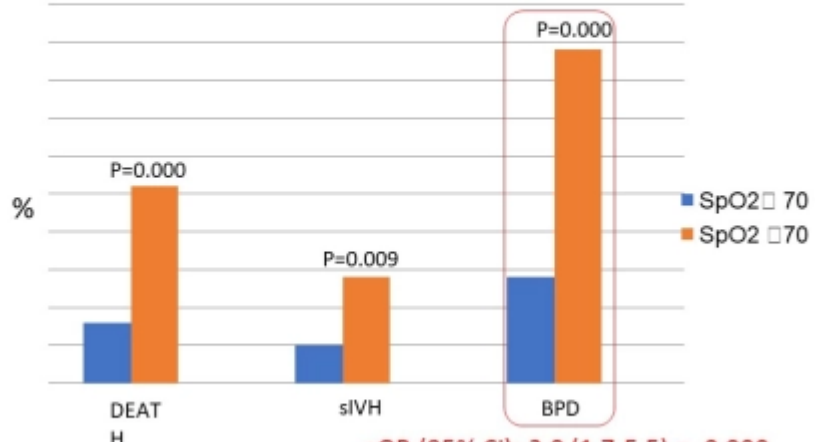
14 RCT , n=1721, BPD vs CP and Death
KD: median (IQR) 3.0mg/kg (1.1-5.0)
BPD_{36} in control group, median (IQR) 50% (28-69)



Doyle, L. W. et al. Pediatrics 2005;115:655-661

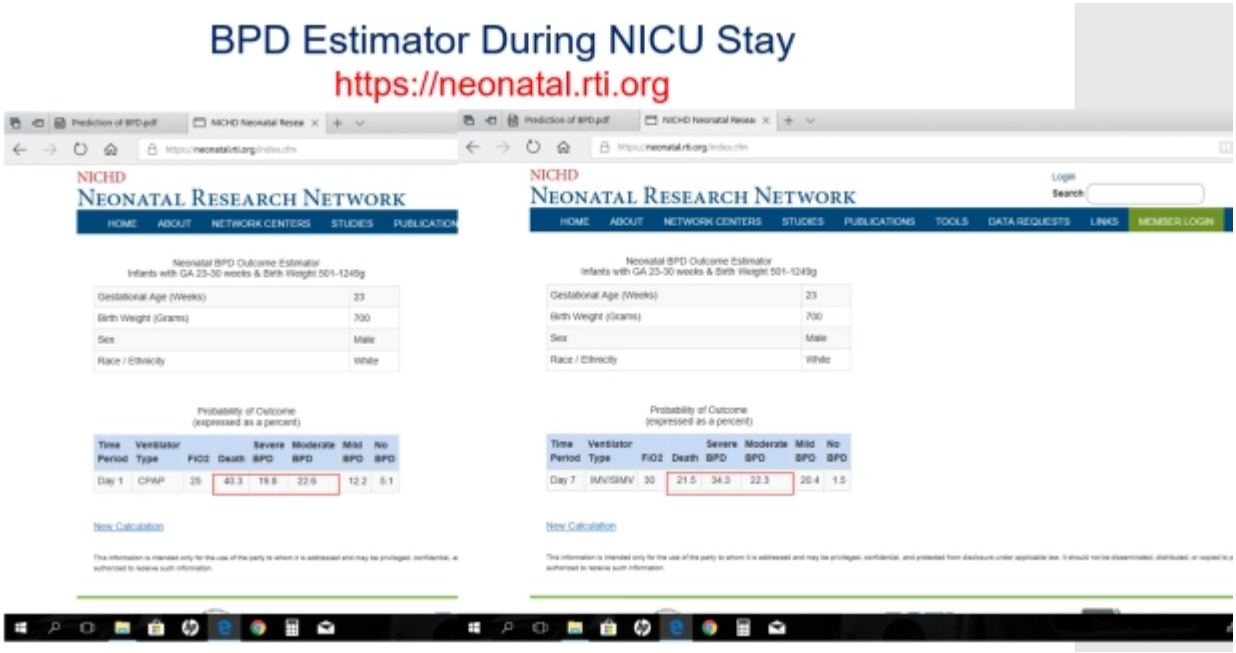
Hypoxemic ELGAI At Five Minutes Of Life Died Or Suffered From SIVH and BPD More Frequently Than Normoxemia Ones

Hypoxemia = SpO2 < 70%



aOR (95% CI): 3.0 (1.7-5.5) p=0.000
Adjusted GA, BW, ANS, intubation, bradycardia

Hypoxemic



NICU

Ureaplasma spp. Increase the risk of BPD

Association Between Pulmonary Ureaplasma Colonization and Bronchopulmonary Dysplasia in Preterm Infants

Updated Systematic Review and Meta-analysis

N 2206, 39 studies, moderate –good quality (22/BPD28, 8/BPD36 and 9/both)

BPD28 OR (95% CI) = 2.22 (1.42-3.47)

BPD36 OR (95% CI) = 3.04 (2.41-3.83)

Lowe J et al. The Pediatric Infectious Disease Journal • Volume 33, Number 7, July 2014

Characteristics of premature who lungs are colonized by Ureaplasma spp.
Extreme prematurity

- The frequency of RT colonization is inversely related to gestational age
- Immaturity of immune defence system – insufficiency SP A a low expression of TLR

PPROM – vertical transmission

Frequent signs of FIRS

- Histologic chorioamnionitis and fetal vasculitis
- Leucocytosis after delivery

Mild RDS in the beginning

Early signs of evolving CLD (X ray)
Viscardi RM and Kallapur SG Clin Perinatol 2015; 42(4): 719-738

Caffeine decreases BPD and improves lung functions!
Caffeine citrate vs Placebo: OR (95CI); **0.64 (0.52 -0.78)** *Schmidt B et al N Engl J Med 2006*

Better forced vital capacity (FVC < 5. percentile) (11years): OR (95CI); **0.31 (0.12-0.77)**
Doyle LW et al Am J Respir Crit Care Med 2017
Early (< 3days) vs Late Caffeine: OR (95CI); **0.74 (0.69-0.80)** *Davis PG et al J Pediatr 2010*
Early < 2 days vs late caffeine: OR (95CI); **0.81 (0.62-0.89)** *Lodha A et al JAMA Pediatr 2015*

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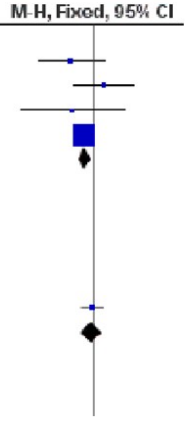
Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birth weight infants

Darlow BA, Graham PJ, Rojas-Reyes MX

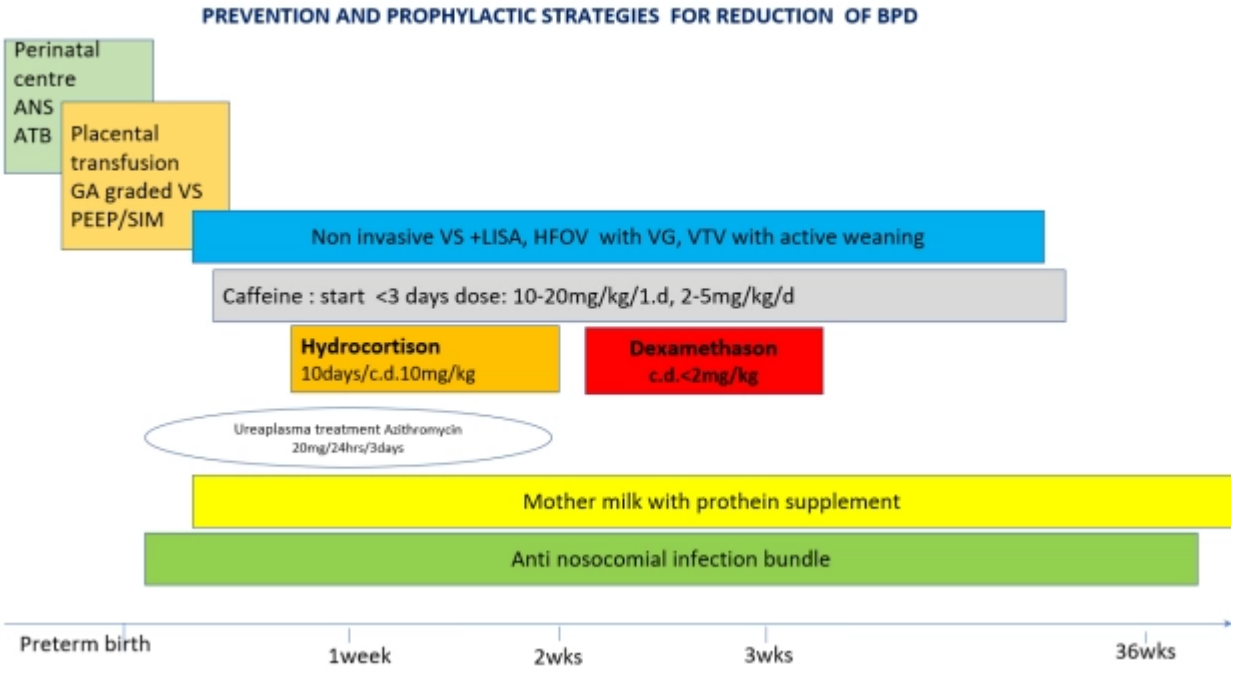
Cochrane Database of Systematic Reviews 2016

Chronic lung disease (oxygen use at 36 weeks' postmenstrual age in survivors)

Study or Subgroup	Vitamin A Events	Vitamin A Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.5.1 Supplementation via intramuscular injection						
Kiatchoosakun 2014	9	40	14	40	5.3%	0.64 [0.31, 1.31]
Mactier 2012	14	39	12	43	4.4%	1.29 [0.68, 2.43]
Ravishankar 2003	4	17	5	14	2.1%	0.66 [0.22, 2.00]
Tyson 1999	163	346	193	347	73.5%	0.85 [0.73, 0.98]
Subtotal (95% CI)		**442**		**444**	**85.3%**	**0.85 [0.74, 0.98]**
Total events	190		224			
Heterogeneity: Chi² = 2.41, df = 3 (P = 0.49); I² = 0%						
Test for overall effect: Z = 2.25 (P = 0.02)						
1.5.2 Supplementation via oral route						
Wardle 2001	40	52	37	48	14.7%	1.00 [0.81, 1.24]
Subtotal (95% CI)		**52**		**48**	**14.7%**	**1.00 [0.81, 1.24]**
Total events	40		37			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.02 (P = 0.98)						



Vitamin A



BPD