3° Congreso Argentino de Neonatologia

Buenos Aeres 1_3 July 2016

Nutrition and Bronchopulmonary dysplasia

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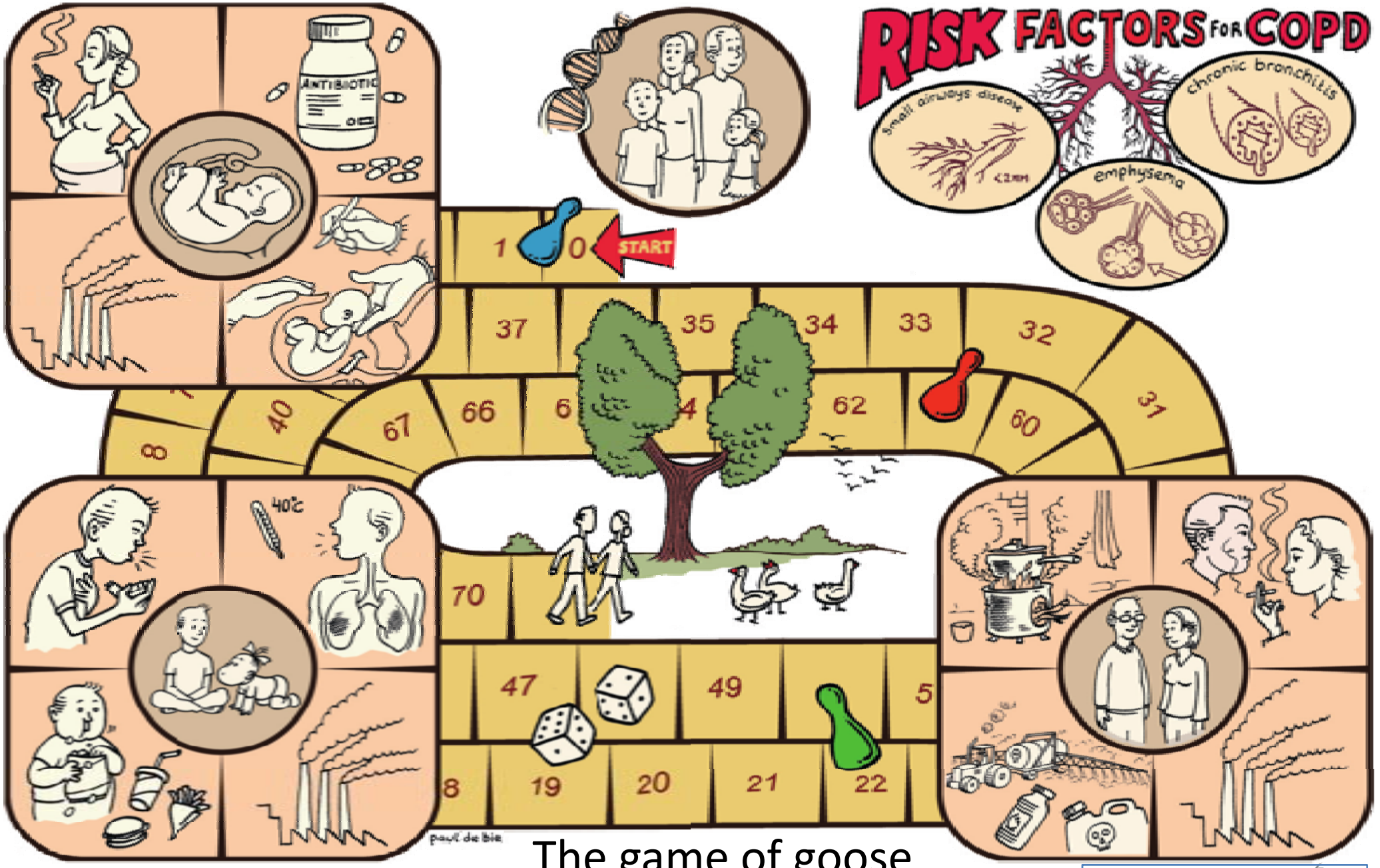
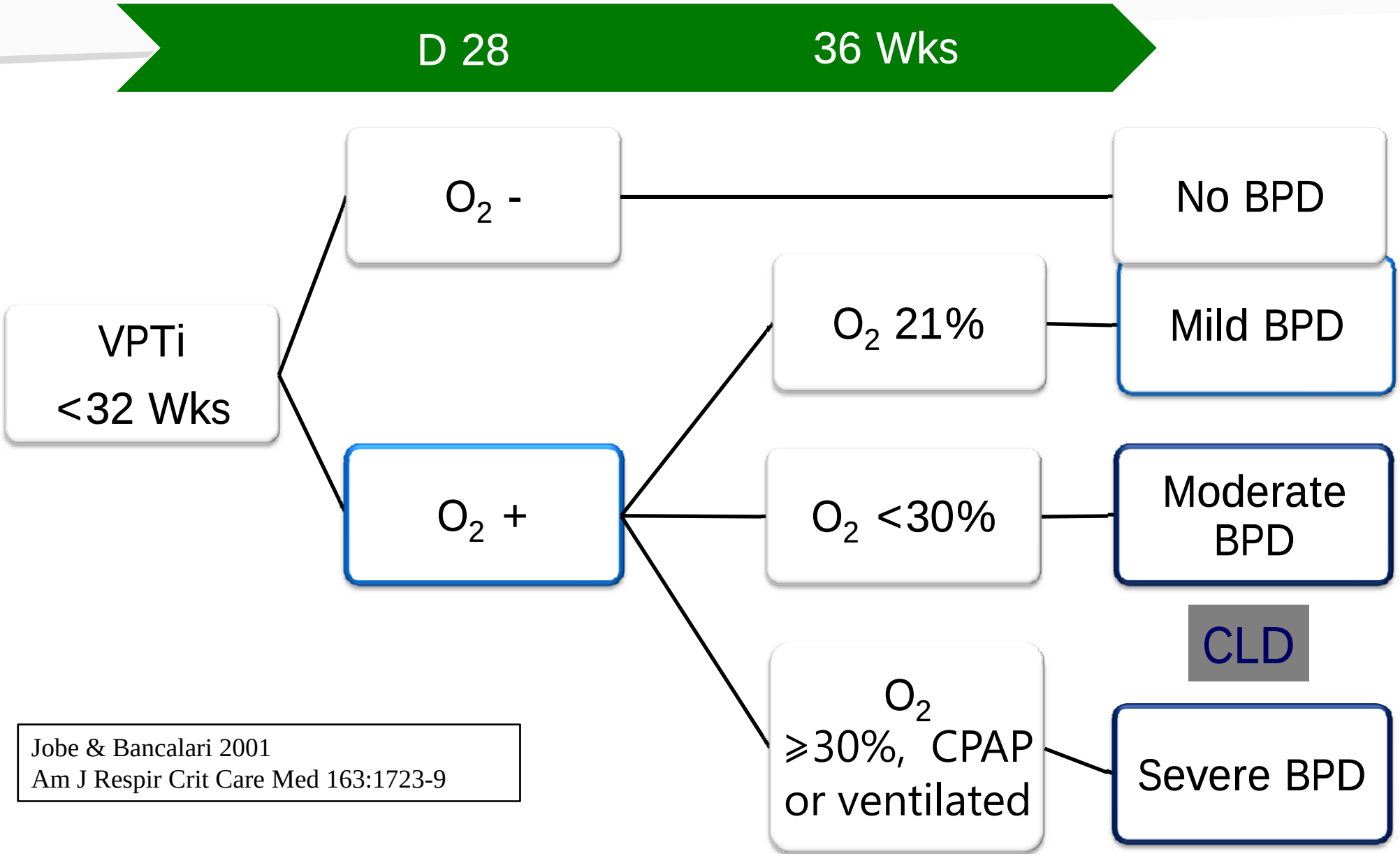


The game of goose

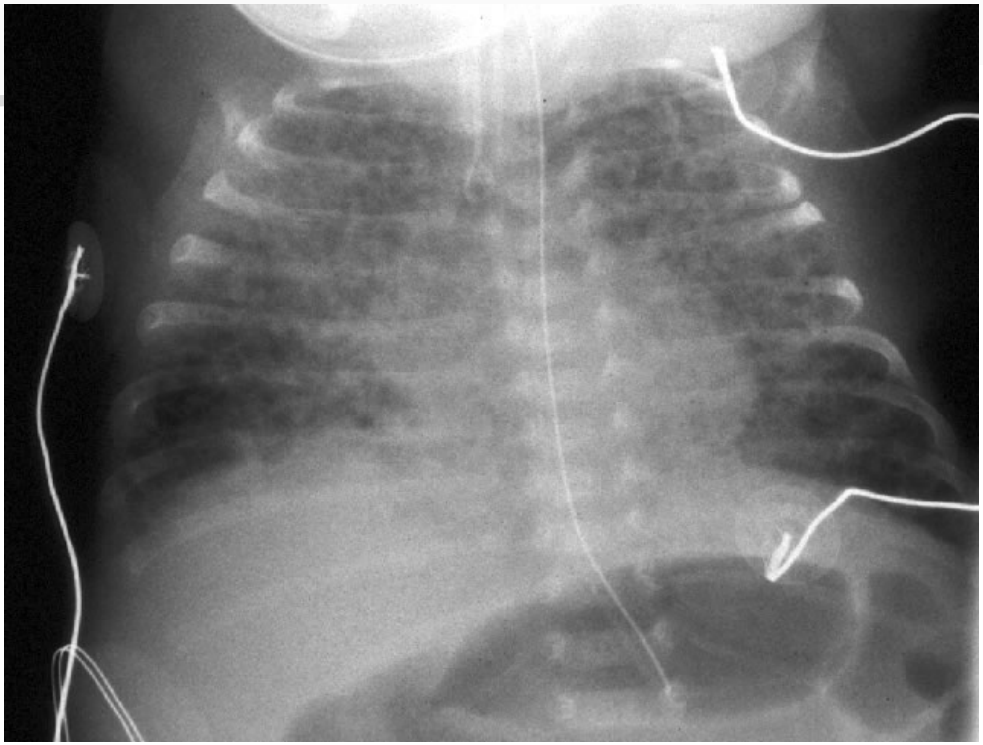
Definitions

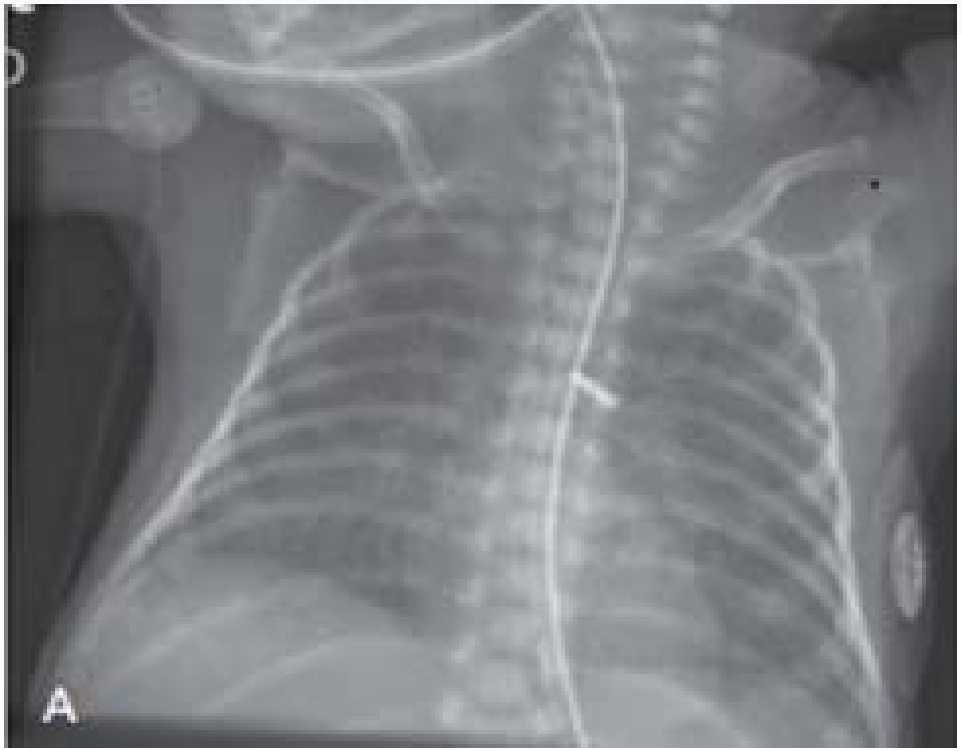


Jobe & Bancalari 2001
Am J Respir Crit Care Med 163:1723-9

Old BPD – New BPD

Keller in Avery's disease of the newborn 2012

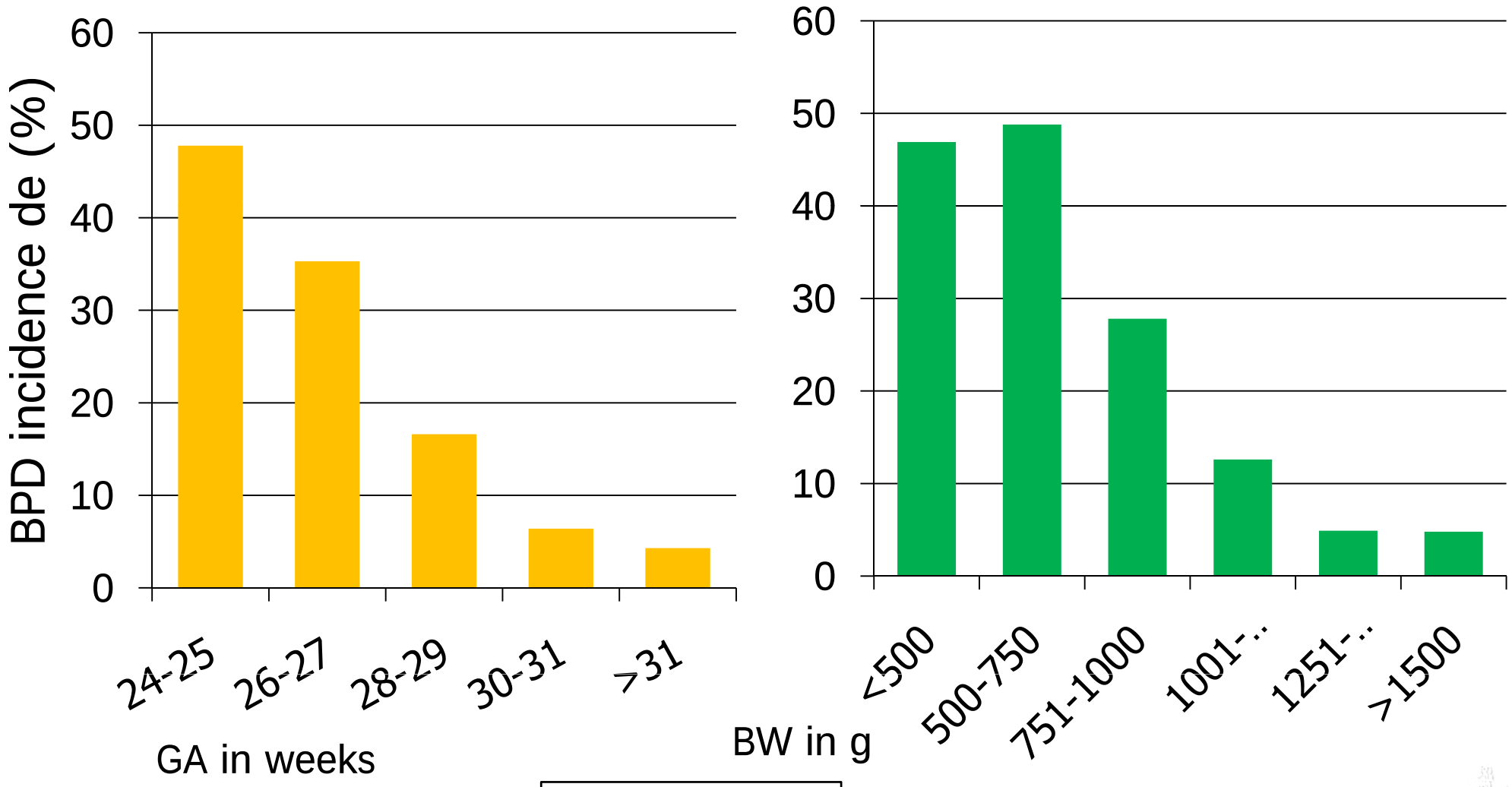




Old BPD
Alternating areas of atelectasis and hyperinflation
Severe airway epithelial lesions
(hyperplasia and squamous metaplasia)
Decreased internal surface area and alveoli
Airway smooth muscle hyperplasia
Extensive fibroproliferation
Prominent vascular hypertensive lesions

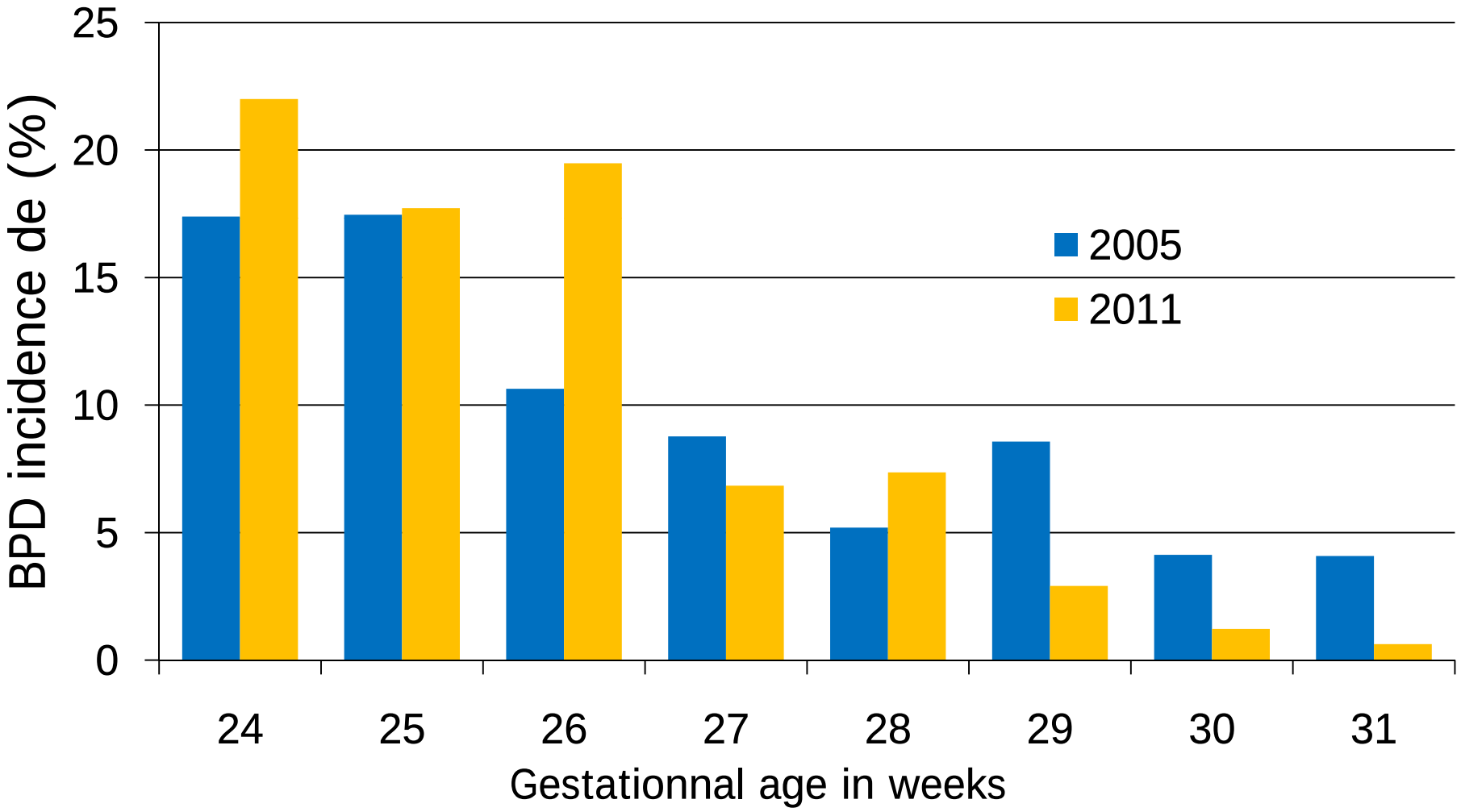
New BPD
Decreased, large and simplified alveoli
(alveolar hypoplasia, decreased acinar complexity)
Negligible airway epithelial lesions
Variable airway smooth muscle hyperplasia
Variable interstitial fibroproliferation
Decreased, dysmorphic capillaries
Less severe arterial/arteriolar vascular lesions
Less septal fibrosis that appears more diffuse

BPD_{36} rate in VPTi- VLBWi



Data EuroNeoNet 2010

BPD_{36}: rate according to GA



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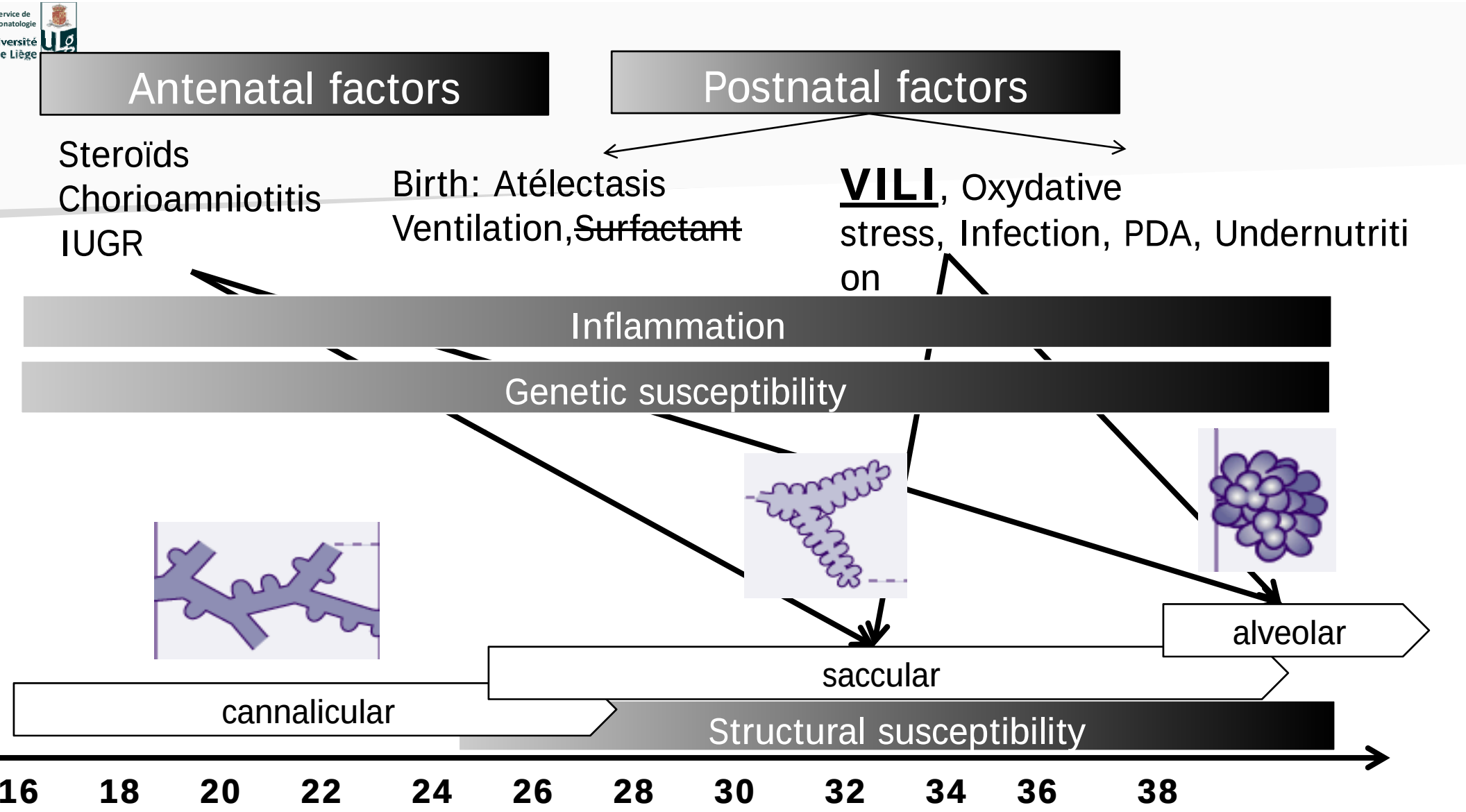


Modified from Parad 2012

VILI=Ventilated-induced lung inflamation

Prevention of BPD : the role of nutrition

1. Caffeine: 20 mg/kg, followed by 5 mg/kg/day as maintenance
2. Parenteral high dose of Vit A 2000-5000 IU 3 times /wks for 4 wks
3. Reduction of oxydative stress
4. Prevention of phtalate exposition
5. LCPUFA
6. Early exclusive human milk diet

Early Caffeine Use in Very Low Birth Weight Infants and Neonatal Outcomes: A Systematic Review and Meta-Analysis

Park HW et al J Korean Med Sci 2015; 30: 1828-1835

The use of caffeine citrate for treatment of apnea in very low birth weight infants showed short-term and long-term benefits.

Objective :To undertaken a systematic review and meta-analysis to document the effect providing caffeine early (0-2 days of life) compared to caffeine late (= 3 days of life) on BPD in VLBW infants ,BW<1500 g.

Method : From a total of 1094 studies, 5 relevant studies including a total of 59,136 infants were evaluated for the primary outcome: **BPD, death, and "BPD and death"**

Primary outcome	Early caffeine	Late Caffeine	OR	CI	P=
Died	1177/30974 (3.8%)	1001/23873 (4.2%)	0.902	0.828-0.983	O.019
BPD	6667/33356 (20.0%)	8785/25405 (34.6%)	0.507	0.396-0.648	<0.001
Died or BPD	7821/32960 (23.7%)	9415/24838 (37.9%)	0.526	0.384-0.719	<0.001

Early Caffeine Use in Very Low Birth Weight Infants and Neonatal Outcomes: A Systematic Review and Meta-Analysis

Park HW et al J Korean Med Sci 2015; 30: 1828-1835

Secondary outcome	Early caffeine	Late Caffeine	OR	CI	P=
IVH	NP	NP	0.540	0.364-0.801	0.02
PVL	(1.4%)	(2.4%)	0.560	0.494-0.635	<0.001
PDA	(8.8%)	(19.3%)	0.402	0.380-0.423	<0.001
ROP + Laser	NP	NP	0.447	0.223-0.897	0.024
NEC	(8.0%)	(8.3%)	0.976	0.715-1.332	0.879
NEC+Surgery	(2.6%)	(2.4%)	1.007	0.652-1.747	0.796

In conclusion, this meta-analysis suggests that early caffeine use (< 3 days of life) in VLBW infants has beneficial effects on neonatal outcomes, including mortality, BPD, IVH, PVL, ROP laser photocoagulation, and PDA requiring treatment, without increasing the risk of NEC.

Vitamin A Supplementation for Prevention of Bronchopulmonary Dysplasia: Cornerstone of Care or Futile Therapy?

Gawronski CA: Annals of Pharmacotherapy 2016

A total of 6 studies were evaluated: 5 RCT and 1 observational study during a national shortage

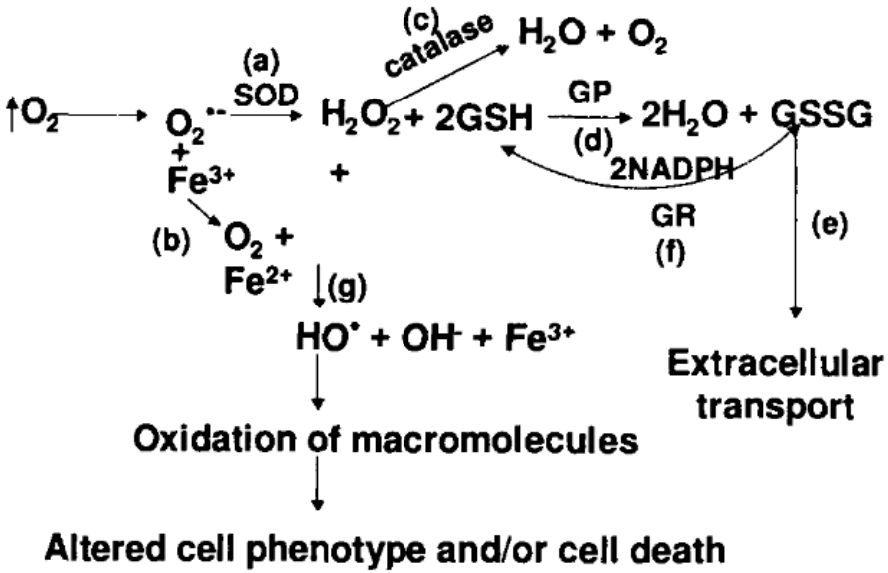
Articles	***Outcomes***	***VAS group***	***Control group***	***p=***
RCT with parenteral Vit A 2000 to 5000 IU 3 times /wks for 4 wks				
Shenai et al1987 Pearson et al1992	BPD at 31 days	22/47 (46.8%)	29/42 (69.1%)	0.034
Tyson et al 1999 Londhe et al 1993	Death or CLD at 36 weeks	248/455 (54.5%)	281/455 (61.7%)	0.028
Chabra et al 2013	CLD at 36 weeks	15/35 (42.8%)	15/32 (46.8%)	0.742
Observational study 2010-12 during the US shortage of parenteral Vit A				
Tolia et al 2014*	Death or CLD at 36 weeks	551/1085 (50.9%)	2460/5125 (48.0%)	0.082*

*In centers with high preshortage use of vit A, with 75% to 100% of eligible infants, the rate of CLD or death remained stable (47%) during, both preshortage and shortage periods.

Rationale for Antioxidant Therapy in Premature Infants to Prevent Bronchopulmonary Dysplasia

Welty SE & Smith CV Nutrirnt review 2001

The association between elevated lipid oxidation products such as exhaled pentane and plasma aldehydes with the development of BPD is highly suggestive of a role for lipid oxidation in the pathogenesis of BPD and supports the theory that antioxidants aimed at interrupting lipid oxidation might reduce the incidence and/or severitv of BPD.



Ascorbylperoxide Contaminating Parenteral Nutrition Is Associated With Bronchopulmonary Dysplasia or Death in Extremely Preterm Infants

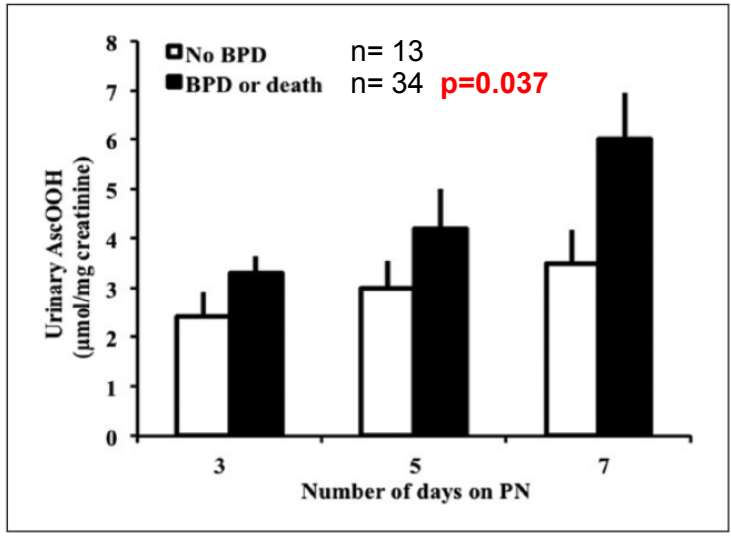
Mohamed I JPEN 2016

Background: Ascorbylperoxide (AscOOH) is a hydrogen peroxide contaminating PN that increases apoptosis, and decreased alveolarization in guinea pigs.

Objective: to explore the association between an early level of urinary AscOOH and later development of BPD or death.

Materials and Methods: urinary AscOOH were collected at d 3, 5, and 7 in 51 infants <29 wks GA and plasma total glutathione, were determined at d7.

Results: Urinary AscOOH increased over time (*P* = .001) and was higher in infants who later developed BPD or died (*P* = .037). Compared with term infants, total plasma glutathione was low.



Conclusion: ELBW infants have limited capacity to detoxify AscOOH and higher first-week urinary AscOOH levels are associated with an increased incidence of BPD or death.

However the causality can only be determined by a RCT

Oxygen and parenteral nutrition two main oxidants for extremely preterm infants: 'It all adds up'.

Mohamed I J Neonatal Perinatal Med 2015;8(3):189-97

*Objective:*To assess the effect of early exposure to O2 and parenteral nutrition (PN) on oxidative stress at 36 weeks post-menstrual age (PMA) and on bronchopulmonary dysplasia (BPD) in extremely preterm infants.

Study Design: In a prospective observational study FiO2 on d 7, PN duration outcomes were collected in 116 infants <29 wks GA. In addition, tot glutathione, oxidized gluthatione and redox potential were evaluated in 39 preterms

Results:

	Fi02>25%	Fi02<25%	PN>14 d	PN≤14 d
BPD (%)	38/42 (90)	25/54 (46)	56/62 (89)	8/34(24)
GSSG (mmol/g prot)	0.29±0.04	0.18±0.02	0.26±0.03	0.13±0.02
Redox Pot (mV) (n)	-191±2 (19)	-198±2 (20)	-193±5(33)	-203±2 (6)

In logistic regression, each 1% increase in FiO2 and each 1 d increase in PN increase the OR for BPD by1.57 (1.09 –2.28) and 1.17 (1.03 –1.33) respectively.

Conclusion: Early O2 supplement and PN have additive effects that were associated with prolonged oxidative stress and increased risk of BPD.

Shielding Parenteral Nutrition Solutions From Light: A Randomized Controlled Trial

S Laborie et al 2015 JPEN 39 729-37

Oxidant stress (OS) is implicated in the pathogenesis of bronchopulmonary dysplasia (BPD). Light induces peroxide generation in parenteral nutrition (PN) solutions, creating an OS

Objective: To determining whether full light protection of PN decreases the rate of BPD and/or death in VLBW infants.

Methods: MC RCT of photoprotection, using amber bags and tubing initiated during compounding of PN and maintained throughout infusion in the light-protected (LP) group. The control group (light exposed [LE]) received PN exposed to ambient light.

Results: In total, 590 infants born <30 wks GA were included. Multivariate analysis showed no significant effect of photoprotection on BPD and/or death. The rate of BPD/death was significantly lower (OR, 0.54; 95% CI, 0.32–0.93; *P = .02)* ***in infants receiving all-in-one PN vs those who received lipids separately.***

From that publication, a metaanalysis on 4 trials including 800 preterms shows that mortality in LP was significantly lower than in LE: OR=0.53; 95% CI (0.32–0.87) , *P = 0.1) Chessex P et al JPEN 2016*

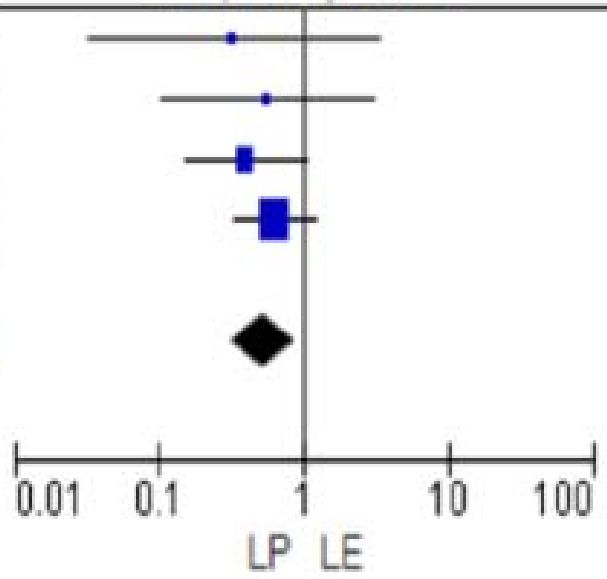
Shielding Parenteral Nutrition From Light Improves Survival Rate in Premature Infants: A Meta-Analysis

Ph Chessex et al JPEN 2016

Study or Subgroup	LP Events	LP Total	LE Events	LE Total	Weight	Odds Ratio M-H, Fixed, 95% CI
J Pediatr 2007	1	38	3	39	6.6%	0.32 [0.03, 3.26]
Free Radic Biol Med 2010	2	18	7	38	9.2%	0.55 [0.10, 2.98]
J Pediatr Gastro Ntr 2009	9	40	17	40	30.2%	0.39 [0.15, 1.04]
JPEN 2014	16	293	25	294	54.1%	0.62 [0.32, 1.19]
Total (95% CI)		**389**		**411**	**100.0%**	**0.53 [0.32, 0.87]**
Total events	28		52			

Heterogeneity: $Chi^2 = 0.77$, $df = 3$ ($P = 0.86$); $I^2 = 0\%$

Test for overall effect: $Z = 2.51$ ($P = 0.01$)



Increased levels of phtalates in very low birth weight infants with septicemia and bronchopulmonary dysplasia

K. Strømmen et al. Environment International 89–90 (2016) 228–234

Phtalate is a endocrine disruptor inducing several deleterious reproductive effects.

Very lowbirth weight infants are exposed to potentially harmful phthalates from medical devices during their hospital stay. In adults, an association between urinary phthalates and lung function has been suggested

Objective: to evaluate the possible relation between urinary phthalate's conc. and BPD

Method: Urinary phthalate metabolites were measured 3 times during the first 5 weeks of life in 46 VLBW infants enrolled in a RC nutritional intervention study.

Increased levels of phthalates in very low birth weight infants with septicemia and bronchopulmonary dysplasia

K. Strømmen et al. Environment International 89–90 (2016) 228–234

Results: During the study, significantly higher levels of phthalate metabolites were seen in infants with lower BW and those diagnosed with BPD In addition, a significant positive correlation between the duration of respiratory support and ∑DEHP metabolites was observed at the three periods.

∑DEHP ng/ml	Without BPD (n=36)	With BPD (n=10)	p=	Correlation to resp support	
				r=	p=
At 0.7 wks	1096	2262	0.13	0.34	0.04
At 2.9 wks	632	2763	0.02	0.44	<0.01
At 4.8 wks	673	2328	0.06	0.54	0.001

Conclusions, As Infants with lower BW and those with BPD experienced prolonged exposure from medical equipments containing phthalates further studies need to evaluate the causality between Phtalate exposition and BPD.

LCPUFA and Bronchopulmonar dysplasia

The LCPUFAs are known to modulate inflammation and are also believed to modulate the neonatal immune response.

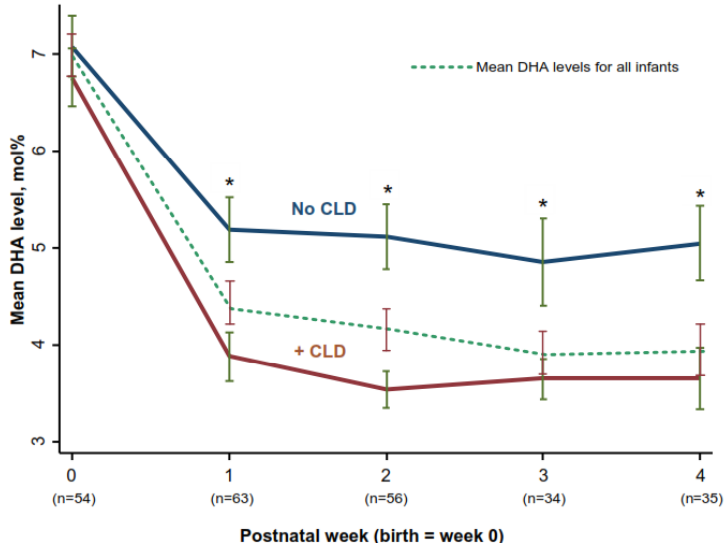
A decreased DHA level was associated with an increased risk of BPD in infants born before 30 weeks of gestation

(OR, 2.5; 95% CI, 1.3-5.0)

An increased LA/DHA ratio was also associated with an increased risk of BPD

(OR, 8.6; 95% CI, 1.4-53.1).

Martin CR 2011



A MC RCT shows that infants with a BW below 1,250 g and boys born <33 wks, BF with DHA suppl in the mother's diet induces a reduced incidence of BPD

Manley BJ.2011

	High dose % (n)	Reg dose % (n)	0R	CI	P=
02 at 36 wks	18.8 (319)	25.1 (334)	0.77	(0.59-1.02)	0.07
<1250 g	34.5 (145)	47.0 (149)	0.75	(0.57-0.98)	0.04
Male	17.7(171)	28.0(182)	0.67	(0.47-0.96)	0.03

The N3RO trial: a randomised controlled trial of DHA to reduce bronchopulmonary dysplasia in preterm infants < 29 wks GA

CT Collins et al BMC Pediatr. 2016; 16: 72

Evidence from animal and human studies has suggested potential benefits of docosahexaenoic acid (DHA), an n-3 LCPUFA, in the prevention of chronic lung disease.

This randomised controlled trial aims to determine the effectiveness of enteral supplementary DHA (60 mg/kg*d) in reducing the rate of BPD in infants less than 29 weeks' gestation.

The target sample size is 1244 infants (622 per group), which will provide 90 % power to detect a clinically meaningful absolute reduction of 10 % in the incidence of BPD between the DHA and control emulsion (two tailed α =0.05).

Does Breastmilk Influence the Development of Bronchopulmonary Dysplasia?

Spiegler J et al J Pediatr 2016;169:76-80

The effect of breastmilk feeding on the development of bronchopulmonary dysplasia (BPD) has been minimally studied with a few, inconsistent, and descriptive reports.

Cohort study; 1433 VLBW <32 weeks, 239 (17%) on exclusive formula , 223 (16%) on exclusive breastmilk and 971 (68%) on mixed diet

	Excl HM	**Excl formula**	**Mixed diet**	**P=**	**0R**	**CI**
BPD	11.2%	20.9%		0.005	2.59	1.33-5.04
	11.2%		19.5%	0.004	1.61	1.15-2.25

Similar data were suggested by Schanler in 2005 with an incidence of 14% versus 28% in HM (n=151) and FF (n=92)p=0.0103 fed VLBW infants.Such a benefit was not reported by O'Connor DL in 2003

Beyond Necrotizing Enterocolitis Prevention: Improving Outcomes with an Exclusive HM based diet

A B Hair et al Breastfeeding medicine 2016;11:70-4

Objective: The aim of this study was to compare outcomes of infants pre and post initiation of a feeding protocol providing an exclusive human milk–based diet (HUM).

Methods: MC retrospective cohort study, infants with a BW<1,250 g receiving either OMM fortified with bovine fortifier and/or PTF (BOV), either exclusive OMM fortified with a HM fortifier (HUM)

Results: A total of 1,587 infants were included

Primary outcome	BOV (768)	HUM (819)	P=	Secondary outcome	BOV (768)	HUM (819)	P=
NEC(%)	16.7	6.9	<0.00001	LOS (%)	30.3	19.0	<0.00001
Surgical NEC (%)	10.6	4.8	0.00002	ROP (%)	9.0	5.2	0.003
Dead (%)	17.2	13.6	0.045	PDA (%)	64.7	55.1	0.0001
NEC+Dead (%)	28.0	18.2	<0.0002	BPD(%)	56.3	47.7	0.0015

BPD and Nutritional support

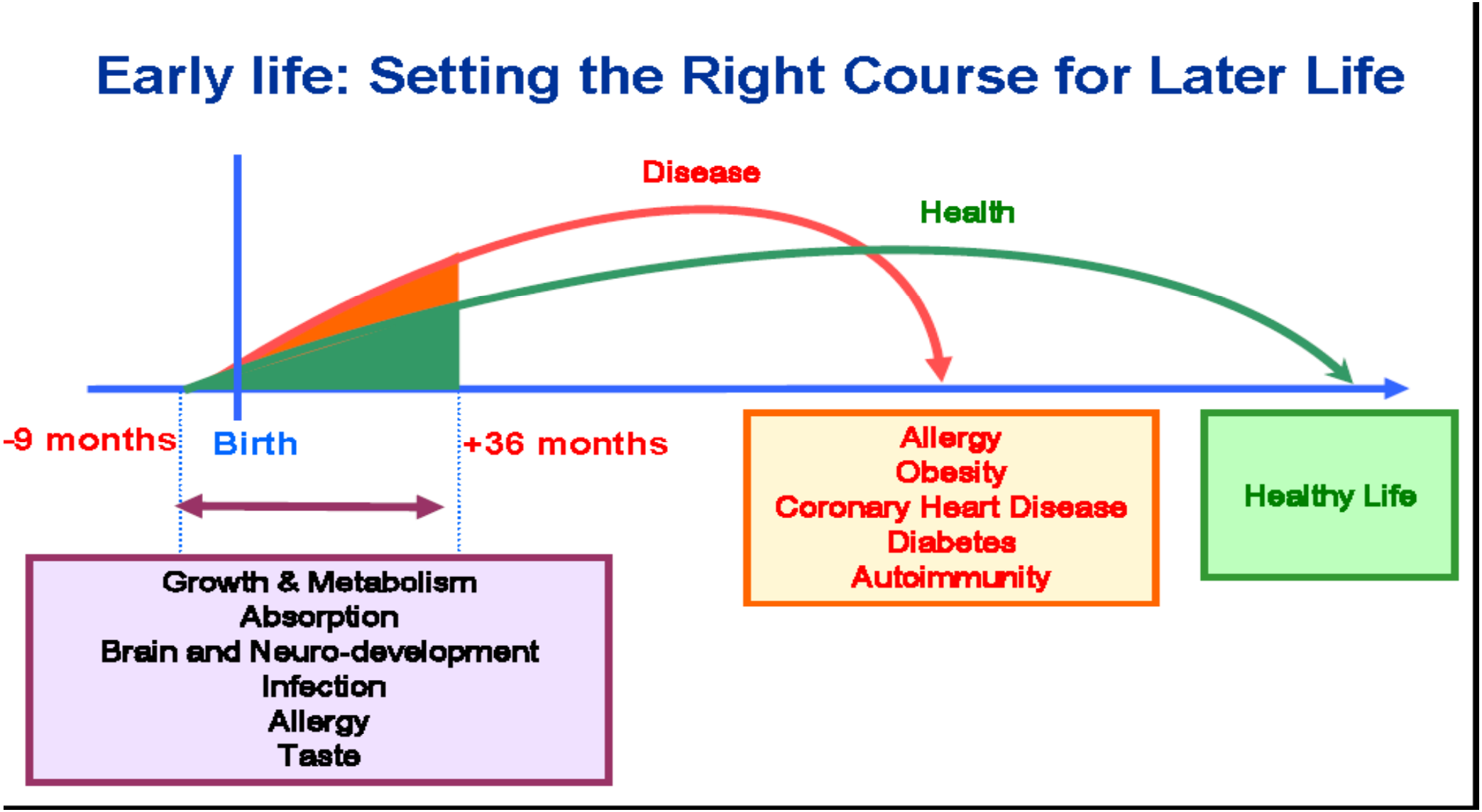
Growth failure among preterm infants due to insufficient protein is not innocuous and must be prevented

WW Hay and EE Ziegler Journal of Perinatology (2016) 36, 500–502

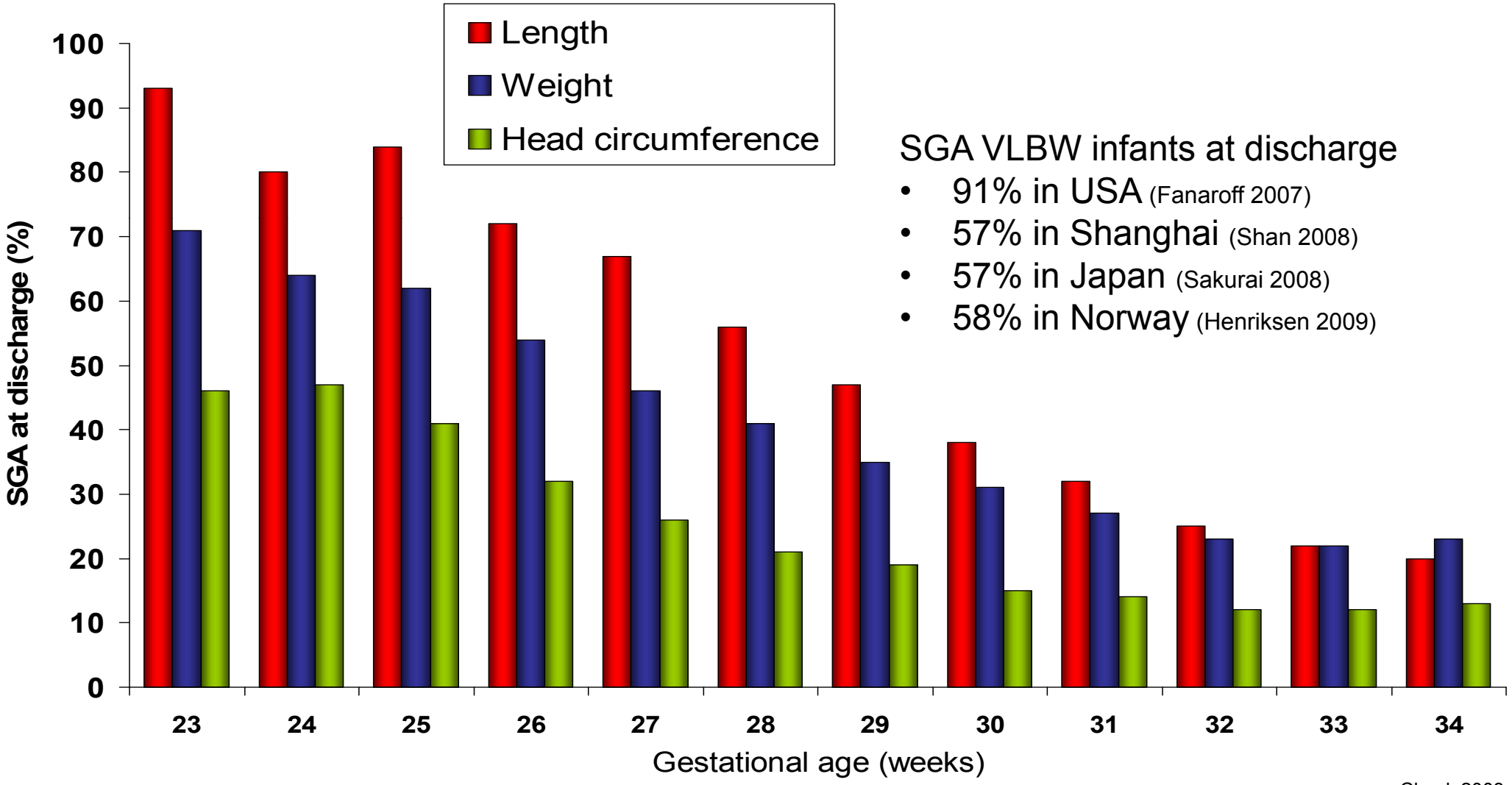
Promotion of growth

Non protein energy partition

Fetal and Neonatal imprinting



Postnatal growth restriction in preterm infants



SGA VLBW infants at discharge

- 91% in USA (Fanaroff 2007)
- 57% in Shanghai (Shan 2008)
- 57% in Japan (Sakurai 2008)
- 58% in Norway (Henriksen 2009)

Clarck 2003

Increased energy intake for preterm infants with (or developing) bronchopulmonary dysplasia/ chronic lung disease.

Lai NM[1], Rajadurai SV, Tan KH. Cochrane Database Syst Rev. 2006 Jul 19;(3):CD005093

Preterm infants with bronchopulmonary dysplasia/chronic lung disease have nutritional deficits that may contribute to short and long term morbidity and mortality. Increasing the daily energy intake for these infants may improve their respiratory, growth and neurodevelopmental outcomes.

AUTHORS' CONCLUSIONS

To date, no randomized controlled trials are available that examine the effects of increased versus standard energy intake for preterm infants with (or developing) CLD/BPD.

Research should be directed at evaluating the effects of various levels of energy intake on this group of infants on clinically important outcomes like mortality, respiratory status, growth and neurodevelopment.

Impact of Nutrition on Bronchopulmonary Dysplasia.

Poindexter BB and Martin CR Clin Perinatol. 2015 Dec;42(4):797-806

- Bronchopulmonary dysplasia (BPD) remains a common morbidity of prematurity.
- Pathogenesis of BPD is recognized to be both multifactorial and complex, but the role of nutrition in the pathophysiology of BPD is typically limited to management after a diagnosis has been made.
- Infants born small for gestational age and those who experience postnatal growth failure are more likely to have BPD.
- Therapies for lung disease, such as fluid restriction, diuretics, and corticosteroids, can negatively impact postnatal growth.
- Future research is needed to optimize nutritional strategies in the neonatal intensive care unit and after hospital discharge.

Effects of quality of energy on substrate oxidation in enterally fed, low-birth-weight infants

Metabolism of carbohydrate and lipid: Energy and CO_2 production

Glucose oxydation:	$C_6H_{12}O_6 + O_2$	➔	6 CO_2	AND	36 ATP
Palmitate oxydation:	$C_{16}H_{32}O_2 + 0_2$	➔	16 CO_2	AND	129 ATP
100 g Glucose		➔	3.33 CO_2	AND	20 ATP
100 g Palmitate		➔	6.25 CO_2	AND	50,4 ATP

In parenteral nutrition

100 kcal Glucose	➔	0.89 CO_2	AND	5,3 ATP
100 kcal Palmitate	➔	0.67 CO_2	AND	5.4 ATP

In enteral nutrition

100 kcal Glucose (100% absorption)	➔	0.89 CO2	AND	5,3 ATP	(100 kcal)
100 kcal Palmitate (75% absorption)	➔	0.50 CO2	AND	4.0 ATP	(75 kcal)

Effects of quality of energy on substrate oxidation in enterally fed, low-birth-weight infants

Kashyap S et al; Am J Clin Nutr 2001;74:374–80.

	130 kcal & 4.1g Protein			154 Kcal & 4.1g Protein	
Lipid (%Non prot E)	66%	52%	34%	65%	37%
Protein retention (g)	2.5	2.7	2.8	2.7	3.1
Metabolisable Energy (kcal)	113	116	121	129	140
VCO_2 (ml)	7.76	8.25	8.58	8.2	9.7

Conclusions,

In enterally fed low-birth-weight infants, due to a relative fat malabsorption, energy supplied as carbohydrate is more effective than energy supplied as fat in sparing protein oxidation. By contrast, energy supplied as fat allows to reduce slightly CO_2 production.

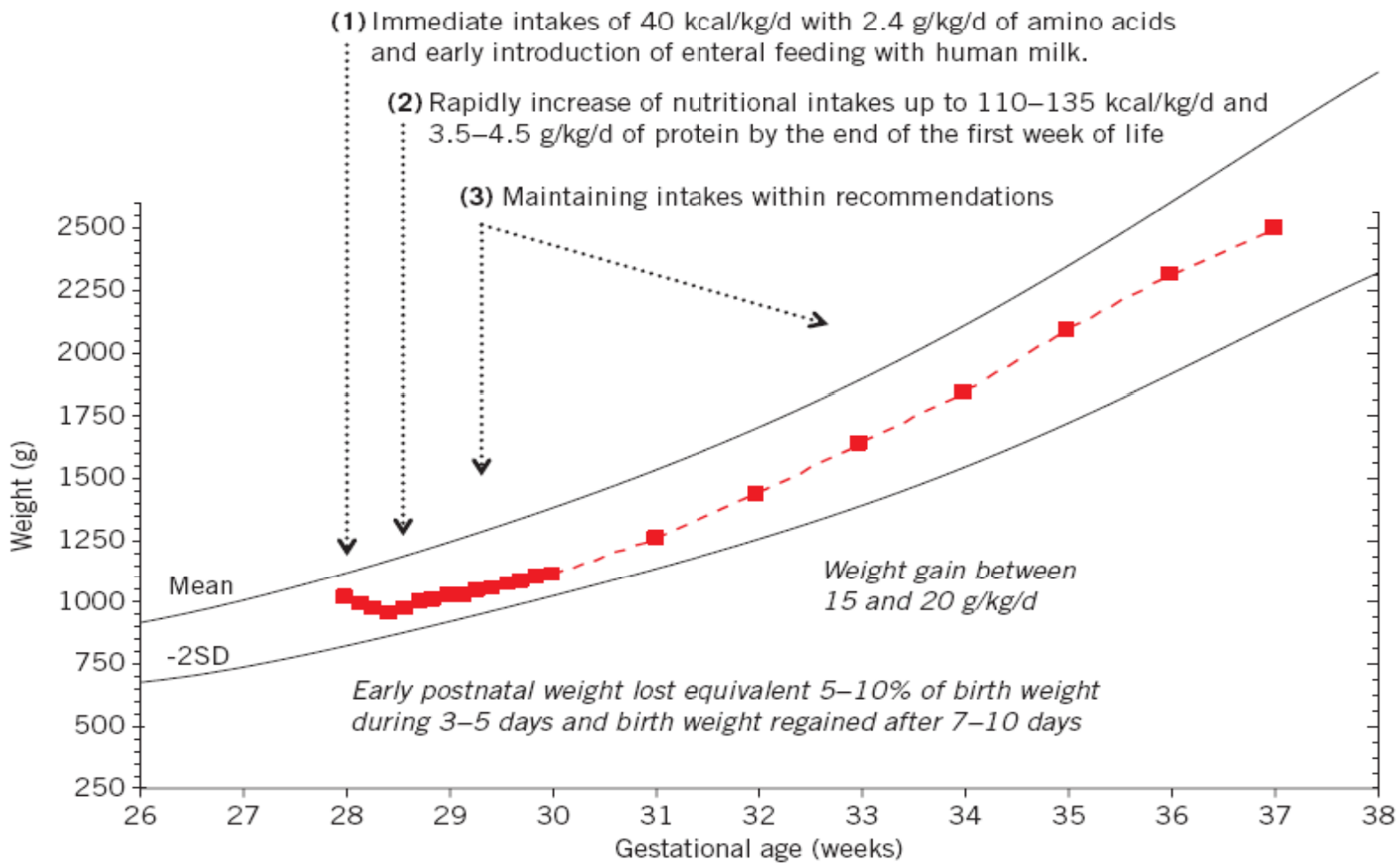


Figure 32-2 Optimizing nutritional support and postnatal growth from the first day of life onwards during postnatal hospitalization in very preterm infants. Adapted from Senterre.[45]

Senterre T and Rigo J. - JPGN 2011;53(5):536-42.
- Acta Paediatrica. 2012;101(2):e64-70

Messages to take home

BPD can be prevented in VLBW infants by relatively simple measures:

•Provides early caffeine
•Reduce oxydative stress in TPN (RTU multichamber bag from industry could be a first choise)
•Use exclusive HM diet with high n3 content (DHA)

Long term side effects of BPD could be minimized in VLBW infants by:

• Reducing early cumulative deficit.
•Limiting postnatal growth restriction.
•Prevent postnatal CMV contamination (OMM)

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Nutrition and Bronchopulmonary dysplasia

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•PN must be initiated within a few hours of birth with at least 2.0 g/kg/day of amino acids, to be increased to 3.5–4.0 g/kg/d over the first 24–48 h for infants >30 weeks gestation (up to 4.0 g/kg/d for ELBWI <27 wks GA).

Glucose should be infused at the highest rate tolerated without causing hyperglycemia and lipids should be started within 24 h of birth, advancing from 2.0 to 3.0–3.5 g/kg/d.

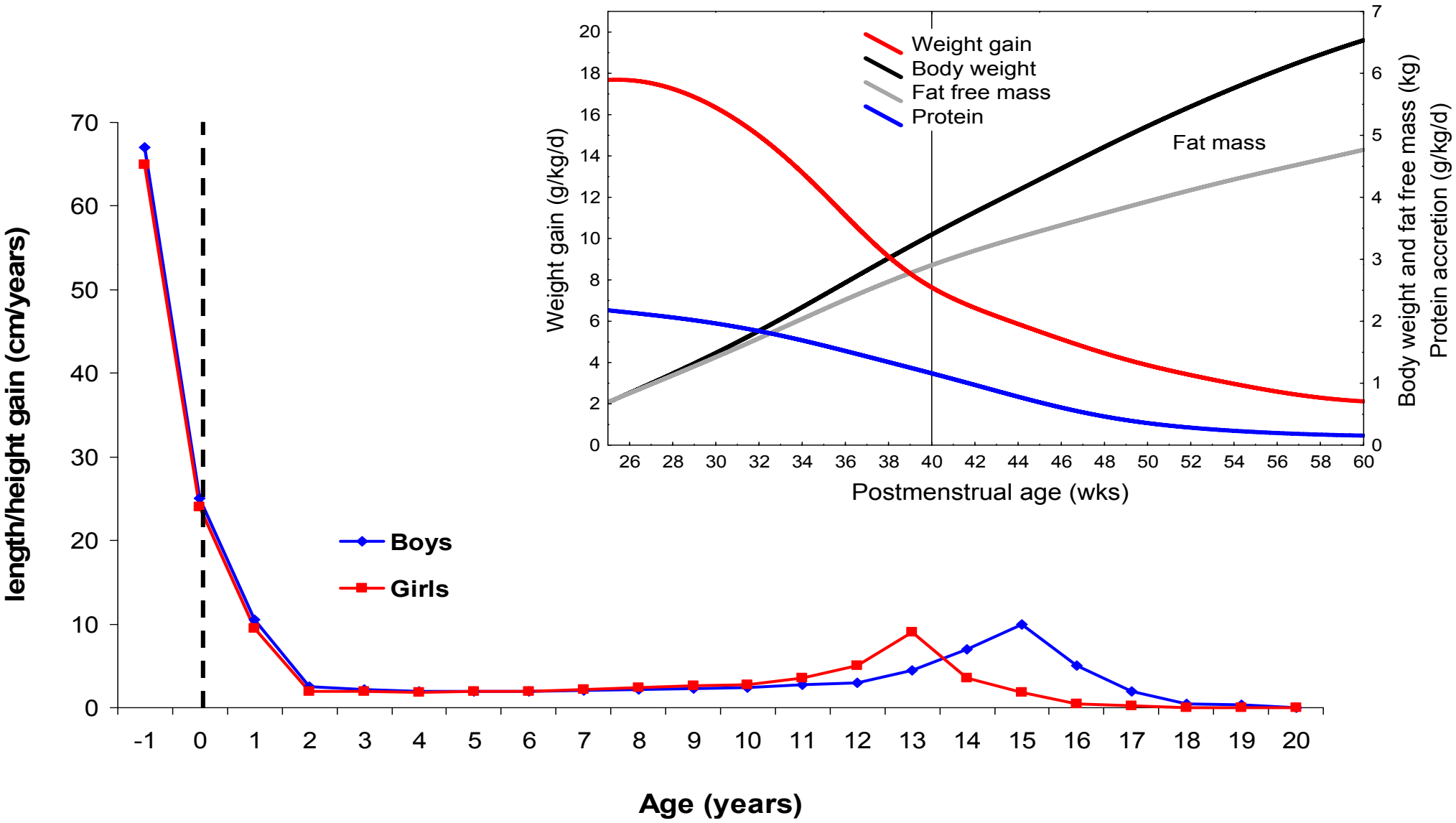
•Gut priming should be initiated on d1 and advanced in volume as tolerance permits.

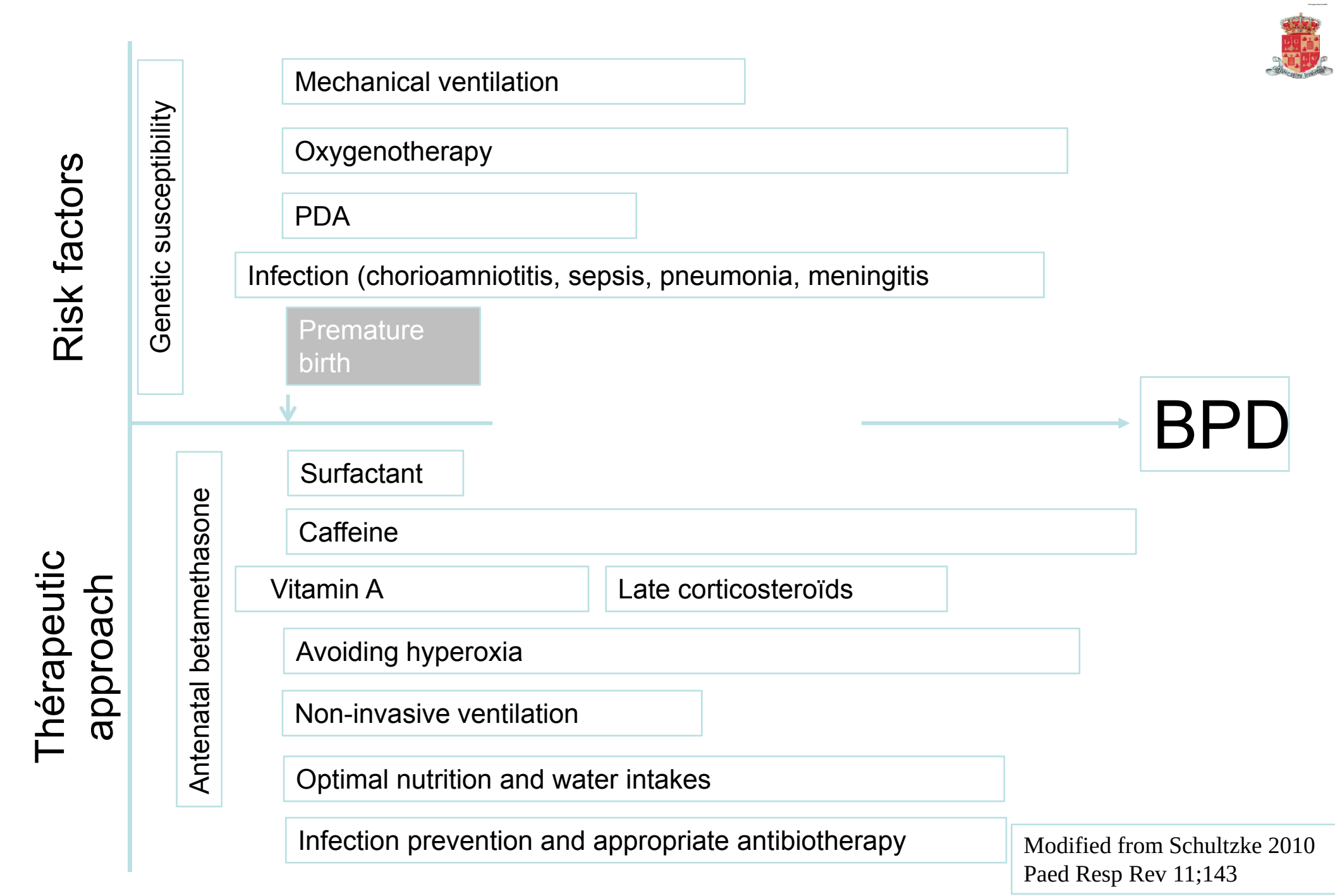
•Fortification of human milk should be started no later than when feedings reach 50 ml/kg/d.

•As parenteral nutrition is phased out, attention must be paid to maintaining adequate total nutrient intakes at all times by concentrating IV nutrition mixes and increasing fortification of milk.

•Feedings should not be reduced in volume or held altogether because of minor GI rregularities, such as slowed gastric emptying defined by residuals.

Growth rate according to age





Modified from Schultzke 2010
Paed Resp Rev 11;143