

# PREVENTION STRATEGIES FOR PREMATURE INFANTS

Prof Joseph HADDAD  
Neonatology

Saint George University Hospital  
University of BALAMAND  
Beirut



# OBJECTIVES

Reduce morbidity and mortality



Cost effectiveness Strategies



Evidence Based Medicine

# Domains of Interventions

- Neonatal resuscitation
- Lung
- Brain
- Nutrition
- Infection
- Toxicology

**NEONATAL  
RESUSCITATION**

# What is the Optimal Oxygen Saturation During resuscitation?



**Fig. D-1.** This extremely preterm baby is cyanotic, has poor muscle tone, and requires assisted ventilation.

# Neonatal Death

<b>Room Air</b>	<b>Oxygen</b>	<b>OR</b>	<b>95% CI</b>
<b>14%</b>	<b>19%</b>	<b>0.69</b>	<b>0.44-1.06</b>

**A 5% reduction in mortality means approx 200,000 saved lives**

*Saugstad, Rootwelt, Aalen on behalf of the Resair 2 Study Group,  
Pediatrics, 1998; 102:e1*

0 1 2 odds ratio  
Neonatal mortality

Term



Preterm



Apgar 1min < 4



All infants



A 5% reduction in mortality indicates approx 200,000 saved lives worldwide

A 3% reduction in mortality indicates approx 6000 saved lives in both North America and Western Europe

Favoring 21%

Favoring 100%

# Oxidative stress

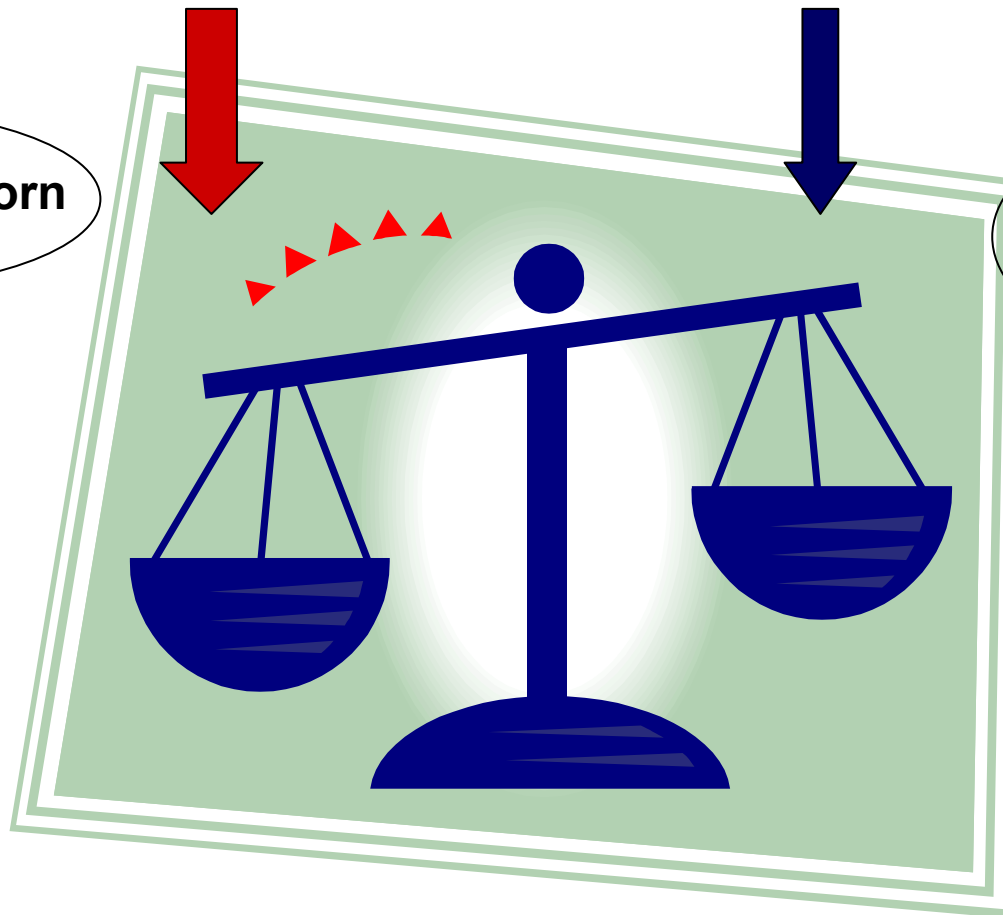
## Pro-oxidative factors

Oxygen, inflammation,  
Free Iron

## Anti-oxidative factors

SOD, Catalase, Glutathione Peroxidase  
Glutathione, Bilirubin, etc, etc

High in the newborn



Low in the preterm

# ROS and Oxidative Stress

## Reactive Oxygen Species are implicated in

- Inflammation
- Hypoxia-reoxygenation injury
- Carcinogenesis
- Atherosclerosis
- Signal transduction
- Cell growth and differentiation
- Apoptosis
- Gene expression

**ROS in low doses stimulate  
and in high doses  
Inhibit cell growth**

*Suzuki et al Free Radic Biol Med 1997;22:269*

*Saugstad OD, Curr Opin Obstet Gynecol 2001;13:147*

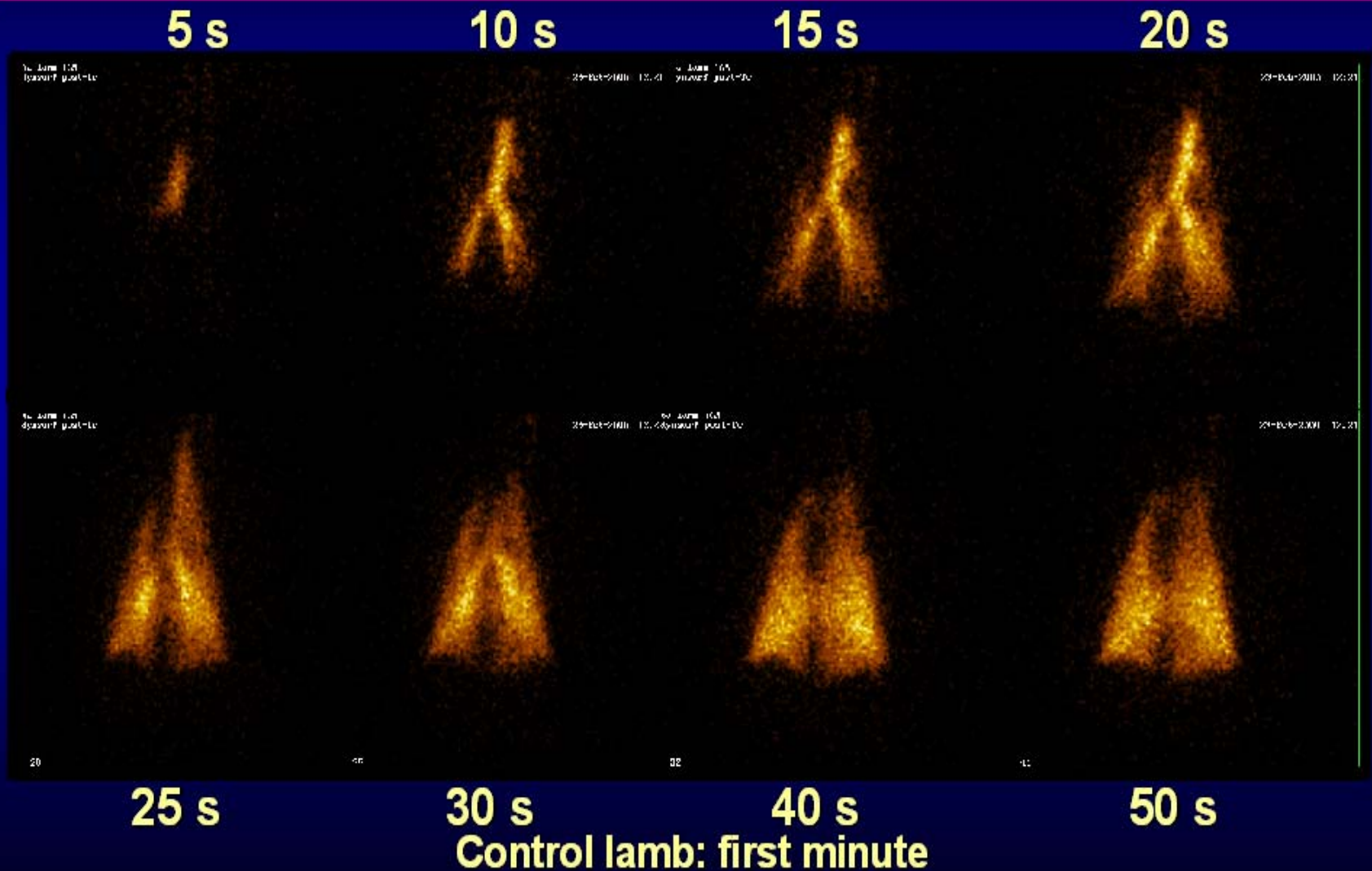
*Jankov et al Pediatr Res 2001;50:681*

*Jankov et al Ped Res 2001;50:681*

***By changing the oxidative load long term effects on  
growth and development might be triggered***

**LUNG**

# Surfactant Distribution



# Results from Systematic Reviews

<b>Mortality</b>	<b>RR</b>	<b>95% CI</b>	<b>NNT</b>	<b>95% CI</b>
Multiple doses	0.63	0.39-1.02	14	7-1000
Natural Surfactant	0.86	0.76-0.98	50	20-1000
Prophylaxis	0.61	0.48-0.77	20	14-50
Early	0.87	0.77-0.99	33	17-1000
Early INSURE	0.38	0.08-1.81	_____	

# Protocol for Surfactant Treatment of RDS and Early CPAP

<b>&lt; 27-28 wk</b>	<b>28-31 wk</b>	<b>≥ 32 wk</b>
<b>Prophylaxis in DR with 100 mg/kg</b>	<b>Early CPAP Surfactant if intubated for resuscitation</b>	<b>Observe CPAP if respiratory distress</b>
<b>Extubate to CPAP as soon as possible (&gt; 24 wk)</b>	<b>Early rescue with 100 mg/kg if <math>FiO_2 &gt; 0.30</math> ± white CXR</b>	<b>Rescue with 100-200 mg/kg if <math>FiO_2 &gt; 0.40</math> ± white CXR</b>

# Conclusions: Surfactant Therapy

- First drug developed only for treatment of neonates
- A major breakthrough in neonatal medicine in the past two decades
- Reduces both neonatal mortality and air leaks in RDS by approximately 50%
- About 6% reduction in overall infant mortality in the first year of life
- No increase in pulmonary or neurodevelopmental problems at long-term follow-up
- Numerous potential applications currently under investigation

# **POSTNATAL STEROID THERAPY: POTENTIAL BENEFITS**

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- **improve lung function**
- **decrease need for supplemental oxygen**
- **decrease need for ventilator support**
- **decrease chronic lung disease**
- **decrease mortality**

# **POSTNATAL STEROID THERAPY: POTENTIAL RISKS**

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- **hypertension**
- **hyperglycemia**
- **infection**
- **cardiomyopathy**
- **g.i. bleeding/perforation**
- **decreased somatic growth**
- **neurodevelopmental problems**

# **Suggested New Recommendations**

- Don't give in the first week of life
- Consider if ventilator-dependent after the first 7-10 days of life
- Discuss risks and benefits with parents
- Use lowest dose for shortest duration
- No role yet for inhaled steroids
- Further studies needed

# OPTIMAL SATURATION

# The BOOST trial (Benefits Of Oxygen Saturation Targeting)

358 infants  
GA < 30 weeks  
O<sub>2</sub> dependent at 32 weeks

Standard



91-94%

High



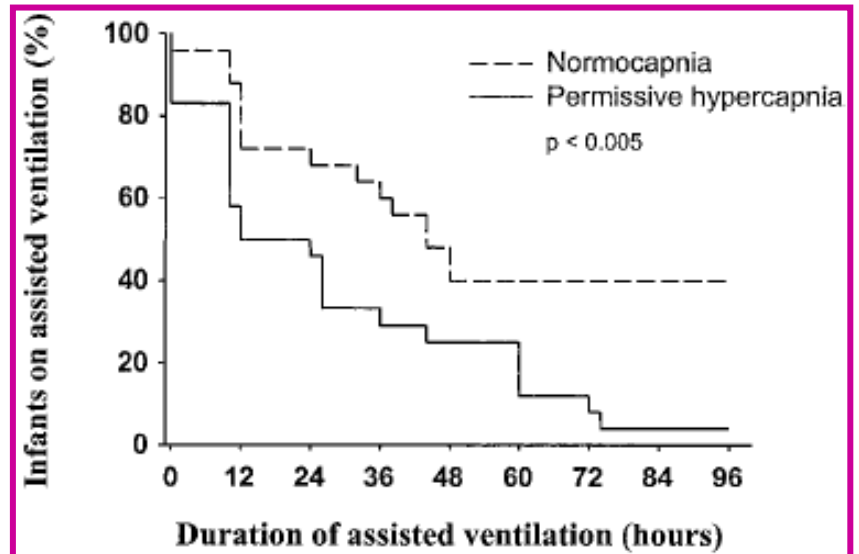
95-98% SaO<sub>2</sub> functional

No long term difference on growth and development  
The high group increased duration of O<sub>2</sub> therapy,  
Home O<sub>2</sub> therapy, and chronic lung disease

**OPTIMAL PCO<sub>2</sub>**

# Permissive hypercapnia

- PHC avoid:
  - High tidal volumes
  - Overdistension
  - Hypocapnia (PVL, CP)
- Potentiel adverse effects
  - Hypercapnic acidosis
  - ↗ CBF → IVH

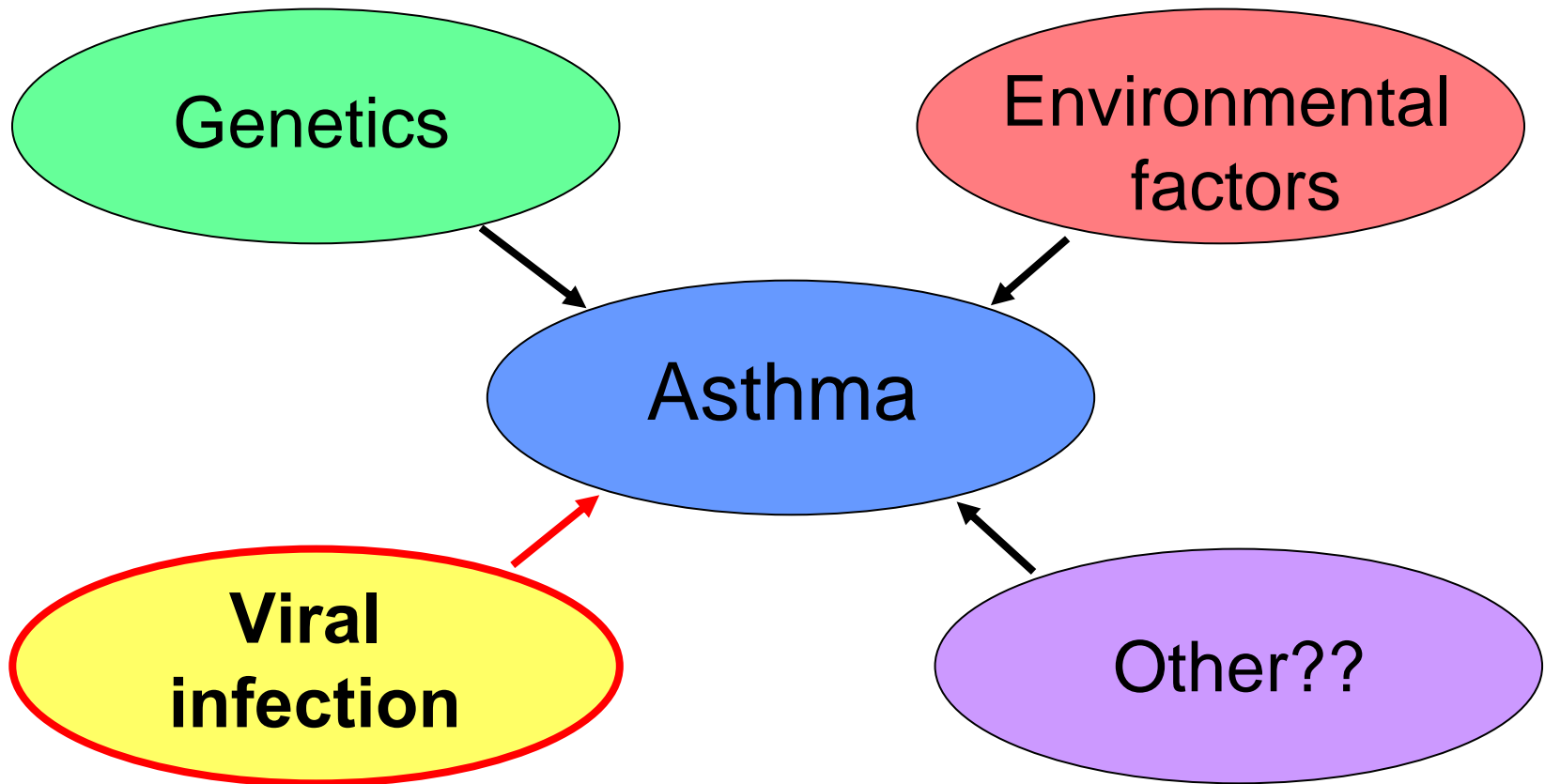


	Hypercapnia Group	NC Group	P Value	RR (95% CI)
Assisted ventilation (d)*	2.5 (1.5–11.5)	9.5 (2.0–22.5)	.17	
Supplemental oxygen (d)*	15 (4–53)	32 (17–50)	.34	
BPD (%)	43 (9/21)	64 (14/22)	.29	0.67 (0.35, 1.29)
Oxygen at 36 weeks (%)	10 (2/21)	9 (2/22)	1.0	1.05 (0.11, 10.10)
Air leaks (%)	8 (2/24)	16 (4/25)	.67	0.52 (0.07, 3.08)
Reintubation rate				
Within 24 h (%)	17 (4/24)	28 (7/25)	.54	0.60 (0.16, 2.0)
Any time (%)	67 (16/24)	48 (12/25)	.30	1.39 (0.80, 2.36)
Reintubations for apnea (%)	21 (5/24)	12 (3/25)	.46	1.74 (0.40, 8.74)
Postnatal steroids (%)	12 (3/24)	24 (6/25)	.46	0.52 (0.11, 2.11)
One course	4 (1/24)	12 (3/25)	.61	0.35 (0.01, 3.55)
More than one course	8 (2/24)	12 (3/25)	1.0	0.69 (0.08, 4.86)
Surfactant (doses)*	2 (1–3)	3 (2–3)	.21	
Extubated to NCPAP (%)	25 (6/24)	40 (10/25)	.27	0.63 (0.23, 1.59)

# Other Preventive strategies

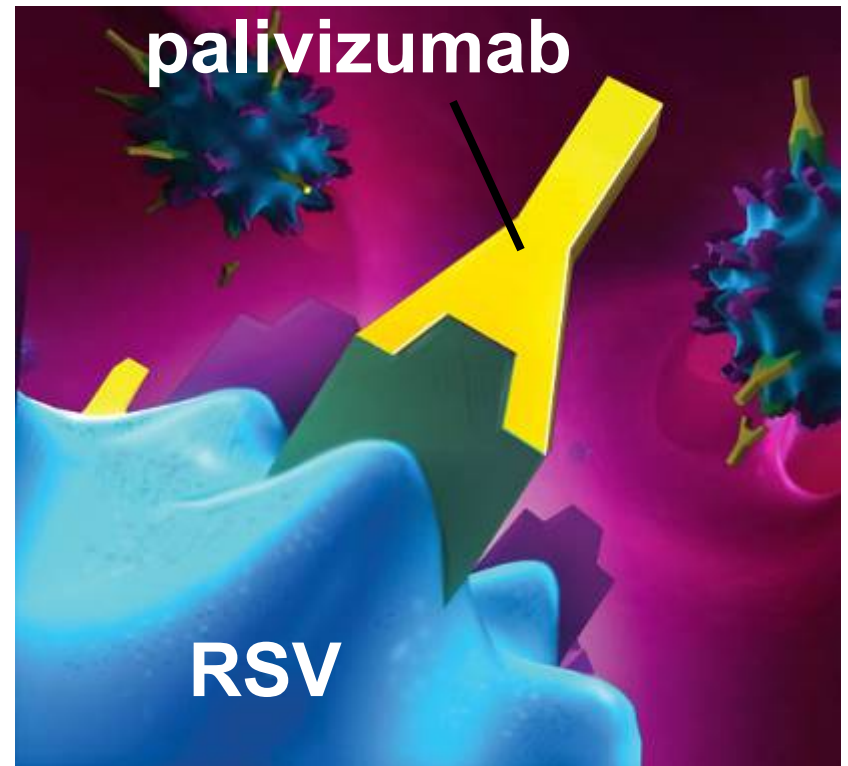
- Nasal CPAP
- HFV v/s Conventional MV
- Protective ventilation strategies including low tidal volume and high PEEP

# Potential Link between RSV and Asthma



# Palivizumab: Mechanism of action

- **Palivizumab is a monoclonal antibody that binds the F protein of RSV**
- **Produced by recombinant DNA technology**
- **Palivizumab blocks the fusion of infected cells**
- **Reduces viral activity and cell-to-cell transmission of the virus**



# BRAIN NEUROPROTECTION

# Hypothermia

# Whole body cooling using a manually controlled cooling blanket



# The 'CoolCap'



# Summary

## Normal Outcome at 18-22 Months of age

### ■ Head Cooling Study (n=218)

- Control Group 34%

- Intervention group 45%

### ■ Total Body Cooling Study (n=205)

- Control Group 38%

- Intervention group 56%

# PHARMACOLOGICAL INTERVENTIONS

- **Phenobarbital**
- **N-acetylcystein**
- **Allopurinol**
- **Deferoxamine**
- **Vitamin C/E**
- **Growth factors**
- **Erythropoietin**
- **Selective NOS-inhibitors**
- **Anti-inflammatory drugs: Melatonin/IL-1RA**
- **Proton-blockers: Amiloride**
- **Ketamin**
- **Thyroxin-derivates**
- **Xenon-inhalation**

# NUTRITION

**BREAST is the BEST**



# **What is the optimal composition of formula feeding of infants if breastfeeding is not successful ?**

Recent trends:

- Adding of prebiotics
- Adding of nucleotides
- Adding of LC-PUFA's (DHA / AA )

# **Suggested composition of preterm infant formula's**

**/ 100 ml**

## **Special preterm formula:**

Protein: 2.2-2.4 g., Ca: 100 mg, P: 50 mg, vit. D: **5**  $\mu\text{g}$

## **Breast milk fortifier :**

Protein: 0.8 g., Ca: 60 mg, P: 35 mg, vit. D: **3-5**  $\mu\text{g}$

## **Post-discharge formula:**

Protein: 1.7-1.9 g., Ca: 70 mg, P: 35 mg, vit. D: **2.5**  $\mu\text{g}$

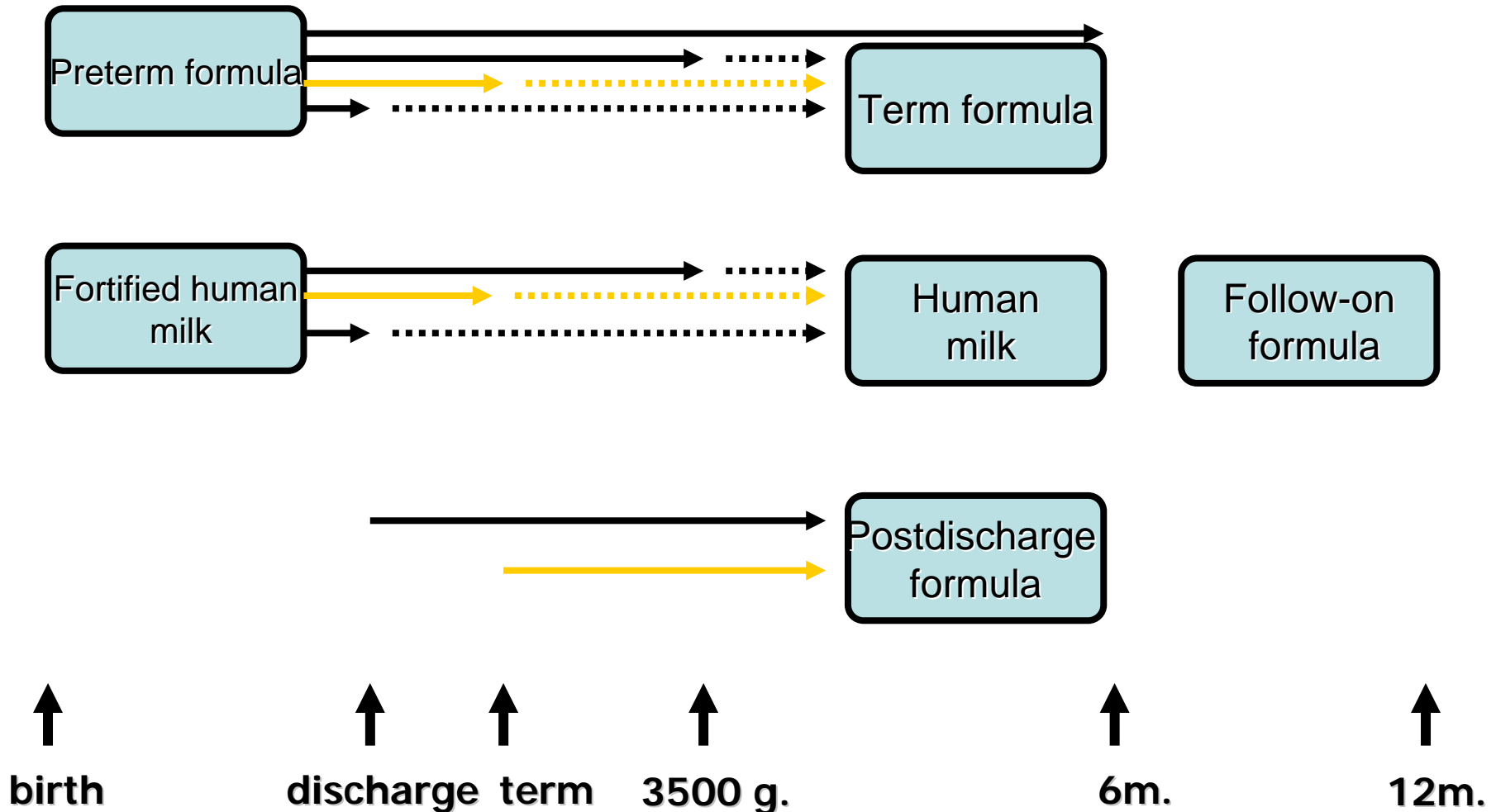
## **Regular term formula:**

Protein: 1.4 g., Ca: 54 mg, P: 27 mg, vit. D: **1.4**  $\mu\text{g}$

## **Average breast milk as comparison:**

(Protein: 1.3 g., Ca: 27 mg, P: 14 mg, vit. D: **0.1**  $\mu\text{g}$ )

# Nutrition possibilities in VLBW infants



# ANEMIA OF PREMATURITY

R-Epo beginning first week

Meta analysis by Kotto et al :

- No reduction in early transfusion
- More in late transfusion

*J Perinatology , 2004*

# Antibiotics in the Neonatal Period : What's the Matter ? Comments...

- *Infectious disease in NICU's*

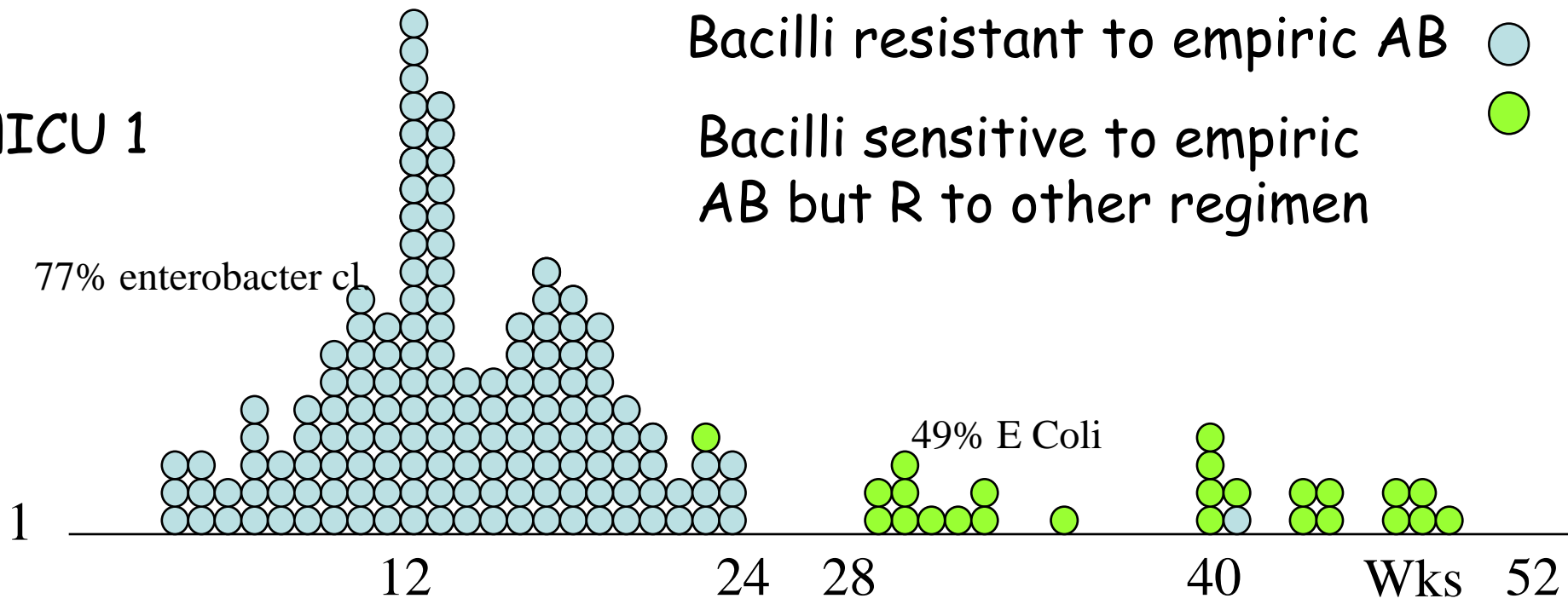
- ❖ Dramatic increase in term of **Antibiotic bacterial resistance** among *Enterobacteriaceae* (*E. coli*, *Enterobacter sp.*, *Klebsiellae*,.....)
- ❖ Not resolved Increase of **Nosocomial Infectious Morbidities**

Common possible Explaining Factor :  
ANTIBIOTIC TREATMENT POLICY IN THE  
PERINATAL PERIOD AND IN THE EARLY STAGE.

- Too much
- Too long
- Too broad spectrum

Bacilli resistant to empiric AB ●  
 Bacilli sensitive to empiric AB but R to other regimen ●

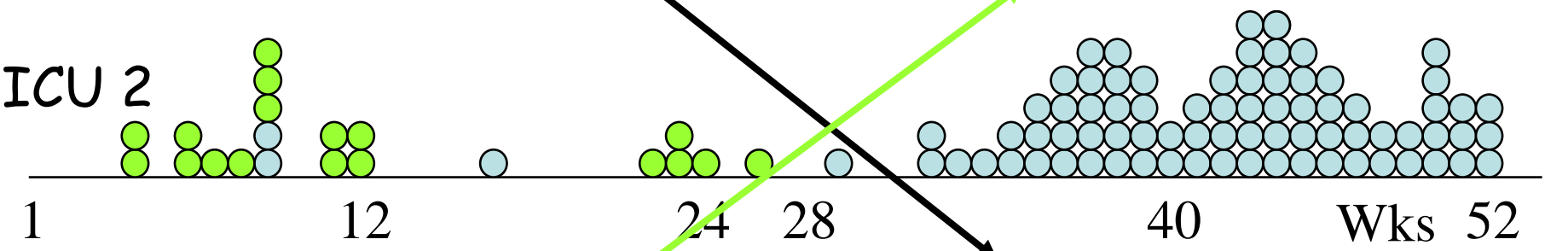
NICU 1



Amoxicillin-Cefotaxime

Pen-Tobramycin

NICU 2



Pen-Tobramycin

Amoxicillin-Cefotaxime

*De Man et al Lancet 2000;355(9208):973-8.*



# Neonatal Infection

- Empiric Use of Ampicilline plus Cefotaxime during the first three days is associated with an increased risk of death compared with Ampicilline and Aminocyclitol antibiotics in a cohort of 128914 neonates

*Clark et al, Pediatrics 2006 , 117*

# THE ISRAELI ATTACKS TO LEBANON JULY – AUGUST 2006











Ali Shaito implored his mother, Muntaha, to stay conscious as she lay near death from shrapnel wounds.

Voice of Hassan M. Fattah

Photo: Ghazi Abdel-Ahad/Getty Images













**Mahmoud Suroor, 8, was severely burned when his family's Mercedes was struck by an Israeli missile. Mohammed Suroor, his father, was killed.**







**WE WILL NEVER FORGET**

**THE WHOLE WORLD HAS TO  
NEVER FORGET**