Prevention of Necrotizing Enterocolitis (NEC) in the High Risk Neonate: Using Human Milk and Beyond!

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Objectives

- Review the history and clinical findings and outcome of *necrotizing enterocolitis*
- Discuss the changing occurrence rates of *necrotizing enterocolitis*
- Define proposed methodologies of prevention of *necrotizing enterocolitis*
- Consider ideas of prevention of *necrotizing enterocolitis* for the future

History of Necrotizing Enterocolitis

- Reported in foundling hospitals in Paris in 1828 and in Vienna in 1850. Since it was noted to occur in clusters, it was considered a nosocomial infection
- First report in the English literature was in 1960 with characterization of clinical and pathologic findings
- Bell's Criteria introduced in 1970
- *After 188 years we are still no closer to eradicating this disease*

Necrotizing Enterocolitis in VLBW infant

Occurrence and Mortality

NECROTIZING ENTEROCOLITIS

Necrotizing Enterocolitis - NEC

- Occurs in 7 – 12% of VLBW infants (< 1500 gms)
- Mortality rate varies between 10 - 30%

VON data 71, 808 VLBW infants (2005-2006)

J Ped Surgery 2009;44:1072

Birth Weight	NEC Risk	Mortality with NEC
501-750 gms	12%	42%
751- 1000 gms	9%	29%
1001-1250 gms	6%	21%
1251-1500 gms	3%	16%

Short and Long Term Complications

NECROTIZING ENTEROCOLITIS

Necrotizing Enterocolitis - NEC

- Associated with short-term complications:

  sepsis, meningitis, peritonitis, intra-abdominal abscess, perforation, DIC, hypotension, shock, respiratory failure, hypoglycemia, metabolic acidosis

- Associated with long-term complications:

  increase length of stay, short gut, colonic strictures, recurrence NEC, abnormal neurodevelopment

Prevention ?

Let’s do something!!

Failed attempts to reduce NEC

- Treatment with antibiotics
- Delayed feeding—did not reduce NEC and was associated with delay in establishing full feedings
- Rate of advancement of feedings – slow v fast was not associated with reduced NEC and was associated with delay in achieving birth weight
- Providing minimal or trophic feedings was not associated with increasing rate of NEC
- Provision of elemental formulas had no effect on occurrence rate

Pre-Intervention Rates of NEC Inborn-Preterm Infants

(VON data 2009-2010 BTGH)

- Very Low Birth Weight Infants – less than or equal to 1500 grams

  –NEC rate is 10%-11%

- Really Very Low Birth Weight Infants– less than or equal to 1250 grams

  -- NEC rate is 14% -17%

Prevention ?

Can we try something better ?

What makes sense ?

Strategy # 1

Human Milk (EBM and DEBM) as NEC Reduction/Prevention

Benefits of breast milk on the gut

- Enhance normal growth of the bowel via growth factors in breast milk
- Develop competent GI barrier function
- Develop competent mucosal immune system
- Enhance the establishment of a “normal” intestinal microbiome

Meta-analysis: Donor Milk vs. Formula

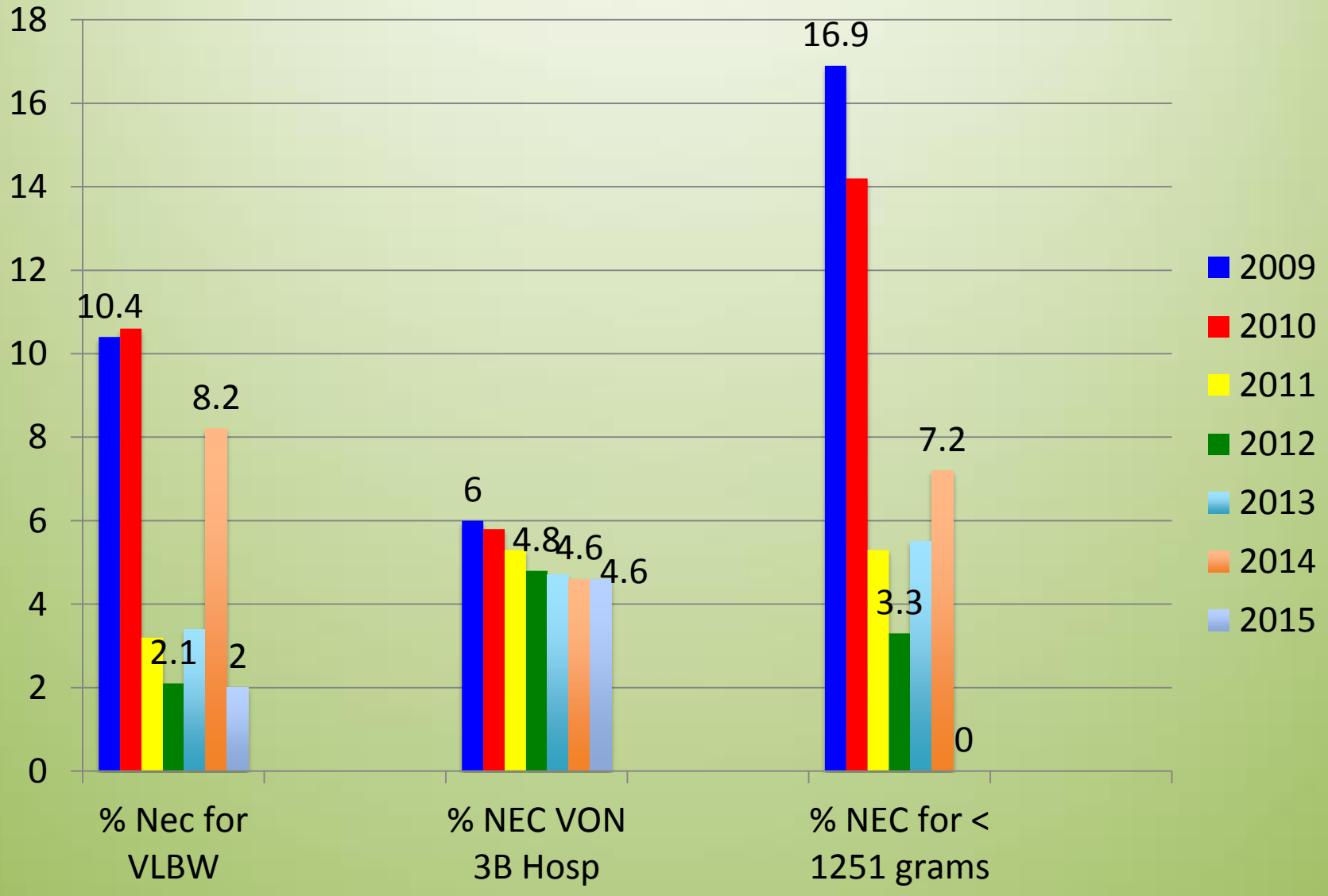
Table 2 Studies of Donor Human Milk and NEC[34,48]

	Donor Milk	Formula
Gross 1983	1/42 (2%)	3/29 (10%)
Cooper 1984	1/24 (4%)	3/15 (20%)
Lucas 1990	1/87 (1%)	4/80 (5%)
Schanler 2005	5/78 (6%)	10/88 (11%)
Overall	8/231 (3%)	20/212 (9%)

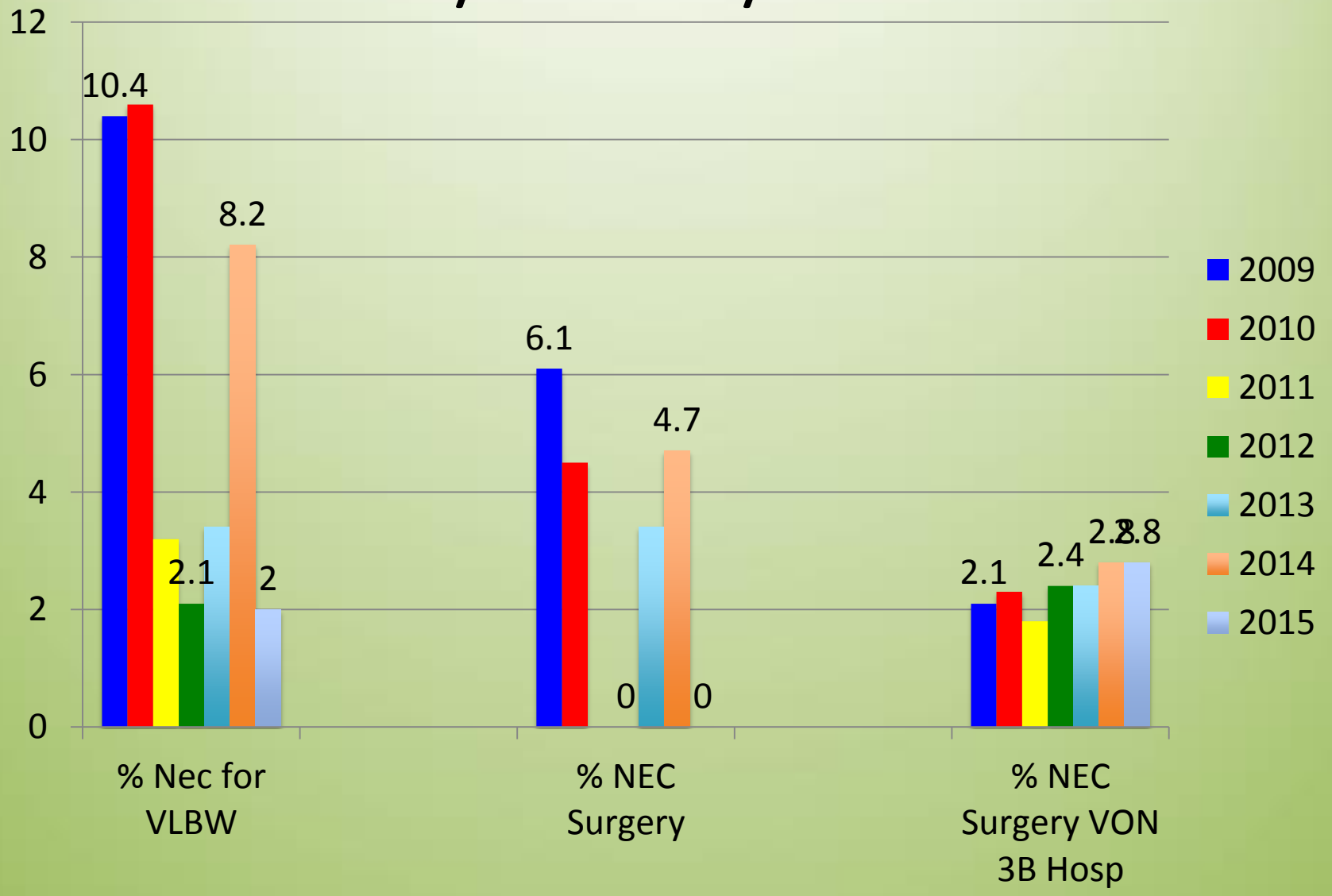
Risk of NEC is reduced significantly with pasteurized donor milk 0.35 (0.15; 0.81).

Morales Y and RJ Schanler. Human milk and clinical outcomes in VLBW infants: how compelling is the evidence of benefit? Semin Perinatol 2007; 31:83.

Rates of NEC/VLBW/In-born/BTGH



Rates of NEC Surgery VLBW/In-born/BTGH



Strategy # 2

Human Milk (EBM and DEBM) and Human Milk Fortifier as a NEC Reduction/Prevention

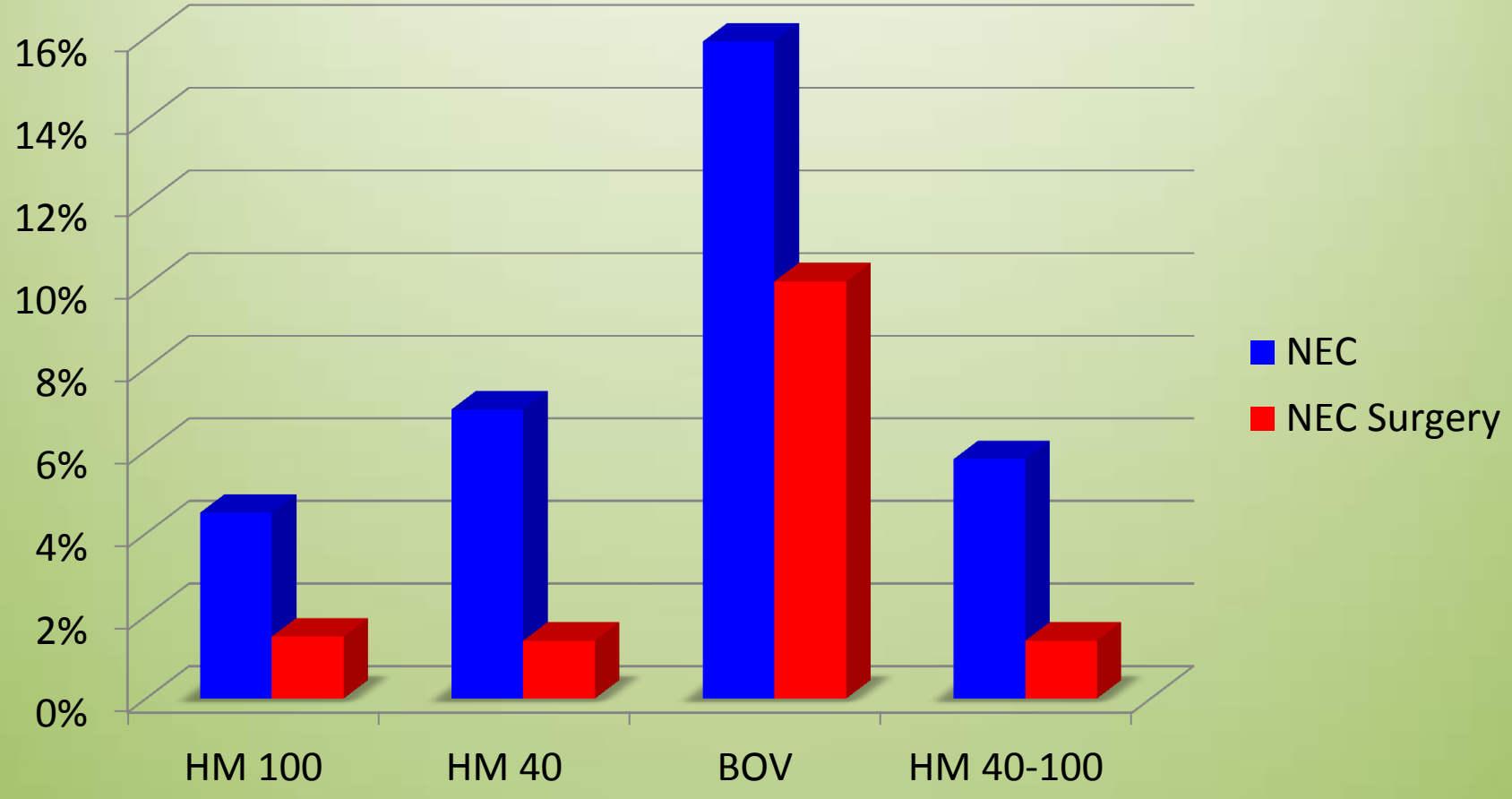
Exclusively Human Milk-Based Diet is Associated with Lower Rate of NEC

Sullivan et al *J Pediatr* 2010

- NEC is reduced using mother's EBM combined with DEBM compared to feeding high risk infants with preterm formula
- Using ***human breast milk fortifier*** instead of bovine based fortified could provide added benefit.

Comparison of NEC/NEC surgery

Sullivan *et al J Pediatr* 2010



AAP Policy Statement 2012

Breastfeeding and the Use of Human Milk

"The potent benefits of human milk are such that all preterm infants should receive human milk. Mother's own milk, fresh or frozen, should be the primary diet, and it should be fortified appropriately for the infant born weighing less than 1.5 kg. If mother's own milk is unavailable despite significant lactation support, pasteurized donor milk should be use."

Improving outcomes with exclusive human milk-based diet

Hair, Peluso et.al. PAS 2014

- Multi center (4) retrospective cohort study
- 1587 preterm infants < 1250 grams
- Population demographics similar
- Primary outcome was NEC
- Compare NEC rates pre and post initiation of exclusive human milk based diet (EBM/DEBM+ Prolacta) vs BOV diet (EBM/DEBM + BOV fortifier or formula)

NEC Rates

Hair, Peluso, et.al 2014 PAS

	BOV (n=768)	HUM (n=819)
All NEC % (n)	16.7 (128) *	6.9 (53)
Medical NEC % (n)	6.1 (47) *	2.1 (16)
Surgical NEC % (n)	10.6 (81) *	4.8 (37)
Mortality %	17.2 ***	13.6

*All comparisons statistically significant $p < 0.0005$

*** Statistically significant <0.04

What part of “I need breast milk” do you not understand??

Other Strategies to Prevent NEC

- Human milk based fortifier ✔
- Prebiotics
- Probiotics
- Lactoferrin
- Oxidents
- Umbilical cord transfusions

Prebiotics and Probiotics

- **Prebiotic** – non digestible food ingredient that promotes the growth of beneficial microorganisms in the intestines
- **Probiotic** - live microorganism that when administered in adequate amounts confer a health benefit on the host
- **Synbiotic** – a combination of prebiotics and probiotics

Prebiotics vs Probiotics

Prebiotics	Probiotics
Prebiotics are defined as nonliving non-digestible special form of fiber or carbohydrates.	Probiotics are referred to as live active microorganisms that when administered in adequate amount will have beneficial effects to its host.
The powder form of prebiotics can survive heat, cold, acid.	• more fragile. • vulnerable to heat. • may be killed over time.
Prebiotics perform their role by nourishing the bacteria that live in the intestines.	Probiotics fight the harmful bacterial species present in the gut.

The ProPre-Save Study: effects of probiotics & prebiotics alone or combined on NEC in VLBW

Dilli et al J Pediatr March 2015

- Prospective, randomized, controlled trial in 5 NICU's in Turkey
- 400 VLBW infants/3 study groups and placebo
- Group 1 probiotic (*Bifidobacterium lactis*);
- Group 2 prebiotic (inulin),
- Group 3 a synbiotic, Control
- Added to EBM or formula for max of 8 weeks

ProPre-Save Study

	Pro Group (n=100)	Pre Group (N=100)	Syn Group (n=100)	Control (n=100)
NEC n (%)	2 (2%) *	12 (12%)	4 (4%) *	18 (18%)
Late onset sepsis	8 (8%)	10 (10%)	8 (8%)	13 (13%)
Mortality	3 (3%) *	2 (2%) 8	3 (3%) *	12 (12%)
Time to full feedings (days)	18 * (14-23)	17 * (12-24)	20 * (20%)	25 (15-37)

* Statistically significant compared to control

ProPre Save Study
J Pediatr 2015

- Findings cannot be generalized to other probiotics with different doses
- Increased number of stools in the prebiotic group
- No safety issues were noted using probiotics in immunocompromised host

Other Strategies to Prevent NEC

- Human milk based fortifier ✔
- Prebiotics ✔
- Probiotics
- Lactoferrin
- Oxidents
- Umbilical cord transfusions

Probiotics in prevention of NEC

Cochrane Database Systematic Review 2014

- Randomized or quasi randomized trials that included 24 trials
- Enrolled preterm infants (<37 wks) or < 2500 grams (5529 infants)
- Highly variable enrollment criteria, baseline risk for NEC in control group, timing, dose, formulation of probiotics, and feeding regimens
- Involved administrations of live microbial organisms

Probiotics in the prevention of NEC

Cochrane Database Systematic Review 2014

- Enteral probiotics supplementation significantly reduced the incidence of severe NEC (20 studies, 5529 infants)
- Enteral probiotics reduced mortality (17 studies, 5112 infants)
- No evidence in the reduction of late onset sepsis (19 studies, 5338 infants)
- No evidence of systemic infection of probiotics organism
- Probiotics containing either *Lactobacillus* alone or in combination with *Bifidobacterium* were found to be effective

Other Strategies to Prevent NEC

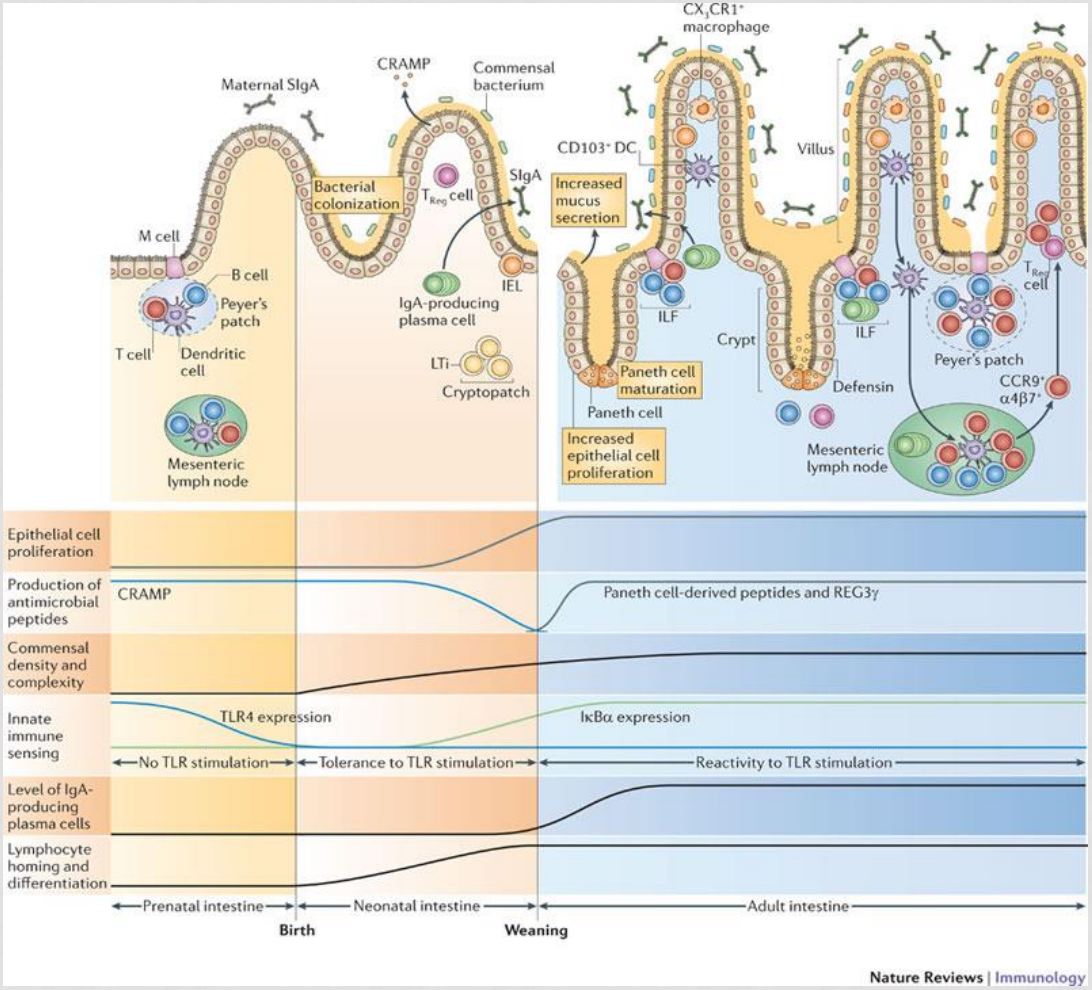
- Human milk based fortifier ✔
- Prebiotics ✔
- Probiotics ✔ ✔
- Lactoferrin
- Oxidents
- Umbilical cord transfusions

Lactoferrin

- A multi functional protein found in various secretory fluids including saliva, tears, and nasal secretions.
- It is found in highest concentrations in human colostrum and breast milk
- It has antimicrobacterial activity and is part of the innate defense, mainly at mucosas.

Barriers - Intestinal

- Breast milk and early nutrition
  - Role of lactoferrin
    - Iron chelation
    - Destabilization of microbial membranes
    - Prevention of microbe adherence
    - Enhancement of neutrophil functions
    - **Lower levels compared to adult**



Oral lactoferrin for the prevention of sepsis and NEC in preterm infants

Pammi and Abrams

Cochrane Database Systemic Reviews 2015

- All RCT using oral lactoferrin at any dose or duration to prevent sepsis or NEC in preterm infants
- Evidence of moderate to low quality suggests that oral lactoferrin prophylaxis with or without probiotics decreases late onset sepsis and but does not reduce NEC stage 2 or greater unless used in combination with a probiotic in preterm infants without adverse affects.

Other Strategies to Prevent NEC

- Human milk based fortifier ✔
- Prebiotics ✔
- Probiotics ✔ ✔
- Lactoferrin ✔
- Oxidents
- Umbilical cord transfusions

Shielding Parenteral Nutrition from Light Improves Survival Rates in Premature Infants: A Meta-Analysis

J Parenter Enteral Nutr 2015

- Preterm infants face an imbalance between high oxidant loads and immature antioxidant defenses.
- Oxidants are generated with treatment such as supplemental oxygen.
- Parenteral nutrition unfortunately represent a further source of oxidants

Shielding Parenteral Nutrition from Light Improves Survival Rates in Premature Infants: A Meta-Analysis

J Parenter Enteral Nutr 2015

- These oxidants originate from the interaction between photoexcited riboflavin contained in multivitamins solutions and ascorbic acid, amino acids, lipids.
- Concentrations of these peroxides contaminating parenteral solutions (TPN) have a lethal effect on endothelial cells in tissue culture.

Shielding Parenteral Nutrition from Light Improves Survival Rates

	Light Exposed	Light Exposed	Light Protected	Light Protected
	Dead	Alive	Dead	Alive
Chessex	3	36	1	37
Bassioumy	17	23	9	31
Chessex	7	31	2	16
Laborle	25	269	16	277
TOTAL	**52 (12.7%)**	**359**	**28 (7.0%)**	**361**

Shielding Parenteral Nutrition from Light Improves Survival Rates in Premature Infants: A Meta-Analysis

J Parenter Enteral Nutr 2015

- Conclusion and speculation of this data will be used to investigate why mortality is reduced??
- Reduction in infection??
- Reduction in NEC ??
- More investigation to come

Other Strategies to Prevent NEC

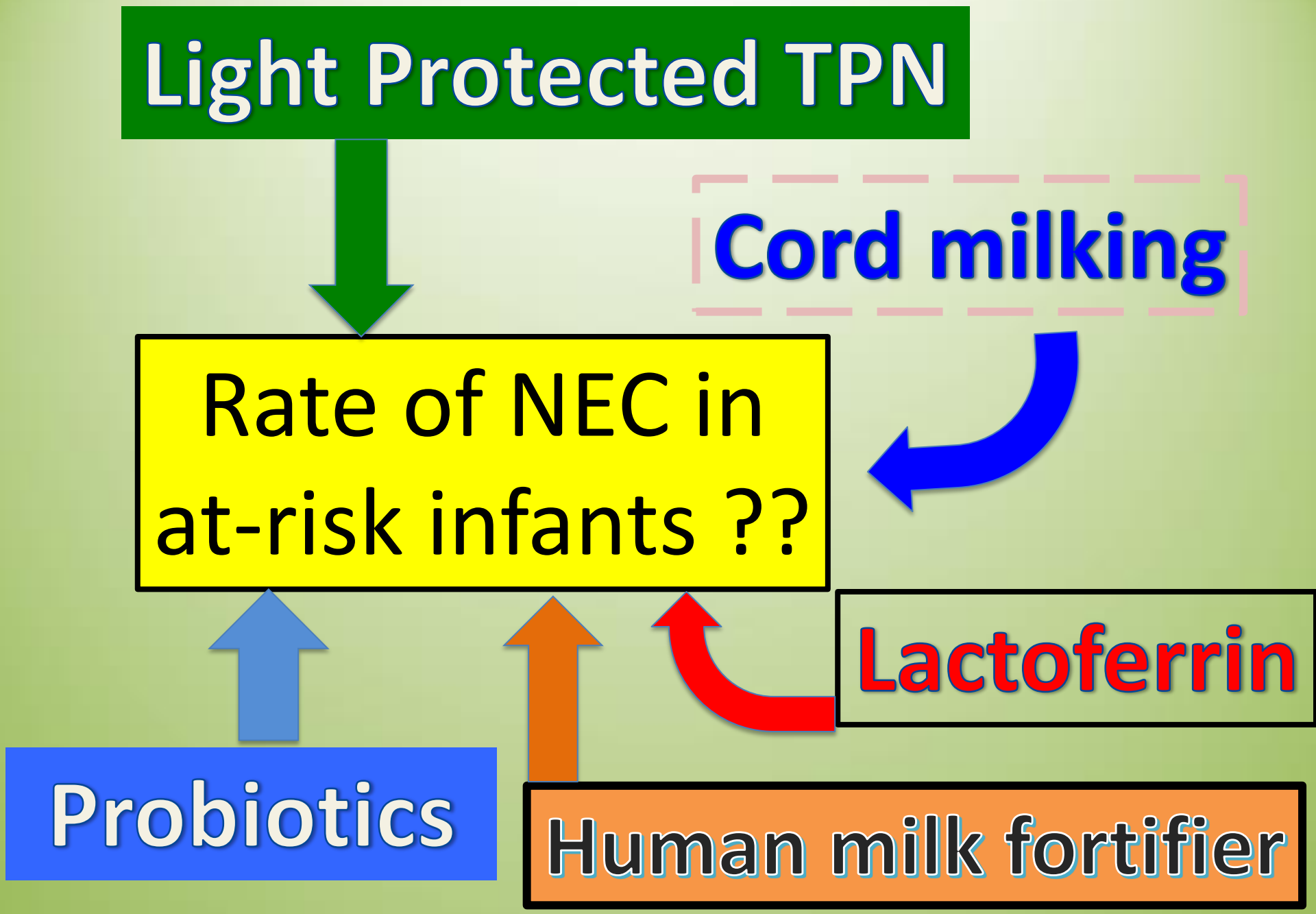
- Human milk based fortifier ✔
- Prebiotics ✔
- Probiotics ✔ ✔
- Lactoferrin ✔
- Oxidents ✔
- Umbilical cord transfusions

Umbilical cord milking reduces need for red cell transfusions and improved neonatal adaptation in preterm infants: Meta-analysis

J Obstet Gynaecol Res 2015

- 6 studies were included using UCM/ICC
- 292 preterm infants received UCM
- 295 preterm infants received ICC
- Significant reduction in IVH and NEC and mortality in the UCM vs the ICC

Conclusion/Speculation

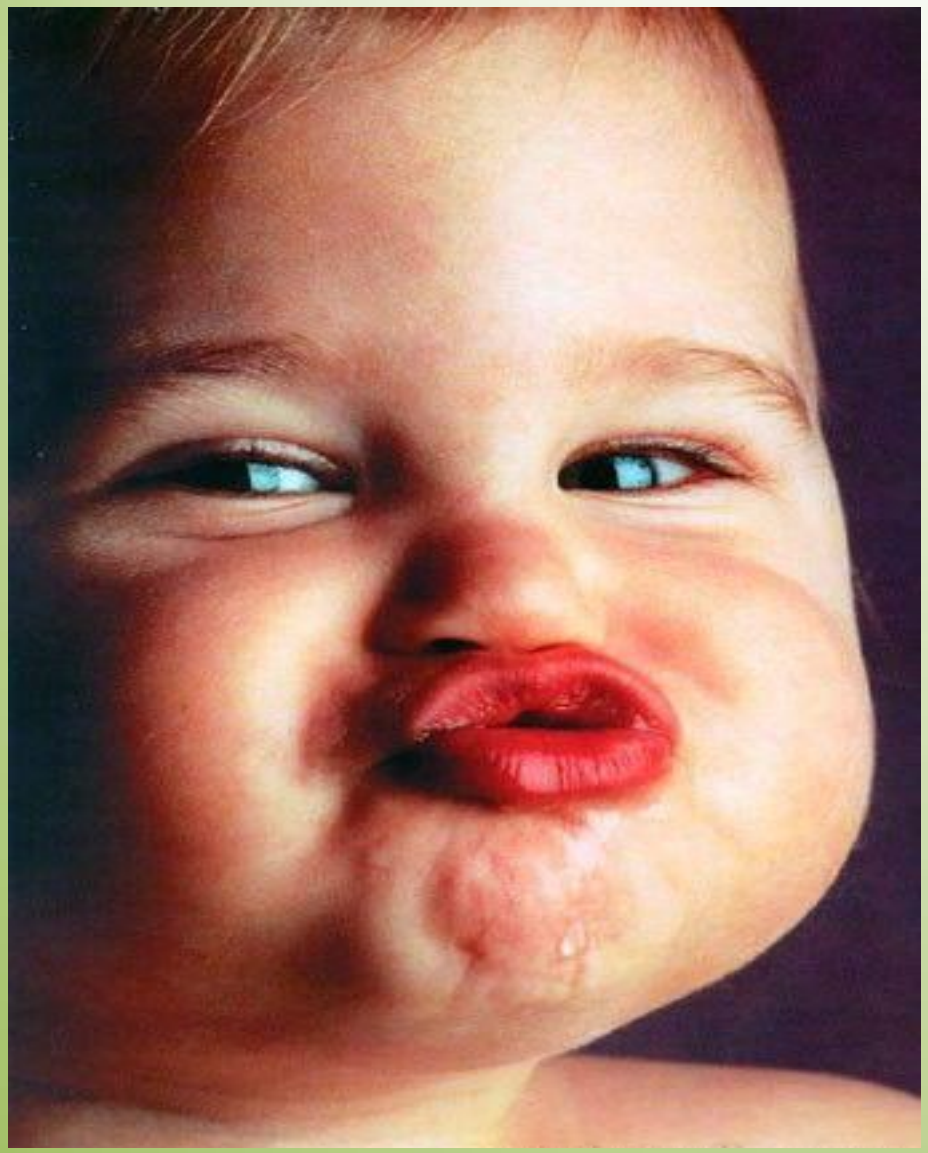

Light Protected TPN
Cord milking
Rate of NEC in at-risk infants ??
Lactoferrin
Probiotics
Human milk fortifier

Summary

- What is the rate of NEC in your nursery for patients with B. Wt < 1500 grams ?
- What is the rate of NEC in your nursery for patients with B. Wt < 1250 grams?
- Do you have a standard approach to feeding these infants at high risk for NEC?
- Do you use exclusive human milk feeding (EBM/DEBM) for these at risk infants?

Summary

- The integration of theses suggested “additional” therapies into your feeding approach for the infant at risk will depend on the research over the next 3-5 years involving
  - Human milk fortifier
  - Lactoferrin
  - Probiotics
  - Umbilical cord milking
  - Shielding Parenteral Nutrition



Thanks for listening!!

Questions??