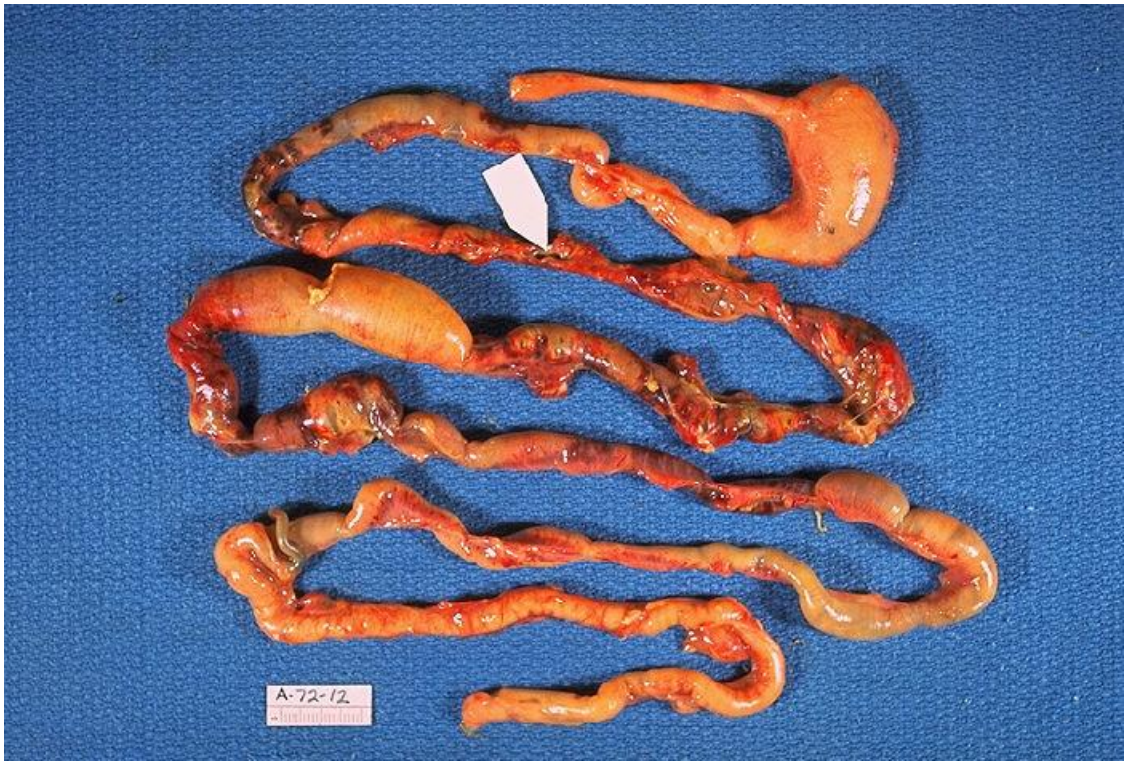
Necrotizing Enterocolitis: What is it and what can we do about it?

Christine Culpepper, MD

Objectives

- Describe the pathophysiology of Necrotizing Enterocolitis (NEC)
- Discuss presentation, diagnosis and management of NEC
- Identify infants at risk for NEC in the NICU
- Apply preventative measures in own units to reduce the incidence of NEC

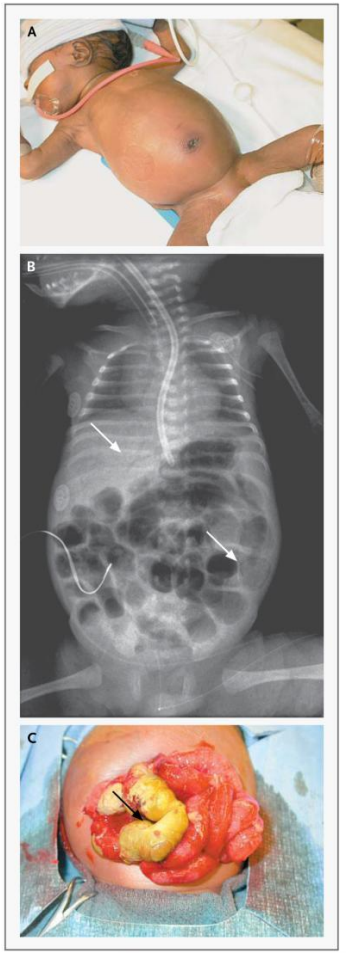


Acute inflammatory necrosis of the bowel

NECROTIZING ENTEROCOLITIS (NEC)

NEC

- Most common severe neonatal gastrointestinal emergency
- Occurs in 1-3 per 1000 live births
  - VLBW infants
  - Term infants with CHD
- Morbidity
  - Intestinal stricture
  - Short bowel syndrome
  - Neurodevelopmental impairment
- Mortality ranges from 25-50%



History

- Pathology was described in 1952, when Schmidt and Quaiser labeled it as *enterocolitis ulcerosa necroticans.*

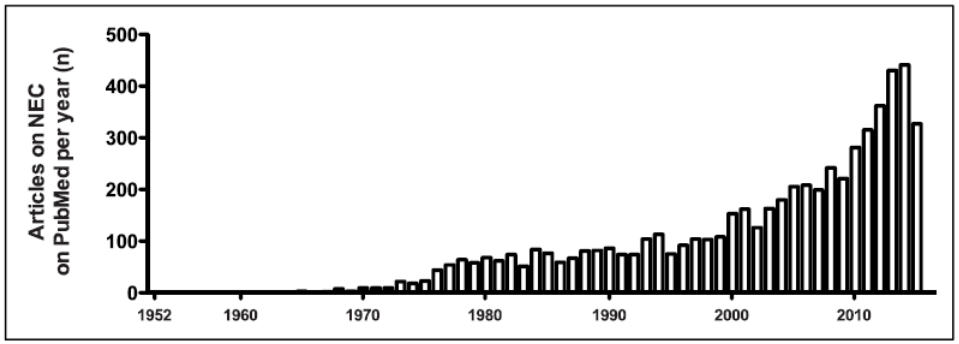
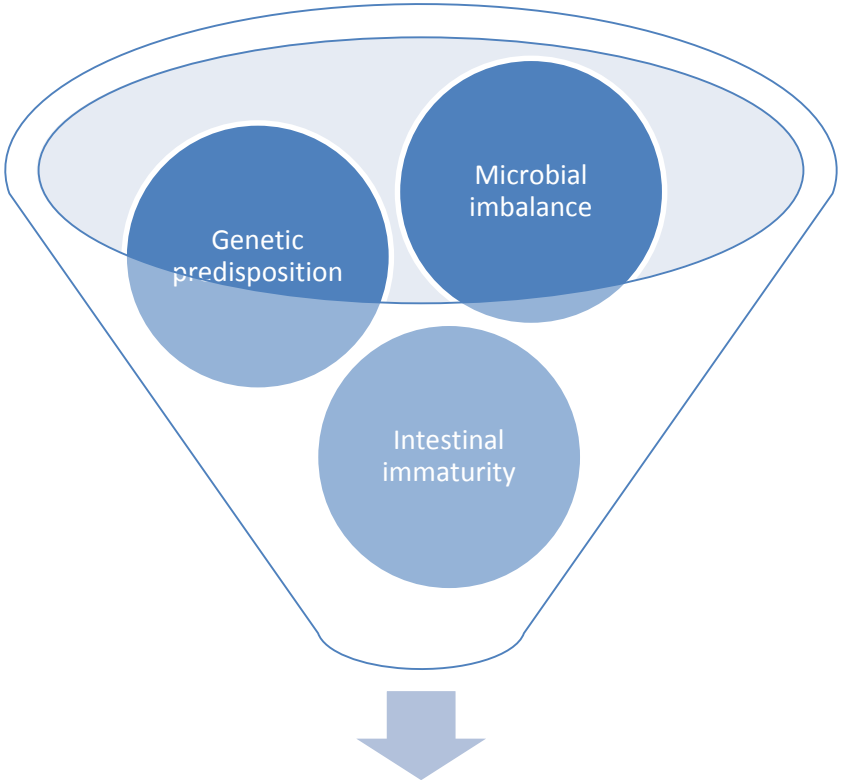


Figure 1. Number of articles published per year on PubMed since 1952 to 2015 (July).

Pathophysiology



Neu 2014

Intestinal Immaturity

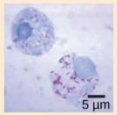
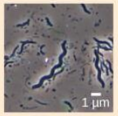
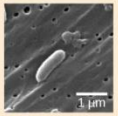
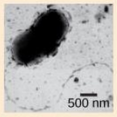
- Premature infants have immature:
  - Intestinal motility
  - Digestion
  - Absorption
  - Immune defenses
  - Barrier function

- Increased risk for intestinal injury

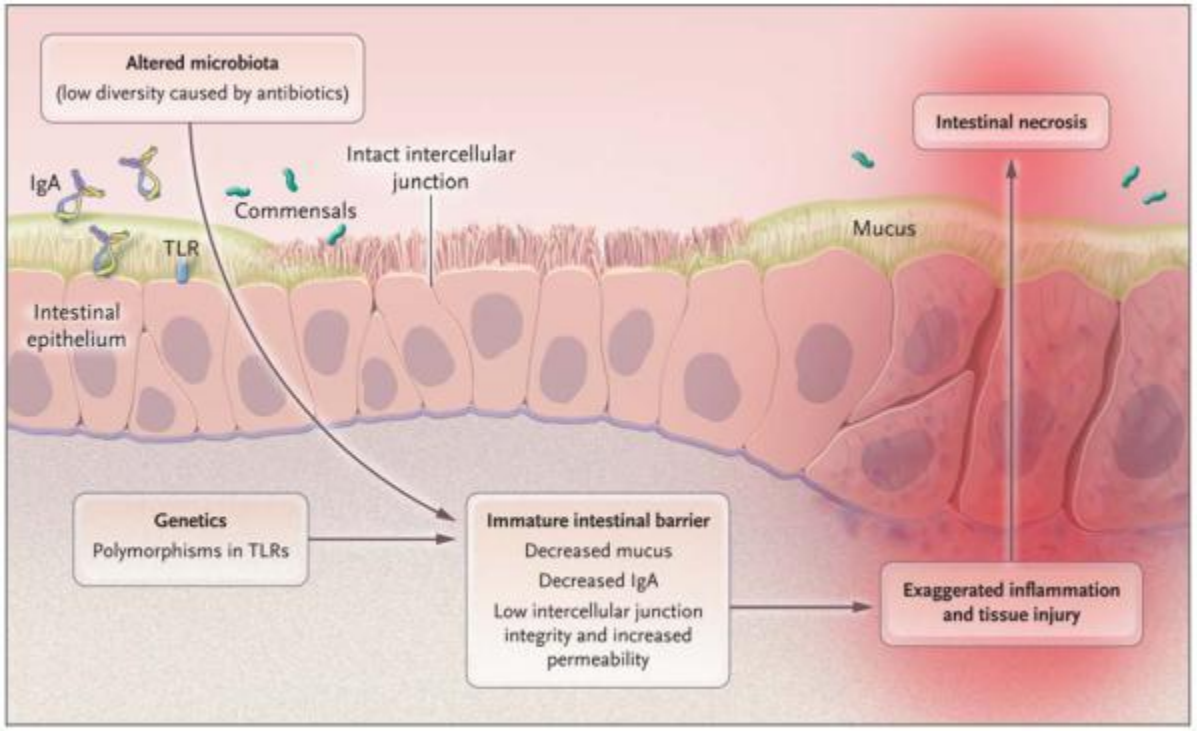
Microbes

- Culture
  - No single organism consistently implicated
- Gas-forming organisms → pneumatosis
- “Outbreaks”
- Molecular methods
  - Proteobacteria
  - Lower diversity of microbiota

Bacteria of Phylum Proteobacteria

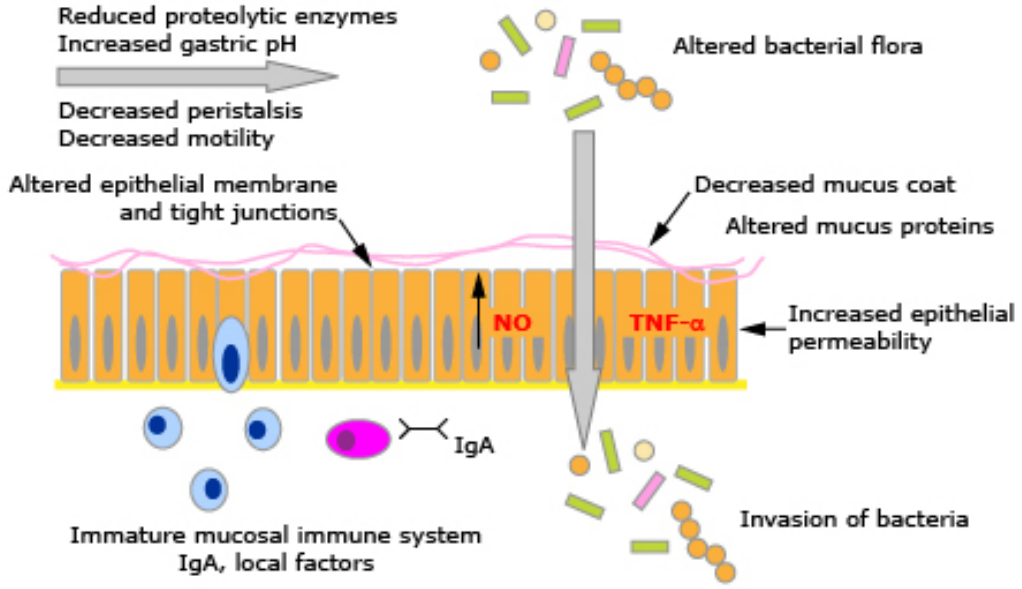
Class	Representative organisms	Representative micrograph
Alpha Proteobacteria Some species are photoautotrophic but some are symbionts of plants and animals and others are pathogens. Eukaryotic mitochondria are thought be derived from bacteria in this group.	*Rhizobium* Nitrogen-fixing endosymbiont associated with the roots of legumes *Rickettsia* Obligate intracellular parasite that causes typhus and Rocky Mountain Spotted Fever (but not rickets, which is caused by Vitamin C deficiency)	 *Rickettsia rickettsia*, stained red, grow inside a host cell.
Beta Proteobacteria This group of bacteria is diverse. Some species play an important role in the nitrogen cycle.	*Nitrosomas* Species from this group oxidize ammonia into nitrite. *Spirillum minus* Causes rat-bite fever	 *Spirillum minus*
Gamma Proteobacteria Many are beneficial symbionts that populate the human gut, but others are familiar human pathogens. Some species from this subgroup oxidize sulfur compounds.	*Escherichia coli* Normally beneficial microbe of the human gut, but some strains cause disease *Salmonella* Certain strains cause food poisoning or typhoid fever *Yersinia pestis* Causative agent of Bubonic plague *Psuedomonas aeruginosa* Causes lung infections *Vibrio cholera* Causative agent of cholera *Chromatium* Sulfur-producing bacteria that oxidize sulfur, producing H_2S	 *Vibrio cholera*
Delta Proteobacteria Some species generate a spore-forming fruiting body in adverse conditions. Others reduce sulfate and sulfur.	*Myxobacteria* Generate spore-forming fruiting bodies in adverse conditions *Desulfovibrio vulgaris* Aneorobic, sulfate-reducing bacterium	 *Desulfovibrio vulgaris*
Epsilon Proteobacteria Many species inhabit the digestive tract of animals as symbionts or pathogens. Bacteria from this group have been found in deep-sea hydrothermal vents and cold seep habitats.	*Campylobacter* Causes blood poisoning and intestinal inflammation *Heliobacter pylori* Causes stomach ulcers	 *Campylobacter*

Exaggerated Inflammation



Neu 2011

Necrotizing enterocolitis: Susceptibility of premature infants

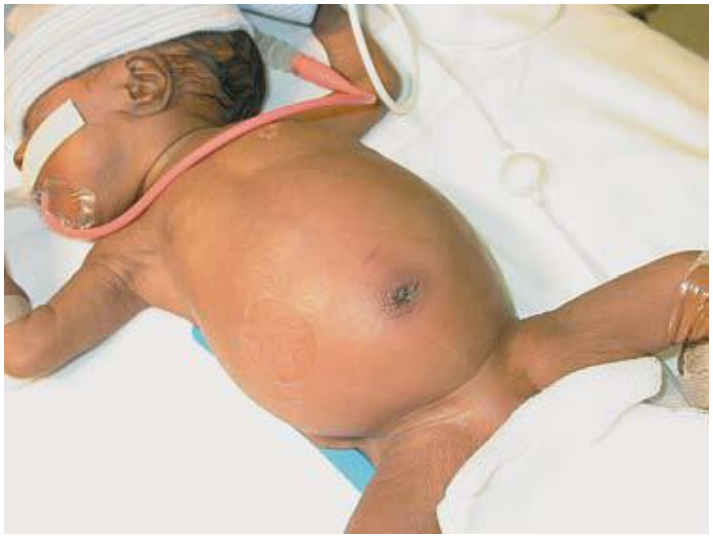


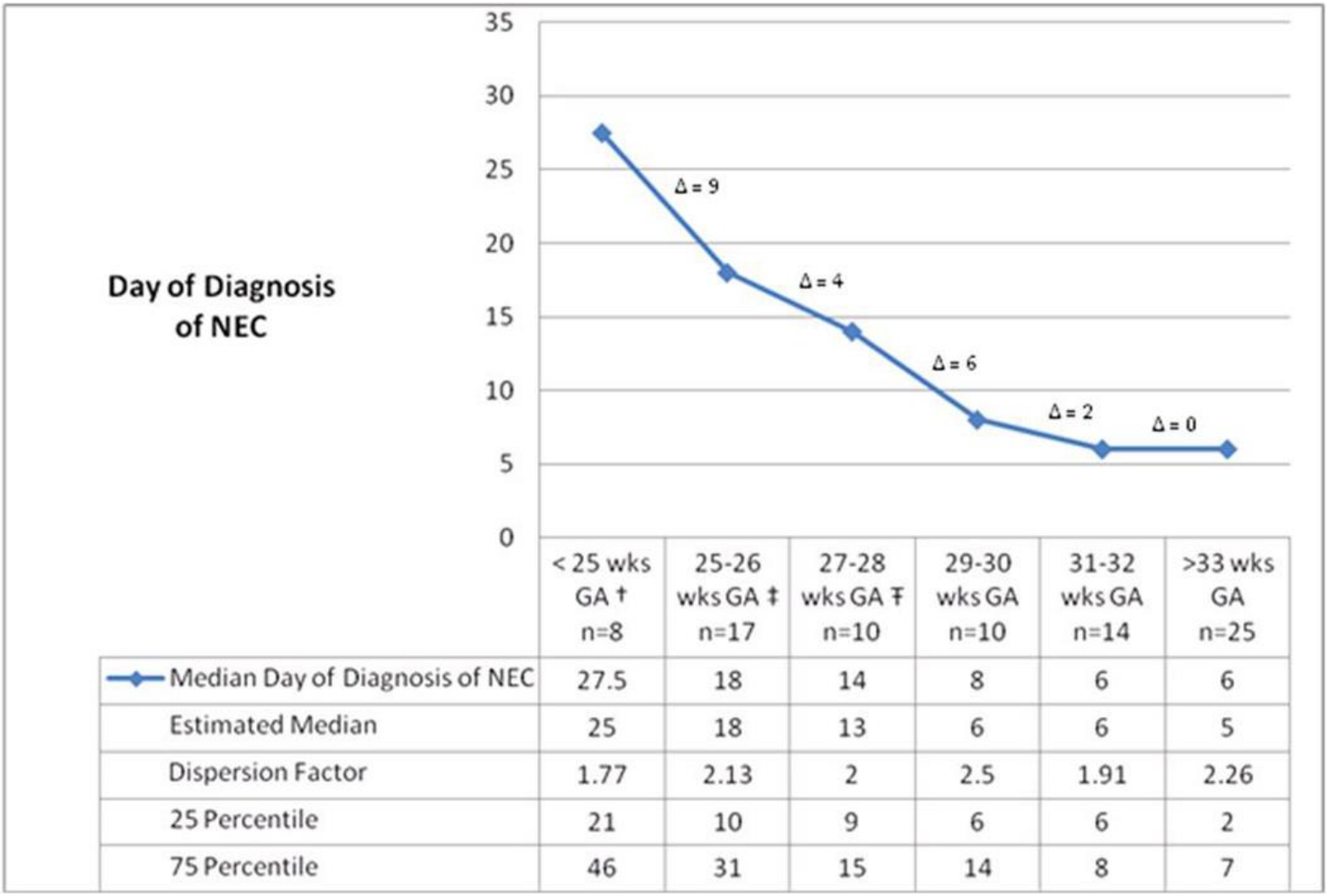
Immaturity of the intestinal epithelial barrier and the neonatal mucosal immune system predispose the premature infant to microbial invasion, which triggers the sequence of events leading to necrotizing enterocolitis (NEC). Stimulation of pro-inflammatory cytokines compromises intestinal defenses. An imbalance between epithelial cell injury and repair leads to a cycle of bacterial invasion, immune activation, uncontrolled inflammation, and gut barrier failure.

NO: nitric oxide; TNF-α: tumor necrosis factor - alpha.

Presentation

- Age at onset inversely related to GA
- Clinical Presentation
  - Abdominal distension
  - Feeding intolerance
  - Hematochezia
  - Non-specific systemic signs



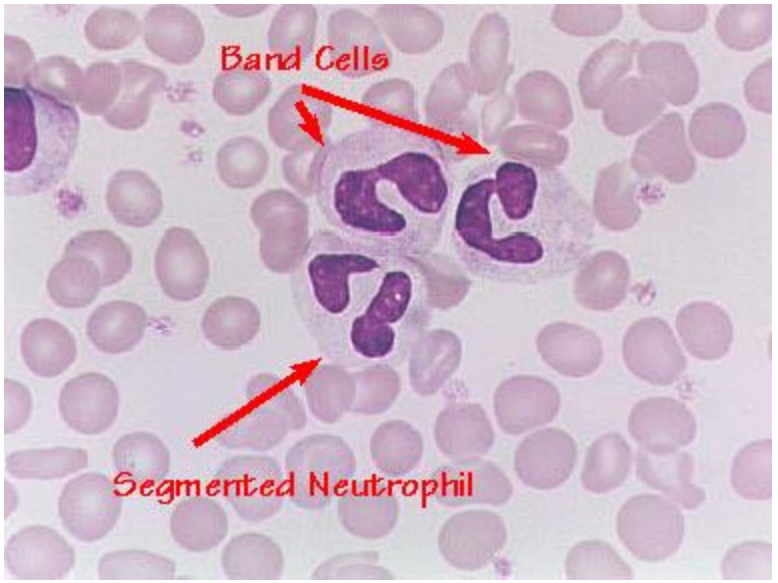


	< 25 wks GA † n=8	25-26 wks GA ‡ n=17	27-28 wks GA ₸ n=10	29-30 wks GA n=10	31-32 wks GA n=14	>33 wks GA n=25
Median Day of Diagnosis of NEC	27.5	18	14	8	6	6
Estimated Median	25	18	13	6	6	5
Dispersion Factor	1.77	2.13	2	2.5	1.91	2.26
25 Percentile	21	10	9	6	6	2
75 Percentile	46	31	15	14	8	7

R Gonzales-Rivera J Perinatol 2011

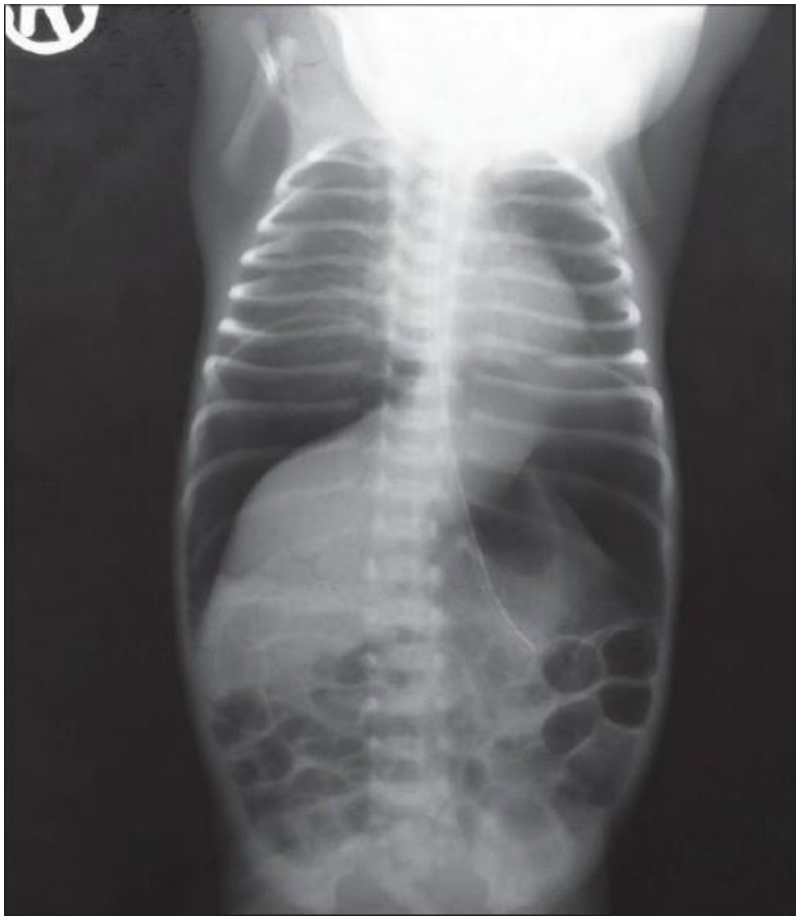
Labs

- Anemia
- L shift neutrophils
- Neutropenia
- Thrombocytopenia
- Raised C-reactive protein (CRP)
- Metabolic acidosis
- Hyponatremia
- Hyperkalemia
- Glucose instability
- Positive blood culture (<40%)



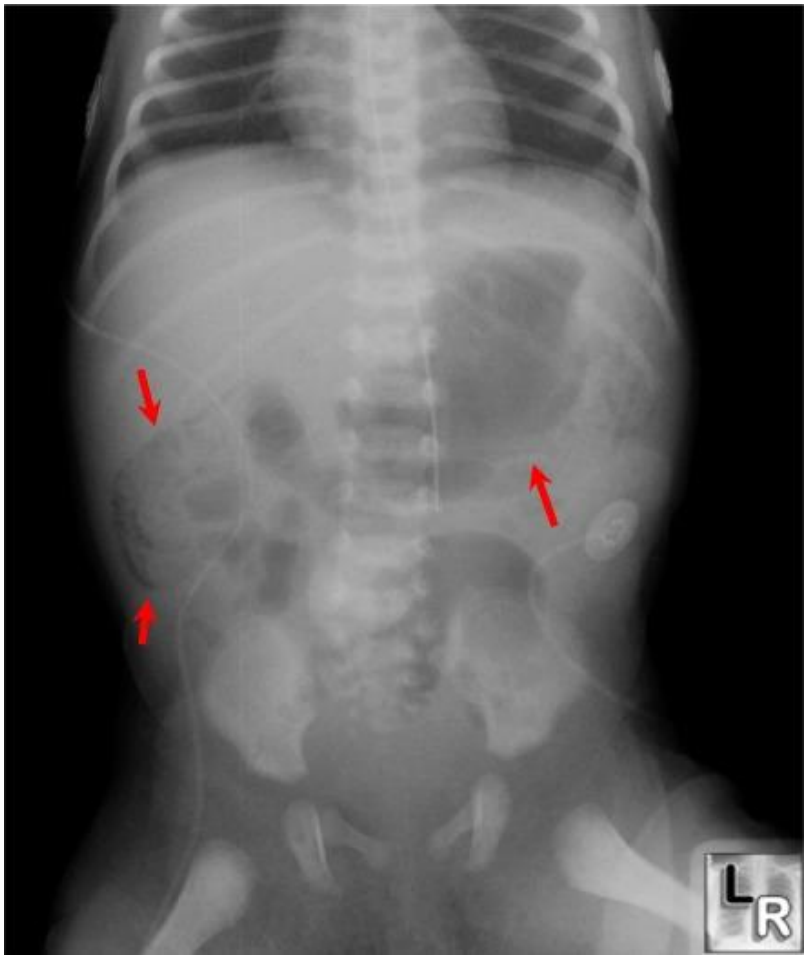
Differential Diagnosis

- Septic ileus
- Hirschsprung disease
- Spontaneous intestinal perforation
- Anal fissure
- Milk protein allergy

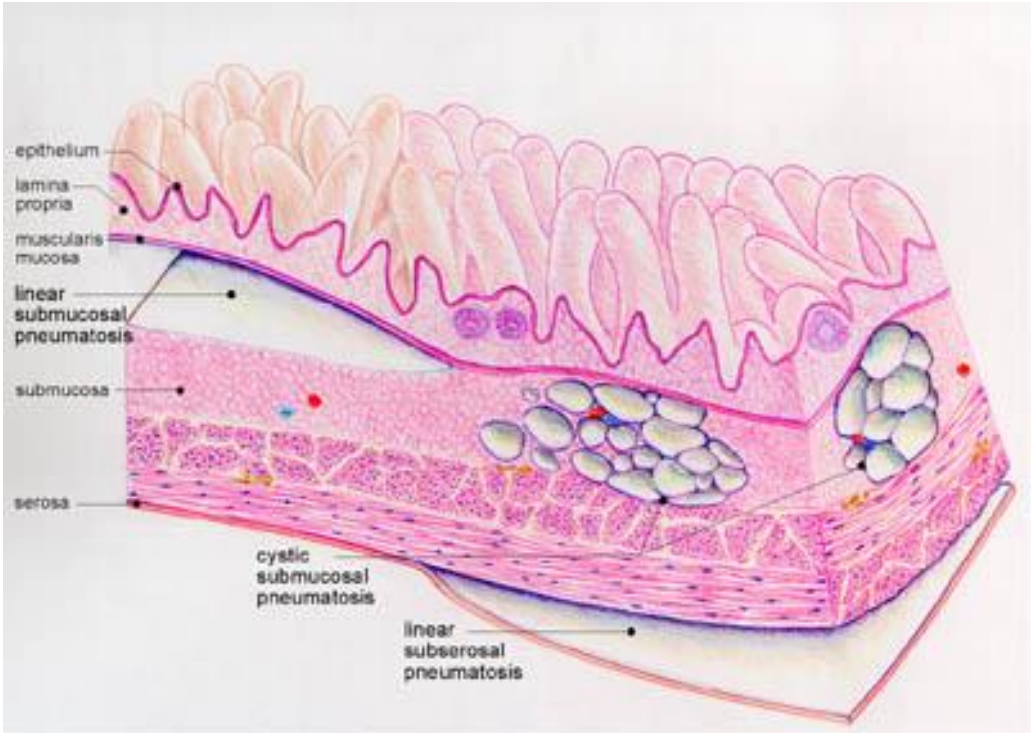


Diagnosis

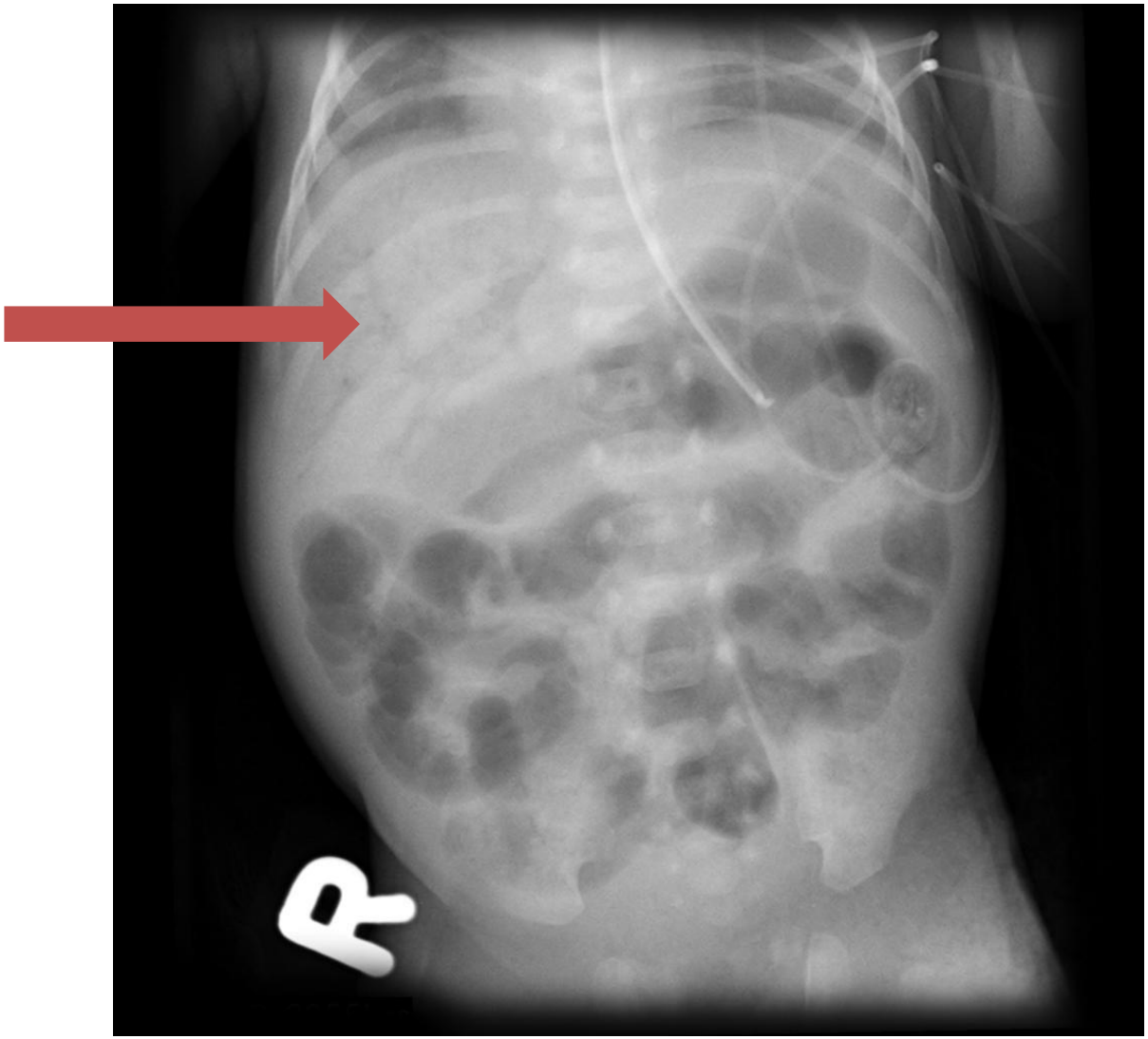
- Pneumatosis intestinalis
- Portal venous gas
- Pneumoperitoneum



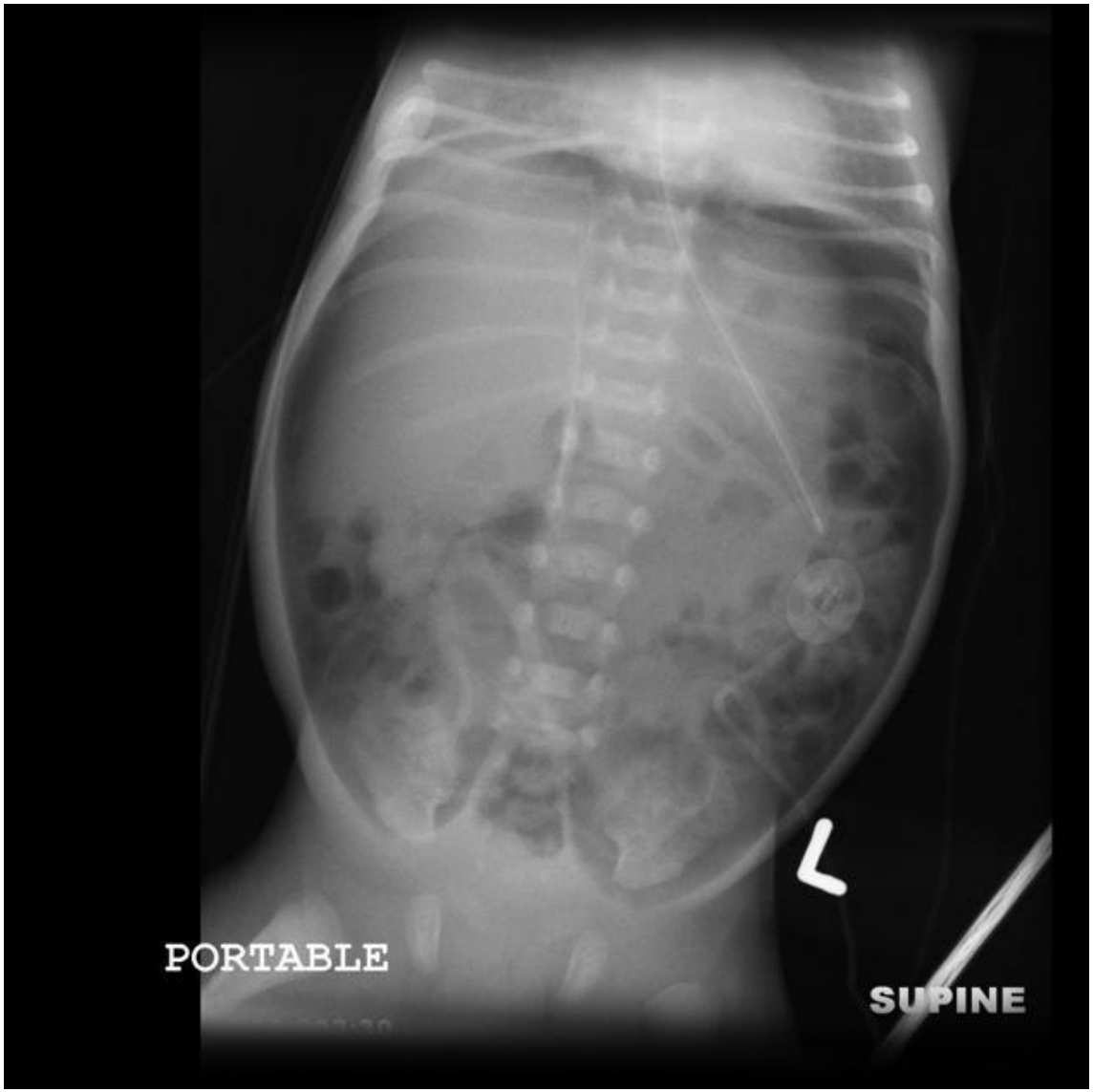
Submucosal and Subserosal Pneumatosis

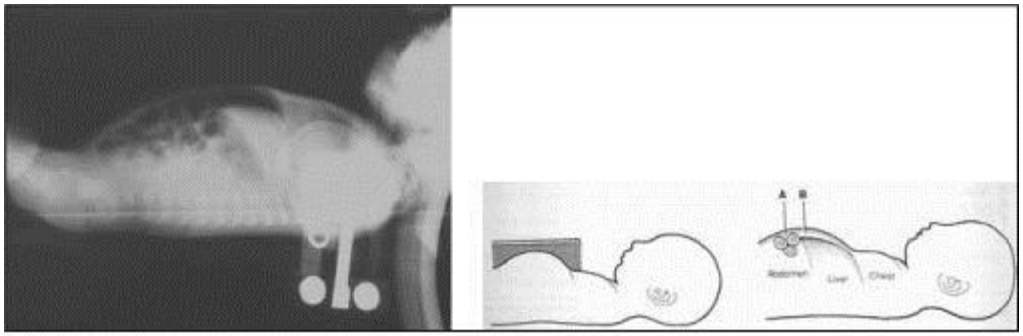


Portal Venous Gas



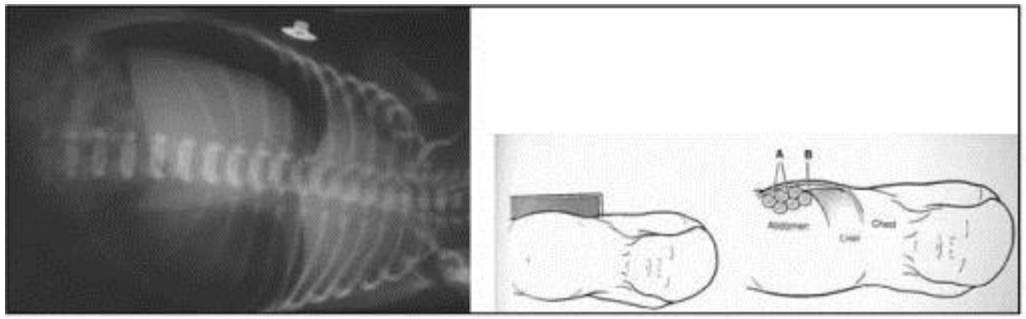
Pneumoperitoneum





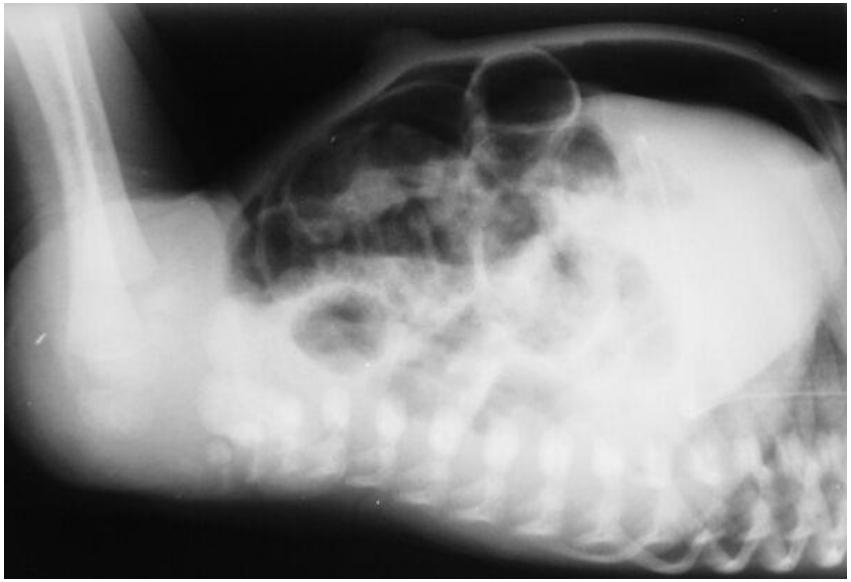
A B

Figure 7(A,B). A: Abdominal plain x-ray obtained in dorsal decubitus with horizontal x-ray beam. Free air movement is observed anteriorly within the abdominal cavity. **B:** Scheme demonstrating the NN positioning to be adopted for study in dorsal decubitus with horizontal beam to demonstrate pneumoperitoneum (reference 16).

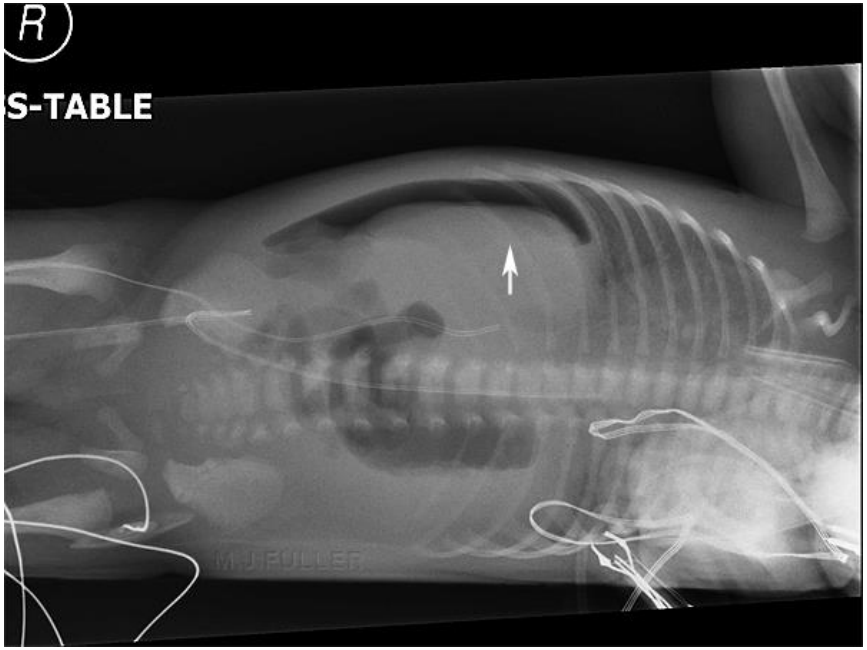


A B

Figure 8(A,B). A: Abdominal x-ray film obtained in left lateral decubitus with horizontal x-ray beams, left lateral decubitus with horizontal x-ray beams, where pneumoperitoneum is demonstrated between the liver and the right abdominal wall. **B:** Scheme demonstrating the NN positioning to be adopted for study in left lateral decubitus with horizontal beam to demonstrate pneumoperitoneum (reference 16).

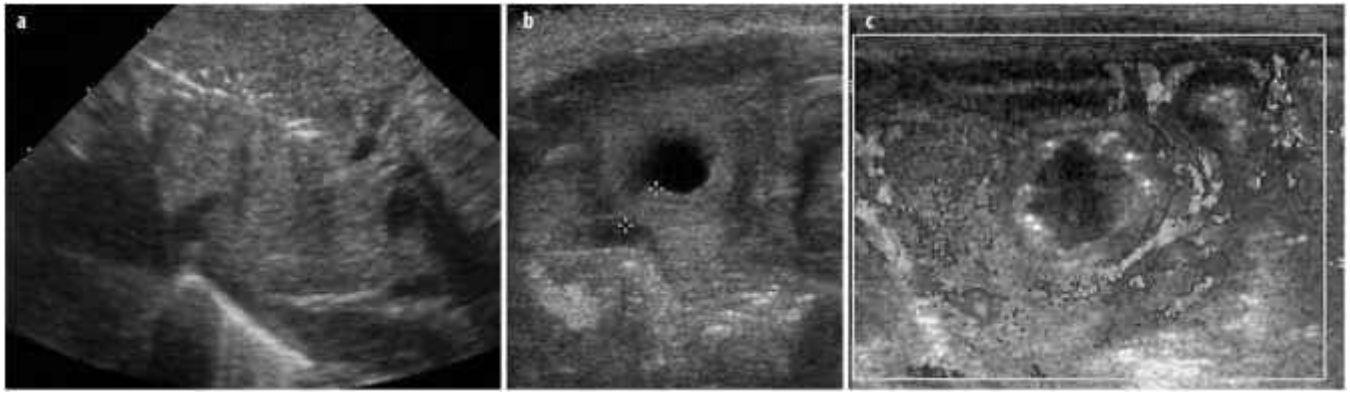


Cross table lateral



Left lateral decubitus

Ultrasound



a. Portal venous gas in liver
b. Thickening of bowel wall
c. Intramural gas and no blood flow to bowel

Modified Bell's Staging Criteria

		Systemic Signs	Intestinal Signs	Radiologic Signs
Suspected	IA	Temperature instability, apnea, bradycardia	Occult blood in stool, mild abdominal distension	Normal or mild ileus
	IB		+ Gross blood in stool	
Definite	IIA		+ Absent bowel sounds	+ Pneumatosis
	IIB	+ mild metabolic acidosis, mild thrombocytopenia	+ Definite abdominal tenderness, abdominal cellulitis	+ Portal venous gas
Advanced	IIIA	+ hypotension, respiratory acidosis, DIC, neutropenia	+ Generalized peritonitis	+ Ascites
	IIIB			+ Pneumoperitoneum

Walsh and Kleigman 1986

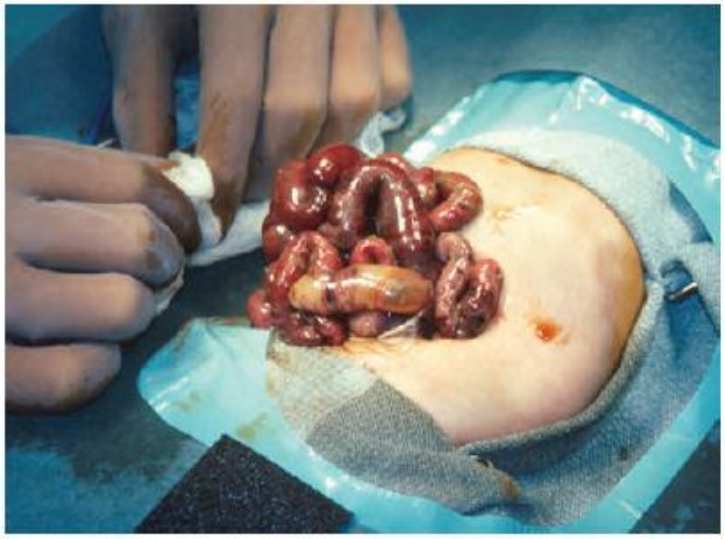
Management

Medical

- Supportive care
- Bowel rest
- Abdominal decompression
- Broad spectrum antibiotics

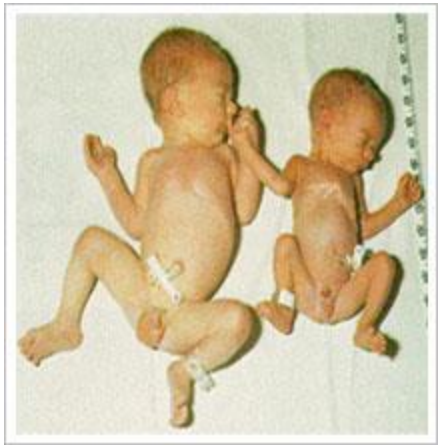
Surgical

- Exploratory laparotomy
- Primary peritoneal drainage



Infants at Risk

- PREMATURITY
- Lower gestational age
- Lower birth weight
- Enteral feedings
- Intrauterine growth restriction



Summary

- NEC is most common severe neonatal gastrointestinal emergency
- Pathophysiology of NEC is multifactorial (intestinal immaturity, microbial imbalance, exaggerated inflammation)
- Diagnose with clinical symptoms and xray/ultrasound
- Management is supportive
- **Prematurity** is greatest risk factor for NEC

Can we change our practice to prevent NEC?

CONTRIBUTING FACTORS

Contributing Factors

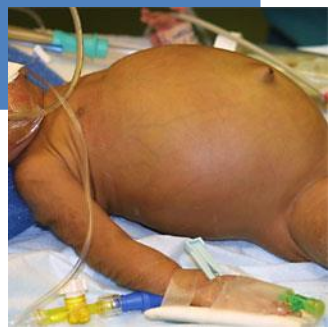
- Treatment with H2 blockers
- Treatment with antibiotics
- Prolonged NPO
- Transfusion with packed red blood cells

Limited gastric acid secretion

Administration of H2 blocker

Gastric bacterial overgrowth

NEC



- Case control study of VLBW infants with NEC
  - Received Zantac, Pepcid or Tagament (IV/PO) > 1 day before diagnosis
    - Median 14 days

TABLE 3 **Conditional Logistic Regression: H2-Blocker Use Truncated According to Gestational Age**

Variable	OR	95% CI	*P*
H2 blocker	1.71	1.34–2.19	<.0001
Male vs female	1.12	0.95–1.31	.1910
Outborn vs inborn	1.51	1.18–1.92	.0008
Apgar score < 7 at 5 min	0.96	0.80–1.16	.6868
Postnatal steroids	1.02	0.83–1.25	.8389

Guillet Pediatrics 2006

Antibiotics

- Most commonly prescribed medication in NICU
- Exposure
  - →Reduce biodiversity
  - →Delay beneficial colonization
  - →Promote pathogenic and/or resistant organisms

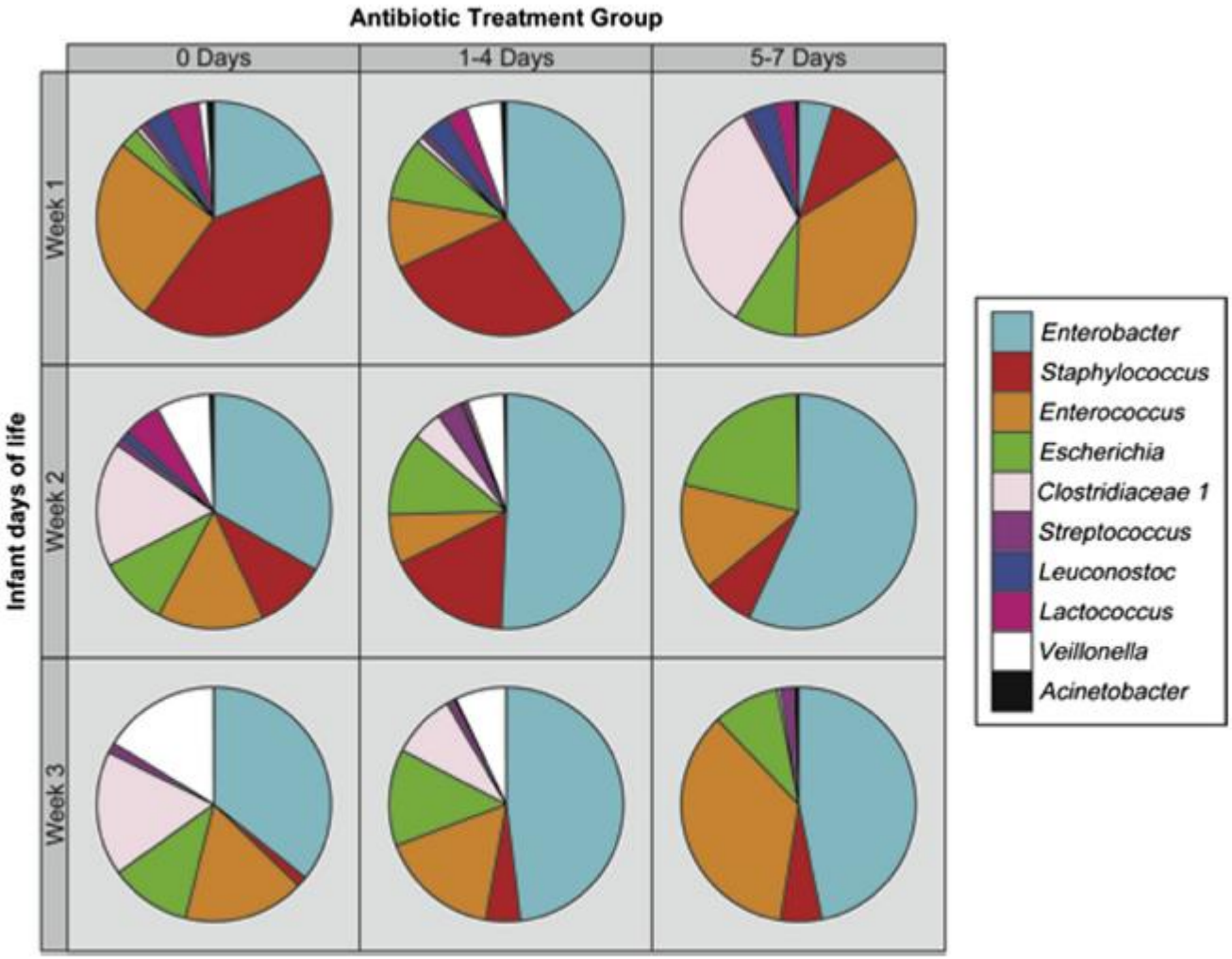
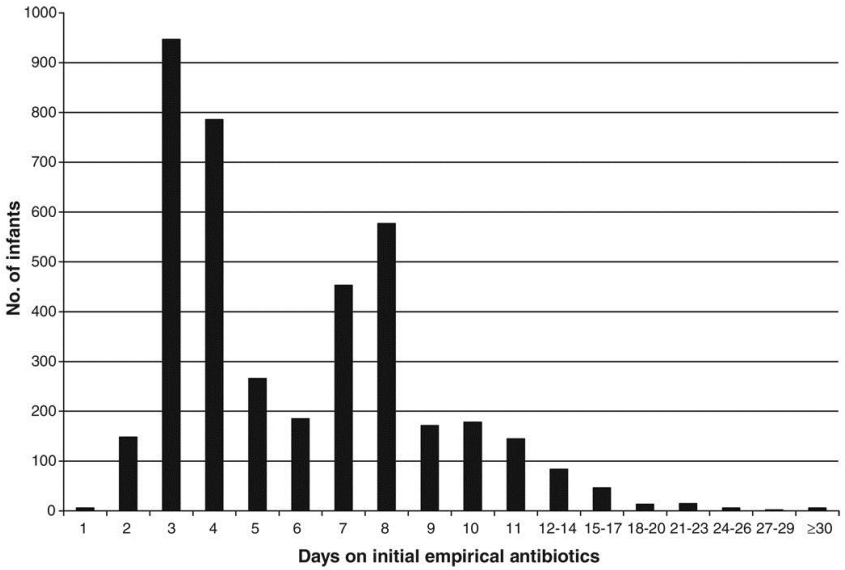


Figure 1. Pie graphs depicting relative abundance of bacterial genera detected in stool specimens from study infants as a function of antibiotic exposure over the first 3 weeks of life.

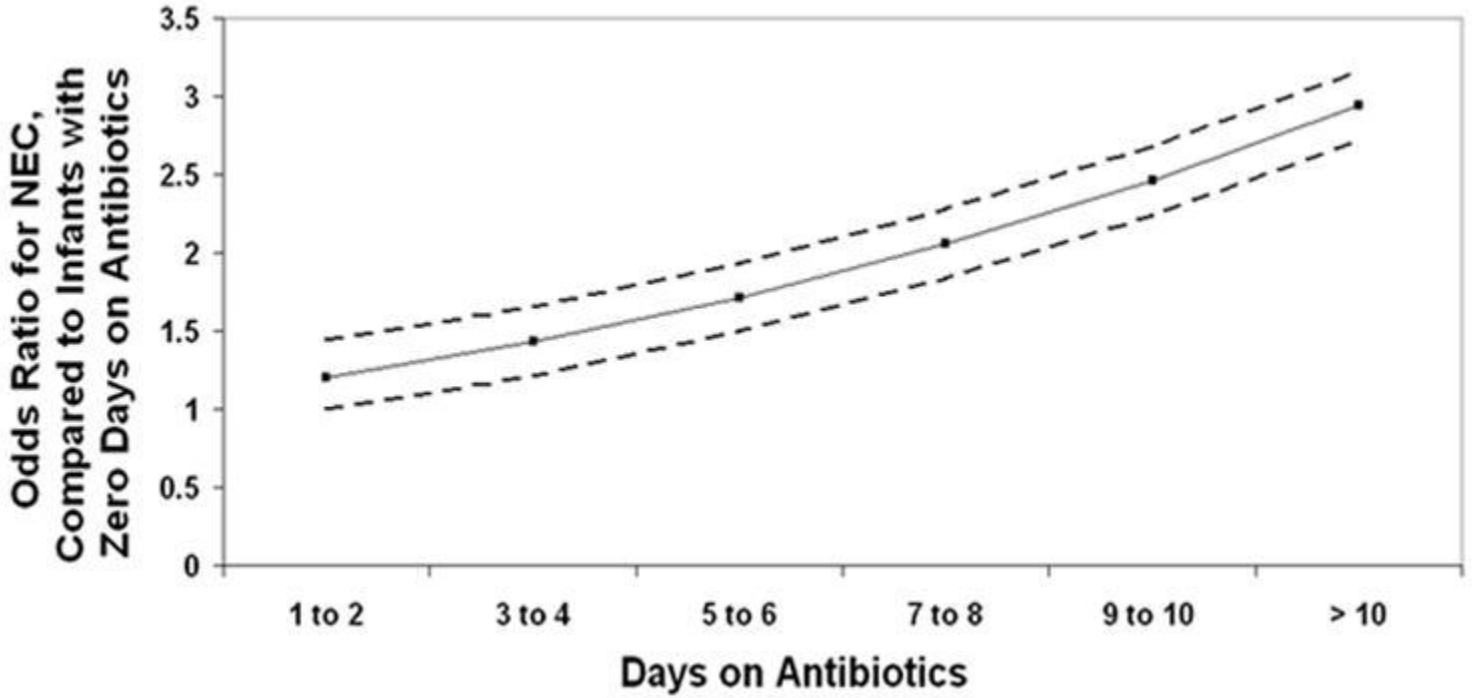
Greenwood J Pediatr 2014

Antibiotics, NEC and ELBW Infants

- ELBW infants with ≥ 1 antibiotic in first 3 days of life
- ~ 4000 infants
- Prolonged treatment: ≥ 5 days with sterile culture results
- ~ 4% increase in odds of NEC or death with each additional day of treatment

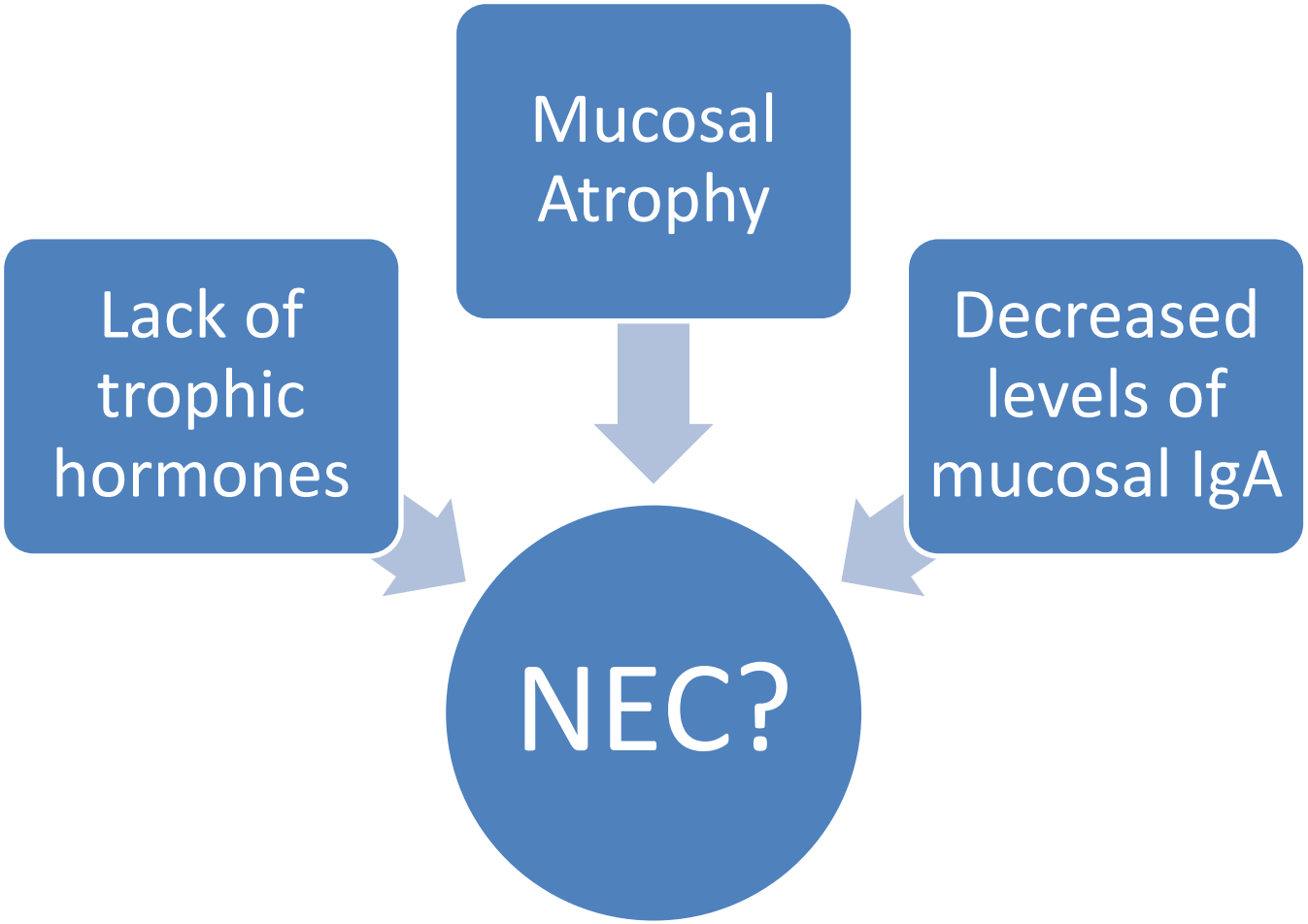


Cotton Pediatrics 2009



Alexander J Pediatr 2011

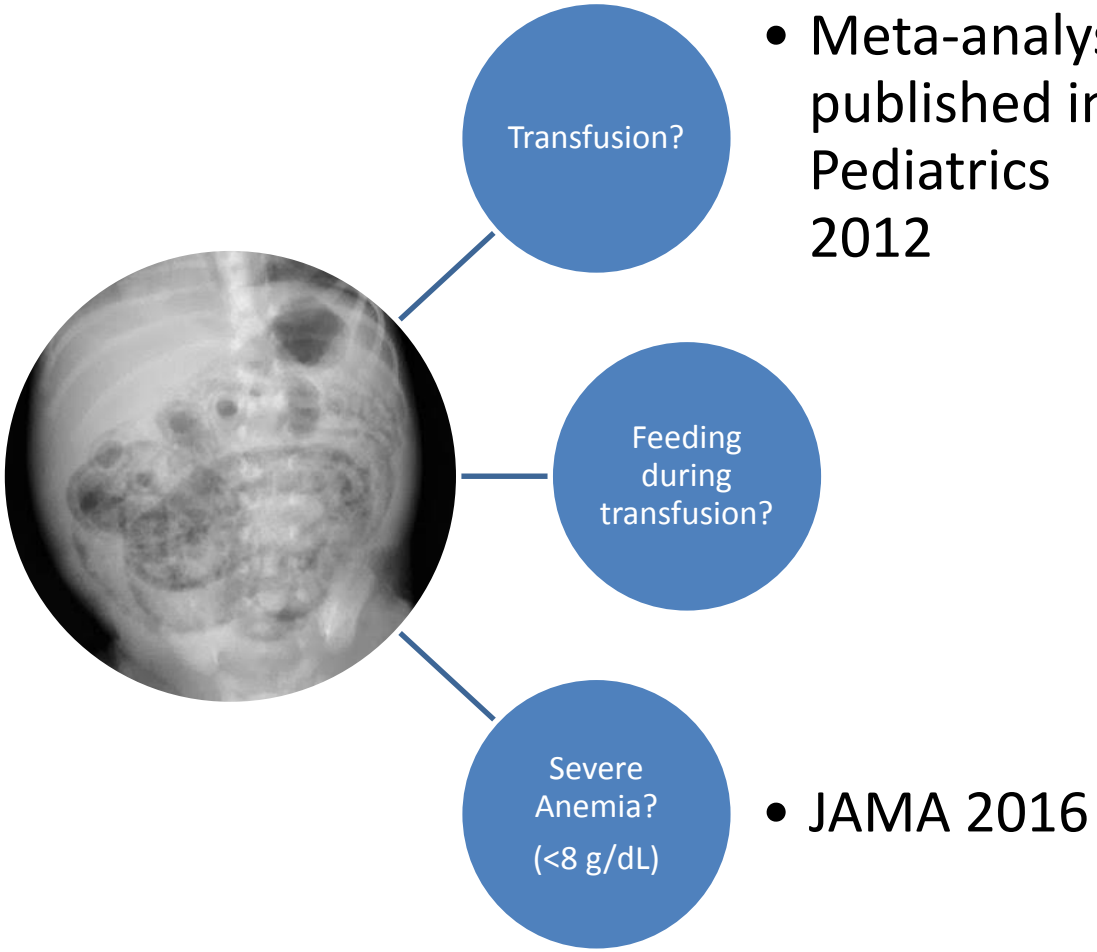
Prolonged NPO



NPO and NEC

- Cochrane Review 2013
  - Nine trials with VLBW infants
    - No difference in NEC
- Am J Perinatol 2015
  - Infants <29 weeks
    - 467 without NEC
      - NPO 3.7 days
    - 234 with NEC
      - NPO 5.6 days

TANEC (Transfusion Associated NEC)



- Meta-analysis published in Pediatrics 2012
- JAMA 2016

Choosing Wisely in Newborn Medicine

1. Avoid routine use of antireflux medications for treatment of symptomatic gastroesophageal reflux disease or for treatment of apnea and desaturation in preterm infants
2. Avoid routine continuation of antibiotic therapy beyond 48 hours for initially asymptomatic infants without evidence of bacterial infection

Potential Changes

- Reflux
  - Reflux precautions
  - If trial medication STOP use if no documented change
- Antibiotics
  - Consider monitoring (with or without blood culture)
  - STOP antibiotics after 48 hours with stable infant and negative culture

Potential Changes

- NPO
  - Minimal enteral feeding, gut priming, or trophic feeding
  - ≤ 24 mL/kg/day
  - SAFE
    - Treatment indomethacin

Potential Changes

- Anemia
  - Threshold for transfusion (asymptomatic)
    - 11.5/34.5 young, sick babies
    - 9.5/28.5 for low FiO2 with NC
    - 7.5/22.5 older, stable babies

Potential Changes

Practice Change to Potentially Reduce TANEC

1. Evaluate unit-specific NEC rate and benchmark unit performance against other unit NEC rates because the rate may be reducible.
2. Communicate the unit-specific NEC rate with every physician, neonatal nurse practitioner, bedside nurse, dietitian and lactation consultant.
2. Encourage mothers to provide human milk as soon as possible by initiating early pumping.[17]
3. Consider feeding pasteurized donor milk if mother's milk is not available.[17]
4. Evaluate unit-specific transfusion practices
    - Are they standardized? [4,5]
    - How are feedings handled before, during and after transfusion?
    - Do most infants < 1500 grams receive > 1 transfusion? [5]
    - Consider developing and implementing a standardized transfusion guideline
5. Consider changing practice to exclusive human milk or nothing by mouth during transfusion and measure the impact on unit-specific NEC rate [14,15]

Gephart Adv Neonatal Care 2012

What else can we do?

PREVENTATIVE STRATEGIES

Prevention of NEC

- Antenatal corticosteroids
- Mother’s own milk (MOM)
- Donor breastmilk
- Standardized feeding protocols
- Probiotics
- Future directions

Antenatal Corticosteroids

Reduces the incidence of respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, sepsis, and neonatal mortality.

MOTHERS' OWN MILK

Feeding preterm infants human milk is associated with a significant reduction in the incidence of NEC

Liquid Gold

- Bioactive components
  - Anti-infectious
    - Immunoglobulins
    - Oligosaccharides
  - Trophic effects
    - Epidermal growth factor
    - Lactoferrin
  - Hormones
    - Pituitary
    - Thyroid
    - Steroid
  - Cells
    - Neutrophils
    - Macrophages
    - T-lymphocytes

Ziegler Karger 2014

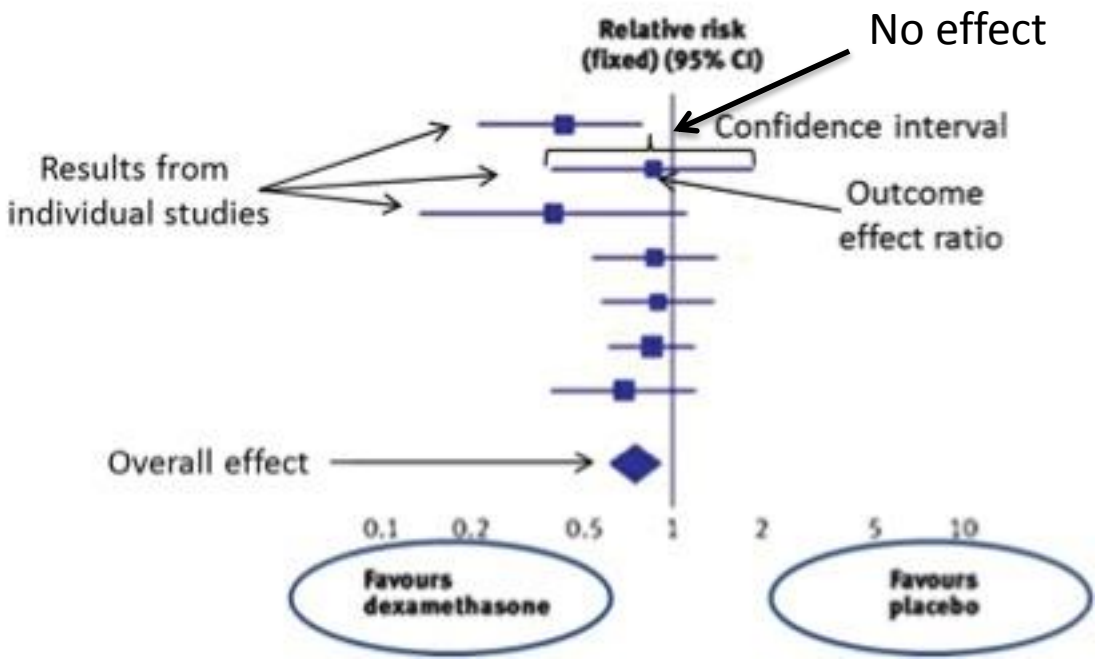
Got Breastmilk?

- Pumping within first hour
- Support for moms
- Breast pumps available through insurance
- Lactation consultants

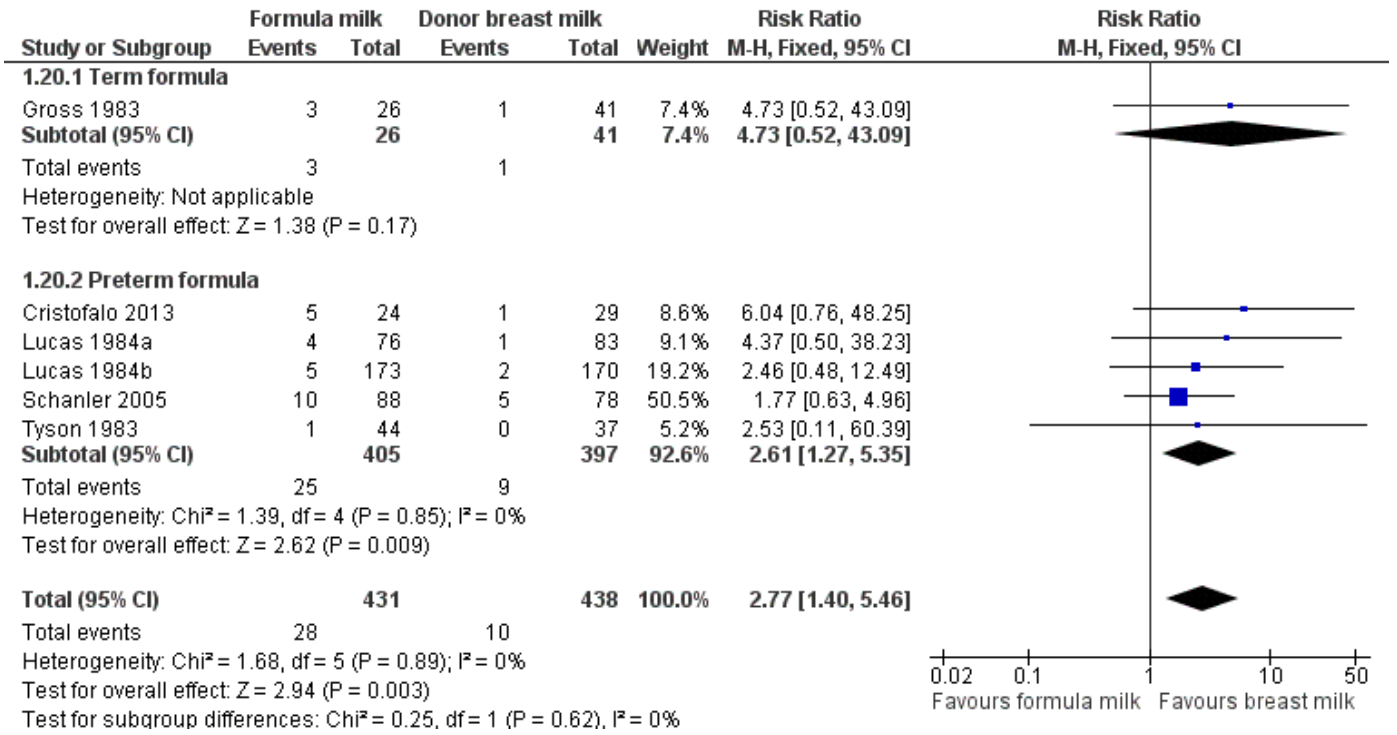
Pasteurized Donor Human Milk (PDHM)

- Strict screening process
- Holder pasteurization
  - ↓ Secretory IgA
  - ↓ Lactoferrin
  - Inactivates lipase

Forest Plots



Formula versus donor breast milk for feeding preterm or low birth weight infants



Cochrane Database of Systematic Reviews
22 APR 2014 DOI: 10.1002/14651858.CD002971.pub3
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002971.pub3/full#CD002971-fig-0006

Standardized Feeding Protocols

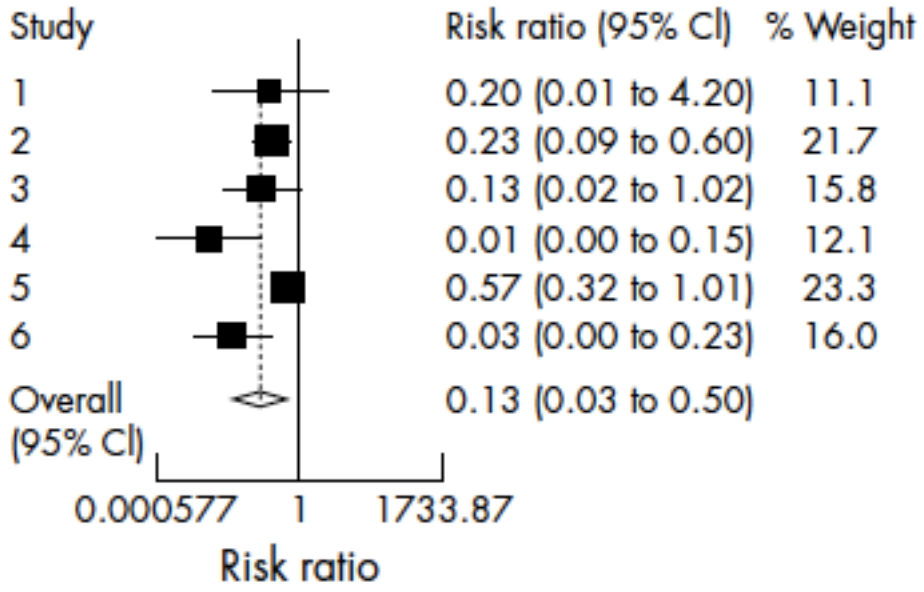


Figure 1 Meta-analysis of the six studies that used a random effects model: 1, Premji *et al*[15]; 2, Kamitsuka *et al*[9]; 3, Brown *et al*[7]; 4, Spritzer *et al*[8]; 5, Kuzma-O'Reilly *et al*[16]; 6, Patole *et al.*[10 11] CI, Confidence interval.

Patole Arch Dis Child Fetal Neonatal Ed 2005

Preventing Necrotizing Enterocolitis With Standardized Feeding Protocols:
Not Only Possible, But Imperative
Sheila M. Gephart, PhD, RN; Corrine K. Hanson, PhD, RD

“ON THE BASIS OF THAT, STANDARDIZED FEEDING PROTOCOLS ARE SIMPLE, CHEAP, EFFECTIVE, AND TRANSMISSIBLE; FURTHERMORE, THEY REDUCE THE RISK OF NEC, IT IS TIME THAT ADOPTION OF STANDARDIZED FEEDING PROTOCOLS IS NO LONGER OPTIONAL BUT IMPERATIVE IN THE QUEST TO PREVENT NEC.”

Figure 1. Feeding Guidelines for Preterm Infants Born <1500grams

Weight (g)	DOF* 1	DOF 2	DOF 3	DOF 4	DOF 5	DOF 6	DOF 7	DOF 8	DOF 9	DOF 10
≤750	≤20	≤20	≤20	≤20	≤20	≤50	≤80 Fortify	≤110	≤140	160
750-1000	≤20	≤20	≤20	≤50	≤80 Fortify	≤110	≤140	160		
1000-1500	≤20	≤20	≤50	≤80 Fortify	≤110	≤140	160			

*DOF = day of feed

Risk Factors supporting conservative advancement of feeds:

Perinatal:

1) Umbilical Cord Gas or infant's first blood gas with metabolic acidosis: *pH <7 and base deficit >-15*
2) Asymmetric IUGR or IUGR with reversed or absent end-diastolic flow
3) Monochorionic twin gestation with Twin-Twin Transfusion Syndrome

Neonatal:

1) Significant cardiovascular instability: *Chest compressions, vasoactive agent requirement, or multiple boluses of crystalloid or colloid.*
2) Symptomatic patent ductus arteriosus
3) Prolonged NPO status greater than 7 days

Probiotics

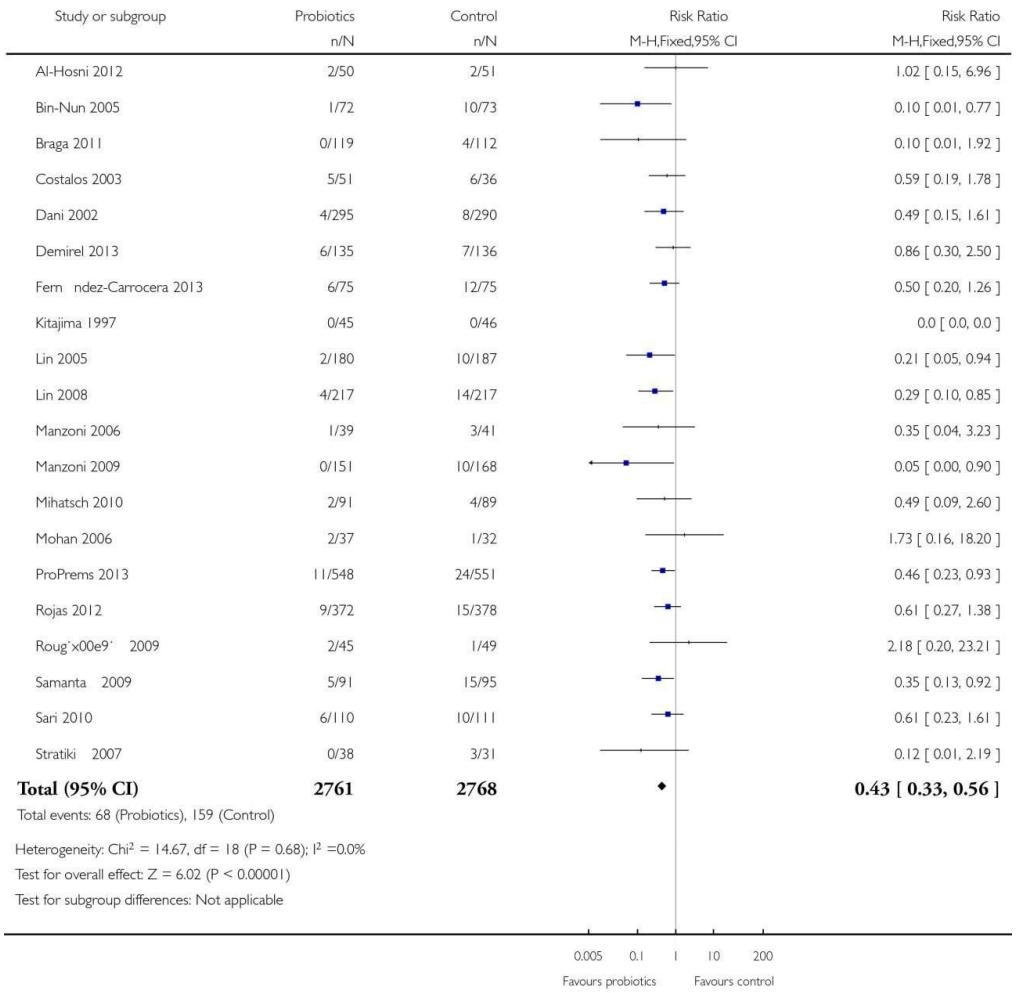
- Live microorganisms
  - Protective barrier
  - Modulate inflammatory response
  - Improved intestinal motility

Probiotics for prevention of necrotizing enterocolitis in preterm infants

Review: Probiotics for prevention of necrotizing enterocolitis in preterm infants

Comparison: 1 Probiotics versus control (all infants)

Outcome: 1 Severe necrotising enterocolitis (stage II-III)



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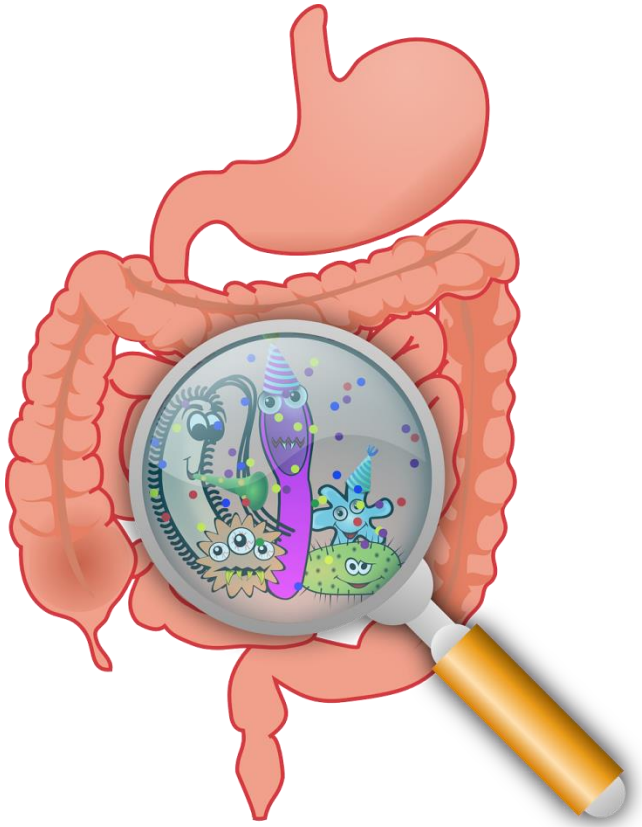
http://onlinelibrary.wiley.com/doi/10.1002/ebch.1976/full#fig1

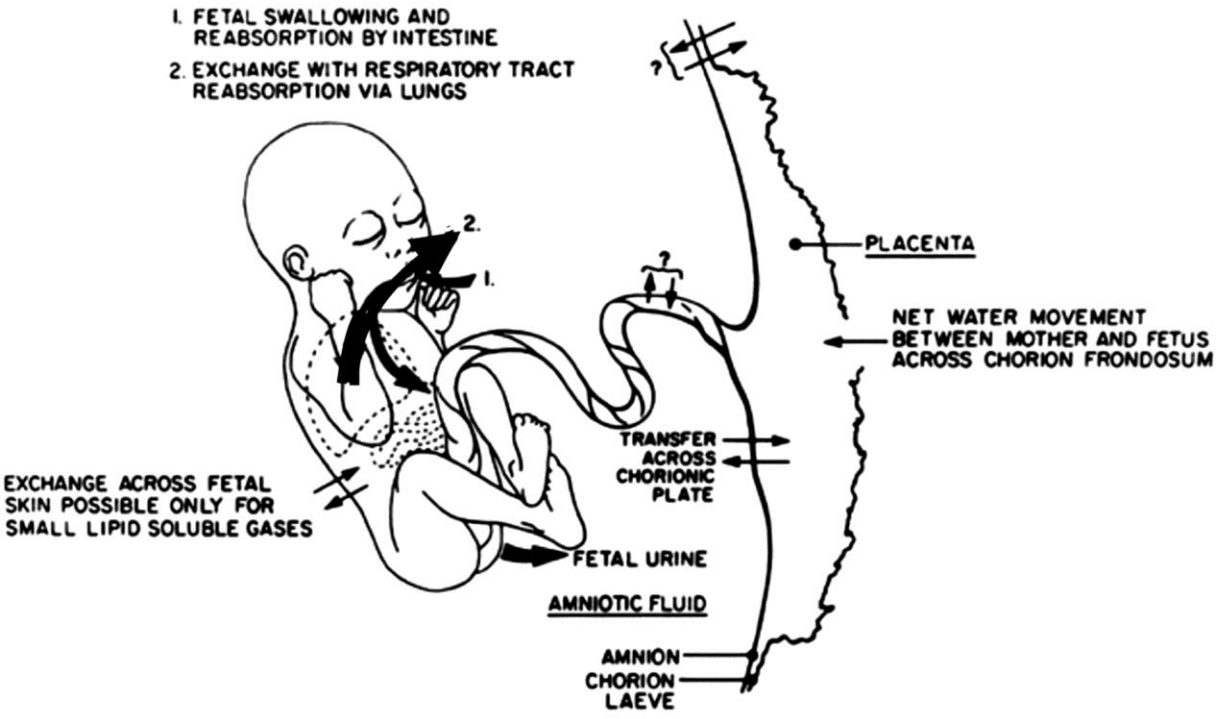
Why isn’t everyone on probiotics?

- Trend for higher incidence sepsis (infants <750g)
- Poor quality control
- Appropriate probiotic and dose?



Future Directions

- Stem cells in **amniotic fluid** as a protective agent against the development of NEC



Conclusion

- NEC is multifactorial
- Prevention is key!
  - Your unit's incidence of NEC compared to other similar units
  - Quality Improvement Project
    - Feeding protocol
      - Use of MOM
      - Decrease days NPO
    - Decrease antibiotic and H2 blocker use
    - Transfusion practice
    - Probiotics

Thank You!

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