



Alphabet soup of preemie problems... MBM & NEC



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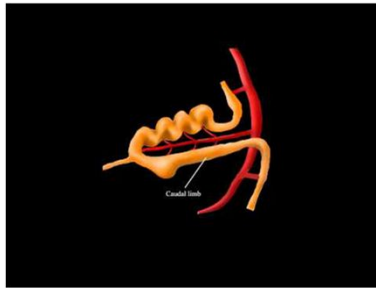
Objectives

Upon completion of this presentation the participant should be able to:

- Describe fetal GI development
- Differentiate between the term and preterm GI system
- Describe nutritional goals for the preterm infant
- Identify risk factors for necrotizing enterocolitis (NEC)
- Identify signs and symptoms of NEC
- Describe medical and surgical treatment plans for NEC

Embryologic GI Development

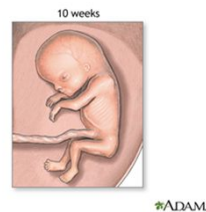
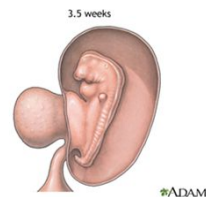
- Fetal gut complete by 20-22 weeks
- Functional development begins in utero and continues into infancy



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Gastrointestinal Development

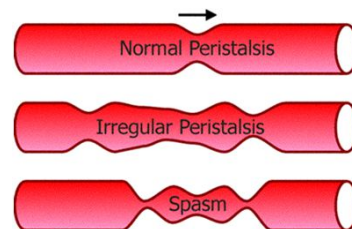
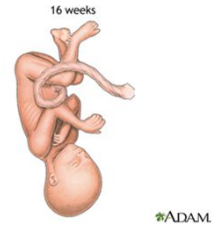
- By 4 weeks the embryo has a single tube intestine, liver bud, and hepatobiliary system
- At 5-9 weeks rapid small intestine growth causes herniation
- By 10 weeks, intestines reenter the abdomen. Villi and microvilli are formed



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Gastrointestinal Development

- At 16 weeks the fetus begins sucking & swallowing, meconium is present
- By 24 weeks the intestines secrete digestive enzymes
- At 32 weeks the fetus begins normal gastric emptying. At 34-36 weeks suck swallow coordination occurs, along with rapid peristalsis



5

Medline Plus. (2017). *Fetal development: MedlinePlus Medical Encyclopedia*. Medlineplus.gov. Retrieved 15 April 2017, from <https://medlineplus.gov/ency/article/002398.htm>


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How long are the small intestines?

- The intestines are the largest part of our body that interact with the external environment

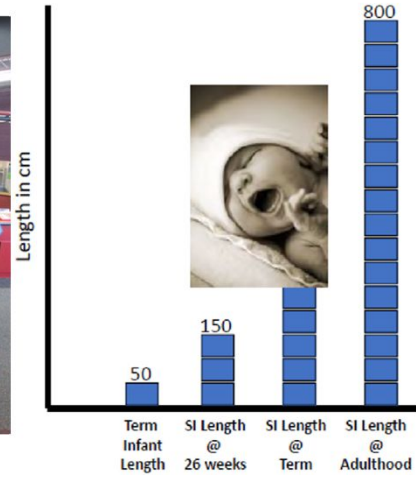


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McElroy, S. (2017). *Innate Immunity and NEC*. Presentation, UC Davis.


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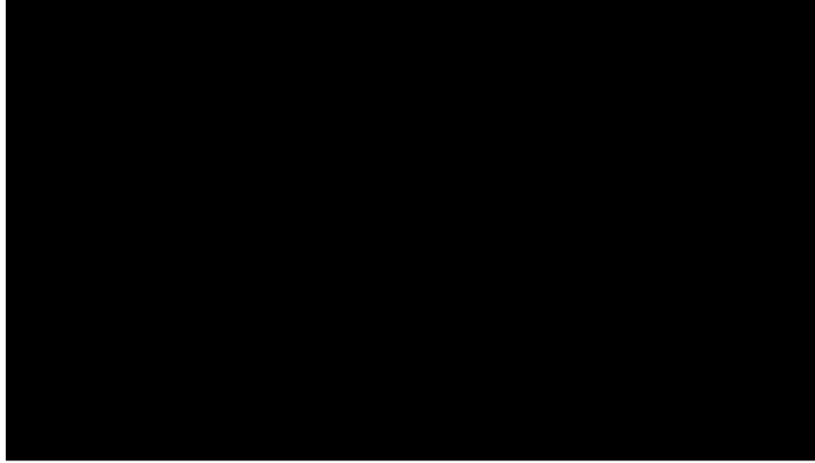
How long are the small intestines?



7 McElroy, S. (2017). *Innate Immunity and NEC*. Presentation, UC Davis.



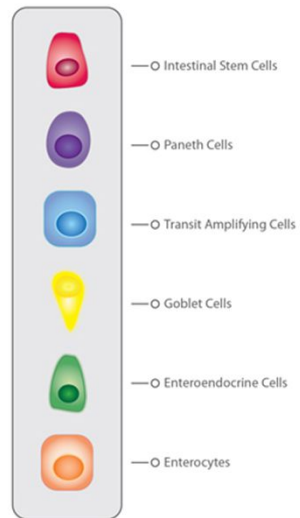
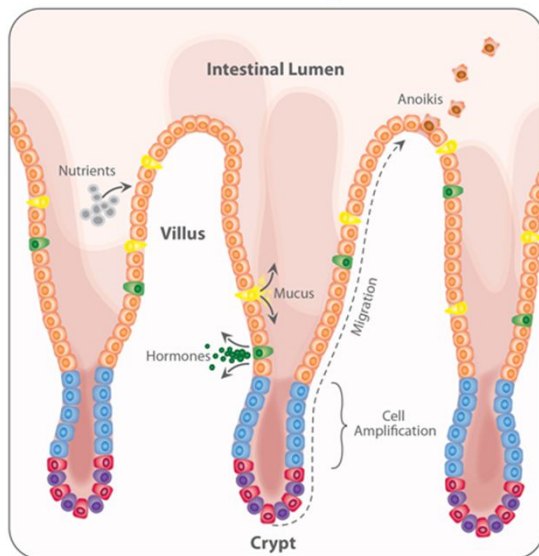
Structure of the Small Intestines



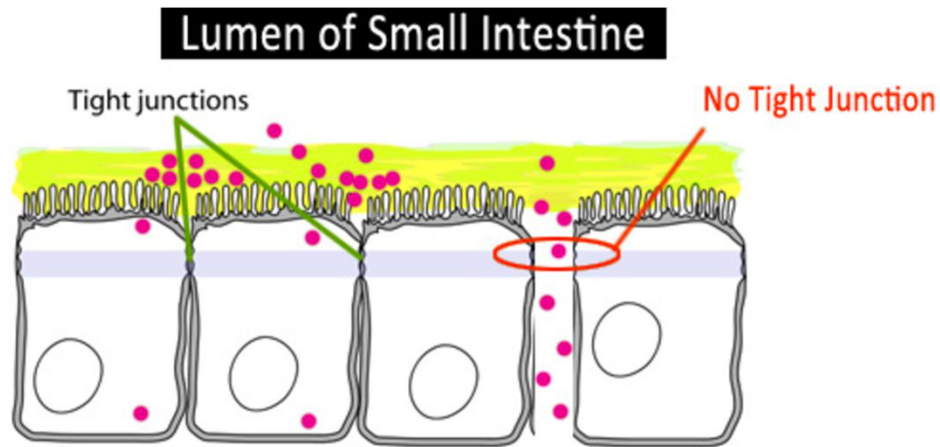
•<https://www.youtube.com/watch?v=qq5k1sWqL00>

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The Intestinal Epithelium



Small Intestines Tight Junctions



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Gastrointestinal Development

Neonatal phase

- Exposure to enteral nutrition leads to rapid differentiation and development
- Development of GIT mucosal immunity due to dietary antigens (or lack of)
- Mucosal immune system begins to distinguish between safe nutrients and foreign pathogens
- What are we putting into our babies??



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Case Study

- DOL 9
 - “small and weak”
 - Copious green-stained diarrhea
 - Intense perianal redness
 - Swollen abdomen

- DOL 11
 - Large bloody stools
 - Vomiting
 - Cold, livid extremities
 - Tense belly
 - Extremely slow heartbeat
 - Intense perianal redness
 - Swollen abdomen
 - Dies that evening with a large liquid black stool

13 Dunn, P. (1990). Charles-Michel Billard (1800-1832): pioneer of neonatal medicine. *Archives Of Disease In Childhood*, 65(7 Spec No), 711-712. http://dx.doi.org/10.1136/adc.65.7_spec_no.711



Case Study Continued

Upon autopsy

- Terminal ileum intensely red and swollen
- Mucosa friable, covered in blood
- “Mucosa is so soft it turns to mash when scraped with the fingernail...”

-Reported by Charles Billard in 1826



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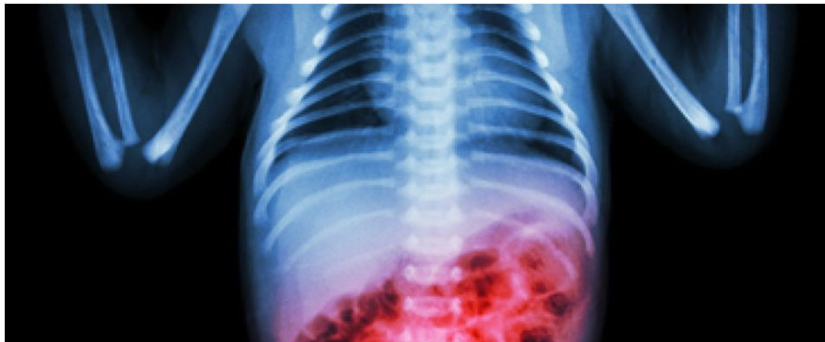


When Good Guts Go Bad...



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Necrotizing Enterocolitis



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What is NEC?

▪ **Definition:** an acquired disease that affects the GI system, particularly that of *premature infants*. It is characterized by **inflammation** of the bowel wall followed by areas of **necrosis**, most commonly in the terminal ileum and proximal colon, but may affect any or all of the small and large intestines.

17

Verklan, M., & Walden, M. (2015). *Core curriculum for neonatal intensive care nursing* (5th ed.).



Incidence

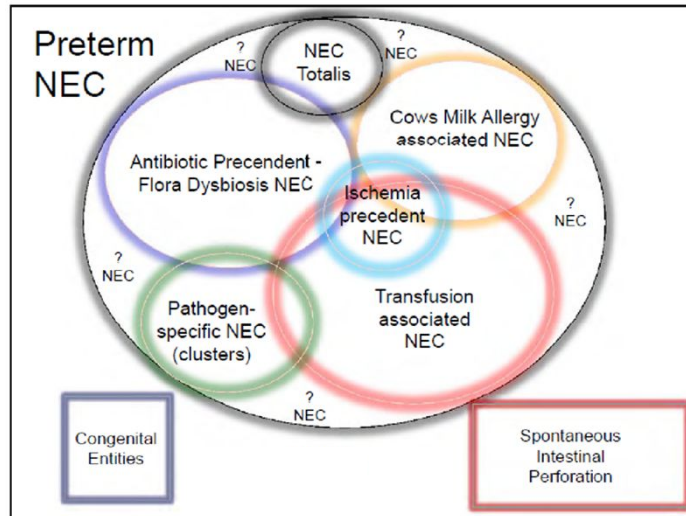
- BW 501 to 750 g – 12 percent risk, 42 percent mortality with NEC
- BW 751 to 1000 g – 9 percent risk, 29 percent mortality with NEC
- BW 1001 to 1250 g – 6 percent risk, 21 percent mortality with NEC
- BW 1251 to 1500 g – 3 percent risk, 16 percent mortality with NEC

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Verklan, M., & Walden, M. (2015). *Core curriculum for neonatal intensive care nursing* (5th ed.).



What is or isn't NEC?



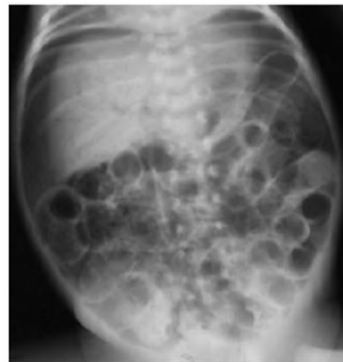
Gordon, P. (2017). *We have to redefine NEC*. Presented at, UC Davis

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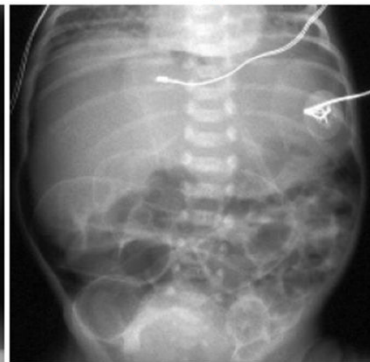


Which baby has NEC?

Baby X



Baby Y



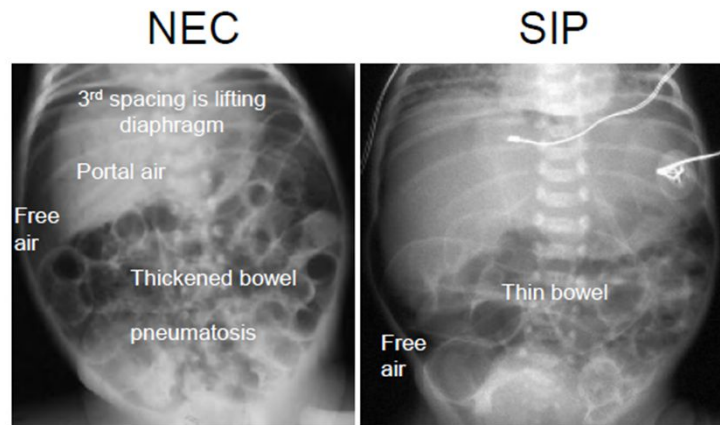
Gordon, P. (2017). *We have to redefine NEC*. Presented at, UC Davis

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Which baby has NEC?

Many cases of NEC and SIP can be differentiated by an x-ray but unfortunately not all



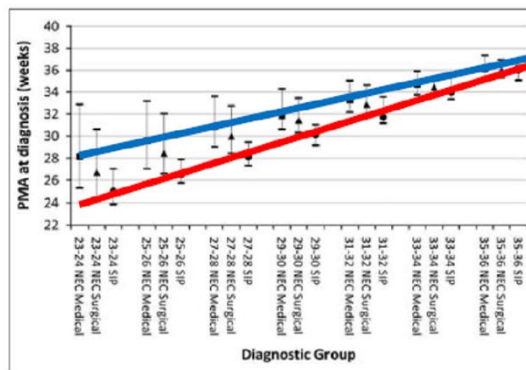
21

Gordon, P. (2017). *We have to redefine NEC*. Presented at, UC Davis



NEC vs SIP

Onset Timing of NEC vs SIP.



Can a national dataset generate a nomogram for necrotizing enterocolitis onset?
 Gordon, P, Clark, R, Swanson, J, Spitzer, A
 Journal of Perinatology. 34(10):732-735, October 2014.
 DOI: 10.1038/jp.2014.137

Figure 3. The median postmenstrual age at diagnosis of NEC-Medical ([black small square]), NEC-Surgical ([DELTA]) and SIP (*) within gestational age groups showing how postmenstrual age at diagnosis increases with increasing gestational age. NEC surgical and SIP were diagnosed earlier in infants with a gestational age <32 weeks. The bars represent the 10th to 90th percentiles for each group.

22

Gordon, P. (2017). *We have to redefine NEC*. Presented at, UC Davis



NEC vs SIP

	NEC	SIP
Incidence < 1500 grams	7 – 10%	2 – 3%
Age of onset	2-6 weeks	0-14 days
Pneumatosis	Yes	No
Enteral feedings	Yes	No
Histologic evidence of villus necrosis	Yes	No
Mortality	10-30% above baseline	5-10% above baseline

SIP

- Can occur in the absence of NEC
- Compared to NEC: less hemodynamic instability, less metabolic acidosis, improved survival rate, lack of coagulation necrosis seen in NEC
- More common in patients with: UAC, administration of indomethacin or ibuprofen

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Gordon, P. (2017). *We have to redefine NEC*. Presented at, UC Davis



Early vs Late onset

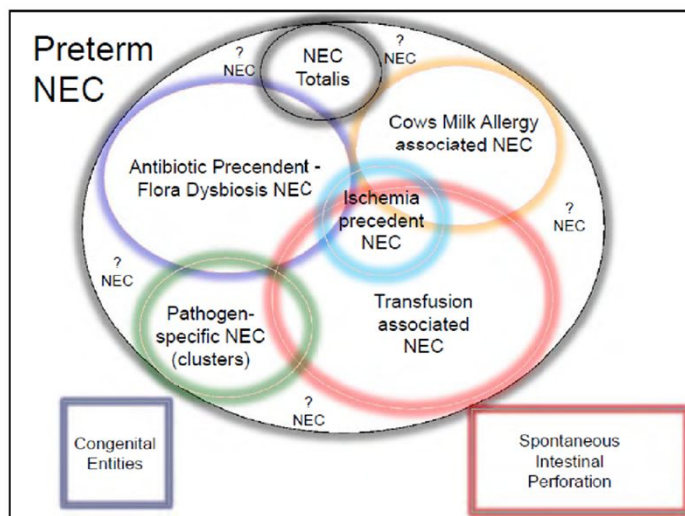
- Early onset
 - Usually term
 - First 7 days
 - Critically ill
 - Never fed
 - Vascular cause of intestinal injury
- Late onset
 - > 7 days
 - Growing preemie
 - Has been fed
 - Luminal cause of intestinal injury



NEC in Term Infants

- Gut vs gut immaturity
- Early onset – perinatal events plausible
- Cannot rely on metabolic acidosis, hemodynamic instability. May have few systemic symptoms due to greater reserve
- Improved survival – probably related to lack of associated problems of prematurity
- May be that NEC results from two different disease processes in premature and term infants
- Most have some risk factor

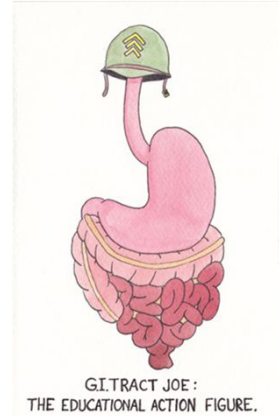
What is or isn't NEC?



NEC Pathogenesis

•Prematurity

- Propensity towards gut inflammation
- Impaired intestinal barrier function
- Decreased intestinal motility
- Deficient mucosal enzymes, hormones, pepsin, and gastric acid
- Immature autoregulation of microcirculation
- Lack of amniotic fluid
- Immature mucin layer

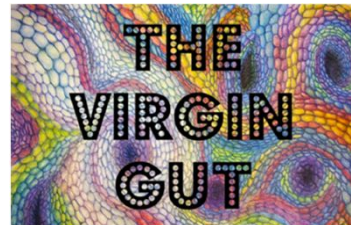


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NEC Pathogenesis

•Enteral Feeds

- Formula feeding
- Fortification



•Abnormal intestinal microbiota

- Decreased commensal flora
- Increased pathogenic bacteria
- Prolonged antibiotic therapy
- Acid suppression medications

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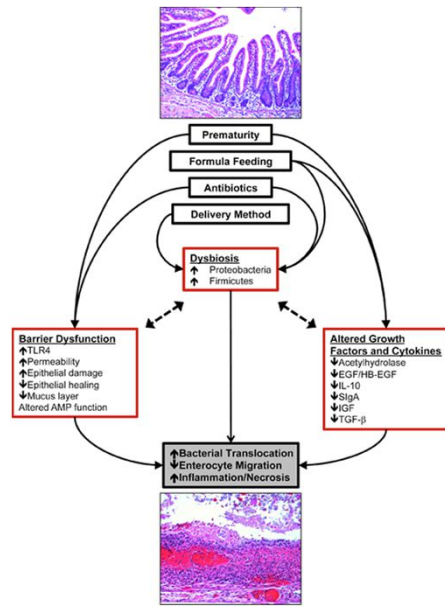
NEC Pathogenesis

•Gut Ischemia

- Abnormal gut vascular regulation
- More prone to hypoxic events

•Inflammatory response

- Genetic factors?
- TLR4?

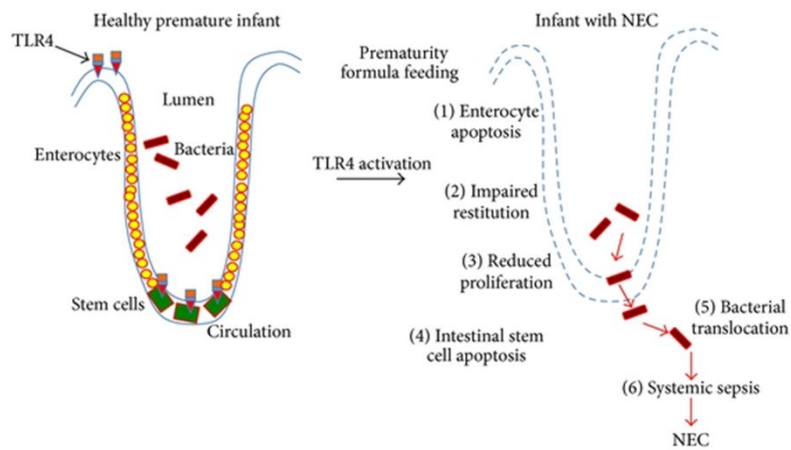


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NEC Pathogenesis

•TLR4

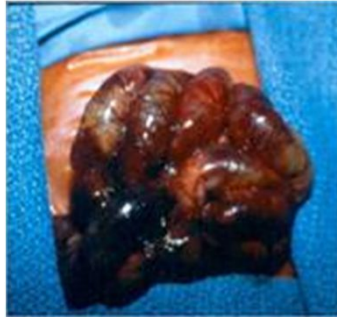
•Toll-like receptor



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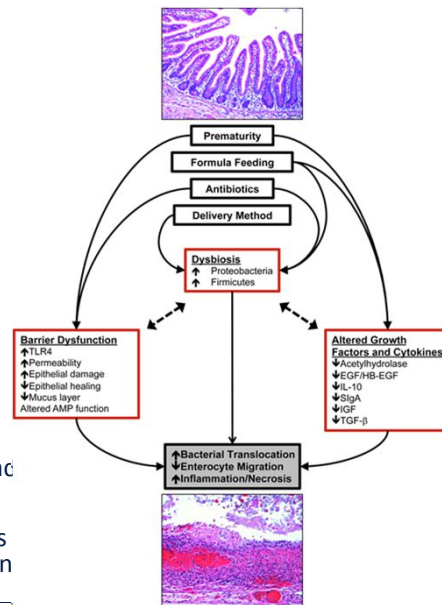
Etiology

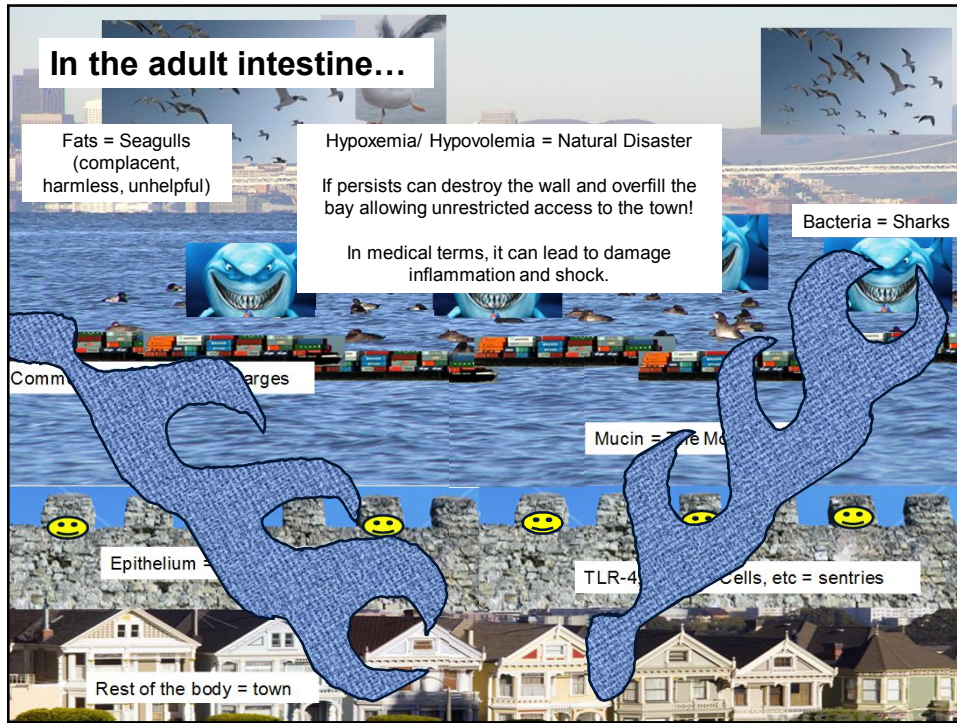
Common final pathway – the endogenous production of inflammatory mediators that precipitate intestinal injury



Model of Pathogenesis


- Subclinical event (hypoxia, ischemia)
- Intestines become colonized
- Bacteria bind to injured mucosa
- Inflammatory response
- Increased permeability of mucosa
- Translocation of bacteria
- Inflammatory response accelerates
- Inflammatory mediators, reactive oxygen species further injure mucosa
- Maladaptive vasoconstrictive response lead to ongoing ischemia/reperfusion injury
- End result – cycle of feedback mechanisms ultimately causing necrosis and perforation





Breast Milk	Formula
<ul style="list-style-type: none">• Has growth factors to increase mucin production• Has HMOs that dist... and feed commens...	<ul style="list-style-type: none">• Less protection against pathogen invasions

Both are still at risk for "natural disasters" but hopefully the breast fed infant can weather the storm a little better



Diagnosing NEC



Bell's Staging for NEC

- Most commonly used in practice
- Staging based on severity of systemic, intestinal, and radiographic findings
- Treatment is directed at the clinical signs rather than the particular stage of NEC
- Each advancing stage includes the characteristics of the previous stage plus additional findings due to increasing severity of the disease

Stage 1-Suspected NEC

- Gastric residuals
- Abdominal distension
- Heme positive stools
- X-ray normal to mild distension
- Temp instability
- A's and B's

Stage 2- Proven NEC

- Absent bowel sounds
- Abdominal tenderness
- Pneumatosis intestinalis
- Portal venous gas
- Mild metabolic acidosis
- ↓ Platelets
- Radiograph findings include intestinal dilation, ileus, pneumatosis intestinalis, and ascites
- Stage IIA “mildly ill”, stage IIB “moderately ill”

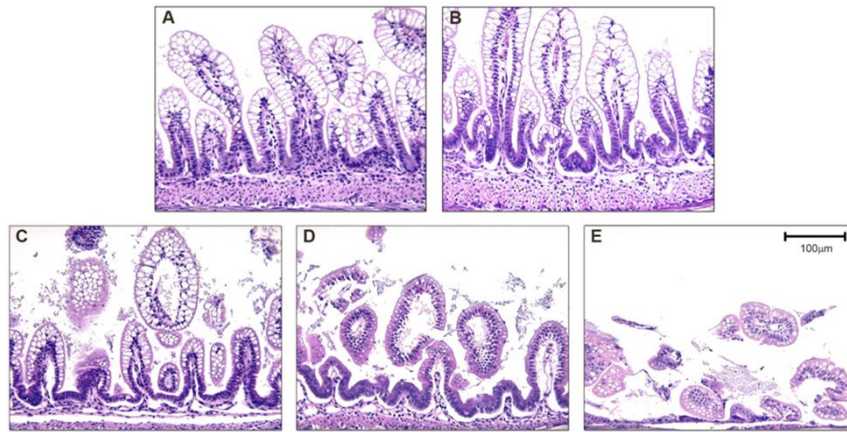


Stage 3-Advanced NEC

- Severely ill
- Marked distension
- Signs of peritonitis
- Hypotension
- Bradycardia
- Severe apnea
- Metabolic and respiratory acidosis
- Disseminated intravascular coagulation (DIC)
- Stage IIIA intact bowel, stage IIIB perforated bowel visualized as a pneumoperitoneum



Diagnosing NEC



Khailova, L., Dvorak, K., Arganbright, K., Halpern, M., Kinouchi, T., Yajima, M., & Dvorak, B. (2017). *Bifidobacterium bifidum* improves intestinal integrity in a rat model of necrotizing enterocolitis. Retrieved 16 April 2017, from

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Diagnosing NEC

- Based on the presence of the characteristic clinical features of:
 - Abdominal distention
 - Rectal bleeding
 - Abdominal radiographic finding of pneumatosis intestinalis.
- Assessment of infants with suspected NEC includes:
 - abdominal imaging, blood studies, stool analysis, and sepsis evaluation
- Future Biomarkers? iFABP? PAF?

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FIGURE 8-61. Pneumatosis intestinalis



FIGURE 8-62. Hemorrhagic intestine



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Presentation – clinical findings

- Abdominal distension
- Feeding residuals, often bilious
- Gross or occult blood in stool
- Abdominal tenderness
- Erythema or bluish discoloration of abdominal wall
- Absent bowel sounds
- Non-specific signs (temp. instability, glucose instability, lethargy, apnea/bradycardia, hypotension)

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Visual Exam






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Abdominal Distension/ Increased AG

- What is the distension from?
- What has been the baseline abdominal exam
- Last stool
- Is he on CPAP or been recently bag/mask ventilated?
Does he have an OGT in place and vented?
- Are there any other concerning signs? – glucose instability, lethargy, temp. instability, apnea, etc.
- Is the infant hungry and eager to nipple feed?


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Residuals

- Is the residual bilious?
- Is the baby stooling at least q12h, moderate amounts?
- Has the infant been recently bag/mask ventilated?
- What position has the baby been in?
- Has the last few hours been stressful for the infant? (blood draws, lots of handling, procedures)
- Is the physical exam benign?
- Could there be an ileus? – morphine, infection, post-op
- Refeed residual if non-bilious, partially digested milk.

Heme Positive Stools

- Is the stool meconium?
- Is the infant receiving glycerin suppositories?
- Does the infant have a fissure?
- Has the infant had abdominal surgery?



Presentation – Laboratory Findings

- Glucose instability
- Abnormally high or low WBC
- Left shift of WBC
- Thrombocytopenia
- Metabolic acidosis
- DIC
- CRP

Radiologic Findings



Normal Abdominal Xray

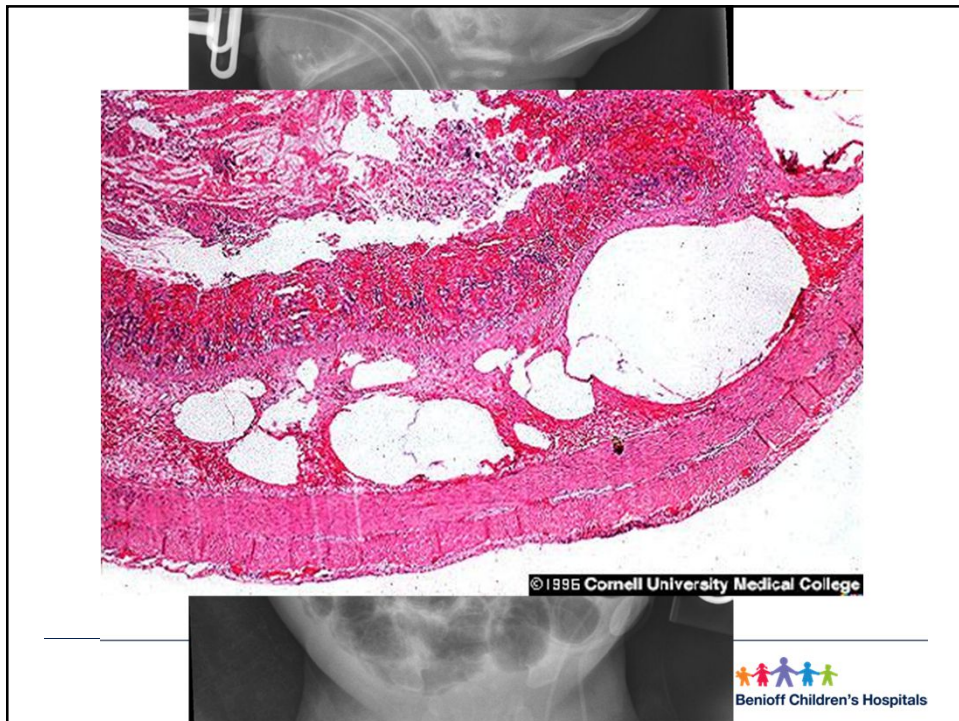
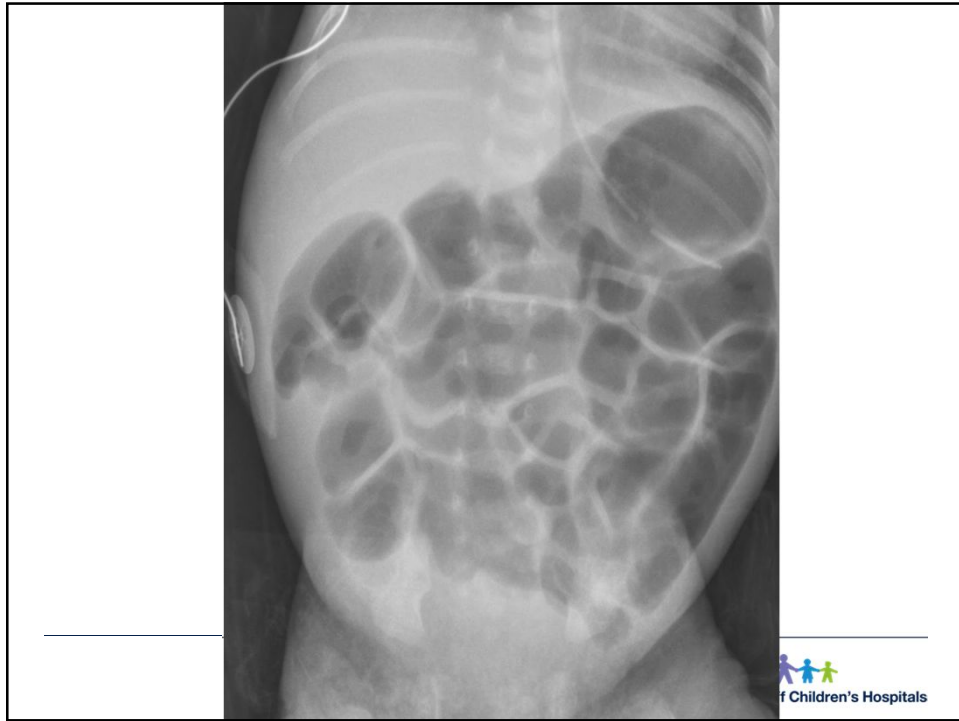
- Uniform size and shape of loops
- Diameter approximates vertebra
- Gas throughout entire bowel tract
- Gas pattern should vary on subsequent x rays
- No free air in abdomen and liver is opaque

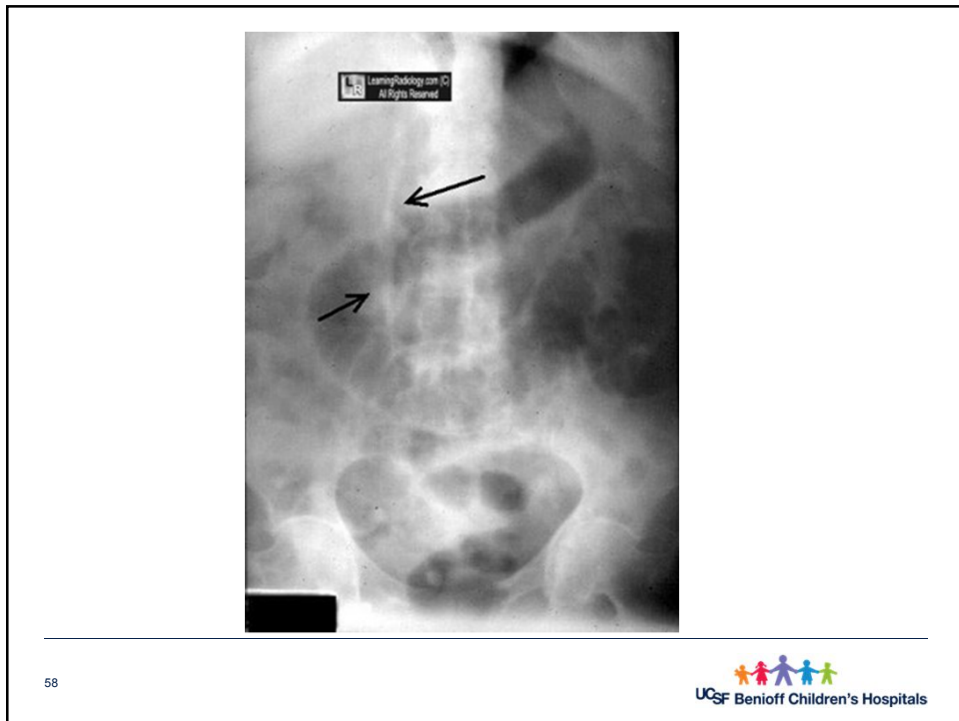
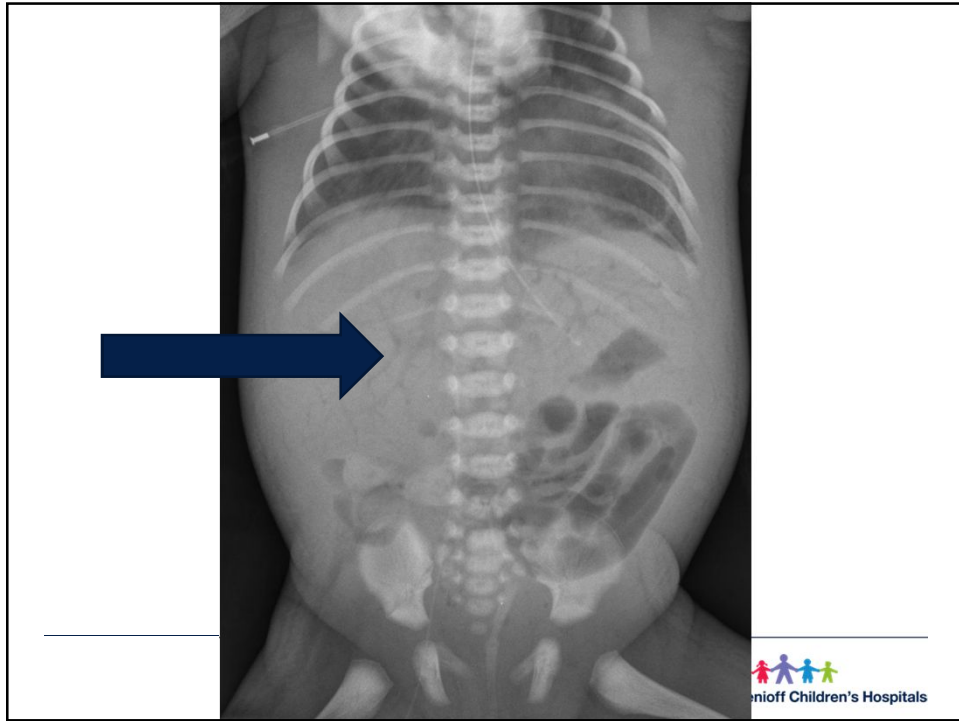


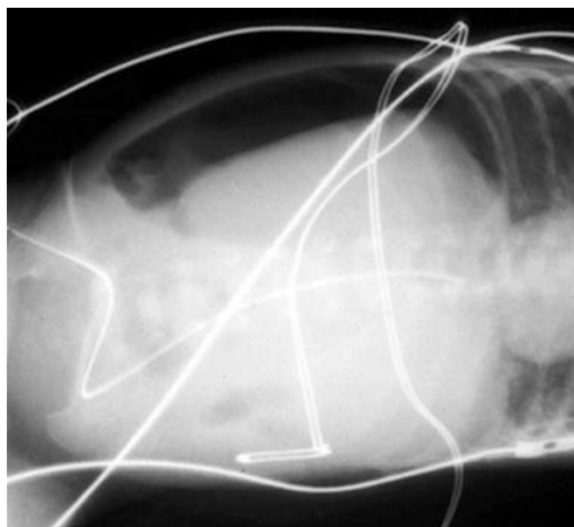
Presentation – Radiographic Findings

- Non-specific bowel dilatation
- Thickening of bowel wall
- Fixed, dilated loop unchanged on >1 radiograph
- Pneumatosis intestinalis
- Portal venous gas
- Pneumoperitoneum
- Falciform ligament may be outlined
- Football sign









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Ultrasound

- Used to look for bowel wall thickening
- Free air
- Portal Venous gas



Management- Suspected NEC

- NPO
- Fluid/electrolyte and parenteral nutrition management
- Gastric decompression
- Labs
- Antibiotics (Ampicillin and Gentamicin, Vancomycin, Cefotaxime, Flagyl?)
- Correct metabolic acidosis
- Serial xrays
- Respiratory & Circulatory support
- Rule out other causes of distension
- Transfusions?
- Close monitoring



Management – Definite NEC

- Obtain consult with surgical team
- Serial KUB's
- NPO 7-10 days
- Careful I/O's – maintain bowel perfusion, may require fluid resuscitation
- Circulatory support
- Respiratory support
- PT, PTT, fibrinogen, platelets
- Frequent abg's, electrolytes
- Antibiotics 7-14 days



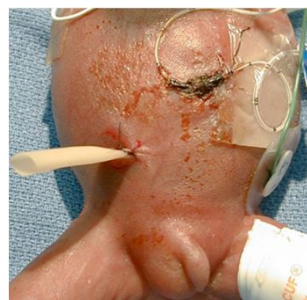
Surgical Treatment

Medical management is appropriate in most cases

- Operative intervention indications:
 - Perforation, evidence of necrotic bowel (fixed loop, metabolic acidosis, DIC, shock), or progressively worsening clinical condition despite intensive medical management
- Surgical Options:
 - Peritoneal drain
 - Exploratory laparotomy for resection of necrotic bowel

Surgical Considerations

- Peritoneal drain +/- irrigation
 - Allows time for baby to stabilize
 - Better able to delineate viable gut when do operate
 - Borderline bowel segments may recover
 - Intestinal perforation may be definitively treated
 - Laparotomy indicated if not improving in 24-48 hrs



Surgical Considerations

- Exploratory laparotomy for resection of necrotic bowel
 - Primary Anastomoses
 - Ostomy & Mucous Fistula
 - Clip & Drop






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Prevention

- Human milk
 - pasteurized MBM is not as protective
- Intestinal priming (gut stimulation feedings)
 - Promotes structural and functional maturation
 - Promotes acquisition of normal flora
 - Stimulate release of gastric hormones
- Slow, but not too slow, feed advance
- Minimize prolonged antibiotic use
- Antenatal glucocorticoids for lung maturation also accelerate intestinal maturation
- Prebiotics, probiotics, postbiotics


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How can Human Milk Prevent NEC?

<http://www.human-milk.com/infographic/eaflet.html>

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The infographic 'The contents of Human Milk' is a circular diagram with 'Human Milk' at the center. It is divided into several segments, each representing a different component of breast milk and its benefits:

- Nucleotides:** Explain that nucleotides are the basic building blocks of DNA and RNA. They are also found in other components of breast milk, such as antibodies, and are essential for the development of the infant's immune system.
- Antinutrients:** These are substances that protect the infant from pathogens. They include lysozyme, lactoferrin, and secretory phospholipase A2. They also help to regulate the growth of the infant's gut microbiome.
- Lipids:** These are essential for the development of the infant's brain and nervous system. They also provide energy for the infant. Breast milk contains a unique profile of lipids that is not found in formula.
- Hormones:** These are chemical messengers that control growth and development. They include growth factors, such as insulin-like growth factor (IGF) and transforming growth factor (TGF). They also help to regulate the infant's immune system.
- Enzymes & Carbohydrates:** These help to break down the milk into nutrients that the infant can absorb. They also help to protect the infant from pathogens. Breast milk contains a unique profile of enzymes and carbohydrates that is not found in formula.

Additional text in the infographic includes: 'Vaccines and antibodies are used in a variety of ways. They are concentrated in breast milk and delivered to the baby, as well as given to the infant through the skin by the mother's touch.' and 'Early in general, breast is a number 1 choice for infants. It is the most natural and healthiest way to feed a baby. It is also the most cost-effective and convenient way to feed a baby. Breast milk is the best source of nutrition for infants. It is the only source of nutrition that is specifically designed for the infant's needs. Breast milk is the best source of nutrition for infants. It is the only source of nutrition that is specifically designed for the infant's needs.'

Oligosaccharides & the Gut

- Human Milk Oligosaccharides
- 3rd most abundant biomolecule in human milk
- Un-digestible by humans

“It’s All About the Breast Milk Sugars, Baby”

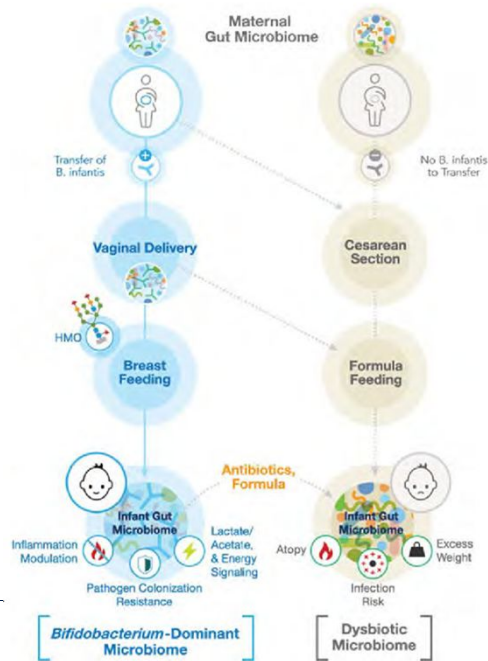
German, B. (2017). *The Evolution of Lactation as a Guide to Understanding Nourishment and Prevention in the 21st Century*. Presentation, UC Davis.

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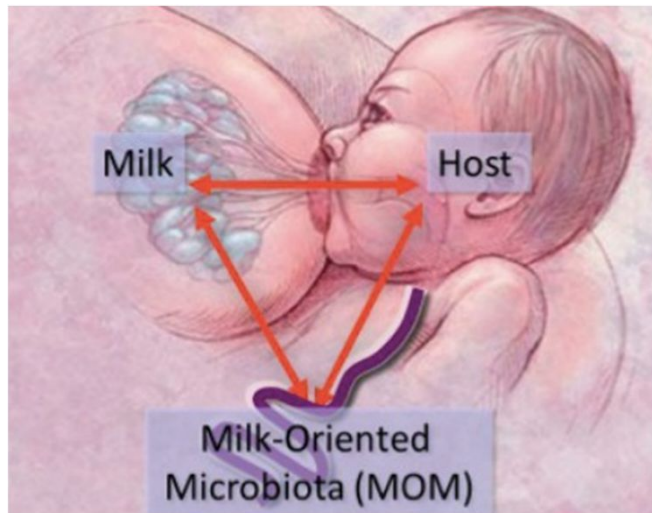
Microbiota

- Modern life has stopped microbial transfer...
- So what are we left with?
- Microbial Dysbiosis...
- Long term consequences



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Milk-Oriented Microbiota



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Probiotics...

The “Golden Age” of Probiotics: A Systematic Review and Meta-Analysis of Randomized and Observational Studies in Preterm Infants

- Probiotics potentially prevent severe NEC and late-onset sepsis, and reduce mortality in preterm infants

Prophylactic Probiotics for Preterm Infants: A Systematic Review and Meta-Analysis of Observational Studies.

- Probiotic supplementation reduces the risk of NEC and mortality in preterm infants. The effect sizes are similar to findings in meta-analyses of RCTs. However, the optimal strain, dose and timing need further investigation.

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Colostrum Care

- Oropharyngeal administration
 - Use syringe to place directly onto the oral mucosa in the buccal cavity for
 - absorption via the mucosa
- Allows for systemic absorption of the cytokines and pancreatic secretory trypsin inhibitor (PSTI)
- Rich source of Oligosaccharides
- May reduce time to full feeds



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Trophic feeds

- Improved feeding tolerance
- More rapid advancement to full feeds
- Improved weight gain
- Shortened duration of TPN
- Less phototherapy
- Reduction in direct bilirubin
- Decreased length of stay
- Does not increase risk of NEC!
- May be considered for an infant who is hemodynamically stable on a low dose of dopamine and/or with an Umbilical Arterial Line in place




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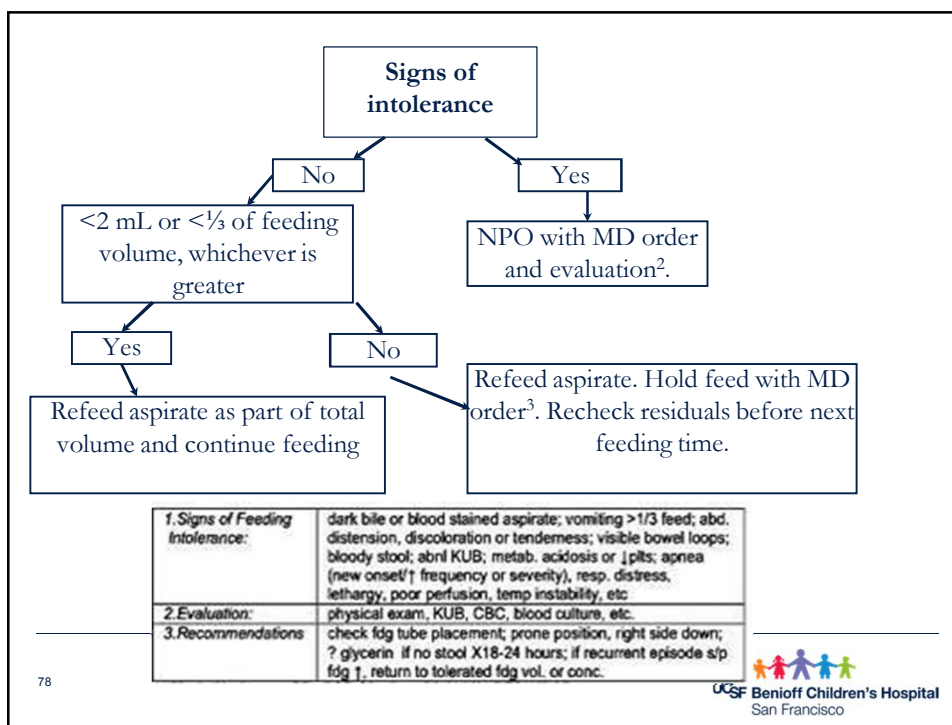
Feeding Protocol for Preterm Infants

- Goal
 - Preterm: 150-160 ml/kg/day of 24cal/oz; fortify when feed volume is 60ml/kg/day
 - Term: 150-165 ml/kg/day of 20cal/oz
- Consider increasing concentration of feeds if poor weight gain, volume intolerance or fluid restriction, or increased energy requirements.
 - Preterm infants should receive 24cal/oz for at least one week before increasing to 27cal/oz
 - Consider hind milk

UCSF BCH Feeding Protocol

Birth GA (wks)	1st day (ml/kg/d)	Advance on Day #	Amount (ml/kg/d)	>60 ml/kg/d Advance by	Achieve Goal Feeds by
< 26	15	6	15	20	Day 13
26 to 27-6/7	15	4	15	20	Day 11
28 to 29-6/7	15	3	15	20	Day 10
30 to 31-6/7	20	Daily	20	20	Day 8
32 to 34-6/7	20	Daily	20-40	20-40	Day 5-8
>35	50 or ad lib	Daily	>20-40 or ad lib	>20-40 or ad lib	Day 4-6





Prevention - Disadvantages of NPO

- “The wisdom of stopping all enteral intake is counter-intuitive to the ontologic processes that started in utero”
Edmund Gamma, Lyle Browne, State Univ. NV
- Has not uniformly provided protection, may simply delay the onset of NEC
- Predisposes to injury when finally fed
 - Gut atrophy
 - Decreased mucin production and enzyme activity
 - Decreased secretion of IgA
 - Increased transmural penetration of bacteria, and antigens
 - Increased susceptibility to infection
 - Autodigestion

Enteral Nutrition

- Breast milk is best
- Donor breast when MBM not available
- Use of standardized feeding guideline
 - Reduced risk of NEC
 - Less variability
 - Achieve full feeds earlier



Prevention – experimental approaches

- Enteral IgG/IgA
- Formula acidification to prevent bacterial overgrowth
- Probiotics supplementation (bifidobacteria)
- L-arginine supplementation: precursor of NO
- Oral antibiotics
- PAF-acetylhydrolase: degrades the inflammatory mediator PAF
- Glutathione (GSH): an antioxidant
- Epidermal Growth Factor (EGF): matures intestinal mucosa



Gut Check NEC (Gephart et al, 2014)

GutCheck ^{NEC} , a Neonatal NEC Risk Index for infants born weighing < 1500 grams © Gephart, 2012				Points
Gestational age (weeks) (9 max.) Calculate GA in weeks at birth based preferably on due date determined by 1 st trimester ultrasound. If that is unavailable, use the gestational age assessment at delivery (Ballard or Dubowitz)	<28 9 points	28-31 6/7 8 points	≥ 32 0 points	
Race (2 max) If the infant is either Black or Hispanic race assign 2 points. If both, assign only 2 points. If not Black or Hispanic, assign 0 points.	Black 2 points	Hispanic 2 points	Other races 0 points	
Outborn (3 max) If the infant is transferred into this center from another hospital at any time after birth, assign 3 points.		Yes 3 points	No 0 points	
NICU NEC rate (23 max.) This is the annual calculated NEC rate for infants weighing less than 1500 grams at delivery. If < 2%, assign 0 points.	2- 4.99% 9 points	5- 7.99% 16 points	8- 11.99% 19 points	> 12 % 23 points
Exclusive human milk feeding (0 max) Defined as human milk fed at both day 7 and day 14 of life. Volume of human milk fed is not defined. If any milk is fed at both day 7 and day 14, <u>subtract 3 points</u> from the total score. Points cannot be subtracted until day of life 14.		Yes -3 points	No 0 points	
Probiotics (0 max) If any probiotic preparation has been given at any dose or any vol		Yes -5 points	No 0 points	
Ho of				

Gut Check NEC (Gephart et al, 2014)

How many culture-proven infections has the infant had since day 3 of life? (6 points max)	One 4 points	Two 6 points	None 0 points
Packed Red Blood Cell transfusion history (8 max) If any PRBC transfusion has been given, regardless of feeding status or volume given. Once the infant receives a transfusion, from that time on it is scored "yes."		Yes 8 points	No 0 points
Hypotension treated with Inotropic Medication (4 max) If hypotension is severe and medications such as dopamine, dobutamine or milrinone are given to treat it, regardless of dose, frequency or duration of treatment.		Yes 4 points	No 0 points
Metabolic Acidosis (3 max) If the infant experiences metabolic acidosis, defined as low pH associated with low serum bicarbonate ($\text{HCO}_3^- < 17$) but normal or near normal pCO_2 ($\text{pH} < 7.30$) or lactate > 6.1 mmol/L. If ordering clinician (physician, NNP, PA-C) documents "metabolic acidosis" code as "yes."		Yes 3 points	No 0 points
TOTAL Score > 32 At Risk; 58 points maximum			
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"You are a better monitor than Hewlett Packard ever made"
(NICU nurse)

- Educate yourself in the signs/symptoms of NEC.
- Know your infant's history. Is this infant at risk?
- Know your infant's baseline exam.
- Be alert to subtle changes.
- Watch for patterns/clusters of concerning symptoms.
- Respect your intuition. It is grounded in expertise.
- If you are worried, assess, obtain a KUB, blood gas, CBC. Remember that these can be normal in the early phase of NEC.
- Nurses by their vigilance and expertise can substantially influence the incidence and outcome of NEC.



Neonatal nurses go beyond the numbers to take in the entire baby. Their nursing is particular, contextual, and holistic. It is an art. Xrays and lab values pale in comparison with the vigilance and commitment of an expert nurse.



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Questions?

Thank you!!

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