

Feeding the Premature Infant

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Disclosure None Pertaining



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Fiona, Cincinnati Zoo's Premie Hippo

Born at 25 lbs. (normal 50 lbs) 6 weeks early. Now 1600 lbs. Mom 3000 lbs.

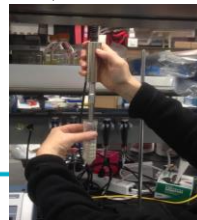


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Analysis of milk



Property	Value
1 Fat	3.91
2 Protein	4.47
3 Carbohydrate	6.87
4 Calories per Ounce	24.0

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Fiona's Journey



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Learning Outcomes

- 1. Assess the pros and cons of measuring gastric residuals to measure feeding tolerance on premature infants.
- 2. Critique the use of individual customized fortification strategies for premature infants.
- 3. List 3 factors that could affect feeding tolerance in premature infants.



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What is feeding intolerance?

- Definitions vary
- Some say inability to progress with feedings due to emesis, abdominal distension, and loose stools
- Others get into gastric residuals > 50% of previous feed.



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Gastric Residuals

- Should you check prior to each feed?
Yes or No
- Should you refeed Gastric Residual?
Yes or No



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Should you refeed a gastric residual?

- Randomized trial by Salas et al should earlier attainment of full feeds in refeeding group
- In their study there was more NEC in the fresh feeding group
- Did not examine labs as throwing out residuals could impact acid/base status, lower serum sodium and chloride, and with rising pH could make a patient more susceptible to enteric organisms and possible NEC. By throwing away the residual, it should make the next feed harder to digest with the loss of digestive juices.



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Electrolyte Loss Estimates

	Sodium mEq/L	Potassium mEq/L	Chloride mEq/L	Bicarbonate mEq/L
Gastric	60-100* Higher in neonatal surgery	10-17	130	0
Duodenum	140	5	80	0
Pancreas	140	5	75	115
Bile	145	5	200	35
Ileostomy	110-140	15	115	30-40
Colon	60-80	30	40	0-20
Diarrhea	10 Secretory 90	10-80	10-110	30
Normal Stool	5 mEq/day	10 mEq/day	10 mEq/day	0



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Gastric Residuals

By checking can you make a difference in necrotizing enterocolitis?
Yes or No

Does the color of residuals make a difference?
Yes or No



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Gastric Residuals

- No evidence that it will be an early warning sign against NEC.
- By the time you have larger residuals, you already have the problem.
- Christiansen
- By pulling up gastric contents through the feeding tube, it influences the bacteria in the biofilm on the interior of the feeding tube. The esophagus and the stomach have different microbiomes.



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So GR have been shown to prolong getting to full enteral feeds and not increase NEC



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Color of residuals?

- In a study by Mihatsch et al, the color made no difference. The green color is a reflection of duodeno-gastric reflux, which a certain amount is regarded as normal.
- Colors other than milky had no impact on the feeding volume



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GER

- Gastroesophageal reflux (GER) is differentiated from GERD which is the disease.
- All infants have some degree of GER. Not very many have GERD
- Infants with GERD are often prescribed H₂ blockers or PPIs.
- H₂ blockers are histamine 2 receptor blocker
- PPIs are proton pump inhibitors



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Medications to decrease the acid in preterm infants.

- PPI use in infants increase 7 fold from 1999 to 2004 (not approved by the FDA. Barron et al.
- No studies that compare the use of H₂ blockers and PPIs on GER symptoms or symptoms.



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Medications to decrease acid.

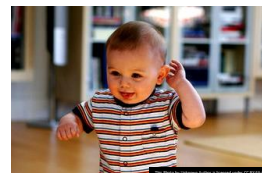
- Omeprazole has been shown to be effective in reducing acid exposure in premature infants with pathological acid reflux by pH probe. Omari et al.
- Another study double blinded placebo study showed that although Omeprazole decreased acid exposure, there was no difference on irritability. Moore et al.
- Lansoprazole was shown to be no different than placebo in another study. Orenstein et al.



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GER

- It peaks at @ 4 months, with a relationship anatomy with pressures in the chest and pressures in the abdomen.
- By 10 months it is becoming rare and by the time 12 months come, very rare unless the child has an anatomical problem like repaired diaphragmatic hernia.



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GER

- Landmark research by Jose Garza using pH – multichannel impedance studies.
- Symptoms that were attributed to GER were cough, pain, and desaturation episodes.
- 186 studies were done with 10, 847 reflux events recorded. 4,159 noted symptoms (counting symptoms documenting within 5 minutes after the event).
- ½ of the infants were being fed by mouth, ½ received tube feeds.



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Garza et al.

- 36% of symptoms were associated with reflux events, 27% nonacid, 9% acid.
- The symptoms commonly attributed to GER in infants are most often not associated with a reflux event. Of those that are associated, non-acid events as likely as acid events to cause symptoms.



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Garza et al.

Gagging was not found to be related to reflux events.
Coughing 3074 instances, 34% reflux related, only 8% was acidic.
Regurgitation- 52% was associated with reflux, only 14% were acidic.
Desaturations: 96 reported, 19% correlated with a reflux event, 1% acid.
"Pain" ~crying, restlessness, head side to side, thrashing, screaming and fussiness: 36 episodes were reported 36% associated with reflux, 0 acid



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Garza et al

Most of the symptoms 64% lacked a temporal association with reflux.
42% of back arching were related to reflux but none acidic



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Conclusions:

- Most symptoms were not related to reflux
- Of those related few that were related, vast majority were non acid.
- Brings to question the use of H₂ blockers and PPIs.
- Side effects: increased rates of necrotizing enterocolitis in preterm infants, community acquired pneumonia, gastroenteritis and candidemia in children. ESPGHAN guidelines.
- There is also some thought that the desats could cause reflux versus being a result of reflux.



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Feeding Tubes and Bacterial Contamination

Studies from Little Rock fueled papers by Dr. Mehall in 2002.

Also found in other studies by Taft et al (2019)

In a scenario where feeding tubes were changed weekly, 50 tube fed patients were studied with a mean of @18 days of tube use.

Fed via bolus with an open gravity drained system.

Tubes were collected and analyzed weekly.

71/125 tubes were "contaminated" or > 1000 CFU/ml



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Feeding Tube Study



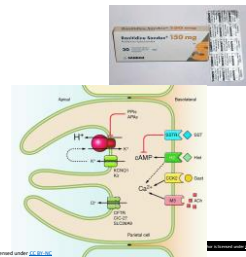
- 3 different bacteria types were seen.
- With formula fed infants, feeding intolerance was seen in 24 of 32 weeks they were used. In contrast in non contaminated tubes there was feeding intolerance in 0/44 weeks the tubes were used.



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H₂ Blockers

- Contamination occurred in 41 of 48 weeks on H₂ blockers versus 32/66 weeks with babies with normal gastric acidity
- NEC developed in 7 infants, all were formula; contamination of >100,000 CFL/ml of gram negative bacteria. Of 4 requiring surgery, the same organism was cultured as was in the tube.



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The role of gastric juices



- Gastric juice is made up of water, electrolytes, hydrochloric acid, lipase, pepsin, mucus, and intrinsic factor (part of the vitamin B₁₂ complex)

Sodium mEq/L 60-100 mEq/L

Potassium mEq/L 10-17 m

Chloride mEq/L 130

Bicarbonate mEq/L 0



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Gastric Juice

- The first line of defense against infections throughout the GI tract.
- At a pH< 4 bacteria are typically killed within 15 minutes.
- Adults taking PPIs or H₂ blockers are at 3 x risk for bacterial diarrhea, and more at risk for community acquired respiratory infections. Martinsen et al.



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Association between H₂ blockers and NEC

- Antecedent use of H₂ blockers was associated with a higher rate of NEC p<.0001.
- Romaine et al found a higher risk of infection, NEC, or death on days exposed to H₂ blockers.
- Santos et al. Meta analysis showed association between infection and NEC but not mortality

P. Pediatrics. 2008;121(1):117-121. doi: 10.1542/peds.2007-1161. Epub 2008 Jan 15.
 Association of H₂-blocker therapy and higher incidence of necrotizing enterocolitis in very low birth weight infants
Romaine Guffee V, Barkans J, Dool C, Michael Collier, Marie Gault, Scott McDonald, W Kenneth Poole, Dale L Peltier
 National Institute of Child Health and Human Development Neonatal Research Network



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Association between H₂ blockers and infection

- Santana et al. Retrospective cohort study of 300 newborns, 115 had received ranitidine, 185 had not.
- No significant association with NEC Bells stage II or greater, but late onset culture positive infection rate was higher 13% vs 3.8%, Mortality risk was 4 fold higher in infants receiving ranitidine. 16.5% vs 8.6%



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Other causes of feeding intolerance

A group in Chicago led by Dr. Tim Sentongo investigated a collection of preterm infants that received more than usual amounts of TPN, multiple courses. Cordova et al.

Some of the infants were diagnosed with Cow Milk Protein Intolerance (CMPI). 14 of the 51 infants in this group (27%) were diagnosed with CMPI. 9 of these infants were initially diagnosed with NEC. After recovery from medical NEC they continued to have feeding intolerance with "NEC-like" illnesses that resolved with a change to a complete protein hydrolysate or amino acid formula.



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Cow Milk Protein Intolerance

- An inflammatory process that affects 3% to 7% of healthy infants during the first year of life.
- Typically appears after exposure and sensitization to cow milk protein which can range in time from 10 days to 10 months. Martorell et al.
- Clinical symptoms include diarrhea, persistent colic, reflux, feeding difficulty, mucous stools, hematochezia, ileus, and intestinal dysmotility mimicking Hirschsprung disease.



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CMPI

No real pathognomic test for this, the clinical diagnosis is confirmed by disappearance of symptoms after elimination of dairy protein from the diet. [And can be reconfirmed with symptoms reappearing after reintroduction into the diet (not always feasible)]

CMPI and NEC are difficult to differentiate and NEC as clinical emergency, must be considered first.

No testing can differentiate at this time.



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Preterm infants and CMPI Cordova et al.

- 2 infants who had presented with a spontaneous intestinal perforation were subsequently diagnosed with CMPI.
- 2 infants fed breast milk only developed NEC like symptoms and were subsequently diagnosed with CMPI



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Proposed Mechanisms

- Disruption of the commensal flora by antibiotic therapy initiated in the immediate perinatal and postnatal period may play a role in sensitization to allergens. Commensal flora is essential to induce mucosal IgA and T regulatory response important on preventing intestinal inflammation. Maynard et al.
- The ability to secrete IgE is present from 11 to 21 weeks of gestation. Miller et al. So preterm infants can mount an antigen induced response.



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NEC or CMPI

- Both may lead to mucosal injury. Profound mucosal injury may predispose to sensitization to allergens.
- Recurring NEC like illnesses may should lead to a consideration of possible CMPI as it could be a case of mis diagnosed CMPI or sensitization after NEC also leading to CMPI.
- Peripheral eosinophilia testing has been suggested but only 14% in a study with infants with hematochezia had this. Christiansen et al.
- Skin prick testing and IgE testing are not helpful in the diagnosis of CMPI, especially in preterm infants.



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Conclusions

- CMPI could be causing some infant's feeding intolerance.
- In infants post medical "NEC" regardless of the etiology if human milk is not available, clinicians should consider switching formula to a complete protein hydrolysate or amino acid formula.
- With human milk, clinicians might consider dietary counseling of mothers to:
 - Discover how much CMPI the mother consumed during pregnancy and now.
 - Consider asking mother to eliminate dairy for a period of time with dietary counseling for calcium in the diet.



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FPIES

Food Protein Induced Enterocolitis

Associated with repeat vomiting, lethargy, can have electrolyte imbalances and need fluid.

Some say more common in premies- often occurs in the first few months of life

Triggers can be cow milk protein, soy, other foods.

Relatively under recognized in medical community outside of GI and allergy.



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Feeding Protocols

- Associated with improved outcomes
- Some references show decreased incidence of NEC or improved nutrition
- Many references discuss difficulties with compliance, especially in the beginning



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Perinatal Institute's Feeding Regimen for Infants < 1500 g

1. Includes SGA infants but not those with GI anomalies, those follow the "spirit" of the protocol. (Feed when able after surgery and sometimes in continuous fashion with windows to po feed when able)
2. Enteral feedings will be started within 48 hours of life. Exceptions to this include:
 1. Vasopressor therapy including hydrocortisone
 2. Persistent hypoxia (Oxygen sats < 85%)
 3. 5 min Apgar < 5

Note: UAC/UVC are not a contraindication to starting or advancing feeds

Trophic feedings may be given while on prophylactic indomethacin



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Small Baby Feeding Protocol

3. Donor milk will be offered to eligible infants for until 34 weeks with parental consent
4. Feedings will be given as intermittent bolus every 3 hours



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Children's Neonatal Feeding Algorithm

- Babies < 1500 gm
- Feed within 48 hrs
- Days 1-3 Begin 15 ml/kg MHM or DHM q3h
- Day 4-6 increase 10 ml/kg bid -20 ml/kg/day
- Day 7 Fortify to 24 kcal/oz using Human Milk Fortify (75 ml/kg)
- Continue to increase 10 ml/kg bid to @160 ml/kg
- Surgical Infants
- Same protocol but do fortification in 2 steps, first to 22 kcal/oz and then if needed to 24 kcal/oz. Even is > 1500 gm, can use HMF at least to 22 kcal/oz.
- They also will need additional Na if they have an ostomy and weekly urine sodium assays. Goal value @ 40. For wound healing add additional zinc to 550 mcg/kg and vitamin C at 100 mg/day not /kg.



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American Academy of Pediatrics

AAP recommendation

- Mother's own milk supplemented with donor milk if necessary and fortified as needed.



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Preference of what to feed

1. Mother's own milk
2. Donor human milk
3. Preterm formula – Cow milk protein, 50% lactose as carbohydrate, 50% MCT as lipid
 - a. Post discharge formula or neonatal follow-up: EnfaCare, NeoSure (basically halfway between a preterm formula and a term formula.)
 - b. Specialty formulas as needed: renal, semi-elemental, elemental



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Maternal Milk: Colostrum

- Best choice, small amount.
- Colostrum is extremely valuable with high amounts of secretory IgA to protect the mucous membranes in the throat, lungs, and intestine.
- Colostrum has higher protein and has more of the following than maternal milk: epidermal growth factor, hepatocyte growth factor, insulin like growth factor, transforming growth factor, fibroblast growth factor, granulocyte colony stimulating factor, heparin binding epidermal growth factor, Martinsen et al,
- Very important to get to baby.



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Maternal Milk

- Academy of Breastfeeding Medicine #21 Guidelines for Breastfeeding and Substance Use or Substance Use Disorder, Revised 2015.
Encourage mothers who want to pump or breastfeed get into treatment with close follow-up. Reece-Stremten et al.
- Babies who receive maternal milk have:
 - Better feeding tolerance
 - Reduced rates of sepsis, NEC, BPD.
 - Shorter hospital stay, fewer hospitalizations
 - Superior developmental outcome at 2-8 years of age. Schanler et al, Schanler et al, Lau et al, Maayan-Metzger et al, Vohr et al, Vohr et al, Lucas et al.



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Donor Milk



- Second best choice
- Not the same – entero-mammary system Schanler et al
- BSS lipase is inactivated, host defense proteins lower.
- Highest in protein and zinc in the beginning.
- WHO first foods for breast fed infants: meats for additional protein and zinc.



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Mother's own milk vs Donor



- Many studies have shown the superiority of maternal milk vs formula and donor milk vs formula.
- MOM vs DHM was studied by Ford et al.
- MOM and DHM fed infants have significantly different microbiota with increased diversity (good) and beneficial bacteria among MOM fed infants. Less feeding intolerance was seen as well.



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What happens to some human milk properties when it is pasteurized for donor use?

- Immunomodulatory proteins in HM are reduced by pasteurization.
- Bacterial pathogens were seen to increase 1.8 to 4.6 x more with donor vs fresh MOM. *Staph aureus*, *Pseudomonas*, or *E coli* were incubated in fresh, frozen and thawed, or donor milk.



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Host Defense Proteins Akinbi et al.

	Fresh HM	Frozen HM	Donor HM
Secretory IgA	100%	51% lower	60% lower
Lysozyme	100%	32% lower	60% lower
Lactoferrin	100%	100%	44% lower
Lactoperoxidase	100%	66% lower	82% lower
Lipase, Bile Salt Stim Lipase (fat digestion) Koh et al.	100%	100%	0%



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What is the most important reason to fortify human milk for a premature infant?

- A. for calories
- B. For protein, calcium, phosphorus, and zinc
- ?



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Reasons to fortify

Per kg	Current Recs Koletzko	HM, preterm, term donor	HM w HMF
Fluids	135-200	150	150
Kcal	110-130	102	120
Protein	3.5-4.5 g/kg	2.4, 1.0, 1.1	4.3
Calcium	120-200 mg/kg	38	182
Phosphorus	60-140 mg/kg	22	102
Zinc	1.4-2.5 mg/kg	0.6	2.0



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Formula Choices

- While we steer away from formulas early on due to the relationship between NEC and early formula use, they are valuable later.
- Categories:
 - Preterm- Special Care, Enfamil Premature
 - Post Discharge- between premature and term, useful for older premie and premie after discharge depending on circumstances potentially to 9 months
 - Term – Enfamil, Good Start, Similac
 - Soy formulas available but try not to use in premature infants due to phytates in soy making minerals less bioavailable* also not for allergies
 - Partial hydrolyzate Soothe, Pro-Sensitive, Gentle Ease * not for allergies



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Specialty Formulas

- Extensively Hydrolyzed* can be used for allergies
 - Alimentum, Pregestimil, Nutramigen
- Renal
 - PM 60/40
- Elemental
 - Elecare Infant, Neocate, PurAmino, Extensive HA
- Spit up formulas added starch- thickens with acid
 - Spit up, Enfamil AR



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Human milk fortification

- Standard bovine based –
 - Similac® Liquid Human Milk Fortifier
 - Enfamil® Liquid Human Milk Fortifier Acidified®
- Enfamil Flex Pro® partially hydrolyzed whey protein
- Similac® HMF Hydrolyzed Protein (Extensively Hydrolyzed) Conc Liquid-
- Similac® Extensively Hydrolyzed protein additive
- Human milk derived Prolacta +4, +6, +8, +10 H²MF, frozen; RTF 24, 26, 28.
- Human milk fat additive Prolacta CR®



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Problems with acidification?

- Cibulskis et al Significantly more infants that received the acidified fortifier had metabolic acidosis, base excess $p=0.006$ and bicarbonate decreased $p<0.001$. More infants were switched off for intolerance or acidosis, than those on the powdered HMF $p<0.001$. Despite the greater amount of protein in the Liquified acidified fortifier, both groups had similar calories with no difference in growth rates between the 2 fortifiers.



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Human milk- based fortifier?

Sullivan et al Lower rate of NEC with HM based fortifier vs powdered HMF, 1 case way out in time in powdered HMF group, this group also used formula as well.

Hair et al Lower NEC compared to bovine fortifiers

Eibensteiner et al no difference in NEC or growth; however Prolacta was given at 26 kcal/oz and bovine fortifier at 24 kcal/oz; both groups were given preterm formula if insufficient mother's milk.



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Microbiome changes

- Preterm infants' microbiome is changeable:
 - Whether c section or vaginal,
 - Whether they have been given antibiotics or not,
 - What they are fed: breast milk or formula.
 - Whether they receive MOM vs DHM.

Ford et al saw distinct differences in the microbiota of infants on DHM vs MOM

- Warner et al looked at stool longitudinally and saw dysbiosis in the stools of infants before they were diagnosed with NEC. Pammi et al confirmed this data.



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Human Milk and Feeding Tubes

About 1/3 of the calories from human milk are from the fat component.

Fat can cling to containers and tubes.

This has been discussed since the 1980s.

Enfit connection systems which were a response to international organization for Standardization standards to reduce errors. Enteral to IV; IV to enteral)

Eccentric (of center) in a study by Abdelrahmen et al had better fat delivery Fat delivery affected by material in tubing, silicone had more fat delivery



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Conclusions



- Maternal Human Milk is the best choice for feedings, then donor milk recognizing it might be lower in protein, zinc, and calories. Not as protective as maternal.
- Would fortify with human milk fortifier; would consider Prolacta at 26 kcal/oz for the most tenuous infants, otherwise would use the liquid HMF (I like the complete hydrolyzed HMF).
- I would avoid an acidified product if possible.



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Conclusions

The literature suggests no advantage to checking gastric residuals.

There appears to be a skewed risk benefit to using acid blocking medications

If an infant does not tolerate feeds with repeat bouts of intolerance, consider avoiding cow milk protein

Acknowledge that when we run human milk feeds over a pump there is nutrient loss especially fat.



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Questions



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