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Feeds, premies and Necrotizing enterocolitis

When to start, how fast, when to restart ?
-Venkatesh Sampath, MBBS, MRCPCh

Red,Yellow,Green Or maybe something in between
– Lovya George,MD

No financial or other conflicts.
Personal Biases are selectively disclosed

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Necrotizing enterocolitis (NEC)

- Incidence: All NEC - 5-12% in infants with birth wt <1500g. Surgical NEC - 2-3%. Mortality of 15-35%.
- Morbidity and mortality in 2000s: Increasing after 2000 [Patel RM. NEJM. 2015]; Many centers reporting decrease after MoM and Donor milk strategies; 7 to 5% stage II NEC [Horbar JD 2017 JAMA Pediatr]; Surgical NEC – stagnant?
- Associated morbidities: Short-bowel syndrome, Growth failure, cystic PVL, Cerebral palsy, Neurodevelopmental Impairment.

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NEC - Feeding practices(**Breast milk protects**)

- No RCT on mothers own milk. Lucas Cole Lancet 1990; 336:1519-23.

TABLE III—NECROTISING ENTEROCOLITIS BY FEED GROUP

	n	No (%) of cases	
		All cases	Confirmed cases
Formula only	236	24 (10·2%)	17 (7·2%)
Formula plus mother's milk	437	16 (3·7%)	11 (2·5%)
Human milk only	253	11 (4·3%)	3 (1·2%)

	All cases		Confirmed cases	
	Formula only	Human milk*	Formula only	Human milk*
Gestation				
25–27 wk	7/35 (20%)	13/83 (16%)	5/35 (14%)	7/83 (8%)
28–30 wk	7/85 (8%)	11/231 (5%)	5/85 (6%)	6/231 (3%)
31–33 wk	6/75 (8%)	3/263 (1%)	3/75 (4%)	1/263 (0·4%)
34–36 wk	4/43 (9%)	0/113	4/43 (9%)	0/113

- Mother's own milk dose-effects: Dose and duration effects from MOM.
  - Schanler RJ et al (1999 Pediatrics): Retrospective study, 50% reduction in NEC when MOM >50ml/kg/day even if mixed with Preterm formula (PF).
  - Meinzen Derr et al (2009 J Perinatol): Retrospective (n=1272), NEC/death after DOL-14 decreased by 0.83/wk for each 10% increase in human milk.
  - Kimak KS et al (2015 JPGN): Observational study (n>1200), 4-fold increase in NEC rates in infants who received < 7 days of MOM.

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Gastric residuals

- Routine practice in NICUs but paucity of evidence
- Wide variations in what to consider significant
- Wide variations in clinical response to "significant residual"

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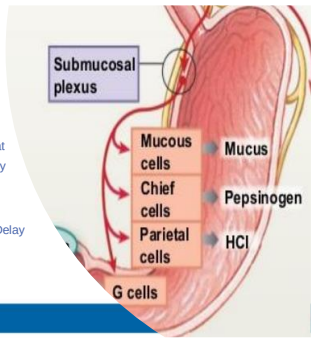
Risks

- Potential damage to delicate gastric mucosa
- May alter secretion of essential GI peptides that are important to the structural and functional development of the GI system → may adversely affect feeding tolerance
- Residuals often discarded → loss of HCl and pepsin →possibly increasing risk of late onset sepsis and NEC
- Decisions regarding enteral nutrition plans → Delay in achieving optimal nutrition and related consequences
- In recent years the practice has shifted to no routine checking of residuals in many centers across the nation



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Why are residuals checked ?

- Verification of feeding tube placement
- Assess residual gastric content
- Monitoring for feeding intolerance or NEC

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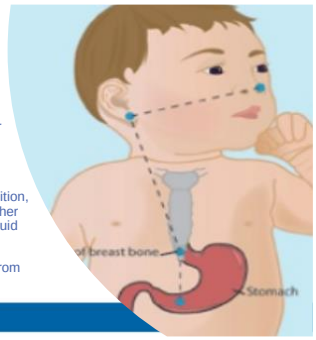
Feeding tube placement

- X-ray is gold standard but not feasible for repeated verification
- Absence of gastric residual does not necessarily indicate malposition
- Dependent on multiple factors –body position, gastric emptying time, feed volume, whether or not tip is positioned in pool of gastric fluid
- 38% of time no residual obtained
- Straw colored aspirate can be obtained from respiratory system



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An indicator of gastric content ?

- Volume often not reflective of actual gastric content
- Errors particularly more in small premature infants
- Simulated model : Aspirated residuals underestimate by 19%
- Size of feeding tube, positioning of the apertures, technique , feeding temperature, viscosity
- Influenced by body position
  - Larger GRs were aspirated from infants positioned left laterally or supine compared to a right lateral or prone position.*(Sangers et al. Outcomes of gastric residuals whilst feeding preterm infants in various body positions. Journal of Neonatal Nursing. 2013)*
  - Left lateral> supine> prone> right lateral *(Cohen et al.Gastric residual in growing preterm infants: effect of body position. Am J Perinatol. 2004)*
  - Lower when positioned prone *(Chen et al. Effects of prone and supine positioning on gastric residuals in preterm infants: a time series with cross-over study.Int J Nurs Stud.2013)*

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Indicator of feeding intolerance / NEC

- VLBW infants : 51 NEC vs 102 controls – gastric residuals in the 6 days prior to NEC diagnosis. Infants with NEC had a maximum GR of 4.5 ml compared to 2 ml in controls (40% or previous feeds vs 14% in controls).Overlap in maximum residual volumes between groups. *(Cobb et al.Gastric residuals and their relationship to necrotizing enterocolitis in very low birth weight infants.Pediatrics. 2004)*

Suggested that GR > 3.5 ml or 33% of previous feeding were at higher risk of NEC.

- Retrospective case control of VLBW infants 17 NEC/17 controls – compared GRs from birth to NEC diagnosis. Max GR of 7.46 vs 4 ml. *(Bertino et al. Necrotizing enterocolitis: risk factor analysis and role of gastric residuals in very low birth weight infants. J Pediatr Gastroenterol Nutr. 2009)*

17 day delay between max GR and diagnosis of NEC

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- Multiple studies have shown that ***omission of routine gastric residual evaluation is not associated with an increase in NEC***
- In the absence of other clinical signs, no correlation between light green GRs and either NEC or feeding intolerance in premature infants.*(Mihatsch et al. The significance of gastric residuals in the early enteral feeding advancement of extremely low birth weight infants. Pediatrics. 2002)*
- Routine aspiration and evaluation of GRs delayed attainment of full feedings (150 mL/kg/d) by 6 days.*(Torrazza et al.The value of routine evaluation of gastric residuals in very low birth weight infants. Perinatol. 2015)*
- Single center RCT – *(Effect of Gastric Residual Evaluation on Enteral Intake in Extremely Preterm Infants. Parker etal,JAMA Pediatrics 2019)* -Infants who did not undergo gastric residual evaluation received considerably *more enteral nutrition without an increase in adverse health outcomes.* Infants advanced feeds more quickly, consumed more enteral nutrition at weeks 5 and 6 after birth.
- Delay in attaining full enteral feeds may increase the duration of parenteral nutrition and its increased risk of associated complications.*(Barr etal.Standardized Nutrition Protocol for Very Low-Birth-Weight Infants Resulted in Less Use of Parenteral Nutrition and Associated Complications, Better Growth, and Lower Rates of Necrotizing Enterocolitis .JPEN 2018)*

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- **Cochrane review 2019**:Abiramalatha et al.

-Routine monitoring of gastric residuals may lead to *delays in the initiation, advancement of feeds, and delay in reaching full enteral feeds*.

- Delays in achieving full enteral feeds *increase the risk of extrauterine growth restriction and neurodevelopmental impairment.*

- Less invasive parameters proven useful in monitoring for feeding intolerance – emesis, visible bowel loops, increased girth, abdominal distension etc.
- Gastric residual aspiration and evaluation **ONLY** in presence of other signs of feeding intolerance

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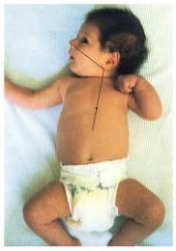
Challenges to a practice change

- Culture change
- Comfort with a reliable method to confirm feeding tube position
- Minimum insertion lengths by weight groups
- Age-related, height-based (ARHB) for only infants > 44.5 cm; Nose-ear-xiphoid (NEX); Nose-ear-mid-umbilicus (NEMU).

RCT showed **NEMU(92%)** and ARHB(100%) are superior to NEX(61%)



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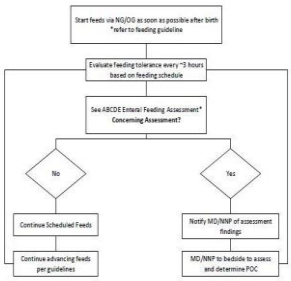

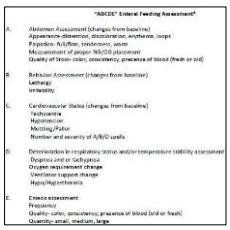

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Conclusions

- Routine evaluation of gastric residuals is not an evidence based practice and may lead to delay in attainment of full enteral nutrition
- Limiting gastric residual evaluation only to infants with symptoms of gastrointestinal dysfunction will optimize nutrition and may lead to improved outcomes in this vulnerable population.

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History – First description of preterm NEC

Bednar A; Vienna hospital for foundlings; 597 infants admitted from 1846-1847: 25 infants with 'entero-colitis' of whom '8 were well nourished, 7 were premature and 10 were emaciated; 15 of them were between 3 and 10 days of age, 4 between 12 and 20 days, 5 between 22 and 30 days and 1 of 1 month and 22 days'. In 20 lethal cases, necropsy showed "the mucosa of small and large intestines swollen, injected, in the colon often a large number of millet-sized dirty-dark red spots. ... In addition, the mucosa including the submucous tissue frequently corroded ... in many areas of the small intestine yellow grey infiltrates with a tendency towards gangrene.'

Bednar: "If we refrain from speculation, we are without knowledge of a specific cause"

Obladen M[1].Neonatology 2009; (Adapted from Siebold AEv: Brand in der kleinen Curvatur des Magens eines atrophischen Kindes. J Geburtsh Frauenzimmer Kinderkrankh 1825; 5:3–4.

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Bolus vs. continuous feeds in VLBW infants

- Issue: Bolus feeds more "physiological" or is it ? Baby vs. "fetus"

Continuous vs. Bolus feeds infants < 1500g. Premji SS, Chessell L (Cochran 2011)

- 7 trials, (n=511 infants), b.wt 500-1500g.
- No difference for time to full feeds or NEC rates.
- One study showed trend towards more apneas with bolus feeds.
- One study- sub-group analysis; Infants <1000g had better weight gain on continuous feeds, earlier discharge to home.

- Impact of Continuous vs Bolus Feeding on Splanchnic Perfusion in Very Low Birth Weight Infants: A Randomized Trial. Bolus feeds increases SMA Doppler flows, NIRS stable. Bozzetti V et al, J Pediatr.

Conclusion: Wash!! Bias towards continuous feeds in ELBW babies.

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NEC - Feeding (Volume of feeds)

- Issue: Increasing feeds by 30-40ml/kg/day vs. <20ml/kg/day is safe.
- Morgan J[1], et al Cochrane Database Syst Rev. 2015 Oct 15;(10):
  - 9 trials in infants < 1500g or < 32 week. (>900 infants).
  - 15-24ml/kg/day *vs.* 30-40ml/kg/day
  - No increase or trend towards increased NEC or mortality.
  - Slow feeding did not confer benefits in ELBW or SGA infants.
  - Time to full feeds, regaining birth weight and rates of invasive infection higher with slow advancement, feed tolerance no different.

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SiFT
Speed of increasing milk feeds

N Engl J Med 2019;381:1434-43. Dorling et al.

- Fast (30ml/kg/day) vs. slow (18ml/kg/day) once feeds were determined to be increased. Age at trial start - 4 days (IQR of 3-6)
- N=2804 (all <1500g); >1000 infants with b.wt <1000gm.
- Fast groups quicker to full feeds; less TPN.
- Survival without moderate or severe neurodevelopmental disability at 24 months, no difference [{65.5% vs. 68.1% (95% CI, 0.92 to 1.01; P=0.16)].
- Late-onset sepsis - No difference {29.8% vs. 31.1% (P=NS)}.
- NEC no differences {5.0% vs. 5.6% (RR - 0.88; 95% CI, 0.68 to 1.16).

Conclusion: No adverse effects of advancing feeds fast. Decrease in CVL/TPN days.

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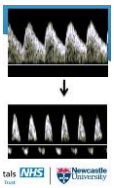
Issue: Feeding high-risk premies - ADEPT trial

- Leaf et al , Pediatrics April 2012; N=404; UK; 52 centers.
  - Infants < 35 week with Absent or reversed diastolic flows, <10% centile for weight randomized.
  - Feeds early **Day 2** vs. Late **Day 6**; once started similar rate of increase.
  - MOM 77% at start on Day 2 vs. 89% at start on Day 6.
  - Full feeds reach 18 days vs. 21 days. (p=0.008).
  - No effect on NEC (18% vs. 15%; stage III NEC 3 vs 5%). Less cholestasis with early feeding.



Courtesy of Nick Embleton, MD (Newcastle upon Tyne)

Conclusion: No advantage in delaying initiation of feeds in high-risk premies.

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New ICN Feeding guidelines – May 2020

< 1kg &/or <27 0/7 weeks GA	
Feeding Day	Volume
1	10 ml/kg/day
2	10 ml/kg/day
3	20 ml/kg/day
4	20 ml/kg/day
5	40 ml/kg/day
6	60 ml/kg/day
7	80 ml/kg/day
8↑	80 ml/kg/day
9↑	100 ml/kg/day
10↑↑	120 ml/kg/day
11↑↑	150 ml/kg/day

1-1.5kg &/or 27-32 weeks GA	
Feeding Day	Volume
1	10 ml/kg/day
2	20 ml/kg/day
3	40 ml/kg/day
4	60 ml/kg/day
5↑	80 ml/kg/day
6↑	100 ml/kg/day
7↑↑	120 ml/kg/day
8↑↑	150 ml/kg/day

1.5-2kg &/or 32-34 weeks GA	
Feeding day	Volume
1	20 ml/kg/day
2	50 ml/kg/day
3↑	80 ml/kg/day
4↑↑	110 ml/kg/day
5↑↑	140 ml/kg/day
6↑↑	150 ml/kg/day

When restarting feeds following a short period of npo (prbc transfusion,

No routine checking of aspirates please !

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Feeding after NEC – When to start back?

Initiation of Enteral Feeding After Necrotizing Enterocolitis Eur J Pediatr Surg 2018;28:44–50

Alvon Maria Hock[1,*] Yong Chen[1,2,*] Hiromu Miyake[1] Yuhki Koike[1] Shogo Seo[1] Agostino Pierro[1]

	Bohnhorst et al (2003)[10]	Boztschi et al (2009)[9]
Study type	Observational	Observational
Setting	NICU Hannover Medical School, Germany	Multicenter (5 NICUs), Switzerland
Participants	Infants < 36 wk gestational age with NEC diagnosis (*n* = 44)	Infants with NEC diagnosis, which was conservatively managed (*n* = 47)
Primary outcome (NEC recurrence, confirmed as follows)	At least one clinical sign (gastric residuals, abdominal distension, blood in stools), plus gas bubbles in portal vein or liver parenchyma, pneumatosis intestinalis, and/or free air (Bell stage 2 +)	Radiologic pneumatosis and/or portal venous gas (international definition of NEC and Bell's stage 2)
Timing of interventions	*Early*: 3 consecutive d without evidence of gas bubbles in portal vein (median: day 4; range: 3–14); (patients admitted between January 1998 and December 2001)	*Early*: median <5 d after NEC diagnosis (range: 1–4 d) (patients admitted between January 2000 and December 2006)
	Delayed: historic comparison group; feeding initiation at discretion of neonatologist (median: day 10; range: 8–22); (patients admitted between April 1993 and March 1997)	*Delayed*: median >5 d after NEC diagnosis (range: 6–16 d) (patients admitted between January 2000 and December 2006)
Type of feeding	*Early*: enteral feeds increased by 20 mL/kg/d formula or breast milk (until full enteral feeding reached at 150 mL/kg/d)	*Early*: enteral feeds increased by 20 mL/kg/d formula or breast milk (until full enteral feeding reached at 150 mL/kg/d)
	Delayed: at discretion of neonatologist	*Delayed*: enteral feeds increased by 20 mL/kg/d formula or breast milk (until full enteral feeding reached at 150 mL/kg/d)

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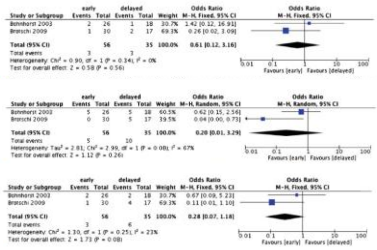
Feeding after NEC – When to start back? Hock et al.

NEC recurrence unchanged (p=0.56)

Catheter-related Sepsis unchanged (p=0.26)

NEC stricture – Trend favors early feeds (p=0.08)



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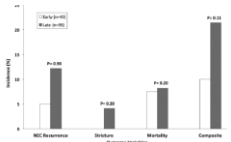
Refeeding early after NEC – Arba et al

- Retrospective chart review over 10 year

	Early[a] (*n* = 40)	Late[b] (*n* = 98)	P-value[c]
Gestational Age at birth (mean, weeks)	30.9	30.3	0.45
Sex (% Male)	50%	50%	1.00
Age at NEC Diagnosis (mean, in days)	19.0	22.6	0.43
Mean Birth Weight (g)	1515.3	1395.5	0.43
Ethnicity (%)			
African American	65.0%	55.1%	0.29
Caucasian	30.0%	37.8%	0.39
Hispanic	2.5%	6.1%	0.38
Other	2.5%	1.0%	0.51
Cardiac Disease (%)	25.6%	38.1%	0.17
Time to First Feed, mean Days after NEC diagnosis (range)	4 (1–6)	12 (7–49)	<0.01
Time to Full Feeds, mean Days after First Feed post-NEC	9.3 (5.6)	10.8 (9.1)	0.32
Bell's Stage (%)			<0.01
I	42.5%	14.3%	<0.01
IIA	55.0%	66.3%	0.21
IIB	2.5%	17.3%	0.02
IIIA	0.0%	2.0%	0.36



Length of stay increased with late feeding strategy

J Pediatr Surg. 2018 Jun;53(6):1187-1191.

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NEC and early refeeding

- Only 3 published studies; all retrospective.
- Early re-feeding (<5 days or < 7 days) after onset not associated with worse outcomes for medical NEC.
- Trend towards less strictures, early discharge with early feeds; No change in mortality. Bias: More severe NEC and later re-feeding.
- *Early refeeding safe in infants who develop stage I/IIA NEC; possibly safe in stage IIB NEC if pneumatosis has resolved.*

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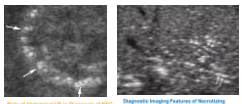
Improving NEC diagnosis – Bowel ultrasound

Abdominal radiography in NEC Pros: Can diagnose free air, pneumatosis, portal venous gas. **Suspicious** - fixed dilated bowel, paucity of gas, thickness.

Limitations: Dynamic bowel function (peristalsis), pneumatosis sometimes subjective (especially bubbly vs. linear), small perforations may be difficult.

Abdominal Ultrasound: Pros: Dynamic, Bowel shape size, wall thickness, dilatation, and ascites. Bowel function and blood flow. **Limitations:** Not readily available, operator dependent, regular monitoring.



Role of Abdominal US in Diagnosis of NEC by Kim, Jae H., MD, PhD Perinatology Clinics, 2018, Volume 46, Issue 1

Diagnostic Imaging Features of Necrotizing Enterocolitis: A Narrative Review. Esposito et al. Quant Imaging Med Surg . 2017 Jun;7(3):336-344.

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Ultrasound in NEC – Useful, not perfect

Table 1
Comparison of specificity and sensitivity of abdominal radiographs to ultrasound

	Abdominal Radiographs		Abdominal Ultrasound	
Findings	Specificity	Sensitivity	Specificity	Sensitivity
Ascites	Low	Low	High	High
Perforation	High	Low	High	High
Bowel wall thickness	Low	Low	High	High
Bowel dilatation	High	Mid (misses fluid-filled loops)	High	High
Pneumatosis	Mid	Mid	High	High
Motility	N/A	N/A	High	High

Role of Abdominal US in Diagnosis of NEC by Kim, Jae H., MD, PhD Perinatology Clinics, 2018, Volume 46, Issue 1

Ultrasound for detection of NEC – meta-analysis . N=462 infants; High specificity and quite low sensitivity. Classic signs of NEC (portal venous gas, pneumatosis, and free air) had pooled sensitivities ranging from 0.27 to 0.48 and pooled specificities ranging from 0.91 to 0.99.

Bowel Ultrasound for the Diagnosis of Necrotizing Enterocolitis: A Meta-analysis. Costa AC, Lee JC, Robinson AL, Allen MH, Foley JE, Chan SS. Ultrasound Q. 2018 Sep;34(3):113-118.

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Ultrasound in NEC – Pragmatic approach

Abdominal radiography and US in NEC: Can complement each other.

- Clinical picture and AXR clear NEC – No need for US diagnosis.
- Clinical picture +/unclear; AXR-negative – Abdominal US can help aid diagnosis.
- Complicated abdominal condition with ascites – AXR is poor; consider US
- Severe medical NEC – need for surgery : Lack of blood flow shows necrotic bowel, abscess, serial imaging will help. AXR not helpful
- Early Re-initiation of feeds: AXR is clear, additional proof is US.

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Feeding during PDA medical treatment

- Issue : Do we need to stop feeds always during medical PDA treatment
  Pros of feeding: Continue nutrition, no delay in time to full feeds
  Cons of feeding: Feed intolerance, bowel perforation, NEC
- Enteral feeding during indomethacin treatment for patent ductus arteriosus: association with gastrointestinal outcomes. Louis D et al. J Perinatol. 2016 Jul;36(7):544-8. Data from single center over 5-yr period.
  - Retrospective chart review: (Group A: NPO, n=229); Group B<60ml/kg/d (n=142); Group C:>60 ml kg/d (n=44). Birth weight (A: 864±239; B: 847±202; C: 932±234 g). Postnatal age at Indomethacin (A: 5.3±2.9; B: 7.2±4.9; C: 15.4±6.6 days).
  - Primary outcome NEC (A: 6.1%, B: 7.8% and C: 4.6%, respectively)
  - Time to full feeds (120ml/kg/day) quicker in infants who were not made NPO.

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Feeding during PDA medical treatment - To Do or Not to Do

- Randomized control trial: Enteral feeding during indomethacin and ibuprofen Rx of PDA J Pediatr. 2013 Aug;163(2):406-11. Clyman R et al.
  - Infants (N = 177, 26.3 ± 1.9 wk) were randomized at 6.5 ± 3.9 days to receive "trophic" feeds ("feeding" group, n = 81: indomethacin 80%, ibuprofen 20%) or no feeds ("fasting [NPO]" group, n = 96: indomethacin 75%, ibuprofen 25%).
  - NEC/perforaton 13% (NPO) vs. 10% (feed). Time to 120ml/kg/day 3 days earlier.
  - Late onset sepsis and other morbidity not different. CVL days – no differences

Conclusion/Recommendation: No adverse effects of maintaining trophic feeds during indomethacin/ibuprofen PDA treatment for most premies.

Consider NPO in Infants with systemic hypotension or acidosis.

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Summary/Conclusion

- Even high-risk premies can start trophic feeds on DOL 1-2.
- Advancing feeds by 20-30ml/kg/day is safe and will decrease CVL days, potentially sepsis rates without adversely impacting outcomes.
- Infants with suspected NEC (stage 1) or mild NEC (stage IIa) can re-start feeds in 3-5 days. Stage IIb NEC (non-surgical) can restart feeds 3 days after resolution of pneumatosis by AXR or ultrasound.
- Abdominal US should be used in conjunction with AXR for NEC diagnosis, when diagnosis is unclear, or as a tool to guide surgery/re-starting feeds.
- Trophic feeds during medical PDA treatment is safe in most babies.

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Acknowledgements

- Mutlidisciplinary Gastric residual and revised feeding protocol taskforce at KU and CMH NICU
- Babies, colleagues and Funding (1R01 DK117296-A1, VS)

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Question

Which of the following is a true statement

A. Routine checking of gastric residuals will shorten time to full enteral feeds

B. Aspirating gastric residual is beneficial to gut mucosal health

C. Green gastric residuals are helpful in predicting the onset of NEC in a clinically stable infant before other symptoms develop

D. Routine checking of gastric residuals has no impact on TPN days

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Bacteria and Humans - Identity Crisis

The following are true about bacteria, viruses and humans except:

1. Neonates have less bacteria, and decreased bacterial diversity in the gut compared to adults.
2. There are 10-100 fold more bacteria living in humans compared to total number of human cells in the body.
3. *1-3%* of the human genome has stretches of viral DNA integrated.
4. In the absence of intrauterine infection, there are no bacterial signatures in the amniotic fluid.
5. Bacteria in the gut secrete metabolites, which may regulate brain neurotransmitter levels, mood, sleep and brain development.

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Necrotizing enterocolitis (NEC)

Regarding the use of donor milk to prevent NEC in premature infants the following statement is true (choose one):

a) It is associated with better 24-month neurological outcomes than preterm formula when used to supplement mothers own milk shortfall.

b) It is associated with comparable linear growth during use.

c) It decreases NEC rates when compared to preterm formula when it is the primary source of nutrition.

d) Pasteurizing donor milk improves its immune-protective properties.

e) Addition of bovine milk fortifier to breast milk decreases NEC risk.

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Necrotizing enterocolitis (NEC)

Literature suggests that Transfusion associated NEC (TANEC) in premature babies is more likely :

a) When more PRBC transfusions are given to maintain a higher hematocrit in study protocols.

b) To occur most commonly in the setting of PRBC transfusions given for an acute drop in hematocrit.

c) To arise from a combination of severe anemia and PRBC transfusion in enteral-fed infants.

d) To cause milder, and less protracted NEC disease.

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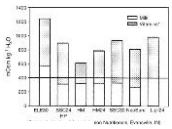
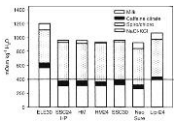
NEC - Osmolality of Feeds

- *Journal of Perinatology* (2012) **32,** 227–229; Milk as a vehicle for oral medications: hidden osmoles. P G Radmacher et al.
  - Tested osmolality of fortified feeds with supplements/drugs.
- ~400mOsm/L is recommended; EBM is 300: most formulas are <450. Additives and drugs can markedly increase osmolality.





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