Preterm Nutrition Consensus

Enteral Feeds

Children's Hospital of Philadelphia®
Division of Neonatology

Title: Preterm Nutrition Consensus Enteral Feeds

Population: Neonates <32 weeks and/or <1500 grams
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Abstract

The nutrition provided to premature neonates, specifically those most at risk, born less than 32 weeks gestation and/or less than 1500 grams can contribute to a multiple outcome for these neonates. Nutrition impacts weight gain, linear growth, neurodevelopment, as well as outcomes such chronic lung disease and sepsis. The goal of this consensus is to provide a consistent and evidenced based approach toward providing optimal nutritional support for neonates balanced with decreasing risk of necrotizing enterocolitis and feeding intolerance.

A multidisciplinary team including physicians, dietitians and lactation consultants worked together to formulate a current enteral feeding guideline and unified feeding advance approach.

Consensus Goals

- Evidenced based approach to feeding less than 32 wk and/or less than 1500 gram at birth.
- Improve weight gain, linear growth and provide optimal feeding advance and fortification goals.
- Decrease Necrotizing Enterocolitis rates.

Background

Standardization of feeding protocols has been shown to decreased the incidence of NEC. Early enteral feeds with human milk is beneficial for premature neonates. Exclusive human milk diet had decreased risk of NEC and NEC requiring surgical repair. Research supports early feeding advances up to 30ml/kg/day does not increase the rates of necrotizing enterocolitis and improves time to full enteral feeds with decreased length of time for requiring TPN or intravenous fluids. Rapid enteral advance also decreases extrauterine growth restriction as well as improves short term outcomes. Earlier fortification of feeds improves protein intake of VLBW without deleterious effects, with positive impact on chronic conditions and long term growth.

Previous Consensus Statement or Data from Division of Neonatology (if applicable)

None Available

Literature Search

Title	Author	Level of Evidence	Primary Outcome	Results	Key Findings/Conclusions
Enteral Feeding of the Preterm Infant	Kate D. Brune and Steven M. Donn	Review Article	Feeds starting by 48hrs of age,		Feeds starting by 48hrs of age, no difference in NEC with slow vs fast advance, fortification no later than 100 ml/kg
Delayed introduction of progressive enteral feeds to prevent necrotizing enterocolitis in very low birth weight infants	Morgan J, Young L, McGuire W Cochrane	Level I	Effect of early trophic feeding versus enteral fasting on feed tolerance, growth and development, and the incidence of neonatal morbidity (including NEC and invasive infection) and mortality in very preterm or VLBW infants	- 9 trials of 1106 infants - Few were extremely preterm (<28wks' GA) or ELBW - Did not detect statistically significant effects on the risk of NEC or all-cause mortality - 4 of the trials restricted participation to IUGR infants with Doppler evidence of abnormal flow. Infants who had delayed introduction of enteral feeds took longer to establish full enteral feeding (2-4 days)	- Delaying the introduction of progressive enteral feeds >4 days after birth did not reduce the risk of developing NEC in very preterm or VLBW infants, including growth-restricted infants - Delaying the introduction of progressive enteral feeds resulted in a few days' delay in establishing full enteral feeds but the clinical importance of this effect was unclear - The applicability of these findings to extremely preterm or ELBW infants was uncertain.

Title	Author	Level of Evidence	Primary Outcome	Results	Key Findings/Conclusions
Controlled Trial of Two Incremental Milk-Feeding Rates in Preterm Infants	SIFT Investigators Group NEJM	Level II	Survival without moderate or severe neurodevelopmental disability at 24 months	Survival without moderate or severe neurodevelopmental disability at 24 months occurred in 65.5% in faster increment and 68.1% in slower increment. Late onset sepsis 29.8% faster vs 31.1% slower, NEC: 5% faster vs 5.6% slower	No significant difference between faster vs slower group
Randomized, controlled trial of slow versus rapid feeding volume advancement in preterm infants	Judith Caple Pediatrics	Level II	Days to reach full feeds 2nd outcome Days to regain BW, days of IV fluid, length of hospital stay, incidence of feeding complications & NEC	Invention group – 30ml/k/d Control group – 20ml/k/d Until 150mL/k/d then fortification for both groups - until weight of 1800-1900gms reached. Invention Group – Mean DOL to reached 150mL/k/d, fewer PN days, regain birth weight shorter duration of	Advancing feedings at a rate of 30mL/k/d is as safe as advancing at the rate of 20mL/k/d

Title	Author	Level of Evidence	Primary Outcome	Results	Key Findings/Conclusions
				hospitalization was significant. No significant difference in NEC, # of feeding intolerance	
Randomized controlled trial of slow vs rapid enteral feeding advancements on the clinical outcomes of preterm infants with birth weight 750-1250 g	Karagol J Parenter Enteral Nutr	Level II	Days to reach full feeds 2nd outcome NEC, Late-onset sepsis, feeding intolerance, growth outcomes	Group 1=slow (20mL/k/d) Group 2=rapid (30mL/k/d) Until 180mL/k/d Rapid feeding – Mean DOL to reached 180mL/k/d, fewer PN days, regain birth weight shorter duration of hospitalization were significant in 750-1000g & 1000-1250g infants. No significant difference in NEC, # of feeding intolerance Incidence of culture-proven late onset sepsis was significant in rapid feeding	Rapid enteral feeding advancement in 750-1250g infants reduces the time to reach full enteral feeding and use of PN. No increase in the risk of sepsis, NEC Also decreased extrauterine growth restriction with improved short-term outcome.

Title	Author	Level of Evidence	Primary Outcome	Results	Key Findings/Conclusions
				Significantly dec. in average number of central line days	
Early trophic feeding versus enteral fasting for very preterm or very low birth weight infants	Morgan Cochrane Database Syst Rev. 2013	Level I	1. Feed intolerance: days to establish full enteral feeding independently of parenteral nutrition 2.NEC	9 trials, 754 very preterm or VLBW infants. No evidence that early trophic feeding affected feed tolerance or growth rates. Meta-analysis did not detect a statistically significant effect on the incidence of NEC: typical risk ratio 1.07 (95% confidence interval 0.67 to 1.70); risk difference 0.01 (-0.03 to 0.05).	- The available trial data do not provide evidence of important beneficial or harmful effects of early trophic feeding for very preterm or very low birth weight infants. - The applicability of these findings to extremely preterm, extremely low birth weight or growth restricted infants is limited.
Slow versus rapid enteral feeding advancement in preterm newborn infants 1000-1499 g: a randomized controlled trial	Kirshnamurthy *et al.*	Level II	Time to full enteral feeds	Neonates in the rapid feeding advancement group (30ml/kg/day) achieved full volume feedings before the slow advancement group (median 7 days vs. 9 days), had	Rapid enteral feeding advancements of 30 mL/kg/day are well tolerated by stable preterm neonates weighing 1000-1499 g

Title	Author	Level of Evidence	Primary Outcome	Results	Key Findings/Conclusions
				significantly fewer days of IVFs, shorter length of stay, and regained BW earlier. No statistical differences in proportion of infants with apnea, feed interruption or feed intolerance.	
Slow advancement of enteral feed volumes to prevent necrotizing enterocolitis in very low birth weight infants	Oddie SJ Cochrane Database Syst Rev 2021	Level I	Determine effects of slow rates of EN advancement on NEC, mortality, and other morbidities in VLVBW infants. Secondary outcome-growth, neurodevelopment, time to reach full feeds, time to establish PO feeds, feeding intolerance, incidence of invasive infection, LOS	No evidence to support slower rates of advancement (15-20ml/kg/d) compared with faster rates (30-40ml/kg/d) reduces risk of NEC in VLBW infants. Infants with slower advancement of feeds reached full feeds and regained BW several days later then infants who had faster rates of advancement.	EN feed advancement at slower rates (slower than 24ml/kg/d) does not reduce risk of feeding intolerance, NEC, or death of very preterm or VLBW infants. Advancing feeds at increased rates (30-40ml/kg daily) shortens time to regain BW, reach full feeds, and may reduce risk of late-onset invasive infection.
Improved outcomes with a standardized feeding protocol for	K R McCallie J Perinatol. 2011	Level III	Days to reach full feeds (160mlc/kg/day)	ELBW infants reached enteral feeds of 120 ml/kg/day and	Implementation of a standardized feeding protocol for VLBE infants result in earlier successful enteral

Title	Author	Level of Evidence	Primary Outcome	Results	Key Findings/Conclusions
very low birth weight infants				160 ml/kg/day significantly faster and had significant fewer days on PN. Decreased NEC in after group among both VLBW and ELBW groups, late onset sepsis decreased in the after group, decrease in discharge weight below 3%	feeding without increased rates of major morbidities
An Exclusively Human Milk-Based Diet is Associated with a Lower Rate of NEC than a Diet of Human Milk and Bovine Milk-Based Products	*Sullivan et al The Journal of Pediatrics 2010*	III	Multicenter, prospective, randomized trial of infants 500-1250g looking at pasteurized donor human milk-based human milk fortifier when enteral intake was 40 vs. 100mL/kg/day vs. bovine milk-based human milk fortifier at 100 mL/kg/day	No difference in duration of parenteral nutrition, length of stay, incidence of LOS, or difference in growth	Groups receiving exclusively human milk diet had significantly lower rates of NEC and NEC requiring surgical intervention
Early vs. Delayed Fortification of Human Milk in Preterm Infants: A Systematic Review	*Alyahya W, Simpson J, Garcia AL, Mactier H, et al.* *Neonatology* 2020	IV	Comparison of effect of early vs. late fortification in VLBW infants on growth, feeding intolerance, NEC, sepsis, length of hospital stay, and		No significant impact of early vs. late fortification on outcomes

Title	Author	Level of Evidence	Primary Outcome	Results	Key Findings/Conclusions
			maturity at discharge Fortification with bovine human milk fortifier 2 studies met inclusion criteria, looking at 171 infants		
Evaluation of Human Milk Fortification from the Time of First Feeding: Effects on Infants of Less Than 31 Weeks Gestational Age	*Tillman S, Brandon DH, & Silva SG. Journal of Perinatology* 2011	IV	Retrospective single center study of infants <31 weeks comparing fortification with powdered human milk fortifier at initial feeding vs. ~85 mL/kg/day (50-100 mL/kg/day)	95 infants included in the analysis (53 in early fortification vs. 42 in delayed fortification)	No difference in weight gain between early and late fortification Early fortification associated with lower alkaline phosphatase levels from 33 weeks corrected age and beyond
Early Fortification of Enteral Feedings for Infants <1250 Grams Birth Weight Receiving a Human Milk Diet Including Human Milk Based Fortifier	*Huston R., Lee M, Rider E, Stawarz M, et al.* *Journal of Neonatal-Perinatal Medicine* 2020	III	Multicenter retrospective cohort study of infants 500-1250g birth weight Breast milk feedings fortified at > 60 mL/kg/day vs. < 60 mL/kg/day with human milk-based fortifier and bovine-based human milk fortifier		Early fortification was associated with improved growth velocity for weight and head circumference Early fortification was associated with decreased occurrence of chronic lung disease No other outcomes, including NEC, were associated with early vs. late fortification
Early versus Delayed Human Milk Fortification in	*Shah SD, Dereddy N, Jones TL, Dhanireddy R, et al.*	II	Prospective, randomized trial of 100 infants to compare the		No difference in time to reach full feedings No significant difference in episodes of feeding

Title	Author	Level of Evidence	Primary Outcome	Results	Key Findings/Conclusions
Very Low Birth Weight Infants: A Randomized Controlled Trial	*The Journal of Pediatrics 2016*		effect of initiating early (20 mL/kg/day) vs. delayed (100 mL/kg/day) human milk fortification on feeding intolerance and time to reach full feeding volume Fortification with bovine human milk fortifier		intolerance, and no increased incidence of NEC in the early fortification group Median daily protein intake was higher in the early fortification group

Literature Summary

- Majority of trials showed safety and improved outcomes with faster feeding advance, especially in the >29 wk and >1000 gram neonates
- Early fortification helps establish improved protein intake, improved growth and decreases chronic issues
- No change in risk of NEC with faster feeding advance and earlier fortification
- Human milk is preferred diet for neonates <32 wks and/or <1500 grams

Delphi Survey Round Results (if applicable)

One round of Delphi survey completed across the Division of Neonatology showed agreement trophic feeds at 20ml/kg for neonates <29 wk or <1000 gram at 74%, and trophic feeds for 3 day period at 82%. Feed advancement of 20 ml/kg/day for neonates <29 weeks or <1000 grams at 87% agreement and for neonates >29 weeks or >1000 gram feed advance rate of 30ml/kg/day agreement at 73%.

Consensus Statement and Clinical Recommendations

Oral immune therapy

- Just colostrum
- Start within 6 hr of birth
- Could be q3-q6 based on the volume obtained

Trophic feeds: Non-advancing feeds

- Start as soon as possible
  - Use of Donor BM for trophic feeds if available to bridge
  - IF no EBM or DBM, may consider formula feeds by 24 hours of life
  - May delay up 72 hours of life if parents want *exclusive* EBM
- No benefit to delay beyond 4 days

<29 weeks or <1000 grams:

- **Trophic feeds**
  - Volume: 20 ml/kg/day
  - Duration: up to 3 days/72 hours
    *TO consider smaller volume or prolonged trophic feeds for IUGR neonates or for clinical concern
- **Advancing feeds**
  - Goal TFL 150-160ml/kg/day
  - Volume: 20ml/kg/day

29 weeks -32 weeks or 1001 to 1500 grams

- **Trophic feeds**
  - Volume: 20ml/kg/day divided q3h
  - Duration: 1-2 days/24- 48 hours
    * TO consider smaller volume or prolonged trophic feeds for IUGR neonates or for clinical concern
- **Advancing feeds**
  - Goal TFL of 150-160ml/kg/day
  - Volume: 30ml/kg/day

Special Circumstances

- **Umbilical Arterial Catheter**
  - Trophic feeds based on weight and GA
    *May use clinical judgement in situations where advance is desired
- **Dopamine (<5mcg/kg/min):**
  - Trophic feeds based on weight and GA
- **Indomethacin/Tylenol for treatment of PDA**
  - Trophic feeds based on weight and GA

Enteral Diet/Fortification

- **Early fortification** is considered safe and may have a positive impact on long-term growth and chronic conditions
- **For all infants <32wks and/or <1500g:**
  - After a minimum of 2 feeds of tolerance at **60mL/kg/d, fortify feeds**:
  - **Prolact+6** (if available at your facility)
  - **HMF 24 kcal/oz (1pk per 25mL)**
  - **Premature formula 24kcal/oz***
    **For facilities without DBM, MBM is not available or the use of DBM has not being consented*
    **Must already be tolerating preterm formula 20kcal/oz*
  - Resume a feed advance after a minimum of 2 feeds of tolerance

- **Feeding calculator**
  - Developed by using the previous recommendations from the feed advance group
  - Enter the weight for calculation and each feed volume will be provided
  - May be for use with units using nurse driven feeds
  - Use birthweight until 7 days and/or birthweight surpassed

Table Representation of Recommended Feeding Advance and Fortification
For Preterm Neonates <32 weeks and/or <1500 grams

	Trophic	Trophic	Trophic	Advancement Vol	Advancment								
	D1	D2	D3		D3/4	D4/5	D5/6	D6/7	D7/8	D8/9	D9/10		
400-499gm	1ml q3h	1ml q3h	1 ml q3h	1ml q24h	2ml	3ml	4ml	5 ml	6 ml	7 ml	8ml		
500-599gm	1ml q3h	1ml q3h	1ml q3h	1.5 ml q24h	2.5 ml	4 ml	5.5 ml	7 ml	8.5 ml	9 ml	10ml		
600-699gm	1.5 ml q3h	1.5 ml q3h	1.5 ml q3h	1.5ml q24h	3ml	4.5 ml	6 ml	7.5 ml	9 ml	10 ml	12ml		
700-799gm	1.5 ml q3	1.5 ml q3	1.5 ml q3	1 ml q12h	3.5 ml	5.5 ml	7.5 ml	9.5ml	11 ml	13 ml	14ml		
800-899 gm	2 ml q3	2 ml q3	2ml q3	1ml q12hr	4ml	6ml	8ml	10ml	12ml	14ml	16 ml		
900-999 gm	2ml Q3	2ml q3h	2ml q3	1.5 ml q12hr	5ml	8ml	11ml	14ml	17ml	18ml			
1000-1099gm	2.5 ml q3	3.5ml q3		2ml q12hr	7.5ml	11 ml	15ml	19 ml	20 ml				
1100-1199gm	3 ml q3	4 ml q3		2ml q12hr	8 ml	12 ml	16 ml	20 ml	22 ml				
1200-1299gm	3 ml q3	4.5 ml q3		2ml q12hr	8.5ml	12 ml	17 ml	21 ml	24ml				
1300-1399 gm	3.5ml q3	4.5 ml q3		2.5 ml q12h	9.5 ml	14 ml	19 ml	24 ml	26ml				
1400-1499 gm	3.5 ml q3	5 ml q3		2.5ml q12hr	10 ml	15 ml	20 ml	25 ml	28 ml				
						For neonates born <29 weeks recommendation for a 20ml/kg/day initial feeding advance							
						Use birthweight up to 7 days or until birth weight is surpassed, than adjust per unit protocol							
						Consider prolonged trophic feeds for IUGR neonates or other clincal concerns							
						Fortification to Prolacta +6; 4pcks HMF/100ml or Preterm formula 24 calories if already tolerating 20 calorie formula							

Considerations for High Risk patients and need to deviate from Feeding Advance Recommendations:

- Medically unstable patients
- Intrauterine Growth Restriction/Small for Gestational Age
- Significant resuscitation needs at time of delivery
- Taking Gestational Age into account when choosing feed advance
  - Small baby who is LGA
  - Consider longer trophic feeds and possible slower advance
- <24-week gestational age consider a more cautious approach
  - Consideration for longer trophic feed period (up tp 5 days, use clinical judgement)
  - Consideration for 10ml/kg/day trophic feed volumes
  - Consideration for slower feed advance

VITAMIN D AND IRON SUPPLEMENTATION FOR PRETERM INFANTS

VITAMIN D

For All Babies, please supplement with 400IU (10mcg) of Cholecalciferol daily
Once feed volumes are at (or approaching) below levels, at which time vitamin D supplementation may not be necessary

Current as of 11/2021

Product*	Vit D Content of Prepared Feeds per 100mL	Volume of feeding that provides 10mcg/day (400IU/day) Vit D
Fortified Human Milk		
Enfamil Liquid HMF[1] @ 22cal/oz	87 IU (47 IU/5mL HMF)	460mL/d (58ml q3hrs)
Enfamil Liquid HMF[1] @24cal/oz	158 IU (47 IU/5mL HMF)	255mL/d (32ml q3hrs)
Similac Hydrolyzed HMF[2] @22cal/oz	65 IU (35 IU/5mL HMF)	620mL/d (78ml q3hrs)
Similac Hydrolyzed HMF[2] @24cal/oz	118 IU (35 IU/5mL HMF)	340mL/d (43ml q3hrs)
Prolacta @ 24cal/oz	3 IU (1.8IU/20mL Prolacta)	n/a due to low vit D content
Prolacta @ 26cal/oz	4 IU (2.5IU/30mL Prolacta)	n/a due to low vit D content
Similac Neosure or Enfamil Enfacare powder @22cal/oz	7 IU	n/a due to low vit D content
Similac Neosure or Enfamil Enfacare powder @24cal/oz	11 IU	n/a due to low vit D content
Formula		
Similac Special Care @22cal/oz	112 IU	365mL/d (46ml q3hrs)
Similac Special Care @24cal/oz	122 IU	335mL/d (42ml q3hrs)
Enfamil Premature @22cal/oz	220 IU	185mL/d (23ml q3hrs)
Enfamil Premature @24cal/oz	240 IU	170mL/d (21ml q3hrs)
Similac Neosure @22cal/oz	52 IU	730mL/d (91ml q3hrs)
Similac Neosure @24cal/oz	57 IU	715mL/d (90ml q3hrs)
Enfamil Enfacare @22cal/oz	56 IU	780mL/d (98ml q3hrs)
Enfamil Enfacare @24cal/oz	61 IU	670mL/d (84ml q3hrs)

*Please consult Registered Dietitian for vitamin D supplementation needs with other caloric densities or feedings

[1]All Enfamil liquid HMFs (acidified, standard protein, high protein) have the same vitamin and mineral content

[2]All Similac liquid HMFs (hydrolyzed, extensively hydrolyzed CL) have the same vitamin and mineral content

SPECIAL CONSIDERATION FOR INFANTS RECEIVING PROLACTA

Given the recognized variability of human milk, exclusive human milk diets will require nutritional supplementation. Thus, Prolacta fortification requires additional vitamin and mineral supplementation. *If receiving Prolacta, regardless of volume, supplement 0.5mL twice daily multivitamin solution (poly-vi-sol without Fe).*

Note: 1 mL of Poly Vi Sol provides 400 IU(10mcg) of Vitamin D.

IRON

Iron intake recommendations for preterm infants: **elemental iron 2 to 4 mg/kg daily, maximum 15 mg total from diet and supplementation** (if receiving rh-Epo, provide 6mg/kg/d)

Age	Diet	Diet provision at 150ml/kg/d	Amount to Supplement[2]
Birth-2 weeks (on full feeds)	Unfortified human milk	0.05mg/kg/d	None
	Fortified human milk (24cal/oz) With Enfamil Liquid HMF With Similac Hydrolyzed HMF With Prolacta	 2.2mg/kg/d 0.6mg/kg/d 0.2mg/kg/d	None
	Formula[1] (preterm or term 20-24cal/oz)	1.8-2.2mg/kg/d	None
>2 weeks (on full feeds)[3]	Unfortified human milk	0.05mg/kg/d	2-4mg/kg/d[4]
	Fortified human milk (24cal/oz) With Enfamil Liquid HMF With Similac Hydrolyzed HMF With Prolacta	 2.2mg/kg/d 0.6mg/kg/d 0.2mg/kg/d	 0-2mg/kg/d[4] 2-4mg/kg/d[4] 2-4mg/kg/d[4]
	Formula[1] (preterm or term 20-24cal/oz)	1.8-2.2mg/kg/d	0-2mg/kg/d[4]

[1] EXCEPT: Similac PM 60/40 will require additional iron supplementation due to its very low iron content

[2] Supplementation required until appropriate (providing 2mg/kg/d) iron-containing complementary foods have been introduced

[3] Consider supplementation for IDM, SGA, and VLBW neonates at 10 to 14 days if they are feeding >100 mL/kg/day

[4] An exception to this practice may be infants who have received an iron load from multiple transfusions of packed red blood cells, who might not need any iron supplementation. However, transfusion-acquired iron overload occurs primarily in neonates with hemolytic disorders

Methods of Supplementation

Supplement	Dose	Elemental Iron Content
Poly-vi-sol with Fe (Mead Johnson)	0.5 ml	5 mg
	1 ml	10 mg
Ferrous Sulfate (FeSO4)	Desired mg/kg/day	15 mg per 1 ml
Fer-In-Sol (Mead Johnson)	Desired mg/kg/day	15mg per 1mL

Note: PVS+Fe may provide excessively high iron supplementation, depending on the weight of the infant. For infants <2.5 kg, consider ordering specific mg/kg/d FeSO4 dosing.

Further Goals
-Continue to add evidence based recommendations with evolving evidence
-Review of integration of feeding advance into Divisional practice

QI Metrics
-Review NEC rates pre and post Preterm Nutrition Consensus