Preterm Nutrition Consensus

Hot Topic 2022

Children's Hospital of Philadelphia®
Division of Neonatology

Preterm Nutrition Consensus, Hot Topic 2022

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Abstract

Preterm nutritional care is multifaceted, in this Hot Topic section the use of supplements including sodium chloride and probiotics were investigated. Probiotics is becoming more commonly used in the term or near-term population, given the latest AAP guidance, there is not sufficient evidence to make a strong recommendation for Probiotic use in preterm neonates. Evidence surrounding the use of probiotics is discussed along with sample formats of current probiotics use in US Neonatal units. Blood transfusions and feeds is a hotly debated topic in preterm nutrition, in this review there is not strong evidence to recommend withholding feeds during a blood transfusion of preterm neonate. The use of modular in order to help growth of the preterm neonate is discussed including dosing for Liquid protein and Medium Chain Triglycerides. Recommendations for Vitamin D and Ferrous Sulfate for discharge of premature neonates is given below.

Consensus Goals

Sodium Chloride requirements and dosing for preterm nutrition
Probiotic recommendations for preterm neonates
Discussion of blood transfusions and feeding for preterm neonates
Use of Modulars for growth in preterm neonates

Background

Sodium chloride is an essential component for preterm neonatal growth, and maternal milk and fortifiers may not provide enough sodium chloride to promote appropriate growth. Probiotics is become a hot national topic in neonatal care, dysbiosis is associated with many disease states including Necrotizing enterocolitis and late onset sepsis; a healthy intestinal biome can help in forming a protective mucosal barrier. In comparison to term infants, preterm infants are higher risk for dysbiosis with fewer probiotic microorganisms. The Cochrane meta-analysis shows weak support in favor of probiotics. Given the no FDA approved pharma and conflicting data at this time Probiotics is not recommended in the preterm neonate. Transfusion related NEC has been reported in observation studies but a causal pathway has yet to be determined versus presumed severe anemia causing intestinal injury. It continues to remain controversial whether continuing to feed during blood transfusions increases the likelihood of NEC. Given the current literature review there is not strong evidence to recommend holding pRBC transfusion during feeds of preterm neonates. Adding modular should be considered if faltering growth in a premature neonate and after multi-nutritional source has been adjusted. Modulars include MCT oil, cream, Liquigen and liquid protein.

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

None

Literature Search

Title	Author	Level of Evidence	Primary Outcome & Results	Key Findings/Conclusions
Impact of Early Sodium Supplementation on Hyponatremia and Growth in Premature Infants: An RCT	Isemann et Al J Parenteral Enteral Nutrition 2014	I	Infants <32w and supplemented DOL 7-35 with Na 4 mEq/kg/d given when at 100 ml/kg/d feeds	Improved % infants maintaining BW at 6 wks and increased velocity of weight gain Significantly increased velocity of wt gain, and percentage increase in wt gain from birth to 6 wks in subgroup analysis of <28w
Effects of Salt Supplementation on Premature Infants on Neurodevelopment at 10-13 years of age	Al-Dahhan et al Arch Dis Child Fetal Neonatal Ed 2002	II	Recalled infants from a prior study in the group that had received sodium supplementation (4mmol/kg/d if 31-34w and 5 mmol/kg/d if <31w) on DOL 4-14	NaCl supplementation resulted in improved scores on some developmental testing
Physiologic Approach to Sodium Supplementation in Preterm Infants	Segar et al American J of Perinatology 2018	II	Developed a urine sodium algorithm to guide supplementation starting at DOL 14 Infants 23w-29+6 compared to historical cohort	Urine sodium decreased with time and does not correlate with serum sodium Weight Z-score between 2-8 wks significantly improved with supplementation
Probiotics for the prevention of Necrotizing Enterocolitis in very preterm or very low birthweight infants	Cochrane Review 2020 Sharif S, Meader N, Oddie SJ, Rojas-Reyes MX, McGuire W	I	Combined analyses showed that giving very preterm and very low birth weight infants probiotics may reduce the risk of necrotizing enterocolitis, and probably reduces the risk of death and serious infection. There is no evidence of an effect on disability or developmental outcomes. Few trials provided data for extremely preterm infants (born more than 12 weeks' early) and extremely low birth weight (less than 1.0 kg), and these analyses did not show effects on necrotising enterocolitis, death and serious infection.	The evidence for an effect on necrotizing enterocolitis is "low-certainty" because of concerns that the effect could have been biased by small trials with unreliable methods.

Title	Author	Level of Evidence	Primary Outcome & Results	Key Findings/Conclusions
Blood transfusion alters the superior mesenteric artery blood flow velocity response to feeding in premature infants.	Krimmel GA et al. 2009	Level II - RCT	- Mean, peak systolic, and end diastolic Doppler mesenteric blood flow velocity 30 minutes before and after feedings at baseline (anemic) and with the first feeding posttransfusion. -22 infants -Anemic infants >1250g had increase in mean and peak systolic MBFV after feeding	- We speculate that the lack of response to feeding in the immediate posttransfusion state may contribute to the development of transfusion-associated necrotizing enterocolitis.
FEEding DURing red cell transfusion (FEEDUR RCT): a multi-arm randomised controlled trial	Schindler et al., 2020	Level II - RCT -Compared 1) Withhold feeds 12 h prior 2) Continue feeds 3) Restrict to 120 kcal/kg/day	- Mean splanchnic-cerebral oxygenation ratio (SCOR) and mean splanchnic fractional oxygen extraction (FOE) before (1 h prior), during (1 h into transfusion) and after (end of transfusion; 12 and 24 h post) transfusion. -60 transfusion episodes, 41 infant -There were no differences in mean SCOR and mean splanchnic FOE -3 groups with similar baseline characteristics -No differences in NEC among group	- There were no differences in splanchnic oxygenation when enteral feeds were either withheld,continued or restricted during a transfusion -Larger scale clinical trial needed for clinical outcomes
The WHEAT pilot trial—WithHolding Enteral feeds Around packed red cell Transfusion to prevent necrotising enterocolitis in preterm neonates: a multicentre, electronic patient record (EPR), randomised controlled point-ofcare pilot trial	Gale et al., 2019	Level II - RCT, Pilot trial	-Comparing continued feeds vs. holding feeds for 4 hrs prior during and 4 hrs afterwards - Primary feasibility outcomes: recruitment, opt-out, retention, compliance, data completeness and data accuracy -clinical outcomes: mortality and NEC. -Ongoing	-To be determined
Effect of withholding feeds on transfusion-related acute gut injury in preterm	Sahin et al., 2020	Level II - RCT pilot trial	-NEC rate -154 transfusion episodes (74 NPO, 80 Fed) -Similar demographics	-Does not support holding feedings, but is not adequately powered to suggest that NPO decreases NEC rates

Title	Author	Level of Evidence	Primary Outcome & Results	Key Findings/Conclusions
infants: a pilot randomized controlled trial.			-No significant difference in NEC rates -Statistically insignificant higher rates of feeding intolerance	
Withholding feeds and transfusionassociated necrotizing enterocolitis in preterm infants: a systematic review.	Jasani et al., 2017	Level V - Meta synthesis of 7 non-RCT	-Transfusion associated NEC rates - *n* = 7492 - withholding feeds during PRBC transfusion significantly reduced the incidence of TANEC (RR: 0.47; 95% CI: 0.28, 0.80; *P* = 0.005; I^2 = 11%). -Moderate GRADE evidence	-Adequately powered RCTs needed
Association of Red Blood Cell Transfusion, Anemia, and Necrotizing Enterocolitis in Very Low-Birth-Weight Infants	Patel et al., 2016	Level III - Observational Cohort Study	-NEC, Stage 2 -Mortality -600 infants enrolled -pRBC not significantly related to NEC in adjusted analyses -NEC rate was significantly increased among VLBW infants with severe anemia	-Severe anemia associated with NEC

Literature Summary

As per above, sodium supplementations helps promote growth in premature neonates and may help with long term neurodevelopment. With regards to probiotics, a large Cochrane Review noted “low-certainty” of evidence an effect on necrotizing enterocolitis given the concerns that the effect could have been biased by small trails with unreliable methods. The AAP recently published a statement not recommending probiotics in premature neonates. With regards to feeding during blood transfusions and incidence of necrotizing enterocolitis, there is not strong evidence to support NPO during blood transfusions at this time.

Delphi Survey Round Results (if applicable)

None

Network Wide Baseline Survey 2022

Comfort with using Probiotics in <32 wk <1500 gram neonates?

Yes 30

No 36

D

o you hold or decrease to torphics during a blood transfusion?

Yes 24

No 41

Consensus Statement and Clinical Recommendations

Sodium Chloride Supplementation for Preterm Neonates

- The amount of sodium in mother's milk as well as in fortifiers may not have sufficient sodium to meet the needs of VLBWs
- Pasteurized donor milk-fed premature infants have a higher incidence of hyponatremia compared to formula-fed
- <35 wk infants have high renal and intestinal sodium losses during first 2 wks of life and develop a negative sodium balance

Recommendation

- If there is concern for growth failure and serum sodium is normal, consider sending a urine sodium level
- Consider supplementing with sodium chloride to augment growth if serum sodium is less than 135 mmol/L or urine sodium is less than 30 mEq/L
- Consider stopping sodium chloride supplementation when fully transitioned to the infant's home diet

Probiotics and Preterm Neonates

Data that SUPPORTS routine probiotic use:

- Plausibility from pre-clinicals studies, many RCTs and non-RCTs, large effects in meta-analysis
- Low relative cost
- NEC remains a major cause of morbidity, mortality, and cost in the NICU

Data that REFUTES routine probiotic use

- No FDA approved formulation
- Contamination concerns
- Large European trials that show no benefit
- Uncertainty about appropriate strain(s)
- Number needed to treat remains high
- Social concern that probiotics cause sepsis

AAP Statement 2021

- Lack of FDA approval for pharma regulated formulation
- Overall conflicting data on safety & efficacy
- Potential for harm
- Extraordinarily high-risk population

Overall recommendation: AAP does not recommend routine, universal administration of probiotics to preterm infants, highlights <1000 g babies particularly

Recommendation
At this time routine use of probiotics in preterm neonates is not recommended

Future Considerations
Discussion on the timing, dosing, strains and duration of use along with commercial availability and licensing issues.

Blood Transfusions and Feeding, Transfusion Associated Necrotizing Enterocolitis

- Low to moderate quality evidence associating holding feeding during transfusion with improved rates of NEC.
- Some evidence that holding feeds during transfusion alone did not lead to short term adverse nutritional outcomes

Recommendation
At this time, not enough evidence to support withholding feeds during a blood transfusion
Modulars for Growth

- Modulars are single nutrient additives that will adjust an individual macronutrient
- Some can be administered as a medication, in addition to the prepared feeds
- When added to the feeding recipe, be mindful of the volume displacement
- Protein:
    - Liquid Protein
    - 0.67 kcal/mL, 0.2 g protein/mL
    - Mix with prepared feeds and administer at each feeding interval
- Fat
    - Cream – from pasteurized donor human milk
        - 2.6 kcal/ 1mL (2.25 fat kcal/mL, 0.28 CHO kcal/mL, 0.04 protein kcal/mL)
        - Mix with prepared MBM or DHM and administer at each feeding interval
    - MCT oil – non-emulsified medium chain triglyceride
        - 7.7 kcal per 1mL
        - Will separate in solution; give as medication via oral/OGT/NGT and administer just prior to a feeding
    - Liquigen – emulsified medium chain triglycerides
        - 4.5 kcal per 1mL

    - Will mix well in solution; mix with prepared feeds and administer at each feeding interval

Vitamin D and Ferrous Sulfate for Discharge
Vitamin D

- *ALL* babies (both human milk and formula fed) should receive 10mcg (400 IU) of Cholecalciferol daily from vitamin supplementation and/or feedings.
- If feeding alone meets this vitamin D provision, additional vitamin D supplementation may not be necessary

Iron intake recommendations for preterm infants:

- Elemental iron 2 to 4 mg/kg daily, maximum 15 mg total from diet and supplementation
- Note: Poly-vi-sol with iron has 11mg iron/mL. This can result in excessively high iron supplementation depending on weight of the infant. For infants <2.5kg, consider specific mg/kg/d dosing using $FeSO_4$ drops.

VITAMIN D AND IRON SUPPLEMENTATION FOR DISCHARGE

VITAMIN D

***ALL* babies (both human milk and formula fed) should receive 10mcg (400 IU) of Cholecalciferol daily from vitamin supplementation and/or feedings. If feeding alone meets this vit D provision, additional vitamin D supplementation may not be necessary.**

Current as of 3/2022

Product*	Discharge with the following Vit D supplementation
Fortified Human Milk	
Human milk with Neosure or Enfacare powder to 22cal/oz or 24cal/oz	Supplement 10mcg (400IU)/day
Human milk + Enfamil Liquid HMF[1] @ 22cal/oz	NO supplementation needed if intake is >460mL/d (58ml q3hrs)
Human milk + Enfamil Liquid HMF[1] @24cal/oz	NO supplementation needed if intake is >255mL/d (32ml q3hrs)
Human milk + Similac Hydrolyzed HMF[2] @22cal/oz	NO supplementation needed if intake is >620mL/d (78ml q3hrs)
Human milk + Similac Hydrolyzed HMF[2] @24cal/oz	NO supplementation needed if intake is >340mL/d (43ml q3hrs)
Formula	
Similac Neosure @22cal/oz	NO supplementation needed if intake is >780mL/d (98ml q3hrs)
Similac Neosure @24cal/oz	NO supplementation required if intake is >715mL/d (89ml q3hrs)
Enfamil Enfacare @22cal/oz	NO supplementation required if intake is >730mL/d (91ml q3hrs)
Enfamil Enfacare @24cal/oz	NO supplementation required if intake is >670mL/d (84ml q3hrs)
Similac Special Care @22cal/oz	NO supplementation required if intake is >365mL/d (46ml q3hrs)
Similac Special Care @24cal/oz	NO supplementation required if intake is >335mL/d (42ml q3hrs)
Enfamil Premature @22cal/oz	NO supplementation required if intake is >185mL/d (23ml q3hrs)
Enfamil Premature @24cal/oz	NO supplementation required if intake is >170mL/d (21ml q3hrs)
Any term formula	Supplement 10mcg (400IU)/day

*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

Available liquid vitamin D supplements - Cholecalciferol (D_3):

Product	Dosing	Comments
Multivitamin (Tri-vi-sol or Poly-vi-sol)	1 mL= 400 units/10mcg	▪ May be covered by insurance ▪ Each bottle only provides 1 month supply
Vitamin D liquid (D-vi-sol)	1 mL= 400 units/10mcg	▪ May be covered by insurance ▪ Each bottle only provides 1 month supply
Baby D-drops (Bio-D-Mulsion)	1 drop (0.04ml)= 400 units/10mcg	▪ Out-patient use: Please ensure that all prescriptions for Baby D-drops are written for a dose evenly divisible by 400 due to drop size. This may necessitate a change in dose. ▪ Available via internet (www.carlsonlabs.com) or CHOP outpatient pharmacy (~$16/bottle). ▪ Each bottle provides supply for ~2years if given as 400 units daily

IRON SUPPLEMENTATION AT DISCHARGE

Methods of Supplementation

Supplement	Dose	Elemental Iron Content
Poly-vi-sol with Fe	0.5 ml	5.5 mg
(Mead Johnson)	1 ml	11 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.

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]
>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	2.2mg/kg/d	0-2mg/kg/d[4]
	With Similac Hydrolyzed HMF	0.6mg/kg/d	2-4mg/kg/d[4]
	With Prolacta	0.2mg/kg/d	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

Registered Dietitian

- Guidelines for Perinatal Care state that at least 1 RD should be available to serve only the NICU (level 3 and level 4)
- National survey completed in 2021 (not yet published), preliminary results support the recommendations already in place through BASPEN and British Dietetic Association

Further Goals

- Develop further criteria about use of Probiotics and preterm and late preterm neonates as more literature becomes available
- Support RD work in CHOP Newborn Care Network
- Develop Growth parameter guidelines, including Z Scores

QI Metrics

Pending

References

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