Working group reports: evaluation of the evidence to support practice guidelines for nutritional care of preterm infants—the Pre-B Project[1–4]

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ABSTRACT

The "Evaluation of the Evidence to Support Practice Guidelines for the Nutritional Care of Preterm Infants: The Pre-B Project" is the first phase in a process to present the current state of knowledge and to support the development of evidence-informed guidance for the nutritional care of preterm and high-risk newborn infants. The future systematic reviews that will ultimately provide the underpinning for guideline development will be conducted by the Academy of Nutrition and Dietetics' Evidence Analysis Library (EAL). To accomplish the objectives of this first phase, the Pre-B Project organizers established 4 working groups (WGs) to address the following themes: *1*) nutrient specifications for preterm infants, *2*) clinical and practical issues in enteral feeding of preterm infants, *3*) gastrointestinal and surgical issues, and *4*) current standards of infant feeding. Each WG was asked to *1*) develop a series of topics relevant to their respective themes, *2*) identify questions for which there is sufficient evidence to support a systematic review process conducted by the EAL, and *3*) develop a research agenda to address priority gaps in our understanding of the role of nutrition in health and development of preterm/neonatal intensive care unit infants. This article is a summary of the reports from the 4 Pre-B WGs. *Am J Clin Nutr* 2016;103(Suppl):648S–78S.

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INTRODUCTION

As highlighted in the Pre-B Executive Summary (1), the meeting was designed to provide the 4 Pre-B working groups (WGs)[16] ample opportunity for within- and between-group conversations in support of their deliberations. After the meeting each WG was provided with additional opportunities to interact via teleconference and e-mail. The following reports represent the summaries of the WG deliberations.

After consultation with the scientific steering committee, 4 broad themes and potential workgroup co-chairs were identified. Once recruited, the co-chairs then worked with the Pre-B Secretariat (NIH staff) to identify and recruit WG members with requisite expertise in the respective WG thematic areas. The WG members are listed as part of the Pre-B Consultative Group [**Supplemental Material** (WG and meeting participant list)]. The 4 thematic areas and co-chairs are listed in **Text Box 1**.

Each WG was asked to develop a summary report organized as follows: a list of priority topics, a review of each topic including

[1] Presented at the meeting "Evaluating the Evidence to Support Guidelines for the Nutritional Care of Preterm Infants: The Pre-B Project" held at the USDA/Agricultural Research Service Children's Nutrition Research Center, Baylor College of Medicine, Houston, TX, 31 July–1 August 2014.

[2] Travel support for the Baylor meeting was provided by the Academy of Nutrition and Dietetics, the American Society for Parenteral and Enteral Nutrition, the American Academy of Pediatrics, ASN, the International Formula Council, and the National Institute of Child Development and Health and Division of Nutrition Research Coordination at the NIH.

[3] The views presented here are those of the authors and not necessarily the NIH.

[4] Supplemental Material is available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

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[16] Abbreviations used: AA, arachidonic acid; AGA, appropriate for gestational age; BPD, bronchopulmonary dysplasia; ELBW, extremely low birth weight; EN, enteral nutrition; EUGR, extrauterine growth restriction; FGF19, fibroblast growth factor 19; FXR, farsenoid X receptor; GA, gestational age; GLP-2, glucagon-like peptide 2; IFALD, intestinal failure–associated liver disease; IQ, intelligence quotient; IUGR, intrauterine growth restriction; LC, long-chain; LGA, large for gestational age; MOM, mother's own milk; NCD, noncommunicable disease; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; PDA, patent ductus arteriosus; PN, parenteral nutrition; PNALD, parenteral nutrition–associated liver disease; ROP, retinopathy of prematurity; SBS, short bowel syndrome; SGA, small for gestational age; VLBW, very low birth weight; WG, working group.

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Text Box 1 Pre-B thematic WGs

WG 1: Nutrient Specifications for Preterm Infants

Chairs: Steven Abrams, University of Texas–Austin
Tay Kennedy, Oklahoma State University
Ian Griffin, University of California–Davis
Susan E Carlson, University of Kansas Medical Center

WG 2: Clinical/Practical Issues in Enteral Feeding of Preterm Infants

Chairs: Diane Anderson, Baylor College of Medicine
William Hay, University of Colorado

WG 3: Gastrointestinal and Surgical Issues

Chairs: Sandra Robins, Inova Children's Hospital
Josef Neu, University of Florida

WG 4: Current Standards of Infant Feeding

Chairs: Michael Georgieff, University of Minnesota
Sharon Groh-Wargo, Case Western Reserve University–School of Medicine
Tanis Fenton, University of Calgary

a brief rationale for the need to address this topic, followed by the associated questions that might be addressed via systematic reviews, and questions to be answered with new research and data. In terms of the presentation of these summaries the following 4 caveats should be noted.

1) Topics within each WG summary are not listed in any particular order of priority.

2) WGs did not always address issues specific to current definitions of preterm infants either by gestational age (GA) or weight. This may be addressed during the systematic review process, as allowed by the existing literature.

3) Postdischarge issues were addressed on a case-by-case basis as each WG deemed necessary.

4) WGs also acknowledged a number of "cross-cutting issues," including the use of human milk (mother's and donor), the role of the caregivers, and all aspects of the evolving appreciation of the human gut microbiome. This was particularly relevant for the topics covered by WGs 2 and 3. These issues were addressed where relevant and feasible, but the lack of focus on them should not be inferred to imply that they are not a priority.

WG 1: NUTRIENT SPECIFICATIONS

Chairs: Ian Griffin and Susan E Carlson

Topic 1: What is the appropriate biological frame of reference for establishing the nutrient needs of parenterally or enterally fed preterm infants? (See Text Box 2.)

Rationale

Infants born early in the third trimester are nutritionally challenged as a result of the interruption of maternal transfer/fetal accretion of micronutrients (vitamins, trace minerals) (2), macronutrients (e.g., protein, fat) (3), and long-chain PUFAs [LC-PUFAs; arachidonic acid (AA, 20:4n–6) and DHA (22:6n–3)] (4). Infants born prematurely may also be developmentally unable to produce the necessary amount of metabolically essential forms of key nutrients (e.g., DHA and AA). Failure to meet these nutrient needs is not uncommon during hospitalization, even for preterm infants who have an uncomplicated course. Moreover, it may also be the case that by hospital discharge, stores of many nutrients are still low compared with the stores that would be found in term-born infants at the same postconceptional age.

The consequences of these deficits can manifest in many ways. For example, most preterm infants do not achieve a growth trajectory similar to the last intrauterine trimester (5). Mineral deficiencies that influence bone or acid-base balance have also been recognized (6). Because of these problems with growth and bone development much research has been focused on the protein, vitamin, mineral, and energy needs of preterm infants. However, it is less recognized that preterm infants who reach term-corrected age have a lower lean mass and a higher percentage of body fat than term infants before and after hospital discharge (7, 8).

These differences in body composition may be related to stresses on protein metabolism associated with early birth. They may also be associated with alterations in amino acid concentrations due to immature metabolic pathways, delayed amino acid administration, and lower than required enteral protein intake (7). However, it is also conceivable that these differences may reflect the different ways that protein and energy are supplied ex utero compared with in utero.

Although little is known about the potential mechanisms to explain long-term effects of higher body fat early in life, it is hypothesized that these changes have implications for future health (9). The ability to more fully understand the potential mechanisms underlying the developmental origins of health and chronic disease demands a better understanding of what is "normal," in terms of the maternal/fetal nutritional environment.

Text Box 2 WG 1: nutrient specification topics

1) What is the appropriate biological frame of reference for establishing the nutrient needs of parenterally or enterally fed preterm infants?

2) What nutrients are conditionally essential in preterm infants?

3) What factors affect nutrient requirements in preterm infants (before hospital discharge)?

4) How do nutrient requirements of otherwise healthy, formerly preterm infants differ from term infants of the same corrected age after hospital discharge?

5) What are the pre- and postnatal modifiers of nutrient requirements of formerly preterm infants, and how do these resulting requirements differ from those of term infants of the same corrected age after hospital discharge?

6) Can we individualize nutrient intakes in preterm infants, and if so, how?

Moreover, our ability to determine the nutritional needs of preterm infants is contingent on having a frame of reference to determine what is "normal" for an infant at a given point in his or her development.

The ability to clarify these relations will be contingent on a better understanding of the role the placenta in moderating the transfer of nutrients. Logic might dictate that the provision of nutrients to preterm infants based on maternal transfer might lead to more biologically relevant formulations. For example, placental transfer of linoleic acid is limited (10), meaning that exposure to high amounts of linoleic acid does not occur until term birth. In contrast, intravenous lipids and preterm formulas provide very large amounts of linoleic acid to the preterm infant, and there might well be long-term health effects. Elevated cord blood linoleic acid has been observed in infants at risk of atopic eczema (11).

Currently, the approach to determining nutrient needs of preterm infants has been empirical and based on extrapolation from the needs of term infants. Only in cases in which frank nutritional deficiencies are recognized or a clinical problem emerges is attention paid to the role of a particular nutrient for preterm infants. Due to this limited frame of reference underlying the unique needs of preterm infants in the hospital and postdischarge, these infants are at risk of being provided either too much or too little of specific essential nutrients either via parenteral or enteral nutrient sources. Moreover, the forms of the nutrients provided might be problematic in the context of developmental metabolism. Finally, it must be recognized that nutrient requirements may be lower when given parenterally, rather than enterally, because parenteral nutrition (PN) does not allow for the moderating effect of $<100\%$ absorption for some nutrients. In summary, the amount, form, and mode of delivery of nutrients to preterm infants must be informed by a better understanding of the baseline with regard to *1*) the maternal/fetal in utero interface and placental function, *2*) an understanding of developmental metabolism as pertains to nutrient utilization, and *3*) unique aspects of different modes of nutrient delivery that might affect form and amount of nutrients delivered.

Suggested systematic review questions

- What are the protein and energy needs of preterm infants to maintain intrauterine growth (linear and body composition) rates?
- What are the mineral and vitamin D needs of preterm infants to support linear growth and to prevent long-lasting osteopenia?
- What is the extent and nature of nutrient transfer in the last intrauterine trimester?
- What are trace element, vitamin, and LC-PUFA requirements in the last intrauterine trimester?

Data and research priorities

- What are the best tools to assess
  - optimal short- and/or long-term bone health in preterm infants;
  - whether premature infants develop osteopenia during early adulthood;
  - normal ranges of protein (total protein, prealbumin), energy biomarkers (serum glucose, proinsulin), lipid biomarkers (triglycerides, cholesterol) that predict better nutrient status and long-term health status in preterm infants; and
  - macronutrients that predict long-term morbidities in preterm infants.
- What are the best biomarkers and cutoffs for defining the status of micronutrients (vitamins and most trace elements) and LC-PUFAs in preterm infants at birth and at discharge?
- Nutrient requirements and outcomes:
  - At what corrected age does micronutrient and LC-PUFA status reach that considered sufficient on the basis of biomarkers appropriate for term infants (and are these same biomarkers as used in term infants appropriate for all nutrients)?
  - Can long-term outcomes be improved by better control of micronutrient and LC-PUFA status?
  - Can long-term outcomes be improved by accelerating recovery from previous insufficiency of micronutrients and LC-PUFA status?
- Implications of timing and formulation of nutrient delivery for nutrient requirements:
  - Do the nutrient compositions of PN and preterm formulas need to be improved?
  - What is the relative impact postdischarge on nutrient status between preterm formula compared with postdischarge formulas?
  - Should breastfed infants continue to receive nutrient fortifier for some period of time after hospital discharge? For how long? What clinical evidence do we need to decide?
  - Is there an optimal macronutrient intake (quantity or quality) to achieve a body composition closer to that of term infants of the same postconceptional age?

Topic 2: What nutrients are conditionally essential in preterm infants?

Rationale

Current nutrient recommendations for preterm infants are based on guidelines that are >30 y old and centered around either term infant needs or data from a preterm population who were considerably older than what is currently seen in today's neonatal intensive care unit (NICU) (12–14). In addition, parenteral nutrients are designed to mimic profiles of term breastfed infants. These recommendations therefore do not adequately account for developmental metabolic differences that can affect nutrient requirements, either in terms of form or amount.

Conditionally essential nutrients are physiologically important compounds that are normally not essential because they can be synthesized from available precursors. They become essential nutrients, and must be provided directly, under specific circumstances, such as physiologic immaturity, higher developmental need, or certain medical conditions. Examples of some potential conditionally essential nutrients for preterm infants are listed in **Text Box 3**.

On the other end of the spectrum, the metabolic immaturity of preterm infants may place them at risk of overexposure to certain nutrients. For example, higher protein supplementation may increase the concentrations of branched-chain amino acids in preterm infants, with potential long-term adverse neurodevelopment (24, 25).

Text Box 3 Developmentally sensitive, potentially conditionally essential nutrients

- Amino acids: in preterm infants, specific amino acids cannot be synthesized adequately from their precursors due to hepatic immaturity (15).
  - L-Cysteine: in human adults L-cysteine can be synthesized de novo from methionine and serine and is therefore a nonessential amino acid.
  - It has been suggested that cysteine might be a conditionally essential in all preterm infants because of biochemical immaturity (16, 17), although more recent studies (18, 19) suggest that this may be true only in preterm infants at <32 wk of gestation.
- Choline and carnitine:
  - Choline and carnitine are historically not included in the earlier recommendations for preterm infants.
  - More recent recommendations suggest that these may also be conditionally essential in the preterm infant (14, 20).
- Vitamin B-6 is provided in the form of pyridoxine added to PN solutions and infant formulas.
  - Pyridoxine must be converted to pyridoxal phosphate requiring an enzyme (pyridoxine phosphate oxidase) that does not reach normal adults concentrations until 1–2 wk postpartum (21).
  - Conversion of pyridoxine to pyridoxal phosphate also requires the enzyme pyridoxal kinase. Pyridoxal kinase is inhibited by theophylline, a drug commonly provided to preterm infants (22).
- LC-PUFAs: synthesis of AA and DHA from their respective precursors, linoleic acid and α-linolenic acid, is inadequate to meet the high needs of preterm infants (23), and the need for AA and DHA is already increased because of early birth (4).

Suggested systematic review questions

- What is the effect of cysteine, arginine, tyrosine, and glutamine supplementation in PN-dependent preterm infants on clinical outcomes and neonatal morbidity/mortality?
- What was the effect of the recent shortages of L-cysteine and vitamin A on clinical outcomes and neonatal morbidity and mortality?
- With regard to timing and need for specific minerals/trace elements, should all preterm infants receive
  - selenium on initiation of PN,
  - fluoride in their PN solutions,
  - iodine in their PN solutions, and
  - molybdenum in their PN solutions?
- Are there other trace minerals that need to be included in PN solutions?
- LC-PUFAs
  - Should LC-PUFA content be increased in preterm formula?
  - Should LC-PUFAs be added to intravenous lipids?
  - What are the functional effects of LC-PUFA supplementation of preterm infants?

Data and research priorities

- What are the optimal dose and form of each amino acid in PN solutions?
- What is the optimal composition of parenteral multivitamins and trace element combinations for preterm infants and should composition vary across the different stages of development [i.e., extremely low birth weight (ELBW), very low birth weight (VLBW), near term]?
- Is it important to provide DHA from birth or can supplementation be postponed until infants are receiving full enteral feedings?
- Is it better to provide AA to parenterally fed preterm infants or is the conversion of linoleic acid to AA adequate?
- Is it better to provide preterm infants the active form of vitamin B-6 (pyridoxal 5′ phosphate) rather than pyridoxine?
- Is choline conditionally essential in parenterally fed preterm infants?

Topic 3: What factors affect nutrient requirements in preterm infants (before hospital discharge)?

Rationale

Preterm birth, especially when it occurs before 34 wk of gestation, is an abnormal pregnancy outcome. Causes of preterm birth include maternal malnutrition (over- or undernutrition), stress, and smoking. These and other environmental factors also influence placental development [e.g., smoking reduces iron transfer to the fetus (26), stress is associated with reduced birth weight (27)] and therefore maternal to fetal transfer of nutrients. Problems with nutrient transfer are manifested as undergrown [intrauterine growth restriction (IUGR) or small-for-gestational-age (SGA)] infants. Fetal access to selected nutrients may also be limited due to low maternal nutrient intake or poor maternal nutrient status. In the absence of deliberate efforts to assess mothers for these nutrient deficiencies, it is unlikely that nutrient deficiencies would be detected.

It is reasonable to consider that preterm infants exposed to such environments are nutritionally compromised compared with infants of the same GA from a more optimal pregnancy. The following briefly summarizes the critical pre- and postnatal factors that may influence nutrient requirements of preterm infants.

GA. As highlighted in topic 1, fetal nutrient requirements vary widely during gestation (28). Most nutritional guidelines for preterm infants were developed for infants >1000 g birth weight and at >28 wk GA (29). However, because of the earlier interruption of nutrient accretion and development immaturity, smaller infants (<1000 g; <28 wk GA) may be at even greater risk of nutritional deficits at birth. Thus, nutritional guidelines based on the needs of preterm infants born at >28 wk of gestation are unlikely to be the same as those of smaller, more premature infants.

SGA and IUGR status. Many preterm infants (up to 50% at the same GAs) may have IUGR (30). IUGR is a heterogeneous syndrome with a common end result, poor fetal growth. In many cases, IUGR may lead to, or necessitate, early delivery of the fetus. Some, but not all, of these etiologies are related to reduced placental function and reduced transfer of nutrients (including oxygen) across the placenta (31). However, it is unclear if all causes lead to similar nutritional consequences or whether the nutritional status (both macronutrient and

micronutrient) is similar in all infants of similar degrees of growth retardation.

It is not certain that the optimal nutrition/growth trajectory of IUGR infants is the same among infants whose causes of IUGR differ. Moreover, it is not clear whether nutrient requirements for IUGR infants are best expressed in terms of kg/d (which implies some commonality in growth rate) or in terms of kcal/d (which implies some commonality in terms of compositional nature of growth) (32).

Route and type of nutrient administration. As referred to above and discussed in greater detail by WG 2 below, the provision of nutrients intravenously (parenterally) compared with orally (enterally) influences requirements, as does the type of enteral feeding provided [e.g., mother's own milk (MOM), banked human milk, formula, etc.]. Issues pertaining to the transition from parenteral to enteral feeding modalities will be addressed by WG 2.

With regard to nutrient specifications, it is important to note that the variety of options for feeding preterm infants (e.g., MOM, with or without a variety of different fortifiers, preterm formula, postdischarge formula, and term formula) leaves many questions in and of themselves about the relative ability to adequately meet the infant's actual requirement. A further layer of complexity is added when factors that influence the choice of any of these options (e.g., developmental stage, metabolic/clinical condition, etc.) is considered.

Growth rate. Human growth is a dynamic process that varies in quantity and quality throughout gestation and in the first year of life (27, 33). Furthermore, many populations are exposed to adverse environmental conditions and inadequate nutritional intakes that affect fetal growth. Maternal diet may be inadequate for fetal transfer. Recent evidence suggests that infant and child growth are more affected by health, social determinants of health, and environmental conditions than by ethnic differences (33). When mothers' nutritional health needs are met and other environmental considerations are minimized, both fetal growth and newborn length are similar across diverse geographical settings (27).

Maternal nutritional status and comorbidities. Maternal comorbidities [e.g., pregnancy-induced hypertension, obesity, diabetes mellitus (type 1, type 2, or gestational)] may reduce nutrient transfer and lead to fetal growth restriction (34) or may lead to increased nutrient transfer and fetal overgrowth. It is reasonable to consider that some nutrient deficiency/excess may influence the physiologic capacity of infants to adapt to extrauterine life, including their response to intensive care or ability to resist infection. Specific examples include the following:

- Vitamin D: maternal vitamin D deficiency in pregnancy is common (35) and leads to infants with poor vitamin D status, which is related to infectious illness (36–38).
- Vitamin A: important for lung function; vitamin A deficiency during mechanical ventilation may be relatively more damaging to the preterm infant's lungs, although results appear to be mixed (39).
- Glucose: excess glucose during the first trimester has been shown to be teratogenic, and hyperglycemia in utero leads to alterations in metabolic and endocrine phenotypes of the offspring (40).

The ability to define nutrient specification across the continuum of preterm births requires a fuller appreciation and more comprehensive clinical assessment of a number of in utero, maternal, and ex utero conditions that can potentially affect nutrient needs of these vulnerable infants.

Suggested systematic review questions

- Does maternal vitamin D deficiency increase the risk of non–bone-related outcomes (e.g., infection) in the postnatal period?
- Does maternal obesity alone or in combination with diabetes mellitus (type 1, type 2, gestational) increase the risk of short-term and long-term morbidities (e.g., persistent hypoglycemia, insulin resistance, metabolic syndrome) in preterm infants?

Data and research priorities

- What are the implications of GA at birth, size at birth ($<$1500, $<$1000, or $<$500 g; SGA, IUGR), obesity/excessive weight gain (overnutrition) during pregnancy, pregnancy-induced hypertension, diabetes mellitus (type 1, type 2, gestational), chronic stress (elevated cortisol), maternal undernutrition, and preeclampsia?
- What are the implications of route and type of nutrient administration for nutrient needs of preterm infants?

Topic 4: How do nutrient requirements of otherwise healthy, formerly preterm infants differ from those of term infants of the same corrected age after hospital discharge?

Rationale

The preterm infant at hospital discharge, or at term corrected age, differs greatly from the newborn term infant. The preterm infant typically weighs substantially less, and has a different body composition, than the term infant of the same corrected age. Evidence suggests that more rapid growth—before hospital discharge, between hospital discharge and term corrected age, and between term corrected age and 4–12 mo corrected age—is beneficial to long-term neurodevelopment, with little evidence of metabolic risk (41). To achieve this catch-up growth, the nutritional needs of preterm infants will be in excess of those of slower growing term infants.

In addition to differences in weight between newborn term infants and preterm infants at the same corrected age, marked differences in body composition have been observed. The weight deficit seen in preterm infants mostly consists of a deficit in lean rather than fat mass (42) as well as deficits in bone mineral content (43). Body composition at term corrected age is significantly affected by prematurity and nutritional and nonnutritional factors.

Less is known about the changes in micronutrient status, but these may also be different between term and preterm infants. An example of one such difference is iron. It has been known for many decades that the iron status of preterm infants is suboptimal at hospital discharge. Iron deficiency is very likely to occur unless supplementary iron is supplied as medicinal iron or as iron-fortified formula (44).

The nutritional requirements of "healthy" preterm infants after hospital discharge are likely to be increased relative to term infants to allow the reversal of these presumed nutrient deficits. In this regard, iron may be considered a "proof of concept," because iron accretion by the preterm infant is far below the in utero rate and significant deficits in total body iron accrue by the

time of term corrected age. This does not appear to lead to clinical problems before hospital discharge or before term, but the reduced iron stores of the preterm infant at term corrected age means that the subsequent need for iron is much greater than in the term infant. It can be surmised that additional iron (either as supplements or as fortificants) is required to prevent significant nutritional effects (iron deficiency anemia) later in infancy.

The increased nutritional needs of preterm infants relative to term infants may be partly met by the increased volume of intake that is seen in formula-fed infants after hospital discharge (7). However, changes in the content of some nutrients within the diet may also be necessary. Because preterm infants are able to adjust their volume of intake in response to changes in the caloric density of formula, increasing the caloric density of a term formula is likely to affect nutrient intake. However, such changes in intake would not affect the nutrient:energy ratio of the diet, which can be altered only through fortification/supplementation.

Trials of postdischarge formulas provide the most evidence on which to base the nutritional management of preterm infants during this time period. These formulas are typically intermediate between the composition of term and preterm formulas, although preterm formulas have also been used during this period. Although interpretations of these data differ (45), postdischarge formulas appear to improve bone mineral content, and probably somatic growth in some populations (46). However, these studies compared different diets (typically different formulas) and provide limited data on the requirements for specific nutrients. Furthermore, the applicability of this information to the human-milk–fed infant is limited. Significant disruption to the mother-infant dyad is required to increase the intake of macronutrients in the human-milk–fed infant, either by replacing some feedings with a concentrated fortified formula or adding a human-milk fortifier to some, or all, of the infant's human-milk feedings. Such an approach has been successfully carried out in research settings, but the effect on growth is inconsistent (47, 48).

Suggested systematic review questions

- How does the macronutrient and micronutrient composition of the diet of healthy preterm infants differ from that of term infants of the same postconceptional age?
- How does a history of common neonatal exposures or medical conditions affect the macronutrient and micronutrient status of healthy preterm infants?
- How does gastrointestinal function, specifically related to nutrient absorption and excretions, differ between term and preterm infants, and how do common neonatal exposures or medical conditions affect nutrient absorption and homeostasis?
- What are the short- and long-term effects of reduced body size and altered body composition at term corrected age in preterm infants?
- What are the short- and long-term effects of catch-up growth at different times?
- How can macronutrient intake be modified in human-milk–fed infants after hospital discharge, and what effect does this manipulation have on the duration of breastfeeding and on the quality of mother-child interaction?

Data and research priorities

- What is the body composition (lean mass, fat mass) of preterm infants at term corrected age?
- What is the body composition of preterm infants during infancy? Does birth weight correlate with alterations in body composition?
- Does increased fat mass in the neonatal period translate into metabolic syndrome, obesity, and diabetes later in life?
- What is the micronutrient status of preterm infants at term corrected age and what micronutrient intakes are required, after hospital discharge, to prevent the overt signs of deficiency and to lead to optimum long-term outcomes?
- What biomarkers are available to estimate the macro-/micronutrient status of preterm infants at, and beyond, term corrected age?

Topic 5: What are the pre- and postnatal modifiers of nutrient requirements of formerly preterm infants and how do these resulting requirements differ from those of term infants of the same corrected age after hospital discharge?

Rationale

As outlined in topic 3, a number of factors inherent to medically compromised preterm infants can influence their nutritional care in the hospital. Those factors may also have implications for the long-term nutritional care of these infants after leaving the NICU. Similarly, those maternal factors that might affect the infants' course may also have longer term implications postdischarge. Moreover, the issues raised in topic 4 may also need to be considered in the care of the medically compromised preterm infant postdischarge. Thus, all of the uncertainties outlined above are also true for preterm infants with more complex medical histories. In addition, the effects on medically complex preterm infants of maternal health, common neonatal morbidities, feeding and nutritional practices, and growth rates on body composition, growth, and macronutrient and micronutrient deficits are unclear. The range of previous exposures that may affect the nutritional needs after hospital discharge (or after term corrected age) in these infants is extremely wide and included in **Text Box 4**.

In general, limited data exist with regard to the long-term effects of these exposures and conditions on nutritional requirements either during hospitalization or after discharge or term corrected age. One exception is the effect of jejunostomies or ileostomies on zinc absorption and excretion. In a small group of such infants, zinc absorption was low and endogenous fecal zinc excretion was high. This resulted in negative zinc balance in the infants, at a time when the zinc requirement for tissue growth would be expected to be high. Even after gut reanastomosis (at a mean corrected GA of 4 wk after term), zinc absorption remained low and was not different from the study before the anastomosis (50). Whether these observations exemplify similar outcomes for other nutrients remains to be determined.

Suggested systematic review questions

- What are the effects of short bowel syndrome (SBS), PN-associated cholestasis/liver disease, and necrotizing enterocolitis (NEC) on micronutrient status at term corrected age?
- What are the effects of SBS, PN-associated cholestasis/liver disease, and NEC on micronutrient absorption before and

Text Box 4 Previous exposures that might affect post-discharge nutritional needs

- Prenatal conditions, such as
  - maternal diabetes (type 1, type 2, gestational),
  - placental insufficiency, and
  - in utero (fetal) growth restriction
- Postnatal exposures, such as
  - necrotizing enterocolitis,
  - chronic lung disease,
  - SGA birth, and
  - exposure to medications (steroids, diuretics, methylxanthines, etc.)
- Previous nutritional management, such as
  - duration and composition of PN (e.g., high-glucose infusion with permissive hyperglycemia, higher protein supplementation),
  - amount and type of enteral nutrition (human milk, preterm formula, term formula), and
  - nature and timing of nutritional supplements [e.g., iron (49), vitamin D]
- Ongoing medical conditions (short bowel syndrome and resulting surgeries, the presence of ostomies, previous gut resections, chronic lung disease)
- Medications (steroids, diuretics, etc.)
- Nature of feedings (human milk, preterm formula, postdischarge formula, term formula etc.)
- Timing of weaning and type of weaning food used (rice cereal, meat-based weaning foods, etc.)

after term corrected age, and how is this affected by the type of enteral feeding (human milk, formula, elemental formula)?
- What are the energy and micronutrient requirements of former preterm infants with congenital heart disease [including patent ductus arteriosus (PDA) and ventricular septal defect] and chronic lung disease on nutrient requirements after term corrected age?

Data and research priorities

- What are the effects of SBS, PN-associated cholestasis/liver disease, and NEC on micronutrient status at term adjusted age?
- What are the effects on micronutrient absorption before and after term corrected age, and how is this affected by the type of enteral feeding (human milk, formula, elemental formula) in infants who had experienced SBS, PN-associated cholestasis/liver disease, or NEC?
- What are the effects of modifications in macronutrients (e.g., higher glucose infusion to compensate for lower lipid intake) in infants with SBS, PN-associated cholestasis/liver disease, and NEC on body composition and long-term associated metabolic disease, obesity, and diabetes?
- What are the effects of maternal diabetes, prediabetes, and obesity on iron absorption and iron status at, and beyond, term corrected age?
- What are the effects of maternal diabetes, prediabetes, and obesity on preterm and term infant body composition and metabolic status?
- What are the long-term effects of crossing weight percentiles in preterm infants? Are there differences if born too small or too large?

Topic 6: Can we individualize nutrient intakes in preterm infants, and if so, how?

Rationale

Preterm infants are an extremely heterogeneous population. Even among VLBW infants (birth weight <1500 g) the range of GAs at birth is wide. Given the differences in body composition, surface area to volume ratio, physiologic maturity, etiologies, etc., it is improbable that the nutritional requirements of infants born at different GAs would be the same. As discussed above, these differences are partly due to differences in growth rate, because weight gain steadily decreases (in terms of $g \cdot kg^{-1} \cdot d^{-1}$) during the last trimester of pregnancy.

When these differences are estimated with the use of a factorial method, the nutritional needs of infants vary widely depending on the weight of the fetus. For example, between weights of 500 and 700 g the fetus gains 21 $g \cdot kg^{-1} \cdot d^{-1}$; to match that rate of weight gain, the preterm infant will likely need enteral intakes of $\sim$105 kcal $\cdot kg^{-1} \cdot d^{-1}$ and 4.0 g protein $\cdot kg^{-1} \cdot d^{-1}$ (equivalent to a protein:energy ratio in the enteral diet of 3.8 g protein/100 kcal of energy) (51, 52). In comparison, to match the in utero growth of the fetus between 1500 and 1800 g, the preterm infant will require somewhat less protein (3.6 $g \cdot kg^{-1} \cdot d^{-1}$), more energy (128 kcal $\cdot kg^{-1} \cdot d^{-1}$), and a lower protein to energy ratio (2.8 g protein/100 kcal of energy) (51, 52). In contrast, mineral requirements change little (**Table 1**), depending on body size.

In Europe, some manufacturers produce different formulas for infants of different weights to mirror these estimated nutrient requirements. For example, a formula intended for use in infants weighing <1500 g may contain 3.7 g protein/100 kcal, one for infants weighing 1500–2500 g may contain 2.7 g protein/100 kcal, and a formula for infants weighing 2500–3500 g may contain 2.4 g protein/100 kcal. These formulas also differ in their mineral and vitamin contents as well. Although these formulations are logical, it is not clear that they improve outcomes. Such formulas are unavailable in North America.

The major limitation of these factorial calculations (Table 1) is the lack of good information on nutrient absorption and balance in preterm infants. Of the studies that exist, many are old, focus on preterm infants of relatively higher GA, and are carried out at older postnatal ages. When studies have been carried out in smaller preterm infants, it appears that nutrient intakes may be considerably lower than is appropriate (54). The absence of recent well-conducted nutrient-balance studies in preterm infants has led to profound uncertainty over the nutrient requirements of these infants and is a critical research need.

The use of different nutritional targets for preterm infants of different GA or different weight might be considered stratified

TABLE 1
Mineral requirements of preterm infants with different weights[1]

	Weight		
Requirements	500 to <1000 g	1000 to <1500 g	1500 to <2000 g
Calcium, $mg \cdot kg^{-1} \cdot d^{-1}$	184	178	173
Phosphate, $mg \cdot kg^{-1} \cdot d^{-1}$	126	124	120
Magnesium, $mg \cdot kg^{-1} \cdot d^{-1}$	6.9	6.7	6.4
Sodium, $mg \cdot kg^{-1} \cdot d^{-1}$	3.3	3.0	2.6

[1]Modified from reference 53 with permission from Karger.

nutrition rather than individualized nutrition, because targeted intakes are still based at the group level. True individualization requires individual-level information to guide intakes, and the most likely source of such information is from the use of nutritional biomarkers. True individualization of nutrient intake in preterm infants has been studied by using blood urea nitrogen to adjust the amount of protein fortification to human-milk–fed preterm infants (55). This approach was shown to lead to both increased protein intakes and to improved growth (55). However, a critical unanswered question is whether the benefits were due to the higher protein intake in the "adjustable" group (the rising tide lifts all ships) or due to the ability to adjust protein intake to the amount required by each individual. Anecdotally, this approach may be far less successful in units in which higher protein intakes are the standard.

Many other factors may modify the nutritional needs of individual preterm infants, including the previous duration of PN and the type of enteral nutrition (EN). Some nutrients may not be added to PN in the expectation that they will soon be supplied by enteral feedings. Conversely, some nutrients (e.g., vitamins) may be added to PN in amounts that meet 100% of the presumed nutrient requirements of preterm infants, even though much (maybe a majority) of nutrition is being provided enterally. For some nutrients, the nature of the enteral supply (e.g., human milk compared with formula) may be just as important as the amount of enteral supply (56).

Some previous disease exposures—for example, gut resection—may alter the nutrient needs of preterm infants; this may be especially true for nutrients whose absorption occurs at limited sites in the gastrointestinal tract. Ongoing diseases, such as chronic lung disease and congenital or acquired heart disease, may increase the nutritional needs of preterm infants (e.g., energy), and the use of diuretics and steroids could increase mineral requirements.

Suggested systematic review questions

- Does adjustable protein fortification of an enteral diet improve outcomes in preterm infants? Is the effect (if present) modified by the basal protein intake of the comparison group? Does this alter body composition?
- Does the type of fat content and additional fat fortification of an enteral diet improve outcomes in preterm infants? Does this translate into better outcomes and body composition?
- Do currently available biomarkers of iron status identify preterm infants who would benefit from higher (or lower) iron intakes?

Data and research priorities

- What are the effects of GA at birth, postnatal age, and corrected GA on nutrient absorption and balance? How do these differences alter body composition?
- What effect does the form of enteral nutrient delivery (MOM compared with donor milk compared with formula, fortified compared with unfortified human milk) have on nutrient absorption in preterm infants? And how is this affected by differences in GA at birth, postnatal age, and corrected GA?
- How is nutrient absorption affected by coexisting morbidities of prematurity?
- What is the relation between biomarkers of iron status and iron absorption, iron utilization, and iron balance in preterm infants?
- Does the use of a wider range of human milk fortifiers or formulas designed for infants of different weights or GAs improve growth and other clinically relevant outcomes in preterm infants?

WG 2: CLINICAL/PRACTICAL ISSUES IN ENTERAL FEEDING

Chairs: Diane Anderson and William Hay

Topic 1: Impact and importance of trophic feedings for VLBW infants (see Text Box 5)

Rationale

As an alternative to enteral fasting in developmentally immature preterm infants who might not be able to tolerate full enteral feedings, trophic feedings are commonly initiated ostensibly to help foster development of the gastrointestinal tract (57). Trophic feedings are defined as enteral feedings with a milk volume up to 24 mg $\cdot$ kg^{-1} $\cdot$ d^{-1} (1 mL $\cdot$ kg^{-1} $\cdot$ h^{-1}), beginning within 96 h of birth and continued for at least 5 d or until at least 1 wk after birth (58). Trophic feedings are frequently introduced as the first feedings for premature infants who are considered at risk of NEC and are generally initiated with infants weighing $<$1500 g at birth. Many NICUs use a longer "trophic feed period" for infants with a birth weight $<$1250 g or $<$1000 g. Although most NICUs do not treat SGA infants differently from those who might be "appropriate for gestational age" (AGA) of the same birth weight, many show more concern about starting or advancing enteral feedings when IUGR/SGA infants had abnormal aortic/umbilical artery velocimetry (from absent to reversed end-diastolic flow). Birth weight is more important than GA in initiating trophic feedings, because SGA/IUGR infants are notoriously difficult to feed and are at increased risk of NEC. The efficacy and safety of trophic feeding compared with enteral fasting were recently systematically reviewed (58), with no reported differences in either benefit or harm in VLBW infants. However, investigations and clinical practices vary and thus present ongoing questions about timing, duration, volume provided, type of milk used, and which

Text Box 5 WG 2: clinical/practice issues in enteral feeding topics

1) What is the impact and importance of trophic feedings for VLBW infants?

2) What, when, and how to feed?

3) How should feeding intolerance be treated?

4) What is the importance of developmental, behavioral, and environmental factors in oral feeding of preterm infants?

5) Should enteral feedings be fortified, and how?

6) What is the impact of support and education of care providers with regard to enteral feeding?

7) What are the goals of enteral feeding and how should progress be assessed?

8) What, when, and how to conduct transitional feeding?

9) What are the special challenges in enteral feeding?

infants by birth weight should be provided with trophic feedings. The common use of trophic feeding demands a concerted effort to address these issues.

Suggested systematic review questions

- What are the effects of trophic feedings on clinical outcomes and neonatal morbidity/mortality?

Data and research priorities

- What are the effects of trophic feedings on growth and development of the gastrointestinal tract?
- Are there differences between continuous and bolus trophic feedings?
- What is the difference in response to trophic feedings in ELBW infants and those with severe IUGR, as documented by abnormal Doppler flow studies of umbilical arteries?
- What are the implications of trophic feedings that are started and stopped a number of times?
- What are the indications to delay trophic feedings beyond 96 h?
- What are the indications to discontinue trophic feedings before a minimum of 5 d?
- On what day of life should trophic feedings be started? For example, before 24 h compared with after 24–96 h?
- Are there differences in the effects of trophic feedings on the basis of type of nutritional source?
- What are the benefits of human milk compared with formula for trophic feedings?
- Are there differences between donor milk and MOM for trophic feedings?

Topic 2: Feeding—what, when, and how?

Rationale

This is one of the most common subjects covered in the newborn/preterm infant populations in the Cochrane Review database (45, 58–66). Thus, the available literature is extensive and has been subjected to many systematic reviews. It is generally recognized that MOM is the preferred source of nutrition for all preterm infants. The need to fortify MOM is a subject of continued research interest and is covered under the WG 2 section entitled "Topic 5" below.

Issues associated with the use of donor milk are less clear. For example, if donor milk is initiated, how long should it be continued if MOM is not available? The implications of using donor milk even if fortified on outcomes such as growth or neurodevelopment remain unclear. Research is needed to determine how long donor milk should be used to achieve decreased morbidity, yet allow for adequate and acceptable growth. The superior growth with special formulas for preterm infants compared with even fortified human milk must be balanced with the increased morbidity and mortality in the absence of human-milk use. Despite the slower growth of infants fed either MOM or banked/donor milk, they have better neurologic outcomes than do infants fed formula, which is referred to as the "breastfeeding paradox" (67).

Suggested systematic review questions

- What is the effect of exclusive feedings of fortified MOM or donor milk on clinical outcomes and neonatal morbidity/mortality?
- What is the ideal exposure time for fortified donor milk compared with infant formula when fortified MOM is not available?
- What effect does the rate of advancement of feeding volumes (with or without trophic feedings) have on clinical outcomes and neonatal morbidity/mortality?
- What infant formulas are appropriate for preterm infants who do not have MOM or who fail to grow with donor milk?

Data and research priorities

- What is the rate of advancement of feeding volumes for best feeding outcomes with the lowest morbidities after an uncertain period of trophic feedings (birth weight <2000 g)?
- What is the ideal timing for the use of milk fortification:
  - during the advancement of feedings or
  - when the full volume of feedings is achieved for VLBW infants?
- What are the benefits of bolus compared with continuous gastric drip feedings via a feeding pump?
- What are the advantages of transpyloric drip feedings with a feeding pump?
- What are the benefits of standardized feeding protocols on growth and morbidities?

Topic 3: Feeding intolerance

Rationale

Feeding intolerance occurs in ~75% of VLBW infants (68, 69). The nonspecific nature of the signs of feeding intolerance have not been *1*) clearly prioritized or *2*) validated to assist in determining who is at greatest risk of developing bowel complications. The clinical signs of feeding intolerance include both gastrointestinal and other system findings. Although no standard ways exist to define abnormal gastric residuals, approximately half of feeding intolerance is associated with the presence of gastric residuals. Factors contributing to feeding intolerance are outlined in **Text Box 6**.

Suggested systematic review questions

- What is the effect of frequent antibiotic use in the NICU on gastrointestinal health in preterm infants?

Text Box 6 Factors contributing to feeding intolerance

- Lower GA and birth weight
- Presence of asphyxia, respiratory distress, and delayed feeding
- The developing gut microbiota:
  - The developing gut microbiome has emerged as a major factor in the overall health of preterm infants (69, 70).
  - Medications such as antibiotics and type of feeding in preterm infants can affect the state of the gut microbiome (71, 72).
- Hemodynamic changes in preterm infants strongly affect feeding tolerance, but it remains unclear what the optimal feeding strategies are for such common cardiovascular problems as PDA (73).
- Gastroesophogeal reflux disease: although gastroesophageal reflux is a normal and common occurrence in preterm infants, gastroesophogeal reflux disease is less common, difficult to diagnose, and difficult to treat effectively (74).

- Does measurement of gastric residuals have any effect on feeding of preterm infants?
- What is the impact of feeding with and/or treatment of a clinically significant PDA in preterm infants?
- Does holding feedings around a blood transfusion reduce NEC in VLBW infants?

Data and research priorities

- What are the effects of altered gut microbiota with use of antibiotics and duration of antibiotic use?
- Does checking and responding to gastric residuals affect clinical outcomes?
- What are defined contraindications to enteral feeding (presence of PDA, hypotension, lines, etc.)?
- What is the effect of a blood transfusion on feeding and gut outcomes?
- When is the optimal time to refeed damaged bowel (gastroschisis, postsepsis, post-NEC)?
- What is the impact of human milk compared with formula on feeding tolerance and long-term health outcomes for late-preterm infants?
- What is the impact of maternal magnesium exposure on feeding tolerance?

Topic 4: Importance of developmental, behavioral, and environmental factors in oral feeding of preterm infants

Rationale

Oral feeding ability is affected both by underlying disease states and by neurodevelopmental readiness (75). Preterm infants develop the ability to feed orally between 32 and 44 wk GA. Studies of predictors for oral feeding success and interventions to optimize preterm infant oral feeding are limited in number. Some of the more common interventions are listed in **Text Box 7**.

Although limited, these studies are laying the foundation for the development of best practices for a problem that is surprisingly complicated. Preterm infant feeding is complicated by infant respiratory health and respiratory support needs, individual infant differences in maturity, the balance of bottle compared with breastfeeding, design of the multidisciplinary team (neonatology, lactation, occupational therapy, speech therapy, parents), and the pressure for hospital discharge when adequate oral feeding is the only remaining obstacle.

Text Box 7 Oral feeding interventions studied to date

- Nonnutritive suckling with a pacifier during gavage feeding (76). It has been reported that this intervention was associated with
  - a significant decrease in length of hospital stay and
  - a reduction in feeding transition time, defined as the number of days from first introduction of bottle feeding to the time when all milk volume is taken from bottles.
- Oral motor stimulation before the initiation of oral feedings and often directed by occupational therapy or speech therapy services (77).
- Other techniques include
  - body positioning (supine, prone, and side-lying),
  - oral support (chin and cheek support during feeding),
  - body sensorimotor intervention, and
  - specific bottle systems.

Suggested systematic review questions

- What is the effect of pre–oral feeding interventions on preterm infant oral feeding skills and associated outcomes, including breastfeeding outcomes?
- What is the effect of initiating oral feeding attempts in preterm infants who are extubated and receiving positive-pressure respiratory support?
- What is the effect of standardized initiation of occupational therapy intervention for feeding on preterm infant feeding outcomes?
- What is the effect of interventions simultaneous with oral feeding on preterm infant oral feeding skills and associated outcomes, including breastfeeding outcomes?

Data and research priorities

- What are the benefits of oral care with colostrum before enteral and particularly nipple feeding is begun?

Topic 5: Fortification of enteral feedings

Rationale

Numerous studies have shown that preterm infants require nutrient fortification of MOM, banked human milk, or standard (nonexempt) term formula to optimize growth and neurodevelopmental outcome (78, 79). Several different fortifiers are available to support growth and sustain enteral feeding tolerance (human-milk fortifiers, formula fortifiers, human-milk–based fortifiers, donor human-milk cream, and high-protein supplements), with minimal data available to show whether any of these products are more or less efficacious. In addition, current consensus guidelines recommend providing a transitional formula or fortified human milk for 6–9 mo after hospital discharge. However, studies that compared nutritionally dense postdischarge formula with term formula provided inconsistent results with regard to improvement in long-term growth and showed no differences in neurodevelopment (65). Multinutrient fortification of human milk after hospital discharge did not affect growth or neurodevelopmental outcomes (80). There are no guidelines on whether or not to fortify milk for the late-preterm infant, even though a substantial amount of brain development occurs during the final month of gestation. The relative impact of type, dose, duration, and timing of enteral feeding fortification on growth and neurodevelopmental outcome requires further investigation.

Suggested systematic review questions

- What is the effect of increasing enteral protein delivery to >3.0 g protein/100 kcal in preterm infants?
- What is the effect of postdischarge fortification of enteral feedings in breastfed preterm infants?
- What is the effect of fortifying human milk in breastfed late-preterm infants?
- What is the effect of using a fortified formula in late-preterm infants who are receiving any formula?

Data and research priorities

- What is the impact of using exclusively human milk–based fortifiers for preterm infants on risk of NEC and long-term growth?

- What is the impact of using centralized milk preparation facilities in the NICU on milk composition, including reproducibility/consistency of composition?
- What is the impact of using centralized milk preparation facilities in the NICU on the attitudes and prevalence of use among the multidisciplinary team?
- What is the impact of manipulating fortification products for the individual patient with growth failure, feeding intolerance, or risk factors for poor absorption (SBS or cholestasis) or allergic colitis?
- What is the relative impact of specific types of formula fortifiers, including partially hydrolyzed whey protein fortifiers, on growth and development?
- What is the relative value of existing and new methods to transition the preterm infant to breastfeeding?
- What are the best methods to maintain the mother's milk supply during the first year of life while continuing human-milk fortification?
- What is the ideal timing of initiation and advancement of fortification?

Topic 6: Impact of support and education of care providers with regard to enteral feeding

Rationale

Approaches to oral feeding of preterm infants at the time of hospital discharge are complicated. Potential problems include limitations in oral feeding ability due to immaturity (discharge before term age) and/or lung disease [bronchopulmonary dysplasia (BPD)], extrauterine growth restriction (EUGR) requiring increased nutritional density for catch-up growth, and restrictions to maternal/infant interactions and therefore limitations in breastfeeding experience.

At hospital discharge, feeding plans may be complex and include feedings with increased nutritional density and/or combinations of breast- and bottle-feeding. These feeding plans are confounded by the use of products in ways other than how they are labeled for preparation (e.g., postdischarge formula mixed to 24 kcal/ounce or postdischarge formula added to MOM), leading to potential misadministration by caregivers. Additional risks are limited oral feeding (breast or bottle) experience by caregivers at hospital discharge and lack of direction to the postdischarge pediatric care team on growth expectations and instructions to decrease nutritional density as intake and growth improve. Therefore, both under- and overfeeding are potential consequences for the preterm infant post–hospital discharge. In addition, preterm infants have significant obstacles to reaching the goal of sustaining breastfeeding through the first postnatal year, including inadequate outpatient education and support of the lactating mother.

Evidence is limited with regard to methods to optimize preterm infant breastfeeding at home. Despite improvements in in-hospital preterm infant/mother lactation support, only 50% of mothers who initiate breast pumping continue to produce milk at their infant's hospital discharge and $\leq$25% are providing milk at 3–6 mo postdischarge. Research must identify methods for preterm infant–mother dyads to overcome the barriers to successful breastfeeding. The barriers are multidimensional and include maintaining the mother's milk supply, measurement of infant nutritional intake adequacy, and the development of infant oral ability at the breast (81–84).

Suggested systematic review questions

- What is the effect of in-hospital educational interventions for parents with regard to preterm infant oral feeding on preterm infant outcomes?
- What is the effect of post–hospital discharge educational interventions for parents with regard to preterm infant oral feeding on preterm infant outcomes?

Data and research priorities

- Identification of methods for preterm infant–mother dyads to overcome the barriers to successful breastfeeding

Topic 7: Goals and assessment of enteral feeding success

Rationale

One of the primary goals for the preterm infant is the successful establishment of full enteral feedings, preferably with human milk. The early initiation of enteral feedings shortens the time to establishment of full enteral feedings and has not been associated with an increase in NEC (58). Enteral feeding adequacy is most commonly assessed anthropometrically (trajectories of weight, length, and head circumference), which have been shown to be reasonable predictors of neurodevelopmental outcome (85). However, there is still a considerable need for more sophisticated methods of measuring enteral feeding adequacy, such as biomarkers, nutrient panels, and more precise measurements of organ growth and body composition. Some of these issues are addressed by WG 4, but WG 2 added the following suggested questions from their specific perspective.

Suggested systematic review questions

- What is the value of serum biomarkers to determine the effectiveness of enteral feeding patterns on nutrient exposure and adequacy and relevant functional outcomes?

Data and research priorities

- What is the relative value of available methods for evaluating enteral feeding adequacy during NICU hospitalization, including the identification of important early-growth milestones, time to regain birth weight, maintenance of growth variables along birth percentile, lack of postnatal growth restriction, or body composition?
- What are new enteral feeding strategies that decrease the time to regain birth weight, maintain consistent growth along birth percentiles, and decrease length of hospital stay?
- What is the effect of routine use of individual plasma amino acid concentrations to assess the adequacy of enteral protein delivery?
- What is the effect of routine use of plasma medium- and long-chain fatty acid concentrations to assess the adequacy of enteral lipid delivery?

Topic 8: Transitional (from parenteral to enteral) feeding

Rationale

There is a paucity of data that describe the optimal method to make the transition from full PN to full EN feedings while maintaining optimal nutrient intakes and growth. A retrospective review of 156 infants born at $<$32 wk of gestation compared the 3 phases of feeding (full PN, transitional PN + EN, and full EN) and found the highest incidence of poor growth (weight gain $<10\ g \cdot kg^{-1} \cdot d^{-1}$) during the transitional phase of feeding. Between the full PN and transitional phases, energy intakes were

stable but protein intake and protein to energy ratio declined as EN volume advanced. Poor growth during the transitional phase was significantly associated with growth failure (weight <10th percentile) at discharge when adjusted for birth weight, GA, and severity of illness (86). Protein intake may be increased during the transitional feeding phase by adjusting the protein content of PN and/or by the use of increased protein-content enteral feedings (fortified breast milk or preterm formula). The impact of individualizing feeding practice to optimize protein intake and protein:energy ratio requires further investigation.

Suggested systematic review questions

- What is the effect of adjusting PN nutrient composition to maintain overall protein intake at >3.5–4 g/kg as PN volume is weaned and EN volume is advanced?
- What is the optimal method to make the transition from full PN to full EN feedings while maintaining optimal nutrient intakes and growth?

Data and research priorities

- What is the impact of fortification of human milk before the infant reaches 100 mL $\cdot$ kg^{-1} $\cdot$ d^{-1} of enteral feedings on growth and nutrient intake (energy, protein, and minerals) during the transitional phase of feeding?
- What is the optimal composition of human-milk fortifiers during the transition period? Is it constant for vitamins and minerals?
- What is the ideal method for fortification of banked milk, which is already variable in nutrient content?

Topic 9: Challenges in enteral feeding—special considerations

Rationale

As highlighted in previous sections, enteral feedings are often either limited to trophic volumes or withheld completely in the critically ill preterm infant, especially when there are concerns for intestinal hypoperfusion. The main concern for feeding under these conditions is risk of developing NEC or spontaneous intestinal perforation, which both are associated with an increased mortality risk or neurodevelopmental impairment (87). Moreover, several conditions result in the interruption of enteral feedings, including hemodynamic instability, symptomatic PDA, administration of a blood transfusion, or prenatal exposures such as IUGR.

Given these myriad contingencies, a need exists to address how best to alter enteral feeding protocols for preterm infants. This also leads to the larger question of whether critically ill preterm infants have different enteral nutrient requirements than do comparable healthy preterm infants, which is an issue that is covered in greater detail by WG 3.

Suggested systematic review questions

- What is the effect of enteral feeding during the treatment of hypotension with low-dose vasopressor support or hydrocortisone in preterm infants?
- What is the effect of early enteral feeding (in the first week of life) in preterm infants who demonstrated Doppler velocimetry changes in the umbilical artery in utero?

Data and research priorities

- What is the impact of administering EN on anabolic growth in preterm infants who are within the acute phase of illness?
- What are the best methods for determining "enteral feeding readiness" in preterm infants?
- What is the need for the development of radiographic or functional assessments to predict enteral feeding readiness in preterm infants (e.g., superior mesenteric artery blood flow)?
- Should a preterm infant receiving medication to treat a symptomatic PDA be fed?
- Is it necessary to interrupt enteral feedings when a preterm infant is receiving a blood transfusion, given concerns for transfusion-related acute intestinal injury?
- When should enteral feedings be restarted and/or advanced after medical and surgical treatment of NEC?

WG 3: GASTROINTESTINAL AND SURGICAL ISSUES

Chairs: Sandra Robins and Josef Neu

Topic 1: Congenital surgical diseases (see Text Box 8)

Rationale

Congenital surgical diseases are associated with major neonatal nutritional morbidity because of both the underlying disease processes and the metabolic issues incurred by treatment. Neonatal gastrointestinal malformations that manifest with almost immediate nutritional problems include the following: esophageal atresia, duodenal atresia, and jejunoileal atresia. Survival for each of these disorders now exceeds 90%. Some of the key features of these conditions are highlighted in **Text Box 9**.

Intestinal atresias are a major cause of SBS, which will be covered in greater detail in WG 3 "Topic 5" below. The advent of multidisciplinary pediatric intestinal failure programs has been associated with both improved mortality and an increase in research activity (93). Despite expanded investigation, many questions remain. Retrospective data suggest that breast milk or elemental formulas enhance the transition to full EN in neonates with SBS (94); however, prospective studies are lacking. In selected neonates, bowel-lengthening operations have been thought to improve enteral tolerance, but evaluation has been restricted to case series and a voluntary registry (95). In addition, hormonal manipulation to promote bowel adaptation, particularly in the form of teduglutide [glucagon-like peptide 2 (GLP-2) analog], has shown show promise for the treatment of SBS (96). The results of a recently completed pediatric trial are pending. Animal research is ongoing with the evolution of novel techniques such as

Text Box 8 WG 3: gastrointestinal and surgical issues topics

1) Congenital surgical diseases

2) Gastroschisis

3) NEC

4) Cholestasis/PN-associated liver disease/intestinal failure–associated liver disease

5) SBS

6) Cardiac surgical issues

7) BPD

8) Retinopathy of prematurity

Text Box 9 Key features of congenital surgical diseases in preterm/term infants

- Esophageal atresias
  - Those with a "long gap" often experience the most pronounced feeding problems, including oral aversion.
  - This subset of patients often has significant lifelong gastrointestinal morbidity (88). The best possible surgical solution to long-gap esophageal atresia remains to be defined.
- Intestinal atresia
  - The surgical techniques to repair intestinal atresias are well established; however, protracted PN is still required.
  - Median (IQR) times for attaining full EN in jejunoileal and duodenal atresia are 17 (9–40) d and 10 (7–20) d, respectively (89).
  - Cisapride appears to be of some benefit in children with secondary intestinal motility problems, but its side effects are potentially fatal and hence its use is highly restricted (90).
  - Safer and more effective prokinetic agents are required, as well as basic studies to characterize why dysmotility is present in neonates with congenital as well as acquired intestinal disorders.
- Thoracic diseases
  - Congenital diaphragmatic hernia and congenital heart disease are also associated with neonatal nutritional difficulties.
  - In congenital diaphragmatic hernia, both elevated caloric demands due to increased work of breathing and reduced intake from gastroesophageal reflux may impede growth.
- Congenital heart disease
  - Fluid restriction is often required and the delivery of adequate quantities of macronutrients is problematic.
  - Not only is protein intake decreased but neonates with cardiorespiratory failure who require heart-lung bypass manifest high rates of net protein catabolism.
  - The provision of adequate protein appears to be central to optimizing anabolism in neonates with both congenital diaphragmatic hernia and congenital heart disease (91, 92).

tension-induced bowel lengthening and tissue-engineered small intestine (97, 98). A further interesting observation is that as survival in SBS improves, significant chronic nutritional problems, including metabolic bone disease, are becoming evident (99).

Although advances in surgery, anesthesia, and critical care have resulted in marked improvements in survival for neonates with congenital anomalies, an area of nutritional research that has been incompletely pursued is the characterization and modulation of the metabolic stress response. It is important to underscore that surgery, anesthesia, and analgesia all interact to affect the perioperative catabolic response in neonates (100). Interesting quantitative studies, some that incorporate the use of stable isotopic techniques, are available, but the best nutritional and metabolic management of both premature and full-term perioperative neonates remains to be defined.

Suggested systematic review questions

- None; there are inadequate data at this time according to the WG.

Research questions

- What interventions will minimize oral aversion in patients with congenital gastrointestinal diseases?
- Can we characterize and treat the intestinal motility disorders attendant to neonatal surgical diseases?
- How can we best organize trials to define the many unknown aspects of the optimal nutritional, medical, and surgical management of SBS neonates?
- What are the long-term nutritional consequences of neonatal gastrointestinal and thoracic disease?
- How can we quantify the metabolic response in surgical neonates and ameliorate its deleterious consequences, including net protein catabolism?

Topic 2: Gastroschisis

Rationale

Gastroschisis is a congenital abdominal wall defect. Infants are born with their intestines, and occasionally other abdominal organs, herniating through a small defect in the abdominal wall. Key features of gastroschisis are outlined in **Text Box 10**.

Little information exists to guide our nutritional management of these infants. After the closure of the hernia, whether staged in a silo or a primary repair, there is often a delay in the return of gut function. Some centers studied having a set time to start enteral feeding postclosure and reported decreasing their length of stay (105). A descriptive study linked earlier enteral feedings to fewer days of PN, fewer infections, and a shorter length of stay (106). Those infants who could be fed early will do well, and those who have a prolonged ileus are more likely to have difficulties with enteral feedings.

Maternal human milk confers many immunologic and neurodevelopmental benefits, and it appears that it is very well tolerated in these infants (107). Another study showed decreased time to full feedings and discharge with the use of human milk but compared human milk with a cow-milk–based formula (108). A recent retrospective cohort study described non–IgE-mediated cow-milk protein allergy (100). The mode of enteral feeding to be used is unknown, with variations from by-mouth ad libitum to nasogastric bolus or to nasogastric continuous feedings, sometimes interspersed with by-mouth feedings in 1-h windows off of the continuous infusion. Continuous feedings have been shown to enhance absorption in patients with damaged gut (109, 110).

Feeding problems are common in infants with gastroschisis, with a delay in achievement of full by-mouth feedings noted. The neuromarkers of esophageal motility in infants with gastroschisis were not normal (103). Some infants therefore may have a physiologic basis to their difficulty with oral feedings. How this information can be integrated into a feeding algorithm is not known.

Neither energy nor protein needs of these infants have been well described, either early in the course with PN or later with enteral feedings. When enteral feeding is delayed or not tolerated, cholestasis and its associated nutritional problems are common.

Text Box 10 Key features of gastroschisis

- Gastroschisis is a congenital abdominal wall defect. Infants are born with their intestines, and occasionally other abdominal organs, herniating through a small defect in the abdominal wall.
- Intestinal atresias have been reported in 10–20% of infants with gastroschisis (101), and infants with gastroschisis are at risk of developing NEC. These infants are generally classified as complex gastroschisis.
- Birth prevalence of gastroschisis is increasing with near doubling between 1995 and 2005 in the United States (101, 102).
- Although most patients with gastroschisis do relatively well, gastroschisis is listed as one of the most common diagnoses in intestinal transplant registries.
- Risk factors for gastroschisis include prematurity and SGA status, which puts infants at risk of growth problems and neurodevelopmental delay (103, 104).
- Gastroschisis is associated with significant morbidities, including gastroesophageal reflux disease, sepsis, cholestasis, motility disorders, and short gut syndrome (103).
- Growth
  - Growth restriction is common in infants with gastroschisis, with ~ 20% noted as SGA at birth (103).
  - Infants with gastroschisis are noted to have continued poor growth throughout the first year, with approximately one-third of infants below the 10th percentile at 16–24 mo (104).

Suggested systematic review questions

- For surgical neonates such as an infant with gastroschisis, when should PN be started?
- Should supplemental albumin be used in surgical infants, or should amino acid content of PN be maximized?
- If human milk is not available, should an elemental formula be used?

Research and data priorities

For surgical neonates such as those with gastroschisis:

- Is there benefit to the use of donor human milk as the initial source of nutrition in the absence of MOM?
- For what length of time should donor milk be used?
- Should infants be started with continuous or bolus feedings or a combination?
- Should MOM and/or donor human milk be fortified and with what?
- If an infant is not growing what should be the best approach, increased volume or density?
- If a more elemental formula is used, how long until switching to a less elemental product and what would be the path?

Topic 3: NEC

Rationale

Progress in the eradication of NEC in the past 50 y has been nearly nil and the disease appears to be increasing in some countries that previously were thought to have an admirably low incidence of this disease (111). There are several reasons for the lack of progress, but one of the factors is the broad terminology of what is included under the term "NEC," a condition that encompasses different diseases on the basis of major differences in pathophysiology. For example, a staging system developed in the 1970s that includes stage I "NEC" (112). This term is misleading because it actually represents a very broad set of conditions and usually is not associated with necrosis as implied.

The terminology with regard to NEC needs to more accurately reflect the clinical continuum. Because the pathophysiology, treatment, and prevention may be very different at different points in the etiology and care of NEC, it will be critical to find ways to differentiate key stages. The diagnosis of NEC is problematic, necessitating better diagnostic and predictive biomarkers. Although several diagnostic biomarkers have been investigated (e.g., intestinal fatty acid binding protein), none are currently used. Predictive biomarkers are needed to determine those infants at highest risk of NEC and to help target preventative therapies.

How to nourish infants without disposing them to NEC is critical. Enteral feeding is clearly a major conundrum with NEC. The lack of enteral feeding may actually have major adverse consequences and may predispose to the disease, whereas overaggressive feeding may exacerbate the development of NEC. The composition of both EN and PN may play a role in NEC.

Although MOM appears to be very helpful, questions remain about the value of donor milk for the prevention of NEC. With the increasing availability of donor milk in pediatric center milk banks, controlled studies are warranted to test whether banked donor milk is as effective as MOM in the prevention of NEC. In addition, other alternatives to human milk need to be considered. Whether the addition of supplements such as arginine or omega-3 fatty acids to human milk may prevent NEC is also not clear (see the WG 1 section for some relevant questions). Finally, as new knowledge emerges with regard to the development and role of the gut microbiome, and its relevance to the prevention, care, and treatment of NEC needs to be considered.

Suggested systematic review questions

- What is the most appropriate composition of feeding to prevent NEC (MOM, donor milk, formula, type of human-milk fortifier, and supplemented immunonutrients)?
- Are there predictive and diagnostic monitoring techniques that can aid in the prevention of NEC (biomarkers such as intestinal fatty acid binding protein; ultrasound; noninvasive, real-time, near-infared spectroscopy; or other technologies)?
- Are there microbial therapies that might be useful in the prevention of NEC? If so, what are they, how can they be most safely provided, and what studies are needed to change practice?
- Does withholding feedings in circumstances such as blood transfusion and sepsis or providing certain drugs such as indomethacin prevent NEC?

Research and data priorities

- What is the best approach to defining and diagnosing NEC? Is there a categorical approach to delineating the different entities that have been termed "NEC" in common databases?
- What is the best approach to delineate the pathophysiology of the most common form of NEC?

- Is the concentration (osmolality) of the feedings an important factor for the prevention of NEC?
- Can bovine colostrum be safely substituted for human milk to provide immune protection and trophic stimulus for the human infant intestine?
- How long should feedings be withheld for an episode of medical NEC (NEC not requiring surgery)?
- What constitutes the most appropriate PN for an episode of medical NEC? How long should it be provided? How can PN for infants who require surgery for NEC be optimized?
- When refeeding is initiated, should human milk (MOM or donor) be used or should a partially hydrolyzed or elemental formula be used?
- How quickly should infants with NEC be allowed to return to full enteral feedings?

Topic 4: Cholestasis/PN-associated liver disease/intestinal failure–associated liver disease

Rationale

PN is an essential component of the care and treatment of premature, low-birth-weight, and other hospitalized infants with SBS and intestinal failure (113). PN-associated liver disease (PNALD) is a common metabolic complication, which presents clinically as increased serum biochemical markers, such as direct bilirubin, bile acids, and liver transaminases. Also at risk are infants who have SBS, especially those who require prolonged (>60 d) PN because of intestinal failure after intestinal resection. In these cases, intestinal failure–associated liver disease (IFALD) occurs, which is a multifactorial disease that often occurs in neonates.

A key element of PN that has been implicated in the pathogenesis of PNALD is the lipid component (114–116). The persistence of PNALD in pediatric clinical care has prompted recent investigations into nutritionally optimal lipid intake and fatty acid composition as well as the safety and health benefits of currently approved and newer-generation lipid emulsions. Some of the key issues associated with lipids in PN are highlighted in **Text Box 11**.

Text Box 11 Key features of the role of lipids in PNALD (114–116)

- Lipids are an essential dietary group of nutrients that must be included in PN.
- In the United States, the only Food and Drug Administration–approved lipid emulsions are enriched with the fatty acids linoleic acid (n–6) and oleic acid (n–9), but are devoid of DHA and EPA, n–3 LC-PUFAs, and medium-chain fatty acids.
- The US-approved emulsions are plant-based seed oils that contain phytosterols, which are cholesterol-like molecules that have been linked as a cause of liver injury in PNALD (114).
- Current attempts at decreasing or eliminating phytosterols include the following:
  - reduced doses of soy-based fat emulsions to $\leq 1\ g \cdot kg^{-1} \cdot d^{-1}$,
  - the use of a fish-oil emulsion (which has no phytosterols), or
  - the use of a mixture of soy oil, medium-chain triglycerides, olive oil, and fish oil (117, 118).

In terms of potential mechanisms that can explain PNALD, research in the past decade has uncovered an important enterohepatic endocrine hormone signaling pathway that is relevant to bile acid homeostasis, which is a critical factor in lipid metabolism. Studies show that lipid emulsions can affect bile acid stimulation of intestinal farsenoid X receptor (FXR)–induced expression of fibroblast growth factor 19 (FGF19).

The significance of FGF19 in human bile acid metabolism is that enteral bile acid activation of intestinal FXR is a key mechanism in the feedback suppression of bile acid synthesis. Thus, during PN, there is diminished bile secretion and reduced activation of intestinal FXR. The loss of gut FXR activation results in a cascade leading to persistent activation of bile acid synthesis and accumulation of bile acids in hepatocytes, a process that contributes to cholestasis. The concept that enteral bile acid can be used therapeutically to reduce PNALD has been tested with promising results (119, 120).

The only Food and Drug Administration–approved bile acids that are available to test this approach are chenodeoxycholic acid (Chenodal; Manchester Pharmaceuticals) and ursodeoxycholic acid (Actigall; Watson Pharmaceuticals), which is a secondary bile acid produced by intestinal bacteria. Neither of these bile acids is Food and Drug Administration–approved for pediatric use, yet ursodeoxycholic acid is often used in pediatric cholestatic conditions. An emerging bile acid designed with maximal FXR agonist activity is obeticholic acid (6α-ethyl-chenodeoxycholic acid). The therapeutic use of obeticholic acid is currently being tested in clinical trials for adult liver diseases.

Suggested systematic review questions

- What is the best fat-emulsion strategy in the prevention and/or treatment of PNALD/IFALD? What are the relative effects of lipid intake compared with lipid fatty acid composition? What is the influence of non–fatty acid components in lipid emulsions, such as phytosterols, cholesterol, and vitamin E?
- With the onset of cholestasis, what are the best strategies for providing adequate micronutrients and/or preventing toxicity? For example:
  - withholding the addition of copper to the PN,
  - decreasing the copper dose to 50%? (i.e., to 10 $\mu g \cdot kg^{-1} \cdot d^{-1}$ from 20 $\mu g \cdot kg^{-1} \cdot d^{-1}$), or
  - keeping the standard copper supplementation (20 $\mu g \cdot kg^{-1} \cdot d^{-1}$).
- What is the impact of cholestasis on macronutrient requirements (fat, protein, carbohydrate) and fat-soluble vitamin requirements?

Research and data priorities

- Can bile acid therapeutic approaches improve the treatment of PNALD/IFALD in preterm infants with intestinal failure? How does bile acid affinity for FXR and FGF19 secretion effect PNALD/IFALD?
- Can ethanol lock prophylactic therapy decrease the risk of central line–associated bloodstream infections in preterm infants at risk of PNALD?

Topic 5: SBS

Rationale

Survival rates for preterm infants, including those with various pathological conditions in the gastrointestinal tract, have increased

dramatically (121). Recent refinements in the provision of PN have further improved these outcomes. However, many of these neonates suffer a major loss of intestinal length due to surgical resection, congenital defect, or disease-associated loss of absorption. SBS leads to an inability to maintain nutrient balance when fed a normal diet (122).

In cases of SBS-associated intestinal failure in which defined enteral diets are not sufficient to meet nutrient needs, prolonged PN is necessary (123). Intestinal failure is defined as the requirement of PN for >60 d. Intestinal adaptation is a complex series of coordinated mucosal, endocrine, and secretory events that ultimately allow for an increase in nutrient absorption, so that the patient can reach nutritional sufficiency without the need for PN.

The major challenges of existing therapy are that *1*) the only method to stimulate intestinal adaptation is enteral feeding and *2*) the use of PN may be detrimental to the adaptive process. There is universal agreement that enteral feeding is preferred to PN to meet the high energy and nutrient requirements of preterm infants. Key features of enteral feeding in the context of SBS are listed in **Text Box 12**.

As a result of an evolving understanding of the physiology of gut development potential, alternative interventions for SBS have emerged, most prominently GLP-2, which has been characterized as follows:

- GLP-2 appears to be a key factor in signaling adaptation because it exerts a variety of functions that are especially beneficial for SBS conditions ranging from
  - suppressing gastric emptying and secretion and
  - improving intestinal barrier function to
  - stimulating bowel growth and nutrient absorption.

Text Box 12 Enteral feeding and SBS

- Enteral nutrients are the primary stimulus for intestinal adaptation by acting
  - directly to provide energy and protein for the intestinal enterocytes or
  - indirectly to trigger the release of intestinal hormones, increase pancreatic-biliary secretions, neural factors, and intestinal blood flow.
- In patients with SBS, the transition from PN to EN should be made as soon as possible; yet, beyond this broad recommendation, there are many areas of controversy in the use of EN in premature infants and infants after surgical resection (124).
- This includes the rate of increase in feedings, the type of EN used, the pattern of feeding (bolus or continuous), and the use of specific types of nutrients and pharmacologic therapies. Human milk is the recommended form of EN in infants with SBS; yet, when human milk is not available, the specific types of formula that provide for optimal intestinal adaptation remain to be established.
- EN triggers the release of multiple trophic gut hormones, but the only ones that have approval for human use are glucagon-like peptide 2 analog and growth hormone.
- The ability to stimulate endogenous GLP-2 secretion in patients with SBS by therapeutic use of parenteral short-chain fatty acids or enteral bile acids has shown promising potential in neonatal animal models (125).
- In adult human SBS studies, parenteral treatment with GLP-2 or its analogs has been shown to improve nutrient and fluid absorption.
- Given the high amounts of endogenous production during the neonatal period, it is likely that GLP-2 treatment of preterm infants with SBS may facilitate the robust intestinal growth during this critical development period.

The recent approval of a commercial GLP-2 analog (Gattex; NPS Pharmaceuticals Inc.) for the treatment of adult SBS in the United States and Europe is promising and may pave the way for the pediatric indication (126). This paucity of translation into clinical practice is related to a number of scientific unknowns about short- and long-term physiologic effects of hormonal therapies, regulatory issues, and safety concerns. Thus, there continues to be a need to establish the mechanisms, efficacy, and safety of various therapies for infants with SBS.

Suggested systematic review questions

- What are the most appropriate enteral formulas (hydrolysates, elemental, human milk, etc.) to use that will improve adaptation and shorten the time with PN?
- Are there potentially therapeutic additives to EN or PN (e.g., glutamine, arginine, short-chain fatty acids, bile acids, GLP-2) that could improve adaptation and shorten time with PN?
- What are the most appropriate bowel-lengthening procedures to improve bowel adaptation and decrease total time with PN?

Research and data priorities

- Are there microbial therapeutic measures or "prebiotic" approaches that could improve the adaptation of the bowel?

Topic 6: Cardiac surgical issues

Rationale

Optimizing nutrition delivery and postnatal growth are relevant issues for the preterm infant cardiac population, because most surgical interventions are not technically feasible until size and weight requirements of a near-term infant have been achieved. However, nutrition delivery in the preterm infant cardiac population is challenging given their multimorbidities of immature intestinal function and cardiac-related intestinal ischemia risk factors. Postnatal growth failure is a widespread health problem among infants with congenital heart disease, specifically infants with single-ventricle lesions including hypoplastic left heart syndrome (127–129).

The morbidities of early postnatal growth failure include poor wound healing, increased infection risk, prolonged hospitalizations, and long-term neurodevelopmental disability, including worse school performance (130, 131). Despite the sobering short- and long-term sequelae of early postnatal growth failure, there is a paucity of knowledge with regard to optimal perioperative nutrition practices for infants with cardiac conditions. The current perioperative nutrition paradigm emphasizes aggressive caloric delivery and enteral feeding algorithms for the term infant (132–135).

For the preterm cardiac population, best-practice guidelines remain elusive, resulting in clinical decisions largely driven by

anecdotal and personal experiences, extrapolation from the term cardiac infant literature, and extrapolation from the preterm noncardiac infant literature. This clinical conundrum highlights the importance of a systematic review to identify best nutrition practices and gaps in research.

Suggested systematic review questions

- What are the specific nutritional requirements for a preterm infant with congenital heart disease during the preoperative period (optimal caloric intake, fluid requirements, electrolyte replacement therapy, micro- and macronutrient supplementation, and sources of fortification)?
- Are there specific groups of cardiac lesions with increased risk of NEC?
- Is there evidence to determine whether preterm infants with congenital heart disease can receive enteral feedings safely without increased incidence of NEC and other gastrointestinal morbidities?
- Are there reliable methods for monitoring or evaluating mesenteric perfusion during enteral feeding (e.g., bedside monitoring, Doppler evaluation, inflammatory biomarkers)?

Research and data priorities

- How does early preoperative enteral feeding affect postnatal intestinal mucosal development and do those effects sustain through the postoperative period?
- What is the characterization of the gut microbiome before and after an infant has undergone cardiac surgery with cardiopulmonary bypass and perioperative antibiotics? How does early enteral feeding affect the microbiome in preterm infants who require neonatal cardiac surgery? Is the gut microbiome a potential target for therapeutic intervention in neonates who experience feeding intolerance after cardiac surgery?
- What are the mechanisms of intestinal injury after exposure to cardiopulmonary bypass?
- What is the best method for defining and confirming milk protein "allergy" or food protein–induced enterocolitis? What is the incidence of food protein–induced enterocolitis in infants with congenital heart disease? Are there associations between preoperative enteral feeding and postoperative food protein–induced enterocolitis?
- What are the indications to transition from human milk to formula?

Topic 7: BPD

Rationale

BPD, also called chronic lung disease, is common in infants born prematurely. It is associated with oxidative injury to developing lungs. For the purposes of this project, the definition of BPD is oxygen supplementation being required at 36 wk corrected GA. With the increasing survival of ELBW infants, a "new BPD" with physiology and outcomes that are different from those of VLBW and larger infants has been described (136, 137). Fluid management, ventilation strategies, inflammation, infection, and conditionally unique nutrient requirements have been studied in the effort to optimize outcomes of infants with BPD (138, 139). Lung development and recovery from injury continues for years; nutrition strategies that support optimal recovery need to be addressed well after the infant leaves the NICU (136).

There is significant interplay between nutrition and risk or prevention of BPD. Early fluid management has been found to play a role in the complex physiologic processes that contribute to lung development and recovery from oxidative stress; once BPD develops, fluid restriction may affect the ability to deliver adequate nutrients for growth (140). Antioxidant and pro-oxidant nutrients have been evaluated in the development of BPD. One antioxidant example is vitamin A, which has been the focus of several studies in relation to lung development (39, 141–144). Inositol's effect on pulmonary surfactant development and the incidence of BPD has been reviewed (145). The work of breathing for infants with BPD may increase energy needs (146), but the method of feeding may affect oxygen consumption (147, 148). Nutrition strategies that result in normal growth may limit the development of BPD (149). The ability to coordinate suck, swallowing, and breathing may be delayed in infants with chronic lung disease, potentially delaying the development of feeding skills, which in turn may affect growth.

Suggested systematic review questions

- Is fluid restriction important in the prevention of BPD? If so, how much fluid restriction is needed and when is this helpful?
- Are there conditionally essential antioxidant nutrient requirements for infants at risk of BPD, such as vitamins A or E or selenium? Are there biomarkers of adequacy for these nutrients in preterm infants? What is the critical time for ensuring the adequacy of these nutrients?
- What is the effect of BPD on energy and protein requirements?
- What feeding mode best minimizes the risk of aspiration of feedings that can exacerbate BPD (bolus compared with continuous, gastric compared with transpyloric, infant-driven feeding compared with scheduled feeding by mouth)?
- Are developmental outcomes as good for infants with BPD than for preterm infants who do not have BPD?

Research and data priorities

- Are there conditionally essential nutrient requirements for infants at risk of BPD: for example, inositol, DHA, calcium, phosphorus, or *N*-acetylcysteine?
- Do the most immature ELBW infants have a different kind of lung disease, resulting in a different kind of BPD compared with infants born at a higher GA? If so, is there a need for different nutritional support and follow-up?
- Are late-preterm infants (those born at 34–36 wk GA) at risk of BPD that can be affected by supplementation of antioxidants or other specialized nutrition support?
- What is the maximum safe feeding concentration (calories/ounce) for premature infants with BPD?
- What feeding strategies best promote the development of gastrointestinal motility and discourage gastroesophageal reflux with aspiration?
- What is the optimal nutritional support for ex-preterm infants with BPD between term age and 2 y of age?
- Does MOM need supplementation beyond the standard recommendations for term infants of the same corrected GA?

Topic 8: Retinopathy of prematurity

Rationale

Retinopathy of prematurity (ROP) is a disorder of the developing retina of preterm infants. In the most severe form, it can lead to blindness. Guidelines for screening and treatment of ROP have been published (150). Although prematurity and the use of

oxygen are risk factors for ROP, nutrition/feeding strategies may play a protective role. Efforts to improve early energy intake along with the use of human milk, vitamin A supplementation, vitamin E supplementation, and intravenous fish oil have been shown to affect the rate of ROP (151–155).

Suggested systematic review questions

- Do intravenous fish-oil emulsions protect preterm infants from the development of ROP? If so, how much for how long is needed?
- Does human milk protect preterm infants from the development of ROP? If so, is donor milk as effective as MOM? If so, how much for long is needed?

Research and data priorities

- Is DHA the effective component of intravenous fish-oil emulsions that reduces ROP?
- Do antioxidants such as vitamins A and E protect infants from the development of ROP? If so, how much is needed for how long and at what age?

WG 4: CURRENT STANDARDS OF INFANT FEEDING

Chairs: Sharon Groh-Wargo, Michael Georgieff, and Tanis Fenton

Topic 1: For preterm AGA, large-for-gestational-age, or SGA infants, how is growth failure defined (weight, length, and occipitofrontal circumference in hospital, at discharge, and after discharge)? (See Text Box 13.)

Rationale

The American Academy of Pediatrics recommends growth of preterm infants to "approximate the growth and composition of weight gain for a normal fetus" (44). The terms "growth failure" and EUGR in neonatology generally refer to weight-for-age $<$10th percentile at discharge from the NICU, at $\sim$36 wk. However, this categorization may not be appropriate after the usual extracellular fluid loss in the first days of life, which results in decreases in percentile/z score losses. This extracellular fluid loss puts many AGA infants in the $<$10th-percentile category. For infants to gain percentiles/z scores to re-cross to above the 10th percentile, many infants would need to gain weight faster than the fetal rate. In addition, EUGR is usually defined by weight-for-age status alone, which is not a recommended practice for any other age group (156, 157); weight-for-length status is recommended for infants older than term age. It has been suggested that length, head circumference, and parental stature (158) should also be considered for the assessment of weight status.

Whether it is more appropriate to reassign a new z score trajectory target once preterm infants decrease their extracellular volume in the postnatal environment, or whether they should return to their birth z score trajectory, remains a theoretical question. Therefore, the use of a weight-gain trajectory beginning after extracellular volume loss, with guidance provided by the size distribution of the fetus, is the most appropriate goal for preterm infants to follow until a more representative and validated growth pattern can supersede this.

The cutoffs for SGA and large-for-gestational-age (LGA) are usually defined as less than the 10th percentile and greater than the 90th percentile compared with the size of infants of the same GA at the time of birth, because being SGA has been associated with adverse outcomes (159). However, these cutoffs may be physiologically arbitrary, based on statistics (186) rather than health status, and do not assess whether the infants are small, appropriate, or large relative to their individual genetic potential.

Text Box 13 WG 4: current standards of infant feeding topics

1) For preterm AGA, LGA, or SGA infants, how is growth failure defined (weight, length, and occipitofrontal circumference in hospital, at discharge, and after discharge)?

2) Are AGA, LGA, or SGA preterm infants at equal or greater risk than similar term infants for the following after discharges or later in life: chronic noncommunicable diseases (e.g., obesity, diabetes, cardiovascular disease, metabolic syndrome) or poorer neurodevelopment?

3) In AGA, LGA, or SGA preterm infants, is growth pattern (i.e., weight, length, occipitofrontal circumference, weight gain velocity, linear growth velocity, body proportionality, and body composition) in the hospital, at discharge, and after discharge specifically associated with noncommunicable diseases, poorer neurodevelopment, or self-reported quality of life after discharge or later in life?

4) Among preterm infants, is feeding type (e.g., MOM, donor milk, formula, mixed, solids) and duration/time of introduction associated with risk of poor neurodevelopmental outcomes, noncommunicable diseases or atopic disease, impaired immune competency, or an altered microbiome after discharge or later in life?

5) Among preterm infants, is the amount of protein intake in the hospital and after discharge associated with noncommunicable diseases, differences in body stature and composition, or different neurodevelopmental outcomes?

6) Among preterm infants, which assessments of neurodevelopment in childhood (e.g., Bayley scales, Wechsler Preschool and Primary Scale of Intelligence) are valid (or sensitive and specific) measurements (i.e., predictive of long-term function)?

7) Is there evidence that levels/cutoffs of essential nutrient biomarkers (e.g., ferritin, prealbumin, phosphate, vitamin B-6) either are the same in preterm infants as those for term infants or change with GA, and is that change driven by postconceptional age or postnatal age?

8) Among preterm infants, are commonly used, clinically available measures (e.g., anthropometric measurements and serum biochemistry values) sensitive or specific "biomarkers" to assess nutritional status (i.e., sufficient, marginal, or deficient) during hospitalization and after discharge?

9) Among preterm infants, which nutritional biomarkers during hospitalization and after discharge are associated with neurodevelopment, bone health, and metabolic health?

10) Among preterm infants, is a specific microbiome, as may be influenced by type of feeding (e.g., MOM or banked human milk) or specific nutrients (e.g., LC-PUFAs, iron), associated with gut health and related functions in childhood or adulthood?

11) Does bone mineral content in hospital, at discharge, and at follow-up predict later body stature and bone mineralization as well as risks of osteoporosis in adulthood?

Studies have found that these designations are arbitrarily based on statistical cutoffs (160), and arbitrary designations are not sensitive or specific to actual growth variables, such as body fat content (161).

Suggested systemic review questions

- Should growth failure be defined by percentile (e.g., <3rd percentile or <10th percentile) or by z score (e.g., <-2) of weight gain, length growth, or head circumference growth?
- Should growth failure be defined differently for AGA, LGA, and SGA infants?
- How is growth failure defined during the NICU hospitalization, at discharge (or at 36 wk or 40 wk postmenstrual age), and after discharge?
- Is there a postnatal age when EUGR is overestimated?

Data and research priorities

- Is weight less than the 10th or 3rd percentiles at the time of hospital discharge associated with adverse health or neurodevelopmental outcomes once neurologic insults (including cerebral palsy, intraventricular hemorrhage, and periventricular leukomalacia) are controlled for?
- Is infant weight recovery to their birth percentile or z score superior to maintaining at their post–initial-weight-loss percentile or z score, in terms of adverse health or neurodevelopmental outcomes, once neurologic insults (including cerebral palsy, intraventricular hemorrhage, and periventricular leukomalacia) are controlled for?
- Should the definition of growth failure take into account the weight loss in the first few days of life and the resulting percentile/z score?
- Should the definition of growth failure consider anthropometric measurements other than weight?

Topic 2: Are AGA, LGA, and SGA preterm infants at equal or greater risk than similar term infants for the following after discharges or later in life: chronic noncommunicable diseases (e.g., obesity, diabetes, cardiovascular disease, metabolic syndrome) or poorer neurodevelopment?

Rationale

Evidence from epidemiologic research exists to suggest that being born "too small or large" or "too early" is associated with greater risk of noncommunicable chronic diseases (NCDs) in later life (162), sometimes appearing as early as childhood. Such events are attributed to exposures to adverse factors or events in the fetal or early neonatal environment that may "program" the metabolic processes of the body to produce different phenotypes.

Whether a causal pathway exists between low birth weight, obesity, and NCDs later in life was recently questioned (163). The hypothesis may be militated by factors such as social determinants of health (163). Recent studies showed an inverse relation between social determinants of health and the prevalence of obesity in children (164). A recent systematic review that examined the relations between growth and neurodevelopment and metabolic outcomes found a lack of congruence between intervention and observational studies, which raises the possibility of confounding by other factors. (165).

With respect to preterm birth as a risk factor for NCDs, a measurable association between preterm birth and insulin sensitivity has been noted among infants and young children; however, in later years, the strength of this association weakens, and current body composition becomes the variable most strongly associated with insulin sensitivity (166).

Severe undergrowth or overgrowth in the early postnatal period in term IUGR infants was related to poorer neurodevelopment in childhood in a J-shaped relation by Pylipow et al. (167), whereas BMI was linearly related. This study supported the idea of developmental origins and critical periods in the neonatal period, and begs the question whether the same principles apply to preterm infants. Were there other factors, such as socioeconomic ones (163), that led to different feeding practices that could have accounted for these findings?

Suggested systematic review questions

- What is the effect of size at birth (small, large) on neurodevelopment, early or long-term risk of obesity, or NCDs?
- What is the effect of preterm birth on neurodevelopment, early or long-term risk of obesity, or NCDs?

Data and research priorities

- Longitudinal, prospective data on birth size and adverse health outcomes in different geographical regions followed to varying ages are needed.
- Data that control for postnatal factors may influence the health outcomes of interest, such as quality of early diet (e.g., MOM, banked human milk, formula, and days with PN), social determinants of health, childhood diet, lifestyle, gender, etc., may be important.
- Does control of current body size create a spurious relation between early factors (infant size and/or early growth) and NCD risk in later life?
- Assessment of the role of confounding and effect modification of the associations between either size at birth or growth with NCDs by extraneous factors such as social determinants of health and neonatal morbidities, including neurologic insults, is needed.
- Improved data on quality of dietary components as a potential modifier of selected outcomes, throughout the clinical care period beginning with PN and including exclusive use of MOM, combined MOM and fortifier, or banked human milk are needed.

Topic 3: In AGA, LGA, or SGA preterm infants, is growth pattern (i.e., weight, length, occipitofrontal circumference, weight gain velocity, linear growth velocity, body proportionality, and body composition) in the hospital, at discharge, or after discharge specifically associated with NCDs, poorer neurodevelopment, or self-reported quality of life after discharge or later in life?

Rationale

An association has been noted between early rapid growth of preterm infants and surrogate markers of later risk of cardiovascular disease or metabolic syndrome (168); however, several studies also controlled for current weight, which may have inadvertently created an association (165). In addition, one of the studies (168) failed to control for size for GA, which was strongly associated with the rapid weight gain in the first 2 wk of life. An association between small size for GA and social determinants of health has been well established (169, 170). Thus, it is entirely possible that adult-onset diseases are due to the many social determinants of health in addition to or rather than small gestational

size. The ability to address the association between growth and later outcomes has a number of methodologic challenges, as outlined in **Text Box 14**.

With specific regard to neurodevelopment, growth failure in the hospital and postdischarge has been associated with poorer subsequent neurodevelopment in preterm infants. However, more data are needed to determine the following: *1*) which aspect of growth failure (stunting, wasting, etc.) is associated with which aspects of neurodevelopment [intelligence quotient (IQ), motor outcomes, processing] and *2*) whether this differs if the growth failure includes an intrauterine component or is strictly postnatal. Moreover, little is known about when catch-up growth is too late to spare neurodevelopment, or whether overgrowth after undergrowth is a risk factor for preterm infants.

Suggested systematic review questions

- What is the relation between IUGR and cognitive or motor outcomes in preterm infants? Stratify by whether the studies controlled for neurologic insults (including cerebral palsy, intraventricular hemorrhage, and periventricular leukomalacia) and social determinants of health.
- What is the relation between EUGR (of varying types including stunting and wasting) and cognitive or motor outcome in preterm infants? Stratify by whether the studies controlled for neurologic insults (cerebral palsy, intraventricular hemorrhage, and periventricular leukomalacia) that could lead to both growth failure and poor cognitive and motor outcomes.
- What is the relation of combined IUGR and EUGR on cognitive or motor outcomes in preterm infants? Stratify by whether the studies controlled for neurologic insults (cerebral palsy, intraventricular hemorrhage, and periventricular leukomalacia) that could lead to both growth failure and poor cognitive and motor outcomes.
- Is there evidence for a critical period for catch-up growth in preterm infants and does this vary with size at birth? Does this growth influence neurodevelopment positively or negatively?
- What is the effect of growth velocity and body composition in early life on disease risk in later life? Stratify by SGA, AGA, or LGA and by social determinants of health.
- Is body composition altered by preterm birth and, if so, does it continue into childhood and adulthood, and does it matter to overall health?
- In observational studies, is a spurious relation created when studies control for later (childhood or adult) obesity in studies of IUGR or preterm birth and neurodevelopmental outcomes?

Data and research priorities

- Define the most appropriate anthropometric measurement or measurements and methods to assess risk to neurodevelopment.
- Define if there is a growth critical period (e.g., a period analogous to what is established for term infants relative to linear growth at birth and up to 1 y, but not afterward).
- Longitudinal data are needed that link growth and body composition observed in the hospital, at discharge from the hospital, and in the first year of life to later health outcomes, with control for neurologic insults (cerebral palsy, intraventricular hemorrhage, and periventricular leukomalacia), size at birth (SGA, AGA, or LGA), and social determinants of health.
- Randomized trials on nutrition interventions in the hospital and/or the first year of life that provide observations of disease risk later in life are needed.
- Assess the role of confounding and effect modification of the associations between either size at birth or growth with adult-onset diseases by extraneous factors such as social determinants of health and neonatal morbidities, including neurologic insults.
- Adapt current assessment tools and discover new assessment tools (e.g., , mid- arm circumference, arm muscle area, abdominal circumference, and ponderal index) to measure body composition, develop normative data sets, and relate measurements to relevant health outcomes.

Text Box 14 Challenges in interpretation of data linking body composition to long-term outcomes

- Several different methods have been used to calculate growth velocity in preterm infants, and the method used influences the magnitude of the result (171).
- Concern has been expressed with regard to the body composition of former preterm infants, upon reaching term-equivalent age. When compared with term infants, former preterm infants are distinguished by their
  - low quantity of lean body mass (42),
  - percentage of body fat (42), and
  - quantity of intra-abdominal fat
- The percentage of body fat has been suggested as an indicator of poor outcomes and risk of adult-onset diseases. However, some studies show that
  - fat deposition may be an extrauterine effect and
  - the higher body fat of preterm infants relative to term infants is not maintained beyond early infancy because of the following:
    - preterm infants do not continue to increase their body fat (172) beyond discharge from the hospital, whereas term infants proceed to their increase body fat percentage through the first months after birth (8, 173) and
    - the difference in intra-abdominal fat between preterm and term infants is not maintained at 5–7 y of age (172).
- Neonatal morbidity: higher intra-abdominal fat in preterm infants, compared with term infants at term age, has been associated with their degree of neonatal morbidity (172) and diminishes with age (172). Therefore, this intra-abdominal fat may be a transient effect, without lasting effects.

Topic 4: Among preterm infants, is feeding type (e.g., MOM, donor milk, formula, mixed, solids) and duration/time of introduction associated with risk of poor neurodevelopmental outcomes, NCDs, or atopic disease, impaired immune competency, or an altered microbiome after discharge or later in life?

Rationale

Aside from its nutrient content, MOM is beneficial due to the presence of diverse bioactive components that confer enhanced digestive capability, immune protection, and immune competency. However, MOM is not always available, sufficiently available, or

capable of meeting desirable somatic growth goals. As a result, other diets must be available as an alternative or supplement for preterm infants. In the preterm or critically ill newborn population, insufficient evidence exists as to the optimal delivery (timing, dose) of MOM to achieve its biological protections and enhanced health in these infants. In addition, the evidence is insufficient with regard to the risks:benefits of either the dietary alternatives to MOM (donor milk, formula, cow-milk–derived human-milk fortifiers, human-milk–derived human-milk fortifiers) or delivery strategies (timing, dose) with particular regard to achieving optimal short- and long-term health outcomes.

Health outcomes along the continuum of life and development that are potentially influenced by dietary type and delivery include neurodevelopment, metabolic health, immune competency, and atopic disease and establishment of the mucosal microbiome, which are reviewed in more detail in **Text Box 15**. The following highlights some of the challenges in making these connections.

Although often compelling, the evidence with regard to the impact of nutrition and feeding practice and neurologic development is not consistent (196), perhaps due to confounding. Such studies are longitudinal, retrospective, or prospective cohort designs that have inherent limitations in factors such as recall bias (for retrospective studies), lack of adjustment for maternal diet in pregnancy, and detailed or frequent dietary assessment of infants/children or other potential confounding variables such as maternal IQ, social determinants of health, and quality of the home environment.

Similarly, studies that relate individual determinants to the development of abnormal metabolic factors, which later can become cardiovascular risk factors, have suggested that after birth, infant nutrition exposure (breastfeeding, formula-feeding, and the energy density of the feedings) is likely to have an impact and may influence the development of abnormal lipid and glucose concentrations and high blood pressure. However, limitations of all of the studies cited are that they were not conducted in only preterm infants and had limited control for potentially confounding variables.

With specific regard to nutrition and immune competence, few, if any, studies were conducted in preterm infants. Nutritive and nonnutritive components of human milk, formula, and solid foods and feeding practices may also shape the infant microbiome, programming growth rates and body composition, promoting differential microfloral colonization, promoting atopic disorders in children, and shaping behavioral responses to foods and eating (197).

Maternal gut dysbiosis may be a result of obesity, poor nutrition, or even stress; and this could ultimately affect the microbes the fetus is exposed to in utero, thus serving to alter fetal gut development. Such variation in fetal gut microbiome composition (and ultimately gut development) may lead to changes in long-term gut function and influence metabolic compromise. Moreover, the rapid colonization initiated by bacteria and substances such as human milk oligosaccharides activates the immune system and initiates host protection against pathogens. Breastfed infants experience fewer infections, perhaps due to increased production of antimicrobial compounds, and decreased intestinal permeability as a result of increased mucin production (198).

Because the nutrients in human milk are used as substrates by the gut microbiota, they may also play a critical role in the ontogeny of the gut microbiome, perhaps by providing selective pressure on the gut microbes. Therefore, changes in maternal nutrition could change the nutritional content of MOM, as well as possibly the milk microbiota, which would directly affect neonatal gut colonization.

Probiotics of various sources have been added to infant formulas fed to preterm infants. The effectiveness of such sources of prebiotics in the prevention of NEC has been evaluated in several studies, with mixed results. The systematic reviews on this topic are not conclusive, which is likely due to the considerable variation in the type and amounts of probiotics tested and heterogeneity among the studies (199). The long-term impact of microbiome diversity in early life to health at older ages has not, to our knowledge, been studied nor have studies of the microbiome focused on preterm infants.

Suggested systematic review questions

- What is the optimal day of exposure for MOM (or colostrum) that shows infant health benefits as defined by (but not exclusive to) each of the short- or long-term outcomes mentioned above?
- What is the optimal dose of MOM (expressed as $mL \cdot kg^{-1} \cdot d^{-1}$ or as a percentage of total feedings) in the first 28 d postnatally that is associated with health benefits as defined by (but not exclusive to) each of the short- or long-term outcomes mentioned above, after control for important confounding variables?
- Compared with MOM, what is the evidence for each of the alternative feeding options in health outcomes defined by (but not exclusive to) each of the short- or long-term outcomes mentioned above, after control for important confounding variables?
- What associations can be established between maternal factors in pregnancy (e.g., overweight status, diet, exposure to cardiometabolic risk factors) and infant outcomes of birth size, growth trajectory, neurodevelopment, cardiometabolic status, and immune function, after control for important confounding variables?
- What nutrition interventions in mothers during pregnancy or in preterm infants in early life (human milk compared with formulas enriched with probiotics) are associated with optimal growth and neurodevelopment, a healthy microbiota, and reduced risk of adverse health outcomes, after control for important confounding variables?
- When data are primarily based on studies conducted in term infants, is it realistic to extrapolate the findings of the impact of fetal/early-life nutrition exposures on long-term health outcomes in prematurely born infants?
- Does the provision of probiotics as supplements or as fortified in infant formulas lead to any adverse health outcomes in or provide any benefit to preterm infants?

Data and research priorities

- Assess the role of confounding and effect modification of the associations between breastfeeding with neurodevelopment (with maternal IQ and sociodemographic and lifestyle factors); metabolic health risks of obesity, diabetes, cardiovascular disease, and metabolic syndrome; risk of atopic disease; immune competency; and the microbiome (with extraneous factors such as social determinants of health and lifestyle-related factors).

Text Box 15 Salient points about key factors affecting functional outcomes of interest

Neurodevelopment

- Begins at conception and is dependent on a web of factors that result in adequate cognitive functioning and emotion regulation (174).
- Major changes occur during the fetal period, a time when neurodevelopment is at its most vulnerable (175).
- Maternal dietary imbalances, nutrient deficiencies, physical inactivity, obesity, and excess weight gain during pregnancy are linked to problems with cognition and emotion regulation in offspring.
- In the early postnatal period, exposure to MOM has associated benefits with such outcomes as cognitive functioning on the Bayley scales in both term and preterm infants.

Body composition and metabolic health

- Multiple studies have shown a protective association between breastfeeding and
  - lower rates of childhood obesity [breastfeeding compared with no breastfeeding was associated with a 15% decrease (95% CI: 1%, 26%) in the odds of childhood overweight (176)] and
  - with reduced blood pressure (177).
- Conversely, early introduction of solids has been associated with adiposity in toddlers in a birth cohort study in the United Kingdom (178) and the United States (179).
- Another study found no association between breastfeeding and adiposity after controlling for family-based sociodemographic, maternal lifestyle, and childhood factors (180).

Immune competency and atopic disease

- Exclusivity and duration of breastfeeding in infancy have been investigated in relation to outcomes of allergic disorders (181) and asthma (182).
- Formula feeding and early introduction of solids have been associated with increased allergic disorders, although inconsistencies remain (183).
- Recent studies and meta-analyses suggest that breastfeeding may protect against recurrent wheeze and asthma in later childhood (184–187).
- Recent birth cohort analyses have not uniformly supported the late introduction of solids as protective against allergy, and there has been a signal for harm in some cohorts.
- Delayed introduction of solids to 6 mo is associated with a greater risk of allergy, although reverse causality bias may account for this (188).

Microbiome

- The infant gut microflora composition may play an important role in the development of immunity and responses to food intake.
- The gut microbiota during infancy is influenced by mode of nutrient delivery, type of infant feeding, hospitalization, antibiotic use, type of delivery (vaginal or cesarean delivery), and prematurity (189).
- Evidence exists that the microbiome of the pregnant mother is associated with metabolic changes in pregnancy, and its transfer to the newborn may influence the metabolic response of the developing infant. Thus, the distinct microbiome signature of the meconium of newborn infants can be altered by maternal metabolic and health status (190).
- The presence of specific strains of maternal enteric bacteria in the meconium implies that the fetus may be exposed to microbes from the maternal gut in utero (191) and points to the maternal gut as a key player in the development of fetal gut microbiome.
- Human milk
  - is a source of macro- and micronutrients (192); differences in human-milk composition have been reported due to maternal nutritional and metabolic status (193);
  - contains bacteria essential for infant gut colonization;
  - is a rich source of carbohydrates that act as prebiotics and promote a healthy neonatal gut microbiota; and
  - contains a number of nonnutritive factors that influence the ontogeny and health of the infant microbiome, most prominently human milk oligosaccharides.
  - Human milk oligosaccharides are of no nutritional value because they are indigestible by the infant; however, they play an essential role in driving microbial diversity and promoting the maturation of the microbiota (194, 195).

- Establish evidence-based dietary practices in the initiation and delivery of MOM in preterm or critically ill newborn infants.
- Establish evidence-based dietary practices in the absence of sufficient MOM.
- Establish evidence-based practices on nutrient fortification of MOM and donor milk.
- Longitudinal cohort studies or randomized clinical trials of EN practices to determine the relative risk in short- and long-term health outcomes as a function of dietary exposures are needed.

- Identify early biomarkers of nutritional exposures linked to health outcomes. These markers will inform nutritional efficacy in a timely manner and with fewer subjects, thus minimizing the costs and intensiveness of large clinical trials of nutritional intervention.

Topic 5: Among preterm infants, is the amount of protein intake in the hospital and after discharge associated with NCDs, differences in body stature and composition, or different neurodevelopmental outcomes?

Rationale

On the basis of estimates of in utero protein accretion and losses and correction for the inefficiency in conversion of dietary protein to body protein, Ziegler (51) estimated that an enteral protein intake of 4.0 and 3.9 $g \cdot kg^{-1} \cdot d^{-1}$ will meet the average requirement of preterm infants weighing $\leq$1200 and 1200–1500 g, respectively. Although there are few empirically derived data for infants weighing <1200 g on which to confirm these estimates, protein intakes of 3.0–3.4 $g \cdot kg^{-1} \cdot d^{-1}$ for infants who weigh >1200 g were shown to produce daily weight gains similar to fetal accretion rates, with higher intakes of 3.7–4.2 $g \cdot kg^{-1} \cdot d^{-1}$ needed to support catch-up growth. Some examples of studies that attempted to address the possibility for deviation from this recommendation are highlighted in **Text Box 16**.

There is an absence of data on the most appropriate protein intake for preterm infants after discharge. Young et al. (65) in their Cochrane Review concluded that there is an inconsistent effect on growth to 12–18 mo from feeding an energy (72–74 kcal/100 mL) and multinutrient postdischarge formula containing 1.8–1.9 g/100 protein compared with a standard term formula (66–68 kcal and 1.4–1.7 g/100 mL) to preterm infants. However, there was some evidence of an advantage of feeding preterm formula containing 2.0–2.4 g protein/100 mL and 80 kcal/100 mL after discharge. It is important to note that many trials in this review excluded infants with significant morbidities or who were not growing well at discharge. Clinicians report that they are most concerned with the growth of predominantly human-milk–fed infants early after discharge. However, few have systematically examined whether a proactive approach to nutrient fortification of human milk might be appropriate. Of the 2 randomized controlled trials available, it appears that nutrient fortification of infants after discharge can be done without significantly influencing breastfeeding, at least in the short term (47). Future studies should focus on predominantly human-milk–fed infants instead of those in whom only a minor proportion of total enteral feedings are from human milk. O'Connor and colleagues showed in a small sample of infants that fortification of half of the human milk fed to predominantly human-milk–fed infants to ~80 kcal and 2.2 protein/100 mL for 12 wk after discharge resulted in better growth, supported bone mineralization, and improved visual development compared with infants discharged to home on human milk alone (47, 206, 207).

Text Box 16 Studies evaluating the impact of protein intake in preterm infants

- Two recent studies of very preterm infants fed human milk showed improved growth when fortified to provide 4.2 and 3.5 $g \cdot kg^{-1} \cdot d^{-1}$ at full enteral feedings (200, 201).
- Kuschel and Harding (79), in a Cochrane review of 4 earlier trials in infants fed human milk, reported that the addition of a protein supplement at ~1.5 $g \cdot kg^{-1} \cdot d^{-1}$ to human milk resulted in small but significant increases in weight gain and linear and head growth.
- Biasini et al. (202) reported improved growth and early neurodevelopment in human-milk–fed infants weighing <1250 g who were fed 4.8 g protein $\cdot kg^{-1} \cdot d^{-1}$ compared with 3.5 g protein $\cdot kg^{-1} \cdot d^{-1}$.
- Fenton et al. (203), in a recent Cochrane review of randomized controlled trials, concluded that protein intakes in the range of 3.0 to <4.0 $g \cdot kg^{-1} \cdot d^{-1}$ from formula accelerated weight gain compared with intakes <3.0 $g \cdot kg^{-1} \cdot d^{-1}$. However, there was insufficient evidence to make specific recommendations with regard to protein intakes >4.0 $g \cdot kg^{-1} \cdot d^{-1}$ and limited information on long-term outcomes such as neurodevelopment.
- An older published study (204) is often cited as reason for concern over "high" protein intake in VLBW infants. In this study,
  - preterm infants were fed bovine-based formula (casein dominant) to provide 3.0–3.6 or 6.0–7.2 g protein $\cdot kg^{-1} \cdot d^{-1}$ during initial hospitalization;
  - at 3 y, infants born weighing <1300 g and fed the higher protein–containing formula had lower IQ scores; and
  - experts in the field have postulated that it was the mix of amino acids supplied and not the absolute amount of protein fed that was explanatory; however, this emphasizes the need for caution (205).

Suggested systematic review questions

- Do high protein intakes in preterm infants (>3.5 $g \cdot kg^{-1} \cdot d^{-1}$) during initial hospitalization result in improved growth and neurodevelopment and the absence of adverse outcomes?
- Does an energy- and nutrient-enriched formula containing at least 1.8 g protein/100 mL or 2.0 g protein/100 mL after discharge improve growth and neurodevelopment in the absence of adverse events in preterm infants?
- What is the optimal protein to energy ratio in the diet for preterm infants before term GA and in the first year of life post–term date?

Data and research priorities

- Do protein intakes in preterm infants (>4.2 $g \cdot kg^{-1} \cdot d^{-1}$) during initial hospitalization result in improved growth, neurodevelopment and in the absence of adverse outcomes?
- Establish the ideal amount of protein (and energy, calcium, phosphorus, and zinc) that should be added to human milk after discharge to support growth, bone mineralization, and neurodevelopment of preterm infants after discharge.
- Determine which specific subgroups of infants should be targeted for nutrient intervention after discharge on the basis of tools (biomarkers) that assess short- and long-term health outcomes.
- Develop tools that assess the longer term impact of higher amounts of protein on obesity and metabolic and cardiovascular outcomes.

Topic 6: Among preterm infants, which assessments of neurodevelopment in childhood are valid (or sensitive and specific) measurements and predictive of long-term function (e.g., Bayley scales, Wechsler Preschool and Primary Scale of Intelligence)?

Rationale

Most studies of preterm infant neurodevelopmental outcomes end at 18–22 mo. The endpoint often coincides with the conclusion of routine clinical follow-up for most VLBW infants and potential attrition of study samples. The assessments are typically general tests of infant performance, because that is what can most easily be performed across multiple sites. This approach is likely misguided for 2 reasons: *1*) the predictive value of general tests of infant performance (e.g., the Bayley scales) conducted at <2 y for IQ at 8 y is poor (208) and *2*) nutrient effects on brain development are relatively subtle (compared with intracranial hemorrhage or birth asphyxia) and may not be demonstrable on generalized testing (209). Conversely, some previous studies have ascribed larger-than-likely effects of growth failure or nutrient deficits (on the basis of the known biology of the nutrients) on general tests of function (suggesting confounding variables such as degree of illness) (210). "Signature" outcomes based on the biology of the nutrient effect on the brain are highly desirable (e.g., if a nutrient affects myelination, the speed of electrical processing, such as evoked responses, should be assessed).

Suggested systematic review questions

- In preterm infants, define whether there is a relation between the Bayley Scales of Infant Development–III at 18–24 mo of age) and relevant middle childhood or adolescent outcomes: performance IQ, frontal lobe function, and grade achievement. How sensitive and specific is the Bayley-III for predicting later function?

Data and research priorities

- Define the predictability relation between neurodevelopmental assessments used in early childhood (e.g., Bayley-III at 24 mo corrected age) and those assessments used at school age and in adolescence.
- Develop and test the sensitivity and specificity of new tests of brain performance that can be applied early in life and that index nutrient-sensitive brain domains. Define their relation to later school-age performance.

Topic 7: Is there evidence that levels/cutoffs of essential nutrient biomarkers (e.g., ferritin, prealbumin, phosphate, vitamin B-6) either are the same in preterm infants as those for term infants or change with GA, and is that change driven by postconceptional age or postnatal age?

Rationale

The American Academy of Pediatrics (44) recommends that preterm infants grow similarly to the fetus and maintain fetal concentrations in blood and tissues. Cord blood sampling provides an accessible method to assess preterm fetal cord blood. Phosphate, magnesium, and alkaline phosphatase in cord blood serum decrease with GA; calcium increases with GA (211).

Phosphate offers an example of the potential effects of GA and clinical course/care on biomarker concentrations and interpretation. Although most of the literature on phosphate for preterm infants emphasizes phosphate's role in bone mineralization, phosphate also has roles in glucose metabolism. Serum phosphate decreases in response to infused glucose in adults (212). Furthermore, low serum phosphate may limit clinical stability, because it is required for tissue sensitivity to insulin in adults (213), as well as glucose-induced insulin secretion in rats (214).

Appropriate standards for concentrations of clinical nutritional biomarkers are necessary to provide useful information about nutrient status in preterm infants. Many nutrients have different reference values during the neonatal period compared with adulthood. Nutrient concentrations in preterm neonates differ from those in term infants because of reduced stores (e.g., incomplete iron or calcium loading during the missed third trimester), immature enzymatic pathways of either synthesis or breakdown (e.g., vitamin B-6, DHA), or reduced protein (e.g., prealbumin, retinol-binding protein) synthesis. Standard curves for some (e.g., ferritin, prealbumin, transferrin), but not all, biomarkers have been generated in preterm infants from cross-sectional cord blood data gathered at various GAs. It is unclear whether biomarker concentrations are driven by postconceptional age, postnatal age, or both.

Suggested systematic review questions

- For each biomarker that assesses a nutrient's status, what evidence is there that GA influences the measure?
- Does postnatal age, irrespective of postconceptional age, modify the biomarker?

Data and research priorities

- Establish GA curves for all biomarkers of all nutrients provided to preterm infants.
- Prioritize by starting with nutrients that have biggest impact on long-term health (including neurodevelopment) and with nutrients that are at greatest risk for deficit or overload in preterm infants.
- Link biomarker values to physiologically relevant outcomes, both acutely (status) and long term.

Topic 8: Among preterm infants, are commonly used clinically available measures (e.g., anthropometric measurements and serum biochemistry values) sensitive or specific to assess nutritional status (i.e., sufficient, marginal, or deficient) during hospitalization and after discharge?

Rationale

The validity of whether a biomarker indexes the nutrient of interest may be affected by other nutrient status or nonnutritional factors—for example, energy (calorie) adequacy, maturity, inflammation, or renal status. For example, alkaline phosphatase and serum phosphorus have been used as markers for inadequate intakes of calcium and phosphorus as well as osteopenia in preterm infants, although not all studies agree on their importance (166, 215, 216). Similarly, blood urea nitrogen has been used as an indicator of protein excess in preterm infants; however, a cutoff to indicate protein excess has not been identified. Blood urea nitrogen is also associated with postnatal age and renal function (217).

The adequacy of nutrient status is generally assessed by comparing a patient's value with reference or standard curves. Abnormal nutrient status is determined by values that lie outside of population statistical cutoffs (e.g., 5th and 95th percentiles).

Although these cutoffs may index either exposure or abnormalities in the physiology of the given nutrient, they do not necessarily relate to functionally relevant health endpoints (e.g., neurodevelopment, obesity, metabolic health). The fact that a measure may indicate a given status does not in and of itself reflect the cause of that status (i.e., due to exposure or a physiologic response to any of a myriad of possible factors). Nor does it necessarily reflect the functional significance. Thus, for preterm infants, it will be necessary to develop data to support the interpretation of a given value as reflecting either exposure or status (adequate, marginal, deficient) compared with a functionally relevant physiologic response.

Suggested systematic review questions

- For each biomarker that assesses a nutrient's status, what evidence is there that values outside of the normal range index of organ dysfunction are related to abnormal health outcome? For example,
  - at what concentration of serum ferritin is neurologic function compromised,
  - at what concentration of alkaline phosphatase is the preterm infant at risk of fractures,
  - at what concentration of zinc is there growth faltering, and
  - at what concentration of vitamin A is there an increased risk of BPD?

Data and research priorities

- Link biomarker concentrations to physiologically relevant outcomes, both acutely and long term.
- Define the relation between clinically available chemistries (blood, urine) or biomarkers and appropriate growth (e.g., between the 10th and 90th percentiles), growth failure (e.g., $<$10th percentile), and excessive growth (e.g., $>$ 90th percentile) during the NICU hospitalization and after discharge for AGA, LGA, and SGA infants or weight-for-height and length-for-age and the 2nd or 98th percentiles as per the CDC 2013 guidelines (156)
- Define the "value" (e.g., positive predictive value, negative predictive value) of clinically available chemistries (blood, urine) or biomarkers during hospitalization and such measures of health status as hematocrit or bone mineral status or of long-term morbidities such as BPD, neurodevelopment, and metabolic and bone health.

Topic 9: Among preterm infants, which nutritional biomarkers during hospitalization and after discharge are associated with neurodevelopment, bone health, and metabolic health?

Rationale

Surrogate intermediary measures of risk of adverse outcomes of neurodevelopment and bone and metabolic health are required to identify infants at risk of adverse health outcomes and to assess the effects of nutritional interventions.

Suggested systematic review questions

- For each of the outcomes noted above, what is the most specific and sensitive nutrient biomarker that reliably predicts adverse clinical outcome?
- What is the earliest age that abnormalities can be detected for the identified health outcomes to be reliably measured?

Data and research priorities

- Any biomarker whose relation to long-term outcomes has not been identified by the above systematic review questions should be investigated. Priority should be given to nutrients that, in preclinical models or from data from term infants, are postulated to affect a clinically relevant outcome, including chronic lung disease, neurodevelopment, metabolic health, risk of cancer, and bone health.
- Identify critical periods for these nutrients (i.e., when is normalizing a previously abnormal nutritional state too late to rescue the desired phenotype to be like the child born at term)

Topic 10: Among preterm infants, is a specific microbiome, as may be influenced by either type of feeding (e.g., MOM or banked human milk) or specific nutrients (e.g., LC-PUFAs, iron), associated with gut health and related functions in childhood or adulthood?

Rationale

The development of the intestinal tract is vital for infant health because it is the largest defense barrier and contributes significantly to the immune system. An understanding of the role of nutrition in these processes will define efficacy of nutritional interventions and provide early markers of nutritional outcomes.

Altered intestinal development (including the microbiome) and barrier function have been linked to NEC (see WG 3 section) and in immune-mediated diseases in later childhood and adulthood, including atopic disease (asthma), autism, celiac disease, inflammatory bowel disease, and obesity. Aspects of intestinal development that may reflect infant and later adult outcomes include the microbiome, intestinal barrier function, Paneth cells and defensin production/function, and goblet cells and mucin production/function.

As highlighted in WG 4 "Topic 4," early delivery results in the cessation of maternally derived and amniotic nutrients that facilitate intestinal development. Postnatally, breastfed infants experience fewer infections, due at least in part to increased production of antimicrobial compounds, and decreased intestinal permeability as a result of increased mucin production. The impact of varying infant gut microbiota on gut health in infancy, childhood, or adulthood has not been well studied in preterm infants. Although WG 4 topic 4 highlighted the implications of feeding regimen on the development and function of the gut microbiome, this topic focuses on the need to further understand the function and short-/long-term health implications of the gut microbiome.

Suggested systematic review questions

- Are the functional components listed (e.g., microbiome, intestinal barrier function, Paneth cells, and defensin production/function and goblet cells and mucin production/function) robust, reproducible markers of postnatal intestinal development that, when aberrant, predict increased vulnerability to disease, after control for sociodemographic and lifestyle factors?
- Are there other aspects of intestinal development that, when aberrant, are linked to disease pathogenesis?
- What is the evidence for dietary influences (including specific nutrients) on markers of intestinal development, after control for sociodemographic and lifestyle factors?

- What is considered sufficient exposure to these dietary influences?
- What is the evidence for the association between these markers with short- and long-term clinical phenotypes—for example, NEC, later atopic disease, etc.?
- For each marker of intestinal development:
  - what is the level of evidence for clinical significance,
  - what are the dietary or nondietary influences (e.g., nothing by mouth status, medications, sociodemographic and lifestyle factors, etc.) in their development,
  - when is each marker best measured,
  - what are "normal" values and how does this relate temporally from fetal development to late infancy, and
  - what is the optimal value (e.g., what is the optimal microbiome of the preterm infant)?
- What is the evidence that the maternal gut microbiota in pregnancy influences the infant gut microbiota at birth or during early life?
- Do variations in human-milk composition related to maternal diet (e.g., n–3 and n−6 fatty acids, total lipid content) influence the infant gut microbiota or health outcomes, after control for sociodemographic and lifestyle factors?
- Does the infant gut microbiota differ between preterm infants fed primarily MOM compared with infant formula, after control for sociodemographic and lifestyle factors? And if so, are there any health benefits to infant health outcomes?

Data and research priorities

- Little, if any, data exist on the relation of maternal factors, maternal microbiota, and infant microbiota and whether such associations convey any health benefits to preterm infants in early life or later childhood.
- Establish a set of intestinal development markers that are critical for infant health and, when aberrant, predict disease. These markers will serve as outcomes of nutritional efficacy.
- Establish evidence-based nutritional practices that are linked to the enhancement of specific markers of intestinal development.
- Animal to infant (translational) studies are needed to define mechanistic pathways of intestinal development that are modulated by diet/specific nutrients and ultimately guide future trials and clinical practice.

Topic 11: Does bone mineral content in the hospital, at discharge, and at follow-up predict later body stature and bone mineralization as well as risks of osteoporosis in adulthood?

Rationale

Preterm infants are known to have lower nutrient reserves and increased nutritional requirements for all nutrients including minerals and vitamins important to bone health. PN, human milk, and standard infant formulas do not meet nutritional needs, so fortified human milk and preterm formulas with higher nutrient density are routinely fed. There is some evidence that improved early nutrition improves bone mineral content in early infancy, although the evidence is conflicting (218–222). Bone mineral content can be measured by dual-energy X-ray absorptiometry but requires careful attention to detail (219, 223, 224).

Suggested systematic review questions

- In preterm infants, does early nutritional intake (specifically calcium, phosphorus, protein, and vitamin D) predict bone mineral content at hospital discharge and during early childhood?
- Is the bone mineral content of former preterm infants in early childhood related to bone mineral content in adolescence and adulthood?
- In former preterm infants, does improved bone mineral content in childhood lower the risk of osteoporosis in adulthood?
- Is dual-energy X-ray absorptiometry the most appropriate tool to measure bone mineral content?

Data and research priorities

- Prospective data are needed on the relation of nutritional intake from various intravenous and enteral sources and bone mineral content followed longitudinally to various ages.
- Randomized trials on nutrition interventions in the hospital and/or the first year of life that provide observations of risk of osteoporosis later in life are needed.

The members of the Pre-B Consultative Working Groups and their affiliations are listed in Supplemental Material.

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