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

Daniel J Raiten,[5] Alison L Steiber,[6] and Rosa K Hand[6]*

[5]*Eunice Kennedy Shriver* National Institute of Child Health and Human Development, NIH, Bethesda, MD; and [6]Academy of Nutrition and Dietetics, Chicago, IL

ABSTRACT

Preterm birth (infants born at <37 wk of gestational age) is a significant clinical and public health challenge in the United States and globally. No universally accepted practice guidelines exist for the nutritional care of preterm infants. To address the current state of knowledge and to support systematic reviews that will be used to develop evidence-informed guidance, a consortium consisting of the American Academy of Pediatrics, the ASN, the American Society for Parenteral and Enteral Nutrition, the Academy of Nutrition and Dietetics, the Food and Drug Administration, the CDC, the USDA/Agricultural Research Service (USDA/ARS), and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development/NIH initiated the Pre-B Project. The project included the constitution of 4 thematic working groups charged with the following tasks: *1*) develop a series of topics/questions for which there is sufficient evidence to support a systematic review process to be conducted by the Academy of Nutrition and Dietetics' Evidence Analysis Library (EAL), leading to the development of new guidelines for nutritional care of preterm infants, and *2*) develop a targeted research agenda to address priority gaps in our understanding of the role of nutrition in the health and development of preterm/neonatal intensive care unit infants. This review consists of a project overview including a summary of a workshop hosted by the USDA/ARS Children's Nutrition Research Center and summary reports of the 4 working groups established to address the following themes: *1*) nutrient specifications, *2*) clinical/practical issues in enteral feeding, *3*) gastrointestinal and surgical issues, and *4*) current standards for assessing infant feeding outcomes. These reports will serve as the basis for the ultimate guideline development process to be conducted by the Academy of Nutrition and Dietetics' EAL.
Am J Clin Nutr 2016;103(Suppl):599S–605S.

Keywords: enteral, neonatal intensive care unit, nutrition, parenteral, preterm birth

INTRODUCTION

Preterm birth continues to be a significant issue in the United States and globally. **Text Boxes 1** and **2** provide some recent data on the magnitude of these problems. Preterm is defined as an infant born alive before 37 wk of gestational age. The WHO (1) defines the following subcategories of preterm birth on the basis of gestational age: extremely preterm (<28 wk), very preterm (28 to <32 wk), and moderate to late preterm (32 to <37 wk). Preterm infants can also be categorized by birth weight as follows: low birth weight (LBW),[7] <2500 g; very low birth weight, <1500 g; and extremely low birth weight, <1000 g.

Because of limited knowledge about what the "normal" maternal-fetal environment confers in terms of providing specific nutrient density for intrauterine growth and development, the implications of these categories for the nutritional care for preterm infants are mostly unknown. Nutritional status as a biological endpoint is achieved via a series of processes that include ingestion, digestion, absorption, transport, metabolism, and functional utilization in dependent biological systems. The preterm infant's ability to achieve a "healthy" nutritional status is challenged, because each of these processes is often compromised due to an interaction of immature development, disease, and general stress.

[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 Infant Formula Council, and the National Institute of Child Development and Health and Division of Nutrition Research Coordination at the NIH.

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

[4] Supplemental Table 1 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.

*To whom correspondence should be addressed. E-mail: raitend@mail.nih.gov.

[7] Abbreviations used: CDER, Center for Drug Evaluation and Research; CFR, Code of Federal Regulations; DGA, *Dietary Guidelines for Americans*; EAL, Evidence Analysis Library (Academy of Nutrition and Dietetics); FDA, Food and Drug Administration; IND, investigational new drug; LBW, low birth weight; MOM, mother's own milk; NICU, neonatal intensive care unit; WG, working group; WIC, Special Supplemental Program for Women, Infants, and Children.

First published online January 20, 2016; doi: 10.3945/ajcn.115.124222.

Text Box 1 Global statistics on preterm birth

- An estimated 15 million preterm (<37 wk of gestational age) infants are born annually.
- Preterm birth complications are the leading cause of death among children <5 y of age, responsible for nearly 1 million deaths in 2013.
- Three-quarters of these deaths are preventable with current, cost-effective interventions.
- Across 184 countries, the rate of preterm birth ranges from 5% to 18% of infants born (1).
- More than 60% of preterm infants were born in South Asia and sub-Saharan Africa, where 52% of the global live births occur.
- Of the 65 countries with estimated time trends, only 3 (Croatia, Ecuador, and Estonia) had reduced preterm birth rates during 1990–2010 (2).
- Preterm birth complications are estimated to be responsible for 35% of the world's 3.1 million annual neonatal deaths and are now the second most common cause of death after pneumonia in children <5 y old (3).

Text Box 2 Prematurity in the United States (1)

Percentage of US infants born premature: 12.8%
Total number of premature infants: 500,000/y
Rate of increase since 1980: 36%
Global rank in terms of total numbers: sixth

Premature birth rate by race/ethnicity

- White: 10.9%
- Black: 17.5%
- Hispanic: 12%

Premature birth survival rates by gestational age

- 23 wk: 17%
- 24 wk: 39%
- 25 wk: 50%
- 26 wk: 80%
- 27 wk: 90%
- 28–31 wk: 90–95%
- 32–33 wk: 95%

Outcome statistics for children born before 26 wk of gestational age (4)

Severe disability (cerebral palsy): 22%
Moderate disability (special needs): 24%
Mild disability [low intelligence quotient (IQ), vision]: 34%
No disability: 20%

As seen in **Supplemental Table 1**, a number of efforts to develop specifications for nutrient intakes for preterm infants have been published (5–8). Although these serve as important points of reference, they are not consistent. Moreover, they are limited to only one aspect of the nutritional care approach, nutrient exposure. Many issues affect the various processes of nutrition in these developmentally challenged infants that must be accounted for beyond the amount of nutrients to which an infant is exposed. Currently, no systematically derived, evidence-based practice/care guidance exists covering the range of issues that confront neonatologists, dietitians, parents, and caregivers who care for these infants.

The Pre-B Project is intended to be the first step in the development of evidence-informed practice guidelines that will address these issues. **Text Box 3** contains a list of some examples of issues that require attention.

EVOLUTION OF THE PRE-B PROJECT

In 2012, an effort was initiated to fill a gap in the primary US public health program designed to address the role of diet in health promotion and disease prevention. Beginning in 1980, the *Dietary Guidelines for Americans* (DGA) represent a congressionally mandated program renewed every 5 y via an active partnership between the Departments of Health and Human Services and the USDA. To date, the DGA do not include infants and children from birth to age 24 mo. To address this public health gap, the project entitled "Evaluation of the evidence to support the inclusion of infants and children from birth to 24 months: B-24 Project" was initiated. That project became phase I of the process that will lead to the eventual inclusion of these infants and children in future iterations of the DGA beginning in 2020. The results of that process were published in 2014 (9).

During the course of the B-24 Project a number of issues fell outside the purview of the DGA process. Although significant, these issues did not fit the DGA public health rubric. One of those was the lack of guidance for nutritional care of preterm infants.

One manifestation of the absence of adequate attention to the nutritional needs of preterm infants was chronicled in May 2013 in an article published in the *Washingtonian* magazine entitled "Children are dying!" (10). The story highlighted the ongoing challenges of feeding preterm infants and presented a complicated scenario of insufficient evidence, regulatory challenges, and a lack of evidence-informed standards of nutrition care to support the efforts of both caregivers in neonatal intensive care units (NICUs) as well as those whose responsibility it is to develop and produce the products needed to respond to the needs of these high-risk infants. That article reinforced the discussions that occurred during the B-24 process and helped to galvanize a consortium of agencies, professional societies, and civil society to address not only why this might be happening but, more importantly, how to develop evidence-informed guidelines for the nutritional care of preterm infants from those born at the limits of viability to those born "late preterm." As a result of the confluence of these issues, the "Evaluation of the evidence to support guidelines for nutritional care of preterm infants: The Pre-B Project." was initiated.

PROCESS

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, in partnership with the Academy of Nutrition and Dietetics, initiated a multiphase process that will lead to the promulgation of evidence-informed guidance for the nutritional care of preterm infants. Phase I involved the creation of a technical support structure to initiate the first step in the systematic review/guidelines development process. **Text Box 4**

Text Box 3 Core questions regarding nutritional care of preterm infants

- What is the level and quality of the evidence to support nutrient specifications to fulfill essential and/or conditionally essential macro- and micronutrient requirements for preterm infants that are distinct from currently established recommendations for term infants?
- What are the unique nutritional needs of high-risk/hospitalized preterm infants including issues such as staging, as follows:
  - first or transition stage including timing of first parenteral or enteral exposure,
  - specific needs during clinically stable stage, and
  - postdischarge stage (from discharge home to ~1 y of age)?
- What are the critically essential outcomes that can be used to assess nutritional status and/or effect of interventions?
- What is the role of human milk for feeding preterm infants, including
  - timing,
  - what we know about composition, and
  - use of fortifiers—need and composition?
- Is there evidence to support the use of specific nutrients in the care/treatment of specific clinical conditions such as the following:
  - vitamin A and bronchopulmonary dysplasia,
  - vitamin E and retinopathy of prematurity, and
  - long-chain PUFAs and neurological growth/development?
- What is the impact of relevant drug-nutrient interactions (e.g., vitamin B-6 and theophylline) (9)?
- What are the technical issues with regard to delivery of nutrients via
  - parenteral nutrition or
  - enteral feeding options?
- What are the implications of specific clinical conditions commonly seen in neonatal intensive care units for the nutritional care of premature and other newborn infants at risk?

Text Box 4 Pre-B Process

Phase I: Develop structure and provide initial report to the Academy of Nutrition and Dietetics

- Identify a scientific steering committee from partner agencies/organizations including the following:

  Academy of Nutrition and Dietetics
  American Academy of Pediatrics
  ASN
  American Society for Parenteral and Enteral Nutrition
  Food and Drug Administration
  Eunice Kennedy Shriver National Institute of Child Health and Human Development/NIH
  USDA/Agricultural Research Service
  CDC
- Identify working group themes
- Recruit working group chair/members
- Conduct 2–3 working group conference calls
- Convene Pre-B workshop (Baylor Children's Nutrition Research Center)
  - Overview of the Evidence Analysis Library (EAL) process
  - Invited speakers to address working group–specific issues, cross-cutting issues
  - Allow working group an opportunity to interact
- Finalize working group reports to include the following:
  - Potential topics
  - Questions for which there are sufficient evidence to support systematic reviews
  - Identify key data/research priorities
- Publish Pre-B report

Phase II: Academy of Nutrition and Dietetics systematic reviews conducted by the Academy of Nutrition and Dietetics' EAL

Phase III: Reconvene scientific steering committee to discuss approaches to implementation

contains an outline of the steps and features of the Pre-B process. The items underlined in Text Box 4 are those summarized in the remainder of this executive summary, including an overview of the Academy of Nutrition and Dietetics' EAL process and invited presentations on cross-cutting issues on the regulation of parenteral and enteral products and the benefits of human milk.

In addition, the workshop included invited speakers to discuss topics of interest to each working group (WG); their articles follow in this supplement. Finally, reports from the 4 WGs are presented.

MEETING SUMMARY AND PRE-B PROCESS INTRODUCTION

After the opening remarks, representatives of the core agencies and organizations of the scientific steering committee provided brief overviews of their respective interests in the care and feeding of preterm infants. This was followed by an overview of the Academy of Nutrition and Dietetics' EAL process. Alison Steiber, Chief Science Officer at the Academy of Nutrition and Dietetics, described the 5-step process that will ultimately lead to evidence-informed practice guidelines. The steps include the following: *1*) formulation of topics/question, *2*) collection of research evidence to be reviewed, *3*) evaluation of the evidence, *4*) summarization of the results of the analyses, and *5*) grading of the strength of the evidence. The Pre-B Project represents step 1, formulating topics/questions.

Once the research questions have been formulated by the phase I WGs, the EAL will recruit a balanced WG to fine-tune the questions, ensuring that they are in the PICO (problem, intervention, comparison, and outcome) format, and develop a search plan that will be executed by the EAL Lead Analyst. The search plan will include key items such as inclusion and exclusion criteria for the literature search, databases to be searched, date ranges for literature to be included, and any variables that might

cause an article to be excluded from the review. The search plan is published along with the systematic review results for transparency.

Trained EAL analysts will perform the literarture search and, on approval by the WG, extract the data from each of the selected articles. These data are used to help inform the data summaries, conclusion statements, and the grading of the conclusion statement. The WG will determine the final grade of each conclusion statement resulting from the review. These conclusion statements are then used to create evidence-based practice guidelines (**Figure 1**). The recommendations will be categorized into the Nutrition Care Process steps (Assessment, Diagnosis, Intervention, and Monitoring and Evaluation) to help practitioners implement the guidelines into everyday practice.

INFANT FORMULA DEVELOPMENT AND REGULATION

Representatives from the US Food and Drug Administration (FDA) involved in the regulation of those nutritional products used in the care of preterm and high-risk infants provided overviews of their coverage. Donna Griebel, Center for Drug Evaluation and Research (CDER), and Leila Beker, Center for Food Safety and Applied Nutrition, provided overviews of the current approaches of the FDA to regulation of drugs, parenteral products, and infant formulas for preterm infants. **Text Box 5** contains a summary of the FDA coverage, categories, and relevant regulations.

Both presentations covered the process and challenges with regard to review (including evidence needed to support new applications) and regulation of products for this special population, thereby providing excellent context for the workshop and Pre-B deliberations.

Griebel described CDER as being involved early in the drug development process, which also applies to parenteral nutrition products, including the pre–investigational new drug (pre-IND) application phase, to help sponsors with the initial IND submission. She noted that CDER works continuously with commercial sponsors throughout the life of the IND to develop a successful drug development plan. An IND is required when human studies are conducted to test investigational new drugs. [Under certain circumstances, which are defined under the regulations at 21 Code of Federal Regulations (CFR) Section 312.2 (b), clinical investigations that study drugs that are already lawfully marketed in the United States may be exempt from IND requirements.] During the development process, and in keeping with its role of protecting human subjects involved in clinical trials, CDER is involved in clinical phases I, II, and III to review protocols and work with sponsors on the drug development strategy. CDER ensures that the design of the scientific evaluation, particularly in phase II and III trials, will be adequate to provide evidence to be considered for supporting drug approval.

To bring a drug to the market, a manufacturer has to submit a New Drug Application or a Biologics License Application, which must include all components as required by regulations 21 CFR Section 314 and 21 CFR Section 600, respectively. Once the drug is approved, CDER works on monitoring postmarketing safety and helps facilitate new drug development plans for new indications.

With specific regard to development programs for drug products intended for preterm infants, CDER is often challenged by issues such as the following:

- design and conduct of adequate and well-controlled trials in this population,
- defining the dose for the full range of pediatric population,
- ensuring safety, and
- blood volume limits and assay validation in the context of these limits.In the event of drug shortages that arise because of manufacturing issues, CDER works with other groups to evaluate medical necessity and health hazards that may be caused by the manufacturing issues, and may work to mitigate the shortage by allowing importation of products that are not approved within the United States (as long as the manufacturing facility has been inspected and passed inspection) through a structured process of regulatory discretion.

To provide additional perspective, Pat Anthony, Fresenius Kabi, discussed product development and regulatory challenges for those developing parenteral nutrition products. She highlighted 3 challenges, which are outlined in **Text Box 6**.

With regard to formulas, Beker described the regulatory process for both exempt and nonexempt products. Exempt infant formula products are used for infants with inborn errors of metabolism, LBW, or with unusual medical or dietary problems. Fortifiers are also regulated as exempt infant formula. Regulations require review of premarket notifications of exempt and nonexempt infant formulas by the Center for Food Safety and Applied Nutrition/FDA. Unlike drugs, there is no preapproval process for infant formula but rather a required notification process that does not have the same level of postmarket evaluation.

Beker described the steps required before a company manufactures new exempt infant formula. The products designed to meet the nutritional needs of LBW infants are often for preterm infants who have higher requirements for specific nutrients than do term infants. When nutrients exceed the regulatory maximum levels specified for nonexempt formulas, an exemption must be requested. The companies are required to submit a detailed description of the formulation, including processing information, and inclusion of medical, nutritional scientific, or technological rationale for any deviation from nutrient requirements. Currently, there are 29 required nutrients for all infant formulas with explicit minimum levels for all of these nutrients and maximum levels for protein, fat, vitamins A and D, iodine, iron, sodium, potassium, and chloride.

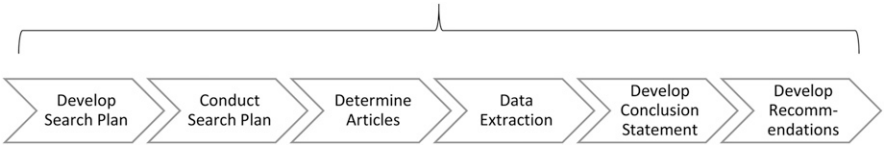

FIGURE 1 Evidence Analysis Library systematic review process.

Text Box 5 Regulatory coverage across FDA for products designed for preterm infants

CDER

- Products regulated are drugs, including small molecules and biological drug products
- The Federal Food, Drug, and Cosmetic Act defines drugs as articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease and articles intended to affect the structure or any function of the body
- The Division of Gastroenterology and Inborn Errors Products is the division within CDER that manages large-volume parenterals (e.g., lipid emulsions, amino acids, mineral additives), in addition to gastrointestinal drugs (e.g., for inflammatory bowel disease, celiac disease, irritable bowel syndrome, gastroesophageal reflux disease, nonviral hepatitis liver diseases, etc.) and drugs intended to treat inborn errors of metabolism (e.g., drugs for phenylketonuria, urea cycle disorders, and enzyme replacement therapies for Gaucher disease, Fabry disease, Pompe disease, Morquio syndrome, and cystic fibrosis)

Center for Food Safety and Applied Nutrition

- The Federal Food, Drug, and Cosmetic Act established a new section 412 (21 U.S.C. 350a) and created a separate category of food designated as infant formula in 1980 and amended in 1986 (11)
- The Current Good Manufacturing Practices, Quality Control Procedures, Quality Factors, Notification Requirements, and Records and Reports, for Infant Formula, final rule was published 10 June 2014 (12)
- **Nonexempt formulas**
  - Healthy term infants
  - Otherwise not meeting exempt criteria
- **Exempt formulas for the following (13):**
  - LBW
  - Inborn errors of metabolism
  - Unusual medical or dietary problem

Amy Mackey, Abbott Nutritionals, provided a manufacturer's perspective of enteral formula product development. She outlined the innovation/renovation process, which takes 2–8 y and includes evaluating unmet needs, seeking input from experts in the field, product feasibility, and regulatory approvals. Mackey highlighted the importance of harmonization across experts while developing recommendations. When designing a product, industry typically considers nutrient recommendations from established technical resources/organizations such as the American Academy of Pediatrics, the American Society for Parenteral and Enteral Nutrition, and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. Ninety days before bringing an exempt infant formula to market, the company is required to prepare and submit infant formula notification. The companies are constantly engaged with FDA, especially with innovative products.

PROVISION OF INFANT FORMULA

A significant portion of the care for postdischarge preterm infants falls within the purview of programs administered by the USDA Food and Nutrition Service. Anne Bartholomew, Chief of the Nutrition Services Branch, USDA/Food and Nutrition Service,

Text Box 6 Challenges for preterm parenteral nutrition/drug development

- Different clinical guidelines across the globe
  - The guidelines for preterm infants in the United States are not the same as the guidelines in Europe and the rest of the world.
  - Manufacturers are required to produce small volumes of intravenous nutrients with different compositions for infants from different countries.
  - This drives higher costs and creates sourcing issues and potentially drug shortages.
- Clinical trial requirements
  - No clear path for approvals for intravenous nutrients because the regulatory burden is the same for drugs to treat specific clinical conditions and nutrients.
  - In general, the clinical trials standards have been slowing the product development process.
- Drug/nutrient shortages.
  - Drug shortages are relatively high in the United States when compared with the rest of the world and could be partially attributed to the trade-off of superior safety and restrictive/cumbersome registration processes.
  - The shortages have been persistent for the past 10 y to the extent that it is unclear in many cases the dose of nutrients received by these infants.
  - The drug shortage is a significant issue and has to be resolved by all the stakeholders involved, including industry, scientists/clinicians, FDA/government, and professional organizations (American Society for Parenteral and Enteral Nutrition, Academy of Nutrition and Dietetics, American Academy of Pediatrics, ASN, European Society for Pediatric Gastroenterology, Hepatology, and Nutrition, etc.).

Text Box 7 Suggested benefits of human-milk feeding for preterm infants

- Dose-related decreases in NICU length of stay and lower morbidity including risk of the following (14–17):
  - sepsis
  - necrotizing enterocolitis
  - urinary tract infection
- Benefits persist beyond NICU stay
- Improved gastrointestinal function and integrity via the following (18):
  - decreased gastric pH
  - increased gastrointestinal motility
  - accelerated mucosal immunity
  - improved gut microflora
  - decreased mucosal permeability leading to reduced bacterial translocation
- Improvement in indexes of neurodevelopment that persists into adolescence (19)

described the role of the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) as 1 of 15 USDA nutrition assistance programs designed to work together to reduce hunger and improve diet quality for children and low-income people in the United States. Together, these programs reach 1 in 4 Americans each year, forming a national nutrition safety net that enables Americans to support a healthy lifestyle throughout the course of their lives. The WIC program reaches women during pregnancy and helps them, their new infants, and their young children eat healthfully during critical times of growth and development. WIC services are provided through 90 state agencies and work in conjunction with state health departments, Indian tribal organizations, >1800 local agencies, >10,000 clinics, and ~47,000 authorized retailers.

The WIC program benefits include the following: healthy supplemental foods, nutrition education, breastfeeding promotion and support, and referrals to health and social services. To receive services, participants have to be in 1 of the following categories: women (pregnant, postpartum up to 6 mo, or breastfeeding up to 1 y postpartum), infants (up to their first birthday), or children (up to 5 y of age.) A nutrition assessment for program eligibility is conducted at no cost to applicants.

The WIC program nutrition assessment includes determination of nutrition and/or medical risk factors for certification. A special food package is available to help meet the nutritional needs of medically fragile participants. To accommodate the needs of low-weight or premature-birth infants, this food package provides a variety of options: for example, medical foods, human-milk fortifier, other supplemental foods if prescribed, exempt infant formula/infant formula, and ready-to-feed formula. The WIC program also offers individualized nutrition education and referrals to other health and social services that will benefit the participant.

MOTHER'S OWN MILK

Because of its critical relation across the developmental and clinical spectrum covered by the Pre-B WGs, the use of human milk for these populations was presented as a cross-cutting issue by Richard Schanler, Hofstra North Shore–LIJ School of Medicine, who provided his perspectives with regard to the benefits of feeding "mother's own milk" (MOM) (**Text Box 7**).

Schanler shared data on the nutrient composition of preterm mother's milk. He noted that the need for human-milk fortifiers is justified by the amounts of a number of nutrients that do not meet the needs of the growing infant including the following: fat, protein, sodium, zinc, calcium, and phosphorus. He highlighted particular concerns about protein (20) and calcium (21, 22). The composition of human milk may contribute to what is an apparent paradoxical effect of human milk. Although infants fed human milk may grow at a "slower" rate (23), perhaps attributable to the variability in nutrient composition (24), they also appear to benefit in terms of immediate and long-term neurodevelopment (19).

Schanler also presented his thoughts about the relative utility of donor human milk as a proxy for MOM. He observed that most of the concerns center around nutrient composition, as follows:

- Nutrient composition of donor milk may not be adequate to meet nutrient requirements for protein, electrolytes (sodium), and energy, which is variable due in part to losses in fat (25).
- The need to pasteurize donor milk has implications for nutrient composition.
- Donor milk generally comes from "term" mothers late in lactation, resulting in a composition that might not meet the needs of preterm infants. The nutrient contents are low in protein, electrolytes, and the energy content is variable.

Despite these challenges, donor milk and particularly exclusive human-milk diets are preferable to formula in terms of protection from feeding intolerances and risk of necrotizing enterocolitis (26, 27). He cautioned against the use of bovine-milk–based fortifiers as human-milk fortifiers for either MOM or donor milk because they have been shown to result in higher rates of infections when compared with exclusive human-milk diets.

Schanler concluded by reinforcing the current American Academy of Pediatrics recommendations (28) (**Text Box 8**) and endorsing the critical role of human milk for the nutritional care of all preterm infants.

The next series of presentations were provided by speakers invited by the individual WGs in support of their deliberations. The articles derived from these presentations are published as part of this supplement.

- WG 1 requested an overview of the current state of understanding with regard to the need for long-chain PUFAs by preterm infants (29).

Text Box 8 American Academy of Pediatrics recommendations on breastfeeding for preterm infants (28)

- All preterm infants should receive human milk.
- Human milk should be fortified with protein, minerals, and vitamins to ensure optimal nutrient intake for infants weighing <1500 g at birth.
- Pasteurized donor human milk, appropriately fortified, should be used if MOM is unavailable or its use is contraindicated.

- WG 2 invited 2 speakers to cover key aspects of the transition from parenteral to enteral feeding: *1*) factors associated with the development of oral feeding skills (30) and *2*) considerations in feeding high-risk infants (31).
- WG 3 invited a talk on the critical issues in fat metabolism and options for feeding in high-risk infants in the NICU (32).
- WG 4 requested an overview of the INTERGROWTH (The International Fetal and Newborn Growth Consortium) study, a multicountry effort to develop fetal growth standards (33).

After these presentations, WG members spent time developing topics and questions for systematic review or further primary research, which are outlined in the final article of this supplement (34).

We acknowledge the contributions of the following Academy of Nutrition and Dietetics' staff members who assisted throughout the process: Deepa Handu, Taylor Wolfram, Lisa Moloney, and Mujahed Kahn. We thank Kripa Raghavan and Alexandra Porter for their role in support of the Pre-B process and meeting. We also thank Dennis Bier, Director of USDA/Agricultural Research Service Children's Nutrition Center, and his staff for hosting and support of the All-hands Meeting at Baylor University.

The authors' responsibilities were as follows—DJR and ALS: conceived of the project and the project plan, provided oversight, and authored the Executive Summary; and RKH: assisted with revisions of the Executive Summary. None of the authors had a conflict of interest to declare.

REFERENCES

1. World Health Organization. Preterm birth: factsheet no 363 [cited 2015 Apr 7]. Available from: http://www.who.int/mediacentre/factsheets/fs363/en/.
2. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller AB, Narwal R, Adler A, Vera Garcia C, Rohde S, Say L, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet 2012;379:2162–72.
3. Liu L, Johnson HL, Cousens S, Perin J, Scott S, Lawn JE, Rudan I, Campbell H, Cibulskis R, Li M, et al. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. Lancet 2012;379:2151–61.
4. Statistic Brain Research Institute. Premature birth statistics [cited 2015 Apr 7]. Available from: http://www.statisticbrain.com/premature-birth-statistics/.
5. Klein CJ. Nutrient requirements for preterm infant formulas. J Nutr 2002;132(Suppl):1395S–549S.
6. Agostoni C, Buonocore G, Carnielli VP, De Curtis M, Darmaun D, Decsi T, Domellof M, Embleton ND, Fusch C, Genzel-Boroviczeny O, et al. Enteral nutrient supply for preterm infants: commentary from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition. J Pediatr Gastroenterol Nutr 2010; 50:85–91.
7. Tsang RD, Uauy R, Koletzko B, Ziotkin SH, editors. Nutrition of the preterm infant. Cincinnati (OH): Digital Educational Publishing; 2005.
8. Koletzko B, Poindexter B, Uauy R, editors. Nutritional care of preterm infants: scientific basis and practical guidelines. Basel (Switzerland): Karger; 2014.
9. Raiten DJ, Raghavan R, Porter A, Obbagy JE, Spahn JM. Executive summary: evaluating the evidence base to support the inclusion of infants and children from birth to 24 mo of age in the Dietary Guidelines for Americans—the B-24 Project. Am J Clin Nutr 2014;99 (Suppl):663S–91S.
10. Robbins A. Children are dying. Washingtonian 2013;May 22.
11. Food and Drug Administration. Exempt infant formulas marketed in the United States by manufacturer and category [cited 2015 Apr 7]. Available from: http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/InfantFormula/ucm106456.htm.
12. Food and Drug Administration. Final rule: Current Good Manufacturing Practices, Quality Control Procedures, Quality Factors, Notification Requirements, and Records and Reports, for Infant Formula. Fed Regist 2014;79(111):33057.
13. Food and Drug Administration. Infant formula guidance documents & regulator information [cited 2015 Apr 7]. Available from: http://www.fda.gov/food/guidanceregulation/guidancedocumentsregulatoryinformation/infantformula/default.htm.
14. Schanler RJ, Shulman RJ, Lau C. Feeding strategies for premature infants: beneficial outcomes of feeding fortified human milk versus preterm formula. Pediatrics 1999;103:1150–7.
15. Schanler RJ, Lau C, Hurst NM, Smith EO. Randomized trial of donor human milk versus preterm formula as substitutes for mothers' own milk in the feeding of extremely premature infants. Pediatrics 2005; 116:400–6.
16. Sisk PM, Lovelady CA, Dillard RG, Gruber KJ, O'Shea TM. Early human milk feeding is associated with a lower risk of necrotizing enterocolitis in very low birth weight infants. J Perinatol 2007;27:428–33.
17. Lucas A, Cole TJ. Breast milk and neonatal necrotising enterocolitis. Lancet 1990;336:1519–23.
18. Hunter CJ, Upperman JS, Ford HR, Camerini V. Understanding the susceptibility of the premature infant to necrotizing enterocolitis (NEC). Pediatr Res 2008;63:117–23.
19. Roze JC, Darmaun D, Boquien CY, Flamant C, Picaud JC, Savagner C, Claris O, Lapillonne A, Mitanchez D, Branger B, et al. The apparent breastfeeding paradox in very preterm infants: relationship between breast feeding, early weight gain and neurodevelopment based on results from two cohorts, EPIPAGE and LIFT. BMJ Open 2012;2: e000834.
20. Rönnholm KA, Sipila I, Siimes MA. Human milk protein supplementation for the prevention of hypoproteinemia without metabolic imbalance in breast milk-fed, very low-birth-weight infants. J Pediatr 1982;101:243–7.
21. Schanler RJ, Garza C, Smith EO. Fortified mothers' milk for very low birth weight infants: results of macromineral balance studies. J Pediatr 1985;107:767–74.
22. Ziegler EE, O'Donnell AM, Nelson SE, Fomon SJ. Body composition of the reference fetus. Growth 1976;40:329–41.
23. Colaizy TT, Carlson S, Saftlas AF, Morriss FH Jr. Growth in VLBW infants fed predominantly fortified maternal and donor human milk diets: a retrospective cohort study. BMC Pediatr 2012;12:124.
24. de Halleux V, Rigo J. Variability in human milk composition: benefit of individualized fortification in very-low-birth-weight infants. Am J Clin Nutr 2013;98:529S–35S.
25. Wojcik KY, Rechtman DJ, Lee ML, Montoya A, Medo ET. Macronutrient analysis of a nationwide sample of donor breast milk. J Am Diet Assoc 2009;109:137–40.
26. Boyd CA, Quigley MA, Brocklehurst P. Donor breast milk versus infant formula for preterm infants: systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed 2007;92:F169–75.
27. Sullivan S, Schanler RJ, Kim JH, Patel AL, Trawoger R, Kiechl-Kohlendorfer U, Chan GM, Blanco CL, Abrams S, Cotten CM, et al. An exclusively human milk-based diet is associated with a lower rate of necrotizing enterocolitis than a diet of human milk and bovine milk-based products. J Pediatr 2010;156:562-7.e1.
28. American Academy of Pediatrics Committee on Nutrition. In: Kleinman RE, Greer FR, editors. Pediatric Nutrition Handbook. Elk Grove Village (IL): American Academy of Pediatrics; 2014.
29. Brenna JT. Long-chain polyunsaturated fatty acids and the preterm infant: a case study in developmentally sensitive nutrient needs in the United States. Am J Clin Nutr 2016;103(Suppl):606S–15S.
30. Lau C. Development of infant oral feeding skills: what do we know? Am J Clin Nutr 2016;103(Suppl):616S–21S.
31. Jadcherla S. Dysphagia in the high-risk infant: potential factors and mechanisms. Am J Clin Nutr 2016;103(Suppl):622S–8S.
32. Nandivada P, Fell GL, Gura KM, Puder M. Lipid emulsions in the treatment and prevention of parenteral nutrition–associated liver disease in infants and children. Am J Clin Nutr 2016;103(Suppl):629S–34S.
33. Giuliani F, Cheikh Ismail L, Bertino E, Bhutta ZA, Ohuma EO, Rovelli I, Conde-Agudelo A, Villar J, Kennedy SH. Monitoring postnatal growth of preterm infants: present and future. Am J Clin Nutr 2016;103 (Suppl):635S–47S.
34. Raiten DJ, Steiber AL, Carlson SE, Griffin I, Anderson D, Hay WW Jr, Robins S, Neu J, Georgieff MK, Groh-Wargo S, et al.; Pre-B Consultative Working Groups. Working group reports: evaluation of the evidence to support practice guidelines for nutritional care of preterm infants—the Pre-B Project. Am J Clin Nutr 2016;103(Suppl):648S–78S.