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The 5 Ps for Promoting Gut Health and Feeding Tolerance in Preterm Infants

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LEARNING OBJECTIVES

1. Describe how feeding protocols and provision of human milk can decrease the risk of necrotizing enterocolitis.
2. Explain a WHO, WHAT, WHERE, WHEN and WHY approach to probiotics in the NICU.
3. Describe how the practice of antibiotic stewardship can impact morbidity and mortality in preterm infants.
4. Identify NICU feeding challenges for parents and encourage parent partnerships.

Introduction

Prematurity can create a nutrition emergency. Following respiratory and hemodynamic stabilization of the preterm infant, the urgent next step is initiating an age- and weight-appropriate feeding plan. Preterm infants have high nutrient requirements during the postnatal period of rapid growth. This occurs in a setting of low nutrient stores and immature organ systems.[1] In addition, early nutrition is of paramount importance as it is a key driver of childhood neurodevelopment and adult health.[2]

Although nearly all very low birth weight (VLBW, <1500 gm) preterm infants are started on parenteral nutrition (PN), the goal is to transition to enteral nutrition (EN) as soon as possible.

The feeding plan requires input from the entire multidisciplinary healthcare team as well as the family. Feeding intolerance is a barrier to achieving full enteral feedings and is often an early sign of necrotizing enterocolitis (NEC). Preterm infants are susceptible to NEC due to intestinal immaturity as well as the permeability of the gut that has an abnormal microbiome. This can lead to bacterial translocation and invasion.[3]

NEC remains a scourge within the NICU. Infection, inflammation and delayed initiation of enteral feeding are all associated with the condition. With the lack of medical treatment options for NEC, only enteral feeding is a modifiable factor. A recent systematic review suggests that overall mortality following NEC remains high – almost 25% for VLBW infants diagnosed with NEC stage 2 disease.[4] Medical NEC is especially dangerous for extremely low birth weight (ELBW, <1000 gm) infants in whom mortality following surgical treatment of NEC is over 50%.[4] Given these poor outcomes, the focus should be on the prevention of NEC by enteral feeding management.

This article describes a five-point strategy for developing a feeding plan. The strategy considers gastrointestinal and neuromuscular development, offers specific evidence-based approaches to minimize complications, maximizes feeding

Figure 1: Protection from NEC by a Diet of Human Milk[3]

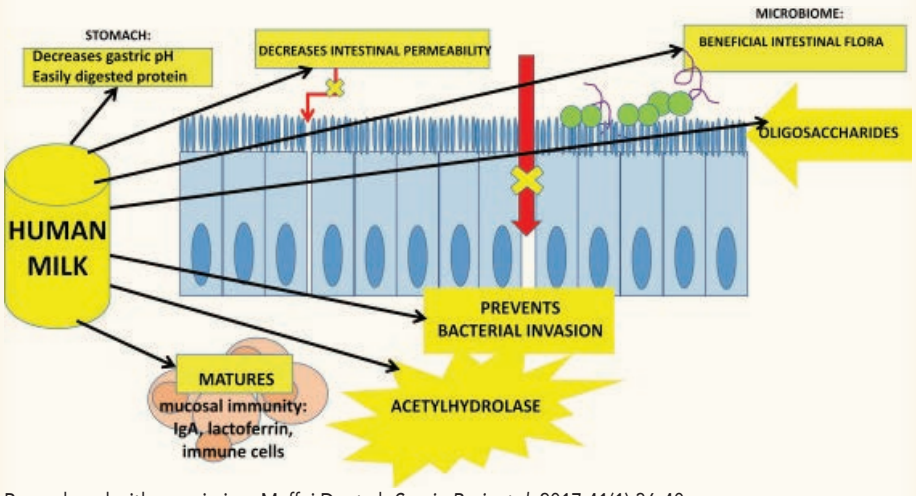

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Table 1: Steps in Developing and Implementing a NICU Feeding Protocol

- Assemble a multidisciplinary feeding team.*
- Set key parameters for the feeding protocol (inclusion and exclusion criteria).
- Review the literature and assign topics to feeding team members.
- Consider other NICU feeding protocols; check list-serves; and reach out to colleagues.
- Report findings to the feeding team.
- Develop a draft protocol.
- Seek feedback from NICU staff.
- Construct a final feeding protocol and educate NICU teams.
- Implement the protocol and collect data over a defined period.
- Share results among feeding team, address issues and revise the protocol as needed.
- Implement the revised protocol.
- Re-visit the protocol annually with feeding team.
- Engage parents in implementing the feeding protocol, educate them on feeding plan and provide support.

*Feeding team members include but are not limited to: physicians, nurse practitioners, registered nurses, registered dietitian nutritionists, lactation consultants, milk/formula technicians, feeding therapists, social workers, case managers, pharmacists and the parent representative.

tolerance and harnesses the power of parents. The 5P approach includes: **P**rovision of human milk, **P**rotocols for feeding, **P**robiotics, **P**ractice of antibiotic stewardship and enlisting **P**arents as partners.

Provision of Human Milk

Human milk is an important evidence-based intervention in reducing the risk of NEC.[5-10] Figure 1 illustrates how human milk protects the intestinal tract. Although most human milk research relies on observational data, multiple studies strongly suggest a role for human milk in the care of the at-risk preterm infant.[11]

Despite the ability of human milk to lower the risk of NEC significant challenges to providing it exist. Initiating and maintaining a supply of human milk is difficult for most mothers of preterm infants. Regardless of support from NICU staff, only about 30% of mothers are able to provide milk to their infants throughout the entire NICU stay.[12]

Although human milk is considered the best feeding for nearly all newborns, to meet the nutritional needs of preterm infants human milk requires fortification with protein and minerals.[5] Fortification is usually provided as either a commercial human milk fortifier containing a bovine protein or a human milk-based fortifier that is mixed in fixed ratios with expressed human milk. The fortification challenge to the provider writing the feeding order is that the nutrient composition of human milk is variable and often unknown.[13,14] Some NICUs provide an individualized approach to fortification with special equipment to analyze the mother's milk. However analyzers are not available in most NICUs.[15]

Pasteurized donor milk is the recommended alternative when mother's own milk is not available.[16] Donor milk lowers the risk of NEC, compared to formula, when fed during the time that infants are most at risk for developing NEC. However, it is not equal in value to mother's own milk. The nutrient density of donor milk is generally lower than mother's own milk because donor mothers are in later stages of lactation. In addition, donor milk is exposed to multiple transfers in and out of plastic containers, resulting in a loss of calorically-rich fat. Moreover, pasteurization, which is critical in ensuring the safety of the milk, destroys bioactive compounds, eliminates bacterial strains with probiotic properties and decreases bile salt-stimulated lipase. Lastly, storage degrades important components in the milk during multiple freeze-thaw cycles.[16,17]

In summary, provision of human milk is a highly recommended therapy to reduce the risk of NEC. Mothers frequently need

staff support to initiate and maintain their milk supply. Donor milk can be an important alternative, but should not be used when mother's own milk is available in adequate amounts.

Protocols for Feeding

In addition to the choice of feeding (mother's milk, donor milk or formula), feeding methods are important. Methods are described for both feeding initiation, minimal enteral nutrition or priming/trophic feedings and feeding advancement. Implementing a standardized feeding protocol has been shown to be an effective strategy in reducing the risk of NEC, according to several systematic reviews and recent single center studies.[18-20] In a study by Kamitsuka et al, researchers demonstrated an 84% reduction in the risk of NEC after the implementation of a standardized feeding protocol.[21] ELBW infants may especially benefit.[22] Other benefits of a unit-based feeding protocol include: higher use of human milk as the first feeding, fewer days on PN, fewer intravenous catheter days, decreased incidence of sepsis, faster achievement of full enteral feeding, optimized nutrient delivery in the transition from PN to EN, improved growth velocity and decreased length of hospital stay.[18,23-26] These benefits appear to result from a combination of factors including: less variation in feeding practices, earlier feeding initiation, encouragement of human milk use, prevention of excessively rapid feeding advancement, and more attention to infant nutrition and feeding tolerance.

Creating a NICU-based feeding protocol requires a multidisciplinary effort. Elements to consider include: patient demographics; healthcare professional staffing; PN practices; availability of human milk, donor milk, fortifiers and formula; variation of current practices for feeding initiation, advancing and transitioning enteral feedings; and resources for discharge plan and follow-up care.[25] Table 1 outlines a series of recommended steps in the development and implementation of a NICU feeding protocol.

In summary, creating a NICU-based feeding protocol is a multidisciplinary team effort that works synergistically with the provision of human milk. The protocols do not necessarily require the purchase of expensive equipment. The development and implementation of feeding protocols focuses the entire unit on the challenge of infant feedings and nutrition. While it is important to never lose sight of the value of critical thinking, a standardized feeding protocol can be an important part of promoting feeding tolerance and preventing NEC in the NICU.

BOX 1: Recommendation regarding probiotics and preterm infants: Position of the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) (2020) [34]

"If all conditions are met, the panel conditionally recommends using the combination of *B infantis* Bb-02, *B lactis* Bb-12, and *Str thermophilus* TH-4 at a dose of 3.0 to 3.5 x 10^8 CFU (of each strain) as it might reduce NEC stage 2 or 3…."

CFU – colony forming unit

Probiotics in the NICU

The infant microbiome is highly vulnerable to environmental influences.[27] Intestinal dysbiosis, an imbalance between homeostasis and inflammation, precedes and is a likely causative factor in the development of NEC.[28,29] Ways to correct dysbiosis in newborn infants include: skin-to-skin contact, oral immune therapy (also known as colostrum swabbing), human milk feeding, antibiotic stewardship and supplemental probiotics.[30,31]

The use of supplemental probiotics in high-risk newborns has been an area of extensive study for several decades.[32,33] To organize the literature on the topic, this article reviews the *WHO, WHAT, WHERE, WHEN and WHY,* starting with *WHY.*

WHY. More than 10,000 preterm infants have participated in randomized controlled trials (RCTs) on probiotics worldwide.[34] In a 2018 systematic review by Patel and Underwood, the authors strongly suggest that probiotics may reduce rates of NEC, sepsis and mortality.[35] However, a significant limitation of the systematic review was that studies used different populations, multiple probiotic strains and varying probiotic doses and treatment durations. Additionally, strain-specific systematic reviews report variable conclusions regarding rates of NEC, sepsis and mortality.[36,37] Single-strain probiotic studies versus multi-strain studies[32,33,38-40] strongly suggest that multi-strain probiotics appear to be more effective in preterm infants.[32,33,38-40] In summary, all probiotic treatments are not equally effective, and the details of strain, dose and duration are very important.

WHO. Most clinical trials of probiotic supplementation in preterm infants evaluate VLBW infants, and it is this group that appears to most likely benefit. Within that group, some data suggest that infants between 1000 to 1500 grams birth weight receive greater benefits from the intervention than infants less than 1000 grams at birth.[40,41] This, however, has not been shown to be universally true.[42] Possibly, ELBW infants cannot colonize the gastrointestinal tract with the probiotic.[43] Regardless, more studies on probiotic supplementation in ELBW infants are needed, as they are at greatest risk for NEC.[34]

WHAT. Multi-strain probiotics are recommended for preterm infants. (See Box 1 for recommendations from the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN)).[34] Single-strain probiotic products are the most widely available, but the least studied in scientific literature.[35,44] Probiotic supplements are largely marketed worldwide as nutritional supplements in an unregulated market, so there may be variability between what is on the label and what is in the product. For example, in a 2015 study by Lewis et al, only one in 16 products labeled as containing *bifidobacteria* actually matched the product.[45] Lack of probiotic regulation also carries the potential for contamination, since

manufacturing of probiotic supplements is not a sterile procedure.

Although the absolute risk of harm is low, probiotic use in vulnerable newborns has led to fungemia, bacteremia and sepsis.[35,46,47] An infant death from a mucormycosis-causing mold associated with a contaminated probiotic led the Centers for Disease Control and Prevention (CDC) to withdraw the product from the market.[48,49] These risks are mitigated by (1) prescribing a strain, or combination of strains, with proven effectiveness and established safety profiles, (2) choosing a product prepared using current Good Manufacturing Practice (cGMP); and (3) having adequate microbiological testing available.[34]

WHERE. If the decision to use a probiotic is made, where it is prepared for dispensing is an important consideration. If a powder packet or capsule is opened for a particular patient within the unit, contamination of surfaces and cross-colonization to other infants can occur, so caution is essential in preparing the probiotic.[50-54]

The practices surrounding probiotic preparation are evolving. Some units draw the probiotic powder into an oral syringe in their milk lab, formula room or pharmacy. It is then carefully mixed with a few milliliters of human milk, formula or sterile water at the patient's bedside. Opening of probiotic products away from the bedside will reduce the risk of inadvertent contamination of the environment.

WHEN (and a little bit of HOW). Available data do not clearly indicate optimal probiotic start time, dose, dosage or treatment duration for the preterm infant.[34] The most common practices include[35,55]:

- Initiation: in the first several days of life;
- Dose: range of 12 million colony forming units (CFU)/day to 12 billion CFU/kg/day. Most common dose is 1 to 6 billion CFU/day;
- Dosage schedule: once daily to twice a day;
- Duration: 10 days – up through entire NICU stay. Most common duration is at least 28 days.

A practical rule is to follow the dose used in a RCT.[34,35,55]

In summary, a multi-strain probiotic supplement manufactured with cGMP, prepared in a secure location and delivered in a dose and duration based on a well-designed RCT, could add protection against NEC and feeding intolerance in VLBW preterm infants.

Practice of Antibiotic Stewardship

Historically, in most NICUs, any infant admitted was started on antibiotics. Until recently, this was viewed almost universally as a best practice. This prophylactic practice was initiated to address the issue of well-appearing newborns dying from Group *B streptococcal* or *Haemophilus influenzae* (HIB) sepsis within hours of birth. However, in 2016 there was a national Call to Action from the CDC to raise the alarm of multi-drug-resistant bacteria.

NICUs now had to challenge the practice that all admitted infants needed antibiotics "just in case" they had an infection. The standard became the right antibiotic for the right patient, treating as specifically as possible for the right amount of time.

In 2011, Kuppala et al[56] completed a retrospective study of 365 premature infants less than 32 weeks, who received more than one week of antibiotics at birth. They found that infants who received extended courses were twice as likely to suffer a major morbidity or mortality. The review also showed that these infants had an increased length of stay in the hospital. In Schulman et al,[57] the researchers described the prescribing practices in 140 NICUs in the state of California. This study demonstrated a 40-fold variation between NICUs in antibiotic prescribing practices. These two noteworthy studies revealed the need for significant practice changes.

Between 2015 and 2018, NICUs partnered worldwide to implement antibiotic stewardship practices, that is, judicious use, in their units. How they accomplished this varied based on unit size and patient population. Some practice changes that were common included the use of a risk scoring tool for healthy newborns and evaluation of empiric antibiotic practices in each unit. As an example, in the author's unit the actual time it took for a blood culture to be positive was noted. It was found that positive cultures appeared in under 24 hours. It was then decided that antibiotics could be safely stopped at 36 hours. Thus, sepsis was ruled out and antibiotic exposure reduced. Emerging evidence shows that the use of antibiotics in the neonatal period, even for a short course of treatment, changes the gut flora of a newborn for up to 6 months.[58]

The gut microbiome is viewed by many as a secondary immune system and the goal is to populate it with healthy bacteria. Neu studied the first stools of newborns to map the common bacteria.[59] Infants born vaginally were found to have different types of bacteria from those delivered by Cesarean, which was not surprising given the differences between bacteria that colonize the skin versus those in the vaginal tract.

There are many factors that cannot be controlled at the time of birth, including delivery method and maternal complications. However, there is strong evidence that the use of human milk helps in epithelial membrane tight junctions, so they are less susceptible to pathogenic bacteria.[10] We now refer to human milk as a medicine important to protect the health of the infant gut. In summary, the practice of judicious antibiotic stewardship is of the essence.

Parents as Partners

The following case study narrative is from one of our authors, Jenné Johns, and written in her own words.

I gave birth to a preterm infant. He weighed 887 grams, and at the time was often referred to as a "micropreemie". We had a nearly three-month journey through the NICU. Although my son was an ELBW infant, he was and still is a fighter!

As a public health professional, I knew the benefits of breastfeeding a baby, but prior to my son's birth I had no personal interest in breastfeeding. I imagined it was easier to feed on the go with formula in a bottle. As I established my first milk supply, it took a while for me to express the milk, and I was hesitant to provide breastmilk for my son's first feeding. That is, until I met our NICU's empowering lactation consultant, who became my son's saving grace. She visited me in the peripartum unit on my son's second day in the NICU. She sat me down to educate and empower me about the vast

BOX 2: Tips for Partnering with Parents to Support Feeding in the NICU

1. Celebrate Big and Small Wins. For the parents of ELBW infants, it is pure joy to receive words of affirmation that they are doing something right for their babies. Offer positive and consistent words of affirmation recognizing parents' big and small wins related to feeding, growth and development. It goes a very long way for the milk production of the mothers of preterm infants.

2. Educate, Re-educate, and Remind. Most parents try to absorb, retain and act upon each piece of information given to them about their infants. Gentle reminders, educating or re-educating parents about their feeding options, are important in meeting the baby's health, growth and developmental needs.

3. Speak Plain Language. Help parents understand, in lay terms, the benefits of each of their feeding options. Discuss the pros and cons and allow them time to process and ask questions, even if they come a week after your conversation.

4. Engage Parents as Members of the Multidisciplinary Feeding Team. Parents value opportunities to share their insights about their preterm infant's development. Parents want to be partners in the delivery of their baby's care. Whenever possible, engage parents as part of the multidisciplinary team reviewing and making decisions about feeding guidelines, protocols and practices.

benefits of supplying my breastmilk for my very small, vulnerable, and fragile baby. After my milk was described as "liquid gold and liquid medicine" for an ELBW infant, I was sold. That very day, I made my way to the NICU to aid in my son's first feeding. It was pure joy to see his reaction after swabbing his cheek with my colostrum. From then on, I became a very proud and, when possible, a consistent milk producer in the NICU. Our family even needed a large cooler to transport my unused milk supply home in the week leading up to his discharge. I felt like celebrating when I heard those magical words "unused frozen milk supply," "cooler," "transport," and "discharge prep." It had not been an easy road.

Throughout my journey as a milk-producing, breastfeeding mother, there were many bumps and unexpected hurdles. I did not fully understanding my feeding options when my milk supply ran low due to stress, exhaustion, or returning to work. I recall having a two to three-week drought when I could barely meet the few ounces of milk required for my son's daily feeding. I cried endlessly, worried sick that the only food he would consume was powdered milk. While I was very briefly introduced to human milk fortification, the full explanation of its benefits was not discussed with me.

Low milk production was terribly stressful, and I needed help to produce more milk. Luckily for me, I had a positive relationship with my son's dietitian, nurses, and the lactation consultant. Each one of these amazing NICU partners offered a variety of recommendations including rest, relaxation, stress reduction techniques, even homemade kale smoothies. While I tried all recommendations, they mostly yielded very little results.

While pumping in the NICU family room one day, a close relative visited. I cried while sharing my milk supply worries. She sat with me quietly, rubbed my hand and gave me warm hugs. Mysteriously, the milk began flowing from me. That one experience gave me what I needed to overproduce milk for my son until it was time for me to return to work.

As my breastmilk was fortified with a bovine protein milk fortifier, my son made steady weight gains almost every day. The NICU provided daily progress emails. The two sections that I recall reading first included the amount of food he tolerated the day before and his weight changes. Any weight loss on his report sent me into overdrive in producing milk. This was heart wrenching, especially if the weight loss lasted over more than one report. I asked lots of questions to understand his change in weight, and what I needed to do differently in my diet.

Reflecting on our feeding journey, I realize our NICU experiences were just a glimpse of what our nutrition and eating challenges would be later, when he came home. The partnerships needed with my son's care team to make informed decisions for his health continue to this day. At six years old, my son remains small for his age but as mighty as he was in the NICU. Although he remains in the underweight classification on the child growth chart, he makes steady weight increases on each clinic visit. He remains healthy, rambunctious, and a picky eater. I continue to supplement his milk with powdered milk during periods of high physical activity.

See Box 2 for tips to successfully partner with parents.

Summary

The birth of a VLBW preterm infant presents a major nutrition challenge. Our 5P program is an evidence-based approach that results in improved outcomes: 1. **P**roviding human milk, 2. Using a feeding **P**rotocol, 3. Considering **P**robiotics, 4. **P**racticing antibiotic stewardship and 5. Having **P**arents as partners.

ABOUT THE AUTHORS

Sharon Groh-Wargo, PhD, RDN is the Senior Neonatal Nutritionist in the Department of Pediatrics at MetroHealth Medical Center and a Professor in Nutrition and Pediatrics at Case Western Reserve University School of Medicine, Cleveland, Ohio, USA.

Dr. Groh-Wargo has over 40 years of experience, is a nationally known speaker and researcher, and has authored numerous publications on neonatal nutrition. She is an editor of both editions of the Academy of Nutrition and Dietetics *Pocket Guide to Neonatal Nutrition* and is a contributor to the Academy's online *Pediatric Nutrition Care Manual*. Dr. Groh-Wargo authored a chapter on "Lactoengineering" for the 3rd edition of *Infant and Pediatric Feedings: Guidelines for Preparation of Human Milk and Formula in Health Care Facilities*. She participates in the Pre-B Project, sponsored by the NIH in cooperation with the Academy of Nutrition and Dietetics, which was convened to perform systematic reviews of neonatal nutrition and to set national dietary guidelines for the premature infant. Dr. Groh-Wargo received the 2019 Academy of Nutrition and Dietetics Medallion Award.

Jenné Johns, MPH is the mother of an ELBW preterm infant, author, speaker, advocate, and President of Once Upon A Preemie. As an advocate for reducing healthcare disparities, Jenné found herself advocating for the needs of her son, as his survival depended on it. She also learned the power of reading to her son daily. Jenné wrote, "Once Upon a Preemie" which is the first of its kind children's book written for the parents of preemies while they are in the NICU. This bedside companion seeks to motivate, encourage and inspire preemie babies and families until they go home. Jenné also created the Once Upon A Preemie Academy, a virtual training program focused on health and racial equity for the NICU and Preemie Professionals.

Her preemie parent contributions include consulting and blogging for fortune 500 companies on preemie parent needs from a cultural lens and reading as a tool for growth, development, and bonding. She serves on numerous advisory committees advocating for preemie babies and eliminating health disparities including: NICU Parent Network, The National Coalition on Infant Health, and March of Dimes Prematurity Prevention Collaborative. Jenné earned a master's degree in public health from Temple University, and a Bachelor of Science Degree in Human Ecology Nutrition with a minor in Chemistry from the University of Maryland Eastern Shore.

Kristen Brown is a Neonatal Nurse Practitioner and Clinical Nurse Specialist currently in the role of Pediatric Quality Liaison at Golisano Children's Hospital in Rochester, NY, USA. Kristen has practiced at many large academic medical centers including The Children's Hospital of Philadelphia, Nationwide Children's Hospital and Dartmouth Hitchcock Medical Center. She has co-authored multiple articles in the areas simulation, medication safety practices and most recently NICU antibiotic stewardship. Kristen graduated with a BSN from Hartwick College, her MSN from the University of Delaware and her Post-Master's from the Ohio State University. Her current areas of focus are on medication safety and error reduction as well as preventable harm to pediatric patients.

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Post-Test: The 5 Ps for Promoting Gut Health and Feeding Tolerance in Preterm Infants

This complete NICU Currents is posted on **www.anhi.org** in "Courses," then filter by keyword "NICU Currents." Complete the following post-test online at no charge to receive CE credit. Please note online questions or answers are randomized and may not appear in the same sequence below. Do not assume that the letter preceding the correct response will be identical to the online version.

1. Human milk reduces the risk of NEC in preterm infants by:
   a. Preventing bacterial invasion
   b. Decreasing absorption of oligosaccharides
   c. Increasing intestinal permeability
   d. Reducing lactoferrin and IgA intake

2. Human milk is the ideal feeding for nearly all newborns. Which of the following statements is true when human milk is fed to preterm infants?
   a. Donor milk is superior to mother's own
   b. Human milk requires fortification of protein and minerals
   c. Most mothers can easily supply enough human milk
   d. Nutrient content is consistent and predictable over time

3. A unit-based feeding guideline is best developed by:
   a. The neonatal dietitian
   b. The nursing staff and leadership
   c. A multi-disciplinary NICU committee
   d. The hospital risk-management team

4. Benefits of a standardized approach to feeding include:
   a. Faster achievement of full enteral nutrition
   b. Decreased risk of NEC
   c. Higher likelihood of human milk as first feeding
   d. All the above

5. Intestinal dysbiosis:
   a. Protects preterm infants from NEC
   b. Is an imbalance between homeostasis and inflammation
   c. Only occurs in preterm infants fed formula
   d. Is improved by antibiotic therapy

6. Thinking about the WHO, WHAT, WHERE, WHEN, WHY and HOW of probiotics in the NICU, which of the following is the best choice for WHY?
   a. Reduce retinopathy of prematurity
   b. Increase one-year survival
   c. Contribute to protection against necrotizing enterocolitis
   d. Increase supply of mother's milk

7. Inappropriate use of antibiotics may lead to:
   a. Growth of multi-drug resistant bacteria
   b. Increased length of NICU stay
   c. Alteration of the gut microbiome for up to 6 weeks
   d. All the above

8. What is the 5th 'P' for promoting gut health and feeding tolerance in preterm infants?
   a. Provision of human milk
   b. Protocols for feeding
   c. Probiotics in the NICU
   d. Parents as partners

9. Why is mother's own milk superior to donor human milk?
   a. The nutrient density is typically lower in donor human milk because donor mothers are in later stages of lactation.
   b. Donor milk is exposed to multiple transfers, which can result in loss of calorically-rich fat.
   c. Pasteurization can destroy protective bioactive compounds within the donor milk.
   d. All the above

10. The most common duration for feeding probiotics in preterm infants is for how many days?
    a. 10
    b. 12
    c. 20
    d. 28

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THE MICROBIOME & THE PRETERM INFANT:

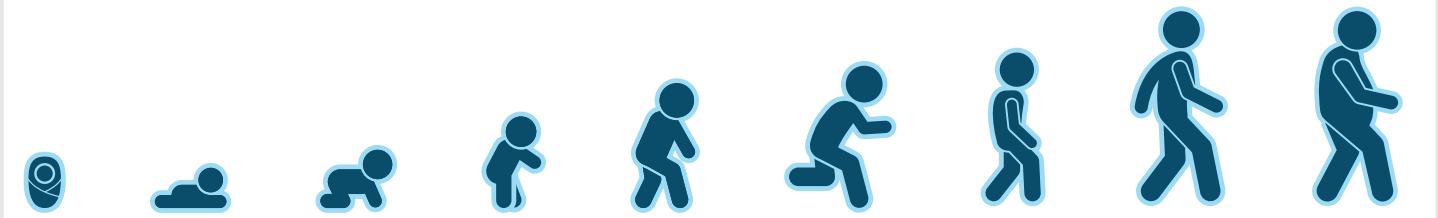
GUT IMMATURITY

The preterm infant's gut motility, digestion, absorption, immune defenses, barrier function, and circulatory regulation are underdeveloped.[1,2]

DYSBIOSIS

The abnormal colonization or the imbalance of microbes.[3]

THE CHALLENGE: The combination of gut immaturity and dysbiosis places preterm infants at risk for impaired nutrient absorption, damaged barrier function, and compromised gut-based immunity, in turn predisposing them to health threats across the lifespan[2, 4, 5]



INFANCY[6]
- Feeding intolerance
- Necrotizing enterocolitis (NEC)
- Infections and sepsis

CHILDHOOD[4, 7, 8]
- Poor bone growth
- Asthma / wheezing

ADULTHOOD[5, 9]
- Obesity
- Inflammatory bowel disease (IBD)
- Psoriasis
- Diabetes (Type 1 and 2)

Infancy is a Critical Window for Microbiome Development

THE SCIENCE: Gut pathophysiology in a preterm infant

For **full term infants**, the gut's immune system and microbiome mature in parallel during the first year of life, leading to better tolerance of foods and beneficial microbes.

In **preterm infants**, gut immaturity and dysbiosis can lead to abnormal immune responses and permeability to pathogens, which can lead to serious, life-threatening, consequences such as NEC and sepsis.[10-13]

NORMAL GUT	DAMAGED GUT
	
• Protects against harmful pathogens • Allows survival of beneficial microbes	• Excessive inflammation • Ischemia and gut barrier breakdown

An immature infant gut has fewer and less diverse microbiota.[3, 14]

Supporting the gut microbiome in preterm infants promotes better health while lowering the risk for adverse health consequences.

GUT IMMATURITY & DYSBIOSIS

NEC is a devastating disease that can affect the intestine of preterm infants. Multiple environmental factors such as: microbial dysbiosis, dysregulated inflammation, and gut immaturity contribute to increased risk.[6]

1 in 14
premature infants with very low birth weight is likely to develop NEC [1,10]

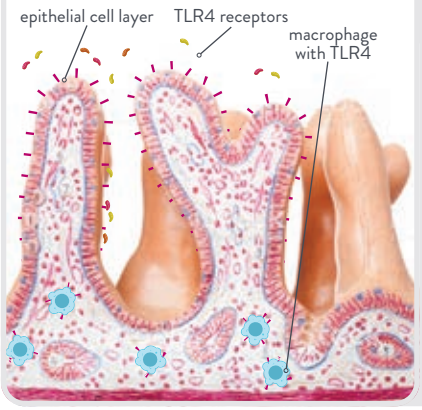
Premature infants who develop the life-threatening condition of NEC have a mortality risk of
20-30% [1,10]

NEC survival rates have remained low and unchanged for 3 decades, despite other advances in care for preterm infants[13]

Why is NEC more likely to affect preterm infants than full-term infants?

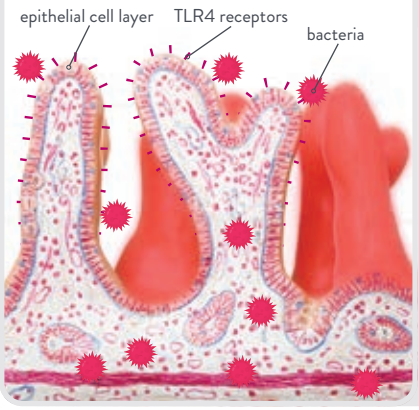
Emerging research shows that a link between prematurity, NEC, and microbes is a membrane protein called toll-like receptor 4 (TLR4)[15]

NORMAL IMMUNE RESPONSE



- Microbes activate receptors on the macrophage
- Pathogens are engulfed and destroyed

IMMATURE GUT INFLAMMATORY RESPONSE



- Lipopolysaccharide (LPS), a component of gram-negative bacteria, activates TLR4 receptors [16]
- This leads to inflammation, cell destruction, and disruption of the intestinal barrier
- Harmful bacteria can then translocate to the bloodstream, triggering sepsis

All part of the rapid-onset, serious condition of NEC

THE SOLUTION: Strategically build a microbiota with gut-friendly bacteria in early life

Use human milk for optimal intake of human milk oligosaccharides (HMOs), which serve as prebiotics to support healthy microbial growth.[17]

Use antibiotics judiciously to minimize overgrowth of harmful pathogens in the gut.[3]

Consider probiotics to help build a balanced population of gut microbes. Evidence suggests that such interventions can reduce intestinal inflammation and lower risk for adverse health outcomes.[18,19] Importantly, giving probiotics to preterm infants can reduce the incidence of NEC. [18]

TAKE-HOME MESSAGES

PRETERM INFANTS CAN HAVE IMPAIRED MATURATION OF GUT MICROBIOTA AND DYSBIOSIS.[2]

1. If sustained, dysbiosis with inflammation may predispose the child to develop serious health consequences.[2,4,5]
2. Dysbiosis and its adverse consequences in preterm infants can now be reduced by using a combination of strategies—human milk feeding, judicious use of antibiotics, and use of probiotics.[3,17-20]

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References: 1. Data on file. Abbott Nutrition. 2020.

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