NEONATAL PROBIOTICS TOOLKIT

NECsociety.org

A resource for clinicians in neonatal intensive care units regarding the use of probiotics, including potential risks, benefits, and other considerations.

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NEC SOCIETY®

NEONATAL PROBIOTICS TOOLKIT

This toolkit is intended as a resource for clinicians in neonatal intensive care units seeking to gain a better understanding of probiotics use in the NICU. **It is not a recommendation for or against the routine use of probiotics in the NICU or for or against the use of any product or preparation.** The information provided may inform a decision-making process and foster discussion amongst key stakeholders specific to your unit.

The decision to initiate routine probiotic administration for preterm infants remains complex. As new evidence becomes available, including data from ongoing clinical trials, we recommend establishing a frequent re-evaluation of literature. The most current evidence available as of the date of publication was used in the development of this toolkit.

The information provided in this toolkit is for educational purposes only and is not a substitute for professional medical advice. If you have a question as to how the information in this toolkit may apply to you or your situation, please consult professional medical advice.

ABOUT US

The NEC Society is a 501(c)(3) nonprofit organization dedicated to building a world without necrotizing enterocolitis (NEC) by advancing research, advocacy, and education. We bring together patient-families, clinicians, and other diverse stakeholders to better understand, treat, and prevent this devastating disease. We are grateful to our Scientific Advisory Council and Key Opinion Leaders for their time and dedication to furthering our mission.

All NEC Society Board, Council, and staff have completed the organization's conflict of interest disclosure. Some members reported financial conflicts, which can be reviewed by contacting jennifer@necsociety.org. All NEC Society statements, actions, and materials are the sole position of the NEC Society and do not necessarily reflect any member's individual institution or place of employment.

This toolkit is dedicated to babies and families affected by necrotizing enterocolitis and all those who care for them.

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THE GUT MICROBIOME

The gut microbiome is a collection of all microbes that live in the intestines and provide protection against pathogens, help develop the immune system, and aid in digestion and energy production.[1] The disruption of the gut microbiome, referred to as intestinal dysbiosis, defines an imbalance of the structure and function of this community of microbes. In neonates, several factors may influence the gut microbiome including gestational age (GA), type of feeding, antibiotic exposure, and the maternal microbiome.[2]

Furthermore, infants born prematurely face several unique environmental factors from stabilization techniques and prolonged hospitalization and the intrinsic conditions of gut and immune system immaturity that are thought to influence the development of their gut microbiome.[3]

NEC DEFINITION

In a 1978 Annals of Surgery article authored by Martin J. Bell et al., a method for clinical staging of necrotizing enterocolitis was proposed. During an 18-month period, 48 infants were classified and treated in a prospective fashion forming the basis for this report nearly five decades ago.

RESOURCE LINK

Bell et al.: Neonatal necrotizing enterocolitis: Therapeutic decisions based upon clinical staging.[4]

Since Bell's initial staging was developed, a number of subsequent definitions have been proposed. Gordon et al. introduced a modified staging to incorporate subsets of Stages II and III in which medical and surgical forms of acquired intestinal disease are tallied at the bedside and revised only if pathology or culture data clearly contradicts that diagnosis.[5] A more recent review by Patel et al. summarized 8 definitions of NEC, including similarities and differences in clinical signs and radiographic findings along with limitations.[6] This review also highlights the importance of a consensus on defining NEC to improve NEC research and outcomes, as well as the important role of patient-families in helping to redefine NEC.

POTENTIALLY BETTER CLINICAL PRACTICES TO HELP PREVENT NEC

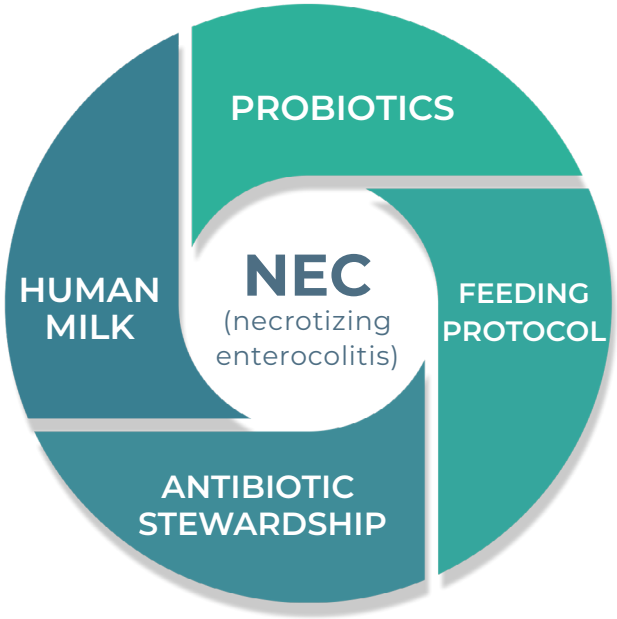
Necrotizing enterocolitis affects approximately 3-9% of infants born prematurely (<37 weeks gestation) each year in the United States.[7] It is the most common disease of the gastrointestinal tract requiring surgery in neonates with a significant morbidity burden on survivors.[8] Abnormal intestinal microbiota has been emphasized as a key component of the multifactorial pathophysiology of NEC.[9]

The mechanisms of NEC pathogenesis are not fully understood. Early NEC research has focused on risk factors such as prematurity, feeding type, intestinal ischemia, and the presence of bacteria.[10-11] Clinical risk factors for NEC include lower gestational age, lower birth weight, small for gestational age, prolonged rupture of membranes, formula feeding, lower oxygen saturation targets, and severe anemia.[12-13] The literature has demonstrated key clinical practices that help to reduce the risk of NEC. For example, human milk, particularly mother's own milk, and standardized feeding protocols have evidence to support reduction in NEC.[13-18]

In addition, prolonged (e.g. > 5 days) early antibiotic exposure has been associated with a higher risk of NEC in multiple studies and antimicrobial stewardship efforts to ensure appropriate antibiotic use is a potentially better practice to reduce the risk of NEC.[19-20] Some studies suggest prolonged antibiotic exposure may increase the risk of NEC[19] and may alter the microbiome[21], although this association has not been seen in all studies.[22]

Ongoing trials are examining approaches to antibiotic use (NaNO trial: NICU Antibiotics and Outcomes Trial), but until the results are available, antimicrobial stewardship efforts on judicious use of antibiotics are recommended.

Centers that are dedicated to reducing or eliminating NEC in their units should consider the various practices that together help to reduce the incidence of NEC.



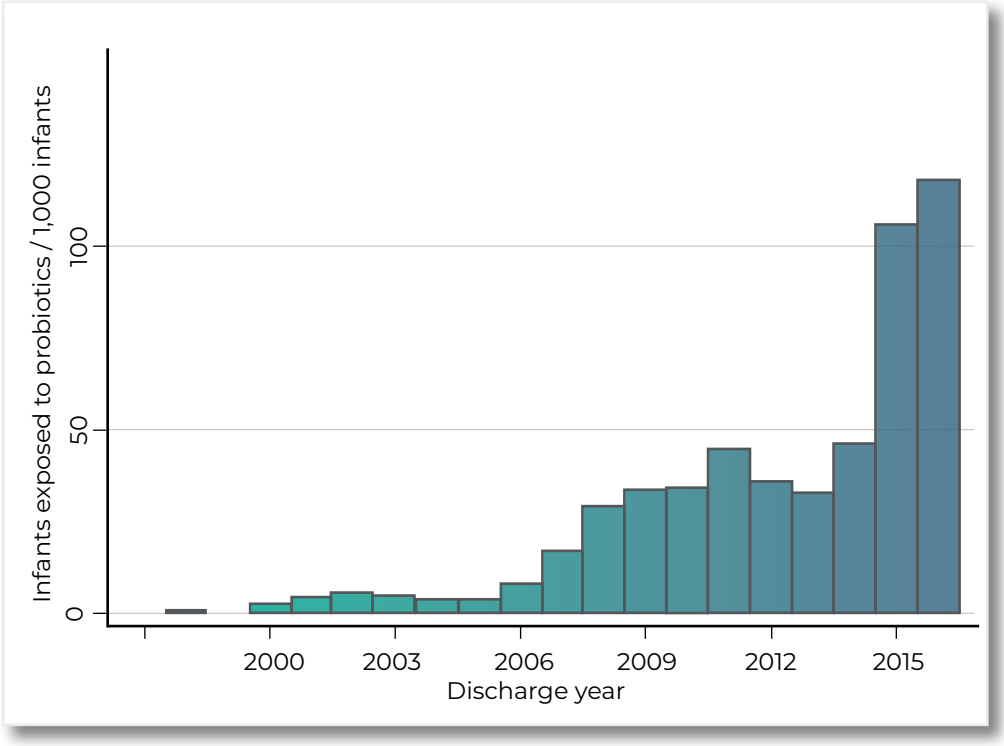
POTENTIALLY BETTER CLINICAL PRACTICES to help prevent NEC

PROBIOTIC USE IN THE NICU

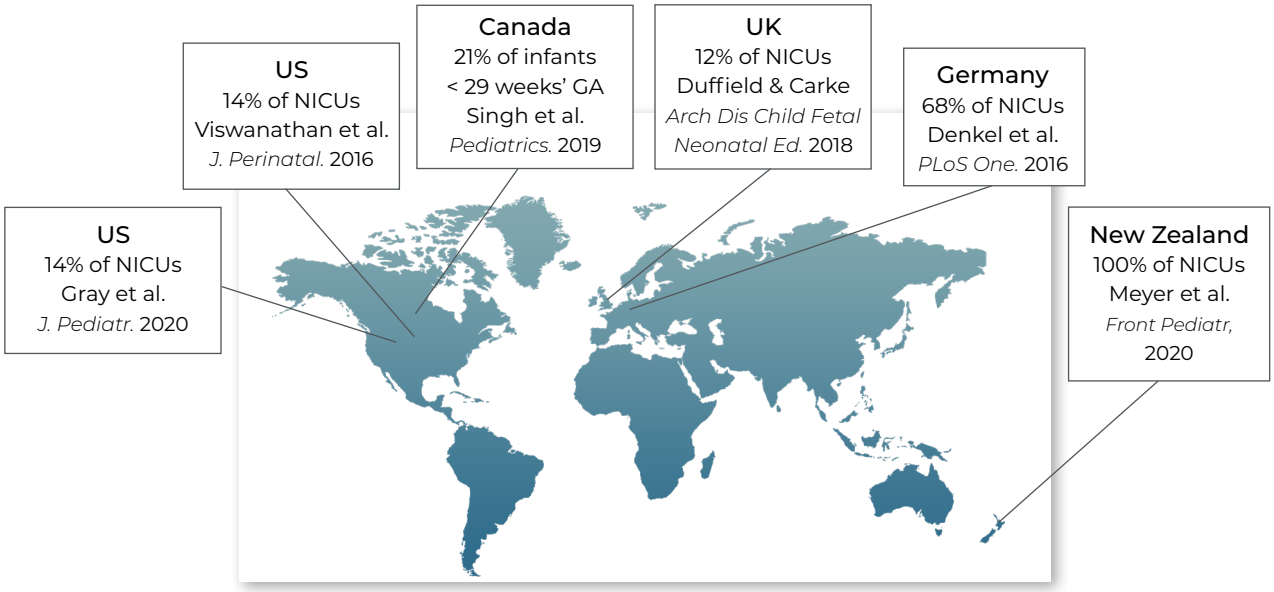
Probiotics are defined as live microorganisms that, when administered in adequate amounts, confer a health benefit on the host.[23] There have been an abundance of observational studies and randomized controlled trials (RCTs) evaluating the effects of probiotics on the risks of NEC, late-onset sepsis, and mortality in preterm infants.[24-30]

Gray et al. studied nearly 20 years of data from over 78,000 infants (23-29 weeks gestation) from 289 NICUs in the United States and found a steady increase in the prevalence of probiotic use.[30] In 1997, at the beginning of the study period, no probiotic use was reported. A small number of NICU sites began probiotic use in 1998–2000, with the greatest increase in use after 2006 and again in 2014.

Viswanathan in 2015 found that 14% of U.S. NICUs (70% response rate) were using probiotics in VLBW infants.[31] The Vermont Oxford Network examined the use of probiotics internationally among VLBW, very preterm infants between 2018-2020 and found European countries had the highest rates (49.1%) while South American countries had the lowest (2.7%).[32] The illustration on the following page provides a summary of additional studies reporting the use of probiotics in neonatal intensive care units around the world.

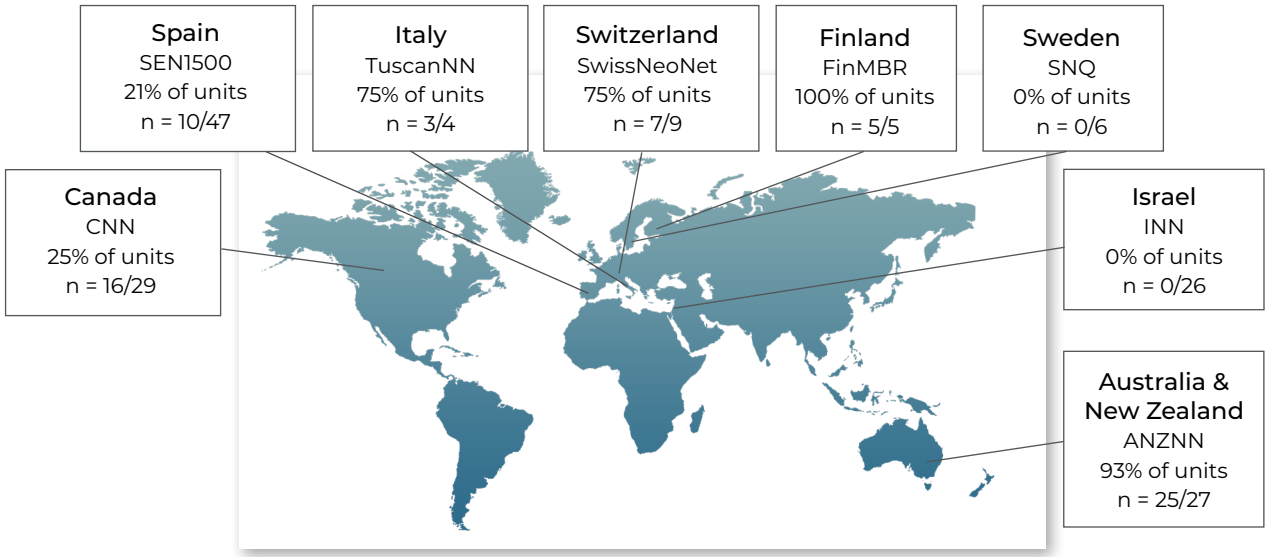


Number of infants exposed to probiotics per 1,000 infants over the study time period in the U.S.: 1997–2016. Reproduced with permission from Gray et al. [30]



Use of probiotics worldwide

Information courtesy Ravi Patel



Use of probiotics in iNeo networks

Information courtesy Ravi Patel

RESOURCES: Human Milk Feeding

Articles

Beyond BFHI: The Spatz 10-Step and Breastfeeding Resource Nurse Model to Improve Human Milk and Breastfeeding Outcomes

CHOP Nurse-Researcher Presents the Spatz 10-Step System as a National Model for Breastfeeding Vulnerable Babies

RESOURCES:
Human Milk Feeding (continued)

NEC-zero recommendations from scoping review of evidence to prevent and foster timely recognition of necrotizing enterocolitis

Promoting Human Milk and Breastfeeding for the Very Low Birth Weight Infant

How to Optimize the Use of Mother's Own Milk in the NICU

Exclusive Maternal Milk Compared With Exclusive Formula on Growth and Health Outcomes in Very-Low-Birthweight Preterm Infants: Phase II of the Pre-B Project and an Evidence Analysis Center Systematic Review

Evidence-Based Methods That Promote Human Milk Feeding of Preterm Infants: An Expert Review

Webinars

Human Milk and the Prevention of Necrotizing Enterocolitis

Pasteurized Donor Milk and the Prevention of Necrotizing Enterocolitis

Donor Milk Advocacy

Other formats

LactaHub by Rush University Medical Center

Human Milk Banking Association of North America

NEC Society donor milk map

Family Educational Materials from the Neonatal Quality Improvement Collaborative of Massachusetts

RESOURCES:
Antibiotic Stewardship

Antimicrobial Stewardship in the Neonatal Intensive Care Unit: An Update

Neonatal ICU antibiotic use trends within an integrated delivery network

RESOURCES: Standardized Feeding Protocols

Impact of Standardised Feeding Regimens on Incidence of Neonatal Necrotising Enterocolitis: A Systematic Review and Meta-Analysis of Observational Studies

NEC-Zero Recommendations from Scoping Review of Evidence to Prevent and Foster Timely Recognition of Necrotizing Enterocolitis

RESOURCES: Feeding Protocol Development

CPQCC Nutrition Toolkit: Nutritional Support of the Very Low Birthweight Infant

Guidelines for Feeding Low Birthweight Infants

Developing a Quality Improvement Feeding Program for NICU Patients

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III

GUIDANCE

IN THIS SECTION

NEC SOCIETY ON PROBIOTICS (2021)

RESOURCE LINK

NEC Society Statement on Probiotics in the NICU

The NEC Society recognizes that there have been numerous randomized controlled trials and observational studies focused on probiotic use in the NICU. However, additional research is still required to:

- Better understand the effectiveness of probiotics in preventing NEC and other outcomes
- Identify whether certain subsets of infants benefit most from probiotics and under what clinical circumstances
- Resolve uncertainties around optimal probiotic strain or combination of strains

Despite these knowledge gaps, NICUs across the United States and elsewhere in the world have implemented the routine use of probiotics as a strategy to reduce the risk of NEC and death at their centers.

It is essential for centers using probiotics or considering use to follow guidelines to ensure consistency in practice. Local data surveillance should be used to assess the impacts of probiotic supplementation on outcomes such as NEC and adverse events such as uncommon infections from the probiotic organism or the rare possibility of contamination of a product.

This statement was developed collaboratively and is supported by 100% of the NEC Society Board, Council, Staff, and Leadership, who unanimously advise:

- Probiotics can be considered as a strategy to help reduce the risks of NEC and death in very low birth weight infants (VLBWs).
- There is a growing awareness of probiotics due to marketing, media coverage, and research. Accordingly, families of VLBWs should be better informed about the potential risks and benefits of probiotic use to prevent NEC and death.
- Clinicians should be prepared to help parents understand their unit's rationale for offering or not offering probiotics in their NICU.
- Detailed implementation and careful data collection are essential to continuously track and understand the effect of probiotic use or the lack thereof.

AMERICAN ACADEMY OF PEDIATRICS (AAP) CLINICAL REPORT (2021)

RESOURCE LINK

AAP Statement: Use of Probiotics in Preterm Infants

In June of 2021, the AAP published a clinical report on the use of probiotics in preterm infants. The stated intentions of the AAP report were to 1.) highlight the differences among available products and the lack of regulatory standards in the US, 2.) outline potential risks associated with routine probiotic use, 3.) provide a review of the evidence, and 4.) emphasize the need for pharmaceutical-grade probiotics with a rigorous evaluation of safety and efficacy.

The report makes 4 summary points: 1.) The lack of a a pharmaceutical-grade probiotic product in the US including less evidence for use in infants <1,000 g; 2.) Centers should discuss the potential risks and benefits of probiotic therapy with parents and develop local guidelines that address probiotic use, including surveillance to assess impacts; 3.) Clinicians should be aware of the manufacturing of probiotics as dietary supplements and risks of contamination; 4.) Centers using probiotics should document outcomes including adverse events.

The NEC Society acknowledges that the AAP report, in summary, does not support the routine universal administration of probiotics to preterm infants, citing the use of different products in diverse settings and populations as well as the lack of availability in the US of an FDA-regulated pharmaceutical-grade product. In December of 2021, the AAP issued a correction to this clinical report, clarifying that probiotics may be classified as a Food for Special Dietary Use (FSDU) and that not all probiotic preparations are categorized as dietary supplements, as previously mentioned in the report.

Per the NCCIH, depending on a probiotic product's intended use, the U.S. Food and Drug Administration (FDA) might regulate it as a dietary supplement, a food ingredient,

or a drug. If a probiotic will be marketed as a drug for treatment, prevention, or mitigation of a disease or disorder, it has to meet stricter requirements. It must be proven safe and effective for its intended use through clinical trials and be approved by the FDA before it can be sold.

CANADIAN PAEDIATRIC SOCIETY POSITION STATEMENT (2022)

RESOURCE LINK

Canadian Paediatric Society: Using probiotics in paediatric populations

The position statement on using probiotics in paediatric populations defines probiotics and reviews the most recent literature on use in pediatric populations. Based on the literature reviewed for this statement, the following recommendations were made:

- There is sufficient evidence to support the use of multi-strain probiotic combinations to lower mortality risk in preterm and low birth weight (LBW) infants with sepsis.

- Probiotics combinations may be of benefit in reducing the incidence of necrotizing enterocolitis (NEC) in preterm neonates >1,000 g, but appears to have no impact on NEC mortality.

EUROPEAN SOCIETY FOR PAEDIATRIC GASTROENTEROLOGY HEPATOLOGY & NUTRITION (ESPGHAN) GUIDANCE (2020)

RESOURCE LINK

ESPGHAN: Probiotics and Preterm Infants

The European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) is a multi-professional organization whose aim is to promote the health of children with special attention to the gastrointestinal tract, liver, and nutritional status. In 2018, the ESPGHAN Working Group for Probiotics and Prebiotics published a strain-specific systematic review and network meta-analysis.

Following this publication, the ESPGHAN Committee on Nutrition and the ESPGHAN Working Group for Probiotics and Prebiotics aimed to develop a document that might serve as a guide for the possible use of probiotics in preterm infants. A writing consensus group convened to support the development of this document and included experts in the fields of neonatology, paediatric gastroenterology, and nutrition. Excerpts:

"The gastrointestinal-related intervention that is both the most safe and efficacious in reducing morbidity and mortality would absolutely be to stimulate the use of unpasteurised own mother's milk. However, especially in NICUs with a high NEC incidence, the use of prophylactic probiotic therapy might be considered as well."

"The panel conditionally recommends that in the clinical setting, the use of a single strain or combination of strains should be practise-based on positive results from well-conducted RCTs (very low certainty of evidence). In research settings, however, it is appropriate to test new strains or new combinations of strains."

AMERICAN GASTROENTEROLOGICAL ASSOCIATION (AGA) CLINICAL PRACTICE GUIDELINES (2020)

RESOURCE LINK

AGA Clinical Practice Guidelines on the Role of Probiotics in the Management of GI Disorders

Following publication of a network meta-analysis on probiotic administration[1], the guideline panel of the AGA published a technical review with the following recommendations[2]:

"The AGA suggests the use of certain probiotic strain or strain combination for the prevention of NEC in preterm infants less than 37 weeks gestational age and low birth weight. Preterm birth is common, affecting 10% of newborns in the United States and 15 million pregnancies worldwide each year. Premature infants have increased risk of mortality and multiple morbidities, including NEC. NEC is the most important gastrointestinal emergency among preterm neonates, characterized by mucosal or even deeper intestinal necrosis of the bowel with common long-term sequelae, including short bowel syndrome and impaired neurodevelopment. Microbiota differs in infants with NEC compared to healthy infants providing a rationale for microbiota-oriented treatments."

..."The overall certainty of evidence across all critical outcomes for probiotics for the prevention of NEC, sepsis and all-cause mortality among preterm, low birth weight infant newborns is moderate/high."

AGA REFERENCES

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WORLD HEALTH ORGANIZATION (WHO) GUIDELINES FOR PRETERM OR LOW BIRTH WEIGHT INFANTS (2022)

RESOURCE LINK

WHO recommendations for care of the preterm or low-birth-weight infant

In 2022, the WHO published a new conditional recommendation that "probiotics may be considered for human-milk-fed very preterm infants (< 32 weeks' gestation) based on moderate-certainty evidence."

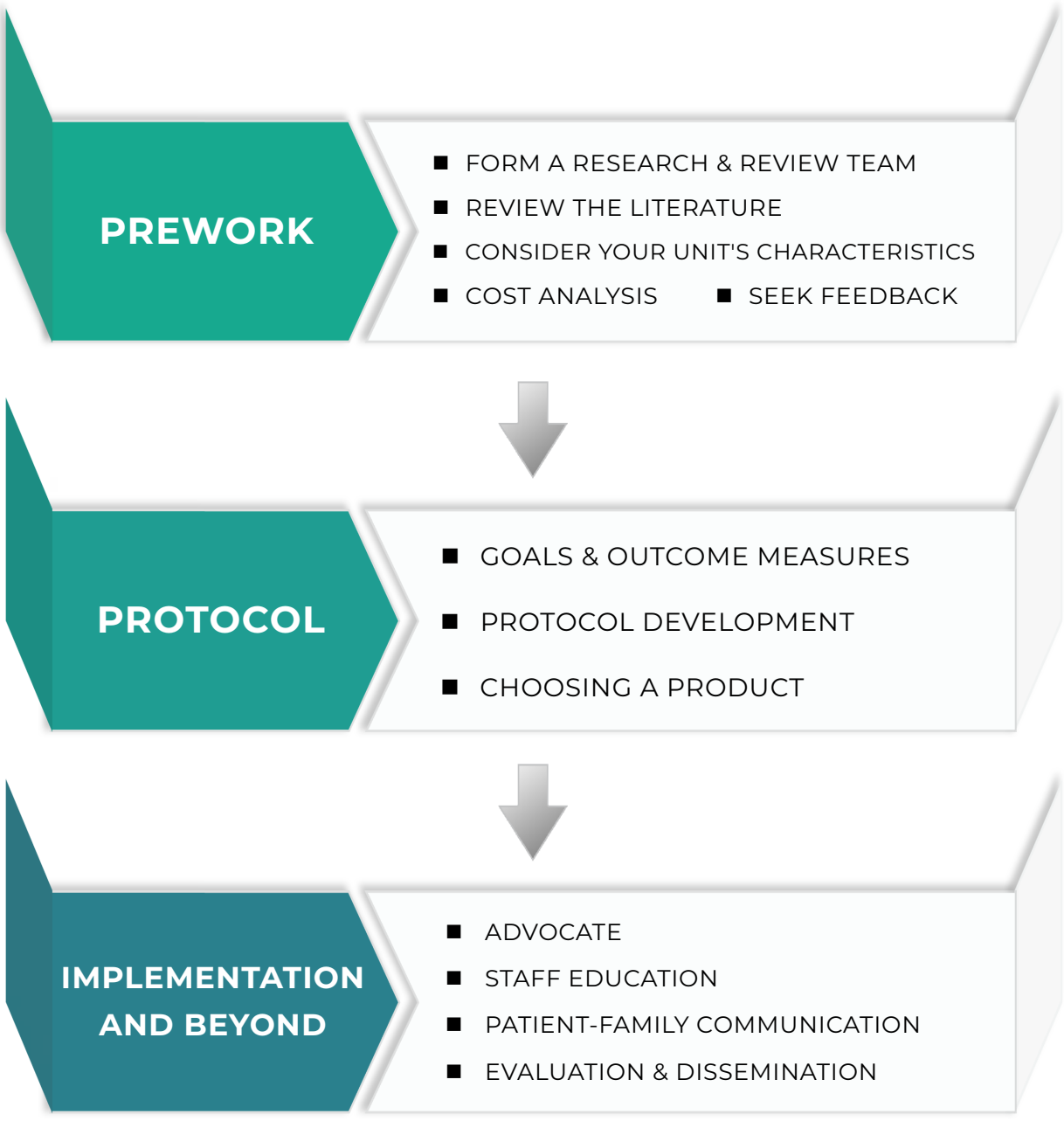
The recommendation was conditional on shared decision-making with parents; this includes informing parents about the benefits and risks and the need for further research. The review added: "The

systematic review about what matters to families about the care of the preterm or LBW infant … reported that families want to be involved in delivering care to infants, and want to take an active role in deciding what interventions are given to infants, including what and how they are fed. A study from the United Kingdom reported that families are willing to consider use of probiotics for their preterm or LBW infants if there is evidence of benefit and safety. There was no other specific evidence available about whether families value probiotic supplements for their preterm or LBW baby or find them acceptable."

The review also "considered that only probiotics especially formulated for preterm or LBW infants that meet regulatory standards should be used, and clear instructions for safe use should be given to health workers."

PROCESS MAP

Consider this sample work flow as you contemplate the use of probiotics in your neonatal intensive care unit.



III

PREWORK

IN THIS SECTION

- FORM A RESEARCH AND REVIEW TEAM
- REVIEW AND DISCUSS CURRENT PROBIOTICS LITERATURE
- ADDITIVE EFFECTS
- SAFETY RISKS AND CONCERNS
- IMPLEMENTATION & MANAGEMENT DECISONS
- CONSIDER YOUR UNIT'S CHARACTERISTICS
- COST ANALYSIS
- SEEK FEEDBACK

There is an abundance of literature on probiotic use spanning decades. Despite limited evidence-based approaches supported by data from clinical trials to reduce NEC incidence, probiotics may warrant consideration as a currently available and effective therapy to help reduce NEC rates.

FORM A RESEARCH AND REVIEW TEAM

Regardless of whether your unit decides to implement routine use of probiotics, an in-depth analysis and thorough decision-making process are essential. We encourage you to establish a research and review team of multidisciplinary members who can use this toolkit as a guide through the decision-making process.

Consider including a physician, neonatal nurse practitioner, bedside nurse, nurse educator/manager, dietitian, pharmacist, infection control specialist, unit or hospital leadership, and a member of your unit's Family Advisory Council. Document and maintain records of your team's discussions (e.g. meeting minutes). Transparency about decisions, reasoning, and supporting evidence, will foster confidence in your care team and ensure consistent communication with patient-families.

REVIEW AND DISCUSS CURRENT PROBIOTICS LITERATURE

RESOURCE LINK

Cochrane Review: Probiotics to prevent necrotising enterocolitis in very preterm or very low birth weight infants[1]

A 2020 Cochrane systematic review and meta-analysis by Sharif et al. of 56 RCTs involving 10,812 infants, mostly very preterm (<32 weeks gestation) and VLBW (<1,500 gm BW), concluded that probiotics may reduce the risk of NEC, mortality, and late-onset sepsis, although the GRADE certainty of evidence was low for NEC and moderate for mortality and late-onset sepsis.

The average birth weight among participants was 1,000 gm to 1,200 gm, and average gestation at birth was 28 to 32 weeks. Few trials provided data for extremely preterm infants (< 28 weeks gestation) and ELBW (< 1,000 gm BW), and these analyses did not show effects on necrotizing enterocolitis, death, and serious infection. Limitations of the studies described in this systematic review led to a low certainty GRADE rating for NEC due to risk of bias due to trial design and possible publication bias.

In a sensitivity analysis of a subset of 16 RCTs meeting the Cochrane criteria for low risk of bias, the relative risk (RR) of NEC was 0.70 (95% CI 0.55-0.89), comparing probiotic administration to control. Although trials differ in product combinations and strains, methodology, dosing strategies, study population, duration of treatment, and type of feeding, statistical heterogeneity was low for NEC (25%), mortality (0%), and late-onset sepsis (8%). In subgroup analyses for NEC comparing trials reporting infant diets (e.g. human milk, formula only, mixed diets), there was no significant difference depending on the type of enteral feed (P=0.15).

The Cochrane meta-analysis evaluated 51 studies (n=10,170) and reported probiotic supplementation resulted in a statistically significant risk reduction in all-cause mortality (RR 0.76; 95% CI 0.65-0.89, NNTB 50 (CI 50-100), moderate certainty evidence).

Forty-seven studies (n=9,762) were evaluated and reported probiotic supplementation resulted in a lower risk of invasive infection (RR 0.89; 95% CI 0.82-0.97, NNTB 50 (CI 33-100), moderate certainty of evidence). Five studies (n=1,518) for severe neurodevelopmental impairment at 18 months to 3 years and found no significant differences (RR 1.03; 95% CI 0.84-1.26, low certainty evidence).

RESOURCE LINK

Prophylactic Probiotic Supplementation for Preterm Neonates—A Systematic Review and Meta-Analysis of Nonrandomized Studies[2]

Multiple cohort studies have evaluated the association between routine use of probiotic supplementation and neonatal outcomes. In a systematic review of 30 studies of 77,018 preterm infants from 18 countries, routine probiotic supplementation was associated with a lower risk of NEC ≥ Stage II (OR 0.60; 95% CI 0.50-0.73), all-cause

mortality (OR 0.77; 95% CI 0.68-0.88) and late-onset sepsis (OR 0.85; 95% CI 0.74-0.97). These data are consistent with the effects observed in the randomized trials, including the aforementioned Cochrane review.

RESOURCE LINK

Patel & Underwood: Probiotics and necrotizing enterocolitis[3]

RESOURCE LINK

Blog Post: Probiotics to Prevent Necrotizing Enterocolitis: Moving to Evidence-Based Use

Patel and Underwood summarized existing evidence in a thorough review of mechanisms of probiotic action, randomized controlled trials, observational studies, and commercial probiotic preparations.

Although there is substantial heterogeneity in study design, this meta-analysis evaluating treatment effects of probiotics on NEC revealed a number of individual studies showing statistically significant effects in the reduction of NEC, while no studies showed an increase in NEC.

RESOURCE LINK

Gray et al.: Probiotic Use and Safety in the Neonatal Intensive Care Unit: A Matched Cohort Study[4]

Gray et al. performed a multicenter, matched cohort study of infants born at 23-29 wks gestational age in 289 NICU's from 1997-2016. Of the more than 75,000 infants evaluated, 4.6% received probiotics. Probiotic use increased throughout the study period and was associated with decreased odds of NEC and death. NEC was defined as Bell Stage II or higher (medical and surgical NEC).

Results showed infants exposed to probiotics had significantly lower odds of any NEC ($p<0.001$) compared with unexposed infants. The odds of death were lower in infants exposed to probiotics ($p<0.001$) and the odds of Candida infection were higher in infants exposed to probiotics ($p=0.004$). There was no significant association between probiotics exposure and surgical NEC ($p=0.32$), bloodstream infection ($p=0.14$), or meningitis ($p=0.76$).

There was a lack of consensus on which strains or products to use. Probiotic treatment varied widely by site depending upon the study population, duration of treatment, and dosing.

RESOURCE LINK

Caplan et al.: Necrotizing Enterocolitis: Using Regulatory Science and Drug Development to Improve Outcomes[5]

Caplan et al. identified randomized controlled trials and recent systematic reviews that evaluated probiotics in neonates and included outcome assessment of NEC. A total of 46 RCTs with over 12,000 infants were identified for inclusion in an analysis revealing inconsistent information on probiotics used, concerns about probiotic quality control, and included potential confounders.

This study also revealed significant variations in baseline NEC rates (0-18%), extent of exposure to human milk, and dosage of probiotics used. Highlighted here is the disagreement globally as to whether probiotics should be used to prevent NEC in preterm babies, and its routine usage as standard of care practice.

Determining the appropriate sample size for dosage-based studies with NEC as the primary outcome is challenging. There are still many questions central to patient safety such as dosing, selection of the strain, and balance between efficacy and safety outcomes. High-quality studies involving pharmaceutical-grade products with large sample sizes are lacking.

RESOURCE LINK

Probiotics in Preterm Infants (PiPs) Study Collaborative[6]

The Probiotics in Preterm Infants (PiPs) Study Collaborative assessed the safety and efficacy of a single strain probiotic (probiotic vs placebo) in over 1300 infants (23-30+6 weeks gestation) in intensive care units in the UK. Primary outcomes included bloodstream infection, NEC Bell Stage II or III, and death before discharge. No difference was found in the primary outcomes and routine use of probiotics in this population was not recommended.

RESOURCE LINK

The ProPrems trial: investigating the effects of probiotics on late onset sepsis in very preterm infants[7]

RESOURCE LINK

Jacobs et al.: Probiotic effects on late-onset sepsis in very preterm infants: a randomized controlled trial[8]

The ProPrems trial recruited and randomized 1,100 infants from 12 perinatal centers in Australia and New Zealand and which, while failing to find evidence of benefit for either sepsis or mortality, did show a protective effect for NEC (2.0% active intervention group vs. 4.4% placebo group). The primary aim of this study was to determine the effect of probiotic organisms in VLBW infants less than 32 weeks gestation at birth on the incidence of late onset sepsis. Necrotizing enterocolitis (Bell Stage II or higher) was considered a secondary outcome.

In a subsequent analysis by Jacbos et al, a statistically significant reduction in NEC Bell stage II+ (p=.03) was found in the probiotic group (n=11) as compared to the control group (n=24). The absolute NEC rate reduction for the probiotic group was 2.4% from the control group rate of 4.4%. The study was not powered to detect a difference by birth weight or gestational age and therefore the data must be interpreted with caution.

WEBINAR LINKS

Probiotics and the Prevention of NEC, Death, and Sepsis

Experiences of Centers Routinely Using Probiotics

Probiotics in the NICU: Considerations Before Routine Use

RESOURCE LINK

Benefits of probiotics on enteral nutrition in preterm neonates: a systematic review.[9]

RESOURCE LINK

Effects of Probiotics on Necrotizing Enterocolitis, Sepsis...in Very Preterm Infants: A Meta-Analysis[10]

A meta-analysis of 19 RCTs (4,527 preterm infants; <2,500 g BW) found shorter time to full enteral feeds with probiotic administration, while a separate analysis of 15 RCTs (3,751 very preterm infants; <1,500 gm BW) found no difference in weight gain.

RESOURCE LINK

Upadhyay et al.: Effect of prebiotic and probiotic supplementation on neurodevelopment in preterm very low birth weight infants: findings from a meta-analysis[11]

Upadhyay et al. summarized results of RCTs in preterm infants <1,500 gms that evaluated the effect of pre and/or probiotics on neurodevelopmental outcomes at 18-22 months corrected age. No significant differences were found in risk of cognitive and motor impairment, cerebral palsy, or visual and hearing impairment (low quality of evidence).

RESOURCE LINK

Association of Hospital Adoption of Probiotics With Outcomes Among Neonates With Very Low Birth Weight[12]

The recent summary of the VON data from 807 U.S. NICUs including more than 300,000 preterm VLBW infants is a thoughtfully presented example of the value of ongoing data collection and analysis. This cohort study adopted statistical approaches to minimize potential confounding and found that the incidence of NEC decreased by 18% at probiotic-adopting NICUs compared with trends at non-adopting NICUs (OR 0.82, 95% CI 0.70-0.95, p=0.01). Similar analyses of other moderate to large data sets would be valuable.

ADDITIVE EFFECTS

A prebiotic is a dietary supplement that stimulates the growth of commensal microbes; the ideal prebiotic would stimulate growth of healthy microbes but not pathogens. Unpasteurized mother's own milk is perhaps as close to the ideal prebiotic as any available product.

Studies of combinations of probiotics and prebiotics have shown benefit in reducing NEC[13] and some studies have demonstrated greater benefit of probiotics in preterm infants receiving their mother's own milk[14], although the aforementioned Cochrane review did not show clear subgroup differences.

SAFETY RISKS AND CONCERNS

Concerns regarding the use of probiotics include potential interference with detecting undesirable organisms, inadvertent cross-contamination, lack of an FDA-regulated pharmaceutical grade product, and organism-related sepsis. As

mentioned, probiotics in the United States are typically regulated as food supplements rather than pharmaceutical products, and are not subject to the same FDA regulatory standards required for medications. Thus, the record of demonstrated safety, purity, or potency may vary by product and is not the same as it would be for an FDA approved pharmaceutical. The references provided below are only a starting point. We encourage a thorough review and discussion of a risk/benefit analysis among your team and a review of data from specific product manufacturers.

RESOURCE LINK

Impact of probiotics on necrotizing enterocolitis[15]

In a review of over 35 randomized controlled trials and 11 cohort studies on probiotic treatment for premature infants, the risks and drawbacks of administration of probiotics were summarized into four categories: sepsis, contamination of product, lack of ingredient/strain label regulation, and cross-colonization among infants not receiving probiotics. Reported adverse events associated with probiotics use for NEC reduction are rare.

RESOURCE LINK

Probiotics and Preterm Infants: A Position Paper by the ESPGHAN...[16]

Probiotics may contribute to certain side effects in the infant population. These include systemic infections, metabolic changes, and gastrointestinal symptoms. Most of the trials done on preterm infants and probiotic use, however, did not fully monitor or report side effects. Probiotic bacteremia may occur because of intestinal translocation or contamination from probiotic preparation and related handling. Especially if probiotics are prepared in the unit in an uncontrolled environment, probiotic spills and contamination may occur to other surface areas, medications, or intravenous catheter sites. Furthermore, cross colonization to other infants in the NICU could occur.

RESOURCE LINK

Probiotic sepsis in preterm neonates-a systematic review. [17]

In a systematic review of probiotic-associated sepsis (1,569 studies), 16 reports (none from randomized trials, 1 non-randomized trial, 8 case-series and 7 case-reports) involving 32 preterm infants were summarized. Bifidobacterium (N = 19), Lactobacillus (N = 10), and Saccharomyces (N = 3) were isolated organisms with 25 of 32 cases confirmed to be due to the administered probiotic strain on full genomic analysis.

RESOURCE LINK

Infant and Pediatric Feedings Guidelines for Preparation of Human Milk and Formula...[18]

There is an increased risk of cross-contamination when probiotic supplements or probiotic-containing formulas are mixed or handled at the bedside, posing an increased risk of sepsis. Careful adherence to aseptic technique and limiting exposure to other feedings will reduce the risk of inadvertent contamination. It is imperative to follow safe handling practices, as recommended by the product manufacturer, to minimize risks.

It is sensible practice to avoid intravenous line access/care or intravenous medication administration at times when probiotics are being administered.

IMPLEMENTATION & MANAGEMENT DECISIONS

Decide who will manage and implement the policy/procedure (pharmacy, nutrition, nursing) and consider what is feasible.

A. Will the probiotic be considered as a milk additive (nutrition) or medication (pharmacy)?

B. If nutrition will own, determine the process for adding the product to your formulary. If your pharmacy will dose and deliver, do you have an in-unit pharmacy or will the product come from a centralized pharmacy? Determine the process for your pharmacy to obtain and deliver the product.

CONSIDER YOUR UNIT'S CHARACTERISTICS

A. Consider if the probiotic will be stored in the feeding preparation room, pharmacy or other location and who will handle or deliver the product to reduce errors. RESOURCE: Technician Training Reduces Formula Preparation Error[19]

Does your unit have the storage space for probiotics? Determine if cold chain storage and monitoring are required. Refer to manufacturers' recommendations for storage. Some are stored at room temperature while some must be stored in the refrigerator or freezer.

B. Consider whether the probiotics preparation is packaged in a single-use container, a bulk container, and how the product is intended to be administered to the infant, including whether, how, and where it may need to be mixed into milk, formula, or sterile water. Adopt clear, written methodologies and training intended to reduce the possibility of contamination and cross-contamination at each point in the process from receipt of the product, through storage of the product, and to administration to the infant.

C. Both environmental factors and healthcare workers' hand hygiene are contributory factors in the genesis and existence of cross colonization of probiotic use.[20] The Infant and Pediatric Feedings Guidelines for Preparation of Human Milk and Formula in Health Care Facilities, recommends providing a separate, designated feeding room for the preparation and handling of human milk and formula. Careful adherence to aseptic technique and limiting exposure of other feedings to probiotic ingredients will reduce the risk of inadvertent contamination of infant feedings.[18] Published best practices (AND, ASPEN, NANN, HMBANA) emphasize the importance of preparation

location, specialty trained staff, and proper identification of human milk and additives.

D. Do you use barcoding for labeling of human milk and/or formula in your NICU?[21] If administered through the nutrition room, will barcoding be available/needed for the probiotic products? RESOURCE: Barcode scanning eliminates breast milk misadministration

E. In some trials (PiPS, ProPrems), it was observed that colonization of the gut with the probiotics that confers the intended benefits of probiotics was not restricted to the intervention group who received the probiotics but occurred in a significant extent in the control group neonates, as well. This may have explained the diminished effect of probiotics in the PiPS trial, but also highlights the potential for effects on gut colonization in the unit. Whether this colonization provides benefit or harm to other non-treated infants is not known at this time.

COST ANALYSIS

Consider a cost analysis and support for adding to the budget.

RESOURCES: COST ANALYSIS

Cost-effectiveness of probiotics for necrotizing enterocolitis prevention in very low birth weight infants[22]

The cost-effectiveness of using banked donor milk in the neonatal intensive care unit: prevention of necrotizing enterocolitis[23]

Cost and Cost-Effectiveness of Donor Human Milk to Prevent Necrotizing Enterocolitis: Systematic Review[24]

SEEK FEEDBACK

Ask for feedback from your medical care team and your Family Advisory Council for their perspective on probiotic use. Discuss the research and review process and provide a summary statement with support and rationale for considering routine probiotic use.

RESOURCES: FAMILY ADVISORY COUNCILS

Institute for Patient- and Family-Centered Care

Building an Effective Family Advisory Council

Consult with other centers of similar size and level of care that use probiotics. The NEC Society is developing a map of US centers using probiotics to foster collaboration.

Consider consulting hospital legal team for guidance on obtaining parent/guardian consent. The NEC Society recommends that NICUs provide written information to parents about their unit's decision to provide/not provide probiotics. As with any potential intervention, the NEC Society recommends that NICUs evaluate whether there is a need to obtain consent or assent when administering probiotics consistent with their standard of care and as evidence continues to develop regarding the benefits and potential risks of probiotics. Consider how consent and information for other care is provided (e.g. donor human milk) and how this may be integrated or consolidated with other guidance.

Consult your hospital (or local) microbiologist when deciding what available products and strain(s) to use, and confirm the ability to lab test for organism specific sepsis. The microbiologist and pharmacist should discuss the considerations for routine antibiotic coverage and treatment of probiotic sepsis. A microbiologist can share any concerns and help perform monitoring for safety as recommended in the AAP statement. For example, this could involve review of blood cultures to identify if any are positive for the probiotic bacteria supplemented

Consult with IT on how to add products to your computerized ordering entry system.

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III

PROTOCOL

IN THIS SECTION

GOALS & OUTCOME MEASURES

If your center has decided to implement the use of routine probiotics, the first step is to set goals and desired outcome measures for the intervention time period. Goals should be specific, measurable, attainable, relevant, and time-sensitive (SMART).

Example: Primary Outcome

By implementing a routine probiotic supplementation protocol in very low birthweight infants, we aim to decrease our medical NEC rate by 50% (from baseline 6% to 3%) over three years. Timeline: July 1, 2023 to June 30, 2026.

Consider the reasons stated in your research and review process when writing these goals and outcome measures. Document all baseline information and determine the time points in which evaluation will occur during the implementation period (i.e. quarterly, bi-annually).

For many centers, the relatively low incidence of NEC and number of supplemented infants (e.g. very low birth weight infants) would support evaluation at quarterly or bi-annual intervals, with a goal to have a minimum denominator size of ~20 infants (e.g. if you have 80 infants per year, quarterly evaluation is reasonable; if your unit has 40 infants per year, bi-annual evaluation should be considered). This will reduce common cause variation in the outcome measure of NEC due to shorter evaluation windows. However, shorter intervals such as monthly should be considered, including time-between event measures as NEC incidence becomes more infrequent.

To detect a reduction in NEC, special cause rules can help to differentiate between a chance increase or decline (common cause variation) and actual change (special cause change). A common rule in improvement science is to have 6-8 data-points below the baseline NEC incidence. For example, if your baseline risk of NEC is 6%, 6 to 8 periods (e.g. quarterly NEC rates) below this would indicate a significant change in a unit's NEC rate. This is important, because short periods of evaluation or few infants per evaluation period may suggest probiotics are not having an effect, when the data likely just reflect common cause variation. Examples of special cause reductions in NEC reported by centers following introduction of probiotics can be found in reports by Rolnitsky et al. and Sekhon et al. as we have highlighted below.

EXAMPLE: Goals & Outcome Measures

A Quality Improvement Intervention to Reduce Necrotizing Enterocolitis in premature infants with Probiotic Supplementation[1]

A quality improvement project done by Rolnitsky et al. aimed to reduce NEC by 30% in a 42-bed NICU by using the following measures:

Primary outcome measures were as follows:

1. Severe NEC rates in infants <33 weeks: for a definition, radiologic diagnosis or surgical diagnosis at laparotomy of Bell's stage 2 or above, was used.
2. Sepsis rates: defined as any positive blood culture.
3. Death before discharge home: defined as mortality in our center or the surgical referral center.

Secondary outcome measures were as follows:

1. Total days NPO, defined as holding feeding for >15 hours, per patient.
2. Growth—weight change per week, as calculated at NICU discharge.
3. Days on antibiotics after the initial 48 hours—total days for a patient.
4. Days on intravenous parenteral nutrition (TPN)—total days for a patient on at least partial intravenous nutrition.

Balancing measures were as follows:

1. Sepsis workups: defined as the drawing of a blood culture after the second day of life. We tracked the number of workups per patient.
2. Feeding intolerance: defined as an event leading to a failure to advance or maintain the unit's feeding protocol (including skipped feed, changes in feeding advancements, or reduction of feed volume). The site monitored the number of episodes per patient and sepsis rates, as defined above.
3. Infections for specific detection of the probiotic agent.

Process measures were as follows:

1. Probiotic supplementation compliance rates—percent of patients who received probiotics from the first day of life or admission.
2. Days on probiotics: percent of hospital stay when the infants received the probiotic product.

Other factors to consider documenting before implementation: average patient census, VLBW census, LOS, and transfers. Also note when any NICU protocol changes occur after probiotic administration is started. Once this information has been assessed and documented, it is time to choose a product and develop a protocol.

PROTOCOL DEVELOPMENT

Inclusion/Exclusion Criteria

Most trials have focused on VLBW infants. Here are some examples of implementation projects to consider as a guide when establishing your inclusion and exclusion criteria.

EXAMPLE: Inclusion/Exclusion criteria to consider

- Born <33 weeks GA or BW< 1,500g
- ≥24 weeks PMA
- At least 72 hr of age
- Tolerating ≥ 6 ml/day enteral feeds for 24 hr
- No lethal anomalies or significant GI anomalies
- Discontinue at 36 weeks CGA, if ever NPO, or ordered D/C by medical provider
- Re-start criteria: if NPO for NEC, restart once the patient is receiving 100 ml/kg/day enteral feeds. If NPO for non-NEC, restart once enteral feeds are resumed.

RESOURCE

Implementation of a probiotic protocol to reduce rates of necrotizing enterocolitis[2]

RESOURCE

Practical Considerations for Probiotics in the NICU

CHOOSING A PRODUCT

One of the most important decisions involved in the use of probiotics to help prevent NEC is product choice. Viswanathan reported that 16 different commercial products were used in 44 NICUs in 2015, as reported by a phone survey.[3-4] There is no data or regulatory approval to support the superiority of a single probiotic strain and/or product. Teams should consider a variety of factors including purity and numbers of viable organisms, whether specific strains have been shown to be effective in NEC prevention, whether a product is recommended for use in the NICU, and ease of administration in your NICU.

Information should also be obtained and reviewed from the product manufacturers. We recommend consulting a microbiologist within your institution, a local university, or your state health department when determining which product to use.

RESOURCES

Articles providing information on specific probiotic products:

Chang HY, Chen JH, Chang JH, Lin HC, Lin CY, Peng CC. Multiple strains probiotics appear to be the most effective probiotics in the prevention of necrotizing enterocolitis and mortality: An updated meta-analysis. PLoS One. 2017;12(2):e0171579. doi:10.1371/journal.pone.0171579

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SAMPLE PROTOCOLS

These sample protocols are provided for reference only. Institution and product names have been removed. Specific guidelines for probiotic administration have not been published. Refer to manufacturer's guidelines for use in unit protocol development.

SAMPLE PROTOCOL #1

(for reference only)

GUIDELINES FOR USE

Inclusion criteria (must meet both):

Birth weight <1,500 grams and
Estimated gestational age <34 weeks at birth

Exclusion criteria:

Congenital gastrointestinal abnormality (omphalocele, gastroschisis, bowel atresia, etc.)
Other reasons at the discretion of the attending physician with documentation in the medical record

Dosing and administration of probiotic:

Initiation: Begin treatment once infant receiving any feeding

Dosing: 5 drops to be given once daily

Administration and preparation: Pharmacy will provide a prepared syringe. Give full syringe contents by NG/OG before feeding. If taking all feeds by mouth, may instead add 5 drops to milk feeding after warmed.

Care: Use gloves at all times and wash hands before and after preparation/administration of probiotics. Do not touch or access vascular access devices (PICC, UVC, PIVs) during times of probiotic administration. Discard syringe immediately after administration. If fluid from syringe spills, decontaminate surfaces in contact with hospital-grade wipes.

- Probiotic therapy should be continued until the infant reaches 35 0/7 weeks postmenstrual (corrected) age
- Therapy may be continued for a longer duration at the discretion of the treating neonatologist
- Probiotic therapy should be held while infant is NPO and restarted as soon as feedings reinitiated
- Families will be provided with an information sheet

SAMPLE PROTOCOL #2

(for reference only)

Eligible patients:

All preterm infants born at less than 32 completed weeks gestation or with birth weight less than 1,500 grams after tolerating 24 hours of trophic feeds. Probiotics will be administered to all multiple gestation infants in cases of discordant eligibility.

Exclusions:

Critical illness with concern for compromised gut integrity
Infants with suspected or confirmed severe immunodeficiency (e.g. SCID)
Infants with known lethal conditions in whom no aggressive intervention is planned/ comfort care
Nothing by mouth (NPO) status

Dose

1 tablet, dissolved in 2-3 mL sterile water, once daily.

Duration

Supplementation to continue until 36 weeks corrected gestational age or at discharge, whichever is earlier.

Administration

Follow institutional guidelines and unit routines for compliance with medication administration requirements and standards. Remove tablet from overwrap, shake or stir vigorously using a closed container or syringe in 2-3 mL* of sterile water for about two minutes or until completely dissolved. Administer immediately. May mix with feed, if needed. Administer slowly. Promptly clean any spills.
*Anecdotal data supports dissolution of product in as little as 2 mL of liquid. Product labeling supports a minimum volume of 3 mL.

Discontinuation of Therapy

Discontinue if NPO status, concern for compromised gut integrity, diagnosis of ileus, or NEC.
Antibiotic therapy is not a contraindication to probiotic supplementation.

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III

IMPLEMENTATION & BEYOND

IN THIS SECTION

ADVOCATE

Consider this checklist for pursuing approval from hospital administration:

SAMPLE CHECKLIST

PREPARING FOR IMPLEMENTATION

- ☐ Identify 2-3 unit champions (or more depending on unit size) who will provide guidance and support during implementation
- ☐ Write a summary report for dissemination to key groups
- ☐ Present and receive feedback from your Family Advisory Council
- ☐ Provide rationale and cost/budget for probiotic chosen
- ☐ Explain consent process and gain approval
- ☐ Present at Grand Rounds

STAFF EDUCATION

For successful implementation and sustainability of any practice or process change in the NICU it is important to ensure the following:

1. Multidisciplinary leadership is in support of the change and the reasoning behind it. In addition to the medical director and physicians, integrate leadership from nursing, nutrition, and pharmacy.

2. There is a dedicated person responsible for allocating and providing resources for nursing/staff education.

3. Multidisciplinary champions who can be known as unit leaders to help answer questions related to the product and the policy/procedure have been identified.

4. A variety of educational formats are used, such as newsletters, visual aids, reference cards, learning boards, pre/post test, informational meetings, huddle reminders, online learning modules/forms, small or large group training with return demonstration and sign off.

5. Fidelity of implementation/standardization of the change, including competency assessment at regular intervals.

6. A work culture where nurses feel comfortable providing honest feedback about the implementation process.

7. Plan, Do, Study, Act (PDSA) cycles are used for evaluation and to improve the process with disseminated results and plans for change when needed.

8. Visual aids are used to show improvement such as graphs and success stories.

- Courtesy of Jenny Quinn, PhD, APRN, NNP-BC, Neonatal Nurse Practitioner, Department of Pediatrics, NorthBay Medical Center
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PATIENT-FAMILY COMMUNICATION

Patient-centered care is essential to optimizing outcomes for infants and families. It is critical for parents to be informed and to be engaged in the decision-making process regarding their child's care. Clinicians and families should work together when considering acceptable risks or benefits of treatment options.

After a thorough review and evaluation process clinicians are encouraged to share the evidence and rationale that led to your center's decision with patient-families. Probiotics and the reasons for implementing or not implementing routine use should be discussed during prenatal consultations for those at high risk of premature birth, and written information should be provided as part of the NICU admission packet.

From ESPGHAN Recommendation: "Because of all of these potential safety and quality issues, we suggest that if a NICU is

implementing probiotics as part of standard care, parents must be actively informed. Communication on the potential benefits and risks of probiotic administration is best undertaken face to face and supplemented with the use of written materials appropriate to the local context."

Your patient-family advisory council should review and provide feedback on your unit's educational and informational resources.

RESOURCES FOR PATIENT-FAMILY COMMUNICATION

Probiotics Handouts:

Probiotics Information sheet for families

NEC Society Probiotics Statement

Other NEC Society Resources:

"What is NEC?" handout for families

"Parents are Care Partners" printable poster

"10 Things to Know When Your Baby Is Diagnosed with NEC" handout for families

"10 Things for Bereaved Parents to Know" handout for families

Patient-families should be informed about probiotics and your unit's rationale for using or not using them. The following are sample questions your patient-families may ask you.

Your team should be prepared to respond thoughtfully to these questions:

- Will my baby receive probiotics? Can you help me understand why/why not?
- What are the risks/benefits of probiotics?
- Are probiotics more helpful to some babies than others?
- When it comes to probiotic use, what are other local NICUs doing?

For units not using probiotics:

- What are you doing to lower my child's risk of developing NEC?
- Can you help me understand how/why the unit has decided against probiotic use?

For units using probiotics:

- Can you help me understand how/why the unit has decided to use probiotics?
- How will the probiotics be given?
- How long will my baby receive probiotics?
- What signs or symptoms show intolerance?
- Can we stop the probiotics after they are started if s/he isn't tolerating them?
- What are the criteria for stopping probiotics?

Probiotics & Necrotizing Enterocolitis

What Parents Should Know

What is necrotizing enterocolitis (NEC?)

Necrotizing enterocolitis (NEC) is a life-threatening intestinal condition that mostly occurs in premature infants, usually between 2 and 8 weeks of age. Full-term infants with health complications such as congenital heart disease are also at an increased risk of NEC. NEC causes an inflammatory process that can lead to intestinal tissue damage and even death. Many infants with NEC require surgery to remove diseased bowel. NEC survivors may experience long-term problems with cognition, behavior, muscle function, and poor intestinal function.

How can we reduce the risks of NEC?

- Breast milk from the baby's mother/parent is the most important way to help reduce NEC risk.
- If mother's milk is unavailable, pasteurized donor milk is the next best option for premature infants.
- Giving probiotics to premature babies, along with breast milk, may reduce the risk of NEC.

What are probiotics?

Probiotics are live microorganisms that, when given in adequate amounts, provide a health benefit to the individual. Probiotics are identified by a genus, species and strain designation, and different strains of even the same species may have different effects. Probiotics support the development of your baby's gut microbiome, which is an important means to maintain gut health.

What do studies show about probiotics and NEC?

When given to premature infants, certain probiotics may reduce the risk of NEC, infections and even death. There is no data or regulatory approval to support the superiority of a single probiotic strain or product.

What are the risks of giving my baby probiotics?

There are risks and benefits to every treatment. Based on scientific studies, it appears that the benefits of probiotic administration may outweigh potential risks. Potential risks include bacterial infection (sepsis), contamination of product, lack of ingredient/strain label regulation, and cross-colonization among infants not receiving probiotics. However, reported adverse events associated with probiotics use for NEC reduction are rare. Talk to your baby's care team about all potential benefits and risks.

How can parents with an infant at risk of NEC advocate for their child?

- Ask your child's physician about the NICU's policy and why they do or do not use probiotics.
- You are an important part of your baby's care team. Ask questions and share your thoughts.
- Learn more about necrotizing enterocolitis at **NECsociety.org**

NEC SOCIETY®

Click **here** for printable version of this info sheet

EVALUATION

The evaluation team should consist of the same members (all or some) as the research and review team. Not all members need to participate in the evaluation process, however we recommend regular convening of the team for discussion of evaluation markers.

For evaluation, consider the following:

- Primary process measure = adherence to the protocol. Determine who will perform audits for protocol adherence.
- Determine who will monitor for and document adverse events.
- Documentation should be based on your previously established outcome measures. Primary outcome measures = NEC rate, surgical NEC rate, morbidity and mortality with NEC, transfer rate d/t NEC.
- Be consistent in the timepoints for evaluation, following the standards of evaluation set earlier as your outcome measures.
- Create a practice timeline. There are many confounding factors and other changes in practice will have been made during the evaluation time period that should be included.
- Write a summary of your evaluation to share with the care team and patient-families. Include rationale for your decision to continue or discontinue routine probiotic use.

CONCLUSION

NEC is a complex disease. There is not just one cause, and there will not be one simple solution. Despite the research that is still needed to properly understand and eliminate NEC, current evidence demonstrates that key care practices can meaningfully influence NEC rates. Even slight variations in a unit's NEC rate translate into profound consequences for patient-families. Modest variations in NEC mean the difference between a child developing a devastating, life-altering, too often fatal disease and a child thriving at home with their family. Given the high morbidity and mortality rates, it is essential for the NEC community to deploy the most promising prevention strategies today. Just as hastily changing care practices can result in unexpected poor outcomes, stalling carries its own risk of subjecting patients to a devastating disease that may otherwise be prevented. It is critical for units to recognize the urgency and gravity of NEC prevention efforts and to thoroughly consider the risks and benefits of inertia.

This probiotic toolkit provides the field with a framework of considerations and guidance for decision-making. You can help us build a world without necrotizing enterocolitis by staying engaged, integrating patient-families, and helping us advance research.

Please provide your feedback on the Probiotics Toolkit **here** and stay in touch with us at **NECsociety.org**

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