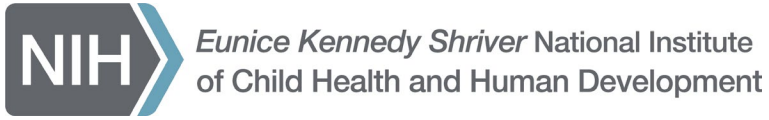
NICHD Necrotizing Enterocolitis (NEC) Working Group of Council

Summary of Findings and Recommendations

September 5, 2024



Health and Human Services Request

In August 2024, at the request of the U.S. Secretary of the Department of Health and Human Services, NICHD convened a “Necrotizing Enterocolitis in Preterm Infants Working Group” of the National Advisory Council of Child Health and Human Development (NACCHD).

NEC Working Group Charge

- Assess the scientific evidence regarding enteral feeding practices in premature infants and factors that may protect against or increase risk for necrotizing enterocolitis
- Identify important research gaps
- Make recommendations for potential future research directions

NEC Working Group Process

- Comprised bench-to-bedside NEC subject matter experts and advocacy leaders, including laboratory scientists, neonatologists, and clinical trials specialists
- Met on August 15, 22, and 28, 2024
- Reviewed portfolio analysis for FY2018-2023
  - >$101 million in NIH funding related to NEC
  - 342 unique projects, 100 unique PIs, 61 unique institutions funded
  - 44% from NICHD, including clinical trials
  - 24% from NIDDK, including many mechanistic studies
  - 40% overall focused primarily on NEC vs. NEC as a secondary aim/outcome
  - 73% research project grants, 10% SBIR/STTRs, 9% cooperative agreements

NEC Working Group Activities

- Reviewed the state of the science for:
  - Risk factors for NEC
  - Nutritional support for preterm infants
  - Associations between feeding practices and risk or severity of NEC
- Developed recommendations to improve the evidence base

Necrotizing Enterocolitis

- A common, serious gastrointestinal illness in which the tissue lining of the intestines becomes inflamed, dies, and can slough off. Symptoms include bloating or swelling of the abdomen, bloody stool, bile in the stomach, and food not moving through the intestines
- One of the leading causes of illness and death in preterm infants born before 28 weeks gestational age
  - 1 infant dies almost every day from NEC in the United States
  - 356 deaths in 2022 (CDC)
- NEC can appear suddenly and progress quickly in infants who otherwise may seem to be getting healthier

Factors That May Be Associated with Risk for NEC

NEC is a multifactorial disease with many associated risk factors

- Maternal/antenatal factors
  - Preeclampsia and hypertension (increased risk)
  - Antenatal steroids and/or tocolysis (e.g., medications used to delay delivery) (protective)
- Infant perinatal factors:
  - Very low birth weight infants (VLBWs) born with birth weight <1500 grams (increased risk)
  - Small for gestational age (increased risk)
- Infant postnatal factors:
  - Antibiotics exposure (variable risk)
  - Human milk exposure (protective)

State of the Science in Brief

The following assessment is of the quality of research evidence and does not represent clinical guidance. Please refer to practice organizations for specific clinical management recommendations.

Foundational Starting Points

- All babies, including those in the NICU, must be fed as soon as is medically feasible by whatever means are available. Nutrition is vital for their brain and other organ development
  - Prolonged fasting increases risk factors for other serious conditions
  - Intravenous feeding increases risk of bloodstream infections
- American Academy of Pediatrics recommends that very low birth weight infants receive human milk, preferably from their own parents
  - If parent's own milk is not available, pasteurized donor human milk is recommended
  - Human milk often requires fortification to meet the nutritional needs of very low birth weight infants

Current State of the Science | Enteral Feeding Practices and Risk of NEC

- Initiation of enteral feeding
  - Early trophic feeding vs. enteral fasting showed no significant effect on risk of NEC, with low certainty
  - Delayed feeding vs. early progressive feeding showed no significant effect, with low certainty
- Advancement of enteral feeding
  - Slow versus faster feeding showed no significant effect on NEC, with moderate certainty

Current State of the Science | Enteral Feeding Practices and Risk of NEC (continued)

- Evidence for base diet
  - When a parent's own milk is insufficient or unavailable, donor human milk (vs. preterm formula) showed lower risk of NEC, with moderate certainty
- Evidence for fortification of the base diet
  - Results have been mixed with recent trials showing no significant differences in rates of NEC between bovine-based vs. human-milk-based fortifiers. Trials have been too small with too few cases of definitive NEC to draw firm conclusions

Limitations of existing evidence about NEC

- Other intestinal conditions may mimic NEC, such as focal/spontaneous intestinal perforation or cow's milk protein-induced enterocolitis syndrome
- Much of the evidence shows associations, not direct or indirect causation linking biological pathways with risk factors for development and/or progression of NEC
- Some risk factors identified in observational data have not been confirmed in clinical trials (e.g., red cell transfusion, empiric antibiotics)
- Because NEC is not a common outcome, studies are often observational or are small clinical trials; generalizability of results may be limited as a result

Recommendations of the NEC Working Group of Council

Recommendations | Overarching

- Expand research into prevention of premature birth, including ways to delay impending births beyond the window of higher NEC risk (~34 weeks gestation) – the best way to prevent most NEC cases is to prevent preterm birth
- Develop a more specific definition of NEC and severity of NEC to improve epidemiologic studies and determine eligibility for trials and treatments
- Ensure that research on NEC incorporates the perspectives of affected families

Recommendations | Epidemiology of NEC

- Improve tracking and reporting of NEC cases as well as deaths
  - Expand epidemiologic data collection, using a common definition, to better quantify the total burden of disease
  - Implement updated ICD-10 codes more specific to NEC and NEC severity, separate out spontaneous intestinal perforation and other conditions (e.g., meconium inspissation)
  - Track NEC cases by gestational age, as there may be differences between NEC that develops in early preterm infants vs. late preterm or term infants
    - NEC in term infants may be associated with cardiac issues
- Expand support for neonatal biorepositories to facilitate research to identify diagnostic, prognostic, predictive, susceptibility and/or surrogate markers of NEC

Recommendations | Epidemiology of NEC (continued)

- Explore innovative methods for collecting and analyzing data
  - Expand data collection to improve estimations for attributable risk for NEC:
    - Disease rate attributable to exposures (e.g., gestational age, antibiotics)
    - Correct diagnosis rate attributable to a positive predictive result (e.g., Bell Stage 3 diagnosis)
    - Beneficial outcome rate attributable to a treatment (e.g., specific feeding strategy)
  - Consider whether open-ended AI or machine-learning analyses of electronic health records of babies with and without NEC could aid in diagnostic criteria or prediction
  - Consider use of biomarkers to better study the disease, given relatively low incidence (e.g., surrogate measures)

Recommendations | Mechanisms of NEC

- Expand research support into the mechanisms of NEC development:
  - Improve early diagnosis of NEC (e.g., biomarkers) to expand the therapeutic window
  - Identify potential prevention and treatment targets (e.g., activated signaling pathways triggering intestinal cell death or gut barrier breakdown) that more clearly link biological pathways with development and progression of NEC
  - Explore genetic and epigenetic pathways for NEC
- Improve animal and laboratory models to better match the disease complexity
  - Expand NEC-in-a-dish, NEC-on-a-chip, gastrointestinal organoid systems, and animal models (e.g., stroma, vasculature, immune cell) and the complexity of the models
  - Collect biospecimens and nutritional data for NEC research and encourage data and specimen sharing

Recommendations | Factors Affecting Risk of NEC

- Explore exposures that may be positively or negatively associated with risk of NEC development, severity, and mortality
  - Nutrition components
  - Antibiotics
  - Bacterial dysbiosis and viruses
- Expand research on feeding practices that may affect NEC risk
  - Timing of initiation/progression and development of NEC
  - Components of human milk, fortifiers, and/or formula

Recommendations | Nutritional Support for Premature Infants and NEC

- Support research to identify the optimal nutritional needs of premature infants and how these may vary by gestational age and nutritional needs of NEC survivors
- Increase research support to optimize parent's lactation performance for preterm and term infants
- Optimize and standardize procedures to collect, process, store, and dispense donor and/or maternal milk for safety and nutritional content (fresh, frozen, pasteurized, etc.)
  - Identify bioactive components of human milk that may be protective for NEC and how to preserve these factors while still protecting against infection
  - Develop point-of-care diagnostics to measure milk components in NICUs and donor banks
  - Research potential standards for donor milk – post-partum donation timing, milk composition, pooling practices, and optimization for specific populations (e.g., VLBWs)

Recommendations | Feeding Practices and NEC

- Support large, independent, comparative effectiveness clinical trials of feeding practices and NEC risk, including timing of onset, severity, mortality, and long-term effects on survivors
  - Fortification methods (human milk-derived fortifiers, bovine milk-derived fortifiers)
  - Timing and method of transiting from donor milk
- Explore innovative clinical trials designs to test, via regulatory pathways when required, the safety and efficacy of promising nutritional additives to prevent and/or treat NEC
  - Ways to manufacture probiotics consistently and test them safely in neonates
  - Ways to test multiple components working together, rather than individual components alone

Recommendations | Feeding Practices and NEC (continued)

- Expand implementation science research to reduce disparities in availability of human milk:
  - Barriers to access donor milk, especially for rural communities and under-represented populations
  - Community support for breastfeeding and milk donation
  - Economic and workplace interventions for lactation support
- Support research on parent education in the NICU about feeding practices and risk of specific conditions, including NEC

Next Steps

- Finalize report
- Submit to the Secretary of HHS by September 16, 2024

Thank you to the NEC Working Group Members

Bonnie Maldonado, MD (Co-Chair)
Ravi M. Patel, MD MSc (Co-Chair)
Steve Abrams, MD
Andrew Bremer, MD PhD MAS
Mandy Brown Belfort, MD MPH
Jennifer Canvasser
Tarah T. Colaizy, MD MPH
Mark Corkins, MD
C. Michael Cotten, MD MHS
Eric C. Eichenwald, MD
Misty Good, MD MS
Janelle Gunn, MPH RDN
Munish Gupta, MD MMSc
Steven James, MD
An Massaro, MD
Joan Meek, MD MS
Clifford McDonald, MD
Jack Moye, Jr., MD
Brenda B. Poindexter, MD MS
Ryan Ranallo, PhD
David Rowitch, MD PhD
Emre Seli, MD
Lisa Stellwagen, MD, FAAP
Stephanie Wilson Archer, MA

Questions and Feedback