Pediatric RESEARCH

SPECIAL ARTICLE

Opportunities for the federal government to advance necrotizing enterocolitis research

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BACKGROUND: Necrotizing enterocolitis (NEC) is a leading cause of morbidity and mortality in the neonatal ICU with minimal progress in the research.
METHODS: Federal webpages were queried to look for funding opportunity announcements (FOAs) and to develop lists of funded projects on NEC to identify gaps in NEC-related research topics.
RESULTS: Over the past 30 years, the National Institutes of Health (NIH) issued two FOAs to stimulate research on NEC with $4.1 million set aside for the first year of respective funding. We identified 23 recently funded studies of which 18 were research projects, 4 training grants, and 1 conference grant support. Only one grant focused on parent and family engagement in the NICU.
CONCLUSION: There are significant research gaps that can be addressed with adequate funding from the federal government on the prevention and treatment of NEC.

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INTRODUCTION

Though neonatal necrotizing enterocolitis (NEC) has very high rates of mortality and morbidity, there has been minimal improvement in the prevalence of NEC over the past decade, and the outcomes after diagnosis remain poor.[1–3] Over the past several decades, no new therapies or effective strategies in clinical practices have emerged for the treatment and prevention of NEC, except for the classic approaches such as bowel rest, hydration, and antibiotics. The lack of randomized clinical trials evaluating the treatment and dearth of quality improvement projects in the prevention of NEC are perhaps reflective of the inadequate funding.

Funding is critical to stimulate research to help develop evidence-based knowledge and multi-center quality improvement projects. Furthermore, the patient–families most impacted by the disease have expressed frustration by the inadequate prioritization of funds, and they are advocating for further advancement of processes of care.[4] We sought to identify the National Institutes of Health (NIH) funding opportunity announcements (FOAs) that were issued to support research in NEC and the use of breast milk, since the latter has been established as protective against NEC. We included ongoing as well as completed studies and expired FOAs.

In this paper, we present a listing of current ongoing studies that are funded by the NIH, focusing on all aspects of NEC: prevention, diagnosis, treatment, long-term outcomes, and most importantly, impact on families and whether families are incorporated in the study methods. We hypothesized that there has been a lack of funding for NEC prevention and treatment strategies, which exacerbated the lack of progress in the management of the disease. Finally, we include a patient–family perspective from a parent-led organization focused on NEC—the NEC Society.

METHODS

Publicly available databases were used to conduct the analysis. Search terms for each database varied based on the format of the entry but focused on all federal funding provided for research on NEC. To understand the patterns of federal support for this devastating disease from the NIH, a broad search of available search engines was conducted, including Google, PubMed, Clinicaltrials.gov, NIH Research Portfolio Online Reporting tools (RePORTer),[5] and the NIH Guide to Grants and Contracts.[6]

Results from the searches were grouped into three sections: funding opportunity announcements, investigator-initiated research projects that succeeded in receiving federal funds, and NEC research conducted by the Eunice Kennedy Shriver National Institute of Child Health Human Development (NICHD) Neonatal Research Network (NRN). FOAs are announcements from the NIH entities inviting researchers to apply for federal grants in the specific areas of research. Request for applications (RFAs) are types of FOA that generally provide set-aside funds to support a specific number of research projects. The NIH announces dollar amounts available to support only the first years of the respective projects, since the US Congress appropriates budget only for the current fiscal year.

Formed in 1986, the NICHD-NRN is a component of the Pregnancy and Perinatology Branch of the NIH. It consists of approximately 15 academic institutions across the United States that conduct research related to neonatal care.[7] The research projects are developed within the network and they are implemented across all NRN sites.

In this report, we also reviewed the components of the NEC-funded research studies and highlighted the gaps in knowledge that need to be rectified.

To understand the patient–family perspective, the founder and director of the NEC Society, Jennifer Canvasser, was approached to

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summarize the opinions of parents and families. Founded in 2014, the NEC Society is a collaborative nonprofit organization comprised of scientists, clinicians, families, and other diverse stakeholders. The NEC Society is directed by two parents who each lost a child to NEC. The organization includes a broad, diverse international network with hundreds of families impacted by the disease from around the globe.

RESULTS

Funded projects

Funding opportunity announcements. Table 1 presents a list of 6 FOAs of which 2 were RFAs with set-aside dollars that could potentially support 8–9 research studies, at the total cost of $4.1 million US dollars the first year of the respective research. The four non-RFAs listed in Table 1 are potentially applicable to NEC, although other conditions fitting the announcement intent could qualify. Since these four FOAs did not have set-aside funds, other applications responding to these RFAs need to compete among the common pool of applications being considered for funding within the institutes' available dollars.

Investigator-initiated research funded by NIH to support NEC research. Information in this area is difficult to discern using publicly available databases. However, using the NIH RePORTer database, we sought to identify *any* research funded by NIH for projects related to NEC. We identified 216 annual awards made by various NIH entities between 1985 and 2019 for 65 projects that contained "necrotizing enterocolitis" in the titles. Since NIH funding mechanisms have multiple years of funding, there are more "awards" than projects. For these 216 awards, the NIH entities spent a *total* of $48,439,181—an average of <$1.5 million per year, which is a tiny fraction of the NIH's annual budget of about $33 billion. Among the 65 projects, there were 23 active studies, of which 18 were research projects (R or P), 4 training grants (Ks and Fs), and 1 conference-support grant (R13) (Table 2).

NEC research support through NIH Network. Though >60 studies have been completed by the group, only a few prominent studies have directly or indirectly focused on NEC. The two ongoing studies include the Transfusion of Prematures (TOP) trial (NCT01702805) and Neurodevelopmental Effects of Donor Human Milk versus Preterm Formula in ELBW infants (the MILK trial—NCT01534481). The TOP and MILK trials look at rates of NEC as secondary outcomes after transfusion and the use of non-maternal milk or formula, respectively. A third NRN study Necrotizing Enterocolitis Surgery Trial (NEST) (NCT01029353) has been completed. The NEST trial evaluates the neurodevelopmental outcome after surgical intervention for NEC after diagnosis.

The TOP trial randomized infants <1 kg and estimated gestational age <29 weeks to receive red blood cell transfusions at a liberal or restrictive hemoglobin threshold. The hypothesis was that a higher level of hemoglobin will improve survival and neurodevelopmental outcomes at 24 months of age; however, the impact of transfusions on the rates of NEC would be a secondary outcome.[7] The MILK trial is testing fortified donor human milk against preterm formula for neurodevelopmental and other outcomes at 2 years of age for extremely low birth weight infants receiving little to no maternal milk. The rates of NEC with each group are once again a secondary outcome. Finally, the NEST trial evaluates whether an initial laparotomy (with subsequent removal of affected intestines) results in improved survival without neurodevelopmental impairment at 18–22 months compared to drainage alone for those <1 kg at birth.

Gaps in funding

Prevention trials for NEC are rare and primarily funded independently. IBP-9414 (NCT02472769) and STP206 (NCT01954017) are

Table 1. NIH funding opportunity announcements.

Title	FOA number	Funding entity	Released	Expired	Activity code	Set-aside dollars[a]
Pathophysiology of NEC (R01)	HD-RFA-94-005	NICHD	April 1993	September 1993	R01	$600,000
New approaches for the prevention and treatment of NEC	HD-RFA-07-018	NICHD NIAID; NIDDK	April 2007	November 2007	R01	$3.5 million
Intestinal failure, short gut syndrome, and small bowel transplantation	PA-02-163	NIDDK	September 2002	October 2005	R01; R21	None set aside[b]
Intestinal failure, short gut syndrome, and small bowel transplantation (R21)	PA-06-229	NIDDK	March 2006	November 2006	R21	None set aside
Drug repurposing for conditions affecting neonates and pregnant women (R01—clinical trial optional)	PAR-18-506[c]	NICHD	December 2017	May 2011	R01	None set aside[b]
Advancing mechanistic probiotic/prebiotic and human microbiome research (R01—clinical trial not allowed)	PA-18-876[c]	NIDCR	July 2018	September 2012	R01	None set aside[b]

[a]NIH identifies the set-aside dollars for the first fiscal year and specifies how many awards will likely to be made.
[b]PA (Program Announcements) and PARs (Program Announcements with Review) generally do not have set-aside dollars.
[c]These funding announcements are active at the time of writing.

Table 2. Funded projects from the NIH reporter.

Activity	Project title	Center	Total cost
P01	Project 2: RBC irradiation and anemia trigger gut injury in preterm infants	NHLBI	$338,617.00
R01	Red cell transfusion-associated necrotizing enterocolitis in premature infants	NHLBI	$376,598.00
R01	Effect of platelet transfusions on neonatal intestinal injury	NHLBI	$409,375.00
K23	Red cell transfusion, severe anemia and necrotizing enterocolitis	NHLBI	$166,212.00
R01	Population genomic analysis of gut microbial colonization in premature infants	NIAID	$709,434.00
R21	Surfactant protein-A as a biomarker to predict development of NEC in infants	NICHD	$231,000.00
R01	Preterm infant susceptibility to NEC due to early intestinal microbiome function	NICHD	$388,817.00
R13	Breaking down the barriers of NEC prevention and treatment	NICHD	$10,000.00
F30	The impact of breast milk on the developing infant microbiome	NICHD	$45,016.00
R21	Antibiotic effects on the developing microbiome metabolome and morbidities in preterm neonates	NICHD	$190,625.00
R01	Phylogenomic, transcriptomic, viromic, and immunoproteomic determinants of necrotizing enterocolitis	NICHD	$625,282.00
R01	Role of the intestinal microvasculature in necrotizing enterocolitis	NIDDK	$541,860.00
R01	Modulation of the intestinal immune response in necrotizing enterocolitis	NIDDK	$350,438.00
R01	Maternal-fetal AHR signaling in the pathogenesis and treatment of necrotizing enterocolitis	NIDDK	$367,390.00
R01	Bile acids in necrotizing enterocolitis	NIDDK	$478,128.00
K08	Defining bacterial virulence; cAMP and PKA in necrotizing enterocolitis	NIDDK	$163,080.00
R03	Rho-associated kinase-dependent cytoskeletal and tight junction dysregulation in necrotizing enterocolitis	NIDDK	$79,000.00
R01	Exosomes and HB-EGF in stem cell-mediated therapy for necrotizing enterocolitis	NIGMS	$284,050.00
R01	Tunable native probiotic formulations for the treatment of NEC	NIGMS	$441,859.00
K08	The role of extracellular histones and neutrophil extracellular traps in necrotizing enterocolitis	NIGMS	$108,557.00
R01	TLR4 signaling in the pathogenesis of surgical necrotizing enterocolitis	NIGMS	$328,050.00
K08	The role of the enteric nervous system in necrotizing enterocolitis	NIGMS	$198,504.00
R21	The influence of the milk microbiome on inflammation of the preterm infant	NINR	$291,592.00

multi-center clinical trials using a drug compared to placebo to evaluate the safety and tolerability in low and extremely low birth weight infants for the prevention of NEC. This is a great opportunity for the federal government to focus on funding studies that could serve as prevention strategies for NEC. Additional strategies that have been suggested include the widespread use of probiotics and/or donor milk but have not been studied in larger clinical trials. Furthermore, as many clinicians and parents are blindsided by the diagnosis, earlier inventions such as education on the protective role of breast milk or consultation with lactation professionals earlier in high-risk pregnancies would be public health interventions that could help to prevent NEC.

Moreover, biomarkers and early predictors such as near-infrared spectroscopy (NIRS) monitoring may be useful for diagnosis and earlier management. Studies from Emory University (NCT02741648) with NIRS monitoring and from Baylor University (NCT03210831) can lead to larger multi-center trials evaluating the role for such predictors. Most of the funding from the federal government focuses on the pathogenesis of NEC and microbiome however, without much dedicated early detection and treatment. None of the funding besides what was provided for the NEC Symposium focuses on the engagement of parents in the diagnosis and management of NEC. This should be a priority for the federal government as the impact on families cannot be overstated.

Several studies, however, have focused on the effect of transfusions on NEC, specifically red blood cells and platelets. These funded studies from the National Heart, Lung and Blood Institute have dedicated >$2 million on transfusion thresholds, speed, and feeding strategies around the transfusion. None of these studies have included the voice of the families.

Finally, the treatment of NEC using novel compounds have primarily focused on modulating gut injury through the innate immune receptor, toll-like receptor 4, or via stem-cell-mediated techniques. No head-to-head studies have been done on the use of antibiotics or bowel rest and timing. The length of antibiotic use for treatment remains unclear.[8] The largest variability is seen in antibiotic use up front and no consensus was noted on a Cochrane review.[9] Moreover, minimal effort has been made to include patient–families in the management of the condition with one exception: the NEC Symposium. The NEC Symposium that received funding from PCORI ($50,000) and NICHD ($10,000) has been led by patient–families working in partnership with clinicians to advocate for additional prevention and treatment strategies.

Priorities for federal government NEC funding should include projects incorporating the patient–family experience, support of the multi-center NEC Society biorepository for biomarker discovery led by Dr. Misty Good (such as the one for Children's Oncology Group for centralizing specimens), and quality improvement projects focused on benchmarking and sharing data on the role of prevention strategies for NEC. In addition, networking with obstetricians and empowering parents with information and resources prenatally, such as with NEC Zero,[10] can be cost-effective prevention strategies. Use of biomarkers and prediction tools can lead to earlier detection and treatment and may enhance outcomes; therefore, additional funding should be focused on these areas. Finally, the study of long-term outcomes including a partnership at diagnosis, parent empowerment, transitions of care after discharge, and short gut syndrome after NEC are crucial to improving the quality of life for families after the initial hospitalization.

DISCUSSION

The patient–families who comprise the NEC Society are eager for the federal government to do more to help advance NEC research. As these families strive to build a world without NEC, they are highlighting the inadequacy of NEC prioritization, resources, and research at the national level, as well as the variability and

disparities in the care of our most vulnerable neonates. The NEC Society's patient–families are motivated to participate in and help drive research that will help to accelerate equitable access to the most promising NEC prevention and interventions strategies. These families, who have witnessed their children suffer from the devastation of NEC, are calling on the federal government to take a comprehensive approach to NEC prevention by not only increasing support for NEC investigators but also ensuring the federal government is not unintentionally thwarting cutting-edge interventions that could potentially save lives.

The death of Patrick Kennedy, son of a sitting President, >55 years ago from what was known as hyaline membrane disease, sparked increased funding from the federal government to find a cause for and treatment of respiratory failure in neonates. Today, respiratory distress syndrome affects >25,000 babies each year and Patrick Kennedy, born at 37 weeks, and placed on a primitive ventilator, would have a nearly 100% survival with universal availability of surfactant.[11] The time has come to translate this urgency to NEC where the progress has been stagnant. Only two active FOAs are available focusing on drug repurposing and microbiome, respectively, with no funding set aside.

Over the past few years, no funding has been dedicated to younger researchers for career development focusing on patient–family engagement in NEC, despite the lack of communication, lack of access to breast milk, and lack of empowerment.[4] By fostering multi-center, interdisciplinary collaboration,[2] outcomes of rare diseases such as NEC, may be improved by quality improvement projects such as the use of probiotics or donor milk.[12,13] Finally, encouragement of centers to join a clinical trial for NEC can help spur progress in a disease that is too often imperceptible and catastrophic.

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AUTHOR CONTRIBUTIONS

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ADDITIONAL INFORMATION

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