



eNeonatal Review VOLUME 10, ISSUE 1

OPTIMAL METHODS FOR PREVENTION AND TREATMENT OF NECROTIZING ENTEROCOLITIS



Editor's Note: As we begin Volume 10, we want to welcome back our returning subscribers and say hello to our newly registered clinicians. In Volume 10, we will continue to provide you with current, clinically relevant data important to helping you improve outcomes in your patients via 6 newsletters and 6 case-based podcasts. Topics scheduled for this volume include: New Evidence-Based Approaches for Treating Neonatal Persistent Pulmonary Hypertension, Management of BPD and RDS, Recognizing and Treating GERD in Neonates, Nutritional Management of Low Birth Weight Preterm Infants, and Kangaroo Care

In this Issue...

Necrotizing enterocolitis (NEC), the most common gastrointestinal emergency in the preterm neonate, is associated with high morbidity, mortality, costs, and long term health problems. Its pathophysiology has been enigmatic; hence little progress has been made in treatment and prevention over the past several decades.

In this issue, we review current publications describing:

- Newly discovered epidemiologic and laboratory-based pathophysiologic clues that may aid in defining NEC
- Newly developed technologies to evaluate the microbial ecology of the intestine prior to the development of NEC
- New diagnostic tools that may improve clinicians' ability to detect NEC in a timely manner
- Controversies in surgical intervention between primary peritoneal drainage and immediate laparotomy
- The evidence-based use of probiotics in the prevention of NEC

LEARNING OBJECTIVES

After participating in this activity, the participant will demonstrate the ability to:

- Describe the evidence that clarifies current knowledge about the pathophysiology of "classic" NEC.
- Identify several developing predictive and diagnostic biomarkers for NEC.
- Appraise several evolving measures that may be useful in the prevention of NEC.

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- 1.0 hour Physicians
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October 31, 2014

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October 30, 2016

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Guest Faculty Disclosure

Josef Neu, MD has indicated that he has received grant funding from and served on a scientific advisory panel for Medela and has served as a consultant to Biogaia/Infant Microbial Therapeutics.

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Unlabeled/Unapproved uses

Josef Neu, MD has indicated that there will be no references to unlabeled/unapproved uses of drugs or products.

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COMMENTARY

Necrotizing enterocolitis (NEC) is the most common severe intestinal emergency that affects predominantly premature infants. It is associated with a mortality between 20% to 30%¹ and also has high associated morbidity, which includes short gut syndrome, severe cholestasis, and significant neurodevelopmental delays.² The precise etiology of NEC remains enigmatic despite considerable research over the past four decades.³ The mean prevalence of NEC is approximately 7% in very low birth weight infants in the United States and Canada.⁴ Of interest, at least in one country where NEC prevalence was previously thought to be extremely low, it appears to be increasing, possibly because of more aggressive intensive care for the most at-risk infants.⁵

Clinical signs, laboratory, and radiologic features at the initial presentation of NEC are highly unreliable and nonspecific. Differentiating early NEC from simple feeding intolerance or late onset sepsis is difficult.⁶ What has been lumped into one disease termed "NEC" is also becoming recognized as probably representing more than one disease. The pathogenesis of even the most classic forms of NEC is multifactorial and this makes it a difficult target for uniform preventive strategies.⁷

The most common reasons provided for susceptibility to NEC in the preterm infant relate to various factors of intestinal immaturity.⁸ These include immature motility, digestion, absorption, barrier function, immune defense, and circulatory regulation. Examination of the bowel and blood from infants with NEC shows an excessive inflammatory response with elevation of proinflammatory cytokines and chemokines.⁹ Another major predisposing factor relates to alterations in intestinal colonization prior to the development of the disease.¹⁰ With the advent of the Human Microbiome project and technological advances that allow for the molecular identification of many more microbes than can be cultured from the intestine, new evidence is being provided pertaining to specific microbial ecologic patterns as well as their effects on the host prior to the development of the disease.¹¹⁻¹⁵ This will be critical for the subsequent preventive measures using microbial therapeutic techniques.

Clinical signs for the development of NEC include the wide array of presentations. These may include feeding intolerance, emesis, abdominal distention, and bloody stools. As the degree of illness advances, the abdomen becomes progressively more distended, shiny and erythematous. Systemic signs with advancing NEC include lethargy, pallor, increased episodes of apnea and bradycardia, hypotension, worsening of respiratory function, and hemodynamic compromise.⁶ Unfortunately these signs cannot be distinguished from late onset sepsis. Commonly used tests include radiographs, which are still considered the "gold standard." Pneumatosis intestinalis (air in the bowel wall), portal venous gas, and free air in the peritoneal cavity are signs that are highly associated with NEC. Unfortunately, free air in the peritoneal cavity may also indicate spontaneous intestinal perforations that are actually a different disease process with a different pathogenesis. Because of this and the fact that NEC can proceed very rapidly from first signs to death, it is imperative to develop better techniques for early detection of this disease.

Current medical management consists primarily of stopping enteral feedings, applying gastric intestinal decompression, and initiating broad-spectrum antibiotics. Frequent evaluation of blood counts, acid-base balance, and abdominal radiographs are used to determine whether the disease is progressing. Free intraperitoneal air is often an indicator for surgical intervention. Current surgical interventions include laparotomy with bowel resection when known necrotic intestine is present or primary peritoneal drainage. Which of these techniques should be used first remains controversial.^{16,17}



Several strategies have been attempted to prevent NEC, but the one that is based on the best evidence appears to be human milk.¹⁸ It is thought that the baby's own mother's milk may provide advantages over donor milk, but donor milk is now commonly used when baby's own mother's milk is not available. Various feeding regimens have been attempted, and it is thought that very rapid advancement of feedings may exacerbate the likelihood of NEC,^{19,20} but the enteral route for careful introduction of nutrition remains highly recommended.²¹

Various other strategies have been suggested for prevention, but many of them remain highly questionable or understudied. Animal models for NEC and evaluation of the preventative modalities in these models remains questionable because some of the most commonly used models rely on procedures that do not closely mimic the timing and presentation of the disease as seen in preterm human infants.²² More recently numerous studies and meta-analyses of these studies using probiotics have been conducted in an attempt to prevent NEC.²³ Some of the approaches appear promising, but many questions remain about the use of these agents and how to best employ them safely for preventing the disease and what kind of quality standards should be used to adequately protect the infant from potential harm by the live microbial agents. A rigorous, prospective trial that is properly powered for NEC, using an agent that meets standards of quality required by the FDA for a pharmacologic agent to prevent a specific disease (NEC) is needed.²⁴

If potentially useful preventive or treatment strategies for NEC are developed, then we need strong diagnostic or predictive tests, such as biomarkers, of the disease.²⁵ To identify which babies are at the highest risk for the development or progression of the disease, such tests must be highly sensitive, specific, and accurate—and have the ability to differentiate NEC from other common inflammatory processes such as sepsis or pneumonia.

In summary, NEC is more than one disease. Preventive strategies must be developed that are specific for the most common forms of NEC. Use of the baby's own mother's milk should be strongly encouraged in neonatal intensive care of these babies. Methods to optimize the quality of donor milk so that it is more highly similar to baby's own mother's milk are needed. Since the microbial ecology prior to the development of NEC appears to be perturbed, a clear understanding of this phenomenon could lead to microbial therapeutic techniques or the use of microbial products that may aid in the prevention of NEC

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REDEFINING NEC

Gordon PV, Clark R, Swanson JR, Spitzer A. Can a national dataset generate a nomogram for necrotizing enterocolitis onset? *J Perinatol*. 2014 Jul 31. doi: 10.1038/jp.2014.137.



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What we have been defining as "necrotizing enterocolitis" (NEC) is probably more than one entity. Different pathophysiologic processes including isolated intestinal perforations and bowel ischemia from various causes have not been clearly differentiated from the most common form of NEC seen in preterm infants. Consequently, datasets that include the different forms of this disease may be misleading and are part of the reason progress in preventing and treating this disease has been slow. This article was chosen not so much because of what the title implies, ie generation of a nomogram for necrotizing enterocolitis onset, but rather because some of the interesting data shown may help us differentiate a "classic," ie, most commonly encountered form of NEC from impostors that represent other pathophysiologic processes.

In this study, Gordon and colleagues used a very large national dataset of patients with acquired intestinal diseases and compared gestational age to the number of days after birth that the diagnosis was first determined. Several entities such as traumatic perforations and meconium ileus were excluded. This study shows an inverse relationship between the onset of NEC and gestational age. Said differently, medical NEC in earlier born preterm infants (ie, those born at the lowest gestational ages) occurs at a later postnatal age than in lesser preterm infants. When evaluating surgical "NEC," a skewing toward younger age groups was found, and the authors suggested this was likely due to many of these infants having spontaneous intestinal perforations, which are a different disease entity. This linear inverse relationship between NEC and gestational age has been known for over a decade and has been described in other publications, but this is the largest dataset to date showing this phenomenon. That the incidence of this "classic NEC"

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peaks at a postmenstrual age of about 29-31 weeks may hold an important clue to pathogenesis and prevention. Whether this information provides any guidance for when these infants may be fed enterally, as implied by the authors, is highly questionable. However, this study does raise the question whether there may be developmental factors that preclude development of "classic NEC" during this peak period. Several potential phenomena come to mind that could provide testable hypotheses:

- 1) The intestinal microbiome matures over a period of weeks, and shifts have been seen in several studies, including a dysbiosis in babies that develop NEC. Could a disease-producing quorum precede the disease?
- 2) Could a host innate an immune phenomenon such as maturation of certain Toll-like receptors and/or could their interaction with the intestinal microbiome play a role?
- 3) Could a host vascular developmental phenomenon such as maturation of the microvasculature (as seen in the retina with vaso-obliterative, proliferative retinopathy of prematurity) or closure of the ductus venosus cause a triggering event?

Several phenomena could be involved either alone or concurrently. Nevertheless, delineating the timing of NEC onset aids our ability to differentiate the most common form of this disease from some of the impostors, which include spontaneous intestinal perforation, ischemic bowel disease as seen in infants with certain forms of congenital heart disease, polycythemia, feeding-induced colitis, and congenital anomalies of the bowel such as Hirschprung's disease.

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INTESTINAL MICROBIAL ECOLOGY AND ENVIRONMENTAL FACTORS AFFECTING NEC

Torrazza RM, Ukhanova M, Wang X, et al. Intestinal microbial ecology and environmental factors affecting necrotizing enterocolitis. *PLoS One*. 2013 Dec 30; 8(12):e83304. doi: 10.1371.



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While the pathophysiology of NEC is poorly understood, there is increasing recognition that a gastrointestinal "dysbiosis" (increased levels of harmful bacteria or reduced levels of beneficial bacteria) may play an important contributing role. Since it is known that a large number of the microbes residing in the human gastrointestinal tract are difficult to culture using standard techniques, new sequencing technologies developed in conjunction with the Human Microbiome Project are being applied to identify the intestinal microbes related to health and disease, as well as to better understand their function and interaction with the host. In this study, 16SrRNA based sequencing of microbial DNA was applied to feces isolated from infants obtained two weeks, one week, and less than 72 hours prior to the onset in patients with NEC and compared to closely matched control subjects (≤ 32 weeks gestational age). Taxonomic evaluation at the phylum level showed a higher proportion of Proteobacteria (61%) in the NEC cases two weeks prior to the onset compared to controls (19%). In some of the earliest fecal samples obtained after birth from these infants, sequences similar to those in *Klebsiella pneumonia* appeared to be strongly associated with NEC development.

Other studies using similar technology have found alterations in the intestinal microbiome prior to the onset of NEC. Claude et al similarly found that three weeks before onset of NEC, microbiota development diverged from the controls.¹ The phylum Proteobacteria was highly represented in both control and NEC infants, but principal component cluster analysis from the 16S sequence data and shotgun metagenomics, which provide additional information about microbial community function, suggested a differential shift in the Proteobacteria and Firmicute phyla before development of the disease. These studies support the concept of a dysbiosis prior to the onset of NEC in preterm infants.

Unfortunately, these studies only show associations with development of NEC and do not provide causal mechanisms, which are crucial for better understanding the pathogenesis



of NEC, as well as for developing science-based strategies for microbial therapeutic preventive measures. Possible approaches for studies to prove causation include the transfaunation of human NEC-associated microbes into animal models. This leaves us with important questions about which animal models would be most appropriate, cost-effective, and useful in fulfilling Koch's postulates for disease causation. The proper choice of microbes for the transfaunation experiments need to be investigated, and simply having the name of candidate microbes that may be associated with the disease will be insufficient. Information about the microbial function using transcriptomics, metabolomics, and systems biology approaches and how the microbe interacts with the host as a pathogen will also be critical in determining which microbes to use for such causality determinations. Nevertheless, these early studies of the intestinal microbiome in preterm infants as it relates to NEC are an important beginning and offer clues to ways to best manipulate the microbial environment of the developing preterm intestine that will help prevent its onset.

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1. Claud EC, Keegan KP, Brulc JM, et al. [Bacterial community structure and functional contributions to emergence of health or necrotizing enterocolitis in preterm infants.](#) *Microbiome*. 2013;1:20.

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INTESTINAL FATTY ACID BINDING PROTEIN (iFABP) AS AN EARLY INDICATOR OF NEC

Gregory KE, Winston AB, Yamamoto HS, et al. Urinary intestinal fatty acid binding protein predicts necrotizing enterocolitis. *JPediatr*. 2014 Jun;164(6):1486-8.



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One of the most challenging conundrums in neonatal intensive care is the prediction and diagnosis of necrotizing enterocolitis (NEC). Warning signs such as increased abdominal girth and gastric residuals are highly nonsensitive or nonspecific, and unfortunately, NEC can progress from mild early symptoms to full-blown disease in the matter of hours. In the late 1970's, Martin Bell and colleagues developed diagnostic criteria that involved staging based primarily on the patients' signs, symptoms, and radiographic findings. Concern has been raised about these criteria, largely because they are highly nonspecific, especially in stage 1, which could represent simply a baby who is having feeding intolerance along with other relatively minor signs of instability, which are seen almost universally in extremely preterm infants. With medical NEC (stage 2) with radiographic evidence, neonatologists, pediatric surgeons and radiologists whether the air represents true pneumatosis intestinalis or a bubbly stool pattern. Surgical NEC (stage 3) is also confounded by the common practice of surgeons placing an abdominal drain rather than directly evaluating the intestine on laparotomy. Many cases that present as NEC may actually be spontaneous intestinal perforations. In some patients, radiographic signs are very concerning, but surgeons are often reluctant to operate without a classic definitive radiographic signs such as pneumoperitoneum. Lab measures such as C-reactive protein, platelet counts, and white blood cell counts are commonly used to aid in the diagnosis of NEC, but these are highly nonspecific and may be abnormal in sepsis or other inflammatory conditions.

This paper by Gregory and colleagues describes the use of intestinal fatty acid binding protein (iFABP) as an early indicator of NEC. iFABP is a water-soluble protein that is released into the blood and urine in conjunction with intestinal mucosal injury. Sensitivity, specificity, receiver operating characteristics, and other criteria for diagnostic validity in previous studies have been promising, and this study with a larger number of subjects supports this notion.

Other markers have also been evaluated—including claudin 3 (a tight junction protein that is also water soluble and can be measured in the urine) and calprotectin (measured in the feces), which have also shown promise.¹ Another study evaluated seven biomarkers with highly accurate diagnostic and prognostic information for infants with suspected NEC,² but these relied on subjective criteria to evaluate onset of NEC rather than actually obtaining

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the samples before development of the disease (as was done in the Gregory study). A problem with fecal samples is that they are not easy to obtain because babies will often defecate only on their own schedule. Although the studies with iFABP suggest that it is likely to be a good diagnostic tool for NEC, questions remain about what it will take to get this test into our clinical armamentarium and why we are not yet using it.

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SURGICAL NEC IN VLBW NEONATES

Hull MA, Fisher JG, Gutierrez IM, et al. Mortality and management of surgical NEC in very low birth weight neonates: a prospective cohort study. *J Am Coll Surg*. 2014 Jun;218(6):1148-55.



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Deciding on when and how to operate in a baby with NEC is controversial. Over the past decade, peritoneal drainage rather than laparotomy has become common practice. Although early randomized, controlled trials of laparotomy vs primary peritoneal drainage for NEC suggested that outcomes were similar between the two groups,¹ many patients who receive peritoneal drainage have also gone on to receive laparotomy.² This has led to concern in that if laparotomy is not performed primarily in many of these patients, it is difficult to discern whether these patients may actually have NEC vs spontaneous intestinal perforations. It is common contention that spontaneous intestinal perforations may heal spontaneously without surgical intervention in the form of a laparotomy, and the same may hold for mild forms of NEC. Furthermore the mortality of doing or not doing these procedures may differ.

This study took a large database of infants from the Vermont Oxford network who were born over a five-year period with birth weights between 401 g to 1500 g. Starting with 215,057 very low birth weight neonates from 655 Vermont Oxford centers in the United States, the incidence of NEC was found to be approximately 9%. Of the infants with NEC, approximately half were considered to have medical NEC and the other half surgical NEC. Of the surgical group, 69% received laparotomy and 31% received primary peritoneal drainage. The primary peritoneal drainage group was divided into those who received primary peritoneal drainage alone and those who subsequently underwent laparotomy. Using this technique, 46% of the primary peritoneal drainage group also had laparotomy.

Several interesting features emerged after mining the data from this large cohort of patients. This investigation demonstrated overall NEC mortality of 28%. Of interest is that medical NEC mortality in this study was 21%, which is higher than reported in previous studies. Previous studies used a definition of NEC that was not uniform and used ICD -9 codes, which very likely resulted in a large number of the babies having Bell's stage I disease, which is highly nonspecific for diagnosing true intestinal necrosis. These previous studies resulted in a mortality of 6.8% for medical NEC, considerably lower than that found in this study (21%), which used the more stringent Vermont Oxford criteria for medical NEC. This is a very interesting example of how databases may misrepresent data. As one would expect, this study also showed a decreasing mortality in patients with NEC as their birth weight increased. However, mortality in surgical NEC infants compared to medical NEC infants did not differ in the birth weights less than 750 g. The mortality among infants who had surgery appeared to plateau at approximately 30% in the highest birth weight stratification, whereas the mortality was only 6% in medical NEC patients at this same birth weight. Of interest is that the background mortality in these infants is approximately 10%, so the medical NEC may not represent death from NEC per se but instead death from comorbidities.



Another point of interest is that the infants who received the laparotomy only and those who received primary peritoneal drainage as well as laparotomy had a similar mortality of approximately 30%, whereas those receiving primary peritoneal drainage alone had a much higher mortality of approximately 50%. The reason for this is poorly understood, but it is of interest to note that the patients who had primary peritoneal drainage were likely to be more severely ill than those receiving laparotomy alone. Furthermore, 27% of neonates undergoing primary peritoneal drainage survive without further surgery. However, it is not comforting to note that so many patients with primary peritoneal drainage died without a definitive diagnosis or the opportunity to evaluate the intestine using laparotomy. It raises the question of whether we may have gone too far with primary peritoneal drainage and whether some of these babies could have been saved had a laparotomy been performed. These questions underline the need for improved diagnostic tools for the neonatologist and pediatric surgeon to be able to diagnose NEC early and to discern whether laparotomy or peritoneal drainage would be most beneficial for an individual patient, rather than relying on group data.

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1. Moss RL, Dimmitt RA, Barnhart DC, et al. [Laparotomy versus Peritoneal Drainage for Necrotizing Enterocolitis and Perforation](#). *N Engl J Med*. 2006;354:2225-34.
2. Pierro A, Eaton S, Rees CM, et al. [Is there a benefit of peritoneal drainage for necrotizing enterocolitis in newborn infants?](#) *J Pediatr Surg*. 2010;45:2117-8.

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PROBIOTICS FOR PREVENTING NEC

Yang Y, Guo Y, Kan Q, Zhou XG, Zhou XY, Li Y. A meta-analysis of probiotics for preventing NEC in preterm neonates. *Braz J Med Biol Res*. 2014 Sep;47(9):804-10.



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Whether to provide routine probiotics for preterm infants to prevent necrotizing enterocolitis has become a major controversy in neonatology over the past decade. This article is a meta-analysis of 27 randomized, controlled trials that included a total of 6655 preterm infants receiving either probiotics or placebo. The differences in NEC incidence between the two groups, as well as reduction of death, appeared to be highly significantly reduced with probiotics. This analysis did not show a difference in incidence of sepsis.

This is one of several meta-analyses, including a Cochrane review published within the past decade, that suggest a decrease in NEC with probiotics.¹ This has led to considerable exuberance on the part of many who have started using probiotics for this purpose. On the other hand, concern has been raised about the use of probiotics without further scrutiny. As with antibiotics, there is a large variety of probiotics, many with different functions. Although it is well established that antibiotics are known to be effective in treating infections, it is clear that targeted therapy with antibiotics depends on the type of infection. At least 150 different forms of probiotics have been used primarily as a food and have not come under the scrutiny that is needed for a pharmacologic agent such as one that can prevent a specific disease entity such as NEC. So the question is, which of the 150 available probiotic preparations should be used? This meta-analysis involved numerous different probiotic agents, some of which appeared to be more effective than others and some that showed no efficacy. However the individual studies were too small to provide the robustness required to specify any one particular probiotic agent for preventing NEC. In the United States, many neonatologists have begun to use probiotics in premature infants in an attempt to prevent NEC, but the probiotic preparations that have commonly been used are not those thought to be efficacious against NEC. As previously mentioned, the standards required for a food preparation are not as stringent as those required for a pharmacologic agent by the Food and Drug Administration of the United States, as well as regulatory agencies in Western Europe. Thus, do we know whether the preparations that are being used are of standardized and utmost quality? Are the infants receiving a highly pure preparation that is standard with each dosage? Is the probiotic preparation being used one that has truly been shown to have benefits and is safe both short- and long-term? Will this probiotic agent interfere with normal development of the preterm infant

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microbiota and not affect the development of the immune system and other important components of health in the long term?

Probiotics by definition are live agents that may survive long-term and change a developing microbial ecosystem in which the effects are not immediately seen. The inability to readily culture some of these agents from the bloodstream may lead to an underestimation of their potential translocation from the gastrointestinal tract into the bloodstream, where they may actually cause septic complications. One study has shown a greater incidence of mortality in adults receiving probiotics,² and several cases of sepsis have been reported in highly susceptible infants receiving probiotics.^{3,4}

Another recent study showed increased association with vancomycin-resistant enterococcus infection in infants given probiotics.⁵ One study showed a higher incidence of sepsis and neurologic damage in babies weighing less than 750 g.⁶ Should this information be disclosed to parents who request their infants be placed on probiotics? Relying on meta-analyses with a high "garbage in – garbage out" potential may be a major mistake in neonatal intensive care if we simply jump to any probiotic preparation to prevent NEC in these infants. Nevertheless, there appears to be a strong signal that begs for additional information in the form of well-designed, carefully controlled, adequately powered randomized trials of probiotic preparations that meet the standards of pharmacologic agents.

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NUTRITION

- Physicians may not be aware of recent evidence-based recommendations on recognizing and treating GERD in neonates.
- Physicians may not be aware of recent evidence-based recommendations on recognizing and treating GERD in neonates.
- Current neonatal nutritional management practices may be enhanced to optimize and meet the specific needs of low birth weight preterm infants.
- Current neonatal nutritional management practices may be enhanced to optimize and meet the specific needs of low birth weight preterm infants.
- Clinicians who treat neonates are uncertain of optimal strategies for prevention and early recognition and treatment of necrotizing enterocolitis.

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- Clinicians may be unfamiliar with some of the newest evidence-based approaches for treating neonatal persistent pulmonary hypertension.

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- Clinicians treating preterm infants may not be fully aware of the most recent developments in optimal management of bronchopulmonary dysplasia and respiratory distress syndrome.

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