ELSEVIER

Pathophysiology 21 (2014) 35–46

ISP PATHOPHYSIOLOGY

www.elsevier.com/locate/pathophys

# Probiotics and prebiotics in neonatal necrotizing enterocolitis: New opportunities for translational research

Pinaki Panigrahi[a,b,*]

[a] *Department of Epidemiology and Pediatrics, University of Nebraska Medical Center, Omaha, NE, United States*
[b] *Center for Global Health and Development, College of Public Health, Omaha, NE, United States*

**Abstract**

Neonatal necrotizing enterocolitis (NEC) in premature infants has been recognized as a defined disease entity for at least four decades. Although survival has increased due to the advent of more sophisticated intensive care, incidence and long term health impacts due to NEC remain unchanged and no preventive therapy is currently available. Different probiotic strains of bacteria have been examined in their ability to prevent NEC with varied but encouraging results. Undigestable prebiotic sugars known to promote the growth of probiotic bacteria in the colon have been used in neonates with no clear benefit. The literature on NEC and probiotics is now cluttered with more reviews and meta-analyses than number of clinical trials. On the other hand, significant new information is available on microbiota and their impact on gut immunity. This review attempts to reiterate the risk factors of NEC and the pathogenesis of NEC with special reference to gut permeability. The reader is then introduced to gut microbiota, uniqueness and differences among probiotic strains, and how multiple resident flora talk to each other in the community setting in the human gut. After presenting a concise review of available clinical research results, the reader is challenged to question as to why no precise answer is available at present. Some modalities to examine the complex microflora and changes in the neonatal gut are then proposed including non-invasive methods and mathematical modeling. The review concludes by attracting the reader's attention to known immunomodulators of inflammation and injury. Justice to this review will be done only if the readers, clinical, and basic science investigators from multiple fields gather courage for a paradigm shift and embark on understanding the pathophysiology of the disease and attempt to discern the difference from equally preterm, equally vulnerable neonates that do not develop NEC. Learning about the developing microbiota in neonatal gut and its immunological impacts on the host in the face of many variables will provide a leap in our pursuit to select better, if not the best candidate probiotics, and put them to work against this stubborn disease that continues to take a toll on our precious neonates and the society.


*Keywords:* Neonatal necrotizing enterocolitis; Probiotics; Prebiotics; Synbiotics; Gut microbiota; Non-invasive technology; Mathematical modeling; Gut immunology; Prematurity

## 1. Introduction

Neonatal necrotizing enterocolitis (NEC) is a disease of premature infants and continues to be one of the most significant causes of mortality and morbidity in the neonatal intensive care units. While the incidence rate has not changed, physicians and surgeons have been treating larger number of infants with NEC now, simply due to the survival of small and micro preemies due to the advanced care available. These infants with NEC have longer hospital stays, long-term neurological deficits, and life-long gastrointestinal dysfunction due to short gut syndrome in cases of large surgical resections of the necrosed gut. The health care expense alone in treating babies with NEC is at least $1B per year [1]. Additional societal burden and toll on parents and family should make NEC a priority disease for physicians, researchers, and policy makers.

## 2. History of NEC, probiotics, and prebiotics

Both NEC and probiotics bring with them at least a century-long recognition. Generisch is cited to have reported the first case of NEC in 1891 in a neonate with abdominal distension and vomiting who did not have intestinal

* Correspondence to: Department of Epidemiology and Pediatrics, Center for Global Health and Development, University of Nebraska Medical Center, Omaha, NE, United States.
*E-mail address:* ppanigrahi@unmc.edu

0928-4680/$ – see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.pathophys.2013.11.016

obstruction [2]. However, others suggest that Paltauf may have reported the first five cases of NEC three years prior to Generisch demonstrating clinical and pathologic findings consistent with NEC [3]. Although sporadic cases were being reported, it was not until the late 1960s and early 1970s when NEC became a well recognized disease entity [4]. The western world took serious notice of this disease as the survival of preterm and low birth weight infants increased over the last several decades. However, in spite of such recognition and active research, there has been no change in practice when it comes to care of newborns with NEC, nor is there a preventative modality for this devastating disease.

Leaving aside the mentions about consumption of fermented milk in the Old Testament, Eli Metchnikoff's mention about the concept of probiotics dates back to 1903. In 1906, Henry Tissier, a pediatrician at Pasteur Institute, described the absence of Bifidobacteria in children with diarrhea. The word probiotics was coined in the 1960s, and Shaedlar used harmless bacteria in a defined cocktail to raise specific pathogen-free animals, followed by introduction of its use in animal feeds by Parker in 1965 [5]. The importance of probiotics somehow was recognized more in Europe, Japan, and Asia compared to the U.S. and these agents have been in use as drugs as well as dietary supplements over the last several decades. During the last fifteen years however, there has been a flurry and an exponential increase on the number of scientific papers from around the world on probiotics.

Prebiotic sugars also bring under their belt at least a half-a-century of scientific evidence on chemistry and their health effects, although tubers containing high concentrations of these sugars have been consumed by humans for many centuries [6,7]. In the early1970s, Baird et al. and Drasar and colleagues started reporting impact of fibers and diet on gut flora [8,9]. By early 1990s prebiotics were well recognized with their biochemistry elucidated that could act as dietary supplements to modulate the colonic microflora in mammals [10]. At present, prebiotics are available on the health food stores, have received GRAS (Generally Regarded As Safe) status by the US FDA, and have been used in multiple clinical studies in adults and children [11].

## 3. Background

### *3.1. Yet another review article in NEC, probiotics, and prebiotics?*

Undoubtedly NEC is a complex and smart disease. But, is it more complex than cancer and HIV/AIDS? At least some therapies are available for certain forms of cancer, and HIV/AIDS is not as deadly a term as it was a decade ago. Is it because NEC is a disease of newborns who cannot speak or complain? Or their value is not fully recognized by the society? May be, newborns are easily replaceable. Otherwise, we would not have done only 12 clinical trials of probiotics and prebiotics in NEC (and just a handful using other interventions) after recognizing the disease for four decades. A July 2013 Pubmed search yielded five times as many reviews and twice as many systematic reviews and meta-analyses on the subject compared to number of original clinical trials (Fig. 1).

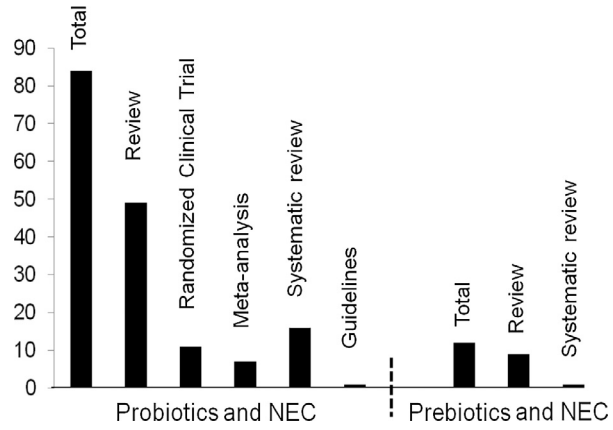


Fig. 1. Number of published papers on *Y* axis. Types of paper (subjects) are described on the "*X*" axis. Retrieved from PubMed using the combination of search terms "NEC and probiotics", and "NEC and prebiotics". Further filters were used to separate randomized clinical trials (RCTs), meta-analyses, and systematic reviews.

On the other hand, now there are 2309 papers on NEC, 6090 papers on probiotics, and 975 on prebiotics. Under prebiotics, we retrieved a total of 12 papers using the terms prebiotics and NEC, of which nine were review articles, and one systematic review. Seven clinical trials used prebiotics of some form, but none had NEC as the primary outcome measure. A systematic review and meta-analysis appeared in the literature during preparation of this manuscript [12].

The purpose of this review is not to clutter the flash drives or IPADs of clinicians and scientists. This author was challenged recently by a pediatrician friend in private practice who commented that "you are serving old wine in the same old bottle – at least use a new bottle!" The current endeavor is not to cater to this friend's wish, but to ask ourselves if we have the ability to design or manufacture a new bottle, are there new and good quality grapes available now? If the answer to these basic questions is "yes", we should refrain from writing reviews and meta-analyses and get busy on making the wine and take it through multiple tastings.

Indeed, there is currently an unfathomable amount of basic science data on probiotic bacteria, we know a lot more about human gut microbiota and how they change during the neonatal period, and many new doors have been opened to witness the exciting immunology as they relate to pathobiology and pathogenesis of human diseases. High throughput techniques and new bioinformatics tools are now routinely used to examine and compare millions of gene sequences at a time, everything at a price tag lower than before and in a much shorter time frame than what many of us are used to. We need new investigators, preferably who have not been jaundiced by us and are seeing everything yellow in NEC: