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Neonatal Gastrointestinal and Respiratory Microbiome in Cystic Fibrosis: Potential Interactions and Implications for Systemic Health

Juliette C. Madan, MD, MS

Division of Neonatology, Department of Pediatrics, Children's Hospital at Dartmouth, Geisel School of Medicine at Dartmouth, Hanover, New Hampshire

ABSTRACT

Purpose: The gastrointestinal microbiome plays a critical role in nutrition and metabolic and immune functions in infants and young children and has implications for lifelong health. Cystic fibrosis (CF) transmembrane conductance regulator (*CFTR*) mutations in CF result in viscous mucous production, frequent exposure to antibiotics, and atypical colonization patterns, resulting in an evolving dysbiosis of the gastrointestinal and respiratory microsystems; dysbiosis in CF results in systemic inflammation, chronic infection, and dysregulation of immune function. Dysbiosis in both the respiratory system and gut contributes to undernutrition, growth failure, and long-term respiratory and systemic morbidity in infants and children with CF. Understanding the role that the gut and respiratory microbiome plays in health or disease progression in CF will afford opportunities to better identify interventions to affect clinical changes.

Methods: Summary was done of the pertinent literature in CF and the study of the microbiome and probiotics.

Findings: New studies have identified bacteria in the respiratory tract in CF that are typically members of the intestinal microbiota, and enteral exposures to breast milk and probiotics are associated with prolonged periods of respiratory stability in CF.

Implications: Understanding the complex interactions between the *CFTR* mutations, microbial colonization, and mucosal and systemic immunity is of major importance to inform new treatment strategies (such as restoring a healthier microbiome with probiotics or dietary interventions) to improve nutritional status and immune competence and to decrease morbidity and mortality in CF. (*Clin Ther*. 2016;▮:▮▮▮–▮▮▮) © 2016 Published by Elsevier HS Journals, Inc.

Key words: Infant, intestinal microbiome, respiratory microbiome, probiotics.

INTRODUCTION

The composition and function of the human microbiome and its critical role in health in infants, young children, and adults is just beginning to be elucidated.[1] The gut microbiome, in particular, which co-evolved with humans, is critical for immune maturation in addition to drug and energy metabolism.[1] Clarifying the role of the microbiome and the metabolome, in particular in the neonatal period, may provide important understanding about immunity and lifetime disease risk, both in high-risk patient populations and in the healthy. Meaningful patterns in the microbiome/metabolome and their associations with disease risk and disease progression have been identified in disorders such as allergic disease, diabetes, obesity, autism, and respiratory disease.[2] Clarifying these patterns affords researchers possibilities for identifying targeted therapies to alter the microbiome to treat disease or to enhance health.[3] The neonatal period is a critical window for immune programming that may affect health for a lifetime, and patterns in the microbiome may allow for prediction of disease risk, disease progression, or elimination of disease altogether.

The role of the gut microbiome in systemic health is a new focus in the care and evaluation of infants and young children with cystic fibrosis (CF). Mutations in CF transmembrane conductance regulator (*CFTR*) fundamentally affect the airway and intestinal microenvironment and result in altered colonization patterns of microorganisms in patients with CF even in the absence of antibiotic exposure.[4] Intestinal dysfunction, secondary to structural and functional

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differences and frequent antibiotic exposure, results in an evolving dysbiosis of the gastrointestinal (GI) microsystem and macrosystem, or the microbe–microbe interactions and microbe–epithelium and immune crosstalk, and its holistic structural and functional role in systemic health.[5–8] This abnormal colonization likely contributes significantly to undernutrition, growth failure, and long-term morbidity from inflammation and infection in children and adults with CF.[5–8] Gut colonization and interactions with systemic immune training likely have implications for respiratory disease progression in CF.[9] Understanding the complex interactions between *CFTR* mutations, microbial colonization, and mucosal and systemic immunity is of major importance to inform new treatment strategies to improve nutritional status and to decrease morbidity and mortality in CF. The role of microbes in systemic health and disease risk in CF has implications for healthy populations as well. The ability to investigate the microbiome of multiple organ systems with the use of high-throughput microbial sequencing methods provides more significant understanding of the landscape of multisystem microbial colonization and disease progression in CF.[10–12] Clarifying further the functional roles these microbes play with investigation of metabolomics has important implications for identifying interventions to alter disease progression in CF.[13]

THE EXPOSOME AND THE DEVELOPING INTESTINAL MICROBIOME IN HEALTHY CHILDREN

The totality of human exposures, beginning in fetal life, and its interaction with the human genome, is called the exposome. The microbiome is established within the first 1 to 3 years of life and remains relatively stable throughout the life span.[14] The developing microbiome in infancy is affected by mode of delivery, gestational age, infant diet, hospitalizations, and medications, particularly antibiotics; environmental toxicants and other exposures and their interaction with the developing microbiome are being investigated.[15] The greatest intrapersonal and interpersonal variation in microbial communities occurs during infancy, potentially reflecting the differential development of the microbiome in relation to environmental factors, many of which can be altered.[14] Human gene–environment interactions, and the interaction between "barrier organs," such as the gut, respiratory tract, and the skin, are an important consideration in the study of the microbiome and its role in health. Environmental exposures and environmental stressors interact with us directly through these barrier organs, which house millions of microbes.[16] Genetic predisposition to patterns of immune regulation or dysregulation direct homeostasis and inflammation of the gut, respiratory tract, and skin; CF is an important example of dysregulation of homeostasis of barrier organs. The microbes in the gut and respiratory tract play an important role in regulation of inflammation, and manipulation of the microbiome may be an important strategy to affect disease in CF.

THE INTESTINAL MICROBIOME AND IMMUNITY

Seminal studies in germ-free animals found that absence of microbial colonization in neonatal life results in altered gut epithelialization, growth, and immune function.[17,18] The establishment of symbiotic bacteria can act as a central stimulus for maturation of the immune system and may alter risk of disease manifestation.[19,20] Both innate and adaptive immunity in humans have evolved to require microbial interactions during their development, including Toll-like receptors, class II major histocompatibility complexes, CD4 T cells, and the gut-associated lymphoid tissue.[21,22] Competent immune maintenance and homeostasis also require ongoing interaction with the gut microbiome.[23] It is theorized that fetal and neonatal exposures and events (such as exposure to toxins, antibiotics, and illness) during gut colonization and immune development are relevant to modifying disease risk for a lifetime.[18] Targeted investigation of neonatal microbial colonization patterns with *Bifidobacterium* found associations between enhanced maturation of protective mucosal immunoglobulins, and early intense colonization with *Bacteroides fragilis* decreases immune responsiveness in infancy.[24] Interestingly, specific bacteria have been associated with early-onset allergy and atopy, particularly an increase in *Clostridia* and a decrease in *Bifidobacteria*.[25] Murine models of type 1 diabetes have found that incidence of diabetes can be attenuated by modifying bacterial exposures[26]; in a separate murine model oral administration of probiotics before