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# Harnessing the Early-Life Microbiota to Protect Children with Cystic Fibrosis

In this issue of *The Journal*, Hoen et al[1] carefully studied 120 fecal and oropharyngeal samples from 13 children with cystic fibrosis (CF) from birth to nearly 3 years of age. They sought to test the hypothesis that patterns of acquisition of the normal microbiome affect the risk of CF-related events, such as pulmonary colonization with *Pseudomonas* and clinically significant pulmonary infections. They showed that a core of dominant microbes, many of them anaerobes, is shared between stools and the oropharyngeal mucosa, dominating the microbiome from birth and during the first few years of life in these patients. This study highlights the substantial diversity in the microbial environments in which pathogens bloom. The small sample size (13 children) limits interpretation, but the results are sufficiently promising to merit the study of larger cohorts for validation.

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This report leads us to consider that the early stages of acquiring the human microbiome might be important in relation to the susceptibility for infections with pathogens in CF. Such susceptibility commonly has been associated with host factors that

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| CF | Cystic fibrosis |
| CFTR | Cystic fibrosis transmembrane conductance regulator |

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increase the individual risk of acquiring a pathogen.[2,3] In CF, impaired antimicrobial activity in the airway mucosa is an example of this type of susceptibility.[4] Host CF genotype is important because there are major CF phenotypic differences based on a patient's particular mutation.[5,6] Thus, the extent of CF transmembrane conductance regulator (CFTR) dysfunction provides varying selection pressure affecting the host's early microbial colonization.

A different kind of susceptibility can be conceived if we consider the individual's microbiome as a supraorganism within each individual, in which its distinct composition and function (or dysfunction) can make it susceptible to the successful seeding and blooming of pathogens. Thus, the newborn period can be considered a vulnerable stage in which the airway microbiome is an important component of the host defense system and normal development of a healthy microbiota provides reduced susceptibility to the introduction of pathogens (**Figure**; available at www.jpeds.com). This may differ in children with CF, however. As such, we considered 3 important questions.

## What Is the Early-Life Microbiota in Children with CF?

Based on this study, specific assemblages of bacteria in intestinal samples were associated with CF exacerbation in early life. Although effects of the intestinal microbiome on the lung phenotype have been suggested previously,[7,8] the findings from this study are consistent with the gut microbiome affecting host immunity, driven by immunologic cross-talk between the gut and lung mucosa. Surprisingly, the composition of the oral microbiota did not appear to be important in the development of pulmonary events. Although this is a critical point, the study was limited, because sampling of the oral cavity does not completely represent the lower respiratory microbiota.[9]

A major limitation of CF studies to date has been the reliance on noninvasive upper respiratory samples to infer the actual composition of the lower airway microbiome. The finding of *Streptococcus* and *Veillonella* as dominant species in oropharyngeal samples is expected because these are known to be abundant oropharyngeal microbes; however, although they are commonly present in the lower airways, many healthy subjects appear to lack them.[10-12] It is possible that the relative abundance of these 2 taxa more accurately represents the upper airway microbiota rather than the lower airway microbiota. Studies are needed to dissect topographical differences related to the airway microbiota to further understand host immune and inflammatory responses in the lung. The role of the upper airway microbiota in preventing or facilitating pathogen acquisition events may be critical. The present study requires confirmation, so that clinicians and scientists can develop proper approaches to therapy.

## Does the Microbial Composition of the Gastrointestinal and Airway Mucosa Make a Difference in the Natural History of the Disease?

Hoen et al report that before the onset of *Pseudomonas aeruginosa* colonization, there were significant changes in relative abundance, including increased *Salmonella* in the oropharyngeal mucosa and decreased *Bacteroides* and *Bifidobacterium* in intestinal samples. We interpret the *Salmonella* observation as representative of the *Enterobacteriaceae*, and consistent with a diathesis for their colonization of patients with CF. The authors speculate that because *Bacteroides* and *Bifidobacterium* have been associated with mucosal immunity, the decrease in their relative abundance may contribute to pathogen acquisition. The authors also report that greater microbial diversity in the gastrointestinal tract and less diversity in the oropharynx were associated with a trend toward longer times to CF exacerbation and *P aeruginosa* colonization. Fluctuations in the abundance of specific bacterial taxa preceded clinical outcomes; a significant decrease in the intestinal genus *Parabacteroides* was noted before the onset of chronic *P aeruginosa* colonization. Taken together, these results are consistent with either of 2 major possibilities: that the composition of oral and fecal microbiota directly affects host susceptibility to pathogens, or that the microbiota composition reflects the state of dysfunctional immune maturation in CF.

Hoen et al found that breast-feeding was associated with delayed exacerbations, an observation consistent with evidence that breast-feeding is associated with increased gut microbial diversity.[13] If confirmed, this observation could make a difference clinically, providing a strong incentive for mothers of children with CF to breast-feed, possibly for as long as reasonably possible and, unless clearly necessary, to avoid taking antibiotics that perturb the microbiota.[14]

## Can We Harness the Microbiome to Protect Children with CF Against Early Infections by Pathogens?

CF is a disease in which recurrent and chronic infection leads to progressively declining lung function and death. Specific CFTR modulators are already available to improve CFTR function and thereby decrease the susceptibility to infections[15]; however, as long as CFTR dysfunction continues, a deeper understanding of human microbial ecology is needed to prevent the acquisition of opportunistic pathogens. Environmental exposures in early life shape the microbiome at this very susceptible stage; thus, it is not surprising that in a host intrinsically susceptible owing to CFTR dysfunction, the characteristics of the early-life microbiome may play critical roles in disease development. Studies of the microbiota and the combined microbial/host metabolome across time may have important diagnostic and prognostic implications, and possibly preventive or therapeutic potential. Steps to