

# Piecing together the preterm infant microbiome

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The human microbiome—the collection of microbes living in the gut—is now recognized as an important contributor to health and disease. The environment, the host, and microbe-microbe interactions are all likely to shape the microbiome's dynamics, but the unique roles of each are not well understood. Now, a Boston Children's Hospital infectious disease researcher reveals how the microbiome develops in the preterm infant gut, an environment where few microbes are in residence at the beginning of life.

"Understanding how the microbiome forms in [preterm infants](#) is essential, as we know it can lead to disease and influence their future health," says Seth Rakoff-Nahoum, MD, Ph.D., a physician-scientist in the Divisions of Infectious Diseases and Gastroenterology whose [paper on the topic](#) was published in *Nature*. "We can't change it unless we know how it develops and functions."

Preterm infants are usually delivered by caesarian section, so they are not exposed to the usual maternal [microbes](#) associated with a vaginal delivery. "That means they are a clean slate, with

virtually no microorganisms in the gut at birth," says Rakoff-Nahoum. "It's a great way to learn how the microbiome develops and how the organisms interact and influence each other."

## Microbial ecology in action

By studying the gut ecology of preterm babies via fecal samples, Rakoff-Nahoum and his colleagues discovered that microorganisms engage in a literal battle to the death. "We know that assembly of the preterm gut microbiome occurs predictably, but we didn't know why," says Rakoff-Nahoum. The authors found that first, an initial pioneer microorganism settles in the gut. Other microbes follow, initially interacting with their predecessors to get established, but then exploiting them, or wiping them out, and building up their own numbers. The process continues as the microbes continue to interact with each other, with the dominant organism establishing a larger presence at the cost of earlier microbes.

Specifically, the team found that interactions between different kingdoms of microorganisms—which include bacteria, fungi, and archaea—influenced how the gut microbiome assembled. "We uncovered, with exquisite precision, blooms and extinctions of each microbe and also an inverse relationship between the amounts of bacteria and fungi," says Rakoff-Nahoum, referring to the finding that a single fungal species, *Candida albicans*, inhibited many dominant types of gut bacteria. "It was shocking to see how much fungi could be found in the gut of a newborn infant and how it could regulate specific bacteria."

## Next-generation sequencing revealed dynamics

To learn how the microbes interacted with each other, known numbers of bacteria, fungi, and archaea were injected into fecal samples from 178 preterm [infants](#) and cultured in the lab.

In a method the team developed called MK-SpikeSeq, DNA was extracted and amplified from the stool samples. Next-generation sequencing revealed exactly how much DNA from each organism was present over time as the microbes interacted with each other.

"We didn't just find the relative amounts of DNA from each organism, but the actual numbers," says Rakoff-Nahoum. This was previously difficult to calculate with existing methods. "And we saw a certain network of interactions between the microbes; some positive, some negative."

Mouse studies confirmed the same findings in a living organism. "We found that these transitions from one microorganism to another are actually direct interactions between pairs of microbes that drive microbiomes in preterm babies," he says.

### **Engineering microbiomes to improve health**

"Our discovery of the precise interactions that shape the development of the preterm infant microbiome is a critical step towards targeted microbiota engineering to improve health or treat disease," says Rakoff-Nahoum.

Moving forward, the team plans on studying how the preterm infant [microbiome](#) affects specific diseases, such as during sepsis or from necrotizing enterocolitis. The researchers hope to find new ways to prevent [disease](#) from gaining a foothold or from progressing.

The team also hopes that the newly developed methods will be used in conservation and environmental microbiology. Potential uses involve understanding the relationships between bacteria and fungi, such as in algae blooms in marine ecosystems, or in soil ecosystems.

**More information:** Chitong Rao et al. Multi-kingdom ecological drivers of microbiota assembly in preterm infants, *Nature* (2021). [DOI: 10.1038/s41586-021-03241-8](https://doi.org/10.1038/s41586-021-03241-8)

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