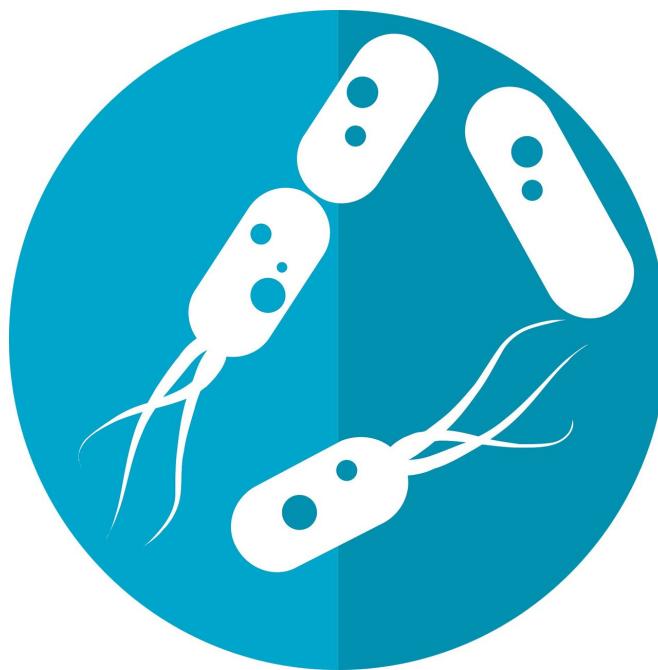


Restoring gut microbes missing in early life dysbiosis can reduce risk of colitis in mice

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A new study at the University of Chicago has determined that restoring a single microbial species—*Bacteroides* sp. CL1-UC (Bc)—to the gut microbiome at a key developmental timepoint can prevent antibiotic-induced colitis in a mouse model of the condition. The results, published on June 7 in *Gastroenterology*, have major implications for humans dealing with inflammatory bowel disease (IBD), and underscore the impact of early childhood exposures on health throughout the lifetime.

Prior studies in human patients have found that [early life exposure](#) to antibiotics can skew the gut [microbiome](#), causing dysbiosis, or an imbalance of the microbial populations in the gut, which is correlated with increase risk for developing pediatric IBD.

"We know that the kinds of microbes that you're exposed to early in life actually determine how your [immune system](#) develops," said senior author Eugene Chang, MD, Martin Boyer Professor of Medicine at UChicago. "Our immune system learns to recognize our own selves, and the trillions of microbes in our gut—they're 'us' as well, so our immune system has to learn to tolerate these organisms, just as it tolerates our own cells. Early exposure to antibiotics can eradicate some of the organisms that are essential for educating the immune system to develop immune tolerance."

Due to the challenges of conducting such studies in [human patients](#), the researchers opted to use a common model for studying colitis: Mice that lack a gene known as IL-10 (IL-10-/-). "This [mouse model](#) has been established as being genetically susceptible to IBD, and we know that the [gut microbiome](#) plays a crucial role in the development of colitis in this model," said first author Jun Miyoshi, MD, Ph.D., a Senior Assistant Professor in the Department of Gastroenterology and Hepatology at Kyorin University School of Medicine, and a former postdoctoral scholar at UChicago.

While only very rarely do these [mice](#) develop spontaneous colitis without any intervention in a clean environment, if their mothers are exposed to antibiotics during pregnancy and nursing, the disrupted microbiome can be transmitted to the pups at an early age. Around 30% of pups with this vertically transmitted disrupted microbiome go on to develop colitis.

The investigators used a technique known as shotgun metagenomic sequencing to screen the fecal microbiomes of IL-10-/- mice that had antibiotic-induced dysbiosis, alongside an untreated control group, and identify specific microbial species that might distinguish the two groups. This led them to members of the bacterial phylum *Bacteroides*.

One clue of the phylum's importance was that *Bacteroides* was very abundant in the microbiomes of untreated mice, but completely lacking in the mice that had been exposed to antibiotics. What's more, the researchers never saw *Bacteroides* in the treated mice that did not go on to develop colitis—but they often found *Bacteroides* in the guts of mice that did end up with the condition.

"These bacteria were eradicated by early exposure to antibiotics and were essential for educating the immune system in developing immune tolerance," said Chang. "When those mice later acquired the bacteria, their immune system had never seen it. It was viewed as foreign, not as self, and their immune systems reacted to it."

In an effort to determine whether restoring important *Bacteroides* back to the microbiome could correct the dysbiosis, the researchers honed in on a particularly abundant species known as *Bacteroides* sp. CL1-UC (Bc). They tried adding Bc back to the microbiomes of the mice with dysbiosis at two timepoints: Around infancy (three weeks of age) and adulthood (11 weeks of age).

Engrafting Bc into the younger mice, during the critical immune system developmental window, corrected their dysbiosis and prevented colitis, but adding Bc back to adult mice could not correct the dysbiosis, and even worsened their colitis.

"This shows that you can't just restore the missing bacteria at any time point, it has to be at a specific time early in life to have a beneficial effect," said Chang. "In young animals, we know that the immune system is developing, it's naive, it has to be taught, and it's taught by being exposed to certain kinds of microbes. In some ways, it's similar to a peanut allergy—[early exposure](#) to the antigen can tolerize the immune system to help avoid a [peanut allergy](#), but it has to happen within a very finite window."

The researchers were surprised to learn that restoring a single microbe was enough to correct lifelong dysbiosis, and said it highlighted how relatively small changes can have a dramatic impact on a system. "It's like the tall trees of the Amazon rainforest," said Chang. "You need the tall

trees, because if you don't have them, the ecosystem below cannot develop properly. But if you have those trees in place, the rest of the ecosystem will flourish."

The results also go against popular theories on the origin of IBD. "There's a misconception that colitis is caused by a classical pathogen, like salmonella, and scientists have spent years looking for a culprit," said Chang. "But what our data are pointing to is that these diseases are caused by our own commensal microbes. They are present in the normal, healthy microbiome, but given the right circumstance and opportunity, they can transform into disease-promoting microbes."

While this early study was proof-of-concept, if the results translate to humans, the ripple effects are likely to be far-reaching. "This shows that we probably have to rethink our approach to these kinds of complex immune disorders," said Chang. "We can see that risk is developing early in life—even in utero—and so this has implications for practices such as C-sections and formula feeding, which can impact the microbes an infant is exposed to. What this says to me is that, as physicians, we need to shift our thinking to not what immediately precedes these diseases but what happens early in life. That's where we need to intervene for these patients."

More information: Jun Miyoshi et al, Early-life microbial restitution reduces colitis risk promoted by antibiotic-induced gut dysbiosis in IL-10^{-/-} mice, *Gastroenterology* (2021). DOI: [10.1053/j.gastro.2021.05.054](https://doi.org/10.1053/j.gastro.2021.05.054)

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