

Use of antibiotics in preemies has lasting, potentially harmful effects

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Nearly all premature babies receive antibiotics in their first weeks of life to ward off or treat potentially deadly bacterial infections. Such drugs are lifesavers, but they also cause long-lasting collateral damage to the

developing microbial communities in the babies' intestinal tracts, according to research from Washington University School of Medicine in St. Louis.

A year and a half after babies leave the neonatal intensive care unit (NICU), the consequences of early antibiotic exposure remain, the study showed. Compared to healthy full-term babies in the study who had not received antibiotics, preemies' microbiomes contained more bacteria associated with disease, fewer species linked to good health, and more bacteria with the ability to withstand antibiotics.

The findings, published Sept. 9 in *Nature Microbiology*, suggest that antibiotic use in preemies should be carefully tailored to minimize disruptions to the gut microbiome—and that doing so might reduce the risk of health problems later in life.

"The type of microbes most likely to survive antibiotic treatment are not the ones we typically associate with a healthy gut," said senior author Gautam Dantas, Ph.D., a professor of pathology and immunology, of molecular microbiology, and of biomedical engineering. "The makeup of your gut microbiome is pretty much set by age 3, and then it stays pretty stable. So if unhealthy microbes get a foothold early in life, they could stick around for a very long time. One or two rounds of antibiotics in the first couple weeks of life might still matter when you're 40."

Healthy gut microbiomes have been linked to reduced risk of a variety of immune and metabolic disorders, including inflammatory bowel disease, allergies, obesity and diabetes. Researchers already knew that antibiotics disrupt the intestinal microbial community in children and adults in ways that can be harmful. What they didn't know was how long the disruptions last.

To find out whether preemies' microbiomes recover over time, Dantas

and colleagues—including first author Andrew Gasparrini, Ph.D., who was a graduate student at the time the study was conducted, and co-authors Phillip I. Tarr, MD, the Melvin E. Carnahan Professor of Pediatrics, and Barbara Warner, MD, director of the Division of Newborn Medicine—analyzed 437 fecal samples collected from 58 infants, ages birth to 21 months. Forty-one of the infants were born around 2 ½ months premature, and the remainder were born at full term.

All of the preemies had been treated with antibiotics in the NICU. Nine had received just one course, and the other 32 each had been given an average of eight courses and spent about half their time in the NICU on antibiotics. None of the full-term babies had received antibiotics.

The researchers discovered that preemies who had been heavily treated with antibiotics carried significantly more drug-resistant bacteria in their gut microbiomes at 21 months of age than preemies who had received just one course of antibiotics, or full-term infants who had not received antibiotics. The presence of drug-resistant bacteria did not necessarily cause any immediate problems for the babies because most gut bacteria are harmless—as long as they stay in the gut. But gut microbes sometimes escape the intestine and travel to the bloodstream, urinary tract or other parts of the body. When they do, drug resistance can make the resulting infections very difficult to treat.

Moreover, by culturing bacteria from fecal samples taken eight to 10 months apart, the researchers discovered that the drug-resistant strains present in older babies were the same ones that had established themselves early on.

"They weren't just similar bugs, they were the same bugs, as best we could tell," Dantas said. "We had cleared an opening for these early invaders with antibiotics, and once they got in, they were not going to let anybody push them out. And while we didn't show that these specific

bugs had caused disease in our kids, these are exactly the kind of bacteria that cause urinary tract and bloodstream infections and other problems. So you have a situation where potentially pathogenic microbes are getting established early in life and sticking around."

Further studies showed that all of the babies developed diverse microbiomes by 21 months of age—a good sign since lack of microbial diversity is associated with immune and metabolic disorders in children and adults. But heavily treated preemies developed diverse microbiomes more slowly than lightly treated preemies and full-term infants. Further, the makeup of the gut microbial communities differed, with heavily treated premature infants having fewer healthy groups of bacteria such as Bifidobacteriaceae and more unhealthy kinds such as Proteobacteria.

The findings already have led Warner, who takes care of premature infants in the NICU at St. Louis Children's Hospital, and her fellow neonatologists to scale down their use of antibiotics.

"We're no longer saying, 'Let's just start them on antibiotics because it's better to be safe than sorry,'" Warner said. "Now we know there's a risk of selecting for organisms that can persist and create health risks later in childhood and in life. So we're being much more judicious about initiating antibiotic use, and when we do start babies on antibiotics, we take them off as soon as the bacteria are cleared. We still have to use antibiotics—there's no question that they save lives—but we've been able to reduce antibiotic use significantly with no increase in adverse outcomes for the children."

More information: Gasparrini AJ, et al. Persistent metagenomic signatures of early-life hospitalization and antibiotic treatment in the infant gut microbiota and resistome. *Nature Microbiology*. 2019. DOI: [10.1038/s41564-019-0550-2](https://doi.org/10.1038/s41564-019-0550-2) , [nature.com/articles/s41564-019-0550-2](https://www.nature.com/articles/s41564-019-0550-2)

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