Microbiome insights found in poop help predict infections in liver transplant patients

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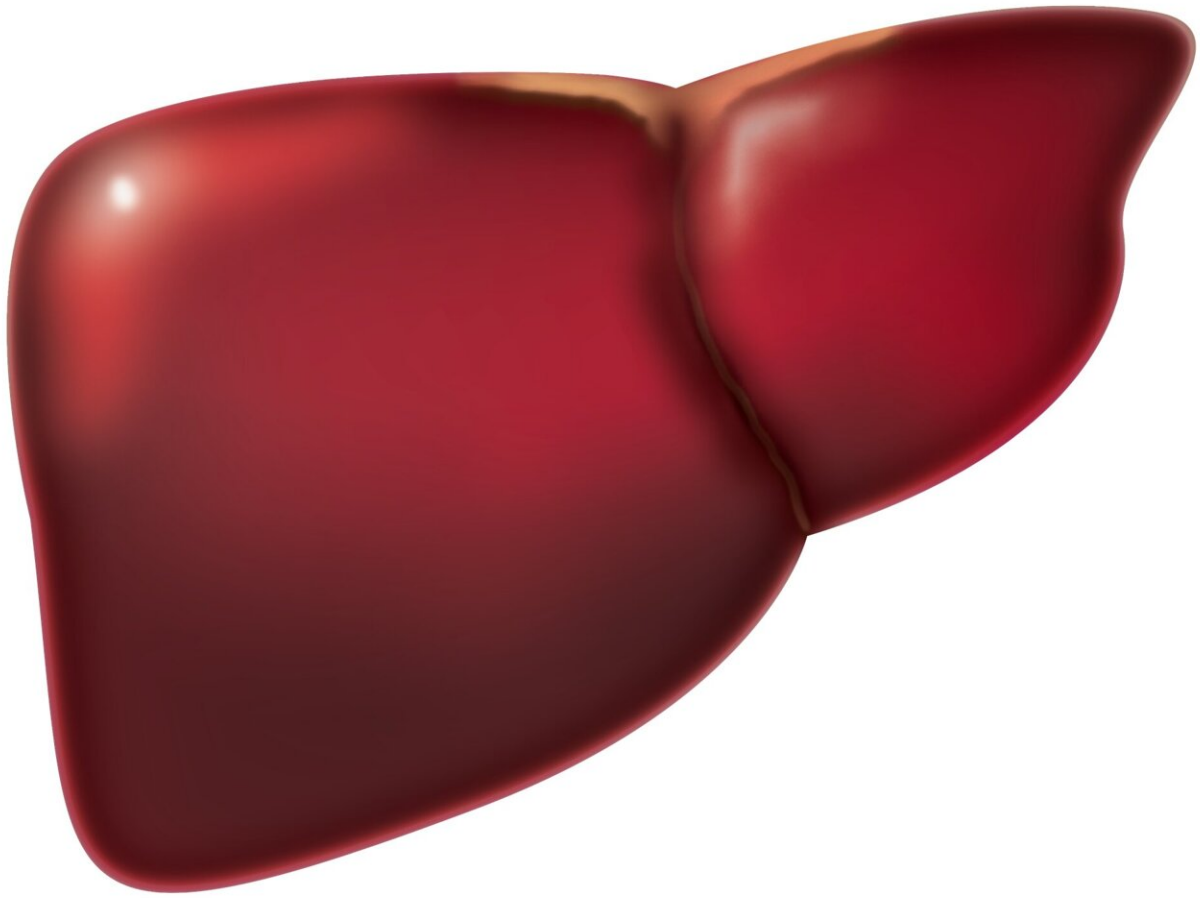

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In a new study, researchers at the University of Chicago were able to predict postoperative infections in liver transplant patients by analyzing molecules in their poop. Their analysis represents a key leap forward in exploring the connection between the gut microbiome—the bacteria that inhabit the human body—and overall health.

"Antibiotic resistance is growing every year and getting worse. Without antibiotics that work, we can't do things like perform surgeries, protect premature infants or treat cancer," said Christopher Lehmann, MD, an assistant professor of medicine at UChicago Medicine and lead author on the study. "It turns out the human microbiome, particularly the gut microbiome, has adapted to fight off drug-resistant bacteria over the course of history. We need to try to understand how that works to fight off these drug-resistant infections."

Liver transplant patients are especially susceptible to drug-resistant infections, so Lehmann and his fellow researchers analyzed fecal samples from over 100 liver transplant patients to see if the microbiome could be influencing their risk of infection.

Healthy versus unhealthy microbiomes

The researchers discovered a wide range of microbiome compositions in different patients.

"A healthy microbiome would be composed of over a trillion bacterial cells, with thousands of unique species—like a diverse rainforest," explained Lehmann. "Some patients have that entire ecosystem wiped out. They still have over a trillion cells, but there's only one single

bacterial species—usually a bad, drug-resistant one. It would be like clear-cutting the rainforest and planting nothing but a single harmful weed species."

The researchers found that healthy microbiomes produce several key metabolites, which are molecules made through digestion or other chemical processes inside an organism. These metabolites include short-chain fatty acids, which are beneficial to human hosts, as well as secondary bile acids produced when the bacteria modify human bile acids to fit their own needs.

It turned out that in a diverse microbiome, those needs include fighting off drug-resistant bacteria. Some of the bile acids are highly toxic to bacteria such as vancomycin-resistant Enterococcus (VRE), a type of antibiotic-resistant bacteria that frequently causes infections in patients who've undergone surgery, cancer treatment or intensive care.

The predictive power of poop

Next, the researchers examined their data to see if there was a correlation between microbiome composition and postoperative infections.

"It turned out that the amount of drug-resistant pathogens in the microbiome predicted postoperative infections with an accuracy we'd normally be looking for in a clinical test," Lehmann said.

The team then took it one step further. Rather than sequencing genomes to identify specific bacterial species, they decided to look just at the metabolites in patients' poop to see if those molecules offered the same predictive value. The metabolites alone allowed them to sort patients into two categories: healthy microbiomes and unhealthy microbiomes. Making the final analytical leap, the scientists found they could use the

metabolites to predict whether a patient would get an infection at all.

"We can go straight from metabolites to predicting a clinical outcome," Lehmann said. "This is important because metabolomic analysis can be performed very quickly, whereas sequencing is relatively slow."

The analytical algorithm is currently very complicated and would need extensive validation before being used as a diagnostic or predictive test in clinical practice. However, these findings lay the groundwork for future studies that could solidify the connection between infection and metabolites in poop, as well as exploring potential causal relationships.

The next step: fixing microbiomes to prevent infection

"The next step of this course of research will be investigating whether we can use these findings to correct people's microbiomes," Lehmann said. Patients who have unhealthy, single-species gut microbiomes and are at high risk of infection could potentially receive healthy gut bacteria from external sources restore production of healthy metabolites, including molecules like the secondary bile acids that can help protect against drug-resistant infections.

In 2023, FDA approved two microbiome restoration products. "Microbiome restoration isn't in the far-off future; it's already in the present," Lehmann said.

UChicago's Biological Sciences Division already has a biobank containing thousands of bacteria, all of which have been analyzed and categorized based on their genomes and what metabolites they produce. UChicago is building a Good Manufacturing Practices (GMP)-compliant facility that will allow scientists to produce, filter, and freeze-dry key gut

bacteria derived from healthy donors and pack them into pharmaceutical-grade capsules that people can take like pills.

"We've already made a handful of cocktails of bacteria that are missing from patients who have bad outcomes but present in patients that have good outcomes," Lehmann said. "Those bacteria can work together to make the metabolites that were missing in patients that got infections, and then they can inhabit the gut and theoretically defend against future negative outcomes."

In patients who have received broad-spectrum antibiotic treatment, such capsules could be used to repopulate healthy gut bacteria that were wiped out. In patients who are at high risk for drug-resistant bacterial infections, supplementing their microbiome metabolites may be able to provide some protection.

"We've been losing the battle against multiple drug-resistant bacteria, so we desperately need more weapons," Lehmann said. "Understanding the microbiome, testing the microbiome's health, and restoring the microbiome are all crucial new tools we can add to our arsenal."

The study, "Fecal metabolite profiling identifies liver transplant recipients at risk for postoperative infection," was published in *Cell Host & Microbe* in December 2023. Co-authors include Nicholas P. Dylla, Matthew Odenwald, Ravi Nayak, Maryam Khalid, Jaye Boissiere, Jackelyn Cantoral, Emerald Adler, Matthew R. Stutz, Mark Dela Cruz, Angelica Moran, Huaiying Lin, Anitha Sundararajan, Ashley M. Sidebottom, Jessica Cleary, Eric G. Pamer, Andrew Aronsohn, John Fung, Talia B. Baker and Aalok Kacha.

More information: Christopher J. Lehmann et al, Fecal metabolite profiling identifies liver transplant recipients at risk for postoperative infection, *Cell Host & Microbe* (2023). DOI:

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