New antibiotic kills pathogenic bacteria, spares healthy gut microbes

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A medical illustration of Clostridioides difficile bacteria, formerly known as Clostridium difficile, presented in the Centers for Disease Control and Prevention (CDC) publication entitled, Antibiotic Resistance Threats in the United States, 2019. Credit: CDC

Researchers have developed a new antibiotic that reduced or eliminated drug-resistant bacterial infections in mouse models of acute pneumonia and sepsis while sparing healthy microbes in the mouse gut. The drug, called lolamicin, also warded off secondary infections with Clostridioides difficile, a common and dangerous hospital-associated bacterial infection, and was effective against more than 130 multidrug-resistant bacterial strains in cell culture.

The findings are detailed in the journal *Nature*.

"People are starting to realize that the antibiotics we've all been taking—that are fighting infection and, in some instances, saving our lives—also are having these deleterious effects on us," said University of Illinois Urbana-Champaign chemistry professor Paul Hergenrother, who led the study with former doctoral student Kristen Muñoz.

"They're killing our good bacteria as they treat the infection. We wanted to start thinking about the next generation of antibiotics that could be developed to kill the pathogenic bacteria and not the beneficial ones."

Numerous studies have found that antibiotic-related disturbances to the gut microbiome increase vulnerability to further infections and are associated with gastrointestinal, kidney, liver and other problems.

"Most clinically approved antibiotics only kill gram-positive bacteria or kill both gram-positive and gram-negative bacteria," Muñoz said.

Gram-positive and gram-negative bacteria differ in the composition of their cell walls. Gram-negative bacteria have a double layer of protection, making them more difficult to kill, Muñoz said.

The few drugs available to fight gram-negative infections also kill other potentially beneficial gram-negative bacteria. For example, colistin, one

of the few gram-negative-only antibiotics approved for clinical use, can cause C. difficile-associated diarrhea and pseudomembranous colitis, a potentially life-threatening complication. The drug also has toxic effects on the liver and kidney, and "thus colistin is typically utilized only as an antibiotic of last resort," the researchers wrote.

The study team included, back row, from left, graduate student Rebecca Ultrich; chemistry professor Paul Hergenrother; Chris Fields, of Roy J. Carver Biotechnology Center, research scientist Po-Chao Wen, graduate student Matt Sinclair; and, front row, from left, senior scientist Hyang Yeon Lee; Jessica Holmes, of the Roy J. Carver Biotechnology Center; and biochemistry professor Emad Tajkhorshid. Credit: Michelle Hassel

To tackle the many problems associated with indiscriminately targeting gram-negative bacteria, the team focused on a suite of drugs developed by the pharmaceutical company AstraZeneca. These drugs inhibit the Lol system, a lipoprotein-transport system that is exclusive to gram-negative bacteria and genetically different in pathogenic and beneficial microbes.

These drugs were not effective against gram-negative infections unless the researchers first undermined key bacterial defenses in the laboratory. But because these antibiotics appeared to discriminate between beneficial and pathogenic gram-negative bacteria in cell culture experiments, they were promising candidates for further exploration, Hergenrother said.

In a series of experiments, Muñoz designed structural variations of the Lol inhibitors and evaluated their potential to fight gram-negative and gram-positive bacteria in cell culture.

One of the new compounds, lolamicin, selectively targeted some "laboratory strains of gram-negative pathogens including Escherichia coli, Klebsiella pneumoniae and Enterobacter cloacae," the researchers found. Lolamicin had no detectable effect on gram-positive bacteria in cell culture. At higher doses, lolamicin killed up to 90% of multidrug-resistant E. coli, K. pneumoniae and E. cloacae clinical isolates.

When given orally to mice with drug-resistant septicemia or pneumonia, lolamicin rescued 100% of the mice with septicemia and 70% of the mice with pneumonia, the team reported.

Extensive work was done to determine the effect of lolamicin on the gut microbiome.

"The mouse microbiome is a good tool for modeling human infections

because human and mouse gut microbiomes are very similar," Muñoz said. "Studies have shown that antibiotics that cause gut dysbiosis in mice have a similar effect in humans."

Treatment with standard antibiotics amoxicillin and clindamycin caused dramatic shifts in the overall structure of bacterial populations in the mouse gut, diminishing the abundance several beneficial microbial groups, the team found.

"In contrast, lolamicin did not cause any drastic changes in taxonomic composition over the course of the three-day treatment or the following 28-day recovery," the researchers wrote.

Many more years of research are needed to extend the findings, Hergenrother said. Lolamicin, or other similar compounds, must be tested against more bacterial strains and detailed toxicology studies must be conducted. Any new antibiotics also must be assessed to determine how quickly they induce drug resistance, a problem that arises sooner or later in bacteria treated with antibiotics.

The study is a proof-of-concept that antibiotics that kill a pathogenic microbe while sparing beneficial bacteria in the gut can be developed for gram-negative infections—some of the most challenging infections to treat, Hergenrother said.

More information: Paul Hergenrother, A Gram-negative-selective antibiotic that spares the gut microbiome, *Nature* (2024). DOI: 10.1038/s41586-024-07502-0.
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