Good bacteria armed with antibiotic resistance protect gut microbiome

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Researchers from Case Western Reserve University in Cleveland have discovered that populating the gastrointestinal (GI) tracts of mice with *Bacteroides* species producing a specific enzyme helps protect the good commensal bacteria from the harmful effects of antibiotics. Their research is published ahead of print in *Antimicrobial Agents and Chemotherapy*.

Antibiotics are powerful weapons against pathogens, but most are relatively indiscriminate, killing the good bacteria, along with the bad. Thus, they may render patients vulnerable to invasion, particularly by virulent, antibiotic-resistant pathogens that frequently populate hospitals.

The novel aspect of the research is that the enzyme produced by these bacteria, beta-lactamase, is a major cause of antibiotic resistance , says first author, Usha Stiefel. Interestingly, the enzyme is not only protecting the bacteria that produce it but also the rest of the bacteria making up the intestinal microbiome.

In the study, the investigators established populations of beta-lactamase producing *Bacteroides* in some mice, but not others. They then gave all the mice ceftriaxone, a beta-lactam antibiotic, for three days and then oral doses of vancomycin-resistant enterococcus, or *Clostridium difficile*, both of which are virulent GI pathogens.

The mice that had been populated with *Bacteroides* maintained their diverse species of commensal gut bacteria, free of pathogens, while the control mice saw their commensals decimated by antibiotics, enabling establishment of the pathogens.

"When patients in the hospital or nursing home setting receive antibiotics, it is doubly dangerous when they lose their native colonic bacteria, because healthcare settings are full of resistant or particularly virulent bacteria, and so patients are especially vulnerable to acquiring these bacteria within their intestinal tracts," says Stiefel.

Since the *Bacteroides*, which comprise roughly one quarter of the intestinal microbiome, are absent elsewhere in the body, the investigators believe that the beta-lactamase will not interfere with treatment of infections in other organ systems, such as in the respiratory tract, or the blood, explains Stiefel.

"The results of our study are exciting because they show how it might be possible to take antibiotics without suffering from the loss of your colonic microbiome and then becoming colonized by virulent pathogens," says Stiefel. For example, beta-lactamase enzymes could be given orally as drugs, to protect the gut bacteria from systemic antibiotics. Alternatively, as with the mice, patients' GI tracts might be populated with antibiotic-degrading bacteria.

One weakness of the strategy is that while it could protect against acquiring a GI infection, *C. difficile*, for example, it could not be used to combat such an infection.

"The recognition of the importance of an intact and diverse microbiome has probably best been demonstrated by the successful treatment of *Clostridium difficile* colitis by fecal microbiota transplantation, or 'stool transplant,'" says Stiefel. "If you have an intact intestinal microbiome, you simply are going to be resistant to acquiring many types of infection."

"If we can find ways to preserve the microbiome in hospitalized patients who are receiving antibiotics, we are on our way to preventing a large proportion of hospital-acquired infections," says Stiefel.

More information: The manuscript can be found online. The final version of the article is scheduled for the August 2014 issue of Antimicrobial Agents

and Chemotherapy.

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