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Resistance to last-line antibiotic makes bacteria resistant to immune system

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Bacteria resistant to the antibiotic colistin are also commonly resistant to antimicrobial substances made by the human body, according to a study in *mBio*, the online open-access journal of the American Society for Microbiology. Cross-resistance to colistin and host antimicrobials LL-37 and lysozyme, which help defend the body against bacterial attack, could mean that patients with life-threatening multi-drug resistant infections are also saddled with a crippled immune response. Colistin is a last-line drug for treating several kinds of drug-resistant infections, but colistin resistance and the drug's newfound impacts on bacterial resistance to immune attack underscore the need for newer, better antibiotics.

Corresponding author David Weiss of Emory University says the results show that colistin therapy can fail patients in two ways. "The way that the bacteria become resistant [to colistin] allows them to also become resistant to the antimicrobials made by our immune system. That is definitely not what doctors want to do when they're treating patients with this last line antibiotic," says Weiss.

Although it was developed fifty years ago, colistin remains in use today not so much because it's particularly safe or effective, but because the choices for treating multi-drug resistant *Acinetobacter baumannii* and other resistant infections are few and dwindling. Colistin is used when all or almost all other drugs have failed, often representing a patient's last hope for survival.

Weiss says he and his colleagues noted that colistin works by disrupting

the inner and outer membranes that hold Gram-negative bacterial cells together, much the same way two antimicrobials of the human immune system, LL-37 and lysozyme, do. LL-37 is a protein found at sites of inflammation, whereas lysozyme is found in numerous different immune cells and within secretions like tears, breast milk, and mucus, and both are important defenses against invading bacteria. Weiss and his collaborators from Emory, the CDC, Walter Reed Army Institute of Research, and Grady Memorial Hospital in Atlanta set out to find whether resistance to colistin could engender resistance to attack by LL-37 or lysozyme.

Looking at *A. baumannii* isolates from patients around the country, they noted that all the colistin-resistant strains harbored mutations in pmrB, a regulatory gene that leads to the modification of polysaccharides on the outside of the cell in response to antibiotic exposure. Tests showed a tight correlation between the ability of individual isolates to resist high concentrations of colistin and the ability to resist attacks by LL-37 or lysozyme.

This was very convincing, write the authors, that mutations in the pmrB gene were responsible for cross-resistance to LL-37 and lysozyme, but to get closer to a causative link between treatment and cross-resistance, they studied two pairs of *A. baumannii* isolates taken from two different patients before and after they were treated for three or six weeks with colistin. The results helped confirm the cross-resistance link: neither strain taken before treatment was resistant to colistin, LL-37, or lysozyme, but the strains taken after treatment showed significant resistance to colistin and lysozyme. (One post-colistin isolate was no more or less resistant to LL-37 than its paired pre-colistin isolate.) Like the resistant strains tested earlier, both post-colistin isolates harbored crucial mutations in the pmrB gene that apparently bestow the ability to resist treatment.

The authors point out that the apparent link between resistance to colistin and cross-resistance to antimicrobial agents of the immune system could well extend to other pathogens that are treated with colistin, including *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. Weiss says he plans to follow up with studies to determine whether this bears out.

For Weiss, the problems with colistin are symptomatic of a much larger trio of problems: increasing levels of drug resistance, cuts in federal funding for antibiotic research, and lack of incentives for pharmaceutical companies to invest in antibiotic R&D. "We don't have enough antibiotics, and it's really important for the research community and the public to support increases in funding for research to develop new antibiotics," says Weiss.

"We got complacent for a while and the bugs are becoming resistant. This is something we can reverse - or make a lot better - if we have the resources."

Provided by American Society for Microbiology