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Novel antibiotic combination therapy overcomes deadly drug-resistant bacteria

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Researchers have known that part of the challenge in treating penicillin-resistant infections lies in understanding the way bacteria inactivate penicillin antibiotics. The enzymes that do this, beta-lactamases, chop up the antibiotics rendering them useless. One particularly problematic group of bacterial beta-lactamases, metallo-beta-lactamases (MBLs), is able to destroy even the newest penicillins. MBLs are often made by bacteria alongside other enzymes, including other beta-lactamases that allow certain bacteria to destroy the entire penicillin arsenal. Now, researchers in Cleveland, Ohio have taken a significant step toward defeating antibiotic-resistant infections by combining two different antibiotics that each block a different kind of drug-destroying enzyme secreted by bacteria. When combined, the antibiotics run interference for each other to fight infections. Now doctors have a new weapon to overcome one of the most pernicious infections caused by deadly bacteria endemic to hospitals.

CRE is shorthand for carbapenem-resistant enterobacteriaceae, which causes approximately one-third of healthcare-associated infections in the United States and kills nearly half its victims, according to a multicenter epidemiologic study just released in *Antimicrobial Agents and Chemotherapy*. The new combination antibiotic drug regimen proved effective against 81% of CRE specimens tested in a second study, published in the same journal issue. Both studies were conducted under the leadership of Robert A. Bonomo, MD, Professor of Medicine, Pharmacology, Biochemistry, Molecular Biology, and Microbiology at Case Western Reserve University School of Medicine and Chief of

Medical Service at the Louis Stokes Cleveland Veterans Affairs Medical Center.

The strategy uses two antibiotic drugs to protect each other from being neutralized by CRE's problematic enzymes. The first half of the antibiotic combination regimen—ceftazidime/avibactam—is vulnerable to the neutralizing effect of the metallo-beta-lactamases. But the other antibiotic in the regimen—aztreonam—is not. But aztreonam is, however, vulnerable to other types of CRE enzymes, which are in turn neutralized by ceftazidime/avibactam. So, when combined, the two antibiotics run interference for each other and in tag-team fashion defeat the infection.

The novel combination helps doctors overcome the antibiotic neutralizing metallo-beta-lactamases. With protection from the other half of the regimen, "aztreonam skirts around the metallo-beta-lactamase and hits its target—the penicillin-binding proteins," Bonomo explained in a Center for Infectious Disease Research and Policy feature. Bacteria with aztreonam attached to their penicillin-binding proteins can't build effective cell walls with the drug in the way, and they quickly die. Said Bonomo, "If we understand the fundamental mechanisms by which bacteria become resistant to antibiotics, we can use what we know to help design better therapies."

Bonomo and his team demonstrated their regimen's promise in laboratory models, but were soon faced with patients who had no other treatment options. Doctors necessarily used the new regimen to treat a young kidney transplant patient at Nationwide Children's Hospital, and an elderly woman who had just received a new hip at University Hospitals. Both patients had various infections that verged on fatal, yet survived because of the cutting edge treatment. The combination approach still needs to go through clinical trials and undergo additional research before it can become a commonly used treatment. It is however

extremely promising news for doctors worldwide low on options to treat patients with antibiotic-resistant infections.

More information: Michael J. Satlin et al, Bacteremia due to Carbapenem-resistant Enterobacteriaceae (CRE): A Multicenter Clinical and Molecular Epidemiologic Analysis in the Nation's Epicenter for CRE, *Antimicrobial Agents and Chemotherapy* (2017). DOI: 10.1128/AAC.02349-16

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