Novel combination therapy overcomes difficult-to-treat form of antibiotic resistance

6 February 2017

Combination therapy with two antibiotic compounds overcame pathogenic Enterobacteriaceae harboring a pernicious form of antibiotic resistance, in a bone-infected patient, where other drugs had failed. The research describing this successful treatment regimen is published in *Antimicrobial Agents and Chemotherapy*, a journal of the American Society for Microbiology.

Corresponding author, Robert A. Bonomo, MD, Professor of Medicine, Pharmacology, Molecular Biology and Microbiology Chief, Medical Service, Louis Stokes Cleveland Department of Veteran Affairs Medical Center, was originally moved to investigate the possibility that these two compounds could treat infections due to this form of resistance, after reading in an online discussion group about a 72 year old female patient with an untreatable bone infection. The resistance is caused by metallo ß-lactamases, resistance causing compounds that have been spreading rapidly around the globe.

The problem this combination therapy overcame is that many so-called class C and class A ß-lactamases present in Gram negative bacteria confer resistance to ß-lactams, a very important class of antibiotics. (ß-lactamases cut ß-lactam antibiotics, destroying their activity.) But ceftazidime/avibactam, one of the compounds, inactivates these ß-lactamases, freeing aztreonam, the other, to prevent the pernicious resistance proteins, called metallo-ß-lactamases, from clipping the antibiotics.

Bonomo's laboratory tested the two compounds in vitro against ß-lactam resistant Enterobacteriaceae, and then against a bacterial infection in animal models. In both cases, the combination therapy killed, and prevented further growth of the Enterobacteriaceae cells. Thus, the combination appeared potent enough to try in the patient, who was being treated by one of Bonomo's coauthors.

The woman had fallen while on vacation in eastern Europe, fracturing her hip. She had had hip replacement surgery there, returning home after two weeks, with the surgical site red and painful from the infection. The clinicians removed the arthroplasty, and tested intraoperative cultures. These grew the pathogen, *Enterobacter cloacae*, which carried the blaNDM-1 metallo-ß-lactam resistance gene.

After all else had failed, the clinicians gave the patient the ceftazidime/avibactam. and aztreonam, combination, which ultimately cleared the resistant infection. Six months after completion of antibiotics, the patient underwent successful final reimplantation of a total hip arthroplasty.

At around the same time, Bonomo explored this same combination in a patient at Nationwide Children's Hospital and The Ohio State University, in a child with a transplanted kidney, who had had prolonged bacteremia caused by another metallo-ß-lactam producing strain , *Stenotrophomonas maltophilia*, and who was thus successfully treated. (That report was also published in *Antimicrobial Agents and Chemotherapy*.)

In both cases, the use of the drug combination was a "desperate, last ditch measure," said Bonomo. Currently, these investigators are working on experimental models, in order to make a more accurate estimation of the best doses for patients. It is hoped that this research will lead to a clinical trial while the medical community awaits the release of other promising agents.

Metallo-ß-lactamase resistance genes are found in a wide variety of pathogens, including *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and *E.coli*, and constitute a growing global public health problem. They are particularly dangerous because they

confer resistance to all beta-lactam antibiotics, severely limiting treatment options.

Provided by American Society for Microbiology