Ineffective antibiotics form strong teams against deadly super bacteria

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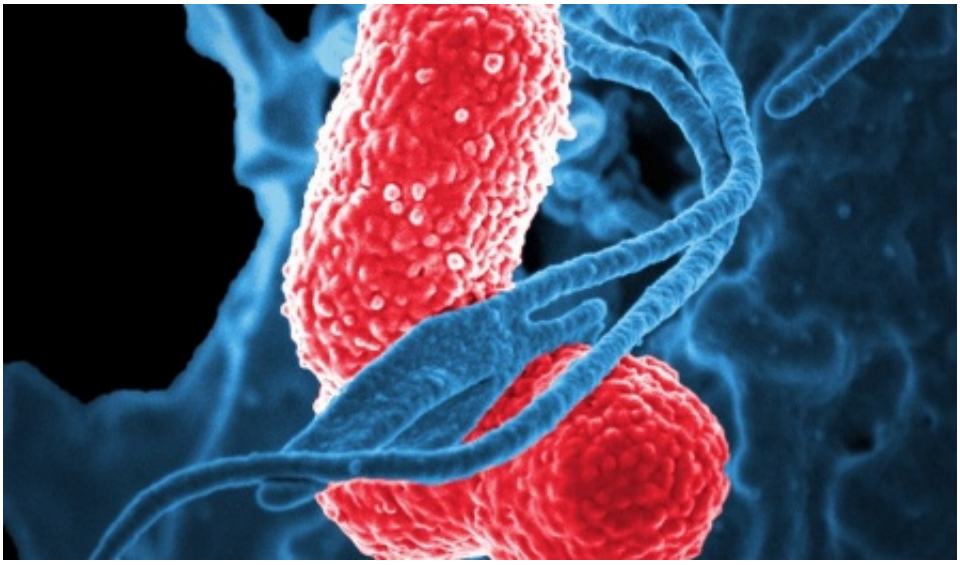

Klebsiella pneumoniae, the pink-colored bacteria in the image, cause more than 2 million infections and nearly 23,000 deaths a year. Credit: NIAID

In the fight against super bacteria, University at Buffalo scientists are relying on strength in numbers to win the battle against drug resistance.

A team of researchers found that combinations of three antibiotics – that are each ineffective against superbugs when used alone – are capable of eradicating two of the six ESKAPE pathogens when delivered together.

ESKAPE pathogens are a group of antimicrobial-resistant bacteria that

pose a grave threat, causing more than 2 million infections and nearly 23,000 deaths a year, according to the Centers for Disease Control and Prevention. The six super bacteria are also responsible for a substantial number of infections in hospitals.

The new, triple combination treatments provide a new weapon in the evolutionary arms race between modern medicine and harmful bacteria.

"These bacteria are extremely problematic and have become resistant to nearly all available antibiotics. We needed to think differently to attack this problem," says Brian Tsuji, PharmD, an author on two recent studies and associate professor in the Department of Pharmacy Practice in the UB School of Pharmacy and Pharmaceutical Sciences.

One study, "Polymyxin-resistant, carbapenem-resistant Acinetobacter baumannii is eradicated by a triple combination of agents that lack individual activity," was published in the May issue of the *Journal of Antimicrobial Chemotherapy*, while another study, "Polymyxin B-Based Triple Combinations Wage War Against KPC-2-producing Klebsiella pneumoniae: New Dosing Strategies for Old Allies," was published in the April issue of *Antimicrobial Agents and Chemotherapy*.

Non-traditional combinations of medication are frequently used to fight against superbug infections, however, questions remain over proper dosage and which combinations are most effective.

The UB researchers tested combinations of the antibiotics polymyxin B, meropenem and ampicillin-sulbactam against the pathogen Acinetobacter baumannii. The bacterium Klebsiella pneumoniae was treated with polymyxin B, meropenem, and rifampin.

"Each antibiotic was chosen to complement the other drugs' mechanisms of bacterial killing," says Justin Lenhard, PharmD, first author on the

investigation of Acinetobacter baumannii, UB School of Pharmacy and Pharmaceutical Sciences alum and former postdoctoral researcher in Tsuji's lab. Lenhard is now an assistant professor at California Northstate University College of Pharmacy.

"By combining antimicrobials that exert their bacterial killing in different ways, it is possible to outmaneuver the ESKAPE pathogens and completely overwhelm the bacteria's defensive countermeasures," he said.

The medications were applied to the bacterial samples individually, in pairs and in triple combinations. Both the time needed for the antibiotics to kill the bacteria and the time it took for the pathogens to repopulate were measured.

For the tests on Acinetobacter baumannii, none of the antibiotics were able to kill the bacteria when used alone. Of the pairs of antibiotics, only the grouping of polymyxin B and meropenem was able to effectively kill the pathogen, but the bacteria gradually regrew over three days.

The triple combination achieved a similar kill rate to the pair of polymyxin B and meropenem, but the addition of ampicillin-sulbactam prevented regrowth of the pathogen. Within 96 hours, no viable bacteria cells were detected after exposure to all three antibiotics.

The tests against Klebsiella pneumoniae were led by Zackery Bulman, PharmD, UB School of Pharmacy and Pharmaceutical Sciences alum and postdoctoral researcher in Tsuji's lab. Individual antibiotics were unable to sustain the killing of bacteria over a 24-hour period. The most effective double combination was polymyxin B and rifampin, which killed bacteria for up to 30 hours before the population regrew to initial levels.

The triple combination of polymyxin B, meropenem, and rifampin produced the highest kill rates and tripled the time it took for bacteria to regrow to 72 hours. Rifampin, the researchers suspect, temporarily suppresses the antibiotic resistance of Klebsiella pneumoniae, allowing the trio to destroy the bacteria.

Additional research is required to validate the treatments against other clinically relevant strains of bacteria, but the results of both studies are promising.

"These new antibiotic combinations may help to guide therapy in infections where no treatments appear to exist," says Tsuji.

More information: Zackery P. Bulman et al. New Polymyxin B Dosing Strategies To Fortify Old Allies in the War against KPC-2-Producing Klebsiella pneumoniae, *Antimicrobial Agents and Chemotherapy* (2017). DOI: 10.1128/AAC.02023-16

Justin R. Lenhard et al. Polymyxin-resistant, carbapenem-resistant Acinetobacter baumannii is eradicated by a triple combination of agents that lack individual activity, *Journal of Antimicrobial Chemotherapy* (2017). DOI: 10.1093/jac/dkx002

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