Resistance to a 'last resort' antibiotic seen in mice

Carbapenemase-resistant *Enterobacteriaceae* (CRE) infections are a significant public health concern due to high mortality rates and a shortage of efficacious treatment options. Dr. David Weiss, Director of the Emory Antibiotic Resistance Center, studies how CRE become resistant to polymyxin antibiotics, which is a drug of last resort against these highly resistant bacteria.

Through the Multi-site Gram-Negative Surveillance Initiative (MuGSI), which operates under the auspices of the CDC's Emerging Infections Program, Dr. Weiss' lab characterized two distinct clinical isolates of carbapenemase-resistant *Klebsiella pneumoniae* (CRKP) collected at hospitals located in Atlanta, GA. Their recent publication in the March/April 2018 edition of mBio has garnered national attention. It was the first report to demonstrate that CRKP strains isolated within the United States exhibited heteroresistance, or a difference in sensitivity, to the last-line polymyxin antibiotic colistin amongst the CRKP strains.

The isolated heteroresistant strains of CRKP harbored a stable subpopulation (as low as 1 in 1,000,000) of colistin-resistant bacteria that exhibited a significant and reversible growth advantage over colistin-susceptible bacteria in the presence, but not in the absence, of colistin. Authors utilized robust gene sequencing techniques to confirm that the two populations of bacteria were identical at the genetic level, which is a hallmark of heteroresistance. Analysis of gene expression patterns revealed changes in two previously identified resistance genes that were likely to be responsible for the observed differences between resistant and susceptible bacteria.

Lastly, mice were treated with a lethal dose of the clinical CRKP isolates that were either colistin-heteroresistant or colistin-susceptible. The colistin-heteroresistant mice did not respond to colistin treatment and rapidly succumbed to the infection while colistin-susceptible mice achieved a 100% survival rate after treatment with colistin.

This report underscores the dangerous disguise of heteroresistance. Only one out of three standard clinical laboratory tests used in this study to evaluate antibiotic susceptibility positively identified colistin resistance in both CRKP isolates. The authors concluded that colistin-heteroresistance could be responsible for treatment failure of CRKP and other related CRE infections in clinical settings and stressed the urgency for more sensitive diagnostics that will accurately identify antibiotic resistance and ultimately improve patient outcomes.

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Reference

Carbapenem-resistant *Klebsiella pneumoniae* exhibiting clinically undetected colistin heteroresistance leads to treatment failure in a murine model of infection. V I Band *et al, mBio*, 2018, **9**, e02448

Colistin | https://www.webmd.com/drugs/2/drug-8761/colistin-colistimethate-sodium-injection/details