Resistance to last resort drug arose in patient over 3 weeks

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French investigators have described development of resistance to one of the last resort therapies used to treat extremely drug-resistant Pseudomonas aeruginosa. That resistance arose in a single patient over a scant 22 days. They subsequently identified the single nucleotide mutation in P. aeruginosa that caused the resistance. The research is published in *Antimicrobial Agents and Chemotherapy*, a journal of the American Society for Microbiology.

Unexpectedly, the mutation partially re-sensitized P. aeruginosa to antimicrobials that have long been in use—carbapenems and piperacilline-tazobactam—to which the bacterium had been fully resistant.

That peculiar finding might prove beneficial for the treatment of extremely drug-resistant P. aeruginosa, by enabling use of piperacilline-tazobactam and carbapenems in such cases, as their minimum inhibitory concentrations (MIC) "decrease significantly," said principal investigator Leurent Dortet, PharmD, Ph.D. Nonetheless, he cautioned that clinicians would need to proceed with caution "since other resistance mechanisms might be present."

Dr. Dortet said that using higher doses of ceftolozane-tazobactam to begin with might limit the appearance of the mutation by killing the pathogens more rapidly. Dr. Dortet is Associate Professor of Microbiology, University Paris-Saclay, France,and Head of the Associated French National Reference Center for Antimicrobial

Resistance, Bacteriology-Hygiene Department, Bicêtre Hospital, Le Kremlin-Bicêtre, France.

To determine the mechanism responsible for causing this resistance, the team analyzed P. aeruginosa clinical isolates, both susceptible and resistant, that had been collected from this patient during the infection, and performed whole genome sequencing on these. That enabled the investigators to identify the single mutation in a gene that encodes a natural enzyme, cephalosporinase. (Overexpression of cephalosporinase causes resistance to nearly all antimicrobials of the β-lactam family.)

Modeling the mutant enzyme in silico confirmed its role as the cause of resistance to ceftolozane-tazobactam, and resensitization to carbapenems and piperacilline-tazobactam.

"Our results demonstrated that resistance to this novel molecule can occur rapidly during treatment," said Dr. Dortet. He noted that at the time the investigators discovered the mutation, the antibiotic, ceftolozane-tazobactam, had only been in clinical use for a couple of years.

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