Study finds new patterns of antibiotic resistance spread in hospitals

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Carbapenem-resistant Enterobacteriaceae bacteria. Credit: Stephanie Rossow, CDC/Antibiotic Resistance Coordination & Strategy Unit

Bacteria that cause infections in hospitals are increasingly becoming resistant to antibiotics, and a group of bacterial species called

Enterobacterales that are able to fend off a type of antibiotic called carbapenems are a particular problem. They cause difficult-to-treat, often fatal infections, and can spread between patients within hospital settings, creating outbreaks that can be hard to contain.

A group led by Ashlee Earl, an institute scientist and senior group leader of the Bacterial Genomics group (BGG) at the Broad Institute of MIT and Harvard, and including BGG-affiliated scientists Rauf Salamzade, Abby Manson, Bruce Walker, and Colin Worby, along with Roby Bhattacharyya, an associate member of the Broad and assistant professor at Massachusetts General Hospital and Harvard Medical School, has investigated the spread of carbapenem-resistant Enterobacterales (CRE) in four hospitals. They developed a new computational method for analyzing the genomes of CRE isolated from patients. Using that method, the scientists were able to track the movement of key genes across different CRE species over time and space, revealing many more connections between patient infections than expected based on standard methods. Their study was recently published in *Genome Medicine*.

"This new approach changed the picture," said Earl. "While we expected to find examples of gene sharing, the results from Rauf's method started to suggest that there is a veritable interstate highway for antibiotic resistance genes to move between bacteria in hospital environments and for a very long time."

Spot the spread

From 2012 through 2016, the team worked with clinical microbiology leaders at four hospitals—Beth Israel Deaconess Medical Center, Brigham and Women's Hospital, and Massachusetts General Hospital in Boston, MA, and the University of California Irvine Medical Center in Orange, CA—to collect all CRE isolates from patient samples as well as an assortment of CRE that had been saved from patients in these

hospitals going back to 2008. Using previously established approaches, the team analyzed the chromosomes of these organisms to see how closely related they were from person to person within a hospital. They identified a small number of very close connections between patient samples within hospitals, suggesting that the movement of the organisms between patients within hospitals had been limited and short-lived. While this suggested the local transfer of CRE was minimal, one large limitation still loomed.

These bacteria typically become resistant to carbapenems by picking up a gene from other bacteria that enables carbapenem resistance. Such genes, which encode an enzyme called a carbapenemase that degrades the antibiotic, typically reside on a piece of the genome, called a plasmid, which is smaller than the chromosome and can be transferred between bacteria through a process called horizontal transfer. The sequence of the carbapenamase gene is highly consistent across CRE from around the world, making it impossible for scientists to confidently track the movement of that gene from one bacterial cell to the next.

Luckily for researchers, the plasmid DNA on either side of the carbapenemase gene varies more than the gene itself, and the team leveraged this to create new analyses for tracking patterns of CRE spread. Rauf Salamzade, now a graduate student at University of Wisconsin, Madison and first author of the study, developed an algorithm to systematically sift through all of the plasmids from the bacterial isolates the team had sequenced. By looking at the entire plasmid rather than just the carbapenemase gene, the researchers identified plasmid segments that were most strongly associated with a specific geographical location—the team called these segments geographic signatures.

Within these signatures, the researchers found additional antibiotic resistance genes, genes that support resistance to hospital disinfectants,

and other genes that they hypothesize help the carbapenemase gene to persist and spread across species even when carbapenems are not present.

The findings suggest that specific genes, rather than entire organisms, were circulating in hospitals—in some cases, for many years. Notably, the team discovered antibiotic resistance gene transfer between bacteria, connecting patient infections in new ways and also helping to explain the large diversity of CRE species and strains in these hospitals. Typically, hospitals would not connect outbreaks of different CRE species such as E. coli and Klebsiella, but the research team says that information from Salamzade's tool could make hospitals more aware of potential hospital reservoirs for gene exchange and inform epidemiological investigations into antibiotic resistant infections.

"Hospital epidemiology would never find this with more traditional methods," said Earl. "I would argue that this is the kind of thing even our standard genomics approaches wouldn't find. It really took having a hypothesis, building up an approach to allow us to test that hypothesis in a really rigorous way, and then stepping back to look at the data."

With this new approach, the team hopes to further investigate how and why CRE can persist in hospitals. They also aim to characterize genes in the geographic signatures with unknown functions to better understand their role in supporting CRE.

More information: Rauf Salamzade et al, Inter-species geographic signatures for tracing horizontal gene transfer and long-term persistence of carbapenem resistance, *Genome Medicine* (2022). DOI: 10.1186/s13073-022-01040-y

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