Real-time deep genomic surveillance for bacterial mutations could inform personalized antibiotic therapy

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Antibiotic-resistant bacterial infections are difficult to treat and cause more than a million annual deaths worldwide, especially in hospitalized patients with pneumonia, bloodstream infections, urinary tract

infections, or abdominal infections. New research finds that rare antibiotic resistance mutations can rapidly expand within days in response to antibiotic treatment, and that real-time genomic surveillance could help physicians keep closer tabs on drug resistance—allowing patients to receive better-matched, better-timed, more effective antibiotic treatment.

Gregory Priebe, MD, at Boston Children's Hospital, Roy Kishony, Ph.D., of Technion–Israel Institute of Technology, and first author Hattie Chung, Ph.D., of the Broad Institute of MIT and Harvard developed the technology in collaboration with the Walter Reed Army Institute of Research. Their work is reported today in *Nature Communications*.

"Clinicians often try a certain antibiotic for a defined time and then switch to a different antibiotic, but how switching therapies affects antibiotic resistance is unknown," says Priebe, who is part of the Department of Anesthesiology, Critical Care and Pain Medicine and the Division of Infectious Diseases at Boston Children's and an associate member of the Broad Institute of MIT and Harvard.

"Clinical trials have largely been conducted at the level of a unit or hospital, with mixed results," he notes. "Our results suggest that antibiotic cycling might be more effective at the level of individual patients. We are looking to use genomic surveillance to inform initial antibiotic therapy—both the type of antibiotic and the timing—and then to inform switches in antibiotic as the frequencies of antibiotic resistance mutations change."

The technique combines whole-genome sequencing with a deep-sequencing method the authors call resistance-targeted deep amplicon sequencing (RETRA-Seq) to track changes in frequencies of antibiotic resistance mutations over time.

"In clinical testing for antibiotic susceptibility, we test a few colonies of bacteria and can miss some that have developed antibiotic resistance," explains Alex McAdam, MD, Ph.D., co-author on the study and medical director of the Infectious Diseases Diagnostic Laboratory. "RETRA-Seq tests the bacterial population as a whole, so it can detect these rare antibiotic-resistant bacteria with much higher sensitivity than routine clinical methods."

Tracking P. aeruginosa's genetic moves

In a prospective study, the team first performed whole-genome sequencing of multiple bacterial colonies cultured from seven mechanically ventilated patients at Boston Children's. They sequenced 420 bacterial colonies cultured from patients' sputum samples, about 24 from each sample. All the patients had acute lower-respiratory infection with Pseudomonas aeruginosa, a common cause of respiratory infections in ventilated patients. Testing began at the onset of each infection and continued during its course (from four to 11 days) as antibiotic therapies were given.

"Remarkably, we found that the bacteria became more genomically diverse in most patients over time," says Priebe. "The mutations we saw impacted not only regulators of virulence but also many antibiotic resistance genes and pathways."

The team next developed the RETRA-Seq technique to measure the frequencies of antibiotic resistance mutations directly from DNA in the sputum samples, skipping the culturing step that can sometimes bias results.

Resembling a game of Whac-A-Mole, antibiotic resistance gene mutations in P. aeruginosa changed rapidly in many of the patients. Mutations conferring antibiotic resistance sprang up soon after that

antibiotic was started and disappeared within days of switching to a different antibiotic—when other mutations emerged to take their place.

"With more study, we hope a technique like RETRA-Seq could help us choose an antibiotic that will not drive expansion of low-frequency resistant bacteria that are lurking in our patients," says Priebe. "RETRA-Seq could also be used during long antibiotic courses, all with the goal of finding the right antibiotic at the right time, which should lead to better patient outcomes."

Better care for chronic infections, COVID-19?

Although this study was conducted in hospitalized patients, real-time genomic surveillance could also potentially be used in the outpatient treatment of chronic lung infections, such as those in patients with chronic obstructive pulmonary disease or cystic fibrosis. It could also benefit critically ill patients with COVID-19, Priebe adds.

"Thirty to 50 percent of adults requiring intubation and mechanical ventilation for COVID-19 develop ventilator-associated pneumonia, and about half of these are due to Gram-negative bacteria such as P. aeruginosa that tend to cause serious infections in hospital settings," he says.

More information: Hattie Chung et al, Rapid expansion and extinction of antibiotic resistance mutations during treatment of acute bacterial respiratory infections, *Nature Communications* (2022). DOI: 10.1038/s41467-022-28188-w

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