

Whole-Genome Sequencing Accurately Identifies Resistance to Extended-Spectrum β -Lactams for Major Gram-Negative Bacterial Pathogens.

Samuel Shelburne, Jiwoong Kim, Jose Munita, Pranoti Sahasrabhojane, Ryan Shields, Ellen Press, Xiqi Li, Cesar Arias, Brandi Cantarel, Ying Jiang, Min Kim, Samuel Aitken and David Greenberg.

Abstract

Background: There is marked interest in using DNA based methods to detect antimicrobial resistance (AMR) with targeted polymerase chain reaction (PCR) approaches increasingly being incorporated into clinical care. Whole genome sequencing (WGS) could offer significant advantages over targeted PCR for AMR detection, particularly for species where mutations are major drivers of AMR.

Methods: Illumina MiSeq WGS and broth microdilution (BMD) assays were performed on 90 bloodstream isolates of the four most common gram-negative bacteria causing bloodstream infections in neutropenic patients. The WGS data, including both gene presence/absence and detection of mutations in an array of AMR relevant genes, were used to predict resistance to four β -lactams commonly used in the empiric treatment of neutropenic fever. The genotypic predictions were then compared to phenotypic resistance as determined by BMD and by commercial methods during routine patient care.

Results: Out of 133 putative instances of resistance to the β -lactams of interest identified by WGS, only 87 (65%) would have been detected by a typical PCR based approach. The sensitivity, specificity, positive and negative predictive values for WGS in predicting AMR were 0.87, 0.98, 0.97, and 0.91 respectively. Using broth microdilution as the gold standard, our genotypic resistance prediction approach had a significantly higher positive predictive value compared to minimum inhibitory concentrations generated by commercial methods (0.97 vs. 0.92, $P = 0.025$).

Conclusions: These data demonstrate the potential feasibility of using WGS to guide antibiotic treatment decisions for patients with life-threatening infections for an array of medically important pathogens.