

Shelby Simar

The Accessory Genome of Vancomycin-Resistant Enterococci and Its Role in Antimicrobial Resistance

Vancomycin-resistant enterococci are important causes of bloodstream infections in severely ill and immunocompromised patients. The plasticity of the enterococcal accessory genome— the genetic material that varies between strains— promotes development of resistance to multiple antibiotics by acquisition of antimicrobial resistance (AMR) determinants through horizontal gene transfer of mobile genetic elements. Evaluating the transmission of AMR determinants among enterococci has previously been challenging due to limitations of existing surveillance and sequencing methodologies, as these approaches generally focus only on a subset of the bacterial genome. Thus, the significant gap in our understanding of the epidemiology and clinical implications of the intricacies of the bacterial genome limits our understanding of the dynamics of infection and prevents the use of robust interventions in clinical settings. The Vancomycin-Resistant Enterococcal Bacteremia Outcomes (VENOUS) study is a prospective study of patients with enterococcal bacteremia being carried out worldwide. VENOUS utilizes cutting-edge sequencing approaches to identify enterococcal genomic elements associated with development of AMR that may impact patient outcomes. Preliminary data has revealed a large amount of genomic heterogeneity in infecting isolates, particularly in *E. faecium*, where accessory genes comprised nearly half of the total genome. Phylogenetic analysis showed the previously described split between Clades A (hospital-adapted) and B (community-associated), with a variety of Clade B isolates causing bloodstream infections. Furthermore, more than half of *E. faecium* isolates harbored the *vanA* gene cluster, and we also identified 15 vancomycin-resistant *E. faecium* strains that harbored W73C and T120A substitutions in *LiaR* and *LiaS*, respectively, that have been associated with daptomycin resistance. These results suggest that accessory genes, including AMR genes, comprise a significant proportion of the enterococcal pan-genome, indicating major genetic plasticity within these organisms that plays a substantial role in expansion of the genomic repertoire in clinical isolates.