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Multifaceted approaches are needed to limit carbapenem-resistant Enterobacteriaceae (CRE) infections, including *Klebsiella pneumoniae*, which have emerged as a worldwide public health problem. These multi-drugresistant organisms are associated with high morbidity and mortality that often exceeds 50%, as highly effective and non-toxic treatment regimens are lacking. While intestinal colonization with CREs has been proposed as a potential risk factor for infections during CRE outbreaks, its actual contribution to infection remains incompletely understood. Moreover, there is a fundamental gap in knowledge on how these antibiotic resistant organisms transition from colonization to infection within affected hosts. The long-term goal of this application is to elucidate at the bacterial genome level how CRE infections emerge and spread. Understanding these processes is critical to developing intervention and real-time clinical monitoring approaches to limit the impact of CRE infections at an individual and population level. We will focus our study on patients after liver transplantation who are at very high risk for CRE infections and adverse outcomes. Our central hypothesis is that the intestine provides a microenvironment in which CRE can expand and adapt with small genetic variations and subsequently lead to infections. To address these questions we propose to establish a cohort study of adult patients undergoing liver transplant, and track CREs within affected patients and across the hospital. In this prospective cohort we will enroll 300 patients pre-transplant, collect stool samples to ascertain intestinal colonization pre- and repeatedly post-transplant, and assess patients for CRE infections over a 6-month period. Our study design will allow us to execute the following Aims: 1) Define the rate and role of colonization on CRE infection in liver transplant patients; 2) Evaluate the within-host evolution from CRE colonization to infection; and 3) Investigate the spread of CRE between liver transplant and other patient populations in the hospital. In Aim 1 we will test the contribution of CRE colonization to infection and characterize outcomes using Kaplan-Meier survival analyses and a Cox proportional hazard model. In Aim 2 we will apply 16S and whole-genome sequencing to answer whether CRE colonization dominance develops prior to infection and how modifiable risk factors (e.g. certain antibiotics) relate to these adaptations. We will also define the clonal diversity of colonizing CRE and assess whether infectious isolates arise from dominant colonizing clones or acquire novel virulence traits. In Aim 3 we will assess the within-hospital evolution and spread of CRE infections by extending whole-genome sequence analyses to infections that occurred in non-liver transplant patients. Our multidisciplinary approach is innovative in its combination of high-resolution genomics with detailed epidemiological investigations to monitor the evolution of CRE infections in real time. This research is significant with direct translational impact in establishing a framework to track the emergence of multi-drug resistant Enterobacteriaceae and to ultimately devise novel containment strategies for CREs.