Microbial Cooperation Enhances *Clostridioides difficile* Pathogenesis

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*Clostridioides difficile* is one of the most common nosocomial pathogens in the United States and an urgent global public health threat. *C. difficile* infection manifests along a broad spectrum of disease severity up to severe diarrhea and/or death. Upon colonization of the gastrointestinal (GI) tract, *C. difficile* is exposed to a dynamic polymicrobial and metabolic environment. Despite the well-established link between the gut microbiota and susceptibility to *C. difficile*, the impact of cooperative interactions between the gut microbiota and pathogens on the outcome of infection is largely unknown. Here we show that *C. difficile* synergizes with bacteria from the genus *Enterococcus*, common GI commensals and opportunistic pathogens, to potentiate infection severity. We have found that *Enterococcus* abundance correlates with clinical metrics of severity in adults with *C. difficile* infection. Additionally, metabolomic analyses of *in vitro* coculture systems and *in vivo* coinfection models reveal that nutrient restriction and cross-feeding of key fermentable amino acids by enterococci provide a reversible cue for *C. difficile* that facilitates increased virulence. Furthermore, we demonstrate that enterococci exploit the inflammatory environment created by the *C. difficile* toxins to gain a fitness advantage in the infected GI tract through aerobic respiration. These results reveal a positive feedback loop between two cooperating pathogens that directly leads to increased pathogenesis. Additionally, this work demonstrates the profound and underappreciated role that ecology plays in *C. difficile* infection and broadens our understanding of ecology in the gut microbiome. Microbiome-targeted ecological interventions present a pathway toward novel therapeutic strategies against *C. difficile*. 