Increased enterococcal abundance and low microbial diversity are early predictive markers of a microbiota primed for development of Clostridioides difficile infection

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Background: Clostridioides difficile (CDI) is the most common form of infectious antibiotic-associated diarrhoea (AAD) causing considerable morbidity and mortality in acute-care facilities. Identification of early markers predictive of CDI in hospitalized patients could substantially contribute to decreasing the CDI burden.

Materials/methods: In this European, prospective, longitudinal cohort-study including 1,007 patients aged ≥50 years receiving broad-spectrum antibiotic treatment with penicillins + beta-lactamase inhibitors, other beta-lactam antibiotics, or fluoroquinolones during hospital stay, we characterized faecal samples using high-resolution, single-nucleotide 16S rRNA gene profiling before (D1, n = 945) and after antibiotic treatment (D6, n = 737). CDI was defined according to the ESCMID diagnostic guidelines.

Results: C. difficile carriage was observed in 51/945 (5.4%, D1) and 50/737 (6.8%, D6) patients. Among patients who developed diarrhoea within 90 days, those with CDI (n=14) exhibited significantly lower diversity (p≤0.016) and a distinctly different microbial composition at D1 compared to those with non-C. difficile AAD (n=64) and no diarrhoea (n=669, 198 lost to follow-up, Figure). At D1, the microbiota was enriched for Enterococcus spp. in patients who later developed CDI, for Clostridiales Incertae Sedis XI, Blautia and Ruminococcus spp. in patients developing non-C. difficile AAD, and for Blautia luti, Porphyromonas, Prevotella, and Bifidobacterium spp. in non-diarrhoeic patients. Antibiotic treatment reduced microbial diversity and induced class-specific dysbiosis; beta-lactam treatment specifically increased enterococcal abundance, and fluoroquinolone treatment depleted Prevotella spp.

Conclusions: Our findings of a distinct, low-diversity CDI-associated microbiota can be exploited for enriching high-risk patients in prospective clinical trials and for the development of predictive, microbiota-based diagnostics for clinical management of patients at high risk of CDI.

Figure. Characterization of microbial diversity in baseline (D1) samples. CDI patients (blue) display significantly lower alpha diversity in terms of Shannon (A) and Chao1 indices (B), compared to AAD (light blue), and ND patients (green) at D1. Cladogram demonstrating significantly higher abundances of Actinobacteria, Alphaproteobacteria and Enterococcus spp. in the gut microbiota of CDI patients at baseline (D1) compared to AAD and ND patients (C). AAD: patients with antibiotic-associated diarrhoea. CDI: patients with confirmed C. difficile infection. ND: non-diarrhoeic patients. *: p<0.05. **: p<0.01. ***:p<0.001.

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