Serum Trace Metal Concentrations in *Clostridium difficile* Infection and Their Relationship to Disease Severity

Introduction: Trace metals play a central role in host-pathogen interactions, impacting both microbial growth/pathogenicity and antimicrobial host immune defences. The main objective of this study was to determine the relationship between serum trace metal concentrations and severity of *C. difficile* infection (CDI).

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Methods:

We analysed biobanked serum samples previously collected from a single-centre prospective observational study in which we recruited consecutive hospitalised patients ≥18 years with symptomatic toxin-positive *C. difficile* diarrhoea. Severe *C. difficile* was defined as WCC ≥15 x 10^9/L or an increase in serum creatinine ≥1.5 above baseline, or pseudomembranous colitis, megacolon, need for colectomy or septic shock requiring ICU admission. Selected trace metal

(iron, selenium, zinc, cadmium, cobalt, copper, magnesium, manganese, nickel and lead) concentrations in sera were determined by inductively-coupled mass spectrometry (ICP-MS). Mean biometal concentrations were compared between mild and severe CDI cases using Mann-Whitney test. Univariate and multivariate regression analyses were used to identify clinical and laboratory factors associated with risk of severe CDI.

Results: A total of 224 serum samples derived from 149 patients [n=65 male; mean age (S.D.) 65.7 yrs (16.4); n= 84 female; 68.3 yrs (19.3)] were included. 46 (32.6%) of cases were defined as severe CDI. The median concentrations (μg/L) of iron, zinc and selenium were significantly lower in severe CDI cases compared with those with mild infection. 16 input variables were initially tested in the CART decision tree analysis including Peak WCC, minimum albumin, age, 10 biometals, immunosuppression status, sex and Charlson co-morbidity score. 4 variables (peak WCC, selenium, Charlson co-morbidity index and magnesium) were found to be good predictors of severe CDI with sensitivity, specificity, accuracy, positive predictive value, negative predictive value and ROC of 84.8%, 98.9%, 94.3%, 97.5%, 93.1% and 0.848, respectively.

Conclusions:

Novel therapeutic interventions that modulate the availability of trace metals may substantially impact on disease outcomes in CDI. Mechanistic studies are required to establish the source of metals detected and to determine their relevance to oxidative stress, impaired immune response and the promotion of *C. difficile* bacterial virulence.