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Vancomycin versus metronidazole for mild acute Clostridium difficile infections, and its impact on subsequent vancomycin-resistant Enterococcus (VRE) isolation

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Background: The epidemiology of *Clostridium difficile* infections (CDI) has evolved dramatically in the past decade. Higher rates of moderate to severe disease states have led to a marked increase in the empirical use of vancomycin. The emergence and dissemination of the hypervirulent BI/NAP1/027 strain, along with its propensity to cause severe disease, and its higher rates of drug resistance (e.g., to metronidazole), has contributed as well to the increased empiric use of vancomycin. Though vancomycin has been suggested to be the treatment of choice for moderate-severe disease, there is lack of controlled efficacy analyses pertaining to the effectiveness of vancomycin versus metronidazole for mild CDI, and the potential impact that the increased use of vancomycin might have on the emergence of vancomycin-resistant *Enterococcus* (VRE); specifically at the individual patient level.

Material/methods: A retrospective cohort analysis was conducted at the Assaf Harofeh Medical Center, for calendar years 2010-15. Adult patients (>18 years) with a first episode of acute CDI, determined per well-defined, pre-established criteria, were enrolled. The efficacy of vancomycin vs. metronidazole was evaluated in the subset of patients with mild CDI. Cox regression multivariable model was used in order to analyze the predictors for future isolation of VRE.

Results: Overall, 260 patients with acute CDI were included. The majority of patients were elderly (75%), with high indices of co-morbidities and acute illness (e.g., 25% had septic shock or multi-organ failure, 35% had a severe to fulminant Horn index, and 56% had moderate to severe CDI). Of the 75 patients with mild CDI who were treated with metronidazole only (n=64) or with vancomycin only (n=11), the outcomes were insignificantly favorable among the group treated with metronidazole (all ORs >1.0, all p-values>0.05). In 16 separate multivariable outcome models, after incorporating a prediction score to control for confounders associated with being a "vancomycin case", metronidazole was still not inferior to vancomycin in any of the outcome models. In a multivariable model of predictors for post-CDI VRE isolation, prior treatment with vancomycin proved to be the strongest independent predictor (aOR=74, p=0.004).

Conclusions: The use of vancomycin for acute CDI has recently increased exponentially due to the evolving epidemiology of the infection. However, our analyses suggest that the practice of prescribing empiric vancomycin for acute CDI should be curbed and controlled since: 1) in mild CDI metronidazole is not inferior to vancomycin, and (2) vancomycin use is associated with increased rates of subsequent VRE carriage on individual patient level.