VANCOMYCIN AND METRONIDAZOLE FOR *CLOSTRIDIUM DIFFICILE*-RELATED COMPLICATIONS

Guideline-based recommendations have driven therapy selection for *Clostridium difficile* infection (CDI) cases contingent on clinical resolution, with relatively limited evidence supporting therapeutic use in favor of secondary outcomes such as recurrence or all-cause mortality. This issue of *CLIPs* briefly summarizes an article that provided insight in addressing this research gap through a large, multi-year comparative effectiveness study within the US Department of Veterans Affairs (VA). Specifically, investigators evaluated the risk of recurrence and all cause 30-day mortality among patients receiving metronidazole or vancomycin for the treatment of mild to moderate and severe CDI. If you need further information, please contact the Center for Healthcare Innovation and Patient Outcomes Research (CHIPOR) at chipor@samford.edu.

Introduction
- The incidence of *Clostridium difficile* infection (CDI) has progressed with approximately 450,000 incident and 83,000 recurrent CDI cases in the U.S.
- According to the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA), metronidazole is the historical drug of choice for an initial episode of mild-to-moderate CDI, at a dosage of 500 mg orally 3 times per day for 10–14 days. Yet, later observational data and clinical trials suggest metronidazole is less efficacious than vancomycin hydrochloride for clinical cure rates.
- For an initial episode of severe CDI, first-line treatment in vancomycin at 125 mg orally 4 times per day for 10–14 days.
- The effect of drug therapy on outcomes such as recurrence, which is estimated to occur in approximately 15-50% of patients, and all-cause mortality, which has been reported as high as 38% is unknown, as there is limited and mixed clinical evidence.

Methods
- This study was a retrospective, propensity-matched cohort study in the US Department of Veterans Affairs health care system from January 1, 2005, through December 31, 2012. Data analysis was performed from February 7, 2015, through November 22, 2016.
- CDI was defined as a positive laboratory test result for the presence of *C. difficile* toxins or toxin genes in a stool sample and severity was defined by criteria according to the SHEA/ISDA guidelines.
- Patients were excluded if they did not receive metronidazole or oral vancomycin or if they received both therapies within 2 days prior to or after the CDI diagnosis.
- A total of 47,471 patients (mean [SD] age, 68.8 [13.3] years; 1,947 women [4.1%] and 45,524 men [95.9%]) were included in the study with 3 separate propensity matched cohorts by selecting up to 4 patients in the metronidazole group for each patient in the vancomycin group. The three cohorts are as follows:
  - Any severity cohort, containing all patients who were matched regardless of severity (n=10,137)
  - Mild to moderate CDI (n=5,452)
  - Severe CDI (n=3,130)
- Outcomes of interest in this study were CDI recurrence and all-cause 30-day mortality. Relative risks (RRs) and risk differences (RDs) were estimated for each cohort for both endpoints using a modified Poisson regression evaluated in STATA software version 14.

Methods (continued)

- o Recurrence was defined as a second positive laboratory test result within 8 weeks of the initial CDI diagnosis.
  - o All-cause 30-day mortality was defined as death from any cause within 30 days of the initial CDI diagnosis.
- Further information was collected on patient demographics, comorbidities, health care utilization, CDI history, laboratory values, and medication use from the Corporate Data Warehouse, the VA's clinical data repository.
- All other statistical procedures were performed using SAS version 9.2.

Results

- Of those 47,471 patients with first eligible treatment episodes, 2068 (4.4%) received vancomycin as ***initial therapy*** stratified as follows in the defined cohorts:
  - o Mild to moderate CDI: 1112 (4.4%) of CDI patients received vancomycin.
  - o Severe CDI: 630 (3.6%) of CDI patients received vancomycin.
  - o Unknown severity: 326 (6.8%) of CDI patients received vancomycin.
- The following number of recurrent CDI cases were observed: 7,449 of 45,661 patients (16.3%) presenting with incident CDI and 191 of 837 patients (22.8%) presenting with recurrent CDI.
- The all-cause 30-day mortality rates were 10.2% for any severity CDI, 6.7% for mild to moderate CDI, and 18.9% for severe CDI.

Table 1: Comparative analysis of adjusted RRs and RDs in CDI patients treated with vancomycin versus metronidazole for recurrence and mortality					
		Recurrence		**30-day mortality**	
Cohort	**No. of patients**	**RR (95% CI)**	**RD (95% CI)**	**RR (95% CI)**	**RD (95% CI)**
Full cohort (any severity)	10,137	0.98 (0.87 to 1.10)	0.00 (-0.02 to 0.02)	0.86 (0.74 to 0.98)	-0.02 (-0.003 to -0.01)
Mild to moderate subcohort	5,452	1.07 (0.93 to 1.15)	0.01 (-0.01 to 0.03)	0.91 (0.72 to 1.14)	-0.01 (-0.02 to 0.01)
Severe subcohort	3,130	0.96 (0.76 to 1.23)	-0.01 (-0.04 to 0.03)	0.79 (0.65 to 0.97)	-0.04 (-0.07 to -0.01)

Abbreviations: RD, risk difference; RR, relative risk.
Adapted from Stevens, *et al*

- Overall, there were no differences in the risk of recurrence between patients treated with vancomycin vs those treated with metronidazole in any of the disease severity cohorts.
- No significant difference was found in the risk of mortality between treatment groups among patients with mild to moderate CDI.
- Mortality benefit was demonstrated amongst patients who were treated with vancomycin in the full cohort group, with a significant risk reduction demonstrated amongst patients with severe CDI.
- The number needed to treat (NNT) to prevent 1 death among patients with severe CDI is approximately 25.
- The use of nitazoxanide, rifaximin, toxin-binding agents, and fidaxomicin was uncommon, and use was similar between patients treated with vancomycin and metronidazole for all severity groups.

Conclusion

- Recurrence rates were similar among patients treated with vancomycin and metronidazole.
- However, the risk of 30-day mortality was significantly reduced among patients who received vancomycin, particularly for patients with severe CDI.
- Even though treatment costs associated with vancomycin treatment are higher than metronidazole and there is concern for vancomycin-resistant Enterococcus, these study results highlight the need for an assessment and integration of new clinical evidence in updating practice guidelines.

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