


2016

There is a trend favoring vancomycin vs. metronidazole in treating severe *C. difficile* infection

Dean D. Fouchia

Wayne State University School of Medicine, dfouchia@med.wayne.edu

Follow this and additional works at: <https://digitalcommons.wayne.edu/crp>

 Part of the [Bacterial Infections and Mycoses Commons](#), [Digestive System Diseases Commons](#), [Medical Education Commons](#), and the [Pharmaceutical Preparations Commons](#)

Recommended Citation

Fouchia DD. There is a trend favoring vancomycin vs. metronidazole in treating severe *C. difficile* infection. *Clin. Res. Pract.* 2016 Sept 15;2(2):eP1082. doi: [10.22237/crp/1473984449](https://doi.org/10.22237/crp/1473984449)

This Critical Analysis is brought to you for free and open access by the Open Access Journals at DigitalCommons@WayneState. It has been accepted for inclusion in Clinical Research in Practice: The Journal of Team Hippocrates by an authorized editor of DigitalCommons@WayneState.

There is a trend favoring vancomycin vs. metronidazole in treating severe *C. difficile* infection

DEAN D. FOUCHIA, B.S., Wayne State University, Detroit, MI, dfouchia@med.wayne.edu

ABSTRACT A critical appraisal and clinical application of Johnson S, Louie TJ, Gerding DN, et al. Vancomycin, metronidazole, or tolevamer for *Clostridium difficile* infection: results from two multinational, randomized, controlled trials. *Clin Infect Dis*. 2014;59(3):345-354. doi: [10.1093/cid/ciu313](https://doi.org/10.1093/cid/ciu313)

Keywords: *Clostridium difficile*, *C. difficile*, *C. diff*, vancomycin, metronidazole

Clinical Context

Patient is a 98 year old Caucasian male with a past medical history of benign prostatic hypertrophy and peripheral arterial disease that presented to a large urban hospital complaining of severe abdominal pain associated with watery, non-bloody diarrhea of four days duration. One month prior to admission, the patient was admitted to the hospital for episodes of non-bloody emesis secondary to non-occlusive small bowel obstruction (SBO) likely due to adhesions from past abdominal surgeries. The patient's symptoms resolved after successful medical management without surgery. However, the patient developed aspiration pneumonia and was treated successfully with antibiotics. Because of this recent hospitalization and antibiotic use, a *Clostridium difficile* DNA amplification was performed and found to be positive. The patient's labs showed a WBC count of 47,100 cells/mm³, a serum albumin of 2.2 g/dL, and a serum creatinine (Cr) of 2.72 mg/dL, which was 2.5x greater than his previous Cr measured one week prior measured at 1.07 mg/dL. According to the clinical practice guidelines for *Clostridium difficile* by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA), this patient met the criteria for severe *C. difficile* infection (CDI), which is defined as WBC >15,000 cells/mm³, serum albumin <3 g/dL, and/or a serum creatinine level ≥1.5 times the pre-morbid level¹. There are two mainstay treatments for *C. difficile* infection (vancomycin and metronidazole), but we wanted to ensure we provided the most appropriate treatment.

Clinical Question

Is oral vancomycin more effective than oral metronidazole for treatment of severe *Clostridium difficile* infection?

Research Article

Johnson S, Louie TJ, Gerding DN, et al. Vancomycin, metronidazole, or tolevamer for *Clostridium difficile* infection: results from two multinational, randomized, controlled trials. *Clin Infect Dis*. 2014;59(3):345-354. doi: [10.1093/cid/ciu313](https://doi.org/10.1093/cid/ciu313)

DEAN D. FOUCHIA, B.S., is a fourth year medical school student at Wayne State University School of Medicine.



ISSN: 2379-4550

<http://digitalcommons.wayne.edu/crp>, © 2016 The Author(s)

Licensed under [Creative Commons Attribution Non-Commercial 4.0](https://creativecommons.org/licenses/by-nc/4.0/)

Literature Review

A literature search was initiated in PubMed using the search phrase "(“C. difficile” OR “Clostridium difficile” OR “difficile”)[title] AND (treat*[tiab] OR therapy*[tiab]) AND (trial[tiab] OR meta-analysis[tiab] OR systematic review[tiab])." My intention was to find primary research studying vancomycin in non-recurrent, severe CDI. I was unable to find any studies, systematic reviews or meta-analyses that primarily studied this population of severe CDI, specifically. Thus, studies had to be stratified by disease severity with subgroup analysis in order to be most appropriate for this particular clinical question.

There are also new therapies being developed for the treatment of *Clostridium difficile* infection, such as surotomycin, tigecycline, fidaxomicin, tolevamer and rifaximin. However, these therapies tend to be less well studied and are not recommended first-line therapies by IDSA or SHEA, and so were not considered.

A meta-analysis by Di X, et al. was found comparing the efficacy of vancomycin and metronidazole, the two mainstay treatment options for CDI. Furthermore, this meta-analysis determined the most effective method of treatment for CDI stratified by disease severity³. The most comprehensive study of the meta-analysis was by Johnson, et al., titled “Vancomycin, metronidazole, or tolevamer for *Clostridium difficile* infection: results from two multinational, randomized, controlled trials,” which used two randomized controlled trials to assess treatment efficacy by both primary and secondary outcomes with three different medications, including vancomycin and metronidazole². The meta-analysis contained two other studies that compared the efficacy of metronidazole with vancomycin in patients with severe CDI. One was a cohort study written by Le, et al.⁴ that had results supporting the study by Johnson, et al. Another was a randomized controlled trial by Zar, et al.⁵ that also had results supporting the study by Johnson, et al. Both the Zar and Johnson studies were comparable in terms of design and assessment. Furthermore, both were equally scored as the highest quality studies on the meta-analysis. Quality was assessed by external validity, internal validity (bias, confounding), power, and quality of reporting. I decided to use the study by Johnson because it is the largest and most recent trial comparing vancomycin to metronidazole, with data stratified by disease severity. It is the study given the most weight in the meta-analysis and has outcomes similar to the other studies analyzed, as well as the overall outcome of the meta-analysis.

Critical Appraisal

Overall, the Johnson, et al. study is a well-designed pair of RCTs (Study 301 and Study 302). Study 301 contained 143 total subjects in the metronidazole group with 57 (40%) defined as having severe CDI. This study also contained 134 total subjects in the vancomycin group with 33 (25%) defined as having severe CDI. Study 302 contained 135 total subjects in the metronidazole group with 35 (26%) defined as having severe CDI. This study contained 125 total subjects in the vancomycin group with 32 (26%) defined as having severe CDI. The two studies together shows that the metronidazole group has a higher percentage (33%) of severe disease compared to the vancomycin group (25%).

The study was designed as two identical randomized, double-dummy, double-blind, parallel studies to limit researcher bias and maximize the study’s internal validity. The study included two RCT: one study included 91 sites in the US and Canada, and the other study included 109 sites in Europe, Australia, and Canada. The wide distribution of clinical sites worldwide supports the study’s generalizability and external validity. Since the study involves providing oral medications, rather than any type of procedures, individual provider characteristics or skill are not of high concern. Each study included 464 randomized patients in a 2:1:1 ratio for three potential treatments for CDI, which, respectively, were tolevamer, metronidazole, and vancomycin. This gave each study a power of 90% for non-inferiority (including tolevamer).

Patients were chosen based on a clear definition of CDI: 3 or more bowel movements in a 24-hour period (BM/day) with a loose or watery consistency, a positive *C. difficile* toxin assay result (enzyme immunoassay or cellular cytotoxicity assay) or pseudomembranes on endoscopy, and no other likely etiology for the diarrhea. The primary outcome was “clinical success,” which was defined as resolution of diarrhea and absence of severe abdominal discomfort due to CDI for more than 2 consecutive days including day 10. The secondary outcomes included time to resolution of diarrhea and recurrence rates of CDI. All assessments had clear criteria to meet. Nonresponse was also clearly defined as an increase in diarrhea or increased abdominal discomfort for more than 48 hours, development of symptomatic ileus or toxic megacolon, persistent fever >38.6°C orally or 39°C rectally, or recurrence of diarrhea attributed to CDI while on study medication.



This study did not use SHEA/IDSA criteria for severe CDI, but instead provided their own criteria based on number of bowel movements, WBC count, and abdominal pain severity. Severe disease was defined as a WBC count of $>20,000$ cells/mm³, more than 9 bowel movements/day, or severe abdominal pain. Though our patient met these criteria with a WBC count of 47,100 cells/mm³ and severe abdominal pain, the choice not to use the SHEA/IDSA criteria reduces this study's generalizability, as practitioners are more likely to use the SHEA/IDSA definition of severe CDI.

Because there were three groups compared in each individual study, the authors should have used a Bonferroni adjustment for testing statistical significance. They incorrectly reported statistical significance when both individual studies merely showed a trend favoring vancomycin in the subgroup of severe CDI. Another caution was this trend was derived from a per protocol analysis instead of an intention to treat analysis. Combining subgroup analyses from two negative studies and claiming superiority should be viewed with some skepticism. Yet, the trend in the literature review and the trends in the paper being reviewed all favor vancomycin, so this evidence has clinical utility. Additionally, adverse events related to the study medication were greater with metronidazole compared to vancomycin (6.3% vs 2.7%).

Since this study contains two RCTs that were analyzed both individually and combined this article meets criteria for Level 1b (individual RCT) in regards to evidence as therapy based on the Oxford Centre for Evidence-based Medicine⁶.

Among patients with severe disease in both studies, 66.3% of patients in the metronidazole group achieved clinical success, and 78.5% of patients in the vancomycin achieved clinical success. Therefore comparing vancomycin and metronidazole, the ARR = 0.785 – 0.663 = 0.122; NNT = $1/0.122 = 8.2$. Tolevamer performed inferiorly to both vancomycin and metronidazole; however, the details are not discussed here since it is not part of the clinical question.

Clinical Application

This literature search was inspired by a patient suffering from severe CDI, as defined by his markedly elevated WBC count. The study by Johnson, et al. provided evidence that vancomycin had higher rates of symptom improvement compared to metronidazole for treatment of severe CDI. Two other studies, Le and Zar, supported these findings. With these results, we started our patient on vancomycin and saw improvement in his CDI. However, these findings may not apply to all patients with severe *Clostridium difficile* infection, depending on how clinicians define the severity of disease in their patients.

Learning points:

- 1.) It is important for physicians to evaluate the severity of *Clostridium difficile* infection, as different degrees of severity may have different methods of management.
- 2.) Vancomycin is probably more effective than metronidazole in reducing symptoms in patients who meet the criteria for severe *Clostridium difficile* infection.
- 3.) When evaluating research trials, it is important to pay attention to the population studied. One must be careful that the definitions and population demographics of the study reasonably apply to the patient that is being cared for.

References

1. Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). *Infect Control Hosp Epidemiol*. 2010 May;31(5):431-455. doi: [10.1086/651706](https://doi.org/10.1086/651706)
2. Johnson S, Louie TJ, Gerding DN, et al. Vancomycin, metronidazole, or tolevamer for *Clostridium difficile* infection: results from two multinational, randomized, controlled trials. *Clin Infect Dis*. 2014;59(3):345-354. doi: [10.1093/cid/ciu313](https://doi.org/10.1093/cid/ciu313)
3. Di X, Bai N, Zhang X, et al. A meta-analysis of metronidazole and vancomycin for the treatment of *Clostridium difficile* infection, stratified by disease severity. *Braz J Infect Dis*. 2015 Jul;19(4):339-349. doi: [10.1016/j.bjid.2015.03.006](https://doi.org/10.1016/j.bjid.2015.03.006)
4. Le F, Arora V, Shah DN, Salazar M, Palmer HR, Garey KW. A real-world evaluation of oral vancomycin for severe *Clostridium difficile* infection: implications for antibiotic stewardship programs. *Pharmacotherapy*. 2012 Jan 24;32(2):129-134. doi: [10.1002/phar.1002](https://doi.org/10.1002/phar.1002)



5. Zar FA, Bakkanagari SR, K. M. L. S. T. Moorthi, Davis MB. A comparison of vancomycin and metronidazole for the treatment of *Clostridium difficile*-associated diarrhea, stratified by disease severity. *Clin Infect Dis*. 2007 Aug 1;45(3):302-307. doi: [10.1086/519265](https://doi.org/10.1086/519265)
6. Oxford Centre for Evidence-based Medicine - Levels of Evidence (March 2009). *Centre for Evidence-based Medicine* website <http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/>. Accessed August 18, 2015.
7. Hu J, Zhang Q, Ren X, Sun Z, Quan Q. Efficacy and safety of acetylcysteine in "non-acetaminophen" acute liver failure: A meta-analysis of prospective clinical trials. *Clin Res Hepatol Gastroenterol*. 2015;39(5):594-599. doi: [10.1016/j.clinre.2015.01.003](https://doi.org/10.1016/j.clinre.2015.01.003).
8. Lee WM, Stravitz RT, Larson AM. Introduction to the revised American Association for the Study of Liver Diseases Position Paper on acute liver failure 2011. *Hepatology*. 2012;55(3):965-967. doi: [10.1002/hep.25551](https://doi.org/10.1002/hep.25551).
9. Trey C, Davidson CS. The management of fulminant hepatic failure. *Prog Liver Dis*. 1970;3:282-298.

