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Comparison of treatment outcomes with vancomycin alone versus combination therapy in severe *Clostridium difficile* infection

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SUMMARY

Background: The recommended treatment for severe *Clostridium difficile* infection (CDI) is oral vancomycin alone. Combination therapy with metronidazole is only recommended in cases complicated by shock, ileus, or toxic megacolon. However, patients with severe infection are often treated with combination therapy despite a lack of data supporting this practice.

Aim: To evaluate differences in outcomes for patients with severe CDI treated with oral vancomycin alone versus combination therapy.

Methods: Medical records of 78 patients with severe CDI receiving either oral vancomycin alone or combination therapy for $\geq$72 h were retrospectively reviewed. The primary outcome was time to clinical cure of CDI, defined as the first day of resolution of diarrhoea for $\geq$48 h without development of a complication. Other endpoints included cure rates, complication rates, and recurrence rates.

Findings: There was no difference in the incidence of clinical cure between monotherapy and combination therapy (57.1% vs 65.1%, $P = 0.49$). Median time to clinical cure was 7.0 days for the monotherapy group and 8.0 days for combination therapy ($P = 0.19$). After adjustment for potential confounders, the hazard ratio of the time to clinical cure for combination therapy compared with monotherapy was 0.58 ($P = 0.10$). There was no difference in recurrence rate or rates of individual complications between groups; however, there was a significantly higher composite complication rate in the combination therapy group.

Conclusion: These data suggest that there is no difference in treatment outcomes between monotherapy and combination therapy for severe CDI.

Introduction

Clostridium difficile infection (CDI) is a large epidemiological problem for hospitalized patients across the world. In the USA, the incidence of CDI is reported to be 3.4–8.4 cases per 1000 admissions; however, the incidence is rising, with rates of hospital discharges for CDI doubling from 1996 to 2003.[1,2] Furthermore, in recent years, numerous outbreaks of CDI have been reported; in some of these reports, rates are as high as 22.5 per 1000 admissions.[1,3–5] Most concerning, CDI-related mortality rates are increasing; in the USA, rates increased approximately fourfold between 2000 and 2004, with similar trends seen in the UK.[6,7]

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Despite the rising incidence and worsening outcomes associated with CDI, there are few treatment options. Metronidazole and oral vancomycin are frequently used in practice for treatment of CDI and are recommended in the recently published Society for Healthcare Epidemiology of America (SHEA)/Infectious Diseases Society of America (IDSA) guidelines for CDI.[8] Both drugs have activity against *C. difficile* with limited resistance reported.[9] Metronidazole is effective for CDI due to secretion into the colon following oral or intravenous administration, although faecal concentrations decrease as treatment continues.[10] Oral vancomycin is not absorbed systemically and maintains exceedingly high faecal concentrations for the duration of treatment.[11]

The selection of treatment for CDI according to SHEA/IDSA guidelines is based on severity of disease with oral metronidazole recommended for mild to moderate infections and oral vancomycin for severe uncomplicated cases.[8] Other guidelines, such as those from the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), also support this practice.[12] When severe infection is complicated by hypotension, shock, toxic megacolon, or ileus, the combination of oral vancomycin and intravenous metronidazole is suggested.[8] Other guidelines recommend combination therapy only in severe cases where patients cannot tolerate oral therapy.[12] Although the SHEA/IDSA guidelines recommend combination therapy only for severe complicated illness, its use is still reported in cases of severe uncomplicated CDI. In a 2010 institutional evaluation performed prior to this study, it was determined that 48% of patients with a first episode of severe uncomplicated CDI were treated with the combination of metronidazole and vancomycin. Furthermore, similar practices are described elsewhere in the literature.[13,14]

Despite the lack of evidence supporting combination therapy in severe uncomplicated CDI, it is often used, thus warranting an investigation comparing the efficacy and safety of monotherapy and combination therapy for severe CDI. The purpose of this study was to evaluate differences in time to clinical cure, overall cure, complication, and recurrence for patients with severe CDI treated with monotherapy with oral vancomycin compared with combination therapy with oral vancomycin and metronidazole.

Methods

Study design

This non-interventional, retrospective medical record review was designed to assess differences in treatment outcomes for patients with severe CDI treated with oral vancomycin alone or with combination therapy. The study was designed based on the SHEA/IDSA guideline definitions of disease severity and recommendations for use of antimicrobial therapy for CDI.[8] The study was performed at a large, tertiary care, academic medical centre and approved by the Cleveland Clinic Institutional Review Board (Cleveland, OH, USA).

Adult patients aged $\geq$18 years, admitted between July 2006 and July 2011 with a diagnosis of severe CDI and who received either oral vancomycin alone or oral vancomycin in combination with metronidazole for $\geq$72 h without cross-over, were included. In this study, CDI was defined as a stool sample positive for *C. difficile* toxin with enzyme immunoassay or polymerase chain reaction and evidence of diarrhoea. Diarrhoea was noted if any of the following thresholds were met or exceeded: three unformed stools, 200 mL watery rectal bag output, or 1 L colostomy output in 24 h.[15] Criteria for severe CDI were defined as white blood cell (WBC) count of $\geq 15 \times 10^3$ cells/μL, serum creatinine of $\geq$1.5 times premorbid level, or inpatient documentation of acute kidney injury.[8]

Patients were excluded if they met criteria for mild–moderate, severe complicated, or recurrent CDI, had treatment cross-over within the first 72 h of therapy, or had baseline conditions potentially influencing the assessment of the primary outcome variable. These disease states included irritable bowel disease, graft-versus-host disease, neutropenia, or cirrhosis. Criteria for mild–moderate CDI were defined as WBC count $<15 \times 10^3$ cells/μL and serum creatinine $<$1.5 times premorbid level. Severe complicated CDI was defined as the presence of ileus, shock with the use of a vasopressor, or evidence of toxic megacolon (including colectomy, colonic perforation, or radiographic evidence) within 48 h preceding CDI onset.[8]

After enrolment, patients were divided into two cohorts: monotherapy with oral vancomycin, or combination therapy with oral vancomycin and metronidazole in any dosage form. The medical record of each patient was reviewed from 48 h prior to onset of CDI to 30 days after completion of treatment. Patient demographic data were recorded and baseline severity of CDI illness was assessed through the Charlson comorbidity index (CCI), sequential organ failure assessment (SOFA) score, and baseline laboratory markers (e.g. WBC count, serum creatinine, lactate).[16,17] Daily medication use for the first 10 days after satisfying inclusion and exclusion criteria was verified through the medication administration record. Medications of interest included vancomycin, metronidazole, and other therapies that might have affected CDI course (fidaxomicin, tigecycline, rifampin, rifaximin, intravenous immunoglobulins, probiotics, nitaxoxanide, and other systemic antibiotics). Physician and nurses' notes were assessed for evidence of complications and symptoms of CDI, such as diarrhoea or pseudomembranous colitis if applicable. Radiographic notes were also evaluated for complications.

Outcomes

The primary outcome was time to clinical cure of CDI, defined as resolution of diarrhoea for 48 h without the development of a complication. Resolution of diarrhoea was defined as the passage of two or fewer formed stools, $<$1 L colostomy output or $<$200 mL rectal bag output in 24 h. Time to clinical cure was the time from initiation of therapy until the first day on which the resolution of diarrhoea criteria were met.

Secondary outcomes were clinical cure rate at day 10 of treatment, mortality rate within 30 days of treatment, CDI-associated complication rates within 10 days, and recurrence rate within 30 days of treatment. Evaluated CDI-associated complication rates included rates of colectomy, colonic perforation, ileus, and toxic megacolon. Recurrence was defined as satisfying the definition of CDI after initial cure.

Statistics

Assuming a 70% cure rate, we determined that 78 patients would be needed to detect a difference of $\geq$25% in cure rate

between treatment groups with a two-sided alpha level of 0.05 and power of 80%.[18] A recent institutional evaluation of oral vancomycin use noted that 48% of patients were treated with combination therapy, while the rest were treated with oral vancomycin alone. Thus a one-to-one allocation between the two groups was assumed.

Nominal data were evaluated using chi-square test or Fisher's exact test, as appropriate. Continuous data were assessed for normalcy using the Shapiro–Wilkes test and normally distributed data were evaluated using Student's *t*-test. Continuous, non-normally distributed data and interval data were evaluated using the Mann–Whitney *U*-test. Kaplan–Meier curves were constructed to show the time to clinical cure and were compared with the log-rank test. A Cox proportional hazards model with adjustments for baseline differences between groups was also developed for time to clinical cure. Variables were entered into the model if they had biological plausibility for affecting the primary outcome and met the *a priori*-determined statistical criteria of $P < 0.20$ on baseline univariate comparisons. The proportional hazards assumption was assessed by inspection of the log(−log(survival function)) versus time plot. All analyses were two-sided and considered statistically significant at $P < 0.05$. All statistics were computed using SPSS software, version 11.5 (SPSS Inc., Chicago, IL, USA).

Results

A total of 651 patients, admitted between July 2006 and July 2011, were initially screened for inclusion, all of whom received oral vancomycin and had a positive stool sample for *C. difficile* toxin. In all, 573 patients were excluded, with 526 not satisfying the inclusion criteria and 47 meeting exclusion criteria (Table I). The majority of patients not satisfying inclusion criteria had either mild–moderate CDI (45%), severe complicated CDI (8%) or a duration of therapy without crossover <72 h (35%). Seventy-eight patients were enrolled with 35 in the monotherapy group and 43 patients in the combination therapy group.

Baseline characteristics are shown in Table II. The average age of the entire cohort was 65.8 ± 15 years and the average weight was 81.9 kg. Number of loose stools, SCr, and lactate on day of CDI onset were similar between groups at baseline. WBC count on day of CDI onset was higher in the combination therapy group (22.6 vs 17.5 × 10^3 cells/μL) although this difference did not reach statistical significance. Both median CCI and SOFA scores were numerically higher in the combination therapy group; however, only SOFA scores reached statistical significance ($P = 0.007$).

Table I
Reasons for patient exclusions ($N = 573$)

Screening criteria	No. (%)
Mild CDI	258 (45)
Severe complicated CDI	47 (8.2)
Recurrent CDI	19 (3.3)
Duration <72 h	202 (35)
Irritable bowel syndrome	14 (2.4)
Neutropenia	3 (0.5)
Cirrhosis	10 (1.7)
Incomplete charting	20 (3.5)

CDI, *Clostridium difficile* infection.

Table II
Patient characteristics by treatment group

Characteristic	Monotherapy ($N = 35$)	Combination therapy ($N = 43$)	*P*
Age (years)	63.1 ± 16.9	68.0 ± 12.9	0.15
Weight (kg)	78.6 ± 19.5	84.5 ± 27.7	0.29
Values on day of CDI onset			
No. of loose stools	4 (3–6)	4 (3–8)	0.71
SCr (mg/dL)	1.9 ± 2.0	2.1 ± 1.6	0.67
WBC count (10^3 cells/μL)	17.5 ± 7.3	22.6 ± 14.2	0.06
Lactate (mmol/L)	1.0 ± 1.0	1.3 ± 1.4	0.27
CCI score	2 (1–4)	3 (2–5)	0.08
SOFA score	2 (0–3)	3 (2–5)	0.007
Systemic antibiotic use [no. (%)]	27 (77.1)	33 (76.7)	0.97
Additional *C. difficile* therapies[a] [no. (%)]	2 (5.7)	0	0.2
Probiotic use [no. (%)]	0	1 (2.3)	1.0

CDI, *Clostridium difficile* infection; SCr, serum creatinine; WBC, white blood cell; CCI, Charlson comorbidity index; SOFA, sequential organ failure assessment.
Ordinal and continuous data reported as median (interquartile range) or mean ± SD, respectively.
Comparison of *P*-values for categorical values was performed using Fisher's exact test or chi-square test, and for continuous variables by Mann–Whitney *U*-test or Student's *t*-test.
[a] Additional *Clostridium difficile* therapies included intravenous immune globulin, nitazoxanide, rifampin, and/or tigecycline.

The median duration of oral vancomycin was similar between groups at 10 days. Metronidazole use was infrequent in the monotherapy group with a median duration of therapy of 0 days (interquartile range: 0–2 days). The most usual route of metronidazole administration in both groups was intravenous (overall 90.7%, combination therapy 64.1%); oral metronidazole use was also frequent (overall 74.4%, combination therapy 48.7%). Overall, vancomycin per rectum was used in 15% of patients; median duration of therapy was 0 days in both groups. Other therapies for CDI were also rarely used, with only two patients in the monotherapy group receiving additional therapies for treatment of *C. difficile*, and one patient in the combination therapy group receiving probiotics during the study period. Systemic antibiotic use was frequent in both monotherapy and combination therapy groups, 77.1% vs 76.7%, respectively ($P = 0.97$).

Overall, 48 patients (61.5%) achieved clinical cure at day 10 after treatment initiation. Within each cohort, the clinical cure rate was 57.1% (20 of 35 patients) in the monotherapy group and 65.1% (28 of 43 patients) in the combination therapy group ($P = 0.49$). The median time to clinical cure was 7.0 days (95% CI: 5.4–8.6) in the monotherapy group and 8.0 days (95% CI: 6.4–9.6) in the combination therapy group ($P = 0.19$) (Figure 1). Multivariate analysis with Cox proportional hazards was performed with adjustment for age, CCI, SOFA score, and WBC count on day of CDI onset. After adjustment, the hazard ratio of the time to clinical cure for combination therapy compared with monotherapy was 0.58 (95% CI: 0.31–1.09; $P = 0.10$).

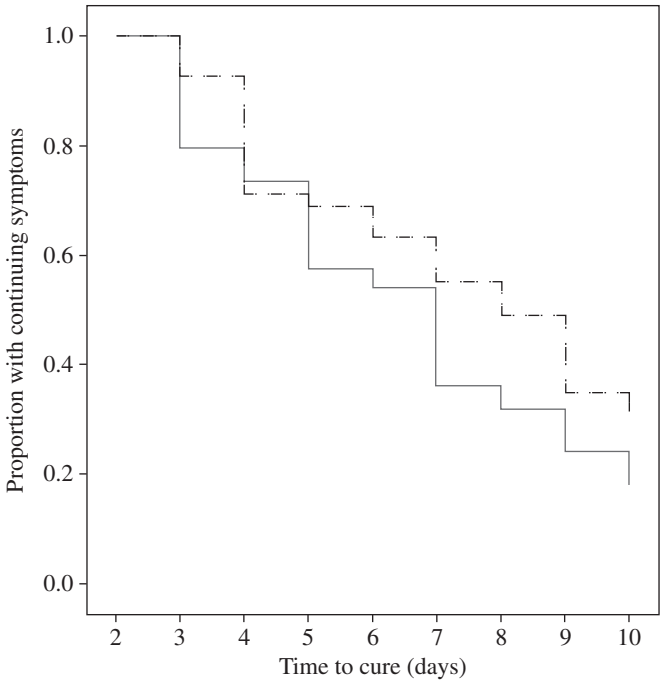

Figure 1. Kaplan–Meier analysis of time to cure for *Clostridium difficile* infection. $P = 0.19$, by log-rank test. Solid line: monotherapy; dashed line: combination therapy.

Death occurred in two (5.7%) of 35 patients in the monotherapy group compared with 10 (23.3%) of 43 patients in the combination group ($P = 0.06$) (Table III). Complication rates, including rates of recurrence, toxic megacolon, colonic perforation, and colectomy, were similar between groups (Table III). The composite complication rate was significantly higher in the combination therapy group (16.3% vs 0; $P = 0.015$).

Discussion

Our study is the first to compare monotherapy using oral vancomycin and combination therapy with oral vancomycin and metronidazole for the treatment of severe CDI. To date, there are few published data on combination therapy for the treatment of CDI. To our knowledge, only one prospective study has addressed combination therapy in the initial treatment of first-episode CDI. The study compared oral metronidazole alone to the combination of oral metronidazole and rifampin and found no differences between groups in time to symptom improvement or time to first relapse.[19] In addition, although no clinical studies have been conducted, an *in vitro* study of the combination of metronidazole and vancomycin failed to demonstrate synergy with the two agents.[20] Clinicians may initiate combination therapy with an assumption of better outcomes compared with monotherapy. It is often held that multiple routes of drug administration used in combination therapy may ensure that there are adequate drug concentrations in the colon when severe CDI is complicated by acute colonic inflammation.[8] Therefore, the recommendation for combination therapy has been reserved for patients with severe complicated CDI. However, this recommendation is based on expert opinion. As there is a paucity of data on combination therapy for CDI, the results from this current study will provide additional insights into the best treatment of severe CDI.

Our study demonstrated that there was no difference in measures of clinical cure between monotherapy and combination therapy for patients with severe CDI. Cure rates were lower overall compared with other studies.[21–23] This may be attributable to our definition of cure as resolution of symptoms for $\geq$48 h by day 10. The 48 h requirement was included to ensure that response to therapy was not a transient phenomenon, as patients may have symptom resolution on one day and subsequently symptoms may recur. Cure rates were not assessed based on alternative definitions in order to assess whether rates were similar to other studies in either group. Lower cure rates may have also been attributable to increased severity of illness at baseline in the study population compared with similar studies; our patient population had higher age, baseline WBC count, and renal function compared with other studies.[18,21–23]

The time to cure found in the current study is comparable with other investigations.[18,19] Our data suggest a trend towards an earlier time to cure in the monotherapy group compared with the combination therapy group (seven versus eight days; $P = 0.19$). Even after adjustment for baseline characteristics, the patients in the combination group appeared to have a slower time to cure (hazard ratio: 0.58; 95% CI: 0.31–1.09; $P = 0.10$). While this finding is not significant, there are data to suggest that metronidazole and vancomycin may increase the risk for the development of CDI. In a systematic review of literature, Bignardi *et al.* determined that the pooled odds ratios for the development of CDI associated with the use of metronidazole and vancomycin were 5.2 and 3.1, respectively.[24] Although their analysis was designed to evaluate for risk factors associated with the development of CDI, the principles of CDI treatments being detrimental to patients' natural flora may also be applied to a recovering colon. This may partially explain the delay in resolution of symptoms associated with combination therapy seen in our study. However, it is important to note that there was no difference between the groups in the secondary outcome of recurrence rate, which would conceivably be increased if gut flora were negatively affected by the addition of an extra antibiotic. Due to the retrospective design of our study, recurrences of CDI outside of our institution were not captured. Furthermore, recurrences may be dictated by a number of other factors that were not

Table III
Rates of death, recurrence, and complication of severe *Clostridium difficile* infection by treatment type

Outcome	Monotherapy ($N = 35$)	Combination therapy ($N = 43$)	*P*
Death	2 (5.7)	10 (23.3)	0.06
Recurrence	2 (5.7)	2 (4.7)	1.0
Any complication	0	7 (16.3)	0.015
Colectomy	0	4 (9.3)	0.12
Colonic perforation	0	1 (2.3)	1.0
Ileus	0	3 (7)	0.25
Toxic megacolon	0	3 (7)	0.25

Data reported as no. (%) of patients.
P-values were calculated using Fisher's exact test.

assessed in the current study, including duration of overall antibiotic use and hospital course beyond the duration of CDI treatments.

Overall, while there was no statistically significant difference in any of the complication rates between groups, each complication rate was numerically higher in the combination therapy group. Furthermore, when the composite of complication rates between groups was assessed, there were significantly more complications in the combination therapy group than in the monotherapy group. Several factors may explain this trend. First, there are known baseline discrepancies between combination therapy and monotherapy, as evidenced by univariate differences in WBC count, CCI, and SOFA score; therefore a potential reason for the higher death and complication rates is the higher severity of illness at baseline in the combination therapy group. There may also be other potentially unaccounted differences between groups which were not evaluated. The decision to administer combination therapy is based frequently on the patient's overall clinical condition and is subject to confounding bias. Finally, despite having excluded diagnoses such as IBD and neutropenia that interfere with assessment of complications, CDI may not be the only explanatory cause for the development of these complications. For instance, ileus may be caused by the use of narcotics or mesenteric ischaemia if the patient requires vasoactive agents, and would therefore occur more frequently in patients at higher severity of illness at baseline. However, these endpoints have been used previously in observational studies of CDI.[25]

An explanation for our findings is that patients with severe disease do not have complications that prevent oral vancomycin alone from achieving adequate faecal concentrations. For example, an ileus in severe complicated disease may prevent orally administered medications from reaching the site of colonic inflammation, and the addition of intravenous metronidazole may be necessary. When these additional circumstances are absent in cases of severe uncomplicated CDI, our data may suggest that concentrations of oral vancomycin alone are sufficient to achieve cure without additional complications and recurrences. Furthermore, there is evidence that faecal concentrations of intravenous metronidazole, which is most often used in combination therapy, may be substantially lower compared with oral metronidazole or vancomycin, leading to worse treatment outcomes.[25] This suggests that the additional therapy may not significantly augment faecal concentrations compared with monotherapy in severe CDI.

There were several limitations to our study. First, this was a retrospective medical record review and the study is subject to the inherent flaws of this design; incomplete medical records were reasons for many excluded patients. Furthermore, despite efforts to adjust for potential confounders, there may still be unaccounted differences between groups that reflect the clinician's decision to administer monotherapy or combination therapy. Second, the study spanned five years and there were institutional practice changes throughout the period; for instance, polymerase chain reaction for detection of CDI was introduced to our institution in 2010. Previous years relied on the enzyme immunoassay test which is less sensitive. Third, as a retrospective review, the 72 h requirement of inclusion ruled out evaluation of patients who changed therapies within the first 72 h. This requirement was incorporated into the design to ensure that patient groups would be easily distinguishable. Patients excluded for cross-over in the first 72 h may have constituted an important group warranting evaluation. For instance, monotherapy that was changed to combination in the first 72 h could be considered a treatment failure, and excluding these patients may have biased the results. Finally, this study had a relatively small sample size. Although we met our target sample size, our observed cure rate is lower than that included in the power analysis. It is possible that some of the outcomes, particularly our secondary outcomes, may have been significant, given a larger sample size. These results then indicate that a randomized controlled trial is warranted to confirm our conclusions, and would be clinically safe.

In conclusion, despite common practice of combination therapy for treatment of severe CDI, our data suggest that there are no outcome differences for patients receiving oral vancomycin alone versus those receiving oral vancomycin and metronidazole as treatment for severe CDI. These data are important as they are the first to directly compare monotherapy with oral vancomycin and combination therapy with oral vancomycin and metronidazole for patients with severe CDI. This supports guideline recommendations that first-line therapy for patients with severe CDI should be oral vancomycin alone and should prompt a prospective investigation into the comparison of monotherapy and combination therapy.

Conflict of interest statement
None declared.

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