Does Extending Clostridium Difficile Treatment In Patients Who Are Receiving Concomitant Antibiotics Reduce The Rate Of Relapse?

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Citation

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Abstract

Purpose: Exposure to concomitant antibiotics during treatment for Clostridium difficile infection (CDI) is a major risk factor for relapse. This study compared the CDI relapse rates among patients who underwent CDI treatment while receiving concomitant antibiotics.

Methods: This retrospective chart review evaluated consecutive adult patients with CDI who were receiving concomitant antibiotics at two acute care sites (Hamilton, Ontario) during 2011–2013. We compared the CDI relapse and mortality rates for regular CDI treatment (10–14 days) and extended CDI treatment (>14 days), and adjusted the analyses for several covariates.

Results: We identified 457 patients with CDI, and 228 (50%) patients were considered eligible. A total of 101 (44.2%) patients were receiving regular CDI treatment and 127 (55.7%) patients were receiving extended CDI treatment. The relapse rates were similar for the regular and extended treatment groups in the univariate (17% and 23%, respectively; odds ratio [OR]: 1.4, 95% confidence interval [CI]: 0.7–2.7, p = 0.286) and multivariate analyses (OR: 0.7, 95% CI: 0.3–1.7, p = 0.425). A composite outcome (in-hospital mortality and/or CDI relapse) was higher for extended treatment (35% vs. 23%; OR: 1.9, 95% CI: 1.0–3.4, p = 0.039), although this difference was not significant in the multivariate analysis (OR: 1.2, 95% CI: 0.6–2.5, p = 0.648).

Conclusions: We found no evidence to support extended CDI treatment among patients who are receiving concomitant antibiotics. However, further studies are needed to identify better methods for reducing the risk of relapse in this population.

BACKGROUND

Clostridium difficile (C. difficile) infection (CDI) is the most common cause of hospital-associated diarrhoea [1] and the leading cause of nosocomial infection [2]. The incidence and severity of CDI has increased in North America and in many other parts of the world during the past 20 years, which is partially due to the emergence of the B1/NAP1/027 strain [3]. The mortality rate that is attributable to CDI has now risen to approximately 6%, and increases with advancing age [4].

Relapsing CDI remains a major challenge, and occurs in 15–35% of cases [5]. Unfortunately, exposure to concomitant antibiotics during CDI treatment is a major risk factor for relapse [6]. Therefore, some healthcare providers extend the duration of CDI treatment beyond the recommended 10–14 days [7] for patients who are receiving concomitant antibiotics, based on the belief that the extended treatment will decrease the risk of relapse. However, we are not aware of any evidence to support this practice.

The purpose of this study was to assess whether extending CDI treatment beyond 14 days affected the risk of CDI relapse and mortality among patients who were receiving concomitant antibiotics.

METHODS

We performed a retrospective review of all patients who were treated for CDI while receiving concomitant antibiotics in two adult tertiary, university-affiliated teaching hospitals (Hamilton, Ontario, Canada) between 2011 and 2013. The study was approved by our local research ethics board.

We included all consecutive patients who were ≥18 years old, were receiving concomitant antibiotics for non-CDI treatment while receiving CDI treatment, and had CDI symptoms (≥3 loose stools during a 24-h period [7]) and detection of C. *difficile* toxin genes via real-time polymerase chain reaction. We excluded patients who had received <10 days of CDI treatment, and only the first episode per patient during the study period was considered. Patients were also excluded if their first episode during the study period was a relapse. The NAP-1 strain was identified via the presence of tcdC and cdtA (binary toxin genes), as previously described [8].

Regular CDI treatment was defined as metronidazole or vancomycin treatment for 10–14 days [7], and extended CDI treatment was defined as >14 days of treatment with these drugs. The primary outcome was CDI relapse, which was defined as recurrent CDI symptoms with confirmatory testing after a symptom-free period and within 8 weeks after successful treatment. The secondary outcomes were a composite of CDI relapse and/or in-hospital mortality, mortality while receiving CDI treatment, and CDI-related death (defined as documented severe CDI or toxic megacolon with CDI listed as the direct of cause of death in the death report) [7, 9].

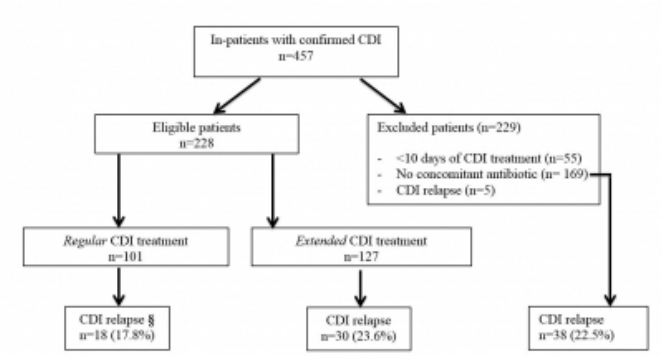
We compared the characteristics and outcomes between the regular and extended treatment groups using the chi-square test or Fisher's exact test, as appropriate. The results were reported as odds ratios (OR) and 95% confidence intervals (CI) for categorical variables, and the Mann-Whitney U-test was used for continuous variables. Predictors of relapse with a p-value of <0.2 in the univariate analysis were included in a step-wise forward multivariate logistic regression analysis. All analyses were performed using PASW software (version 18; SPSS Inc., Chicago, IL).

RESULTS

During the study period, we identified 457 patients with CDI, and 228 (50%) cases fulfilled our eligibility criteria (Fig. 1). Among the included cases, 163 (71%) were hospital-associated cases, with substantial in-hospital mortality (27, 11.8%). A total of 101 (44.2%) patients were receiving regular CDI treatment and 127 (55.7%) patients were receiving extended CDI treatment (Table 1). The two groups were similar in their age, sex, use of proton pump inhibitors, incidence of presumed NAP-1/027 strain vs. non-NAP-1/027 strain, and underlying disease (Table 1). However, patients in the extended treatment group had a longer median hospital stay (39 days vs. 17 days; p < 0.001), were more likely to be treated with combination of metronidazole and vancomycin (36.2% vs. 18.8%; OR: 2.6, 95% CI: 1.4–4.8, p = 0.003), and were more likely to receive intravenous or intravenous/oral combinations of CDI treatment (15% vs. 5%; OR: 3.4, 95% CI: 1.2–9.4, p = 0.014). Furthermore, the median duration of concomitant antibiotic treatment was significantly longer in the extended group (19 days vs. 8 days; p < 0.001), and the use of betalactams and carbapenems was also more common in the extended group.

Figure 1

Flow Chart



§ CDI relapse: recurrence of symptoms of CDI (after symptom free-period) within 8 weeks after successful treatment along with confirmatory testing

Table 1

Patient characteristics and outcomes of regular (10-14 days) and extended (>14 days) CDI treatment groups

Patient characteristic and outcome	Regular CDI treatment (n=101)	Extended CDI treatment (n=127)	Univariate analysis OR (95% CI)	*p*-value
	n (%)	n (%)		
Age – years, median (IQR)	72 (59-82)	71 (58-80)	n/a	0.385
Male	49 (48.5)	70 (55.1)	1.3 (0.8-2.2)	0.321
Hospital Site #1 vs #2	53 (52.4)	50 (39.3)	0.6 (0.3-1.0)	**0.048**
Hospitalization – days, median (IQR)	17 (8-41.5)	39 (20-69)	n/a	**<0.001**
Presumed NAP-1/027 strain	27 (26.7)	32 (25.1)	0.9 (0.5-1.7)	0.758
Underlying disease				
- Diabetes	30 (29.7)	43 (33.8)	1.2 (0.7-2.1)	0.504
- Hypertension	56 (55.4)	63 (49.6)	0.8 (0.5-1.3)	0.381
- Coronary artery disease	34 (33.6)	44 (34.6)	1.0 (0.6-1.8)	0.877
- Chronic kidney disease	12 (11.8)	22 (17.3)	1.6 (0.7-3.3)	0.252
- Malignancy	25 (24.7)	37 (29.1)	1.3 (0.7-2.3)	0.460
- Immunosuppression	16 (15.8)	32 (25.1)	1.8 (0.9-3.5)	0.085
- Inflammatory bowel disease	1 (1)	3 (2.3)	2.4 (0.2-23.6)	0.632
Use of proton pump inhibitor	64 (63.3)	81 (63.7)	1.0 (0.6-1.8)	0.949
CDI treatment				
- Drug for CDI treatment				**0.006**
o Metronidazole	80 (79.2)	75 (59)	reference	
o Vancomycin	2 (2)	6 (4.7)	3.2 (0.6-16.4)	0.162
o Metronidazole and vancomycin	19 (18.8)	46 (36.2)	2.6 (1.4-4.8)	**0.003**
- IV or IV/oral combination	5 (5)	19 (15)	3.4 (1.2-9.4)	**0.014**
Concomitant antibiotics				
- Antibiotic treatment 8 weeks before CDI treatment	84 (83.2)	107 (84.3)	1.1 (0.5-2.2)	0.826
- Duration of concomitant antibiotics while on CDI treatment until end of 8 week follow up	8 (3.5-15.5)	19 (10-28)	n/a	**<0.001**
- Group of antibiotic while on CDI treatment				
- Betalactam (-combinations)	33 (32.6)	62 (48.8)	2.0 (1.1-3.4)	**0.014**
- Cephalosporin	41 (40.5)	56 (44)	1.2 (0.7-2.0)	0.595
- Carbapenems	8 (7.9)	26 (20.4)	3.0 (1.3-6.9)	**0.008**
- Glycopeptides	23 (22.7)	38 (29.9)	1.4 (0.8-2.6)	0.226
- Fluoroquinolone	38 (37.6)	47 (37)	1.0 (0.6-1.7)	0.924
- Other systemic antibiotics	12 (11.8)	16 (12.5)	1.1 (0.5-2.4)	0.870
- Systematic antibiotic in 8 weeks following CDI treatment	38 (37.6)	78 (61.4)	2.6 (1.5-4.5)	**<0.001**
Outcomes				
- CDI relapse†	18 (17.8)	30 (23.6)	1.4 (0.7-2.7)	0.286
- CDI relapse and/or in-hospital mortality	23 (22.8)	45 (35.4)	1.9 (1.0-3.4)	**0.038**
- CDI related death§	2 (7.4)	3 (7.6)	1.2 (0.2-7.3)	1.000
- Death while on CDI treatment	8 (29.6)	8 (20.5)	0.8 (0.3-2.2)	0.643

Abbreviations: CDI: *C. difficile* infection; IV: intravenous

† CDI relapse: recurrence of symptoms of CDI (after symptom free-period) within 8 weeks after successful treatment along with confirmatory testing

§ CDI related mortality: sepsis due to CDI or toxic megacolon related to CDI

Among the 228 eligible patients, 48 (21%) experienced a CDI relapse. The relapse rates were similar in the regular and extended treatment group (17% vs. 23%, respectively; OR: 1.4, 95% CI: 0.7–2.7, p = 0.286). In the multivariate analysis, the risk of experiencing a relapse was also similar between the two groups (OR: 0.7, 95% CI: 0.3–1.7, p = 0.425). The statistically significant independent predictors of relapse were female sex (OR: 2.6, 95% CI: 1.1–5.8, p = 0.025), duration of hospital admission (10-day increase; OR: 1.2, 95% CI: 1.1–1.4, p < 0.001), presumed presence of the NAP-1 strain (OR: 4.0, 95% CI: 1.8–9.2, p = 0.001), and diabetes (OR: 3.1, 95% CI: 1.4–7.0, p = 0.007). In contrast, the CDI relapse rate was 22.5% among the patients who were excluded for not receiving concomitant antibiotics.

The mortality outcomes were similar between the two groups, with the exception of the composite outcome of in-hospital mortality and/or CDI relapse, which was higher in the extended treatment group (OR: 1.9, 95% CI: 1.0–3.4, p = 0.039). However, this increase was not significant in the multivariate analysis (OR: 1.2, 95% CI: 0.6–2.5, p = 0.648).

DISCUSSION

CDI treatment was extended beyond the recommended 14 days in >50% of the patients who were receiving concomitant antibiotics. However, we found no evidence that extended treatment improved patient outcomes. Although the patients who underwent extended CDI treatment were exposed to a greater number and longer duration of concomitant antibiotics, and had a longer average stay, we did not observe an effect for extended CDI treatment on relapse rates, even after adjusting for these factors and other relapse risk factors. Our findings support the recommendation in the current guidelines, which do not recommend extending the treatment duration in non-relapse cases [7]. Furthermore, our study corroborates the findings of previous studies that have demonstrated that adherence to CDI treatment guidelines is suboptimal, with reported adherence rates of 43–52% [10, 11]. We also found a higher relapse rate among patients with the presumed NAP-1 strain, which also corroborates the findings of previous studies [12, 13].

To the best of our knowledge, this is the first study to assess the potential benefit of extended CDI treatment for patients who are receiving extended antibiotic treatment. The strengths of the present study include comprehensive data collection from consecutive patients. However, our study also has a number of limitations. First, despite our best efforts to gather all relevant information, 27 (11.8%) patients had missing information regarding their CDI treatment duration. For these patients, we assumed a treatment duration of 10–14 days, as recommended in the major guidelines. Second, given the observational design, confounding by indication may have biased our findings. To minimize this potential bias, we adjusted for measurable confounding factors in the multivariate analysis. Fourth, in-hospital mortality was substantial (11.8%) in our study, and similar results have been previously reported [4]. Nevertheless, because death is a competing outcome, we used a composite of CDI relapse and/or in-hospital mortality as a secondary outcome to confirm the findings from the primary analysis. Fifth, it is possible that we missed relapses, because patients may have presented to providers outside of our hospital network. However, the related effect on our analyses would likely be minimal, as our hospital

network is the largest in the region and our microbiology lab handles all specimens from throughout the region.

In conclusion, we found no evidence to support extending CDI treatment for patients who are receiving concomitant antibiotics. However, further studies are needed to confirm these findings, and to identify better methods for reducing the risk of relapse in this population.

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