Antibiotic Regimen after a Total Abdominal Colectomy with Ileostomy for Fulminant *Clostridium difficile* Colitis: A Multi-Institutional Study

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Abstract

Background: Fulminant *Clostridium difficile* colitis (fCDC) is a highly lethal disease with mortality rates ranging between 12% and 80%. Although often these patients require a total abdominal colectomy (TAC) with ileostomy, there is no established management protocol for post-operative antibiotics. In this study we aim to make some recommendations for post-operative antibiotic usage, while describing the practice across different institutions.

Methods: Multi-institutional retrospective case series including fCDC patients who underwent a TAC between January 1, 2007, and June 30, 2012. We first analyzed the complete cohort and consecutively performed a survivor analysis, comparing different antibiotic regimens. Additionally we stratified by time interval (antibiotics for ≤ 7 d, or ≥ 8 d). Primary outcome was in-hospital mortality. Additional secondary outcomes included hospital length of stay (HLOS), ICU LOS, number of ventilator-free days, and occurrence of intra-abdominal complications (proctitis, abscess, sepsis, etc.).

Results: A total of 100 fCDC patients that underwent a TAC were included across five institutions. Four different antibiotic regimens were compared; A (metronidazole IV + vancomycin PO), B (metronidazole IV), C (metronidazole IV + vanco PO and PR), and D (metronidazole IV + vancomycin PR). The combination of IV metronidazole with or without PO vancomycin showed superior outcomes in terms of a shorter ICU length of stay and more ventilator-free days. However, when comparing metronidazole alone vs. metronidazole and any combination of vancomycin, no significant differences were found. Neither the addition of vancomycin enema, nor the time interval changed outcomes.

Conclusion: Patients, after a TAC for fCDC, may be placed on either IV metronidazole or PO vancomycin depending upon local antibiograms, and proctitis may be treated with the addition of a vancomycin enema (PR). There was no data to support routine treatment of more than 7 d.

COLONIZATION WITH *CLOSTRIDIUM DIFFICILE* can result in a wide range of disease patterns from asymptomatic colonization, to a mild infection (CDI), and sometimes even a severe, fulminant, colitis [1,2]. Fulminant *C. difficile* colitis (fCDC) is a disease of increasing incidence, with high morbidity and mortality [3–5]. Often these patients require surgical treatment, namely a total abdominal colectomy (TAC).

Although this procedure has been performed and described many times [4–17], not much has been written about the post-operative antibiotic course of these patients. There is literature describing post-operative complications such as enteritis and surgical site infections [12,13,18]; however, there is no established antibiotic management protocol for patients with fCDC who underwent a TAC. For almost three decades now,

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vancomycin and metronidazole have been the two most frequently used antimicrobial agents for the treatment of CDI [19], but no guidelines recommend one specific antibiotic regimen for patients after a TAC. In this study the practice across different institutions is described. Our aim is to make some recommendations for post-operative antibiotic usage with regard to length of treatment, and the effect on outcomes such as residual *C. difficile* infections.

Patients and Methods

Design

This is a multi-institutional retrospective case series including fCDC patients who underwent a total abdominal colectomy (TAC) between January 1, 2007, and June 30, 2012. The primary outcome was in-hospital mortality. Secondary outcomes included hospital length of stay (HLOS), intensive care unit (ICU) LOS, number of ventilator-free days, and occurrence of intra-abdominal complications (e.g., proctitis, abscess, sepsis).

Definitions and data collection

Fulminant CDC is defined as [4] CDC with major systemic toxic effects and shock, resulting in need for ICU admission, colectomy, or death. Normally, a TAC is performed in patients with fCDC who were determined to be too toxic for a trial of non-operative management or who failed medical therapy. In all patients undergoing a TAC, CDC was confirmed by histopathologic analysis of the surgical specimen.

The focus was on the post-operative course of these patients, and initially we compared patients that received antibiotics post-operatively for ≤ 7 d, or ≥ 8 d. The following variables from patient electronic records were collected: 1) Age, gender, race, and ethnicity; 2) Charlson Comorbidity Index [20], Acute Physiology and Chronic Health Evaluation (APACHE II) score, vasopressor requirement, transfusion requirements, $\text{PaO}_2:\text{FiO}_2$ (P:F) ratio, and total fluid balance; 3) laboratory values: Red blood cell count, white blood cell count, platelets, hemoglobin, hematocrit, sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, and glucose; 4) hospital length of stay, ICU length of stay, ventilator-free days, time to full enteral feeds, mortality, and discharge disposition; and 5) complications: Proctitis, sepsis, abscess, breakdown of rectal staple line, and surgical site infection.

Statistical analysis

Descriptive statistics were tabulated to give an overview of our study cohort. When comparing groups, continuous variables were summarized as mean $\pm$ standard deviation, and compared by *t*-tests when variables were normally distributed. Otherwise, data were summarized as median (interquartile range [IQR]), and compared by Wilcoxon rank sum tests. Categorical variables were compared by Fisher exact test. To examine the outcomes in the post-operative course, we conducted an additional analysis limited to survivors, defined as patients that were still alive after the regular period of 28 d post-operatively. We compared outcomes between antibiotic regimen, length of treatment, and with and without the addition of an enema. We also compared antibiotic groups stratified by length of treatment. Additionally, we compared survivors vs. non-survivors, and variables significant at the

$p \leq 0.1$ level were considered as candidates for a multivariable logistic regression model to identify independent predictors of mortality. Because of the small number of events, the final model included the two predictors significant at the $p < 0.05$ level and adjusted odds ratios (aOR) with 95% confidence intervals (CI) were reported. A two-tailed $p < 0.05$ was considered to be significant for all analyses. All analyses were performed in SAS version 9.3 (The SAS Institute, Cary, NC). This study was approved by our Institutional Review Board.

Results

A total of 100 patients from five institutions were collected. All patients underwent a total abdominal colectomy (TAC) for fCDC. The mean ($\pm$ standard deviation) age was 66 ± 15 years, and 58% were male. The average age-adjusted Charlson Comorbidity Index (CCI) was 4.4 ± 2.7 . Pre-operatively, the mean APACHE II score was 18 ± 9 points, 43% required a vasopressor, mean P:F was 332 ± 147 , and median total fluid balance (TFB) was 2.6 L positive (IQR 0.6–5.4 L). Our primary outcome, mortality, was 26% (26/100) overall. The median (IQR) HLOS was 19 d (11–37), with a median ICU LOS of 6.5 d (3–15), and median ventilator-free days of 25 (0–27). All other variables, including the intra- and post-operative status, as well as the complications that occurred, can be found in Table 1.

The antibiotics studied in the post-operative course of fCDC patients were metronidazole (per OS, PO, and intravenous, IV) and vancomycin (PO and per rectum, PR). In total, 14 different combinations could be made (Table 2). There was a substantial amount of variability within institutions and across institutions in preferred regimen and length of treatment. When dividing the length of treatment into two groups, ≤ 7 d and ≥ 8 d, we found that a majority of the centers (57% of patients) preferred post-operative antibiotic treatment for ≥ 8 d. There was a significant difference in in-hospital mortality between patients who received antibiotics for ≤ 7 d vs. ≥ 8 d (41.7% vs. 17.5%, $p = 0.016$). In the survivor analysis, there were no significant differences in outcomes between patients that received antibiotics for ≤ 7 d vs. ≥ 8 d.

Because of low numbers in some of the subgroups, we decided to compare the four largest groups; subgroup A (metronidazole IV + vancomycin PO), B (metronidazole IV), C (metronidazole IV + vancomycin PO and PR), and D (metronidazole IV + vancomycin PR). None of the combinations turned out to be superior in mortality. When comparing groups A and C, as well as A and D, a shorter ICU LOS and more ventilator-free days were found in favor of group A. The same results were found when comparing ICU LOS between groups B and C, as well as B and D, with group B being superior. No significant differences were found between groups A and B or between groups C and D (Table 3).

Additionally, we compared patients per time interval (≤ 7 d vs. ≥ 8 d), stratified by antibiotic regimen (group A–D), with no significant differences found. Similarly, there were no significant differences when comparing metronidazole alone vs. metronidazole with any combination of vancomycin (with and without stratification by time interval). An extra focus was the addition of a rectal enema of vancomycin to the antibiotic regimen. Overall, patients who received an enema in addition to IV/PO vancomycin or metronidazole had a

TABLE 1. OVERALL COHORT WITH FULMINANT *CLOSTRIDIUM DIFFICILE* COLITIS (fCDC),
MANAGED WITH A TOTAL ABDOMINAL COLECTOMY (TAC)

Parameter	Overall cohort (n = 100)
Demographics	
Age, mean (SD), y	66.3 ± 15.3
Age > 70 y, No. (%)	44 (44)
Male, no. (%)	58 (58)
Race, no. (%)	
Caucasian	86 (86)
African-American	12 (12)
Asian	1 (1)
Unknown	1 (1)
Charlson Comorbidity Index (CCI), mean (SD)	4.4 ± 2.7
Pre-operative status	
APACHE II score, mean (SD)	18.3 ± 8.6
Vasopressor requirement, no. (%)	43 (43)
P:F, mean (SD)	331.7 ± 146.7
TFB, median (IQR), mL	2,584 (608– 5384)
Intra-operative status	
EBL, median (IQR), mL	250 (100– 500)
Blood transfusions, median (IQR), units	0.5 (0– 3.5)
Post-operative status	
Vasopressor requirement, no. (%)	65 (65)
PF ratio 24 h post-op, mean (SD), mmHg	302.4 ± 126.8
TFB post-op day 1, median (IQR), mL	7,438 (4,771–11,659)
TFB post-op day 2, median (IQR), mL	9,181 (5,221–13,095)
TFB post-op day 3, median (IQR), mL	8,245 (4,610–14,174)
Outcomes	
Hospital length of stay, median (IQR), d	19 (11– 37)
ICU length of stay, median (IQR), d	6.5 (3– 15)
Ventilator free days, median (IQR), d	25 (0– 27)
Time to full enteral feeds, median (IQR), d	4 (2– 6)
Proctitis + pouchitis, No. (%)	6 (6)
Sepsis, no. (%)	28 (28)
Abscess, no. (%)	7 (7)
Breakdown rectal staple line, no. (%)	3 (3)
Surgical site infection, no. (%)	8 (8)
Mortality, no. (%)	26 (26)
Discharge disposition, no. (%)	
Home	32 (32)
Deceased	28 (28)
Rehabilitation	26 (26)
Nursing home	14 (14)

SD=standard deviation; APACHE=Acute Physiology and Chronic Health Evaluation; PF=PaO (partial pressure of oxygen):FiO (fraction of inspired oxygen); mm Hg=millimeters of mercury; TFB=total fluid balance; mL=milliliter; EBL=estimated blood loss; IQR=interquartile range; ICU=intensive care unit.

longer ICU LOS (median [IQR] of 11 d [6–19] vs. 5 d [2–11], $p=0.001$), and a greater incidence of proctitis (13.9% vs. 0, $p=0.006$). When stratified by time interval, adding an enema to any antibiotic regimen of ≤ 7 days was associated with a delay to full enteral feeds (median [IQR] of 6 d [5–7] vs. 3 d [2.5–4], $p=0.047$). Receiving antibiotics including an enema for ≥ 8 days was associated with a longer ICU LOS (median [IQR] of 11.5 d [9–22] vs. 5 d [4–13], $p=0.008$), and a greater percentage of patients with proctitis (13.9% vs. 0, $p=0.019$). Similar results were observed when the analyses were limited to survivors.

In the multivariable logistic regression analysis for mortality, we identified two predictors significant at the $p < 0.05$ level: Requiring a vasopressor before the operation increased

the risk of mortality significantly (OR, 6.46), as well as the total units of FFP transfused during hospital admission; for every extra unit of FFP the odds of dying increased by 17% (Table 4). The final model had a c statistic of 0.81 with no evidence of lack of fit (Hosmer-Lemeshow goodness-of-fit $p=0.21$). However, the combination of antibiotics did not turn out to be a risk factor for mortality.

Discussion

In this multicenter study of 100 fCDC patients who underwent a TAC, we looked at the differences in antibiotic regimen postoperatively. Four different combinations of metronidazole and vancomycin were compared, and the IV

TABLE 2. DIFFERENT COMBINATIONS OF ANTIBIOTICS AND NUMBER OF TREATMENT DAYS

Combination of antibiotics	Total (n=100)	Treatment 1–7 d (n)	Treatment > 8 d (n)
Metronidazole IV and vancomycin PO	26	12	14
Metronidazole IV	21	11	10
Metronidazole IV and vancomycin PO+PR	12	1	11
Metronidazole IV and vancomycin PR	12	4	8
Metronidazole PO+IV and vancomycin PR	7	2	5
Metronidazole PO+IV	6	2	4
Metronidazole PO+IV and vancomycin PO	3	1	2
Vancomycin PO	2	1	1
Metronidazole PO+IV and vancomycin PO+PR	2	0	2
Metronidazole PO	1	0	1
Metronidazole PO and vancomycin PO+PR	1	0	1
Vancomycin PR	1	1	0
Vancomycin PO+PR	1	1	0
No antibiotics at all or unknown	5	-	-

IV=intravenous; PO=per OS; PR=per rectum.

metronidazole with or without PO vancomycin showed superior outcomes in terms of a shorter ICU length of stay and more ventilator-free days. However, when comparing metronidazole alone vs. metronidazole and any combination of vancomycin, no significant differences were found. The majority of patients (57%) within our study were treated for ≥ 8 d, but that did not result in any significant differences in outcomes. In addition we showed that adding an enema (PR) of vancomycin did not improve outcomes.

For the past 30 y, vancomycin and metronidazole have been the two drugs of choice for the treatment of CDI [21–23]. Current guidelines recommend metronidazole for the treatment of an initial episode of mild to moderate CDI, as well as for a first recurrence, whereas vancomycin (with or without the addition of metronidazole) is the antibiotic of choice for more severe and complicated episodes, and a second recurrence [19]. These recommendations are supported by studies

of Belmares et al. and Zar et al. that looked specifically into disease severity stratification and found superior results for vancomycin in more severe cases [24,25].

Early studies have shown that metronidazole and vancomycin are equally efficient, and have similar relapse rates in regular CDI, with a side note that metronidazole is more economical than vancomycin [22]. The efficacy of metronidazole was more recently challenged by a study of Vardakis et al., who showed in a systematic review that metronidazole had a greater treatment failure rate than vancomycin [26]. Additionally, Musher and colleagues also showed higher recurrence rates in patients treated with metronidazole [27].

However, vancomycin has been shown to have varying results as well; Pepin et al. reported that vancomycin lost its superiority over metronidazole, coinciding with the emergence of NAP1/027 in the early 2000s, implying that vancomycin would not work as well in severe cases [28]. A

TABLE 3. COMPARISON OF THE FOUR MOST FREQUENTLY USED ANTIBIOTIC REGIMEN

	A (n=26)	B (n=21)	C (n=12)	D (n=12)	p
Mortality, No. (%)	10 (38)	7 (33)	3 (25)	4 (33)	None
Hospital length of stay, median (IQR), d	17 (9–31)	21 (11–46)	19.5 (14.5–29.5)	16.5 (10–29)	None
ICU length of stay, median (IQR), d	4.5 (1–15)	4.5 (2–10.5)	11.5 (9.5–29)	11.5 (4.5–17.5)	A vs. C: 0.017 B vs. C: 0.009
Ventilator-free d, median (IQR), d	24.5 (0–28)	25.5 (0–27)	16 (0–25.5)	12 (0–22)	None
Limited to survivors	A (n=16)	B (n=14)	C (n=9)	D (n=8)	
Hospital length of stay, median (IQR), d	16.5 (11–28)	22.5 (13–46)	20 (19–33)	21 (11–29)	None
ICU length of stay, median (IQR), d	4 (0–5.5)	5 (3–8)	11 (10–29)	13.5 (7–17.5)	A vs. C: 0.007 A vs. D: 0.031
Ventilator-free days, median (IQR), days	26.5 (25–28)	27 (25–27)	22 (12–26)	17.5 (8.5–25.5)	B vs. C: 0.01 B vs. D: 0.038 A vs. C: 0.021 A vs. D: 0.021

Total cohort, n=100; subanalysis shown here of the four most frequently used antibiotic regimen, n=71

Group A: Metronidazole IV+vancomycin PO

Group B: Metronidazole IV

Group C: Metronidazole IV+vancomycin PO+vancomycin PR

Group D: Metronidazole IV+vancomycin PR

IV=intravenous; PO=per oral; PR=per rectum; IQR=interquartile range; ICU=intensive care unit.

TABLE 4. INDEPENDENT PREDICTORS OF MORTALITY

Predictor	Odds Ratio	95% CI	p
Vasopressor requirement pre-operative	6.46	1.96–21.24	0.0021
Total units of FFP transfused during hospital admission	1.17	1.06– 1.3	0.0021

CI = confidence interval; FFP = fresh-frozen plasma.

Cochrane database review in 2011 concluded that when looking at both symptomatic and bacteriologic cure, there was no overwhelming evidence that either metronidazole or vancomycin was superior in treating CDI. One explanation of discrepancies was small sample size.

Regarding our study, there is no literature on the ideal post-operative antibiotic regimen. Although vancomycin might be recommended for severe disease, patients that have undergone a TAC are technically moving away from their complicated course, because the source of infection is removed. Given there is no difference in outcome measures when comparing metronidazole alone vs. metronidazole and any combination of vancomycin, and considering that CDI is being caused by antibiotic usage in the first place [1,2], for post-operative patients it is reasonable to place them on either IV metronidazole or PO vancomycin depending upon local antibiograms. Although it is known that PO vancomycin is not significantly absorbed in the gastrointestinal tract, it is the most effective antibiotic against *C. difficile* because it remains intraluminal. The rationale that many investigators have for using PO vancomycin after a subtotal colectomy was the notion that spores remain in the terminal ileum and that perhaps treatment will minimize effects of *C. difficile* on the terminal ileum. Naturally, any effects produced by the PO vancomycin would be limited to the terminal ileum because it does not reach the rectal stump, a limitation not shared by IV metronidazole. Complications such as proctitis or pouchitis should therefore be treated with the addition of an enema (PR) of vancomycin (500mg Q8 h). Regarding duration of postoperative antibiotic treatment, we found no data to support routine use of more than 7 d.

We have to emphasize that our study has its limitations. First, this is a retrospective review of patients with a complicated disease course; although many parameters were collected, certain causality cannot be ascertained. However, our goal was to create some guidelines since this matter normally is decided only based on physician discretion. The sample size was small and therefore we were unable to evaluate all antibiotic regimens. Lastly, new drugs such as fidaxomicin were not included in this study, because this drug was only approved in 2011. Although good results in two trials (fidaxomicin was found to be equally effective to vancomycin in achieving a clinical response at end of therapy but superior in preventing a recurrence), data are lacking for critically ill patients. Future studies are warranted to test the usage of fidaxomicin in the post-operative course after a TAC for fCDC [29,30].

Despite these limitations, this multicenter initiative is the largest collection of data of this specific population. Fulminant CDC, after which a TAC is undertaken, is a rare event, and single centers are unlikely to acquire sufficient numbers to make meaningful comparisons. This study was designed to give some insight into this procedure and especially its post-

operative course, with the understanding that the conclusions would be limited by the construct of the database.

In conclusion, there is no justification for mandated use of vancomycin rather than IV metronidazole in the post-operative period and routine duration of therapy should not exceed 7 d unless warranted by clinical status. We recommend future studies to design definite guidelines about antibiotic usage after a TAC for fCDC.

Author Disclosure Statement

No competing financial interests exist.

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