Patterns of Antibiotic Use for the Treatment of Colon Ischemia Before and After Guideline Publication: Has Anything Changed?

Shaya Noorian[1,2]*, Joann Kwah[1], Olga Aroniadis[1,3], Paul Feuerstadt[4] and Lawrence J Brandt[1]

[1]*Department of Medicine, Albert Einstein College of Medicine, Montefiore Medical Center, USA*

[2]*Department of Medicine, UCLA Medical Center, USA*

[3]*Department of Gastroenterology and Hepatology, Renaissance School of Medicine at Stony Brook University, USA*

[4]*Department of Medicine, Yale University School of Medicine, USA*

Abstract

Objective: To determine whether there was a difference in guideline-recommended antibiotic use in the three years following, compared to the three years preceding, release of the 2015 American College of Gastroenterology (ACG) Clinical Guideline on Colon Ischemia (CI).

Patients and Methods: This study included 253 patients diagnosed with CI from January 01st, 2012 through December 31st, 2014 (CI_{12-14}) and January 01st, 2015 through December 31st, 2017 (CI_{15-17}) at Montefiore Medical Center and Yale-New Haven Hospital. The primary outcome was guideline-recommended antibiotic use: For mild CI, no antibiotics; for moderate-severe CI, either: (i) metronidazole + ciprofloxacin or cephalosporin (ii) piperacillin-tazobactam. Secondary outcomes were specific antibiotic use, overall antibiotic use (irrespective of guideline adherence), and clinical outcomes.

Results: Guideline-recommended antibiotic use was similar in CI_{12-14} and CI_{15-17} (58.3% *vs.* 50.3%, P=0.23). Overall antibiotic use also was similar between CI_{12-14} and CI_{15-17} (77.4% vs. 69.8%, P=0.21). Ciprofloxacin use decreased in CI_{15-17} compared with CI_{12-14} (44.6% *vs.* 61.0%, P=0.03). CI_{15-17} experienced higher 30-day mortality (8.0% *vs.* 1.3%, P=0.01) and 30-day mortality or colectomy rates (16.0% *vs.* 6.0%, P=0.01) compared with CI_{12-14}. The remaining outcomes were similar between groups.

Conclusion: Guideline adherence was unchanged post-guideline publication with a significant (>40%) remaining deficit in guideline-recommended antibiotic use. The decrease in ciprofloxacin use follows a nationwide trend and may be attributed to antimicrobial stewardship efforts to minimize the risk of *Clostridioides difficile* infection. Further research is needed to explain worsened outcomes post-guideline release, and the impact of specific antimicrobials on outcomes.

Abbreviations

ACG: American College of Gastroenterology; AGA: American Gastroenterological Association; CI: Colon Ischemia; CI_{12-14}: Colon Ischemia cases admitted from 1/1/2012 to 12/31/2014; CI_{15-17}: Colon Ischemia cases admitted from 1/1/2015 to 12/31/2017; ICU: Intensive Care Unit

Introduction

Colon Ischemia (CI) occurs when blood supply to the colon is reduced to levels inadequate to maintain cellular metabolic function, ultimately leading to colonocyte dysfunction and death [1]. It is one of the three most common causes of lower gastrointestinal bleeding [2-4], and is associated with significant healthcare expenditures, approximating $13,000 per hospital admission [5]. The incidence of CI has been estimated to be 16 cases per 100,000 person-years [6]. While most cases are benign and reversible, severe cases do occur and account for mortality rates of 7% to 13% [6-9]. The spectrum of injury caused by CI may vary from reversible disease such as transient colitis or submucosal hemorrhage to irreversible processes including fulminant colitis, chronic colitis, stricture, and rarely gangrene [10].

Management of CI includes bowel rest, volume replacement, and correction of precipitating

conditions, antimicrobial therapy and surgical intervention in the most severe cases. Although antimicrobial therapy has long been used for treatment of CI, indications for such treatment and the types of antimicrobials that should be utilized have not been established. Some publications support the general use of antimicrobial therapy. In 2000, the American Gastroenterological Association (AGA) released the "AGA Technical Review on Intestinal Ischemia," which consisted of a literature review and therapeutic recommendations for acute mesenteric ischemia, chronic mesenteric ischemia, and CI [11]. With regards to the use of antimicrobial agents for the management of CI, the AGA Technical Review stated that "most authorities recommend the routine use of antibiotics in all patients with moderate or severe acute presentations of colon ischemia" [11]. This review also stated that while there was no clinical proof supporting the benefits of antimicrobial therapy, the recommendation stemmed from animal studies demonstrating decreased intestinal damage and increased survival after ischemic events when antimicrobial therapy was administered [12-15], as well as the theoretical protection of antimicrobial therapy against mucosal translocation of gut bacteria.

In 2015, the American College of Gastroenterology (ACG) released a comprehensive set of clinical guidelines addressing the clinical presentation, evaluation, diagnosis, and treatment of CI [1]. Similar to the AGA recommendations in 2000, this guideline stated that although a very low level of evidence existed to support the use of antimicrobial therapy, antimicrobials should be considered for patients whose disease severity was rated as moderate or severe. Along with this recommendation, the guideline proposed an algorithm for classifying disease severity (mild, moderate, or severe) based on the presence of risk factors (e.g. male gender, hypotension, and tachycardia) for poor outcomes. For those with moderate-severe disease, the guideline recommended broad antimicrobial coverage with regimens including an "anti-anaerobic agent plus a fluoroquinolone or an aminoglycoside or a third-generation cephalosporin".

The 2015 ACG clinical guideline is the first and only clinical guideline to recommend specific antimicrobial therapy for CI based on disease severity. Given the novelty of this guideline, we sought to investigate whether clinical practice changed after its publication. Specifically, the primary goal of our study was to assess retrospectively whether there was a difference in guideline-recommended antimicrobial use (i.e. the proportion of CI cases in which antimicrobials were administered in accordance with guideline recommendations) in the three years preceding (2012-2014) and three years following (2015-2017) guideline release.

Materials and Methods

Study design

Study population: A database of consecutive patients diagnosed with CI at Montefiore Medical Center (Moses, Einstein, and Wakefield campuses) and Yale-New Haven Hospital (York Street and Saint Raphael campuses) was reviewed for this study. Patients were initially identified through International Classification of Diseases, 9th revision (ICD-9) codes (557.0- vascular insufficiency of the intestine; 557.9- unspecified vascular insufficiency of intestine) and International Classification of Diseases, 10th revision (ICD-10) codes (K55.0- acute vascular disorders of intestine; K55.9- vascular disorder of intestine, unspecified). Only patients admitted between January 01st, 2012 and December 31st, 2017 were included in the study. Patients were included in the database only if their electronic health record revealed

the following criteria for a diagnosis of CI: (i) the pathology report of colon biopsy specimens described findings pathognomonic of CI (i.e., infarction or ghost cells); and/or (ii) the clinical presentation was consistent with CI (i.e., abdominal pain and tenderness associated with bloody or non-bloody diarrhea), in addition to colonoscopic findings consistent with CI (e.g., mucosal/submucosal hemorrhage, edema, ulceration, and/or gangrene); and biopsy findings consistent with CI (mucosal/submucosal hemorrhage, edema, and/or capillary fibrin thrombi). Patients were excluded if data were unavailable regarding date of admission, antibiotic treatment, CI severity, or clinical outcomes.

Outcomes

The primary outcome was guideline-recommended antibiotic use, which was defined independently for each CI severity class. In accordance with the 2015 clinical guideline on CI [1], patients with mild CI met the guideline-recommended antibiotic use if no antibiotics were administered, while patients with moderate and severe CI met guideline-recommendations if either (i) metronidazole in addition to ciprofloxacin or cephalosporin; or (ii) piperacillin-tazobactam alone were administered. Guideline-recommended antibiotic use was met if the aforementioned regimens were administered specifically for the treatment of CI within 72 h of presentation or at the time of diagnosis.
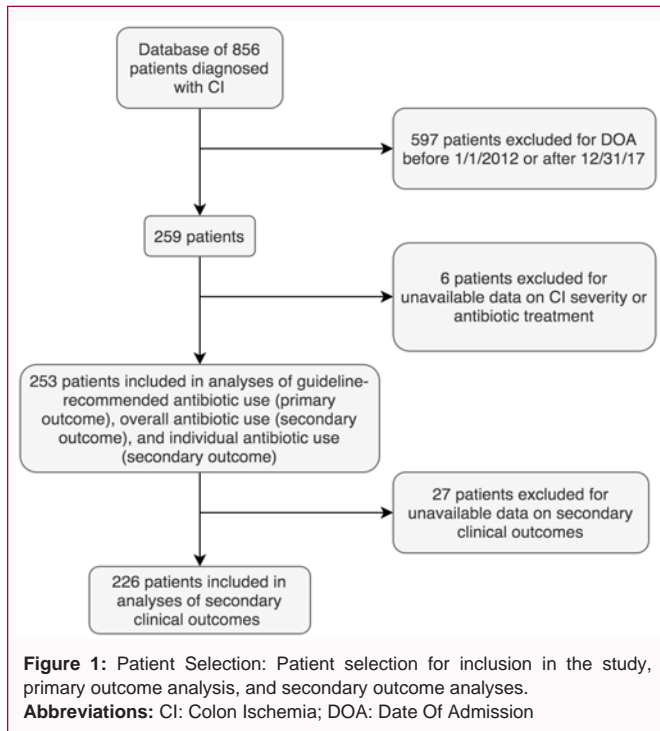
Secondary antibiotic-related outcomes included overall antibiotic use (the proportion of CI cases in which one or more antibiotics were administered, irrespective of guideline adherence) and specific antibiotic use (the proportions of CI cases in which ciprofloxacin, metronidazole, ceftriaxone, cephalosporin, and piperacillin-tazobactam were used). As in the case of the primary outcome, these secondary outcomes were specific to antibiotics administered for treatment of CI within 72 h of presentation or at the time of diagnosis. Secondary clinical outcomes included the frequency of ICU requirement, 90-day readmission rate, 90-day recurrence rate, 30-day colectomy rate, 30-day mortality rate, 30-day mortality or colectomy rates, and length of hospital stay.

Data extraction and definitions

For each patient, data were extracted from the CI database for the following: age, gender, date of admission, symptoms, physical examination findings, colonoscopy findings, biopsy findings, comorbidities, antibiotic use, clinical outcomes (ICU requirement, 90-day readmission rate, 90-day recurrence rate, 30-day colectomy rate, 30-day mortality rate, length of stay), and additional information required for determination of CI severity (systolic blood pressure, heart rate, blood urea nitrogen, hemoglobin, lactate dehydrogenase, serum sodium, white blood cell count, imaging findings). CI severity (mild, moderate, or severe) was classified as in the 2015 clinical guideline on CI [1]. Information was extracted on whether an antibiotic was given and whether the following specific antibiotics or classes of antibiotics were given: Ciprofloxacin, metronidazole, ceftriaxone, cephalosporin, piperacillin-tazobactam. The pre- and post-guideline cohorts in this study were those admitted from 1/1/2012-12/31/2014 (CI_{12-14}) and 1/1/2015-12/31/2017 (CI_{15-17}) respectively.

Statistical analysis

Demographic data and clinical outcomes were compared between CI_{12-14} and CI_{15-17} groups. Categorical variables were compared using a Chi-squared test or Fisher's exact test for frequencies of less than 5. Continuous variables were compared between groups using the Wilcoxon rank-sum test. A *P* value of <0.05 was considered statistically significant.

Figure 1: Patient Selection: Patient selection for inclusion in the study, primary outcome analysis, and secondary outcome analyses.
Abbreviations: CI: Colon Ischemia; DOA: Date Of Admission

Results and Discussion

Study population

856 patients who met diagnostic criteria for CI and for whom data had been completely extracted were available in the CI database. Of these patients, 603 patients were excluded for admission dates outside of the target time frame (1/1/2012-12/31/2017) for this study (Figure 1). Six additional patients were excluded because CI severity and antibiotic treatment could not be determined from available data. This yielded 253 patients for the analysis of outcomes related to antibiotic treatment and, of these, and additional 27 did not have data available for one or more secondary clinical outcomes and were thus excluded from these analyses.

Of the 253 patients analyzed for all antibiotic-related outcomes, 169 patients and 84 patients were included in the CI12-14 and CI15-17 cohorts respectively (Table 1). Patients in both cohorts were similar in terms of age, Charlson comorbidity score [16], and distribution of CI severity. Of note, only 2 cases in the entire study met criteria for mild CI. Also, although a higher proportion of women were included

Table 1: Patient characteristics.

	CI 12-14	CI 15-17	P value
Number of patients (n)	169	84	
Age (years)	68.2 ± 16.7	69.5 ± 11.3	0.47
Female gender	110 (65.1%)	64 (76.2%)	0.07
Colon ischemia severity[a]			
Mild	2 (1.2%)	0 (0.0%)	0.55
Moderate	70 (41.4%)	40 (47.6%)	0.35
Severe	97 (57.4%)	44 (52.4%)	0.45
Charlson comorbidity score[b]	5.3 ± 3.2	5.1 ± 2.7	0.65

Abbreviations: *CI* 12-14: Colon Ischemia cases admitted from 1/1/2012 to 12/31/2014; *CI* 15-17: Colon Ischemia cases admitted from 1/1/2015 to 12/31/2017
[a] defined in the ACG clinical guideline on colon ischemia1
[b] derived from the Charlson comorbidity index16

in the CI_{15-17} cohort, this difference was not statistically significant (P=0.07).

Primary outcome

In this retrospective analysis, guideline-recommended antibiotic use was similar in the CI_{15-17} and CI_{12-14} cohorts (58.3% *vs.* 50.3%; P=0.23; Figure 2).

Secondary outcomes

Antibiotic-related outcomes: There was a 7.6% increase in overall antibiotic use in the CI_{15-17} cohort compared with the CI_{12-14} cohort (Figure 3); this difference, however, did not reach statistical significance (77.4% *vs.* 69.8%; P=0.21). Ciprofloxacin accounted for a significantly lower proportion of cases in which antibiotics were given for treatment of CI in the CI_{15-17} compared with the CI_{12-14} cohort (44.6% *vs.* 61.0%; P=0.03); no other change in the use of specific antibiotics or antibiotic classes reached statistical significance (Figure 4). Notably, while there was a modest increase in cephalosporin use in the CI_{15-17} compared with the CI_{12-14} cohort (29.2% *vs.* 20.3%; P=0.17), there was actually a decrease in ceftriaxone use in the CI_{15-17} compared with the CI_{12-14} cohorts (6.2% *vs.* 13.6%; P=0.12); neither of these
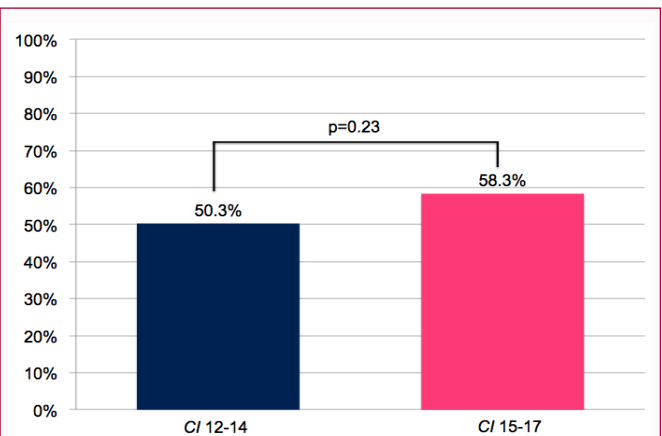

Figure 2: Guideline-recommended Antibiotic Use: Comparison of guideline-recommended antibiotic use between *CI* 12-14 and *CI* 15-17 cohorts.
Abbreviations: CI 12-14: Colon Ischemia cases admitted from 1/1/2012 to 12/31/2014; CI 15-17: Colon Ischemia cases admitted from 1/1/2015 to 12/31/2017

Figure 3: Overall Antibiotic Use: Comparison of overall antibiotic use between *CI* 12-14 and *CI* 15-17 cohorts.
Abbreviations: CI 12-14: Colon Ischemia cases admitted from 1/1/2012 to 12/31/2014; CI 15-17: Colon Ischemia cases admitted from 1/1/2015 to 12/31/2017
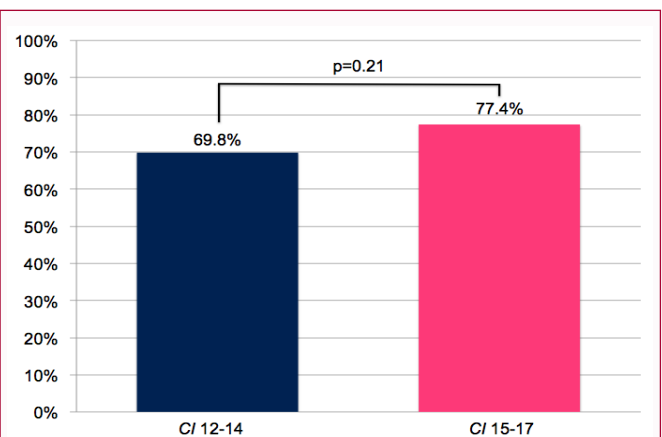
Figure 4: Specific Antibiotic Use: Comparison of specific antibiotic use between *CI* 12-14 and *CI* 15-17 cohorts.
Abbreviations: CI 12-14: Colon Ischemia cases admitted from 1/1/2012 to 12/31/2014; CI 15-17: Colon Ischemia cases admitted from 1/1/2015 to 12/31/2017
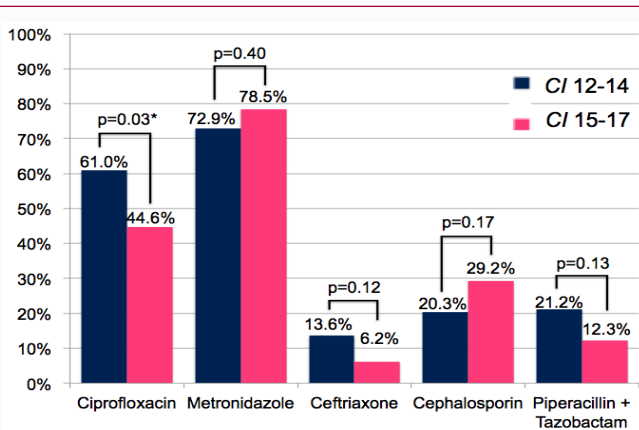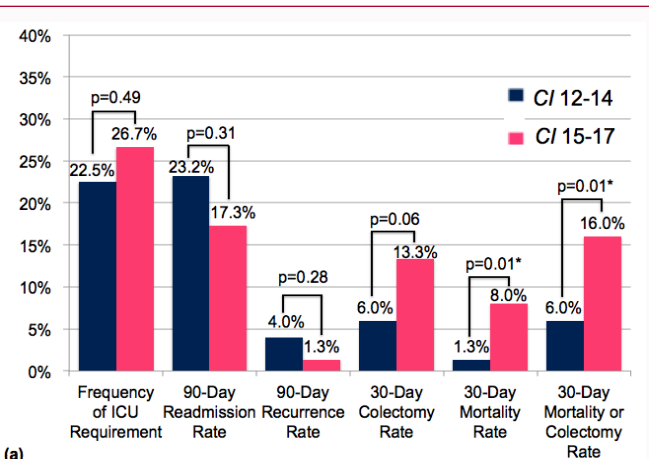
findings were statistically significant. A non-significant 8.9% decrease in piperacillin-tazobactam use was observed in the CI_{15-17} compared with the CI_{12-14} cohort (12.3% *vs.* 21.2%; *P*=0.13). Metronidazole was used more frequently than any other antimicrobial and accounted for similar proportions for those in the CI_{12-14} (72.9%) and CI_{15-17} (78.5%) cohorts (*P*=0.40).

Clinical outcomes: The CI_{15-17} cohort had a significantly higher 30-day mortality rate (8.0% *vs.* 1.3%; *P*=0.01) and 30-day mortality or colectomy rates (16.0% *vs.* 6.0%; *P*=0.01) compared with CI_{12-14} (Figure 5a). When analyzed separately, 30-day colectomy rates were higher in the CI_{15-17} cohort compared with the CI_{12-14} cohort, however, this difference was not statistically significant (13.3% *vs.* 6.0%; *P*=0.06). Average length of stay was higher in the CI_{15-17} cohort compared with the CI_{12-14} cohort, but this did not achieve statistical significance (25.9 *vs.* 9.3 days; *P*=0.97, Figure 5b). Non-significant differences also were observed for the remaining clinical outcomes, including frequency of ICU requirement (26.7% *vs.* 22.5%; *P*=0.49), 90-day readmission rates (17.3% *vs.* 23.2%; *P*=0.31) and 90-day recurrence rates (1.3% *vs.* 4.0%; *P*=0.28).
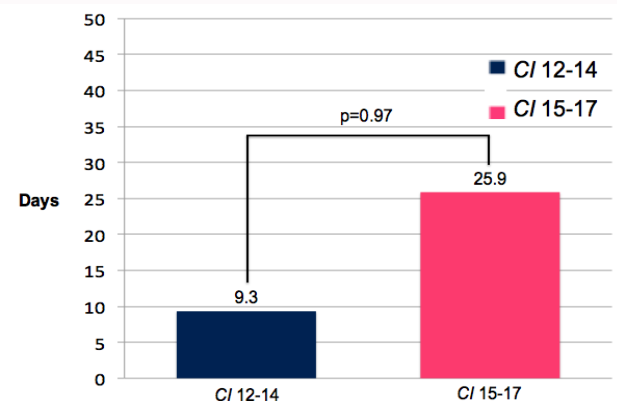
Discussion

Our study demonstrated a similar use of guideline-recommended antimicrobials before and after publication of the ACG 2015 clinical guideline on CI. Most patients (99.2%) met criteria for moderate and severe CI, likely due to the sole inclusion of inpatients in this study. Based on the clinical guidelines, broad-spectrum antimicrobial regimens would be indicated in the treatment of moderate and severe CI; however, only 58% of these patients were given this recommended therapy. While this statistic suggests a deficit in guideline adherence, it is important to note that the ACG 2015 guideline recommendations regarding antimicrobial use for CI are based on a very low level of evidence and the impact of adherence on clinical outcomes is uncertain.

To better understand the trends in antimicrobial use for CI, we believe that it is important to consider overall antimicrobial use, i.e., the proportion of cases in which at least one antibiotic was administered, and whether the antibiotic was prescribed in accordance with the guidelines or not. Our observed increase of ~8% in overall antibiotic use (Figure 3), however, may reflect the trend that more patients with

(a)

(b)

Figure 5: Clinical Outcomes:
A. Comparison of frequency of ICU requirement, 90-day readmission rate, 90-day recurrence rate, 30-day colectomy rate, 30-day mortality rate, 30-day mortality or colectomy rate between CI 12-14 and CI 15-17 cohorts.
B. Comparison of length of stay between CI 12-14 and CI 15-17 cohorts.
Abbreviations: CI 12-14: Colon Ischemia cases admitted from 1/1/2012 to 12/31/2014; CI 15-17: Colon Ischemia cases admitted from 1/1/2015 to 12/31/2017; ICU: Intensive Care Unit

CI in the post-guideline period received antimicrobials in general, regardless of regimen. Thus, it is important to consider the possibility that the observed increase in guideline-recommended antibiotic use might be a byproduct of general increases in antibiotic use in the more recent time-frame rather than a result of physicians choosing to administer antibiotics in accordance with the ACG guidelines. In fact, in both the pre- and post-guideline periods (Figure 2), approximately 20% of patients who were prescribed antibiotics did not receive them in accordance with guideline-recommendations (Figure 2 and 3).

In addition to evaluating overall antibiotic use, this study highlights differences in the frequencies of specific antibiotic types and classes used between the pre- and post-guideline periods. The only statistically significant change was a ~16% decrease in ciprofloxacin use, which follows a nationwide trend of decreasing fluoroquinolone use that has been observed even before the time period of our study [17]. A major driving force behind efforts to limit fluoroquinolone use has been the identification of fluoroquinolone exposure as a significant risk factor for *C. difficile* infection [18]. This is compounded by the recognition of fluoroquinolone use as a risk factor for *C. difficile* infection with the BI/NAP1/027 strain [19], a hypervirulent strain associated with decreased cure rates and worse clinical outcomes than other strains [20,21]. Other factors that

may have also contributed to the decrease in fluoroquinolone use include a 2016 Food and Drug Administration advisement to restrict fluoroquinolone administration for certain uncomplicated infections [22], as well as the increasing identification of fluoroquinolone-resistant infections [23-25].

In regards to the remaining evaluated antibiotics, cephalosporin use increased more than any other evaluated antibiotic type/class, suggesting that cephalosporin use had a large part in compensating for the decreased ciprofloxacin use in guideline-recommended regimens. Not surprisingly, metronidazole, a preferred antibiotic for anaerobic coverage [26], was used with the highest frequency in both periods of our study. Given that metronidazole was a component of regimens in over 70% of all cases in which antibiotics were utilized, it is likely that antibiotic regimens including metronidazole also accounted for the majority of guideline-recommended antibiotic use in this study.

Aside from trends in antimicrobial usage, this study also aimed to assess differences in clinical outcomes pre- and post-guideline publication. While differences in 30-day mortality and 30-day mortality or colectomy rates were the only clinical outcomes that differed significantly between groups, all clinical outcomes except for 90-day recurrence and readmission rates tended to be worse in the post-guideline period. Given that both cohorts in our study were similar (e.g., age, gender, CI severity, Charlson comorbidity score), these differences in clinical outcomes likely are not attributable to baseline differences in patient health or CI severity at presentation. The minimal observed differences in antimicrobial use between the two cohorts, similarly, would be unlikely to account for these large differences in clinical outcomes. It remains possible that a difference in a factor not directly related to CI, such as the rate of hospital-acquired infections or body mass index, which is not accounted for in the Charlson comorbidity score, could account for the observed differences in clinical outcomes.

While the results of this study do not point to a particular etiology for the worsened clinical outcomes in the post-guideline period, these findings are concerning and warrant further investigation. It is worth noting, however, that the 30-day mortality rates in both periods of this study fall below the mortality rates of 11% to 13% associated with CI in other studies [3-5]. In this context, it seems that the 30-day mortality rate of 1.3% in the pre-guideline period might be an aberration whereas the 30-day mortality rate of 8.0% in the post-guideline period would represent a mortality rate more typical of CI. Since the post-guideline 30-day mortality rate is comparable to mortality rates seen in other studies, it seems unlikely that the increase in mortality rates over time in our study would be indicative of a larger and general trend towards poor outcomes in CI. The worse, though not significantly different, clinical outcomes in the post-guideline period also introduces another important consideration, namely, that increased use of guideline-recommended antimicrobials in the post-guideline era, may be accounted for by providers choosing to administer broad-spectrum antimicrobials to patients who have may been more acutely ill during that time frame, as opposed to choosing to administer antibiotics according to guideline recommendations.

Given our study observed similar levels of guideline adherence before and after guideline release, it is important to consider reasons for such static practice patterns. Previous studies have identified that passive guideline dissemination strategies such as publication, or simply singular intervention methods, are among the least effective methods for driving guideline implementation [27,28]. One

review of studies evaluating dissemination strategies for consensus recommendations found 8 of 10 studies using passive dissemination had no or only minor impact on practice behavior. Additionally, when passive dissemination strategies were used, awareness of consensus recommendations was measured to be 30% to 60% [29]. In this context, our post-guideline guideline-recommended antibiotic usage rate of 58% is not surprising. It is also possible that antimicrobial usage patterns are not a reflection of overall guideline adherence. Perhaps adherence to recommendations specifically regarding antimicrobial use has not increased because such recommendations are based on a low level of evidence. Clinicians may also find the CI severity classification cumbersome to use in clinic practice given the diversity of information (demographics, vital signs, laboratory results, imaging findings, physical exam findings, and colonoscopic findings) required for its use.

Our study does have limitations and weaknesses including those associated with a retrospective study. First, the uneven distribution between the CI_{12-14} (n=169) and CI_{15-17} (n=84) cohorts may have limited this study's power to detect statistically significant differences. This limitation in sample size, however, was a byproduct of the stringent criteria used to establish a diagnosis of CI and thus limit potential alternative diagnoses. We believe that our use of stringent diagnostic criteria is a strength confirming the accuracy of diagnosis. Second, broad-spectrum antimicrobials in this study did not include all antibiotics commonly considered as part of such a regimen, with notable exclusions of aminoglycosides and fluoroquinolones other than ciprofloxacin. We do not believe the impact of this possibility, however, would be expected to be large given that ciprofloxacin is the most commonly used fluoroquinolone [30], and is the fluoroquinolone on formulary at both academic centers. Also, the lack of inclusion of aminoglycosides would not be expected to significantly impact our results as these agents are less commonly used than other antimicrobial classes of interest in this study (e.g. cephalosporins, metronidazole, fluoroquinolones), and this class is declining in use [17,31].

In summary, our study identified similar guideline-recommended antimicrobial use before and after release of the 2015 ACG clinical guideline on CI. Ciprofloxacin use decreased post-guideline release, following a nationwide trend that may be attributed to antimicrobial stewardship efforts to minimize the risk of *Clostridioides dificial* infection. Our study also demonstrated worsened clinical outcomes post-guideline release, a finding that should be investigated in future studies. Additionally, research should be directed at identifying the effects of specific antimicrobial regimens on clinical outcomes, especially given the paucity of evidence that exists to support current recommendations.

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