Corticosteroids Do Not Increase the Likelihood of Primary Clostridioides difficile Infection in the Setting of Broad-Spectrum Antibiotic Use

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Background. The pathogenesis of Clostridioides difficile infection (CDI) involves a significant host immune response. Generally, corticosteroids act by suppressing the host inflammatory response, and their anti-inflammatory effects are used to treat gastrointestinal disorders. Although previous investigations have demonstrated mixed results regarding the effect of corticosteroids on CDI, we hypothesized that the anti-inflammatory effect of corticosteroids would decrease the risk of CDI in hospitalized patients.

Methods. This was a case-control study of hospitalized adults. The case population included patients diagnosed with primary CDI who received at least 1 dose of a high-risk antibiotic (cefepime, meropenem, or piperacillin-tazobactam) in the 90 days before CDI diagnosis. The control population included patients who received at least 1 dose of the same high-risk antibiotic but did not develop CDI in the 90 days following their first dose of antibiotic. The primary study outcome was the development of CDI based on receipt of corticosteroids.

Results. The final study cohort consisted of 104 cases and 153 controls. Those who received corticosteroids had a lower odds of CDI after adjusting for age, proton pump inhibitor use, and antibiotic days of therapy (odds ratio, 0.54; 95% CI, 0.30–0.97; P = .04). We did not observe an association between corticosteroid dose or duration and CDI.

Conclusions. We demonstrated a 46% relative reduction in the odds of developing CDI in patients who received corticosteroids in the past 90 days. We believe that our results provide the best clinical evidence to further support mechanistic studies underlying this phenomenon.

Keywords. antibiotic; Clostridium difficile; corticosteroid; diarrhea; steroid.

Corticosteroids blunt the host inflammatory response via multiple mechanisms [7, 8] and are used to treat other inflammatory gastrointestinal (GI) disorders, such as inflammatory bowel disease (IBD) [9–11]. Although the benefit of an anti-inflammatory agent in an inflammation-driven disease state makes intuitive sense, the immunosuppressive effects of corticosteroids could increase the likelihood of CDI in a susceptible patient population. It is worth noting that the anti-inflammatory effects of corticosteroids are quite rapid, while the immunosuppressive effects are not maximal until at least several weeks of dosing [7, 8, 12]. Numerous case-control studies have suggested that corticosteroid use increases a patient’s risk of developing CDI [13–19], while others have found corticosteroid use to be protective against the development of CDI [20, 21]. However, these studies have a number of limitations, including an inability to control for predisposing antibiotic use [13, 15, 19], lack of corticosteroid dosing documentation [13, 15–17, 19], changes in CDI diagnostic testing over time [17, 19, 20], and the inclusion
of populations that limit generalizability (eg, IBD [14, 16, 18, 19] or hematopoietic stem cell transplant [21]).

Given this mechanistic understanding of CDI and corticosteroids, we hypothesized that the anti-inflammatory effects of corticosteroids would decrease the risk of CDI when studied in a generalizable population. To test this hypothesis, we conducted a case–control study examining the association between corticosteroid use and CDI risk.

**METHODS**

**Study Population**

This case–control study included hospitalized patients admitted to a single quaternary care hospital in the Texas Medical Center in Houston, Texas. The case population was derived from our ongoing cohort study of patients with CDI and included adults (age ≥18 years) consecutively diagnosed with primary CDI between October 2015 and August 2017 who received at least 1 dose of a high-risk antibiotic (cefepime, meropenem, or piperacillin-tazobactam) in the 90 days before CDI diagnosis. The control population consisted of adult patients who received at least 1 dose of the same high-risk antibiotic during the same time frame but did not develop clinically significant diarrhea or other symptoms that would warrant testing for *C. difficile* toxins in the 90 days following their first dose of antibiotic. Patients with a documented history of CDI were excluded.

**Patient Consent**

The study was approved by the University of Houston Committee for the Protection of Human Subjects with a waiver of informed consent (UH CPHS IRB study 00000128).

**Covariates and Definitions**

Electronic medical records (EMRs; Epic Systems Co., Verona, WI, USA) were reviewed retrospectively for demographic information, underlying comorbidities, medication administration records (MARs), laboratory data, and clinical outcomes. Charlson Comorbidity Index (CCI) scores were calculated using comorbidities documented on or before the date of hospital admission [22]. Options for residence before admission included home, skilled nursing facility, nursing home/long-term care facility, another hospital, or hospice, but were coded and reported as a binary variable of admission from home vs nonhome. Recent GI surgery was defined as any invasive GI procedure (ie, laparoscopic or open) in the 6 months before CDI diagnosis (cases) or last day of follow-up (controls). The 90-day study period refers to the 90 days preceding the date of the positive *C. difficile* toxin test for cases and the 90 days after initiation of a high-risk antibiotic for controls. The primary outcomes, corticosteroids and antibiotic days of therapy (DOT), were defined as the aggregate sum of days for which any amount of high-risk corticosteroid or antibiotic was administered within the 90-day study period. Our EMR’s interoperability platform, Care Everywhere, enabled us to collect medication use before hospital admission (cases) and following hospital discharge (controls) assuming the patient was seen in a facility within the Epic Network.

All corticosteroid doses were converted into prednisone equivalents [23, 24]. Daily doses were averaged for individuals receiving >1 steroid and/or >1 daily dose. Corticosteroid use was expressed as receipt (administration of at least 1 dose of any corticosteroid) within the 90-day study period, average daily dose (prednisone dose equivalent per day), and duration of therapy.

Multiple prespecified subgroup analyses were planned in those who received corticosteroids in order to assess whether an association between dose or duration and CDI risk existed. In these analyses, corticosteroid dose and duration were used as predictor variables while CDI remained the outcome variable. Furthermore, an additional subgroup analysis using the receipt of an “immunosuppressive dose” of corticosteroid as the predictor variable to investigate the potential for a ceiling effect was performed. An immunosuppressive dose of corticosteroid was defined as the receipt of ≥20 mg of prednisone or equivalent for ≥2 weeks [12].

**Outcomes**

The primary study outcome was the development of CDI. Patients were tested for CDI at the discretion of the treating physician and medical team. The CDI testing standard of care in our facility during the study time frame was a *C. difficile* nucleic acid amplification test (NAAT) in patients with unexplained new-onset diarrhea (≥3 unformed stools in 24 hours). The Epic Care Everywhere Network was accessed to limit attrition bias by ensuring that outcome data were captured as completely as possible.

**Statistical Analysis**

For baseline characteristic comparison, binary variables were compared using the χ² test while continuous variables were compared using the Student *t* test or the Wilcoxon rank-sum test, depending on the distribution of the data for the given variable. A logistic regression model was developed modeling CDI diagnosis as a function of relevant patient covariates. To prevent overfitting the model, only covariates whose univariate Wald test had a *P* value <.20 were considered as candidates for the multivariable model. A stepwise backwards elimination procedure was performed by which variables with a *P* value >.05 were removed 1 at a time, and the partial likelihood ratio test was used to compare the new, smaller model with the old model. Variables that did not improve the model fit remained excluded. Subgroup analyses were completed using the same variables included in the multivariable model for the primary analysis. Odds ratios (ORs) and 95% CIs were calculated. All *P* values resulted from 2-sided tests, and outcomes were deemed significant at *P* <.05.
RESULTS

Patient Characteristics

A total of 313 patients were identified, with 56 excluded due to a history of CDI, leaving a final study cohort of 257 patients (104 cases and 153 controls) aged 65 ± 14 years (female, 43%; median CCI, 2). Demographic and baseline characteristics of the patients are shown in Table 1. More patients in the control arm had documented proton pump inhibitor (PPI) use (P < .001). Conversely, more patients in the case arm had had corticosteroids. The results of these analyses can be seen in Figure 1. Corticosteroid dose and duration did not increase the risk of development of CDI.

Clinical Outcomes

In the univariate analysis, the odds of CDI were lower among patients who received corticosteroids (Table 2). Receipt of corticosteroids remained protective in the multivariable model after adjusting for age, PPI use, and antibiotic DOT (OR, 0.54; 95% CI, 0.30–0.97; P = .04).

Table 1. Comparison of Patient Demographics, Comorbidities, and Medication Use

| Covariate                  | Cases (n = 104) | Controls (n = 153) | P Value |
|----------------------------|----------------|-------------------|---------|
| Age, mean (SD), y          | 63.5 (16.8)    | 66.4 (13.0)       | .13     |
| Female, No. (%)            | 53 (51.0)      | 60 (39.2)         | .06     |
| CCI, median (IQR)          | 2 (1–4)        | 3 (1–4)           | .39     |
| SOT, No. (%)               | 8 (7.7)        | 24 (15.7)         | .06     |
| Residence PTA, No. (%)     | 78 (75.0)      | 112 (73.2)        | .75     |
| Recent GI surgery, No. (%) | 15 (14.4)      | 24 (15.7)         | .78     |
| Corticosteroid use, No. (%)| 45 (43.3)      | 89 (58.2)         | .02     |
| Prednisone equivalent/d, median (IQR), | 40 (25–86)    | 27 (13–48)        | .006    |
| mg (n = 104)               |               |                   |         |
| ≥20 mg                     | 39 (86.7)      | 58 (65.2)         |         |
| 10–19 mg                   | 3 (6.7)        | 18 (20.2)         |         |
| 5–9 mg                     | 3 (6.7)        | 7 (79)            |         |
| <5 mg                      | 0 (0.0)        | 6 (6.7)           |         |
| Corticosteroid DOT, median (IQR) | 5 (2–11)      | 9 (4–35)          | .01     |
| PPI use, No. (%)           | 72 (69.2)      | 52 (34.0)         | <.001   |
| Antibiotic use, No. (%)    |                |                   |         |
| Cefepime                   | 67 (64.4)      | 91 (59.5)         | .42     |
| Meropenem                  | 41 (39.4)      | 77 (50.3)         | .09     |
| Piperacillin-tazobactam    | 49 (47.1)      | 80 (52.3)         | .42     |
| Antibiotic DOT, median (IQR) | 6 (3–10)      | 10 (6–19)         | <.001   |

Abbreviations: CCI, Charlson Comorbidity Index; DOT, days of therapy; GI, gastrointestinal; IQR, interquartile range; PPI, proton pump inhibitor; PTA, prior to admission; SOT, solid organ transplantation.

Our prespecified subgroup analyses were done in the 134 patients who received corticosteroids. The results of these analyses can be seen in Figure 1. Corticosteroid dose and duration did not increase the risk of development of CDI.

We conducted a post hoc analysis of all patients diagnosed with CDI to determine risk factors that may have mitigated the protective effects of corticosteroids (Table 3). A significantly higher proportion of patients who received corticosteroids and subsequently developed CDI had received solid organ transplantation in the past (P = .02). Although not reaching statistical significance, these patients also had numerically higher CCI scores and rates of PPI use.

DISCUSSION

Although previous investigations have demonstrated mixed results regarding the effect of corticosteroids on CDI risk [13–21], we hypothesized that the anti-inflammatory effect of corticosteroids would decrease the risk of CDI in a generalizable population of hospitalized patients. This single-center, retrospective study demonstrated a 46% relative reduction in the odds of developing CDI in patients who received corticosteroids in the past 90 days, thereby supporting our hypothesis. Our long-term hypothesis is that an anti-inflammatory agent may aid in the prevention, severity, and treatment of CDI. We believe that the results of this study provide preliminary evidence for our long-term hypothesis and help to justify a drug development program targeting the host inflammatory response to CDI.

The anti-inflammatory effects of corticosteroids are not completely understood; however, the binding of corticosteroid to glucocorticoid receptors is known to lead to a decrease in the production of cytokines and chemokines [7]. Elevated cytokines have been associated with poor CDI outcomes including death in mice [3], prolonged symptomology in humans [4], and increased severity of disease in humans [5, 6]. Therefore, it is reasonable to hypothesize that administering an anti-inflammatory agent such as corticosteroid might abrogate CDI pathogenesis and lessen symptomatic disease severity. It is possible that...
corticosteroids reduce disease severity, resulting in subclinical disease and/or underdiagnosis. As cytokine and chemokine production relies on transcription, the effects of corticosteroids can persist even after discontinuation of the agent [7]. As these effects are cytokine/chemokine specific, further research will be needed to assess the pharmacologic activity of corticosteroids or other future anti-inflammatory agents in relation to the pathophysiology of CDI. Furthermore, glucocorticoid receptors are subject to saturation and are completely occupied following the administration of ~100–200 mg of prednisolone [7]. Thus, higher doses of corticosteroid will not be of benefit. Our study was designed with these pharmacokinetic (PK) and pharmacodynamic (PD) characteristics in mind. We measured corticosteroid use in the previous 90 days rather than 30 days and collected both dose and duration data. Not surprisingly, our findings support these PK/PD characteristics: We observed an association between receipt of corticosteroid in the past 90 days (regardless of time since administration) and CDI, but we did not observe an association between corticosteroid dose or duration and CDI.

A strength of this study was the ability to assess the effect of corticosteroid dose and duration of therapy, which has not previously been done. Another strength was the inclusion of a large population of hospitalized adults receiving broad-spectrum antibiotics without a history of CDI, thus controlling for a known predisposing risk factor of CDI. In addition, we controlled for antibiotic DOT, which is positively correlated with CDI risk [25]. The non-CDI control group was selected based on no subsequent occurrence of CDI, and thus the unexpected increase in antibiotic DOT in the control group was simply an artefact of the matching process. Three of the 7 previously mentioned case–control studies that concluded that

| Steroid potency | OR (95% CI) |
|----------------|-------------|
| Average daily dose | 1.08 (1.00–1.16) |
| Age | 0.99 (0.96–1.02) |
| Antibiotic DOT | 0.95 (0.91–0.99) |
| PPI use | 5.10 (2.16–12.02) |

| Steroid duration | OR (95% CI) |
|----------------|-------------|
| Steroid DOT | 0.99 (0.96–1.01) |
| Age | 0.99 (0.96–1.02) |
| Antibiotic DOT | 0.95 (0.91–1.00) |
| PPI use | 4.83 (2.09–11.13) |

| Immunosuppressive regimen | Odds ratio |
|----------------|-------------|
| 20 mg x 2 weeks | 1.15 (0.40–3.30) |
| Age | 0.99 (0.96–1.02) |
| Antibiotic DOT | 0.94 (0.90–0.99) |
| PPI use | 5.05 (2.19–11.62) |

Table 3. Stratified Analysis of Corticosteroid Use Among Patients Diagnosed With *Clostridioides difficile* Infection

| Covariate | Steroids (n = 45) | No Steroids (n = 59) | P Value |
|-----------|-------------------|----------------------|---------|
| Age, mean (SD), y | 62.1 (15.2) | 64.5 (18.1) | .47 |
| Female, No. (%) | 24 (53.3) | 29 (49.2) | .67 |
| CCI, median (IQR) | 3 (1–4) | 2 (1–4) | .12 |
| SOT, No. (%) | 7 (15.6) | 1 (1.7) | .02 |
| Residence PTA, No. (%) | 33 (73.3) | 45 (76.3) | .73 |
| Recent GI surgery, No. (%) | 7 (15.6) | 8 (13.6) | .77 |
| PPI use, No. (%) | 34 (75.6) | 38 (64.4) | .22 |
| Antibiotic use, No. (%) | 28 (62.2) | 39 (66.1) | .68 |
| Cefepime | 20 (44.4) | 21 (35.6) | .36 |
| Meropenem | 24 (53.3) | 25 (42.4) | .27 |
| Piperacillin-tazobactam | 6 (4–12) | 6 (3–10) | .31 |
| Albumin, mean (SD), g/dL | 2.9 (0.6) | 2.8 (0.6) | .38 |

Abbreviations: CCI, Charlson Comorbidity Index; DOT, days of therapy; GI, gastrointestinal; IQR, interquartile range; PPI, proton pump inhibitor; PTA, prior to admission; SOT, solid organ transplantation.
corticosteroid use increases a patient’s risk of developing CDI were unable to adequately control for predisposing antibiotic use [13, 15, 19]. Our ability to control for these variables decreases the likelihood of residual confounding and increases the robustness of our findings.

Our study also has several limitations. First, the inherent disadvantages of a retrospective design were present, including attrition and misclassification bias. We attempted to minimize attrition bias by using the Epic Care Everywhere Network but cannot rule out the possibility that some patients in the control group were lost to follow-up. This may have led to the misclassification of a case patient as a control patient and an overestimation in the protective effect of corticosteroids. Patient who receive corticosteroids are inherently different than those who do not require them. Likewise, case–control studies cannot assess temporality, and controls may not have had the same baseline risk for CDI or corticosteroid use as the cases despite matching on the receipt of high-risk antibiotics. Additionally, although MAR data were used for medication exposure while inpatient, we relied on accurate documentation of before-admission and/or discharge medications in the EMR to capture exposures received outside of the hospital. We were unable to account for patient adherence (which would overestimate exposure) and the receipt of medications omitted from the before-admission and/or discharge medication lists in the EMR (which would underestimate exposure). However, as both groups would be equally affected by this, it is unlikely to have biased our conclusions.

In summary, corticosteroid use significantly reduced the odds of developing CDI in patients without a history of CDI who received cefepime, meropenem, or piperacillin-tazobactam. These results are hypothesis-generating and provide support for further investigation into the mechanism behind this phenomenon and future drug development targeting the CDI inflammatory host response.

**Acknowledgments**

**Financial support.** This study was funded in part by the Society of Infectious Diseases Pharmacists (SIDP) and the National Institutes of Health (NIH) National Institute of Allergy and Infectious Diseases (NIAID) U54 AI124290-01.

**Potential conflicts of interest.** All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

**Guarantor of the article.** Kevin W. Garey accepts full responsibility for the conduct of this study. He had access to the data and had control of the decision to publish.

**Author contributions.** T.J.C. made substantial contributions to this work including the acquisition of the data, data interpretation and analysis, and drafting of the manuscript. He approved of the final draft submitted and agrees to be accountable for the accuracy and integrity of the work. A.J.G.-L. made substantial contributions to this work including the conception and design of the study, data acquisition, and critical revision of the manuscript. He approved of the final draft submitted and agrees to be accountable for the accuracy and integrity of the work. E.J.Z. made substantial contributions to this work including the conception and design of the study, data interpretation and analysis, and drafting of the manuscript. He approved of the final draft submitted and agrees to be accountable for the accuracy and integrity of the work. B.K.A. made substantial contributions to this work including the acquisition of the data and critical revision of the manuscript for important intellectual content. She approved of the final draft submitted and agrees to be accountable for the accuracy and integrity of the work. F.S.A. made substantial contributions to this work including the acquisition of the data, data interpretation and analysis, and drafting of the manuscript. He approved of the final draft submitted and agrees to be accountable for the accuracy and integrity of the work. P.P. made substantial contributions to this work including the acquisition of the data and critical revision of the manuscript for important intellectual content. He approved of the final draft submitted and agrees to be accountable for the accuracy and integrity of the work. K.W.G. made substantial contributions to this work including the conception and design of the study, data interpretation and analysis, and drafting of the manuscript. He approved of the final draft submitted and agrees to be accountable for the accuracy and integrity of the work.

**Ethics statement.** The study was approved by the University of Houston Committee for the Protection of Human Subjects with a waiver of informed consent (IRB study 0000128).

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