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Emergency department eosinophil counts and mortality in Clostridium difficile: a multihospital retrospective cohort study

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Abstract

Background: Clostridium difficile (Clostridioides difficile) infection (CDI) is the most common nosocomial infection in the United States, with mortality rates approaching 25% within 2 months of diagnosis. While current guidelines focus on CDI management once systemic symptoms develop, limited research has explored early predictors of disease severity. Eosinophils play a key role in gut immunity, and prior studies suggest absolute eosinopenia may be associated with severe CDI. This study evaluates the relationship between initial emergency department eosinophil counts and in-hospital mortality, with secondary assessments of admission rates, length of hospital stay, vasopressor use, and the need for surgical intervention.

Methods: We conducted a retrospective cohort study across 3 hospitals from July 1, 2018, to September 1, 2019. Adult patients with a positive Clostridium difficile stool assay and a documented eosinophil count during their emergency department evaluation were included. Patients already on CDI treatment, those younger than 18 years, and those without eosinophil counts were excluded. The primary outcome was in-hospital mortality. Secondary outcomes included admission rates, length of hospital stay, vasopressor use, and surgical intervention. Eosinophil counts were categorized 0.0 cells/μL (absolute eosinopenia) and >0.0 cells/μL. Odds ratios and relative risks were calculated with 95% confidence intervals.

Results: Among 326 patients, 56 had eosinophil counts of 0.0 cells/μL, while 270 had counts >0.0 cells/μL. Patients with eosinophil counts of 0.0 cells/μL had higher mortality (16% vs. 6%, OR: 2.98, 95% CI: 1.25–7.15), increased admission rates (87% vs. 57%, OR: 5.05, 95% CI: 2.23–11.41), and longer hospital stays (7.1 vs. 3.4 days, $P < .001$). No significant differences were observed in vasopressor use or surgical intervention.

Conclusions: An initial emergency department eosinophil count of 0.0 cells/μL is associated with increased mortality, admission rates, and prolonged hospital stays in CDI. Absolute eosinopenia may serve as an early prognostic marker for disease severity, warranting further prospective investigation.

Keywords: clostridium difficile, eosinophils, mortality, emergency medicine, retrospective studies, hospitalization, length of stay, vasopressors

Introduction

Clostridium difficile infections are the most common nosocomial infections in the United States, with mortality rates nearing 25% within 2 months of diagnosis.[1] Clostridium difficile occurs when gram-positive, spore-forming anaerobic bacteria disrupt the normal colonic microbiota, leading to infection.[2] Risk factors include recent antibiotic use, surgery, advanced age, chronic comorbidities, proton pump inhibitor use, and immunosuppression.[3] Clinical manifestations vary widely, ranging from profuse watery diarrhea and mild abdominal pain to severe complications, such as sepsis, toxic megacolon, and intestinal perforation.[2-4] Patients with suspected Clostridium difficile should have a Clostridium difficile toxin assay performed via stool sample and if positive, should proceed with medically management.[3] Management typically involves the first-line treatment of oral vancomycin for 10 days.[3] Patients with normal vital signs and mild symptoms can be discharged home, but hospitalization is recommended for patients with fever, leukocytosis, severe

Conflicts of Interest: none.

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Ethical approval for this study (Protocol #1494644-1) was provided by the institutional review board of Atlantic Health System, Morristown, New Jersey, on September 11, 2019, and deemed exempt under the guidelines for retrospective chart reviews. Ethical considerations for patient data privacy and confidentiality were adhered to in compliance with Health Insurance Portability and Accountability Act regulations.

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diarrhea, severe pain, or failure of outpatient therapy.[4] In recurrent cases, which encompass approximately 25% of patients, the same agent as initial treatment should be considered.[3] In cases of multiple recurrences, alternative second-line agents, including fidaxomicin or metronidazole, or additional interventions, such as fecal microbiota transplantation, may be necessary. Emergency surgery is reserved for life-threatening complications, such as perforation or toxic megacolon.[3]

Current guidelines focus on managing Clostridium difficile once systemic symptoms develop, but limited research has evaluated predictors of disease severity at the time of initial diagnosis.[1] Historically, the mechanism by which gut commensal bacteria protect against Clostridium difficile has been linked to the ability of healthy microbiota to outcompete the bacterium.[2,5] Neutrophils, lymphocytes, and eosinophils play a critical role in promoting local immunity through healthy gut bacteria and maintaining intestinal barrier integrity.[2,4,5] To regulate gut permeability, Interleukin-25, a key glycoprotein, is produced and its production is induced by eosinophilia.[2] Eosinophils are multifunctional leukocytes abundant in the gastrointestinal tract, where they promote local immunity and maintain intestinal barrier integrity.[6] Yet, while other markers such as neutrophil count, C-reactive protein, and albumin have been studied as highly prognostic for short-term mortality in Clostridium difficile, the prognostic value of eosinophil count has received limited attention.[4] Evidence from animal studies underscores the importance of eosinophils in maintaining gut homeostasis with eosinophil depletion proven to be linked to endogenous gut microflora that are more susceptible and have impaired responses to gut pathogens, notably Clostridium difficile.[2,7] In an effort to translate these findings to human populations, one inpatient study demonstrated that peripheral eosinophil depletion in the setting of Clostridium difficile infection was associated with increased in-hospital mortality and severe complications.[1] This study theorized that the Clostridium difficile toxin itself induces significant eosinopenia, thereby increasing disease morbidity and mortality.[1,5]

While patients with Clostridium difficile infection are often first diagnosed in the emergency department, no studies to date have explored the relationship between initial eosinophil levels in the emergency department setting with subsequent in-hospital mortality and disease prognosis. The primary objective of this study was to evaluate the relationship between initial emergency department eosinophil counts and mortality in patients diagnosed with Clostridium difficile infection. Secondary objectives include assessing admission rates, length of hospital stay, vasopressor use, and the need for surgical intervention. By evaluating a potential early predictor of poor outcomes, this study aims to improve management and disposition decisions for emergency department patients with Clostridium difficile infection.

Methods

A retrospective multihospital cohort study was conducted from July 1, 2018, to September 1, 2019. To evaluate the association between eosinophil counts and clinical outcomes in patients with Clostridium difficile infection via retrospective chart review, data collection occurred between October 2019 and February 2020. The study was conducted within a health system comprising 3 hospitals in Northern New Jersey. Two of these hospitals are rural community emergency departments with annual patient volumes of approximately 35,000 and 20,000 visits. The third hospital is a large suburban, teaching community emergency department with an annual volume of 95,000 patient visits. Patient records were accessed using Epic Systems electronic medical record. Total Clostridium difficile cases were identified by searching for stool assays positive for Clostridium difficile during the study period.

Inclusion criteria for the study consisted of adults (≥18 years) who presented to one of the 3 emergency departments with a positive Clostridium difficile stool assay and had a documented eosinophil count during their emergency department evaluation. Exclusion criteria included patients already receiving treatment of Clostridium difficile infection at the time of presentation, patients younger than 18 years, and those without documented eosinophil counts.

The primary outcome variable was in-hospital mortality. Secondary outcome variables included hospital admission rates, length of hospital stay, vasopressor use, and surgical interventions. The primary predictor variable was eosinophil count, categorized as 0.0 cells/μL (absolute eosinopenia) and >0.0 cells/μL. Demographic variables such as age and sex were also collected. Eosinophil counts were obtained from complete blood count results documented in the electronic medical record. Patient charts were reviewed to extract demographic and clinical outcome data, including admission status, length of stay, treatment received, complications, intensive care unit admission, vasopressor use, surgical interventions, and mortality outcomes. The reliability of eosinophil count measurements was ensured by standardized hematology laboratory protocols, and the accuracy of data extraction from the electronic medical record was validated by the health system's research support staff.

The study followed best practices for optimal retrospective chart reviews, fulfilling 9 of the 12 recommended methodological criteria including abstractor training, defined case selection criteria, variable definition, use of structured abstraction forms, identification of the medical record database, a plan for missing data, and institutional review board approval.[8] A trained clinical information specialist conducted manual chart reviews with each chart reviewed twice to ensure consistency and minimize errors. However, the chart reviewer was not blinded to the study hypothesis.

A total of 372 patients were initially identified, of whom 45 were excluded due to missing data for key variables. Missing data were handled using complete case analysis, leaving 326 patients who met inclusion criteria. The sample size was determined based on convenience sampling. Eosinophil counts were categorized as 0.0 cells/μL (absolute eosinopenia) and >0.0 cells/μL. Statistical analyses were performed using standard calculations in Microsoft Excel. Group differences were assessed using a 2-tailed *t* test. While a formal test for normality was not conducted, the central limit theorem was considered sufficient justification for the use of parametric methods given the sample size. In addition, odds ratios and relative risks were estimated calculated with 95% confidence intervals calculated to assess the precision of differences.

Efforts to minimize bias included the use of predefined inclusion and exclusion criteria to standardize data collection and reduce variability, along with the categorization of eosinophil counts into clear groups to minimize misclassification and improve comparability between patient cohorts. In addition, requiring the chart reviewer to systematically review each chart twice helped minimize the risk of misclassification bias. Despite these measures, observer bias due to reviewer awareness of the study hypothesis and selection bias from convenience sampling remain potential limitations to the generalizability of the findings.

Table 1

Characteristic data of patients with Clostridium difficile infection used in study design, with respect to their eosinophil counts on arrival

Characteristic	Eosinophil count of 0.0 cells/μL (n=56)	Eosinophil count greater than 0.0 cells/μL (n=270)	Patients with Clostridium difficile infection included (n=326)	Significance
Mean age (y)	69 (SD: 20, CI: 64, 74)	65 (SD: 15, CI: 63, 68)	67.2 (100%)	NS ($P = .17$)
Male	25 (45%; CI: 32, 58)	111 (41%; CI: 35, 47)	136 (42%)	NS ($P = .63$)
Female	31 (55%, CI: 42, 68)	159 (59%, CI: 53, 65)	190 (58%)	NS ($P = .63$)

Results

Of the 326 patients who were included in the study, 56 patients had eosinophil counts of 0.0 cells/μL (absolute eosinopenia) and 270 patients had eosinophil counts greater than 0.0 cells/μL. Demographically, both groups were similar, with no significant differences in age (69 vs. 65 years) or gender distribution (45% vs. 41% male) (Table 1).

Patients with eosinophil counts of 0.0 cells/μL had a significantly higher mortality rate (16% vs. 6%, difference 11%, CI: 3, 18, $P < .01$) (Table 2). The odds ratio for mortality was 2.98 (95% CI: 1.25, 7.15), and the relative risk was 2.67 (95% CI: 1.24, 5.72). In addition, patients with eosinophil counts of 0.0 cells/μL had a significantly higher rate of admission (88% vs. 57%, difference 31%, CI: 17, 44, $P < .001$) (Table 2). The estimated odds ratio for admission was 5.05 (95% CI: 2.23, 11.41), and the relative risk was 1.53 (95% CI: 1.32, 1.76). Those with eosinophil counts of 0.0 cells/μL also had a longer length of hospital stay (7.1 days vs. 3.4 days, difference 3.7 days, CI: 2.1, 5.3, $P < .001$) compared with those with eosinophil counts greater than 0.0 cells/μL (Table 2).

Interestingly, the study results also showed several clinical outcomes that did not demonstrate significant differences between groups (Table 2). First, there were no significant differences in the use of vasopressors (11% vs. 6%, difference 4%, CI: 11, −3, $P = .24$) between patients with eosinophil counts of 0.0 cells/μL and those with eosinophil counts greater than 0.0 cells/μL. The odds ratio for vasopressor use was 1.94 (95% CI: 0.73, 5.14), and the relative risk was 1.83 (95% CI: 0.76, 4.43). Second, the number of patients requiring surgery (7% vs. 9%, difference −2%, CI: 6, −10, $P = .62$) was not significantly different between groups. The odds ratio for surgical intervention was 0.76 (95% CI: 0.25, 2.30), and the relative risk was 0.78 (95% CI: 0.28, 2.17). Regarding data analysis, initial exploratory analyses considered excluding outliers, but this did not change the results. When evaluating eosinophil count as a continuous variable, no clear linear correlation with mortality was observed, leading to the decision to categorize eosinophil count as a binary variable for analysis.

Discussion

In this multihospital retrospective cohort study, we evaluated patients diagnosed with Clostridium difficile infection and the relationship between emergency department peripheral eosinophil counts and in-hospital mortality, with secondary assessments of admission rates, length of hospital stay, vasopressor use, and the need for surgical intervention. Our findings indicate that patients presenting with absolute eosinopenia experience increased in-hospital mortality, increased rates of hospital admission, and prolonged hospital stays compared with those with detectable eosinophil counts.

The significantly higher mortality rate (16% vs. 6%), increased admission rate (88% vs. 57%), and prolonged hospital stays (7.1 vs. 3.4 days) among patients with initial absolute eosinopenia highlight a potential prognostic role for emergency department eosinophil counts in Clostridium difficile infection severity along with a suggestion that absolute eosinopenia serves as a marker of disease severity. These results align with prior studies demonstrating an association between eosinopenia, increased in-hospital mortality, and disease severity among patients with Clostridium difficile infection.[1,9,10] Recognizing this trend may assist emergency department clinicians in risk stratification and disposition decisions.

Eosinopenia has been observed in multiple clinical conditions associated with systemic illness and increased disease severity. Table 3 summarizes conditions in which eosinopenia is commonly identified, including sepsis, COVID-19, and glucocorticoid use, as well as conditions where eosinopenia has been linked to increased mortality risk.[11-20] Recognizing these broader associations may further support the role of eosinopenia as a marker of systemic illness, particularly in the emergency setting. Future studies should explore whether eosinopenia is simply a reflection of disease severity or has mechanistic implications in disease progression.

Of note, no significant differences were observed in vasopressor use or surgical intervention between the 2 groups. This contrasts with prior studies, possibly due to differences in sample size, patient populations, or institutional management strategies, warranting further investigation.[1]

The generalizability of our findings is constrained by the study setting, which included 3 hospitals—a large suburban teaching hospital and 2 rural community hospitals. These results may not fully apply to urban academic medical centers or institutions with differing patient populations and treatment protocols. Furthermore, as data were collected from 2018 to 2019, evolving Clostridium difficile infection management strategies, including

Table 2

Outcomes of patients with Clostridium difficile infection with respect to their eosinophil counts upon initial emergency department evaluation

Outcomes	Eosinophil count of 0.0 cells/μL	Eosinophil count greater than 0.0 cells/μL	Difference	P
Mortality rate	9 (16% CI: 6, 26)	15 (6% CI: 3, 8)	10% (CI: 3–18)	<.01
Rate of admission	49 (88% CI: 79, 96)	154 (57% CI: 51, 63)	31% (CI: 17–44)	<.001
Length of hospital stay (d)	7.1 (SD: 6.3; CI: 5.4, 8.7)	3.4 (SD: 5.2; CI: 2.8, 4.1)	3.7 days (CI: 2.1–5.3)	<.001
Vasopressor use	6 (11% CI: 3, 19)	17 (6% CI: 3, 9)	5% (CI: 11, −3)	.24
Surgical Intervention	4 (7% CI: 0, 14)	25 (9% CI: 6, 13)	−2% (CI: 6, −10)	.61

Table 3

Clinical situations associated with eosinopenia and its prognostic implications

Clinical situations eosinopenia is regularly identified	Clinical situations that have been shown to have increased severity/risk of mortality in the presence of eosinopenia
Acute infection with COVID-19[11]	Bronchiectasis[12]
Cushing syndrome[13]	Chronic obstructive pulmonary disease[14]
Glucocorticoid use[15]	Pneumonia[14]
Sepsis[16]	COVID-19[17]
Systemic lupus erythematosus[18]	Return of spontaneous circulation[19]
Aplastic anemia[18]	Myocardial infarction[20]

This table summarizes common clinical conditions in which eosinopenia is observed, as well as those where its presence is linked to increased disease severity or mortality.

newer antimicrobial stewardship efforts, may influence current applicability.

The retrospective design relies on the accuracy and completeness of medical records, introducing the potential for misclassification bias. However, this risk was mitigated by standardized hematology protocols and laboratory documentation. Second, selection bias is possible due to the use of convenience sampling, which may have disproportionately included sicker patients with complete data, potentially overestimating the severity of absolute eosinopenia in Clostridium difficile infection. Third, confounding remains a concern, as we did not adjust for key clinical factors such as immunosuppression, recent antibiotic or proton pump inhibitor use, or chronic comorbidities, all of which may influence Clostridium difficile infection severity and outcomes. The magnitude of this confounding effect is difficult to quantify, but it could moderately overstate the association between absolute eosinopenia and poor outcomes. In addition, patients with recurrent Clostridium difficile infection were excluded, which may limit the applicability of our findings to all Clostridium difficile infection cases.

In summary, our study suggests that initial emergency department absolute eosinopenia is associated with increased mortality, higher admission rates, and longer hospital stays among patients with Clostridium difficile infection. While these findings underscore the potential utility of absolute eosinopenia as an early prognostic marker, the limitations of our study highlight the need for prospective research to confirm these associations and better understand the underlying mechanisms. Clinicians may consider incorporating eosinophil counts into Clostridium difficile infection risk stratification models to improve patient management and outcomes.

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