Ischemic Colitis Is a Risk Factor for Clostridium difficile Infection

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Abstract

Introduction: Clostridium difficile infection (CDI) is an anaerobic infection that can carry detrimental outcomes for patients and is a growing burden to the US healthcare system. Various theories have been proposed for the etiopathogenesis of CDI, including antibiotic use, dysbiosis, and acid suppression. The role of ischemia in CDI has not been explored. We hypothesize that tissue ischemia is a risk factor for the development of CDI. The study aimed to assess whether ischemia was a risk factor for CDI using ischemic colitis as a target population.

Methods: We performed a case-control study using the National Inpatient Sample (NIS) database in 2013. The study group included all patients with ischemic colitis (ICD 9 Code: 557.0, 557.1, 557.9) and the control group included all patients with diverticulitis (ICD 9 Code: 562.11, 562.13). Univariable and multivariable analyses were performed to assess the risk factors associated with CDI (ICD 9 Code: 008.45). The case and control groups were compared using the chi-square test for analysis. Continuous variables were compared using t-tests and categorical variables were compared using Rao-Scott chi-square tests. In addition, multivariable logistic regression analysis was performed to assess the association between disease group and CDI while adjusting for confounders. Univariable analysis was performed to assess differences between subjects with ischemic colitis and those with diverticulitis; continuous variables were compared using t-tests and categorical variables were compared using Rao-Scott chi-square tests. All analyses were done using SAS (version 9.4, The SAS Institute, Cary, NC).

Results: We analyzed more than 30 million hospitalizations in 2013, with 120,490 being Ischemic colitis-related admissions and 309,940 being diverticulitis-related admissions. The rate of CDI was more in the ischemic colitis group than in the diverticulitis group (odds ratio [OR] = 1.39; 95% confidence interval [CI] [1.03-1.88], p=0.03). After adjusting for all variables, multivariate analysis showed CDI was associated with ischemic colitis (OR = 2.06; 95% CI 1.59-2.65, p<0.001).

Conclusion: CDI was shown to be more prevalent in ischemic colitis than in diverticulitis control in this population-based study. As C. difficile is an anaerobe, we hypothesize that tissue hypoxia is a risk factor for its development. Further studies are needed to validate our findings.

Categories: Internal Medicine, Gastroenterology, Infectious Disease
Keywords: hospitalization outcomes, diverticulitis colon, gut dysbiosis, ischemic colitis, clostridium difficile

Introduction

Clostridium difficile infection (CDI) is a major source of healthcare burden, including cost, morbidity, and mortality. It is the most common pathogen isolated in healthcare-associated infections, accounting for 12.1% [1], and the most common nosocomial infectious diarrhea [2]. Some of the most well-known risk factors for CDI that have been studied include antibiotics, acid-suppressing agents, age over 65 years, comorbid conditions, antineoplastic chemotherapy, and increased length of hospital stay [3].

The presence of tissue ischemia has been linked to CDI remotely but has not been extensively studied [4]. We hypothesized that ischemic colitis is a risk factor for the development of CDI for several reasons related to its pathogenesis that leave the colon vulnerable. Clostridium difficile is an anaerobic bacteria with spore formation that can survive hypoxic and acidic conditions. Ischemic colitis is a condition in which both of these factors are present in addition to decreasing innate intestinal defenses and causing microbiological dysbiosis. We aimed to assess whether ischemia was a risk factor for CDI using ischemic colitis as a target population.

The preliminary results of this article were presented in a poster form at the American College of Gastroenterology 2017 Annual Scientific Meeting (October 15-18 in Orlando) and published in the American...
Materials And Methods

We performed a case-control study using the National Inpatient Sample (NIS) database in 2013. The National Inpatient Sample is the largest all-payer inpatient database in the United States, and its large sample size is ideal for analyzing rare conditions and associations. No IRB is required by our institution for this research work.

Case group

Our case group included all patients ≥18 years old with an ICD-9 code indicating a discharge diagnosis of ischemic colitis. This included acute ischemic colitis (ICD 9 Code 557.0), chronic ischemic colitis (557.1), and unspecified vascular insufficiency of the intestine (557.9).

Control group

Our control group included all patients ≥18 years old with an ICD-9 code indicating a discharge diagnosis of uncomplicated diverticulitis. This included diverticulitis of the colon without mention of hemorrhage (ICD 9 Code: 562.11) and diverticulitis of the colon with mention of hemorrhage (562.13). We excluded patients with complicated diverticulitis.

Data collection

Once the patients with ischemic colitis were identified, an excel sheet was used to gather information regarding the frequency of the diagnosis of CDI (ICD-9 code 008.45) and the risk factors associated with CDI.

Statistical analysis

Univariable and multivariable analyses were performed to assess the risk factors associated with CDI (008.45). The case and control groups were compared using the chi-square test for analysis. Continuous variables were compared using t-tests and categorical variables were compared using Rao-Scott chi-square tests. In addition, multivariable binomial logistic regression analysis was performed to assess the association between disease group and CDI while adjusting for confounders. Univariable analysis was performed to assess differences between subjects with ischemic colitis and those with diverticulitis; continuous variables were compared using t-tests and categorical variables were compared using Rao-Scott chi-square tests. All analyses were done using SAS (version 9.4, The SAS Institute, Cary, NC).

Results

Overall analysis

We analyzed more than 30 million hospitalizations in 2013. 120,490 patients were admitted for Ischemic colitis, which comprised the case group. The control group included 309,940 patients admitted for diverticulitis in 2013. CDI was diagnosed in 65/120,490 patients with ischemic colitis, with an incidence of 0.054%. CDI had an incidence of 0.039% (120/309,940) in patients with diverticulitis. The rate of CDI was significantly higher in the ischemic colitis group compared to the diverticulitis group (odds ratio [OR] = 1.39; 95% confidence interval [CI] [1.03 - 1.88], p=0.03).

Baseline characteristics of hospital demographics and patients with ischemic colitis, diverticulitis, and C. difficile

Baseline characteristics of C. Difficile patients were studied (Table 1). We compared baseline characteristics of ischemic colitis and diverticulitis patients. Females were more likely to have ischemic colitis (64% vs 58%; p<0.001). There were no significant differences in race, household income, or insurance. Ischemic colitis patients were more likely to fall under the class 3 (36.5%) and class 4 (29.6%) Diagnosis Related Group (DRG) risk of mortality subclass. Diverticulitis patients were more likely to fall under the class 1 (39%) and class 2 (23.5%) DRG risk of mortality subclass (Table 2).
## TABLE 1: Patient and hospital demographics and outcomes for patients in ischemic colitis versus diverticulitis.

|                          | Ischemic colitis and CDI | Diverticulitis and CDI | P-Value |
|--------------------------|--------------------------|-------------------------|---------|
| Region of hospital       |                          |                         |         |
| 1                        | 9.9%                     | 14.2%                   |         |
| 2                        | 23.6%                    | 22.8%                   |         |
| 3                        | 37.2%                    | 38.9%                   |         |
| 4                        | 19.7%                    | 17.4%                   | <0.001  |
| Location/teaching status of hospital (STRATA) |                       |                         |       |
| 2                        | 39.8%                    | 43.5%                   |         |
| 3                        | 50.4%                    | 42.3%                   | <0.001  |

**Race**

|                  | Hispanic | Other |
|------------------|----------|-------|
|                  | 7.3%     | 2.2%  |
| Total            | 100.0%   | 100.0%|

**Median household income national quartile for patient ZIP Code**

| Income Range          | Ischemic colitis and CDI | Diverticulitis and CDI | P-Value |
|-----------------------|---------------------------|------------------------|---------|
| $1 - $38,999          | 26.0%                     | 25.9%                  |         |
| $39,000 - $47,999     | 26.8%                     | 26.2%                  |         |
| $48,000 - $62,999     | 26.0%                     | 25.0%                  |         |
| $63,000 or More       | 21.3%                     | 23.0%                  | <0.001  |

**Primary expected payer**

|                  | Ischemic colitis and CDI | Diverticulitis and CDI | P-Value |
|------------------|--------------------------|------------------------|---------|
| Medicare         | 68.3%                    | 50.9%                  |         |
| Medicaid         | 7.7%                     | 7.1%                   |         |
| Private including HMO | 21.6%           | 39.2%                  |         |
| Other            | 2.4%                     | 2.8%                   | <0.001  |

**All Patient Refined DRG: Risk of Mortality Subclass**

| Subclass | Ischemic colitis and CDI | Diverticulitis and CDI | P-Value |
|----------|--------------------------|------------------------|---------|
| 0        | 0.0%                     | 0.0%                   |         |
| 1        | 14.6%                    | 59.0%                  |         |
| 2        | 19.5%                    | 23.5%                  |         |
| 3        | 36.3%                    | 12.7%                  |         |
| 4        | 29.6%                    | 4.8%                   | <0.001  |

**Bed size of hospital (STRATA)**

| STRATA | Ischemic colitis and CDI | Diverticulitis and CDI | P-Value |
|--------|--------------------------|------------------------|---------|
| 1      | 12.8%                    | 16.5%                  |         |
| 2      | 28.6%                    | 28.2%                  |         |
| 3      | 60.6%                    | 55.4%                  | <0.001  |

**CDI**

|                  | Ischemic colitis and CDI | Diverticulitis and CDI | P-Value |
|------------------|--------------------------|------------------------|---------|
| Present          | 100.0%                   | 100.0%                 | 0.03    |

**Sepsis**

|                  | Ischemic colitis and CDI | Diverticulitis and CDI | P-Value |
|------------------|--------------------------|------------------------|---------|
| Present          | 100.0%                   | 100.0%                 | <0.001  |

**Bowel perforation**

|                  | Ischemic colitis and CDI | Diverticulitis and CDI | P-Value |
|------------------|--------------------------|------------------------|---------|
| Present          | 100.0%                   | 100.0%                 | <0.001  |

**Bowel surgery**

|                  | Ischemic colitis and CDI | Diverticulitis and CDI | P-Value |
|------------------|--------------------------|------------------------|---------|
| Present          | 100.0%                   | 100.0%                 | <0.001  |

**Died during hospitalization**

|                  | Ischemic colitis and CDI | Diverticulitis and CDI | P-Value |
|------------------|--------------------------|------------------------|---------|
| Dead             | 100.0%                   | 100.0%                 | <0.001  |

**DRG:** Diagnosis-related group

**CDI:** Clostridium Difficile infection
| Category                              | N %    | N %    |
|--------------------------------------|--------|--------|
| **Age**                              |        |        |
| Mean (SD)                            | 71 (11) | 73 (8) |
| **Indicator of sex**                 |        |        |
| Male                                 | 53.8%  | 45.8%  |
| Female                               | 46.2%  | 54.2%  |
| Total                                | 100.0% | 100.0% |
| **Race (uniform)**                   |        |        |
| White                                | 69.2%  | 66.7%  |
| Black                                | 7.7%   | 4.2%   |
| Hispanic                             | 23.1%  | 20.8%  |
| Other                                | 0.0%   | 8.3%   |
| **Median household income national quartile for patient ZIP Code** | | |
| $1 - $38,999                         | 25.0%  | 25.0%  |
| $39,000 - $47,999                    | 8.3%   | 29.2%  |
| $48,000 - $62,999                    | 33.3%  | 29.2%  |
| $63,000 or More                      | 33.3%  | 16.7%  |
| **Primary expected payer (uniform)** | | |
| Medicare                             | 61.5%  | 70.8%  |
| Medicaid                             | 15.4%  | 0.0%   |
| Private including HMO                | 15.4%  | 25.0%  |
| Other                                | 0.0%   | 0.0%   |
| Self-Pay                             | 7.7%   | 4.2%   |
| No Charge                            | 0.0%   | 0.0%   |
| **All Patient Refined DRG: Risk of Mortality Subclass** | | |
| 1                                    | 7.7%   | 29.2%  |
| 2                                    | 15.4%  | 8.3%   |
| 3                                    | 38.5%  | 50.0%  |
| 4                                    | 38.5%  | 12.5%  |
| **Bed size of hospital (STRATA)**    |        |        |
| 1                                    | 7.7%   | 12.5%  |
| 2                                    | 30.8%  | 41.7%  |
| 3                                    | 61.5%  | 45.8%  |
| **Region of hospital**               |        |        |
| 1                                    | 30.8%  | 16.7%  |
| 2                                    | 15.4%  | 20.8%  |
| 3                                    | 23.1%  | 50.0%  |
| 4                                    | 30.8%  | 12.5%  |
| **Location/teaching status of hospital (STRATA)** | | |
| 1                                    | 0.0%   | 8.3%   |
| 2                                    | 46.2%  | 45.8%  |
| 3                                    | 53.8%  | 45.8%  |
| **Sepsis**                           |        |        |
| Present                              | 30.8%  | 33.3%  |
| Absent                               | 69.2%  | 66.7%  |
| **Bowel perforation**                |        |        |
| Present                              | 0.0%   | 4.2%   |
Patients with CDI were significantly more likely to be older than patients without CDI (mean: 50 vs 48 years old; p=0.003). CDI was associated with an increased length of stay (mean: 5.39 days vs 4.55 days; p<0.001). Patients with CDI had higher odds of having ischemic colitis, diverticulitis, or sepsis as a diagnosis (p<0.001). CDI patients were less likely to undergo bowel surgery (0.2% vs 23%; p<0.001); however, not more likely to have bowel perforation. Patients with CDI diagnosis were more likely to have coagulopathy (1.5% vs 0.5%; p<0.05), and electrolyte abnormalities (37% vs 73%; p<0.05) during their hospital stay. We found that some chronic diseases were also associated with CDI. These included chronic anemia, Congestive heart failure, and hypertension. Patients with CDI had greater odds of death than patients without CDI (p<0.001) (Table 3).

### TABLE 2: Patient and hospital demographics and outcomes for patients in ischemic colitis and CDI versus diverticulitis and CDI.

CDI: Clostridium difficile infection.

|                      | No CDI | Percentage | CDI Present | Percentage | P- Value |
|----------------------|--------|------------|-------------|------------|----------|
| **Sepsis**           |        |            |             |            |          |
| Total                | 53565  | 3.067%     | 60          | 0.935%     |          |
| Ischemic colitis     | 28570  | 23.710%    | 20          | 30.769%    | 0.19     |
| Diverticulitis       | 24995  | 8.062%     | 40          | 33.333%    | 0.000    |
| **Bowel surgery**    |        |            |             |            |          |
| Total                | 81380  | 23.227%    | 15          | 0.234%     | 0.003    |
| Ischemic colitis     | 30535  | 25.340%    | 10          | 15.385%    | 0.07     |
| Diverticulitis       | 50845  | 16.401%    | 5           | 4.167%     | 0.000    |
| **Bowel perforation**|       |            |             |            |          |
| Total                | 6555   | 17.939%    | 5           | 0.078%     | 0.17     |
| Ischemic colitis     | 4910   | 4.075%     | 0           | 0.000%     | 0.116    |
| Diverticulitis       | 1645   | 0.531%     | 5           | 4.167%     | 0.000    |
| **History of ischemic colitis** | | | | | |
| Total                | 1835   | 10.019%    | 0           | 0.000%     | 0.000    |
| Ischemic colitis     | 1485   | 1.232%     | 0           | 0.000%     | 1.000    |
| Diverticulitis       | 350    | 0.113%     | 0           | 0.000%     | 1.000    |
| **Died**             |        |            |             |            |          |
| Total                | 22360  | 3.325%     | 5           | 0.076%     | 0.719    |
| Ischemic colitis     | 18140  | 15.054%    | 5           | 7.692%     | 0.117    |
| Diverticulitis       | 4220   | 1.361%     | 0           | 0.000%     | 0.418    |
| **Age**              |        |            |             |            |          |
| Total                | 48.65  | (+- 27.61) | 50.21       | (+-25.257) | 0.000    |
| Ischemic colitis     | 67.65  | (+-16.84)  | 71          | (+-10.68)  | 0.572    |
| Diverticulitis       | 62.51  | (+-15.76)  | 72.58       | (+-8.229)  | 0.001    |
| **Length of stay**   |        |            |             |            |          |
| Total                | 4.55   | (+-6.655)  | 5.39        | (+-7.918)  | 0.000    |
| Ischemic colitis     | 9.02   | (+-13.684) | 21.77       | (+-24.061) | 0.000    |

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| Condition                      | Total | Ischemic colitis | Diverticulitis |
|-------------------------------|-------|-----------------|----------------|
| **AIDS**                      | 380   | 150             | 230            |
| **Alcohol abuse**             | 8740  | 15              | 8725           |
| **Iron deficiency anemia**    | 72950 | 26185           | 46765          |
| **Rheumatoid arthritis**      | 15795 | 4870            | 10925          |
| **Chronic blood loss anemia** | 6635  | 3290            | 3345           |
| **Congestive heart failure**  | 38635 | 16870           | 21765          |
| **Chronic pulmonary diseases**| 83660 | 28090           | 55570          |
| **Coagulopathy**              | 24065 | 13965           | 10100          |
| **Depression**                | 49075 | 15245           | 33830          |
| **Diabetes-uncomplicated**    | 77565 | 23995           | 53570          |
| **Diabetes-complicated**      | 13785 | 6040            | 7745           |
| **Drug abuse**                | 8815  | 3015            | 5800           |
| **Hypertension**              | 250725| 77640           | 5.36 (±5.740)  | 8.33 (±8.320) | 0.000 |

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- **diverticulitis**: 5.36 (±5.740) 8.33 (±8.320) 0.000
- **Alcohol abuse**: Total 8740 0.598% 0.574% 0.000 0.855
- **Iron deficiency anemia**: Total 72950 1.385% 0.000
- **Rheumatoid arthritis**: Total 15795 1.914% 0.000
- **Chronic blood loss anemia**: Total 6635 0.889% 0.000
- **Congestive heart failure**: Total 38635 1.500% 0.000
- **Chronic pulmonary diseases**: Total 83660 1.467% 0.000
- **Coagulopathy**: Total 24065 1.551% 0.000
- **Depression**: Total 49075 1.474% 0.000
- **Diabetes-uncomplicated**: Total 77565 1.367% 0.000
- **Diabetes-complicated**: Total 13785 0.967% 0.000
- **Drug abuse**: Total 8815 0.607% 0.000
- **Hypertension**: Total 250725 1.685% 0.000
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| Diagnosis                                      | Total       | Perc. | Ischemic colitis | Perc. | Diverticulitis | Perc. |
|------------------------------------------------|-------------|-------|-----------------|-------|---------------|-------|
| **Hypothyroidism**                             | 62870       | 1.790%| 5               | 0.078%| 0             | 0.000%|
| Ischemic colitis                              | 19725       | 16.369%| 0               | 0.000%| 0             | 0.000%|
| Diverticulitis                                | 43145       | 13.917%| 5               | 4.167%| 0.002         |       |
| **Liver diseases**                             | 17235       | 1.839%| 15              | 0.234%|               |       |
| Ischemic colitis                              | 6895        | 5.722%| 10              | 15.385%| 0.004         |       |
| Diverticulitis                                | 10340       | 3.335%| 5               | 4.167%| 0.372         |       |
| **Lymphoma**                                  | 3265        | 1.357%| 0               | 0.000%|               |       |
| Ischemic colitis                              | 1020        | 0.846%| 0               | 0.000%| 0.575         |       |
| Diverticulitis                                | 2245        | 0.724%| 0               | 0.000%| 0.418         |       |
| **Fluid and electrolyte disorder**            | 151225      | 2.037%| 135             | 2.104%|               |       |
| Ischemic colitis                              | 62380       | 51.768%| 45              | 69.231%| 0.004         |       |
| Diverticulitis                                | 88845       | 28.658%| 90              | 75.000%| 0.0000        |       |
| **Metastatic cancer**                         | 7840        | 1.192%| 5               | 0.078%|               |       |
| Ischemic colitis                              | 3495        | 0.846%| 0               | 0.000%| 0.148         |       |
| Diverticulitis                                | 4345        | 1.402%| 5               | 4.167%| 0.028         |       |
| **Other neurologic disorder**                 | 26335       | 1.126%| 30              | 0.468%|               |       |
| Ischemic colitis                              | 10455       | 8.676%| 5               | 7.692%| 0.5           |       |
| Diverticulitis                                | 15880       | 5.122%| 25              | 20.833%| 0.000         |       |
| **Obesity**                                   | 58755       | 1.567%| 10              | 0.156%|               |       |
| Ischemic colitis                              | 13340       | 11.071%| 5               | 7.692%| 0.26          |       |
| Diverticulitis                                | 45415       | 14.649%| 5               | 4.167%| 0.001         |       |
| **Paralysis**                                 | 6005        | 0.779%| 0               | 0.000%|               |       |
| Ischemic colitis                              | 3345        | 2.776%| 0               | 0.000%| 0.16          |       |
| Diverticulitis                                | 2660        | 1.666%| 0               | 12.500%| 0.355         |       |
| **Peripheral vascular disorder**              | 67300       | 3.793%| 50              | 0.779%|               |       |
| Ischemic colitis                              | 50770       | 42.133%| 45              | 69.231%| 0.000         |       |
| Diverticulitis                                | 16530       | 5.332%| 5               | 4.167%| 0.378         |       |
| **Psychoses**                                 | 14135       | 0.975%| 0               | 0.000%|               |       |
| Ischemic colitis                              | 5020        | 4.166%| 0               | 0.000%| 0.063         |       |
| Diverticulitis                                | 9115        | 2.940%| 0               | 0.000%| 0.028         |       |
| **Pulmonary circulation disorder**            | 9710        | 1.449%| 15              | 0.234%|               |       |
| Ischemic colitis                              | 4545        | 3.772%| 0               | 0.000%| 0.082         |       |
| Diverticulitis                                | 5165        | 1.666%| 15              | 12.500%| 0.000         |       |
| **Renal failure**                             | 49315       | 1.351%| 45              | 0.701%|               |       |
| Ischemic colitis                              | 22020       | 18.274%| 20              | 30.769%| 0.01          |       |
| Diverticulitis                                | 27295       | 8.804%| 25              | 20.833%| 0.000         |       |
| **Solid tumor without metastasis**            | 8355        | 1.363%| 0               | 0.000%|               |       |
| Ischemic colitis                              | 3070        | 2.548%| 0               | 0.000%| 0.187         |       |
| Diverticulitis                                | 5285        | 1.705%| 0               | 0.000%| 0.122         |       |
We performed a multivariate analysis of the risk factors for CDI. After adjusting for all variables, multivariate analysis showed CDI was associated with ischemic colitis (OR = 2.06; 95% CI 1.59-2.65, p<0.001) (Table 4).

### TABLE 3: Univariate analysis comparing ischemic colitis versus diverticulitis in CDI positive patients.

CDI: Clostridium difficile infection.

| Condition                          | Total | Crude % | Ischemic colitis | Diverticulitis |
|------------------------------------|-------|---------|------------------|----------------|
| **Peptic ulcer diseases with no bleeding** |       |         |                  |                |
| Total                              | 195   | 2.216%  | 95               | 100            |
| Ischemic colitis                   | 95    | 0.079%  | 0                | 0              |
| Diverticulitis                     | 100   | 0.032%  | 0                | 0              |
| **Valvular diseases**              |       |         |                  |                |
| Total                              | 18445 | 1.689%  | 7205             | 11240          |
| Ischemic colitis                   | 7205  | 5.979%  | 5                | 10             |
| Diverticulitis                     | 11240 | 3.626%  | 10               | 0              |
| **Weight loss**                    |       |         |                  |                |
| Total                              | 36250 | 2.438%  | 18720            | 17530          |
| Ischemic colitis                   | 18720 | 15.535% | 25               | 25             |
| Diverticulitis                     | 17530 | 5.654%  | 25               | 25             |

### TABLE 4: Multivariate analysis of factors associated with C. difficile infection.

| Factor                              | Sig.  | Odds Ratio | 95% C.I.     |
|-------------------------------------|-------|------------|--------------|
|                                    |       |            | Lower        | Upper        |
| Age                                 | .000  | .996       | .994         | .997         |
| Race - White                        | .000  | .629       | .570         | .694         |
| Race - Black                        | .000  | 1.548      | 1.429        | 1.677        |
| Race - Hispanic                     | .004  | 1.251      | 1.076        | 1.455        |
| Medicare                            | .590  | .974       | .884         | 1.072        |
| Medicaid                            | .000  | 1.253      | 1.160        | 1.353        |
| Private insurance                   | .015  | .854       | .751         | .970         |
| Died                                | .000  | .592       | .489         | .717         |
| Length of Stay                      | .000  | 1.011      | 1.008        | 1.014        |
| Anemia                              | .000  | 1.158      | 1.082        | 1.240        |
| Congestive Heart Failure            | .003  | .843       | .755         | .942         |
| Coagulopathy                        | .000  | 1.510      | 1.372        | 1.661        |
| Hypertension                        | .000  | 1.160      | 1.086        | 1.239        |
| Electrolyte imbalance               | .000  | 9.963      | 9.370        | 10.593       |
| Obesity                             | .483  | 1.034      | .942         | 1.134        |
| Renal failure                       | .063  | 1.089      | .995         | 1.191        |
| Weight loss                         | .000  | 1.510      | 1.375        | 1.657        |
| Ischemic colitis                    | .000  | 2.055      | 1.590        | 2.656        |
Discussion

Our study found that ischemic colitis was twice as likely to be seen in patients with CDI than in patients without C. difficile. In addition, C. difficile was 39% more likely to be seen in ischemic colitis than in acute diverticulitis patients. These findings support our hypothesis that tissue ischemia is a risk factor for CDI. As previously mentioned, very few previous studies have suggested a link between ischemia and CDI [4,5]. To our knowledge, there have been no studies analyzing the association between Ischemic colitis and CDI. This is the first of its kind.

The microbiology of C. difficile supports ischemia as a risk factor for this infection. C. difficile is an anaerobic gram-positive bacteria transmitted through the fecal-oral route via the ingestion of spores. Its spores are resistant to heat, acid, and antibiotics; in addition, its anaerobic nature allows C. difficile to thrive in low oxygen states [6]. Thus, in low oxygen and acidic conditions, C. difficile naturally survives while other bacteria die, leading to dysbiosis. Once in the colon, C. difficile converts from its spore form to its functional form, producing exotoxins (toxin A and toxin B) that act upon the intestinal epithelial cells and inflammatory cells causing tissue injury and diarrhea. The body normally protects itself from CDI through immune defense mechanisms in the epithelial layer of the intestine, producing antibodies to the toxins and toxic receptors, and by increasing IL-8. However, ischemia may damage these innate immune responses leading to increased infection risk.

The pathogenesis of ischemic colitis may also contribute to an increased risk of infectious colitis, including CDI. It involves decreased blood flow and ischemia of the mucosal layer, submucosal layer, and/or transmural involvement; this is followed by reperfusion injury. These states of ischemia and reperfusion injury lead to transient sub-epithelial hemorrhage, edema, ulceration of the mucosa, and occasionally permanent necrosis of the bowel wall. Thus, there are two mechanisms by which the risk of CDI may be increased in ischemic colitis. One is the presence of a low oxygen state, which allows the spores of C. difficile to survive while other normal flora perishes, causing dysbiosis. The other is the presence of edema and ulceration in the mucosa, which leads to a decrease in the intrinsic defense mechanism in the epithelium. This is similarly seen in ulcerative colitis, which is associated with an increased risk of CDI. Thus, the pathophysiology of C. difficile and ischemic colitis interprets the statistically significant association seen in our study.

Patients with ischemic colitis had 39% higher odds of contracting CDI than patients with acute diverticulitis. This is likely due to differences in pathogenesis, as ischemic colitis causes tissue ischemia, while diverticulitis tends to cause micro-perforations of the gut wall. To our knowledge, there has been no past data comparing the rates of CDI in both groups.

Acute diverticulitis was chosen as a control group for several similarities that it shares with ischemic colitis while being considered a more benign disease. Acute diverticulitis is a major differential diagnosis of ischemic colitis. Demographics are similar in terms of age. Ischemic colitis patients are in their 60s-70s while the mean age at admission of acute diverticulitis is 63 years old [7]. In our study, patients with ischemic colitis had a mean age of 68-71 years. Both disorders affect the colon, where C. difficile primarily infects. Treatment is similar in both disease entities, consisting of supportive care (bowel rest and intravenous fluids) and broad-spectrum antibiotics.

Previous studies have shown that the use of antibiotics in uncomplicated diverticulitis may be equivocal to not using antibiotics, suggesting that the prevalence of infection in these patients is not significant [8]. There is also a lack of strong evidence to support the use of antibiotics in ischemic colitis [9]. That being said, empiric antibiotics are a commonly used therapy in both diverticulitis and ischemic colitis. They usually empirically cover gram-negative and anaerobes for 7-10 days [10,11]. Thus, one of the major risk factors for CDI, the use of antibiotics, is present in both ischemic colitis and diverticulitis patients. Empiric antibiotic regimens for both colonic diseases usually include PO or IV metronidazole, which would empirically cover for C. difficile infection. Thus, antibiotic use was not thought to disproportionately affect either group in this study. Unfortunately, we could not measure the proportion of patients that received antibiotics in either group.

Ischemic colitis patients are generally considered to have a worse prognosis compared to diverticulitis patients. The results of our study reflect this. In our study, mortality for ischemic colitis patients was 15%, while the mortality for diverticulitis patients was 1.4%. In comparison, the literature says mortality is 1%-3% [12] in uncomplicated diverticulitis. Meanwhile, mortality in ischemic colitis patients has been estimated to be approximately 22% [13], including 6% in medically managed patients and 59% for surgically managed patients [14]. Similarly, patients with ischemic colitis and CDI had higher mortality (7%) than patients with diverticulitis and CDI (0%). In addition, patients with ischemic colitis required a higher rate of surgeries (20%) than patients with diverticulitis (15%).

Our study also looked at other risk factors that may contribute to CDI. Older patients were more likely to have CDI; this is consistent with what has been found in the literature [15]. In addition, older patients are more likely to develop severe CDI [16]; we did not assess CDI severity in our study. Black and Hispanic patients were more likely than white patients to contract C. difficile. In our literature search, one study
found that white patients had greater CDI rates than nonwhite patients, although these differences disappeared in a population for which healthcare access was presumed to be less racially biased [16]. In another study, CDI incidence was higher for white patients, but black race was independently associated with mortality and CDI [17]. Medicaid increased a patient’s risk of developing CDI while having private insurance or Medicare did not correlate. No studies comparing CDI infection rates depending on insurance were found during the literature search. The cost of vancomycin and other antibiotics may contribute to this as patients may not be able to treat severe recurrent CDI [17].

Patients with chronic diseases such as anemia and hypertension had greater odds of having CDI in our study. No studies were found in our literature search associating these diseases to CDI; this may be a false positive given their high prevalence. Interestingly, renal failure was not associated with CDI and Congestive Heart failure decreased the odds of having CDI in our study. This is inconsistent with the literature. Studies have found that patients with CKD have a higher risk of CDI [18]. Heart failure has also been associated with higher rates of CDI [18]. In addition, the Charlson Comorbidity Index, which takes into account the presence of CHF and CKD among other diseases, was found to be a predictor of the need for hospitalization and complicated CDI [19]. Coagulopathy, electrolyte imbalance, and weight loss were also associated with CDI. This can be explained by sepsis and diarrhea.

It is important to note that CDI was associated with increased length of stay and increased risk of death in our study. Ischemic colitis patients with CDI had a mean length of stay of 22 days compared to 9 days in ischemic colitis patients without CDI. Diverticulitis patients with CDI had a mean length of stay of 8 days compared with a mean LOS of 5 days if they did not have CDI. This was expected as previous studies have suggested that CDI contributes to a longer length of stay [20]. Length of stay is very important because it proportionally increases healthcare resource expenditure. A retrospective study in the American Journal of Infection Control found that patients with CDI were associated with increased length of stay (by 4.7 days) which led to increased attributable costs (by $7,286) and increased mortality. These results are broadly similar to those of Kyne et al. [21] (attributable LOS, 3.6 days; attributable cost, $5,669) and Song et al. [20] (attributable LOS, 5.5 days; attributable cost, $6,326).

The main strength of our study is the large sample size which was obtained from a reliable representative database. There are few studies linking ischemic colitis to CDI, and no studies directly studying the two diseases were found during the literature search. Thus, this is the first study to do so. The use of multivariate analysis helped eliminate confounding variables. The observational characteristic of the study was beneficial as it is not an intervention and is of no harm to the patient.

Our study had a few limitations. For one, it is a retrospective study. Thus, it is not considered the highest level of evidence and is subject to confounders, such as the presence of comorbidities that may increase the risk of CDI. We performed a multivariable logistic regression analysis to assess the association between disease group and CDI while adjusting for confounders. Another limitation was that the diagnosis of the diseases and risk factors from the National inpatient survey is based on ICD-9 codes; thus, the correct data collection in this study is dependent on correct billing by physicians and staff. This could lead to record bias from under-reporting of diseases and variables. The possible underdiagnosis of ischemic colitis, as discussed previously, could also be a limitation. Given the retrospective nature and longitudinal nature of the study, it was not possible to establish whether the disease (CDI or diverticulitis) was causing an increase in the variables (such as LOS) or the variables caused an increase in the disease. We had no data on antibiotic regimens used or their duration, which is an important risk factor for CDI. Similarly, we had no data on the severity of CDI.

Conclusions

Our study is novel in that it aimed to assess whether there is an association between tissue ischemia and CDI. The results of our study supported our hypothesis as we found that ischemic colitis was twice as likely to be seen in patients with CDI. The pathogenesis of C. difficile and ischemic colitis likely both contribute to this finding. CDI was associated with increased hospital stay and mortality. This undoubtedly leads to higher healthcare costs and utilization. The hope is that these findings will reintroduce the discussion and lead to more research on ischemic colitis as a risk factor for CDI. Increased awareness of ischemic colitis as a CDI risk factor can lead to improved surveillance strategies, more prompt treatment, more judicious use of antibiotics, and hopefully decrease healthcare utilization and costs in this patient population. This is important given the currently increasing economic burden of CDI in the healthcare system in the US and worldwide.

Additional Information

Disclosures

Human subjects: All authors have confirmed that this study did not involve human participants or tissue.

Animal subjects: All authors have confirmed that this study did not involve animal subjects or tissue.

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from
any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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