

# Impact of Acid Suppressants on the Development of *Clostridioides difficile* Infection and Possible Preventive Effects of Probiotic Formulations

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**Background:** The comparative effectiveness and potential impact of individual proton pump inhibitors (PPIs) on the development of *Clostridioides difficile* infection (CDI) remain unclear. Additionally, there is insufficient evidence to support the use of probiotics for CDI prevention outside clinical trials. This study aimed to identify the PPIs that are most associated with CDI development and to determine whether probiotic co-administration can reduce this risk.

**Methods:** We retrospectively analyzed the data of 3287 patients tested for CDI at Mie University Hospital between January 2014 and June 2024, excluding 1917 patients who had received antibiotics within the prior 3 months. The PPIs studied included esomeprazole, omeprazole, rabeprazole, and lansoprazole.

**Results:** Univariate logistic regression analysis revealed age and esomeprazole use as potential risk factors for CDI ( $p = 0.009$ ). Although not significant, the co-administration of probiotics tended to reduce the incidence of CDI in patients receiving esomeprazole (3.8% vs 10.4%,  $p = 0.060$ ). Patients prescribed vonoprazan had a significantly higher rate of concomitant probiotic use than did those prescribed esomeprazole ( $p = 0.025$ ).

**Conclusion:** Our findings suggest that esomeprazole use and advanced age may increase the risk of CDI. Additionally, probiotics may help prevent CDI during PPI therapy. Selecting PPIs based on individual bleeding profiles and considering probiotics could be beneficial to mitigate the risk of CDI.

**Plain Language Summary:** Esomeprazole use and advanced age may increase the risk of *Clostridioides difficile* infection (CDI). Probiotics may help prevent CDI during PPI therapy. Therefore, selecting PPIs based on bleeding risk and considering adjunctive probiotic may be beneficial in mitigating CDI incidence.

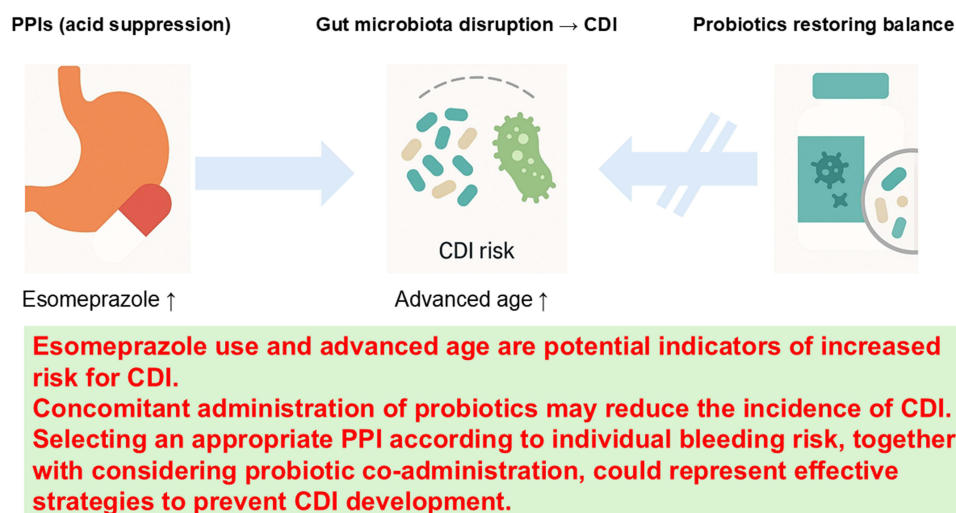
**Keywords:** proton pump inhibitors, *Clostridioides difficile* infection, probiotics

## Introduction

*Clostridioides difficile* infection (CDI) primarily affects the colon and typically occurs in patients whose intestinal microbiota is disrupted by antibiotic therapy. The hallmark clinical symptom of CDI is diarrhea. In most cases, CDI develops in hospitalized patients after exposure to *Clostridioides difficile* spores, which germinate, proliferate, and release toxins that damage the colonic mucosa. The clinical spectrum ranges from mild to fulminant colitis, and in severe cases, death.<sup>1</sup>

Proton pump inhibitors (PPIs) are considered the first-line agents for the treatment of various acid-related gastrointestinal disorders, including gastroesophageal reflux disease, non-steroidal anti-inflammatory drug-associated ulcers, esophagitis, peptic ulcer disease, Zollinger–Ellison syndrome, non-erosive reflux disease, and functional dyspepsia.<sup>2,3</sup>

## Graphical Abstract



However, long-term gastric acid suppression is associated with intestinal dysbiosis, which potentially increases the risk of CDI. Multiple studies have explored the relationship between acid suppression therapy and CDI, indicating a potential link.<sup>4</sup> PPIs have been implicated not only in the development of CDI but also in worse clinical outcomes.<sup>5</sup> Overprescription of acid-suppressive agents is a growing concern.<sup>6</sup>

Numerous head-to-head comparisons of PPIs have been performed. For example, esomeprazole 40 mg has demonstrated superior intragastric pH control in patients with gastroesophageal reflux disease, compared with omeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg, and rabeprazole 20 mg.<sup>7</sup> One study also reported that esomeprazole 40 mg, pantoprazole 40 mg, esomeprazole 20 mg, and lansoprazole 30 mg were more effective for treating erosive esophagitis than were other PPIs.<sup>8</sup> However, most analyses failed to identify significant differences in healing rates, heartburn relief, or discontinuation rates among PPIs administered at commonly used doses, such as omeprazole 20 mg, pantoprazole 40 mg, lansoprazole 30 mg, rabeprazole 20 mg, and esomeprazole 20 mg.<sup>9–12</sup> Although CD exhibits pH-dependent effects on strain growth, toxin production, motility, and sporulation,<sup>13</sup> the comparative effectiveness and potential impact of individual PPIs on the development of CDI remain unclear.

Probiotics, defined as live microorganisms that confer health benefits to the host when administered in adequate amounts, are naturally present in the intestinal tract. They exert protective effects through several mechanisms, including the inhibition of pathogenic microorganisms, production of antimicrobial compounds, and prevention of antibiotic-associated diarrhea.<sup>14</sup> Several meta-analyses have suggested a potential role for probiotics in preventing CDI.<sup>15,16</sup> However, most major international guidelines currently do not recommend the routine use of probiotics for CDI prevention, mainly due to insufficient evidence of benefit and concerns about potential harm. Specifically, the American College of Gastroenterology advises against probiotic use for primary CDI prevention in patients receiving antibiotics (conditional recommendation, moderate-quality evidence) as well as for prevention of recurrence (strong recommendation, very low-quality evidence).<sup>17</sup> Similarly, the European Society of Clinical Microbiology and Infectious Diseases discourages routine probiotic use during antibiotic therapy (strong recommendation, low-quality evidence),<sup>18</sup> whereas the Infectious Diseases Society of America states that insufficient evidence exists to support the use of probiotics for CDI prevention outside clinical trials.<sup>19</sup>

In real-world clinical settings, it is essential to carefully assess the necessity of PPI use and ensure appropriate use in indicated cases to minimize the risk of CDI. Herein, we aimed to identify the PPIs that are most strongly associated with CDI development and determine whether the concomitant use of probiotics may help reduce this risk.

## Methods

We analyzed the data of patients tested for CDI at Mie University Hospital between January 2014 and June 2024. The CDI testing methods employed included culture, rapid diagnostic tests (glutamate dehydrogenase and toxin assays), and nucleic acid amplification tests. Patients who had received antibiotics within 3 months prior to testing were excluded. To evaluate its potential preventive effects, probiotic administration was defined as concomitant use for more than 1 week prior to CDI development. We also collected data on concomitantly administered medications known to be associated with drug-induced CDI (selective serotonin reuptake inhibitors, ticlopidine,  $\alpha$ -glucosidase inhibitors, non-steroidal anti-inflammatory drugs, amino acid preparations, antifungal drugs, immunosuppressants, prednisolone, probiotic preparations, PPIs, vonoprazan, and histamine type 2 receptor antagonists).<sup>20</sup> The PPIs analyzed in this study included esomeprazole, omeprazole, rabeprazole, and lansoprazole. The estimated glomerular filtration rate (eGFR) was calculated using the following prediction equation for Japanese patients:  $\text{eGFR (mL/min/1.73 m}^2\text{)} = 194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287}$  ( $\times 0.739$  if women).<sup>21</sup>

## Statistical Analyses

Statistical analyses were performed using JMP Pro 16 statistical package (SAS Institute, Cary, NC, USA). Categorical data were summarized as numbers (%) and analyzed using the chi-square test. Continuous data were summarized as medians (interquartile range [IQR]) and analyzed using the Mann–Whitney *U*-test. Statistical significance was defined as a two-tailed *p*-value  $< 0.05$ .

Univariate and multivariate logistic regression analyses were performed to identify independent variables associated with CDI development. Variables with a *p*-value  $< 0.05$  were included in the multivariate model. Using a stepwise forward selection method, potential independent variables were examined to construct the final model. This was performed not only based on the criterion of the *p*-value but also on clinical validity, as in previous reports.<sup>7–13</sup> Multivariate logistic regression analysis was performed to determine the multivariate regression equation for CDI development. These interactions were verified by focusing on each significant independent variable. Clinical characteristics were compared and stratified using independent variables as needed. When multicollinearity was present, an independent variable was selected based on its clinical relevance using sensitivity analyses. The missing values were handled without correction. The acid-suppressive effects of PPIs were compared in terms of omeprazole equivalents.<sup>22</sup>

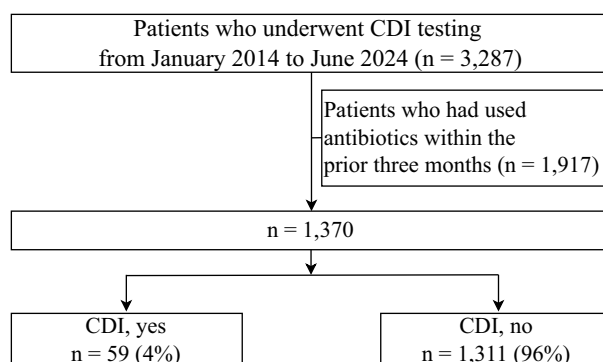
## Ethics Approval

This study was conducted in accordance with the Declaration of Helsinki and its amendments, after obtaining approval from the Clinical Research Ethics Review Committee of Mie University Hospital (No. H2024–132). In this retrospective observational study, informed consent was obtained through an opt-out procedure.

## Results

### Patient Characteristics

During the study period, 3287 patients underwent CDI testing. [Figure 1](#) shows the flowchart of the patient selection process. We excluded 1917 patients who had used antibiotics within the prior 3 months as antibiotic use is the most influential modifiable risk factor for CDI development.<sup>23</sup> Finally, this retrospective observational study enrolled 1370 patients. The baseline characteristics of the patients are summarized in [Table 1](#). None of the patients consumed supplements or health foods. The median (IQR) age, body weight, and hospitalization period were 67.0 (52.0–75.0) years, 52.7 (44.2–62.0) kg, and 9.0 (4.0–18.0) days, respectively. Regarding the concomitant use of drugs that may interact with CDI development, probiotic preparations were used in 313 (22.8%) patients, PPIs in 364 (26.6%), vonoprazan in 129 (9.4%), and histamine type 2 receptor antagonists in 117 (8.5%). The number of patients who received each PPI and their median administration periods, respectively, were as follows: esomeprazole: 103 (7.5%) patients and 18.0 (5.8–125.8) days, omeprazole: 3 (0.2%) patients and 8.0 (2.0–1323.0) days, rabeprazole: 167 (12.2%) patients and 47.0 (8.0–389.0) days, and lansoprazole: 191 (13.9%) patients and 7.0 (3.0–19.0) days. Among the 1370 patients enrolled, 59 developed CDI and four experienced recurrences. Among the 59 patients, 24 were treated with vancomycin alone, one with metronidazole alone, and two with fidaxomicin.



**Figure 1** Flow chart. During the study period, 3287 patients underwent CDI testing. Figure 1 shows the flow chart of the patient selection process. We excluded 1917 patients who had used antibiotics within the prior 3 months, as antibiotic use is the most influential modifiable risk factor for CDI development. Finally, this retrospective observational study enrolled 1370 patients.

**Abbreviation:** CDI, *Clostridioides difficile* infection.

The remaining patients received no treatment. Among those with recurrence, 2 received vancomycin and 2 received no treatment. Our analysis did not identify any characteristic or predictive factor associated with recurrence. Regarding medical history, 815 (59.5%) patients had a history of cancer, 162 (11.8%) had inflammatory bowel disease, 711 (51.9%) had kidney disease, 711 (51.9%) had diabetes, and 504 (36.8%) had undergone gastrointestinal surgery.

## Univariate and Multivariate Logistic Regression Analysis for CDI Development

Univariate logistic regression analysis revealed that age and esomeprazole use were potential independent variables associated with CDI development. The final model, using the stepwise forward selection method, included age (odds ratio [OR] = 1.017, 95% confidence interval [CI] = 1.001–1.033,  $p = 0.038$ ) and esomeprazole use (OR = 2.164, 95% CI = 1.029–4.550,  $p = 0.042$ ) (adjusted coefficient of determination = 0.189,  $p = 0.009$ ; Table 2). The cutoff value for age was 63 years (area under the

**Table 1** Baseline Patient Characteristics

| Variables                        | n (%)            |
|----------------------------------|------------------|
| Men                              | 831 (60.7)       |
| Age, year                        | 67.0 [52.0–75.0] |
| Body weight, kg                  | 52.7 [44.2–62.0] |
| Cancer                           | 815 (59.5)       |
| Inflammatory bowel disease       | 162 (11.8)       |
| Kidney disease                   | 711 (51.9)       |
| Diabetes                         | 711 (51.9)       |
| Gastrointestinal surgery         | 504 (36.8)       |
| Hospitalization period, days     | 9.0 [4.0–18.0]   |
| Alb, g/dL                        | 3.7 [3.2–4.1]    |
| BUN, mg/dL                       | 15.0 [10.9–22.0] |
| SCr, mg/dL                       | 0.8 [0.6–1.1]    |
| CRP, mg/dL                       | 0.5 [0.1–3.3]    |
| eGFR, mL/min/1.73m <sup>2</sup>  | 69.9 [48.9–89.1] |
| WBC, $\times 10^3/\mu\text{L}$   | 7.1 [5.2–10.2]   |
| SSRI                             | 9 (0.7)          |
| Ticlopidine                      | 2 (0.1)          |
| $\alpha$ -glucosidase inhibitors | 15 (1.1)         |
| NSAIDs                           | 363 (26.5)       |
| Amino acid preparations          | 137 (10.0)       |
| Antifungal drugs                 | 55 (4.0)         |

(Continued)

**Table 1** (Continued).

| Variables                               | n (%)            |
|-----------------------------------------|------------------|
| Immunosuppressants                      | 33 (2.4)         |
| Prednisolone                            | 86 (6.3)         |
| Probiotic preparations                  | 313 (22.8)       |
| PPI                                     | 364 (26.6)       |
| PPI administration period, day          | 9.0 [4.0–18.0]   |
| Esomeprazole                            | 103 (7.5)        |
| Esomeprazole administration period, day | 18.0 [5.8–125.8] |
| Omeprazole                              | 3 (0.2)          |
| Omeprazole administration period, day   | 8.0 [2.0–1323.0] |
| Rabeprazole                             | 167 (12.2)       |
| Rabeprazole administration period, day  | 47.0 [8.0–389.0] |
| Lansoprazole                            | 191 (13.9)       |
| Lansoprazole administration period, day | 7.0 [3.0–19.0]   |
| Vonoprazan                              | 129 (9.4)        |
| H <sub>2</sub> receptor antagonists     | 117 (8.5)        |

**Notes:** eGFR [mL/min/1.73 m<sup>2</sup>] =  $194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287}$  ( $\times 0.739$  if women).<sup>21</sup> Chi-square test or Mann–Whitney *U*-test. Data are presented as median [interquartile range].

**Abbreviations:** Alb, serum albumin; BUN, blood urea nitrogen; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; H<sub>2</sub>, histamine type 2; NSAIDs, non-steroidal anti-inflammatory drugs; PPI, proton pump inhibitor; SCr, serum creatinine; SSRI, selective serotonin reuptake inhibitor; WBC, white blood cell.

**Table 2** Univariate and Multivariate Logistic Regression Analyses

|                                     | Univariate Analysis |         | Multivariate Analysis (Variable Selection) |         |
|-------------------------------------|---------------------|---------|--------------------------------------------|---------|
|                                     | OR [95% CI]         | p-value | OR [95% CI]                                | p-value |
| Men                                 | 0.877 [0.517–1.487] | 0.628   | 1.017 [1.001–1.033]                        | 0.038   |
| Age, year                           | 1.018 [1.002–1.033] | 0.018   |                                            |         |
| Body weight, kg                     | 0.988 [0.971–1.006] | 0.191   |                                            |         |
| Cancer                              | 0.744 [0.441–1.255] | 0.270   |                                            |         |
| Inflammatory bowel disease          | 0.388 [0.120–1.255] | 0.069   |                                            |         |
| Kidney disease                      | 0.830 [0.493–1.400] | 0.486   |                                            |         |
| Diabetes                            | 0.830 [0.493–1.400] | 0.486   |                                            |         |
| History of gastrointestinal surgery | 0.628 [0.350–1.126] | 0.108   |                                            |         |
| Hospitalization period, day         | 1.001 [0.998–1.013] | 0.213   |                                            |         |
| Alb, g/dL                           | 0.816 [0.521–1.312] | 0.394   |                                            |         |
| BUN, mg/dL                          | 1.003 [0.987–1.019] | 0.708   |                                            |         |
| SCr, mg/dL                          | 1.106 [0.996–1.229] | 0.089   |                                            |         |
| CRP, mg/dL                          | 0.982 [0.934–1.032] | 0.444   |                                            |         |
| eGFR, mL/min/1.73m <sup>2</sup>     | 0.992 [0.984–1.000] | 0.056   |                                            |         |
| WBC, $\times 10^3/\mu\text{L}$      | 0.994 [0.946–1.043] | 0.788   |                                            |         |
| NSAIDs                              | 1.129 [0.634–2.009] | 0.683   |                                            |         |
| Amino acid preparations             | 1.020 [0.430–2.418] | 0.965   |                                            |         |
| Antifungal drugs                    | 0.401 [0.055–2.952] | 0.298   |                                            |         |
| Immunosuppressants                  | 0.689 [0.083–5.131] | 0.700   |                                            |         |
| Prednisolone                        | 1.742 [0.727–4.175] | 0.243   |                                            |         |
| Probiotic preparations              | 0.952 [0.508–1.786] | 0.879   |                                            |         |
| PPI                                 | 1.685 [0.980–2.896] | 0.066   |                                            |         |

(Continued)

**Table 2** (Continued).

|                                     | Univariate Analysis |         | Multivariate Analysis (Variable Selection) |         |
|-------------------------------------|---------------------|---------|--------------------------------------------|---------|
|                                     | OR [95% CI]         | p-value | OR [95% CI]                                | p-value |
| Esomeprazole                        | 2.330 [1.12–4.885]  | 0.040   | 2.164 [1.029–4.550]                        | 0.042   |
| Rabeprazole                         | 1.270 [0.448–3.604] | 0.663   |                                            |         |
| Lansoprazole                        | 1.440 [0.734–2.825] | 0.306   |                                            |         |
| PPI administration period           | 1.000 [0.999–1.001] | 0.535   |                                            |         |
| PPI >365 days                       | 0.628 [0.142–2.773] | 0.515   |                                            |         |
| Vonoprazan                          | 1.093 [0.461–2.595] | 0.841   |                                            |         |
| H <sub>2</sub> receptor antagonists | 0.178 [0.024–1.294] | 1.021   |                                            |         |

**Notes:** The adjusted coefficient of determination was 0.189 ( $p = 0.009$ ).  $\text{eGFR [mL/min/1.73 m}^2\text{]} = 194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287}$  ( $\times 0.739$  if women).<sup>21</sup>

**Abbreviations:** Alb, serum albumin; BUN, blood urea nitrogen; CI, confidence interval; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; H<sub>2</sub>, histamine type 2; NSAIDs, non-steroidal anti-inflammatory drugs; OR, odds ratio; PPI, proton pump inhibitor; SCr, serum creatinine; WBC, white blood cell.

receiver operating characteristic curve, 0.593; specificity, 0.591; sensitivity, 0.780;  $p = 0.001$ ). There was no association between the duration of PPI administration and CDI development.

The relationship between the incidence of CDI and the degree of acid suppression was evaluated based on omeprazole equivalents ([Supplementary Table 1](#)). Patients receiving esomeprazole 20 mg showed higher incidence of CDI than did those receiving other PPIs.

## Comparison of CDI Incidence in Patients Stratified Based on the Receipt of Esomeprazole and Probiotic Preparations

[Table 3](#) shows a comparison of CDI incidence in patients stratified based on the receipt of esomeprazole and probiotic preparations. CDI occurred in 1/26 (3.8%) patients who received esomeprazole and probiotic preparations, 8/77 (10.4%) of those who received only esomeprazole, 12/287 (4.2%) of those who received only probiotic preparations, and 38/980 (3.9%) of those who did not receive esomeprazole or probiotic preparations ( $p = 0.060$ ).

## Comparison of Backgrounds of Patients Who Received Esomeprazole and Those Who Received Vonoprazan

[Table 4](#) shows a comparison of backgrounds of patients who received esomeprazole and those who received vonoprazan. The rate of administration of probiotic preparations was significantly higher in patients who received esomeprazole than in those treated who received vonoprazan (25.2% vs 39.5%,  $p = 0.025$ ). In contrast, no significant differences in other clinical characteristics were observed between the two patient groups.

**Table 3** Comparison of Incidence of *Clostridioides Difficile* Infection in Patients Stratified Based on the Receipt of Esomeprazole and Probiotic Preparations

|     | Esomeprazole, Yes<br>Probiotic Preparations, Yes | Esomeprazole, Yes<br>Probiotic Preparations, No | Esomeprazole, No<br>Probiotic Preparations, Yes | Esomeprazole, No<br>Probiotic Preparations, No |
|-----|--------------------------------------------------|-------------------------------------------------|-------------------------------------------------|------------------------------------------------|
| CDI | 1/26 (3.8%)                                      | 8/77 (10.4%)                                    | 12/287 (4.2%)                                   | 38/980 (3.9%)                                  |

**Note:**  $p = 0.060$  (Fisher's exact test).

**Abbreviation:** CDI, *Clostridioides difficile* infection.

**Table 4** Comparison of Backgrounds of Patients Who Received Esomeprazole and Those Who Received Vonoprazan

|                                     | Esomeprazole (n = 103) | Vonoprazan (n = 129) | p-value |
|-------------------------------------|------------------------|----------------------|---------|
| Men                                 | 63 (61.2)              | 85 (65.9)            | 0.337   |
| Age, year                           | 70.0 [60.0–76.0]       | 71.0 [63.0–78.0]     | 0.419   |
| Body weight, kg                     | 53.3 [44.5–62.1]       | 53.6 [45.2–61.0]     | 0.691   |
| Cancer                              | 64 (62.1)              | 78 (60.5)            | 0.892   |
| Inflammatory bowel disease          | 9 (8.7)                | 7 (5.4)              | 0.435   |
| Kidney disease                      | 65 (6.3)               | 87 (67.4)            | 0.578   |
| Diabetes                            | 66 (64.1)              | 86 (66.7)            | 0.781   |
| History of gastrointestinal surgery | 29 (28.2)              | 53 (41.1)            | 0.053   |
| Administration period, day          | 11.0 [4.5–19.5]        | 11.0 [8.0–19.0]      | 0.573   |
| Alb, g/dL                           | 3.8 [3.3–4.0]          | 3.7 [3.3–4.1]        | 0.971   |
| BUN, mg/dL                          | 16.6 [11.5–21.5]       | 16.0 [11.1–22.3]     | 0.716   |
| SCr, mg/dL                          | 0.8 [0.6–1.0]          | 0.8 [0.6–1.0]        | 0.721   |
| CRP, mg/dL                          | 0.6 [0.2–2.2]          | 0.3 [0.09–2.2]       | 0.273   |
| eGFR, mL/min/1.73m <sup>2</sup>     | 69.5 [49.4–89.3]       | 7.03 [51.2–86.8]     | 0.817   |
| WBC, ×10 <sup>3</sup> /μL           | 6.7 [5.1–9.9]          | 6.6 [5.1–10.1]       | 0.798   |
| SSRIs                               | 0 (0.0)                | 0 (0.0)              | 1.000   |
| Ticlopidine                         | 0 (0.0)                | 0 (0.0)              | 1.000   |
| α-glucosidase inhibitors            | 0 (0.0)                | 2 (1.6)              | 0.504   |
| NSAIDs                              | 38 (36.9)              | 48 (37.2)            | 1.000   |
| Amino acid preparations             | 18 (17.5)              | 14 (10.9)            | 0.180   |
| Antifungal drugs                    | 4 (3.9)                | 2 (1.6)              | 0.410   |
| Immunosuppressants                  | 4 (3.9)                | 3 (2.3)              | 0.703   |
| Prednisolone                        | 8 (7.8)                | 9 (7.0)              | 1.000   |
| Probiotic preparations              | 26 (25.2)              | 51 (39.5)            | 0.025   |

**Notes:** eGFR [mL/min/1.73 m<sup>2</sup>] =  $194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287}$  ( $\times 0.739$  if women).<sup>21</sup> Chi-square test or Mann–Whitney U-test. Data are presented as median [interquartile range].

**Abbreviations:** Alb, serum albumin; BUN, blood urea nitrogen; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; NSAIDs, non-steroidal anti-inflammatory drugs; SCr, serum creatinine; T-Bil, total bilirubin; SSRIs, selective serotonin reuptake inhibitor; WBC, white blood cell.

## Discussion

Our study suggests that both esomeprazole use and advanced age are potential indicators of an increased risk of CDI. Furthermore, the concomitant administration of probiotics appears to reduce the incidence of CDI. Our findings suggest that selecting an appropriate PPI based on individual bleeding risk and considering the co-administration of probiotics may be effective strategies for preventing CDI development.

Advanced age is a well-established risk factor not only for CDI development but also for poor clinical outcomes, including increased severity and mortality.<sup>24,25</sup> Notably, many reported cases of CDI have involved older individuals with chronic and/or multiple comorbidities, which may increase their susceptibility to infection. Microbiological studies have demonstrated significantly reduced bacterial diversity in the fecal microbiota of older adults than of younger individuals.<sup>26</sup> These findings highlight the importance of minimizing unnecessary prescription of PPIs in older populations to preserve or restore gut microbial diversity. For instance, for patients receiving medications such as low-dose aspirin,<sup>27</sup> oral anticoagulants,<sup>28</sup> or non-steroidal anti-inflammatory drugs,<sup>29</sup> for which co-administration with PPIs is supported by evidence to reduce gastrointestinal bleeding, clinicians should tailor PPI selection based on bleeding risk and consider concomitant probiotic use. However, for patients receiving glucocorticoids, the protective role of PPIs remains controversial.<sup>30,31</sup> Regarding stress-related gastric mucosal hemorrhage, hospital-acquired gastrointestinal bleeding is rare in non-critically ill patients,<sup>32</sup> although acid suppression remains an effective strategy in critically ill patients.<sup>33</sup> Overall, the decision to initiate or continue PPI therapy should be individualized, based on the patient's clinical condition.



The influence of PPIs on intragastric pH control varies depending on the type and dosage.<sup>7–13</sup> Esomeprazole maintains intragastric pH above 4.0, which is significantly higher than the pH maintained by other PPIs.<sup>8,34</sup> In our study, multivariate logistic regression analysis revealed a significant association between esomeprazole use and increased risk of CDI (Table 2). Bacterial overgrowth in the stomach is strongly influenced by elevated gastric pH, and CD can survive under high pH conditions.<sup>13</sup> Therefore, the use of PPIs with potent and sustained acid-suppressive effects may be associated with an increased risk of CDI. Further studies are needed to clarify the threshold of acid suppression and duration of PPI use that influence the development of CDI.

Vonoprazan is a potent acid blocker that inhibits the proton pump activity of cytoplasmic tubulovesicles and secretory canaliculi, resulting in stronger and more sustained inhibition of gastric acid secretion, compared with conventional PPIs.<sup>35,36</sup> Night-time acid suppression (measured as the percentage of time with pH  $\geq$  4 at night) was significantly higher in patients receiving vonoprazan than in those receiving esomeprazole.<sup>37</sup> However, vonoprazan was not identified as a risk factor for CDI in the present study. Based on the comparison of backgrounds of patients who received vonoprazan and those who received esomeprazole, the former patients had a significantly higher rate of concomitant probiotic use, compared with the latter patients. Although our sample size was limited and the difference did not reach statistical significance, patients who received both esomeprazole and probiotics showed a lower incidence of CDI than did those who received esomeprazole alone. Previous studies have suggested that probiotics help mitigate PPI-associated dysbiosis and play a preventive role in CDI development during potent acid suppression therapy.<sup>38</sup>

Several mechanisms may underlie the beneficial effects of probiotics in reducing the risk of CDI during PPI therapy. PPIs are known to cause intestinal dysbiosis. One key mechanism through which probiotics exert their protective effect is competitive exclusion, by outcompeting pathogenic organisms for receptor sites in the gastrointestinal tract. However, the specific pathways involved in this process remain poorly understood.<sup>39</sup> Additionally, probiotics produce bacteriocins that inhibit pathogenic bacteria, influence bile acid metabolism, exhibit enzymatic activity, and modulate host immune responses.<sup>40</sup> Collectively, these actions contribute to the protective effect of probiotics when used in combination with PPIs.

This study has some limitations. First, owing to its retrospective design based on medical record review, the potential for bias and confounding cannot be excluded. Second, a substantial number of patients (1370 of 3287, 41.7%) were excluded from the analysis, introducing a significant risk of selection bias. Third, medication adherence was not fully verified, which may have influenced the outcomes. Fourth, although most patients received *Clostridium butyricum* as a probiotic, we did not conduct a subgroup analysis based on the probiotic type. Fifth, probiotic administration was defined as concomitant use for more than 1 week prior to CDI development; however, we did not analyze the impact of dosage and duration on CDI development in detail. Sixth, we could not evaluate the association between CDI therapy or disease severity and the importance of probiotics due to the small number of patients. Further studies with larger patient populations (eg, real-world data analyses) will be conducted to address this question. Additionally, owing to the limited sample size, we were unable to perform stratified analyses based on disease severity or recurrence. Considering these limitations, the findings of this retrospective cohort study should be interpreted with caution.

## Conclusions

PPIs change the composition of the gut microbiota by altering the pH and thereby affect their modulation of host immune responses. Esomeprazole has been shown to be associated with a higher incidence of CDI, compared with other PPIs. Probiotics may inhibit intestinal dysbiosis after PPI therapy and may help alleviate its side effects. Further studies involving larger patient populations will be needed to evaluate the association between CDI therapy or disease severity and the role of probiotics.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically



reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare no conflicts of interest in this work.

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