Proton pump inhibitor use and risk of community-acquired Clostridium difficile-associated disease defined by prescription for oral vancomycin therapy

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Background: The association between the use of proton pump inhibitors and the risk of Clostridium difficile-associated disease (CDAD) is controversial. In this study we re-examined a previously reported association between the use of proton pump inhibitors and the development of community-acquired CDAD, this time using an alternative case definition of the disease.

Methods: We performed a case–control study of community-acquired CDAD using a United Kingdom clinical research database. Patients receiving oral vancomycin therapy were identified as having CDAD, the only indication for this drug. Each case subject was matched with up to 10 control subjects. Neither the cases nor the controls had been admitted to hospital in the year before the date of the vancomycin prescription (index date). Conditional logistic regression analysis was used to adjust for key covariates.

Results: We identified 317 cases of community-acquired CDAD treated with oral vancomycin therapy and 3167 matched control subjects. Exposure to a proton pump inhibitor in the 90 days before the index date was associated with an increased risk of CDAD (odds ratio [OR] 3.5, 95% confidence interval [CI] 2.3–5.2). Antibiotic exposure in the 90 days before the index date was also a significant risk factor for community-acquired CDAD (OR 8.2, 95% CI 6.1–11.0), even though 45% of the case subjects had not received a prescription for an antibiotic during that period. Certain comorbidities, in particular renal failure, inflammatory bowel disease and malignant disease, as well as prior methicillin-resistant Staphylococcus aureus infection, were also associated with an increased risk.

Interpretation: Proton pump inhibitor use was associated with an increased risk of community-acquired CDAD, when cases were defined by receipt of prescription for oral vancomycin therapy. Prior antibiotic exposure was also a significant risk factor, but a significant proportion of the patients with community-acquired CDAD had no such exposure.

Interpretation: Proton pump inhibitor use was associated with an increased risk of community-acquired CDAD, when cases were defined by receipt of prescription for oral vancomycin therapy. Prior antibiotic exposure was also a significant risk factor, but a significant proportion of the patients with community-acquired CDAD had no such exposure.
are removed. Several validation studies of the GPRD have confirmed the quality and completeness of the data. \(^2,3\)

A case–control approach was used. All patients with a first prescription of oral vancomycin therapy recorded in the database between Jan. 1, 1994, and Dec. 31, 2004, were included as the case series. To avoid including patients receiving treatment for relapses, we excluded patients who had either a clinical diagnosis of MRSA infection or toxin-positive assay result recorded 30 days to 1 year before the prescription date. To define community-acquired CDAD, patients were limited to those who had not been admitted to hospital in the year before their first prescription for oral vancomycin therapy. Using this definition, we observed that there was no overlap between these cases and the cases included in a previous study. The date of the vancomycin prescription was defined as the index date. For each case, up to 10 control subjects were selected from patients attending the same general practice, matched by age (± 2 years), who had not been admitted to hospital in the year before the index date, had not received a prescription for oral vancomycin therapy and were neither toxin positive nor had had a clinical diagnosis of CDAD recorded by the index date. Both cases and controls had to have had at least 2 years of follow-up in the database before the index date.

Patients were classified as currently exposed to a drug of interest (i.e., gastric acid suppressant agent or antibiotic) if they received a prescription for the drug in the 90-day period before the index date. Otherwise they were considered unexposed.

**Table 1: Characteristics of patients with community-acquired Clostridium difficile-associated disease (CDAD)***

| Characteristic                          | Cases   | Controls |
|----------------------------------------|---------|----------|
|                                       | n = 317 | n = 3167 |
| Age, yr, mean (SD)                     | 65.0 (19.6) | 64.9 (19.5) |
| Sex, male                              | 116 (36.6) | 1315 (41.5) |
| Comorbid conditions in the 2 yr before index date† |         |          |
| Gastrointestinal                       |         |          |
| Inflammatory bowel disease             | 18 (5.7) | 6 (0.2)  |
| Diverticular disease                   | 7 (2.2)  | 32 (1.0) |
| Peptic ulcer disease                   | 1 (0.3)  | 3 (0.1)  |
| Gastroesophageal reflux disease        | 13 (4.1) | 67 (2.1) |
| Other                                  |         |          |
| Renal failure                          | 17 (5.3) | 22 (0.7) |
| Diabetes                               | 14 (4.4) | 139 (4.4) |
| MRSA                                   | 5 (1.6)  | 3 (0.1)  |
| Cancer (solid tumour)                  | 5 (1.6)  | 12 (0.4) |
| Leukemia or lymphoma                   | 3 (0.9)  | 3 (0.1)  |
| Pernicious anemia                      | 1 (0.3)  | 3 (0.1)  |
| COPD                                   | 21 (6.6) | 98 (3.1) |

Note: SD = standard deviation, MRSA = methicillin-resistant Staphylococcus aureus, COPD = chronic obstructive pulmonary disease.

*Cases of CDAD are defined by receipt of prescription for oral vancomycin therapy.
†Unless stated otherwise.
‡The index date is the date of prescription for oral vancomycin therapy.

**Results**

There were 481 eligible patients who received a prescription for oral vancomycin therapy during the study period. Of these patients, 317 (65.9%) had not been admitted to hospital in the year before and were retained as cases in the study. None of these cases had been coded in the database as being toxin positive at any time, including in the 30 days before the vancomycin prescription date (index date). The 317 patients who received vancomycin had a mean age of 65.0 years and were predominantly female (Table 1). After controlling for all covariates shown in Table 1, as well as exposure to antibiotics, NSAIDs and ASA, we observed a strong association between treated CDAD and current proton pump inhibitor exposure (OR 3.5, 95% confidence interval [CI] 2.3–5.2). Use of an H₂-receptor antagonist was not significantly associated with an increased risk of CDAD (OR 1.4, 95% CI 0.8–2.5). Prior antibiotic exposure was the most important of the medication exposures (OR 8.2, 95% CI 6.1–11.0), even though 45% of the cases were not exposed to antibiotics within 90 days before the index period. The cases were also significantly more likely than the controls to have a history of renal failure, inflammatory bowel disease and cancer and to have had a previous diagnosis of MRSA infection (Table 2).

**Interpretation**

In this study of community-acquired CDAD, with cases defined on the basis of the patient having received a prescription for oral vancomycin therapy (whose only indication is the treatment of CDAD), we observed an increased risk of CDAD associated with current use of proton pump inhibitors. The es-
timate of effect for H₂-receptor antagonists was not found to be statistically significant. Comorbid illnesses determined to be associated with CDAD in previous studies (i.e., renal failure, inflammatory bowel disease, cancer and MRSA infection) remained significantly associated with CDAD in this study.

As in the previous study, antibiotics presented the highest risk of all the medications assessed; however, 45% of the case subjects had not received a prescription for antibiotics in the 90 days before vancomycin prescription. Most studies of CDAD have involved patients in acute care hospitals, where the prevalence of antibiotic exposure is high,¹⁴ which has likely contributed to the high rates of antibiotic exposure among CDAD patients in this setting. Also, because antibiotics frequently cause diarrhea and are believed to be in the causal pathway of CDAD, selection and ascertainment bias may be occurring. Patients receiving antibiotics are more likely than those not taking antibiotics to be admitted to the hospital and therefore receive a diagnosis of CDAD, especially with recommendations that testing only be performed in patients with recent antibiotic exposure.¹⁵ In 3 studies performed in settings where the rate of antibiotic exposure in the source population was low (less than 15%), rates of prior antibiotic exposure of 49%,¹⁶ 50%¹⁷ and 52%¹⁸ among the CDAD cases were observed. At a recent workshop on clostridial disease, low rates of antibiotic exposure among patients with community-acquired CDAD were also reported.¹⁹,²⁰ Therefore, patients with community-acquired CDAD may be less likely than those with hospital-acquired CDAD to have been previously exposed to antibiotics.

The use of 3 different case definitions for CDAD from a validated research database — laboratory diagnosis based on a positive toxin assay result (n = 833), physician diagnosis (n = 400) and receipt of a prescription for oral vancomycin therapy (n = 317) — yielded similar proportions of patients with prior proton pump inhibitor exposure (24%, 21%³ and 19%). The proportion of patients who had previously been exposed to antibiotics was higher among cases defined on the basis of vancomycin treatment (55%) than among those defined on the basis of a positive toxin assay result (34%) or physician diagnosis (38%).¹ Because vancomycin is significantly more expensive than metronidazole and because metronidazole is suggested as the first-line agent for the treatment of CDAD, it is possible that a case definition based on a prescription for oral vancomycin therapy may have resulted in certain biases.³ For example, if being given oral vancomycin therapy is a marker for more severe CDAD, our estimates of drug effects may only be applicable to the risk of severe disease. It is possible that we included patients with relapses whose risk factors may have differed from those of patients with a first occurrence of CDAD. Also, if oral vancomycin therapy was prescribed as a second-line agent,

### Table 2: Factors associated with increased risk of community-acquired Clostridium difficile-associated disease (CDAD)*

| Factor                              | % of cases† | % of controls† | Crude OR | Adjusted OR (95% CI)‡ |
|-------------------------------------|-------------|----------------|----------|-----------------------|
| **Sex, male, no. (%)**              | 116 (36.6)  | 1315 (41.5)    | 0.8      | 1.0 (0.8-1.3)         |
| **Comorbid conditions in the 2 yr before index date§** |            |                |          |                       |
| **Gastrointestinal**                |             |                |          |                       |
| Inflammatory bowel disease          | 5.7         | 0.2            | 36.0     | 46.1 (14.5-146.7)     |
| Diverticular disease                | 2.2         | 1.0            | 2.3      | 1.5 (0.5-4.4)         |
| Peptic ulcer disease                | 0.3         | 0.1            | 2.5      | 2.9 (0.3-30.0)        |
| Gastroesophageal reflux disease     | 4.1         | 2.2            | 2.0      | 0.9 (0.4-1.9)         |
| **Other**                           |             |                |          |                       |
| Renal failure                       | 5.3         | 0.7            | 8.7      | 6.2 (2.7-13.9)        |
| Diabetes                            | 4.4         | 4.4            | 1.0      | 0.9 (0.4-1.7)         |
| MRSA                                | 1.6         | 0.1            | 15.3     | 8.9 (1.7-46.6)        |
| Cancer (solid tumour)               | 1.6         | 0.4            | 4.3      | 4.9 (1.5-16.5)        |
| Leukemia or lymphoma                | 0.9         | 0.1            | 10.0     | 10.3 (1.3-81.5)       |
| Pernicious anemia                   | 0.3         | 0.1            | 5.1      | 6.0 (0.2-149.9)       |
| COPD                                | 6.6         | 3.1            | 2.3      | 1.1 (0.6-1.9)         |
| **Medications received in the 90 d before index date,§ no. (%) of patients** |          |                |          |                       |
| Proton pump inhibitor               | 61 (19.2)   | 157 (5.0)      | 5.1      | 3.5 (2.3-5.2)         |
| Antibiotic                          | 174 (54.9)  | 405 (12.8)     | 9.4      | 8.2 (6.1-11.0)        |
| H₂-receptor antagonist              | 23 (7.3)    | 112 (3.5)      | 2.2      | 1.4 (0.8-2.5)         |

Note: OR = odds ratio, CI = confidence interval, MRSA = methicillin-resistant Staphylococcus aureus, COPD = chronic obstructive pulmonary disease.
*Cases of CDAD are defined by receipt of prescription for oral vancomycin therapy.
†Unless stated otherwise. All variables in table were included in multivariate model to estimate adjusted ORs.
§The index date is the date of prescription for oral vancomycin therapy.

| Medications received in the 90 d before index date,§ no. (%) of patients | % of cases† | % of controls† | Crude OR | Adjusted OR (95% CI)‡ |
|---------------------------------------------------------------------------|-------------|----------------|----------|-----------------------|
| Proton pump inhibitor                                                     | 61 (19.2)   | 157 (5.0)      | 5.1      | 3.5 (2.3-5.2)         |
| Antibiotic                                                               | 174 (54.9)  | 405 (12.8)     | 9.4      | 8.2 (6.1-11.0)        |
| H₂-receptor antagonist                                                    | 23 (7.3)    | 112 (3.5)      | 2.2      | 1.4 (0.8-2.5)         |
The patients may have had diarrhea that was actually undiagnosed CDAD and in whom other antibiotic therapies (e.g., metronidazole or a quinolone) had failed. This could have increased our effect estimate of exposure to previous antibiotic agents (protopathic bias). This could also explain, in part, differences in the prevalence of antibiotic exposure between the cases seen in this study and those in a previous study, where the rate of prior antibiotic exposure was 37%.

The UK health care system differs from the Canadian system in that general practitioners in the United Kingdom are responsible for overseeing the care of the patients in their practice, and budgetary adjustments are based on this premise. There may have been some unrecorded prescription information related to specialist visits, but it is unlikely to account for a high proportion of patients. Although the accuracy of the data is always a concern with database research, it has been reported that prescription information in the GPRD is extremely accurate and has been consistent throughout the period of study. Although the accuracy is shown to be of high quality for certain diagnoses, routine collection of such large amounts of data is inevitably subject to some constraints, since detailed diagnostic criteria cannot be laid down as in prospective studies. However, we believe that the consistency of the associations using the 3 different case definitions suggests that our definitions are valid.

In a community-based cohort, patients are less likely to be exposed to antibiotics and rarely receive multiple antibiotics concurrently. Under these conditions, it may be possible to gain a clearer estimate of the effect of nonantibiotic drugs on the risk of CDAD than in a hospital-based study, where antibiotic use is highly prevalent. The inability to demonstrate an association between antibiotic agents and CDAD in some hospital-based studies could have been due to residual confounding by indication. This is highlighted by the fact that underlying disease severity, a known risk factor for CDAD (as well as other nosocomial complications) may be highly correlated with both broad-spectrum and multiple antibiotic use. Recent hospital-based studies and a large community study have described an increased risk of CDAD associated with proton pump inhibitor use. The results of this study, involving a different community cohort and a different case definition of CDAD, add additional weight to the evidence that proton pump inhibitor use is associated with an increased risk of CDAD.

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