Use of Gastric Acid–Suppressive Agents and the Risk of Community-Acquired Clostridium difficile–Associated Disease

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Context Recent reports suggest an increasing occurrence and severity of Clostridium difficile–associated disease. We assessed whether the use of gastric acid-suppressive agents is associated with an increased risk in the community.

Objective To determine whether the use of gastric acid-suppressive agents increases the risk of C difficile–associated disease in a community population.

Design, Setting, and Patients We conducted 2 population-based case-control studies using the United Kingdom General Practice Research Database (GPRD). In the first study, we identified all 1672 cases of C difficile recorded between 1994 and 2004 among all patients registered for at least 2 years in each practice. Each case was matched to 10 controls on calendar time and the general practice. In the second study, a subset of these cases defined as community-acquired, that is, not hospitalized in the prior year, were matched on practice and age with controls also not hospitalized in the prior year.

Main Outcome Measures The incidence of C difficile and risk associated with gastric acid-suppressive agent use.

Results The incidence of C difficile in patients diagnosed by their general practitioners in the General Practice Research Database increased from less than 1 case per 100 000 in 1994 to 22 per 100 000 in 2004. The adjusted rate ratio of C difficile–associated disease with current use of proton pump inhibitors was 2.9 (95% confidence interval [CI], 2.4-3.4) and with H2-receptor antagonists the rate ratio was 2.0 (95% CI, 1.6-2.7). An elevated rate was also found with the use of nonsteroidal anti-inflammatory drugs (rate ratio, 1.3; 95% CI, 1.2-1.5).

Conclusions The use of acid-suppressive therapy, particularly proton pump inhibitors, is associated with an increased risk of community-acquired C difficile. The unexpected increase in risk with nonsteroidal anti-inflammatory drug use should be investigated further.

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risk of community-acquired CDAD. We thus evaluated whether the use of gastric acid-suppressant drugs is associated with the risk of community-acquired CDAD.

METHODS

Data Source

The data were obtained from the United Kingdom General Practice Research Database (GPRD), which has been described in detail elsewhere. More than 3 million people in the United Kingdom are enrolled with more than 400 general practitioners who use office computers and have agreed to provide data for research purposes. General practitioners have been trained to record medical information including demographic data, medical diagnoses, details of hospital stays, and deaths using a standard anonymous form. The physicians generate prescriptions directly with their study computer; this information is automatically transcribed into the computer record. A modification of the Oxford Medical Information System classification (similar to the International Classification of Diseases, Eighth Revision) is used to enter medical diagnoses, and a coded drug dictionary based on the UK Prescription Pricing Authority Dictionary is used for recording prescriptions. The recorded information on drug exposure and diagnoses has been validated and proven to be of high quality. The study was approved by the Scientific and Ethical Advisory Group of the GPRD and the ethics review board of the McGill University Health Centre.

Study Design

The study population included all patients with at least 2 years of follow-up in the GPRD. The strategy was to first use a case-control approach with all cases of CDAD including both hospital- and community-acquired cases identified in the database to first examine widely acknowledged risk factors for the development of CDAD such as antibiotic use, prior hospitalization, and age. A second case-control analysis was then performed using the subset of cases defined as community-acquired who were matched with another set of controls.

Cases and Controls

For the first case-control study, all patients from the study population with a first occurrence of CDAD recorded in the medical record between January 1, 1994, and December 31, 2004, were identified based on the presence of a first positive C difficile toxin assay and/or a clinical diagnosis recorded by their general practitioner. For each case, 10 controls were randomly selected from all patients in the study population and in the same practice as the case, but who were neither toxin positive nor had a clinical diagnosis of C difficile recorded by the time the case was diagnosed (index date). Cases and controls had to be aged 18 years or older and had to have at least 2 years of records in the GPRD prior to the index date. Cases and controls were matched on practice to control for possible physician-related and geographical variations in the exposure.

In the second case-control study, the community-acquired cases were defined as the subset of CDAD patients who had not been hospitalized in the year prior to the index date. For each such case, a new set of 10 controls was identified. The controls were selected from patients attending the same general practice as the case, matched on age (±2 years), were not hospitalized in the year prior to the index date, and were neither toxin positive nor had a clinical diagnosis of C difficile recorded by the time the case was diagnosed (index date).

Exposure Assessment

All prescriptions for antibiotics and gastric acid-suppressant agents, which included proton pump inhibitors and H2RAs, written during the 2-year period prior to the index date were identified. Patients were classified as currently exposed to a drug if they received a prescription for the drug in the 90-day period prior to the index date and unexposed otherwise.

Covariates

Comorbid gastrointestinal illnesses present in the 2 years prior to the index date, including inflammatory bowel disease, diverticular disease, peptic ulcer disease, and gastroesophageal reflux disease, H pylori-associated disease, and pernicious anemia as a marker of gastric hypochlorhydria, were identified from physician diagnoses. Prescriptions for nonsteroidal anti-inflammatory agents and aspirin given in the 90 days before the index date were also evaluated. Other comorbid illnesses identified from physician diagnoses were renal failure including dialysis, cancer including solid tumor and hematologic malignancies, methicillin-resistant Staphylococcus aureus positive, diabetes mellitus, chronic obstructive pulmonary disease, and cirrhosis.

Data Analysis

All analyses were based on conditional logistic regression to estimate the odds ratio as an approximation of the rate ratio (RR) of CDAD for the risk factors under study. In the first analysis, based on the entire series of cases and their controls, RRs of CDAD were estimated for age, sex, hospitalization in the year prior to the index date, and current antibiotic exposure.

For the second analysis, the adjusted RRs of community-acquired CDAD were estimated for current use of proton pump inhibitors, H2RAs, nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, and antibiotics after adjustment for sex, comorbidity, and coprescription with NSAIDs and aspirin. Because of insufficient numbers, we were not able to assess dose response within the gastric acid-suppressive classes of agents. A sensitivity analysis that included patients recorded as having a clinical diagnosis of CDAD vs being recorded based on toxin assay alone was conducted to examine the effect of potential case misclassification. As acid-suppressive therapy is frequently used in patients with gastrointestinal disorders and in patients prescribed NSAIDs or aspirin, analysis restricted to patients without prior
for current proton pump inhibitor exposure is 2.9 (95% confidence interval [CI], 2.4-3.4). The adjusted RR for H,RAs is 2.0 (95% CI, 1.6-2.7). Current exposure to NSAIDs but not aspirin was also associated with an increased rate of C difficile (RR, 1.3; 95% CI, 1.2-1.5) (TABLE 4). Renal failure (adjusted RR, 3.7; 95% CI, 2.4-5.6); inflammatory bowel disease (RR, 3.6; 95% CI, 2.6-5.1); malignancy (RR, 1.9; 95% CI, 1.4-2.7); and being methicillin-resistant Staphylococcus aureus-positive (RR, 4.2; 95% CI, 2.7-6.4) were also associated with an increased risk of community-acquired CDAD.

In the first analysis that compares all 1672 cases with their controls, age, prior hospitalization, and exposure to antibiotics in the 90 days prior to the index date were all highly associated with a significantly increased risk of CDAD (TABLE 1). Age older than 65 years is associated with a particularly elevated risk of CDAD.

In the second analysis of cases and controls not hospitalized in the year prior to the index date, there were 1233 cases of which 400 were identified based on a clinical diagnosis and 833 were identified based on a positive toxin assay. As shown in TABLE 2, cases that were identified based on a toxin assay only or based on clinical diagnosis were similar with respect to age, sex, antibiotic, and gastric acid-suppressive therapy. TABLE 3 shows that the 1233 community-acquired C difficile cases had a mean age of 71 years and were more likely to be women than their age-matched controls. Cases were also more likely to have a history of renal failure, inflammatory bowel disease, malignancy, and to be methicillin-resistant Staphylococcus aureus-positive.

After controlling for all covariates shown in Table 3, antibiotic, NSAID, and aspirin exposure, the adjusted RR of C difficile per 100 000 persons in 1994 to 22 per 100 000 in 2004. During this period, the rate of prescriptions of antibiotics decreased and that of proton pump inhibitors increased.

The sensitivity analysis performed on patients with a clinical diagnosis only showed an adjusted RR for proton pump inhibitors of 2.8 (95% CI, 2.1-3.9) and 1.4 (95% CI, 0.9-2.3) for H,RAs, while for cases identified based on toxin assay only, the RRs were 3.0 (95% CI, 2.5-3.7) and 2.5 (95% CI, 1.8-3.4), respectively, for current proton pump inhibitor and H,RA exposure. The estimates for proton pump inhibitor exposure in patients without a prior history of gastrointestinal disease was 3.2 (95% CI, 2.6-3.9) and 3.7 (95% CI, 2.8-4.8) in patients without current NSAID exposure. The esti-
mates for H2RAs was 2.1 (95% CI, 1.5-2.9) and 1.6 (95%CI, 1.0-2.5) respectively, in patients without prior gas-

Table 2. Baseline Characteristics of the 1233 Community-Acquired Cases of Clostridium difficile Based on Identification From a Clinical Diagnosis vs Identification Based on Toxin Assay Only

<table>
<thead>
<tr>
<th>Variable</th>
<th>Clinical Diagnosis</th>
<th>Toxin Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>400 (32)</td>
<td>833 (68)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>71.2 (17)</td>
<td>70.8 (16)</td>
</tr>
<tr>
<td>Age &gt;65 y</td>
<td>286 (72)</td>
<td>641 (77)</td>
</tr>
<tr>
<td>Women</td>
<td>260 (65)</td>
<td>550 (66)</td>
</tr>
<tr>
<td>Medication exposures in the 90 d prior</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td>158 (39)</td>
<td>284 (34)</td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
<td>82 (21)</td>
<td>201 (24)</td>
</tr>
<tr>
<td>H2-receptor antagonists</td>
<td>29 (7)</td>
<td>55 (7)</td>
</tr>
</tbody>
</table>

Table 3. Comparison of Community-Acquired Matched Cases and Controls—Medical History Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nonhospitalized Incident Cases</th>
<th>Nonhospitalized Age- and Practice-Matched Controls</th>
<th>Crude Rate Ratio (95% CI)</th>
<th>Adjusted Rate Ratio (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>1233</td>
<td>1230</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>71.0 (16)</td>
<td>70.8 (16)</td>
<td>1.2 (0.9-1.5)</td>
<td>1.1 (0.9-1.4)</td>
</tr>
<tr>
<td>≤35</td>
<td>66 (5)</td>
<td>666 (6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>36-50</td>
<td>87 (7)</td>
<td>872 (7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>51-65</td>
<td>150 (12)</td>
<td>1661 (13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;65</td>
<td>930 (75)</td>
<td>9141 (74)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>803 (65)</td>
<td>7130 (58)</td>
<td>1.4 (1.1-1.6)</td>
<td>1.3 (1.1-1.5)</td>
</tr>
<tr>
<td>Medical history in the 2 years prior</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastritis intestinal disease</td>
<td>57 (5)</td>
<td>144 (1)</td>
<td>4.1 (3.0-5.7)</td>
<td>3.6 (2.6-5.1)</td>
</tr>
<tr>
<td>Diverticular disease</td>
<td>119 (10)</td>
<td>763 (6)</td>
<td>1.6 (1.3-2.0)</td>
<td>1.1 (0.9-1.4)</td>
</tr>
<tr>
<td>Peptic ulcer disease</td>
<td>9 (1)</td>
<td>116 (1)</td>
<td>0.8 (0.4-1.5)</td>
<td>0.5 (0.2-1.1)</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>153 (12)</td>
<td>1022 (8)</td>
<td>1.6 (1.3-1.9)</td>
<td>1.0 (0.8-1.2)</td>
</tr>
<tr>
<td>Helicobacter pylori</td>
<td>15 (1)</td>
<td>90 (0.6)</td>
<td>1.7 (1.0-3.0)</td>
<td>0.9 (0.5-1.6)</td>
</tr>
<tr>
<td>Other comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal failure</td>
<td>37 (3)</td>
<td>99 (1)</td>
<td>3.9 (2.6-5.7)</td>
<td>3.7 (2.4-5.6)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>175 (14)</td>
<td>1451 (10)</td>
<td>1.3 (1.1-1.5)</td>
<td>1.1 (0.9-1.3)</td>
</tr>
<tr>
<td>Methicillin-resistant</td>
<td>39 (3)</td>
<td>72 (0.2)</td>
<td>3.6 (1.1-11.4)</td>
<td>4.2 (2.7-6.4)</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer (solid tumor)</td>
<td>50 (4)</td>
<td>258 (2)</td>
<td>2.1 (1.5-3.0)</td>
<td>1.9 (1.4-2.7)</td>
</tr>
<tr>
<td>Leukemia or lymphoma</td>
<td>17 (1.4)</td>
<td>68 (0.6)</td>
<td>2.5 (1.5-4.3)</td>
<td>1.9 (1.1-3.5)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>2 (0.2)</td>
<td>17 (0.2)</td>
<td>1.1 (0.1-8.8)</td>
<td>0.9 (0.2-4.6)</td>
</tr>
<tr>
<td>Pernicious anemia</td>
<td>16 (1.3)</td>
<td>76 (0.6)</td>
<td>1.7 (0.7-4.5)</td>
<td>1.8 (1.0-3.3)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>211 (17)</td>
<td>1545 (12)</td>
<td>1.6 (1.3-2.1)</td>
<td>1.0 (0.9-1.2)</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval. *Adjusted for all variables in the table.

**Table 2**

**Table 3**

**Comment**

This large population-based study found that gastric acid-suppressive drug use was associated with an increased risk of community-acquired CDAD. We confirmed the effect of age, prior hospitalization, and antibiotic exposure as known important risk factors for the diagnosis of C difficile.1 We also found associations with less-recognized risk factors such as female sex,28 renal failure,18,29 and a history of inflammatory bowel disease.30,31

Four previous case-control studies have shown an association between proton pump inhibitor use and CDAD in hospitalized patients or institutionalized patients.17-20 The odds ratios for exposure to proton pump inhibitors are all remarkably similar in the 3 studies and to the RR of 2.9 found in this study (2.5,17 2.7,18 and 2.420). One report29 also observed the same odds ratio for H2RA exposure as this study. The current study examined the risk of community-acquired CDAD and found that both proton pump inhibitors and H2RAs are associated with an increased risk, although more so with proton pump inhibitors. This finding supports the hypothesis that the mechanism of increased risk of CDAD may be related to the degree of gastric acid suppression as H2RAs are associated with less suppression than proton pump inhibitors. Decreased gastric acidity is a known risk factor for other infectious diarrheal illnesses such as travelers’ diarrhea, salmonellosis, and cholera.16 Moreover, gastric acid-suppressive use has been associated with colonization of the normally sterile upper gastrointestinal tract11 and therefore alters upper gastrointestinal flora. Because the major mode of transmission of C difficile is believed to be via spores, which are acid resistant,31 the biological plausibility of an elevated risk of CDAD with gastric acid–suppressive agents has been questioned. It has been demonstrated in a hamster model that 75% of ingested spores transformed into the vegetative state within an hour of ingestion12 at which time they were located in the small intestine. It is possible that, in humans, if conversion of C difficile to the vegetative phase is occurring while the spores are still in the stomach, their survival may be facilitated by elevated gastric pH levels. Other mechanisms are also possible, such as gastrin-mediated direct effects on colonic mucosa,33 effects on immune function,12-14,34 or possibly effects on the organism’s toxin production. Two studies did not find an association with gastric acid–suppressive use.35,36 In the first,35 the choice of controls as C difficile–negative nosocomial diarrhea was not necessarily representative of the source population. Moreover, there were significant differences in antibiotic and other exposures that may have biased the results toward a null effect. In the more
recent study, there was no adjustment for type of hospital ward that may be very correlated with risk of exposure, multiple episodes of care were analyzed as independent events, as well as the absence of time-dependent analysis of covariates in the model may have resulted in the inability to demonstrate an association.

The striking exponential rise in the rate of community-acquired CDAD diagnosed since 1994 may be partly due to increased testing for C difficile, but the pattern is very similar to that reported in the hospital setting. However, most of the study period that was analyzed predated the introduction of mandatory reporting in Great Britain that began in 2004. In fact, CDAD is believed to be underdiagnosed in the community.

Antibiotic exposure has been considered to be almost a prerequisite for the diagnosis of CDAD; furthermore, the majority of studies on CDAD have been performed in hospitals. As the prevalence of antibiotic use is high in hospitals and testing is likely to be more common in patients with prior antibiotic exposure, this may have contributed to possible overestimation of the effect of antibiotic exposure. The crude RR of 5.5 found in this study is similar in magnitude to the pooled odds ratio of 5.9 reported in a meta-analysis of nosocomial CDAD. Therefore the magnitude of the association between antibiotics and CDAD in this study is consistent with results reported in hospital-based populations in which rates of antibiotic exposure in the control population are usually 50% or more. Nonetheless, rates of only 50% of prior antibiotic exposure in cases of CDAD have been reported in nonhospital settings in which antibiotic exposure is lower. In the current study, although antibiotic use was the most important medication-related risk factor for the disease, only 37% of the cases were prescribed an antibiotic in the 90-day period prior to the diagnosis, likely related to the lower prevalence of antibiotic use in a community setting. In light of these results and other reports, including a recent French study in which 47% of the cases were not hospital-associated and 26% did not have a history of antibiotic exposure, the belief that prior antibiotic exposure is practically a prerequisite for C difficile infection needs to be reevaluated.

The independent association between NSAID use and the risk of C difficile has not been described previously although case reports of a possible association have been reported in patients without prior antibiotic exposure. Animal models also suggest an association, as pretreatment with indomethacin markedly increased the incidence of antibiotic-induced cecitis in hamsters. We are unable to adjust for over-the-counter use of NSAIDs, which if it resulted in nondifferential exposure misclassification would be likely to underestimate the actual effect. More research to evaluate this association should be undertaken.

Our case definition included patients identified either based on positive toxin assay, clinical diagnosis, or both. From observations of different recording patterns by physicians for diagnoses in the GPRD, we included both test result based and clinical-based diagnoses to capture all episodes. This may have resulted in case misclassification, especially as details of diarrhea were not available. It is possible that patients identified based solely on positive toxin assay could represent individuals colonized only, but we believe this is unlikely because the majority of laboratories in Great Britain will only perform testing based on a specific request from the physician for community-based specimens. In view of the testing practices and the fact that C difficile is rare in the community, it is likely that patients were tested based on a suspicion of disease by their treating physician, and therefore would have been symptomatic. The similarity of the patients identified based on a clinical diagnosis vs identified by positive toxin assay (Table 2) as well as the stability of the estimates of gastric acid—suppressant effects in the sensitivity analysis supports such an assumption.

The study design has several strengths, including the population-based nature of the data source and the size of the study. Matching on calendar time and practice was useful to control for time-dependent, physician-related and geographical variations in the outcome and exposure. By excluding all patients hospitalized within the year preceding the diagnosis, we controlled for many confounding factors related to hospitalization such as clustering on susceptible hosts, and higher risk of exposure to the organism. This is also the largest case-control study performed to date, and examines endemic CDAD in the community, unlike hospital-based studies, many of

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nonhospitalized Incident Cases</th>
<th>Nonhospitalized Age- and Practice-Matched Controls</th>
<th>Crude Rate Ratio (95% CI)</th>
<th>Adjusted Rate Ratio (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td>456 (37)</td>
<td>1649 (13)</td>
<td>3.9 (3.4-4.4)</td>
<td>3.1 (2.7-3.6)</td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
<td>280 (23)</td>
<td>1038 (8)</td>
<td>3.3 (2.9-3.9)</td>
<td>2.9 (2.4-3.4)</td>
</tr>
<tr>
<td>H2-receptor antagonists</td>
<td>83 (8)</td>
<td>367 (4)</td>
<td>2.4 (1.9-3.1)</td>
<td>2.0 (1.6-2.7)</td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory drugs</td>
<td>467 (38)</td>
<td>3043 (24)</td>
<td>1.9 (1.8-2.4)</td>
<td>1.3 (1.2-1.5)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>245 (20)</td>
<td>2148 (17)</td>
<td>1.2 (1.0-1.4)</td>
<td>1.0 (0.9-1.2)</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.
*Adjusted for all variables in Table 2 plus use of medications listed in this table in the past 90 d.
which were single-center outbreak investigations. We cannot exclude with certainty the possibility that unknown risk factors may have biased or confounded the analysis. However, we controlled for a variety of risk factors both by matching and adjustment in multivariate analysis. We also performed an analysis restricted to patients without gastrointestinal diseases or current NSAID use, to control for potentially significant confounders of diarrhea and gastric acid suppressant use. We could not adjust for the effect of chemotherapy as this information was not available in the GPRD but did control for the diagnoses of cancer, including solid tumor and hematologic malignancies in the model.

While the increase in the number of CDAD cases may be due to increased reporting and testing, and while it is possible that patients with gastrointestinal disorders with diarrhea may be more likely to be tested for CDAD, gastric–acid–suppressive agents are more commonly prescribed for upper gastrointestinal symptoms and would not necessarily influence testing for CDAD, and should not have contributed to significant confounding of the association. The persistence of the effect of gastrointestinal suppressive exposure in this study in patients without a prior diagnosis of gastrointestinal disease also supports an independent drug effect. Antibiotics, proton pump inhibitors, and NSAIDs are all associated with an increased risk of diarrhea, which could have resulted in ascertainment bias, but if anything would preferentially favor an antibiotic effect as they are the most well-known risk factor for CDAD and have higher rates of diarrhea than the other medications studied.54-56

Clostridium difficile–associated disease is becoming an important public health issue. Significant increases in the number of cases of CDAD in Great Britain since the 1990s3-37 have been observed, including the exponential increase in the community observed in this study. Genetic mutations that may be associated with increased transmissibility and increased severity are also being reported.57-61 These factors combined with reports of outbreaks in the United States32 and the recent outbreak of in the Canadian province of Quebec7 justify considering CDAD as an important public health concern. While the overall rate of CDAD in the GPRD is much lower than in the hospital setting, it appears to be increasing significantly even in the face of both our data and another report to suggest that outpatient antibiotic prescribing in the GPRD is decreasing.44 Acid-suppressive agents are among the most frequently prescribed medications63 in the United Kingdom and North America, and it is in this context that the contribution of these agents by potentially increasing the pool of susceptible hosts to the increasing rates of CDAD needs to be considered and more completely characterized.

Author Contributions: Dr Dial had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Dial, Barkun, Suissa. Acquisition of data: Sussa. Analysis and interpretation of data: Dial, Delaney, Barkun, Suissa. Drafting of the manuscript: Dial, Barkun, Suissa. Critical revision of the manuscript for important intellectual content: Delaney, Barkun, Suissa. Statistical analysis: Dial, Delaney, Suissa. Obtained funding: Suissa. Administrative, technical, or material support: Dial, Delaney, Suissa. Study supervision: Suissa.

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