MAJOR ARTICLE

Use of Acid Suppression Medication is Associated With Risk for *C. difficile* Infection in Infants and Children: A Population-based Study

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Background. Acid suppression medication is associated with *Clostridium difficile* infection (CDI) in adults and is increasingly prescribed to children. This study evaluated the relationship between acid suppression medication and incident CDI in children.

Methods. This was a population-based, nested case-control study. Patients were eligible if they were aged 0–17 years with 3 or more visits or 1 year or more of follow-up in the dataset. Patients were excluded if they had comorbidities that associate with CDI and might also associate with acid suppression medication. Patients with codes for CDI were matched 1:5 with control patients by age, sex, medical practice, time of entry into the dataset, and follow-up time. The primary exposure was use of acid suppression medication with proton pump inhibitors (PPIs) or histamine-2 receptor antagonists (H2RAs) within 8–90 days.

Results. We identified 650 CDI cases and 3200 controls. The adjusted odds ratio (OR) for CDI and acid suppression medication was 7.66 (95% confidence interval [CI], 3.24–18.1). Acid suppression medication was associated with CDI in infants aged <1 year (OR, 5.24; 95% CI, 1.13–24.4) and children aged 1–17 years (OR, 9.33; 95% CI, 3.25–26.8). There was increased risk for CDI with PPIs compared with H2RAs and with recent compared with distant exposure.

Conclusions. Acid suppression medication associated with CDI in infants and children in the outpatient setting, with an effect based on medication timing. Increased risk for CDI should be factored into the decision to use acid suppression medication in children.

Keywords. proton pump inhibitors; histamine-2 receptor antagonists; *Clostridium difficile* infection; microbiome; pharmacoepidemiology.

Clostridium difficile infection (CDI) is associated with hospitalization, exposure to antibiotics, inflammatory bowel disease (IBD), and immune compromise. Rates of CDI in children are increasing, with a 10-fold rise from 1991 to 2009 [1]. CDI has recently emerged as a problem in relatively healthy, ambulatory children who lack traditional risk factors. In a large, active surveillance program, the majority of children with confirmed CDI had neither underlying medical comorbidities nor recent antibiotic exposure [2]. The factors underlying the shift in the epidemiology of pediatric CDI are unknown.

Proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs) are the most common acid suppression medication in children. The use of acid suppression medication in the pediatric population has risen dramatically during the past 10–15 years [3]. Acid suppression medication is effective treatment for gastroesophageal reflux disease (GERD) in adults [4], but is often used for long periods in otherwise healthy infants and children with nonspecific symptoms [5, 6].

In adults, acid suppression medication is a recognized risk factor for incident CDI [7–10]. However, there is little data regarding acid suppression and risk

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for CDI in pediatric outpatients and no data regarding acid suppression and risk for CDI in nonhospitalized infants aged <1 year. To evaluate the relationship between acid suppression and CDI in infants and children, we performed a case-control study nested within a large, outpatient dataset of children aged 0–17 years.

METHODS

Study Design

We conducted a population-based, case-control study nested within the Health Improvement Network (THIN) using data collected from 1995 to 2014. We selected 1995 because it was a date by which PPI use was widespread and also allowed up to 18 years of follow-up time. The institutional review board of Columbia University Medical Center approved the study.

Data Source

THIN is a database of electronic medical records maintained by general practitioners (GPs) throughout the United Kingdom. It includes records for more than 13 million individuals who are required to register with a GP to receive nonemergent care. For practitioners who use THIN, it represents the entire medical record. CDI has previously been studied within the General Practice Research Database (GPRD) [10], and recording of THIN data is similar to that for GPRD data [11]. THIN data have been extensively validated for health outcomes research [12] and use of acid suppression medication [13, 14]. THIN records contain demographic information, diagnoses, and complete prescribing information, which is captured electronically.

Study Population

Patients were eligible for inclusion in the study if they were aged 0–17 years on the index date, which was the date of CDI diagnosis for cases or the matched case's date of CDI for controls. To ensure adequate follow-up, we required ≥3 visits for patients aged <1 year or >1 year of follow-up time for patients aged ≥1 years. Follow-up time was calculated as the time from inclusion in the dataset to the index date. To address potential confounding by indication, we carefully excluded all patients with chronic conditions associated with long-term acid suppression that may also be associated with CDI. To identify these conditions, we referenced studies of children who receive long-term acid suppression [15] and studies of children with CDI [16]. The conditions that we identified included neurological disorders, which may be linked to risk for CDI through increased healthcare interactions [17], malignancy, chronic pulmonary conditions, and chronic gastrointestinal mucosal diseases (complete list in Supplementary Table 1). Using keyword searches and a hierarchical search strategy, we excluded children with codes for these conditions prior to the index date.

Case Selection

Cases of CDI were patients with their first diagnostic code for CDI within THIN. THIN diagnoses are linked to the hierarchical Read Code system. For clinicians who use THIN, the most effective way to communicate to other clinicians that a patient has a new diagnosis is to assign the patient an appropriate Read Code; the purpose of these codes is communication rather than billing [18].

Control Selection

The control group was selected using incidence density sampling, which yields odds ratios (ORs) interpretable as unbiased estimates of incidence rate ratios from a cohort study [19]. For each case, the control pool was the study population without a diagnosis of CDI at the time when the case had his or her first diagnosis. Up to 5 eligible control patients were randomly matched with each case by age (within 1 year), sex, THIN practice, entry into the dataset (within 1 year), and follow-up time (within 1 year).

Exposure

The primary exposure was defined a priori as use of acid suppression medication with H2RAs or PPIs within 90 days of the index date, with the prescription issued at least 8 days prior to the index date. The minimum of 8 days was set to ensure that exposure to acid suppression sufficiently preceded diagnosis of CDI, and the maximum of 90 days was set because studies of antibiotics and CDI show that the CDI risk associated with antibiotics wanes after 90 days [20]. To calculate the last day that acid suppression medication was used, we assumed that children would take medication as prescribed. For example, if a prescription issued on 1 January 2013 called for acid suppression to be given daily for 28 days, we assumed that the last use of acid suppression would be 29 January 2013. To assess for the possibility that acid suppression was prescribed for nonspecific abdominal symptoms that represented early but undiagnosed CDI (ie, protopathic bias), we performed a sensitivity analysis with patients classified as exposed to acid suppression only if the first prescription for acid suppression was issued more than 90 days before the index date *and* the last use was within 8–90 days of the index date.

Covariates

As potential confounders, we extracted information related to age, sex, body mass index (BMI; kg/m^2), healthcare exposures, and use of other medications that have been associated with CDI. To calculate BMI, we used the last simultaneously recorded height and weight measurements within 1 year prior to the index date. We then calculated a sex-specific BMI Z-score (standard deviation score) relative to age based on UK growth charts [21, 22]. We classified patients as overweight if they were ≥85th percentile for age and as underweight if they were ≤5th percentile for age.

BMI for the remaining patients was classified as normal or missing if no valid data were available. Children were classified as exposed to other medications only if these exposures occurred within 90 days of the index date; medications examined were oral antibiotics, oral glucocorticoids, and other immunosuppressants. Healthcare exposures were also classified dichotomously based on whether they occurred within 90 days [23].

Statistical Analysis

Categorical variables were summarized by frequencies and rates and compared using χ^2 tests. Continuous variables were summarized by computing medians and interquartile ranges and compared using *t* tests (for normally distributed data) or Wilcoxon rank-sum tests. We used conditional logistic regression to estimate the multivariable adjusted ORs and associated 95% confidence intervals (CIs) for CDI risk associated with use of acid suppression. For the multivariable model, we selected variables that exerted a ≥10% change on the beta-coefficient representing acid suppression in the acid suppression–CDI relationship. The final model included the following variables: use of antibiotics, use of oral glucocorticoids, and prior hospitalization. Because the epidemiology of CDI varies by age [1, 2], we performed an analysis with patients stratified into infants aged <1 year and children aged 1–17 years on the index date. All data were analyzed using Stata 12.1 (StataCorp, College Station, Texas) at the alpha 0.05 level of significance.

RESULTS

We identified 650 case patients with CDI. From an eligible pool of more than 3 million potential controls, we matched 3200 controls. A total of 14 children were exposed to PPIs with or without H2RAs within 8–90 days of the index date; an additional 11 children were exposed to H2RAs only. The median age of the study population was 5 years, and 10% of patients were <1 year old (Table 1). Comparing cases with controls, there were no significant differences in the matching variables of age, follow-up time, and sex. Of the total population, 0.7% was exposed to acid suppression medication within 8–90 days of the index date and 3.1% of patients were ever exposed. The median duration from the first day that acid suppression medication was prescribed to the last day of use was 2.0 years (interquartile range, 0.9–3.5). The most common indications for acid suppression medication were abdominal pain and vomiting/regurgitation (Supplementary Table 2).

The crude OR for CDI and acid suppression medication exposure was 10.5 (95% CI, 4.55–24.4). In multivariable analysis, the adjusted OR for CDI and acid suppression was 7.66 (95% CI, 3.24–18.1). In the final multivariable model, variables with independent associations with CDI were antibiotics, glucocorticoids, and hospitalization (Table 2). Stratifying the study population into infants aged <1 year and children aged 1–17 years, there was no evidence of an age-based interaction on the acid suppression–CDI relationship ($P = .49$).

There was significantly increased risk for CDI with more potent PPIs compared with less potent H2RAs (Table 3; *P* for trend <.01). There was also significantly increased risk for CDI when use of acid suppression medication was recent compared with distant (Table 4; *P* for trend <.01). Both of these trends persisted when infants were excluded from the analyses (Supplementary Tables 3 and 4).

Table 1. Baseline Data From Children With and Without *Clostridium difficile* Infection

Characteristic	Cases (n = 650)	Controls (n = 3200)	*P* Value
Age, y (median, IQR)	5.1 (2.4–11.7)	5.2 (2.5–11.5)	.89
Infants <1 y	68 (11%)	334 (10%)	.98
Children 1–17 y	582 (90%)	2866 (90%)	
Follow-up time, y (median, IQR)	4.0 (2.1–7.7)	3.8 (2.0–7.8)	.90
Sex			.96
Male	370 (57%)	1818 (57%)	
Female	280 (43%)	1382 (43%)	
Body mass index			<.01
Underweight	18 (2.8%)	116 (3.6%)	
Normal	141 (22%)	683 (21%)	
Overweight	77 (12%)	232 (7.3%)	
Not recorded	414 (64%)	2169 (68%)	
Acid suppression medication			<.01
Exposed within 8–90 d	17 (2.6%)	8 (0.3%)	
Not exposed within 8–90 d	633 (97.4%)	3192 (99.7%)	
Use of other medication			
Antibiotics	151 (23%)	387 (12%)	<.01
Glucocorticoids	11 (1.7%)	20 (0.6%)	.01
Other immunosuppressants	0	0	. . .
Healthcare exposures			
Hospitalization	37 (5.7%)	71 (2.2%)	<.01
Emergency room visit without hospitalization	45 (6.9%)	96 (3.0%)	<.01

Abbreviation: IQR, interquartile range.

Table 2. Final Multivariable Model for Exposures and Risk for *Clostridium difficile* Infection

Exposure Variable	Cases (n = 650)	Controls (n = 3200)	Odds Ratio (95% Confidence Interval)[a]
Acid suppression	17 (2.6%)	8 (0.3%)	7.66 (3.24–18.1)
Antibiotics	151 (23%)	387 (12%)	2.18 (1.74–2.73)
Glucocorticoids	11 (1.7%)	20 (0.6%)	1.97 (.88–4.40)
Hospitalization	37 (5.7%)	71 (2.2%)	2.51 (1.59–3.97)

[a] Conditioned on age, sex, follow-up time, and practice.

Table 3. Relationship Between Exposure to Acid Suppression Medication Within 8–90 Days and Risk for *Clostridium difficile* infection, by Type of Acid Suppression

Type of Acid Suppression	Cases (n = 650)	Controls (n = 3200)	Odds Ratio (95% Confidence Interval)[a]
Neither (n = 3825)	633	3192	Reference
H2RA only (n = 11)	5	6	2.64 (.93–10.4)
Proton pump inhibitor with or without H2RA (n = 14)	12	2	21.5 (4.71–98.6)

Abbreviation: H2RA, histamine-2 receptor antagonist.

[a] Conditioned on age, sex, follow-up time, and practice; adjusted for use of antibiotics or steroids and hospitalization.

We performed several additional restriction analyses. When we excluded all those hospitalized within 90 days of the index date (n = 3742 remaining), the acid suppression–CDI relationship was unchanged (OR, 7.49; 95% CI, 2.94–19.1). This was also true when we excluded another 141 children who had emergency room visits within 90 days of the index date but were not hospitalized (OR, 9.29; 95% CI, 3.16–27.3) and when we restricted the analysis to 3321 children who had not been exposed to antibiotics within 90 days (OR, 11.1; 95% CI, 3.50–35.5). To assess for protopathic bias, we reclassified patients as exposed to acid suppression medication only if the first prescription was more than 90 days before the index date and the last use was within 8–90 days of the index date. The association was attenuated, but acid suppression medication remained significantly associated with risk for CDI (OR, 4.17; 95% CI, 1.60–10.8).

We explored potential misclassification of CDI in 2 ways. First, we examined CDI cases for documentation of diarrhea within the 90 days preceding CDI diagnosis. In 392 cases with diarrhea and their corresponding controls, the independent association between exposure to acid suppression medication and CDI persisted (OR, 5.78; 95% CI, 1.35–24.7). Second, we examined a scenario of differential misclassification of CDI where we assumed that 15% of children who were exposed to acid suppression were incorrectly coded with CDI but that unexposed children were always coded correctly with CDI. Because the relationship between acid suppression and CDI remained strong (crude OR, 6.39; 95% CI, 2.89–14.1), we then varied the assumed rate of differential misclassification until the lower bound of the 95% CI for the acid suppression–CDI relationship crossed 1.0. The relationship between acid suppression and CDI remained statistically significant until the rate of differential misclassification exceeded 53%.

Table 4. Relationship Between Exposure to Acid Suppression Medication and Risk for *Clostridium difficile* Infection, by Time Elapsed since Last Use of Acid Suppression Medication

Last Use of Acid Suppression Medication	Cases (n = 650)	Controls (n = 3200)	Odds Ratio (95% Confidence Interval)[a]
Never (n = 3738)	608	3130	Reference
More than 1 y ago (n = 57)	14	43	1.56 (.83–2.93)
Within 91 d to 1 y (n = 30)	11	19	2.75 (1.26–5.97)
Within 8 to 90 d (n = 25)	17	8	8.02 (3.38–19.0)

[a] Conditioned on age, sex, follow-up time, and practice; adjusted for use of antibiotics or steroids and hospitalization.

DISCUSSION

Use of acid suppression medication within 8–90 days was associated with significantly increased risk for incident *C. difficile* infection in children. The relationship between acid suppression and CDI showed a dose–response effect based on the type of acid suppression, with a stronger association for PPIs compared with H2RAs. The relationship was also affected by the timing of the last use of acid suppression, with increased risk for CDI seen when acid suppression was used during recent compared with distant periods. There was significantly increased risk for CDI in both infants aged <1 year and in children aged 1–17 years.

Studies in adults show that patients who take acid suppression medication have more comorbidities than those who do not [24]. For this reason, it has been questioned whether the observed relationship between acid suppression and CDI in adults is causal or due to residual confounding [25]. We addressed this by carefully excluding from the study all patients who had comorbidities that might be associated with both use of acid suppressive therapy and risk for CDI [15]. Also, we performed a sensitivity analysis that excluded all patients who had been hospitalized within 90 days. In addition to hospitalization and these comorbid conditions, the main reason for acid suppressive therapy in this population would be GERD, which is not likely to be an important confounder because it does not have a known direct effect on risk for CDI [6]. Although confounding is possible in all observational studies, it is unlikely that residual confounding alone explains our study results.

Acid-related disorders can present with nonspecific symptoms such as abdominal pain. These symptoms may prompt treatment with acid suppression medication and have the potential to overlap with the symptoms of CDI, so it is possible that acid suppression medication could be given for early but undiagnosed CDI. We addressed this potential problem (known as protopathic bias) through a sensitivity analysis in which we reclassified exposure to acid suppression medication as occurring only if the *last* use was within 8–90 days of the index date and the *first* prescription was at least 90 days before the index date. Acid suppression medication remained significantly associated with increased risk for

CDI, indicating that protopathic bias is unlikely to explain our study results.

Previous pediatric studies regarding acid suppression and risk for CDI have focused on hospitalized children. Among hospitalized children, acid suppression with PPIs and H2RAs has been associated with significantly increased risk for CDI [26, 27]. However, studies have shown that 85%–90% of hospitalized children with CDI have serious comorbidities compared with only 40% of pediatric outpatients with CDI [28]. To address whether acid suppression medication is a risk factor for children who lack these comorbidities, we used an outpatient dataset and excluded patients with serious comorbidities. Acid suppression medication was associated with increased risk for CDI in this relatively healthy outpatient population, consistent with studies of hospitalized children.

There is controversy regarding the significance of CDI in infants. Because up to half of all infants aged <1 year are constantly colonized with *C. difficile* [29], the presence or absence of *C. difficile* in infants' stools does not predict diarrhea [30]. However, recent data suggest that *C. difficile* may nonetheless be an important cause of diarrhea in infants as well as older children. The ongoing active surveillance program for *C. difficile* conducted by the Centers for Disease Control and Prevention excludes infants aged <1 year, but the incidence of CDI in children aged 1–2 years was higher than the incidence in children of any other age [2]. A population-based study of children aged 0–18 years found more cases of CDI in infants than in children in any other age range; in this study, CDI cases were confirmed clinically, by a positive stool test for *C. difficile* toxin, and by stool testing to exclude alternative etiologies for diarrhea [1]. PPIs have been associated with increased risk for CDI in hospitalized neonates [31]. We found that acid suppression medication was associated with increased risk for CDI in infants, and the magnitude of risk seen in infants was similar to the magnitude of risk seen in older children. This is concerning because use of PPIs has expanded rapidly in infants despite a paucity of evidence that acid suppression is beneficial in this population. However, given the uncertainty surrounding CDI in infants, our results should be interpreted with caution for children aged <1 year.

Acid suppression medication may increase risk for CDI by causing alterations in the gastrointestinal microbiome. Children who take H2RAs or PPIs have altered gastric flora compared with children who do not take acid suppression medication, with increased gastric abundance of *Streptococcus* and other gram-positive bacteria [32]. *Streptococcus* is easily disrupted by antibiotics and has been linked to risk for CDI, thus providing potential connections between acid suppression, specific microbial changes, and risk for CDI [33, 34]. Recent studies in adults using bacterial 16S rRNA gene sequencing showed that acid suppression medication may alter the colonic microbiome [35, 36]. The pediatric microbiome differs substantially from the adult microbiome, with relative instability through the first 4 years of life [37]. The impressive magnitude of the association between acid suppression medication and risk for CDI seen in our study suggests that acid suppression may have a greater potential impact on the developing microbiome of children compared with the more stable microbiome of adults. A previous study in hospitalized children also showed that the risk for CDI associated with acid suppression in the pediatric population may be greater than the risk observed in adults [26].

Our study has several strengths. We used a large, population-based dataset that has been extensively validated [11]. Also, we used multiple strategies to address confounding, including restriction, adjustment, and sensitivity analyses, and we found powerful supporting evidence of a dose–response effect. Our study has some limitations. CDI was assessed retrospectively based on diagnostic codes. However, similar codes have been validated within our data and similar datasets [10, 12, 38]. THIN medication records do not capture over-the-counter use of acid suppression medication, but such use appears to be minimal in the United Kingdom, where children receive prescription medications for free [39, 40]. Finally, we could not assess medication nonadherence, but this would likely bias results toward the null.

Use of acid suppression medication was associated with increased risk for incident CDI in children in the outpatient setting. In stratified analyses, the association was present for both infants aged <1 year and children aged 1–17 years. Use of acid suppression medication continues to expand, and future studies should explore the mechanisms that may link acid suppression and CDI in children. Knowledge of these mechanisms would improve understanding of the pathogenesis of CDI as well as other conditions that affect the health of children that may be mediated by similar mechanisms. Increased risk for CDI should factor into the decision of whether to use acid suppression medication in children.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Contributors. D. E. F. and J. A. A. conceived the project, designed the study, and obtained the data. Y.-X. Y. was involved in study design. D. E. F., E. S. L.-S., J. R. L., J. A. A., and Y.-X. Y. performed the literature search. D. E. F. drafted the first version of the manuscript. D. E. F., Z. J., Y.-X. Y., and J. A. A. performed the statistical analyses. All authors participated in interpretation of the analyses and critical revisions of the final manuscript.

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