Association of *Clostridium difficile* Infections with Acid Suppression Medications in Children

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Objective Multiple studies have confirmed associations between acid suppression medication and *Clostridium difficile* infections (CDIs) in adults. Therefore, we sought to evaluate an association between acid suppression medications and CDI in children.

Study design A retrospective self-controlled case series was performed utilizing billing records from the TRICARE Management Activity military health system database. Children ages 2-18 years from October 1, 2001 to July 31, 2013, who had an outpatient or inpatient record of CDI diagnosis were included. The relative incidences (RIs) of CDI or recurrent CDI were calculated comparing time periods prescribed and not prescribed proton pump inhibitors (PPIs) or histamine-2 receptor antagonists (H2RAs).

Results There were 2531 cases of CDI among 2437 patients, and 1190 (48.8%) were prescribed acid suppression medications. CDI were more likely to occur during periods when patients were prescribed a PPI (RI 2.36; 95% CI 2.22-2.52), H2RA (RI 1.95; 95% CI 1.63-2.34), or during periods while prescribed both simultaneously (RI 2.40; 95% CI 1.90-3.04). There were 265 (10.4%) cases that were classified as recurrent among 217 (8.9%) patients. Recurrent CDI also was found to be more likely during prescription periods of PPI (RI 1.74; 95% CI 1.51-2.00) and H2RA (RI 2.63; 95% CI 1.89-3.66).

Conclusions Acid suppression medications are associated with an increased risk of CDI and recurrent CDI. Judicious use of acid suppression medication should be considered, especially among those at highest risk for CDI. *(J Pediatr 2014;165:979-84)*.

Clostridium difficile is a gram-positive, spore forming, anaerobic bacillus that can colonize the gastrointestinal lumen and lead to *Clostridium difficile* infection (CDI). CDI can vary in its presentation including diarrhea, pseudomembranous colitis, and toxic megacolon. CDI is associated with an increased risk for both colectomy and death in children.[1] There have been several epidemiologic changes in CDI over the last decades. These include increasing rates of CDI in hospitalized children, increasing rates of community-acquired CDI, and emergence of hypervirulent strains.[1-5] These epidemiologic changes of CDI may be due to other factors including changing host factors such as exposure to medications.

Gastric acid suppression medications are used for a variety of conditions in children including gastroesophageal reflux disease, erosive esophagitis, gastric and duodenal ulcers, *Helicobacter pylori* gastritis, and eosinophilic esophagitis.[6-8] Indications for acid suppression without evidence of esophagogastrointestinal inflammation are expanding. These include optimization of pancreolipase therapy, stress ulcer prophylaxis, treatment of respiratory symptoms, and treatment of sleep disorders.[9-12] Many clinicians feel that acid suppression medications also are prescribed inappropriately as in cases of overmedicalized physiologic infant reflux or functional gastrointestinal disorders.[13]

There are 3 main classes of acid suppression medications: neutralizing antacids, histamine-2 receptor antagonists (H2RAs), and proton pump inhibitors (PPIs). There has been a rapid increase over the last decade in prescriptions for both PPIs and H2RAs.[14] For example, prescriptions of PPI in children increased 3-fold from 2002-2009, with the majority of these prescriptions in children aged 1-12 years old.[15] Although acid suppression medications generally are perceived to be relatively benign, adverse effects of acid suppression include an increased risk for respiratory and enteric infections such as CDI.[16]

There is ample evidence of an association of both PPIs and H2RAs with CDI in adults. Three meta-analyses have been published, with Janarthanan reporting a collective risk ratio of PPI for CDI of 1.69 (1.40-1.97), Deshpande reporting

CDI	*Clostridium difficile* infection
H2RA	Histamine-2 receptor antagonist
ICD-9-CM	*International Classification of Diseases, Ninth Revision, Clinical Modification*
MHS	Military health system
PPI	Proton pump inhibitor
RI	Relative incidence
SCCS	Self-controlled case series

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an OR of CDI with PPI therapy of 2.15 (1.81-2.55), and Tleyjah reporting a pooled effect estimate for H2RA of 1.44 (1.22-1.70).[17-19] In addition, the Food and Drug Administration released a drug safety communication warning that PPIs may be associated with an increased risk of *Clostridium difficile*-associated diarrhea.[20] The current evidence for the risk of acid suppression and CDI in children has been reviewed and is less clear because of insufficient studies in children.[21] Utilizing a large health care database, we sought to confirm the risk of acid suppression for the development of CDI in children.

Methods

A self-controlled case series (SCCS) method was chosen to study the association of a diagnosis of CDI with the prescription of PPI or H2RA. SCCS can be used to study associations between an acute event and an exposure without requiring a control group.[22] This method investigates the incidence of events within well-defined risk periods relative to the incidence of events during control periods. The control periods can include periods before or after the cases experienced exposure. The major benefit of the SCCS method is that all time independent known or unknown confounders are controlled for implicitly. Applied to this study, the incidence of CDI during periods when subjects were prescribed PPI or H2RA was compared with periods when acid suppression medications were not prescribed.

Data were obtained from the TRICARE Management Activity military health system (MHS) database covering the period of October 1, 2002 to July 31, 2013. The TRICARE Management Activity oversees health care delivery for US uniformed services members and their families in the US and abroad. The MHS database includes all outpatient and inpatient billing records, and outpatient pharmacy utilization, for all eligible military dependents in both military and civilian facilities. TRICARE provides medication coverage for either no cost/copay at military pharmacies or for very low copays at civilian pharmacies; this includes coverage for both PPIs and H2RAs. Data were selected for all children ages 2-18 years who were dependent beneficiaries of US uniformed service members. Children less than 2 years old were excluded because of the uncertainty about the true morbidity of CDI in young children and infants.[23]

Variable Definition

Case selection was performed by searching the MHS database for the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnostic code 008.45. This is the sole diagnostic code dedicated to CDI. All outpatient and inpatient billing records for both military and civilian medical facilities were investigated over the time period. Visits or hospitalization with a code for CDI must have been greater than 60 days apart to be counted as unique. The typical treatment course for CDI is 10 days, and repeat testing for recurrent CDI is not recommended prior to 4 weeks after initial testing.[24] We selected this 60-day time period between events as a conservative measure to distinguish independent cases of CDI.

Outpatient pharmacy records for the identified cases were queried utilizing American Hospital Formulary Service therapeutic class codes for PPI and H2RA. Data for the prescriptions included the number of days supplied. Cases were considered within the exposed medication time frame if they occurred during periods after a prescription was billed by a pharmacy (through the number of days supplied). For cases with multiple prescriptions, the exposure time periods were combined if the next prescription was filled within 14 days of the anticipated exhausted supply of the previous prescription, with the assumption of continued use. This grace period was to account for partial noncompliance and accumulation of medication. The exposure time periods were divided into 3 groups: PPI, H2RA, or both. Dose or patient weight information was not available. Inpatient pharmacy records were not available. If an inpatient CDI case occurred during an exposure period based on outpatient pharmacy records, it was considered to be within the at-risk exposure period. In addition, if an inpatient CDI case occurred during a nonexposure period based on outpatient pharmacy records, the case was assumed to not be exposed to antacid medications. Any subject within the greater SCCS who had 2 or more cases of CDI 60 days or greater apart was considered to have recurrent CDI. Only the CDI cases after the subject's first case were utilized for analysis for recurrent CDI.

Statistical Analyses

Univariate analyses were conducted to investigate normality of the data. We summarized normally distributed data with mean and SD and skewed data with median and IQR. The χ^2 test was used to test differences of categorical variables. The Kruskal-Wallis Test was used to compare age across groups and the Mantel-Haenszel χ^2 test was used to compare sex distribution across risk groups. Relative incidence (RI) was calculated utilizing a conditional Poisson regression. The dependent variable was a visit or hospitalization with a diagnosis of CDI and the independent variables were PPI exposure, H2RA exposure, simultaneous PPI and H2RA exposure, age, sex, and calendar year. Calendar year was included in the model to both evaluate and control for the linear trend of CDI cases over time. For purposes of calculating and presenting trends, only rates with whole year data were used (2003-2012), although all years were included in the calculation of adjusted RIs. Two-way interactions between the dependent variables were evaluated and retained in the model if significant. The assumptions of the SCCS were validated. These included the following: CDI does not affect the observation periods, CDI was unlikely to alter the probability of a prescription of PPI, and that cases of CDI were independent. We required recurrent events to be greater than 60 days apart. To validate this assumption of independence, a sensitivity analysis was performed with successive increasing interval requirements between cases of CDI. Statistical analyses were performed using SAS v 9.3 (SAS

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