Association Between Proton Pump Inhibitor Therapy and *Clostridium difficile* Infection in a Meta-Analysis

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BACKGROUND & AIMS: In the past decade, there has been a growing epidemic of *Clostridium difficile* infection (CDI). During this time, use of proton pump inhibitors (PPIs) has increased exponentially. We evaluated the association between PPI therapy and the risk of CDI by performing a meta-analysis. **METHODS:** We searched MEDLINE and 4 other databases for subject headings and text words related to CDI and PPI in articles published from 1990 to 2010. All observational studies that investigated the risk of CDI associated with PPI therapy and used CDI as an end point were considered eligible. Two investigators screened articles independently for inclusion criteria, data extraction, and quality assessment; disagreements were resolved based on consensus with a third investigator. Data were combined by means of a random-effects model and odds ratios were calculated. Subgroup and sensitivity analyses were performed based on study design and antibiotic use. **RESULTS:** Thirty studies (25 case-control and 5 cohort) reported in 29 articles met the inclusion criteria (n = 202,965). PPI therapy increased the risk for CDI (odds ratio, 2.15, 95% confidence interval, 1.81–2.55), but there was significant heterogeneity in results among studies ($P < .00001$). This association remained after subgroup and sensitivity analyses, although significant heterogeneity persisted among studies. **CONCLUSIONS: PPI therapy is associated with a 2-fold increase in risk for CDI. Because of the observational nature of the analyzed studies, we were not able to study the causes of this association. Further studies are needed to determine the mechanisms by which PPI therapy might increase risk for CDI.**

Keywords: Gastric Acid Suppression; Infectious Diarrhea; Systematic Analysis; Bacteria.

Clostridium difficile infection (CDI) is the leading cause of nosocomial infectious diarrhea in the developed world.[1] In the past decade, health care facilities across North America and Western Europe have reported a dramatic increase in the incidence of CDI. Based on current estimates, there are between 450,000 and 750,000 cases of CDI annually in the United States alone,[2] with an estimated 3 billion dollars spent on related health care costs.[3]

A major factor driving the CDI epidemic is the emergence of a hypervirulent strain of *C difficile* known most commonly by the pulsed-field gel electrophoresis pattern of its DNA as the North American pulse-field type 1 strain.[4] Infection with the North American pulse-field type 1 strain typically predisposes to more severe disease and higher mortality rates when compared with other *C difficile* strains.[5]

Historically, broad-spectrum antimicrobial therapy has been the most consistently identified causative factor involved in CDI pathogenesis including the use of fluoroquinolones.[6] More recently, a possible association between CDI and the use of proton pump inhibitors (PPIs) has been suggested.

Although numerous studies have investigated a possible association between gastric acid–suppressive therapy and CDI, their results have been quite conflicting.[7] Given the magnitude of the prevailing CDI epidemic and the widespread use of PPI therapy, this is a question of extreme clinical significance.

In this meta-analysis, our aim was to summarize the association between PPI therapy and the risk of CDI in the published literature.

Methods

All procedures used in this meta-analysis were consistent with Preferred Reporting Items for Systematic reviews and Meta-analyses guidelines.[8]

Data Sources and Searches

We performed a systematic search of the literature using the following predetermined inclusion criteria: (1) observational studies, including cross-sectional, case-control, and cohort studies that evaluated the risk of CDI associated with PPI therapy; (2) a study population that comprised adult patients (>18 y) who received PPI therapy; (3) CDI was a study end point; and (4) date of publication between 1990 and 2010 in any language. We used 1990 as a cut-off year because the first PPI received Food and Drug Administration approval in 1989. There was no restriction on study site (in-patient and/or outpatient). We excluded studies if: (1) there was no control group (case-control studies) or an unexposed group (cohort studies) of patients; (2) PPI use data were not available for either of the study groups; or (3) data were presented based on CDI episodes and not the number of actual patients. We identified no prospective studies evaluating PPI therapy and the risk of CDI.

Abbreviations used in this paper: CDI, *Clostridium difficile* infection; CI, confidence interval; H2RA, histamine 2 receptor antagonist; NNH, number needed to harm; OR, odds ratio; PPI, proton pump inhibitor.

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This search was performed in October 2010. The following databases were searched: MEDLINE (PubMed) (1990–2010), Web of Science (1990–2010), Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1990–2010), Cochrane Library, and Scopus (1990–2010). Search terms included "*Clostridium difficile*, *C. diff*, *C. difficile*, CDAD, CDI, proton pump inhibitors, proton pumps, PPI." Reference lists from included studies and several previously published reviews on *C difficile* and PPI therapy also were searched. The electronic search strategy of PubMed is available in Appendix 1.

Study Selection

A list of retrieved articles was reviewed by 2 investigators independently (V.P. and A.D.) using the earlier-detailed eligibility criteria. Any disagreement about a particular study was decided in consensus with a third investigator (C.P.). Where more than one article for a single study was found to have been published by the same investigators, we used the most relevant publication and supplemented it, if necessary, with data from the other publications.

Data Extraction and Quality Assessment

Two investigators (A.D. and V.P.) independently extracted data from the full text of the included studies. Any disagreements or discrepancies were resolved in consensus with a third investigator (C.P.). Study authors were contacted if the relevant information was not available for a particular study. The methodologic quality for each article was assessed by 2 investigators independently (A.D. and V.P.). Case-control and cohort studies were assessed. Each study was assessed for study quality based on the criteria proposed by the Meta-analysis of Observational Studies in Epidemiology collaboration.[9] The study quality criteria are available in Appendix 2.

Data Synthesis and Analysis

The primary outcome of interest under evaluation was the association between PPI therapy and the risk of developing CDI. Although there were several potential reasons for this heterogeneity, we considered 2 a priori hypotheses to explain potential variability between studies and accordingly performed subgroup analyses: (1) study design (ie, case-control vs cohort studies); and (2) percentage of antibiotic use: for each study, antibiotic use for cases and controls in case-control studies and exposed and unexposed groups in cohort studies were calculated. Next, a median for percentage of antibiotic use was calculated for all studies (ie, case-control and cohort studies). Based on this number, studies were divided into 3 groups. These were as follows: (1) studies with percentage of antibiotic use greater than the median; (2) studies with percentage of antibiotic use less than or equal to the median; and (3) studies in which antibiotic use data were unavailable.

Three a priori sensitivity analyses were planned for the primary outcome: (1) case-control studies by percentage of antibiotic use and exclusion of studies in which there was no information about antibiotic use; (2) case-control studies by percentage of antibiotic use as defined in the CDI group (ie, cases) only; and (3) exclusion of studies that evaluated recurrent CDI.

We computed pooled odds ratios (ORs) and 95% confidence intervals (CIs) for our primary and all subgroup analyses. Meta-analyses were not stratified by type of PPI because all types of PPI have similar efficacy and can be used interchangeably.[10]

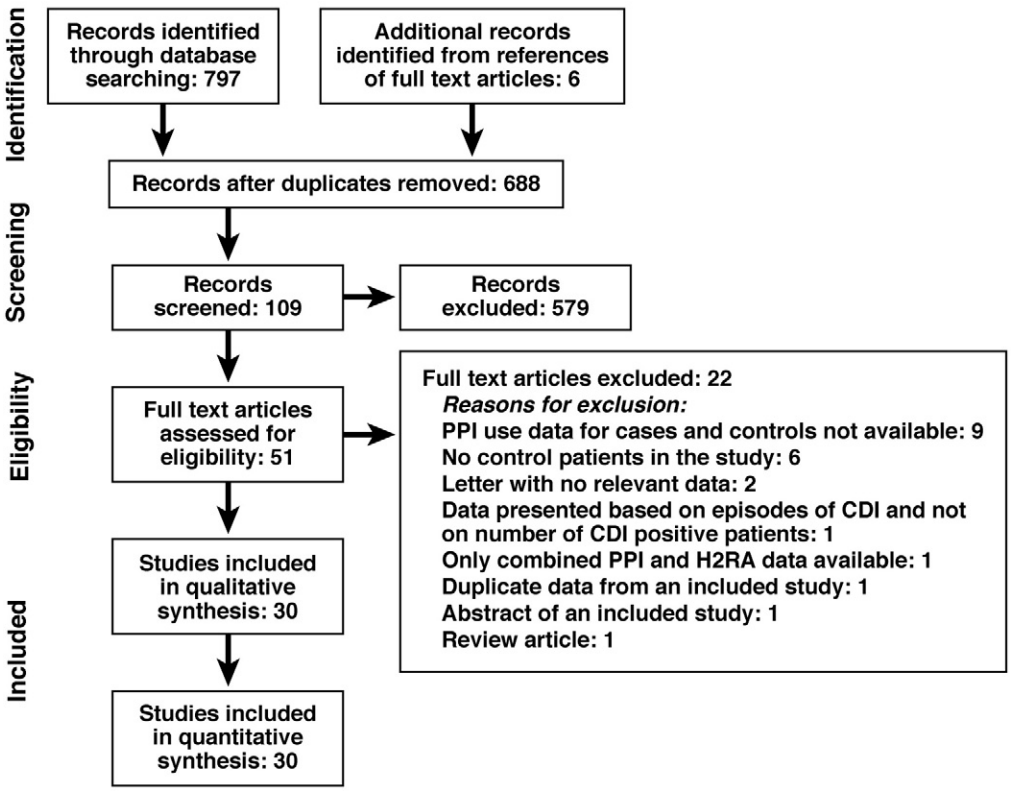

Figure 1. Study selection process.