

Comparison of the Hospital-Acquired *Clostridium difficile* Infection Risk of Using Proton Pump Inhibitors versus Histamine-2 Receptor Antagonists for Prophylaxis and Treatment of Stress Ulcers: A Systematic Review and Meta-Analysis

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Background/Aims: Although proton pump inhibitors (PPIs) have been widely used for the prevention and treatment of stress gastric ulcers in hospital settings, there are concerns that PPIs increase the risk of *Clostridium difficile* infection (CDI). However, little is known about the risk of CDI following PPI and histamine-2 receptor antagonist (H2RA) use. We evaluated the comparative hospital-acquired CDI occurrence risk associated with the concurrent use of PPIs versus H2RAs. **Methods:** A systematic search of PubMed, MEDLINE/Ovid, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science, and Google Scholar through August 19, 2016, identified 12 studies that reported the hospital-acquired CDI occurrence following H2RA and PPI use for the prevention and treatment of stress gastric ulcers. Random-effects pooled odds ratios and 95% confidence intervals were estimated. Heterogeneity was measured using I^2 , and a meta-regression analysis was conducted. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was used to assess the overall quality of the evidence. **Results:** A total of 74,132 patients from 12 observational studies were analyzed. Compared to H2RAs, PPIs increased the risk of CDI by 38.6% (pooled odds ratio, 1.386; 95% confidence interval, 1.152 to 1.668; $p=0.001$; $I^2=42.81\%$). Subgroup analyses of the purpose of study medication use, study site, and study design confirmed the consistency of a greater CDI risk with PPIs than

with H2RAs. The overall quality of evidence was rated as low.

Conclusions: The use of PPIs for both the prevention and treatment of stress ulcers was associated with a 38.6% increased risk of hospital-acquired CDI occurrence compared to H2RA use. (**Gut Liver 2017;11:781-788**)

Key Words: *Clostridium*; Stomach ulcer; Histamine antagonists; Meta-analysis; Proton pump inhibitors

INTRODUCTION

Clostridium difficile is a spore forming, toxin producing, gram positive anaerobic bacterium. It was first identified as the cause of antibiotic associated diarrhea in 1978.¹ Annually, 453,000 new cases occur in the United States with one in four cases occurring in the hospital and a mortality rate of approximately 6%.² Since *C. difficile* infection (CDI) is highly transmissible via the fecal-oral route, strict contact isolation is required per hospital infection control.^{3,4} Beyond well-known risk factors, proton pump inhibitor (PPI) use for gastric acid suppression treatment has been an emerging risk factor of CDI.⁵⁻¹⁶ Studies have shown that both PPIs and histamine-2 receptor antagonists (H2RAs) are associated with an increased risk of CDI.^{9,11,12} Bacterial overgrowth resulting from gastric acid suppression treatment has been suggested as an explanation for the vulnerable gut environment that increases CDI occurrence.¹⁷ In addition, since 2012, the Food and Drug Administration (FDA) has expressed public concerns of CDI occurrence by gastric acid suppression treatment.¹⁸ A series of meta-analysis studies sup-

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Received on November 23, 2016. Revised on December 21, 2016. Accepted on December 21, 2016. Published online May 17, 2017

pISSN 1976-2283 eISSN 2005-1212 <https://doi.org/10.5009/gnl16568>

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ported this public concern of the association between gastric acid suppression and CDI occurrence.¹⁹⁻²² Gastric acid suppression can be achieved by two different classes of medications PPI and H2RA. There is an urgent need of comparing CDI risk from PPI and H2RA. In 2012, Kwok *et al.*²⁰ reported subgroup analysis that H2RAs were less likely to cause CDI compared to PPIs. However, this meta-analysis encountered a substantial heterogeneity (I^2 , 60% to 85%).²⁰ Then after, MacLaren *et al.*²³ reported greater risk of gastrointestinal (GI) hemorrhage, pneumonia and CDI with PPI compared to H2RA use in an intensive care unit setting. This study limited study participants to critically ill patients on mechanical ventilation.²³ As such, there is little insight regarding the relation between PPI or H2RA and hospital-acquired CDI. Current meta-analysis is an important addition to medical literature which will guide the health care professional on gastric acid suppression choices in the hospital setting.

MATERIALS AND METHODS

1. Search strategy

We performed a literature search using the keywords “*Clostridium*,” “Proton pump inhibitor,” “Histamine antagonist,” “Gastric ulcer,” or “Stress ulcer” in various combinations to identify original studies published in English from PubMed,

MEDLINE/Ovid, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science, and Google Scholar databases through August 19, 2016.

2. Inclusion and exclusion criteria

We included studies that compared the CDI occurrence risks from PPI and H2RA in hospitalized adults. We excluded studies that analyzed patients in nursing homes or living at home.

3. Study selection and data extraction

Two authors (M. Azab and J.W.Y.) independently screened titles and abstracts. They obtained full articles that met the inclusion and exclusion criteria and after an independent review, they extracted the data. For all phases, discrepancies were resolved in consultation with three other authors (L.D., D.H.D., and Y.E.). We also hand-searched the eligible articles. Twenty-nine studies relevant to inclusion criteria were added. The actual numbers of CDI cases were collected from tables and manuscript text in each study. When actual data was not presented in certain studies, three authors (M. Ahmed, J.J.C., and X.B.L.) directly contacted corresponding authors of their studies to obtain the data. Since data was from previously published studies, an Institutional Review Board approval was waived. Finally, twelve studies were selected. Fig. 1 presents the study selection process

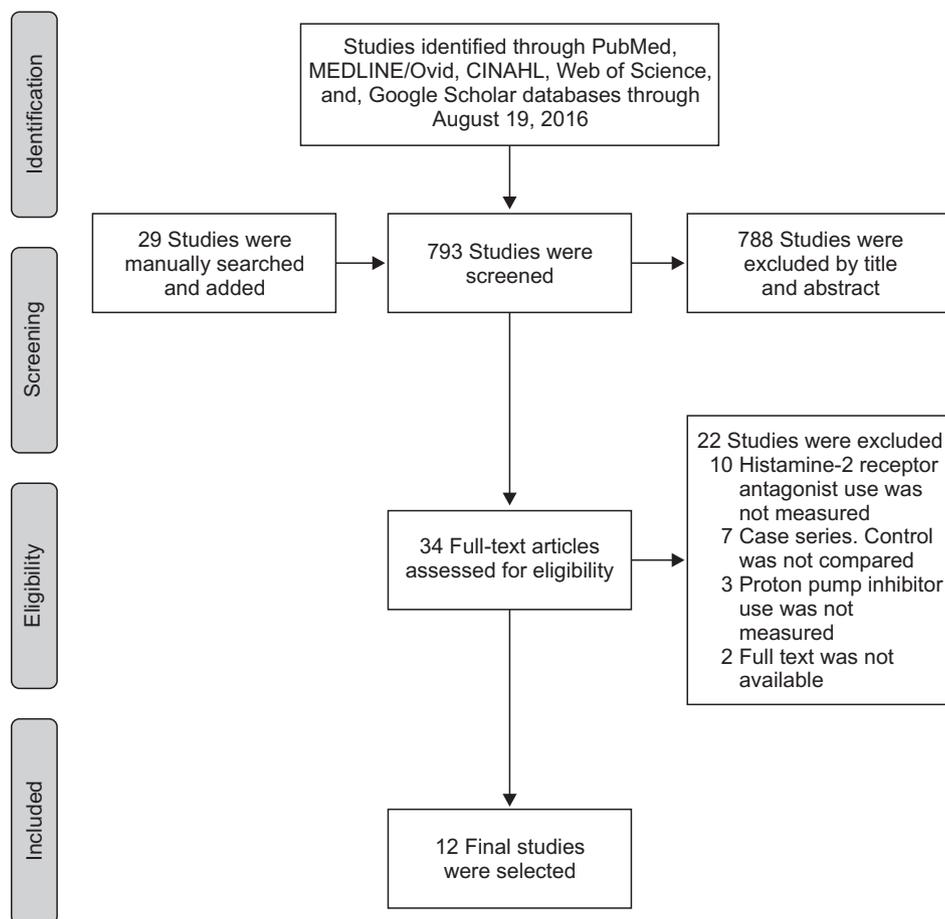


Fig. 1. Study selection process. CINAHL, Cumulative Index of Nursing and Allied Health Literature.

Table 1. Summary of Studies

| Author (year) | Study participants | Study site | Study design | <i>Clostridium difficile</i> infection risk | | | |
|--|--------------------|------------------|--------------|---|---------|------|-----------------|
| | | | | PPI | | H2RA | |
| | | | | OR* | p-value | OR* | p-value |
| Shah <i>et al.</i> (2000) ⁵ | 95 | South Wales | Case-control | NA | | NA | |
| Muto <i>et al.</i> (2005) ⁶ | 432 | USA | Case-control | 2.4 | - | 2.0 | - |
| Kazakova <i>et al.</i> (2006) ⁷ | 70 | USA | Case-control | 3.14 | 0.003 | 2.69 | 0.02 |
| Jayatilaka <i>et al.</i> (2007) ⁸ | 322 | USA | Case-control | 2.61 | <0.001 | 1.06 | Non-significant |
| Dubberke <i>et al.</i> (2007) ⁹ | 1,451 | USA | Case-control | 4.2 | - | 3.0 | - |
| Aseeri <i>et al.</i> (2008) ¹⁰ | 123 | USA | Case-control | 3.6 | <0.001 | 2.14 | 0.082 |
| Howell <i>et al.</i> (2010) ¹¹ | 60,531 | USA | Cohort | 1.74 | <0.001 | 1.53 | 0.001 |
| Loo <i>et al.</i> (2011) ¹² | 2,145 | Canada | Case-control | 2.64 | - | 0.98 | - |
| Stevens <i>et al.</i> (2011) ¹³ | 7,405 | USA | Cohort | 4.50 | <0.001 | 1.7 | 0.25 |
| Barletta <i>et al.</i> (2013) ¹⁴ | 148 | USA | Case-control | 1.14 | 0.018 | | NA |
| Barletta <i>et al.</i> (2014) ¹⁵ | 429 | USA (ICU only) | Case-control | 2.19 | 0.005 | 1.12 | 0.628 |
| Ro <i>et al.</i> (2016) ¹⁶ | 981 | Korea (ICU only) | Cohort | 3.0 | 0.003 | | NA |

PPI, proton pump inhibitor; OR, odds ratio; H2RA, histamine-2 receptor antagonist; NA, not applicable; ICU, intensive care unit.

*OR >1 indicates that either PPI or H2RA increases the risk of *C. difficile* infection compared to no treatment.

Table 2. Quality of Evidence

| Outcome | Anticipated absolute effects* (95% CI) | | Relative effect OR [†] (95% CI) | No. of participants (studies) | Quality of the evidence (GRADE) | Comment |
|--|---|----------------------|---|--------------------------------------|---------------------------------------|--|
| | Risk with H2RA | Risk with PPI | | | | |
| <i>Clostridium difficile</i> infection occurrence from PPI vs H2RA | 26 per 1,000 (95% CI) | 36 per 1,000 (30–43) | 1.38 (1.15–1.67) | 74,132 (12 observational studies) | 2/4 Low | No serious limitations were found in risk of bias, consistency, directness, precision, and publication bias. |

CI, confidence interval; H2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor; OR, odds ratio; GRADE, Grading of Recommendations Assessment, Development, and Evaluation.

*Number of *C. difficile* infection per 1,000 persons; [†]OR >1 indicates *C. difficile* risk from PPIs is higher than the risk from H2RAs.

in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.²⁴ A summary of studies is shown in Table 1.

4. Quality assessment

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system to assess overall quality of evidence for each outcome.²⁵ The overall quality of evidence took into consideration the following five domains: risk of bias, consistency, directness, precision, and publication bias.²⁵ The GRADE system can be used for rating the quality of evidence (high, moderate, low, and very low).²⁵ Meta-analysis from observational studies starts from low quality of evidence. The quality of evidence may decrease when there is serious limitation of any of the five domains. We used optimal information size (OIS) calculations as an objective measure of imprec-

ision for grading evidence, as a priori of risk increase by 25% from PPI with an $\alpha=0.05$ and $\beta=0.80$ compared to CDI occurrence risk from H2RA.²⁶ Publication bias was assessed by visual inspection of funnel plots and Egger regression analysis. The GRADEpro software (McMaster University and Evidence Prime Inc., Hamilton, ON, Canada) was used to prepare the quality of evidence as shown in Table 2.²⁷

5. Data synthesis and analysis

We combined individual study results to calculate the pooled odds ratio (OR) and 95% confidence intervals (CI) using the random effects method.²⁸ Between-study heterogeneity was assessed using the I^2 static values of 50%, representing extensive statistical inconsistency. Subgroup analysis was performed to examine effects of medication use purpose, study site, and study design. Meta-regression analysis was performed to predict

Table 3. Baseline Characteristics of the Study Participants by *Clostridium difficile* Infection Status

| Variable | <i>C. difficile</i> infection (n=2,235) | Absence of <i>C. difficile</i> infection (n=71,897) | p-value |
|-----------------------------|---|---|---------|
| Age, yr | 68.74±3.41 | 67.88±2.20 | 0.294 |
| Sex (male), % | 52.20 (3.28) | 51.96 (2.54) | 0.539 |
| Race (white), % | 79.28 (13.42) | 78.84 (14.70) | 0.360 |
| Intensive care unit stay, % | 58.32 (16.72) | 39.57 (7.14) | <0.001 |
| Antibiotics use, % | 86.58 (6.09) | 84.90 (7.13) | 0.328 |

Data are presented as mean±SD or observed (SD).

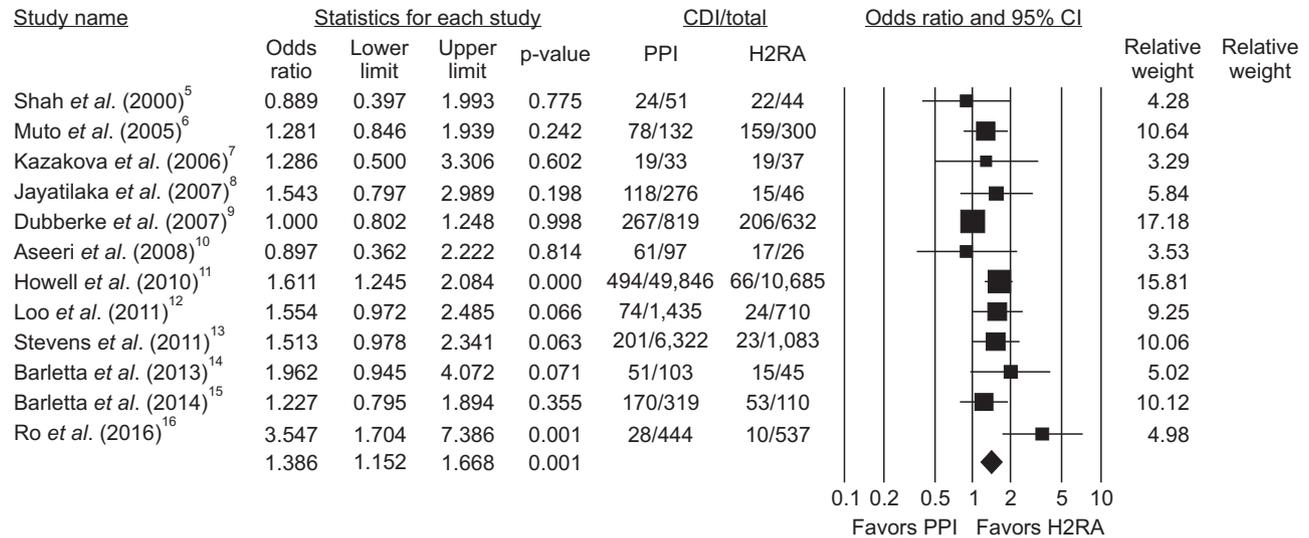


Fig. 2. Meta-analysis results. Comparison of the *Clostridium difficile* infection (CDI) risk following proton pump inhibitor (PPI) and histamine-2 receptor antagonist (H2RA) use. CI, confidence interval.

whether age, gender, or antibiotics use would be associated with hospital-acquired CDI occurrence risk. Baseline characteristics of study participants were aggregated from 12 analyzed studies as shown in Table 3. To compare the baseline characteristics by CDI status, chi-square analysis for categorical variables and t-test analysis for continuous variable was performed. Kwok *et al.*²⁰ performed subgroup analysis of CDI occurrence risks from “PPI vs control” and “H2RA vs control.” Supplementary Table 1 compared the studies analyzed by current and Kwok’s meta-analysis.²⁰ All analyses were performed in SPSS version 24 (IBM Corp., Armonk, NY, USA) and Comprehensive Meta-Analysis version 3 (Biostat Inc., Englewood, NJ, USA). A two-sided p-value <0.05 was considered statistically significant.

RESULTS

A total of 74,132 patients from 12 observational studies were analyzed. Baseline characteristics from pooled study participants are reported in Table 3. Characteristics were grouped by CDI status: CDI (n=2,235) versus absence of CDI (n=71,897). There was no statistical significance between the participants of CDI and non-CDI except for intensive care unit use. CDI group par-

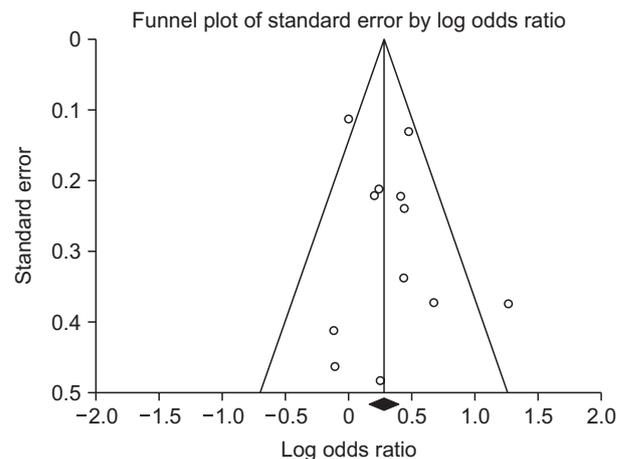
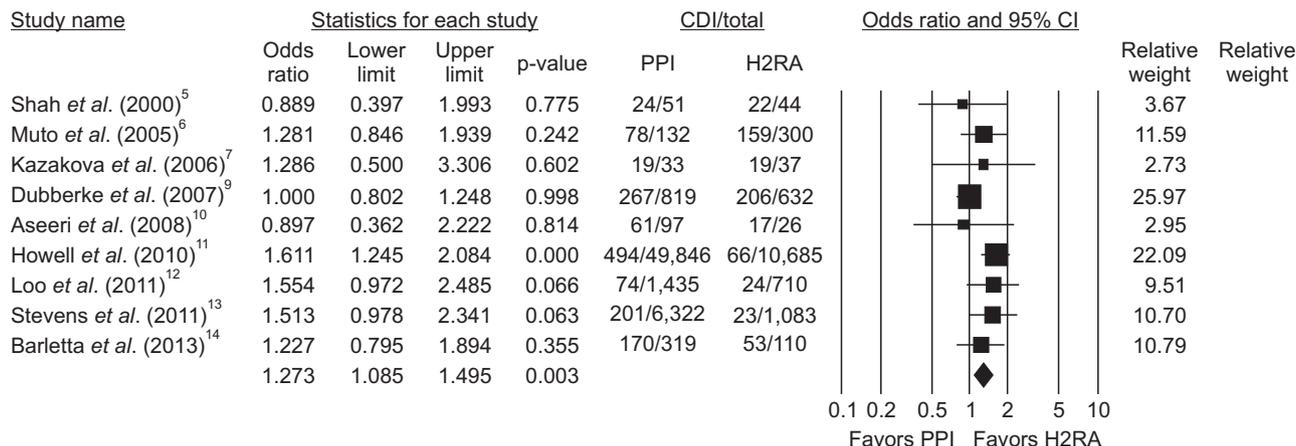


Fig. 3. Publication bias.

ticipants were more likely to be in the intensive care unit than non-CDI group participants (58.32% vs 39.57%, p<0.001).

Fig. 2 presents meta-analysis results, CDI risk comparisons between PPI and H2RA. PPIs were associated with an increase in CDI occurrence risk (pooled OR, 1.386; 95% CI, 1.152 to 1.668; p=0.001). Heterogeneity was low (n=4, Q=7.639, p=0.157,

A



B

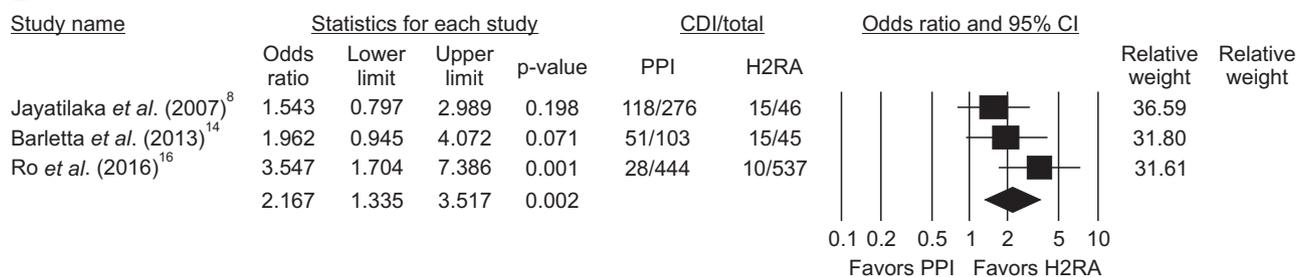


Fig. 4. Subgroup analysis by purpose of medication use; (A) unspecified and (B) prevention.

CDI, *Clostridium difficile* infection; CI, confidence interval; PPI, proton pump inhibitor; H2RA, histamine-2 receptor antagonist.

$I^2=42.81\%$).

The quality of evidence started low because analyzed studies were all observational. Fig. 3 presents symmetrical funnel plot consistent with absence of publication bias. No evidence of publication bias by the Egger regression test for all-cause was found. The total number of study patients (17,397) exceeded OIS (6,220). The final quality of evidence remained low because no serious limitation was found in all domains of the GRADE system as shown in Table 2.

Fig. 4 presented subgroup analysis results by the purpose of acid suppression therapy. Nine of 12 studies did not specify the purpose of therapy. Only three studies specified the purpose of therapy for prevention of gastric ulcers. PPIs were associated with an increase in CDI occurrence risk in both subgroups (unspecified purpose in Fig. 4A: pooled OR, 1.273; 95% CI, 1.085 to 1.495; $p=0.003$, random effect, $I^2=22.9\%$ and prevention purpose in Fig. 4B: pooled OR, 2.167; 95% CI, 1.335 to 3.517; $p=0.002$, random effect, $I^2=28.9\%$). Subgroup analysis by intensive care unit (pooled OR, 1.616; 95% CI, 1.112 to 2.347; $p=0.012$) and non-intensive care unit (pooled OR, 1.321; 95% CI, 1.11 to 1.563; $p=0.001$) confirmed consistent results that PPI is associated with higher CDI risk than H2RA. Subgroup analysis by study design confirmed consistency that PPI's CDI risk was higher than that of H2RA: nine case-control studies (pooled

OR, 1.166; 95% CI, 1.003 to 1.355; $p=0.046$); three cohort studies (pooled OR, 1.821; 95% CI, 1.257 to 2.638; $p=0.002$).

Dubberke *et al.*'s study⁹ could be an outlier resulting in increasing the degree of heterogeneity. When this study was removed from current meta-analysis, the magnitude of pooled OR increased to 1.492 (95% CI, 1.279 to 1.741; $p<0.001$) and heterogeneity dropped to near zero ($I^2=4.41\%$). Little is known whether either characteristic study design (nested case control), CDI definition (confirmation by stool toxin assay), or other factor in Dubberke *et al.*'s 2007 study would generate the outlier effect.⁹

Meta-regression analysis found that there was absence of CDI predictor among age, gender, and antibiotics use. The results of meta-regression analysis were confirmed even at sensitivity analysis using a second-order term for age, gender, and antibiotics use.

DISCUSSION

To the best knowledge, the current meta-analysis is the first meta-analysis comparing CDI occurrence risk in two different stress ulcer treatment and prevention. Current meta-analysis found PPIs increased CDI occurrence risk by 38.6% compared with H2RAs.

Multiple medical societies have raised concerns about the unnecessary use of gastric acid suppression in the hospital.^{29,30} Indications for stress ulcer prophylaxis (SUP) in hospitalized patients have been identified in these literature: patients on mechanical ventilation and those with coagulopathy are strongly recommended. Other indications include prior history of GI bleeding, acute renal failure, high dose of steroids, burn, sepsis and increased severity of illness with prolonged intensive care unit stay.^{29,30} In critically ill patients, PPIs seem to be more effective than H2RAs in preventing overt upper GI bleeding.³¹ SUP use in lower risk groups is not specified by the professional societies. Indeed, SUP is commonly overused in hospitals, with as many as 71% of patients in general medicine wards receiving some sort of SUP without an appropriate indication.³² Anticoagulant therapy has been identified as a risk factor for GI bleeding in hospitalized patients, but the use of SUP has not been found to lower that risk.³³ Therefore, routine use of SUP in non-ICU services should seriously be reconsidered.^{32,33} Moreover, future studies highlighting the comparative efficacy between PPI and H2RA among patients at low GI bleeding risk are needed. Studies have also shown better cost-effectiveness with the use of PPI compared to H2RA for SUP.³⁴⁻³⁶ However, applying these results to current practice would be limited because these studies did not include CDI occurrence as one of the outcomes.³⁴⁻³⁶

CDI is a significant burden on the health care system. CDI incidence in the United States has increased by approximately 3-fold between 2000 and 2012.^{2,37} In 2008, CDI may have resulted in as much as \$4.8 billion in excess healthcare costs in acute-care facilities alone.^{2,37} Additionally, it is critical to include cost as main outcome in future studies determining the choice of SUP use. It is also largely unknown which acid suppressive

therapy group has better preventive efficacy than the other group in other conditions such as acute renal failure, sepsis, chronic steroid use, and burns. Further studies are urgently needed to compare the efficacy of H2RAs versus PPIs in these patient groups.

Current meta-analysis raised public concerns and suggests future studies. Olsen *et al.*³⁸ analyzed nationally representing administrative databases and reported the incidence of CDI in Medicare population was 10-fold higher than that in the privately insured younger patients. Long-term PPI use in nursing homes could increase the risk of CDI occurrence, especially in elderly patients who have been recently discharged from hospital and are more vulnerable to intestinal mucosal injury.³⁹ In addition, according to recent nationally representing database analysis, Medicare beneficiaries with recent hospitalization, invasive procedures, urinary tract infection, and pneumonia were more vulnerable to have the CDI.⁴⁰ Public health dimension should identify more high risks and maximize the effectiveness of preventing CDI occurrence attributed by SUP from hospital-level and regional health authorities' perspectives. Suggested future studies would be highlighted by exploring how these high risks on CDI would be influenced when PPI or H2RA is used for SUP.

Our confidence in current meta-analysis results is strengthened by the following few points. First, current meta-analysis has higher homogeneity ($I^2=42.81\%$) compared with previous meta-analyses as shown in Table 4. Second, current meta-analysis focused on study participants to hospitalized adults. Current analysis findings could be more specifically applied to the development of hospital quality and infection control. Third, current meta-analysis was free of publication bias. For example,

Table 4. Meta-Analysis Comparisons of Acid Suppression Therapy and *Clostridium difficile* Infection

| Author (year) | Search engine | Acid suppression therapy | No. of studies | Degree of heterogeneity (I^2), % | Pooled effect estimates, OR* (95% CI) | Quality grading system |
|--|--|--------------------------|----------------|--------------------------------------|---------------------------------------|-------------------------------|
| Current study | PubMed, MEDLINE/Ovid, CINAHL, Web of Science, and Google Scholar | PPI vs H2RA | 12 | 42.81 | 1.386 (1.152–1.668) | GRADE |
| Tleyjeh <i>et al.</i> (2012) ¹⁹ | MEDLINE, EMBASE, Web of Science, and Scopus | PPI vs control | 51 | 89.9 | 1.65 (1.47–1.85) | Newcastle-Ottawa Scale; GRADE |
| Kwok <i>et al.</i> (2012) ²⁰ | MEDLINE and EMBASE | PPI vs control | 39 | 85 | 1.74 (1.47–2.85) | GRADE |
| Janarthanan <i>et al.</i> (2012) ²¹ | MEDLINE | PPI vs control | 23 | 91.93 | 1.648 (1.424–1.908) | MOOSE |
| Deshpande <i>et al.</i> (2012) ²² | MEDLINE, CINAHL, Cochrane, Web of Science, and Scopus | PPI vs control | 30 | 87 | 2.15 (1.81–2.55) | MOOSE |

OR, odds ratio; CI, confidence interval; CINAHL, Cumulative Index of Nursing and Allied Health Literature; PPI, proton pump inhibitor; H2RA, histamine-2 receptor antagonist; GRADE, Grading of Recommendations Assessment Development and Evaluations; MOOSE, Meta-Analysis of Observational Studies in Epidemiology.

*OR >1 indicates that PPIs increase the risk of *C. difficile* infection compared to H2RAs (current meta-analysis) or the control (Tleyjeh, Kwok, Janarthanan, and Deshpande's meta-analyses).

newer studies were added after previous meta-analyses were published in 2012 and studies of small number cases (n<10) were excluded. Lastly, subgroup analysis results confirmed consistency of current meta-analysis results.

We acknowledge several limitations in the current meta-analysis. First, the diagnosis methods of CDI occurrence were not unified by the microbiologic or/and clinical diagnosis. Second, despite being an important risk factor for CDI, we could not obtain information on the specific dose, duration and frequency of the antibiotics used in most of the included studies. We could not perform further analysis to investigate the potential influence of antibiotics use. Third, the purpose of current analysis was not aimed at evaluating other comparative efficacies between PPI and H2RA (e.g., GI bleeding prevention). Finally, more specific H2RA and PPI use data (strength and duration) were not reported. Therefore, current meta-analysis findings should be interpreted with caution.

In conclusions, in either prevention or treatment of stress ulcers, the use of PPIs was associated with increased risk of hospital-acquired CDI occurrence by 38.6% compared to the use of H2RAs.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGEMENTS

This work was supported by University of Nevada School of Medicine, Faculty Career Development Award (recipient: J.W.Y.).

Author contributions: M. Azab, D.H.D., L.D., Y.E., and J.W.Y. contributed to the conception and design; M. Azab, M. Ahmed, and J.J.C. contributed to the acquisition of data. D.H.D. and L.D. contributed to the quality assessment; X.B.L. and J.W.Y. undertook the statistical analysis; M. Azab, D.H.D., L.D., A.S., X.B.L., and J.W.Y. drafted the report and contributed to the critical revision of the manuscript.

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