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META-ANALYSIS

Proton pump inhibitors therapy and risk of *Clostridium difficile* infection: Systematic review and meta-analysis

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Abstract

AIM

To perform a systematic review and meta-analysis on proton pump inhibitors (PPIs) therapy and the risk of *Clostridium difficile* infection (CDI).

METHODS

We conducted a systematic search of MEDLINE/PubMed and seven other databases through January 1990 to March 2017 for published studies that evaluated the association between PPIs and CDI. Adult case-control and cohort studies providing information on the association between PPI therapy and the development of CDI were included. Pooled odds ratios (ORs) estimates with 95% confidence intervals (CIs) were calculated using the random effect. Heterogeneity was assessed by I^2 test and Cochran's Q statistic.

Potential publication bias was evaluated *via* funnel plot, and quality of studies by the Newcastle-Otawa Quality Assessment Scale (NOS).

RESULTS

Fifty-six studies (40 case-control and 16 cohort) involving 356683 patients met the inclusion criteria and were analyzed. Both the overall pooled estimates and subgroup analyses showed increased risk for CDI despite substantial statistical heterogeneity among studies. Meta-analysis of all studies combined showed a significant association between PPI users and the risk of CDI (pooled OR = 1.99, CI: 1.73-2.30, $P < 0.001$) as compared with non-users. The association remained significant in subgroup analyses: by design-case-control (OR = 2.00, CI: 1.68-2.38, $P < 0.0001$), and cohort (OR = 1.98, CI: 1.51-2.59, $P < 0.0001$); adjusted (OR = 1.95, CI: 1.67-2.27, $P < 0.0001$) and unadjusted (OR = 2.02, CI: 1.41-2.91, $P < 0.0001$); unicenter (OR = 2.18, CI: 1.72-2.75, $P < 0.0001$) and multicenter (OR = 1.82, CI: 1.51-2.19, $P < 0.0001$); age ≥ 65 years (OR = 1.93, CI: 1.40-2.68, $P < 0.0001$) and < 65 years (OR = 2.06, CI: 1.11-3.81, $P < 0.01$). No significant differences were found in subgroup analyses (test for heterogeneity): $P = 0.93$ for case-control *vs* cohort, $P = 0.85$ for adjusted *vs* unadjusted, $P = 0.24$ for unicenter *vs* multicenter, $P = 0.86$ for age ≥ 65 years and < 65 years. There was significant heterogeneity across studies ($I^2 = 85.4\%$, $P < 0.001$) as well as evidence of publication bias (funnel plot asymmetry test, $P = 0.002$).

CONCLUSION

This meta-analysis provides further evidence that PPI use is associated with an increased risk for development of CDI. Further high-quality, prospective studies are needed to assess whether this association is causal.

Key words: Proton pump inhibitors; *Clostridium difficile* infection; Risk; Systematic review; Meta-analysis

Core tip: A possible association between the use of proton pump inhibitors (PPIs) and the risk of *Clostridium difficile* infection (CDI) have been suggested by several studies. This meta-analysis, including the largest number of studies published to date found the risk of CDI almost two-times higher in PPIs users than in nonusers. Because all the studies analyzed were observational, the causality could not be confirmed. Nevertheless, clinicians should be aware of such potential association and prescribe the PPIs only where they are clearly indicated.

Trifan A, Stanciu C, Girleanu I, Stoica OC, Singeap AM, Maxim R, Chiriac SA, Ciobica A, Boiculese L. Proton pump inhibitors therapy and risk of *Clostridium difficile* infection: Systematic review and meta-analysis. *World J Gastroenterol* 2017; 23(35): 6500-6515 Available from: URL: http://www.wjgnet.com/1007-9327/full/v23/i35/6500.htm DOI: http://dx.doi.org/10.3748/wjg.v23.i35.6500

INTRODUCTION

Over the past two decades *Clostridium difficile* (*C. difficile*) infection (CDI) has registered an increasing trend worldwide both in incidence and severity[1-5], with healthcare costs varying between 1.2 and 4.7 billion dollars each year in the United States alone[6-9]. In addition to the broad-spectrum antimicrobial therapy which has been the most prominent causative factor for CDI[10,11], other potential risk factors have been identified such as: advanced age, hospitalization [particularly in intensive care units (ICU)], immunosuppression, renal insufficiency, hypoalbuminemia, lengthy hospital stay, the use of nasogastric tubes, invasive gastrointestinal procedures, chemotherapy, the presence of comorbidities, environment-related factors, and the emergence of a hypervirulent strain of the bacterium known as North American pulso-type 1 in some areas[12-21]. However, there might be some other risk factors for the CDI epidemic in the recent years despite tighter control on the use of antibiotics and stricter control policies on hospital-related infections[17]. A possible association between the use of proton pump inhibitors (PPIs) and the development of CDI has been suggested and numerous studies have examined it, reporting conflicting results[22-43].

Since their release in the late 1980s, PPIs have become some of the most widely prescribed agents both in outpatient and inpatient settings throughout the world[44-53], with sales totalling billions dollars worldwide[54,55]. These drugs have proven effective in the treatment of ulcer disease (including bleeding peptic ulcer), gastroesophageal reflux disease, *Helicobacter pylori* (in combination with antibiotics), Zollinger-Ellison syndrome, in the prophylaxis of upper gastrointestinal complications with nonsteroidal anti-inflammatory drugs (NSAIDs) therapy, stress ulcer prophylaxis in ICU patients, and functional dyspepsia[50,53,56-60]. The widespread use of PPIs during the last 25 years in clinical practice is the result not only of their high efficacy but also of their excellent safety profile, proving to be one of the safest class of medication used in gastroenterology[57,61-64].

Nevertheless, like in the case of other drugs, PPIs are not as safe as it has been thought and more recently, concerns have been raised about their potential association with pneumonia[65-67], bone fractures[68-70], interstitial nephritis and acute kidney injury[71]. More recently, reports of other potential PPIs adverse events such as risk for chronic kidney disease[72,73], dementia[74], spontaneous bacterial peritonitis[75,76], acute myocardial infarction[77,78], micronutrient

deficiency (magnesium, calcium, iron)[79,80] were published, although the quality of evidence for these is consistently low to very low[81].

An association between PPIs use and CDI is, at least theoretically, rational. Thus, intestinal homeostasis is maintained by host defense mechanisms in which gastric acid plays an important role as a barrier to ingested bacteria and bacterial overgrowth[82]. PPIs therapy profoundly inhibits gastric acid production leading to the proliferation of spores and their ability to convert to a vegetative form of *C. difficile* [83]. Moreover, PPIs impair leukocyte function by inhibiting phagocytosis and acidification of phagolysosome[84].

Several systematic reviews and meta-analyses have reported conflicting results regarding the association between PPIs use and increased risk of CDI. Thus, no less than six meta-analyses[85-90] found a significant association between PPIs therapy and increased risk of CDI. These findings were also supported by several studies[19,22-26,39,91-114] which reported a risk for CDI two or three times higher in PPIs users than in nonusers. Moreover, the United States Food and Drug Administration (FDA) informed the public about a possible correlation between PPIs use and CDI[115]. Still, other studies and meta-analyses have failed to associate PPIs use with the development of CDI[11,27,34,38,40-43,116-123]. It should be mentioned that PPIs continue to be among the most used drugs despite the above mentioned concerns about long-term side effects. Furthermore, beside a marked overuse of PPIs, over half of prescriptions are for non-indicated reasons[29]. One study reported that 60.7% of patients with CDI used PPIs, of whom only 47.1% had an evidence-based indication[30].

The aim of this systematic review and meta-analysis is to summarize data on the association between PPIs use and the risk of CDI as presented in the published studies.

MATERIALS AND METHODS

Information sources

A systematic literature search was independently conducted by four study investigators (Girleanu I, Stoica OC, Singeap AM and Chiriac SA) using a variety of databases including MEDLINE/PubMed, Web of Science (ISI Web of Knowledge), Scopus, EMBASE, Science Direct, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Excerpta Medica Database, and Cochrane Library, from January 1990 (the first PPI received FDA approval in 1989) to March 2017. The database searches were performed using the following medical subject heading (MeSH) terms: "proton pump inhibitors", "acid suppressive therapy", "omeprazole", "pantoprazole", "lansoprazole", "rabeprazole", "esomeprazole", combined with "*C. difficile* infection", "*C. difficile*-associated diarrhea", "pseudomembranous colitis". Reference lists of all retrieved papers were hand-searched to identify any additional studies that may have been missed in the computed-assisted literature search. The investigation was limited to studies performed in adult human beings, written and published in English, French, and German, in any geographic region.

Inclusion and exclusion criteria

Selection of the studies. Inclusion and exclusion criteria were established a priori by two authors (Trifan A and Stanciu C). First, duplicate citations were identified and removed, then three of us (Ciobica A, Maxim R and Singeap AM) independently reviewed the titles and abstracts of the studies and excluded those which did not answer the search question. Adult case-control and cohort studies providing information on the association between PPI therapy and the development of CDI were included. Studies conducted on pediatric patients, systematic reviews and meta-analyses, consensus documents, studies using PPIs simultaneously with H2 receptor antagonists (H2RA) or reporting exclusively on H2RA, case reports, editorials, protocols, and studies presented only as abstracts were excluded. There was no restriction related to the type of PPI regimen or diagnostic methods of CDI. Any disagreements about study inclusion were resolved in consensus with a third author (Stanciu C or Trifan A) after the full-text of the potential study had been reviewed; all eligible studies were assessed in full. They were subsequently included in this meta-analysis only if reported odds ratios (ORs) or risk ratios (RRs) for (adjusted or unadjusted) case-control and cohort studies, respectively, or data for their calculation were available.

Data extraction

Extracted data were cross-checked independently by four authors (Girleanu I, Stoica OC, Chiriac SA and Ciobica A) from each included study using a standardized data extracting sheet which included the last name of first author, journal and year of publication, country where the study was carried out, study design, sample size, age (mean or median) and gender distribution of patients, duration of the PPI treatment, effect estimates ORs or RRs, and 95% confidence intervals (CIs) of PPI exposure with and without adjustment for confounding variables. Any disagreement between reviewers was resolved in consensus with a third reviewer (Stanciu C or Trifan A).

Study quality assessment

Assessment of study quality was made independently by two authors (Boiculese L and Girleanu I) using the Newcastle-Ottawa Quality Assessment Scale (NOS; ranging 0-9)[124] as recommended by the Cochrane Handbook for Systematic Reviews of Interventions[125]. The NOS comprises three domains: selection, comparability, and outcome for cohort studies or exposure for case-control studies. A maximum of

four stars were awarded for selection, two stars for comparability, and three stars for exposure/outcome. Studies with cumulative score ⩾ 7 were considered high quality, 6 stars to be of moderate quality, and less than 6 stars to be of low quality. When disagreement, after discussion with the third author (Trifan A or Stanciu C) a consensus was reached. The final analysis included 56 high and moderate quality studies.

As none of the studies was randomized, and all were observational (case-control and cohort), the methods used in our systematic review and meta-analysis followed the MOOSE (Meta-Analysis of Observational Studies in Epidemiology) criteria[126].

Statistical analysis

Meta-analyses were performed both for all studies together and separately for case-control and cohort studies using DerSimonian and Laird[127] random effects model due to expected heterogeneity between studies. Our primary analysis focused on the association between PPIs therapy and the risk for developing CDI and because all of PPIs have similar efficacy we have not performed meta-analyses stratified by type of PPIs. The results are reported as pooled ORs with 95%CIs for primary and subgroup analyses.

Heterogeneity between studies was assessed by I^2 statistic and Cochran's *Q*-statistic. The level of heterogeneity was considered as high when I^2 > 75% or P < 0.10 for the *Q* statistic[128]. I^2 values between 61%-75%, 30%-60%, and < 30% were considered to represent substantial, moderate and low level of heterogeneity, respectively[129]. Seven potential confounders were considered: study design, effect estimate (adjusted *vs* unadjusted), setting (community *vs* inpatient), number of centers (single center *vs* multicenter), age, study quality, and geographical region.

Publication bias was assessed quantitatively using Egger's regression asymmetry test[130] and a P < 0.1 was considered statistically significant for asymmetry, and qualitatively by visual inspection of funnel plots of the logarithmic OR *vs* their standard errors[131]. Asymmetrical funnel plots were regarded to indicate high risk of publication bias.

Number needed to harm (NNH) estimates the number of patients needed to be treated with PPI for one additional person to have a CDI, and was calculated using the pooled OR (95%CI) from the meta-analysis and Patient Expected Event Rate (1.67%)[120].

All statistical tests were two tailed, and results associated with P < 0.05 (except for heterogeneity and publication bias) were considered significant. All analyses were performed using R version 3.2.3 software for the metaphor package 1.9-8, which provides a comprehensive collection of validated functions[132]. The statistical analyses of this study were performed by an expert in biostatistics from "Grigore T. Popa" University of Medicine and Pharmacy, Department of Medical Informatics and Biostatistics.

RESULTS

Search results

The initial online databases search identified 944 studies and 12 more were found from the reference lists of the articles retrieved. After reviewing all titles and abstracts, 216 studies were selected for full-text review, from which 56 studies were found to fulfill the inclusion criteria and were included in meta-analysis. Five of the 56 studies were published after the last meta-analysis (Figure 1).

Characteristics of included studies

The characteristics of the included studies are shown in Table 1. Of the included 56 studies, 40 (71.4%) were case-control, and 16 (28.6%) cohort studies, addressed to hospital-acquired (n = 43), community-acquired (n = 6), and both hospital and community-acquired CDI (n = 7). Most of the studies (n = 31) were single-center. The size of the study population ranged from 40 to 101796. In total, 356683 subjects were included, most of them from North-American and European studies (n = 46).

Quality assessment

The median value of NOS quality assessment was 7, with a mean 6.67 ± 0.74, range 6-8. In studies reporting gender, the proportion of men ranged from 47% to 67%, and from those that reported the age, the average age ranged between 18 and 82.2 years. Thirty-eight studies identified confounding factors (sex, age, antibiotic use, comorbidities) used for adjustment of the association between PPI therapy and risk of CDI. The majority of the studies were retrospective (85.7%) and only 8 were prospective (14.3%). None of the studies was randomized.

Meta-analysis

Meta-analysis of all studies combined. The results of pooled analysis for all 56 studies showed a significant association between PPI therapy and the risk of CDI as compared with non-PPI users (OR = 1.99, CI: 1.73-2.30, P < 0.001) (Figure 2). There was significant heterogeneity of effects across studies (I^2 = 85.41%; P < 0.001).

Subgroup analyses of case-control and cohort studies also showed a significant higher risk of CDI with PPI use (Table 2). There was no significant difference of effects between cohort and case-control studies (P = 0.931). The pooled OR for the cohort studies was 1.98 similar to OR for case-control that was 2.0.

The association remained also significant after limiting meta-analysis to studies with both adjusted (OR = 1.95, CI: 1.67-2.27, P < 0.001) and unadjusted

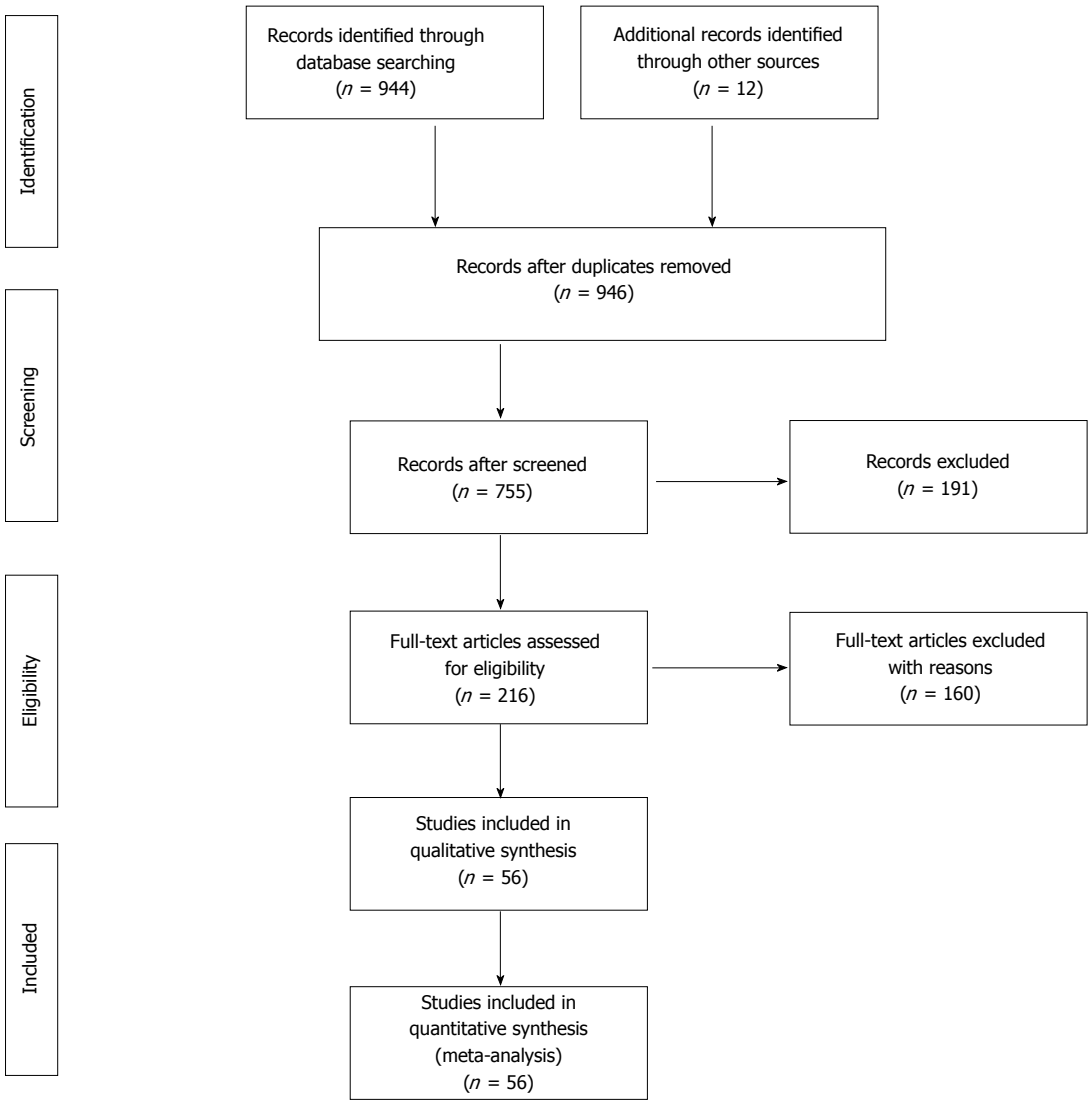

Figure 1 Study selection process.

data (OR = 2.02, CI: 1.41-2.91, $P < 0.001$). There was also no significant difference of effects between adjusted and unadjusted studies ($P = 0.856$).

PPIs use was found to be associated with an increased risk of CDI in both single-center studies (OR = 2.18, 95%CI: 1.72-2.75) and multicenter studies (OR = 1.82, 95%CI: 1.51-2.19).

There was no significant difference between inpatients and outpatients regarding CDI risk ($P = 0.868$). For both inpatients and outpatients the PPIs use almost doubled the risk of CDI (OR = 1.95, OR = 2.10, respectively).

When grouped by region, a direct association was found in the European group (OR = 1.78, 95%CI: 1.35-2.34), the North American group (OR = 2.00, 95%CI: 1.67-2.40), while the highest risk of CDI after PPI treatment was demonstrated in the Asian group (OR = 2.31, 95%CI: 1.96-2.72).

The subgroup of high-quality studies (NOS $\geqslant$ 7) showed a direct association (OR = 1.88, 95%CI: 1.55-2.28) between PPIs and risk of CDI, and this association was also significant in the medium-quality group (OR = 2.11, 95%CI: 1.69-2.62), with no difference between the two groups ($P = 0.441$).

There was no statistical difference regarding the risk for CDI for elderly ($\geqslant$ 65 years) compared with younger group (< 65 years) ($P = 0.860$).

Publication bias

We have drawn the funnel plot for 3 levels of confidence interval (90%, 95% and 99% corresponding to shades white, gray and dark gray) (Figure 3). The Egger's test of asymmetry proved no significance ($Z = 0.3699$, $P = 0.711$).

Number needed to harm

Based on reported incidence of CDI (at 14 d after hospital admission) of 1.67% in patients who have not used PPI, we estimate a NNH of 63 (95%CI: 48-78), if these patients will receive PPIs.

Table 1 Characteristics of studies included in the meta-analysis

Author, yr	Region	Study design	Centers	Setting	Sample size, *n*	Mean age, yr	Identified confounders	OR (95%CI)
Akhtar *et al* Shaheen[91], 2007	America	Case-control	Unicenter	Inpatient	1290		Adjusted for age, sex, comorbidities, antibiotics, chemotherapy	2.1 (1.6-2.7)
Al-Tureihi *et al*[19], 2005	America	Case-control	Unicenter	Inpatient	53		Adjusted for age, antibiotics	3.1 (1.0-9.7)
Aseeri *et al*[23], 2008	America	Case-control	Unicenter	Inpatient	188		Adjusted for admission date, sex, age group, antibiotic use, patient location, and room type	4.4 (2.3-8.2)
Bajaj *et al*[133], 2010	America	Case-control	Multicenter	Mixt	162		Adjusted for antibiotics, PPI	37.6 (6.2-227.6)
Barletta *et al*[92], 2014	Asia	Case-control	Unicenter	Inpatient	408		Adjusted for PPI exposure, antibiotics, immunosuppression	2.1 (1.2-3.8)
Baxter *et al*[93], 2008	America	Case-control	Multicenter	Inpatient	4493		Adjusted for antibiotics, age, hospital stay, other infections	1.2 (1.0-1.4)
Beaulieu *et al*[27], 2007		Cohort	Unicenter	Inpatient	827		Adjusted for age, sex, length of stay, comorbidities, APACHE score, NGT feeding, tracheal tube placement, antibiotics	1.3 (0.9-2.0)
Branch *et al*[94], 2007	America	Case-control	Unicenter	Inpatient	787	66.02	No	13.0 (7.5-22.7)
Buendgens *et al*[95], 2014	Europe	Case-control	Multicenter	Inpatient	3286		Adjusted for age, sex, antibiotics, comorbidities, other treatment	3.1 (1.1-8.7)
Campbell *et al*[38], 2013	America	Case-control	Unicenter	Inpatient	96		Adjusted for antibiotics, hospitalization	2.2 (0.6-8.0)
Cunningham *et al*[96], 2003	Europe	Case-control	Unicenter	Inpatient	320		Adjusted for antibiotics and chemotherapy	2.5 (1.5-4.1)
Dalton *et al*[22], 2009	America	Cohort	Multicenter	Inpatient	14719	74.7	Adjusted for number of medication groups, antibiotic days, age, length of stay, medical service, PPI days	1.9 (1.4-2.7)
Debast *et al*[116], 2009	Europe	Case-control	Unicenter	Inpatient	154		Adjusted for age, hospital stay, comorbidities, antibiotics	1.1 (0.5-2.4)
Dial *et al*[26], 2004 (case-control)	America	Case-control	Multicenter	Inpatient	188		Adjusted for age, antibiotics	2.6 (1.3-5.0)
Dial *et al*[26], 2004 (cohort)	America	Cohort	Multicenter	Inpatient	1187		Adjusted for age, antibiotics	2.1 (1.2-3.5)
Dial *et al*[98], 2005	Europe	Case-control	Multicenter	Outpatient	13563		Adjusted for age, sex, antibiotics	2.9 (2.4-3.5)
Dial *et al*[97], 2006	Europe	Case-control	Multicenter	Outpatient	3484		Adjusted for PPI and antibiotics	3.5 (2.3-5.3)
Dial *et al*[134], 2008	America	Case-control	Multicenter	Outpatient	9196	79.8	Adjusted for age, sex, antibiotics, comorbidities, physician visits, hospital admissions, length of stay	1.6 (1.3-1.9)
Dubberke *et al*[99], 2007	America	Cohort	Unicenter	Inpatient	36086		Adjusted for age, admissions, antibiotics, albumin level, leukemia/lymphoma, mechanical ventilation, antimotility agents	1.6 (1.3-2.1)
Elseviers *et al*[100], 2015	Europe	Case-control	Multicenter	Inpatient	743	71.9	Adjusted for age, co-morbidity, endoscopic procedures	1.9 (1.1-3.4)
Faleck *et al*[42], 2016	America	Cohort	Unicenter	Inpatient	11230	66	Adjusted for age, sex, antibiotics, comorbidities, length of stay	0.6 (0.4-0.8)
Garzotto *et al*[43], 2015	Europe	Case-control	Multicenter	Inpatient	225		No	0.4 (0.2-0.8)
Hebbard *et al*[135], 2017	Asia	Case-control	Unicenter	Inpatient	200	59.7	Adjusted for age, chemotherapy, abdominal surgery, antibiotics	2.4 (1.0-5.7)
Hensgens *et al*[117], 2011	Europe	Case-control	Unicenter	Inpatient	169		Adjusted for age, co-morbidity, antibiotics, ICU stay	1.1 (0.5-2.5)
Howell *et al*[136], 2010	America	Cohort	Unicenter	Inpatient	101796	65.4	Adjusted for age, comorbidities, antibiotics	1.7 (1.3-2.1)
Ingle *et al*[40], 2011	Asia	Cohort	Unicenter	Mixt	99	47	Adjusted for immunosuppression	1.8 (0.4-7.4)
Ingle *et al*[118], 2013	Asia	Case-control	Unicenter	Community	150	45.3	no	2.3 (0.6-9.2)
Jayatilaka *et al*[101], 2007	America	Case-control	Unicenter	Inpatient	366		Adjusted for PPI	2.7 (1.6-4.8)

Kazakova *et al*[102], 2006	America	Case-control	Unicenter	Mixt	195		Adjusted for antibiotics, PPI, length of stay, psychosis, depression	5.0 (1.3-19.3)
Khan *et al*[39], 2012	Asia	Cohort	Unicenter	Inpatient	123		Adjusted for surgery, PPI, antibiotics, hospitalization, Underlying debilitating conditions	3.2 (1.2-8.5)
Khanafer *et al*[119], 2013	Europe	Cohort	Unicenter	Inpatient	40			2.5 (0.6-9.6)
Kuntz *et al*[2], 2011	America	Case-control	Unicenter	Mixt	3344		no	2.3 (1.5-3.3)
Kurti *et al*[3], 2015	Europe	Case-control	Multicenter	Inpatient	979	72.4	Adjusted for antibiotics, PPI, length of stay,	1.6 (1.1-2.2)
Kutty *et al*[41], 2010	America	Case-control	Multicenter	Outpatient	144	62	No	1.7 (0.7-4.0)
Lewis *et al*[103], 2016	America	Cohort	Unicenter	Inpatient	41663		No	6.4 (3.6-11.5)
Lin *et al*[137], 2013	Asia	Case-control	Multicenter	Inpatient	86	59	Age, sex, unit, antibiotics, length of stay	10.1 (1.2-87.4)
Linney *et al*[24], 2010	America	Case-control	Unicenter	Inpatient	284		Age, sex, discharge date and hospital unit, antibiotics, diabetes mellitus, IBD, cancer, enteral feeding, length of stay	2.4 (1.4-4.3)
Loo *et al*[120], 2005	America	Case-control	Multicenter	Inpatient	474		no	1.0 (0.7-1.4)
Loo *et al*[138], 2011	America	Cohort	Multicenter	Inpatient	4143	67.4	Adjusted for age, PPI, antibiotics, chemotherapy	2.6 (1.7-4.0)
Lowe *et al*[121], 2006	America	Case-control	Multicenter	Inpatient	13692	78.7	Adjusted for antibiotics, other medications, and comorbidities	0.9 (0.7-1.0)
McFarland *et al*[122], 2007	America	Case-control	Multicenter	Mixt	368		No	0.8 (0.5-1.4)
Mizui *et al*[104], 2013	Asia	Case-control	Multicenter	Inpatient	2716	71.7	No	3.2 (1.4-7.3)
Modena *et al*[105], 2005	America	Case-control	Unicenter	Inpatient	250		Adjusted for macrolides, ICU, length of stay, infections	3.3 (1.6-6.8)
Mori *et al*[123], 2015	Asia	Case-control	Unicenter	Outpatient	78	58.2	No	0.4 (0.1-2.0)
Muto *et al*[106], 2005	America	Case-control	Multicenter	Inpatient	406		Adjusted for PPI, antibiotics, diabetes mellitus, organ transplantation	2.4 (1.3-4.4)
Pakyz *et al*[107], 2014	America	Case-control	Multicenter	Inpatient	14164		No	1.4 (1.3-1.5)
Peled *et al*[108], 2007	America	Cohort	Unicenter	Inpatient	217		Adjusted for PPI, low albumin level,	3.7 (1.5-9.3)
Pepin *et al*[11], 2005	America	Cohort	Unicenter	Inpatient	5619		Adjusted for age, length of stay, antibiotics	1.0 (0.7-1.2)
Ro *et al*[139], 2016	Asia	Cohort	Unicenter	Inpatient	1005	64.8	Adjusted for age, antibiotics, comorbidities	3.3 (1.5-7.2)
Roughead *et al*[109], 2016	Asia	Cohort	Multicenter	Mixt	54957		Adjusted for antibiotics, PPI, length of stay,	2.4 (1.9-3.1)
Shah *et al*[34], 2000	Europe	Case-control	Unicenter	Inpatient	252		No	0.8 (0.4-1.5)
Southern *et al*[110], 2010	Europe	Cohort	Multicenter	Inpatient	3904	65.5	No	2.3 (1.1-4.5)
Vesteinsdottir *et al*[111], 2012	Europe	Case-control	Multicenter	Mixt	333		No	1.6 (1.0-2.6)
Yang *et al*[112], 2011	Asia	Case-control	Multicenter	Inpatient	1420	67.12	No	1.9 (1.3-2.7)
Yearsley *et al*[25], 2006	Europe	Case-control	Unicenter	Inpatient	308	79.1	Adjusted for PPI, antibiotics, female sex	1.9 (1.1-3.2)
Yip *et al*[140], 2001	America	Case-control	Unicenter	Inpatient	54		No	3.0 (0.8-11.1)

CI: Confidence interval; IBD: Inflammatory bowel disease; ICU: Intensive care unit; PPI: Proton pump inhibitor; NGT: Naso-gastric tube; OR: Odds ratio.

DISCUSSION

This systematic review and meta-analysis which includes 56 studies and 356683 subjects[2,3,11,19,22-27,34,38-43,91-112,116-123,133-140] found a significant association between PPI therapy and the risk for CDI development. Both the overall pooled estimates (OR = 1.99, CI: 1.73-2.30, $P < 0.001$) and subgroup analyses showed a significant increased risk for CDI in patients on PPI therapy compared to nonusers, despite substantial statistical heterogeneity among studies and evidence of publication bias. Thus, in line with previous meta-analyses, our results add further evidence to PPIs use as a risk factor for development of CDI [85-89].

Since 2001, when Yip *et al*[140] first suggested a possible association between PPIs use and the risk of CDI, other studies, systematic reviews, and meta-analyses have reported such an association. It should be mentioned that a decade earlier (1993), Walker *et al*[141] suggested that the H2RAs therapy was a potential risk factor for CDI. In an earlier systematic review which included 11 studies with 126999 patients, Leonard *et al*[113] reported a significant association between PPI therapy and CDI (OR = 2.05, 95%CI: 1.47-2.85) although there was significant heterogeneity among the studies ($\chi^2 = 50.9$, $P <$

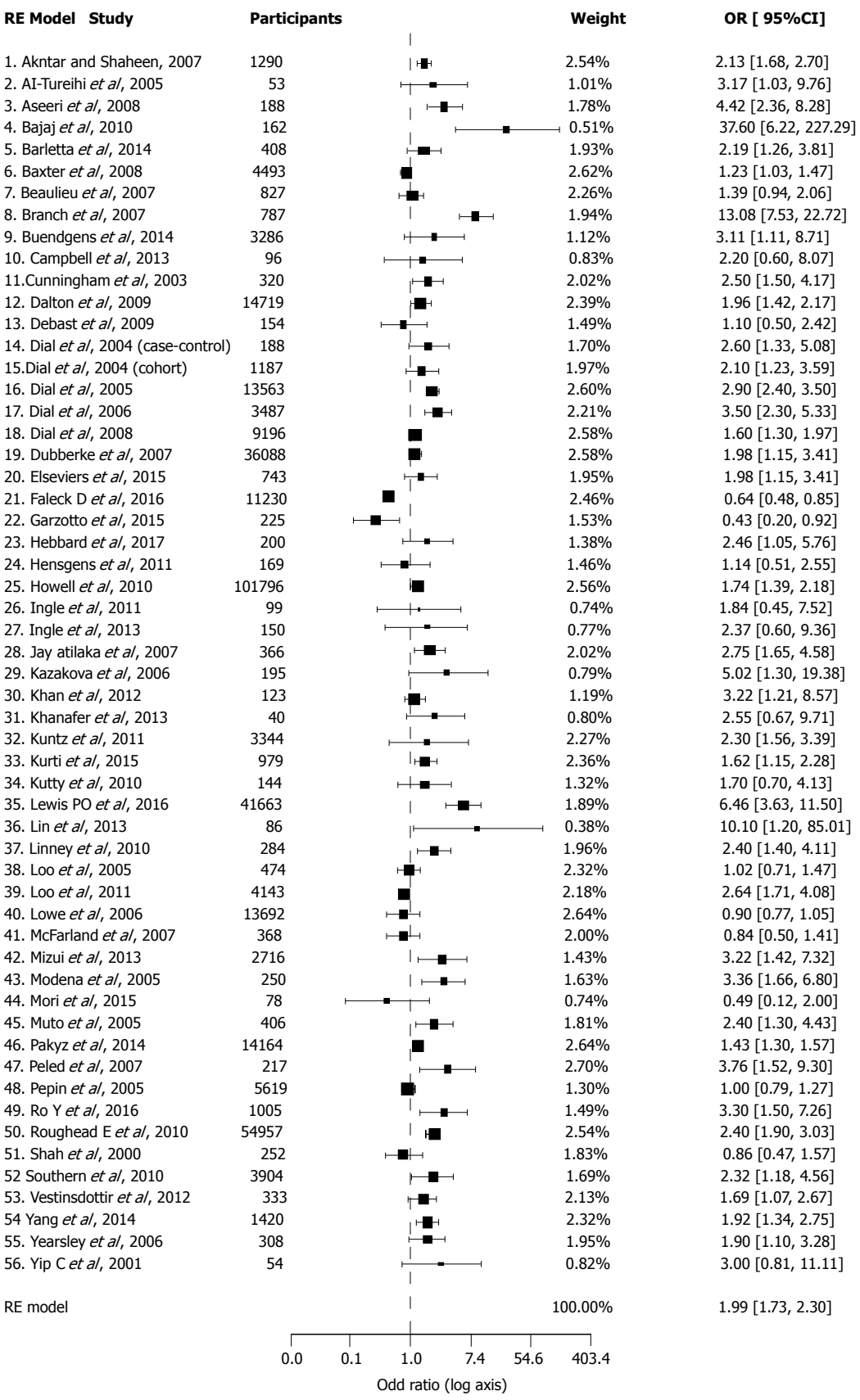

Figure 2 Forest plot of the meta-analysis.

0.0001). During the last years, six meta-analyses have been published on this topic, and all reported a positive association between PPIs use and the risk for CDI. Thus, Janarthanan *et al*[88] in a meta-analysis including

Table 2 Subgroup analysis

Subgroup analysis	No. of studies (n = 56)	ORs	95%CI	Heterogeneity, I^2, %	Heterogeneity between groups, P value
Study design					
Case-control	40	2	1.68-2.38	85.54	0.931
Cohort	16	1.98	1.51-2.59	85.99	
Study type					
Adjusted	38	1.95	1.67-2.27	85.02	0.856
Unadjusted	18	2.02	1.41-2.91	85.58	
Centers					
Unicentric	31	2.18	1.72-2.75	83.99	0.241
Multicentric	25	1.82	1.51-2.19	86.97	
Type					
Inpatient	43	1.95	1.67-2.29	84.99	0.868
Outpatient	6	2.1	1.36-3.24	84.84	
Mixt	7	2.19	1.39-3.45	76.77	
Region					
Europe	14	1.78	1.35-2.34	74.33	0.231
America	31	2	1.67-2.40	88.58	
Asia	11	2.31	1.96-2.72	89.18	
Age					
Age < 65 yr	6	2.06	1.11-3.81	35.39	0.86
Age ⩾ 65 yr	13	1.93	1.40-2.68	92.11	
NOS					
NOS ⩾ 7	26	1.88	1.55-2.28	87.65	0.441
NOS < 7	30	2.11	1.69-2.62	81.98	

CI: Confidence interval; NOS: Newcastle-Ottawa Quality Assessment Scale; ORs: Odds ratio.

23 observational studies with nearly 300000 patients found a 65% increase in the incidence of CDI among PPIs users with an estimated risk of 1.69 and 95%CI from 1.395 to 1.974. In another meta-analysis (30 studies, 202965 patients), Desphande *et al*[85] reported that PPI therapy was associated with a 2-fold increase in risk for CDI, but their study is limited by unadjusted risk estimates. Recently, the same team[90] performed a meta-analysis examining the relationship between PPI therapy and the risk for recurrent CDI, and found a positive association with the pooled risk ratio of 1.58 (95%CI: 1.13-2.21). A third meta-analysis by Kwok *et al*[87] including 42 studies (313000 participants) also found a statistically significant association between PPIs use and the risk for CDI compared with nonusers (OR = 2.51; 95%CI: 1.47-2.85; P = 0.05). Tleyjeh *et al*[86] in a systematic review and meta-analysis including 51 observational studies (37 case-control and 14 cohort) examining healthcare and community-associated CDI, found a very low quality evidence for an association between PPI therapy and CDI not supporting a cause-effect relationship. Authors reported a pooled OR of 1.65 (95%CI: 1.47-1.85) with evidence of publication bias and significant statistical heterogeneity among the studies (I^2 = 89.9%). More recently, Arriola *et al*[89] suggest, in a meta-analysis including only inpatients, that PPIs use significantly increases the risk of hospital-acquired CDI (OR = 1.81). Bavishi *et al*[114] in a systematic review regarding the use of PPI and increased susceptibility to enteric infection found 27 studies evaluating an association between PPI therapy and the risk of CDI, 17 of which reported a significant association. Based on an analysis of 28 studies, US FDA issued a warning on the risk of CDI with PPIs use[115], and similar warnings are found in CDI treatment guidelines[142].

Several studies reported that PPIs use is also a risk factor for community-acquired CDI. Dial *et al*[26], in a study including over 1000 cases of community-acquired CDI, found that patients who had received PPIs within the previous 90 d had a nearly 3-fold increased risk for CDI. A similar result was reported by Kutty *et al*[41] who found a 2-3-fold increased for community-acquired CDI in patients treated with PPIs within the previous 6 mo. Marwick *et al*[143] in a study including patients aged 65 years or older identified all cases of community-acquired CDI and found that patients prescribed PPIs within the previous 6 mo had a 1.7-fold increased risk for CDI compared to matched controls. A study assessing the epidemiology of community-acquired CDI found rates of PPI use of nearly 30% among patients with this infection compared to less than 3% in the general population[144]. These results indicate a similar degree of association between PPIs use and CDI risk, be it community-acquired CDI or hospital-acquired CDI[145].

Nevertheless, the association between PPIs use and the risk for CDI remains to a certain extent controversial despite the results reported above, as several studies failed to find such an association[11,27,34,94,122]. Beaulieu *et al*[27] found that the use of gastric acid-suppression therapy does not predispose to development of CDI, while McFarland *et al*[122] reported no relation between CDI and the use of PPIs. Branch *et al*[94] found that

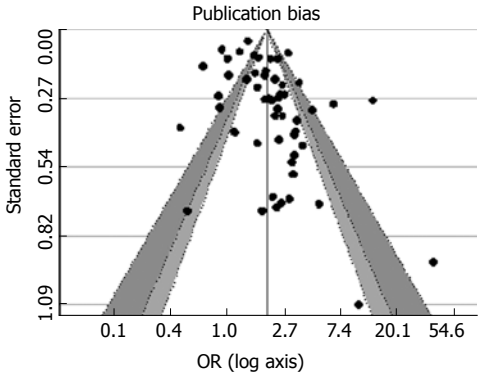

Figure 3 Funnel plot with 95% confidence limits.

PPI use did not increase the incidence of CDI in hospitalized patients.

The mechanism by which PPI therapy contributes to an increased risk of CDI is unclear. It has been proposed that a vegetative form of *C. difficile* survives in conditions of gastric pH greater than 4[114]-the threshold for enteric infections acquisition, including *C. difficile*. Howell *et al*[136] reported that the risk of nosocomial CDI rose with increasing levels of acid suppression. Hegarty *et al*[146] reported that PPI therapy decreased the expression of genes holding an important role in colonocyte integrity, thus favoring the development of CDI. Other studies show that long-term use of PPIs decreases microbial diversity, a condition found in patients with CDI[147].

As we have already mentioned, our subgroup analyses also showed an increased risk for CDI. There were no significant differences of effects between cohort and case-control studies, adjusted and unadjusted data, single-center and multicenter studies, hospitalized-and community-acquired CDI or among geographic regions. Advanced age is a well-known risk factor for CDI. To our surprise, we found no increased risk of CDI in elderly patients (≥ 65 years) using PPIs compared with youngers (OR = 1.93 *vs* OR = 2.06, P = 0.860). A possible explanation is that many of such patients may have atrophic gastritis with low gastric acid output[148] and PPIs use cannot further lower gastric acid secretion, without any additional risk of CDI[32].

As data regarding the association between PPI therapy and risk of CDI are supported only by observational studies, a final estimation of the real risk is not possible. It should be mentioned that randomized placebo-controlled clinical trials evaluating the association of PPIs use and the risk for CDI are ethically unfeasible and therefore, such studies could not be performed in the future. Thus, a weak association between PPI therapy and CDI does not confirm causality and could be the result of bias and uncontrolled confounding (*e.g.*, comorbidities, comedication use, *etc.*) which were lacking in most studies.

Our meta-analysis has some strengths such as the largest number of studies published to date, adjusted effect estimates concerning the association between PPI use and the risk of CDI, and subgroup analyses based on age, region, type, design and quality of the study. However, it also has several limitations: the included studies were observational, influenced by confounding variables despite statistical adjustment, the significant heterogeneity among most of them and lack of information regarding the dose and duration of PPI use as well as patient compliance to PPI therapy.

Although the above presented data from several meta-analyses and many studies demonstrated an association between PPI therapy and the risk for development of CDI, PPIs continue to be overused even in patients who are at high risk of CDI, because they are still considered "safe" drugs by most physicians. There is evidence that over half of PPI users who developed CDI had no valid indications for such therapy[25]. While in many countries PPIs are now totally available as over-the-counter medication, clinicians should inform their patients about the risk of CDI when PPIs are used on the long-term and without valid indication.

In spite of the aforementioned limitations of our and several other meta-analyses, clinicians should be aware of the risk of CDI when prescribing long-term PPI therapy, particularly in patients at high risk (*e.g.*, hospitalized patients on antibiotics). It should be underlined that PPIs remain, on the whole, a safe group of drugs[149], providing enormous benefits when prescribed for well-established indications. Unfortunately, many prescriptions fall outside accepted indications[90].

In conclusion, this systematic review and meta-analysis provides further evidence that PPI use significantly increases the risk for developing CDI, despite the substantial heterogeneity and publication bias present among studies. Due to the fact that all the studies included in our analysis are observational and cannot confirm causality, further large, high quality, prospective studies are needed to assess the association between PPI use and the risk of CDI.

COMMENTS

Background

Proton pump inhibitors (PPIs) are among the most widely prescribed agents by gastroenterologists because of their high efficacy and excellent safety profile. However, more recently, concerns have been raised about association between PPI therapy and several potentially serious adverse events including *Clostridium difficile* (*C. difficile*) infection (CDI). This systematic review and meta-analysis explored the existing evidence regarding the association of PPI therapy and CDI.

Research frontiers

Many observational studies and meta-analyses have reported conflicting results regarding the association between PPI therapy and the risk for CDI.

Innovations and breakthroughs

This systematic review and meta-analysis, including the largest number

of studies published to date, provides further evidence that PPI therapy is associated with an increased risk for development of CDI. Because all the studies analyzed were observational, with inherent limitations, the causality could not be confirmed.

Applications

Although our systematic review and meta-analysis, in line with previous studies and meta-analyses, reported an association between PPI therapy and the risk for development of CDI, such association remains controversial and a final estimation of the real risk has not been established. Further high-quality, prospective studies are needed to assess whether this association is causal. Until then, clinicians should be aware that long-term PPI therapy may be associated with the risk of CDI, and prescribe the PPIs in the lowest effective dose only to patients with a clear indication.

Terminology

PPIs are a group of potent inhibitors of gastric acid secretion. CDI is a symptomatic infection due to the spore-forming bacterium *C. difficile*.

Peer-review

This manuscript is an interesting, informative and well-presented meta-analysis on PPI therapy and risk of *C. difficile* infection.

REFERENCES

1 **Khanna S**, Pardi DS. The growing incidence and severity of Clostridium difficile infection in inpatient and outpatient settings. *Expert Rev Gastroenterol Hepatol* 2010; **4**: 409-416 [PMID: 20678014 DOI: 10.1586/egh.10.48]

2 **Kuntz JL**, Chrischilles EA, Pendergast JF, Herwaldt LA, Polgreen PM. Incidence of and risk factors for community-associated Clostridium difficile infection: a nested case-control study. *BMC Infect Dis* 2011; **11**: 194 [PMID: 21762504 DOI: 10.1186/1471-2334-11-194]

3 **Kurti Z**, Lovasz BD, Mandel MD, Csima Z, Golovics PA, Csako BD, Mohas A, Gönczi L, Gecse KB, Kiss LS, Szathmari M, Lakatos PL. Burden of Clostridium difficile infection between 2010 and 2013: Trends and outcomes from an academic center in Eastern Europe. *World J Gastroenterol* 2015; **21**: 6728-6735 [PMID: 26074711 DOI: 10.3748/wjg.v21.i21.6728]

4 **Honda H**, Dubberke ER. The changing epidemiology of Clostridium difficile infection. *Curr Opin Gastroenterol* 2014; **30**: 54-62 [PMID: 24285002 DOI: 10.1097/MOG.0000000000000018]

5 **Dubberke ER**, Butler AM, Yokoe DS, Mayer J, Hota B, Mangino JE, Khan YM, Popovich KJ, Fraser VJ. Multicenter study of Clostridium difficile infection rates from 2000 to 2006. *Infect Control Hosp Epidemiol* 2010; **31**: 1030-1037 [PMID: 20695799 DOI: 10.1086/656245]

6 **Peery AF**, Dellon ES, Lund J, Crockett SD, McGowan CE, Bulsiewicz WJ, Gangarosa LM, Thiny MT, Stizenberg K, Morgan DR, Ringel Y, Kim HP, Dibonaventura MD, Carroll CF, Allen JK, Cook SF, Sandler RS, Kappelman MD, Shaheen NJ. Burden of gastrointestinal disease in the United States: 2012 update. *Gastroenterology* 2012; **143**: 1179-1187.e1-e3 [PMID: 22885331 DOI: 10.1053/j.gastro.2012.08.002]

7 **Depestel DD**, Aronoff DM. Epidemiology of Clostridium difficile infection. *J Pharm Pract* 2013; **26**: 464-475 [PMID: 24064435 DOI: 10.1177/0897190013499521]

8 **Reveles KR**, Lee GC, Boyd NK, Frei CR. The rise in Clostridium difficile infection incidence among hospitalized adults in the United States: 2001-2010. *Am J Infect Control* 2014; **42**: 1028-1032 [PMID: 25278388 DOI: 10.1016/j.ajic.2014.06.011]

9 **Gabriel L**, Beriot-Mathiot A. Hospitalization stay and costs attributable to Clostridium difficile infection: a critical review. *J Hosp Infect* 2014; **88**: 12-21 [PMID: 24996516 DOI: 10.1016/j.jhin.2014.04.011]

10 **Thomas C**, Stevenson M, Riley TV. Antibiotics and hospital-acquired Clostridium difficile-associated diarrhoea: a systematic review. *J Antimicrob Chemother* 2003; **51**: 1339-1350 [PMID: 12746372 DOI: 10.1093/jac/dkg254]

11 **Pépin J**, Saheb N, Coulombe MA, Alary ME, Corriveau MP, Authier S, Leblanc M, Rivard G, Bettez M, Primeau V, Nguyen M, Jacob CE, Lanthier L. Emergence of fluoroquinolones as the predominant risk factor for Clostridium difficile-associated diarrhea: a cohort study during an epidemic in Quebec. *Clin Infect Dis* 2005; **41**: 1254-1260 [PMID: 16206099 DOI: 10.1086/496986]

12 **Taslim H**. Clostridium difficile infection in the elderly. *Acta Med Indones* 2009; **41**: 148-151 [PMID: 19752488]

13 **Lawrence SJ**, Puzniak LA, Shadel BN, Gillespie KN, Kollef MH, Mundy LM. Clostridium difficile in the intensive care unit: epidemiology, costs, and colonization pressure. *Infect Control Hosp Epidemiol* 2007; **28**: 123-130 [PMID: 17265392 DOI: 10.1086/511793]

14 **Eddi R**, Malik MN, Shakov R, Baddoura WJ, Chandran C, Debari VA. Chronic kidney disease as a risk factor for Clostridium difficile infection. *Nephrology* (Carlton) 2010; **15**: 471-475 [PMID: 20609100 DOI: 10.1111/j.1440-1797.2009.01274.x]

15 **Schneeweiss S**, Korzenik J, Solomon DH, Canning C, Lee J, Bressler B. Infliximab and other immunomodulating drugs in patients with inflammatory bowel disease and the risk of serious bacterial infections. *Aliment Pharmacol Ther* 2009; **30**: 253-264 [PMID: 19438424 DOI: 10.1111/j.1365-2036.2009.04037.x]

16 **Dubberke ER**, Olsen MA, Stwalley D, Kelly CP, Gerding DN, Young-Xu Y, Mahé C. Identification of Medicare Recipients at Highest Risk for Clostridium difficile Infection in the US by Population Attributable Risk Analysis. *PLoS One* 2016; **11**: e0146822 [PMID: 26859403 DOI: 10.1371/journal.pone.0146822]

17 **Ananthakrishnan AN**. Clostridium difficile infection: epidemiology, risk factors and management. *Nat Rev Gastroenterol Hepatol* 2011; **8**: 17-26 [PMID: 21119612 DOI: 10.1038/nrgastro.2010.190]

18 **Raza S**, Baig MA, Russell H, Gourdet Y, Berger BJ. Clostridium difficile infection following chemotherapy. *Recent Pat Antiinfect Drug Discov* 2010; **5**: 1-9 [PMID: 19929843 DOI: 10.2174/157489110790112608]

19 **Al-Tureihi FI**, Hassoun A, Wolf-Klein G, Isenberg H. Albumin, length of stay, and proton pump inhibitors: key factors in Clostridium difficile-associated disease in nursing home patients. *J Am Med Dir Assoc* 2005; **6**: 105-108 [PMID: 15871884 DOI: 10.1016/j.jamda.2005.01.003]

20 **Morfin-Otero R**, Garza-Gonzalez E, Aguirre-Diaz SA, Escobedo-Sanchez R, Esparza-Ahumada S, Perez-Gomez HR, Petersen-Morfin S, Gonzalez-Diaz E, Martinez-Melendez A, Rodriguez-Noriega E; Hospital Civil de Guadalajara, Fray Antonio Alcalde Clostridium difficile Team. Clostridium difficile outbreak caused by NAP1/BI/027 strain and non-027 strains in a Mexican hospital. *Braz J Infect Dis* 2016; **20**: 8-13 [PMID: 26620948 DOI: 10.1016/j.bjid.2015.09.008]

21 **Rotramel A**, Poritz LS, Messaris E, Berg A, Stewart DB. PPI therapy and albumin are better predictors of recurrent Clostridium difficile colitis than choice of antibiotics. *J Gastrointest Surg* 2012; **16**: 2267-2273 [PMID: 23007285 DOI: 10.1007/s11605-012-2037-9]

22 **Dalton BR**, Lye-Maccannell T, Henderson EA, Maccannell DR, Louie TJ. Proton pump inhibitors increase significantly the risk of Clostridium difficile infection in a low-endemicity, non-outbreak hospital setting. *Aliment Pharmacol Ther* 2009; **29**: 626-634 [PMID: 19183143 DOI: 10.1111/j.1365-2036.2008.03924.x]

23 **Aseeri M**, Schroeder T, Kramer J, Zackula R. Gastric acid suppression by proton pump inhibitors as a risk factor for clostridum difficile-associated diarrhea in hospitalized patients. *Am J Gastroenterol* 2008; **103**: 2308-2313 [PMID: 18702653 DOI: 10.1111/j.1572-0241.2008.01975.x]

24 **Linney S**, Fernandes T, Einarson T, Sengar A, Walker JH, Mills A. Association Between Use of Proton Pump Inhibitors and a Clostridium difficile-Associated Disease Outbreak: Case-Control Study. *Can J Hosp Pharm* 2010; **63**: 31-37 [PMID: 22478951 DOI: 10.4212/cjhp.v63i1.866]

25 **Yearsley KA**, Gilby LJ, Ramadas AV, Kubiak EM, Fone DL, Allison MC. Proton pump inhibitor therapy is a risk factor for Clostridium difficile-associated diarrhoea. *Aliment Pharmacol Ther* 2006; **24**: 613-619 [PMID: 16907893 DOI: 10.1111/j.1365-2036.2006.03015.x]

26 **Dial S**, Alrasadi K, Manoukian C, Huang A, Menzies D. Risk of Clostridium difficile diarrhea among hospital inpatients prescribed proton pump inhibitors: cohort and case-control studies. *CMAJ* 2004; **171**: 33-38 [PMID: 15238493 DOI: 10.1503/cmaj.1040876]

27 **Beaulieu M**, Williamson D, Pichette G, Lachaine J. Risk of Clostridium difficile-associated disease among patients receiving proton-pump inhibitors in a Quebec medical intensive care unit. *Infect Control Hosp Epidemiol* 2007; **28**: 1305-1307 [PMID: 17926283 DOI: 10.1086/521664]

28 **Pant C**, Madonia P, Minocha A. Does PPI therapy predispose to Clostridium difficile infection? *Nat Rev Gastroenterol Hepatol* 2009; **6**: 555-557 [PMID: 19713988 DOI: 10.1038/nrgastro.2009.128]

29 **Rashid S**, Rajan D, Iqbal J, Lipka S, Jacob R, Zilberman V, Shah M, Mustacchia P. Inappropriate Use of Gastric Acid Suppression Therapy in Hospitalized Patients with Clostridium difficile-Associated Diarrhea: A Ten-Year Retrospective Analysis. *ISRN Gastroenterol* 2012; **2012**: 902320 [PMID: 22701180 DOI: 10.5402/2012/902320]

30 **Choudhry MN**, Soran H, Ziglam HM. Overuse and inappropriate prescribing of proton pump inhibitors in patients with Clostridium difficile-associated disease. *QJM* 2008; **101**: 445-448 [PMID: 18411220 DOI: 10.1093/qjmed/hcn035]

31 **Patil R**, Blankenship L. Proton Pump Inhibitors and Clostridium Difficile Infection: Are We Propagating an Already Rapidly Growing Healthcare Problem? *Gastroenterology Res* 2013; **6**: 171-173 [PMID: 27785249 DOI: 10.4021/gr575w]

32 **Cunningham R**, Dial S. Is over-use of proton pump inhibitors fuelling the current epidemic of Clostridium difficile-associated diarrhoea? *J Hosp Infect* 2008; **70**: 1-6 [PMID: 18602190 DOI: 10.1016/j.jhin.2008.04.023]

33 **McCarthy DM**. Proton pump inhibitor use and Clostridium difficile colitis: cause or coincidence? *J Clin Gastroenterol* 2012; **46**: 350-353 [PMID: 22495812 DOI: 10.1097/MCG.0b013e31824b228f]

34 **Shah S**, Lewis A, Leopold D, Dunstan F, Woodhouse K. Gastric acid suppression does not promote clostridial diarrhoea in the elderly. *QJM* 2000; **93**: 175-181 [PMID: 10751237 DOI: 10.1093/qjmed/93.3.175]

35 **Naggie S**, Miller BA, Zuzak KB, Pence BW, Mayo AJ, Nicholson BP, Kutty PK, McDonald LC, Woods CW. A case-control study of community-associated Clostridium difficile infection: no role for proton pump inhibitors. *Am J Med* 2011; **124**: 276.e1-276.e7 [PMID: 21396512 DOI: 10.1016/j.amjmed.2010.10.013]

36 **Vindigni SM**, Surawicz CM. C. difficile Infection: Changing Epidemiology and Management Paradigms. *Clin Transl Gastroenterol* 2015; **6**: e99 [PMID: 26158611 DOI: 10.1038/ctg.2015.24]

37 **Rostom A**, Moayyedi P, Hunt R; Canadian Association of Gastroenterology Consensus Group. Canadian consensus guidelines on long-term nonsteroidal anti-inflammatory drug therapy and the need for gastroprotection: benefits versus risks. *Aliment Pharmacol Ther* 2009; **29**: 481-496 [PMID: 19053986 DOI: 10.1111/j.1365-2036.2008.03905.x]

38 **Campbell KA**, Phillips MS, Stachel A, Bosco JA 3rd, Mehta SA. Incidence and risk factors for hospital-acquired Clostridium difficile infection among inpatients in an orthopaedic tertiary care hospital. *J Hosp Infect* 2013; **83**: 146-149 [PMID: 23313026 DOI: 10.1016/j.jhin.2012.11.009]

39 **Khan FY**, Abu-Khattab M, Anand D, Baager K, Alaini A, Siddique MA, Mohamed SF, Ali MI, Al Bedawi MM, Naser MS. Epidemiological features of Clostridium difficile infection among inpatients at Hamad General Hospital in the state of Qatar, 2006-2009. *Travel Med Infect Dis* 2012; **10**: 179-185 [PMID: 22800937 DOI: 10.1016/j.tmaid.2012.06.004]

40 **Ingle M**, Deshmukh A, Desai D, Abraham P, Joshi A, Rodrigues C, Mankeshwar R. Prevalence and clinical course of Clostridium difficile infection in a tertiary-care hospital: a retrospective analysis. *Indian J Gastroenterol* 2011; **30**: 89-93 [PMID: 21553102 DOI: 10.1007/s12664-011-0097-5]

41 **Kutty PK**, Woods CW, Sena AC, Benoit SR, Naggie S, Frederick J, Evans S, Engel J, McDonald LC. Risk factors for and estimated incidence of community-associated Clostridium difficile infection, North Carolina, USA. *Emerg Infect Dis* 2010; **16**: 197-204 [PMID: 20113547 DOI: 10.3201/eid1602.090953]

42 **Faleck DM**, Salmasian H, Furuya EY, Larson EL, Abrams JA, Freedberg DE. Proton Pump Inhibitors Do Not Increase Risk for Clostridium difficile Infection in the Intensive Care Unit. *Am J Gastroenterol* 2016; **111**: 1641-1648 [PMID: 27575714 DOI: 10.1038/ajg.2016.343]

43 **Rodríguez Garzotto A**, Mérida García A, Muñoz Unceta N, Galera Lopez MM, Orellana-Miguel MÁ, Díaz-García CV, Cortijo-Cascajares S, Cortes-Funes H, Agulló-Ortuño MT. Risk factors associated with Clostridium difficile infection in adult oncology patients. *Support Care Cancer* 2015; **23**: 1569-1577 [PMID: 25410088 DOI: 10.1007/s00520-014-2506-7]

44 **Devlin JW**, Welage LS, Olsen KM. Proton pump inhibitor formulary considerations in the acutely ill. Part 2: Clinical efficacy, safety, and economics. *Ann Pharmacother* 2005; **39**: 1844-1851 [PMID: 16204393 DOI: 10.1345/aph.1G176]

45 **Attwood SE**, Ell C, Galmiche JP, Fiocca R, Hatlebakk JG, Hasselgren B, Långström G, Jahreskog M, Eklund S, Lind T, Lundell L. Long-term safety of proton pump inhibitor therapy assessed under controlled, randomised clinical trial conditions: data from the SOPRAN and LOTUS studies. *Aliment Pharmacol Ther* 2015; **41**: 1162-1174 [PMID: 25858519 DOI: 10.1111/apt.13194]

46 **Kyne L**, Hamel MB, Polavaram R, Kelly CP. Health care costs and mortality associated with nosocomial diarrhea due to Clostridium difficile. *Clin Infect Dis* 2002; **34**: 346-353 [PMID: 11774082 DOI: 10.1086/338260]

47 **Jacobson BC**, Ferris TG, Shea TL, Mahlis EM, Lee TH, Wang TC. Who is using chronic acid suppression therapy and why? *Am J Gastroenterol* 2003; **98**: 51-58 [PMID: 12526936 DOI: 10.1111/j.1572-0241.2003.07186.x]

48 **Kelly OB**, Dillane C, Patchett SE, Harewood GC, Murray FE. The Inappropriate Prescription of Oral Proton Pump Inhibitors in the Hospital Setting: A Prospective Cross-Sectional Study. *Dig Dis Sci* 2015; **60**: 2280-2286 [PMID: 25840918 DOI: 10.1007/s10620-015-3642-8]

49 **Craig DG**, Thimappa R, Anand V, Sebastian S. Inappropriate utilization of intravenous proton pump inhibitors in hospital practice--a prospective study of the extent of the problem and predictive factors. *QJM* 2010; **103**: 327-335 [PMID: 20211846 DOI: 10.1093/qjmed/hcq019]

50 **Moayyedi P**, Delaney BC, Vakil N, Forman D, Talley NJ. The efficacy of proton pump inhibitors in nonulcer dyspepsia: a systematic review and economic analysis. *Gastroenterology* 2004; **127**: 1329-1337 [PMID: 15521002 DOI: 10.1053/j.gastro.2004.08.026]

51 **Sebastian SS**, Kernan N, Qasim A, O'Morain CA, Buckley M. Appropriateness of gastric antisecretory therapy in hospital practice. *Ir J Med Sci* 2003; **172**: 115-117 [PMID: 14700112 DOI: 10.1007/BF02914494]

52 **Haroon M**, Yasin F, Gardezi SK, Adeeb F, Walker F. Inappropriate use of proton pump inhibitors among medical inpatients: a questionnaire-based observational study. *JRSM Short Rep* 2013; **4**: 2042533313497183 [PMID: 24040498 DOI: 10.1177/2042533313497183]

53 **Pappas M**, Jolly S, Vijan S. Defining Appropriate Use of Proton-Pump Inhibitors Among Medical Inpatients. *J Gen Intern Med* 2016; **31**: 364-371 [PMID: 26553337 DOI: 10.1007/s11606-015-3536-7]

54 **Ladd AM**, Panagopoulos G, Cohen J, Mar N, Graham R. Potential costs of inappropriate use of proton pump inhibitors. *Am J Med Sci* 2014; **347**: 446-451 [PMID: 24270078 DOI: 10.1097/

MAJ.0b013e31829f87d5]
55 **Shaheen NJ**, Hansen RA, Morgan DR, Gangarosa LM, Ringel Y, Thiny MT, Russo MW, Sandler RS. The burden of gastrointestinal and liver diseases, 2006. *Am J Gastroenterol* 2006; **101**: 2128-2138 [PMID: 16848807 DOI: 10.1111/j.1572-0241.2006.00723.x]
56 **Barkun AN**, Bardou M, Pham CQ, Martel M. Proton pump inhibitors vs. histamine 2 receptor antagonists for stress-related mucosal bleeding prophylaxis in critically ill patients: a meta-analysis. *Am J Gastroenterol* 2012; **107**: 507-520 ; quiz 521 [PMID: 22290403 DOI: 10.1038/ajg.2011.474]
57 **Yachimski PS**, Farrell EA, Hunt DP, Reid AE. Proton pump inhibitors for prophylaxis of nosocomial upper gastrointestinal tract bleeding: effect of standardized guidelines on prescribing practice. *Arch Intern Med* 2010; **170**: 779-783 [PMID: 20458085 DOI: 10.1001/archinternmed.2010.51]
58 **Alhazzani W**, Alenezi F, Jaeschke RZ, Moayyedi P, Cook DJ. Proton pump inhibitors versus histamine 2 receptor antagonists for stress ulcer prophylaxis in critically ill patients: a systematic review and meta-analysis. *Crit Care Med* 2013; **41**: 693-705 [PMID: 23318494 DOI: 10.1097/CCM.0b013e3182758734]
59 **Xiao YL**, Peng S, Tao J, Wang AJ, Lin JK, Hu PJ, Chen MH. Prevalence and symptom pattern of pathologic esophageal acid reflux in patients with functional dyspepsia based on the Rome III criteria. *Am J Gastroenterol* 2010; **105**: 2626-2631 [PMID: 20823838 DOI: 10.1038/ajg.2010.351]
60 **Cohen ME**, Hathway JM, Salmasian H, Liu J, Terry M, Abrams JA, Freedberg DE. Prophylaxis for Stress Ulcers With Proton Pump Inhibitors Is Not Associated With Increased Risk of Bloodstream Infections in the Intensive Care Unit. *Clin Gastroenterol Hepatol* 2017; **15**: 1030-1036.e1 [PMID: 28110095 DOI: 10.1016/j.cgh.2016.12.035]
61 **Yang YX**, Metz DC. Safety of proton pump inhibitor exposure. *Gastroenterology* 2010; **139**: 1115-1127 [PMID: 20727892 DOI: 10.1053/j.gastro.2010.08.023]
62 **Heidelbaugh JJ**, Goldberg KL, Inadomi JM. Overutilization of proton pump inhibitors: a review of cost-effectiveness and risk [corrected]. *Am J Gastroenterol* 2009; **104** Suppl 2: S27-S32 [PMID: 19262544 DOI: 10.1038/ajg.2009.49]
63 **Brunner G**, Athmann C, Schneider A. Long-term, open-label trial: safety and efficacy of continuous maintenance treatment with pantoprazole for up to 15 years in severe acid-peptic disease. *Aliment Pharmacol Ther* 2012; **36**: 37-47 [PMID: 22531114 DOI: 10.1111/j.1365-2036.2012.05106.x]
64 **Haastrup PF**, Paulsen MS, Christensen RD, Søndergaard J, Hansen JM, Jarbøl DE. Medical and non-medical predictors of initiating long-term use of proton pump inhibitors: a nationwide cohort study of first-time users during a 10-year period. *Aliment Pharmacol Ther* 2016; **44**: 78-87 [PMID: 27137875 DOI: 10.1111/apt.13649]
65 **Lambert AA**, Lam JO, Paik JJ, Ugarte-Gil C, Drummond MB, Crowell TA. Risk of community-acquired pneumonia with outpatient proton-pump inhibitor therapy: a systematic review and meta-analysis. *PLoS One* 2015; **10**: e0128004 [PMID: 26042842 DOI: 10.1371/journal.pone.0128004]
66 **de Groot MC**, Klungel OH, Leufkens HG, van Dijk L, Grobbee DE, van de Garde EM. Sources of heterogeneity in case-control studies on associations between statins, ACE-inhibitors, and proton pump inhibitors and risk of pneumonia. *Eur J Epidemiol* 2014; **29**: 767-775 [PMID: 25154551 DOI: 10.1007/s10654-014-9941-0]
67 **Eurich DT**, Sadowski CA, Simpson SH, Marrie TJ, Majumdar SR. Recurrent community-acquired pneumonia in patients starting acid-suppressing drugs. *Am J Med* 2010; **123**: 47-53 [PMID: 20102991 DOI: 10.1016/j.amjmed.2009.05.032]
68 **Cai D**, Feng W, Jiang Q. Acid-suppressive medications and risk of fracture: an updated meta-analysis. *Int J Clin Exp Med* 2015; **8**: 8893-8904 [PMID: 26309543]
69 **Leontiadis GI**, Moayyedi P. Proton pump inhibitors and risk of bone fractures. *Curr Treat Options Gastroenterol* 2014; **12**: 414-423 [PMID: 25209137 DOI: 10.1007/s11938-014-0030-y]
70 **Eom CS**, Park SM, Myung SK, Yun JM, Ahn JS. Use of acid-suppressive drugs and risk of fracture: a meta-analysis of observational studies. *Ann Fam Med* 2011; **9**: 257-267 [PMID: 21555754 DOI: 10.1370/afm.1243]
71 **Sierra F**, Suarez M, Rey M, Vela MF. Systematic review: Proton pump inhibitor-associated acute interstitial nephritis. *Aliment Pharmacol Ther* 2007; **26**: 545-553 [PMID: 17661758 DOI: 10.1111/j.1365-2036.2007.03407.x]
72 **Arora P**, Gupta A, Golzy M, Patel N, Carter RL, Jalal K, Lohr JW. Proton pump inhibitors are associated with increased risk of development of chronic kidney disease. *BMC Nephrol* 2016; **17**: 112 [PMID: 27487959 DOI: 10.1186/s12882-016-0325-4]
73 **Arora S**, Dellon ES. PPIs and Chronic Kidney Disease: Another Association to Worry About? *Gastroenterology* 2016; **151**: 366-368 [PMID: 27371880 DOI: 10.1053/j.gastro.2016.06.028]
74 **Wijarnpreecha K**, Thongprayoon C, Panjawatanan P, Ungprasert P. Proton pump inhibitors and risk of dementia. *Ann Transl Med* 2016; **4**: 240 [PMID: 27429966 DOI: 10.21037/atm.2016.06.14]
75 **Dam G**, Vilstrup H, Watson H, Jepsen P. Proton pump inhibitors as a risk factor for hepatic encephalopathy and spontaneous bacterial peritonitis in patients with cirrhosis with ascites. *Hepatology* 2016; **64**: 1265-1272 [PMID: 27474889 DOI: 10.1002/hep.28737]
76 **Xu HB**, Wang HD, Li CH, Ye S, Dong MS, Xia QJ, Zhang AQ, Pan K, Ge XL, Dong JH. Proton pump inhibitor use and risk of spontaneous bacterial peritonitis in cirrhotic patients: a systematic review and meta-analysis. *Genet Mol Res* 2015; **14**: 7490-7501 [PMID: 26214428 DOI: 10.4238/2015.July.3.25]
77 **Zhu W**, Hong K. Potential Cardiovascular Risks of Proton Pump Inhibitors in the General Population. *Int Heart J* 2017; **58**: 163-166 [PMID: 28321021 DOI: 10.1536/ihj.16-208]
78 **Shah NH**, LePendu P, Bauer-Mehren A, Ghebremariam YT, Iyer SV, Marcus J, Nead KT, Cooke JP, Leeper NJ. Proton Pump Inhibitor Usage and the Risk of Myocardial Infarction in the General Population. *PLoS One* 2015; **10**: e0124653 [PMID: 26061035 DOI: 10.1371/journal.pone.0124653]
79 **Heidelbaugh JJ**. Proton pump inhibitors and risk of vitamin and mineral deficiency: evidence and clinical implications. *Ther Adv Drug Saf* 2013; **4**: 125-133 [PMID: 25083257 DOI: 10.1177/2042098613482484]
80 **Hashimoto R**, Matsuda T, Chonan A. Iron-deficiency anemia caused by a proton pump inhibitor. *Intern Med* 2014; **53**: 2297-2299 [PMID: 25318791 DOI: 10.2169/internalmedicine.53.2743]
81 **Freedberg DE**, Kim LS, Yang YX. The Risks and Benefits of Long-term Use of Proton Pump Inhibitors: Expert Review and Best Practice Advice From the American Gastroenterological Association. *Gastroenterology* 2017; **152**: 706-715 [PMID: 28257716 DOI: 10.1053/j.gastro.2017.01.031]
82 **Thorens J**, Froehlich F, Schwizer W, Saraga E, Bille J, Gyr K, Duroux P, Nicolet M, Pignatelli B, Blum AL, Gonvers JJ, Fried M. Bacterial overgrowth during treatment with omeprazole compared with cimetidine: a prospective randomised double blind study. *Gut* 1996; **39**: 54-59 [PMID: 8881809 DOI: 10.1136/gut.39.1.54]
83 **Amir I**, Konikoff FM, Oppenheim M, Gophna U, Half EE. Gastric microbiota is altered in oesophagitis and Barrett's oesophagus and further modified by proton pump inhibitors. *Environ Microbiol* 2014; **16**: 2905-2914 [PMID: 24112768 DOI: 10.1111/1462-2920.12285]
84 **Zedtwitz-Liebenstein K**, Wenisch C, Patruta S, Parschalk B, Daxböck F, Graninger W. Omeprazole treatment diminishes intra- and extracellular neutrophil reactive oxygen production and bactericidal activity. *Crit Care Med* 2002; **30**: 1118-1122 [PMID: 12006811 DOI: 10.1097/00003246-200205000-00026]
85 **Deshpande A**, Pant C, Pasupuleti V, Rolston DD, Jain A, Deshpande N, Thota P, Sferra TJ, Hernandez AV. Association between proton pump inhibitor therapy and Clostridium difficile infection in a meta-analysis. *Clin Gastroenterol Hepatol* 2012; **10**: 225-233 [PMID: 22019794 DOI: 10.1016/j.cgh.2011.09.030]
86 **Tleyjeh IM**, Bin Abdulhak AA, Riaz M, Alasmari FA, Garbati MA, AlGhamdi M, Khan AR, Al Tannir M, Erwin PJ, Ibrahim T, Allehibi A, Baddour LM, Sutton AJ. Association between proton pump inhibitor therapy and clostridium difficile infection:

a contemporary systematic review and meta-analysis. *PLoS One* 2012; **7**: e50836 [PMID: 23236397 DOI: 10.1371/journal.pone.0050836]
87 **Kwok CS**, Arthur AK, Anibueze CI, Singh S, Cavallazzi R, Loke YK. Risk of Clostridium difficile infection with acid suppressing drugs and antibiotics: meta-analysis. *Am J Gastroenterol* 2012; **107**: 1011-1019 [PMID: 22525304 DOI: 10.1038/ajg.2012.108]
88 **Janarthanan S**, Ditah I, Adler DG, Ehrinpreis MN. Clostridium difficile-associated diarrhea and proton pump inhibitor therapy: a meta-analysis. *Am J Gastroenterol* 2012; **107**: 1001-1010 [PMID: 22710578 DOI: 10.1038/ajg.2012.179]
89 **Arriola V**, Tischendorf J, Musuuza J, Barker A, Rozelle JW, Safdar N. Assessing the Risk of Hospital-Acquired Clostridium Difficile Infection With Proton Pump Inhibitor Use: A Meta-Analysis. *Infect Control Hosp Epidemiol* 2016; **37**: 1408-1417 [PMID: 27677811 DOI: 10.1017/ice.2016.194]
90 **Deshpande A**, Pasupuleti V, Thota P, Pant C, Rolston DD, Hernandez AV, Donskey CJ, Fraser TG. Risk factors for recurrent Clostridium difficile infection: a systematic review and meta-analysis. *Infect Control Hosp Epidemiol* 2015; **36**: 452-460 [PMID: 25626326 DOI: 10.1017/ice.2014.88]
91 **Akhtar AJ**, Shaheen M. Increasing incidence of clostridium difficile-associated diarrhea in African-American and Hispanic patients: association with the use of proton pump inhibitor therapy. *J Natl Med Assoc* 2007; **99**: 500-504 [PMID: 17534007]
92 **Barletta JF**, Sclar DA. Proton pump inhibitors increase the risk for hospital-acquired Clostridium difficile infection in critically ill patients. *Crit Care* 2014; **18**: 714 [PMID: 25540023 DOI: 10.1186/s13054-014-0714-7]
93 **Baxter R**, Ray GT, Fireman BH. Case-control study of antibiotic use and subsequent *Clostridium difficile*-associated diarrhea in hospitalized patients. *Infect Control Hosp Epidemiol* 2008; **29**: 44-50 [PMID: 18171186 DOI: 10.1086/524320]
94 **Branch K,** Yahl V, Kier K, Mertz N, Marques S. Gastric acid suppression by proton pump inhibitors as an independent risk factor for-associated diarrhea. *P&T* 2007; **32**: 432-437
95 **Buendgens L**, Bruensing J, Matthes M, Dückers H, Luedde T, Trautwein C, Tacke F, Koch A. Administration of proton pump inhibitors in critically ill medical patients is associated with increased risk of developing Clostridium difficile-associated diarrhea. *J Crit Care* 2014; **29**: 696.e11-696.e15 [PMID: 24674763 DOI: 10.1016/j.jcrc.2014.03.002]
96 **Cunningham R**, Dale B, Undy B, Gaunt N. Proton pump inhibitors as a risk factor for Clostridium difficile diarrhoea. *J Hosp Infect* 2003; **54**: 243-245 [PMID: 12855243 DOI: 10.1016/S0195-6701(03)00088-4]
97 **Dial S**, Delaney JA, Schneider V, Suissa S. Proton pump inhibitor use and risk of community-acquired Clostridium difficile-associated disease defined by prescription for oral vancomycin therapy. *CMAJ* 2006; **175**: 745-748 [PMID: 17001054 DOI: 10.1503/cmaj.060284]
98 **Dial S**, Delaney JA, Barkun AN, Suissa S. Use of gastric acid-suppressive agents and the risk of community-acquired Clostridium difficile-associated disease. *JAMA* 2005; **294**: 2989-2995 [PMID: 16414946 DOI: 10.1001/jama.294.23.2989]
99 **Dubberke ER**, Reske KA, Olsen MA, McMullen KM, Mayfield JL, McDonald LC, Fraser VJ. Evaluation of Clostridium difficile-associated disease pressure as a risk factor for C difficile-associated disease. *Arch Intern Med* 2007; **167**: 1092-1097 [PMID: 17533213 DOI: 10.1001/archinte.167.10.1092]
100 **Elseviers MM**, Van Camp Y, Nayaert S, Duré K, Annemans L, Tanghe A, Vermeersch S. Prevalence and management of antibiotic associated diarrhea in general hospitals. *BMC Infect Dis* 2015; **15**: 129 [PMID: 25888351 DOI: 10.1186/s12879-015-0869-0]
101 **Jayatilaka S**, Shakov R, Eddi R, Bakaj G, Baddoura WJ, DeBari VA. Clostridium difficile infection in an urban medical center: five-year analysis of infection rates among adult admissions and association with the use of proton pump inhibitors. *Ann Clin Lab Sci* 2007; **37**: 241-247 [PMID: 17709687]
102 **Kazakova SV**, Ware K, Baughman B, Bilukha O, Paradis A, Sears S, Thompson A, Jensen B, Wiggs L, Bessette J, Martin J, Clukey J, Gensheimer K, Killgore G, McDonald LC. A hospital outbreak of diarrhea due to an emerging epidemic strain of Clostridium difficile. *Arch Intern Med* 2006; **166**: 2518-2524 [PMID: 17159019 DOI: 10.1001/archinte.166.22.2518]
103 **Lewis PO**, Litchfield JM, Tharp JL, Garcia RM, Pourmorteza M, Reddy CM. Risk and Severity of Hospital-Acquired Clostridium difficile Infection in Patients Taking Proton Pump Inhibitors. *Pharmacotherapy* 2016; **36**: 986-993 [PMID: 27455386 DOI: 10.1002/phar.1801]
104 **Mizui T**, Teramachi H, Tachi T, Tamura K, Shiga H, Komada N, Umeda M, Koda A, Aoyama S, Goto C, Tsuchiya T. Risk factors for Clostridium difficile-associated diarrhea and the effectiveness of prophylactic probiotic therapy. *Pharmazie* 2013; **68**: 706-710 [PMID: 24020129]
105 **Modena S**, Bearelly D, Swartz K, Friedenberg FK. Clostridium difficile among hospitalized patients receiving antibiotics: a case-control study. *Infect Control Hosp Epidemiol* 2005; **26**: 685-690 [PMID: 16156324 DOI: 10.1086/502603]
106 **Muto CA**, Pokrywka M, Shutt K, Mendelsohn AB, Nouri K, Posey K, Roberts T, Croyle K, Krystofiak S, Patel-Brown S, Pasculle AW, Paterson DL, Saul M, Harrison LH. A large outbreak of Clostridium difficile-associated disease with an unexpected proportion of deaths and colectomies at a teaching hospital following increased fluoroquinolone use. *Infect Control Hosp Epidemiol* 2005; **26**: 273-280 [PMID: 15796280 DOI: 10.1086/502539]
107 **Pakyz AL**, Jawahar R, Wang Q, Harpe SE. Medication risk factors associated with healthcare-associated Clostridium difficile infection: a multilevel model case-control study among 64 US academic medical centres. *J Antimicrob Chemother* 2014; **69**: 1127-1131 [PMID: 24327619 DOI: 10.1093/jac/dkt489]
108 **Peled N**, Pitlik S, Samra Z, Kazakov A, Bloch Y, Bishara J. Predicting Clostridium difficile toxin in hospitalized patients with antibiotic-associated diarrhea. *Infect Control Hosp Epidemiol* 2007; **28**: 377-381 [PMID: 17385141 DOI: 10.1086/513723]
109 **Roughead EE**, Chan EW, Choi NK, Griffiths J, Jin XM, Lee J, Kimura M, Kimura T, Kubota K, Lai EC, Man KK, Nguyen TA, Ooba N, Park BJ, Sato T, Shin JY, Wang T, Wong IC, Yang YK, Pratt NL. Proton pump inhibitors and risk of Clostridium difficile infection: a multi-country study using sequence symmetry analysis. *Expert Opin Drug Saf* 2016; **15**: 1589-1595 [PMID: 27645304 DOI: 10.1080/14740338.2016.1238071]
110 **Southern WN**, Rahmani R, Aroniadis O, Khorshidi I, Thanjan A, Ibrahim C, Brandt LJ. Postoperative Clostridium difficile-associated diarrhea. *Surgery* 2010; **148**: 24-30 [PMID: 20116817 DOI: 10.1016/j.surg.2009.11.021]
111 **Vesteinsdottir I**, Gudlaugsdottir S, Einarsdottir R, Kalaitzakis E, Sigurdardottir O, Bjornsson ES. Risk factors for Clostridium difficile toxin-positive diarrhea: a population-based prospective case-control study. *Eur J Clin Microbiol Infect Dis* 2012; **31**: 2601-2610 [PMID: 22441775 DOI: 10.1007/s10096-012-1603-0]
112 **Yang BK**, Do BJ, Kim EJ, Lee JU, Kim MH, Kang JG, Kim HS, Kim KH, Jang MK, Lee JH, Kim HY, Shin WG. The simple predictors of pseudomembranous colitis in patients with hospital-acquired diarrhea: a prospective observational study. *Gut Liver* 2014; **8**: 41-48 [PMID: 24516700 DOI: 10.5009/gnl.2014.8.1.41]
113 **Leonard J**, Marshall JK, Moayyedi P. Systematic review of the risk of enteric infection in patients taking acid suppression. *Am J Gastroenterol* 2007; **102**: 2047-2056 [PMID: 17509031 DOI: 10.1111/j.1572-0241.2007.01275.x]
114 **Bavishi C**, Dupont HL. Systematic review: the use of proton pump inhibitors and increased susceptibility to enteric infection. *Aliment Pharmacol Ther* 2011; **34**: 1269-1281 [PMID: 21999643 DOI: 10.1111/j.1365-2036.2011.04874.x]
115 **US Food and Drug Administration.** Clostridium difficile-associated diarrhea can be associated with stomach acid drugs known as proton pump inhibitors (PPIs). RDA Drug Safety Communication; 2012 Available from: URL: http://www.fda.gov/Drugs/DrugSafety/ucm 290510.htm
116 **Debast SB**, Vaessen N, Choudry A, Wiegers-Ligtvoet EA, van

den Berg RJ, Kuijper EJ. Successful combat of an outbreak due to Clostridium difficile PCR ribotype 027 and recognition of specific risk factors. *Clin Microbiol Infect* 2009; **15**: 427-434 [PMID: 19416295 DOI: 10.1111/j.1469-0691.2009.02713.x]

117 **Hensgens MP**, Goorhuis A, van Kinschot CM, Crobach MJ, Harmanus C, Kuijper EJ. Clostridium difficile infection in an endemic setting in the Netherlands. *Eur J Clin Microbiol Infect Dis* 2011; **30**: 587-593 [PMID: 21194003 DOI: 10.1007/s10096-010-1127-4]

118 **Ingle M**, Deshmukh A, Desai D, Abraham P, Joshi A, Gupta T, Rodrigues C. Clostridium difficile as a cause of acute diarrhea: a prospective study in a tertiary care center. *Indian J Gastroenterol* 2013; **32**: 179-183 [PMID: 23526401 DOI: 10.1007/s12664-013-0303-8]

119 **Khanafer N**, Touré A, Chambrier C, Cour M, Reverdy ME, Argaud L, Vanhems P. Predictors of Clostridium difficile infection severity in patients hospitalised in medical intensive care. *World J Gastroenterol* 2013; **19**: 8034-8041 [PMID: 24307797 DOI: 10.3748/wjg.v19.i44.8034]

120 **Loo VG**, Poirier L, Miller MA, Oughton M, Libman MD, Michaud S, Bourgault AM, Nguyen T, Frenette C, Kelly M, Vibien A, Brassard P, Fenn S, Dewar K, Hudson TJ, Horn R, René P, Monczak Y, Dascal A. A predominantly clonal multi-institutional outbreak of Clostridium difficile-associated diarrhea with high morbidity and mortality. *N Engl J Med* 2005; **353**: 2442-2449 [PMID: 16322602 DOI: 10.1056/NEJMoa051639]

121 **Lowe DO**, Mamdani MM, Kopp A, Low DE, Juurlink DN. Proton pump inhibitors and hospitalization for Clostridium difficile-associated disease: a population-based study. *Clin Infect Dis* 2006; **43**: 1272-1276 [PMID: 17051491 DOI: 10.1086/508453]

122 **McFarland LV**. Update on the changing epidemiology of Clostridium difficile-associated disease. *Nat Clin Pract Gastroenterol Hepatol* 2008; **5**: 40-48 [PMID: 18174906 DOI: 10.1038/ncpgasthep1029]

123 **Mori N**, Aoki Y. Clinical characteristics and risk factors for community-acquired Clostridium difficile infection: A retrospective, case-control study in a tertiary care hospital in Japan. *J Infect Chemother* 2015; **21**: 864-867 [PMID: 26482373 DOI: 10.1016/j.jiac.2015.09.004]

124 **Wells G,** Shea B, O'connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa: Ottawa Hospital Research Institute; Accessed on 2017-3-15 Available from: URL: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

125 **Higgins JPT,** Green S. Cochrane Handbook for Systematic Reviews of Interventions: Version 5.1.0. The Cochrane Collaboration 2011. Available from: URL: http://www.cochrane-handbook.org

126 **Stroup DF**, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; **283**: 2008-2012 [PMID: 10789670 DOI: 10.1001/jama.283.15.2008]

127 **DerSimonian R**, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7**: 177-188 [PMID: 3802833 DOI: 10.1016/0197-2456(86)90046-2]

128 **Higgins JP**, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**: 557-560 [PMID: 12958120 DOI: 10.1136/bmj.327.7414.557]

129 **Higgins JP**, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; **21**: 1539-1558 [PMID: 12111919 DOI: 10.1002/sim.1186]

130 **Egger M**, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315**: 629-634 [PMID: 9310563 DOI: 10.1136/bmj.315.7109.629]

131 **Easterbrook PJ**, Berlin JA, Gopalan R, Matthews DR. Publication bias in clinical research. *Lancet* 1991; **337**: 867-872 [PMID: 1672966 DOI: 10.1016/0140-6736(91)90201-Y]

132 **Viechtbauer W**. Conducting meta-analyses in R with the metafor package. *J Stat Softw* 2010; **36**: 1-48 Available from: URL: https://doi.org/10.18637/jss.v036.i03

133 **Bajaj JS**, Ananthakrishnan AN, Hafeezullah M, Zadvornova Y, Dye A, McGinley EL, Saeian K, Heuman D, Sanyal AJ, Hoffmann RG. Clostridium difficile is associated with poor outcomes in patients with cirrhosis: A national and tertiary center perspective. *Am J Gastroenterol* 2010; **105**: 106-113 [PMID: 19844204 DOI: 10.1038/ajg.2009.615]

134 **Dial S**, Kezouh A, Dascal A, Barkun A, Suissa S. Patterns of antibiotic use and risk of hospital admission because of Clostridium difficile infection. *CMAJ* 2008; **179**: 767-772 [PMID: 18838451 DOI: 10.1503/cmaj.071812]

135 **Hebbard AIT**, Slavin MA, Reed C, Trubiano JA, Teh BW, Haeusler GM, Thursky KA, Worth LJ. Risks factors and outcomes of Clostridium difficile infection in patients with cancer: a matched case-control study. *Support Care Cancer* 2017; **25**: 1923-1930 [PMID: 28155020 DOI: 10.1007/s00520-017-3606-y]

136 **Howell MD**, Novack V, Grgurich P, Soulliard D, Novack L, Pencina M, Talmor D. Iatrogenic gastric acid suppression and the risk of nosocomial Clostridium difficile infection. *Arch Intern Med* 2010; **170**: 784-790 [PMID: 20458086 DOI: 10.1001/archinternmed.2010.89]

137 **Lin YC**, Huang YT, Lee TF, Lee NY, Liao CH, Lin SY, Ko WC, Hsueh PR. Characteristics of patients with Clostridium difficile infection in Taiwan. *Epidemiol Infect* 2013; **141**: 2031-2038 [PMID: 23218131 DOI: 10.1017/S0950268812002749]

138 **Loo VG**, Bourgault AM, Poirier L, Lamothe F, Michaud S, Turgeon N, Toye B, Beaudoin A, Frost EH, Gilca R, Brassard P, Dendukuri N, Béliveau C, Oughton M, Brukner I, Dascal A. Host and pathogen factors for Clostridium difficile infection and colonization. *N Engl J Med* 2011; **365**: 1693-1703 [PMID: 22047560 DOI: 10.1056/NEJMoa1012413]

139 **Ro Y**, Eun CS, Kim HS, Kim JY, Byun YJ, Yoo KS, Han DS. Risk of Clostridium difficile Infection with the Use of a Proton Pump Inhibitor for Stress Ulcer Prophylaxis in Critically Ill Patients. *Gut Liver* 2016; **10**: 581-586 [PMID: 27021503 DOI: 10.5009/gnl15324]

140 **Yip C**, Loeb M, Salama S, Moss L, Olde J. Quinolone use as a risk factor for nosocomial Clostridium difficile-associated diarrhea. *Infect Control Hosp Epidemiol* 2001; **22**: 572-575 [PMID: 11732787 DOI: 10.1086/501954]

141 **Walker KJ**, Gilliland SS, Vance-Bryan K, Moody JA, Larsson AJ, Rotschafer JC, Guay DR. Clostridium difficile colonization in residents of long-term care facilities: prevalence and risk factors. *J Am Geriatr Soc* 1993; **41**: 940-946 [PMID: 8104968 DOI: 10.1111/j.1532-5415.1993.tb06759.x]

142 **Surawicz CM**, Brandt LJ, Binion DG, Ananthakrishnan AN, Curry SR, Gilligan PH, McFarland LV, Mellow M, Zuckerbraun BS. Guidelines for diagnosis, treatment, and prevention of Clostridium difficile infections. *Am J Gastroenterol* 2013; **108**: 478-498; quiz 499 [PMID: 23439232 DOI: 10.1038/ajg.2013.4]

143 **Marwick CA**, Yu N, Lockhart MC, McGuigan CC, Wiuff C, Davey PG, Donnan PT. Community-associated Clostridium difficile infection among older people in Tayside, Scotland, is associated with antibiotic exposure and care home residence: cohort study with nested case-control. *J Antimicrob Chemother* 2013; **68**: 2927-2933 [PMID: 23825381 DOI: 10.1093/jac/dkt257]

144 **Chitnis AS**, Holzbauer SM, Belflower RM, Winston LG, Bamberg WM, Lyons C, Farley MM, Dumyati GK, Wilson LE, Beldavs ZG, Dunn JR, Gould LH, MacCannell DR, Gerding DN, McDonald LC, Lessa FC. Epidemiology of community-associated Clostridium difficile infection, 2009 through 2011. *JAMA Intern Med* 2013; **173**: 1359-1367 [PMID: 23780507 DOI: 10.1001/jamainternmed.2013.7056]

145 **Freedberg DE**, Salmasian H, Friedman C, Abrams JA. Proton pump inhibitors and risk for recurrent Clostridium difficile infection among inpatients. *Am J Gastroenterol* 2013; **108**: 1794-1801 [PMID: 24060760 DOI: 10.1038/ajg.2013.333]

146 **Hegarty JP**, Sangster W, Harris LR 3rd, Stewart DB. Proton pump

inhibitors induce changes in colonocyte gene expression that may affect Clostridium difficile infection. *Surgery* 2014; **156**: 972-978 [PMID: 25151556 DOI: 10.1016/j.surg.2014.06.074]

147 **Seto CT**, Jeraldo P, Orenstein R, Chia N, DiBaise JK. Prolonged use of a proton pump inhibitor reduces microbial diversity: implications for Clostridium difficile susceptibility. *Microbiome* 2014; **2**: 42 [PMID: 25426290 DOI: 10.1186/2049-2618-2-42]

148 **Husebye E**, Skar V, Høverstad T, Melby K. Fasting hypochlorhydria with gram positive gastric flora is highly prevalent in healthy old people. *Gut* 1992; **33**: 1331-1337 [PMID: 1446855 DOI: 10.1136/gut.33.10.1331]

149 **Scarpignato C**, Gatta L, Zullo A, Blandizzi C; SIF-AIGO-FIMMG Group; Italian Society of Pharmacology, the Italian Association of Hospital Gastroenterologists, and the Italian Federation of General Practitioners. Effective and safe proton pump inhibitor therapy in acid-related diseases - A position paper addressing benefits and potential harms of acid suppression. *BMC Med* 2016; **14**: 179 [PMID: 27825371 DOI: 10.1186/s12916-016-0718-z]

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