Clinical Infectious Diseases

MAJOR ARTICLE

Acid Suppression Medications During Hospitalization as a Risk Factor for Recurrence of *Clostridioides difficile* Infection: Systematic Review and Meta-analysis

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Background. Studies have had conflicting results regarding the influence of acid-suppression medications (ASMs) during hospitalization on the recurrence of *Clostridioides difficile* infection (CDI).

Methods. A systematic review and meta-analysis investigating the association between recurrent CDI and ASM use in inpatients was performed. Relevant literature was identified using Medline, Google Scholar, and Web of Science. All human studies were considered regardless of publication date. Case-control and cohort studies and clinical trials were included if they contained the necessary information to calculate appropriate statistics related to the objective of this study. Review articles, meta-analyses, and commentaries were excluded; however, their references were searched to identify any studies missed. The random-effects model was selected since significant heterogeneity in study design was identified. To evaluate the sensitivity of the analysis various subgroup analyses were performed.

Results. Our search identified 9 studies involving 5668 patients of whom 1003 (17.7%) developed recurrent CDI. Patients on ASM were 64% more likely to develop recurrent CDI than patients not on ASM (OR, 1.64; 95% CI, 1.13–2.38; $P = .009$; $I^2 = 79.54\%$). Proton pump inhibitor (PPI) use was associated with an 84% increased risk of recurrent CDI versus no ASM (OR, 1.84; 95% CI, 1.18–2.85; $P = .007$; $I^2 = 83.4\%$).

Conclusions. ASM use during hospitalization was associated with a 64% increase in recurrent CDI. The association was greater with PPI use. Due to significant heterogeneity in the analyses, additional studies are essential to further elucidate iatrogenic effects of ASM. Unnecessary PPI use should be discontinued.

Keywords. acid suppression; *Clostridioides difficile* infection; proton pump inhibitors; histamine 2 receptor antagonists; meta-analysis.

Clostridioides difficile infection (CDI) is associated with significant morbidity and mortality. An estimated 500 000 cases of CDI are diagnosed in the United States annually [1]. Recurrence of infection is common, with 1 report suggesting that 83 000 patients will have a least 1 recurrence [2]. While traditional risk factors for recurrent CDI include antibiotic exposure, recent hospitalization, and increasing age, the use of acid-suppressive medications (ASMs), particularly proton pump inhibitors (PPIs), has also proven to be an important risk factor to consider, particularly because ASM use is modifiable [2, 3].

Both histamine-2 receptor antagonists (H2RAs) and PPIs are commonly used ASMs that are available as both prescription and over-the-counter medications to treat acid-related disorders [4]. However, these medications are often overprescribed [4]. Up to 73.9% of ASMs used in hospitalized patients have been reported to be unnecessary; furthermore, the use of ASMs during CDI treatment is common (up to 50% of patients) and they are rarely discontinued [5]. Multiple studies suggest an increased risk of CDI and CDI recurrence with the use of ASMs [5–14]; however, many of these studies included small sample sizes, had variable definitions of exposure and outcome, used different study designs, and combined multiple forms of ASMs into 1 composite. Due to small sample sizes the point estimates suggested by some of these studies may be imprecise and subgroup analyses are not possible [10]. Previous meta-analyses have been performed, but these analyses did not provide evaluations by filtering out inpatient studies alone [15]. This distinction is important because it is commonly seen that studies that contain an outpatient population often display less integrity or accuracy in terms of data, since compliance cannot be monitored. Furthermore, the inpatient setting presents an opportunity to discontinue and counsel patients on the importance of

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avoiding ASM, during CDI treatment and to reduce the risk of recurrence. Therefore, we performed a systematic review and meta-analysis to study specifically the inpatient population and the association between ASMs and recurrence of CDI.

METHODS

Data Sources and Search Strategy

A literature search using Ovid MEDLINE, PubMed, and Google Scholar with no limitations on date (from inception to 1 December 2019) and language to ensure that the search would be as inclusive as possible was performed. Controlled vocabulary, keywords, and Medical Education Subject Heading (MeSH) terms were used to identify relevant studies. The terms "*Clostridium/Clostridioides difficile* infection," "proton pump inhibitors," "histamine-receptor 2 antagonists," and "acid suppression" were used in various combinations. Article titles and abstracts were reviewed by 2 investigators independently (P. M. and L. B.) for inclusion. Results were compared and discrepancies were resolved in group discussions. All study references were scanned to identify literature not captured using the search strategy above. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was used to guide reporting of the systematic review and meta-analysis [16].

Selection Criteria

The studies considered in the analysis included case-control studies, cohort studies, and clinical trials. To be eligible for inclusion in the meta-analysis, statistics or raw numbers relating to a population of patients with recurrent CDI and previous CDI treatment with concomitant use of PPIs, H2RAs, or any ASM was required. We excluded studies that did not provide statistics relating to both exposures to ASMs during the index CDI treatment and nonexposure, which would prevent the calculation of appropriate statistics. The analysis was limited to studies that included adult patients. The investigators extracted all pertinent data from the individual studies. A summary of this information may be reviewed in Table 1 [6, 8, 9, 11–13, 17–19]. The Newcastle-Ottawa Scale was used to assess the quality of cohort and case-control studies and is included in Supplementary Table 1 [20].

Outcomes Assessed

Our primary analysis focused on the risk of CDI recurrence in patients on any ASM. We performed subgroup analyses including individuals on PPI therapy during CDI to identify whether recurrence was dependent on ASM drug class. While there were various definitions for CDI recurrence reported in the literature, they ranged from 10 to 90 days after resolution and generally incorporated some form of testing for active disease.

Statistical Analyses

We deduced that because data were extracted from a variety of study designs, populations, and geographic locations, the random-effects model would represent the optimal choice for analysis. However, to ensure accuracy and for completeness,

Table 1. Summary of Study Characteristics

Study	Design	Location	Recurrent CDI Definition[a]	ASM/Exposure Assessment/ Intensity	Diagnostics	Adjusted for Confounding/ Accounted for Death
Abdelfatah et al, 2015 [6]	Retrospective case-control	United States	Recurs between day 10 and 90	PPI/extracted from health record/intensity not defined	PCR	Hierarchal linear regression/ 30-day mortality
Freedburg et al, 2013 [8]	Retrospective cohort	United States	Recurs between day 15 and 90	PPI/daily for at least 2 days during CDI/intensity defined	PCR	Multivariable regression/90-day death
Herbert et al, 2013 [9]	Retrospective cohort	United States	Recurs between day 15 and 56	PPI/extracted from clinical data warehouse/intensity not defined	PCR	Multivariable regression/ removed encounters within 56 days of death
Kim et al, 2010 [11]	Retrospective case-control	Korea	Recurs within 90 days	PPI/at least 3 days before and then continued during CDI/ intensity not defined	ELISA	Multivariate analysis/not reported
Kyne et al, 2001 [12]	Prospective cohort	United States	Recurs within 60 days	Not specified/recorded at study entry/intensity not defined	ELISA	Multivariable regression/not reported
McDonald et al, 2015 [13]	Retrospective cohort	Canada	Recurs within 15–90 days	PPI/detailed exposure data/ intensity defined	PCR	Cox proportional hazards/ 90-day mortality
Rodríguez-Pardo et al, 2013 [17]	Prospective cohort	Spain	Recurs within 8 weeks	PPI/assessed with questionnaire and adjudication by site investigator/intensity not defined	ELISA	Multivariate analysis/death included in endpoint
Samie et al, 2013 [18]	Retrospective cohort	Germany	Recurs within 60 days	PPI/not defined/intensity not defined	ELISA	Multinominal logistic regression/not described
Weiss et al, 2015 [19]	Prospective cohort	United States, Canada, Europe	Recurs within 30 days	PPI or H2RA/extracted from phase III case report forms/ intensity defined	Not specified	Multivariate analysis/death included in endpoint

Abbreviations: ASM, acid-suppression medication; CDI, *Clostridioides difficile* infection; ELISA, enzyme-linked immunosorbent assay; H2RA, histamine-2 receptor antagonist; PCR, polymerase chain reaction; PPI, proton pump inhibitor.

[a]The timeline for endpoints began after therapy CDI discontinuation.

we evaluated both models. Using these models, the odds ratios (ORs), 95% confidence intervals (CIs), z values, and P values were calculated. Heterogeneity was assessed via calculation of the I^2 value, and publication bias was assessed via visual inspection of the funnel plot.

For all of the inferential statistics performed, a P value of less than .05 was considered significant. Sensitivity analysis was performed by removing outlier studies. Subgroup analyses were performed for ASM drug class, study design, follow-up period to assess recurrence, and diagnostic test used to identify CDI. All statistical analyses were performed using Comprehensive Meta-Analysis v3.0 (BioStat, Englewood, NJ).

RESULTS

Search Results

The search strategy identified a total of 221 studies, of which 9 met all selection criteria for the meta-analysis (Figure 1). These 9 studies (Table 1) comprised 5668 patients of whom 3027 were on ASMs. The studies included data from over a decade (2001–2015), and the majority of studies were retrospective. Only 2 prospective studies met the inclusion/exclusion criteria. Studies represented several geographic locations including the United States, Korea, Japan, Israel, Spain, Germany, Canada, and some unspecified European countries.

Acid Suppression With Any Agent and Recurrence

A meta-analysis of all of the studies demonstrated that there was a greater risk of recurrence of CDI in patients who were concurrently taking ASM during an episode of CDI (OR, 1.64; 95% CI, 1.13–2.38; P = .009) (Figure 2). Of note, there was significant heterogeneity, with an I^2 value of 79.5%. Furthermore, visual inspection of the funnel plot analysis identified potential publication bias in 2 studies (Figure 3). The performance of sensitivity analysis by removing these studies did not substantially alter findings (OR, 1.58; 95% CI, 1.28–1.95; P < .001).

Subgroup Analyses

Proton Pump Inhibitor Use and Clostridioides difficile Infection Recurrence

Many studies only included patients who were prescribed PPIs concomitantly with CDI treatment, while others that included patients prescribed either a PPI or an H2RA also reported data to differentiate populations. Subsequently,

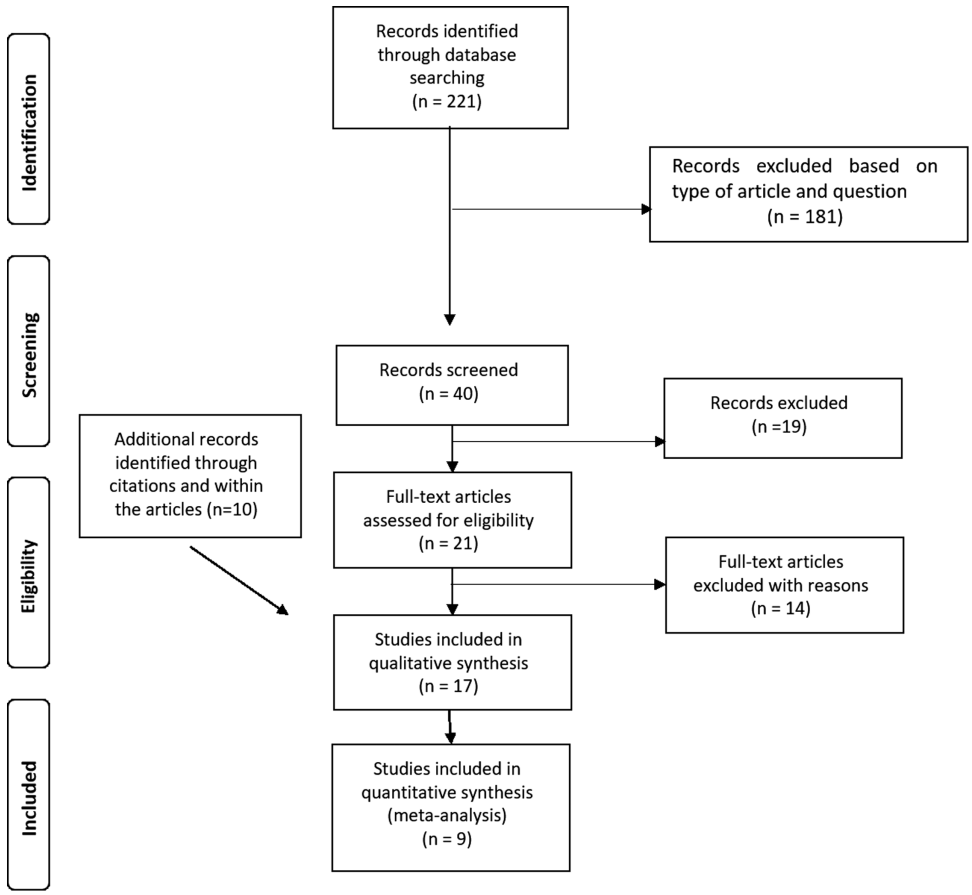

Figure 1. PRISMA flowchart. Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

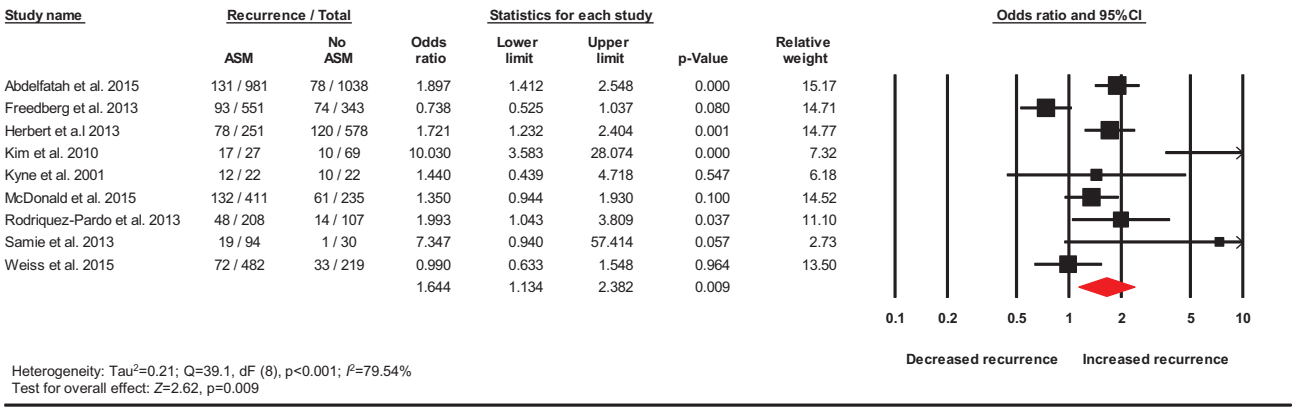

Figure 2. Overall meta-analysis of inpatient studies evaluating the association between ASMs and recurrent CDI. Abbreviations: ASM, acid-suppression medication; CDI, *Clostridioides difficile* infection; CI, confidence interval.

the availability of data supported a subgroup analysis of patients on ASMs with PPIs. This analysis included 7 studies (Figure 4) and confirmed an 84% increased risk of recurrence among patients on PPIs during CDI treatment (OR, 1.84; 95% CI 1.18–2.85; P = .007; I^2 = 83.4%). Sensitivity analyses excluding studies deemed to be outliers via inspection of the funnel plot did not significantly alter the findings. There were not enough data to perform a subgroup analysis involving only H2RAs.

Study Design

A subgroup analysis was conducted based on study design, in which the groups of interest were divided between case-control and cohort design. Meta-analysis of the 7 cohort-design studies (Figure 5A) identified without significance a 31% increase in the risk of recurrence (OR, 1.31; 95% CI, .928–1.86; P = .124; I^2 = 68.1%). Meta-analysis of the 2 case-control studies (Figure 5B) revealed a 4-fold increase in the risk of recurrence (OR, 4.04; 95% CI, .80–20.54; P = .092; I^2 = 89.2%).

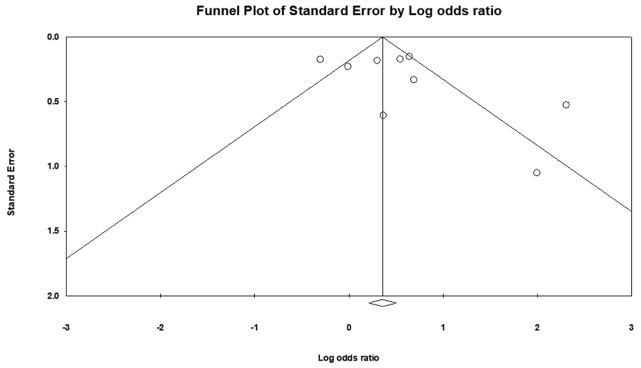

Figure 3. Funnel plot for overall meta-analysis.

Duration of Follow-up for Recurrent *Clostridioides difficile* Infection Identification

Various follow-up periods were used for identification of recurrent CDI, ranging from 10 to 90 days after completion of treatment. Studies were stratified according to the duration of follow-up after completion of CDI treatment from the index episode. In studies that used a definition with a follow-up period of more than 60 days (Figure 6A), a 78% increase in the risk of CDI recurrence was identified (OR, 1.78; 95% CI, .92–3.45; P = .007; I^2 = 90.54%). Studies with a shorter follow-up (<60 days) (Figure 6B) identified a 55% increase in CDI recurrence (OR, 1.55; 95% CI, 1.06–2.26; P = .024; I^2 = 42.9%). In addition, excluding only Weiss et al [19] from the meta-analysis yielded a greater association between ASM and recurrent CDI (OR, 1.79; 95% CI, 1.19–2.71; P = .006; I^2 = 80.7%).

DISCUSSION

In this meta-analysis, ASM use during hospitalization was associated with a 1.3- to 4-fold increased risk of CDI recurrence depending on the subgroup. While an increase in the risk of CDI recurrence with ASMs was identified in the North American and cohort-design subgroups, the results failed to reach significance. Overall, this analysis takes into account many important variables including type of ASM, study design, and duration of follow-up for identification of recurrence. Additional subgroup analyses are also available in Supplementary Figures 1 and 2.

Numerous factors such as age older than 60 years, antibiotic exposure, and hospitalization are associated with CDI recurrence [2, 3]; however, in many cases, these risk factors are nonmodifiable. Antibiotic use can be modifiable and specific antibiotic drug classes have a greater risk than others, but in the setting of infection antibiotics are essential. ASM is modifiable and is often prescribed (or self-prescribed) without appropriate indications. In fact, 1 study reported that 65% of ASMs prescribed in inpatients were without indication [21]. ASM carries many

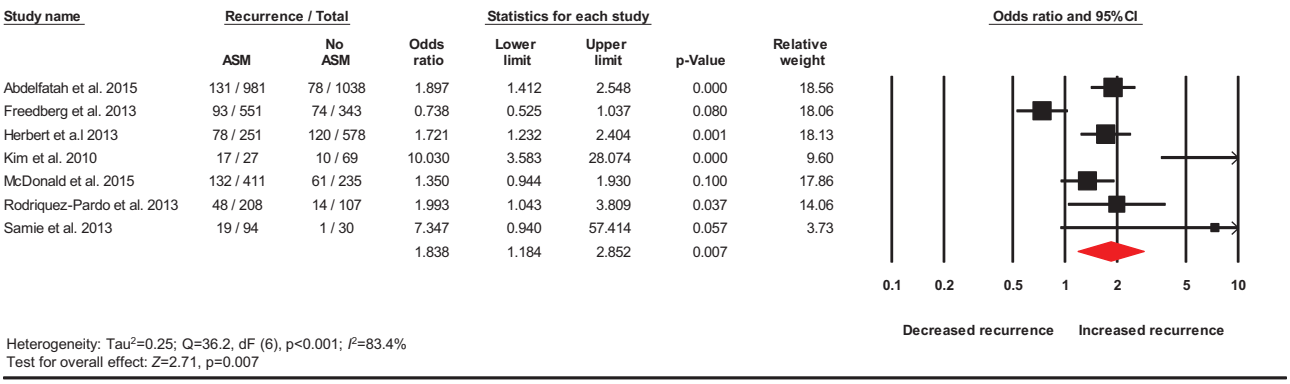

Figure 4. PPI subgroup analysis evaluating the association between ASM and recurrent CDI. Abbreviations: ASM, acid-suppression medication; CDI, *Clostridioides difficile* infection; CI, confidence interval; PPI, proton pump inhibitor.

risks, especially with long-term use, that are often ill considered. ASM may increase the risk of pneumonia, bone fractures, hypomagnesemia, and CDI/recurrent CDI [22]. The mechanism of increased risk of CDI is likely related to the impact of altered pH on gut microbial diversity [23]. *Clostridioides difficile* spores are acid resistant, making it unlikely that acid suppression directly impacts their survival. Further PPIs do not significantly impact the pH of the colon. Rather, the mechanism is likely related to altered pH in the upper gastrointestinal tract, leading to an imbalance of the colonic microbiome favoring *C. difficile* [8]. Proton pump inhibitors have a more pronounced effect on gastric pH compared with acid suppressants overall and may have a more significant effect on microbial biodiversity [23]. This postulation is supported by our findings and others [15], suggesting that PPIs have a pronounced effect on recurrent CDI. Further studies are necessary to confirm this finding prospectively as the implications are clinically important. One strategy to provide insight into the mechanism may be to perform microbiome analysis of patients with recent CDI on ASM versus those who are not and follow until recurrence. Another may be to prospectively compare individuals with CDI requiring ASM versus those who do not and evaluate recurrence. Prospective

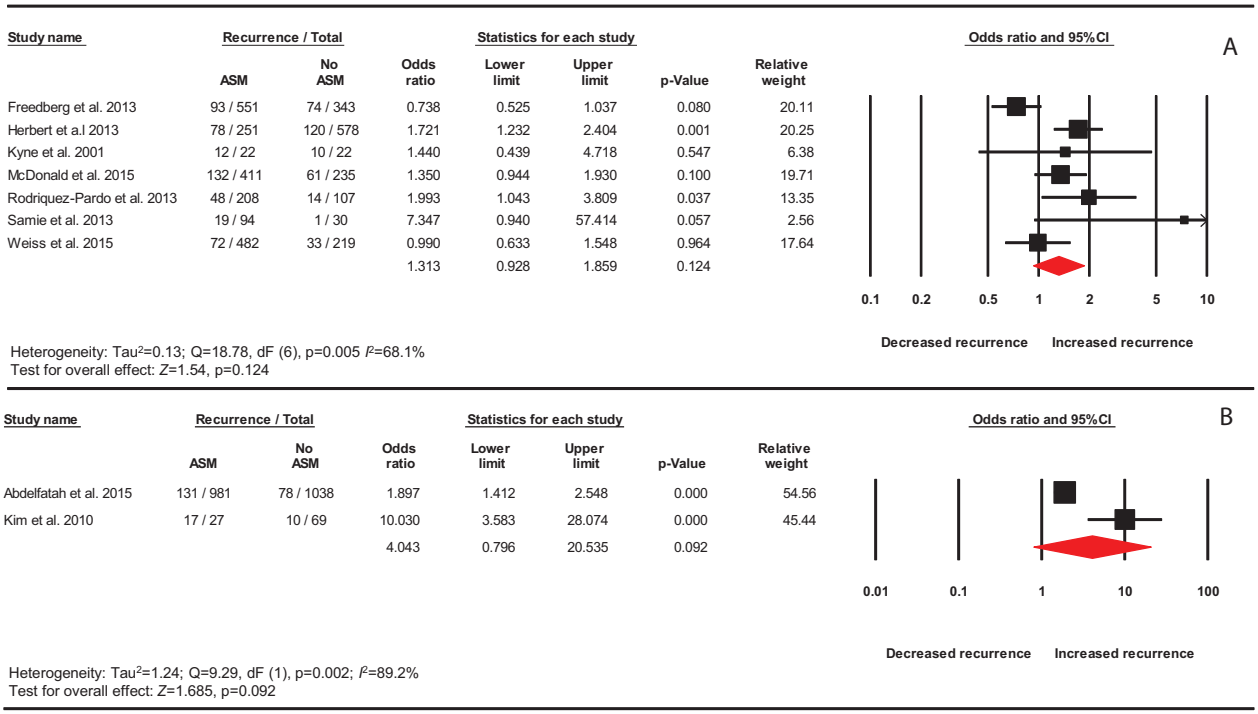

Figure 5. Stratified meta-analysis according to study design: cohort (*A*) versus case-control (*B*) study. Abbreviations: ASM, acid-suppression medication; CI, confidence interval.

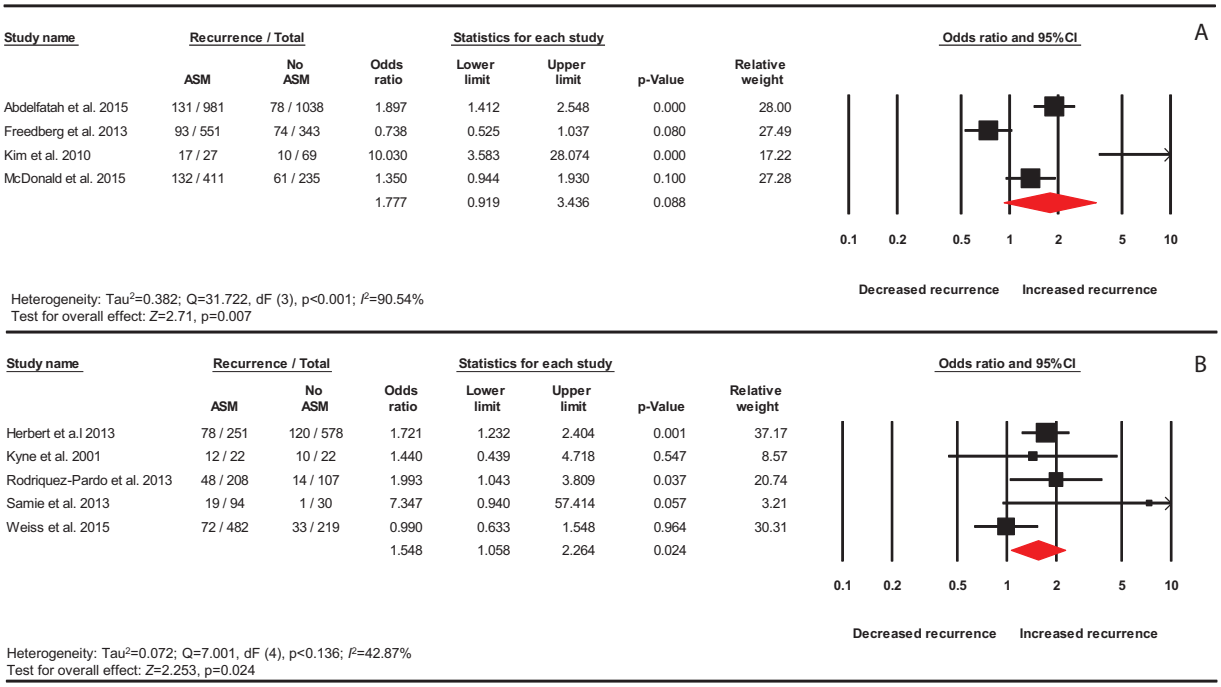

Figure 6. Stratified meta-analysis based on duration of follow-up used for identification of CDI recurrence. *A*, More than 60-day follow-up. *B*, Less than 60-day follow-up. Abbreviations: ASM, acid-suppression medication; CDI, *Clostridioides difficile* infection; CI, confidence interval.

data collection may allow collection of the necessary data for robust analysis including biomarkers. Finally, future studies are also needed to identify the best ASM strategy in patients with CDI or at risk of CDI. While previous studies suggest that a large number of patients do not require ASMs, some patients clearly do. A re-assessment of ASMs, as suggested by the Infectious Diseases Society of America, seems clinically prudent.

Strengths and Limitations

A strength of this meta-analysis includes a large population (n = 5668), which expanded upon a previously complete meta-analysis in terms of focus on the inpatient population. Since previous meta-analyses did note the presence of a great deal of heterogeneity, we attempted to address the heterogeneity with sensitivity analyses. Conducting subgroup analyses still displayed a high level of heterogeneity. However, conducting analyses with and without studies falling outside the funnel plot did not yield substantially different point estimates, another strength of our analysis. While most of the ORs did not significantly change with our sensitivity analyses, the strategy confirms that even without outlier studies the association between ASMs and recurrent CDI remains.

Some limitations must also be addressed. First, the studies encompass many definitions of CDI recurrence, ranging in the time frame and diagnostic criteria. This lack of a set definition contributes to significant heterogeneity. A subgroup analysis was performed based on follow-up period to identify CDI recurrence, but heterogeneity remained. Furthermore, lack of information about the age and sex for each of the patients prevented further stratification. Moreover, since we had no information about compliance and dosing of the ASM, we were unable to investigate how many of the patients recorded as taking ASMs took them in significant doses, if at all. The inconsistent definition of ASM exposure in the studies can be a source of misclassification bias. This concern is lightened by the inpatient status of the patients in the study. This meta-analysis used raw data from each of the studies rather than the adjusted point estimates because of the variety of covariates collected and those considered in adjustments. Performing a crude analysis may introduce confounding and fail to account for the competing risk of death; however, we performed subgroup analyses for studies that controlled for confounding and reported ORs or hazard ratios (Supplementary Figure 2), allowing individuals to compare results. Finally, an important limitation is the small population sizes for individual studies leading to large 95% CIs and imprecise point estimates.

Despite these limitations, our analyses provide additional evidence that ASM is an important modifiable risk factor for recurrent CDI. During CDI treatment, clinicians should carefully review the indication for ASMs and, if no clear indication is evident, ASMs should be discontinued. Given the high risk of recurrence of CDI and the significant morbidity, mortality, and cost burden associated with CDI recurrence, this modifiable risk factor cannot be neglected.

Conclusions

The use of ASMs during CDI treatment in the inpatient setting is associated with a 1.5- to 4-fold increase in recurrence. The association remained significant for most subgroup analyses. Clinicians should consider discontinuation of ASMs during the treatment of CDI whenever possible.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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