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ORIGINAL ARTICLE

Comorbidities, Exposure to Medications, and the Risk of Community-Acquired *Clostridium difficile* Infection: A Systematic Review and Meta-analysis

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BACKGROUND. *Clostridium difficile* infection (CDI) has been extensively described in healthcare settings; however, risk factors associated with community-acquired (CA) CDI remain uncertain. This study aimed to synthesize the current evidence for an association between commonly prescribed medications and comorbidities with CA-CDI.

METHODS. A systematic search was conducted in 5 electronic databases for epidemiologic studies that examined the association between the presence of comorbidities and exposure to medications with the risk of CA-CDI. Pooled odds ratios were estimated using 3 meta-analytic methods. Subgroup analyses by location of studies and by life stages were conducted.

RESULTS. Twelve publications (n = 56,776 patients) met inclusion criteria. Antimicrobial (odds ratio, 6.18; 95% CI, 3.80–10.04) and corticosteroid (1.81; 1.15–2.84) exposure were associated with increased risk of CA-CDI. Among the comorbidities, inflammatory bowel disease (odds ratio, 3.72; 95% CI, 1.52–9.12), renal failure (2.64; 1.23–5.68), hematologic cancer (1.75; 1.02–5.68), and diabetes mellitus (1.15; 1.05–1.27) were associated with CA-CDI. By location, antimicrobial exposure was associated with a higher risk of CA-CDI in the United States, whereas proton-pump inhibitor exposure was associated with a higher risk in Europe. By life stages, the risk of CA-CDI associated with antimicrobial exposure greatly increased in adults older than 65 years.

CONCLUSIONS. Antimicrobial exposure was the strongest risk factor associated with CA-CDI. Further studies are required to investigate the risk of CA-CDI associated with medications commonly prescribed in the community. Patients with diarrhea who have inflammatory bowel disease, renal failure, hematologic cancer, or diabetes are appropriate populations for interventional studies of screening.

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INTRODUCTION

Although the previous literature has focused largely on healthcare-associated (HA) *Clostridium difficile* infection (CDI), the incidence, prevalence, and severity of community-acquired (CA) CDI has also increased.[1] Kuntz et al[2] reported similar incidence rates for CA-CDI (11.2 cases/100,000 person-years) and HA-CDI (12.1 cases/100,000 person-years) in the United States. Moreover, the emergence of "hypervirulent" strains of *C. difficile* in the community among patients previously considered to be at low risk of CDI (ie, young adults without antimicrobial exposure) clearly shows that the epidemiology of CDI is changing and that CDI is no longer exclusively a nosocomial infection, as it was previously considered.[1] It seems that the risk profile of patients from the community points more to increased numbers of younger patients without comorbidities, whereas in the hospital setting, elderly inpatients with multiple morbidities and exposed to polypharmacy remain most at risk.

Research, including through meta-analysis, has attempted to describe the risk of CDI specifically in the community setting and found that clindamycin, fluoroquinolones, cephalosporins, macrolides, penicillins, and sulphonamides/trimethoprim are associated with an increased CA-CDI risk.[3,4] The evidence, however, remains uncertain because these meta-analyses used the random effects (RE) model, which has been questioned for its overconfident results.[5] Exposure to gastric-acid suppressive drugs[6–11] and the presence of comorbidities[12–14] are associated with an increased risk of HA-CDI; but as with antimicrobials, the

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evidence remains inconclusive in the community setting. Therefore, the current meta-analysis was undertaken to pool the evidence from observational studies so that the magnitude and direction of the association between commonly prescribed medications and comorbidities with CA-CDI can be documented.

METHODS

Search Methodology

A systematic search was undertaken in 5 medical and life sciences databases (PubMed, Embase, Cochrane CENTRAL, Cumulative Index to Nursing and Allied Health Literature [CINAHL], and Scopus) from their inception to March 1, 2014 (Appendix 1). A related citation search was also performed; by combining the systematic search with the first 20 studies from the related citation search of selected articles in PubMed, a comprehensive evaluation of the published evidence can be achieved.[15]

Eligibility Criteria

The inclusion of studies was restricted to human studies, full-text articles written in English, studies reporting CA-CDI, and data presented in an extractable format. Conference presentations and abstracts, studies that exclusively compared CA-CDI with HA-CDI, and studies that presented data in a nonextractable format (ie, graphical representations) were excluded. Exclusions were also made for studies that investigated specific groups (ie, patients with human immunodeficiency virus or cirrhosis) because these were not considered representative of the general population.

Study Selection and Data Extraction

Two authors (L.F.-K. and J.C.S.) independently evaluated all the citations by titles and abstracts for studies that met the eligibility criteria. Full-text version articles of all potentially relevant studies were retrieved and independently assessed for eligibility. Data from the included studies were then independently extracted using a predefined tool (Appendix 2) and summarized in a spreadsheet by the same 2 authors. Extracted data were cross-checked by the 2 authors, and discrepancies during the selection of studies or data extraction were resolved through discussion and consensus following independent evaluation by another author (S.A.R.D.).

Quality Assessment

The quality of each study was assessed using a modified version of the Newcastle-Ottawa quality assessment scale for case-control studies. The modified scale assessed whether 7 safeguards against bias had been undertaken by the authors: (1) definition of cases and methods employed for *C. difficile* diagnosis, (2) selection of CA infection, (3) control definition and the method used to rule out *C. difficile*, (4) selection of controls from the community, (5) analysis adjusted for confounders, (6) method used for ascertainment of exposure, and (7) same method used to ascertain exposure for cases and controls. The quality criteria were combined into a univariate score as outlined in Table 1. The quality score was rescaled between zero and 1 (called *Qi*); this was done by summing the points of each component (maximum sum = 17) and dividing it by the highest sum obtained by a study within the meta-analysis, ensuring that the best quality study always had a *Qi* of 1.

Statistical Analyses

The outcome measure was the odds ratio (OR) for the association of CA-CDI with exposure to risk factors, such as antimicrobial drugs, gastric acid suppressant drugs (proton-pump inhibitors [PPI] and histamine-2-receptor antagonists), nonsteroidal anti-inflammatory drugs, aspirin, steroids, and the presence of comorbidities. The OR was pooled using 3 meta-analytic models. This was justified because some have expressed skepticism regarding the appropriateness of the conventional RE model[16] owing to its documented underestimation of the statistical error, which leads to overconfident results.[5,17–19] The other 2 models that were used were the quality effects (QE) model [20–21] and a novel method, the inverse variance heterogeneity (IVhet) model.[22] The QE model uses the *Qi* to redistribute the inverse variance weights in favor of the studies with higher methodologic quality and thus studies that provided higher quality of evidence contributed with a higher weighting towards the overall effect size.[21] This use of quality information via a univariate score does not imply that quality deficiencies can quantify bias. Rather, the quality score is used to rank studies by methodologic rigor and this rank is then linked with a synthetic bias variance that is added to the random error variance.[20] The other model used was the IVhet model that does not require input of quality information and so is less rigorous than the QE model.[22] Both of the latter models use a quasi-likelihood-based variance structure without distributional assumptions and thus have coverage probabilities for the confidence interval (CI) well above the nominal level.[22] The reported results are based on the IV het model; results using the QE and RE models have been presented for comparative purposes.

Statistically significant heterogeneity was defined as tau-squared statistic (τ^2) > 0, Cochran's Q test $P < .1$, or I^2 index >0%. A sensitivity analysis was conducted to determine the degree to which the findings vary depending on the geographic location where the studies were conducted (America or Europe) and life stages of the participants (children aged <2 years, children and adults, adults, or adults aged >65 years).

The *Doi* plots were used to evaluate the presence of publication bias, which plots the lnOR against the absolute value of the z-score for each study.[23] Funnel plots were not reported because the graphical assessment of publication bias requires at least 10 studies and even then can be difficult to interpret.[24]

The results of the analyses were considered statistically significant if the 95% CI did not include zero. Analyses were conducted using MetaXL, version 2.0 (EpiGear International).

TABLE 1. Modified Newcastle-Ottawa Quality Assessment Scale for Case-Control Studies Included in the Meta-analysis

Author, publication year	Definition of cases[a]	Case selection for community-acquired infection[b]	Definition of controls[c]	Control selection[d]	Analysis adjusted for confounders[e]	Ascertainment of exposure[f]	Method of ascertainment of exposure for cases and controls[g]	Total score (points)	*Qi* (total score/13)
Dial et al 2005[25]	1	1	1	2	2	3	1	11	0.85
Dial et al 2006[27]	0	1	0	2	2	3	1	9	0.69
Dial et al 2008[46]	1	1	1	1	3	3	1	11	0.85
Kuntz et al 2011[2]	1	2	1	2	3	3	1	13	1.00
Kutty et al 2010[30]	2	2	2	1	1	3	0	11	0.85
Lowe et al 2006[32]	1	2	0	1	2	3	1	10	0.77
Marwick et al 2013[31]	2	1	0	2	1	3	1	10	0.77
Naggie et al 2011[47]	2	2	2	1	2	1	1	11	0.85
Soes et al 2014[28]	3	2	3	2	0	1	1	12	0.92
Suissa et al 2012[48]	0	1	0	2	2	3	1	9	0.69
Vesteinsdottir et al 2012[44]	2	2	2	2	0	1	1	10	0.77
Wilcox et al 2008[49]	2	0	2	2	0	2	1	9	0.69

[a]Definition of cases: Method used for *Clostridium difficile* diagnosis: stool culture (3 points), toxin detection (2 points), clinical diagnosis or *International Classification of Diseases* (ICD) code (1 point), other or no description (0 points).

[b]Case selection for community-acquired infection: Patient not previously hospitalized and not a resident of a nursing home (2 points), patient not previously hospitalized or not a resident of a nursing home (1 point), no description (0 points).

[c]Definition of controls: Method used for exclusion (noninfection) of *C. difficile*: stool culture (3 points), toxin detection (2 points), clinical diagnosis or ICD code (1 point), other or no description (0 points).

[d]Control selection: Community (2 points), community and hospital (1 point), no description (0 points).

[e]Analysis adjusted for exposures other than the primary exposure of interest (sex, age, antimicrobial exposure, gastric acid–suppressive medication exposure or presence of comorbidities). Adjusted for 5 factors (3 points), 3–4 factors (2 points), 1–2 factors (1 point), or nonadjusted (0 points).

[f]Ascertainment of exposure: Objective methods, ie, charts or medical records (3 points), reported by the general practitioner (2 points), self-reported (1 point), no description (0 points).

[g]Method of ascertainment of exposure for cases and controls: Same (1 point), different (0 points).

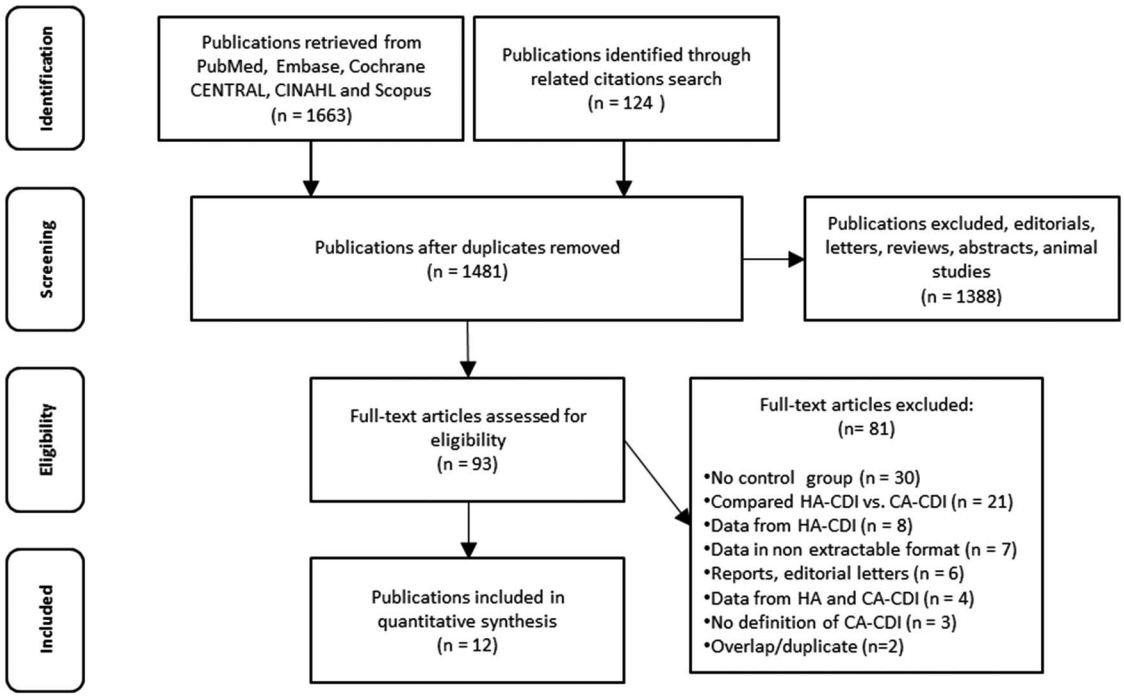

FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis flowchart of the literature search conducted on March 1, 2014, for the meta-analysis.

RESULTS

Yield of Search Strategy

The initial search identified 1,663 publications. An additional 124 publications were retrieved throughout the related citations search. After excluding duplicate citations, 1,481 publications remained. After screening the publications by title and abstract, 1,388 were excluded. A full-text review of 93 publications was conducted, and 12 met the eligibility criteria and were selected for the meta-analysis (Figure 1).

There was overlap in subjects between 2 sets of publications. Two publications (Dial et al[25] and Delaney et al[26]) used data from the UK General Practice Research Database between 1994 and 2004 and a positive toxin test result for CDI as case definition to assess the risk of CA-CDI with antimicrobial exposure. Although Dial et al[27] also used data from the UK General Practice Research Database, the authors reported that there was no overlap between this and Dial et al[25] because they used different case definitions for CDI.[27] Additionally, 2 publications (Soes et al[28] and Soes et al[29]) reported results from the same Danish cohort. Therefore, Delaney et al[26] and Soes et al[29] were excluded from the analyses.

Characteristics of the Included Studies

Twelve publications were included in the meta-analysis. Two publications reported results divided into groups. Kutty et al[30] presented the results of 2 populations (Veterans Affairs and Durham County residents), whereas Soes et al[28,29] presented the results divided into 2 age groups (<2 years and ≥2 years). Among the included studies, 7 were case-control studies and 5 were nested case-control studies. The studies included covered more than 35 years of research and 56,776 patients in 6 different countries. The age of the participants ranged from 3 months to 101 years. Only one study[28,29] used exclusively positive *C. difficile* culture in the case definition and another study[31] used a combination of *C. difficile* culture or toxin test results in the case definition. All studies evaluated exposure to medication for at least 6 weeks and presence of comorbidities for at least 12 weeks prior to the index date, respectively (Table 2). The quality score of the studies ranged from 9 to 13 of 17 (Table 1).

Quantitative Synthesis

When examining the association between drug exposures and CA-CDI using the IVhet model, exposure to antimicrobials (OR, 6.18; 95% CI, 3.80–10.04) and corticosteroids (1.81; 1.15–2.84) were significantly associated with CA-CDI. Gastric acid–suppressing drugs were not associated with increased odds of CA-CDI (both PPIs and histamine-2-receptor antagonists: OR,1.58; 95% CI, 0.90–2.75; just PPIs: 1.61, 0.90–2.88; just histamine-2-receptor antagonists:1.24, 0.76–2.01). Statistically significant associations were found between CA-CDI and the presence of inflammatory bowel disease (OR, 3.72; 95% CI, 1.52–9.12), renal failure (2.64, 1.23–5.68), leukemia or

TABLE 2. Characteristics of the Studies Included in the Meta-analysis

Author, publication year	Data source	Study period	Study design	Study population	Age, mean (SD), years case/control	Male sex, % case/control	Community-acquired definition	Case definition	Control definition	Matching	Exposure to medication or presence of comorbidity, days prior to index date	N case/control
Dial et al 2005[25] & Delaney et al 2007[26]	GPRD, UK	1 Jan 1994–31 Dec 2004	Case-control	≥2 years registered in a general practice in the UK and ≥18 years old	71.0(16)/70.8(16)	35/42	Not hospitalized the year prior to the index date	Clinical diagnosis or positive toxin test results for CDI	No clinical diagnosis nor positive toxin test result for CDI	Practice location, age (±2 years)	Gastric acid suppressant, antimicrobials, NSAID, aspirin, 90 Comorbidity, 720	1,233/12,330
Dial et al 2006[27]	GPRD, UK	1 Jan 1994–31 Dec 2004	Case-control	Registered in the GPRD without clinical diagnosis or positive toxin test results for CDI 30 days to 1 year prior to the index date	65.0 (19.6)/64.9 (19.5)	36.6/41.5	Not hospitalized the year prior to the index date	Prescription of oral vancomycin therapy	No prescription for oral vancomycin	Practice location, age (±2 years)	Gastric acid suppressant, antimicrobials, 90 Comorbidity, 720	317/3,167
Dial et al 2008[46]	Régie de l'assurance maladie du Québec and MED-ECHO, Canada	1996–2004	Nested case-control	Hospitalized during the study period, ≥65 years old, and have not received metronidazole or oral vancomycin 90 days prior the index date	79.8 (6.8)/77.5 (6.3)	33.7/40.9	Not admitted to any type of institution in the 90-day period before the index date	First hospital admission with primary diagnosis of CDI (ICD-9 code 008.45)	No primary diagnosis of CDI during the first hospital admission	Unmatched Index date and date of first hospital admission	Antimicrobials, 45 Comorbidity, 720	836/8,360
Kuntz et al 2011[2]	University of Iowa Wellmark Data Repository, USA	1 Jan 2004–31 Dec 2007	Nested case-control	Patients with at least 1 year of health and pharmacy insurance	NR/NR	39.47/48.36	No history of long-term care facility 6 months or hospitalized 12 weeks before the index date	Primary or secondary diagnosis of CDI (ICD-9 code 008.45)	No diagnosis of CDI on or before the index date	Unmatched Index date	Gastric acid suppressant, antimicrobials, 180 Comorbidity,	304/3,040
Kutty et al 2010[30a]	VA infection control database and Surveillance database of the Duke University Hospital network, USA	Jan 2005–Dec 2005	Case-control	≥18 years old	VA: 62 (38–85)/64 (38–86)[c] Durham County: 61 (20–101)/55 (22–87)[c]	VA: 88/96 Durham County: 42/29	No history of healthcare exposure within 8 weeks of the index date	Nonformed stool specimen with positive toxin test results for CDI	Outpatients with no clinical diagnosis of diarrhea or positive toxin test results for CDI	Unmatched	Gastric acid suppressant, antimicrobials, NSAID, 90 Comorbidity, NR	VA: 36/108 Durham County: 73/48
Lowe et al 2006[32]	Ontario Drug Benefit Program, Canadian Institute for Health Information Discharge Abstract Database, Ontario Health Insurance Plan Database and Ontario Registered Persons Database, Canada	1 Apr 2002–31 Mar 2005	Nested case-control	≥66 years old, exposed to antimicrobials	78.7 (7.2)/78.0 (6.8)	59.8/60.5	Not hospitalized during the 90-day period prior to the index date nor patients from long-term care or nursing homes	Hospitalized with diagnosis of CDI (ICD-10 code A04.7)	Outpatient	Index date, sex, age (±1 years), antimicrobials prescribed	Gastric acid suppressant, 90 Antimicrobials, 60 Comorbidity, 180–720	1,389/12,303
Marwick et al 2013[31]	Health Information Center at the University of Dundee, Scotland	1 Nov 2008–31 Oct 2009	Nested case-control	≥65 year old	81 (8.9)/81 (8.9)	27.4/27.4	Not hospitalized during the 120-day period prior to the index	Diarrhea and a positive toxin test result for CDI or positive *C. difficile* culture and pseudomembranous colitis	NR	Sex, age (±1 years)	Gastric acid suppressant, antimicrobials, 180 Comorbidity, 360	62/620

Naggie et al 2011[47]	Duke University Medical Center, Durham Regional Hospital, Durham VA Medical Center, Salisbury VAMC and Asheville VAMC, USA	1 Oct 2006–31 Nov 2007	Case-control	≥18 years old	64 (50–73)/ 63 (52–74)[c]	44/45	Symptom onset in the community or within 72 hours of admission to a healthcare facility. Not hospitalized during the 12-week period prior to the index	Diarrhea and a positive toxin test results for CDI	Outpatient with no diagnosis of CDI	Unmatched Geographic location	Gastric acid suppressant, antimicrobials, NSAID, aspirin, 90 Comorbidity, 720	66/114
Soes et al 2014[28,29 b]	NR, Denmark	24 Aug 2009–28 Feb 2011	Nested case-control	Patients who had fecal sample submitted by their GP for microbiological testing due to diarrhea or other gastrointestinal symptoms	<2 years: 0.95 (0.30–1.98)/1.06 (0.25–1.98) ≥2 years: 50 (2–94)/ 50 (2–90) [c]	<2 years: 53/55 ≥2 years: 25/28	Not hospitalized during the 12-week period prior to the index or onset of symptoms within 48 hours of admission	Positive *C. difficile* culture	Negative *C. difficile* culture	Laboratory location, sex, age (±2 years if ≥5years; ± 5 months if ≥6months and < 4years; ± 6 weeks if < 6months)	Antimicrobials, 56 Gastric acid suppressant, NSAID, aspirin, 120 Comorbidity, 120	<2 years: 121/213 ≥2 years: 138/242
Suissa et al 2012[48]	GPRD, UK	1 Jan 1994–31 Dec 2005	Case-control	≥2 years registered in a general practice in the UK and ≥18 years old	NR/NR	NR/NR	Not hospitalized the year prior to the index date	First positive toxin test results for CDI, or first prescription of oral vancomycin	No clinical diagnosis, positive toxin test result for CDI or prescription of oral vancomycin	Practice location, age (±2 years)	Gastric acid suppressant, antimicrobials, NSAID, aspirin, 90 Comorbidity, 720	929/10,242
Vesteinsdottir et al 2012[44]	National University Hospital of Iceland, Iceland	1 Jul 2010–30 Jun 2011	Case-control	≥18 years old	65 (56–80)/ 65 (55–80)[c]	42.3/42.3	Not hospitalized during the 6-week period prior to the index or lived in a nursing facility and if hospitalized, diagnosed with CDI within the 72 hours of admission	Positive toxin test results for CDI	Negative toxin test results for CDI	Sex, age (±5 years)	Gastric acid suppressant, antimicrobials, 42 Comorbidity, 84	111/222
Wilcox et al 2008[49]	Cornwall and Leeds, UK	Jan 1999–Dec 1999	Case-control	Patients who had fecal sample submitted by their GP for microbiological testing	78 (4–100)/NR[c]	44/NR	Patients that attended the GP	Diarrhea and a positive toxin test results for CDI	Negative toxin test results for CDI	Sex, age categories	Antimicrobials, 180 Comorbidity, NR	40/112

NOTE. CDI, *Clostridium difficile* infection; GP, general practitioner; GPRD, General Practice Research Database; ICD, *International Classification of Disease*; index date, the date when the cases were identified; MED-ECHO, provincial hospital discharge summary; NR, not reported; NSAID, nonsteroidal anti-inflammatory drug; VA, Veterans Affairs.

[a]Presented in 2 groups: Patients from the VA and Durham County.

[b]Presented in 2 groups: Patients aged < 2 years and ≥2 years.

[c]Age, median (range), years.

TABLE 3. Pooled Effect Size Using the IVhet Model, QE Model, and the RE Model

Exposure	IVhet model OR (95% CI)	QE model OR (95% CI)	RE model OR (95% CI)	Heterogeneity I^2 index %
Antimicrobials	**6.18 (3.80–10.04)**	**6.11 (3.92–9.55)**	**5.92 (4.21–8.32)**	87.90
Cephalosporins	1.80 (0.38–8.46)	2.09 (0.55–7.98)	**3.29 (1.20–9.05)**	98.39
Clindamycin	2.32 (0.14–37.99)	3.21 (0.30–34.55)	**8.35 (1.54–45.20)**	97.73
Fluoroquinolones	1.55 (0.32–7.57)	1.90 (0.51–7.05)	**3.59 (1.60–8.06)**	96.97
Macrolides	1.26 (0.49–3.24)	1.45 (0.64–3.28)	**2.15 (1.11–4.17)**	93.38
Penicillins	1.31 (0.57–3.01)	1.54 (0.75–3.16)	**2.40 (1.40–4.11)**	93.50
Tetracyclines	0.98 (0.68–1.41)	0.98 (0.67–1.41)	0.98 (0.68–1.41)[a]	0
TMP-SMX	1.26 (0.75–2.12)	1.30 (0.80–2.10)	1.37 (0.87–2.15)	77.37
Gastric acid suppressant	1.58 (0.90–2.75)	1.58 (0.95–2.63)	**1.58 (1.06–2.34)**	68.89
H2RA	1.24 (0.76–2.01)	1.24 (0.78–1.96)	1.37 (0.96–1.96)	73.95
PPI	1.61 (0.90–2.88)	1.63 (0.95–2.80)	**1.68 (1.11–2.55)**	92.23
Other medication				
Aspirin	0.97 (0.87–1.08)	0.96 (0.85–1.08)	0.97 (0.87–1.08)[a]	0
NSAIDs	1.14 (0.67–1.93)	1.04 (0.63–1.71)	0.83 (0.56–1.23)	90.42
Corticosteroids	**1.81 (1.15–2.84)**	**1.84 (1.22–2.77)**	**1.65 (1.14–2.38)**	34.79
Comorbidities				
Congestive heart disease	0.95 (0.45–2.01)	0.98 (0.46–2.06)	1.40 (0.77–2.54)	68.70
COPD	1.04 (0.93–1.16)	1.04 (0.93–1.16)	1.04 (0.93–1.16)[a]	0
Diabetes mellitus	**1.15 (1.05–1.27)**	**1.14 (1.04–1.26)**	**1.15 (1.05–1.27)[a]**	0
Diverticular disease	1.15 (0.98–1.36)	1.15 (0.98–1.35)	1.15 (0.98–1.36)[a]	0
GERD	1.02 (0.74–1.43)	1.03 (0.74–1.43)	1.07 (0.80–1.44)	45.53
Inflammatory bowel disease	**3.72 (1.52–9.12)**	**4.11 (1.78–9.49)**	**5.19 (2.49–10.83)**	89.39
Leukemia or lymphoma	**1.75 (1.02–3.03)**	**1.74 (1.01–3.01)**	**1.88 (1.09–3.21)**	38.95
Peptic ulcer	0.97 (0.60–1.57)	0.96 (0.59–1.56)	0.94 (0.58–1.51)	14.72
Renal failure	**2.64 (1.23–5.68)**	**2.59 (1.20–5.59)**	**3.02 (1.66–5.48)**	85.96
Solid cancer	1.34 (0.83–2.17)	1.35 (0.84–2.17)	**1.51 (1.01–2.27)**	81.64

NOTE. COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; H2RA, histamine-2-receptor antagonists; IVhet, inverse variance heterogeneity; NSAIDs, nonsteroidal anti-inflammatory drugs; OR, odds ratio; PPI, proton-pump inhibitors; QE, quality effects; RE, random-effects; TMP-SMX, trimethoprim-sulfamethoxazole. Boldface type indicates statistically significant ORs.
[a]No heterogeneity, pooled estimated report using the inverse variance model.

lymphoma (1.75, 1.02–3.03), and diabetes mellitus (1.15, 1.05–1.27) (Table 3).

Visual inspection of the forest plots, Cochran's Q test (Appendix 3), τ^2 (results not shown), and I^2 index (Table 3 and Appendix 3) confirmed heterogeneity across studies, except for exposure to tetracyclines or aspirin and the presence of chronic obstructive pulmonary disease, diabetes, or diverticular disease.

Sensitivity Analysis

A sensitivity analysis was possible only for antimicrobial and PPI exposure because of the small number of studies in the other categories. When stratifying the studies by geographic location, the sensitivity analysis showed that antimicrobial exposure had a greater association with CA-CDI in the United States (OR, 9.16; 95% CI, 5.47–15.34) compared with European countries (4.54, 2.68–7.70; Appendix 4.1). Conversely, exposure to PPIs had a stronger association with CA-CDI in Europe (OR, 2.56; 95% CI, 1.40–4.71) compared with the United States (1.12, 0.64–1.95; Appendix 4.2).

The subgroup analysis by life stages showed that older adults (>65 years) had the highest risk (OR, 10.16; 95% CI, 5.56–18.58) of CA-CDI when exposed to antimicrobials, followed by children and adults (5.98, 4.67–7.67; Appendix 4.3). When exposed to PPIs, adults had the highest risk of CA-CDI (OR, 2.78; 95% CI, 2.02–3.81; Appendix 4.4).

Publication Bias

On visual inspection of the *Doi* plots, there was gross asymmetry for some exposures, suggesting publication bias in relation to cephalosporins, fluoroquinolones, macrolides, penicillin, presence of congestive heart failure, and presence of gastroesophageal reflux disease. The bias was toward selective publication that reported medication exposure and presence of comorbidities as risk factors for CA-CDI (Appendix 3).

DISCUSSION

Exposure to antimicrobials remained the strongest risk factor associated with CA-CDI. No statistical significance was observed in most analyses by antimicrobial class, likely because

the largest study (Lowe et al[32]) reported ORs close to the null value. However, point estimates confirmed a trend toward an association with CA-CDI regardless of antimicrobial class exposure. These observations corroborated previous findings published by Deshpande et al[3] and Brown et al[4] that suggested an increased risk of CA-CDI as a result of antimicrobial exposure.

Despite the growing evidence in the past decade with respect to increased risk of HA-CDI after exposure to PPIs[6,7,9–11] or histamine-2-receptor antagonists,[8,25] no significant association was observed in the community setting. The observed difference between the risk of CA-CDI and HA-CDI with gastric-acid suppressive medication can be explained by the overuse of these medications in healthcare facilities.[33] Exposure to corticosteroids was associated with CA-CDI. In contrast to antimicrobials that disrupt the normal gut microbiome, facilitating the proliferation of *C. difficile*,[34] and in contrast to gastric-acid suppressive medication that may allow survival of vegetative forms of *C. difficile*,[35] a plausible biological mechanism for the observed association could be the negative impact of corticosteroids on the gastrointestinal mucosal integrity.[36]

Previous studies found that gastrointestinal comorbidities such as inflammatory bowel disease[12] and cirrhosis[14] were associated with a worse prognosis in patients with CDI. Similarly, congestive heart disease, chronic pulmonary disease, renal failure, and malignant neoplasms were also associated with higher mortality rates among inpatients with CDI.[13] Among the comorbidities examined in this meta-analysis, inflammatory bowel disease was the strongest risk factor for CA-CDI, followed by renal failure and hematologic cancers. In patients with the described comorbidities, early identification and prompt treatment of CA-CDI may reduce mortality rates. The associations found between CA-CDI and comorbidities may be confounded by medication exposure, given that polypharmacy is common among patients with multiple comorbidities. Furthermore, the heterogeneous definition of CA-CDI across the studies (ie, not hospitalized the year prior to the index date versus not hospitalized 6 weeks prior to the index date) may also be a source of misclassification between CA- and HA-CDI, considering that patients with multiple comorbidities are more likely to be admitted to hospitals.

The sensitivity analyses suggested that risk of CA-CDI with exposure to antimicrobials and PPI differed between Europe and America. The observed difference might be due to the dissimilar prescription of antimicrobials[37] and/or the presence of different strains of *C. difficile* in Europe and America.[38] Similarly, the risk of CA-CDI with exposure to antimicrobials and PPI varied among the life stages. These findings were consistent with Sandora et al,[39] who reported a negative correlation between age and CA-CDI among pediatric populations, and with Lessa et al,[40] who reported a higher incidence of CDI among patients at both extremes of life (1–4 years of age and older than 65 years). In the past 2 decades, a 12-fold increased incidence of CA-CDI among the pediatric population[41] and numerous outbreaks in long-term care facilities[42] have been reported, indicating that infants, toddlers, and older adults should be considered at high risk of CA-CDI.

Although a comprehensive systematic search for studies was performed, publication bias could have resulted in additional positive associations being published, such as those between CA-CDI and exposure to cephalosporins, fluoroquinolones, macrolides, and penicillins and the presence of congestive heart disease and gastroesophageal reflux disease. The actual risks attributable to these risk factors could be less than what we have reported. Nevertheless, heterogeneity across studies could also result in effect size asymmetry, and this represents an alternative explanation to selective publication of positive results.

Recent meta-analyses have investigated the risk of CDI associated with exposure to antimicrobials[3,4,6] and gastric acid suppressant drugs[6–9] using the widely adopted RE model.[16] However, the coverage probability of the RE CI can be substantially below the nominal level of 95% and thus does not adequately reflect the statistical error, especially when there are few included studies.[5,22,43] By underestimating the statistical error, the RE model produces tight CIs that potentially cause overconfident results prone to type 1 error. Moreover, the assumption of normally distributed random effects is not easily verified.[43] The use of a moment-based common variance[16] within this model is in the redistribution of the weights from larger to smaller studies.[18] The QE and IVhet models have both been created to do away with the problems that affect the RE model and both have coverage of the CI at or above the nominal level.[22] As an example, with the clindamycin pooled estimates, the IVhet model distributed the weight (83.5%) toward the biggest study (Lowe et al[32]; n = 13,692). The QE model took into account the extra information regarding the quality of the studies and penalized the biggest study by reducing the assigned weight (from 83.5% to 69.0%) because it had the lowest quality score; whereas the RE model redistributed the weights by equalizing weights (by transferring from big to small studies) and thus, it gave a weight percentage to the biggest study (Lowe et al[32]; n = 13,692; weight 25.85%) that was similar to that of the smallest study (Vesteinsdottir et al[44]; n = 333; weight 23.98%). Moreover, the RE model produced a tighter CI (with a statistically significant result), but its coverage may have been under the nominal level and thus may not have captured the true value of the effect (Appendix 3.3).

Several limitations of the present meta-analysis were noted. Kuntz et al[2] and Marwick et al[31] reported a positive relationship between duration of exposure to antimicrobials and CA-CDI. However, the small number of studies precluded a subgroup analysis by duration of exposure to antimicrobials. All studies included in this meta-analysis were conducted in Northern Hemisphere countries. A recent study has described a different seasonal pattern of CDI in Australia that remains largely unexplained.[45] The epidemiologic patterns of *C. difficile* transmission and infection may differ between hemispheres and thus generalizability of the findings to Southern Hemisphere countries is limited.

In conclusion, while antimicrobial use remains the dominant risk factor for CA-CDI, corticosteroid use should also

be considered an important risk factor. Given these are commonly prescribed medications in the community, the attributable risk of CDI due to exposure may be high and thus further research is warranted. In addition, patients with inflammatory bowel disease, renal failure, and hematologic cancer are at higher risk of CA-CDI, making them appropriate populations for interventional studies of screening for *C. difficile*.

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SUPPLEMENTARY MATERIAL

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