Clostridium difficile Infection: An Epidemiology Update

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Abstract

Clostridium (reclassified as "*Clostridioides*") *difficile* infection (CDI) is a healthcare-associated infection and significant source of potentially preventable morbidity, recurrence, and death, particularly among hospitalized older adults. Additional risk factors include antibiotic use and severe underlying illness. The increasing prevalence of community-associated CDI is gaining recognition as a novel source of morbidity in previously healthy patients. Even after recovery from initial infection, patients remain at risk for recurrence or reinfection with a new strain. Some pharmaco-epidemiologic studies have suggested an increased risk associated with proton pump inhibitors and protective effect from statins, but these findings have not been uniformly reproduced in all studies. Certain ribotypes of *C. difficile*, including the BI/NAP1/027, 106, and 018, are associated with increased antibiotic resistance and potential for higher morbidity and mortality. CDI remains a high-morbidity healthcare-associated infection, and better understanding of ribotypes and medication risk factors could help to target treatment, particularly for patients with high recurrence risk.

Keywords
- *Clostridium difficile*
- healthcare associated infection
- proton pump inhibitor
- statins
- ribotype

Introduction

Clostridium difficile[a] is an anaerobic, gram-positive, spore-forming bacillus, and the most common cause of healthcare-associated (HA) infectious diarrhea. Initially thought to be a nosocomial pathogen, increasing discovery of asymptomatic carriage and identification that 35% of *Clostridium difficile* infections (CDI) occur in the community led to additional proposed fecal–oral transmission sources, such as food, compost, manure, zoonotic sources, and other environmental exposures.[1,2] Precautions against nosocomial transmission include isolation gown and gloves for health care providers and hand hygiene with soap and water, as alcohol-based cleansers are ineffective against spores. *C. difficile* spores are persistent and require dedicated disinfection efforts with sporicidal agents.[3]

Clinical manifestations of CDI range from asymptomatic carriage to mild diarrhea to severe with life-threatening fulminant infection with sepsis, toxic megacolon, and transmural pancolitis that may require colectomy. The overall mortality of *C. difficile* infection ranges from 2 to 6%, though mortality is significantly higher in patients with inflammatory bowel disease and those admitted to intensive care units.[4–6]

In 2011, nearly half–a-million cases of CDI occurred in the United States, with approximately 29,000 deaths.[7] The vast majority of CDI deaths occurred in adults over 65 years; CDI was the 18th leading cause of death among that age group in 2008.[8] Many countries have instituted protocols and guidelines to decrease CDI in the acute-care setting through antibiotic stewardship, outbreak management, case detection and appropriate contact precautions, personal protective equipment, and environmental cleaning; the United States noted an 8% decrease in CDI between 2011 and 2014.[9–11] The financial burden of CDI in the United States is estimated at 1.9 to 7 billion U.S. dollars annually, as CDI prolongs hospitalization by 2.8 to 10.4 days[4,12,13] at a cost over $42,000 per case.[12]

Risk Factors

The most common risk factor for CDI is antibiotic use, specifically clindamycin, third- and fourth-generation cephalosporins,

[a] The genus name "*Clostridium*" was reclassified as "*Clostridioides*" in 2016.

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Table 1 Risk factors for *Clostridium difficile infection* (CDI), recurrent CDI, community-associated CDI, and severe CDI

C. difficile infection	Recurrent CDI	Community-associated CDI	Severe CDI
Antibiotic use	Antibiotic use	Antibiotic use	Antibiotic use
Older age (65+ years)	Older age (65+ years)	Younger age (children–65 years)	Older age (70+ years)
PPI use	PPI use	PPI use	Immunocompromised state
Multimorbidity	Heart disease	Female sex	Previous hospitalization
IBD	MRSA colonization	Proximity to infants	Renal dysfunction
Liver disease	VTE	Outpatient health care exposure	Hypoalbuminemia
Immunosuppression	Community-associated CDI	Proximity to farm	Nursing facility stay
Prolonged hospitalizations	Long hospital LOS		Rehabilitation facility stay
Multiple hospitalizations			
Long term care facility resident			
Abdominal operations			

Abbreviations: CDI, *C. difficile* infection; IBD, inflammatory bowel disease; LOS, length of stay; MRSA, methicillin resistant *Staphylococcus aureus*; PPI, proton pump inhibitor; VTE, venous thromboembolism.

fluoroquinolones, or combinations of antibiotics.[14] Patient factors associated with CDI include older age, multimorbidity, inflammatory bowel disease, chronic liver disease, immunosuppression, prolonged or multiple hospitalizations, intensive care unit (ICU) admission, and residency in a long-term care facility (►**Table 1**).[14–17] Abdominal operations and lower extremity amputations are associated with an increased risk of CDI as compared with other operations.[18,19] Geographic location has also been identified as a risk factor, with greater incidence in the Northeastern United States.[14]

Asymptomatic Carriage

Asymptomatic carriage of *C. difficile* is present in approximately 4 to 15% of normal hosts. Development of symptomatic CDI with frequent, watery stool occurs when the balance of intestinal flora is disrupted in the setting of antibiotic use, other medications, or dysmotility.[20–22] Asymptomatic carriage may be even more common among older adult patients in residential nursing facilities.[23] Why some patients are unaffected by *C. difficile* and others progress to severe disease is unclear, though a study evaluating antibodies to *C. difficile* toxins found increased levels of antibodies against toxin A in those who were asymptomatic carriers.[24] Development of antibodies may be a mechanism for some patients to remain asymptomatic despite *C. difficile* colonization.

CDI

The Infectious Diseases Society of America and Society for Healthcare Epidemiology of America (IDSA/SHEA) defines CDI as three or more unformed stools in 24 hours, a positive stool toxin, and positive result to one or both of the following tests: nucleic acid amplification test (NAAT) and glutamate dehydrogenase test (GDH).[3]

Severe CDI

IDSA/SHEA further defines severe CDI as CDI with presence of a white blood cell count (>15,000 per microliter) or serum creatinine of >1.5 mg/dL.[3,25] Other guidelines add fever, presence of ICU admission, endoscopically visualized pseudomembranes, abdominal pain, hypoalbuminemia (serum albumin <3 g/dL), or age ≥ 65 years as indicators of severe disease.[26,27] Progression from severe to fulminant CDI, also termed "severe and complicated" CDI, includes development of shock, ileus, and/or megacolon. Another epidemiologic classification score of severe CDI included ICU admission, requirement of surgery, and death within 30 days, but this post hoc classification of CDI cannot be used in clinical settings to prospectively identify those with severe CDI.[28]

Patient risk factors for severe CDI include increasing age (>70 years), immunocompromised state, previous hospitalizations, nursing facility or rehabilitation stay, hypoalbuminemia, and renal dysfunction.[29]

Recurrent CDI

Approximately 18 to 35% of individuals treated for CDI experience at least one more episode within 2 to 8 weeks of initial CDI.[28] Subsequent episodes can be classified as either "relapse" with the same strain, or "reinfection" with a new strain of *C. difficile*.[30] In one study, after a first recurrence, 9% of patients had at least one additional recurrence.[31] Risk factors for recurrent CDI include older age, heart disease, methicillin-resistant *Staphylococcus aureus* (MRSA) colonization, venous thromboembolism (VTE), continuous proton pump inhibitor (PPI) use, antibiotic use, hypoalbuminemia, community-associated CDI, longer hospital length of stay, and less-severe CDI.[32–35] Risk for reinfection was more strongly associated with an interval hospital admission.[36] A Korean retrospective study investigating the ribotypes (RTs) of consecutive CDI episodes found that about half were a relapse with the same RT of *C. difficile* and half were reinfections with a different RT.[36] Another study found 65% of second episodes to be relapses.[37] In patients who relapsed, time to second CDI episode was shorter as compared with those reinfected with a new RT, and relapses were more common for RTs 017, 018, and BI/NAP1/027.[36]

A potential mechanism for susceptibility to recurrent CDI includes persistent disruption of microbiota diversity.[38] Failure of host response[39] may also be a mechanism, as low-serum antibodies against toxins A and B are associated

with CDI recurrence, and antibodies to toxin A are associated with asymptomatic carriage, as previously discussed, but also protective against recurrent CDI.[24,40]

Community-Associated CDI

Conventionally, CDI is considered a hospital-acquired infection. However, the identification of symptomatic CDI among young, healthy, community-dwelling individuals suggested novel community-associated CDI (CA-CDI).[32] The SHEA defines CA-CDI as onset of diarrhea before or within 48 hours of hospitalization, with no hospital or health care facility discharge in the previous 12 weeks.[28]

CA-CDI has been increasing, with approximately one-third of U.S. CDI cases now originating in a nonhospital setting.[30] CA-CDI patients are typically younger than their HA-CDI counterparts, with a median age of 51 for CA-CDI patients in one study.[41] Many studies identified antibiotic use as a risk factor for CA-CDI, with up to three quarters of patients receiving antibiotics in the 12 weeks prior to infection,[41,42] but other studies showed either decreased exposure to antibiotics as compared with HA-CDI patients, or no association to antibiotics at all.[43–45] Additional risk factors for CA-CDI include hospitalization within the last year, female sex, proximity to infants, use of proton pump inhibitors (PPIs), or farm proximity.[44,46] Though CA-CDI is defined as symptom onset in the community or first 48 hours of hospital admission, many afflicted patients have prior contact with the health care system. In one study, 82% of patients with CA-CDI had exposure to health care, but not admission, in the 12 weeks prior to infection, and approximately half of those had an outpatient office visit, and the other half had a procedure, emergency department visit, inpatient care, or other "high-level" exposure to health care.[41] Thus, some of what is classified as CA-CDI may in fact have been acquired through health care exposure. For those with no exposure to HA sources of infection, a potential source of CA-CDI could be environmental exposures, including food, compost, animals, and public sandboxes; over 50% of samples from public sandboxes in a Madrid study were positive for *C. difficile*, and seven of eight toxigenic samples were epidemic RTs 014 or 106.[47] The RT/strain of *C. difficile* may vary between HA-CDI and CA-CDI as well.[45]

In efforts to identify modifiable risk factors and provide risk stratification, recent research efforts have focused on concomitant medication use, as well as identifying specific strains, and RTs of *C. difficile*.

Proton Pump Inhibitors

After a handful of studies investigated a correlation between *Helicobacter pylori* therapy and CDI,[48,49] a small case-control study in 2003 identified an association between use of proton pump inhibitor (PPI) in the 2 months prior to diagnosis, more than doubling of the odds of CDI.[50] Once this association between PPI use and CDI was identified, investigation into potential mechanisms and many additional studies have followed, but the findings and conclusions have been inconsistent.

Few prospective trials have been performed, though a small, likely under-powered, multicenter randomized controlled trial of pantoprazole versus placebo in 91 ICU patients found no statistically significant difference in incidence of CDI.[51] Of those retrospective studies that found no association between PPI use and CDI, most were case control with varying control group definitions, some by age, gender, antibiotic status, ward, dates of hospital admission, and presence of diarrhea.[52–57] Three were cohort studies in general and ICU populations with CDI.[58–60]

Nine meta-analyses found statistically significant associations between PPI use and either primary or recurrent CDI when evaluating case-control and cohort studies, with pooled odds ratios (ORs) listed in ►**Table 2**, and included number of studies ranging from 23 to 67 for all CDI and 3 to 16 for recurrent CDI.[61–68] Validity of these analyses is limited because of significant heterogeneity, with variable definitions of PPI use, lack of identification of specific PPI and/or dose, duration of PPI exposure (definitions range from 3 days to any use within the last year),[52,69] and numerous potential confounding factors at the patient level. A time association between the prevalence of negative studies has been identified, with positive studies dominating after 2007.[61] PPI use and recurrent CDI have been linked as well, also shown in ►**Table 2**, and when controlling for confounding factors including age and comorbid conditions, nine pooled studies continued to demonstrate an association (1.38, 95% confidence interval [CI]: 1.08–1.76).[65,66,70] Definitions of recurrence are heterogeneous, but when studies were grouped into 60 or 90 days from initial infection, ORs were minimally different (OR = 1.54; 95% CI: 1.04–2.28 and OR = 1.53; 95% CI: 1.07–2.19, respectively).[70] Overall, the heterogeneous evidence seems insufficient to recommend avoidance of PPIs for the purposes of CDI prevention,[3,67,71] yet the United States Food and Drug Administration (FDA) issued a Safety Announcement to the public regarding an increased risk of CDI for patients taking PPIs.[72] The 2018 IDSA/SHEA guidelines do not provide a recommendation regarding PPI use, acknowledging the association but also lack of evidence for PPI discontinuation.[3]

PPIs result in several physiological changes that may affect CDI risk (►**Table 3**), including decreased hydrochloric acid production in the stomach, which results in somatostatin release, increased gastrin production, increased bile salts, and bacterial overgrowth. The resulting multifactorial disruption of both gastrointestinal environment and drug metabolism is associated with many adverse effects including hypomagnesemia, vitamin B-12 deficiency, small-intestinal bacterial overgrowth, osteoporosis-related fractures, acute and chronic kidney disease, pneumonia, and diarrheal illness.[73,74]

A variety of proposed mechanisms exist to explain the correlation between CDI and PPI use.[75] Many focus on the gut microbiome, as PPIs disrupt bacterial ratios, decrease microbial diversity, and increase oropharyngeal commensal bacteria.[76–79] High-bile salts could enhance *C. difficile* spore germination and CDI.[75,80–82] Some studies theorize that decreased gastric acidity may improve *C. difficile* survival, but the exact mechanism remains unclear. A study of *C. difficile* spores in the gastric contents of patients on PPI did not show increased spore germination in the higher pH environment of PPI[83] and in vitro studies have shown bile salts are needed

Table 2 Characteristics of nine meta-analyses of the association between proton pump inhibitors and primary and/or recurrent *Clostridium difficile* infection (CDI)

Publication	No. of studies included	No. of patients included	OR	95% CI	I^2 (%)[a]
Primary CDI					
Deshpande[63]	29	202,965	2.15	1.81–2.55	87.0
Janarthanan[64]	23	288,620	1.69	1.40–1.97	91.9
Kwok[65]	42	313,000	1.74	1.47–2.85	85.0
Tleyjeh[67]	47	NS	1.65	1.47–1.85	89.9
Arriola[62]	23	186,033	1.81	1.52–2.14	82.0
Oshima[66]	67	NS	2.34	1.94–2.82	>40
Trifan[68]	56	356,683	1.99	1.73–2.30	85.4
Cao[61]	50	342,532	1.26	1.12–1.39	80.6
Recurrent CDI					
Kwok[65]	3	NS	2.51	1.16–5.44	78.0
Oshima[66]	9	NS	1.73	1.39–2.15	>40
Tariq[70]	16	7,703	1.52	1.20–1.94	64.0

Abbreviations: CDI, *Clostridium difficile* infection; CI, confidence interval; NS, not specified; OR, odds ratio.
[a] I^2 is a value indicating heterogeneity of the included studies, with >50% generally characterized as significant heterogeneity.

Table 3 Proposed mechanisms for association between proton pump inhibitors (PPI) and *Clostridium difficile* infection (CDI)

Potential mechanisms for PPI-related CDI
• Disruption of gut microbiome
• Increased gastric bile salts
• Decreased gastric acidity
• Increased inflammation

for sporulation.[83] Increased inflammatory response may predispose to CDI, as colon biopsies in patients taking PPIs have demonstrated increased intraepithelial lymphocytes and inflammation[84] and mouse models of PPI use develop intestinal inflammation, disrupted colonic integrity, increased bacterial load, increased weight loss, and worse stool consistency.[85,86] Changes in colonocyte gene expression have been observed with omeprazole treatment in vitro.[87]

Because of the acid-reducing mechanism of PPIs, histamine H2 receptor antagonists (H2-blockers) have been studied as well, with a lower risk of CDI in H2-blockers as compared with PPIs.[16,65,88] Based on the observational nature of the studies and significant heterogeneity, it is unclear whether the association between PPI use and CDI derives from proposed downstream effects of the medication or confounding by the indications for therapy among patients receiving PPIs.

Statins

Statins, or 3-hydroxy-3-methylgutaryl-coenzyme A (HMG-CoA) reductase inhibitors, were first linked to protection from infection through observational studies of patients with sepsis. Data supporting an association between statins and CDI, and also statins and sepsis, are limited. A recent meta-analysis of statins and CDI included eight studies, three of which were abstracts, and demonstrated a 20% decreased risk of CDI (OR = 0.80, 95% CI: 0.66–0.97) among patients taking statins.[89] When limited to the five studies that attempted to account for confounding variables, such as age, race, gender and comorbid conditions, meta-analysis did not identify a significant protective effect of statins.[89] A small study found a 22% reduction in the odds of CDI development in statin users compared with nonusers, whereas no effect was observed for other cholesterol-reducing medications, including niacin, ezetimibe, and fibrates.[90] In two studies assessing the effect of statins on CDI recurrence, one found a greater than 50% decrease in recurrence, while the other found no effect.[91,92] A small study of patients with CDI did not find a difference in mortality, severity, or complication of CDI in statin users as compared with nonusers.[93]

Proposed mechanisms for statins to protect against CDI relate to the disruption of cholesterol production. Because statins interfere with cholesterol production at the beginning of the synthesis pathway, many downstream cholesterol-independent, pleotropic effects on inflammatory, and immunomodulation pathways have been observed and studied.[94–99] With these pathways affected, the main proposed mechanisms for statin protection against CDI are anti-inflammatory or antimicrobial effects.[100,101] However, studied statin dosages required for antimicrobial activity are higher than those seen in blood concentrations of patients taking statins at a standard dose.[102]

Emerging Strains and Epidemic Ribotypes

Efforts to decrease CDI have focused on patient risk factors, medications, and also particular strains or RTs of *C. difficile*, particularly after epidemics attributed to select RTs.

C. difficile RTs are geographically distributed by nation and region, but also by hospital.[103] The population of *C. difficile* RTs is expansive, but dominated by a few RTs, and population balance changes over time.[104,105] A few major strains, as follows, are dominant: BI/NAP1/027, 014, 001/072, and 078 predominated in a population of 99 RTs identified in European stool samples.[106] These varieties of *C. difficile* differ in antibiotic resistance and detectability by immunoassays.[105–107] Some RTs are associated with specific populations, such as RT 078 and younger patients with CA-CDI.[108] Others have regional specificity: RT 356 is seen in Italy, with RT 018 predominantly in Italy, Japan, and Korea, and RT 176 in Czech Republic and Germany. RT BI/NAP1/027, a common epidemic RT is found in the United States, Canada, Mexico, England, Denmark, Hungary, Italy, Germany, Serbia, Romania, and Poland.[105,109,110] RTs 591, 106, and 002 are the prevailing RTs in Colombia.[111] Antibiotic resistance is associated with outbreaks, nearly all strains of RTs, such as BI/NAP1/027, 001, and 106 are resistant to erythromycin, many are resistant to fluoroquinolones, and some strains of BI/NAP1/027 and 001 are resistant to clindamycin as well.[105,112] RTs BI/NAP1/027, 017, and 198 have resistance to five or more antibiotics.[105] Maintaining a diverse population is important: diversity is inversely related to antibiotic resistance.[105]

Ribotype BI/NAP1/027

An increased incidence and severity of CDI outbreaks in the United States, Canada, Mexico, and Europe led to identification of RT BI/NAP1/027 as an epidemic strain.[113] Subsequent research was directed toward identifying any potential virulence factors influencing the observed more frequent, severe CDI, particularly in older adults.[114] RT BI/NAP1/027 demonstrates increased toxin A and B production, as well as production of *C. difficile* binary toxin (CDT), though the role of CDT in severity is unclear.[115] RT BI/NAP1/027 is resistant to multiple antibiotics, particularly fluoroquinolones.[105,113,114] A small study of BI/NAP1/027 found trends toward higher 3-day and 28-day mortality than other strains, with greater incidence of toxic megacolon.[116] Relapses are more common for BI/NAP1/027, as compared with other RTs.[36] The predominance of BI/NAP1/027 strain has decreased over time.[117]

Ribotype 018

RT 018, also identified as smz initially in the Asian literature, is a predominant strain in some Italian, South Korean, and Japanese hospitals.[118–120] It tends to affect older patients and produce higher levels of toxin.[121–123] Patients with RT 018 had higher C-reactive protein and greater 90-day all-cause mortality in a prospective Italian cohort study, as compared with the other identified RTs.[122] The vast majority, 95.7%, of nosocomial transmission cases in one study were caused by RT 018.[123] In Korean studies, RT 018 affected more female patients, caused more azotemia and more severe CDI than the next most common strain, RT 017, but increased recurrence or mortality were not observed.[124]

Genetically, RT 018 produces toxins A and B and has a mutation (gyrA C245T) which confers high resistance to fluoroquinolones.[123] Antibiotic resistance to erythromycin, clindamycin, and moxifloxacin have been identified with some Italian strains of RT 018 resistant to rifampicin.[105]

Ribotype 106

Another emerging strain, RT 106, is gaining prominence in the United Kingdom, Ireland, and Spain and has been responsible for outbreaks.[125–127] Its prevalence has increased in all Canadian provinces in recent years.[114] RT 106 is resistant to at least three antibiotics and produces more spores as compared with other RTs.[105,128]

Summary and Future Directions

Infection with *C. difficile* remains a costly, morbid, and potentially life-threatening hospital-acquired infection particularly for the older and sicker patients. CDI is now recognized in younger, healthier patients living in the community. Research continues to investigate modifiable risk factors and medication use; however, the associations between PPI and statins with CDI are insufficient to guide medical decision making. The sheer volume of studies identifying an association with PPI is compelling, though the lack of definition in PPI exposure, dose relationship, and patient factors that may confound the association are considerable detractors from this observation. Perhaps the association will encourage providers to reconsider discontinuation of marginally-indicated PPIs or be more thoughtful when initiating PPIs in hospitalized patients with weak indications for treatment or prophylaxis. The evidence from the statin studies is not strong enough to recommend initiating statins in at-risk patients, though may provide additional benefit for those with cardiovascular risk and other comorbidities at higher risk for CDI. The RTs and emerging strains of *C. difficile* have geographic trends and cause CDI of varying severity. Importantly for clinicians, the treatment of these specific strains remains the same as for any other CDI, though identification of high-relapse strains may spur providers to earlier fecal-microbiota transplant.

In summary, CDI remains a significant healthcare-associated infection, but its community-associated affects are increasingly recognized. A multifaceted approach to control this healthcare-associated infection through patient risk factors, medication associations, and identification of particular strains and RTs that may allow risk stratification of patients are part of the path toward better CDI care.

Conflict of Interest
Dr. De Roo reports grants from National Clinical Scholars Program, grants from Agency for Healthcare Quality and Research, during the conduct of the study.

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