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FIELD OF VISION

Clostridium difficile infection in the community: Are proton pump inhibitors to blame?

Daniel E Freedberg, Julian A Abrams

Daniel E Freedberg, Julian A Abrams, Division of Digestive and Liver Diseases, Columbia University Medical Center, New York, NY 10032, United States

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Correspondence to: Daniel E Freedberg, MD, Division of Digestive and Liver Diseases, Columbia University Medical Center, 630 West 168th Street, PH Bldg Floor 7, New York, NY 10032, United States. def2004@columbia.edu

Telephone: + 1-212-3420238 Fax: +1-212-3425759

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Abstract

Once a nosocomial disease, *Clostridium difficile* infection (CDI) now appears frequently in the community in the absence of exposure to antibiotics. Prior studies have shown that patients with community-acquired CDI are younger, more likely to be female, and have fewer comorbidities compared to patients with hospital-associated CDI. Because most studies of CDI are hospital-based, comparatively little is known about community-acquired CDI. The recent study by Chitnis has received widespread attention because it used active surveillance to capture all cases of community-acquired CDI within a large population and assessed key risk factors. The authors found that low-level healthcare exposure and proton pump inhibitor use were common among those with non-antibiotics associated, community-acquired CDI. In this commentary, we discuss the changing epidemiology of community-acquired CDI and the evidence basis for the controversial association between proton pump inhibitors and community-acquired CDI.

Key words: *Clostridium difficile*; Pseudomembranous enterocolitis; Proton pump inhibitors; Anti-bacterial agents; Pharmacoepidemiology; Public health; Disease outbreaks; Epidemics

Core tip: Population-based studies demonstrate that non-antibiotic associated, community-acquired *Clostridium difficile* infection (CDI) is increasingly common. Patients with community-acquired CDI are younger and have fewer co-morbidities compared to patients with hospital-associated CDI. Proton pump inhibitors may be a risk factor for non-antibiotic associated, community-acquired CDI.

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COMMENTARY ON HOT TOPICS

Clostridium difficile (*C. difficile*) infection (CDI) is the most feared gastrointestinal epidemic in the developed world with increasing incidence, virulence, and case fatality rates[1-5]. Formerly a nosocomial disease, CDI has become common in the community[6,7]. Early reports suggested that the risk factors associated with community-acquired CDI differ from the traditional risk factors associated with nosocomial CDI with relatively young and healthy individuals affected[8]. Thus we read with great interest the recent article by Chitnis *et al*[9] describing a multi-center study of the factors associated with community-acquired CDI.

COMMUNITY-ACQUIRED *CLOSTRIDIUM DIFFICILE* INFECTION

Pseudomembranous colitis was reported in the 19th cen-

tury and has long been understood as an antibiotic-associated phenomenon[10,11]. In 1978, *C. difficile* was identified as the causative agent of disease; subsequent reports recognized that pseudomembranous colitis caused by *C. difficile* could occur without antibiotics[12]. But it was only beginning in 2005 that it became understood that *C. difficile* infection was frequently occurring in the community[7].

Community-acquired CDI differs from hospital-associated disease, although many uncertainties remain. In the United States and Europe, 15%-44% of CDI occurs in the community without an identifiable antecedent healthcare exposure[8,13-15]. Compared to individuals with nosocomial CDI, those with community-acquired CDI are younger, have fewer comorbidities, and are more likely to be female[7]. Most surprisingly, patients with community-acquired CDI often do not report exposure to antibiotics[16].

If antibiotics are not essential in community-acquired CDI, what are the crucial risk factors? This question has been difficult to answer, in part because it is challenging to study community-acquired CDI in the United States. Cases of CDI arising in the community rarely require hospital admission. However, many studies of community-acquired disease are hospital-based and thus miss a large proportion of disease that both arises and is treated in the community[17-21]. In 2009, to address this problem, the Centers for Disease Control and Prevention (CDC) began a population-based program of active surveillance encompassing 11 million people[22]. Working with laboratories within the active surveillance area, all newly positive *C. difficile* stool tests were prospectively identified. Based on interviews with affected individuals, cases were classified as hospital-associated (defined as diarrhea and stool collected > 3 d to < 12 wk from a hospitalization) or community-acquired (all other cases). Community-acquired cases were assessed for risk factors including use of antibiotics or proton pump inhibitors (PPIs) and healthcare exposures within the previous 12 wk (classified as high-level exposure for dialysis or emergency department visits or low-level exposure for visits to a physician's office).

Chitnis *et al*[9] report on the first results of this valuable project. The authors identified 984 patients with confirmed community-acquired *C. difficile* infection. Patients were relatively young (median age 51 years old) and predominantly female (67%). Yet morbidity and mortality were surprisingly high. One quarter of patients with community-acquired CDI were hospitalized for treatment and there was a 6% combined rate of death, colectomy, or admission to an intensive care unit. Overall, 41% of patients reported a high-level healthcare exposure, 41% of patients reported a low-level healthcare exposure, and 18% of patients reported no healthcare exposure. Sixty-four percent of patients recalled antibiotic use within the preceding 12 wk. Compared to patients who reported recent antibiotic use, those that did not report antibiotic use were slightly more likely to report PPI use (31% *vs* 26%) but not histamine 2-receptor antagonist use (10% *vs* 9% respectively). The study has no comparison group so its most important findings are essentially descriptive. Nonetheless, the concerning implication is that non-antibiotic associated CDI is rising. Are PPIs to blame?

CLOSTRIDIUM DIFFICILE INFECTION AND PPIS

Over thirty observational studies and multiple meta-analyses indicate that PPIs are a risk factor for *C. difficile* infection[17,18]. Citing these findings in 2012, the United States Food and Drug Administration issued a warning regarding increased risk of CDI among patients taking long term PPIs[23]. Yet many questions remain regarding the relationship between PPIs and *C. difficile*. The data connecting PPIs and CDI is observational. Because patients who are prescribed PPIs differ in many ways from those who are not prescribed PPIs[24,25], it is possible that the observed association between PPIs and CDI is attributable to unmeasured confounding[26]. And there is comparatively little data that specifically addresses PPIs in community-acquired CDI.

There are a few reasons to suspect that the relationship between PPIs and CDI might be different among those with community-acquired compared to hospital-associated CDI. First, the highly toxigenic North American pulsed-field 1 (NAP1) strain has been linked to hospital-associated[3,27] rather than community-acquired cases; it is possible that the relationship between PPIs and CDI is affected by *Clostridial* strain. Second, a potential mechanism by which PPIs increase risk for CDI may be via alteration of the colonic microbiome[28-31]. Thus hospitalized patients, who can have altered microbiomes compared to those in the community[32], may be affected differently by PPIs. Finally, antibiotic exposure, which differs between hospitalized and non-hospitalized patients, may modify the relationship between PPIs and CDI[33].

So what is the evidence that PPIs are a risk factor for CDI in the community? Only a handful of studies include disease that is both acquired and treated in the community. A large, population-based study conducted within a United Kingdom dataset identified over 1000 cases of community-acquired CDI from 1994 to 2004[34]. The authors found that only 37% of cases had been prescribed antibiotics within the previous 90 d; compared to matched controls, patients prescribed PPIs within the previous 90 d had a nearly 3-fold increased risk for CDI. A Scottish study conducted among adults ≥ 65 years old identified all cases of community-acquired CDI[35]. After adjusting for covariables, the authors found that patients prescribed PPIs within the previous 6 mo had a 1.7-fold increased risk for CDI compared to matched controls. Finally, a study using a large United States insurance claims database identified all cases of CDI from 2004 to 2007 in Iowa and South Dakota[13]. Seventy-three percent of cases had been prescribed antibiotics within the previous 180 d; patients prescribed PPIs or histamine-2 receptor antagonists within the previous 180 d had a 2.3-fold increased

risk for community-acquired CDI compared to matched controls. These findings imply that the association between PPIs and CDI is at least as strong in community-acquired disease as in its more familiar hospital-associated form.

The study by Chitnis *et al*[9] was not designed to directly test the hypothesis that PPIs are associated with CDI in the community. Instead, this study yields valuable lessons regarding the epidemiology and risk factors for community-acquired *C. difficile* infection. Using active surveillance to capture all cases of community-acquired CDI, the authors have shown that non-antibiotic associated, community-acquired CDI is common, and that affected patients frequently have some form of healthcare exposure that falls short of actual hospitalization. Overall, rates of PPI use were extraordinarily high, nearly 30% among patients with community-acquired CDI compared to less than 3% in the general population[36]. Future studies should test the hypothesis that PPIs are a risk factor for non-antibiotic associated, community-acquired *C. difficile* infection and assess whether interventions causing decreased PPI use can also decrease rates of CDI. For now, the findings of Chitnis *et al*[9] highlight the fact that community-acquired CDI is a very real problem and remind us that PPIs should be prescribed only in situations where they are indicated.

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