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

FreedbergDE *et al. C. difficile* in the community

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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-associatedCDI. 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.

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**Keywords:** 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 comorbidities 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* infection (CDI) is the most feared gastrointestinal epidemic in the developed world with increasing incidence, virulence, and case fatality rates[[1-5](#_ENREF_1)]. Formerly a nosocomial disease, CDI has become common in the community[[6](#_ENREF_6),[7](#_ENREF_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](#_ENREF_8)]. Thus we read with great interest the recent article by Chitnis *et al*[[9](#_ENREF_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 century and has long been understood as an antibiotic-associated phenomenon[[10](#_ENREF_10),[11](#_ENREF_11)]. In 1978, *Clostridium difficile* was identified as the causative agent of disease; subsequent reports recognized that pseudomembranous colitis caused by *C. difficile* could occur without antibiotics[[12](#_ENREF_12)]. But it was only beginning in 2005 that it became understood that *C. difficile* infection was frequently occurring in the community[[7](#_ENREF_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](#_ENREF_8), [13-15](#_ENREF_13)]. Compared to individuals with nosocomial CDI, those with community-acquired CDI are younger, have fewer comorbidities, and are more likely to be female[[7](#_ENREF_7)]. Most surprisingly, patients with community-acquired CDI often do not report exposure to antiobitics[[16](#_ENREF_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](#_ENREF_17)]. 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](#_ENREF_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](#_ENREF_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-year-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 *Clostridium difficile* infection[[17](#_ENREF_17),[18](#_ENREF_18)]. Citing these findings in 2012, the United States Food and Drug Administration issued a warning regarding increased risk of CDI among patients taking longterm PPIs[[23](#_ENREF_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 than those who are not prescribed PPIs[[24](#_ENREF_24),[25](#_ENREF_25)]. It is possible that the observed association between PPIs and CDI is attributable to unmeasured confounding[[26](#_ENREF_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](#_ENREF_3),[27](#_ENREF_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](#_ENREF_28)]. Thus hospitalized patients, who can have altered microbiomes compared to those in the community[[32](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_35)]. After adjusting for covariables, the authors found that patients prescribed PPIs within the previous 6 months 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](#_ENREF_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](#_ENREF_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 *Clostridium 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](#_ENREF_36)]. Future studies should test the hypothesis that PPIs are a risk factor for non-antibiotic associated, community-acquired *Clostridium 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.

**REFERENCES**

1 **O'Brien JA**, Lahue BJ, Caro JJ, Davidson DM. The emerging infectious challenge of clostridium difficile-associated disease in Massachusetts hospitals: clinical and economic consequences. *Infect Control Hosp Epidemiol* 2007; **28**: 1219-1227 [PMID: 17926270 DOI: 10.1086/522676]

2 **Kelly CP**, LaMont JT. Clostridium difficile--more difficult than ever. *N Engl J Med* 2008; **359**: 1932-1940 [PMID: 18971494 DOI: 10.1056/NEJMra0707500359/18/1932]

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

4 **Gravel D**, Miller M, Simor A, Taylor G, Gardam M, McGeer A, Hutchinson J, Moore D, Kelly S, Boyd D, Mulvey M. Health care-associated Clostridium difficile infection in adults admitted to acute care hospitals in Canada: a Canadian Nosocomial Infection Surveillance Program Study. *Clin Infect Dis* 2009; **48**: 568-576 [PMID: 19191641 DOI: 10.1086/59670310.1086/596703]

5 **Cohen SH**, Gerding DN, Johnson S, Kelly CP, Loo VG, McDonald LC, Pepin J, Wilcox MH. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). *Infect Control Hosp Epidemiol* 2010; **31**: 431-455 [PMID: 20307191 DOI: 10.1086/651706]

6 **Kyne L**, Merry C, O'Connell B, Keane C, O'Neill D. Community-acquired Clostridium difficile infection. *J Infect* 1998; **36**: 287-288 [PMID: 9661938]

7 Centers for Disease Control and Prevention. Severe Clostridium difficile-associated disease in populations previously at low risk: four states, 2005. *MMWR Morb Mortal Wkly Rep* 2005; **54:** 1201-1205.

8 **Khanna S**, Pardi DS, Aronson SL, Kammer PP, Orenstein R, St Sauver JL, Harmsen WS, Zinsmeister AR. The epidemiology of community-acquired Clostridium difficile infection: a population-based study. *Am J Gastroenterol* 2012; **107**: 89-95 [PMID: 22108454 DOI: 10.1038/ajg.2011.398ajg2011398]

9 **Chitnis AS**, Holzbauer SM, Belflower RM, Winston LG, Bamberg WM, Lyons C, Farley MM, Dumyati GK, Wilson LE, Beldavs ZG, Dunn JR, Gould LH, Maccannell DR, Gerding DN, McDonald LC, Lessa FC. Epidemiology of Community-Associated Clostridium difficile Infection, 2009 Through 2011. *JAMA Intern Med* 2013; **173**: 1359-1367 [PMID: 23780507 DOI: 10.1001/jamainternmed.2013.70561697791]

10 **Rifkin GD**, Fekety FR, Silva J. Antibiotic-induced colitis implication of a toxin neutralised by Clostridium sordellii antitoxin. *Lancet* 1977; **2**: 1103-1106 [PMID: 73011]

11 **Climo MW**, Israel DS, Wong ES, Williams D, Coudron P, Markowitz SM. Hospital-wide restriction of clindamycin: effect on the incidence of Clostridium difficile-associated diarrhea and cost. *Ann Intern Med* 1998; **128**: 989-995 [PMID: 9625685]

12 **Bartlett JG**, Chang TW, Gurwith M, Gorbach SL, Onderdonk AB. Antibiotic-associated pseudomembranous colitis due to toxin-producing clostridia. *N Engl J Med* 1978; **298**: 531-534 [PMID: 625309 DOI: 10.1056/NEJM197803092981003]

13 **Kuntz JL**, Chrischilles EA, Pendergast JF, Herwaldt LA, Polgreen PM. Incidence of and risk factors for community-associated Clostridium difficile infection: a nested case-control study. *BMC Infect Dis* 2011; **11**: 194 [PMID: 21762504 DOI: 10.1186/1471-2334-11-1941471-2334-11-194]

14 **Naggie S**, Miller BA, Zuzak KB, Pence BW, Mayo AJ, Nicholson BP, Kutty PK, McDonald LC, Woods CW. A case-control study of community-associated Clostridium difficile infection: no role for proton pump inhibitors. *Am J Med* 2011; **124**: 276.e1-276.e7 [PMID: 21396512 DOI: 10.1016/j.amjmed.2010.10.013S0002-9343(10)00925-3]

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

16 **Bauer MP**, Goorhuis A, Koster T, Numan-Ruberg SC, Hagen EC, Debast SB, Kuijper EJ, van Dissel JT. Community-onset Clostridium difficile-associated diarrhoea not associated with antibiotic usage--two case reports with review of the changing epidemiology of Clostridium difficile-associated diarrhoea. *Neth J Med* 2008; **66**: 207-211 [PMID: 18490799]

17 **Kwok CS**, Arthur AK, Anibueze CI, Singh S, Cavallazzi R, Loke YK. Risk of Clostridium difficile infection with acid suppressing drugs and antibiotics: meta-analysis. *Am J Gastroenterol* 2012; **107**: 1011-1019 [PMID: 22525304 DOI: 10.1038/ajg.2012.108ajg2012108]

18 **Janarthanan S**, Ditah I, Adler DG, Ehrinpreis MN. Clostridium difficile-associated diarrhea and proton pump inhibitor therapy: a meta-analysis. *Am J Gastroenterol* 2012; **107**: 1001-1010 [PMID: 22710578 DOI: 10.1038/ajg.2012.179]

19 **Lowe DO**, Mamdani MM, Kopp A, Low DE, Juurlink DN. Proton pump inhibitors and hospitalization for Clostridium difficile-associated disease: a population-based study. *Clin Infect Dis* 2006; **43**: 1272-1276 [PMID: 17051491 DOI: CID39734]

20 **Dial S**, Kezouh A, Dascal A, Barkun A, Suissa S. Patterns of antibiotic use and risk of hospital admission because of Clostridium difficile infection. *CMAJ* 2008; **179**: 767-772 [PMID: 18838451 DOI: 10.1503/cmaj.071812179/8/767]

21 **McFarland LV**, Clarridge JE, Beneda HW, Raugi GJ. Fluoroquinolone use and risk factors for Clostridium difficile-associated disease within a Veterans Administration health care system. *Clin Infect Dis* 2007; **45**: 1141-1151 [PMID: 17918075 DOI: CID50655]

22 **Centers for Disease Control and Prevention.** Emerging Infections Program-Healthcare-associated Infections Project. Technical Information — Measuring the Scope of Clostridium difficile Infection in the United States. Available from: http: //www.cdc.gov/hai/eip/cdiff\_techinfo.html. Accessed July 30

23 **Food and Drug Administration.** FDA Drug Safety Communication: Clostridium difficile-associated diarrhea can be associated with stomach acid drugs known as proton pump inhibitors (PPIs). Available from: http: //www.fda.gov/drugs/drugsafety/ucm290510.htm. Accessed March 15, 2013

24 **Ho PM**, Maddox TM, Wang L, Fihn SD, Jesse RL, Peterson ED, Rumsfeld JS. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. *JAMA* 2009; **301**: 937-944 [PMID: 19258584 DOI: 10.1001/jama.2009.261301/9/937]

25 **Brophy S**, Jones KH, Rahman MA, Zhou SM, John A, Atkinson MD, Francis N, Lyons RA, Dunstan F. Incidence of Campylobacter and Salmonella infections following first prescription for PPI: a cohort study using routine data. *Am J Gastroenterol* 2013; **108**: 1094-1100 [PMID: 23588238 DOI: 10.1038/ajg.2013.30ajg201330]

26 **Leontiadis GI**, Miller MA, Howden CW. How much do PPIs contribute to C. difficile infections? *Am J Gastroenterol* 2012; **107**: 1020-1021 [PMID: 22764024 DOI: 10.1038/ajg.2012.174ajg2012174]

27 **McDonald LC**, Killgore GE, Thompson A, Owens RC, Kazakova SV, Sambol SP, Johnson S, Gerding DN. An epidemic, toxin gene-variant strain of Clostridium difficile. *N Engl J Med* 2005; **353**: 2433-2441 [PMID: 16322603 DOI: NEJMoa051590]

28 **Garcia-Mazcorro JF**, Suchodolski JS, Jones KR, Clark-Price SC, Dowd SE, Minamoto Y, Markel M, Steiner JM, Dossin O. Effect of the proton pump inhibitor omeprazole on the gastrointestinal bacterial microbiota of healthy dogs. *FEMS Microbiol Ecol* 2012; **80**: 624-636 [PMID: 22324305 DOI: 10.1111/j.1574-6941.2012.01331.x]

29 **Jakobsson HE**, Jernberg C, Andersson AF, Sjölund-Karlsson M, Jansson JK, Engstrand L. Short-term antibiotic treatment has differing long-term impacts on the human throat and gut microbiome. *PLoS One* 2010; **5**: e9836 [PMID: 20352091 DOI: 10.1371/journal.pone.0009836]

30 **Bühling A**, Radun D, Müller WA, Malfertheiner P. Influence of anti-Helicobacter triple-therapy with metronidazole, omeprazole and clarithromycin on intestinal microflora. *Aliment Pharmacol Ther* 2001; **15**: 1445-1452 [PMID: 11552917 DOI: apt1033]

31 **Jernberg C**, Löfmark S, Edlund C, Jansson JK. Long-term ecological impacts of antibiotic administration on the human intestinal microbiota. *ISME J* 2007; **1**: 56-66 [PMID: 18043614 DOI: ismej20073]

32 **Manges AR**, Labbe A, Loo VG, Atherton JK, Behr MA, Masson L, Tellis PA, Brousseau R. Comparative metagenomic study of alterations to the intestinal microbiota and risk of nosocomial Clostridum difficile-associated disease. *J Infect Dis* 2010; **202**: 1877-1884 [PMID: 21050115 DOI: 10.1086/657319]

33 **Stevens V**, Dumyati G, Brown J, Wijngaarden E. Differential risk of Clostridium difficile infection with proton pump inhibitor use by level of antibiotic exposure. *Pharmacoepidemiol Drug Saf* 2011; **20**: 1035-1042 [PMID: 21833992 DOI: 10.1002/pds.2198]

34 **Dial S**, Delaney JA, Barkun AN, Suissa S. Use of gastric acid-suppressive agents and the risk of community-acquired Clostridium difficile-associated disease. *JAMA* 2005; **294**: 2989-2995 [PMID: 16414946 DOI: 294/23/2989]

35 **Marwick CA**, Yu N, Lockhart MC, McGuigan CC, Wiuff C, Davey PG, Donnan PT. Community-associated Clostridium difficile infection among older people in Tayside, Scotland, is associated with antibiotic exposure and care home residence: cohort study with nested case-control. *J Antimicrob Chemother* 2013; [Epub ahead of print] [PMID: 23825381]

36 **Jacobson BC**, Ferris TG, Shea TL, Mahlis EM, Lee TH, Wang TC. Who is using chronic acid suppression therapy and why? *Am J Gastroenterol* 2003; **98**: 51-58 [PMID: 12526936 DOI: S0002927002058549]

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