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# Community-Acquired *Clostridium Difficile* Infection: Awareness and Clinical Implications

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## Abstract

The epidemiology of *Clostridium difficile* infection *(CDI)* is changing. CDI, usually depicted as a nosocomial infection in the elderly, is now occurring in community-dwelling persons who are younger and otherwise dissimilar. A more virulent isolate (North American Pulsed Field type $_1$ ($NAP_1$) associated with increased morbidity and mortality, has been identified. In 2005, similar strains were associated with severe disease in community-dwelling patients at a rate of 7.6/100,000. Screening patients with potential CDI symptoms and implementing preventative measures, including judicious use of antibiotics, can reduce disease burden.

## Introduction

*Clostridium difficile (C. difficile)* is typically defined as a nosocomial infection occurring in the elderly. Although about 500,000 Americans acquire *Clostridium difficile* infection (CDI)

in institutions each year, an estimated 15,000 to 180,000 cases occur in community settings.[1]

In 2000, a more severe strain $NAP_1$ was identified, leading to increased morbidity and mortality.[2] This strain appears more virulent due to increased spore germination, secretion of potentially hyper-virulent forms of toxins A and B, and production of an additional virulence factor, binary toxin.[2] In 2005, such strains were associated with severe disease in patients in the community (7.6/100,000 people).[3]

Compared to patients with Hospital Acquired CDI (HA-CDI), patients with Community Acquired CDI (CA-CDI) have lower mortality and shortened hospitalizations,[4] but some may have poorer prognosis. A large Centers for Disease Control and Prevention (CDC) funded study assessed rates of colectomy due to CDI in 5 tertiary-care hospitals between 2000 to 2006. While 75 of 8,569 cases identified with CDI required a colectomy due to disease severity, colectomy rates for patients with HA-CDI were lower than those with CA-CDI ( 4.3/1,000 versus 16.5/1,000 cases[5]). Appropriate screening and treatment of patients presenting with potential CDI symptoms may avoid such severe consequences.

Recent interest also has focused on differentiating CA-CDI from another diagnosis, Community-Onset Hospital-Associated CDI (CO-HA-CDI). CDI surveillance recommendations indicate symptoms beginning within four weeks post-discharge from hospital/institutional settings are defined CO-HA-CDI, while those beginning ≥ 12 weeks post-discharge are considered CA-CDI.[6] However, controversy still exists in definitions, and failure to distinguish may contribute to confusion in study findings.

## Clinical Vignette

A 25 year old woman presents to the clinic with a chief complaint of “diarrhea” for 7 days. Symptoms began with 4–5 loose stools daily and mild abdominal cramps, but have worsened, and she reports 5–10 watery stools daily, abdominal cramps and tenderness, and a low-grade temperature since yesterday. She tried non-prescription medication (loperamide hydrochloride) without relief. Her medical history is significant for recent sinusitis treated with ciprofloxacin for 14 days. She denies known food or drug allergies, recent travel out of the country, or eating salads, uncooked vegetables, meats, or exotic foods.

## Differential Diagnosis & Discussion

Differential diagnosis for infectious diarrhea includes viruses, bacteria, and protozoa. Viral agents are usually self-limiting; infected patients present with vomiting, nausea, occasional headache, fever, watery diarrhea, and generalized or periumbilical abdominal cramping.[7,8] Symptoms of protozoal agents commonly include weight loss, loose stools, meteorism, hyperperistalisis, perianal itching, wheezing, and rectal prolapsed,[8] while symptoms of bacterial agents consist of fever, blood and/or mucous in the stool, small-volume stools, and suprapubic pain.[8]

Since this patient has not traveled, agents associated with “traveler’s diarrhea” are unlikely. Nor has she eaten foods commonly associated with shiga-like toxins such as *Escherichia coli 0157H7*. Other diagnoses, such as *Giardia*, might be considered, but *Giardia* is more commonly associated with daycare stay, travel, or immunocompetence.[8] Although this patient is young and has not recently been hospitalized, the primary differential diagnosis for consideration is CDI, especially given her recent use of ciprofloxacin.

## Pathophysiology

*C. difficile*, a gram-positive, anaerobic spore-forming bacillus[2,9] is present in approximately 70% of healthy infants. In the 1970's, *C. difficile* was first deemed pathogenic, due to association with antibiotic use and development of pseudomembraneous colitis.[9]

*C. difficile spores are* noninfectious until ingested and germination occurs. Ingested spores remain dormant in the colon until normal bowel flora are disrupted, at which time spores germinate, into the pathogenic bacteria, releasing two toxins (Toxins A and B) responsible for *C. difficile* colitis or pseudomembraneous colitis.[2,9,10]

## Epidemiology

*C. difficile* is often found in the environment and can survive for long periods as spores.[10] It is transmitted via the fecal-oral route, usually after contact with contaminated surface areas (e.g., bathtubs, rectal thermometer probes), or frequently after contact with contaminated hands of health care workers.[2] CDI symptoms typically present as watery diarrhea, fever, anorexia, abdominal pain or tenderness, and nausea. CDI risk factors include use of antibiotics or proton pump inhibitors, increased age, gastrointestinal surgery, immunocompetence, complicated chronic illness, or prolonged stays in healthcare settings.[2,10,11]

## Clinical Impact

Historically, CDI was regarded as a nosocomial infection occurring among the elderly, with its frequent occurrence attributed to immunocompetence.[2,10,11] Reported HA-CDI incidence in 2005 was 84/100,000.[12] However, more recent evidence suggests that CA-CDI occurs in younger patients without co- morbidity, with estimates ranging from 3.2–16.2 cases/ 100,000.[13,14] Additionally, according to 2010 Emerging Infections Program data, 94% of CDI cases occurred in persons receiving health care; 75% had symptoms that presented outside hospital settings.[9,15]

While CDI risk factors appear to be changing, few studies have compared HA-CDI and CA-CDI risk factors. Khanna *et al.* examined CAS-CDI and HA-CDI in Olmsted County, Minnesota, from 1991–2005.[16] Persons with CA-CDI were younger (median age 50 vs. 72 years), female (76% vs. 60%), had fewer co-morbidities, and less likely to have severe infection (20% vs. 31%) or exposure to antibiotics (78% vs. 94%) than patients with HA-CDI.[16]

Kuntz *et al.* examined CA-CDI in a population-based, retrospective, nested, case-control study. Incidence rates for CA-CDI were lower than HA-CDI (11.16 versus 12.1/100,000 person-years). CA-CDI cases were more likely than controls to receive antibiotics drugs (adjusted OR 6.09, 95% CI 4.59–8.08) and gastric acid suppressants (adjusted OR 2.30, 95% CI 1.56–3.39) within six months prior to diagnosis.[17] CA-CDI in this article was termed as Community-Associated CDI but defined as no history of hospital discharge pre diagnosis.

The economic burden associated with CDI is significant. An estimated 178,000–246,139 CDI cases occur annually with an average attributable cost of $2,848 to $3,791 per case.[18,19] Based upon these assumptions, CDI cost estimates are from $433 to $797 million annually.[20]

## Diagnostics

CDI diagnosis is based on symptom presentation and diagnostic confirmation. Patients with three or more watery stools for more than two days, low-grade temperature elevation, nausea, anorexia, and abdominal pain and tenderness should have diagnostic testing for toxigenic *C. difficile*.[2,10] Costs, sensitivity and specificity of molecular diagnostic tests vary (see Table 1). Stool culture of *C. difficile* is the most sensitive test, but is labor intensive, results may be delayed 48–96 hours, and can yield false-positives due to presence of non-toxigenic strains.[2] The most common method in the U.S. is enzyme immunoassay (EIA), which detects toxins A and B, but lacks good sensitivity and specificity.[11,21,26,27] A two-step method glutamate dehydrogenase (GDH) assay is recommended. GDH, an antigen associated with *C. difficile*, is present in both toxigenic and non-toxigenic strains, but largely absent for other bacteria. A GDH-negative specimen is reported as negative for *C. difficile* with a high level of confidence. A positive GDH result requires additional testing for *C. difficile* toxin,[11] using a polymerase chain reaction (PCR).[11,31] Sensitive assays eliminate necessity for more than one stool specimen for confirmation. Repeat testing within 7 days is not beneficial unless patients' health deteriorates.[28,29,30]

## Clinical Vignette Continued

The patient's stool specimen tested positive for *C. difficile* toxin. Though she completed metronidazole 500mg TID P.O. for 10 days, three weeks later, diarrhea has recurred. She has not traveled nor eaten out lately and is very concerned.

## Treatment

Treatment of CDI differs according to disease severity. Discontinuing an offending antibiotic may be effective in very mild cases.[10] However, in most cases, an antibiotic is needed. The Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) recommend initial episodes of mild to moderate cases of CDI (Leukocytosis with White Blood Cell count [WBC] of 15,000 cell/ul or less) be treated with metronidazole 500mg TID P.O. for 10–14 days. Severe cases of CDI (Leukocytosis with WBC > 15,000 cells/ul or elevated serum creatinine ≥ 1.5 times premorbid levels) should be treated with vancomycin 125mg QID P.O. for 10–14 days.[11]

Approximately 20% of patients with CDI develop a recurrent episode of *C. difficile* colitis, typically within 3–10 days after completing antibiotics.[10] The etiology of recurrent episodes of CDI is not well understood, but may be related to incomplete eradication of *C. difficile* by prescribed antibiotics or inadequate production of antibodies to bacterial toxins.[10] CA-CDI versus HA-CDI rates of recurrence are not well documented and further research is needed.

Treatment for a first recurrent case may include the medication prescribed initially, depending on disease severity.[11] Metronidazole should not be used after the first recurrence due to drug -associated neurotoxic effects.[32] Second recurrences should be treated with pulsed or tapered doses of vancomycin.[11] Other treatment options include therapies such as nitazoxamide[33] or intravenous immunoglobulins.[34,35,36,37] Further recurrent or severe cases should be referred to an infectious disease consultant. Use of antimotility drugs such as loperamide has been discouraged in patients with CDI but supporting evidence is limited,[38] and more research is indicated.

## New Treatment Strategies

High CDI recurrence rates demonstrate need for new treatment strategies. Antibiotic development and testing has produced several new drugs currently in Phase III clinical

trials.[39] The newest antibiotic approved in the USA and Europe is fidaxomicin, a novel macrocyclic antibiotic thought to inhibit bacterial RNA synthesis. Equally effective to vancomycin in treating active infection, fidaxomicin is superior in reducing rates of recurrence[40] though cost may limit its use in clinical practice and it should be considered for patients at increased risk for recurrence. Also in Phase III clinical trials are a number of non-antibiotic treatments, including monoclonal antibodies and probiotics.[39] Fecal transplants have proved to be highly effective in treating recurrent infections, through re-establishing balanced intestinal microbiota.[41] A *C. difficile* toxoid vaccine (ACAM-CDIFF) designed to prevent CDI recurrence has recently completed Phase II clinical trials,[39] but study results have not yet been posted. SHEA and IDSA do not recommend probiotics due to potential risk of septicemia.[11]

## CDI Control Measures

The most effective control measure is prevention. Preventive measures, include effective hand hygiene and cleansing of patients' rooms, exam rooms, bathrooms, or other environments with antimicrobial disinfectant. Exam tables should be cleaned with a sporicidal agent registered with the Environmental Protection Agency.[2]

Hand washing with soap and water is recommended for healthcare workers in hospital settings with outbreaks,[2,42] and caregivers in community settings. Although research has demonstrated no actual decrease in CDI with use of soap and water versus alcohol-based products, SHEA and IDSA recommend use of soap and water in settings with outbreaks.[2,42]

Given the association between use of antibiotics and development of severe CDI illness or complications, clinicians are encouraged to prescribe antibiotics judiciously to prevent disease development. Clinicians who follow IDSA guidelines for optimal antibiotics for targeted bacteria, drug doses, and treatment duration also minimize drug resistance.[43]

Other useful clinical advice includes teaching patients about disease pathophysiology, diagnosis, course, various treatments, and outcomes. Clinicians should advise patients to complete antibiotics as prescribed and not to take medications belonging to others.

## Conclusion

Much remains unknown about CDI and its effective treatment. More research is indicated to determine its epidemiology, including risk factors, as well as control measures and effective treatment strategies. Clinicians must be alert to patients presenting with CDI symptoms and to screen, treat appropriately, and implement preventative measures.

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## TABLE 1

Diagnostic performance and cost of C. difficile detection assays[a]

| Assay | Performance characteristics (%)[b] | | Cost[c] |
|---|---|---|---|
| | Sensitivity | Specificity | |
| Toxin A, B IA | 60–85.4 | 90.9–99.7 | ~$6 |
| Cytotoxin assay | 86.4 | 99.2 | ~$25 |
| GDH | 87.6–96.2 | 76.4–94.3 | – |
| GDH/toxin 2-step algorithm | 82.9–100 | 99.7–100 | ~$8–$14 |
| NAAT | 88.5–100 | 95.4–100 | ~$25–$48 |

[a] Compiled from references Vasoo et al., Chapin et al., Eastwood et al., Kvach et al., Pancholi et al.

[b] Compared to toxigenic culture.

[c] Materials and labor (U.S. dollars).

Abbreviations: IA, immunoassay; GDH, glutamate dehydrogenase; NAAT, nucleic acid amplification test