**Review**

*Clostridium difficile* Infection in Travelers—A Neglected Pathogen?

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**Background.** Until recently, *Clostridium difficile* infection (CDI) has been mostly diagnosed in hospitalized elderly patients treated with antibacterial agents. The epidemiology of *C difficile* is changing as the ribotype 027 strain is spreading worldwide, and more infections are diagnosed in patients residing in the community. Although only few data about the epidemiology of CDI in developing countries are available, a number of reports seem to indicate that the incidence of CDI may be high in some such countries. Transmission of CDI may be more common in hospitals that lack the resources for efficient infection control programs. Theoretically, travelers to low-income countries may be exposed to *C difficile* both in the community and within hospitals.

**Methods:** Data for this article were identified by searches of PubMed and MEDLINE, and references from relevant articles using the search terms “clostridium” and “travel.” Abstracts were included when related to previously published work.

**Results and conclusions.** A total of 48 cases of travelers with CDI were located. CDI among travelers was more commonly acquired in low- and medium-income countries, although 20% of all reported cases occurred in travelers returning from high-income countries. All travelers with CDI for whom a detailed history was available acquired the infection in the community. CDI in travelers occurred in relatively young patients and was frequently associated with the empiric use of antibacterial agents, notably fluoroquinolones. A sizable minority of travelers with CDI had no exposure to antibacterial agents at all. The incidence of travel-related CDI is unknown, but may be higher than previously suspected. A prospective study among travelers with unexplained acute or chronic diarrhea is warranted.

Diarrhea occurs commonly during or after travel in low-income countries.1,2 Bacterial and viral infections account for most cases of acute diarrhea,3 while many of the cases of recurrent, persistent (duration 2–4 weeks), or chronic (duration > 4 weeks) diarrhea are caused by various parasitic infections, or by non-infectious diseases such as acquired disaccharidase deficiency, postinfectious irritable bowel syndrome, or inflammatory bowel disease. In many of the cases of diarrhea among travelers a specific etiology is not identified.4–6

*Clostridium difficile* is known to be a major cause of health-care-associated diarrhea. The clinical manifestations of *C difficile* infection (CDI) vary greatly. Asymptomatic carriage of the bacteria is common among infants and also exists among healthy adults.7 Some patients with CDI have only a self-limiting diarrhea that resolves spontaneously, while in others the disease takes a fulminant course manifested by the development of characteristic pseudomembranes within the colon, and progression to toxic megacolon, colonic perforation, and death. The diarrhea in CDI can be acute, persistent, chronic, or recurrent—all of which are common clinical syndromes among travelers with diarrheal diseases. Over the past few years, the epidemiology of CDI has changed considerably.5 In many high-income countries community-acquired cases in populations previously considered to be at a low risk are on the increase, and recurrence rates and mortality attributed directly to CDI increased as well.9–11

As CDI can be acquired within hospitals also in the community, it is possible that *C difficile* accounts for some of the undiagnosed cases of travelers presenting...
with diarrhea. Factors such as empiric use of antibiotics during travel, contact with a low-resource health-care system, concurrent gastrointestinal infections, or close contact with animals may contribute to the occurrence of CDI among travelers. We aim to review what is already known about the epidemiology and clinical aspects of CDI in low-income countries and among travelers. The possible implications on the management of returning travelers presenting with diarrhea are discussed.

Health-Care-Associated CDI

Clostridium difficile has been recognized for many years as a leading cause of health-care-associated diarrhea. Prior antibiotic therapy, prolonged use of antibacterial agents, prolonged hospitalization, chemotherapy, enteral feeding, and the use of proton pump inhibitors have been repeatedly identified as factors associated with acquisition of CDI.12

The epidemic NAP1/027 strain (North American pulsed-field type 1 and PCR ribotype 027) has been reported initially in Canada, but then spreading rapidly to the United States, Europe, Asia, and Australia. CDI with this epidemic strain was associated with an increased rate of complicated cases, and a significant rise in attributable mortality.8,11 Following this rapid rise in the incidence, morbidity, and mortality attributed to C difficile, many high-income countries developed programs aimed at reducing CDI rates. These programs included various combinations of active surveillance (including, in some countries, centrally funded programs for ribotyping strains of C difficile), improved infection control measures, restrictions imposed on the use of cephalosporins and fluoroquinolones, and education of health-care workers. A subsequent decrease in rate of infections caused by the NAP1/027 strain, and a parallel decrease in mortality directly caused by C difficile have been reported in the United States and in several European countries.8,13–15

These measures, aimed at reducing CDI rates within hospitals, require enormous resources which are often not available in low-income countries.

CDI in the Community

Even in patients not exposed to any of the “classical” risk factors associated with CDI, the acquisition of the infection within the community hardly comes as a surprise, when one considers the many possible reservoirs of these bacteria outside health-care facilities. Clostridium difficile is ubiquitous in the environment and frequently colonizes newborns and some asymptomatic adults.12,16 – The organism has also been isolated from raw vegetables, rivers, tap water, seawater, swimming pools, farm animals, and pets such as cats and dogs.17–23

Farm animals are often treated with antibiotics, and C difficile is known to colonize asymptomatic animals, and to cause a clinical disease quite identical to human CDI.24 Clostridium difficile has been isolated from various food products, and although food-borne CDI has not been reported, its occurrence remains theoretically possible.18,25,26

Guidelines published by the Infectious Diseases Society of America suggest using strict standardized case definitions for (1) health-care facility (HCF)-onset, HCF-associated CDI, (2) community-onset, HCF-associated CDI, and (3) community-associated CDI.27

Although these definitions are not universally applied in all published studies, it is increasingly evident that C difficile can cause clinical disease in people with no known risk factors residing in the community.28–31 Using stringent definition criteria, a surveillance program for community-associated CDI performed in the United States revealed an annual incidence of 6.9 cases per 100,000 persons.12 In England, 2.1% of the stool samples taken from patients residing in the community and suffering from diarrhea were positive for C difficile toxin. These are astonishing figures for a clinical syndrome that was rarely reported in such settings in previous decades.33 Different studies reported that around 25% to 33% of patients with community-associated CDI had not been exposed to either of the two most significant risk factors for such infection: admission to a health-care facility and use of antibiotics.32–34

When compared to patients with health-care-associated CDI, these patients were typically younger and had a milder disease, although fatal cases among previously healthy adults including young women during the peripartum period have been reported.32,35

A change in the pattern of antibiotic prescription, an effect of new epidemic strains with different transmission patterns or virulence factors, increasing indirect contact with health-care facilities, and an ascertainment bias resulting from a growing interest in C difficile within the medical community could contribute to the increase in the diagnosis of community-acquired CDI.5

CDI in Low- and Middle-Income Countries

National active surveillance programs for C difficile do not exist in low-income countries, and no studies have evaluated the incidence of community-acquired CDI in such countries. The data regarding CDI in low- and medium-income countries come from the few studies conducted in Latin America,36–41 Africa,42,43 and Asia.34–47 Most of these studies report a very high incidence of CDI among hospitalized patients, but since national incidence or mortality rates are not available, a reporting bias is possible. A prospective observational study conducted in a tertiary hospital in Peru, for example, demonstrated a high incidence of CDI among patients with nosocomial diarrhea in all wards. When medical wards were analyzed separately, the incidence rate surpassed even the one reported in the often-mentioned
outbreak of *C. difficile* NAP1/027 strain in Quebec, Canada.\(^\text{4}\)\(^\text{7}\)

As *C. difficile* spores can be transmitted by health-care workers or directly from patient to patient, infection control measures are crucial in avoiding the spread of CDI within hospitals. Some of the recommended infection control measures (ie, active surveillance programs, isolation or cohorting of patients, and use of gloves and gowns) are simply not available in most public health-care facilities in developing countries.\(^\text{4}\)\(^\text{8}\)\(^\text{,}\)\(^\text{4}\)\(^\text{9}\)

The burden of health-care-associated infections, in general, has been shown to be higher in low-income countries.\(^\text{1}\)\(^\text{0}\)

A significant obstacle to the control of CDI within hospitals in low-income countries is the lack of laboratory tests for diagnosing CDI in many such institutions. A multitude of diagnostic tests for CDI exist, and this issue is beyond the scope of this article. In general, a screening test with a sensitive method (such as the glutamate dehydrogenase) and a confirmatory test (such as a cytotoxity test) are optimal. In a resource-limited setting, an enzyme immunoassay detecting the *C. difficile* toxins can be used despite its lower sensitivity. However, empiric treatment for presumed bacterial pathogens and intestinal parasites is frequently administered to patients with diarrhea without using any diagnostic tool. This approach results in an unrestricted use of antibiotics and the delay of treatment for CDI. Such use of antibiotics creates ideal conditions for the proliferation of *C. difficile*. Ultimately, excess morbidity, mortality, and increased transmission of CDI to other patients may ensue.

As previously mentioned, several potential reservoirs of *C. difficile* have been recognized (eg, soil, farm animals, water). In addition, infants and healthy adults are occasionally asymptomatic carriers of these bacteria. In low-income countries, these reservoirs may play a more prominent role in the spread of community-acquired CDI. Throughout much of the developing world clean water is not universally available, sewage infrastructure is suboptimal, and drinking water is frequently contaminated with human or animal excretions. Whether transmission of *C. difficile* is enhanced by such unfortunate circumstances is unknown. In addition, the close proximity of humans to domestic animals known to carry pathogenic strains of *C. difficile* and the higher number of persons per household may also pose additional risks of contracting the bacteria. Thus, although the incidence of community-acquired CDI in low-income countries is unknown, it is likely to be high.

An association between human immunodeficiency virus (HIV) infection and CDI has been long observed in the United States.\(^\text{3}\)\(^\text{1}\)

A study conducted in Peru demonstrates that this important association is also evident in low-income countries.\(^\text{5}\)\(^\text{2}\)

In this study, the most common pathogen causing persistent diarrhea in HIV-positive patients was *C. difficile*, and CDI was associated with increased mortality, even after adjustment for coinfection, CD4 lymphocyte count, and weight loss. Similar findings were reported in Africa.\(^\text{3}\)\(^\text{2}\)

One would expect to find a high incidence of CDI in hospitals within some developing countries in which a large proportion of the patients are infected with HIV.

### CDI in Travelers

When one considers the increased awareness to CDI, its increased incidence, and its widespread occurrence within the community, it is surprising to find that very little is known about the epidemiology of CDI among travelers. In a recent comprehensive review of 51 studies examining the global etiology of travelers' diarrhea, *C. difficile* was not mentioned. In most studies the occurrence of CDI was not assessed at all.\(^\text{5}\)\(^\text{3}\)

We are aware of only two prospective studies in which CDI was assessed in travelers with diarrhea. In a study which was performed during 1987 among US military personnel in Egypt, no cases of CDI were detected among the 183 patients with a diarrheal disease.\(^\text{5}\)\(^\text{4}\)

In contrast, a large prospective study conducted in Sweden 10 years later (1996–1997) included 851 patients with diarrhea.\(^\text{5}\)\(^\text{4}\) CDI was diagnosed in 101/851 (13%) of all patients with diarrhea and was one of the two predominant recovered pathogens. Most patients had both a positive culture and a positive *C. difficile* toxin assay. Notably, in this cohort of 851 patients with diarrhea, 510 were returning travelers, and among them CDI accounted for 25 (4.9%) of all cases. Most cases of CDI, that were related to travel, occurred after trips to low- or medium-income countries. Most patients with CDI (61%) were younger than 60, and 41% had not received antibiotics during the month preceding the onset of diarrhea.

However, in general, the results of this study might not reflect the true incidence of CDI among travelers. The study was conducted in an infectious-diseases referral hospital, possibly overrepresenting returning travelers with more severe diarrhea not responsive to previous empiric treatments, and overestimating the incidence of CDI in this population. In addition, interpretation of the study’s results is clouded by the inclusion of travelers to both low- and high-income countries. Empiric fluoroquinolone therapy is usually provided only to the former, making these populations essentially different with regard to the risk of CDI acquisition.

In the past few years, there have been accumulating case reports of travelers with CDI. A retrospective study performed in a Tropical Medicine Referral Unit in Madrid, Spain, and published in 2008 reported six travelers returning from low- and middle-income countries.\(^\text{5}\)\(^\text{5}\) All patients had both a positive *C. difficile*...
toxin assay and a positive culture in selective media. In this study, only travelers who had previously been treated with antibacterial agents and had persistent or recurrent diarrhea were included in this study, so cases of CDI among travelers without exposure to antibiotics, or travelers with acute diarrhea caused by C difficile may have been missed. Four of these patients were treated with ciprofloxacin with or without additional antibiotics, and two patients were treated with an unknown antibacterial agent during their trip.

In 2011, another case series of nine returning American travelers diagnosed with CDI in a single center was presented in an abstract form. In this study, a retrospective chart review was performed, and patients with CDI and a history of international travel within the previous 6 months were included. Only 5/9 of these travelers were exposed to antibacterial agents during their travel—most commonly to ciprofloxacin.

Several other reports described cases of presumed travel-related CDI: Australian travelers returning from South-East Asia and Africa, aid-workers in Haiti, and a traveler returning from South America.

The methodological limitations of case-series studies make drawing definite conclusions about travel-related CDI impossible. However, the existing data, although limited, highlight several interesting aspects regarding CDI in travelers (Table 1).

- Although CDI was reported more often after traveling to low- and middle-income countries, ~20% of cases occurred after returning from industrialized countries. In sharp contrast to many other pathogens that cause diarrhea in travelers, C difficile is widely prevalent both in high- and low-income countries.
- Patients were relatively young, probably reflecting the lower average age of travelers to low-income countries.
- All travelers with CDI for whom a detailed history was available acquired the infection in the community.
- A sizable number of travelers with CDI had no exposure to antibacterial agents. When prior use of antibiotics was reported, fluoroquinolones were by far the most common agent.

Fluoroquinolones and the Risk for CDI Among Travelers

Fluoroquinolones are used frequently as a first-line agent for the treatment or prevention of travelers’ diarrhea. In general, the use of fluoroquinolones has been strongly associated with the risk of developing CDI, and has emerged as a dominant risk factor for the acquisition of the fluoroquinolones resistant, epidemic ribotype 027 strain. The risk of CDI in a traveler using a short course of fluoroquinolones is unknown, but many of the cases of CDI among travelers were indeed associated with the use of this class of antimicrobials (Table 1). As fluoroquinolones are used extensively by travelers, we would have expected to find more reported cases of CDI following the use of fluoroquinolones. It is possible that the use of fluoroquinolones by a young and healthy host is normally not sufficient to create the conditions for a clinical infection with C difficile, or that many cases are simply not diagnosed and resolve spontaneously.

Malaria Chemoprophylaxis and CDI

A single case series of three Australian travelers who acquired CDI after using doxycycline for malaria chemoprophylaxis has been published in 1995. On the basis of this single observation, the Centers for Disease Control and Prevention (CDC) guidelines specifically mention CDI as a potential complication of malaria chemoprophylaxis. We have previously suggested that this association is not supported by available data. Since 1995, no additional cases have been documented despite the widespread use of doxycycline for malaria chemoprophylaxis. One study comparing doxycycline and mefloquine chemoprophylaxis for malaria given to US military personnel in Thailand reported similar rates of diarrheal disease in the two groups. In addition, the association between the use of doxycycline and CDI in general is weak at best; in at least one large study, its use was actually associated with a significant reduction in the risk of acquiring CDI.

The Potential Spread of New Strains of C difficile by Travelers

The first reported case of CDI involving the hypervirulent epidemic 027 strain in Australia was...
reported in 2008. The patient probably acquired CDI during a stay in the United States and suffered a recurrence after returning to Australia.66 This case illustrates the ease with which a virulent strain of *C. difficile* can be transported inadvertently by travelers. A small epidemiologic study from England suggested that travel outside the UK might be associated with an increased risk of community-onset CDI.67 A recent review from the *Clinical Infectious Diseases* journal lists hypervirulent *C. difficile*—alongside organisms like multiresistant *Klebsiella pneumoniae* as well as *Acinetobacter* spp, methicillin-resistant *Staphylococcus aureus*, and vancomycin-resistant enterococci—as a potential health-care threat transmissible through international travel. The so-called “medical tourists” pose an increased risk of transmitting *C. difficile* through contact with under-resourced health-care systems, and because of an increased exposure to infected patients and to antibacterial agents.68

**Conclusions**

CDI is traditionally considered a rare cause of diarrhea in travelers, but several factors led us to assume that this may be changing. The increasing incidence of community-associated CDI, the occurrence of CDI in patients without a history of prior antibiotic use, the appearance of hypervirulent strains spread through international travel, the epidemiologic data showing that CDI may be common in low-income countries, and the frequent use of antibacterial agents including fluoroquinolones by travelers—all suggest that CDI should be considered in all travelers with diarrhea. It is unclear why the total number of reported CDI cases among travelers is low. It is theoretically possible that CDI does not commonly occur among travelers, despite the risk factors mentioned above. However, underdiagnosis may play a role in the current situation. In addition, health-care-associated CDI may be uncommon because most travelers to low-income countries do not require inpatient care.

The existing case series of travelers with CDI are not sufficient to draw definite conclusions about the true epidemiology of CDI in this population. Theoretically underdiagnosis, underreporting, overrepresentation of patients from specialized referral centers, and publication bias favoring more “exotic” pathogens could have affected the current available data.

A prospective study of the incidence of CDI among travelers with diarrhea is warranted. Reliable diagnostic tests should be used to evaluate travelers with acute, chronic, and recurrent diarrhea. Both travelers with and without health-care exposure and prior antibiotic use should be evaluated, and a special emphasis should be placed on travelers who have used fluoroquinolones during their travel.

**Declaration of Interests**

The authors state that they have no conflicts of interest to declare.

**References**


