Bacterial Diarrhea in HIV-Infected Patients: Why *Clostridium difficile*, and Why Now?

Sumathi Sivapalasingam and Martin J. Blaser

Departments of Medicine and Microbiology, Division of Infectious Diseases, New York University School of Medicine, New York, New York

(See the article by Sanchez et al. on pages 1621–7)

*Clostridium difficile*, the most common cause of nosocomial diarrhea in the United States [1], is responsible for a substantial proportion of antibiotic-associated diarrhea [2]. After fecal-oral transmission, *C. difficile* spores colonize the colonic lumen, especially after antibiotic suppression of the normal protective biota [3]. In highly *C. difficile*-contaminated environments, such as intensive care units and long-term care facilities, ~30% of patients who receive antibiotics are colonized [4], but the majority of such patients do not develop diarrheal illnesses [4].

*Clostridium difficile*-associated diarrhea (CDAD) and its most severe form, pseudomembranous colitis, are mediated by exotoxins A and B of pathogenic *C. difficile* strains. Host immunity, especially humoral responses to the toxins, now is believed to be a major determinant of the consequences of *C. difficile* acquisition [5]. Asymptomatic carriers of *C. difficile* have higher titers of antitoxin A IgG than patients who develop CDAD [4], and patients with high titer antitoxin A antibodies during a first CDAD episode are much less likely to develop recurrent disease than those with lower titers [6]. Variation in antibody responses may be a principal explanation for the association of symptomatic *C. difficile* infections with advanced age and immunodeficiency-associated conditions, such as HIV infection.

HIV infection deranges both cellular and humoral immunity. Although B lymphocyte hyperactivation and polyclonal hypergammaglobulinemia are frequent among HIV-infected persons [7, 8], antigen-specific B cell memory responses are, paradoxically, severely impaired [9, 10]. HIV-infected patients with few memory B cells have reduced titers of IgG against recall antigens, such as tetanus toxoid [11], and against neoantigens [12]. The ability of B cells to release immunoglobulins in vitro is dependent on the CD4+ T cell count [11, 13]. Therefore, HIV-infected patients, especially those who are severely immunosuppressed, may be particularly susceptible to symptomatic *C. difficile* infection requiring medical attention (figure 1). Although *C. difficile* carriage is detected in 1%–3% of healthy adults [14], serum antibody responses to its toxins are evident in 60% of the general population [15], suggesting persistent memory responses or frequent subclinical infections. The prevalence of serum antitoxin A IgG in HIV-infected persons is not known. However, the abnormalities in humoral immunity described above suggest that a significant proportion of severely immunosuppressed HIV-infected patients have inadequate serum antibodies to protect against *C. difficile* toxin–mediated disease once the organism is acquired.

The introduction of HAART has not eliminated *C. difficile* as a problem for hospitalized HIV-infected patients [16, 17]. However, estimates of the incidence of bacterial diarrheal illnesses among HIV-infected persons before and during the HAART era have been lacking, until now. In this issue of *Clinical Infectious Diseases*, Sanchez et al. [18] report the analysis of data from a national, longitudinal, medical record–review study of HIV-infected subjects enrolled in the Adult/Adolescent Spectrum of HIV Disease (ASD) Project. Since its inception in 1990, the Centers for Disease Control and Prevention–ASD Project partnership with 11 state and local health departments in a prospective sentinel surveillance system has provided important information about the conditions diagnosed in HIV-infected persons [19–21]. For HIV-infected persons ≥13 years old who were identified and enrolled during their first health care encounter at either an inpatient or outpatient facility, data are abstracted in 6-month intervals until death or loss to follow-up. Because of incomplete reporting from 2 study sites, data from only 9 sites were analyzed by Sanchez et al. [18]. Nevertheless, from 1992 through 2002, more than 44,000 persons from diverse medical settings, comprising >115,000 person-years of follow-up, were reported. The participants, primarily young, non-Hispanic homosexual men, have demographic characteristics...
that, overall, are typical of HIV-infected persons in the United States [22]. That 67% of the cohort had a diagnosis of an opportunistic infection at some point during the observation period indicates a severely immunosuppressed population overall.

Among the 11,320 episodes of diarrheal illness reported through the ASD Project, only ∼10% had a bacterial pathogen documented, which is consistent with the prevalently poor application of contemporary bacteriologic methods to the study of diarrheal diseases, especially in HIV-positive persons. The authors defined infectious diarrhea as laboratory- or physician-documented identification of at least 1 of the known bacterial agents of diarrhea. However, a clinical definition of “diarrhea” was not provided, nor were there uniform indications for stool cultures; these considerations limit the study’s utility.

Nevertheless, Sanchez et al. [18] report that C. difficile was the most commonly identified bacterial pathogen, followed by the following typical diarrhea-causing pathogens: Shigella, Campylobacter, and Salmonella species. Not surprisingly, Sanchez and colleagues found that the group of patients with clinical AIDS had the highest incidence of CDAD and diarrhea due to other bacteria, compared with the group with immunologic AIDS or with HIV infection without AIDS. They also report a significant decrease in the incidence of bacterial diarrhea in those with clinical AIDS from 1992 to 2002. The Centers for Disease Control and Prevention definition of clinical AIDS involves the diagnosis of opportunistic infections or malignancy, complications that frequently require hospitalization, admission to intensive care or long-term care facilities, and, almost always, treatment with antimicrobial agents [23]. For patients with clinical AIDS who are exposed to C. difficile, the absence of antitoxin A antibodies could be important in pathogenesis (figure 1). Patients with immunologic AIDS (but without clinical manifestations of AIDS) are less likely to receive anti-infectives or to be hospitalized, reducing the risk of exposure.

Shigella organisms were the second most common bacterial agents isolated, and Shigella flexneri was the most common serogroup. In the general US population, Shigella organisms are usually less common than Salmonella and Campylobacter organisms, and the most common Shigella serogroup is Shigella sonnei [24]. The fact that 75% of the S. flexneri isolates were isolated from men who have sex with men suggests sexual transmission, as opposed to nosocomial transmission, for C. difficile and foodborne transmission for Campylobacter and Salmonella organisms.

Understanding trends in common diarrheal pathogens identified in the general US population helps provide context for the results of this study. Diarrheal pathogens often are foodborne. According to the active surveillance system FoodNet, the incidence of Campylobacter, E. coli O157, Salmonella, and Yersinia infections decreased substantially between 1996 and 2003, coinciding with improvements in animal slaughter and processing practices and with new regulations implemented to reduce contamination of produce, juices, and seafood [25]. By contrast, most C. difficile infections are acquired in hospitals or long-term care facilities. National hospital-based surveillance system data reveal significant increases in the incidence of C. difficile isolations from stool during 1987–2001, particularly in intensive care units and in large hospitals [26].

Why did the incidence of CDAD among patients with clinical AIDS decrease, despite the increased incidence of CDAD across the country as a whole [26]? To unravel this apparent paradox, the definition of clinical AIDS used in this report is critical: “any previous diagnosis of at least 1 AIDS-defining opportunistic infection, regardless of CD4+ cell count” [18, p. 1622]. Therefore, this subgroup of patients included patients with resolved opportunistic infections who had achieved successful immune reconstitution with HAART. With the widespread use of HAART after 1996, a majority of patients in the subgroup with clinical AIDS probably had high CD4+ cell counts and did not require antibiotics for prophylaxis or treatment of opportunistic infections. These changes in the characteristics of the subgroup could explain the decrease in incidence of CDAD and other bacterial di-

![Figure 1. Proposed pathogenesis of Clostridium difficile-associated diarrhea in HIV-infected hosts](image-url)
arrheal infections. After receipt of HAART, the diminished antigen-specific antibody responses to immunizations with recall or presumed neoantigens that are due to polyclonal B cell activation improve [27], leading to a more immunologically competent group than the term “clinical AIDS” would suggest. Because no information about CD4+ cell counts or HAART status is reported, the contributions of changes in these 2 factors to the decrease in the incidence of CDAD remains speculative.

The data described by Sanchez et al. [18] are not wholly representative. Although data sources included outpatient and inpatient sites, the surveillance system is facility-based and likely captures data on patients who are more ill and immunosuppressed than the general HIV-infected population in the United States. The absence of systematic culture of stool specimens introduces other potential biases, and the lack of information about exposure to inpatient facilities, broad-spectrum antibiotic therapy, and HAART during the study period also curtails interpretation. Despite these limitations, Sanchez and colleagues demonstrate that the prevalence and etiologies of diarrheal diseases for HIV-infected persons are changing but that there is continuing exposure to diarrheagenic bacteria with its attendant consequences in HIV-infected patients in the HAART era. Perhaps the most immediate implication of these important data is the need for ongoing implementation of preventive measures against nosocomial, foodborne, and sexually transmitted diarrheal pathogens in the HIV-infected population.

Acknowledgments

Potential conflicts of interest. S.S. and M.J.B.: no conflicts.

References


