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Use of probiotics in prevention and treatment of patients with *Clostridium difficile* infection

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A B S T R A C T

Clostridium difficile is an anaerobic, gram positive, sporulating, toxin-producing bacillus which causes a spectrum of clinical disease ranging from an asymptomatic carrier state to toxic megacolon and fulminant disease. Infection with *C. difficile* is an expensive and pervasive health care burden. The current theory regarding the development of *C. difficile* infection (CDI) suggests that disruption of the structure and/or function of an individual's normal intestinal microbiota enables colonization by *C. difficile*, and in the absence of an effective immune response, the bacteria causes illness. In this article we discuss the role of the colonic microbiota in the development of CDI and the potential role of probiotics in preventing and treating CDI. We review the evidence from *in vitro* laboratory and pre-clinical studies, as well as evidence from clinical studies and discuss the current recommendations for the use of probiotics for CDI in clinical practice.

Abbreviations: CDAD, clostridium difficile associated disease; FMT, fecal microbiota transplantation; CDI, clostridium difficile infection.

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Introduction

Clostridium difficile is an anaerobic, gram positive, sporulating, toxin-producing bacillus. Pathogenic *C. difficile* strains produce multiple toxins. The most well-characterized are Toxin A (enterotoxin) and Toxin B (cytotoxin), both of which may cause diarrhea and colonic inflammation in infected patients [1].

C. difficile infection (CDI) causes a spectrum of clinical disease ranging from an asymptomatic carrier state to toxic megacolon and fulminant disease. The occurrence of a particular clinical presentation is not fully understood but may be related to a complex interplay between host and pathogen factors. As a result, the term CDI has supplanted the earlier use of *C. difficile* associated diarrhea/disease (CDAD) in order to reflect this wider range of clinical manifestations.

In the United States, *C. difficile* is an expensive and pervasive health care burden. A recently published population-based study shows that the incidence of CDI has tripled over the past 15 years with an estimated 453,000 cases of CDI in 2011 and nearly 30,000 associated deaths [2]. The majority of CDI are nosocomial and up to 40% are community associated [3]. It is the most frequently reported nosocomial pathogen in hospitals in the United States that has also quadrupled the annual cost of hospitalization by $1.5 billion [4,5].

The rationale for targeting the intestinal microbiota in the management of *C. difficile* infection

The current theory regarding the development of CDI suggests that disruption of the structure and/or function of an individual's normal intestinal microbiota (e.g. following exposure to antibiotics) enables colonization by *C. difficile*, and in the absence of an effective immune response, the bacteria may cause a spectrum of illnesses due to colonic injury from diarrhea to toxic megacolon and death [1].

The mainstay of treatment for CDI since the 1970s has been antibiotic therapy with metronidazole or vancomycin [1]. Regardless of treatment choice, CDI frequently recurs despite no clinically significant antibiotic resistance of the organism to metronidazole or vancomycin [1]. Recurrence of symptoms after successful initial therapy for CDI develops in 10–25 percent of cases and may be due to relapse of the initial infecting strain or reinfection with a new strain [6]. Recurrent CDI, defined as those that recur more than once, occurs in 40–60 percent of cases [7] and often represents relapse rather than reinfection, regardless of the interval between episodes [6].

The reasons for recurrences are not clear, but recent microbiological data demonstrated ongoing and more severe alterations in the diversity and structure of the intestinal microbiota in recurrent CDI compared to initial infection and healthy controls [8]. Antibiotic treatment of CDI itself may further disrupt the intestinal microbiota, facilitating *C. difficile* colonization. Supporting this, fidaxomicin, a new poorly absorbable antibiotic, has been shown to be more effective than vancomycin in preventing recurrences; a phase III randomized controlled trial of over 600 patients receiving either fidaxomicin or vancomycin for the treatment of CDI showed that fidaxomicin was associated with fewer recurrences [9]. This was theorized to occur because of increased specificity of fidaxomicin for Clostridial species including *C. difficile* resulting in less dysbiosis in the normal microbiota sparing protective species such as the genus Bacteroides much more so than vancomycin [9].

Since the host's healthy microbiota is essential in preventing and treating CDI, a number of therapies aiming to help reconstitute a diverse microbiota have been proposed and investigated in patients with CDI. For example, several recent studies have demonstrated highly successful cure rates for patients treated with Fecal Microbiota Transplantation (FMT) for multiple recurrent CDI [10,11]. Microbiological studies following FMT have shown that beneficial effects in these patients are associated with significant increases in the Simpson's diversity index of their intestinal microbiota. This further emphasizes the important relationship between a diverse population in the microbiota and colonization resistance to protect against CDI [10,11].

The use of probiotics for prevention and treatment of *C. difficile* infection

The pivotal role that the colonic microbiota has in the development of CDI has raised interest in the potential role probiotics may have in promulgating a diverse gut microbiome and in doing so preventing and treating CDI. Probiotics are live nonpathogenic bacteria capable of colonizing the human