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Review article

Probiotics as adjunctive therapy for preventing *Clostridium difficile* infection – What are we waiting for?

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ABSTRACT

With the end of the golden era of antibiotic discovery, the emergence of a new post-antibiotic age threatens to thrust global health and modern medicine back to the pre-antibiotic era. Antibiotic overuse has resulted in the natural evolution and selection of multi-drug resistant bacteria. One major public health threat, *Clostridium difficile*, is now the single leading cause of hospital-acquired bacterial infections and is by far the most deadly enteric pathogen for the U.S. population. Due to the high morbidity and mortality and increasing incidence that coincides with antibiotic use, non-traditional therapeutics are ideal alternatives to current treatment methods and also provide an avenue towards prevention. Despite the need for alternative therapies to antibiotics and the safety of most probiotics on the market, researchers are inundated with regulatory issues that hinder the translational science required to push these therapies forward. This review discusses the regulatory challenges of probiotic research, expert opinion regarding the application of probiotics to *C. difficile* infection and the efficacy of probiotics in preventing this disease.

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1. Introduction

We are on the verge of a global antibacterial resistance crisis [1,2], where deaths due to common infections will rival heart disease and cancer and erase 70 years of progress combating life-threatening bacterial infections. This crisis was presaged by Sir Alexander Fleming in his 1945 Nobel Prize speech [3] where he predicted that the misuse of antibiotics by the public at large would be the undoing of the "golden era" of antibiotics. A major risk factor of antibiotic therapy is acquiring *Clostridium difficile* infection (CDI), with approximately half a million cases contributing to ~30,000 deaths per year in the United States at annual costs of $4.8 billion [4]. The majority of these cases occur following disruption of the gastrointestinal microbiota through antibiotic use (Fig. 1) for non-related events. The current standard of care for CDI involves additional antibiotic therapy in the face of a disease already caused by

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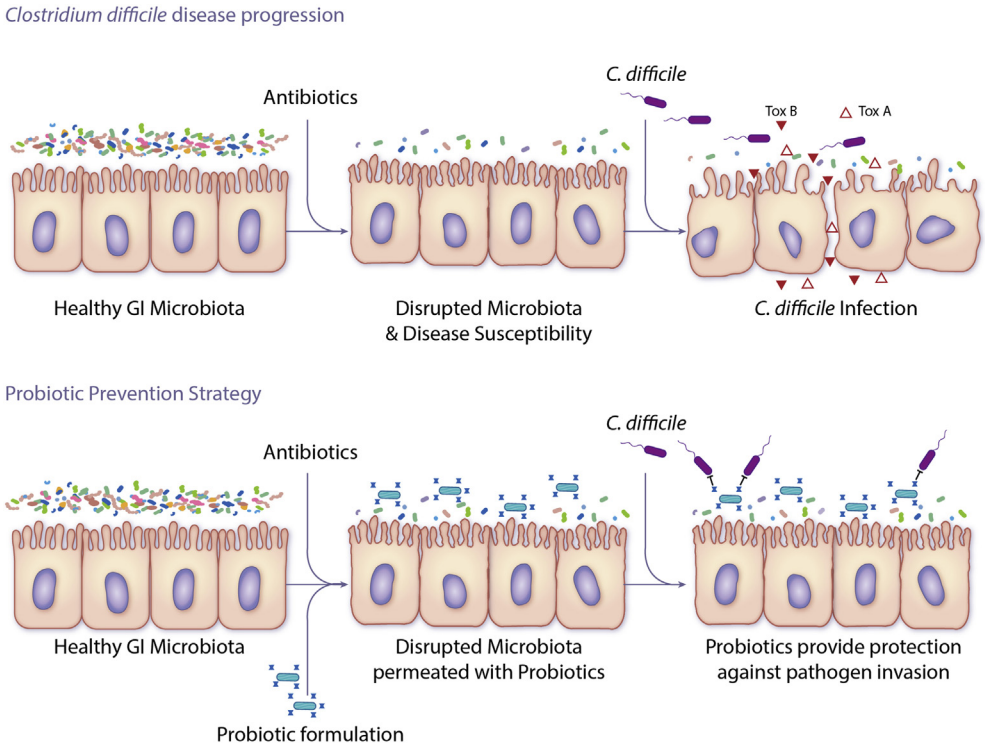

Fig. 1. Disruption of a healthy GI microbiota by antibiotics increases CDI susceptibility. Adjunctive probiotic therapy provides protection against CDI by stabilizing the GI microbiota, protecting the host by various mechanisms and preventing *C. difficile* invasion.

previous antibiotic administration. *C. difficile* is not significantly resistant to drugs currently used to treat the disease; however some concerns about antibiotic resistance exist. Hypervirulent BI/NAP1/027 strains that emerged in the early 2000s are associated with fluoroquinolone resistance [5–9], and more recently the European EUCAST epidemiological marker of resistance for metronidazole and vancomycin has increased for *C. difficile* isolates in the U.S [10]. Even more concerning is the prophylactic use of vancomycin or metronidazole to prevent CDI [11,12]; oral administration of these drugs has been linked to a decline in intestinal microbiota colonization that imposes a greater risk for developing CDI [13]. Despite a lack of significant antibiotic resistance by *C.difficile*, the unique relationship of CDI with antibiotic treatment and escalating incidence and mortality rates have driven the Centers for Disease Control and Prevention (CDC) to classify *C. difficile* as an urgent public health threat requiring urgent and aggressive action [14].

A steady rise in CDI is accompanied by increased incidences of disease recurrence, an arguably larger problem with increased morbidity and mortality and fewer treatment options. Current treatment options for CDI are limited to extended antibiotic regimens with only three antibacterial drug choices and/or fecal microbiota transplantation (FMT). Most patients with CDI will respond to vancomycin or off-label use of metronidazole as the first line of treatment, although approximately 35% of patients will undergo a recurrence after antibiotic treatment [15–17]. Almost 50% of these recurrent cases will face multiple recurrences, contributing further to the rise in patient morbidity [18]. Severe recurrent cases are currently treated by FMT with 90% efficacy, demonstrating the efficacy of microbiota-based therapy. While FMT is an effective treatment option for patients with recurrent CDI [15,19], it is deemed an investigational therapy by the US Food and Drug Administration that may not be covered by third-party payers [20]. Long-term health effects of FMT are still unknown; a recent case report highlighting new-onset obesity in a patient receiving stool from an overweight donor [21] raises serious concerns about the lasting effects of FMT and emphasizes the importance of finding alternative treatment and prevention options for CDI. The ability to transfer obesity via FMT was first shown in animals [22]. Similar animal studies are also demonstrating that other chronic conditions like high blood pressure, atherosclerosis, and potentially heart failure can be transferred via gastrointestinal microbiome transplantation [23–25]. Probiotics have the most potential for use as adjunctive treatment to antibacterial therapy as a means to prevent primary and recurrent CDI. In spite of mounting literature reporting that probiotics are safe and effective for preventing CDI, clinicians are working from outdated 2010 SHEA/IDSA guidelines [26] that do not offer a consensus on the best treatment for recurrent CDI and deter use of probiotics for disease prevention.

The use of probiotics to treat gastrointestinal disease was well underway before Sir Alexander Fleming discovered the antagonistic effects of penicillin. The beneficial effects of bacteria were first described by Elie Metchnikoff, who touted that lactic acid bacteria could “replace the harmful microbes by useful microbes” in the intestine [27]. In 1917, Alfred Nissle isolated the non-lactic acid *Escherichia coli* Nissle 1917 strain [28] which has since been used traditionally in Germany and other European countries to treat gastrointestinal afflictions [29]. More than a century later, instead of clinical use of defined microbes that are generally regarded as safe [30], modern medicine is relying on >1,700-year-old, non-standardized FMT practices [31]. Several recent reviews [32–39] and meta-analyses [40–47] have covered the literature supporting probiotics as an alternative preventative method for CDI. For a summary of probiotic formulations tested in human trials for efficacy against CDI see Table 1. This review highlights the current opinion of experts in the field and the most recent clinical success stories that directly support continued effort towards developing alternative probiotic therapies for CDI prevention (Fig. 1).