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Manipulation of the gut microbiota: probiotics and fecal microbiota transplantation as a treatment option for recurrent *Clostridium difficile* infection

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ABSTRACT

Diarrhea and other gastrointestinal symptoms are possible side effects of long-term antibiotic therapy. The most common etiology of hospital-acquired diarrhea is *Clostridium difficile* infection (CDI). It has been demonstrated that probiotic use may be beneficial in the prevention of antibiotic-associated diarrhea. There is also growing evidence that a fecal microbiota transplant may reduce the duration and recurrence of CDI. In this review, we update the current knowledge on both modalities in the prevention of resistant CDI and as useful adjuncts to standard treatment.

Keywords: fecal microbiota transplantation; clostridium difficile; probiotics; microbiome; microbiota.

INTRODUCTION

Antibiotic-associated diarrhea has become a prominent global health problem in recent years as antibiotic therapy is one of the most common therapies in healthcare facilities and in the community. The term "gut microbiota" refers to all the microorganisms that inhabit the gastrointestinal tract, mainly bacteria, but also fungi, archaea, or viruses, all of which are responsible for maintaining host homeostasis. Antibiotics can alter the composition of gut microbiota leading to a predominance of opportunistic microorganisms and thus increasing the incidence of various diseases. *Clostridium difficile* or *Clostridioides difficile*, an anaerobic, spore-forming and toxin producing Gram-positive bacillus, is an etiological factor for most of the cases of antibiotic-acquired diarrhea (AAD) [1]. Approximately 5% of the adult population is colonized with *C. difficile*, and the prevalence is higher in residents of nursing homes and highest in hospitalized patients [2]. *Clostridioides difficile* infections (CDI) can vary in terms of severity, ranging from asymptomatic infections, diarrhea and colitis to life-threatening *megacolon toxicum* [3]. Asymptomatic colonization does not require medical intervention; however, in other clinical manifestations, targeted treatment is obligatory. The standard management for CDI includes oral vancomycin and fidaxomicin intake (less effectively, oral metronidazole). Nevertheless, novel anti-CDI therapies have been implemented recently, with an increasing importance given to non-antimicrobial interventions in the form of gut microbiota modifications. In this paper, the authors summarize current knowledge regarding the role of probiotics and fecal microbiota transplantation in the management of various CDI scenarios.

PROBIOTICS

The term "probiotics" refers to selected strains of microorganisms that are administrated orally, transfer to the intestine in an active form and exert positive effects on one's health. Probiotics may be both of natural and commercially produced origin. They display various mechanisms of action that are strain-specific. The most important of these include the protection of the integrity of the intestinal barrier, reduction in adherence of pathogens to the epithelial of the intestine, competitive inhibition of pathogenic microorganisms or production of anti-microbial metabolites and stimulation of the immune system [4, 5, 6]. Probiotics have well-documented benefits in the prevention of AAD when administrated simultaneously with antibiotic therapy. In a meta-analysis from 2012, the positive effect of adjunct probiotic treatment resulted in a reduced risk for developing an AAD (RR 0.58) [7]. Cochrane meta-analysis displayed the significant effectiveness of probiotics in preventing *C. difficile* related diarrhea (CDRD) when administrated alongside antibiotics in a population with a baseline risk of >5% for developing CDRD [8]. Recently published meta-regression and network meta-analysis showed a reduction in the incidence rate of CDRD in a group receiving probiotics, with *Lactobacillus casei* being the most effective strain. However, no difference has been found in terms of the duration of diarrhea and the time until its onset between the study and control groups [9]. A relatively high rate of adverse effects, including CDI, is linked to short-term clindamycin use in stomatology – the adverse drug reaction incidence is almost 15 times higher when compared to widely-used amoxicillin [10]. These data suggest that

it should become a standard of care to add a probiotic strain to oral clindamycin treatment as a prophylaxis, although no specific strain is preferred to date. A work by Aabed et al. promotes *Lactobacillus paracasei* as having the strongest ameliorative affect, though the study was done on a rodent model and supported by prebiotics such as propolis [11].

In spite of their preventative role, probiotics are also currently being assessed as a promising adjunct therapy to standard management in CDI. Wei et al. investigated the role of *Bifidobacterium longum* JDM301 as an anti-toxin agent of CDI both *in vitro* and *in vivo* [12]. The *in vitro* study showed an inhibitory effect of JDM301 on *C. difficile*, as well as a beneficial role in the degradation of *C. difficile* toxins. The *in vivo* study confirmed the down-regulatory effect of JDM301 on inflammatory markers, such as interleukin 6 and tumor necrosis factor alfa in the CDI mice model, indicating its antagonistic effect in *C. difficile* induced inflammation. In another study, *Pediococcus pentosaceus* LI05 has been investigated as a protective strain against CDI in mice [13]. Oral administration of *P. pentosaceus* resulted in an increased survival rate and decreased levels of serum inflammatory markers. Alongside this, the histopathological assessment of colonic tissues indicated improved tight-junctions via the protection of ZO-1, occludin and claudin-1 proteins. Golić et al. confirmed the antimicrobial effect of a probiotic combination of *Lactobacillus helveticus* BGRA43, *Lactobacillus fermentum* BGHI14 and *Streptococcus thermophilus* BGVLJ1-44 against *C. difficile in vitro* [14]. In a randomized, double-blind controlled study, implementation of probiotics consisting of *Lactobacillus helveticus* R0052 and *Lactobacillus rhamnosus* R0011 resulted in a shortened duration of diarrhea-like defecations in healthy adults with AAD secondary to amoxicillin–clavulanic (AC) acid treatment [15]. A pilot randomized controlled trial was performed in 2017 determining the effect of a 4-strain probiotic containing *Lactobacillus acidophilus* NCFM, *Lactobacillus paracasei* Lpc-37, *Bifidobacterium lactis* Bi-07 and *Bifidobacterium lactis* Bl-04 on initial mild to moderate CDI in humans. Authors concluded that the primary duration of diarrhea, total diarrhea days and rate of diarrhea all decreased in the study group compared to control, however, there was no statistically significant difference in the rate of CDI episode recurrence [16]. A 1994 randomized placebo-controlled study in CDI patients displayed a reduction in *C. difficile* diarrhea recurrence rates when treated with a combination of standard antibiotics and *Saccaromyces boulardii* [17]. In another prospective randomized controlled study on *Saccharomyces boulardii* CNCM I-745 AC in relation to gut microbiota, authors concluded that the simultaneous intake of AC and probiotics reduces microbial alterations and decreases *Escherichia* concentrations thus lowering the diarrhea score [18].

GUT MICROBIOTA TRANSPLANT

Patients with at least 3 consecutive reinfections of *C. difficile* despite proper treatment are considered candidates for a gut microbiota transplant. The above-mentioned group of patients has a much less diversified intestinal flora than healthy people. Stool transplantation can help them to be recolonized by missing strains and regain the balance of the intestinal barrier. A meta-analysis of controlled trials from 2019 regarding the effectiveness of treatment with stool transplantation shows that as much as 60–75% of patients undergoing this procedure did not experience another CDI recurrence [19]. Other sources state that the effectiveness of CDI treatment highly depends on the number of consecutive fecal microbiota transplant procedures. Lee et al. reported therapeutic success in 50% of cases after 1st administration, approx. 75% after 2 administrations and up to 90% after 3 or more administrations of fecal microbiota from a healthy donor [20]. However, there are some technical as well as ethical considerations regarding the procedure. It should be stated that, to date, the Food and Drug Administration has not officially approved stool transplantation as a therapeutic method despite the promising outcomes of multiple small studies. In the USA, it is allowed under enforcement discretion. There are still no strict guidelines when it comes to qualifying for the procedure: no clear requirements for the donor, and no specific inclusion or exclusion criteria for the recipient. Although the entire procedure is considered as generally safe and with a low risk of severe complications, no large-scale clinical trials with long-term follow up have been conducted, so no longitudinal effects can be clearly assessed. Side effects reported following a fecal microbiota transplant are minor and mainly include abdominal discomfort. However, there were some cases of ESBL-producing bacteria transmission from the donor to the recipient, one of which was fatal [21, 22, 23]. Thus, qualifying patients as fecal microbiota recipients should be conducted carefully, as it carries the potential risk of transmitting multidrug-resistant bacterial strains and other pathogens from the donor [21].

As mentioned above, there are no strictly regulated criteria for being a stool donor. To ensure maximum safety of the procedure, each donor should be screened virologically and for a specific subset of fecally transmitted pathogens, i.e., ESBL-producing *E. coli* or vancomycin-resistant *Enterococci*. An assumption widely adopted is that an ideal donor is a person with a normal body mass index and no underlying comorbidities. The candidate should not be under any antibiotic therapy for at least 3 months before the donation procedure. It is interesting to note that the lower age limit for becoming a donor is 10 years old. Importantly, the donor does not have to be compatible with the recipient in the human leukocyte antigen (HLA) system, in comparison to "classic" transplantations – no differences in outcome were found between HLA-compatible donor-recipient pairs and strangers [24].

Stool transplantation can be performed in several ways: either by oral administration of capsules containing the isolate, during colonoscopy, using rectal enema, or by passing the isolate through the nasoduodenal tube beyond the Treitz ligament (suspensory ligament of the duodenum) [25]. None of the above-mentioned methods have clear advantages over the others when it comes to the effectiveness of the procedure. One of the studies conducted by Cohen et al. showed

that the administration of fecal microbiota through the lower gastrointestinal tract is more effective than through the upper gastrointestinal tract [26]. However, the study group in this paper was too small (n = 22) to be able to draw firm conclusions in favor of stool transplant during colonoscopy. The safest route seems to be, in the absence of contraindications, through oral administration – simply swallowing the capsule with the microbial isolate [25].

CONCLUSION

Based on the already available and still emerging promising clinical data on the effectiveness of stool transplant and probiotic support in recurrent CDI treatment, the authors believe that it should become a permanent element of therapy in a selected group of patients and be more widely available in many centers in Poland. Nevertheless, both require unified guidelines to ensure maximum safety and effectiveness to the treated individuals.

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