Anaerobe 45 (2017) 114–119

Contents lists available at ScienceDirect

Anaerobe

journal homepage: www.elsevier.com/locate/anaerobe

Probiotics and prevention of *Clostridium difficile* infection

E.J.C. Goldstein [a, b, *], S.J. Johnson [c], P.-J. Maziade [d], C.T. Evans [e, f], J.C. Sniffen [g], M. Millette [h], L.V. McFarland [i]

[a] *R M Alden Research Laboratory, Santa Monica, CA, USA*
[b] *UCLA School of Medicine, Los Angeles, CA, USA*
[c] *Loyola School of Medicine, Chicago, IL, USA*
[d] *Pierre-Le Gardeur Hospital, Quebec, Canada*
[e] *Department of Preventive Medicine and Center for Healthcare Studies, Northwestern University, Chicago, IL, USA*
[f] *Edward Hines Jr VA Hospital, Chicago, IL, USA*
[g] *Florida Hospital, Orlando, FL, USA*
[h] *Bio-K Plus International Inc., Laval, Canada*
[i] *Department of Medicinal Chemistry, University of Washington, Seattle, WA, USA*

ARTICLE INFO

Article history:
Received 30 October 2016
Received in revised form
4 December 2016
Accepted 7 December 2016
Available online 14 December 2016

Handling Editor: Casey Michelle Theriot

Keywords:
Probiotic
Bio-K+
Saccharomyces boulardii
C. difficile
Lactobacillus rhamnosus GG
Lactobacillus acidophilus CL1285
Lactobacillus casei LBC80R
Lactobacillus rhamnosus CLR2

ABSTRACT

The role of probiotics as adjunctive measures in the prevention of *Clostridium difficile* infection (CDI) has been controversial. However, a growing body of evidence has suggested that they have a role in primary prevention of CDI. Elements of this controversy are reviewed and the proposed mechanisms of action, the value and cost effectiveness of probiotics are addressed with a focus on three agents, *Saccharomyces boulardii*, *Lactobacillus rhamnosus* GG and the combination of *Lactobacillus acidophilus* CL1285, *Lactobacillus casei* LBC80R, *Lactobacillus rhamnosus* CLR2 (Bio-K+).

Clostridium difficile infection (CDI) is a multifactorial disease whose pathogenesis consists of a complex interaction of factors including the alteration of the normally protective intestinal microbiome, the acquisition of a toxin producing strain of *C. difficile* (isolates may produce two homologous toxins Toxin A and Toxin B and possibly Binary toxin) and an insufficient immune response. CDI has been declared an urgent threat by the Centers for Disease Control and Prevention (CDC) [1] and is estimated to result in more than $1 billion of excess medical care costs [2]. Despite a call to arms to combat this illness, the optimal therapy of CDI remains in need of improvement. Two antibiotics, metronidazole and vancomycin have been the mainstays of therapy for more than 30 years. Patients respond to therapy while on these agents, but relapse rates have been unacceptably high and reported from 15–30% [3–6]. Even with the newly approved anti-CDI antibiotic fidaxomicin, there is still a relapse rate of ~15% and some collateral damage due to the continued disruption of the microbiome [6]. A search for alternative therapies with different mechanisms of action for the prevention of CDI and relapse of CDI has included monoclonal antibodies [7], vaccination [8] and fecal microbiota transplantation (FMT) [9]. This latter approach has a reported ~90% success rate, but its long term consequences have yet to be fully studied [10]. The theory behind FMT is the repopulation of the patient's gastrointestinal tract with a restored and healthy microbiome.

Others have focused on adjunctive measures such as the administration of probiotics as reviewed by Johnson et al. [11].

* Corresponding author. 2021 Santa Monica Blvd, Suite #740E, Santa Monica, CA 90404, USA.
E-mail address: ejcgmd@aol.com (E.J.C. Goldstein).

http://dx.doi.org/10.1016/j.anaerobe.2016.12.007
1075-9964/

Probiotics are defined as live organisms that when given in sufficient quantities confer a health benefit to the patient [12]. Not all live microorganisms or *Lactobacillus* species have probiotic properties, but rather the efficacy of probiotic organisms is strain specific [13]. Yet, the shelves of food stores and pharmacies are often stocked with a multitude of different products called probiotics and are loosely regulated as dietary supplements by the Food and Drug Administration (FDA). It is estimated that probiotic sales will reach $48 billion/year globally by 2017 [14]. A literature review showed the most common indication (17%) was the prevention of antibiotic associated diarrhea (AAD) and 3% were specifically to prevent or treat CDI [15] (Fig. 1). In 2012 it was estimated that 3.9 million Americans, 1.6% of the population, used probiotics which was four-times more than in 2007 [16]. Consumers often get selection advice from people such as the stocking clerk or by selection based on package design and claims. Physicians are often undereducated about probiotic agents, do not ask their patients about probiotics as part of the medical history and be may be unaware of their patients' utilization. Yet, probiotics are increasingly given to patients receiving antibiotics in US hospitals [17]. In a 2012 prevalence study of 145 US hospitals, it was reported that 96% used some form of probiotic, but the specific products used were quite varied. Those receiving probiotics were more likely have received antimicrobials and patients with established CDI are 21 times more likely to receive probiotics [17]. The hypothesis that probiotics can help prevent CDI is supported by the observation that lactobacilli remain present in the colon during and after their ingestion [18,19]. While there are a plethora of agents available there is only extremely limited control trial data available. Both the Infectious Diseases Society of America's (IDSA) [20] and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) [21] guidelines for the therapy of CDI do not yet recommend probiotic use as an adjunctive measure to prevent or treat CDI.

A literature search and meta-analysis [11,22] found probiotic trials were usually small, uncontrolled, sponsored by industry and not powered to either find significant conclusions or support their hypotheses. Yet, a Forrest plot of these studies suggested that the use of probiotics was consistently advantageous [22]. Johnson et al. [11] suggested that the use of probiotics was more likely to be efficacious for the primary prevention of CDI where there is less fecal microbiome disruption rather than for the secondary prevention of CDI where there have been significant changes in the diversity, goodness and richness of the patients' microbiome. Some of the potential confusion about the value of probiotics in CDI might emanate from combining primary and secondary prophylaxis as well as combining different strains into pooled analyses in a variety of prior studies [11,23].

Johnson et al. [11] reviewed the literature from 1976 to 2010 and found 11 studies where adult patients who received antibiotics were randomized to receive either a probiotic or placebo and in which CDI was a measured outcome. They then selected for meta-analysis those probiotics with at least two randomized, controlled trials for inclusion. Only two probiotics, *Saccharomyces boulardii*, and the combination of *L. acidophilus* CL1285, *L. casei* LBC80R and *L. rhamnosus* CLR2 (Bio-K+) were selected as qualified. A Forrest plot of the three trials using Bio-K + and the four that used *S. boulardii* are shown in Fig. 2 [11]. Despite some variability in study design, the combined overall effect was fewer cases of CDI in those receiving a probiotic, especially those on Bio-K+, than those in the placebo group.

There are many reasons for confusion about the value of probiotics in CDI. These have included a number of medical claims without proven scientific evidence advanced by manufacturers and the varied and less stringent regulation of over-the-counter products by governmental agencies. Additionally, issues of product purity, strength and the level of quality control were raised by Grzeskowiac et al. [24] who studied 15 *L. rhamnosus* GG products produced by different manufacturers. They found that the production and methods of the manufacturing process, as well as the food carrier used, could influence the properties of the finished

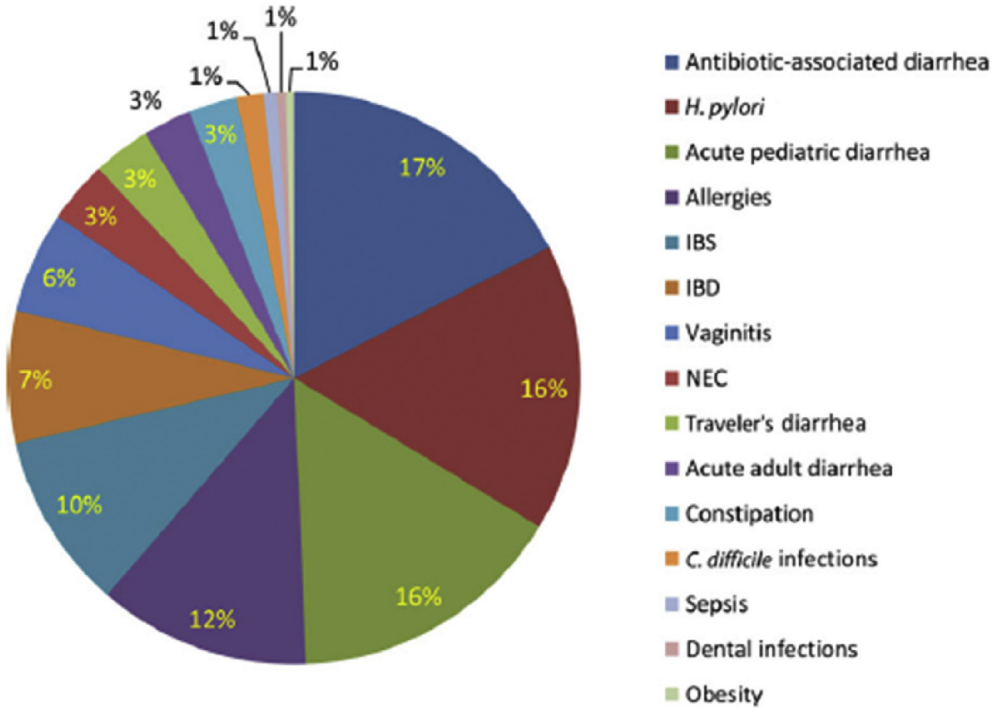

Fig. 1. The 15 most commonly studied indications for probiotics from 420 randomized controlled trials, 1977–2014. Abbreviations: IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; NEC, necrotizing enterocolitis. McFarland [15].