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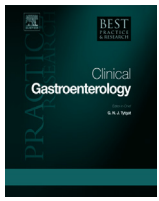

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Probiotics and prebiotics in ulcerative colitis

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A B S T R A C T

The intestinal microbiota is one of the key players in the etiology of ulcerative colitis. Manipulation of this microflora with probiotics and prebiotics is an attractive strategy in the management of ulcerative colitis. Several intervention studies for both the induction and maintenance of remission in ulcerative colitis patients have been performed. Most of these studies evaluated VSL#3 or *E. Coli* Nissle 1917 and in general there is evidence for efficacy of these agents for induction and maintenance of remission. However, studies are frequently underpowered, lack a control group, and are very heterogeneous investigating different probiotic strains in different study populations. The absence of well-powered robust randomized placebo-controlled trials impedes the widespread use of probiotics and prebiotics in ulcerative colitis. However, given the promising results that are currently available, probiotics and prebiotics may find their way to the treatment algorithm for ulcerative colitis in the near future.

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Introduction

Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), is a chronic relapsing inflammatory disorder of the gastrointestinal tract with variable prevalences between 37.5 and 248.6 per 100.000 in North America and 4.9–505 per 100.000 in Europe [1]. Clinical features involve (hemorrhagic) diarrhea, abdominal pain, weight loss and/or fatigue and some patients develop IBD-related extra-intestinal manifestations such as primary sclerosing cholangitis, skin lesions or joint problems. Current strategies for the treatment of IBD involve first induction of remission, followed by maintaining remission. UC patients with disease activity are usually treated with topical or systemic 5-aminosalicylic acids (5-ASA) or corticosteroids. Subsequently, 5-ASA is the first choice for maintenance therapy followed by immunomodulators, including azathiopurine and 6-mercaptopurine in case of persistent disease activity or adverse events to 5-ASA. In case of severe refractory UC, intravenous corticosteroids, cyclosporine, anti-TNFα agents and lately the anti-integrin vedolizumab are options to induce remission in order to avoid colectomy.

The therapies outlined above have significant disadvantages. First, immunosuppressive therapies and anti-TNFα agents are associated with a higher risk of infectious complications [2]. Second, a third of patients eventually requires surgical intervention, indicating that current therapeutic options are insufficient for many patients [3]. Third, the high costs of biological therapies contribute to the increasing financial burden of health care and are topic of discussion among health policy makers. This emphasizes the need for other (non-pharmacological) options, preferably based on pathways that contribute to chronic mucosal inflammation in UC.

Although a multi-factorial etiology in IBD is widely acknowledged, the exact etiology remains unclear. It is assumed that an exaggerated mucosal immune response to commensal gut bacteria drives the inflammatory process in genetically susceptible individuals [4]. The role for the intestinal microbiota is supported by the finding that intestinal inflammation often occurs in anatomical areas with high bacterial numbers [5,6]. Furthermore, diversion of the fecal stream proximal to the inflamed area decreased disease activity in CD [7–10]. In addition, a meta-analysis showed better induction of remission rates in antibiotic versus placebo treated CD patients [11]. After the identification of the first CD gene, NOD2, many genetic IBD loci have been identified [12]. Many of these loci are associated with the innate immunity responsible for the primary defensive system against enteric bacteria, further underscoring the interaction between the gut microbiota and mucosal inflammation.

Given the overwhelming evidence for the involvement of the intestinal microbiota in the pathogenesis of IBD, the strategy of manipulation of the microbial composition has been a topic of research in recent decades. Indeed, promising results were shown for fecal microbiota transplantation to induce remission in UC [13]. Similarly, pre- and probiotics that also act on the microbial composition, could be of benefit in IBD. This review aims to give an overview of the rationale and role of pre- and probiotics in UC.

The intestinal microbiota in inflammatory bowel disease

Microbiota in general

The gut microbiota refers to all microorganisms colonizing the gut, not only including bacteria but also other microbes such as fungi and viruses. Collectively, this complex ecosystem contains 10^{13-14} bacteria including more than 35.000 bacterial species with an increasing density and diversity from stomach to colon [14]. The microbiota develops soon after birth, when the sterile gastrointestinal tract is colonized by successive waves of microorganisms. The individual gut microbiota is relatively stable over time and differs between subjects. It is mainly dominated by the bacterial phyla *Firmicutes* and *Bacteroidetes* and contains a core microbiome with shared functionality [15–18]. In general, three robust clusters (enterotypes) with balanced community compositions can be identified around which individual gut microbiota congregate. These enterotypes are driven by enrichment of the genera *Bacteroides* (enterotype 1), *Prevotella* (enterotype 2), and *Ruminococcus* (enterotype 3) [19].

The microbiota contains several critical functions that contribute to the overall health of the host. These functions include nutrient and mineral absorption, synthesis of vitamins and amino acids,