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REVIEW

# Diet and microbiome in the beginning of the sequence of gut inflammation

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## Abstract

Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the gastrointestinal tract due, at least partially, to an aberrant and excessive mucosal immune response to gut bacteria in genetically-predisposed individuals under certain environmental factors. The incidence of IBD is rising in western and newly industrialized countries, paralleling the increase of westernized dietary patterns, through new antigens, epithelial function and permeability, epigenetic mechanisms (*e.g.*, DNA methylation), and alteration of the gut microbiome. Alteration in the composition and functionality of the gut microbiome (including bacteria, viruses and fungi) seems to be a nuclear pathogenic factor. The microbiome itself is dynamic, and the changes in food quality, dietary habits, living conditions and hygiene of these western societies, could interact in a complex manner as modulators of dysbiosis, thereby influencing the activation of immune cells' promoting inflammation. The microbiome produces diverse small molecules *via* several metabolic ways, with the fiber-derived short-chain fatty acids (*i.e.*, butyrate) as main elements and having anti-inflammatory effects. These metabolites and some micronutrients of the diet (*i.e.*, vitamins, folic acid, beta carotene and trace elements) are regulators of innate and adaptive intestinal immune homeostasis. An excessive and unhealthy consumption of sugar, animal fat and a low-vegetable and -fiber diet are risk factors for IBD appearance. Furthermore, metabolism of nutrients in intestinal epithelium and in gut microbiota is altered by inflammation, changing the demand for nutrients needed for homeostasis. This role of food and a reduced gut microbial diversity in causing IBD might also have a prophylactic or therapeutic role for IBD. The relationship

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between dietary intake, symptoms, and bowel inflammation could lead to dietary and lifestyle recommendations, including diets with abundant fruits, vegetables, olive oil and oily fish, which have anti-inflammatory effects and could prevent dysbiosis and IBD. Dietary modulation and appropriate exclusion diets might be a new complementary management for treatment at disease flares and in refractory patients, even reducing complications, hospitalizations and surgery, through modifying the luminal intestinal environment.

**Key Words:** Diet; Microbiome; Inflammatory bowel disease; Pathogenia



**Core Tip:** Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the gastrointestinal tract. The incidence of IBD is rising in western and newly industrialized countries, paralleling the increase of westernized dietary patterns. Microbiome is changing in western societies and can influence the activation of immune cells promoting inflammation. Change in the composition and functionality of the gut microbiome seems to be a nuclear pathogenic factor. An excessive and unhealthy consumption of sugar, animal fat and a low vegetables and fiber diet are risk factor for IBD appearance. This role of food and a reduced gut microbial diversity in cause of IBD might have also a prophylactic or therapeutic role for IBD. Dietary modulation and appropriate exclusion diets might be a new complementary management for treatment at disease flares and in refractory patients.

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## INTRODUCTION

The intestine of monogastric animals, including humans, is inhabited by populations of microorganisms after the birth of the host; these are mostly bacterial but also include archaea, fungi (mainly Ascomycota and Basidiomycota) and viruses (mainly bacteriophages)[1]. All these microorganisms constitute what is called a microbiota, which is functionally very active and on which eukaryotes depend for the absorption of certain substances, such as vitamins, essential amino acids and monocarboxylic fatty acids of up to six carbon atoms (short-chain fatty acids, SCFAs) including butyrate, acetate and propionate, the main energy source of the colonocyte. This makes animals holobionts that carry a greater prokaryote genome than their own, and whose composition depends on host genetics, diet, hygienic conditions and the environment. The microbiota, its genetics, and the habitat they occupy, we call the microbiome.

Not all regions of the intestine are suitable for microbial life, since the acid secreted in the stomach and the fastening or flow of content in the proximal bowel ensure that those segments contain only microorganisms in transit in healthy hosts[2], with *Lactobacillus* and Proteobacteria being the main residents. In addition, the partial oxygen pressure and fermentable content of conditional intestinal lumen support the presence and particular type profile of microorganisms. The terminal ileum and colon (especially the cecum) are easily proliferation environments and represent the seat of a complex ecosystem of *Bacteroides* and *Clostridium*.

Many of the quantitatively relevant members of the gut microbiome have not been laboratory-grown and have been identified in recent decades from their stable genetic marker sequences, such as ribosome RNA fragment 16S (rRNA) with variable regions characteristic of each genus that are compared to reference libraries[3], and preserved regions that allow the appropriate laboratory techniques to be used for amplification. This has made it possible to highlight the significant complexity in the composition of the microbiome, which has been defined up to 1150 species of bacteria[4]. The RNA extracted from bacterial cells is mainly rRNA and can be used as an indicator of metabolic activity since the ribosome-cell ratio is approximately proportional to the

growth rate of bacteria; although, this measurement could overestimate the number of microorganisms in cases harboring multiple copies of the rRNA gene being studied. In addition, a new perspective has been gained on the prevalence of bacterial species, such as *Clostridium* and related genera, as they are among the predominant bacteria, a dataset not recognized with the results of non-invasive studies based on *in vitro* growth[5]. Finally, DNA-based identification procedures provide an adequate phylogenetic image of the community but do not reflect metabolic activity because DNA could come from living (active), latent, or dead cells. It is precisely the metabolism of the microbiota that connects the fermentation of dietary fiber and the generation of useful metabolites to the intestinal epithelium, such as SCFAs, as can be seen in Figure 1.

The composition of each individual's fecal microbiota with respect to quantitatively-prevalent species is unique and remarkably stable in adulthood. At least three distinct microbiomes (called enterotypes and considered normal, eubiosis) have been recognized, with predominance of Bacteroidetes or Firmicutes[6]. Against this normal or non-pathological microbiome is coined the term dysbiosis, representing an alteration with respect to the normal pattern. While it is true that there is no single and clear definition, the concept assumes the presence of a loss of stability or homeostasis by increasing resident germs with pathogenic potential, decreasing commensals or reducing diversity.

The colon microbiome is either regulated or able to resist minor changes induced by a varied daily diet or small fluctuations in the physiological parameters of the host. The uniqueness in the composition of bacterial communities probably reflects consistent physiological and immunological idiosyncrasies of humans that are controlled by the genetic constitution of the host, among many other factors[7]. Demonstration of lies in monozygotic twins having microbiological profiles more similar to each other than those of non-genetically related subjects[8]. Antibiotics that aim at eliminating pathogenic bacteria have led to changes in the microbiome of the industrialized societies that use them[9]. The use and abuse (half of the requirements are inadequate) of them is also directly proportional to the growing number of pathogen resistances, which has become a severe alert from World Health Organization[10].

Although the phylogeny of individual bacterial communities seems unique among humans, the overall metabolic profile of the microbiota in terms of fermenting capacity is reasonably similar; regardless of bacterial profile, the same SCFAs are detected in similar proportions. This common metabolic profile might suggest redundancy between bacteria that can inhabit the gut. Several bacterial species may occupy a specific ecological niche, and each niche can be occupied differently between different humans. Therefore, regardless of the specific composition of the complex microbiota, the intestinal ecosystem works in the same way and the human gut provides habitat for a diversity of bacterial species when composition varies between individuals. The presence of the microbiome is essential for the necessary maturation of the immune system of the intestinal epithelium present from birth.

The nucleus of this gut microbiota could be composed of relatively few populations that provide the main metabolic activities. Physiological interactions between the host and microbiome cells and metabolic products are relevant for the thin line between health and disease. In this sense, the environmental factor that constitutes the change in the microbiome associated with the habits of western industrialized societies appears to be a more relevant element than the disease susceptibility polymorphisms whose association is already documented.

## HOST AND RESIDENT AND TRANSITING MICROBIOTE

The physiology of germ-free or axenic animals has shown that the gut microbiota has a considerable influence on local and systemic immunology, and on low-level resistance to intestinal infections. The immune system of the intestinal epithelium, which constitutes 70% of the body's leukocytes, must mature and function in coexistence with the microbiome, as it serves to balance protection against pathogens and tolerance to food antigens and resident microorganisms that are commensals or symbionts. Immunotolerance allows permanent contact with environmental epitopes of the microbiota and food. Brake of this tolerance initiates immunologic reactions that can lead to a disproportionate and unnecessary inflammation in inflammatory bowel disease (IBD)[11]. Now that it is possible to measure the transcription of mammalian genes as a result of the animal's exposure to specific bacteria and *vice versa*, the mutual

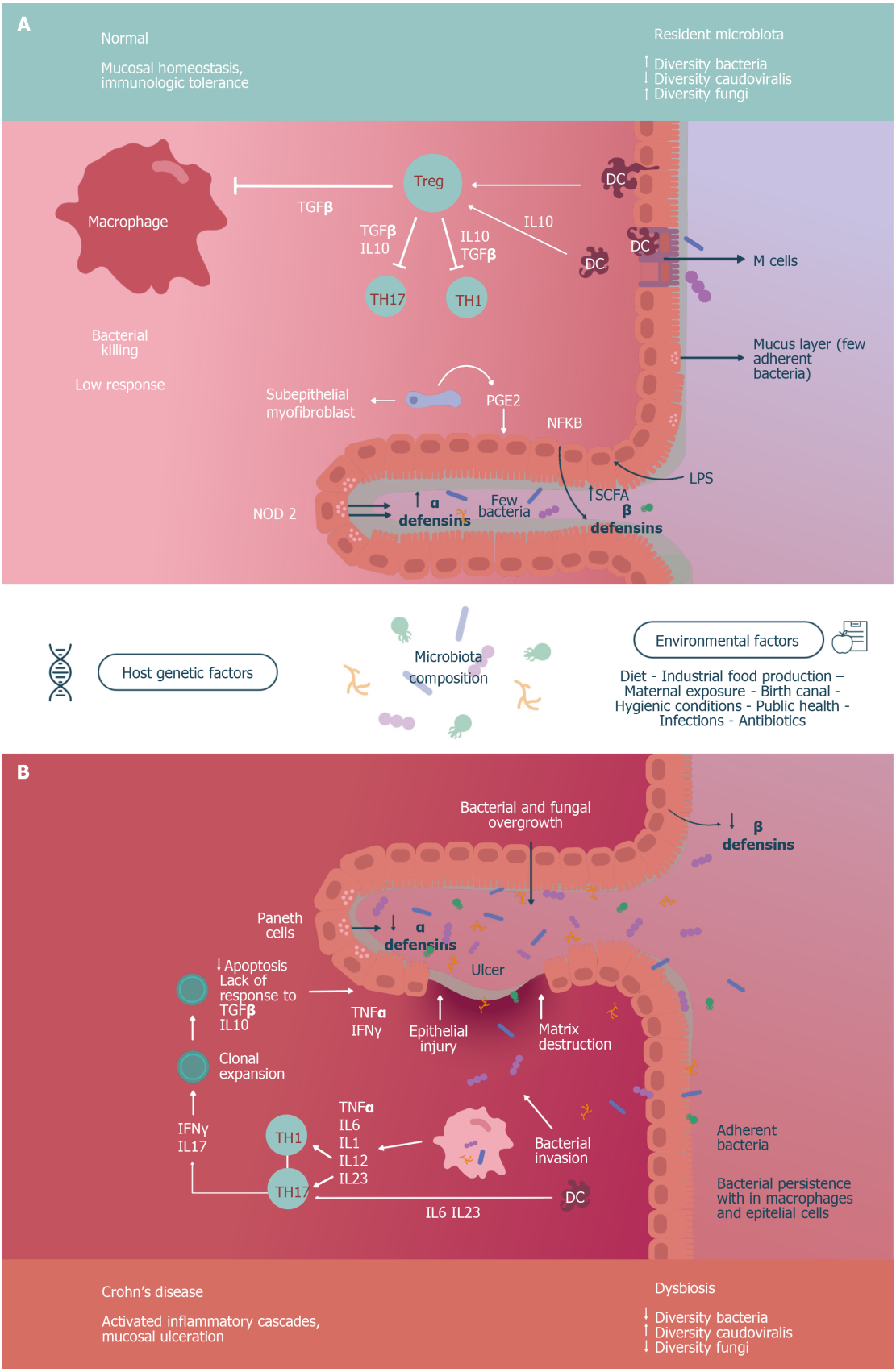


**Figure 1 Commensal microbiota modulates the response of the immune system in the intestinal mucosa and participates in the metabolism of the epithelium.** A: In the case of immune regulation, dendritic cells (DCs), activated in M cells, modulate regulatory T lymphocytes (Tregs) through anti-inflammatory signals (such as interleukin [IL]-10), which in turn inhibit other anti-inflammatory signals (such as IL-10 and transforming growth factor-beta [TGFβ]) of T helper cells 1-17 and macrophages. In the case of epithelial metabolism, the synthesis of short chain fatty acids (SCFAs), the secretion of prostaglandins (PGEs, such as PGE2) and the activity of nuclear factor-kappa B (NF-kB) contributes to an adequate secretion of defensins α and β, to the appropriate functioning of

the mucus layer and even the microbiome state in homeostasis; B: The persistence of bacteria adhering to a deteriorated mucus film, the decrease in defensins and the invasion of the epithelium produces the activation of DCs and macrophages, that in turn activate the T helper (Th) cells, Th1 and Th17, by proinflammatory signals (IL-1, IL-6, IL-12, and IL-23), thereby promoting a low apoptosis, clonal expansion with loss of response to anti-inflammatory signals, and contributing to tissue damage mediated by interferon gamma (INFγ) and tumor necrosis factor alpha (TNFα). This figure is based upon data published in Reference 11.

consequences of the presence and composition of the microbiome can be demonstrated. However, since the phylogeny of the intestinal community could be metabolically irrelevant, gene expression studies may focus on alterations in the functioning of the ecosystem as a whole, rather than evidence of the impact of individual bacterial species.

Recent studies of the composition of the fecal bacterial community in humans have shown that the detection of a particular bacterial species does not necessarily mean that bacteria are inhabitants of the intestinal ecosystem. Fluctuations in *Lactobacillus* populations in human stools have been shown in subjects receiving a specific probiotic contribution[12]. Perhaps these species of *Lactobacillus* were transient in the gut because they were present in food and are often used as starting organisms in food production, as well as probiotics. Food-associated *Lactobacillus* survive passage through the gut, but do not persist in the microbiome in the absence of continued consumption[13]. Their presence in the gut depends on external factors, such as the consumption of food in which they are present, and may be considered foreign or "transiting" microorganisms. In contrast, some species of *Lactobacillus* can be detected steadily in stools of a given human host for long periods after becoming residents.

Knowledge of the molecular traits that confer native or resident property on a particular bacterial species is essential. Bacteria residing in the intestine of mammals have evolved in parallel with their host and have developed a high degree of symbiosis and specialization. These bacteria must have traits that allow them to establish and persist in an environment of high competition between various species of microorganisms. The challenge for bacteria is to meet their own growth requirements, as well as to address the hostile conditions generated by competing members of the microbiome and by host defense mechanisms.

Although quantitatively less relevant in the human gut, *Lactobacillus* are relatively numerous in the proximal regions of other animals' gut due to the presence of a non-secretor squamous epithelium. *Lactobacillus* are directly adhered to epithelial cells, forming a layer of bacterial cells, which can be released with the flow of luminal content. Adhesive capacity to the epithelium should be a critical factor in the persistence of these germs in the gut; when they are joined and replicated on a host surface, a microbe can persist in a flowing habitat, while non-adherent microbes are swept away by the flow of secretions and food.

Three specifically induced genes have been detected during *Lactobacillus* colonization[1]. Homologies have been detected for at least two, namely xylose isomerase (xylA) and methionin-sulfoxide reductase (msrB). Xylose is a plant-derived sugar commonly found in straw and bran, and introduced into the gut in food. Xylose in the gut could be derived from hydrolysis of xylans and pectins by the microbiota. *L. reuteri* can also use isoprimeverose, which is the building block of xyloglucans, as described for *L. pentosus*. The selective expression of xylA suggests that *L. reuteri* maintains its energy requirements in the gut, at least in part by fermentation of xylose or isoprimeverose. On the other hand, msrB is a repair enzyme that protects bacteria from oxidative damage caused by reactive nitrogen and oxygen intermediaries. Nitric oxide is produced by epithelial cells of the ileum and colon and possibly acts as an oxidative barrier, maintaining intestinal homeostasis, reducing bacterial translocation, and providing a means of defense against pathogens. Therefore, *L. reuteri* could play a role in promoting a hostile ecosystem for pathogens.

The ability of bacterial cells to alert their resident neighbors to increase prokaryote density is well known[14]. Typically, cells produce a small extracellular signaling molecule, known as autoinducer, and simultaneously detect it on the cell surface. If the concentration of autoinducer exceeds a certain threshold, gene expression is induced, which often results in the production of other extracellular substances, such as those involved in the establishment of biofilms. Artificial addition of signaling molecules can reverse the creation of defective biofilms in mutant strains. Oligopeptides seem the most likely proposition in Gram-positive bacteria[15], but the most common signaling molecule is autoinducer 2 (AI-2). A wide range of Gram-positive and Gram-negative bacterial species produce AI-2 by a common metabolic pathway, and it has been proposed that AI-2 is a universal signaling molecule that functions in communication between bacteria. AI-2 is produced from S-adenosylmethionine (SAM). The use of

SAM as a methyl donor in metabolic processes such as DNA synthesis produces a toxic intermediary, S-adenosylhomocistein (a SAM-dependent methyltransferase inhibitor) that is hydrolyzed to S-riboadenosylhomocistein by a nucleosidase. LuxS protein catalyzes SRH cleavage to form homocysteine and 4,5-dihydroxy2,3-pentanedione. This molecule is cycled to form pro-AI-2, which is then transformed into AI-2 by addition of boron[1]. The argument that AI-2 has a cellular signaling function is based on extracellular accumulation proportional to the number of prokaryotes. In addition, the link between AI-2 production and cell synthesis (SAM utilization) could make AI-2 accumulation a tool for measuring the metabolic potential of a cell population[14]. If AI-2 molecules produced by all bacterial species capable of doing so are identical, then AI-2 could only inform bacterial cells that other bacterial cells are present but would not allow cells to determine the specific identity of their neighbors. In this way, the signal allows for the homeostasis of a prokaryote volume that is not as extensive as its phylogenetic composition.

## BACTERIAL DYNAMICS IN THE GUT

The biological dynamics that occur in the human gut include changes over time, from neonate to adulthood[16]. Particularly notable are the higher proportions of optional anaerobics (Enterococcus, Enterobacteriaceae) and Bifidobacterium relative to the total microbiota in infants compared to adults. An overall decrease in the number of Enterococcus and Enterobacteriaceae in the stool occurs as babies' gut microbiota matures and as SCFAs increase in quantity and diversity in the gut[17]. Phylogenetic diversity expands up to 3 years of age, reaching a state that will remain stable, with small fluctuations due to stimuli such as diet or medications. Antibiotics produce diversity reduction, loss of *Faecalibacterium* sp. loss of SCFA-producing germs, loss of Bifidobacterium, predominance of *Bacteroides*, growth of resistant and potentially pathogenic opportunistic resident bacteria, and increased total bacterial load[18].

Unlike in mice, where *Lactobacillus* are notable members of the microbiota, Bifidobacterium are predominant members of the low-diversity gut microbiota of human neonates, accounting for 60%-91% of the total bacterial community in breastfed infants and 28%-75% in formula-fed infants[19]. Proteobacteria is the other main group of bacteria in neonates. The formation of this first microbiome depends on initial factors such as maternal microbiome, type of delivery (vaginal *vs* C-section) and breastfeeding or formula-feeding[20].

Gut is the most extensive surface of contact with the external environment and the initial maturation site of the immune system *via* a process of learning antigenic recognition to numerous epitopes. The influence of the neonate gut microbiota on the immune system is of particular interest due to the increase in incidence of allergies among children in developed countries that has occurred in recent decades. Pediatricians have developed the "hygiene hypothesis" to try to explain this increase in the prevalence of those diseases[21,22]. This hypothesis states that in developed countries, the pattern of microbial exposure in the early years of life has changed, in particular: families are smaller; epidemics of childhood infectious diseases have become uncommon; contact with mud, soil bacteria and helminths, and infections caused by them, are rarer; living standards and hygienic-dietary practices are higher; there is little contact with farm animals; food is produced industrially, with more additives present; foods are commonly preserved by refrigeration; antibiotics are widely used as a treatment in childhood; and, finally, there is a significant percentage of C-section deliveries. This altered exposure to microorganisms has been able to predispose children's immune systems to react inappropriately to saprophyte microbiota and diet-related environmental antigens. A correlation has been reported between the onset of atopic disease and asthma and the frequency of antibiotic treatments during the first year of life. Examination of the fecal microbiota of babies treated with antibiotics has shown that the profile of the microbiota changes during the treatment period, including elimination of Bifidobacterium during periods of antibiotic administration[1] and risk of IBD in infants receiving antibiotics is significantly higher than those who do not receive antibiotics[23]. From the age of 65, a change in the composition of the microbiota, predominantly *Bacteroides* and *Clostridium*, has been seen[24], with a reduction in their SCFA-producing metabolism and an increase in proteolysis.

## IBD AND MUCOSA-ASSOCIATED MICROBIOTA

Both Crohn's disease (CD) and ulcerative colitis (UC) are the result of a genetically-predisposed loss of tolerance by the immune system to the presence of the gut microbiota. Bacteria provides a constant antigenic stimulus for the host's immune system. Normally, immune tolerance to the gut microbiota prevents continued intestinal inflammation[25]. This tolerance is lost in genetically-susceptible hosts with a dysfunctional and hyperreactive immune system, which thus develop chronic enteritis and colitis mediated by their own immune system.

Gastrointestinal tract of humans presents difficulties in the formation of typical *Lactobacillus*'s biofilms because it is covered by an epithelium of secretory columnar cells. *Lactobacillus* and other bacteria could also become trapped and possibly multiply in the mucus layer that is continuously secreted in human intestinal epithelium. The characterization of specific bacterial populations of the mucus layer-associated microbiota could help unravel the bacteriology of IBD[11], as can be seen in Table 1.

Targeted deletion or overexpression of a variety of genes that regulate immune or mucous barrier function in experimental animal models leads to an overly aggressive cellular immune response confined to the gut[26]. Results of experiments with germ-free rodents, in which intestinal inflammation is absent or only expressed very slightly, have indicated that bacteria are indispensable contributors to the pathogenesis of chronic intestinal inflammation mediated by gamma interferon-secreting T helper 1 CD4+ cells[27]. In addition, decreased bacterial load by administering broad-spectrum antibiotics reduces the intensity of colitis[28].

An additional argument for the role of the microbiota is that CD lesions are mainly found in regions of the intestine colonized by a large number of bacteria (the ileum and right colon) and the bypass fecal flow of the inflamed segments usually produces clinical benefit. In addition, infusion of intestinal contents into the ileum excluded from patients with post-surgical CD recurrence causes new inflammation[29].

It remains unclear whether the disease is due to the presence of specific bacterial species in the intestine of IBD patients[30] or if it results from an overly aggressive immune response to substances associated with many of the bacterial types that are able to reside or transit through the gut, causing inflammation, increased permeability and changes in the ecosystem. With the evidence in studies on experimental patients and animals that shows gut bacteria or their products at least promote chronic inflammation associated with IBD, immune and clinical knowledge brings us closer to exactly defining the gut microbiota in health and disease as well as the different losses of diversity in identical ecosystems (a diversity) and between different locations (b diversity). Changes in intestinal viroma have also been detected in the context of IBD, with predominance of *Caudovirales* phages that could promote bacteria associated with proinflammatory dysbiosis in IBD[31] and with increased prevalence of *Faecalibacterium prausnitzii* phages that may play an etiopatogenic role[32]. Finally, the fungoma, even though it involves only 0.1% of the total microbiota[4], has certain particularities associated with IBD, with changes in diversity[33], increase in *Candida* and Basidiomycota, and decrease in Ascomycota and *Saccharomyces*[34]. In addition, there are synergistic relationships of high pathogenicity by forming biofilms[35] in the case of the association between *Candida*, *Serratia* and *Escherichia coli*.

From the basis that the composition of the microbiome in the human gut is highly variable between individuals and depends on the factors already mentioned, the comparison of fecal microbiota between healthy and sick subjects may not lead to conclusions regarding etiology. The uniqueness of the human microbiota makes comparisons difficult, given the absence of a specific causal agent. In addition, the composition of the human fecal microbiota reflects that of the colon, but the bacterial community is more metabolically active in the proximal colon as a result of the increased availability of fermentable substrates. On the other hand, bacteria attached to mucus layer and epithelium are inadequately expressed in stool studies due to their location, but may be more related to the immune system of the gut and modulate inflammatory processes.

The precise definition of the mucosal-associated microbiota is complex because mucosal biopsy samples should be collected through heterogeneous invasive procedures between different studies. In addition, prior to colonoscopy for biopsy, the patient receives intestinal preparation to remove the content of the colon and the effect of this prior treatment on the composition of the microbiome is unknown. However, the colon is not completely clean after this procedure and fecal fluid persists on the mucous surface. Therefore, it is not clear exactly what is being biopsied: the mucosal surface contaminated with luminal bacteria or true inhabitants associated with the mucosa. We must be cautious in advancing knowledge about the microbiota

**Table 1 Role of microbioma in inflammatory bowel disease patients and mouse models[11]**

| Aggressive | Protective |
|---|---|
| Proteobacteria | Bifidobacterium sp. |
| *Escherichia coli* (adherent/invasive) | Clostridium (groups IV and XIVA) |
| *Fusobacterium sp.* | *Faecalibacterium prausnitzii* |
| Pasteurellaceae | *Bacteroides fragilis* |
| Veillonellaceae | *Saccharomyces cerevisiae* |
| Caudovirales | *Roseburia sp.* |
| *Ruminococcus gnavus* | *Suterella sp.* |
| *Candida albicans* | |
| *Candida tropicalis* | |

associated with the mucosa of humans because of all these biases.

If there are native bacteria associated with the mucosa, they may vary from patient to patient. Therefore, comparisons between healthy and sick subjects will be of little use in addressing etiology. However, comparisons of the microbiota within an individual (inflamed and non-inflamed mucosa) could be useful, as recognition of a microbiota of so-called "abnormal" composition could provide a diagnostic or even therapeutic target. However, this will not necessarily allow specific bacterial populations to be assigned a causal role in IBD. Alterations in the mucosal-associated microbiota could occur as a result of inflammation-induced changes in the ecosystem and therefore be consequential, and not causal.

Infinite heterogeneity of the immune system in relation to human leukocyte antigen (HLA) increases the complexity of understanding the relationship of the microbiota and IBD. HLA genes determine the specificity of the immune response, so the immune systems of different humans and other animals recognize different epitopes. Identifying intestinal ecosystem antigens produced by the redundant metabolism of the microbiota to which the dysfunctional immune system responds abnormally can lead to new therapeutic targets.

Finally, the similarities of HLA between IBD patients are likely to increase the likelihood that their immune systems will react inappropriately to the same antigens. A classic example of an association of an HLA with a disease is HLA-B27 and spondyloarthropathies. In the case of IBD, 30% of CD and UC patients have this genetic marker[36], so HLA polymorphisms must intervene in the relationship between the immune system and the microbiome. In fact, the genes identified in the genetic predisposition are related to the two-way interaction between the microbiota and the immune system[37].

## DIET, PREBIOTICS, PROBIOTICS AND MICROBIOTA

Targeted and intentional modification of the gut microbiota using probiotics, dietary supplements or foods containing live non-pathogenic microorganisms is a developing therapeutic pathway. However, the probiotic designed to modify the gut microbiota only achieves that effect transiently and for a particular microbiological population. For example, the ingestion of *Lactobacillus* modifies the population of this genus but in a study with the DR20 strain of *Lactobacillus rhamnosus*, easily identifiable by genetic fingerprint of other members of the same genus, 9 out of 10 subjects showed detectable strain in stool culture during the probiotic consumption period; however, in 8 of these 9 subjects, the ingested strain was no longer detectable a month after discontinuation of probiotic consumption[12]. Administration of the probiotic did not cause other alterations in the composition of the microbiota. In fact, as is commonly observed, *Lactobacillus* comprise less than 1% of the total fecal microbiota, even when administered in a relatively large number.

This resistance or resilience of the microbiota to return to its previous stable state also occurs after alterations caused by antibiotics. On the contrary, the persistence of changes capable of overcoming the resilience of the microbiome would constitute dysbiosis, by moving away from the classic enterotypes considered normal[6]. The

maintenance of a self-regulating community structure explains the stability in the composition of the fecal microbiota. The basis on which this homeostasis operates is competitive exclusion. A mature bacterial community makes it difficult for a foreign organism to settle down because the community is complete and homeostatic for that specific host[38]. Dysbiosis can cause metabolic change, even more crucial than phylogenetics, initiator of a vicious cycle of loss of SCFA production, increased oxygen stress in the mucosa, loss of strict anaerobes, such as *Faecalibacterium*, increased Proteobacteria, perpetuation of fermentation loss and synthesis of SCFAs[39], as can be seen in Figure 2. This metabolic disorder causes a deterioration in the functioning of the epithelium immune system, with increased immunoglobulin (Ig)A degradation, Toll-like receptor modulation and nuclear factor-kappa B (NF-kB) inhibition[40]. This alteration could occur at the beginning of the pathogenic sequence of diseases of self-inflammatory origin[41]. The phylogenetic and especially metabolomic characterization of dysbiosis could lead to a diagnostic and therapeutic target in IBD[42].

Under these basal resilience conditions, it is doubtful that probiotics will have an impact on the colon ecosystem but could be effective in the bowel. After all, consuming a probiotic product provides more than $10^9$ foreign bacterial cells per dose. A realistic probiotic goal should not be modification of the colonic microbiota but stimulation of the bowel immune system.

Another microbiota modulation alternative, effective from the point of view of changing the ecological environment of the microbiome, is based on the intake of prebiotics, which are potential substrates for gut bacteria[43]. The argument behind this practice is that the proliferation of resident bacterial strains with beneficial consequences for host health can be promoted in the gut. Different oligosaccharides and inulin have been proposed to selectively increase the number of Bifidobacterium. These supplements seem to promote more intense changes in metabolic activity (measured by rRNA) than in microbiota phylogeny (measured by DNA), and are also limited by meteorism and abdominal pain that can lead to increased intraluminal fermentation. In relation to metabolism, the performance of bacterial cells is directly proportional to the amount of adenosine triphosphate produced, but there is no zero balance between anabolism and catabolism[1,44]. Latent bacteria suspensions consume energy sources in total absence of growth from maintenance energy expenditure. In addition, this energy loss can occur when growth is limited by nutrients other than energy sources. DNA fragments depicting *Bifidobacterium adolescentis* and *Colinsella aerofaciens* were found to be present in the microbiota following prebiotic supplementation[45]. These bacteria could have been in a metabolically restive state prior to supplementation and when the usual diet was enriched with oligosaccharides, the substrate for metabolism might have been available in the colon, but because other nutrients were limiting in the bacterial community, there was no increase in the cell numbers of *Bifidobacterium* and *Colinsella*. Therefore, populations remained constant in size, but RNA provided evidence of increased metabolic activity.

Diet has a fundamental impact on the original composition of the microbiota and on the maintenance of its homeostasis. Fiber-enriched diets in developing countries, along with numerous characteristics associated with non-urban and non-industrialized environments, promote an increase in Bacteroidetes and a decrease in Enterobacteriaceae. Fiber, the prebiotic element by antonomasia, can influence the profile of the most prevalent bacterial genera by promoting a widespread increase in diversity, and commensal bacteria in particular[46]. Given the inability to digest and therefore absorb fiber degradation products, most of this dietary element is fermented by bacteria. Soluble fiber seems to be crucial in this role. In addition, there is selectivity of different bacterial species by certain substrates to be fermented, so a dietary intervention can promote certain species against other[47].

Certain specific elements of the diet, such as the essential amino acid tryptophan [48], through its metabolites, such as quinurenic acid and indol-3-acetic acid, or arginine[49], involved in tissue repair and macrophage differentiation, may have a specific role as immunomodulators. In the context of IBD, the production and demand balance of certain amino acids is altered and could be a therapeutic target. Other dietary elements could also modify the microbiome, such as sweeteners that alter Bifidobacterium and *Lactobacillus*[50], emulsifiers by solubilizing mucus and direct effect on bacteria[51], dyes by decreasing mucus production[52], and salt by decreasing *Lactobacillus*, increasing Firmicutes[53] and promoting the proinflammatory pathway of interleukin (IL)-17/IL-23.

Mediterranean diet, rich in consumption of vegetables, fruits, legumes, olive oil, cereals, nuts and seeds, and with moderate consumption of fish, poultry and dairy, has been associated with a decrease in the risk of IBD[54]. This diet is characterized by polyunsaturated fatty acids such as omega-3, fermentable fiber and polyphenols, and

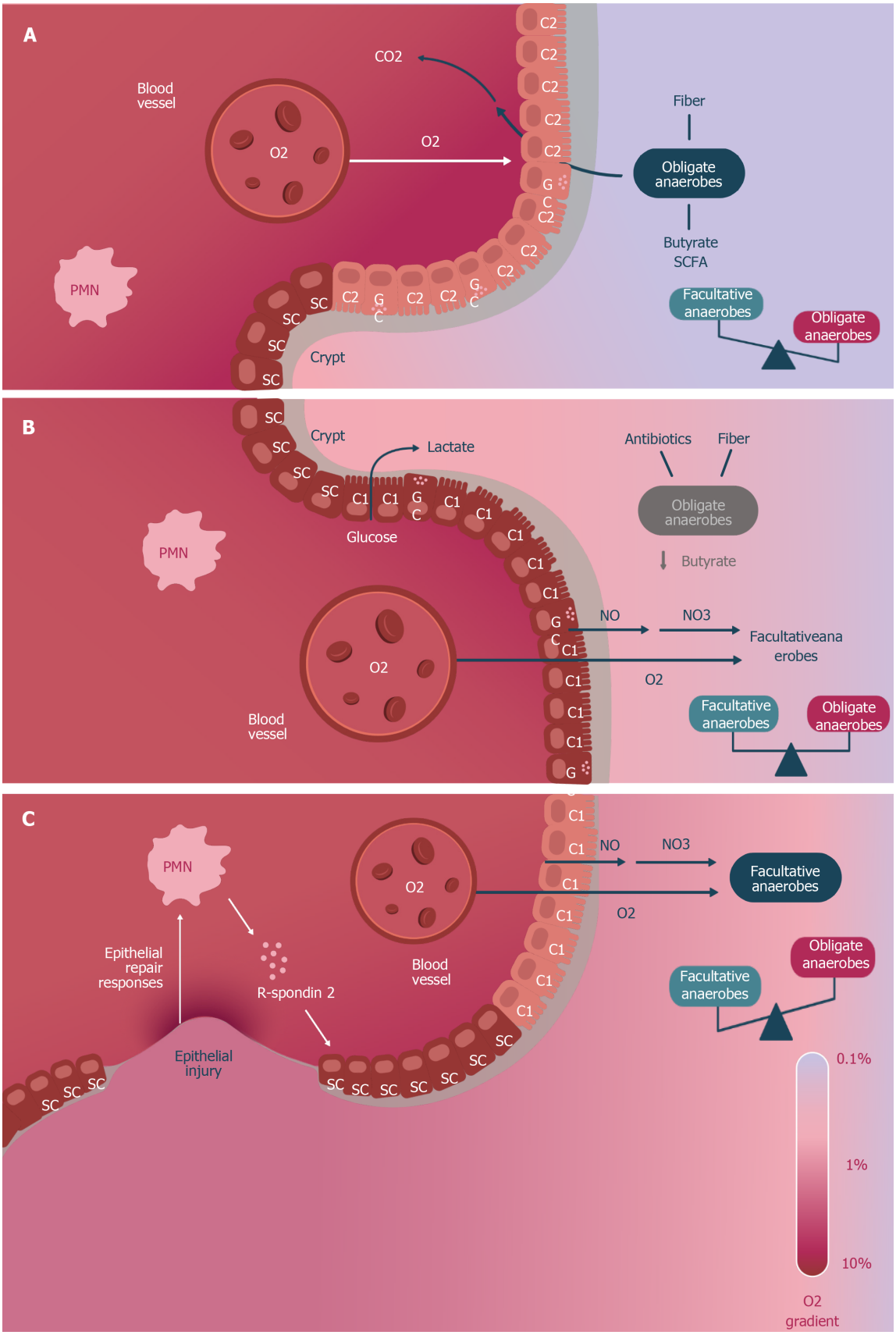


**Figure 2 Metabolic epithelial changes in dysbiosis due to loss of obligate anaerobes.** A: The eubiosis microbiome contains a significant number of obligate anaerobes that convert dietary fiber into short chain fatty acids (SCFAs), contributing to a C2-type epithelial trophism with high oxygen consumption ($O_2$), which limits its diffusion to the intestinal lumen and maintains the epithelium in relative hypoxia; B: The deterioration of the microbiome with loss of obligate anaerobes and SCFAs orients the metabolism of the epithelium to a C1-type, with greater glucose fermentation, low $O_2$ consumption, and generation of lactic acid and nitric oxide (NO). The higher partial pressure of the $O_2$ not consumed by the C1 colonocytes and the conversion of NO to nitrate ($NO_3^-$) causes an overgrowth of facultative

anaerobes; C: The persistence of the loss of strict anaerobes and their fermentation products ends up causing epithelial damage (*via* polymorphonuclear neutrophils R-spondin 2), the response of which is crypt hyperplasia and the multiplication of stem cells (SCs). The sustained increase in $NO_3^-$ and $O_2$ contributes to the persistence of facultative anaerobes and dysbiosis. This figure is based upon data published in reference 39.

is low in red meats and processed products. Diets rich in fats and refined sugars are usually low in fiber, so they impoverish butyrate production, among that of other SCFAs, promoting a proinflammatory ecosystem by increasing cytokine transcription and decreasing regulatory T cells[55] and loss of epithelium barrier functions[56], particularly the bacterial degradation of mucus, which facilitates the adhesion of bacteria and their translocation. These unhealthy, high-fat diets can increase the expression of tumor necrosis factor alpha (TNFa), modulating the immune system towards proinflammatory responses[57].

## DIETARY FOOD COMPONENTS AS RISK FACTORS FOR IBD

There is strong evidence to state that the influence of the dietary pattern, on which certain foods may be individually involved, as a risk factor for the onset of IBD, is more important. Among the environmental factors related to the etiopathogenesis of IBD, diet has demonstrated the capacity to modify the composition of the microbiota and the products of its metabolism with an action on the immune and intestinal barrier function in the gut[58]. Diet is a modifiable factor and our dietary intervention should try to increase those nutrients with an anti-inflammatory effect and avoid proinflammatory ones, in order to reduce the risk of developing IBD and to maintain remission of the inflammatory activity of the disease.

The increased incidence of IBD in industrialized countries, as well as in the migrant population coming from less developed areas, suggests that the typical western diet is promoting the development of IBD[59]. The western diet model exhibits an increased consumption of refined sugar, omega n-6 polyunsaturated fats, red meat and processed food, associated with a diet deficient in fruit, vegetables, and fiber[60]. The western diet model is hypothesized to increase proinflammatory cytokines, disrupt epithelial barrier, and alter the intestinal microbiota (with an increase in Bacteroides and Enterobacteriaceae, and a decrease in Bifidobacterium and *Lactobacillus*) promoting a low-grade chronic inflammation in the gut[50,61,62].

### *Dietary fiber intake*

A negative association between dietary fiber and fruit intake and CD risk as well a high vegetable intake association with decreased risk of UC were reported from a systematic review ($n$ = 2609 IBD subjects)[63]. In a prospective cohort ($n$ = 170776 women from the Nurses' Health Study), high intake of fiber predominantly from fruits was associated with a significant reduction in risk of CD but not UC[64]. A recent meta-analysis concluded that consumption of vegetables was associated with decreased risk of UC alone, while higher consumption of fruits was associated with decreased risk of both UC and CD[65]. Increased consumption of sweets is positively associated with CD[66]. Diets high in fiber, or fiber supplementation, increase the diversity of bacterial genes and are associated with growing proportion of Bifidobacterium and producers of SCFAs with an anti-inflammatory profile[50,67]. Overall, complex carbohydrates including fruit, vegetables and fiber should be included in the diet to prevent and manage IBD.

### *Protein intake*

In a large prospective cohort study ($n$ = 67581 and 10 years of follow-up), high protein intake, specifically animal protein from meat, was positively associated with an increased risk of CD and UC[68]. A systematic review ($n$ = 2609 IBD patients) found an association with high total protein intake and the onset of IBD[69]. The con-sumption of animal proteins (meat) causes an increase of Bacteroides, *Alistipes* and *Bilophila* (related to pathological processes as atherogenesis) and a reduction of Bifidobacterium, *Roseburia*, *Eubacterium* and *Ruminococcus*[70,71]. Overall, a diet high in animal protein is a major risk factor for the development of IBD.

### *Dairy intake*

Milk consumption may be associated with a decreased risk of developing CD but not UC, based on the European Prospective Investigation into Cancer and Nutrition cohort

(*n* = 401326 participants)[72]. In a meta-analysis (*n* = 1935 IBD patients), dairy foods were suggested to decrease risk of IBD, with dairy restrictions suggested as having the potential to adversely affect disease outcome[73]. Overall, the consumption of dairy products is not a risk factor for IBD.

### Dietary fat intake

The effect of fats on the microbiota differs according to the type of fatty acid, which include saturated fatty acids, monounsaturated fatty acids or polyunsaturated fatty acids (PUFAs). Moreover, the PUFA family is classified into omega-3 (n-3) and omega-6 (n-6) fatty acids.

Dietary n-6 PUFAs are present in high amounts in red meat, margarines and cooking oils (*e.g.*, sunflower and corn oil). A prospective cohort study (*n* = 203193) conducted over 4 years found that intake of linoleic acid was associated with an increased risk of UC[74]. An analysis from the European Investigation into Cancer and Nutrition study (*n* = 260686) found an increased risk of UC with a higher total PUFA intake[75]. Frequent intake of fast foods (high in trans-unsaturated fatty acids) defined as more than once a week was significantly associated with a risk of UC (43%, odds ratio [OR]: 5.78, 95% confidence interval [CI]: 2.38-14.03) and CD (27%, OR: 2.84, 95%CI: 1.21-6.64)[76]. Dietary n-3 PUFAs, contained in fish oils and olive oil, were inversely associated with risk of UC, whereas no association has been found with CD [77]. High n-3 PUFA/n-6 PUFA ratio in the diet is inversely associated with the risk of IBD[78] and a dietary intervention trial with an increasing n-3 PUFA/n-6 PUFA ratio found it to be effective in maintaining disease remission in patients with both UC and CD, through the increasing n-3 PUFA intake[79]. High intakes of fats and saturated fatty acids had a negative impact on the diversity of microbiota associated with an increase in anaerobic microbiota and Bacteroides[62]. Overall, total fat should not be restricted but an increase in olive and fish oils rich in n-3 PUFA should be promoted.

### Emulsifiers and food additives

A high intake of processed and fast foods has been shown to confer a 3- to 4-fold greater risk of developing IBD[80]. Maltodextrine is one of the frequently consumed dietary additives, and animal models have demonstrated a direct effect of maltodextrins on the intestinal mucosal barrier, which translates to exacerbation in intestinal inflammation or increased bacterial burden[81]. Overall, processed food is a risk factor for the onset of IBD.

## DIET INTERVENTIONS TO MAINTAIN REMISSION IN IBD

Diet interventions have been studied in IBD to manage active disease or to maintain remission. Even some of these regimes have shown to be effective, the precise components that are important for each diet are not clearly defined. Although the study on diet interaction over microbiota is increasing, the available data regarding modifications in the composition and immune effect of microbiota are still limited due to the complexity of the study techniques and the interpretation of its results.

### Low-residue diet

A low-residue diet requires the elimination of whole grains, legumes and all fruits and vegetables. It is usually recommended when intestinal strictures are present in IBD patients, to reduce the risk for intestinal obstruction and the frequency and volume of stools[82]. Only case series have demonstrated improvement in symptoms in CD patients with obstructive symptoms and strictures when following a diet low in fiber (total daily fiber intake < 10 g)[83]. A small pilot study in CD (*n* = 6)[84] found a marked decrease in microbial diversity with a low-residue diet but with no changes in inflammatory markers[85]. Overall, a low-residue diet cannot be recommended, except in individualized cases such as those with obstructive symptoms, because its long-term use with reduced fiber intake may not be beneficial for IBD patients.

### Semi-vegetarian diet

The semi-vegetarian diet is a lacto-ovo vegetarian regime, in which eggs and milk are allowed with small portions of meat offered once every 2 wk and fish offered weekly. A prospective trial was conducted in Japan to evaluate the effect of a semi-vegetarian diet in maintenance of remission in 22 adult patients in medical remission[86]; after 2 years of follow-up, 16/22 patients continued the semi-vegetarian diet and 15/16 maintained remission compared with 2/6 in the control group ($P$ = 0.0003). However,

a randomized clinical trial of 213 patients with CD[87] did not show a lower risk of flare-up in those who consumed red or processed meat less than once per month. Overall, there is no sufficient evidence to recommend a semi vegetarian-diet in IBD patients.

### *Low-fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) diet*

The low diet FODMAPs diet consists of eliminating high-fermentable but poorly absorbed carbohydrates and polyols[88] for a short period (4-8 wk), including wheat, rye, onion, garlic, legumes, dairy, honey, syrups, fruits such as apple, pear and plum, and light foods and sweeteners.

Irritable bowel syndrome (commonly known as IBS)-like symptoms are common in IBD[89] and have been reported in 57% of patients with CD and 33% of patients with UC, and retrospective studies including IBD patients with functional gut symptoms who received low-FODMAPs diet advice displayed a significant reduction in symptoms and improvements in stool consistency and frequency[90]. Nevertheless, the FODMAPs diet promotes dysbiosis and does not improve biological inflammatory biomarkers, so it is not recommended for prolonged use[91]. Overall, a low FODMAPs diet may be recommended to manage concurrent IBS-symptoms in IBD patients.

### *Anti-inflammatory diet (IBD-AID)*

The IBD-AID restricts the intake of particular carbohydrates (*i.e.*, lactose, and refined and processed complex carbohydrates), includes the ingestion of prebiotic and probiotic foods, and modifies dietary fatty acid intake, specifically decreasing the total fat and increasing the intake of foods rich in n-3 PUFA. Only one retrospective case series[92] using IBD-AID ($n$ = 40) has demonstrated improvement in symptoms and stool frequency (*via* patient self-report). Overall, there is not sufficient evidence to recommend an IBD-AID-diet in IBD patients.

### *Mediterranean diet*

The Mediterranean diet is a regime of fiber-rich plant-based foods (*e.g.*, cereals, fruits, vegetables, legumes, nuts, seeds and olives) relying on olive oil as the principle source of added fat, high intakes of fish and seafood, moderate consumption of eggs, poultry, dairy products (*i.e.*, cheese and yogurt), wine and low consumption of red meat[93]. A case-control study ($n$ = 264 IBD subjects and 203 controls) showed that a significant risk factor in the development of pediatric UC was a low adherence to the Mediterranean diet[94]. The omega n-6/n-3 ratio of the Mediterranean diet (35% total fat, 15% monounsaturated fatty acids mainly from olive oil, 13% saturated fatty acids, and 6% PUFA)[95] might explain the protective effect over the gut microbiome and gut metabolome[96]. An intervention study examining the use of the Mediterranean diet pattern in CD[97] ($n$ = 8) demonstrated a tendency towards inflammatory biomarker reduction ($P$ = 0.39) and "normalization" of the gut microbiota. Overall, however, there is not sufficient evidence to recommend a Mediterranean Diet, but it is a promising option for IBD patients.

### *Specific carbohydrate diet (SCD)*

The SCD is one of the most used exclusion diets in IBD, and is based on the idea that patients with IBD may have malabsorption of disaccharides and complex carbohydrates. Therefore, higher amounts of disaccharides would be present in the colon, with the consequent bacterial overgrowth and bowel injury increasing intestinal permeability. The toxic substances produced by dysbiosis of the luminal microbiota in the bowel may cause damage to intestinal cell membranes and destroy brush border enzymes[98-100].

The SCD is a strict grain-free, sugar-free and complex carbohydrate-free diet regimen[98]. It is based on the avoidance of starches (*i.e.*, cereals, rice, and potato), refined sugars, dairy (except yogurts and cured cheese) and almost all preservatives or additives, but it allows for fruits, vegetables, nuts, fish, meat, eggs, honey, some legumes, coffee, oil, mustard and tea. An internet survey ($n$ = 451) that examined the IBD patient's perceptions of the SCD found that symptoms decreased[99] (*e.g.*, abdominal pain, diarrhea, and blood in stool). Another patients' self-report of the effectiveness of the SCD ($n$ = 50 IBD patients in remission)[100] was rated as a mean of 91.3% effectiveness in controlling acute flare symptoms (range: 30%-100%) and a mean of 92.1% effectiveness in maintaining remission (range: 53%-100%). SCD showed higher bacterial diversity in the SCD group ($n$ = 20) compared to controls but the difference did not reach statistical significance. Overall, there is no sufficient evidence

to recommend the SCD for IBD patients.

### *Autoimmune diet (modified-Paleo diet)*

The autoimmune diet is a modified Paleolithic regime which includes avoidance of processed food, refined sugars, legumes, dairy, grains and cereals, and instead it advocates for grass-fed meat, wild fish, fruit, vegetables, nuts and "healthy" saturated fat. After an initial elimination phase, and once clinical symptoms and inflammation are controlled, a 5-wk maintenance phase is started with one-by-one reintroduction of foods, in order to identify trigger items. Only in one open-label observational study [101] did the authors evaluate the efficacy of an autoimmune diet in patients with UC or CD, finding clinical evidence and objective evidence of inflammation (biochemical/imaging/endoscopic inflammation). There was improvement in the subjects' clinical symptoms and in their quality of life, and 11 of the 15 patients maintained remission during the 11 wk maintenance phase. Overall, however, there is not sufficient evidence to recommend an autoimmune diet, but is a promising option for IBD patients.

### *Partial enteral nutrition (PEN)*

PEN is the use of < 100% of total energy requirements from nutrition enteral formula, in addition to consuming food. PEN is an effective therapy for induction of remission in CD[102] but not in UC. However, PEN is difficult to adhere to, particularly in adults, because of its poor tolerability due to its taste. A systematic review assessed the efficacy of enteral nutrition (EN) for maintenance of remission in CD[103] and included two studies: one of which was a randomized clinical trial, which found significantly lower relapse rates in patients who received half of their total daily caloric requirements as elemental diet and the remaining half as normal diet compared to patients who received unrestricted normal diet (9 of 26 *vs* 16 of 25; OR: 0.3, 95%CI: 0.09-0.94)[104]; and, in the second study, elemental and polymeric feeds (providing between 35% and 50% of patients' pretrial caloric intake in addition to unrestricted normal food) were found to be equally effective for maintenance of remission and allowing for withdrawal of steroid therapy (8 of 19 *vs* 6 of 14; OR: 0.97, 95%CI: 0.24-3.92)[105]. A recent systematic review[106] included 12 studies (1169 patients, including 95 children), of which 11 showed that PEN was either better than or as effective as its comparator in maintaining remission in patients with inactive CD. Several changes in the taxon abundance of certain species and metabolites were described in children with CD on EN, specifically the abundance of genera belonging to Actinobacteria, Bacteroidetes, and Firmicutes[107]. Overall, there is not sufficient evidence to recommend PEN but is a promising option for maintenance of remission in IBD patients.

## DIET AS TREATMENT FOR INFLAMMATION AND DYSBIOSIS

Dietary modulation and appropriate exclusion diets might be a new complementary management for treatment at disease flares and in refractory patients, even reducing complications, hospitalization and surgery, through modifying the luminal intestinal environment.

The complex relationship between intestinal homeostasis and dietary nutrients makes dietary intervention a complicated task due to interactions between host immunity, the intestinal epithelium, the gut microbiota[47] and the antigenic load of food. In IBD, cellular and microbial metabolisms changed by intestinal inflammation, genetic polymorphisms, and the scarcity or overabundance of some nutrients makes everything more complicated[47].

Despite several research investigations, the role of diet in the management of IBD is not well understood[108]. The current dietary recommendations for disease management are scarce and controversial, non-evidence based and from different across regions/countries[109]. A lack of solid dietary recommendations has emerged from the sparse data, and good quality clinical trials are needed in this context. Other issues are the difficulty to differentiate between active disease symptoms and remission with symptoms that are functional, because therapeutic approaches are quite different and there is risk of compromising nutritional status with a restrictive diet in a population where under-nutrition is common.

The exclusion diets are based on the effect that certain dietary patterns have on the composition of the microbiome, the impact of dietary antigens on the immune response or that of the metabolites produced by the microbiota, altering the mucosa

layer and the immune response.

Recently, some efforts have been made towards evaluating specific diets for the management of IBD; nevertheless, there remains no general strategy that can be recommended to induce remission in IBD patients with active disease[110].

### Exclusive enteral nutrition (EEN)

EEN is recommended as a first-line therapy to induce remission in children with active luminal CD[108] with a strong, rapid and durable anti-inflammatory effect[91,111,112], according to the ECCO-ESPGHAN consensus. EEN is first-line therapy for CD in Asian countries[109,113] for adults and children. A Japanese study found that EN therapy with elemental diet has a higher rate of induction of remission in CD patients compared with corticosteroids, and especially improves luminal lesions[114,115].

EEN improves the nutritional status and disease activity, and significantly reduced surgical intervention in one study[113]. Clinical trials comparing EEN to steroids based on remission rates as the outcome parameter showed an overall remission rate of 75% for EEN at the end of exclusive treatment. While in children[116,117], EEN has demonstrated similar efficacy to both EN and corticosteroids; in adults[118], EEN was inferior. However, it is difficult to draw clear conclusions because studies in adults are sparse and of poor quality[112]. EEN has not been shown to be effective for UC[119].

In a prospective study[120], 58% of patients had early endoscopic response, and one-third had complete transmural healing on bowel imaging. Open-label trials in children have demonstrated endoscopic healing, and improved quality of life[119]. The long-term durability of the achieved remission in patients on EEN is over 2 years, *via* reducing corticosteroid dependency and lowering relapse rates over 12 mo[113].

EEN implies the exclusive consumption of an elemental or polymeric substance for many weeks, so treatment failures are due to poor compliance (dropouts are frequently due to poor acceptance of a nasogastric tube and unpalatable formulations [118]); however, there is scarce experience between adult-IBD patients with the use of this nutritional intervention[111]. In a recent meta-analysis[121], the efficacy of an elemental EEN (based on amino acids, sugars, fats, vitamins and minerals) or a polymeric EEN (composed of whole protein or oligopeptide sources) have the same potential for inducing remission. However, polymeric diet could decrease the level of C-reactive protein better than an elemental one.

EEN may restore epithelial barrier, excluding certain dietary components known to increase intestinal permeability, adherence of *E. coli* and reducing the antigenic load [119,122]. Disease improvement with EEN is associated with extensive modulation of the gut microbiome, particularly an increase in relative abundance of genes involved in cell growth and renewal and possibly in tissue healing[107,117,123]. Nevertheless, its impact on dysbiosis is paradoxical, depleting the gut microbiome of potentially detrimental bacteria rather than restoring a totally healthy microbiome; thus, EEN decreases bacterial microbiota diversity[124-126]. Species-specific effects induced by EEN were reported in different studies, particularly a significant decrease in Bacteroides[123] and specific beneficial bacteria like *Faecalibacterium prausnitzii*[124].

After achieving clinical remission with EEN, there exists a correlation of disease recurrence with the re-colonization of eradicated taxa post-EEN. Specific species within Lachnospiraceae, Ruminococcaceae, and Erysipelotrichaceae were among the key taxa identified as potentially involved in the perpetuation of gut inflammation in CD[125]. It has been suggested that a sequential EEN-probiotic therapy may prove beneficial in the improvement of long-term efficacy of EEN therapy in pediatric CD, but there is not yet enough data to make a definitive recommendation.

Some authors[127-130] have demonstrated a decrease in proinflammatory and an increase in anti-inflammatory molecules, like transforming growth factor-beta (TGF-β), in CD patients treated with EEN. EEN is an alternative to immunosuppressive therapy in adult active luminal CD patients, providing an important therapeutic effect on the microbiota, enhancing barrier defense and reducing proinflammatory cytokines[121]. More studies have deepening of the mechanisms of action, the duration of treatment, its use in other clinical settings are needed.

### PEN

PEN has been studied for maintenance of remission or treatment of active IBD[123]. It arises as an alternative to abstinence and the monotony of drinking enteral formula that limits the compliance and success of EEN. Type, dose, duration and method of delivery of the supplementation, the volume, and the range of total energy requirements as well as the profile of foods consumed (*i.e.*, free diet or a defined restrictive diet) varies widely in clinical practice and among the different studies[104,131-134].

PEN did not impact disease activity in a randomized clinical trial comparing it with normal diet in the treatment of active CD and malnutrition in adults[135], although some nutritional markers were improved. Other trials have compared elemental PEN and EEN for induction of remission in children with moderate to severely active. PEN has been reported to result in fewer patients entering remission[136], and has not demonstrated superiority in providing clinical remission, in children or adolescents, compared to ENN or anti-TNF treatment in a non-randomized trial[137].

One uncontrolled trial[138] studied PEN in conjunction with a CD exclusion diet in children/young adults, and found a clinical response in 78.7% and 70.2% entering full disease remission. A greater number and methodologically more robust studies are needed to assess the efficacy of PEN in induction of remission of IBD.

### SCD

Evidence of SCD ability to induce and maintain remission in IBD is based on several case-series, most of them involving children. A prospective study[139] found that there were significant clinical and mucosal improvements at 12 and 52 wk, but in only 10 children with CD. A cases-based study with 50 adult IBD patients[100] showed that SCD-followers had decreased symptom scores and a high quality of life; some of them were even able to maintain clinical remission without maintenance medications. SCD is well associated with improvements in biochemical laboratory parameters and Lewis score on capsule endoscopy[139,140,141], and the patients perceive substantial clinical benefit to its use[99]. SCD also helps to improve symptoms in IBD patients, due to its effects on decreasing inflammation and increasing diversity of the microbiome[84,119,142,143].

This dietary alternative can be an option, alone or combined with medical treatment, in patients with active IBD, producing improvement in symptoms and increasing quality of life; however, special caution must be taken in CD patients with bowel strictures, because it can tend to be higher in fiber and may lead to an obstruction[144].

### CD exclusion diet

The CD exclusion diet (also known as CDED) involves exclusion of those dietary components which impair innate immunity, increase intestinal permeability, cause microbial dysbiosis, or allow bacteria to adhere and translocate through the intestinal epithelium in animal models. These components are animal and saturated fats, gluten, and emulsifiers. Half of the diet is provided as EEN, thereby allowing the double effect of avoiding nutritional deficiencies and improving dysbiosis. Some studies have confirmed the effectiveness of CDED for the induction of remission in children with CD[122,138]. A randomized controlled study that compared CDED plus PEN *vs* EEN in pediatric CD patients[145] demonstrated similar response and remission rates at week 6 and sustained remission at week 12. The results of this new therapeutic approach could change the recommendation for EEN in the future.

### Low-FODMAPs diet

Many patients within a flare of IBD and beyond can develop functional IBS type symptoms, and for them, the FODMAP diet could be an option[100]. However, there is not enough data yet to recommend it to induce remission.

### Mediterranean diet

The Mediterranean diet is considered inappropriate for patients during flares, due to the high amount of fiber. However, some of the main foods have shown isolated benefit in this context. Olive oil, bluefish, almond milk and rice all have known anti-inflammatory effects in the gut mucosa[108]. A recent prospective cohort study with a dietary intervention based on the Mediterranean diet[146] demonstrated a significant reduction of malnutrition-related parameters and a spontaneous improvement of disease activity and inflammatory markers after 6 mo.

### Gluten-free diet

Scientific evidence related to the use of a gluten-free diet in active IBD is scarce (cross-sectional reports) and there are no reported interventional studies. Nevertheless, is the most widely used for IBD patients in order to relieve gastrointestinal symptoms[113]. Due to a lack of high-quality prospective clinical studies, though, the current data do not support the universal use of a gluten-free diet in IBD[147].

**Table 2 Dietary intervention in inflammatory bowel disease**

| Intervention feature | Prevent IBD | Maintain remission | Treat IBD |
|---|---|---|---|
| Protein intake | Limit red meat consumption | - | - |
| Fat intake | Limit 6-PUFA and trans-saturated fatty acid consumption | - | - |
| Fiber intake | Not limited | - | - |
| Low-residue diet | - | No recommendation[1] | - |
| Semi-vegetarian diet | - | No recommendation | - |
| Low-FODMAPs diet | - | Optional (if IBS symptoms) | No recommendation |
| Anti-inflammatory diet | - | No recommendation | - |
| Mediterranean diet | - | Optional | No recommendation |
| Specific carbohydrate diet | - | No recommendation | No recommendation |
| Autoimmune diet (Paleo diet) | - | No recommendation | - |
| Partial enteral diet | - | Optional | No recommendation |
| Exclusive enteral nutrition | - | - | First-line in children with active CDOptional in active CD[2]; No recommendation in UC |
| Crohn's disease exclusion diet | - | - | No recommendation |
| Gluten-free diet | - | - | No recommendation |
| Caloric restrictions | - | - | No recommendation |

[1]Except in intestinal strictures.
[2]Firstline in adults (only in Asian countries).
CD: Crohn's disease; FODMAPs: Fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; IBD: Inflammatory bowel disease; IBS: Irritable bowel syndrome; PUFA: Polyunsaturated fatty acid; UC: Ulcerative colitis.

### *Caloric restriction*

Different types of caloric restriction diet like periodic fasting and fasting-mimicking diets (also known as FMDs) have been shown to be effective in increasing healthy lifespan, as therapies in mouse models of some diseases can reduce cancer incidence and aging-associated immunosuppression or immunosenescence, an hematopoietic stem-cell-based regeneration[148,149]. Cycles of FMD ameliorate intestinal inflammation, promote intestinal regeneration, and stimulate the growth of protective gut microbial populations in a mouse model displaying symptoms and pathology associated with IBD. FMD could be a safe, feasible and effective option in reducing systemic inflammation and the consequent high levels of immune cells in humans, but these findings need to be tested in randomized clinical trials.

### *IGG4 exclusion diet*

The IgG4 exclusion diet is a personalized/customized IBD patient diet, in which the patient is tested for IgG4 antibodies to 14 specific food antigens and the four most reactive foods then excluded for 4 wk; notably, beef, pork and egg are most commonly excluded[100,150]. This strategy demonstrated significant improvements in clinical activity and quality of life in a randomized controlled trial[151].

## CONCLUSION

Dietary habits and hygiene conditions are powerful factors influencing microbiota [61]. Changes in dietary patterns in western societies could lead to dysbiosis[62], an etiologic factor that could explain the significant incidence of IBD[11] in those countries.

An excessive and unhealthy consumption of sugar and animal fat and a low-vegetable and low-fiber diet are risk factors for IBD appearance[54]. Regarding other diets, different dietary approaches have been described but with very poor scientific evidence, like the low-fat, fiber-limited exclusion (known as LOFFLEX) dietary protocol which uses an elemental formula to induce remission in CD, a diet with carbohydrate exclusions[100], or the Paleo diet, based on an evolutionary hypothesis that the digestive tract is insufficiently evolved to handle foods resulting from modern agricultural techniques and promoting the intake of lean, non-domesticated meats and non-cereal plant-based foods[111], as can be seen in Table 2. One important counterpart is the potential of creating deficiencies of particular nutrients.

A recent Cochrane revision[152] values the effect of low refined carbohydrates, low microparticle diet, low calcium diet, symptom-guided diet, and a highly restricted organic diet on inducing remission in active CD, concluding that there are insufficient data for its recommendation in this context as well in UC considering uncertainty whether symptom-guided diets improve the induction of remission. As undernutrition is common in IBD, the use of restrictive diets should be supervised by a dietitian who is part of a wider multidisciplinary care team.

Ultimately, there is not enough scientific evidence to suggest a specific diet to prevent and maintain remission in IBD, except for that of EN. Patients should be advised to pursue a healthier diet, consuming a well-balanced diet containing predominantly fruits and vegetables and avoiding, as much as possible, processed foods and foods identified by the patient as prejudicial, capable of worsening symptoms, or even triggering flares.

Further high-quality research studies of various dietary interventions that may induce and maintain remission in active IBD are needed, as well as to answer the many questions that remain about dietary interventions from patients in flare and quiescent states of their illness.

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