

THE INTESTINAL MICROBIOTA AND THE ROLE OF PROBIOTICS IN IRRITABLE BOWEL SYNDROME: a review

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Received 14/7/2015
Accepted 13/8/2015

ABSTRACT - Irritable bowel syndrome is a common, chronic relapsing gastrointestinal disorder that affects 7%–22% of the population worldwide. According to Rome III Criteria, the disorder is defined by the coexistence of abdominal discomfort or pain associated with an alteration in bowel habits. Its pathophysiology is not completely understood but, in addition to some important abnormalities, the disturbed intestinal microbiota has also been described supported by several strands of evidence. The treatment of irritable bowel syndrome is based upon several therapeutic approaches but few have been successful or without adverse events and more recently the gut microbiota and the use of probiotics have emerged as a factor to be considered. Probiotics are live micro-organisms which when consumed in adequate amounts confer a health benefit to the host, such as Lactic bacteria among others. An important scientific rationale has emerged for the use of probiotics in irritable bowel syndrome, although the data regarding different species are still limited. Not all probiotics are beneficial: it is important to select the specific strain which should be supported by good evidence base. The mechanisms of action of probiotics are described and the main strains are quoted.

HEADINGS - Irritable bowel syndrome. Microbiota. Therapeutics. Probiotics.

INTRODUCTION

The commensal bacteria that normally colonize the gastrointestinal tract (previously referred to as the gut flora but now included in the term microbiota) play a critical role in human health and have been considered an important factor in the pathophysiology of some digestive disorders. This narrative review considers recent advances in our understanding of the gut microbiota, as well as their interactions with the host, in the pathophysiology of irritable bowel syndrome (IBS) and analyzes the role of probiotics in the management of IBS.

To achieve a comprehensive review the relevant literature was assessed in Pubmed, Medline and other online sources using the following search terms: probiotics, irritable bowel syndrome, gastrointestinal, enteric flora, spastic colon, gut microbiota, gut microflora, diarrhea, constipation, motility, functional disorders, dietary guidelines.

IRRITABLE BOWEL SYNDROME

Definition and classification

IBS is defined by the coexistence of abdominal

discomfort or pain associated with an alteration in bowel habits. The diagnostic criteria currently used in clinical research and, to some extent in clinical practice, are the Rome III criteria⁽³⁴⁾. (Figure 1). IBS is a common, chronic, relapsing and remitting gastrointestinal disorder estimated to affect 7%–22% of the general worldwide population^(28, 31).

Recurrent abdominal pain or discomfort* at least 3 days per month in the last 3 months** associated with 2 or more of the following:

1. Improvement with defecation
2. Onset associated with a change in frequency of stool
3. Onset associated with a change in form (appearance) of stool

FIGURE 1. Rome III criteria for IBS⁽³⁴⁾.

* Discomfort means an uncomfortable sensation not necessarily described as pain. In clinical trials, a pain and/or discomfort frequency of at least 2 days/week during screening evaluation is needed for subject eligibility.

** Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.

Declared conflict of interest of all authors: none

Disclosure of funding: no funding received

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IBS is commonly diagnosed based upon these symptom criteria and in the absence of alarm signals. The cardinal symptom in IBS is abdominal pain occurring in association with an alteration in bowel habit; diarrhea and/or constipation. Accordingly, given that pain is a defining feature, painless, unexplained diarrhea or constipation would not be included in the definition of IBS. Bloating is reported by the majority of patients with IBS and may be associated with visible abdominal distention⁽³¹⁾. Complete details on the diagnostic approach to IBS diagnosis are beyond the scope of this paper; the common clinical features supporting the diagnosis of IBS are presented in Figure 2.

- Presence of Rome III Criteria (Figure 1)
- No alarm features
- Bloating and/or distension
- Variability of symptoms over time
- Exacerbations triggered by life events and stressful situations
- Symptoms exacerbated by eating
- Psychiatric comorbidity (depression, anxiety and somatoform disorders)

FIGURE 2. IBS diagnosis: clinical features supportive of IBS

The American College of Gastroenterology IBS Task Force recommended that diagnostic testing (blood tests, colonoscopy, celiac disease serology, etc) should not be performed on a routine basis on patients with typical IBS symptoms, except when alarm features are present^(3, 16). However, in some cases and in certain contexts, the differential diagnosis of IBS from other intestinal disorders can be difficult. In such instances it is important to consider, among others, enteric infections and infestations, food intolerance, inflammatory bowel disease, adverse drugs reactions (e.g. to antibiotics, tricyclic antidepressants, proton pump inhibitors) and small bowel bacterial overgrowth.

In developing a management strategy in IBS it is important, where possible, to define the predominant bowel pattern. Accordingly, four IBS sub-types have been proposed by the Rome Foundation Committee on functional bowel disorders (Figure 3):

- Constipation predominant IBS (IBS-C);
- Diarrhea-predominant IBS (IBS-D);
- Mixed IBS (IBS-M);
- Unsubtyped IBS.

1. IBS-C
 - Hard or lumpy stools $\geq 25\%$ of bowel movements
 - Loose (mushy) or watery stools $< 25\%$ of bowel movements
2. IBS-D
 - Loose (mushy) or watery stools $\geq 25\%$ of bowel movements
 - Hard or lumpy stools $< 25\%$ of bowel movements
3. IBS-M
 - Hard or lumpy stools $\geq 25\%$ of bowel movements
 - Loose (mushy) or watery stools $\geq 25\%$ of bowel movements
4. Un-subtyped IBS

FIGURE 3. IBS subtype classification according to bowel habit⁽³⁴⁾

The importance to society of IBS rests, not only in its high prevalence but also, for some affected individuals, on the occurrence of very bothersome symptoms which significantly impact on quality of life and social functioning and, as a consequence, impose a substantial economic impact on health-care systems and the community at large⁽⁴⁹⁾. Precise, early diagnosis will minimize exposure to unnecessary and potentially risky investigations and may alleviate suffering and improve quality of life.

Pathophysiology

As a multifactorial functional disorder, the pathophysiology of IBS is not completely understood, but it is commonly viewed as representing dysregulation along the brain-gut axis, which may include abnormalities at any one or more levels in the enteric, autonomic and/or central nervous systems, or altered interactions between these systems⁽⁵³⁾. Peripheral contributors to IBS symptomatology may include abnormal motility⁽⁴⁰⁾, a dysregulated intestinal immune response⁽⁷⁾, low grade inflammation, altered gastrointestinal permeability⁽⁷²⁾ and a disturbed intestinal microbiota⁽⁷²⁾. Of late, considerable interest has surrounded the possibility that intestinal bacteria could play an important role in triggering symptoms and even in the basic pathophysiology of IBS.

A role for the microbiota in IBS is, indeed, supported by several strands of evidence that include: differences in the colonic microbiota between IBS and non-IBS populations, the development of IBS in the aftermath of infectious gastroenteritis, symptomatic responses to antibiotic, prebiotic and probiotic administration and, more recently, by anecdotal reports of responses to fecal microbial transplantation^(14, 21, 30, 66). Perhaps the most convincing illustration of the role of bacteria in IBS is provided by observations that indicate that the risk for IBS is increased sevenfold in patients who have previously experienced an infectious gastroenteritis⁽²¹⁾. Indeed, it would appear that any intervention that can lead to changes in intestinal ecology may lead to the occurrence of IBS and its discomforting symptoms⁽⁴⁾.

In assessing the role of any putative pathophysiological factor in IBS one must bear in mind the potential impact of an important confounder: co-morbid psychopathology. Co-morbid depression and anxiety, so common in IBS, can modulate and even intensify the patient's perception of their symptoms⁽⁴⁾, increase the likelihood of medical consultation and investigation and even impact directly on many of the aforementioned factors thought relevant to the pathophysiology of IBS.

Treatment

The ideal therapeutic approach to any disease or disorder is to consider its pathophysiology and how direct therapy accordingly. However, given its heterogenous phenotype, varying presentation, broad range of severity and, undoubtedly, multifactorial pathophysiology, this approach is not possible in IBS. Given a multitude of possibly relevant therapeutic

targets, a simple, unitary approach is currently impossible; not surprisingly many therapeutic approaches have been proposed but few have been very successful or without adverse events (Figure 4).

Treatment approach	Comments
Diet and dietary manipulations	FODMAP restricted diet may be beneficial to IBS-C. FODMAP: rapidly fermentable, short-chain carbohydrates, present in apples, pears, mango, lactose, fructose sweeteners, etc.
Fiber and bulking agents	Soluble fibers and bulking agents may be effective in the treatment of IBS-C. Bulking agents include psyllium, methyl-cellulose and polycarbophyl.
Antispasmodics	Pinaverium bromide, mebeverine, trimebutine and some others may be effective to reduce the pain as well as diarrhea.
Loperamide	Opioid antimotility drug may be effective in patients with IBS-D.
Antidepressants and psychological therapies	By different mechanisms, desipramine, amitriptyne, fluoxetine, paroxetine, citalopran and some psychological therapies (cognitive behavioral therapy, dynamic psychotherapy) may be effective treatments for IBS.
Rifaximin	Is a semi-synthetic derivative of rifamycin with a benzimidazole ring that prevents its systemic absorption. It may be effective in patients with IBD-D.
5-HT ₃ antagonists and 5-HT ₄ agonists	Alosetron, cilansetron, lubiprostone may be effective in the treatment of IBS.
Probiotics	Most probiotics are lactic acid-producing bacteria. Probiotics may be beneficial in the treatment of IBS.
Acupuncture	By proposed different mechanisms, acupuncture treatment may benefit IBS symptoms.
Hypnotherapy	Gut-directed hypnotherapy may have durable efficacy in patients with IBS.
Physical activity	Increased physical activity may improve symptoms in IBS. Physically active patients with IBS may face less symptom deterioration compared with physically inactive patients.

FIGURE 4. Some treatment approaches to IBS^(14, 20, 26, 42, 47, 56, 59, 73)

Given the aforementioned interest in the gut microbiota and its interactions with the host in this common disorder, the gut microbiota, through the use of antibiotics, prebiotics and probiotics, has emerged as a factor to be considered in the treatment of IBS. Two non-pharmacological approaches have emerged as being of particular interest: dietary and lifestyle changes^(22, 41, 54) and the use of probiotics^(22, 66, 72).

THE GUT MICROBIOTA

Humans are colonized with microorganisms that inhabit the skin, oral cavity, vagina and gastrointestinal tract from birth⁽³³⁾. In the gastrointestinal tract, 500 to 1,000 different species of bacteria coexist (gut microbiota), with the precise composition of the gut microbiome varying between individuals⁽¹⁸⁾. The adult human gastrointestinal tract is estimated to contain 10¹⁴ viable microorganisms, which is 10 times the number of eukaryotic cells found within the human body⁽⁶⁴⁾. This is a complex ecosystem with the largest population of microorganisms in the gastrointestinal tract residing in the lumen and within, or adjacent to, the mucus layer of the colon⁽¹⁹⁾.

The development of the gut microbiota starts at birth. Its composition is influenced by both the mode of delivery and how the infant is fed: the gut microbiota of breastfed babies, for example, being mainly dominated by *Bifidobacteria*, in comparison to babies nourished with infant formulas. Early environmental exposure is of primary importance in shaping the microbiota⁽⁷¹⁾; by 3-4 years of age the microbiota becomes stable and similar to that of adults.

In adults, the composition of the microbiota is influenced by such factors as diet, geographic location and the use of oral antibiotics⁽²⁴⁾. It is also thought that further changes occur in old age.

The microbiota performs many critical roles, such as the maintenance of mucosal integrity, the protection against pathogens (by means of bacterial antagonism and priming of host immune responses⁽²⁴⁾), immune system modulation, synthesis of vitamins and cholesterol, metabolism of bile acids and indigestible dietary components. With the intestinal epithelium, the microbiota of the gut provides the first line of defense against orally introduced invaders⁽¹⁴⁾.

A relationship between the microbiota and intestinal motility has also been described⁽⁵⁷⁾ and may be mediated through substances released by bacteria, by the end products of bacterial fermentation, through the effects of cytokines and chemokines elaborated as part of the immune response, as well as via the release of intestinal neuroendocrine factors^(18, 36).

Dysbiosis (also called *dysbacteriosis*) refers to microbial imbalance on or inside the body, and is most commonly reported in terms of changes in the digestive tract. Many factors can negatively impact on gut commensals and promote dysbiosis, such as antibiotic use, psychological and physical stress, radiation, altered peristalsis and dietary changes. It should be remembered that although dysbiosis has been recognized in various intestinal diseases, in most cases a definitive cause-and-effect relationship remains to be established.

The gut microbiota is considered to be an important factor in the pathophysiology of IBS, either alone or in combination with other factors^(16, 18, 55). In some studies, specific changes in the microbiota have been associated with particular IBS presentations and/or phenotype⁽²⁴⁾. Commensal function though especially relevant to IBS will be explored further in the discussion of probiotics in IBS.

PROBIOTICS

Probiotics are live micro-organisms which when consumed in adequate amounts, confer a health benefit to the host⁽²⁷⁾.

Most probiotic bacteria are lactic bacteria (lactic acid-producing bacteria), that include *Lactobacillus*, *Lactococcus*, *Bifidobacterium* and *Streptococcus*⁽⁶³⁾. This group of bacteria has the capacity to anaerobically digest dietary sugars and produce lactic acid. Probiotic properties have also been ascribed to the yeast *Saccharomyces cerevisiae ssp boulardi* (*S. Boulardi*) and other species of bacteria of the genera *Escherichia* and *Bacillus*. The natural ecosystem of lactic acid bacteria is the digestive tract.

The use of probiotics has been extensively investigated and efficacy, to a greater or lesser extent, demonstrated in a number of intestinal disorders, as presented in Figure 5. However, not all probiotics all beneficial in all circumstances: it is important to carefully select the specific strain which is supported by a good evidence base for a given indication. A large volume of *in vitro* and *in vivo* data has clearly shown that the various biological effects of probiotics are strain specific and it is not possible to extrapolate efficacy or failure from one strain to another, unless a common mechanism of action has been described and appropriate clinical studies performed⁽⁶⁰⁾.

Disease	Effect
Ulcerative colitis	Promotes maintenance of remission (children) ⁽²⁵⁾
Irritable bowel syndrome	There is reasonable evidence for efficacy on abdominal pain, bloating, diarrhea and constipation ^(5, 9, 10, 16, 17, 39, 50, 68)
<i>Clostridium difficile</i> infection	May prevent infection and recurrence of infection ⁽⁵⁷⁾
Antibiotic-associated diarrhea	Prevention of diarrhea ⁽⁶²⁾ and reduction of symptoms ⁽³⁵⁾
Necrotizing enterocolitis	Reduces mortality ⁽²⁾
Infectious diarrhea	Decrease the severity and duration of diarrhea ^(8, 70)

FIGURE 5. Effects of probiotics in randomized, clinical trials of intestinal disease^(19 mod.)

Probiotic mechanisms of action

Not all the mechanisms of action of the probiotics are well understood and some have been primarily, if not exclusively, documented *in vitro* or in animal models studies. Care should be exerted in extrapolating these results to man. Taking into consideration such limitations, these are some known modes of action of probiotics that may be especially relevant to IBS.

• Actions in the intestinal lumen and on the mucosal surface

One mode of action of a probiotic may relate to its effects on the host's microbiota. This includes the so called "barrier" effect whereby resistance to colonization is exerted against pathogenic bacteria thus limiting or even preventing their colonization of the host. Bacterial inhibition by probiotics may be mediated through their production of bacteriocins or biosurfactants with antimicrobial activity or to the elaboration of metabolites that induce a decrease in luminal pH and, thereby, an environment which is less favourable for the growth of certain bacteria⁽⁶⁾. In addition to the production of antimicrobials, probiotics may also modify the metabolic behaviour of the indigenous microbiota⁽⁶⁷⁾. Paneth cells, stimulated by probiotics, produce antimicrobial peptides and mucus that function to prevent direct contact between luminal pathogens and the epithelium. All of these effects could be important in the prevention of post-infections IBS.

Probiotics can also enhance epithelial integrity by promoting mucus secretion, the production of defensins and the synthesis of proteins critical to the structure of tight junctions between enterocytes; effects that collectively improve gut barrier function, whose function may be compromised in IBS^(6, 55, 60, 63, 67).

Metabolic effects, though little studied in the context of IBS, could also be relevant. Thus changes in bacterial fermentation could impact on "gas-related" symptoms and modulation of bile salt conjugation influence stool volume and consistency.

• Immune effects and systemic actions

Probiotics modulate the immune system and, in particular, that important population of immune cells that exist in the small bowel, the gut-associated (or mucosa-associated) lymphoid tissue (GALT or MALT). Peyer's patches constitute a gateway for entry for antigens and the activation of immune responses involves recognition of antigen by the specific receptors on innate immune cells, epithelial cells, dendritic cells and macrophages. Some probiotics protect against pathogen-induced tissue damage by stimulating induction of regulatory T-cells, as has been described with the probiotic *B. Infantis* 35624 in mice⁽⁵²⁾. These receptors are recognized by structural components on the surface of the micro-organisms, the microbial associated molecular patterns (MAPS), which may interact with the intestinal epithelium and stimulate the cells of the intestinal immune system at the lamina propria level⁽⁴²⁾. Subsequently, T-cells are activated and the differentiation of T-helper lymphocytes promoted with the production of anti-inflammatory cytokines. Various probiotics and, especially, lactic acid bacteria, may exert differing biological effects depending on the cytokine profile they induce⁽⁴²⁾. Furthermore, effects may be local, limited to the stimulation of the intestinal immunity, or may be systemic⁽⁶⁷⁾. Given that a number of immunological changes have been demonstrated, albeit not consistently, in IBS, any one or combination of these immunological effects of probiotics could be relevant to their benefits.

PROBIOTICS IN GASTROENTEROLOGY

Probiotic effects are strain dependent. A wide range of probiotics are currently available as presented in Figure 5. In this regard, it is important to emphasize that the clinical efficacy of a probiotic product is determined by factors such as the dosage (number of colony forming units, cfu's), the formulation, the viability (outside and inside the intestine), the method of dosing and the specific microbial species and strain(s) that it includes. A good product should be characterized at the level of the genome, its range of biological effects defined and its stability in the conditions and over the duration of time that it is recommended to be stored, validated⁽⁶¹⁾.

Currently, gastrointestinal disorders for which the use of probiotics has been proposed include: acute infectious diarrhea^(11, 65), traveler's diarrhea^(38, 65), antibiotic-associated diarrhea^(37, 69), constipation^(17, 29, 46), necrotizing enterocolitis⁽⁴⁵⁾, inflammatory bowel disease^(15, 23, 25, 44) and IBS^(7, 37, 66, 72) (Figure 6). It must be emphasized that not all of these indications are supported by compelling clinical data.

Lactobacillus acidophilus NCFM
L. acidophilus LA5
L. acidophilus LA14
L. acidophilus ATCC SD5221
L. acidophilus R0052
L. acidophilus LB
L. acidophilus CUL 60
L. acidophilus CUL 21
L. rhamnosus HN001 (DR20)
L. rhamnosus R0011
L. paracasei CRL 431
L. fermentum VR1003 (PCC)
L. reuteri RC-14
L. reuteri ATCC 55739
L. paracasei F19
L. casei Shirota
L. casei DN-114001
L. rhamnosus GR-1
L. rhamnosus 271
L. rhamnosus GG ("LGG")
L. rhamnosus LB21
L. johnsonii Lj-1
L. plantarum 299v
L. salivarius UCC118

Lactococcus lactis L1A

Bacillus coagulans BC3
B. infantis 35264
B. longum BB536
B. animalis DN-173 01

Saccharomyces cerevisiae boulardii

Bifidobacterium animalis lactis Bi-07
B. lactis HN019 (CR10)
B. lactis Bb-12
B. lactis CUL 34
B. lactis HN019
B. bifidum CUL 20
B. infantis 35264
B. animalis DN-173 010

FIGURE 6. Probiotics strains available in most countries^(61mod.,50mod.).

* This figure is only a reference and may not include all strains/mixtures currently available.

Probiotics in IBS

IBS is a good example of the limitations of clinical data; though many studies have been published, few have achieved standards appropriate for clinical trials in man. Recommendations for probiotic use in man continue to be constrained by poor methodological standards in many studies resulting in low levels of evidence and, at best, conditional recommendations. Recognizing these limitations, the observations included here represent a summary of an extensive and updated review of the current literature of the role of the probiotics in the therapeutic approach of the IBS.

Studies in patients with IBS have shown alterations in microbiota such as an increased ratio of *Firmicutes* to *Bacteroides* and a reduction in *Lactobacillus* or *Bifidobacterium* species⁽⁵⁸⁾. It is known that *Lactobacillus* and *Bifidobacterium* species have anti-inflammatory effects in the intestine and their depletion could contribute to low-grade inflammation⁽⁵¹⁾. Proinflammatory cytokine levels (e.g. interleukin (IL)-6, IL-8, tumor necrosis factor- α , and IL-1 β) are elevated in the systemic circulation of patients with IBS⁽¹³⁾; phenomena that may be triggered and perpetuated by the alterations in the gut microbiota observed in IBS, as evidenced by experiments in germ-free animals⁽⁴⁸⁾.

Taking into consideration the large number and highly variable characteristics and properties of microorganisms that have been studied, it may be inappropriate to combine the results of different trials⁽⁴⁾. Furthermore, probiotic formulations may contain a single strain or a combination of multiple species and/or strains. In IBS, the most studied strains belong to *Lactobacillus sp.* and *Bifidobacterium sp.* As such, a consistent trend toward an improvement of bloating and constipation has been reported with the use of *Bifidobacterium infantis*, *B. brevis* and *B. Animalis* and abdominal pain, bloating, diarrhea and constipation have been shown to improve with *Lactobacillus plantarum*, *L. casei*, *L. reuteri*, *L. acidophilus*, *L. Rhamnosus*^(1, 9, 12, 17, 32, 51, 68, 74). *Bifidobacterium infantis* 35624 has been shown to, not only improve individual symptoms, but also produce global improvement^(5, 51, 74).

Management strategies in IBS are highly variable (Figure 4) and may be driven by illness severity, predominant symptoms and physician preference. In this context, certain probiotics, by virtue of their safety and tolerability are options to consider as they have been shown to improve global symptoms, bloating and flatulence. A number of reviews^(5, 17, 39, 46, 50) as well as a recent well conducted systematic review and meta-analysis have demonstrated that probiotics have a therapeutic benefit in the IBS and may improve global symptoms, abdominal pain, bloating and flatulence⁽¹⁷⁾ although the quality of evidence, according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) assessment, was low.

CONCLUSIONS

The relative lack of effective therapeutic options for the treatment of IBS opens the way for new approaches and, among these, probiotics, which are generally regarded as safe and may act on the global symptoms, bloating and flatulence, which have considerable appeal. Furthermore, a rather impressive scientific rationale has emerged for the use of probiotics in gastrointestinal conditions, including IBS. Such data is, of course, highly strain specific⁽¹⁰⁾. However,

recommendations regarding individual species or strains continue to be limited by a lack of data and the poor quality of much of the available data⁽¹⁷⁾.

Authors' contributions

Moraes-Filho JP: acquisition of data; interpretation of data; drafting of the manuscript. Quigley EMM: critical revision of the manuscript for important intellectual content; interpretation of data; supervision of the final manuscript.

The authors approved the final version of the manuscript.

Moraes-Filho JP, Quigley EMM. Microbiota intestinal e função dos probióticos na síndrome do intestino irritável: uma revisão. *Arq Gastroenterol.* 2015,52(4):xxx.

RESUMO - A síndrome do intestino irritável é uma enfermidade crônica recidivante, que afeta 7%-22% da população mundial. Segundo os denominados Critérios de Roma III, a síndrome do intestino irritável é definida pela coexistência de dor ou desconforto abdominal associados à alteração do hábito intestinal. A fisiopatologia não é completamente esclarecida mas, além algumas importantes alterações descritas, alterações na microbiota intestinal têm também sido relatadas, suportadas por diferentes graus de evidência. O tratamento da síndrome do intestino irritável é baseado em diversas abordagens terapêuticas, mas, poucas tem resultados efetivamente satisfatórios ou sem a ocorrência de eventos adversos. Mais recentemente, a microbiota intestinal e o uso de probióticos têm sido considerados como fatores importantes a serem considerados. Probióticos são microrganismos vivos que, quando consumidos em quantidades adequadas, contribuem para a saúde do hospedeiro, como por exemplo, *Lactobacillus acidophilus*, dentre outras. Importantes justificativas científicas têm sido citadas sobre o uso de probióticos na síndrome do intestino irritável, embora sejam ainda limitados dados sobre as diferentes espécies bacterianas constituintes dos probióticos. Não todos os probióticos são benéficos nesse caso: é importante selecionar as cepas específicas as quais devem ser suportadas por evidências científicas satisfatórias. Os mecanismos de ação dos probióticos são descritos e citadas as principais cepas.

DESCRITORES - Síndrome do intestino irritável. Microbiota. Terapêutica. Probióticos.

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