



REVIEW IN GASTROENTEROLOGY

Review of the role of probiotics in gastrointestinal diseases in adults[☆]



Juan José Sebastián Domingo

Servicio de Aparato Digestivo, Hospital Royo Villanova, Zaragoza, Spain

Received 12 October 2016; accepted 2 December 2016

Available online 31 May 2017

KEYWORDS

Probiotics;
Lactobacillus;
Bifidobacterium;
Clostridium difficile;
Gastrointestinal
diseases;
Diarrhoea;
Pouchitis;
Irritable bowel
syndrome;
Constipation;
Helicobacter pylori;
Colitis, Ulcerative;
Crohn disease

Abstract

Background: Probiotics may act as biological agents that modify the intestinal microbiota and certain cytokine profiles, which can lead to an improvement in certain gastrointestinal diseases.

Objectives: To conduct a review of the evidence of the role of probiotics in certain gastrointestinal diseases in adults.

Search methods: Review conducted using appropriate descriptors, filters and limits in the PubMed database (MEDLINE).

Selection criteria: The MeSH terms used were *Probiotics* [in the title] AND *Gastrointestinal Diseases*, with the following limits or filters: *Types of study:* Systematic Reviews, Meta-Analysis, Guideline, Practice Guideline, Consensus Development Conference (and Consensus Development Conference NIH), Randomised Controlled Trial, Controlled Clinical Trial and Clinical Trial; *age:* adults (19 or older); *language:* English and Spanish; *in humans*, and with at least one abstract.

Data collection and analysis: Full texts of all the Systematic Reviews and meta-analyses directly related to the review's objective were obtained, as well as the Randomised Controlled Trials of the studies that were considered relevant and of sufficient quality for this review.

Main results: Certain probiotics, different for each process, have proven to be effective and beneficial in cases of acute infectious diarrhoea, antibiotic-associated diarrhoea, *Clostridium difficile*-associated diarrhoea, pouchitis and *Helicobacter pylori* infection eradication.

Authors' conclusions: Although some probiotics have not demonstrated any benefit, there are certain gastrointestinal diseases in which the use of probiotics, true biological agents, can be recommended.

© 2017 Elsevier España, S.L.U., AEEH and AEG. All rights reserved.

[☆] Please cite this article as: Sebastián Domingo JJ. Revisión del papel de los probióticos en la patología gastrointestinal del adulto. Gastroenterol Hepatol. 2017;40:417–429.

E-mail address: jjsebastian@salud.aragon.es

PALABRAS CLAVE

Probióticos;
Lactobacillus;
Bifidobacterium;
Clostridium difficile;
 Diarrea;
 Reservoiritis;
 Síndrome del
 intestino irritable;
 Estreñimiento;
Helicobacter pylori;
 Colitis ulcerosa;
 Enfermedad de Crohn

Revisión del papel de los probióticos en la patología gastrointestinal del adulto**Resumen**

Antecedentes: Los probióticos pueden actuar como agentes biológicos que modifican la microbiota intestinal y ciertos perfiles de citoquinas, lo que puede conllevar una mejora en ciertos procesos gastrointestinales.

Objetivos: Realizar una revisión basada en la evidencia del papel de los probióticos en determinadas patologías gastrointestinales del adulto.

Métodos de búsqueda: Revisión realizada utilizando los descriptores, filtros y límites adecuados en la base de datos PubMed (MEDLINE).

Criterios de selección: Se han empleado los términos MeSH *Probiotics* [en el título] AND *Gastrointestinal Diseases*, con los siguientes límites o filtros: *tipos de estudios:* Systematic Reviews, Meta-Analysis, Guideline, Practice Guideline, Consensus Development Conference (y Consensus Development Conference NIH), Randomised Controlled Trial, Controlled Clinical Trial y Clinical Trial; *edad:* adultos (19 o más años); *idioma:* en inglés y español; *en humanos*, y que dispusieran, al menos, de un *abstract*.

Recogida y análisis de datos: Se recuperaron los textos completos de todas las revisiones sistemáticas y metaanálisis directamente relacionados con el objetivo de la revisión, así como los ensayos clínicos aleatorizados de los estudios que se consideraron relevantes y de calidad para realizar esta revisión.

Resultados principales: Determinados probióticos, diferentes para cada proceso, se han demostrado eficaces y beneficiosos en caso de diarrea aguda infecciosa, diarrea asociada a antibióticos, diarrea asociada a *Clostridium difficile*, pouchitis y en la erradicación de la infección por *Helicobacter pylori*.

Conclusiones de los autores: Hay ciertas patologías gastrointestinales en las que se puede recomendar el uso de los probióticos, verdaderos agentes biológicos, y otras en las que no se ha demostrado beneficio.

© 2017 Elsevier España, S.L.U., AEEH y AEG. Todos los derechos reservados.

The human gastrointestinal tract (GIT) houses the *gastrointestinal microbiome*, a complex and dynamic microbial ecosystem, which is estimated to feature more than 400 different species of bacteria,¹ and which is responsible for important functions, including metabolic activities, trophic effects on the intestinal epithelium and interactions with the host immune system.²

The term “*microbiome*” (previously known as “*intestinal flora*”) refers to all microbes (bacteria, fungi, viruses, etc.) and their genetic components and environmental interactions in a particular environment.³ The term was added to the MeSH database in 2014.

The microbiota, the community of live micro-organisms residing in a particular ecological niche, such as the human large bowel (colon), acts as a barrier and prevents the colonisation of opportunistic and pathogenic micro-organisms.² The intestinal microbiome is essential in the interaction between the intestinal epithelium and the mucosal immune system, and affects the development and homeostasis of normal mucosal immunity.³

Probiotics are defined as “live microorganisms which when administered in adequate amounts confer a health benefit on the host”.^{2–10} This is the definition proposed by the United Nations (UN) for the Food and Agriculture Organisation (FAO) and the World Health Organisation (WHO). The Royal Academy of the Spanish Language (RAE) has not yet added the term “probiotic” to its dictionary.

Probiotics may be ingested in the form of any food supplement or as drugs.^{3,5,7} However, most commercial products are derived from food sources, especially cultured and fermented dairy products.⁴ They are available in multiple formulations that may contain just one or a combination of several probiotics, whose quantity varies widely from one product to another.³

The micro-organisms that are most commonly used as probiotics belong to the group of lactic acid bacteria (*Lactobacillus*) and *Bifidobacterium*. These are important constituents of the normal human GI microbiota.^{1,7} Other probiotics that are less commonly used but are also being researched due to their possible probiotic functions are strains of *Streptococcus*, *Escherichia coli* (*E. coli*) and *Bacillus*.^{2–4} Some non-pathogenic yeasts, such as *Saccharomyces boulardii* (*S. boulardii*) (from *Litchi chinensis*, a tropical fruit originating in southern China) that are not normally found in the GIT are also used.^{1,10}

Probiotics improve the nutritional and microbiological balance of the GIT.¹ They act as vectors that deliver their active components to several target sites in the GIT.⁶ Their destinations and effects vary by strain.⁷ Most effects occur only when live micro-organisms are ingested⁶; however, this may not always be necessary to achieve benefits.⁴

For a probiotic to be effective, it should survive the acidic environment of the stomach and transit through the bowel. This explains, in part, the requirement that

probiotics should be ingested in high concentrations.³ Their survival during GI transit varies widely,^{3,4,6} since it depends on genera, species, strains, dose ingested, host-related factors (acid, biliary, and pancreatic secretions) and vector-related factors (foods, microencapsulation).⁶

Probiotics vary in their capacity to resist gastric acid and bile, their capacity to colonise the GIT and to have an influence on cytokines secreted by intestinal epithelial cells. As a result, the clinical benefits observed in some cannot necessarily be generalised to others.⁴ Their capacity for adhesion to the intestinal mucosa also varies by strain, thereby promoting competitive exclusion of pathogens and immunomodulation.⁶

The appropriate probiotic for each indication should be selected.³ Although probiotics are perceived and cause responses by immune and/or intestinal cells, their mechanisms of action are not entirely clear.^{4,8}

The beneficial effects of probiotics on GI function are attributed to normalisation of permeability, restoration of the microbiota, improvement of barrier immune function, down-regulation of the pro-inflammatory immune response and rebalancing of pro-inflammatory and anti-inflammatory cytokines.³

The use of probiotics in different diseases is becoming increasingly widespread. A specific journal called *Probiotics and Antimicrobial Proteins* collects the main research studies being conducted on probiotics. This journal has an impact factor of 1.283.

The beneficial effects of probiotics on gastrointestinal diseases may be considerable (and demonstrated), possible or anecdotal. The gastrointestinal diseases on which probiotics have considerable beneficial effects include acute (viral) gastroenteritis, antibiotic-associated diarrhoea,¹¹ travellers' diarrhoea, pouchitis and irritable bowel syndrome (IBS). Those on which probiotics have possible beneficial effects include chronic idiopathic constipation (CIC; functional constipation, in the Rome IV classification), chronic gastritis due to *Helicobacter pylori* (*H. pylori*) and ulcerative colitis (UC). The benefits of probiotics have been anecdotal in other processes, such as acute pancreatitis, microscopic colitis (collagen), Crohn's disease (CD) and lactose intolerance.³⁻⁶

Review strategy

The literature search was performed in the PubMed database of the US National Library of Medicine (pubmed.gov). To review the scientific evidence, the Medical Subjects Headings (MeSH) terms *Probiotics* [in the title] AND *Gastrointestinal Diseases* were used, with the following limits or filters: *study type*: Systematic Reviews, Meta-Analysis, Guideline, Practice Guideline, Consensus Development Conference (and NIH Consensus Development Conference), Randomised Controlled Trial, Controlled Clinical Trial and Clinical Trial; *age*: adults (19 years of age or older); *language*: English (there are no studies on the general role of probiotics in GI disease in Spanish); *in humans*; and availability of at least an *abstract*.

All this was done according to the recommendations in a study by Shojania,¹² but using the Systematic Reviews tool in addition to the Clinical Queries tool.

With this search strategy, 51 studies were retrieved. Of these, 28 were selected due to their relevance after ruling out childhood processes and others outside of the topics relevant to the review (colon cancer, HIV, surgery, concomitant use with other drugs).

All other studies were selected after searching for evidence with the strategy Probiotics[ti] AND each of the MeSH descriptors of the concrete entities reviewed (Diarrhoea; *Clostridium difficile* [*C. difficile*]; Pouchitis; Irritable Bowel Syndrome; Constipation; *H. pylori*; Colitis, Ulcerative; Crohn's Disease).

As the highest level of evidence and degree of recommendation correspond to systematic reviews (SRs) and meta-analyses (MAs), the most outstanding data and the data most applicable in clinical practice extracted from the evidence used to prepare this manuscript, a total of 33 studies, have been collected in Table 1.

Fig. 1 summarises the search strategy for that evidence and how the evidence used to draft the manuscript was selected.

The use of different probiotics in the groups of gastrointestinal diseases on which they have considerable effects and possible effects, in which they are recommended and are currently being used, are reviewed below, with variable results, as shall be seen.

Disease entities in which probiotics are being used with considerable beneficial effects

Acute infectious diarrhoea

Most studies have been conducted in infants and children. In a SR from the Cochrane database¹³ that analysed 63 studies including a total of 8014 participants, only 352 participants (4.4%) were adults 19 years of age or older. This MA found that probiotics reduce the overall risk of diarrhoea lasting four or more days by 59% and the average duration thereof by 25 h. The two most commonly studied probiotics were *Lactobacillus* GG and *S. boulardii*.

Despite the great variability in the methodological quality of the trials, in general, probiotics, regardless of the strain(s) used, doses, causes (bacterial or viral), seriousness and country of study, demonstrated themselves to be safe and effective in reducing the duration and seriousness of diarrhoea, in addition to preventing the progression of the acute form (<14 days) to the persistent form. This goes against the general consensus that the effects of probiotics are strain-specific and that the results obtained with a probiotic cannot be extrapolated to other organisms, including related strains.¹⁴ Well-designed studies of specific regimens of probiotics in specific contexts are required. These studies must be as homogeneous as possible so that definitive conclusions may be drawn. Even so, the results are encouraging.¹⁵

Antibiotic-associated diarrhoea

A SR of the literature on the use of probiotics in treating antibiotic-associated diarrhoea (AAD) in adults (18–64 years of age) and elderly patients (≥65 years of age) analysed 30

Table 1 SRs and MAs on the use of probiotics in different gastrointestinal processes.

Std.	Type of study	Disease	Probiotics	Effects
13	Cochrane SR (63 RCTs: 56 in children; 7 in adults)	Acute infectious diarrhoea	Mixed. Most with <i>L. rhamnosus</i> GG and <i>S. boulardii</i> and other strains of <i>Lactobacillus</i>	Probiotics appear to be safe and have clear beneficial effects in shortening the duration and reducing the frequency of bowel movements in acute infectious diarrhoea
16	MA (30 RCTs)	Antibiotic-associated diarrhoea	Several strains of <i>Lactobacillus</i> and <i>S. boulardii</i>	Reduce the risk of AAD in adults but not in elderly people
17	SR and MA (82 RCTs)	Antibiotic-associated diarrhoea	Several strains of <i>Lactobacillus</i> and <i>S. boulardii</i>	Reduce the risk of AAD
18	SR and MA (12 RCTs)	Antibiotic-associated diarrhoea	<i>L. rhamnosus</i> GG	Effective in preventing AAD in children and adults
19	SR and MA (21 RCTs)	Antibiotic-associated diarrhoea	<i>S. boulardii</i>	Reduce the risk of AAD in adults and children, and the risk of CDAD
20	SR and MA (2 RCTs)	Antibiotic-associated diarrhoea	Yoghurt (<i>L. delbrueckii</i> , <i>L. bulgaricus</i> and <i>Streptococcus salivarius thermophilus</i>)	Inconsistent effect in preventing AAD
21	Cochrane SR (23 RCTs)	<i>C. difficile</i> -associated diarrhoea	Several strains of <i>Lactobacillus</i> and <i>S. boulardii</i>	Significantly reduce the risk of CDAD
22	SR and MA (20 RCTs)	<i>C. difficile</i> -associated diarrhoea	Several strains of <i>Lactobacillus</i> and <i>S. boulardii</i>	Major reduction in the risk of CDAD
23	SR and MA (26 RCTs)	<i>C. difficile</i> -associated diarrhoea	Several strains of <i>Lactobacillus</i> and <i>S. boulardii</i>	Significant reduction in the risk of CDAD
26	MA (12 RCTs)	Travellers' diarrhoea	<i>S. boulardii</i> and mixture of <i>L. acidophilus</i> and <i>B. bifidum</i>	Significantly prevent travellers' diarrhoea
27	MA (5 RCTs)	Travellers' diarrhoea	Several strains of <i>Lactobacillus</i> and <i>S. boulardii</i>	Are not effective in preventing travellers' diarrhoea
30	MA (23 RCTs)	Pouchitis, ulcerative colitis	VSL#3, <i>E. coli</i> strain Nissle 1917, <i>L. GG</i> , <i>B. longum</i> , alone or in combination with oral 5-ASA	Benefit in inducing UC remission and reducing UC recurrence (improves maintenance of remission) with VSL#3 (also in pouchitis) and <i>E. coli</i> strain Nissle 1917
31	MA (5 RCTs)	Pouchitis	VSL#3 (4 RCTs) and <i>Lactobacillus rhamnosus</i> GG (1 RCT)	Benefit in maintaining remission in patients with an ileal pouch with an ileoanal anastomosis
34	Cochrane SR (11 RCTs)	Pouchitis	<i>Lactobacillus</i> GG VSL#3	<i>Lactobacillus</i> GG was not superior to placebo in inducing remission of acute pouchitis. VSL#3 was more effective than placebo in maintaining remission of chronic pouchitis and preventing pouchitis

Table 1 (Continued)

Std.	Type of study	Disease	Probiotics	Effects
37	SR (19 RCTs, mixed)	Irritable bowel syndrome	Mixed. Several strains of <i>Lactobacillus</i> and <i>Bifidobacterium</i> , VSL#3, yoghurt	Very effective in improving symptoms (NNT = 4). Very promising strategy
38	SR (16 RCTs, mixed)	Irritable bowel syndrome	Mixed. Several strains of <i>Lactobacillus</i> alone and in combination, and several strains of <i>Bifidobacteria</i> alone and in combination; combination of <i>Lactobacillus</i> and <i>Bifidobacteria</i>	Only <i>B. infantis</i> 35,624 causes a significant improvement in abdominal pain and distension, as well as a change in intestinal habits
39	SRs and MAs (14 RCTs, mixed)	Irritable bowel syndrome	Mixed. Several combinations of <i>Lactobacillus</i> , <i>Bifidobacterium</i> , VSL#3	Mixed. Modest improvement in some/all symptoms of IBS, depending on the species/combination used
40	MA (20 RCTs, mixed)	Irritable bowel syndrome	Mixed (23 types). Several strains of <i>Lactobacillus</i> , <i>B. infantis</i> , <i>Streptococcus</i> , VSL#3, mixtures	Overall improvement in IBS symptoms compared to placebo. "It is too soon to recommend their use in clinical practice." 2008
42	SR and MA (43 RCTs, 35 of them with probiotics; mixed)	– Irritable bowel syndrome (and chronic idiopathic constipation or functional constipation)	Mixed (<i>Lactobacillus</i> , <i>Bifidobacterium</i> , <i>Streptococcus</i> , <i>Saccharomyces</i> , <i>Escherichia</i> ; combinations)	Beneficial effects on overall IBS symptoms, on abdominal pain, bloating and flatulence. Prebiotics and symbiotics (limited studies), whose effect on IBS is unknown, are also assessed
46	SR of SRs (9 SRs and 35 RCTs)	Irritable bowel syndrome	Mixed (29 probiotic formulations)	In 2016, no specific probiotic may be recommended for the treatment of IBS in adults "Probiotics are unlikely to provide a substantial benefit in IBS symptoms in adults, although they are safe"
53	MA (10 RCTs) – author's study-	Irritable bowel syndrome	Mixed. Several strains of <i>Lactobacillus</i> and <i>Bifidobacterium</i>	Probiotics improved pain if they contained the species <i>Bifidobacterium breve</i> , <i>B. longum</i> or <i>L. acidophilus</i> . Distension improved if they contained the species <i>B. breve</i> , <i>B. infantis</i> , <i>L. casei</i> or <i>L. plantarum</i> . All species of probiotics evaluated improved flatulence (<i>B. breve</i> , <i>B. infantis</i> , <i>L. casei</i> , <i>L. plantarum</i> , <i>B. longum</i> , <i>L. acidophilus</i> , <i>L. bulgaricus</i> and <i>S. salivarius</i> ssp. <i>thermophilus</i>)

Table 1 (Continued)

Std.	Type of study	Disease	Probiotics	Effects
54	MA (32 RCTs) – author's study-	Irritable bowel syndrome	Mixed. Several strains of <i>Lactobacillus</i> and <i>Bifidobacterium</i> , alone or in combination; <i>E. coli strain Nissle 1917</i> , <i>S. boulardii</i>	Mixtures of <i>B. bifidum</i> BGN4 with <i>B. lactis</i> AD011 and <i>L. acidophilus</i> AD031, and <i>L. casei</i> IBS41 and <i>L. acidophilus</i> SDC 2012 and 2013 showed a significant effect on pain relief in patients with IBS (antinociceptive effect)
58	SR and MA (14 RCTs)	Functional constipation	Mixed. Several strains of <i>Lactobacillus</i> and <i>Bifidobacterium</i>	Probiotics may improve intestinal transit time, frequency of bowel movements and consistency of stools, with <i>B. lactis</i> in particular
59	SR (5 RCTs)	Functional constipation	Several strains of <i>Lactobacillus</i> ; <i>B. lactis</i> and <i>E. coli strain Nissle 1917</i>	The data published to date (2010) do not provide sufficient scientific evidence to support a general recommendation on the use of probiotics in treating functional constipation
63	MA (14 RCTs)	<i>Helicobacter pylori</i> infection (eradication therapies)	Several strains of <i>Lactobacillus</i> (in particular GG and <i>acidophilus</i>), one with <i>Bifidobacterium</i> and <i>S. boulardii</i>	Supplementation with probiotics could be effective for increasing <i>H. pylori</i> eradication rates (85.4% versus 77.6%; OR 1.82), in particular in patients in whom eradication has failed previously
66	SR and MA (45 RCTs)	<i>H. pylori</i> infection (eradication therapies)	Combinations of <i>Lactobacillus</i> + <i>Bifidobacterium</i> + <i>Streptococcus</i> , <i>Lactobacillus</i> or <i>Saccharomyces</i> alone	Increased overall rates of eradication in the probiotic group (82.31%) versus the control group (72.08%)
68	MA (9 RCTs)	<i>H. pylori</i> infection (eradication therapies)	Several types of <i>Lactobacillus</i> alone or in combination with others (<i>Streptococcus thermophilus</i> , <i>Bifidobacterium</i>)	Rates of eradication significantly increased by 17% in the group treated with <i>Lactobacillus</i> alone. With the combination of probiotics they only improved by 2.8%
73	SR and MA (11 RCTs)	<i>H. pylori</i> infection (eradication therapies)	<i>S. boulardii</i>	Adding <i>S. boulardii</i> significantly increased the rate of eradication (with standard triple therapy), although under the desired level. <i>S. boulardii</i> significantly reduced some treatment-related side effects
74	Cochrane SR (4 RCTs)	Ulcerative colitis	<i>E. coli strain Nissle 1917</i> , <i>L. acidophilus</i> and <i>B. animalis</i> , <i>Lactobacillus</i> GG	There are no sufficient tests to support the use of probiotics for inducing or maintaining remission in UC (2011)

Table 1 (Continued)

Std.	Type of study	Disease	Probiotics	Effects
82	SR and MA (43 RCTs)	Inflammatory bowel disease (UC and CD)	<i>E. coli strain Nissle 1917</i> BIO-THREE (see text) VSL#3 Several species of <i>Bifidobacterium</i> , alone or in combination with <i>Lactobacillus</i> <i>S. boulardii</i>	Promising results with <i>E. coli strain Nissle 1917</i> in inactive UC (maintaining remission) and VSL# 3 in inducing remission in active UC and for maintaining remission in inactive pouchitis. There is no evidence available supporting the use of probiotics in CD
Std.	Type of study	Disease	Probiotics	Effects
83	MA (5 RCTs)	Ulcerative colitis (moderately active)	VSL#3	VSL#3 associated with conventional treatment (5-ASA and/or immune modulators) is safe and more effective than conventional therapy alone in achieving response and remission in active UC of mild to moderate severity
90	Cochrane SR (1 RCT)	Crohn's Disease	<i>Lactobacillus</i> GG	There are no sufficient tests to draw conclusions on the efficacy of probiotics for inducing remission in CD (2008)
91	Cochrane SR (7 RCTs)	Crohn's Disease	<i>Lactobacillus</i> GG VSL#3 <i>S. boulardii</i> <i>E. coli strain Nissle 1917</i>	There is no sufficient evidence to suggest that probiotics are beneficial for maintaining remission in CD (2006)

randomised controlled trials that met the pre-established inclusion criteria. The MA of these trials suggested that administering probiotics as an adjuvant therapy to antibiotics is associated with a lower risk of AAD in adults, but not in elderly people.¹⁶ These results confirmed the results of prior MAs.¹⁷

Probiotics that have demonstrated their efficacy in preventing AAD include *Lactobacillus rhamnosus* (*L. rhamnosus*) GG¹⁸ and *S. boulardii*,¹⁹ but not yoghurt (*Lactobacillus delbrueckii* [*L. delbrueckii*] *bulgaricus* or *Streptococcus salivarius* [*S. salivarius*] ssp. *thermophilus*), as confirmed by the PROSPERO study.²⁰ However, more studies are needed to pinpoint the optimal probiotic preparation dose, administration time and treatment duration.

C. difficile-associated diarrhoea (CDAD)

Antibiotics are widely prescribed drugs that may cause disruptions in the gastrointestinal microbiota, which may in turn reduce resistance to some pathogenic agents such as *C. difficile*. This may lead to *C. difficile*-associated diarrhoea (CDAD), a serious complication. As probiotics are live micro-organisms, it is believed that they may balance the

gastrointestinal microbiota, thereby preventing this disorder.

In this regard, several studies have demonstrated that some probiotics are safe and effective in preventing CDAD. A SR from the Cochrane Collaboration (including 23 clinical trials, with a total of 4213 participants) suggested that probiotics significantly reduce the risk of CDAD by 64%. The incidence of CDAD was 2.0% in the probiotic group, compared to 5.5% in the control group with no treatment or with placebo.²¹

Other SRs and MAs, including 20 RCTs and 3818 patients, demonstrated that probiotics reduce the incidence of CDAD by 66%. In a population with an incidence of CDAD of 5%, probiotic prophylaxis would prevent 33 episodes per 1000 people.²²

Another MA, which included 26 RCTs with 7957 patients, confirmed that the use of probiotics significantly reduces the risk of developing CDAD by 60.5%. Probiotics proved beneficial in both adults and children (reduction of 59.5% and 65.9%, respectively), especially among hospitalised patients. *Lactobacillus*, *Saccharomyces* and a mixture of probiotics were all beneficial in reducing the risk of developing CDAD.²³ *Lactobacillus acidophilus* (*L. acidophilus*)

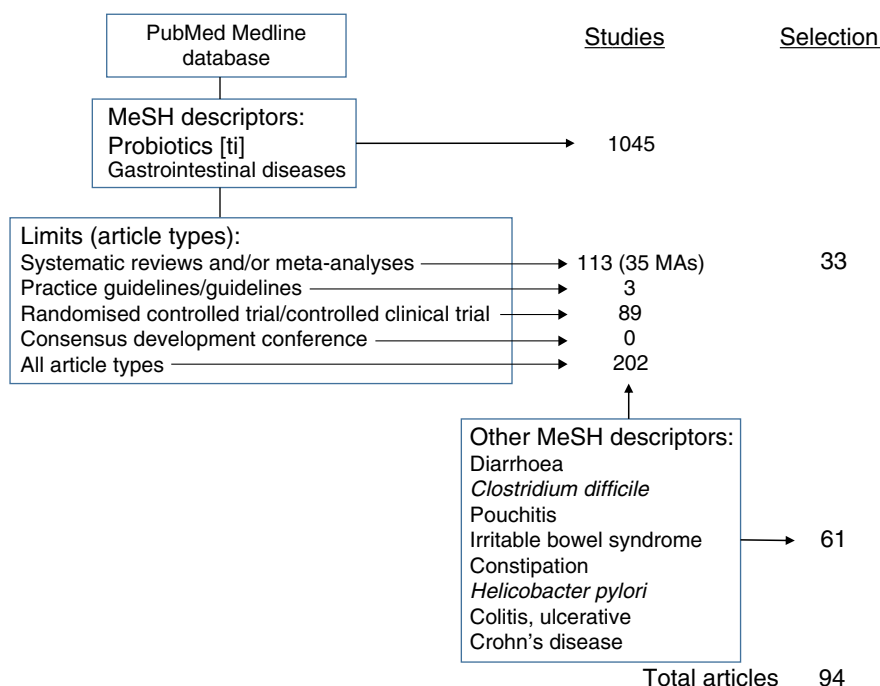


Figure 1 Summary of the strategy for searching for evidence and selection.

CL1285 and *Lactobacillus casei* (*L. casei*) LBC80R have also been shown to be effective.²⁴

However, not all studies have demonstrated these results: an extensive RCT, which enrolled 2941 adults with exposure to antibiotics, confirmed that patients who received probiotics (a multi-strain preparation of *L. acidophilus* and *Bifidobacterium bifidum* [*B. bifidum*]) were not at reduced risk of CDAD.²⁵

Regarding treatment, a MA published in 2012 evaluated the efficacy of probiotics in treating CDAD and suggested that probiotics are beneficial in treating this condition,¹⁷ although very few of the trials included had been designed specifically to evaluate this process.

Travellers' diarrhoea

Acute diarrhoea is common in travellers, ranging from 5% to 50% depending on the destination.^{3,6} Most cases (80%) are due to bacterial infections. The most common infection is one of the seven types of diarrhoeagenic *E. coli*.^{2,3}

One MA²⁶ showed that some probiotics are safe and effective in preventing travellers' diarrhoea and estimated that up to 85% of these cases may be prevented with probiotics. However, another subsequent meta-analysis²⁷ did not confirm these results.

S. boulardii appeared to provide significant protection in these cases. *L. rhamnosus* GG and a mixture of probiotics consisting of *L. acidophilus*, *Lactobacillus bulgaricus* (*L. bulgaricus*), *B. bifidum* and *Streptococcus thermophilus* (*S. thermophilus*) also had a significant protective effect versus placebo.^{2,3,26}

Pouchitis

Proctocolectomy with an ileoanal anastomosis and ileal pouch is the treatment of choice for reconstructing intestinal continuity in severe refractory ulcerative colitis (UC) (and familial adenomatous polyposis) requiring surgery. The long-term complications observed following this procedure are most often acute and/or chronic inflammation of the ileal pouch, i.e. pouchitis. Up to 46% of patients with UC have at least one episode of pouchitis in the first 5 years following surgery,²⁸ and 10–15% of patients with an ileoanal pouch develop serious pouchitis requiring long-term antibiotic use or removal of the pouch.²⁹

Some observations and the high rate of response to several antibiotics have suggested that certain intestinal bacteria (increase in levels of *Clostridium perfringens* and absence of *Streptococcus*) play a significant role in the pathogenesis of pouchitis. Thus, it has been hypothesised that administering some probiotics may alter the microbiota and restore the intestinal mucosal barrier, thereby reducing the risk of inflammation of the mucosa of the pouch.⁴

In this regard, different studies have been conducted with certain probiotics that have confirmed their efficacy and safety in maintaining remission of pouch inflammation, achieved following antibiotic treatment, like 5-aminosalicylic acid,^{30,31} as well as in preventing acute pouchitis³² and recurrence of chronic pouchitis following induction treatment with antibiotics.³³

The probiotic mixtures used in the different studies were VSL#3 (*L. acidophilus*, *L. casei*, *Lactobacillus plantarum* [*L. plantarum*], *L. bulgaricus*; *Bifidobacterium longum* [*B. longum*], *Bifidobacterium breve* [*B. breve*], *Bifidobacterium*

infantis [*B. infantis*] and *S. thermophilus*)^{29,30}; Trilac, which contains *L. acidophilus*, *L. delbrueckii* ssp. *bulgaricus* and *Bifidobacterium bifidum*, for 9 months; and Ecologic 825, a mixture of strains of *B. bifidum*, *Bifidobacterium lactis* (*B. lactis*), *L. acidophilus*, *L. casei*, *Lactobacillus paracasei*, *Lactobacillus plantarum* (*L. plantarum*), *Lactobacillus salivarius* and *Lactococcus lactis*,³² for 8 weeks.

In all cases, the Pouchitis Disease Activity Index significantly improved and the results were superior to placebo.

Finally, a SR from the Cochrane Collaboration³⁴ concluded that VSL#3 was more effective than placebo in maintaining remission of chronic pouchitis and preventing the onset of pouchitis.

Irritable bowel syndrome

The pathophysiology of IBS remains unknown. However, several lines of epidemiological, physiological and clinical data have suggested that intestinal bacteria play a role in the pathogenesis of the disease.^{35,36}

In addition, some physiological studies have demonstrated that manipulating the intestinal microbiota with probiotics may affect certain intestinal functions, such as motility and sensitivity, which appear to be relevant to the pathogenesis of IBS.³⁷

Several systematic reviews and meta-analyses,^{37–43} as well as some clinical trials,^{44,45} although not others,^{46,47} appear to have confirmed that certain probiotics have overall beneficial effects in IBS on abdominal pain and distension as well as flatulence, compared to placebo, and may improve these patients' quality of life.

However, in general, these are very mixed studies that have analysed and compared highly disparate combinations and doses of probiotics, and some have significant methodological deficiencies. Consequently, general recommendations cannot be established.

No specific strain or dose of any probiotic analysed appears to be consistently effective for improving IBS symptoms or quality of life.⁴⁶ However, one study^{48,49} confirmed that symptoms significantly improved in the group of patients that received *B. infantis* (35,624) compared to placebo. In addition, the serum IL-10/IL-12 ratio normalised, suggesting that the probiotic may help to reduce a pro-inflammatory state associated with IBS.

L. plantarum is another probiotic that has been used with good results, superior to placebo, in the management of some symptoms in patients with IBS. Specifically, the DSM 9843 strain significantly reduced flatulence,⁵⁰ and the LPO 1⁵¹ and 299 V⁵² strains significantly reduced abdominal pain.

Our working group performed two meta-analyses to assess the effect of probiotics on IBS symptoms in general⁵³ and abdominal pain in particular,⁵⁴ and concluded that the beneficial effects of probiotics on each IBS symptom are probably strain-specific.

More data from high-quality RCTs dealing with specific profiles and symptoms are needed for probiotics to be recommended in the management of IBS.

Disease entities on which probiotics have possible beneficial effects

Chronic idiopathic constipation (functional constipation)

There are several potential mechanisms of action by which probiotics may be beneficial in functional constipation. First, they modify the gastrointestinal microbiota, which is abnormal in constipation.⁵⁵ Second, probiotic metabolites may alter intestinal motility.⁵⁶ Third, some probiotics increase production of lactic acid and short-chain fatty acids, thereby reducing luminal pH, which may improve colon peristalsis and shorten intestinal transit time.⁵⁷

Based on this evidence, hypotheses as to the possible beneficial effect of certain probiotics on the management of CIC have been formulated. Several systematic reviews and meta-analysis have been conducted to assess this.^{42,58,59} These have concluded that, although probiotics have demonstrated some promising results in this regard, specifically an increase in the mean number of bowel movements per week, more high-quality RCTs are needed before they may be recommended in a standardised fashion in the management of CIC.

H. pylori infection

When *H. pylori* eradication is recommended,⁶⁰ the rate of success is approximately 90% using a first-line treatment (in particular with concomitant quadruple therapy without bismuth, which has better results than classic triple therapy),⁶¹ and around 70% using a second-line treatment.⁶²

In a 2007 MA, Tong et al.⁶³ demonstrated that administering probiotics may both improve the rate of eradication and reduce the incidence of adverse events.

Subsequently, different studies and meta-analyses confirmed this,^{64–68} finding that the use of probiotics to supplement standard eradication therapy in patients infected with *H. pylori* may end up increasing the rate of eradication of the micro-organism by approximately 13% and decreasing the overall rate of adverse effects by approximately 41%, regardless of the patient's age, gender or dose of probiotics.⁶⁶

Notable among the different types of probiotic used to improve the results of eradication therapies were *Lactobacillus reuteri* (*L. reuteri*),⁶⁹ which demonstrated an ability to inhibit the colonisation of the human gastric mucosa by *H. pylori*,⁷⁰ in addition to an ability to produce reuterin, a broad-spectrum antibiotic active against *H. pylori*.⁷¹ The DSM17648 strain of *L. reuteri* seemed especially effective for this.⁷²

Adding *S. boulardii* also seemed to significantly increase the rate of eradication, although under the desired success level (80% versus 71% in the control group). This yeast also significantly reduced some treatment-related side effects.⁷³

An economic evaluation is needed to establish the rate of cost-effectiveness of adding probiotics to *H. pylori* eradication treatment, since this undoubtedly increases treatment costs.

Ulcerative colitis

Although, initially, a 2011 SR from the Cochrane Collaboration⁷⁴ concluded that there were no sufficient tests to support the use of probiotics to induce or maintain remission in UC, most studies, though small, have concluded that probiotics are equivalent, or at least not inferior, to standard therapy for maintaining UC remission.⁷⁵

One trial⁷⁶ reported that therapy with *Lactobacillus* GG may be more effective than standard therapy, with mesalamine, for prolonging recurrence-free time.

Most studies with probiotics in UC have been conducted with VSL#3 or *E. coli* strain Nissle 1917.^{77–79} Results with these probiotics have a degree of recommendation of A for maintaining UC remission and a degree of recommendation of B for inducing UC remission, according to the 4th^o Triennial Yale/Harvard Workshop on Probiotic Recommendations.⁸⁰

Thus, *E. coli* strain Nissle 1917 was as effective as a low dose of 5-ASA in preventing UC recurrence in adults.⁸¹

A MA that included RCTs comparing VSL#3 to controls (placebo or 5-ASA) demonstrated this probiotic to have a significant benefit versus controls for inducing UC remission.⁸² Another subsequent MA, which compared VSL#3 to placebo, demonstrated remission rates of 43.8% in patients treated with this probiotic versus 24.8% in patients with placebo.⁸³ Previously, another RCT⁸⁴ found that patients who received VSL#3 tended to experience a decrease of at least 50% on the Ulcerative Colitis Disease Activity Index (UCDAI) after eight weeks of treatment, compared to patients who received placebo (63 versus 41 per cent). Remission rates were also higher in the VSL#3 group (48 versus 32 per cent). However, histological results did not significantly improve with treatment with VSL#3.

Finally, although benefits with probiotics have generally been anecdotal, studies have also been conducted with probiotics in Crohn's disease.

Crohn's disease

The vast majority of RCTs that have used probiotics in CD have been conducted in patients with inactive disease (in remission), to prevent clinical reactivation and/or endoscopic recurrence.

Studies conducted with different types of *Lactobacillus*^{85–87} and with *E. coli* strain Nissle 1917^{88,89} have not demonstrated any of them to be superior to placebo in terms of preventing recurrence of the disease.

Two SRs from the Cochrane Collaboration concluded that the data available did not support the clinical efficacy of probiotic treatment in patients with CD either for inducing⁹⁰ or for maintaining remission.⁹¹

In addition, one study⁹² demonstrated that *S. boulardii*, together with 2 g daily of mesalamine, was superior to 3 g daily of mesalamine alone in reducing clinical recurrences in patients with CD in remission. Another subsequent study⁹³ did not confirm these results.

In general, with the possible exception of *S. boulardii* in certain populations (e.g. non-smokers), long-term treatment with probiotic micro-organisms does not seem to yield benefits in maintaining remission in patients with CD.⁹⁴

Regarding induction of clinical remission, in general, there is no convincing evidence that probiotics show a significant capacity to increase the efficacy of conventional treatments in patients with CD.⁹⁴

Table 1 presents the most outstanding data from all SRs and MAs used to prepare the article. From these, the following conclusions and recommendations may be drawn:

- (1) Most of the studies reviewed were small, and many had significant methodological limitations. Consequently, it is difficult to draw unequivocal conclusions on the efficacy of the probiotics used. Large, well-designed, multi-centre, controlled clinical trials are needed to clarify the role of specific probiotics in different well-defined patient populations.
- (2) There are considerable differences in terms of composition, doses and biological activity among various commercial probiotic preparations. Consequently, results with one preparation cannot be extrapolated to other preparations or all probiotic preparations.
- (3) No strategy with a probiotic may currently be considered the standard primary treatment in any of the diseases reviewed above.
- (4) Following assessment of the quality and consistency of the available evidence reviewed, in the author's opinion, certain probiotics, which vary by process, have been shown to be effective and beneficial in acute infectious diarrhoea, antibiotic-associated diarrhoea, *C. difficile*-associated diarrhoea and pouchitis and in *H. pylori* infection eradication, and thus may be recommended for use in these processes:
 - *L. rhamnosus* GG and *S. boulardii* have clear beneficial effects in shortening the duration and reducing the frequency of bowel movements in acute infectious diarrhoea. Similarly, they appear to significantly decrease the risk of antibiotic-associated diarrhoea and *C. difficile*-associated diarrhoea. Supplementation with these two probiotics could be effective for increasing *H. pylori* eradication rates.
 - VSL#3 in primary and secondary prevention of pouchitis, in addition to standard medical therapy.
 - *E. coli* strain Nissle 1917 appears to be promising in maintaining UC remission and could be considered as an alternative in patients who are intolerant or resistant to 5-ASA preparations.

Conflicts of interest

The author declares that he has no conflicts of interest.

References

1. Penner R, Fedorak RN, Madsen KL. Probiotics and nutraceuticals: non-medicinal treatments of gastrointestinal diseases. *Curr Opin Pharmacol.* 2005;5:596–603.
2. Sullivan A, Nord CE. Probiotics and gastrointestinal diseases. *J Intern Med.* 2005;257:78–92.
3. Girardin M, Seidman EG. Indications for the use of probiotics in gastrointestinal diseases. *Dig Dis.* 2011;29:574–87.
4. Sullivan A, Nord CE. Probiotics and gastrointestinal diseases. *J Intern Med.* 2005;257:78–92.

5. Passariello A, Agricola P, Malfetheriner P. A critical appraisal of probiotics (as drugs or food supplements) in gastrointestinal diseases. *Curr Med Res Opin.* 2014;30:1055–64.
6. Islam SU. Clinical uses of probiotics. *Medicine (Baltimore).* 2016;95:e2658.
7. Marteau P. Living drugs for gastrointestinal diseases: the case for probiotics. *Dig Dis.* 2006;24:137–47.
8. Bergonzelli GE, Blum S, Brüssow H, Corthésy-Theulaz I. Probiotics as a treatment strategy for gastrointestinal diseases? *Digestion.* 2005;72:57–68.
9. Wasilewski A, Zielińska M, Storr M, Fichna J. Beneficial effects of probiotics, prebiotics, synbiotics, and psychobiotics in inflammatory bowel disease. *Inflamm Bowel Dis.* 2015;21:1674–82.
10. Issa I, Moucari R. Probiotics for antibiotic-associated diarrhea: do we have a verdict? *World J Gastroenterol.* 2014;20:17788–95.
11. Allen SJ. The potential of probiotics to prevent *Clostridium difficile* infection. *Infect Dis Clin N Am.* 2015;29:135–44.
12. Shojania KG, Bero LA. Taking advantage of the explosion of systematic reviews: an efficient MEDLINE search strategy. *Eff Clin Pract.* 2001;4:157–62.
13. Allen SJ, Martinez EG, Gregorio GV, Dans LF. Probiotics for treating acute infectious diarrhoea. *Cochrane Database Syst Rev.* 2010;CD003048.
14. Rijkers GT, Bengmark S, Enck P, Haller D, Herz U, Kalliomaki M, et al. Guidance for substantiating the evidence for beneficial effects of probiotics: current status and recommendations for future research. *J Nutr.* 2010;140:671S–6S.
15. Preidis GA, Hill C, Guerrant RL, Ramakrishna BS, Tannock GW, Versalovic J. Probiotics, enteric and diarrheal diseases, and global health. *Gastroenterology.* 2011;140:8–14.
16. Jafarnejad S, Shab-Bidar S, Speakman JR, Parastui K, Daneshi-Maskooni M, Djafarian K. Probiotics reduce the risk of antibiotic-associated diarrhea in adults (18–64 years) but not the elderly (>65 years): a meta-analysis. *Nutr Clin Pract.* 2016;31:502–13.
17. Hempel S, Newberry SJ, Maher AR, Wang Z, Miles JN, Shanman R, et al. Probiotics for the prevention and treatment of antibiotic-associated diarrhea: a systematic review and meta-analysis. *JAMA.* 2012;307:1959–69.
18. Szajewska H, Kolodziej M. Systematic review with meta-analysis: *Lactobacillus rhamnosus* GG in the prevention of antibiotic-associated diarrhoea in children and adults. *Aliment Pharmacol Ther.* 2015;42:1149–57.
19. Szajewska H, Kolodziej M. Systematic review with meta-analysis: *Saccharomyces boulardii* in the prevention of antibiotic-associated diarrhoea. *Aliment Pharmacol Ther.* 2015;42:793–801.
20. Patro-Golab B, Shamir R, Szajewska H. Yogurt for treating antibiotic-associated diarrhea: systematic review and meta-analysis. *Nutrition.* 2015;31:796–800.
21. Goldenberg JZ, Ma SS, Saxton JD, Martzen MR, Vandvik PO, Thorlund K, et al. Probiotics for the prevention of *Clostridium difficile*-associated diarrhea in adults and children. *Cochrane Database Syst Rev.* 2013;CD006095.
22. Johnston BC, Ma SS, Goldenberg JZ, Thorlund K, Vandvik PO, Loeb M, et al. Probiotics for the prevention of *Clostridium difficile*-associated diarrhea: a systematic review and meta-analysis. *Ann Intern Med.* 2012;157:878–88.
23. Lau CS, Chamberlain RS. Probiotics are effective at preventing *Clostridium difficile*-associated diarrhea: a systematic review and meta-analysis. *Int J Gen Med.* 2016;9:27–37.
24. Maziade PJ, Andriessen JA, Pereira P, Currie B, Goldstein EJ. Impact of adding prophylactic probiotics to a bundle of standard preventative measures for *Clostridium difficile* infections: enhanced and sustained decrease in the incidence and severity of infection at a community hospital. *Curr Med Res Opin.* 2013;29:1341–7.
25. Allen SJ, Wareham K, Wang D, Bradley C, Hutchings H, Harris W, et al. Lactobacilli and bifidobacteria in the prevention of antibiotic-associated diarrhoea and *Clostridium difficile* diarrhoea in older inpatients (PLACIDE): a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet.* 2013;382:1249.
26. McFarland LV. Meta-analysis of probiotics for the prevention of traveler's diarrhea. *Travel Med Infect Dis.* 2007;5:97–105.
27. Takahashi O, Noguchi Y, Omata F, Tokuda Y, Fukui T. Probiotics in the prevention of traveler's diarrhea: meta-analysis. *J Clin Gastroenterol.* 2007;41:336–7.
28. McLaughlin SD, Clark SK, Tekkis PP, Ciclitira PJ, Nicholls RJ. Review article: restorative proctocolectomy, indications, management of complications and follow-up – a guide for gastroenterologists. *Aliment Pharmacol Ther.* 2008;27:895–909.
29. Turrone S, Vitali B, Candela M, Gionchetti P, Rizzello F, Campieri M, et al. Antibiotics and probiotics in chronic pouchitis: a comparative proteomic approach. *World J Gastroenterol.* 2010;16:30–41.
30. Shen J, Zuo ZX, Mao AP. Effect of probiotics on inducing remission and maintaining therapy in ulcerative colitis, Crohn's disease, and pouchitis: meta-analysis of randomized controlled trials. *Inflamm Bowel Dis.* 2014;20:21–35.
31. Elahi B, Nikfar S, Derakhshani S, Vafaie M, Abdollahi M. On the benefit of probiotics in the management of pouchitis in patients underwent ileal pouch anal anastomosis: a meta-analysis of controlled clinical trials. *Dig Dis Sci.* 2008;53:1278–84.
32. Tomasz B, Zoran S, Jarosław W, Ryszard M, Marcin G, Robert B, et al. Long-term use of probiotics *Lactobacillus* and *Bifidobacterium* has a prophylactic effect on the occurrence and severity of pouchitis: a randomized prospective study. *Biomed Res Int.* 2014;2014:208064.
33. Persborn M, Gerritsen J, Wallon C, Carlsson A, Akkermans LM, Söderholm JD. The effects of probiotics on barrier function and mucosal pouch microbiota during maintenance treatment for severe pouchitis in patients with ulcerative colitis. *Aliment Pharmacol Ther.* 2013;38:772–83.
34. Holubar SD, Cima RR, Sandborn WJ, Pardi DS. Treatment and prevention of pouchitis after ileal pouch-anal anastomosis for chronic ulcerative colitis. *Cochrane Database Syst Rev.* 2010;CD001176.
35. Ringel Y, Carroll IM. Alterations in the intestinal microbiota and functional bowel symptoms. *Gastrointest Endosc Clin N Am.* 2009;19:141–50.
36. Salonen A, de Vos WM, Palva A. Gastrointestinal microbiota in irritable bowel syndrome: present state and perspectives. *Microbiology.* 2010;156:3205–15.
37. Moayyedi P, Ford AC, Talley NJ, Cremonini F, Foxx-Orenstein AE, Brandt LJ, et al. The efficacy of probiotics in the treatment of irritable bowel syndrome: a systematic review. *Gut.* 2010;59:325–32.
38. Brenner DM, Moeller MJ, Chey WD, Schoenfeld PS. The utility of probiotics in the treatment of irritable bowel syndrome: a systematic review. *Am J Gastroenterol.* 2009;104:1033–49.
39. Hoveyda N, Heneghan C, Mahtani KR, Perera R, Roberts N, Glasziou P. A systematic review and metaanalysis: probiotics in the treatment of irritable bowel syndrome. *BMC Gastroenterol.* 2009;9:15.
40. McFarland LV, Dublin S. Meta-analysis of probiotics for the treatment of irritable bowel syndrome. *World J Gastroenterol.* 2008;14:2650–61.
41. Parkes GC, Sanderson JD, Whelan K. Treating irritable bowel syndrome with probiotics: the evidence. *Proc Nutr Soc.* 2010;69:187–94.
42. Ford AC, Quigley EM, Lacy BE, Lembo AJ, Saito YA, Schiller LR, et al. Efficacy of prebiotics, probiotics, and synbiotics in irritable bowel syndrome and chronic idiopathic constipation: systematic review and meta-analysis. *Am J Gastroenterol.* 2014;109:1547–61.

43. Ringel Y, Ringel-Kulka T. The rationale and clinical effectiveness of probiotics in irritable bowel syndrome. *J Clin Gastroenterol*. 2011; Suppl.:S145–8.
44. Lorenzo-Zúñiga V, Llop E, Suárez C, Alvarez B, Abreu L, Espadaler J, et al. I.31, a new combination of probiotics, improves irritable bowel syndrome-related quality of life. *World J Gastroenterol*. 2014;20:8709–16.
45. Yoon JS, Sohn W, Lee OY, Lee SP, Lee KN, Jun DW, et al. Effect of multispecies probiotics on irritable bowel syndrome: a randomized, double-blind, placebo-controlled trial. *J Gastroenterol Hepatol*. 2014;29:52–9.
46. McKenzie YA, Thompson J, Gulia P, Lomer MC, (IBS Dietetic Guideline Review Group on behalf of Gastroenterology Specialist Group of the British Dietetic Association). British Dietetic Association systematic review of systematic reviews and evidence-based practice guidelines for the use of probiotics in the management of irritable bowel syndrome in adults (2016 update). *J Hum Nutr Diet*. 2016, <http://dx.doi.org/10.1111/jhn>.
47. Begtrup LM, de Muckadell OB, Kjeldsen J, Christensen RD, Jarbøl DE. Long-term treatment with probiotics in primary care patients with irritable bowel syndrome—a randomised, double-blind, placebo controlled trial. *Scand J Gastroenterol*. 2013;48:1127–35.
48. Whorwell PJ, Altringer L, Morel J, Bond Y, Charbonneau D, O'Mahony L, et al. Efficacy of an encapsulated probiotic *Bifidobacterium infantis* 35624 in women with irritable bowel syndrome. *Am J Gastroenterol*. 2006;101:1581–90.
49. O'Mahony L, McCarthy J, Kelly P, Hurley G, Luo F, Chen K, et al. *Lactobacillus* and *bifidobacterium* in irritable bowel syndrome: symptom responses and relationship to cytokine profiles. *Gastroenterology*. 2005;128:541–51.
50. Nobaek S, Johansson ML, Molin G, Ahrné S, Jeppsson B. Alteration of intestinal microflora is associated with reduction in abdominal bloating and pain in patients with irritable bowel syndrome. *Am J Gastroenterol*. 2000;95:1231–8.
51. Saggioro A. Probiotics in the treatment of irritable bowel syndrome. *J Clin Gastroenterol*. 2004;38 Suppl.:S104–6.
52. Carroll IM, Ringel-Kulka T, Keku TO, Chang YH, Packey CD, Sartor RB, et al. Molecular analysis of the luminal- and mucosal-associated intestinal microbiota in diarrhea-predominant irritable bowel syndrome. *Am J Physiol Gastrointest Liver Physiol*. 2011;301:G799–807.
53. Ortiz-Lucas M, Tobías A, Saz P, Sebastián JJ. Effect of probiotic species on irritable bowel syndrome symptoms: a bring up to date meta-analysis. *Rev Esp Enferm Dig*. 2013;105:19–36.
54. Ortiz Lucas M, Tobías A, Saz Peiró P, Sebastián JJ. Probiotics for specific treatment of pain in irritable bowel syndrome: a review. *Rev Col Gastroenterol*. 2014;29:146–55.
55. Khalif IL, Quigley EM, Konovitch EA, Maximova ID. Alterations in the colonic flora and intestinal permeability and evidence of immune activation in chronic constipation. *Dig Liver Dis*. 2005;37:838–49.
56. Quigley EM. Bacteria: a new player in gastrointestinal motility disorders—infections, bacterial overgrowth, and probiotics. *Gastroenterol Clin N Am*. 2007;36:735–48.
57. Waller PA, Gopal PK, Leyer GJ, Ouwehand AC, Reifer C, Stewart ME, et al. Dose-response effect of *Bifidobacterium lactis* HN019 on whole gut transit time and functional gastrointestinal symptoms in adults. *Scand J Gastroenterol*. 2011;46:1057–64.
58. Dimidi E, Christodoulides S, Fragkos KC, Scott SM, Whelan K. The effect of probiotics on functional constipation in adults: a systematic review and meta-analysis of randomized controlled trials. *Am J Clin Nutr*. 2014;100:1075–84.
59. Chmielewska A, Szajewska H. Systematic review of randomised controlled trials: probiotics for functional constipation. *World J Gastroenterol*. 2010;16:69–75.
60. Gisbert JP, Calvet X, Bermejo F, Boixeda D, Bory F, Bujanda L, et al. III Spanish Consensus Conference on *Helicobacter pylori* infection. *Gastroenterol Hepatol*. 2013;36:340–74.
61. Campillo A, Ostiz M, Amorena E, Kutz M, La Iglesia M. Quadruple concomitant non-bismuth therapy vs. classical triple therapy as first line therapy for *Helicobacter pylori* infection. *Med Clin (Barc)*. 2016, pii:S0025-7753(16)30165-8.
62. Gisbert JP, Calvet X, O'Connor A, Mégraud F, O'Morain CA. Sequential therapy for *Helicobacter pylori* eradication: a critical review. *J Clin Gastroenterol*. 2010;44:313–25.
63. Tong JL, Ran ZH, Shen J, Zhang CX, Xiao SD. Meta-analysis: the effect of supplementation with probiotics on eradication rates and adverse events during *Helicobacter pylori* eradication therapy. *Aliment Pharmacol Ther*. 2007;25:155–68.
64. Dajani AI, Abu Hammour AM, Yang DH, Chung PC, Nounou MA, Yuan KY, et al. Do probiotics improve eradication response to *Helicobacter Pylori* on standard triple or sequential therapy? *Saudi J Gastroenterol*. 2013;19:113–20.
65. Wilhelm SM, Johnson JL, Kale-Pradhan PB. Treating bugs with bugs: the role of probiotics as adjunctive therapy for *Helicobacter pylori*. *Ann Pharmacother*. 2011;45:960–6.
66. Zhang MM, Qian W, Qin YY, He J, Zhou YH. Probiotics in *Helicobacter pylori* eradication therapy: a systematic review and meta-analysis. *World J Gastroenterol*. 2015;21:4345–57.
67. Ma F, Zhou C, Wang J, Liu T, Liu J. Probiotics in the treatment of peptic ulcer infected by *Helicobacter pylori* and its safety. *Pak J Pharm Sci*. 2015;28 Suppl.:1087–90.
68. Zheng X, Lyu L, Mei Z. *Lactobacillus*-containing probiotic supplementation increases *Helicobacter pylori* eradication rate: evidence from a meta-analysis. *Rev Esp Enferm Dig*. 2013;105:445–53.
69. Dore MP, Goni E, di Mario F. Is there a role for probiotics in *Helicobacter pylori* therapy? *Gastroenterol Clin N Am*. 2015;44:565–75.
70. Mukai T, Asasaka T, Sato E, Mori K, Matsumoto M, Ohori H. Inhibition of binding of *Helicobacter pylori* to the glycolipid receptors by probiotic *Lactobacillus reuteri*. *FEMS Immunol Med Microbiol*. 2002;32:105–10.
71. Dore MP, Soro S, Rocchi C, Loria MF, Bibbò S, Pes GM. Inclusion of *Lactobacillus Reuteri* in the treatment of *Helicobacter pylori* in sardinian patients: a case report series. *Medicine (Baltimore)*. 2016;95:e3411.
72. Holz C, Busjahn A, Mehling H, Arya S, Boettner M, Habibi H, et al. Significant reduction in *Helicobacter pylori* load in humans with non-viable *Lactobacillus reuteri* DSM17648: a pilot study. *Probiotics Antimicrob Proteins*. 2015;7:91–100.
73. Szajewska H, Horvath A, Kolodziej M. Systematic review with meta-analysis: *Saccharomyces boulardii* supplementation and eradication of *Helicobacter pylori* infection. *Aliment Pharmacol Ther*. 2015;41:1237–45.
74. Naidoo K, Gordon M, Fagbemi AO, Thomas AG, Akobeng AK. Probiotics for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev*. 2011;CD007443.
75. Do VT, Baird BG, Kockler DR. Probiotics for maintaining remission of ulcerative colitis in adults. *Ann Pharmacother*. 2010;44:565–71.
76. Zocco MA, dal Verme LZ, Cremonini F, Piscaglia AC, Nista EC, Candelli M, et al. Efficacy of *Lactobacillus GG* in maintaining remission of ulcerative colitis. *Aliment Pharmacol Ther*. 2006;23:1567–74.
77. Derikx LA, Dieleman LA, Hoentjen F. Probiotics and prebiotics in ulcerative colitis. *Best Pract Res Clin Gastroenterol*. 2016;30:55–71.
78. Chibbar R, Dieleman LA. Probiotics in the management of ulcerative colitis. *J Clin Gastroenterol*. 2015;49 Suppl. 1:S50–5.

79. Meijer BJ, Dieleman LA. Probiotics in the treatment of human inflammatory bowel diseases: update 2011. *J Clin Gastroenterol*. 2011; Suppl.:S139–44.
80. Floch MH, Walker WA, Sanders ME, Nieuwdorp M, Kim A, Brenner DA, et al. Recommendations for probiotic use—2015 update: proceedings and consensus opinion. *J Clin Gastroenterol*. 2015;49 Suppl. 1:S69–73.
81. Kruis W, Frick P, Pokrotnieks J, Lukás M, Fixa B, Kascák M, et al. Maintaining remission of ulcerative colitis with the probiotic *Escherichia coli* Nissle 1917 is as effective as with standard mesalazine. *Gut*. 2004;53:1617–23.
82. Jonkers D, Penders J, Masclee A, Pierik M. Probiotics in the management of inflammatory bowel disease: a systematic review of intervention studies in adult patients. *Drugs*. 2012;72:803–23.
83. Mardini HE, Grigorian AY. Probiotic mix VSL#3 is effective adjunctive therapy for mild to moderately active ulcerative colitis: a meta-analysis. *Inflamm Bowel Dis*. 2014;20:1562–7.
84. Tursi A, Brandimarte G, Papa A, Giglio A, Elisei W, Giorgetti GM, et al. Treatment of relapsing mild-to-moderate ulcerative colitis with the probiotic VSL#3 as adjunctive to a standard pharmaceutical treatment: a double-blind, randomized, placebo-controlled study. *Am J Gastroenterol*. 2010;105:2218–27.
85. Prantera C, Scribano ML, Falasco G, Andreoli A, Luzi C. Ineffectiveness of probiotics in preventing recurrence after curative resection for Crohn's disease: a randomised controlled trial with *Lactobacillus GG*. *Gut*. 2002;51:405–9.
86. Schultz M, Timmer A, Herfarth HH, Sartor RB, Vanderhoof JA, Rath HC. *Lactobacillus GG* in inducing and maintaining remission of Crohn's disease. *BMC Gastroenterol*. 2004;4:1–5.
87. Marteau P, Lémann M, Seksik P, Laharie D, Colombel JF, Bouhnik Y, et al. Ineffectiveness of *Lactobacillus johnsonii* LA1 for prophylaxis of postoperative recurrence in Crohn's disease: a randomised, double blind, placebo controlled GETAID trial. *Gut*. 2006;55:842–7.
88. Malchow HA. Crohn's disease and *Escherichia coli*. A new approach in therapy to maintain remission of colonic Crohn's disease? *J Clin Gastroenterol*. 1997;25:653–8.
89. Guslandi M. Role of probiotics in Crohn's disease and in pouchitis. *J Clin Gastroenterol*. 2015;49 Suppl. 1:S46–9.
90. Butterworth AD, Thomas AG, Akobeng AK. Probiotics for induction of remission in Crohn's disease. *Cochrane Database Syst Rev*. 2008;CD006634.
91. Rolfe VE, Fortun PJ, Hawkey CJ, Bath-Hextall F. Probiotics for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev*. 2006;CD004826.
92. Guslandi M, Mezzi G, Sorghi M, Testoni PA. *Saccharomyces boulardii* in maintenance treatment of Crohn's disease. *Dig Dis Sci*. 2000;45:1462–4.
93. Bourreille A, Cadiot G, le Dreau G, Laharie D, Beaugier L, Dupas JL, et al. *Saccharomyces boulardii* does not prevent relapse of Crohn's disease. *Clin Gastroenterol Hepatol*. 2013;11:982–7.
94. Lichtenstein L, Avni-Biron I, Ben-Bassat O. Probiotics and prebiotics in Crohn's disease therapies. *Best Pract Res Clin Gastroenterol*. 2016;30:81–8.