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REVIEW ARTICLE

Microbiota, gastrointestinal infections, low-grade inflammation, and antibiotic therapy in irritable bowel syndrome (IBS): an evidence-based review☆

Max Schmulson[a,*], María Victoria Bielsa[b], Ramón Carmona-Sánchez[c], Angélica Hernández[d], Aurelio López-Colombo[e], Yolanda López Vidal[f], Mario Peláez-Luna[a], José María Remes-Troche[g,h], José Luis Tamayo[i], Miguel Angel Valdovinos[j]

[a] *Laboratory of Liver, Pancreas, and Motility (HIPAM), Department of Experimental Medicine, Universidad Nacional Autónoma de México (UNAM) Hospital General de México, Mexico City, Mexico*
[b] *Department of Gastroenterology, School of Medicine, Universidad Autónoma de Guadalajara, Guadalajara-Jal., Mexico*
[c] *Gastroenterology Service, Internal Medicine Service, Hospital Ángeles-CMP, San Luis Potosí-S.L.P., Mexico*
[d] *Endoscopy Service, Instituto Nacional de Cancerología. Mexico City, Mexico*
[e] *Coordination of Health Research Delegation, Instituto Mexicano del Seguro Social, Puebla-Pue., Mexico*
[f] *Molecular Microbial Immunology Program, Universidad Nacional Autónoma de México (UNAM), Mexico City, Mexico*
[g] *Laboratory of Digestive Physiology and Gastrointestinal Motility, Medical and Biological Research Institute, Universidad Veracruzana, Veracruz, Veracruz*
[h] *School of Medicine, Miguel Alemán Valdés, Veracruz-Ver, Mexico*
[i] *Health Sciences Research and Teaching Center, Universidad Autónoma de Sinaloa. Hospital Civil de Culiacán, Culiacán-Sin., Mexico*
[j] *Department of Gastroenterology. Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico*

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KEYWORDS
Irritable bowel syndrome;
Bacterial overpopulation;

Abstract
Background: Post-infectious irritable bowel syndrome (PI-IBS) prevalence, small intestinal bacterial overgrowth (SIBO), altered microbiota, low-grade inflammation, and antibiotic therapy in IBS are all controversial issues.

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* Corresponding author. Laboratorio de Hígado, Páncreas y Motilidad (HIPAM), Departamento de Medicina Experimental, Facultad de Medicina-Universidad Nacional Autónoma de México (UNAM). Hospital General de México. Dr. Balmis #148. Col. Doctores. México D.F. México. C.P. 06726. Tel.: +52-5556232673; fax: +52-5556232669.
E-mail address: maxjulio@prodigy.net.mx (M. Schmulson).

Post-infectious;
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Low-grade inflammation;
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Adults;
Children;
Evidence-based review;
Mexico

Aims: To conduct an evidence-based review of these factors.
Methods: A review of the literature was carried out up to July 2012, with the inclusion of additional articles as far as August 2013, all of which were analyzed through the Oxford Centre for Evidence-Based Medicine (OCEBM) system.
Results: 1. There is greater SIBO probability in IBS when breath tests are performed, but prevalence varies widely (2-84%). 2. The gut microbiota in individuals with IBS is different from that in healthy subjects, but a common characteristic present in all the patients has not been established. 3. The incidence and prevalence of PI-IBS varies from 9-10% and 3-17%, respectively, and the latter decreases over time. Bacterial etiology is the most frequent but post-viral and parasitic cases have been reported. 4. A sub-group of patients has increased enterochromaffin cells, intraepithelial lymphocytes, and mast cells in the intestinal mucosa, but no differences between PI-IBS and non PI-IBS have been determined. 5. Methanogenic microbiota has been associated with IBS with constipation. 6. Rifaximin at doses of 400 mg TID/10 days or 550 mg TID/14 days is an effective treatment for the majority of overall symptoms and abdominal bloating in IBS. Retreatment effectiveness appears to be similar to that of the first cycle.
Conclusions: Further studies are required to determine the nature of the gut microbiota in IBS and the differences in low-grade inflammation between PI-IBS and non PI-IBS. Rifaximin has shown itself to be an effective treatment for IBS, regardless of prior factors.

PALABRAS CLAVE
Síndrome de intestino irritable;
Sobrepoblación bacteriana;
Postinfeccioso;
Microbiota;
Inflamación de bajo grado;
Tratamiento con antibióticos;
Rifaximina;
Adultos;
Niños;
Revisión sistemática basada en evidencias

Microbiota, infecciones gastrointestinales, inflamación de bajo grado y antibioticoterapia en el síndrome de intestino irritable. Una revisión basada en evidencias

Resumen
Antecedentes: Existen controversias sobre la prevalencia del síndrome de intestino irritable (SII)-postinfeccioso (PI), sobrepoblación bacteriana (SPB), alteraciones en la microbiota, inflamación de bajo grado y antibioticoterapia en SII.
Objetivos: Realizar una revisión basada en evidencia de estos factores.
Métodos: Se realizó una revisión de la literatura hasta julio del 2012 y se incluyeron artículos adicionales hasta agosto del 2013, los cuales fueron analizados mediante el sistema del Centro para Medicina Basada en Evidencia de la Universidad de Oxford (OCEBM).
Resultados: 1. Existe mayor probabilidad de SPB mediante pruebas de aliento pero la prevalencia es muy variable (2-84%). 2. La microbiota intestinal es diferente en SII que en sujetos sanos, pero no se ha establecido una característica común presente en todos los pacientes. 3. La incidencia y prevalencia del SII-PI varía del 9-10% y 3-17%, respectivamente; esta última disminuye con el tiempo. La etiología bacteriana es la más frecuente, pero se han reportado casos posvirales y parasitarios. 4. Existe un subgrupo de pacientes con incremento de células enterocromafines, linfocitos intraepiteliales y mastocitos en la mucosa intestinal, pero no se han determinado diferencias entre SII-PI y SII-No PI. 5. La microbiota metanogénica se asocia con el SII con estreñimiento. 6. La rifaximina en dosis de 400 mg TID/10 días o 550 mg TID/14 días es efectiva en la mejoría de síntomas globales y distensión abdominal en SII. La efectividad del retratamiento parece ser similar a la del primer ciclo.
Conclusiones: Se requieren más estudios para determinar la microbiota intestinal propia del SII y las diferencias en inflamación de bajo grado entre SII-PI y SII-No PI. La rifaximina ha demostrado efectividad en el tratamiento del SII independientemente de los factores anteriores.

1. Introduction

The pathophysiology of irritable bowel syndrome (IBS) is not completely understood, but various mechanisms such as gastrointestinal motility disturbances, visceral hypersensitivity, altered bidirectional brain-gut communication, psychosocial alterations, and stress have been proposed.[1] More recently a group of patients has been described that develop IBS after gastrointestinal infections, known as post-infectious (PI) IBS.[2] Likewise, the presence of small intestinal bacterial overgrowth (SIBO) in quantitative and qualitative gut and fecal microbiota disruptions has been reported.[3–4] IBS has

also been associated with the presence of low-grade inflammation in the intestinal mucosa resulting from an increase in the number of intraepithelial lymphocytes, mast cells, and enterochromaffin cells,[5] without minimizing the fact that immunity alterations have been described at the peripheral level; such is the case with low levels of interleukin (IL)-10 and the increase of some pro-inflammatory interleukins such as tumor necrosis factor alpha (TNF-α) and other inflammation mediators.[6] In fact, it is thought that alterations in the microbiota or SIBO in the small bowel could increase intestinal permeability, activating submucosal immunologic mechanisms that in turn could lead to low-grade inflammation.[7] Furthermore, the mediators of this immunologic activation could stimulate enteric nervous system terminals, and even the autonomic nervous system, triggering the visceral sensitivity and motility alterations that have been described in IBS.[7–8] On the other hand, the presence of PI-IBS, changes in the microbiota, and the association with SIBO in IBS have brought about the justification of antibiotic use in IBS treatment.[8–9]

Nevertheless, despite all the above, evidence is sometimes controversial. On the one hand, only one group of patients develops PI-IBS and not all the patients present with SIBO.[9–10] The latter is even more limited due to the fact that the breath tests for diagnosing SIBO have not been standardized and vary among studies.[11] Moreover, the disturbances in the microbiota are diverse and there is a wide variety of techniques for studying them, including the most sophisticated genomic tests.[12] Similarly, the presence of low-grade inflammation is not universal and the alterations described differ among studies, in fact, it is uncertain whether these changes that present in some IBS patients are related only to PI-IBS.[13] Finally, the studies on antibiotics in IBS have evaluated different doses, for different periods of time, and different outcome variables.[14–15]

Consequently, our aim was to carry out an evidence-based review on the following aspects of IBS: 1. The frequency of SIBO in IBS. 2. The incidence and prevalence of PI-IBS and its risk factors. 3. To determine the alterations in the intestinal and/or fecal microbiota in IBS. 4. To determine the presence of bowel inflammation in IBS, analyzing the differences between PI-IBS and non PI-IBS. 5. To understand the altered intestinal function (motility, secretion, visceral sensitivity) in IBS, in relation to PI-IBS, SIBO, and microbiota disturbances. 6. To evaluate antimicrobial treatment in IBS.

2. Methods

2.1. Coordinator and reviewers

This initiative was carried out by a group of Mexican gastroenterologists interested in the subject. The coordinator of the group is an IBS expert (MS) and the participants were chosen based on their experience in gastroenterology and their training and participation in clinical and basic research related to the theme. An expert in the classification of levels of evidence and grades of recommendation (MP) with experience and training in gastroenterology, as well as clinical and statistical research, but who is not an IBS expert, was also included in the group. This was purposely done so that there would be both a different perspective and a more objective evidence evaluation. The 9 reviewers were divided into 6 reviewer groups (MB, RC-AH, ALC-JLT, YLV-MAV, MRT and MS), each receiving one of the 6 issues to be reviewed.

The project coordinator did a preliminary literature review in PubMed, using the MEDLINE database and including articles written up to July 2012. The following search terms were employed: «*IBS*» AND «*SIBO*», «*abnormal breath test*», «*incidence of post infectious IBS*», «*prevalence of post infectious IBS*», «*microbiota*», «*Post infectious IBS*» AND «*risk factors*», «*epidemiology*», «*low grade inflammation*», «*Microbiota*», «*dysbacteriosis*», «*SIBO*», «*methane*» AND *intestinal function*», «*intestinal motility*», «*sensory function*», «*sensory abnormalities*», «*visceral hypersensitivity*».

Once identified, the articles were distributed to those responsible for each theme to be reviewed. Systematic reviews with or without meta-analyses and original articles were selected. Narrative reviews were not included. In addition, the reviewers were authorized to include articles that were not selected in the initial review, but that were identified from other sources, such as from the references of an article originally chosen, or articles published after July 2012 and up to August 31, 2013, when the preparation of the manuscript concluded. All participants received a set of instructions by email with respect to the information to be obtained from the publications, as well as the methodology for classifying the levels of evidence and grades of recommendation.

2.2. Evidence grading

The reviewers analyzed the evidence and elaborated statements based on the available information. The levels of evidence and grades of recommendation were evaluated and graded using the Oxford Centre for Evidence-Based Medicine (OCEBM) system.[16] This system utilizes numbers and letters to evaluate the quality and the level of evidence of clinical studies. Quality and methodology are established with the numbers 1 through 5 and the lower case letter «a», «b», or «c». The numbers indicate the quality of the studies and the letters indicate the methodology employed. For example, a 1a study is usually a systematic review that only includes high quality, homogeneous, controlled clinical trials (the number 1 indicates that only high quality homogeneous controlled clinical trials were included and the letter «a» indicates that it is a systematic review); a 2 a study is a systematic review (letter «a») that includes cohort studies of different quality that are methodologically considered to be of lower quality and level (number 2) than the controlled clinical trials. A final example: 2 b is a single individual cohort or a single controlled clinical trial (letter «b») of low quality (number 2).

The grade of recommendation is given in the upper case letters A through D. The letter A is for statements, conclusions, or recommendations based on information obtained from high quality or level 1 evidence, whereas letter D is given to recommendations based on studies of low scientific quality or level 5 evidence.[16]

2.3. Evidence analysis

The first face-to-face meeting of the group was held in August 2012 and lasted 9 hours. First the OCEBM system was discussed and then the reviewers presented a summary of each selected article in tables, including authors, journal, year, country, type of article (systematic review or original) and design, diagnostic criteria for IBS, and other selection criteria for the subjects, study methods and/or evaluated treatment, outcome variables, and results or conclusions. In addition, the reviewers responsible for each theme proposed a level of evidence for each of the studies and then presented the statements or declarations and their grades of recommendation. Each of the assigned levels of evidence was discussed and were modified and accepted by consensus; the same was done for the grades of recommendation. Finally, the coordinator presented a summary of each one and its pending work. In January 2013 the second meeting was held, lasting 8 hours, and only the 6 updated reviews were presented. Then in March 2013 each reviewer sent his or her written participation to the coordinator who then sent each of the sections to be cross-reviewed. In other words, each reviewer or reviewer group went over another group's section. Once this cross-review was completed, the coordinator proceeded to edit the manuscript, after which it was reviewed again by all the participants.

3. Results

In the preliminary PubMed review, 183 references were identified; 60 were eliminated because they were duplicated, leaving 123 selected articles. Later, 9 additional articles from other sources were added. The articles identified in the initial search and those selected from other sources are described in each section. The results of the 6 aspects covered in the review are described below. Each section begins with the statements and their respective levels of evidence and grades of recommendation, followed by the corresponding summary.

3.1. 1. Frequency of small intestinal bacterial overgrowth (SIBO) in irritable bowel syndrome

- *Different studies have suggested that patients with IBS have a greater probability of having SIBO, determined through hydrogen breath tests* (level 3 evidence, grade B recommendation).
- *The reported prevalence of SIBO in patients with IBS varies widely due to the different criteria for defining a positive breath test and the methodology employed (28 to 84% with the lactulose breath test [LBT], 2 to 31% with the glucose breath test [GBT], and 2 to 6% based on cultures)* (level 3-4 evidence, grade C recommendation).

Twenty-four articles were identified that reported on the prevalence of SIBO in IBS; [3,11,17–38] 23 articles during the initial search,[3,11,17–35,37–38] and an additional article identified through manual search during the preparation of the document.[36] Two systematic reviews with a meta-analysis that included more than 3,400 subjects and compared patients with IBS and healthy controls showed that the breath tests for SIBO were abnormal in the patients, with a 4-times higher probability than the controls.[3,17] An extensive bibliographic search was carried out in both reviews, the studies were adequately selected, and the authors made a clear reference to the heterogeneity of the studies (Table 1).

On the other hand, a case series of patients with IBS that participated in an open study with rifaximin, showed a SIBO prevalence of 71% with LBT in IBS.[37] In addition, 16 case-control studies[11,18–30,36,38] provided information on SIBO prevalence in IBS, including the study by Pimentel et al.;[18] the prevalence of this comparative controlled clinical trial with placebo was the result of a sub-analysis of the study population. A second study analyzed a series of consecutive patients with diverse digestive disorders that were referred for upper endoscopy; they had duodenal aspiration culture done to determine SIBO and IBS was considered a posteriori.[36] In this same study SIBO was also compared in those patients with IBS-D and IBS-Non D, which made it incomparable with all the other studies.[36] Of the 14 remaining studies, 5 demonstrated greater SIBO prevalence in IBS compared with the controls;[3,17,19,24,38] 7 showed equal prevalence,[11,20–22,26–27,30] one showed lower prevalence in IBS,[28] and one did not report the p value, although there appeared to have been a greater prevalence in IBS[23] (Table 1). Among the analyses with greater prevalence in IBS, the study by Pimentel et al. stands out because it analyzed the prevalence of SIBO among patients with fibromyalgia, IBS, and healthy controls.[19] The patients with fibromyalgia were selected regardless of their digestive symptoms and were the group with the highest SIBO prevalence, above that of the IBS patients and the healthy controls (100, 84, and 20%, respectively). It should be stressed that only one Latin American study was identified.[21] In this study, Madrid et al., in Chile, found that the prevalence of SIBO was similar in patients with IBS, compared with that of other functional gastrointestinal disorders (IBS: 76%; functional constipation: 73%; functional diarrhea: 69%; and functional bloating: 68%).[21] Another study analyzed patients treated with proton pump inhibitors (PPIs) vs those that were not, finding no apparent differences in SIBO frequency.[25] And finally, two other studies compared IBS vs other functional gastrointestinal disorders (FGIDs).[26,29] Six case series with a combined total of 478 patients were analyzed as well, and a prevalence of SIBO was reported in patients with IBS that varied from 36 to 74%, depending on the methods employed.[31–35,37]

The use of breath tests for diagnosing SIBO has been characterized by the lack of a standardized methodology and validated criteria for defining an abnormal test. In the majority of the studies lactulose was the substrate, but with a wide variety of doses, protocols for carrying out the tests, and criteria for determining that a test is abnormal. Walters et al. used the LBT and applied 2 different criteria in their interpretation.[20] They included 39 patients with IBS and 20 healthy controls, finding a radically different SIBO prevalence in patients with IBS, even though there was no difference in the comparison with the healthy controls, regardless of the criterion used: 28% of the patients with IBS vs 30% of the control subjects when the criterion of more than 20 ppm of H_2 in the first 90 min of the test was used, compared with 69% of the patients with IBS vs 75% of the controls when the criterion of more than 20 ppm of H_2 at

Table 1 Prevalence of SIBO in IBS.

Author, journal, year	Country	Type of study	Diagnostic criteria/Study groups	n	Test employed	Outcome variables	Results/Conclusions	LE
Ford et al., Clin Gastroenterol Hepatol, 2009[3]	Canada USA	Systematic review of case-control studies	Manning, Kruis, Rome IBS vs healthy subjects	1,921 vs 326	LBT, GBT, XBT, Culture	Prevalence of SIBO and positive tests	IBS, LBT: 54%; GBT: 31%; XBT (a single study): 33%, culture: 4% (a single study). The accumulated probability of one test for +SIBO in IBS vs controls is: OR 3.4 (95% CI 0.9-12.7) to OR 4.7 (95% CI 1.7−12.9), depending on the criteria used	3a
Shah et al., Dig Dis Sci, 2010[17]	USA	Systematic Review + meta-analysis of case-control studies	Rome I, II, III IBS vs healthy subjects	1,076 vs 509	LBT, GBT, FBT, XBT	Probability of abnormal tests	IBS vs controls: OR 4.46 (95% CI 1.7 11.8)	3a
Pimentel et al., Am J Gastroente-rol, 2003[18]	USA	Case-control	Rome I IBS vs healthy subjects	111 vs 15	LBT	SIBO prevalence	IBS: 84% vs controls: 20%; ($p < 0.01$)	3b
Pimentel et al., Ann Rheum Dis, 2004[19]	USA	Case- control	Rome I IBS vs FM ACR 1990	111 vs 42	LBT	SIBO prevalence	IBS: 84% vs controls: 20%, ($p < 0.01$), vs FM: 100%; ($p < 0.05$)	3b
Walters et al., Am J Gastroenterol, 2005[20]	Canada	Case- control	Rome II IBS vs healthy subjects	39 vs 20	LBT, XBT	SIBO prevalence	H2 > 20 ppm between 90 and 180 min, IBS: 28% vs controls: 30%, ($p = NS$) H2 > 20 ppm in the first 90 min, IBS: 69% vs controls: 75%, ($p = NS$)	3b
Madrid et al., Rev Med Chile, 2007[21]	Chile	Case- control	Rome II IBS vs controls (functional bloating vs functional constipation vs functional diarrhea)	225 vs 83 vs 33 vs 26	LBT	SIBO prevalence	IBS: 76% vs controls: 76%; ($p = NS$); IBS-C: 73%, IBS-D: 76%, IBS-A: 79.7%	3b
Posserud et al., Gut, 2007[22]	Sweden	Case- control	Rome II IBS vs healthy subjects	162 vs 42	Culture	SIBO prevalence	IBS: 4% vs controls: 4%; ($p = NS$). Of the patients with SIBO, IBS-C: 43%, IBS-D: 28.5%, IBS-A: 28.5%	3b

Table 1 (*Continued*)

Author, journal, year	Country	Type of study	Diagnostic criteria/Study groups	n	Test employed	Outcome variables	Results/Conclusions	LE
Bratten et al., Am J Gastroenterol, 2008[11]	USA	Case- control	Rome II IBS vs healthy subjects	224 vs 30	LBT	SIBO prevalence	IBS: 20% vs controls: 15%; (p = 0.79)	3b
Grover et al., J Neurogastro Motil, 2008[23]	USA, Japan	Case- control	Rome II IBS vs healthy subjects	158 vs 34	XBT	SIBO prevalence	IBS: 32.9 vs controls: 17.9% (p = not reported); SIBO according to IBS subtype, IBS-C: 30.8%, IBS-D: 30.8%, IBS-M: 38.5%	3b
Scarpellini et al., J Pediatr, 2009[38]	Italy	Case- control	Children with IBS Rome II vs healthy subjects	43 vs 56	LBT	SIBO prevalence	IBS: 65% vs controls: 7%; (OR 3.9, 95% CI: 7.3-80.1, p < 0.001)	3b
Parodi et al., J Clin Gastroenterol, 2009[24]	Italy	Case- control	Rome III IBS vs Rome III functional bloating vs healthy subjects	130 vs 70 vs 70	GBT	SIBO prevalence	IBS: 16.5% vs functional bloating: 2.8% vs controls: 4.2%; (p = 0.0137); SIBO according to IBS subtype, IBS-D: 52.3%, IBS-C and IBS-M: the exact frequency is not reported	3b
Law et al., Dig Dis Sci, 2010[25]	USA	Case- control	Rome I IBS with PPI vs without PPI	106 vs 449	LBT	SIBO prevalence	IBS: 54.4%; IBS + PPI: 46.2% vs IBS - PPI: 56.3%, (OR 0.67, 95% CI 0.436-1.017, p = 0.06)	3b
Park et al., Korean J Gastroeterol, 2010[26]	South Korea	Case- control	Rome II IBS vs Rome II other FGID vs healthy subjects	76 vs 70 vs 40	LBT	SIBO prevalence	IBS: 45% vs FGID: 41% vs controls: 40%, (p = 0.97); IBS-C: 11.8%, IBS-D: 58.8%, IBS-M: 29.4%	3b
Ghoshal et al., Neurogastro-enterol Motil, 2010[27]	India	Case- control	Manning IBS vs NSCD vs healthy subjects	129 vs 73 vs 51	GBT	SIBO prevalence	IBS: 8.5% vs NSCD: 21.9% vs controls: 2%; (IBS vs NSCD, p = 0.007; IBS vs controls, p = 0.18; NSCD vs controls, p = 0.003)	3b
Choung et al., Aliment Pharmacol Ther, 2011[28]	USA, Australia	Case- control	IBS vs endoscopy patients	148 vs 527	Duodenal aspirate culture	SIBO prevalence in IBS	IBS: 2% vs controls: 10%, (p = non-specific)	3b

Table 1 (*Continued*)

Author, journal, year	Country	Type of study	Diagnostic criteria/Study groups	n	Test employed	Outcome variables	Results/Conclusions	LE
Yakoob et al., Saudi J Gastroente-rol, 2011[29]	Pakistan	Case- control	Rome III IBS-D vs NSCD	119 vs 115	LacBT	SIBO prevalence	IBS-D: 19% vs NSCD: 9%; ($p = 0.03$). Only patients with IBS-D were included	3b
Rana et al., Digestion, 2012[30]	India	Case- control	Rome II IBS-D vs healthy subjects	175 vs 150	LBT GBT	SIBO prevalence	LBT, IBS: 34 vs controls: 30%, ($p = NS$) GBT, IBS: 6.2 vs controls: 0.7%, ($p < 0.01$)	3b
Pyleris et al., Dig Dis Sci, 2012[36]	Greece	Case- control	Rome II IBS, IBS-D, IBS-Non D that underwent endoscopy	42	Culture from the third portion of the duodenum	SIBO prevalence in IBS and IBS-D vs IBS-Non D	IBS: 37.5% and IBS-D: 60% vs IBS-Non D: 27.3%, ($p = 0.004$)	3b
Pimentel et al., Am J Gastroenterol, 2003[31]	USA	Case series	Rome II IBS-D	20	LacBT, LBT, concordance between the 2	SIBO prevalence	LacBT: 53%; LBT: 74%; correlation: $\kappa = 0.29$, +H > 166 ppm in LacBT, it was a predictor of +LBT	4
Esposito et al., World J Gastro, 2007[32]	Italy	Case series	Rome II IBS	73	LBT	SIBO prevalence	SIBO prevalence, IBS: 45%	4
Peralta et al., World J Gastroente-rol, 2009[33]	Italy	Case series	Rome II IBS	97	LBT	SIBO prevalence	SIBO, IBS: 55.6%, IBS-C: 52.2%, IBS-D: 61.3%, IBS-M: 52%	4
Reddymasu et al., BMC Gastroente-rol, 2010[34]	USA	Case series	Rome II IBS	98	GBT	SIBO prevalence	SIBO, IBS:36% (IBS-C: 54%, IBS-D: 43%, IBS-M: 3%)	4
Yu et al., Gut, 2011[35]	Canada	Case series	Rome II IBS	40	LBT	SIBO prevalence	SIBO, IBS: 63%	4
Meyrat et al., Aliment Pharmacol Ther, 2012[37]	Switzerland	Case series	Rome III IBS	150	LBT	SIBO prevalence	SIBO, IBS: 71%	4

The studies are organized from higher to lower level of evidence and then in the progressive order of publication year. The prevalence of SIBO is only given according to the IBS subtypes in the studies that reported them.

ACR: American College of Rheumatology; FBT: fructose breath test; FGID: functional gastrointestinal disorders; FM: fibromyalgia; GBT: glucose breath test; H2: exhaled hydrogen; IBS: irritable bowel syndrome; IBS-A: alternating irritable bowel syndrome; IBS-C: irritable bowel syndrome with constipation; IBS-D: irritable bowel syndrome with diarrhea; IBS-M: mixed irritable bowel syndrome; LacBT: lactose breath test; LBT: lactulose breath test; LE: level of evidence; 95% CI: 95% confidence interval; NSCD: non-specific chronic diarrhea; NS: not significant; N: number; OR: odds ratio; ppm: parts per million; PPI: proton pump inhibitors; SIBO: small intestinal bacterial overgrowth; XBT: xylose breath test.

any time during the first 180 min of the test was employed.[20] Furthermore, the accuracy of the LBT has been questioned because the decomposition of this substrate by the bacteria of the cecum usually produces a second spike in hydrogen detection that reduces its specificity. In contrast, the GBT, in which the substrate is completely absorbed in the proximal small bowel (duodenum), has shown a greater sensitivity and specificity for the detection of SIBO than the LBT.[11] Rana et al. found a similar SIBO prevalence in IBS patients and healthy subjects utilizing the LBT (34 vs 30%, p = NS), but a higher prevalence of SIBO in IBS utilizing the GBT (6.2 vs 0.66%, $p < 0.01$).[30] Despite its apparently being a more precise test, it has been employed in fewer studies.[24,27,32,36] Sucrose, another substrate that is totally absorbed in the small bowel and therefore theoretically more accurate, was used in only one of the selected studies.[23]

On the other hand, the presence of SIBO has also been defined based on the detection of an elevated bacterial count from small bowel fluid culture. The quantitative culture should then be regarded as the benchmark test for SIBO, but it has been utilized in very few studies. However, it would depend on the culture site and many bacteria are unculturable. Only 2 of the selected studies employed culture for detecting SIBO,[22,28] and as mentioned before, one of them reported a lower SIBO frequency in IBS vs control subjects with different pathologies that underwent endoscopy.[28]

We can therefore conclude that there is evidence suggesting a greater probability of SIBO in IBS according to breath test data, but there is not enough evidence for recommending the routine use of these tests for diagnosing SIBO in IBS.

3.2. 2. Alterations in the gut microbiota (dysbiosis) in irritable bowel syndrome

- *The composition of the microbiota in patients with IBS is different from that of normal subjects* (level 3 b evidence, grade B recommendation).
- *Alterations in the composition of the microbiota - dysbiosis- occur in both adult and pediatric patients with IBS* (level 3 b evidence, grade B recommendation).
- *Due to the heterogeneity of IBS and the use of different methods for studying the gut microbiota, it is not possible to establish a microbial composition characteristic of IBS* (level 3 b evidence, grade B recommendation).

Twenty-six published articles were identified that studied the composition of the microbiota in patients with IBS; 24 in the initial search[41–64] and 2 from other sources.[39,40] All of them are case-control studies conducted in Europe, Asia, and the United States; none from Latin America or Africa. Twenty-five were carried out on adult population[39–55,57–64] and only one on children.[56] In 11 of the studies, the cases were classified according to the IBS subtype.[41,43,46–48,52,55–56,60,62,64] The microbiota was analyzed with molecular methods in the majority of the studies, whereas just fecal culture was used in 2,[39,40] and both methodologies were used in 4 studies.[42,48,51,58] Even though the majority of the studies analyzed the composition of the microbiota in samples of fecal matter, the microbial composition was also examined in biopsies of the colonic mucosa in 4 of the studies. The predominant results of each of these studies and the summary of the microbial ecology of the gut microbiota in IBS are shown in Table 2.

The investigations that used fecal cultures for studying the gut microbiota have shown that IBS patients, unlike healthy subjects, have a diminished population of bifidobacteria and lactobacilli and an increased population of streptococci, coliforms, and *Clostridium* species.[39,40,42,51] Moreover, the majority of the studies used molecular methods independent of the culture, such as tests based on DNA extraction and amplification of the 16S genes of ribosomal RNA, quantitative PCR, the products of PCR through denaturing gradient gel electrophoresis, and probe-specific fluorescence in situ hybridization. The many different molecular strategies employed in these studies (Table 3) is the reason for the inconsistent and even contradictory results in relation to the composition and diversity of the microbiota in patients with IBS, as well as a single determination of the microbiota in the variable of time and the limited knowledge of new bacterial species that are still waiting to be described. Thus, even though it seems that the gut microbiota of patients with IBS is different from that of the controls, it is not yet possible to establish an intestinal microbial composition characteristic of IBS.

3.3. 3. Incidence and prevalence of post-infectious irritable bowel syndrome (PI-IBS)

- *The average incidence of PI-IBS has been reported as 9 to 10% with a 4 to 36% interval* (level 1 a evidence, grade A recommendation).
- *The prevalence of PI-IBS varies from 3 to 17% and decreases over time after gastrointestinal infection* (level 3 b evidence, grade B recommendation).
- *The most studied etiology in relation to PI-IBS is that of bacterial origin, and even though the viral and parasitic causes have scarcely been studied, they also appear to be risk factors for PI-IBS* (level 2 b evidence, grade B recommendation).

Twenty-three studies on PI-IBS were reviewed, 19 of which were identified in the initial search[10,65–82] and 4 afterwards from other sources.[83–86] Twelve studies reported the incidence of PI-IBS (new onset IBS),[65–67,71–72,75,77,80,83,85] 8 reported the prevalence,[65,69,73,74,78,79,82,84] and 8 analyzed the risk factors related to the development of PI-IBS.[10,66,70,72,82,84,86] All the studies were conducted on adult population, with the exception of one on pediatric population[71] (Table 4).

The incidence of clinical symptoms of IBS after a gastrointestinal infection has been reported at an average of 9-10% based on 2 systematic reviews, but varies depending on the case from 4 to 36%.[65,67] There are no differences if IBS develops after an acute gastroenteritis episode during epidemics, due to isolated infections, or after traveler's diarrhea.[65] Likewise, the probability of developing IBS is 6 times higher in subjects that have been exposed to gastrointestinal infections than in those that have not.[66]

The prevalence of PI-IBS has been reported in 7 to 33% of patients, but there are wide variations depend-

Table 2 Studies on the composition of the intestinal microbiota in patients with IBS.

Author, journal, year	Country	Type of study	Diagnostic criteria/Study groups	n	Sample	Method	Results/Conclusions	LE
Balsari et al., Microbiologica, 1982[39]	Italy	Case-control	Nonspecified IBS criteria vs healthy controls	20 vs 20	Stool	Culture	Composition of the microbiota, IBS vs controls: < *Lactobacillus* spp, < *Bifidobacterium spp*, < Coliforms	3b
Si et al., World J Gastroenterol, 2004[40]	China	Case-control	Rome II IBS vs healthy controls	25 vs 20	Stool	Culture	Number of bacteria, IBS vs controls: < *Enterobacteriaceae*, > *Bifidobacterium*, (both $p < 0.05$)	3b
Malinen et al., Am J Gastroenterol, 2005[41]	Finland	Case-control	Rome II IBS vs healthy controls	27 vs 22	Stool	qPCR	Total bacteria, IBS vs controls: < *C. coccoides*, ($p < 0.04$) IBS-D: <*Lactobacillus* spp, ($p < 0.019$) IBS-C: >*Veillonella* spp, ($p < 0.045$)	3b
Matto et al., Immunol Med Microbiol, 2005[42]	Finland	Case-control	Rome II IBS vs healthy controls	26 vs 25	Stool	Culture, PCR-DGGE	Composition of the microbiota, IBS vs controls: > Coliforms, > Aerobic/Anaerobic Temporal stability, IBS < controls	3b
Maukonen et al., J Med Microbiol, 2006[43]	Finland	Case-control	IBS-D vs IBS-C vs IBS-M nonspecified criteria vs healthy controls	7 vs 6 vs 3 vs 16	Stool	PCR-DGGE	Predominant microbiota, in all: *C. coccoides-Eubacterium rectale*, IBS-C: 30% vs IBS-D: 50% vs controls: 43%; temporal stability, IBS < controls	3b
Kassinen et al., Gastroenterology, 2007[44]	Finland	Case-control	Rome II IBSD vs IBS-C vs IBS-M vs healthy controls	10 vs 8 vs 6 vs 23	Stool	16S rRNA sequencing, qPCR	Composition of the microbiota, IBS: < *Lactobacillus* (almost nonexistent) and *Collinsella* (especially in IBS-D and IBS-M) vs controls; IBS-D: abundant *Streptococcus* and < Bifidobacteria, IBS-C: abundant Ruminococcus, IBS-M: Predominance of Bacteroides and *Allisonella*	3b

Table 2 (*Continued*)

Author, journal, year	Country	Type of study	Diagnostic criteria/Study groups	n	Sample	Method	Results/Conclusions	LE
Kerckhoffs et al., World J Gastroenterol, 2009[45]	The Netherlands	Case-control	Rome II IBS vs healthy controls	41 vs 26	Stool, duodenal mucosa	FISH, qPCR	Composition of the microbiota, IBS vs controls: Bifidobacteria, 4.2 ± 1.3 vs 8.3 ± 1.9 ($p < 0.01$), *Bifidobacterium catenulatum*, 6 ± 0.6 vs 19 ± 2.5, ($p < 0.001$)	3b
Krogius-Kurikka et al., BMC Gastroenterol, 2009[46]	Finland	Case-control	Rome II IBS-D vs healthy controls	10 vs 23	Stool	16S rRNA sequencing	Composition of the microbiota, IBS-D vs controls: > Proteobacteria, Firmicutes (family *Lachnospiraceae)*, < Actinobacteria, Bacteroidetes	3b
Lyra et al., World J Gastroenterol, 2009[47]	Finland	Case-control	Rome II IBS-C vs healthy controls	20 vs 15	Stool	qPCR	Characteristic phylotypes, 85%≈C. *thermosuccinogenes*, IBS-D: -4.08 ± 0.90 vs controls: -3.33 ± 1.16 ($p = 0.04$), vs IBS-M: -3.08 ± 1.38 ($p = 0.05$); 94% ≈*R. torques*, IBS-D: -2.43 ± 1.49 vs controls: -4.02 ± 1.63 ($p = 0.01$); 93%≈*R. torques*, controls: -2.41 ± 0.53 vs IBS-M: -2.92 ± 0.56 ($p = 0.00$); *R. bromii-like* in IBS-C: -1.61 ± 1.83 vs controls: -3.69 ± 2.42 ($p = 0.01$)	3b
Carroll et al., Gut Pathog, 2010[48]	USA	Case-control	Nonspecified IBS-D criteria vs healthy controls	10 vs 10	Stool, colonic mucosa	Culture, qPCR	Composition of the fecal microbiota, IBS-D: 1.4×10^7 vs controls: 8.4×10^8 CFU/g feces ($p = 0.002$) > 3.6 *Lactobacillus* spp ($p = 0.002$); colonic mucosa, with no differences	3b
Codling et al., Dig Dis Sci, 2010[49]	Ireland	Case-control	Rome II IBS vs healthy controls	47 vs 33	Stool, colonic mucosa	DGGE of the 16S rRNA gene	Composition of the fecal microbiota, IBS vs controls: < variability ($p < 0.001$); with no differences between stool and mucosa	3b
Noor et al., BMC Gastroenterol, 2010[50]	United Kingdom	Case-control	Rome II IBS vs UC vs healthy controls	11 vs 13 vs 22	Stool	PCR-DGGE and 16S rRNA sequencing	Number of bacterial bands, IBS: 39 ± 6 vs UC: 37 ± 5 vs controls: 45 ± 3 ($p = 0.01$); < Bacteroides and Parabacteroides biodiversity, IBS, UC < controls ($p = 0.01$)	3b

Table 2 (*Continued*)

Author, journal, year	Country	Type of study	Diagnostic criteria/Study groups	n	Sample	Method	Results/Conclusions	LE
Malinen et al., World J Gastroenterol, 2010[64]	Finland	Case series	Rome I IBS	44	Stool	qPCR	Composition of the microbiota, 94%≈*R. torques*-like, was associated with IBS symptom severity; IBS with 94%≈*R. torques*: < *C. cocleatum*, *C. aerofaciens*-like and *C. eutactus* 97%	4
Tana et al., Neurogastroenterol Motil, 2010[51]	Japan	Case-control	Rome II IBS vs healthy controls	26 vs 26	Stool	Culture, qPCR	Altered microbiota (log_{10} bacteria g^{-1}), *Veillonella* spp, IBS: 7.2 ± 0.8 vs controls: 6.8 ± 0.7 (p = 0.046), *Lactobacilli* spp, IBS: 5.6 ± 1.9 vs controls: 4.6 ± 1.6, (p = 0.031)	3b
Carroll et al., Am J Physiol Gastrointest Liver Physiol, 2011[52]	USA	Case-control	Rome III IBS-D vs healthy controls	16 vs 21	Stool, colonic mucosa	PCR with 16S rRNA primers	Biodiversity in stool, IBS-D vs controls: < 1.2 times (p = 0.008); no differences in the colonic mucosa	3b
Kerckhoffs et al., J Med Microbiol, 2011[63]	Holland	Case-control	Rome II IBS vs controls	37 vs 20	Stool, duodenum	PCR-DGGE	Composition of the microbiota, *Pseudomonas* 48% of clones duodenum, IBS: 8.3 ± 0.9 vs controls: 0.1 ± 0.007 (p < 0.001); stool, IBS: 2.34 ± 0.31 vs controls: 0.003 ± 0.0027 (p < 0.001)	3b
Ponnusamy et al., J Med Microbiology, 2011[53]	Korea	Case-control	Rome II IBS vs healthy controls	11 vs 8	Stool	qPCR DGGE of 16S rRNA genes	Bacterial diversity, IBS-D > controls, (p = 0.004), < *Bifidobacter* and *C. coccoides*; Number of bacteria, IBS = controls	3b
Rajilic-Stojanovic et al., Gastroenterology, 2011[54]	Holland	Case-control	Rome II IBS vs healthy controls	62 vs 46	Stool	16S phylogenetic microarrays and qPCR	Firmicutes-Bacteroides ratio, IBS vs controls: x2 (p = 0.0002), x1.5 *Dorea*, *Ruminococcus* and *Clostridium* spp (p = 0.005), x2 *Bacteroidetes* (p = 0.0001), x1.5 *Bifidobacterium* and *Faecalibacterium* spp (p = 0.05); methanogens, IBS: 3.50 ± 107 vs controls: 8.74 ± 106 cells/g feces (p = 0.003)	3b

Table 2 (*Continued*)

Author, journal, year	Country	Type of study	Diagnostic criteria/Study groups	n	Sample	Method	Results/Conclusions	LE
Rinttila et al., Gut Pathog, 2011[55]	Finland	Case-control	Rome I IBS-D vs healthy controls	96 vs 23	Stool	qPCR	*S. aureus* prevalence, IBS: 17% vs controls: 0 ($p < 0.05$), *C. perfringes*, IBS: 13% vs controls: 17% (NS)	3b
Saulnier et al., Gastroenterology, 2011[56]	USA	Case-control	Children with Rome III IBS-C vs healthy controls	22 vs 22	Stool	16S rRNA metagenomic sequencing and DNA microarrays	Composition of the microbiota, IBS-C vs controls: > 0.07% Proteobacterias (*Haemophilus parainfluenzae);* a novel *Ruminococcus*-like microbe, was associated with IBS	3b
Carroll et al., Neurogastroenterol Motil, 2012[57]	USA	Case-control	Rome II IBS-D vs healthy controls	23 vs 23	Stool	High performance DNA sequencing	Composition of the microbiota, IBS: > *Enterobacteriacea*, ($p = 0.03$), < Fecalibacterium ($p = 0.04$) vs controls	3b
Chassard et al., Aliment Pharmacol Ther, 2012[58]	France	Case-control	Rome II IBS-C vs healthy controls	14 vs 12	Stool	Culture and FISH	Composition of the microbiota, Enterobacteria, IBS-C: 7.4 ± 0.8 vs controls: 6.4 ± 0.9 ($p = 0.01$), Bifidobacteria, 6.8 ± 0.7 vs 7.8 ± 0.5 ($p < 0.0001$), lactobacilli, 5.5 ± 0.9 vs 6.9 ± 0.7 ($p = 0.0007$), lactate utilizers, 7.9 ± 1.2 vs 9.3 ± 0.4 ($p = 0.0046$), sulfate utilizers, 8.4 ± 0.3 vs 5.9 ± 0.4 ($p = 0.0002$), < butyrate producers, *Roseburia-E. rectale* (*Lachnospiraceae*) ($p < 0.05$)	3b
Duboc et al., Neurogastroenterol Motil, 2012[59]	France	Case-control	Rome III IBS vs healthy controls	14 vs 18	Stool	qPCR	Number of bacteria, IBS-D vs controls: the same number of bacteria, > *E. coli* ($p = 0.002$), < *Leptum* ($p < 0.001$), < Bifidobacteria ($p = 0.007$)	3b

Table 2 (*Continued*)

Author, journal, year	Country	Type of study	Diagnostic criteria/Study groups	n	Sample	Method	Results/Conclusions	LE
Jeffery et al., Gut, 2012[60]	Sweden	Case-control	Rome II IBS-D vs IBS-C vs IBS-A vs healthy controls	15 vs 10 vs 12 vs 20	Stool	16S rRNA pyrosequencing	3 IBS subgroups were identified, 1: microbiota similar to the controls; 2 and 3: > Firmicutes and < Bacteroidetes vs controls	3b
Maccaferri et al., Gut Microbes, 2012[61]	Italy	Case-control	IBS-D vs IBS-M vs IBS-C vs controls	10 vs 5 vs 20 vs 24	Stool	Microarrays	Composition of the microbiota, IBS vs controls: > Lactobacilli, > *B. cereus*, > *B. clausii*, > Bifidobacteria, > Clostridia IX, > *E. rectale*, < Bacteroides/genus *Prevotella* and < *Veillonella*	3b
Parkes et al., Neurogastroenterol Motil, 2012[62]	United Kingdom	Case-control	Rome III IBS-D vs IBS-C vs healthy controls	27 vs 26 vs 26	Colonic mucosa	FISH, confocal micros-copy	Number of bacteria/mm^3 (IQR), IBS: 218 (209) vs controls: 128 (121), ($p = 0.007$); Bacteroides, 69 (67) vs 14 (41), ($p = 0.001$), *E. rectale–Clostridium coccoides*, 52 (58) vs 25 (35), ($p = 0.03$), Bifidobacteria, IBS-D: 24 ± 32 vs IBS-C: 54 ± 88 vs controls: 32 ± 35, ($p = 0.011$)	3b

The studies are organized from higher to lower level of evidence and then in the progressive order of publication year.
A: alternating; C: constipation; D: diarrhea; DNA: deoxyribonucleic acid; FISH: fluorescence in situ hybridization; H2: hydrogen; IBS: irritable bowel syndrome; IQR: interquartile range; LE: level of evidence; N: number; PCR-DGGE: polymerase chain reaction-denaturing gradient gel electrophoresis; qPCR: quantitative polymerase chain reaction; RCT: randomized controlled trial; rRNA: ribosomal ribonucleic acid; spp: all the species of the genus referred to; UC: nonspecific chronic ulcerative colitis; >: increase; <:decrease;.

Table 3 Molecular methods used in the microbiota analysis.

FISH (Fluorescence in situ hybridization)	FISH is a technique that detects the sequences of nucleic acids in bacteria and tissue. In situ detection provides direct visualization of the special location of specific sequences, which is crucial for explaining the genetic organization and function. For this reason the in situ hybridization method is an important technique in the diagnosis of chromosomal rearrangement in microorganism detection. In situ hybridization is based on the complementariness of the nucleic acids of DNA and/or RNA through the hydrogen bridges formed between the bases: adenine-thymine (DNA) or uracil (RNA) and cytosine-guanine (DNA and RNA)
PCR-DGGE (amplification by polymerase chain reaction- denaturing gradient gel electrophoresis)	The genetic blueprint technique is useful for identifying bacteria (isolated or in community) at the end of a polymerase chain amplification of its DNA. The genetic print consists of a profile based on the physical separation of the unique sequence of the 16S ribosomal RNA gene through DGGE. It also enables the simultaneous analysis of numerous bacteria from a clinical sample or tissue. Thus the technique makes it possible to compare the genetic diversity of bacteria and the study of their behavior at the same time
16S rDNA (deoxyribonucleic acid)	16S rDNA is the gene that encodes for 16s ribosomal RNA. It is a component of the small subunit of prokaryotic ribosomes. The 16S rDNA gene is used for phylogenetic studies because it is highly conserved among the different bacterial and archaeal species; in addition it contains hypervariable regions that provide specific species sequences that are useful for bacterial identification. The use of these sequences has made it possible to become aware of the existence of a large number of genera and species
16S rRNA (ribonucleic acid)	16S rRNA is a polyribonucleotide of approximately 1.500 nt, encoded by the RRS gene. It is also designated 16s ribosomal DNA (16S rDNA) and phylogenic and taxonomic information can be obtained from its sequencing. Regarded as a molecular chronometer due to the fact that it is an ancient molecule present in all bacteria, 16S ribosomal RNA (rRNA) is the most widely used macromolecule in studies of bacterial phylogeny and taxonomy. The changes in its sequence data occur slowly and its variability enables it to distinguish organisms both nearby and distant
Quantitative PCR (deoxyribonucleic acid)	Quantitative polymerase chain reaction (qPCR) or real-time PCR is a variation of the standard PCR technique that is employed to determine the number of DNA or mRNA copies present in a sample (measurement of gene expression). The microorganisms in a sample can be identified and quantified by this technique, which is very useful for the diagnosis and treatment of patients
Phylogenetic microarray	Microarrays are made up of biologic or synthetic material and a solid support in which it is immobilized or the biologic material is adsorbed. Microarrays have different applications, such as the detection of genes in a sample (DNA microarrays), the presence of polymorphisms, or the determination of different gene expressions (mRNA microarrays). Microarrays have the advantage that the presence and/or expression of a large number of genes can be analyzed simultaneously. Dendograms, which enable the genetic relation of different samples to be observed, can be constructed through bioinformatic analysis
Pyrosequencing	Pyrosequencing is a non-fluorescent massive sequencing technique that enables the determination of nucleotide sequences in a sample. One of the advantages of this technique is that if a sample contains a mixture of bacterial species, they can each be identified through the bioinformatic analysis

ing on the reported series and particularly on the time of observation.[65] Prevalence also varies depending on the geographic region and Mexico appears to have one of the lowest prevalence rates in the world, at only 5.0%.[79] Prevalence is also higher if it is evaluated sooner rather than later after an infectious outbreak. For example, 2 years after an outbreak of bacterial gastroenteritis in Walkerton (Canada), PI-IBS prevalence was reported in 30.4% of the subjects exposed to acute gastroenteritis.[87] Contrastingly, in the following years the prevalence had decreased and at 8 years it was 15.4%.[70,88] Similarly, in Sweden the initial PI-IBS prevalence of 12% was reduced to 9%, 5 years later.[84] In large reviews it has been reported that the probability (odds ratio: OR) of developing IBS 3 months after an episode of infectious diarrhea was 7.58-8.47 times higher than in the control population, but at 24 to 36 months the OR had descended to 3.85-4.05.[10,66]

Regarding the causal agent of PI-IBS, the studies on incidence and prevalence generally refer to clinical presentations of IBS after bacterial infections or the cause is not specified. The most frequently identified bacteria have been *E. coli, Campylobacter, Shigella*, and *Salmonella*.[10,67,68,77,80] *E. coli* was the cause in the majority of the patients presenting with PI-IBS after an episode of traveler's diarrhea acquired in Mexico.[80] In a group of patients in Houston (Texas) 16.1% of the patients with PI-IBS had previously travelled abroad, whereas only 7.5% of the patients with non PI-IBS had done so.[69] A study conducted on children

Table 4 Incidence, prevalence, and risk factors for PI-IBS.

Author, journal, year	Country	Type of study	Diagnostic criteria/Study groups	n	Outcome variables	Results/Conclusions	LE
Thabane et al., Aliment Pharmacol Ther, 2007[86]	Canada	Systematic review of prospective controlled studies	Manning, Rome I, II, III IBS in subjects exposed to acute GE vs non-exposed	2,977 vs 586,523	Risk for PI-IBS, risk factors	Overall risk: (OR = 5.86, 95% CI 3.60–9.54) 3 months: OR = 7.58 (95% CI 4.27–13.45) 6 months: OR = 5.18 (95% CI 3.24–8.26) 12 months: OR = 6.37 (95% CI 2.63–15.40) 24-36 months: OR = 3.85 (95% CI 2.95–5.02); Risk factors for PI-IBS vs non PI-IBS: younger age, greater anxiety and depression	1a
Schwille-Kiuntke et al., Z Gastroenterol, 2011[65]	Germany	Systematic review	Subjects exposed to acute diarrhea (epidemics, individual GE, traveler's diarrhea) Manning, Rome I, II IBS	6,404 (2,414; 3,764; 226) 811	Incidence, prevalence of PI-IBS at 12 months	Incidence, post-epidemics: 7-32%; post-individual GE: 4-36%; post-traveler's diarrhea: 4-14%; prevalence: 7-32%	1a
Dai et al., Hepatogastro-enterology, 2012[66]	China	Systematic review of case-control studies	Rome, Manning IBS in subjects exposed to bacterial GE vs non-exposed	2,721 vs 586,297	Incidence of PI-IBS, risk factors	Global: OR = 6.03 (95% CI 3.58-10.13); 3 months: OR = 8.47 (95% CI 4.85-14.76); 6 months: OR = 4.58 (95% CI 2.94-7.14); 12 months: OR = 6.19 (95% CI 2.82-13.58); 24-36 months: OR = 4.05 (95% CI 3.13-5.24); risk factors: female sex, younger age, severity of initial insult, enteritis duration, adverse psychological factors	3a

Table 4 (*Continued*)

Author, journal, year	Country	Type of study	Diagnostic criteria/Study groups	n	Outcome variables	Results/Conclusions	LE
Haagsma et al., Epidemiol Infect, 2010[67]	Hollan-d	Case-control outcome	Rome, Manning IBS in subjects exposed to bacteria vs *Campylobacter* vs *Salmonella* vs *Shigella* vs controls	318 vs 108 vs 266 vs 322 vs 585,178	Incidence of PI-IBS at 1 year post GE, AR at 10-12 months	Incidence: 4-17%; AR: 8.8% (90%CI 7.2-10.4)	2b-c
Okhuysen et al., Am J Gastroenterol, 2004[80]	USA	Cohort study	Rome II IBS, traveler's diarrhea from enteropathogenic and enterotoxigenic *E. coli* in Mexico	169	Incidence PI-IBS at 6 months	10%	2b
Moss-Morris et al., Psychosom Med, 2006[81]	New Zealand	Cohort study	Rome I, II IBS in subjects exposed to GE from *Campylobacter* vs infectious mononucleosis	592 vs 243	Risk for PI-IBS after 3 and 6 months	Risk for PI-IBS: *Campylobacter* > Mononucleosis, 3 months: OR = 3.45 (95% CI 1.75-667) 6 months: OR = 2.22 (95% CI 1.11-6.67)	2b
Törnblom et al., Clin Gastroenterol Hepatol, 2007[84]	Sweden	Cohort study	Rome II IBS in subjects exposed to bacterial, viral, and parasitic GE	333	Prevalence of PI-IBS, risk factors	Prevalence of GI symptoms, 3 months: 12%; 5 years: 9% (68% IBS); risk factors: female sex, OR = 2.65 (95% CI 1.28-5.50); antibiotic use, OR = 2.37 (95% CI 1.07-5.25)	2b
Marshall et al., Clin Gastroenterol Hepatol, 2007[85]	Canada	Cohort study	Rome I IBS in subjects exposed to GE due to *Norovirus*	135	Incidence PI-IBS after 3 months, risk factors	Incidence in exposed subjects: 23.6% vs non-exposed: 3.4% (OR 6.9, 95% CI 1.0–48.7, p = 0.014); Risk factor: Vomiting during the GE, OR = 10.5 (95% CI 1.3-85.5, p = 0.028)	2b

Table 4 (*Continued*)

Author, journal, year	Country	Type of study	Diagnostic criteria/Study groups	n	Outcome variables	Results/Conclusions	LE
Thabane et al., Am J Gastroenterol, 2010[71]	Canada	Cohort study	Rome I IBS in children exposed to *E. coli* 0157:H7, *Campylobacter* spp	467	Incidence of PI-IBS	Exposed subjects: 10.5 vs non-exposed: 2.5%, OR = 4.6 (95% CI 1.6-13.3)	2b
Pitzurra et al., J Travel Med, 2011[72]	Switzerland	Cohort study	Rome III IBS	2,476	Incidence of PI-IBS in Europeans traveling to destinations with limited resources	IBS: 1.0% (95% CI 0.6-1.4) PI-IBS: 2.8% (95% CI 1.7-3.9) Unselected IBS: 0.9% (95% CI 0.5-1.4); Risk factors 6 months after travel: traveler's diarrhea OR = 3.61 (95% CI 1.74−7.51); adverse life events 1 year prior to travel, OR = 2.58 (95% CI 1.09-6.07); diarrhea 4 months before travel OR = 2.5 (95% CI 1.19−5.24)	2b
Thabane et al., Am J Gastroenterol, 2009[10]	Canada	Cohort study	Nonspecified PI-IBS criteria in subjects exposed to GE from *E. coli* 0157:H7, *C. jejuni* and others vs non-exposed	1,368 vs 701	To determine and validate PI-IBS predictive factors	Predictors: female sex, age < 60, longer duration of diarrhea, more frequent bowel movements, abdominal colic, bloody stools, weight loss, fever, psychological alterations (anxiety and depression), OR = 1.05 (95% CI 1.03-1.06, p < 0.0001); these factors derive from a numerical scale that determines low moderate to high risk for PI-IBS	1b
Schwille-Kiuntke et al., Neurogastroenterol Motil, 2011[82]	Germany	Cohort study	Rome III IBS in GE from *Salmonella* vs *Campylobacter*	223 vs 249	Prevalence of PI-IBS, moderate to severe cases	Prevalence, *S. enteritidis*: 8.1% vs *C. jejuni*: 12.8%; severe PI-IBS, *Salmonella* > *Campylobacter*: $X^2 = 3.984$, p = 0.047; risk factors for IBS, *Salmonella* > *Campylobacter*: female sex, younger age	2b
Villani et al., Gastro-enterology, 2010[76]	Canada	Case-control study within a cohort study	Rome I IBS in subjects exposed to GE vs Exposed subjects without IBS	228 vs 581	To establish genetic variants associated with PI-IBS susceptibility	CDH1, tight junction protein promoters (rs16260, -C160A, p = 0.0352); IL6, cytokine (rs1800795, -G174C, p = 0.0420); TLR9, innate immune receptor (rs352139, P545P, p = 0.0059) and (rs5743836, -T1237C; p = 0 .0250)	2a

Table 4 (*Continued*)

Author, journal, year	Country	Type of study	Diagnostic criteria/Study groups	n	Outcome variables	Results/Conclusions	LE
Ji et al., J Gastroen-terol Hepatol, 2005[67]	South Korea	Case-control study within a cohort study	Rome I, II IBS in subjects exposed to *Shigella* vs non-exposed	101 vs 102	Incidence of PI-IBS after 12 months, risk factors	Incidence in exposed subjects: 14.85% vs non-exposed: 5.88, OR = 2.9 (95% CI 1.1-7.9); Independent risk factor: diarrhea	2b
Marshall et al., Gut, 2010[70]	Canada	Case-control study with a cohort study	Rome I IBS in subjects exposed to GE due to *E. coli* 0157:H7 and *C. jejuni* vs non-exposed subjects	742 vs 424	Prevalence of PI-IBS, risk factors	Prevalence, 2-3 years: 28.3% vs 8 years: 15.4%; risk in exposed subjects vs non-exposed OR = 3.12 (95% CI 1.99-5.04); independent risk factors at 8 years: female sex, younger age, previous anxiety/depression, fever, weight loss during the acute infection	2b
Kim et al., Korean J Gastroenterol, 2006[77]	South Korea	Case-control study within a cohort study	Rome II IBS in subjects exposed to *Shigella* spp vs non-exposed	95 vs 105	PI-IBS at 3 years	Incidence, 1 year: 13.8% vs 1.1% OR = 11.9 (95% CI 1.49-95.58); 3 years: 14.9% vs 4.5% OR = 3.93 (95% CI 1.20-12.86); recovery from PI-IBS at 3 years: 25%	2b
Morgan et al., Gastroen-terol Res Pract, 2012[73]	Nicara-gua	Case-control study within a cohort study	Rome II IBS	163 vs 194	Prevalence of IBS in accordance with parasite burden	With parasitosis: 16.6% vs controls: 15.4%, (p = NS); IBS-D: 25%, IBS-C: 32%, IBS-M: 43%	2b
Zanini et al., Am J Gastroenterol, 2012[75]	Italy	Case-control study within a cohort study	Rome III IBS, in subjects exposed to norovirus vs non-exposed	186 vs 198	Incidence of PI-IBS after 1 year	Exposed subjects: 21.5% vs non-exposed: 1.5%, OR = 11.40 (95% CI 3.44-37.82), p < 0.0001; IBS-C: 10%, IBS-D: 17.5%, IBS-M: 40%, IBS-U: 32.5%	2b
Soyturk et al., Am J Gastroenterol, 2007[83]	Turkey	Case-control study within a cohort study	Rome II IBS in subjects exposed to GE from *Trichinella britovi* vs non-exposed	72 vs 27	Incidence of PI-IBS at 2 months, persistence and symptoms at 4, 6, and 12 months	Incidence at 2 months in exposed subjects: 13.9% vs non-exposed: 0; persistence, 4 months: 13.9%; 6 months: 13.9%; 12 months: 7%	2b

Table 4 (*Continued*)

Author, journal, year	Country	Type of study	Diagnostic criteria/Study groups	n	Outcome variables	Results/Conclusions	LE
DuPont et al., Am J Trop Med Hyg, 2010[69]	USA	Case-control	Rome II IBS PI, non PI (after acute symptom presentation)[a]	221	Prevalence of PI-IBS and non PI-IBS, history of traveler's diarrhea in IBS	Prevalence, PI-IBS: 11.4% vs non PI-IBS: 24.9% traveler's diarrhea, PI-IBS: 14.0% vs non PI-IBS: 4.5, (p = 0.006)	3b
Porter et al., Dig Dis Sci, 2011[78]	USA	Case-control	FGID ICD-9 564.1 in soldiers deployed in Afghanistan vs deployed soldiers without FGID	129 vs 396	Prevalence of diarrhea, to determine whether diarrhea, vomiting, and war-related stressors were risk factors for PI- IBS	Prevalence of IBS: 17%; risk factors, diarrhea: OR = 5.27 (95% CI 2.28-12.21, p < 0.001); vomiting: OR = 7.00 (95% CI 2.70-18.14, p < 0.001) stress: OR = 2.30 (1.06-4.96, p < 0.05)	3b
Wensaas et al., Gut, 2012[74]	Norway	Case-control	Rome III IBS in subjects exposed to giardiasis vs non-exposed	817 vs 1,128	Prevalence of PI-IBS vs non PI-IBS after 3 years	PI-IBS: 46.1% vs non PI-IBS: 14% RR = 3.4 (95% CI 2.9-3.8)	3b
Rodríguez-Fandiño et al., Neurogas-troenterol Motil, 2013[79]	Mexico	Case-control study within an experi-mental study	Rome II IBS Spiller PI-IBS questionnaire	20	Prevalence of PI-IBS	5.0%	3b

The studies are organized from higher to lower level of evidence and then in the progressive order of the year of publication.
AR: attributable risk; C: constipation; CDH1: cadherin 1; D: diarrhea; FGID: functional gastrointestinal disorder; GE: gastroenteritis; IBS: irritable bowel syndrome; LE: level of evidence; M: mixed; 95% CI: 95% confidence interval; N: number; NS: not significant; OR: odds ratio; PBMC: peripheral blood mononuclear cells; PI: post-infectious; RR: relative risk; spp: species; TLR9: Toll-like receptor 9; U: unclassifiable.

[a] The acute clinical presentation considered to be GE for determining PI-IBS: fever, vomiting, abdominal pain, dysentery; urgency.

reported PI-IBS in 10.5% after *Campylobacter* infection, compared with IBS in 2.5% of the children that were not exposed.[71] On the other hand, bacterial gastroenteritis due to *Campylobacter* is followed by IBS more frequently than by infectious diseases that do not affect the digestive tract, such as infectious mononucleosis, for example.[81] With respect to gastroenteritis of viral etiology, *Norovirus* has been described as causing PI-IBS; the results of the 2 published studies on this[75,85] coincide, reporting that 21.5 and 23.6% of the patients had PI-IBS, whereas only 1.5 and 4.4% of the controls had IBS. In relation to the role of intestinal parasites, the results are less conclusive. A Central American study found no differences in IBS prevalence according to the Rome II criteria in individuals with a history of parasitosis vs subjects with no such history (16.6% vs 15.4%).[73] On the other hand, after a giardiasis outbreak that infected a large number of Norwegians, the prevalence of IBS according to the Rome III criteria was noticeably higher than in the control population (46 vs 14%).[74] Likewise, in an outbreak of *Trichinella britovi* in Turkey that resulted in 72 cases of infection, 10 developed IBS (13.9%).[83]

In reference to the risk factors for developing PI-IBS, the female sex, the severity of gastroenteritis, and the presence of anxiety and depression have been described.[10] Villani et al. analyzed the subjects that developed PI-IBS 2 to 3 years after the Walkerton epidemic, and found that genetic variations associated with the expression of the Toll-like receptor (TLR)-9 related to innate immunity, interleukin (IL)-6 associated with immune activation, and cadherin-1 (CDH1) involved in tight epithelial junctions, were independent risk factors for PI-IBS. [76]

The above allows us to conclude that the incidence and prevalence of PI-IBS are variable and even though the bacterial etiology has been studied the most, it appears that viruses such as the *Norovirus* and parasites such as *Giardia* may also be related to PI-IBS. In addition, risk factors such as the female sex, severity of gastroenteritis, and previous anxiety and depression, as well as genetic factors associated with immunity, have been determined.

3.4. 4. Low-grade intestinal inflammation related to post-infectious and non-post-infectious irritable bowel syndrome

- *There is evidence that suggests the presence of low-grade intestinal inflammation in a subgroup of IBS patients, which involves an increase in intraepithelial T lymphocytes (IEL), mast cells and enterochromaffin cells* (level 3 a evidence, grade B recommendation).
- *The increase in IEL and mast cells appears to be more commonly observed in patients with IBS-D, compared with IBS-C and IBS-M; however, whether there are differences between PI-IBS and non PI-IBS cannot be concluded* (level 3 a-b evidence, grade B recommendation).
- *There is insufficient evidence to determine whether there are differences in the enterochromaffin cells between PI-IBS and non PI-IBS* (level 5 evidence, grade D recommendation).

A total of 29 articles were identified; 2 were systematic reviews [89,90] and the rest were original ones.[91–117] Twenty-seven studies were identified in the initial search[90–115,117] and 2 [89,116] were later selected from other sources. All the studies were conducted on adult population, with the exception of one on pediatric population. Twenty-four studies analyzed the presence of chronic inflammatory cells (T lymphocytes, mast cells, and enterochromaffin cells) in the mucosa of the colon and rectum in IBS patients and controls[89,91,94–104,107–108,110–118] (Table 5).

For several years there have been reports on the increase in the number of enterochromaffin cells in rectal biopsies of PI-IBS patients.[99–100,106] Spiller et al. reported an up to 5 times higher increase in the number of enterochromaffin cells positive for synaptophysin in patients with *C. jejuni* infection.[95] A gradual decrease in the number of enterochromaffin cells was observed in these patients in biopsies taken 6 and 12 weeks after infection; however, one year after the acute infection in the subgroup of patients that remained symptomatic, that is, those with PI-IBS, the number of enterochromaffin cells remained elevated, in a range similar to that observed 2 weeks after the *C. jejuni* infection. The higher number of enterochromaffin cells may have pathophysiologic importance because these cells are the main source of serotonin (5-HT) storage in the organism and there is evidence of an increase in 5-HT release in IBS patients.[119–120] The prokinetic and secretory effect of 5-HT may be related to the diarrhea or liquid stools that accompany IBS-D. A recent systematic review[89] concluded that despite the fact that some researchers have observed an increase in the number of enterochromaffin cells and in the production of serotonin in the mucosa of the colon and rectum in IBS patients, compared with healthy controls, many others have not confirmed such findings. The results show that these changes are not consistent.

In addition, some studies have demonstrated a rise in the number of IEL in both IBS-D and PI-IBS, mainly after acute gastroenteritis due to *C. jejuni* or *Shigella*.[95,111,117] Nevertheless, it is not completely known if there is also an increase in T lymphocytes in non PI-IBS. In fact, only 7 studies compare PI-IBS and non PI-IBS with respect to the inflammatory changes encountered through histology.[92,94,99–100,108,110–111] Dunlop et al. found a higher number of enterochromaffin cells and IEL in PI-IBS than in non PI-IBS and the controls in 2 studies, and therefore suggest that they could be markers for PI-IBS.[99–100] Likewise, Lee et al. observed a greater number of enterochromaffin cells, IEL, and mast cells in rectal biopsies in PI-IBS patients, compared with non PI-IBS patients and healthy controls.[108] An increase in the number of mast cells in non PI-IBS was observed only in those patients with IBS-D, not in patients with IBS-C or IBS-M. The rise in the number of mast cells had been previously described by Weston et al. in biopsies of the terminal ileum in patients with IBS, compared with the control group, but no differentiation was made between PI-IBS and non PI-IBS.[93] Other researchers later confirmed the increase in the number of these cells in IBS,[96,98,101,106] mainly in the IBS-D subgroup, in the patients with PI-IBS, as well as in those with non PI-IBS. Furthermore, the mast cells[95–96,98,101,106] appear to be near the sensory neurons, and there is a positive correlation with the severity and frequency of pain and/or abdominal discomfort when they are in closer proximity. [101]

Table 5 Low-grade inflammation in PI-IBS and non PI-IBS.

Author, journal, year	Country	Type of study	Diagnostic criteria/Study groups	n	Biopsy site	Inflammatory cells studied	Results/Conclusions	LE
Matricon et al., Aliment Pharmacol Ther, 2012[89]	France	Systematic review of case-control studies and RCT	Manning, Rome I, Rome II, Rome III IBS vs healthy subjects	1,282 vs 789	Terminal ileum, cecum, colon, and rectum	Mast cells, IEL, T lymphocytes, ECC	Mast cells, IEL, in the ileum, cecum, colon, and to a lesser degree in the rectal mucosa: IBS > controls; ECC: inconsistent results	3a
Ortíz-Lucas et al., Rev Esp Enferm Dig, 2010[90]	Spain	Systematic review of case-control studies and a RCT	Manning, Rome I, Rome II, Rome III IBS vs controls (healthy subjects, UC, microscopic colitis, FD, NCCP, CD, depression)	999 vs 706	Small bowel, colon	IEL, mast cells	IEL: there is evidence of an increase in IBS patients vs controls, even though results are contradictory; mast cells: there is evidence of an increase in the terminal ileum and ascending colon in IBS patients vs controls	3a
Klooker et al., Gut, 2010[91]	Holland	RCT	Rome II IBS (hyper and normosensitive patients) vs healthy subjects	60 (30, 30) vs 22	Descending colon, rectum	Mast cells	Mast cells +tryptase, IBS < controls, ($p < 0.05$); mast cells CD117, IBS normosensitive patients < controls ($p = 0.001$) and tendency in hypersensitive patients ($p = 0.06$)	2b
De Silva et al., Scand J Gastroenterol, 2012[92]	Sri Lanka	Case- Control study within a cohort	Rome III IBS (PI-IBS) vs family history of colon cancer	49 (16) vs 14	Ileum, colon	Mast cells, eosinophils, neutrophils	Mast cells/median (range), ileum, IBS: 14.67 (8-24) vs controls: 5.75 (4-8), ($p < 0.001$); cecum, IBS: 8.71 (2-14) vs controls: 4.00 (2-6), ($p < 0.001$); ascending colon, IBS: 5.54 (3-8) vs controls: 3.20 (1-5), ($p = 0.012$); descending colon, IBS: 8.67 (4-20) vs controls: 3.50 (3-4), ($p = 0.042$); rectum, IBS: 10.08 (7-16) vs controls: 4.13 (2-7), ($p < 0.001$); no differences in eosinophils, neutrophils; PI-IBS vs non PI-IBS was not analyzed	2b
Weston et al., Dig Dis Sci, 1993[93]	USA	Case-control	Manning IBS vs healthy subjects	20 vs 15	Terminal ileum	Mast cells	Cells/HPF, IBS: 23.3 ± 3.1 vs controls: 6.8 ± 1.1, ($p = 0.0001$); greater number in IBS-D without specifying if they were PI-IBS or non PI-IBS	3b
Gwee et al., Gut, 1992[94]	Great Britain	Case-control	Rome I PI-IBS vs exposed subjects without IBS vs healthy subjects	10 vs 19 vs 18	Rectum	Mononuclear cells	PI-IBS: 105.7 ± 23.3 vs exposed subjects without IBS: 83.2 ± 29.4 vs controls: 79.1 ± 16.9, ($p < 0.05$)	3b

Table 5 (*Continued*)

Author, journal, year	Country	Type of study	Diagnostic criteria/Study groups	n	Biopsy site	Inflammatory cells studied	Results/Conclusions	LE
Spiller et al., Gut, 2000[95]	Great Britain	Case-control study within a cohort	Rome I PI-IBS vs GE from *Campylobacter* vs healthy subjects	10 vs 21 vs 12	Rectum	ECC, IEL	ECC, PI-IBS: 12.7 ± 0.4 vs GE: 5.7 ± 1.0* vs controls: 1.8 ± 0.4, ($p < 0.001$); IEL CD8, PI-IBS 1.8 ± 0.3 vs GE: 0.9 ± 0.2* vs controls: 0.5 ± 0.2, ($p < 0.001$); (*12 weeks); the changes can persist up to 1 year	2b
Walker et al., Aliment Pharmacol Ther, 2009[109]	Sweden	Case-control study within a cohort	IBS-D, IBS-C vs Rome I FD vs healthy subjects	41 vs 51 vs 48	Duodenum	Mast cells, eosinophils, IEL	IEL/medians, IBS-C: 18 vs controls: 14, ($p = 0.005$), vs FD: 14, ($p = 0.003$); mast cells/medians, IBS-C: 255 vs IBS-D: 233, vs controls: 145, (IBS-C vs controls $p < 0.001$, IBS-D vs controls $p = 0.004$); eosinophils/medians, FD: 31 vs controls: 17, IBS-C: 17.5, IBS-D: 14, (FD vs controls $p < 0.001$, vs IBS-C $p = 0.001$ vs IBS-D $p < 0.001$); PI-IBS vs non PI-IBS was not specified	2b
O'ullivan et al., Neurogastro-enterol Motil, 2000[96]	Ireland	Case-control s	Rome I IBS vs healthy controls	14 vs 7	Cecum, ascending, descending colon, rectum	Mast cells	Cecum, IBS: 0.91 ± 0.18 (95% CI 0.79-1.0) vs controls: 0.55 ± 0.14 (95% CI 0.40-0.69); No differences in the ascending, descending colon, or rectum	3b
Chadwick, Gastroentero-logy, 2002[117]	New Zealand	Case-control	Rome I IBS vs controls	77 vs 28	Colon biopsies	To determine histology	3 IBS groups were found, G1: normal histology and > IEL, LPL-CD3, CD25 G2: > Neutrophils, mast cells G3: Microscopic lymphocytic colitis	3b
Törnblom et al., Gastroenterolo-gy, 2002[97]	Sweden	Case-control	Rome I IBS vs degenerative visceral neuropathy vs controls that underwent colonoscopy vs autopsies	10 vs 10 vs 20 vs 15	Intestinal wall biopsy in the proximal jejunum and colon	T-lymphocytes and IEL	Greater number of IEL in the jejunum of IBS vs controls: 13.9 ± 4.0 in controls. There was peri and intraganglionic location of the IEL in IBS; PI-IBS vs non PI-IBS was not specified	3b
Park et al., J Korean Med Sci, 2003[98]	South Korea	Case-control	Rome II IBS vs healthy subjects	14 vs 14	Cecum, rectum	Mast cells	Cecum, IBS-D: 262.7 ± 35.5/mm^2 vs controls: 165.1 ± 25.3/mm^2, ($p < 0.05$); rectum, IBS-D: 184.1 ± 27.0/mm^2 vs controls: 124.6 ± 10.7/mm^2, ($p < 0.05$); increased degranulated mast cells in the proximity of the enteric nerves; PI-IBS vs non PI-IBS was not specified	3b

Table 5 (*Continued*)

Author, journal, year	Country	Type of study	Diagnostic criteria/Study groups	n	Biopsy site	Inflammatory cells studied	Results/Conclusions	LE
Dunlop et al., Gastroenterology, 2003[99]	Great Britain	Case-control	Rome I PI-IBS vs GE due to Campylobacter vs healthy subjects	28 vs 28 vs 34	Rectum	ECC, IEL, mast cells	ECC/HPF, PI-IBS: 35.8 ± 1.2 vs GE: 30.6 ± 1.9, (p = 0.022) vs controls: 29.1 ± 1.8 (p = 0.006); IEL/HPF, PI-IBS: 127.1 ± 8.7 vs GE: 113.4 ± 6.2, (p = 0.006) vs controls: 97.1 ± 5.7, (p = 0.058); No differences in mast cells; ECC were PI-IBS predictors	3b
Dunlop et al., Am J Gastroenterol, 2003[100]	Great Britain	Case-control	Rome II IBS Spiller PI-IBS questionnaire vs Non PI-IBS subjects vs healthy subjects	23 vs 52 vs 36	Rectum	ECC, LPL, IEL, mast cells	ECC/HPF, PI-IBS: 39.4 ± 2.9 vs non PI-IBS: 31.1 ± 1.5 vs controls: 31.8 ± 1.6, (p = 0.012); LPL/HPF, PI-IBS: 120.5 ± 6.8 vs non PI-IBS: 118.5 ± 4.6 vs controls: 101.6 ± 5.9, (p = 0.042); IEL surface/500 cells, PI-IBS: 41.4 ± 4.3 vs non PI-IBS: 32.8 ± 2.7 vs controls: 43.1 ± 3.1, (p = 0.036); mast cells/HPF, PI-IBS: 41.9 ± 3.0 vs non PI-IBS: 53.0 ± 2.4 vs controls: 45.9 ± 2.8, (p = 0.017)	3b
Barbara et al., Gastroenterology, 2004[101]	Italy	Case-control	Rome II IBS vs healthy subjects	44 vs 22	Proximal descending colon	Mast cells, degranulated mast cells	Mast cells, IBS: 9.2 ± 2.5 vs controls: 3.3 ± 0.8, (p < 0.001); IBS greater number of degranulated mast cells, increased histamine and tryptase activity; PI-IBS vs non PI-IBS was not specified	3b
Wang et al., World J Gastroenterol, 2004[106]	China	Case-control	IBS-D vs Rome III non PI-IBS-C vs healthy subjects	20 vs 18 vs 20	Duodenum, jejunum, terminal ileum	ECC, mast cells	ECC, IBS = controls; Mast cells/HPF in terminal ileum, IBS-C: 38.7 ± 9.4 vs IBS-D: 35.8 ± 5.5 vs controls: 29.8 ± 4.4, (p < 0.001); no differences in the duodenum and jejunum	3b
Ohman et al., Clin Gastroenterol Hepatol, 2005[102]	Sweden	Case-control	Rome II IBS (PI-IBS) vs UC vs healthy subjects	33 (5) vs 23 vs 15	Ascending colon and sigmoid colon	LPL CD4, CD8	LPL CD8 ascending colon, IBS: 16.9 ± 5.9 vs UC in remission: 20.4 ± 5.1 vs active UC: 16.4 ± 6.9 vs controls: 10.6 ± 4.4 (IBS, UC remission vs controls, p = 0.01; active vs controls, p = 0.05); no differences in the sigmoid or CD4 in the ascending or sigmoid; PI-IBS vs non PI-IBS was not analyzed	3b

Table 5 (*Continued*)

Author, journal, year	Country	Type of study	Diagnostic criteria/Study groups	n	Biopsy site	Inflammatory cells studied	Results/Conclusions	LE
Tunc et al., Acta Médica, 2005[103]	Turkey	Case-control	Nonspecified criteria IBS vs IBD vs healthy subjects	11 vs 5 vs 5	Cecum	Mast cells	IBS: 39.3 ± 11.2 vs IBD: 22.2 ± 4.2 ($p < 0.01$) vs controls: 13.2 ± 1.9 ($p < 0.001$); PI-IBS vs non PI-IBS was not specified	3b
Park et al., Gastroenterol Hepatol, 2006[104]	South Korea	Case-control	Rome II IBS-D Non-PI vs healthy subjects	18 vs 15	Terminal ileum, ascending colon, rectum	Mast cells	Terminal ileum, IBS: 49.1 ± 7.4 vs controls: 37.9 ± 5.8, ($p < 0.01$); Ascending colon, IBS: 47.7 ± 7.1 vs controls: 37.4 ± 6.2, ($p < 0.01$); Rectum, IBS: 47.8 ± 7.6 vs controls: 37.3 ± 6.0, ($p < 0.01$)	3b
Guilarte et al., Gut, 2007[105]	Spain	Case-control	Rome II IBS-D (PI-IBS) vs healthy subjects	20 (6) vs 14	Jejunum	IEL, mast cells	IEL CD3+ IBS-D: 15.3 ± 5.5 (95% CI 12.7-17.9) vs controls: 10.3 ± 3.9 (95% CI 8.0-12.5), ($p = 0.006$); mast cells/HPF, IBS-D: 34 ± 9.3 vs controls: 15.3 ± 4.4, ($p < 0.001$), higher tryptase levels; mast cells, PI-IBS: 32.3 ± 5.9 (95% CI 26.0-38.5) vs non PI-IBS: 34.7 ± 10.2 (95% CI 28.8-0.6), (p = NS)	3b
Piche et al., Gut, 2008[107]	France	Case-control	Rome II non PI-IBS vs healthy subjects vs depression/ fatigue	50 vs 21 vs 11	Cecum	Cellularity, IEL, mast cells	Cellularity/HPF, IBS: 94.5 (95% CI 48-110) vs controls: 68 (95% CI 58-82), ($p = 0.005$), vs depression: 78 (95% CI 87-90), ($p = 0.05$); mast cells, IBS: 9.3 (95% CI 5.6-11.7) vs controls: 4.0 (2.7-6.8), ($p = 0.001$) vs depression: 4.3 (95% CI 2.8-7.8), ($p = 0.005$)	3b
Lee et al., Gastroenterol Hepatol, 2008[108]	South Korea	Case-control	Rome III (PI-IBS) vs healthy subjects	42 (5) vs 12	Rectum	ECC, mast cells, LPL	ECC/HPF, IBS: 10.9 ± 4.5 vs PI-IBS: 16.8 ± 0.8 vs non PI-IBS: 10.1 ± 4.1 vs controls: 8.0 ± 3.9, (IBS vs controls $p < 0.05$, PI-IBS vs controls $p < 0.01$); mast cells/HPF, IBS: 8.6 ± 2.6 vs PI-IBS: 10.6 ± 3.8 vs non PI-IBS: 8.3 ± 2.8 vs controls: 6.8 ± 2.0, (all vs controls $p \leq 0.05$); LPL/HPF, IBS: 34.0 ± 12.2 vs PI-IBS: 43.4 ± 8.7 vs non PI-IBS: 32.7 ± 12.2 vs controls: 30.2 ± 12.6, (PI-IBS vs controls $p < 0.05$); mast cells, non PI-IBS-D: 8.8 ± 2.2 vs controls: 6.8 ± 2.0; ($p < 0.05$)	3b

Table 5 (*Continued*)

Author, journal, year	Country	Type of study	Diagnostic criteria/Study groups	n	Biopsy site	Inflammatory cells studied	Results/Conclusions	LE
Cremon et al., Am J Gastroenterol, 2009[113]	Italy	Case-control	Rome II IBS vs healthy subjects	25 vs 12	Colon	ECC (5-HT+), mast cells	ECC, greater area of the crypt epithelium occupied by these cells in IBS: 0.56 ± 0.26% vs controls: 0.37 ± 0.16%, (p = 0.039), and greater in IBS-D: 0.69 ± 0.24% vs IBS-C: 0.44 ± 0.22%, (p = 0.34) Mast cells, greater area of the lamina propria occupied by these cells in IBS: 9.8 ± 2.9% vs 4.5 ± 2.8%, (p < 0.01), with no differences in IBS-D vs IBS-C; PI-IBS vs non PI-IBS was not specified	3b
Bhuiyan et al., Mymensingh Med J, 2010[110]	Bangla-desh	Case-control	Rome II PI-IBS vs non PI-IBS vs healthy subjects	18 vs 32 vs 10	Sigmoid colon	IEL, mast cells	IEL: IBS > controls (p < 0.001), lymphoid follicles: IBS > controls (p < 0.05); mast cells: IBS > controls (p < 0.05) and in PI-IBS vs non PI-IBS (p < 0.001)	3b
Kim et al., Yonsei Med J, 2010[111]	South Korea	Case-control	IBS-D Rome II vs PI-IBS Post Shigellosis vs non PI-IBS vs healthy subjects	7 vs 4 vs 7 vs 10	Descending, sigmoid colon, rectum	ECC, IEL, LPL, Mast cells	IEL/HPF, sigmoid colon, PI-IBS: 13.41 ± 5.57 vs non PI-IBS: 7.22 ± 1.20 vs IBS: 11.49 ± 1.31 vs controls: 5.91 ± 0.82, (p = 0.024); rectum, PI-IBS: 11.40 ± 4.17 vs non PI-IBS: 5.83 ± 0.73 vs IBS: 8.19 ± 0.73 vs controls: 4.77 ± 0.85 (p = 0.033); CD3, descending, PI-IBS: 30.4 ± 3.09 vs non PI-IBS: 25.97 ± 4.57 vs IBS: 25.90 ± 3.77 vs controls: 17.69 ± 5.82, (p = 0.024); sigmoid colon, PI-IBS: 29.80 ± 7.37 vs non PI-IBS: 24.09 ± 3.07 vs IBS: 25.51 ± 3.20 vs controls: 13.82 ± 2.83, (p = 0.039); rectum, PI-IBS: 25.0 ± 2.96 vs non PI-IBS: 25.31 ± 3.57 vs IBS: 20.67 ± 1.29 vs controls: 14.89 ± 1.53, (p = 0.013); CD8/HPF, descending colon, PI-IBS: 69.00 ± 10.87* vs non PI-IBS: 36.11 ± 3.91 vs IBS: 35.00 ± 5.37 vs controls 32.56 ± 18.57, (p = 0.031), (*PI-IBS vs non PI-IBS, p < 0.05); mast cells, with no differences except in the descending PI-IBS: 105.3 ± 13.3 vs non PI-IBS: 52.8 ± 13.44, (p < 0.05)	3b

Table 5 (*Continued*)

Author, journal, year	Country	Type of study	Diagnostic criteria/Study groups	n	Biopsy site	Inflammatory cells studied	Results/Conclusions	LE
Goral et al., Hepatogastro-enterology, 2010[112]	Turkey	Case-control	Rome III IBS-C, IBS-D vs healthy subjects	32, 40 vs 50	Rectum	Mast cells	Mast cells present in patients with IBS-D: 77.5% vs IBS-C: 59.4% vs controls: 56.0% ($p < 0.0001$); PI-IBS vs non PI-IBS was not specified	3b
Arévalo et al., Rev Gastroenterol Perú, 2011[114]	Peru	Case-control	Rome III IBS vs healthy subjects	16 vs 9	Ascending, descending colon	IEL, mast cells, eosinophils, ECC	LIE/100 epithelial cells, IBS: 9.81 vs controls: 4.66 ($p = 0.002$); no differences in mast cells, eosinophils, and ECC, or IBS-D vs IBS-C; PI-IBS vs non PI-IBS was not specified	3b
Braak et al., Am J Gastroenterol, 2012[115]	Holland	Case-control	Rome II IBS (PI-IBS) vs healthy subjects	66 (9) vs 20	Descending, sigmoid colon	Mast cells, T lymphocytes	Descending colon LT-CD3, IBS: 493 ± 34 vs controls: 587 ± 66, ($p = NS$); LT-CD8, IBS: 388 ± 28 vs controls: 526 ± 50, ($p = 0.02$); mast cells, IBS: 370 ± 39 vs controls: 186 ± 10, ($p < 0.001$) macrophages, IBS: 729 ± 64 vs controls: $1,261 \pm 146$ ($p < 0.003$); ascending, no differences; PI-IBS vs non PI-IBS was not analyzed, only acute onset IBS < macrophages vs gradual onset IBS, ($p = 0.02$)	3b
Chang et al., Am J Gastroenterol, 2012[116]	USA	Case-control	Rome II non PI-IBS vs healthy subjects	45 vs 41	Sigmoid colon	Immune cells	CD3, CD4, CD8 lymphocytes, ECC, EEC, Mast cells, IBS = controls, ($p = 0.059$-0.892)	3b

The studies are organized from higher to lower level of evidence and then in the progressive order of the year of publication. In regard to the Systematic Reviews, the country corresponds to that of the authors that conducted the study. In the diagnostic criteria/study groups and n columns the corresponding subgroup of those with IBS is in parentheses.
C: constipation; CD: celiac disease; D: diarrhea; ECC: enterochromaffin cells; FD: functional dyspepsia; GE: gastroenteritis; HPF: high power field; IEL: intraepithelial lymphocytes; IBD: inflammatory bowel disease; IBS: irritable bowel syndrome; LE: level of evidence; LPL: lamina propria lymphocytes; NCCP: noncardiac chest pain; Non PI: non-post-infectious; N: number; PI: post-infectious; RCT: randomized controlled trial; UC: ulcerative colitis.

In contrast, Braak et al. reported a decrease in the IEL, macrophage, and mast cell count in the colonic mucosa in 66 patients with IBS, compared with 20 healthy controls.[115] In that study, the difference between PI-IBS and non PI-IBS was not specifically analyzed, but rather the patients with acute and gradual IBS onset were compared, and a lower number of macrophages was observed in those with gradual IBS onset.[115] It is likely that the sudden onset group corresponds to PI-IBS, but we cannot conclude that. Previously, another study by the same group in Holland not only found a lower number of mast cells in biopsies of the rectum and descending colon in IBS, but also reduced tryptase release, compared with the controls.[91] Finally, Chang et al. found no differences in the number of immune cells in the colonic mucosa between patients with non PI-IBS and the controls.[116]

The above suggests that there is an increase in IEL, mast cells, and enterochromaffin cells in the intestinal mucosa in a group of patients with IBS that appears to be more frequent in those with IBS-D. However, it cannot be determined whether this low-grade inflammation is characteristic of PI-IBS or non PI-IBS.

3.5. 5. Altered bowel function in irritable bowel syndrome related to post-infectious irritable bowel syndrome, SIBO and/or microbiota alterations

- *The evidence suggests that the differences in the composition of the microbiota in subjects with IBS are related to alterations in the visceral sensitivity and motility function of the gastrointestinal tract* (level 1 b evidence, grade A recommendation).
- *The presence of methanogenic microbiota is significantly associated with constipation predominant IBS (IBS-C)* (level 3a evidence, grade B recommendation).

Eight articles related to bowel function[22–23,35,60,94,121–123] were identified in the initial search and 3 additional articles[104,124–125] were identified from other sources (Table 6). The evidence suggests that the changes in the microbiota of the patients with IBS have an influence on visceral sensitivity and gastrointestinal motility, especially at the antroduodenal and colorectal level.[22–23,35,60,94,121–126] Regarding the sensory distubances, the studies have shown that some patients with IBS and dysbiosis (PI-IBS and IBS with SIBO) develop rectal hypersensitivity, one of the most characteristic pathophysiologic findings in IBS.[94]

Various studies have also described that patients with PI-IBS have faster colonic transit time. For example, Gwee et al. demonstrated that subjects with a history of gastroenteritis and IBS had faster colonic transit than a control group of healthy subjects (median colonic transit time of 34.4 vs 55.2 min, $p = 0.01$).[94] In contrast, Yu et al. found that the orocecal transit time correlated with the IBS subtype.[35] Thus, orocecal transit is longer in patients with IBS-C than in those with IBS-D ($p = 0.0023$).

Moreover, in patients with IBS and evidence of SIBO alterations in the number and frequency of phase III activities of the migrating motor complex (MMC) have been described.[22–23,121] For example, in a group of patients with IBS according to the Rome I criteria and SIBO based on a positive LBT, Pimentel et al. demonstrated that the number of events of phase III of the MMC was lower in patients with IBS and SIBO than in the healthy controls (0.7 vs 2.2, $p < 0.001$); the same was true for the phase III duration (305 vs 428 s, $p < 0.001$).[121]

Numerous studies have suggested that patients with IBS have qualitative changes in the colonic flora. For example, there are descriptions of patients that can develop a proliferation of bacterial species that produce more gas, specifically methane. The presence of methanogenic flora in patients with IBS has been associated with a slower colonic transit time, rectal hyposensitivity, and altered intestinal motility.[122–125] In a recent analysis of the microbiota in patients with IBS through the technique of pyrosequencing, Jeffery et al. demonstrated that 17 taxas are associated with a slow colonic transit time (including those of the following phylotypes: *Euryarchaeota*, those of the class: *Methanobacteria*, and those of the families: *Methanobacteriaceae* and *Desulfohalobiaceae)*.[60] Likewise, the presence of *Proteobacteria* is described as being associated with an increase in the pain threshold during rectal distension, evaluated using a barostat. In addition, the first evidence in IBS of the detection of different levels of acetic acid, propionic acid, and total fatty acids has been reported. The highest levels are associated with poor outcome IBS.

In summary, the evidence suggests that changes in the composition of the microbiota or its instability (dysbiosis) have an influence on the gastrointestinal physiology, producing abnormalities in visceral sensitivity and gastrointestinal motility. However, further studies are required in order to determine the effect of the microbiota on those sensory and motor alterations. On the other hand, it is not known whether these disturbances contribute to symptom generation or whether they are the consequence of primary motility disorders. Finally, it should be stressed that there are other factors that have an influence on the microbiota of patients with IBS, such as the type of diet (i.e. FODMAPs: fermentable oligosaccharides, disaccharides, monosaccharides and polyols) and the use of antibiotics.

3.6. 6. Antimicrobials in the treatment of irritable bowel syndrome

- *In patients with non-constipation IBS, rifaximin at doses of 400 mg TID for 10 days or 550 mg TID for 14 days, is superior to placebo in the adequate response of global IBS symptoms and in abdominal bloating. It also improves pain and abdominal discomfort, as well as the consistency of loose/liquid stools during treatment and for up to 10 weeks post-treatment* (level 1 b evidence, grade A recommendation).
- *Rifaximin at a dose of 400 mg TID for 7 days may neutralize the LBT in approximately half the patients with IBS, which is associated with reduced IBS symptom severity* (level 4 evidence, grade C recommendation).
- *The frequency of adverse events is similar between rifaximin and placebo, and the most frequent are: headache, upper respiratory tract infections, nausea, nasopharyngitis, diarrhea, and abdominal pain* (level 1 b evidence, grade A recommendation).
- *In the patients that require retreatment with rifaximin, effectiveness appears to be similar to that of the first*

Table 6 Altered bowel physiology in relation to PI-IBS, SIBO, and microbiota alterations.

Author, journal, year	Country	Type of study	Diagnostic criteria/Study groups	n	Outcome variables	Results/Conclusions	LE
Kunkel et al., Dig Dis Sci, 2011[124]	USA	Systematic review + Meta-analysis of case-control studies	IBS unreported criteria CH4+ vs CH4-	319 vs 958	Relation of CH4+ to constipation	CH4, constipation: OR = 3.51 (95% CI 2.00-6.16); IBS-C: OR = 3.60 (95% CI 1.61-8.06)	3a
Gwee et al., Gut, 1999[94]	Great Britain	Case-control	Rome I PI-IBS subjects exposed to GE vs Non-IBS exposed to GE vs healthy subjects	94 vs 22 vs 72	Symptom questionnaire, HADS, Bx of the rectum, rectal distension with syringe, colonic transit with radio-opaque markers	Colonic transit, PI-IBS < healthy subjects; rectal hypersensitivity and hyperactivity, PI-IBS > healthy subjects	3b
Pimentel et al., Dig Dis Sci, 2002[121]	USA	Case-control	Rome I IBS +SIBO vs healthy subjects	68 vs 30	LBT, AD manometry	Phase III of MMC, number of events, IBS: 0.7 vs controls: 2.2, ($p < 0.000001$); duration, IBS: 305 s vs controls: 428 seconds, ($p < 0.001$)	3b
Pimentel et al., Dig Dis Sci, 2003[122]	USA	Case-control	Subjects given breath test IBD vs Rome I IBS (IBS-C, IBS-D)	78 vs 296 (120, 111)	LBT, symptom questionnaire	Methane+: > symptom severity in IBS-C ($p < 0.05$) and < IBS-D ($p > 0.001$). Methane+, IBS-C: 52.3% vs IBS-D: 0, ($p < 0.001$)	3b
Posserud et al., Gut, 2007[22]	Sweden	Case-control	Rome II IBS vs Controls	162 vs 26	LBT, duodenal aspirate culture, duodenal Bx, AD manometry	Dysmotility, IBS with SIBO: 86% vs without: 39% ($p = 0.02$); N of phases III of the MMC, SIBO: Median 0.6 (Range 0-1.8) vs 1.2 (0–4) / 3 hours, ($p = 0.08$)	3b

Table 6 (*Continued*)

Author, journal, year	Country	Type of study	Diagnostic criteria/Study groups	n	Outcome variables	Results/Conclusions	LE
Grover et al., Neurogastroenterol and Motility, 2008[23]	USA	Case-control	Rome II IBS vs healthy subjects	158 vs 34	SBT and CH4, barostat, colonic manometry (MI), IBS-QOL and IBS-SS	IBS patients had an increase in MI after rectal distension vs HC. There was no difference between IBS with SIBO and IBS without SIBO. The CH4-producers had a greater sensitivity threshold for urgency to defecate (28 vs 18 mmHg, $p < 0.05$) and higher MI (461 vs 301.45, $p < 0.05$) vs IBS without SIBO.	3b
Park et al., Gut and Liver, 2009[126]	South Korea	Case-control	Rome II IBS vs healthy subjects	38 vs 12	LBT, intestinal permeability with PEG	Intestinal permeability, IBS: 0.82 ± 0.09 vs controls: 0.41 ± 0.05, ($p < 0.05$); IBS with SIBO: 0.90 ± 0.13 vs without: 0.80 ± 0.11, ($p = NS$)	3b
Jeffery et al., Gut., 2011[60]	Ireland and Sweden	Case-control	Rome II IBS vs healthy subjects	37 vs 20	Microbiota through pyrosequencing in fecal matter, colonic transit with radio-opaque markers, rectal barostat	Microbiota and ST, phylotype: *Euryarchaeota*, class: *Methanobacteria* and families: *Methanobacteriaceae* and *Desulfohalobiaceae* *Firmicutes:Bacteroides* ratio to pain and rectal distension, IBS > controls	3b
Furnari et al., J Gastrointes Liv Dis, 2012[125]	Italy	Case-control	Symptom-based IBS patients given GBT vs healthy subjects	629 vs 40	GBT (H2 and CH4), symptom diary	CH4, IBS-C: 32.3% vs controls: 30% ($p = NS$); constipation: 27.4% vs diarrhea: 17.1%, ($p < 0.001$); CH4 production (ppm), FC vs controls, ($p = 0.04$), vs diarrhea ($p = 0.002$)	3b
Yu et al., Gut, 2010[35]	Canada	Case series	Rome II IBS	40	LBT, orocecal transit with Tc99 scintigraphy	Orocecal transit, IBS: 7167 min (range10-220 min); IBS-C vs IBS-D: > 2.2 times, ($p = 0.0023$)	4

The studies are organized from higher to lower level of evidence and then in the progressive order of the year of publication.
AD: antroduodenal; C: constipation; CH4: methane; CI: confidence interval; D: diarrhea; FC: functional constipation; GBT: glucose breath test; HADS: hospital anxiety and depression scale; HC: healthy controls; H2: exhaled hydrogen; IBD: inflammatory bowel disease; IBS: irritable bowel syndrome; IBS-QOL: quality of life questionnaire for irritable bowel syndrome; IBS-SS: irritable bowel syndrome severity scale; LBT: lactulose breath test; MMC: migrating motor complex; MI: motility index; NS: not significant NT: normal transit; OR: odds ratio; PEG: polyethylene glycol; ppm: parts per million; SBT: sucrose breath test; SIBO: small intestinal bacterial overgrowth; ST: slow transit.

treatment; however, further studies are required in order to determine the effectiveness of retreatment and the appropriate interval for carrying it out (level 4 evidence, grade C recommendation).

- *Studies are required for evaluating the long-term safety and effectiveness of rifaximin in IBS* (level 5 evidence, grade D recommendation).

Twenty articles that analyzed antibiotic therapy in IBS were identified, 5 reviews [15,127–130] and 15 original articles,[18,33,131–143] all studies on adults, except one conducted on the pediatric population.[135] An additional original article that had been published in December 2013 was added [37] (Table 7).

Basically 2 antibiotics have been studied in IBS: rifaximin and neomycin. Rifaximin is a semi-synthetic antibiotic, an analog of rifamycin, designed to have little gastrointestinal absorption. It inhibits the bacterial synthesis of RNA by binding to the RNA polymerase β subunit that is dependent on bacterial DNA.[144] Its absorption is less than 0.4%, making it an almost completely luminal-acting antibiotic, and most of it is excreted in the fecal matter, unchanged. It has a broad spectrum of activity against Gram-positive, Gram-negative, aerobic, and anaerobic enteropathogens[145–146] with a low probability of bacterial resistance.[147–148] In vitro it induces CYP3A4, but its interaction with other medications is almost null.[129]

In the selected reviews,[15,127–131] a short cycle of non-absorbable antibiotics, like rifaximin, has been recommended for improving global IBS symptoms.[131] The authors of a systematic review with only 3 original articles on rifaximin treatment of IBS with or without SIBO concluded that rifaximin at a dose of 400 mg BID for 7 to 10 days, improves IBS symptoms, regardless of whether SIBO is present or not.[129] In 2 later systematic reviews with meta-analyses published 2 years apart, the second one with 10 times more patients treated with rifaximin vs placebo, it was concluded, and with a good level of evidence, that the antibiotic at doses of 400 to 550 mg, 2 to 3 times/day, was twice as effective as the placebo at improving IBS symptoms.[15,127] Additionally, rifaximin showed a therapeutic gain of 9.8 over the placebo and a number needed to treat (NNT) of 10.2 for global IBS improvement and very similar values for abdominal bloating improvement.[15,127] In another systematic review on the treatment of abdominal bloating, it was concluded that rifaximin was superior to placebo in the proportion of patients with IBS-Non C that reported subjective improvement in abdominal bloating.[129]

The original articles analyzed rifaximin and neomycin, as well as a few other antibiotics. However, the studies have different designs and include retrospective studies, case series, and randomized controlled trials with placebo or other antibiotics and different doses. For example, rifaximin has been studied from doses of 200 mg QID,[137] 400 mg BID or TID for 7 to 14 days, to 550 mg TID for 14 days.[15] Likewise, the outcome variables analyzed were very different in each of the studies, from global IBS improvement to improvement of secondary symptoms such as pain and/or abdominal bloating, to the frequency and consistency of bowel movements.[131,132,134] The effect of rifaximin on GBT[136,137] or LBT[33] has been evaluated as well. These differences in the studies make it difficult to arrive at a conclusion. Nevertheless, the best evidence comes from the recent Target 1 and Target 2 studies by Pimentel et al., with more than 1,200 patients between the 2 investigations.[134] They show that rifaximin at a dose of 550 mg TID for 14 days in patients with IBS-Non C by Rome II criteria resulted in a greater proportion of patients with adequate relief from IBS symptoms, abdominal bloating, daily symptom intensity, abdominal pain, and stool consistency.[134] In the follow-up at 10 weeks post-treatment, adequate relief defined as the subjective report of symptom improvement in at least one of every 2 weeks, rifaximin remained significantly superior to placebo. It is worth noting that it had previously been reported that at lower doses, such as 400 mg BID or TID for 10 days, rifaximin was also superior to placebo in the percentage of patients that reported overall improvement of IBS.[131–132] Regarding secondary effects, in the Target 1 and 2 studies, which are the largest, frequency was similar to the placebo (1.6% with rifaximin and 2.4% with placebo) and the main effects in order of frequency were headache, followed by respiratory tract infections, abdominal pain, nausea, and diarrhea.[134]

Furthermore, rifaximin can neutralize LBT in 52% of the patients with Rome II-IBS and in this subgroup symptom severity improved, but the corresponding study was not controlled,[33] and neither were those that evaluated the effect on GBT.[136,137] Regarding the effect on children, a dose of 550 mg TID for 10 days showed no differences from the placebo or in LBT normalization, which was achieved in only 20%.[135] This suggests that children most likely require higher doses or a different type of antibiotic, probably due to a more resistant microbiota. In reference to rifaximin retreatment, only one retrospective study analyzed this modality; patients treated up to 5 times had a mean interval of symptom recurrence of 4 months.[143] Effectiveness was 75%, similar to that of the first treatment. However, well-designed studies are required in order to determine how often rifaximin can be repeated.[143] Finally, no studies have evaluated the long-term effects of rifaximin in IBS.

Regarding neomycin, it is a systemic aminoglycoside that has been evaluated in 2 original studies on IBS,[18,138] both of which are randomized and controlled with placebo. At a dose of 500 mg BID for 7 to 10 days in patients with IBS in general in one study, and IBS-C by Rome I criteria in the other, neomycin was superior to the placebo in the percentage of patients, mainly those with a positive LBT, that reported improvement in a composite score of symptoms including abdominal pain, diarrhea, bloating, and bowel habit.[18] Neomycin normalized LBT in only 20% of the patients, but in the methane-positive patients, the percentage that reported improvement in regard to constipation was 9 times higher with neomycin than with placebo.[138] Despite this, neomycin is not an ideal drug for IBS because of its characteristics in relation to systemic absorption and its safety spectrum.

With regard to other antibiotics, a retrospective study was conducted that compared rifaximin with neomycin, doxycycline, and amoxicillin-clavulanic acid that were used in the management of the treatment and retreatment of SIBO in patients with IBS;[141] however, these agents were not as effective as rifaximin. Erythromycin has also been studied, evaluating the number of days until IBS symptom recurrence after LBT neutralization, but it was much less

Table 7 Antibiotic therapy in IBS.

Author, journal, year	Country	Type of study	Diagnostic criteria/Study groups	Treatment dose	N	Outcome variables	Results/Conclusions	LE
Rezaie et al., Arch Med Sci, 2010[127]	Iran	Systematic review + meta-analysis	Any criteria IBS	Rifa 400 mg vs Pb *BID-TID* x 7-10 days	80 vs 74	Efficacy of antibiotics in IBS	Rifa superior to Pb, clinical response in IBS: RR = 2.04, (95% CI 1.23-3.40, p = 0.0061); symptom response: RR = 2.06, (95% CI 1.3-3.27, p = 0.002)	1a
Menees et al., Am J Gastroente-rol, 2012[15]	USA	Systematic review + Meta-analysis	Any criteria IBS	Rifa 400-550 mg vs Pb *BID-TID* x 10-14 days	895 vs 908	Efficacy and tolerability of rifa in IBS	Global relief, rifa superior to Pb: OR = 1.57, (95% CI: 1.22-2.01); therapeutic gain: 9.8, NNT: 10.2; Abdominal bloating: OR = 1.55, (95% CI: 1.23-1.96); therapeutic gain: 9.9, NNT: 10.1; adverse events: rifa = Pb	1a
Schmulson, Chang, Aliment Pharmacol Ther, 2011[129]	Mexico, USA	Systematic review	Any criteria, abdominal bloating	Rifa 400-550 mg vs Pb *BID-TID* x 7-14 days	704 vs 708	Efficacy in abdominal bloating	Rifa is effective in abdominal bloating improvement in non-constipation IBS	1a
Fumi, Trexler, Ann Pharmacol, 2008[128]	USA	Systematic review	Any criteria IBS with or without SIBO	Rifa 400 mg vs Pb *BID-TID* x 7-10 days	113 vs 30	Efficacy of rifa in IBS symptoms	A third of the IBS patients show clinical improvement with rifa, particularly if they have SIBO	2a
Kwon et al., Korean J Gastroente-rol, 2011[130]	South Korea	Review	Rome I or II IBS	Rifa, neo, other antibiotics, controls	127, 44, 61, 63	Evidence-based consensus and the Delphi Method	A short cycle of non-absorbable antibiotics (rifa or neo) can improve the overall symptoms of IBS, particularly in IBS-D	3
Scarpellini et al., Aliment Pharmacol Ther, 2007[133]	Italy	RCT	SIBO + Rome II IBS	Rifa 400 mg *TID* vs Rifa 400-800-400 mg x 7 days	33 vs 30	GBT	GBT normalization, rifa-1200: 58% vs rifa-1600: 80%, (p < 0.05)	1b

Table 7 (*Continued*)

Author, journal, year	Country	Type of study	Diagnostic criteria/Study groups	Treatment dose	N	Outcome variables	Results/Conclusions	LE
Pimentel et al., New Eng J Med, 2011[134]	USA	RCT	Rome II IBS Non-C	Rifa 550 mg vs Pb, *TID* x 14 days, follow-up for x 10 weeks; 2 studies	Target 1 309 vs 314 Target 2 315 vs 320	% of adequate relief of overall symptoms in 2/4 weeks (weeks 3-6), daily symptom intensity	Adequate improvement, rifa: 40.7 vs Pb: 31.7, ($p < 0.001$); abdominal bloating, rifa: 40.2 vs Pb: 30.3 ($p < 0.001$); daily intensity (overall symptoms, abdominal pain, bloating, stool consistency), rifa > Pb (all significant)	1b
Pimentel et al., Am J Gastroente-rol, 2003[18]	USA	RCT	Rome I IBS	Neo 500 mg vs Pb *BID* x 7 days	55 vs 56	Improvement >50% in composite score (pain, diarrhea, constipation), bowel habit normalization	Improvement > 50%, neo: $35.0 \pm 5.0\%$ vs Pb: $11.4 \pm 9.3\%$, ($p < 0.05$); bowel habit, neo: $40.1 \pm 5.3\%$ vs Pb: $15.1 \pm 3.6\%$, ($p < 0.001$); IBS + LBT, improvement >50%, neo: $35.4 \pm 5.6\%$ vs Pb: $3.7 \pm 10.6\%$, ($p < 0.01$)	2b
Pimentel et al., Dig Dis Sci, 2006[138]	USA	RCT	Rome I IBS-C	Neo 500 mg vs Pb *BID* x 10 days	20 vs 19	% of global improvement, constipation and/or abdominal pain, constipation improvement in CH4+	Global improvement, neo: 36.7 ± 7.9 vs Pb: $5.0 \pm 3.2\%$, ($p < 0.001$); constipation, neo: $32.6 \pm 9.9\%$ vs $18.7 \pm 7.2\%$, ($p = 0.26$); CH4+, neo: $44.0 \pm 12.3\%$ vs Pb: $5.0 \pm 5.1\%$, ($p = 0.05$)	2b
Pimentel et al., Ann Intern Med, 2006[131]	USA	RCT	Rome I IBS	Rifa 400 mg vs Pb *TID* x10 days & follow-up x 10 weeks	43 vs 44	Global improvement, secondary symptoms (pain, bloating, diarrhea, constipation)	Global improvement, rifa: $36.40 \pm 31.46\%$ vs Pb: $21.00 \pm 22.08\%$ ($p < 0.020$); only bloating improved ($p < 0.010$)	2b
Sharara et al., Am J Gastroen-terol, 2006[132]	Lebanon	RCT	Bloating and flatulence-IBS Rome II subgroup	Rifa 400 mg vs Pb, *BID* x 10 days and follow-up x 10 days	37 vs 30	Subjective global relief (pain, bloating, number and frequency of bowel movements, incomplete evacuation)	At 10 days, patients improved with rifa: 40.5% vs Pb: 18.2% ($p = 0.04$); ten-day follow-up, patients improved with rifa: 27.0 vs Pb: 9.1%, ($p = 0.05$)	2b

Table 7 (*Continued*)

Author, journal, year	Country	Type of study	Diagnostic criteria/Study groups	Treatment dose	N	Outcome variables	Results/Conclusions	LE
Collins, Lin, J Pediatr Gastroen-terol Nutr, 2011[135]	USA	RCT	Children with CAP Rome II-IBS subgroup	Rifa 550 mg vs Pb *TID* x 10 days & follow-up x 2 weeks	26 vs 15	Symptoms (bloating, gas, incomplete evacuation, pain, diarrhea, constipation, urgency, mucus, straining, incontinence) VAS: 0-10, LBT	Symptoms, rifa = Pb; LBT normalization, rifa: 80% vs Pb: 86%	2b
Cuoco et al., Minerva Gastroente-rol Dietol, 2006[136]	Italy	Case series	IBS symptoms and +GBT	Rifa 400 mg *TID* x14 days	23	GBT and post-treatment symptoms vs basal	GBT, normalized in 82.6% ($p < 0.01$); IBS symptoms disappeared, in 42%, ($p < 0.05$); diarrhea, bloating, and abdominal pain improvement, (all: $p < 0.05$)	4
Majewski et al., Adv Med Sci, 2007[137]	USA	Case series	Rome II IBS and +GBT	Rifa 200 mg *QID* x 30 days	8	Overall improvement(bowel movement frequency, pain, bloating, gas) and GBT	Rifa normalized symptoms in 7 patients and GBT in 6 patients	4
Morken et al., Scand J Gastroente-rol, 2009[139]	Sweden	Case series	Rome II IBS-D post-*Giardia* eradication	Rifa 200 mg *TID* x 8 days + metro 400 mg *BID* x 10 days vs live fecal flora instilled in the duodenum	18 vs 10	Symptom score (nausea, pain, bloating, diarrhea, constipation, anorexia) and H+ through LBT	Symptoms, rifa+metro: tended to decrease at 4 weeks ($p = 0.07$); fecal flora: diminished at 7 weeks ($p = 0.0009$) but were the same 12 months later; H+, rifa: decreased at 90-120 min, fecal flora: no changes, there was no group comparison	4
Weinstock et al, Dig Dis Sci, 2008[140]	USA	Case series	IBS symptoms and +LBT and restless legs syndrome	Rifa 400 mg, *TID* x 10 days. Then tegaserod 3 mg + zinc 200 mg + probiotic, *QD* x 30 days	13	N with global symptom and % of individual symptom improvement	Improvement above 80%: in 10 patients; complete resolution: in 5; abdominal pain: 74%; diarrhea: 73%; bloating: 70%; postprandial fullness: 65%; constipation: 64%; flatulence: 47%	4

Table 7 (*Continued*)

Author, journal, year	Country	Type of study	Diagnostic criteria/Study groups	Treatment dose	N	Outcome variables	Results/Conclusions	LE
Yang et al, Dig Dis Sci, 2008[141]	USA	Case series	Rome I IBS and +LBT	Rifa 400 mg *TID*, neo, others: doxycycline, augmentin	84, 24, 61	% of responders (improvement > 50%), LBT	Rifa: 68% vs neo: 38% vs others: 44%, (both: $p < 0.01$); normal LBT was a response predictor: 81% of responders ($p < 0.001$)	4
Peralta et al., World J Gastroenterol, 2009[33]	Italy	Case series	Rome II IBS +LBT	Rifa 400 mg *TID* x 7 days	54	LBT normalization (N), symptom severity (Likert 0-4)	LBT normalization: 52, symptom severity, -LBT: 2.3 ± 0.6 vs 0.9 ± 0.8 ($p = 0.003$); +LBT: no changes	4
Pimentel et al, Gastroen-terol Hepatol (NY), 2009[142]	USA	Case series	IBS Nonspecified criteria and SIBO (LBT) + Symptom resolution	Eryth 50 mg, teg 2-6 mg, eryth followed by teg, no treatment followed by eryth or teg, *QD*	42, 16, 20, 6	Time until recurrence (days free from symptoms)	Eryth: 138.5 ± 132.2 vs teg: 241.6 ± 162.2, ($p = 0.004$) vs no treatment ($p = 0.08$); no treatment followed by eryth: 41.0 ± 44.8 vs followed by teg: 195.6 ± 153.3, ($p = 0.06$); eryth followed by teg: extended 105.8 ± 73.3 to 199.7 ± 162.9 ($p = 0.04$)	4
Pimentel et al., Dig Dis Sci, 2011[143]	USA	Case series	Nonspecified criteria IBS Non-C	Rifa nonspecified dose	148	N with re-treatments, % of re-treatment response	1 re-treatment: 71; 2: 48; 3: 22; 4: 7; 5: 4; improvement with first treatment: 75%; subsequent improvement: 75%; recurrence minimum: 4 months	4
Meyrat et al., Aliment Pharmacol Ther, 2012[37]	Switzerland	Case series	Rome III	Rifa 200 mg *QID* x 14 days	106	Symptom severity (Likert: 0-10) weeks 4 and 14 post-treatment and LBT at 4 weeks (N = 64)	Symptoms at 4 weeks, bloating: 5.5 ± 2.6 vs 3.6 ± 2.7, ($p < 0.001$); flatulence: 5.0 ± 2.7 vs 4.0 ± 2.7, ($p = 0.015$); diarrhea: 2.9 ± 2.4 vs 2.0 ± 2.4, ($p = 0.005$); abdominal pain: 4.8 ± 2.7 vs 3.3 ± 2.5, ($p < 0.001$); general well being: 3.9 ± 2.4 vs 2.7 ± 2.3, ($p < 0.001$); LBT normalization: 86%	4

The studies are organized from higher to lower level of evidence and then in the progressive order of the year of publication.
BID: twice a day; CAP: chronic abdominal pain; CH4: methane D: diarrhea; Eryth: erythromycin; GBT: glucose breath test; H+: exhaled hydrogen; IBS: irritable bowel syndrome; LBT: lactulose breath test; LE: level of evidence; N: number; Neo: neomycin; 95% CI: 95% confidence interval; NNT: number needed to treat; OR: odds ratio; Pb: placebo; *QD*: once a day; *QID*: 4 times a day; RCT: randomized controlled trial; Rifa: rifaximin; RR: relative risk; SIBO: small intestinal bacterial overgrowth; Teg: tegaserod; *TID*: 3 times a day; VAS: visual analog scale

effective than tegaserod.[142] And finally, rifaximin together with metronidazole has been evaluated in post-giardiasis-IBS, but no conclusion can be reached in relation to this study.[139]

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5. Conflict of interest

Max Schmulson has been a consultant for Procter and Gamble, Novartis, Schering-Plough, Alfa-Wasserman, Janssen, Nestle Ltd, and Almirall. He has been a speaker for Takeda México SA de CV, Schering-Plough, Mayoli-Spindler, Alfa-Wasserman, Janssen, and Novartis. He has received research support from Takeda México SA de CV and Nestlé Ltd.

María Victoria Bielsa has been a consultant for Alfa-Wasserman, Takeda México SA de CV, and Astra Zeneca. She has been a speaker for Takeda México SA de CV, GlaxoSmithKline México, Mayoli-Spindler, and Alfa-Wasserman.

Ramón Carmona-Sánchez is a member of the Advisory Counsel of Takeda Pharmaceuticals, Alfa-Wasserman, and Mayoly-Spindler. He has been a speaker for Nycomed-Takeda, Mayoly-Spindler, Asofarma, and Janssen-Cilag.

Angélica Hernández has been a consultant for Alfa-Wasserman and Astra Zeneca and a speaker for Astra Zeneca, Menarini, Boston Scientific, Olympus, and Ferring.

Aurelio López-Colombo has been a consultant for Novartis and a speaker for Takeda, Alfa Wasserman, Janssen, and Novartis.

Yolanda López-Vidal has been a consultant for Alfa-Wasserman and she has received research support from and been a speaker for Nestlé Ltd.

Mario Peláez-Luna has no conflict of interest to declare.

José María Remes-Troche is a member of the Advisory Counsel for Takeda Pharmaceuticals, Alfa-Wasserman, Almirall, and Janssen. He has been a speaker for Nycomed-Takeda, Advance Medical, Endomedica, Astra-Zeneca, and Bristol-Myers-Squibb. He has received research funding from Sanofi-Pasteur, Asofarma, and Astra Zeneca.

José Luis Tamayo is a member of the Advisory Counsel for Alfa-Wasserman, Malloly-Spindler, and Takeda. He has been a speaker for Astra Zeneca, Malloly-Spindler, Janssen, and Takeda Pharmaceuticals.

Miguel A. Valdovinos has been a member of the Consultancy Counsels of Takeda, Malloly-Spindler, Almirall, Sanofi, and Danone. He has been a speaker for Takeda, Almirall, Merck, Ferrer, Janssen, Endomédica, Novartis, and Danone and has received research support from Endostim Inc, Ferrer, and Danone.

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