Spanish physicians' point of view on irritable bowel syndrome (IBS). Results of a Delphi survey

C. Almansa, E. Rey, E. Bolaños¹, M. Palma¹, A. Álvarez Sánchez and M. Díaz-Rubio

Service of Digestive Diseases. San Carlos Clinical Hospital. Madrid, Spain. 'Agencia de Evaluación de Tecnologías. Carlos III Institute. Madrid, Spain

RESUMEN

Introducción: el síndrome del intestino irritable (SII) es una patología controvertida, donde ante la escasez de evidencia científica las recomendaciones sobre su manejo clínico y su definición vienen determinadas por métodos de consenso de expertos.

Objetivo: obtener la opinión de los médicos de nuestro país implicados en el manejo de pacientes con SII y conocer los puntos de acuerdo en las principales cuestiones clínicas que plantea.

Material y métodos: se realizó un estudio Delphi a nivel nacional mediante dos envíos a 100 médicos de atención primaria y gastroenterólogos. El cuestionario incluía preguntas sobre el concepto, diagnóstico y tratamiento del SII, evaluando el grado de acuerdo entre los participantes.

Resultados: el 55% de los encuestados completó los dos envíos. Se obtuvo acuerdo respecto a los síntomas que caracterizan al SII y los de alarma. No existió una actitud clara ante el paciente sin síntomas de alarma, pero sí acuerdo respecto a la realización de colonoscopia en su presencia. Se señaló la necesidad de realizar estudios complementarios en mayores de 40 años. En el tratamiento no encontramos una actitud uniforme, aunque parece existir una orientación diferente según el síntoma predominante.

Conclusiones: los médicos participantes en el estudio demuestran a través de sus respuestas un buen conocimiento conceptual del SII, si bien las discrepancias observadas en las cuestiones sobre diagnóstico y tratamiento demuestran la complejidad y falta de uniformidad que existe en el manejo diario de este síndrome.

Palabras clave: Síndrome del intestino irritable. Estudio Delphi.

ABSTRACT

Introduction: lack of evidence in most clinical situations regarding irritable bowel syndrome (IBS) enhances the importance of an expert's opinion, which will guide management and even the concept underlying the disease.

Objective: to delve into the knowledge and degree of agreement on main clinical skills for this syndrome among physicians involved in its management.

Material and method: two rounds of a Delphi survey were conducted on 100 physicians: general practitioners (GPs) and gastroenterologists. The questionnaire evaluated agreement among participants in some aspects regarding the definition, diagnosis, and treatment of IBS.

Results: fifty-five percent of participants completed the two-round survey. Agreement was achieved regarding the definition of typical symptoms and red flags characterizing IBS. Although there was no consensus regarding the appropriate management of patients without alarm symptoms, the performance of a colonoscopy on any patient presenting red flags was suggested. Patients were thought to require a wider examination when older than 40. A well defined line of IBS treatment was not found, albeit most physicians tended to choose it depending on the main complaint.

Conclusion: interviewed physicians showed adequate theoretical knowledge of IBS, but lack of uniformity on diagnosis and treatment approach reflects the controversial day-by-day management of this syndrome.

Key words: Irritable bowel syndrome. Delphi survey.

Almansa Menchero C, Rey E, Bolaños E, Palma M, Álvarez Sánchez A, Díaz-Rubio M. Spanish physicians' point of view on irritable bowel syndrome (IBS). Results of a Delphi survey. Rev Esp Enferm Dig 2007; 99: 210-217.

This study has been supported by the Fundación de Investigación Médica Mutua Madrileña.

Received: 25-09-06. Accepted: 21-12-06.

Correspondence: Manuel Díaz-Rubio. Servicio de Aparato Digestivo. Hospital Clinico San Carlos. C/ Martín Lagos, s/n. 28040 Madrid.

INTRODUCTION

IBS is a functional digestive disorder that affects up to 12% of the Spanish population, depending on the diagnostic criteria used (1). IBS symptoms represent the main complaint in 3% of GP consultations, and up to 25% of gastroenterology visits (2). It has a deep impact on quali-

ty of life, and on the socio-economic field due to medical expenses and other indirect costs, including those derived from work absenteeism (3-5).

As there are few well-designed studies available to answer the main questions arising from a majority of physicians about IBS, current guidelines on IBS have a low scientific evidence level (6).

Expert recommendations weigh heavily in the scientific literature regarding IBS, beginning with a definition arising from their consensus (7). However, the impact of these guidelines on medical practice is probably lower than expected (8).

In a context where evidence-based medicine is barely applied because of the little evidence available, and where most attitudes are guided by experience-based medicine (understanding experience as becoming an expert), it is really important that the opinion of all physicians involved in IBS management (practice-based medicine) be known.

In order to know the generalized opinion on any subject, we could employ different poll methods such as Delphi surveys. This kind of survey offers some advantages over other consensus methods, making it a useful instrument in situations where there is not enough empiric evidence available, and where there are decisive factors that may be subjective. A Delphi survey prevents problems commonly related to consensus meeting from arising, including low geography-based representation and some people dominating the communication process; as it is a controlled interaction, no one in the panel can identify the opinions of other members, which allows for personal freedom (9-11).

The aim of this study was to obtain the opinion of physicians directly involved in the management of IBS (GPs and gastroenterologists), as well as common points of view regarding its principal clinical questions.

MATERIAL AND METHODS

The method chosen for this study was a two-round Delphi survey.

Questionnaire

We elaborated the questionnaire following a previously defined systematic procedure. We designed the first draft considering desired responses: clinical features (characteristic symptoms), factors influencing our management (temporary correlation, red flags, personal and family records, diagnostic criteria, proposed classifications), diagnosis (different tests depending on the situation), and therapeutic approach (drugs and follow-up). We used four types of questions: two possible answers (yes/no), three options (yes, no, sometimes or I don't know), or five alternatives (completely disagree, some-

what disagree, somewhat agree, agree, completely agree), and numerical questions. In addition, we included some open-ended questions to get some additional information. Afterwards, the first draft was analyzed by our consultants, and the second draft was developed from their opinions.

We selected two medical centers, one of them formed by GPs and the other by gastroenterologists, to perform a preliminary test for our questionnaire. We selected ten doctors from each center who answered the questions and relayed their impressions and suggestions. We considered all their proposals in designing the third draft.

The definitive questionnaire was elaborated following the opinion of our consultants.

Identification of participants

The necessary number of participants was estimated at 100-50 GPs and 50 gastroenterologists. We used two ways of identifying potential participants for our survey: a database of doctors who attended an annual update course in gastroenterology for GPs, performed yearly between 2001 and 2004 (these courses did not include IBS), and a directory of specialists was used in order to identify gastroenterologists. In those regions that were underrepresented we performed a random contact of GP centers and gastroenterology departments from a directory.

Selection of participants

We called up every potential participant in order to find out their availability and willingness to participate in the survey. Those who accepted chose the way they wanted to keep in touch (email, fax, postal service).

Mailing

If we did not get a reply from a participant three weeks after the mailing, we sent the questionnaire again with a reminder note, and three contact attempts were made before a participant was rejected. In the second round we added to the questionnaire the results obtained in the first round, and deleted some items for simplification.

Analysis

We obtained the frequency of every answer except for those that were numerical, where we calculated the mean value and interquartilic range. For questions with 5 options we obtained the mean and median values.

Agreement criteria

We preestablished as agreement the following:

- —Questions with 2 answers: a frequency of answers higher than 75%.
- —Questions with 3 answers: a frequency of answers higher than 66%.
- —Questions with 5 answers: a frequency of answers lower than 25% in the opposite direction, and/or a median equal to or higher than 4; in addition, we translated the replies in fictitious variables with values ranging from 1 to 5, requiring a mean higher than 3.75.

RESULTS

Response rate

From a population of 50 GPs initially selected, only 36 (72%) replied to the first round, and 27 replied to the second round (54%). From all 50 gastroenterologists contacted, 31 replied to the first round and 28 (56%) replied to the second round. Overall, the final response was 55%, which included 49% from GPs and 51% from gastroenterologists without any existing bias regarding gender, age, or years of practice among those who replied and those who did not.

Geographical distribution and experience

The geographical distribution and response rate of participants is shown in table I. According to years of practice of GPs, 14.8% had 5 or less, 33.3% had 6-15, 48.1% had 15-30, and 3.7% had more than 30 years. Among gastroenterologists, 21.4% had 5 years or less, 39.3% had 6-15, 25% had 15-30 years, and 14.3% had more than 30 years. According to gender, 32.7% of samples were females.

Table I. Initial distribution and response rate per geographical origin

		9
Regions	Number of	Response data
	physicians selected	n (%)
Andalusia	10	5 (50%)
Aragón	6	3 (50%)
Asturias	6	3 (50%)
Balearic Islands	2	0 (0%)
Canary Islands	2	1 (50%)
Catalonia	18	12 (66%)
Castille-La Mancha	10	5 (50%)
Castilla León	8	4 (50%)
Extremadura	4	2 (50%)
Galicia	4	3 (75%)
Madrid	18	11 (61%)
Basque Country	4	3 (75%)
Valencia	8	3 (37%)

Table II. Characteristic IBS symptoms

	Disagreement rate	Median	Mean	Agreement
Abdominal pain	0%	4.01	4	Yes
Epigastric pain	50.9%	2.54	2	No
Hypogastric pain	1.8%	3.94	4	Yes
Relieved by defecation	0%	4.25	4	Yes
Relieved by passing gases	3.6%	3.92	4	Yes
Worsened by meals	70.9%	2.36	2	No
Increase in stool frequency	2%	3.93	4	Yes
Decrease in stool frequency	9%	3.51	4	Yes
Changes in stool consistency	0%	3.95	4	Yes
Straining	7%	3.22	3	No
Urgency	7%	3.64	4	Yes
Feeling of incomplete evacuation	on 20%	3.18	3	No

Agreement: median \geq 4 and/or mean \geq 3.75.

Characteristic symptoms

Participants considered the following as characteristic symptoms of IBS: abdominal pain, hypogastric pain, changes in frequency and form, or stools associated with pain and abdominal distension.

Alarm symptoms

In the questionnaire we included some questions to assess the value of alarm symptoms regarding both their presence and absence –96% of physicians considered that the presence of alarm symptoms must lead to consider entities other than IBS, and to perform complementary studies; 58% considered that their absence was not sufficient to confirm an IBS diagnosis in spite of typical symptoms

Table III shows all symptoms considered alarm or red flags.

Table III. Alarm symptoms

	Disagreement rate	Median	Mean	Agreement
Anorexia	0%	4	4.04	Yes
Weakness	18%	3.2	3	No
Fever	4%	4	4.22	Yes
Weight loss	0%	5	4.63	Yes
Rectal bleeding	0%	5	4.65	Yes
Nocturnal diarrhea	4%	4	3.98	Yes
Narrow stools	55%	2.55	2	No
Vomiting	16%	3.05	3	No
Feeling of incomplete evacuati	on 24%	2.94	3	No
Abdominal distension	78%	2.18	2	No

Agreement: median \geq 4 and/or mean \geq 3.75.

Temporal features and usefulness of diagnosis criteria

Ninety-six per cent of participants agreed that time of evolution was an important issue in the diagnosis of IBS, 87% considered that times of symptom evolution lower than 3 months should prompt to look for a different diagnosis. Physicians estimated that symptom duration should be 8 months in order to make a diagnosis of IBS (mean 8.48 ± 4.78 , median 7.5).

According to clinical criteria, 70% considered that these make the diagnosis approach easier, and only 2% disagreed with them. When asked about which criteria did they know and use, more than 75% indicated their knowing and using, at least sometimes, Rome II criteria, in comparison to less than 25% who occasionally used Manning criteria.

Ninety-six percent of physicians also reported that they used the classification by symptomatic groups (diarrhea, constipation or alternating), and 76% said that they used it habitually. Most of them agreed to consider it a right classification (4% of responses differed), and up to 65% suggested a modification of the diagnostic approach according to the main complaint.

Patient characteristics

Age was not considered a key element in performing a clinical diagnosis. They disagreed (70% negative responses) in considering that symptoms can be enough for reaching a diagnosis in young patients.

They considered that the limit between young and old was 40 years of age (mean 40.24 ± 5.92 , median 40). One hundred percent of participants recommended asking for a complementary test in patients older than 40 years despite characteristic symptoms.

Concerning personal records, there was agreement in performing a thorough study in those who have first-degree relatives diagnosed with colon cancer (100% agreement) or inflammatory bowel disease (84%).

Diagnosis approach

We suggested different possibilities to them for each symptomatic group (diarrhea, constipation, and alternating habit), distinguishing between those who have alarm symptoms and those who do not. After the first round most physicians agreed to order basic biochemistry testing and hematimetry for all patients, so in the second round we integrated this test as a part of clinical diagnosis. Table IV shows our proposal for complementary tests.

Treatment

More than 90% of physicians surveyed thought that in early IBS patients stand a good chance of improving by simply relaxing; 85% admitted their use of empirical treatment for 4 to 6 weeks against the main complaint.

Concerning therapeutic approach and drugs used, we found a wide variety of combinations. Figures 1, 2, and 3 show overall results.

Concerning the first step in the therapeutic approach:

—*Diarrhea:* As first line of treatment they suggested lifestyle changes and an increase in dietary fiber, but 51% signaled that sometimes you can employ anti diarrheal and spasmolytic drugs.

—Constipation: 60% of participants considered fiber and lifestyle changes as the first-step treatment, although 25% stated that they would offer laxatives at the first consultation.

Table IV. Proposed diagnostic approach regarding symptoms in IBS

					_		, ,	, ,				
	Diarrhea without alarm symptoms		Diarrhea with alarm symptoms		Constipation without alarm symptoms		Constipation with alarm symptoms		Alternating without alarm symptoms		Alternating with alarm symptoms	
	Mean	Agreement	Mean	Agreement	Mean	Agreement	Mean	Agreement	Mean	Agreement	Mean	Agreement
Clinical diagnosis	2.95	No	1.70	No	2.95	No	1.89	No	3.00	No	1.73	No
Acute phase reagents	3.7	Yes	4.3	Yes	3.1	No	3.8	Yes	3.4	No	4.0	Yes
TSH	3.6	No	4.1	Yes	3.2	No	-	-	3.4	No	-	-
Tumoral markers	-	-	3.51	No	-	-	3.54	No	-	-	3.53	No
Stool culture	3.5	No	3.6	No	-	-	-	-	2.8	No	3.3	No
Barium enema	2.40	No	2.83	No	2.85	No	2.87	No	2.64	No	2.89	No
Colonoscopy	2.8	No	4.4	Yes	2.85	No	4.5	Yes	3.0	No	4.6	Yes

Agreement if mean ≥ 3.75.

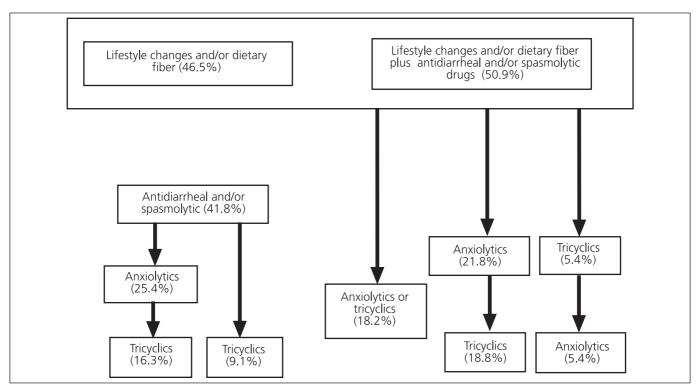


Fig. 1. Diarrhea-predominant IBS.

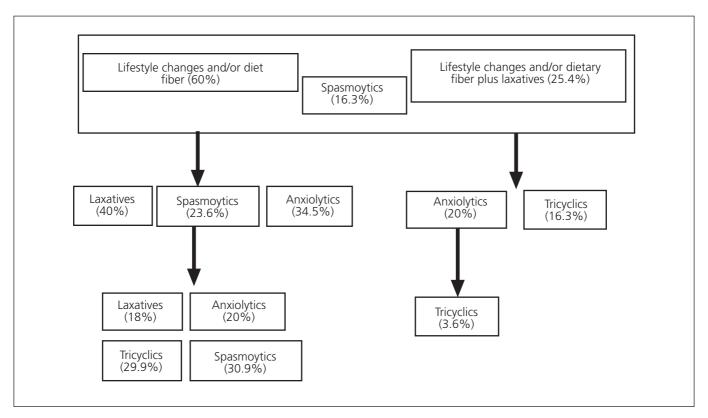


Fig. 2. Constipation-predominant IBS.

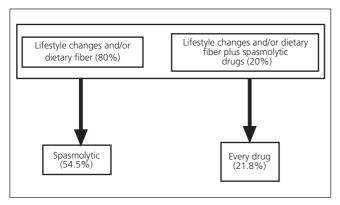


Fig. 3. Alternating IBS.

—Alternating: 80% of physicians consulted recommended lifestyle changes and fiber initially, while 20% suggested spasmolytic drugs as first-step treatment.

Follow up

Twenty percent of doctors agreed on self-reported follow-up on an as-needed basis, but the remaining 80% preferred follow-up at fixed intervals. The majority recommended follow-up every six months.

DISCUSSION

The aim of this work was to gather the various opinions of Spanish physicians concerning IBS and focusing on the most relevant clinical areas. Although response rate was only around 55%, this response is higher than that obtained in previous similarly designed studies (12).

Overall, comparing our physicians' points of view and the scientific evidence available nowadays, which includes national and international guidelines (6, 13,14), we find many similarities as well as some differences.

Every physician questioned defined IBS in the same way: abdominal or hypogastric pain relieved with defecation or passing gas, associated with a change in stool frequency or form, and also related to bloating or a feeling of abdominal distension. This latter fact is interesting because, even though abdominal distension is not included in the Rome II definition, it is a typical and well-documented feature in IBS (15).

As in current guidelines, Spanish physicians interviewed considered it essential to identify potential alarm symptoms before reaching a diagnosis of IBS,

considering as general alarm symptoms anorexia, fever, and weight loss, and as digestive alarm symptoms rectal bleeding and nocturnal diarrhea. An abrupt onset of symptoms is also considered a red flag by both physicians interviewed and experts.

Obtaining family records is also mandatory, especially in cases such as colon cancer or IBS in first-degree relatives. In this case we should order additional tests to gain a better understanding of the patient as a whole.

Spanish doctors suggest 40 years of age as the limit for the ordering of complementary tests to exclude other serious illnesses, reflecting a more conservative and defensive attitude than that recommended for 45-to-50-year-old subjects by guidelines. Regarding this issue we have not found much scientific evidence available, although a study pointed to 50 years of age as a more appropriate limit (16).

The majority of doctors interviewed considered that clinical criteria make IBS easier to diagnose, and more than 75% consider and use, at least sometimes, Rome II criteria in their daily practice. This is in contrast with other previously published data in that it points out that, in their daily practice, a high rate of physicians, mainly GPs, do not use or know about the aforementioned criteria (2,17,18). Our data do not allow us to understand the reason for this discrepancy. Separating patients according to their main symptom (diarrhea, constipation, or alternating) is a well-established classification for the majority, who think that this is also a reasonable instrument to lead the management of these patients.

Most participants estimate that a duration of symptoms of 8 months is necessary in order to consider an IBS diagnosis, and most do not clearly agree that symptoms should be present 25% of the time. Both data are in line with the modifications included in the recently published Rome III criteria, in contrast with the previous Rome II criteria (19).

Concerning the diagnostic approach, our doctors preferred to include a basic blood test as part of the clinical diagnosis in the first visit, adding TSH and a stool culture when diarrhea is the main complaint. Just in case of alarm symptoms physicians opted for adding other complementary tests such as acute reagents and colonoscopy. Comparing this approach to experts' recommendations we obtain a reasonable similitude but with two important discrepancies -first of all, our physicians do not agree in performing screening tests for celiac disease in diarrhea-predominant patients, as recommended by its high prevalence (20) in IBS-like symptoms patients, concluding that this screening is not commonly performed by our physicians and, on the other hand, because there is a tendency to perform a colonoscopy for colon cancer screening in patients younger than recommended by international guidelines.

According to the information given by responding physicians the therapeutic management of IBS has a really uniform approach. Their opinion is that sometimes the best treatment is patient relaxation, as can be confirmed by different clinical essays. A good patientdoctor relationship is essential for the prognosis of this disease (6,21), and may influence medical consultation in the future (22). It is interesting to see the trust of Spanish doctors in lifestyle and dietary changes, and how they insist in recommending fiber to every patient regardless of symptoms presented. This finding could mean two things - one, that a majority of patients visiting our practices have mild symptoms that can improve only with these measures; two, that this is a medical attitude based on a positive experience that could be explained by a placebo effect, which according to clinical essays is higher than 40% in IBS

The empirical pharmacological approach in IBS does not enjoy an unanimous consensus, but there is a tendency to direct drugs against the patient's main complaint, according to published guidelines (13,14); it is however striking that spasmolytic drugs are used as first-line therapy just in diarrhea-predominant patients, and not in constipation-predominant or alternating ones.

Our physicians usually recommend short treatment steps immediately leading to an upper level by adding psychotropic drugs with anxiolytic or relaxing properties.

Doctors, both GPs and gastroenterologists, show an adequate understanding of the IBS concept, but in their practice they expressed an attitude only partially guided by medical guidelines because of the difficult management of IBS. Sometimes physicians move from evidence-based medicine to experience-based medicine while attempting to improve their patients' wellbeing.

ACKNOWLEDGEMENTS

We acknowledge the participation as consultants of Fermín Mearin (Barcelona), Antonio Caballero (Granada), Julio Ponce (Valencia), Jesús García-Cano (Cuenca) and Cristina Moreno (Madrid). We also thank the cooperation of primary care physician and gastroenterologists, because this project had not been possible without them. We thank Peace Fernee and Ana Linares their inestimable aid in the preparation of the English version of the manuscript.

Dra. Cristina Almansa is currently receptor of a scholarship AGA-SEPD (grant Jon Isenberg), in the Department of Gastroenterology of Mayo Clinic. Jacksonville, USA.

REFERENCES

- Mearin F, Badia X, Balboa A, Baro E, Caldwell E, Cucala M, et al. Irritable bowel syndrome prevalence varies enormously depending on the employed diagnostic criteria: Comparisons of Rome II versus previous criteria in a general population. Scand J Gastroenterol 2001; 36: 1155-61.
- Thompson WG, Heaton KW, Smyth GT, Smyth C. Irritable bowel syndrome in general practice: Prevalence, characteristics, and referral. Gut 2000; 46: 78-82.
- 3. Badia X, Mearin F, Balboa A, Baro E, Caldwell E, Cucala M, et al. Burden of illness in irritable bowel syndrome comparing Rome I and Rome II criteria. Pharmacoeconomics 2002; 20: 749-58.
- 4. Sandler RS, Everhart JE, Donwitz M, Adams E, Cronin K, Goodman C, et al. The burden of selected digestive diseases in the United States. Gastroenterology 2002; 122: 1500-11.
- Hungin AP, Whorwell PJ, Tack J, Mearin F. The prevalence, patterns and impact of irritable bowel syndrome: an international survey of 40,000 subjects. Aliment Pharmacol Ther 2003; 17: 643-50.
- 6. Jones J, Boorman J, Cann P, Forbes A, Gomborone J, Heaton K, et al. British Society of Gastroenterology guidelines for the management of the irritable bowel syndrome. Gut 2000; 47 (Supl. II): ii1-ii9.
- Drossman DA, Corazziari E, Talley NJ, Thompson WG, White-head WE. Rome II: the functional gastrointestinal disorders. Diagnosis, pathophysiology and treatment: a multinational consensus. 2nd ed. McLean, Va: Degnon Associates; 2000.
- 8. Yawn BP, Lydick E, Locke GR, Wollan PC, Bertran SL, Kurland MJ. Do published guidelines for evaluation of irritable bowel syndrome reflect practice? BMC Gastroenterology 2001, I: II.
- Verhagen AP, De Vet HC, De Brie RA, Kessels AG, Boers M, Bouter LM, et al. The Delphi list a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. J Clin Epidemiol 1998, 51: 1235-41.
- Powell C. The delphi technique: myths and realities. J Adv Nurs 2003; 41: 376-82.
- Mokkink LB, Terwee CB, Knol DL, Stratford DW, Alonso J, Patrick DL, et al. Protocol of the COSMIN study: Consensus based standards for the selection of health measurement instruments. BMC Med Res Methodol 2006; 24: 2.
- 12. Almasio PL, Niero M, Anglioli D, Ascione A, Gullini S, Minoli G, et al. Experts' opinions on the role of liver biopsy in HCV infection: a Delphi survey by the Italian Association of Hospital Gastroenterologist (A.I.G.O.). J Hepatol 2005; 43(3): 381-7.
- AGA Technical Review on Irritable Bowel Syndrome. Gastroenterology 2002; 123: 2108-31.
- 14. American College of Gastroenterology Functional Gastrointestinal Disorders Task Force. Evidence based position statement on the management of irritable bowel syndrome in North America. AJG 2002; 97: 11(Supl.): S1-S5.
- Chang L, Lee OY, Naliboff B, Schmulson M, Mayer EA. Sensation of bloating and visible abdominal distension in patients with irritable bowel syndrome. Am J Gastroenterol 2001; 96: 3341-7.
- Hammer J, Eslick GD, Howell SC, Altiparmak E, Talley NJ. Diagnostic yield of alarm features in irritable bowel syndrome and functional dyspepsia. Gut 2004; 53: 666-72.
- Gladman LM, Gorard DA. General practitioner and hospital specialist attitudes to functional gastrointestinal disorders: Aliment Pharmacol Ther 2003; 17: 651-4.
- Lea R, Hopkins V, Hastleton J, Houghton LA, Whorwell PJ. Diagnostic criteria for irritable bowel syndrome: Utility and applicability in clinical practice. Digestion 2004; 70: 210-3.
- Longstrech GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. Gastroenterology 2006; 130: 1480-91.
- Sanders DS, Carter MJ, Hurlstone DP. Association of adult coeliac disease with irritable bowel syndrome: A case-control study in patients fulfilling the ROME II criteria referred to secondary care. Lancet 2001; 358:1504-8.

- Owens DM, Nelson DK, Talley NJ. The irritable bowel syndrome: Long term prognosis and the physician patient interaction. Ann Intern Med 1995; 122: 107-12.
 Izquierdo S, Rey E, Garcia Alonso M, Almansa C, Díaz-Rubio M.
- Izquierdo S, Rey E, Garcia Alonso M, Almansa C, Díaz-Rubio M. Has the identification of rectal hypersensitivity any implication in the clinical outcome of irritable bowel syndrome? Rev Esp Enferm Dig 2005; 97: 223-8.
- 23. Spiller RC. Problems and challenges in the design of irritable bowel syndrome clinical trials: experience from published trials. Am J Med 1999; 107(5A): 91S-97S.
 24. Patel SM, Stason WB, Legedza A, Ock SM, Kaptchuk TJ, Con-
- Patel SM, Stason WB, Legedza A, Ock SM, Kaptchuk TJ, Conboy L, et al. The placebo effect in irritable bowel syndrome trials: A meta-analysis. Neurogastroenterol Motil 2005; 17: 332-40