CHAPTER

61

Management if Irritable Bowel Syndrome: A Practical Approach

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INTRODUCTION

According to recently describe Rome IV criteria published in May 2016, irritable bowel syndrome (IBS) is a chronic (onset at least 6 months ago and symptoms present during the last 3 months) functional bowel disorder in which recurrent abdominal pain is associated with defecation or a change in bowel habits (altered stool form and/or passage), which are not explained by any organic cause detected on routine investigations.[1] However, it is being realized more and more that many of these patients, if investigated with highly sensitive investigations, may reveal organic causes that could not have been picked-up by routine investigations challenging the concept of functional basis for all patients with IBS.[2, 3] These data suggest that IBS is multi-dimensional in nature with several micro-organic factors contributing to the pathogenesis.[4] Although it is considered to be a functional disorder without increase in mortality, it has significant impact on quality of life.[5-9] It is highly prevalent in almost all countries and is one of the most common disorders seen by gastroenterologists worldwide.[6, 10-17] There has been major paradigm shift in understanding of epidemiology, pathophysiology, diagnosis and management of IBS in the last decade.[6, 18, 19] This chapter will review some aspects of advances in diagnosis and treatment of this disorder.

DIAGNOSIS OF IBS

IBS used to be considered as a diagnosis of exclusion earlier. However, Manning's criteria brought a revolution in diagnosis of IBS as it brought a paradigm shift; Manning's criteria (Table 1) encourage a positive diagnosis of IBS without the need of multiple unnecessary investigations to exclude organic diseases before diagnosing IBS.[20]

In the Manning's criteria, the authors found fulfilling four of these criteria often turned out to have functional disorder such as IBS on subsequent investigations. However, one must remember that in this study organic disorders excluded included peptic ulcer, gastrointestinal malignancy and stricture. Hence, in true sense, fulfilling Manning's criteria does not exclude other organic diseases such as lactose intolerance, celiac disease, microscopic colitis, small intestinal bacterial overgrowth, fecal evacuation disorder, collagenous colitis and microscopic etc.[20] Other limitation of Manning criteria is lack of any consideration for duration of symptoms, which is important to exclude organic disorders, which are expected to present with short duration of symptoms.[20]

Currently, Rome IV criteria (Table 2), developed after several iterations through Rome I, II and III criteria, are used to diagnose IBS.[21-23]

Table 1: The Manning criteria

- Onset of pain associated with more frequent bowel movements
- Onset of pain associated with more loose bowel movements
- Relief of pain with defecation
- Abdominal distension
- Sense of incomplete evacuation
- Passage of mucus

ALARM FEATURES

There are certain alarm features in presence of which, one should especially look for organic diseases before labelling patients as IBS. These 'red flags' include age 45 years or older, presence of anemia, blood in the stools, unintended weight loss, nocturnal symptoms, fever, abdominal mass, and a family history of colorectal cancer. The relevance of these alarm features may vary in different regions of the world and also from patient to patient. The differential diagnosis of IBS symptoms (Table 3) is broad, which can lead to multiple, but often unnecessary, diagnostic tests.[24, 25] It is the role of clinician to curtail the battery of tests as per the patient's clinical history and examination.

Various expert committees have given guidelines regarding investigations in a suspected case of IBS.[24, 25] For clinical trials, all patients should have at least full blood counts, erythrocyte sedimentation rate, C-reactive protein, and limited colonoscopic examination, and other investigations, if indicated.[24]

RECENT ADVANCES IN DIAGNOSIS OF IBS

Diagnosis of IBS is popularly made by symptom-based

Table 2: Rome IV criteria[1]

Recurrent abdominal pain, on average, at least 1 day per week in the last 3 months, associated with 2 or more of the following criteria:

1. Related to defecation
2. Associated with a change in frequency of stool
3. Associated with a change in form (appearance) of stool

Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

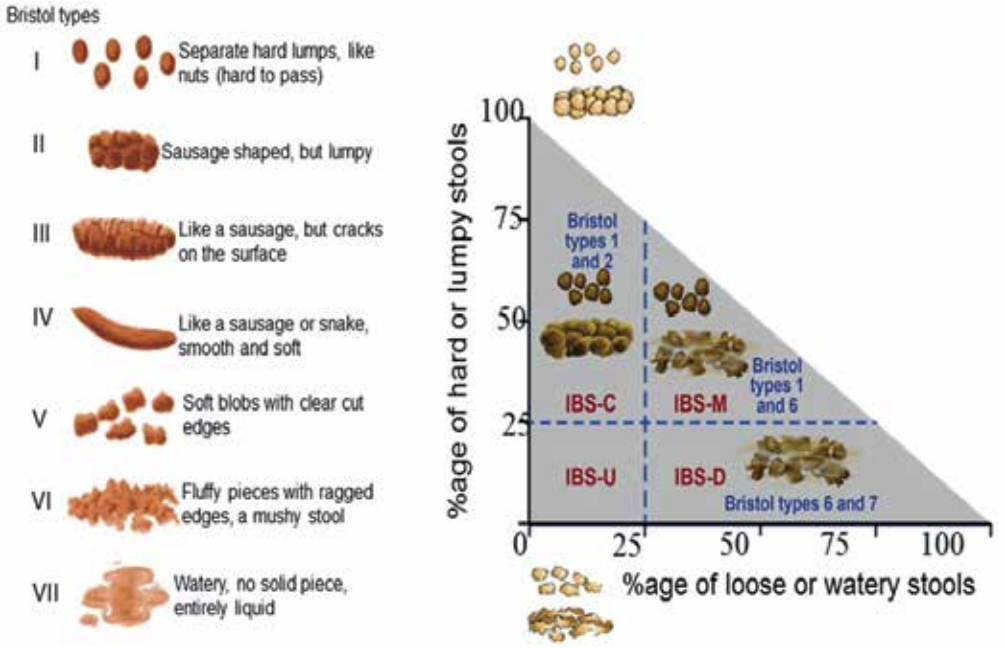

Fig. 1: Bristol stool types and method of sub-typing of IBS according to Rome IV system. IBS subtypes should be established according to stool consistency, using the Bristol stool form scale. Whether 25% of the stools are constipating types (type I and II) or 25% of the stools are diarrheal types (type VI or VII) determine IBS subtypes according to Rome IV criteria.

Table 3: Differential Diagnosis of IBS Symptoms

- Celiac disease
- Food intolerance
- Lactose intolerance
- Inflammatory bowel disease (IBD)
- Infective colitis
- Small intestinal bacterial overgrowth (SIBO)
- Colonic diverticulosis
- Colorectal carcinoma
- Giardiasis

Table 4: Multi-dimensional clinical profile (MDCP)

- Categorical Rome diagnosis
- Additional information that sub-classifies the diagnosis leading to more specific treatment (e.g. diarrhea-predominant, constipation-predominant, pain-predominant etc. overlapping)
- The personal impact of the disorder on the patient (severity)
- Physiological abnormalities or biomarkers
- Psychological influences of the disorder

criteria with reasonable investigation to exclude organic disorders. In a proportion of patients, clinical evaluation and evaluation of past medical records including available investigations may be sufficient. However, there is a paradigm shift in understanding the pathophysiology of IBS in the recent time. Emerging evidence suggest that a sub-set of IBS may have micro-organic basis such as gut dysbiosis including small intestinal bacterial overgrowth (SIBO), low grade inflammation, dietary intolerance, abnormal gut transit, prior gastrointestinal infection and infestation, abnormal intestinal permeability and neuro-hormonal dysregulation.[26-31] Recognizing some of these pathophysiological abnormalities may have important therapeutic implications. For examples, patients with SIBO and IBS are expected to respond more often with antibiotic treatment than those without SIBO.[32-34] Moreover, with recent introduction of the explanatory model, which requires explaining the specific abnormality responsible for the symptom generation and aggravation necessitate physician to first understand the pathophysiological basis of symptoms himself/herself. It is also important to understand that patients with less severe symptoms, those with considerable psychological co-morbidity may not require such extensive investigations and specific treatment for a micro-organic cause. Considering all these, the Rome IV algorithm, brought a new dimension to management of IBS, the multi-dimensional clinical profile (MDCP).[35]

MDCP necessitate the physician to assess several important issues in addition to the categorical diagnosis of functional gastrointestinal disorders such as IBS (Table 4).

Sub-typing (Figure 1) is absolutely essential to treat patients with IBS as drugs useful in one sub-type of disease (e.g. IBS-C) would be counter-productive in another sub-type.[21] Moreover, those with alternating (change in symptoms over weeks to months) and mixed type is more difficult to treat and may require pathophysiology modifying measures such as attempt at manipulating gut microbiota.

Severity assessment is another important aspect of MDCP as patient with mild disease may be managed with less aggressive approach than those with severe disease. Most clinicians try to assess severity of IBS to plan for

investigations and recommend treatment but quite often it is subjective. Few studies have addressed this issue and no consensus criterion for assessing severity assessment of IBS is available. Although neglected in the development of diagnostic criteria for IBS, recent studies have demonstrated the clinical importance of IBS severity. It has been observed that patients who self-reported their IBS as severe or very severe incurred greater indirect medical costs in the form of decreased productivity compared to patients who reported their IBS as mild or moderate.[36,37] Besides cost, severity of IBS is also determines impairment of health related quality of life (HRQOL).[38] It has been shown in many studies that patients with severe IBS had lower HRQOL scores and incurred more direct medical costs.[5,39,40] These studies emphasize the importance of severity in IBS, especially QOL, and also have implications for public health, including the burden of illness. There are several factors which may influence the severity of IBS symptoms. First, whether the patient or doctor think that severity assessment is important? Difference in perception of severity of symptoms between physicians and patients is far greater in patients with functional bowel disorders than in patients with organic diseases. Type of scale used to assess severity may have impact on results. Similarly, the social background and literacy status of patient is also important. Finally, the degree of disability or impairment is another factor that will influence IBS severity.[41] Perhaps due to so many issues involved in severity assessment of IBS symptoms, till date no single set of criteria is universally accepted. Table 5 summarizes some of the criteria used for assessment of severity of IBS.

Table 5: Severity assessment for IBS

Functional Bowel Disorder Severity Index (FBDSI)[42]
IBS Symptom Severity Score (IBS-SSS)[43]
Health-related quality of life (IBS-QOL)[5]
Hospital Anxiety and Depression Scale (HADS)[44]
IBS 36[45]

TREATMENT

Multi-disciplinary approach is often required for optimal treatment. Besides the treating physician expert opinion from dietician and psychologist may also be required. It is often best to focus on the predominant symptom: diarrhea (Figure 2), constipation, or pain/gas/bloat and then treat accordingly (Table 6).

Variable response rates have been reported for each of these drugs in various trials. This may be due to use

Table 6: Current symptom based management of IBS

Symptom	First Line	Second Line	Future
Constipation	Fiber Osmotic laxative including polyethylene glycol Lactulose/Lactitol Stool softner eg, docusate	Bisacodyl Sodium picosulfate Tegaserod (withdrwan) Lubiprostone Linaclotide Prucalopride (5-HT4 agonist)	Elobixibat (ileal bile acid transporter inhibitor)
Diarrhea	Loperamide Diphenoxylate	Alosetron Ramosetron Ondasetron Bile acid sequestrant (cholestyramine, cholestipol) Rifaximin Clonidine	
Bloating	Treat constipation	Probiotic Antibiotic (rifaximin)	
Pain		Antispasmodics Anticholinergics Mebeverine Pinnaverium Otilonium bromide Antidepressant • Tricyclic anti-depressants • SSRI SNRI	

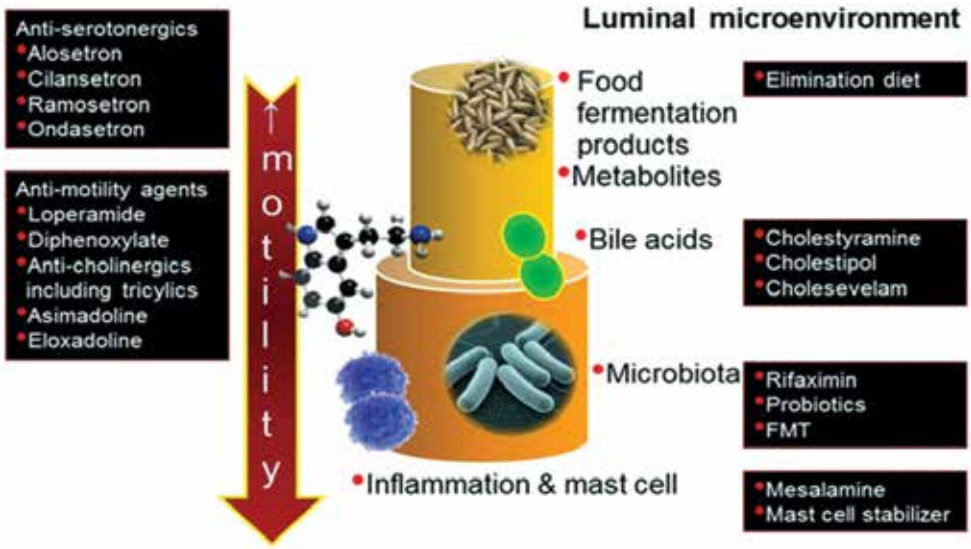

Fig. 2: Abnormalities in luminal micro-environment in diarrhea-predominant IBS, that are used as therapeutic targets with different pharmacological agents. Abbreviation used: FMT: fecal microbiota transplant (currently in experimental stage)

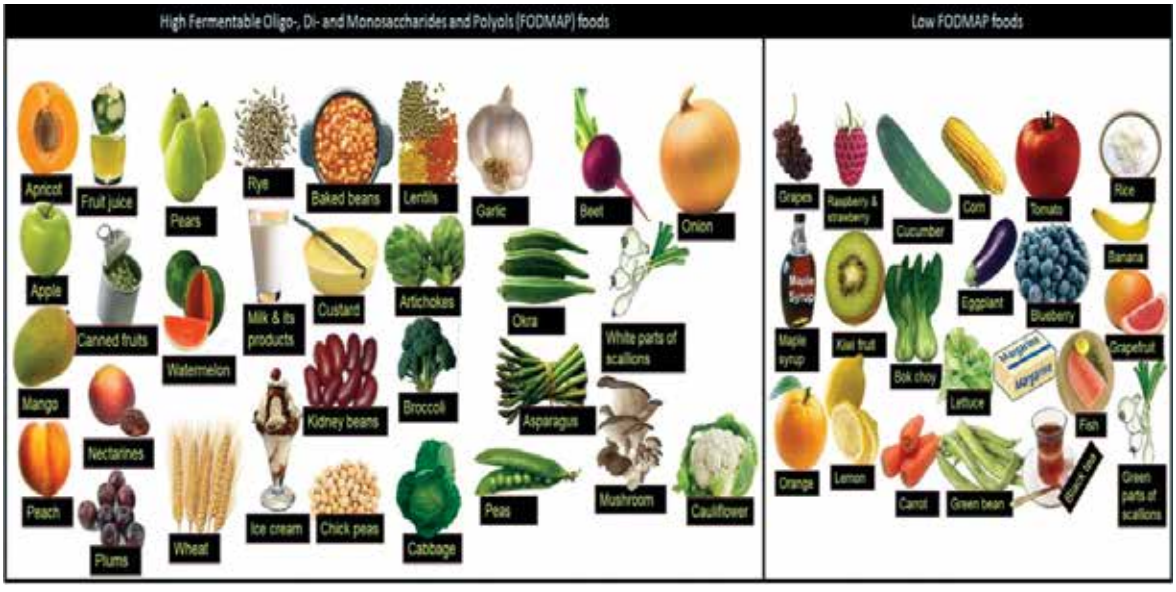

Fig. 3: High and low Fermentable Oligo-, Di- and Monosaccharides and Polyols (FODMAP) foods

of different inclusion criteria and also due to regional, dietary and cultural factors. Another important aspect is that in most of the trials significant proportion of the placebo response rates have been observed. Therefore, more trials are required for many of the therapies that claim on their efficacy in treatment of IBS.

Initial treatment for patients with IBS should include various combinations of antispasmodic, laxative, and anti-diarrheal agents as they are quite safe and relatively inexpensive. Antispasmodics are effective when pain is the predominant symptom.[46,47] Antispasmodics encompass several different drug classes, including anti-muscarinics, smooth-muscle relaxants and anticholinergics. Common side effects, including dry mouth, dizziness, blurry vision, confusion (particularly in elderly patients), urinary retention, and constipation, often limit the usefulness of these agents in the treatment of IBS. The propensity of these agents to promote constipation makes them a less attractive option for patients with IBS-C. Bulking agents are another group of commonly prescribed drugs especially for IBS-C. Evidence for this group of agents in IBS is surprisingly lacking. Moreover, they may even aggravate abdominal pain and bloating.[46, 47] For the control of diarrhea, loperamide has the best quality of evidence, but has not been shown to improve abdominal pain or distension.[48,49] Recently, a few drugs have been used in treatment of IBS which target serotonin receptors (Aloseteron, tegaserod, prucalopride).[31,50] The major concern with some of these agents (e.g. tegaserod) has been the cardiovascular side-effects limiting their utility.

Besides the above-mentioned peripherally acting agents, there are a quite a few centrally-acting therapies for IBS. Antidepressants (tricyclic anti-depressants and SSRI) have been shown to have efficacy in IBS even in absence of any psychiatric illness.[51-53] Both group of anti-depressants were found to be equally effective. They act at multiple levels in IBS, such as by altering pain perception, by improving sleep, and by improving

any associated psychological illness.[54] Another unique approach of treating IBS is psychotherapy. Aims of psychotherapy include reframing maladaptive beliefs, reduction of over-responsiveness to stress, reduction of maladaptive psychological responsiveness and modification of maladaptive behaviors.[54] The specific content of the therapy is based on a biopsychosocial assessment of the patient's background and current difficulties. Hypnotherpay is one of the important tools in psychotherapy.[55] The essence of hypnotherapy is to create a relaxing and calming environment and allowing the patient to refocus away from uncomfortable symptoms and towards a more pleasant perception of his or her current state. There is little evidence for efficacy of such an approach in IBS.[56] Major drawback of hypnotherapy is requirement of a well-trained mental health professional.

Recently, rifaximin has been evaluated for treatment of IBS without constipation (TARGET 1 and Target 2).[57] Rifaximin is a poorly absorbed antibiotic with broad-spectrum activity against Gram-negative bacteria, Gram positive bacteria, and anaerobes. In these trials, 41% patients with IBS reported improvement with two-weeks course of rifaximin as compared to 30% in placebo arm. Symptoms recur in most patients within 2-3 months after therapy. Long term symptom relief with this antibiotic is still not known. Also no attempt was made to test for SIBO in this study. However, in spite of these limitations, this study is important as it brings a novel concept of treating a "functional disorder", which is now believed to result from altered gut microbiota, with antibiotic.

Lastly, dietary modifications have also been tried in IBS. Many people complain of adverse reactions to specific food. Gastrointestinal symptoms are the commonest manifestations of food intolerance. Studies from West show that dairy products and cereals are most important food items which aggravate the symptoms of IBS.[58] In Asian countries, chilli and curry are the possible food triggers for pain in patients with IBS.[59] Lactose intolerance has been found to be equally common in IBS and healthy controls but patients with IBS complain of symptoms more commonly following the lactose load.[60] Similarly, some investigators have studied fructose intolerance in IBS.[61] Presently, the role of fructose malabsorption in IBS is less understood. Recently, a new concept of dietary management of functional gastrointestinal symptoms "FODMAP approach" has been introduced (Figure 3).[62] FODMAP stands for fermentable olio-di-mono-sacchrides and polyols. Basically, these consist of a group of rapidly fermentable short chain carbohydrates. Dietary FODMAPs induce prolonged hydrogen production in the intestine that is greater in IBS, influence the amount of methane produced, and induce gastrointestinal and systemic symptoms experienced by patients with IBS.[63] In view of these dietary triggers involved in generation of symptoms in some patients with IBS, it is necessary to take detailed dietary history including excessive consumption of dairy and lactose-rich products, dietary fibres (especially in the form of bran or other cereals), and fructose or fructan-rich foods. Elimination of high FODMAP foods and encouragement to use low FODMAP foods may help in improving symptoms of IBS, particularly abdominal bloating.

REFERENCES

1. Mearin F, Lacy BE, Chang L, Chey WD, Lembo AJ, Simren M, Spiller R. Bowel Disorders. Gastroenterology 2016.
2. Pimentel M, Soffer EE, Chow EJ, Kong Y, Lin HC. Lower frequency of MMC is found in IBS subjects with abnormal lactulose breath test, suggesting bacterial overgrowth. *Dig Dis Sci* 2002; 47:2639-43.
3. Sanders DS. Celiac disease and IBS-type symptoms: the relationship exists in both directions. *Am J Gastroenterol* 2003; 98:707-8.
4. Barbara G, Feinle-Bisset C, Ghoshal UC, Quigley EM, Santos J, Vanner S, Vergnolle N, Zoetendal EG. The Intestinal Microenvironment and Functional Gastrointestinal Disorders. Gastroenterology 2016.
5. Patrick DL, Drossman DA, Frederick IO, DiCesare J, Puder KL. Quality of life in persons with irritable bowel syndrome: development and validation of a new measure. *Dig Dis Sci* 1998; 43:400-11.
6. Gwee KA. Irritable bowel syndrome in developing countries--a disorder of civilization or colonization? *Neurogastroenterol Motil* 2005; 17:317-24.
7. Levy RL, Von Korff M, Whitehead WE, Stang P, Saunders K, Jhingran P, Barghout V, Feld AD. Costs of care for irritable bowel syndrome patients in a health maintenance organization. *Am J Gastroenterol* 2001; 96:3122-9.
8. Vandvik PO, Wilhelmsen I, Ihlebaek C, Farup PG. Comorbidity of irritable bowel syndrome in general practice: a striking feature with clinical implications. *Aliment Pharmacol Ther* 2004; 20:1195-203.
9. Whitehead WE, Palsson O, Jones KR. Systematic review of the comorbidity of irritable bowel syndrome with other disorders: what are the causes and implications? *Gastroenterology* 2002; 122:1140-56.
10. Drossman DA, Camilleri M, Mayer EA, Whitehead WE. AGA technical review on irritable bowel syndrome. *Gastroenterology* 2002; 123:2108-31.
11. Gaburri M, Bassotti G, Bacci G, Cinti A, Bosso R, Ceccarelli P, Paolocci N, Pelli MA, Morelli A. Functional gut disorders and health care seeking behavior in an Italian non-patient population. *Recenti Prog Med* 1989; 80:241-4.
12. Gwee KA, Lu CL, Ghoshal UC. Epidemiology of irritable bowel syndrome in Asia: something old, something new, something borrowed. *J Gastroenterol Hepatol* 2009; 24:1601-7.
13. Ghoshal UC, Abraham P, Bhatt C, Choudhuri G, Bhatia SJ, Shenoy KT, Banka NH, Bose K, Bohidar NP, Chakravartty K, Shekhar NC, Desai N, Dutta U, Das G, Dutta S, Dixit VK, Goswami BD, Jain RK, Jain S, Jayanthi V, Kochhar R, Kumar A, Makharia G, Mukewar SV, Mohan Prasad VG, Mohanty A, Mohan AT, Sathyaprakash BS, Prabhakar B, Philip M, Veerraju EP, Ray G, Rai RR, Seth AK, Sachdeva A, Singh SP, Sood A, Thomas V, Tiwari S, Tandan M, Upadhyay R, Vij JC. Epidemiological and clinical profile of irritable bowel syndrome in India: report of the Indian Society of Gastroenterology Task Force. *Indian J Gastroenterol* 2008; 27:22-8.
14. Masud MA, Hasan M, Khan AK. Irritable bowel syndrome in a rural community in Bangladesh: prevalence, symptoms

pattern, and health care seeking behavior. *Am J Gastroenterol* 2001; 96:1547-52.

15. Sandler RS. Epidemiology of irritable bowel syndrome in the United States. *Gastroenterology* 1990; 99:409-15.
16. Talley NJ, Zinsmeister AR, Melton LJ, 3rd. Irritable bowel syndrome in a community: symptom subgroups, risk factors, and health care utilization. *Am J Epidemiol* 1995; 142:76-83.
17. Ghoshal UC, Singh R. Frequency and risk factors of functional gastro-intestinal disorders in a rural Indian population. J Gastroenterol Hepatol 2016.
18. Gwee KA. Defining IBS in India: a brave new world. *Indian J Gastroenterol* 2008;27:3-4.
19. Gerson CD, Gerson MJ, Awad RA, Chowdhury A, Dancey C, Poitras P, Porcelli P, Sperber A, Wang WA. Irritable bowel syndrome: an international study of symptoms in eight countries. *Eur J Gastroenterol Hepatol* 2008;20:659-67.
20. Manning AP, Thompson WG, Heaton KW, Morris AF. Towards positive diagnosis of the irritable bowel. *Br Med J* 1978;2:653-4.
21. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. *Gastroenterology* 2006; 130:1480-91.
22. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. *Scand J Gastroenterol* 1997;32:920-4.
23. Gwee KA, Ghoshal UC. The Rome criteria divides, distorts and dilutes the prevalence of irritable bowel syndrome. *Saudi J Gastroenterol* 2010; 16:143-4.
24. Gwee KA, Bak YT, Ghoshal UC, Gonlachanvit S, Lee OY, Fock KM, Chua AS, Lu CL, Goh KL, Kositchaiwat C, Makharia G, Park HJ, Chang FY, Fukudo S, Choi MG, Bhatia S, Ke M, Hou X, Hongo M. Asian consensus on irritable bowel syndrome. *J Gastroenterol Hepatol* 2010; 25:1189-205.
25. Brandt LJ, Chey WD, Foxx-Orenstein AE, Schiller LR, Schoenfeld PS, Spiegel BM, Talley NJ, Quigley EM. An evidence-based position statement on the management of irritable bowel syndrome. *Am J Gastroenterol* 2009; 104:S1-35.
26. Shukla R, Ghoshal U, Dhole TN, Ghoshal UC. Fecal Microbiota in Patients with Irritable Bowel Syndrome Compared with Healthy Controls Using Real-Time Polymerase Chain Reaction: An Evidence of Dysbiosis. Dig Dis Sci 2015.
27. Srivastava D, Ghoshal U, Mittal RD, Ghoshal UC. Associations between IL-1RA polymorphisms and small intestinal bacterial overgrowth among patients with irritable bowel syndrome from India. *Neurogastroenterol Motil* 2014; 26:1408-16.
28. Ghoshal UC, Shukla R, Ghoshal U, Gwee KA, Ng SC, Quigley EM. The gut microbiota and irritable bowel syndrome: friend or foe? *Int J Inflam* 2012; 2012:151085.
29. Osadchuk MA, Burdina VO. [Irritable bowel syndrome with extraintestinal manifestations from a position of neuroendocrine pathology]. *Eksp Klin Gastroenterol* 2015; 29-34.
30. Ohman L, Tornblom H, Simren M. Crosstalk at the mucosal border: importance of the gut microenvironment in IBS. *Nat Rev Gastroenterol Hepatol* 2015; 12:36-49.
31. El-Salhy M, Hatlebakk JG, Gilja OH, Hausken T. Irritable bowel syndrome: recent developments in diagnosis, pathophysiology, and treatment. *Expert Rev Gastroenterol Hepatol* 2014; 8:435-43.
32. Shah SC, Day LW, Somsouk M, Sewell JL. Meta-analysis: antibiotic therapy for small intestinal bacterial overgrowth. *Aliment Pharmacol Ther* 2013; 38:925-34.
33. Ford AC, Spiegel BM, Talley NJ, Moayyedi P. Small intestinal bacterial overgrowth in irritable bowel syndrome: systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2009; 7:1279-86.
34. Ghoshal UC, Srivastava D, Misra A, Ghoshal U. Randomized double-blind placebo-controlled trial of antibiotic treatment in patients with irritable bowel syndrome directed against small intestinal bacterial overgrowth diagnosed using upper gut aspirate culture. Neurogastroenterol Motil (submitted).
35. Drossman DA. Guidelines for use of the multi-dimensional clinical profile. In: Multi-dimensional clinical profile (MDCP) for the functional gastrointestinal disorders (1st Edition). North Carolina; Rome Foundation 2015:7-14.
36. Hahn BA, Kirchdoerfer LJ, Fullerton S, Mayer E. Patient-perceived severity of irritable bowel syndrome in relation to symptoms, health resource utilization and quality of life. *Aliment Pharmacol Ther* 1997; 11:553-9.
37. Longstreth GF, Wilson A, Knight K, Wong J, Chiou CF, Barghout V, Frech F, Ofman JJ. Irritable bowel syndrome, health care use, and costs: a U.S. managed care perspective. *Am J Gastroenterol* 2003; 98:600-7.
38. Drossman DA, Li Z, Andruzzi E, Temple RD, Talley NJ, Thompson WG, Whitehead WE, Janssens J, Funch-Jensen P, Corazziari E, et al. U.S. householder survey of functional gastrointestinal disorders. Prevalence, sociodemography, and health impact. *Dig Dis Sci* 1993; 38:1569-80.
39. Drossman DA, Whitehead WE, Toner BB, Diamant N, Hu YJ, Bangdiwala SI, Jia H. What determines severity among patients with painful functional bowel disorders? *Am J Gastroenterol* 2000; 95:974-80.
40. Coffin B, Dapoigny M, Cloarec D, Comet D, Dyard F. Relationship between severity of symptoms and quality of life in 858 patients with irritable bowel syndrome. *Gastroenterol Clin Biol* 2004; 28:11-5.
41. Reilly MC, Bracco A, Ricci JF, Santoro J, Stevens T. The validity and accuracy of the Work Productivity and Activity Impairment questionnaire--irritable bowel syndrome version (WPAI:IBS). *Aliment Pharmacol Ther* 2004; 20:459-67.
42. Drossman DA, Li Z, Toner BB, Diamant NE, Creed FH, Thompson D, Read NW, Babbs C, Barreiro M, Bank L, et al. Functional bowel disorders. A multicenter comparison of health status and development of illness severity index. *Dig Dis Sci* 1995; 40:986-95.
43. Francis CY, Morris J, Whorwell PJ. The irritable bowel severity scoring system: a simple method of monitoring irritable bowel syndrome and its progress. *Aliment Pharmacol Ther* 1997; 11:395-402.
44. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; 67:361-70.
45. Groll D, Vanner SJ, Depew WT, DaCosta LR, Simon JB, Groll A, Roblin N, Paterson WG. The IBS-36: a new quality of life measure for irritable bowel syndrome. *Am J Gastroenterol* 2002; 97:962-71.
46. Poynard T, Naveau S, Mory B, Chaput JC. Meta-analysis of smooth muscle relaxants in the treatment of irritable bowel

syndrome. *Aliment Pharmacol Ther* 1994; 8:499-510.

47. Ford AC, Talley NJ, Spiegel BM, Foxx-Orenstein AE, Schiller L, Quigley EM, Moayyedi P. Effect of fibre, antispasmodics, and peppermint oil in the treatment of irritable bowel syndrome: systematic review and meta-analysis. BMJ 2008;337:a2313.
48. Cann PA, Read NW, Holdsworth CD, Barends D. Role of loperamide and placebo in management of irritable bowel syndrome (IBS). *Dig Dis Sci* 1984; 29:239-47.
49. Efskind PS, Bernklev T, Vatn MH. A double-blind placebo-controlled trial with loperamide in irritable bowel syndrome. *Scand J Gastroenterol* 1996; 31:463-8.
50. Ford AC, Brandt LJ, Young C, Chey WD, Foxx-Orenstein AE, Moayyedi P. Efficacy of 5-HT3 antagonists and 5-HT4 agonists in irritable bowel syndrome: systematic review and meta-analysis. *Am J Gastroenterol* 2009; 104:1831-43; quiz 1844.
51. Ford AC, Talley NJ, Schoenfeld PS, Quigley EM, Moayyedi P. Efficacy of antidepressants and psychological therapies in irritable bowel syndrome: systematic review and meta-analysis. *Gut* 2009; 58:367-78.
52. Tabas G, Beaves M, Wang J, Friday P, Mardini H, Arnold G. Paroxetine to treat irritable bowel syndrome not responding to high-fiber diet: a double-blind, placebo-controlled trial. *Am J Gastroenterol* 2004; 99:914-20.
53. Masand PS, Gupta S, Schwartz TL, Kaplan D, Virk S, Hameed A, Lockwood K. Does a preexisting anxiety disorder predict response to paroxetine in irritable bowel syndrome? *Psychosomatics* 2002; 43:451-5.
54. Grover M, Drossman DA. Centrally acting therapies for irritable bowel syndrome. *Gastroenterol Clin North Am* 2011; 40:183-206.
55. Whorwell PJ, Prior A, Faragher EB. Controlled trial of hypnotherapy in the treatment of severe refractory irritable-bowel syndrome. *Lancet* 1984; 2:1232-4.
56. Webb AN, Kukuruzovic RH, Catto-Smith AG, Sawyer SM. Hypnotherapy for treatment of irritable bowel syndrome. Cochrane Database Syst Rev 2007:CD005110.
57. Pimentel M, Lembo A, Chey WD, Zakko S, Ringel Y, Yu J, Mareya SM, Shaw AL, Bortey E, Forbes WP. Rifaximin therapy for patients with irritable bowel syndrome without constipation. *N Engl J Med* 2011; 364:22-32.
58. Nanda R, James R, Smith H, Dudley CR, Jewell DP. Food intolerance and the irritable bowel syndrome. *Gut* 1989; 30:1099-104.
59. Gonlachanvit S, Mahayosnond A, Kullavanijaya P. Effects of chili on postprandial gastrointestinal symptoms in diarrhoea predominant irritable bowel syndrome: evidence for capsaicin-sensitive visceral nociception hypersensitivity. *Neurogastroenterol Motil* 2009; 21:23-32.
60. Gupta D, Ghoshal UC, Misra A, Choudhuri G, Singh K. Lactose intolerance in patients with irritable bowel syndrome from northern India: a case-control study. *J Gastroenterol Hepatol* 2007; 22:2261-5.
61. Shepherd SJ, Gibson PR. Fructose malabsorption and symptoms of irritable bowel syndrome: guidelines for effective dietary management. *J Am Diet Assoc* 2006; 106:1631-9.
62. Gibson PR, Shepherd SJ. Evidence-based dietary management of functional gastrointestinal symptoms: The FODMAP approach. J Gastroenterol Hepatol 2010;25:252-8.
63. Ong DK, Mitchell SB, Barrett JS, Shepherd SJ, Irving PM, Biesiekierski JR, Smith S, Gibson PR, Muir JG. Manipulation of dietary short chain carbohydrates alters the pattern of gas production and genesis of symptoms in irritable bowel syndrome. *J Gastroenterol Hepatol* 2010; 25:1366-73.