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Review

Second Asian Consensus on Irritable Bowel Syndrome

Kok Ann Gwee,[1] Sutep Gonlachanvit,[2]* Uday C Ghoshal,[3] Andrew S B Chua,[4] Hiroto Miwa,[5] Justin Wu,[6] Young-Tae Bak,[7] Oh Young Lee,[8] Ching-Liang Lu,[9] Hyojin Park,[10] Minhu Chen,[11] Ari F Syam,[12] Philip Abraham,[13] Jose Sollano,[14] Chi-Sen Chang,[15] Hidekazu Suzuki,[16] Xiucai Fang,[17] Shin Fukudo,[18] Myung-Gyu Choi,[19] Xiaohua Hou,[20] and Michio Hongo[21]

[1]Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, and Gleneagles Hospital, Singapore; [2]Center of Excellence on Neurogastroenterology and Motility, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; [3]Department of Gastroenterology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India; [4]Gastro Centre, Ipoh, Malaysia; [5]Division of Gastroenterology, Department of Internal Medicine, Hyogo College of Medicine, Mukogawa-cho, Nishinomiya, Hyogo, Japan; [6]Department of Medicine and Therapeutics, Faculty of Medicine, The Chinese University of Hong Kong, New Territories, Hong Kong; [7]Department of Internal Medicine, Korea University College of Medicine, Seoul, Korea; [8]Department of Gastroenterology, College of Medicine, Hanyang University, Seoul, Korea; [9]Endoscopy Center for Diagnosis and Treatment, Taipei Veterans General Hospital, Taipei, Taiwan; [10]Division of Gastroenterology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea; [11]Department of Gastroenterology and Hepatology, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China; [12]Division of Gastroenterology, Departement of Internal Medicine, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia; [13]Division of Gastroenterology, P D Hinduja Hospital, Mumbai, India; [14]Department of Internal Medicine, Division of Gastroenterology, University of Santo Tomas, Manila, Philippine; [15]Taichung Veterans General Hospital, Taiwan Boulevard, Taichung City, Taiwan; [16]Department of Gastroenterology and Hepatology, Tokai University School of Medicine, Isehara, Kanagawa, Japan; [17]Department of Gastroenterology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [18]Department of Behavioral Medicine, Tohoku University Graduate School of Medicine, Aoba Sendai, Japan; [19]Division of Gastroenterology and Hepatology, Department of Internal Medicine, The Catholic University of Korea, Seoul, Korea; [20]Union Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; and [21]Department of Medicine, Kurokawa General Hospital, Kurokawa, Miyagi, Japan

Background/Aims

There has been major progress in our understanding of the irritable bowel syndrome (IBS), and novel treatment classes have emerged. The Rome IV guidelines were published in 2016 and together with the growing body of Asian data on IBS, we felt it is timely to update the Asian IBS Consensus.

Methods

Key opinion leaders from Asian countries were organized into 4 teams to review 4 themes: symptoms and epidemiology, pathophysiology, diagnosis and investigations, and lifestyle modifications and treatments. The consensus development process was carried out by using a modified Delphi method.

Results

Thirty-seven statements were developed. Asian data substantiate the current global viewpoint that IBS is a disorder of gut-brain interaction. Socio-cultural and environmental factors in Asia appear to influence the greater overlap between IBS and upper gastrointestinal symptoms. New classes of treatments comprising low fermentable oligo-, di-, monosacharides, and polyols diet, probiotics, non-absorbable antibiotics, and secretagogues have good evidence base for their efficacy.

Conclusions

Our consensus is that all patients with functional gastrointestinal disorders should be evaluated comprehensively with a view to holistic management. Physicians should be encouraged to take a positive attitude to the treatment outcomes for IBS patients.
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Key Words

Asia; Constipation; Diarrhea; Intestines; Irritable bowel syndrome

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*Correspondence: Sutep Gonlachanvit, MD
Center of Excellence on Neurogastroenterology and Motility, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand
Tel: +66-2-256-4265, Fax: +66-2-252-7839, E-mail: gsutep@hotmail.com

Introduction

The first Asian Consensus on Irritable Bowel Syndrome (IBS) was published in 2010.[1] Since then, there has been major progress in our understanding of this condition and novel treatment classes have emerged. The international standard for diagnostic criteria in functional gastrointestinal disorders (FGIDs) was updated with the release of the Rome IV documents in 2016.[2] FGIDs are now described as disorders of gut-brain interaction, shifting the emphasis to the gut, with greater prominence given to the intestinal microenvironment. Furthermore, there is now recognition of the roles of cross-cultural differences, the socio-cultural and environmental factors in the development and manifestation of IBS. The Asian Neurogastroenterology and Motility Association (ANMA) felt it is appropriate to examine the literature from an Asian perspective and to update the Asian IBS Consensus.

Methods

On April 1, 2016, ANMA convened a working team of 21 key opinion leaders from Asian countries on the basis of their scientific activities and published articles on IBS. Participants were organized into 4 teams to review 4 themes: symptoms and epidemiology, pathophysiology, diagnosis and investigations, and lifestyle modifications and treatments. The consensus development process was carried out by using a modified Delphi method.[3]

The consensus team members collected and reviewed original publications on IBS (in English and other languages) since the first consensus, through available global and domestic online literature-search systems. Manual search was also performed for publications that were not available online. Other important original and review articles from Asia and other parts of the world were also collected and reviewed. New publications that were published during the consensus process were also reviewed. Each team then generated 6 to 12 consensus statements through intra- and inter-team e-mail discussions.

On March 22, 2017, the working team met in Osaka during the ANMA Scientific Congress. All statements were presented along with supporting evidence, debated, and modified based on feedback. A grade of evidence was applied to every statement according to the GRADE Working Group.[4] The final complete set of statements was subsequently circulated to all 21 members for anonymous voting. All members were asked to choose 1 of the following 6 levels of agreement on each statement: (a) accept completely, (b) accept with minor reservation, (c) accept with major reservation, (d) reject with major reservation, (e) reject with minor reservation, and (f) reject completely. The members were also asked to provide comments to each statement, if any. When the proportion of members who voted (a) or (b) was greater than or equal to 80.0%, the statement was regarded as acceptable and a consensus was considered to have been reached.

Team 1: Symptoms and Epidemiology

Statement 1: Bowel-related symptoms in IBS consist of abdominal pain, bloating, or discomfort that is either improved or aggravated by passing stool or flatus. The symptoms can be associated with change in stool form or frequency and other symptoms including urgency, straining, and feeling of incomplete defecation.

Grade of evidence: moderate

Level of agreement: a. 80.9%; b. 0.0%; c. 14.3%; d. 0.0%; e. 4.8%; f. 0.0%

These characteristics of IBS symptoms are derived from the original studies by Manning and by Thompson.[5,6] In the subsequent diagnostic criteria for IBS (Rome I to III), abdominal pain and/or discomfort are important components in the evaluation. In the Rome IV era, the term "discomfort" has been eliminated from the criteria because the term is thought to be ambiguous to patients.[7] The current Rome IV definition for IBS required the patients to have recurrent abdominal pain, which is associated with defecation or a change in bowel habits. However, a recent global experts survey indicated that 53.8% felt that bloating was the most important feature of IBS, while only 25.6% felt that abdominal pain was.[8] A study from China by using Rome III defined IBS, only 64.6% of them complained of recurrent abdominal pain and 44.2% with abdominal bloating alone.[9] A large population-based internet survey from Japan also suggests that abdominal bloating has a great impact on the daily life of the patients with constipation-predominant IBS.[10] Studies of IBS patients in India and Bangladesh suggested that frequency and/or severity of abdominal pain may not be so common, ranging from 33.0% to 70.0%, which will result in a low prevalence of Rome IV IBS in India.[11] In a multicenter Indian study using various IBS diagnostic criteria, the Manning criteria had the highest sensitivity (91.0%), followed by Asian criteria (74.5%), Rome I(68.0%), Rome III (52.5%), and Rome II (40.0%) to diagnose IBS.[12] The differences observed may be due to the fact that "abdominal pain" was not absolutely necessary for the diagnosis of IBS by both Manning and Asian criteria. Furthermore, "abdominal bloating" had been included in combination with

"abdominal pain or discomfort" by the Asian criteria.[1] Similar data has been reported from Romania.[13] These data suggested that besides recurrent abdominal pain, abdominal bloating should also be included in the IBS diagnostic criteria, while the pain component in IBS may be de-emphasized in Asia.

Since the words for bloating symptom in several Asian countries have meanings overlapping with other abdominal symptoms, doctors in these countries should explore in detail to confirm whether the patient symptom is a real bloating symptom or not, according to the symptom concept described by the Rome committee.

Statement 2: The patient's bowel pattern should be described according to the Bristol stool form scale (BSFS) with consideration to stool frequency, straining, incomplete evacuation, and urgency.

Grade of evidence: moderate

Level of agreement: a. 71.4%; b. 19.1%; c. 9.5%; d. 0.0%; e. 0%; f. 0.0%

According to Western studies, stool frequency of normal bowel habit varies from 3 stools per week to 3 per day.[14] However, wide variation in normal bowel frequency is noted throughout Asian countries. For example, normal stool frequency is once per day in Chinese and twice per day in Iranians.[15,16] In Indian community, 90.0% of healthy subjects had more than 1 bowel movement per day, less than 1.0% had number of bowel movement fewer than 3 per week, while the median stool frequency was twice a day in IBS patients, regardless of whether they had constipation or diarrhea.[17] It has consistently being shown that stool form rather than stool frequency better represent colonic transit time.[18,19] Therefore, evaluating stool form using the Bristol scale is suggested as the tool of choice in the classification of IBS subtypes in Asia. Bristol stool scale has been reported to be a better marker of constipation and slow colonic transit.[19-21] A recent validation study has also shown that IBS patients could more often be classified as having constipation- or diarrhea-predominant bowel pattern by the Bristol stool form and by the patients' own perception than by the stool frequency criteria.[22]

Statement 3: IBS patients may complain of meal-related symptoms, which include abdominal pain, bloating or distension.

Grade of evidence: moderate

Level of agreement: a. 76.1%; b. 14.3%; c. 4.8%; d. 4.8%; e. 0.0%; f. 0.0%

Several studies provide strong evidence that eating is an important trigger of symptoms in IBS patients.[23-26] A study in Sweden required IBS patients to record in detail the timing of symptoms throughout the day for up to 6 weeks. This study demonstrated that pain was relieved with defecation on only 10.0% of occasions, whereas 50.0% of pain episodes developed within 90 minutes of eating.[27] This study suggests that the pain experienced by IBS patients had a stronger temporal relationship to eating than to defecation. This could be a particular problem in Asia because Asian patients appear to present more frequently with upper abdominal pain than in Western patients.[28,29] In a study from Taiwan, more than 50% of patients initially classified as dyspepsia were reclassified as IBS because their upper abdominal pain was exclusively relieved with defecation.[30] We believe that it is important to highlight the relationship of symptoms to meals in IBS. Mistaking meal-related IBS symptoms as dyspepsia could lead to excessive investigation with tests, such as upper gastrointestinal (GI) endoscopy and ultrasound scans, inappropriate treatments, such as acid suppression, and unnecessary surgery, such as cholecystectomy.[31,32]

Statement 4: IBS is as prevalent in men as in women in most Asian countries.

Grade of evidence: moderate

Level of agreement: a. 80.9%; b. 14.3%; c. 4.8%; d. 0.0%; e. 0.0%; f. 0.0%

Globally the prevalence of IBS in women is approximately 1.5- to 3-fold higher than those seen in men.[33,34] In Western populations, women usually report more IBS symptoms than men, irrespective of the employed diagnostic criteria.[35] However, if the IBS prevalence is stratified according to geographic region, no significant sex difference can be observed in South Asia, South America, and Africa.[33] In Asia, most studies showed no gender difference (female vs male in India: 7.9% vs 6.9%, 4.3% vs 4%, 3.2% vs 4.8%; Korea: 7.1% vs 6.0%; Hong Kong: 6.6% vs 6.5%; Pakistan: 13.1% vs 13.4%; Taiwan: 21.8% vs 22.8%; Singapore: 7.8% vs 9.4%; Malaysia: 10.6% vs 10.5%; Japan: 6.5% vs 5.5%).[28,36-38] Untill now, only 2 reports showed significantly higher IBS prevalence in females.[39,40]

Statement 5: Dyspeptic symptoms including upper abdominal pain are prevalent in Asian IBS patients, and may result in a misdiagnosis of FD.

Grade of evidence: moderate

Level of agreement: a. 76.2%; b. 14.2%; c. 4.8%; d. 0.0%; e. 4.8%; f. 0.0%

In Asia the prevalence of dyspeptic symptoms in IBS patients has been variously reported (India 58.0%, China 25.0-64.0%, and South Korea 14.0%).[41-44] Furthermore Asian patients tend to present more with upper abdominal pain than Western patients. In a

Taiwan study, Lu et al initially classified more than 50.0% of their patients as dyspepsia who were later reclassified as IBS when their upper abdominal pain was exclusively relieved with defecation.[30] Similarly in a study performed in Singapore, 44.0% of patients who had functional chronic upper abdominal pain had IBS, while a later study demonstrated that more than 50.0% of IBS subjects localized their pain to the upper abdomen.[45,46]

Population-based studies demonstrated that 3.5% to 4.5% of the general adult population in India and Bangladesh have dyspepsia-IBS overlap.[47,48] A community-based survey carried out involving 3000 people in Bangladesh, including both rural and urban populations, demonstrated that 42.0% of FD subjects had IBS and 27.0% IBS subjects had FD.[48] Bowel symptoms frequency scores were higher in IBS-FD than IBS alone.[47,48] In a hospital based study of patients with FD from China, postprandial fullness was a predictor of overlapping IBS.[43] In a large study from Japan, abdominal bloating appears to be the most bothersome symptom in IBS with constipation (IBS-C) patients.[10] Correspondingly, early satiety, epigastric pain, and bloating were important factors associated with IBS-FD overlap syndrome in Bangladesh.[48] Bloating is a commonly encountered symptom in Asian IBS patients, in keeping with observations from Western countries. The challenge is not to misclassify these patients as functional dyspeptics when they actually suffer from IBS. An alternative is to view them as a spectrum of functional bowel disorders, focusing treatment on the main symptoms, or using combination therapy for the myriad of symptoms.

Statement 6: Stress relates to the exacerbation of IBS.

Grade of evidence: moderate

Level of agreement: a. 95.2%; b. 4.8%; c. 0.0%; d. 0.0%; e. 0.0%; f. 0.0%

Experience of psychosocial stress and exacerbation of GI symptoms in IBS patients show higher correlation than that in healthy individuals.[49] IBS patients show more exaggerated colonic motility in response to experimental stress than healthy subjects.[50] A meta-analysis showed that colorectal distension in IBS patient is more likely to activate the anterior cingulate cortex, amygdala, and midbrain, which are important brain regions for stress response, but deactivates the medial and lateral prefrontal cortex than healthy controls.[51] Furthermore, the right dorsolateral prefrontal cortex in IBS patients was less activated than healthy controls when subjects were exposed to the situation with necessity of cognitive flexibility and stress-coping.[52]

Systematic review indicated that psychosocial stress likely alters gut microbiota, increases mucosal permeability, motility, and induces visceral hyperalgesia in IBS patients.[53-55] Systematic review of epidemiology supports psychosocial stress (adverse life events) as one of risk factors of post-infection IBS (PI-IBS).[56] When the severity of IBS increases, the impact of psychological distress in IBS patients increases.[57] The interaction between IBS and psychological symptoms are bi-directional. In a 12-year prospective study, functional GI disorder including IBS and functional dyspepsia at onset were found to increase the risk of developing depression and anxiety, while. depressive or anxiety disorder was a risk factor for the development of IBS.[58] A 1-year prospective study indicates that in the majority of patients it is likely that IBS leads to depression and anxiety than the other way around.[59]

Team 2: Pathophysiology

Statement 7: IBS is a multi-dimensional disorder with a variable combination of gut dysbiosis, GI low grade inflammation, mucosal immune activation, increased gut permeability, food intolerance, GI dysmotility, visceral hypersensitivity, altered gut-brain interaction, genetic, and psychosocial factors.

Grade of evidence: moderate

Level of agreement: a. 80.9%; b. 14.3%; c. 4.8%; d. 0.0%; e. 0.0%; f. 0.0%

It is now appreciated that multiple pathophysiological mechanisms may operate in individual patients contributing to symptoms and their exacerbation, health care seeking behavior, and treatment response. The important role that the gut micro-environment plays in the pathophysiology has been increasingly recognized.[60] In the recently published Rome IV guidelines, the term "functional" is de-emphasized, and FGIDs are now defined as "disorders of gut-brain interaction."[2]

Statement 8: Gut microbial dysbiosis is associated with IBS, especially IBS with predominant diarrhea (IBS-D).

Grade of evidence: moderate

Level of agreement: a. 71.4%; b. 23.8%; c. 4.8%; d. 0.0%; e. 0.0%; f. 0.0%

Multiple case-control studies from Asia and elsewhere demonstrated fecal microbial dysbiosis among patients with IBS as compared to controls.[61-63] Since a fecal sample might not be representative of the small bowel, a few studies assessed small bowel aspirate among patients with IBS as compared to controls and showed dysbiosis even in the upper gut of patients with IBS.[64] Multiple studies using quantitative upper gut aspirate culture and glucose and lactulose hydrogen breath tests also revealed occurrence of small

intestinal bacterial overgrowth (SIBO) more often among patients with IBS than healthy subjects.[65] Moreover, multiple studies documenting improvement in IBS symptoms following treatment with antibiotics including rifaximin also supports the role of gut dysbiosis in pathogenesis of IBS.[66,67] Patients with IBS-D more often had SIBO than other sub-types of IBS.[63,67] However, a few studies showed that methane production on lactulose hydrogen breath test is associated with constipation and its reduction with rifaximin accelerates colon transit time and improves constipation suggesting role of gut microbial dysbiosis even in a subset of patients with IBS-C.[68,69]

Statement 9: IBS is associated with immune activation, low grade gut inflammation, and increased gut permeability.

Grade of evidence: high

Level of agreement: a. 71.4%; b. 28.6%; c. 0.0%; d. 0.0%; e. 0.0%; f. 0.0%

A large body of evidence supports the presence of immune activation, low grade inflammation, and increased gut permeability in the pathogenesis of IBS, particularly in PI-IBS and the diarrhea-predominant sub-type.[70-75] In a study from India, over-producer polymorphisms of IL-1 receptor antagonist (which controls inflammation) were found to be infrequent and under-producers frequent among patients with IBS than controls.[76] The same study also revealed patients with SIBO had higher duodenal mucosal levels of IL-1α and β and the latter correlated with looser stools (Bristol type VI) and bloating.[76] Another recent Indian study showed that altered immune activation in response to dysbiotic microbiota may promote intestinal inflammation in a subset of IBS patients.[77] A Chinese study showed that IL-10, an anti-inflammatory cytokine level in serum, was significantly lower in SIBO-positive than negative IBS patients.[78] Nerve growth factor is known to mediate visceral hypersensitivity and gut mucosal barrier dysfunction through interactions with mast cells and sensory nerves. In a recent Chinese study, elevated mucosal nerve growth factor has been suggested to interact with mast cells and sensory nerve fibers, contributing to visceral hypersensitivity and impaired gut barrier function in IBS-D.[79]

Statement 10: GI infection predisposes to development of IBS.

Grade of evidence: high

Level of agreement: a. 80.9%; b. 14.3%; c. 4.8%; d. 0.0%; e. 0.0%; f. 0.0%

More than half a century ago, Chaudhary and Truelove described occurrence of IBS like syndrome following acute GI infection.[80] Subsequently, Gwee et al[81] reported that 27.0% of patients with acute gastroenteritis from Sheffield, England continued to have symptoms sufficient to fulfill the criteria for IBS for 6 months. Four studies on PI-IBS have been reported from Asia to date. In one cohort study from Beijing, China, the incidence of IBS by Rome II criteria among 295 patients following bacillary dysentery was 8.1% compared to 0.8% among controls.[75] In a study from Seoul investigating an outbreak of Shigella infection among 181 health-care workers, the odds ratio of developing IBS was calculated to be 2.9 at 1 year.[82] A 3-year follow-up study from Korea showed that PI-IBS may last for 3 years after onset.[83] A recent study conducted in Bangladesh showed gastroenteritis patients developed PI-IBS and PI-FD more often than controls (16.5% vs 2.6% and 7.4% vs 0.6%, respectively).[84] The same study also showed that 9.0% of patients developing Rome criteria-positive IBS after acute gastroenteritis actually developed post-infectious malabsorption syndrome (tropical sprue).

PI-IBS is defined as new development of IBS following acute infectious diarrhea, characterized by 2 of the followings, (1) diarrhea, (2) vomiting, (3) fever, and (4) positive stool culture for enteropathogens.[85] PI-IBS is usually of diarrhoea-predominant subtype. In Asia, post-infective malabsorption, previously known as Tropical sprue, should be considered as a differential diagnosis.[86] SIBO has been proposed as a possible link between the 2 conditions.[85]

Statement 11: Visceral hypersensitivity plays an important role in the development of symptoms in IBS patients.

Grade of evidence: moderate

Level of agreement: a. 85.7%; b. 9.5%; c. 4.8%; d. 0.0%; e. 0.0%; f. 0.0%

Exaggerated visceral sensitivity is well known in patients with IBS as compared to controls based on studies on luminal distension using balloon and gas during colonoscopy and lactose hydrogen breath test.[87,88] Such luminal distension has also been shown to reproduce patient's abdominal pain. Visceral hypersensitivity in patients with IBS spans beyond the colon. It has been demonstrated in the esophagus, stomach, duodenum, and ileum, suggesting that these patients have irritable gut syndrome.[89] Studies from Asia, like those from the rest of the world, also demonstrated hypersensitivity beyond the gut such as bladder dysfunction and fibromyalgia among patients with IBS. In an Indian study, following 50 g lactose ingestion, IBS patients experienced symptoms more than healthy subjects though the amount of breath hydrogen exhaled was comparable between the 2 groups.[89] A Chinese study also showed similar results.[90] Another Chinese study demonstrated that cold water

intake lowered the visceral perception threshold.[91] Abdominal pain could be elicited in 78.0% of patients with IBS in Singapore by distending the rectum with air insufflation.[92]

Statement 12: Dysregulated entero-endocrine system may contribute to pathogenesis of IBS.

Grade of evidence: low

Level of agreement: a. 80.9%; b. 4.8%; c. 14.3%; d. 0.0%; e. 0.0%; f. 0.0%

Evidence includes increased enterochromaffin cell numbers as well as rectal mucosal serotonin (5-hydroxytryptamine [5-HT]) in PI-IBS, presence of 5-HT-transporter-gene-linked polymorphic region mutation in IBS-C (in China and Korea), and altered serotonergic signaling (increased and decreased plasma serotonin levels in IBS-D and IBS-C respectively).[71,93-95] Of particular interest in Asia is the possible role that 5-HT_3 receptors may play in chili induced abdominal symptoms associated with IBS.[96] However, a recent study compared enterochromaffin cells numbers in the colon of IBS and controls from subjects in Norway and Thailand demonstrated increased enterochromaffin cell numbers in IBS patients compared to controls only in Norwegian patients but not in Thai patients.[97]

Statement 13: GI motility disturbances in IBS patients can arise from an exaggerated physiological response to environmental stimuli, such as meals and stressors.

Grade of evidence: high

Level of agreement: a. 80.9%; b. 14.3%; c. 0.0%; d. 4.8%; e. 0.0%; f. 0.0%

Exaggerated gastro-colic reflex among patients with IBS is well known. In an American study, colonic spike and motor activity were higher following a meal among patients with IBS compared to healthy subjects.[26] Diarrhea-predominant IBS patients have higher colonic motility than constipation-predominant subset. A Korean study showed that patients with diarrhea-predominant IBS showed higher colonic motility than those with constipation-predominant IBS.[98] Lactose malabsorption are common among patients with IBS in Asia. An Indian study showed that though levels of breath hydrogen were comparable among patients with IBS and healthy controls, IBS patients showed greater frequency of symptom development following lactose load than healthy subjects.[88] This may be related to greater degree of visceral hypersensitivity among IBS patients as has been demonstrated in a recent Chinese study.[90] An Indian study demonstrated induction of IBS symptoms following chili ingestion.[99] A study from Thailand also showed that chili ingestion produced more abdominal pain and burning in IBS-D patients than in healthy volunteers.[100] Several Japanese studies showed that patients with IBS showed greater colonic motor response than healthy controls to experimental stress, and suggested that corticotropin releasing factor liberated from the hypothalamus to be the possible mediator.[101,102]

Statement 14: Some diarrhea-predominant IBS patients have been shown to have rapid GI transit, while some constipation-predominant IBS is associated with slow transit.

Grade of evidence: high

Level of agreement: a. 85.7%; b. 4.8%; c. 4.8%; d. 0.0%; e. 0.0%; f. 4.8%

A few landmark studies showed that stool form is determined largely by colon transit time.[19] A recent study, however, showed that the number of bacteria in the small bowel also determines stool forms; larger the number of bacteria in the small bowel, the looser the stools.[64] Patients with IBS-D have shorter colonic transit time than those with IBS-C.[103,104] Colonic transit time has been reported to be faster in Asian populations such as in India, Hong Kong, and Taiwan than in the West.[105,106]

Statement 15: IBS patients can show altered brain activations in specific regions, which might be involved in the perception of pain and emotional arousal.

Grade of evidence: low

Level of agreement: a. 90.5%; b. 9.5%; c. 0.0%; d. 0.0%; e. 0.0%; f. 0.0%

Like somatic sensation, visceral sensation including that from the gut is primarily presented to sensory cortex. However, visceral sensation can also lead to varying degree of emotional arousal due to activation of the emotional arousal system (limbic system and paralimbic structures), particularly among patients with IBS. Due to advances in functional imaging studies using functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), understanding of cerebral processing of visceral sensation in patients with IBS as compared to healthy controls have been possible.

A few Asian studies showed that patients with IBS have exaggerated cerebral activation and abnormal emotional area activation following visceral and somatic stimulation, which is agreement with the Western studies. A Japanese study using PET showed that colonic distension resulted in enhanced activation of specific brain regions, including the limbic system and prefrontal cortex.[107] An fMRI-based study from China showed that rectal balloon distension resulted in increased activity in the anterior cingulate cortex,

insula, prefrontal cortex, and thalamus, more so among IBS patients than controls.[108] A study from Singapore showed abnormal cerebral activation on fMRI in anticipation of rectal pain among IBS patients during rectal stimulation.[109] Cerebral and emotional response to pain is well known to differ among males and females. A recent Indian study on male IBS subjects and healthy controls showed differential brain response to rectal balloon distension and among patients with IBS-C and IBS-D.[110]

Statement 16: Psychosocial factors have significant role in the development and aggravation of IBS symptoms.

Grade of evidence: moderate

Level of agreement: a. 80.9%; b. 14.3%; c. 4.8%; d. 0.0%; e. 0.0%; f. 0.0%

Several case-control studies both from the West and Asia showed that patients with IBS have more psychological co-morbidities than healthy subjects.[111] It is important, however, to note that a cause and effect relationship cannot be assigned based on such case-control studies. Authors of a recent Australian study suggested that in most patients with functional GI disorders gut symptoms drives psychological morbidity rather than the brain being the primary origin of GI symptoms.[59] However, studies on PI-IBS demonstrated that psychosocial co-morbidity are predictors of development of IBS following an episode of acute gastroenteritis.[81] A Korean study showed that depressed women had greater severity of GI symptoms in relation to the degree of depression.[112] Japanese studies also suggested role of psychosocial stress exacerbating IBS symptoms.[113]

Some of the Asian data, like the Western studies, do suggest a role of psychosocial factors determining consultation behavior among patients with functional GI disorders including IBS. Anxiety was the only independent predictor for medical consultation in a study from Hong Kong.[114] In Pakistan, a high psychological distress score was a strong predictor of IBS in men, but not in women, while in India, there appeared to be more consulters in the higher socioeconomic classes.[18,115] However, in Korea, India, and Japan, psychological factors appear to be less important to influence consultation for IBS.[18,116,117] These data may suggest that psychological co-morbidity may influence health care seeking in addition to sociocultural factors.

Statement 17: Genetic factors can contribute to the development of IBS, and gene–environmental interactions need to be further investigated.

Grade of evidence: low

Level of agreement: a. 76.2%; b. 14.2%; c. 4.8%; d. 4.8%; e. 0.0%; f. 0.0%

It is well known that functional GI disorders, including IBS, occurs more often in families having members affected with these conditions. Though it has been argued that this may be related to environmental and socio-cultural factors, a role of genetic factors has also been considered. Polymorphisms in several genes involved inflammation, immune regulation, antigen recognition, defense mechanisms, tissue repair, neuro-transmission, lactose malabsorption etc have been studied in Asia.[118] However, most of these studies suffer from limitation due to inadequate power resulting from relatively small sample size.

Team 3: Diagnosis and Investigations

Statement 18: IBS is a condition characterized by recurrent abdominal pain/discomfort, occurring in association with defecation or a change in bowel habits, in the absence of organic causes that are detectable by routine medical tests.

Grade of evidence: low

Level of agreement: a. 80.9%; b. 14.3%; c. 4.8%; d. 0.0%; e. 0.0%; f. 0.0%

The Rome IV criteria eliminated the term "discomfort" to reduce ambiguity and improve consistency of the criteria across different languages. The frequency of abdominal pain should be at least 1 day per week during the past 3 months with onset at least 6 months earlier. In daily clinical practice, however, a pragmatic and flexible diagnostic approach should be adopted: pain is not universal in patients with IBS, who may have only abdominal discomfort or bloating as the predominant symptom, the threshold for symptom frequency and duration also needs validation in Asian countries.[6,119]

The BSFS is recommended as a reliable tool for evaluation of bowel habits. The subtyping of IBS is based on the stool consistency on days with abnormal bowel habits when the patients are not taking any medication used for the treatment of the bowel habit abnormalities. Based on the BSFS, IBS can be classified into IBS-D, IBS-C, mixed bowel habits, and unclassified. A recent study from Thailand suggested the BSFS type 3 is also associated with constipation. Thus, the correlation of BSFS with IBS classification in Asian patients may be different from that in the West. [120-122]

Statement 19: The diagnosis of IBS requires careful history taking with reference to the diagnostic criteria of IBS, physical examination, and investigations may be performed if indicated, but there is no single diagnostic or confirmatory test for IBS.

Grade of evidence: low

Level of agreement: a. 85.7%; b. 4.8%; c. 4.8%; d. 4.8%; e. 0.0%; f. 0.0%

For the majority of patients with IBS, a positive clinical diagnosis can be based on symptoms and physical examination, with limited investigations. Routine investigations are not warranted in all patients. However, a Canadian center analyzed the performance of symptom-based criteria in secondary-care centers and found a modest specificity of only 71-82% and positive predictive value of < 50%.[123]

Statement 20: Alarm features that needed to be excluded when considering the diagnosis of IBS include the presence of blood in the stools, unintended weight loss, anaemia, nocturnal symptoms, fever, abdominal mass, ascites, a family history of colorectal cancer, and age of onset > 50 years.

Grade of evidence: low

Level of agreement: a. 76.2%; b. 14.3%; c. 9.5%; d. 0.0%; e. 0.0%; f. 0.0%

The presence of alarm features should prompt for investigations including colonoscopy, whereas the absence of alarm symptoms and negative physical examination are associated with lower likelihood of organic disease in patients with IBS symptoms.[1] However, data to support this approach are weak.[124,125]

Statement 21: In the primary-care setting, a positive symptom-based diagnosis of IBS is recommended to minimize unnecessary investigations. A step-wise approach, with special attention to the presence of alarm features and the judicious use of selected diagnostic tests to rule out organic disease, is recommended.

Grade of evidence: low

Level of agreement: a. 85.7%; b. 9.5%; c. 0.0%; d. 0.0%; e. 0.0%; f. 4.8%

In the primary-care setting, selected non-invasive laboratory tests to exclude organic causes in patients without alarm features include full blood counts with erythrocyte sedimentation rate, blood chemistry with C-reactive protein, and stool examination for occult blood and fecal calprotectin.[126-129] Normal C-reactive protein and fecal calprotectin in patients with non-constipation IBS can help exclude inflammatory bowel disease.[130] Evidence to support this approach is however weak.[7]

Stool examination for intestinal parasites should be performed in countries with high prevalence of intestinal parasites. However, the association of intestinal parasites with symptoms of IBS is still controversial and limited.[131]

Statement 22: In the referral-center setting, recommended investigations include full blood counts, erythrocyte sedimentation rate, blood chemistry, C-reactive protein, thyroid function test, stool examination for occult blood, parasites and *Clostridium difficile* infection, and colonoscopy.

Grade of evidence: low

Level of agreement: a. 66.6%; b. 23.8%; c. 4.8%; d. 0.0%; e. 0.0%; f. 4.8%

Colonoscopy for exclusion of colorectal cancer is indicated in patients with symptom onset at age 50 years or older, regardless of other alarm features. In younger patients, colonoscopy is indicated in the presence of alarm symptoms or signs, positive family history of colorectal cancer, and poor symptom response to empiric medical therapy.[1,132] Patients included in clinical trials must have a colonoscopy and/or other examinations as required by the entry criteria or study design.

Further work-up may be considered in selected patients for the diagnosis of other conditions such as SIBO, celiac disease, bile-acid diarrhea, malabsorption syndrome, and pancreatic or small bowel neoplasm. These investigations should be individualized according to the regional prevalence of each condition.[64,85,133-135]

Statement 23: Fecal evacuation disorder may present as constipation-predominant IBS.

Grade of evidence: low

Level of agreement: a. 85.7%; b. 4.8%; c. 4.8%; d. 4.8%; e. 0.0%; f. 0.0%

Normal defecation requires coordination between contraction of the abdominal muscles that increase intra-rectal pressure and relaxation of the pelvic floor including the anal sphincter. Pubo-rectal dyssynergia is a common type of fecal evacuation disorder (FED). Different types of pubo-rectal dyssynergia are characterized by lack of increase in intra-rectal pressure or reduction in residual pressure in the anal canal during attempted defecation. An Indian study showed that the Rome III criteria for IBS were equally fulfilled among patients with constipation with or without FED.[136] In a Thai study, of 50 patients with FED, 29 (58.0%) fulfilled Rome II criteria for IBS; patients with or without IBS demonstrated similar responses to biofeedback therapy.[137] These Asian studies suggest that patients with FED may present as constipation-predominant IBS.[138]

Statement 24: Wheat sensitivity or non-celiac gluten sensitivity (NCGS) and IBS patients are distinct entities although their symptoms may overlap.

Grade of evidence: moderate

Level of agreement: a. 71.4%; b. 14.3%; c. 9.5%; d. 0.0%; e. 0.0%; f. 4.8%

NCGS is an increasingly recognized entity in the spectrum of gluten-related disorders, and is characterized by bowel symptoms similar to IBS. Evidence has emerged from several Asian countries for the presence of NCGS in patients fulfilling IBS criteria.[133-135,139,140] The pathophysiology of NCGS is poorly understood and a causal relationship between NCGS and IBS is still a subject of debate.[141] Moreover, the symptom benefit obtained from a gluten-free diet may be attributed to its low fermentable oligo-, di-, monosacharides, and polyols (FODMAP) content.

Statement 25: In addition to symptom severity, evaluation of health-related quality of life (QOL), functional impairment, psychological stressors and distress is recommended in the clinical evaluation of disease morbidity and monitoring of treatment response.

Grade of evidence: moderate

Level of agreement: a. 85.7%; b. 0%; c. 14.3%; d. 0.0%; e. 0.0%; f. 0.0%

IBS is associated with significant impairment in the QOL, social functioning, sleep, and psychological well-being.[142-144] Validated questionnaires should be considered as supportive instruments for quantitative and objective assessment of quality-of-life impairment and psychological distress. Short form 36, EuroQol 5 dimension, Hospital Anxiety and Depression Scale, Patient Health Questionnaire, and IBS-QOL have been used in Asian studies.

Team 4: Life Style Modifications and Treatments

Introduction/General Comments

In the first Asian IBS consensus,[1] it was generally agreed that the aims of IBS management are symptom relief as well as improving QOL, with the establishing of a good doctor–patient relationship being a cornerstone. Physicians were recommended to identify contributing factors and the patient's specific concerns, so that the management of IBS may be individualized. Specifically, all bothersome symptoms should be targeted, taking into account specific IBS subtypes, symptom severity, and contributing factors including psychosocial issues. It was generally agreed that these remain fundamental to effective management of IBS. Since the last iteration, there has been substantial new information in dietary and pharmacological management.[145]

Statement 26: A low FODMAPs diet could be helpful in IBS.

Grade of evidence: moderate

Level of agreement: a. 85.7%; b. 4.8%; c. 9.5%; d. 0.0%; e. 0.0%; f. 0.0%

As diet is a frequent concern, a detailed dietary history was commended. New data involving diets in Western populations suggest that a diet low in FODMAPs may be effective in improving bloating, flatulence, and abdominal pain.[146,147] As these are non-absorbable sugars, they are osmotically active, and subjected to fermentation in the colon, resulting in the production of metabolites and gases, that may contribute to causing diarrhea, abdominal pain, and bloating. Patients of all IBS subtypes had greater satisfaction with stool consistency while on the low-FODMAPs diet, while diarrhea-predominant IBS appeared to benefit from improved stool consistency and frequency.[147] Specifically to Asian populations, the role of a low FODMAPs diet in the management of IBS requires further study as studies are lacking.[148,149] While in some communities (eg, India with high prevalence of vegetarianism) diets may be high in FODMAPs, others may traditionally be relatively low (eg, China and Japan).[48,148,149] Lactose as a FODMAP is of specific relevance to Asia as lactase deficiency is almost universal in Asians.[88,150] However, as the average daily consumption is relatively low, the role of lactose-containing dairy foods in Asia is uncertain.[48,151]

Statement 27: Antispasmodic agents are efficacious for the treatment of abdominal pain in IBS.

Grade of evidence: high

Level of agreement: a. 85.7%; b. 14.3%; c. 0.0%; d. 0.0%; e. 0.0%; f. 0.0%

Meta-analysis of antispasmodics as well as several Asian clinical trials support the efficacy of this class of drugs to relief IBS symptoms, especially when abdominal pain is the predominant symptom.[145,152-157] As a class, anti-spasmodics have a favorable profile with number needed to treat (NNT) of 5 and number needed to harm of 17.5.[152] However, some antispasmodics may have anticholinergic side effects.

Statement 28: Antidiarrheal agents are effective in controlling diarrhea in IBS.

Grade of evidence: moderate

Level of agreement: a. 76.2%; b. 14.3%; c. 9.5%; d. 0.0%; e. 0.0%; f. 0.0%

Common antidiarrheal agents studied for the treatment of IBS were loperamide and smectite. Loperamide is an opioid agonist that is frequently used to control diarrhea both in infectious and

non-infectious conditions. A limited number of randomized control trials (RCTs) are available that support its efficacy in IBS, and confidence in the estimate of effect was further limited by the small sample sizes.[158-160] Data on the use in IBS of natural adsorbent clay compounds such as dioctahedral smectite that is frequently used to treat diarrhea in children, is very limited and suggests effect on abdominal discomfort or bloating.[161,162]

Statement 29: Some 5-HT_3 antagonists are effective in IBS-D.

Grade of evidence: high

Level of agreement: a. 80.9%; b. 14.3%; c. 4.8%; d. 0.0%; e. 0.0%; f. 0.0%

Serotonin is a neurotransmitter functioning in GI sensation, motility, and secretion. In the GI tract, 5-HT receptor subtype 3 and 4 mediate key functions that have been targeted for amelioration of IBS symptoms.[163] 5-HT_3 antagonists have been shown to slow intestinal transit and to decrease abdominal pain.[164,165] Examples of 5-HT_3 antagonists that have been tested in IBS are alosetron, ramosetron, and ondansetron. Alosetron encountered serious side effect of ischemic colitis and is now available only in the USA. Ramosetron was newly developed in Japan for the treatment of IBS-D. In a trial comparing ramosetron with placebo, patients with IBS-D treated with ramosetron showed significant improvements in global IBS symptoms, abdominal pain, and bowel habits.[166] A Japanese study for the effect of ramosetron on IBS-D patients also showed significantly increased rate of symptom improvements in ramosetron group (47.0%) than placebo group (27.0%).[167] In a recent randomized, placebo-controlled study of 576 Japanese women with IBS-D, 2.5 μg ramosetron per day reduced abdominal pain and discomfort, increased stool consistency, and improved QOL as well as global IBS symptoms.[168]

Although in these studies, there have not been any reports regarding significant adverse reactions including ischemic colitis to this drug, significant proportions of 1 in 5 reported constipation after treatment of ramosetron.[166-168] Ramosetron is also approved for managing patients with IBS-D in Japan, Korea, and Thailand.[169] Ondansetron is an established anti-emetic with good safety record. In an investigator initiated RCT from the UK, a pragmatic approach was employed whereby starting at 4 mg once a day, the dose could be titrated up to 8 mg 3 times a day, ondansetron was found to be more effective than placebo in improving loose stools, bowel frequency and urgency.[170]

Statement 30: Some serotonin 5-HT_4 receptor agonists are effective in constipation-predominant IBS.

Grade of evidence: high

Level of agreement: a. 85.7%; b. 9.5%; c. 4.8%; d. 0.0%; e. 0.0%; f. 0.0%

Tegaserod is a partial 5-HT_4 agonist with high quality data from Asia for efficacy in IBS-C, both in women and men.[171-173] Unfortunately, a controversial alert by Food and Drug Administration regarding cardiovascular safety has led to its withdrawal from most countries.[174] An alternative, prucalopride is a selective 5-HT_4 agonist, that has high quality efficacy data for relieving bloating, hard stool, and straining, symptoms commonly associated with IBS-C.[175-179] While prominent side effects include diarrhea, headache, abdominal pain, and nausea, no cardiovascular safety concerns have been reported.[174,177] Studies involving tegaserod and prucalopride, including 3 involving Asian subjects, provide evidence of efficacy in male subjects.[173,178,179]

Statement 31: The effectiveness of probiotics has not been fully validated in IBS.

Grade of evidence: moderate

Level of agreement: a. 85.7%; b. 4.8%; c. 9.5%; d. 0.0%; e. 0.0%; f. 0.0%

Probiotics are live micro-organisms that confer health benefits. Several meta-analysis provide evidence that some probiotics have beneficial effect in IBS, but not all probiotics have demonstrated benefit.[180] Thus, which species or combination was the most beneficial is unclear. Where a beneficial effect has been demonstrated, improvements in abdominal pain, bloating, and flatulence have been reported.

It is specifically noted that these meta-analyses were carried out on heterogeneous studies. While *Lactobacillus rhamnosus* GG has strong evidence in children, this was lacking in adult IBS patients.[181,182] In a study of adult IBS patients, *Bifidobacterium infantis* was found to improve symptoms over placebo, whereas *Lactobacillus salivarius* did not.[183] In a related study from the same investigators treatment with the same strain produced significant improvement of IBS symptoms only for intermediate dose.[184,185] The authors emphasized the need for clinical data in the final dosage form and dose of a probiotic before confirming efficacy in clinical use. This was endorsed and emphasized in a recently published Asian consensus on probiotics.[185]

Statement 32: Antidepressants are effective for IBS, but it is unclear which patient will benefit.

Grade of evidence: moderate

Level of agreement: a. 71.4%; b. 14.3%; c. 14.3%; d. 0.0%;

e. 0.0%; f. 0.0%

A meta-analysis of 16 RCTs, found RR of IBS symptom not improving with antidepressants vs placebo was 0.67 and NNT of 4.[186] The quality of the data appeared to be better for tricyclic antidepressant (TCA) than selective serotonin reuptake inhibitor (SSRI). Doses of TCA used in IBS trials were frequently below therapeutic range for depression; in particular, 3 Asian studies used low doses of TCAs.[187-189] This suggests the possibility of a peripheral effect. On the other hand, doses of SSRIs used in IBS especially the studies from the West, were at anti-depressant levels.[190,191] In one RCT of citalopram where non-depressed patients were excluded, there was no evidence of benefit.[190] This suggests that SSRI may be acting at the central level. It should be noted that these agents are only used off label in many countries, and it is important to be familiar with known side-effects.

Statement 33: Secretagogues are effective in IBS-C.

Grade of evidence: high

Level of agreement: a. 85.7%; b. 14.3%; c. 0.0%; d. 0.0%; e. 0.0%; f. 0.0%

Linaclotide, a guanylate cyclase-C agonist, with very low oral bioavailability, acts locally in the intestinal tract to stimulate fluid secretion, increase colonic transit, and inhibit colonic nociceptors.[192-194] In Asia, a recent study with linaclotide 290 μg, involving close to 700 patients from China, found significant efficacy over placebo for abdominal pain (60.0% vs 49.0%) and diarrhea was the commonest side effect (9.0%).[195] This reinforces the findings of 2 pivotal studies where abdominal pain endpoints were met by about 54.0% on linaclotide vs 36.0-42.0% on placebo.[196-198] Similarly, the commonest adverse event of linaclotide was diarrhea (19.7%).[199]

Lubiprostone is a luminally acting prostone that selectively activates the type-2 chloride ion channel (ClC-2 chloride channel) expressed in the small intestinal epithelial cells, thereby increasing the amount of water content it the intestinal lumen.[200] In Asia, efficacy of lubiprostone for IBS-C has been evaluated in only 42 patients in a Japanese study with only the 48 μg dose showing superiority over placebo.[201] Initial dose ranging studies had found that the 48 μg dose was associated with more GI adverse events than the 16 μg dose which was considered the optimal dose for efficacy and safety.[202] Nausea was the commonest side effect, occurring in as many as 31%, and is dose dependent.[203] Furthermore, long-term safety data is available only for the 16 μg dose, but not for the 48 μg dose.[204] A recent systematic review and meta-analysis observed that while lubiprostone was efficacious in the short term, and except for bloating all other outcomes including abdominal pain did not appear to be different from placebo.[205]

Statement 34: Non-absorbable antibiotics are effective in IBS.

Grade of evidence: high

Level of agreement: a. 47.6%; b. 42.9%; c. 9.5%; d. 0.0%; e. 0.0%; f. 0.0%

Rifaximin is a rifamycin derived non-absorbable antibiotic which is associated with anti-inflammatory activity. Meta-analysis involving 5 high quality studies, found efficacy for global IBS symptoms, with secondary outcome analysis indicating that bloating could be the key symptom responding to rifaximin in non-constipated IBS.[206] Adverse effects were similar among patients receiving rifaximin or placebo in all studies.[207] Repeat treatments with rifaximin also appear to be safe.[208,209] While the role of antibiotics was premised on the presence of low-grade SIBO, none of the pivotal studies actually evaluated this. One study from China reported that identifying SIBO among patients with IBS criteria produced better outcome.[210] A study from India employing norfloxacin similarly observed better response in those with demonstrable SIBO.[66] However, data on the efficacy of rifaximin for IBS in Asia are lacking. One study from Hong Kong found that a 2-week course produced significant relief of symptoms in functional dyspepsia, but in this study, patients with overlapping IBS were actively excluded. [211]

Statement 35: Some complementary and alternative medicine (CAM) (specifically peppermint oil and Kampo) could be effective in treating IBS.

Grade of evidence: low

Level of agreement: a. 71.4%; b. 14.3%; c. 9.5%; d. 0.0%; e. 0.0%; f. 4.8%

Its heterogeneity makes it difficult to evaluate the efficacy of CAM as a single treatment class. The 4 commonest CAM treatments were evaluated. Chinese herbal medicine has the biggest evidence base and will be evaluated separately. Peppermint oil, thought to alleviate IBS symptoms by relaxing smooth muscles via calcium channels, has been shown in a meta-analysis to be efficacious for IBS.[152] A review of Japanese herbal medicine (Kampo) found little clinical trial evidence for a role in IBS.[212] Daikenchuto was reported to reduce symptoms of constipation in children, while Hangeshasin-to was reported to have anti-diarrheal effect in drug-induced diarrhea. Two single-blind clinical trials involving a total of 273 subjects found no difference between acupuncture and sham acupuncture.[213,214]

Statement 36: Traditional Chinese medicines including herbal

and patent prescriptions could be helpful for some IBS patients, but the efficacies should be validated with high quality RCT.

Grade of evidence: moderate

Level of agreement: a. 76.2%; b. 9.5%; c. 9.5%; d. 0.0%; e. 0.0%; f. 4.8%

A meta-analysis of 14 RCTs of Chinese herbal medicines, involving 1551 subjects with IBS-D, found efficacy for global IBS symptoms, abdominal pain and diarrhea, but recognized that there was high heterogeneity and study sample sizes were generally small.[215] One formulation known as Shugan Jianpi Zhixie had 7 trials of 954 IBS-D patients.[216] Another formulation known as Tongxie Yaofang had 23 publications involving 1972 IBS-D patients.[217] A very recently published RCT had 1044 patients with Rome III criteria IBS randomized to 3 treatments for 4 weeks, and found that Tongxie Yaofang was significantly better than placebo for improving abdominal pain and stool parameters, but not better than pinaverium for abdominal pain.[218]

Statement 37: Psychotherapy is possibly useful in IBS, but data only supports its use in tertiary care patients.

Grade of evidence: low

Level of agreement: a. 90.5%; b. 9.5%; c. 0.0%; d. 0.0%; e. 0.0%; f. 0.0%

A meta-analysis of 41 RCTs of psychotherapy for adults with IBS, found that none of the trials were at low risk of bias for every domain.[219] The majority of studies were from USA, Sweden, and UK. On review of the demographic characteristics of study participants, it was acknowledged that the majority of patients were white and female. Asian experience with psychotherapy is limited to only one study each from Korea[220] and from Japan.[221] The Korean study employed cognitive behavioral therapy and recruited only female nursing students.[220] This limits the generalizability of the outcome as the expectation is that these subjects were young and familiar with clinical science. The Japanese study employed autogenic training as a relaxation technique.[221] The sample size was small (10 male and 11 female) and subjects were recruited from a psychosomatic department. Thus, the acceptance and understanding of this technique by a broader group of IBS subjects are unknown.

Another meta-analysis of 36 RCTs involving a variety of psychotherapies (including cognitive behavioral therapy, relaxation therapy, hypnotherapy, dynamic psychotherapy and mindfulness) involving a total of 2189 patients found that overall IBS symptoms did not improve in 52% compared with 76% receiving control in the form of symptom monitoring, physician's usual management, supportive therapy or placebo.[186] There were serious issues regarding the validity of the findings as none of the trials were at low risk of bias, 22 (61.0%) studies were based in tertiary care setting, 30 (83.0%) studies were unblinded and concealment of allocation was not stated in 24 (67.0%) studies. It remains unclear whether psychotherapy is effective for the treatment of IBS in primary care, with only 2 of the RCTs conducted entirely within this setting.[222] A further concern was that 9 of the eligible studies originated from the same center, and when a subgroup analysis was conducted examining this issue there appeared to be a greater treatment effect in these 9 studies than in the 11 studies emanating from other centers.

A number of weaknesses common to several RCTs of psychological therapies were their failure to use the Rome criteria, absence of a power calculation, use of non-validated outcome measures, and inadequate blinding.[222] Furthermore, the effect of psychotherapy on IBS symptoms in the long term remains unknown.[219,222,223]

Conclusions

Our consensus sought to represent current knowledge in a way that will be clinically useful to doctors treating IBS in Asia. The first and rate-limiting step in its management is to be able to make an early and confident diagnosis of IBS. Thus, it is important that physicians in Asia are able to recognize IBS based on the Asian experience, rather than parameters set by the West. In a landmark pan-Asian study, the pattern of symptom clusters in FGID patients was found to be quite different from the classification system proposed by the Rome committee.[224] A greater emphasis was placed on meal-related symptoms by Asian patients with IBS criteria. In fact, subsequent reports from Australia and from a Rome Foundation study group also found that there are important issues with the Rome IV criteria.[225,226] Future research in Asia should test the Asian symptom clusters against the Rome-proposed symptom clusters. We should also test whether socio-cultural and environmental factors influence the greater overlap between IBS and upper GI symptoms in Asia, and whether this makes it more challenging to recognize IBS here.

Asian data substantiate the global research that now places IBS as a disorder of gut-brain interaction, recognizing the key role of the intestinal micro-environment. Previous emphasis on the psychological disturbance could have contributed to a lack of interest in IBS within the GI community in Asia. The emergence of more effective treatments with peripheral targets should encourage greater effort to recognize IBS in our patients. Furthermore, our rich heritage of traditional Asian treatments, together with emerging data on the potential of herbal medicines, earmarks this as an important field of exploration for future treatments. All patients with IBS should be

evaluated comprehensively with a view to holistic management.

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Author contributions: Participants were organized into 4 teams to review the evidence and develop statements comprising: symptoms and epidemiology (Hiroto Miwa, Ching-Liang Lu, Minhu Chen, Hyojin Park, Andrew S B Chua, and Shin Fukudo), pathophysiology (Uday C Ghoshal, Xiaohua Hou, Myung-Gyu Choi, Sutep Gonlachanvit, and Michio Hongo), diagnosis and investigations (Justin Wu, Ari F Syam, Philip Abraham, Jose Sollano, and Young-Tae Bak), and lifestyle modifications and treatments (Kok Ann Gwee, Chi-Sen Chang, Hidekazu Suzuki, Oh Young Lee, and Xiucai Fang). All other faculty members contributed by reviewing and discussing the statements and supporting evidence, voting, reading, and approving the manuscript.

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