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SPECIAL ARTICLE

Evidence-based clinical practice guidelines for irritable bowel syndrome

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Abstract New strategies for the care of irritable bowel syndrome (IBS) are developing and several novel treatments have been globally produced. New methods of care should be customized geographically because each country has a specific medical system, life style, eating habit, gut microbiota, genes and so on. Several clinical guidelines for IBS have been proposed and the Japanese Society of Gastroenterology (JSGE) subsequently developed evidence-based clinical practice guidelines for IBS. Sixty-two clinical questions (CQs) comprising 1 definition, 6 epidemiology, 6 pathophysiology, 10 diagnosis, 30 treatment, 4 prognosis, and 5 complications were proposed and statements were made to answer to CQs. A diagnosis algorithm and a three-step treatment was provided for patients with chronic abdominal pain or abdominal discomfort and/or abnormal bowel movement. If more than one alarm symptom/sign, risk factor and/or routine examination is positive, colonoscopy is indicated. If all of them, or the subsequent colonoscopy, are/is negative, Rome III or compatible criteria is applied. After IBS diagnosis, step 1 therapy consisting of diet therapy, behavioral modification and gut-targeted pharmacotherapy is indicated for four weeks. Non-responders to step 1 therapy proceed to the second step that includes psychopharmacological agents and simple psychotherapy for four weeks. In the third step, for patients non-responsive to step 2 therapy, a combination of gut-targeted pharmacotherapy, psychopharmacological treatments and/or specific psychotherapy is/are indicated. Clinical guidelines and consensus for IBS treatment in Japan are well suited for Japanese IBS patients; as such, they may provide useful insight for IBS treatment in other countries around the world.

Keywords Functional gastrointestinal disorders (FGIDs) · Functional bowel disorder (FBD) · Definition · Epidemiology · Pathophysiology · Diagnosis · Treatment · Prognosis · Complications · Rome III criteria · Psychosocial stress · Infection · Microbiota · Inflammation · Mucosal permeability · Brain-gut interactions · Probiotics · Antibiotics · Gut epithelial modifier · 5-HT_3 antagonist · 5-HT_4 agonist · Antidepressant · Psychotherapy

Introduction

New strategies for the care of irritable bowel syndrome (IBS) are developing and several novel pharmacological agents have been produced globally. New care should be customized geographically because each country has a specific medical system, life style, eating habit, gut microbiota, genes and so on. Several clinical guidelines for IBS have been proposed. The Japanese Society of Gastroenterology (JSGE) (president, Shimosegawa T., past-president, Sugano K.,

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The members of the Working Committee are listed in the Appendix in the text.

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directors, Kinoshita Y.) has developed diagnostic and therapeutic guideline for IBS with co-operation for the same for functional dyspepsia (chair, Miwa H). A twelve-member working committee (chair, Fukudo S., vice-chair, Kaneko H., Akiho H., Inamori M., Endo Y., Okumura T., Kanazawa M., Kamiya T., Sato K., Chiba T., Furuta K., Yamato M.), an evaluation committee with five members (chair, Arakawa T., vice-chair, Fujiyama Y., Azuma T., Fujimoto K., Mine T.) and an observer (Miura S.) participated in the development. One hundred and two clinical questions (CQs) on important target procedures were proposed and filtered down to 62 CQs. Published articles in English or Japanese from 1983 to 2011 were searched for 3–10 key words using Medline, PubMed and the Web Japan Medical Abstractis Society. The search produced 7,508 articles of which 3,664, with 41 articles manually searched, were utilized to answer the CQs. We used a modified GRADE system (Ann Intern Med 2010; 153: 194–199) to evaluate the articles: grade A (high); B (moderate); C (low); and D (very low). Sets of articles for answering a CQ were evaluated using rate-down or rate-up procedures and finally judged as evidence of grade A, B, C or D. A statement with explanations for each CQ was made based on evidence with a strong recommendation for or against, or a weak recommendation for or against, the target procedure.

Main Text of the Japanese IBS Guideline

1. Definition and Epidemiology

(Definition)

CQ. How is irritable bowel syndrome (IBS) defined?

- IBS is defined as a representative functional gastrointestinal disorder characterized by chronic or recurrent abdominal pain and/or abdominal discomfort associated with abnormal bowel movement.

Comment: Functional gastrointestinal disorders are characterized by a lack of evidence of organic disease upon routine clinical examination, despite the presence of continuous chronic or recurrent gastrointestinal symptoms, and thus demonstrate them as idiopathic disorders. Functional gastrointestinal disorders are classified into several categories, including functional bowel disorder, which is a functional gastrointestinal disorder affecting the mid to lower digestive system. Functional bowel disorder includes IBS, functional abdominal bloating, functional constipation, functional diarrhea and unspecified functional bowel disorder [1].

(Epidemiology)

CQ. Is the prevalence of IBS increasing?

- It is unlikely the prevalence of IBS is increasing.

Comment: From the world-wide systematic review/meta-analysis in 2012, the prevalence of IBS from 1981–1990 (11,000 subjects in 6 studies), from 1991–2000 (639,000 subjects in 33 studies) and from 2001–2010 (160,000 subjects in 38 studies) was 10, 12 and 11 %, respectively [2].

CQ. Does the prevalence of IBS depend on sex, age, residential area or occupation?

- The prevalence of IBS depends on sex, age, residential area or occupation.

Comment: The prevalence of IBS among women is 1.6 times higher than that among men [2]. That decreases with age, differs among geographic regions (e.g., 2 % in France, 7 % in South–East Asia, 10 % in the US and 21 % in South America) and occupations.

CQ. Does obesity have a high prevalence of IBS?

- The prevalence of IBS is not higher among obese individuals.

Comment: In a study conducted by Kubo et al. [3], routine medical examination of 2,717 Japanese subjects revealed that the body mass index (BMI) was significantly lower in an IBS group compared to a control group (BMI: 21.6 vs. 22.5). Although no correlation was observed with lower abdominal pain or constipation, an increase in a patients BMI was positively correlated with upper abdominal pain and diarrhea in a 2001 meta-analysis investigating the association between gastrointestinal symptoms and obesity [4], thereby demonstrating a positive correlation between BMI and diarrhea, but not IBS.

CQ. Does post-infectious (PI)-IBS have a high rate among whole IBS?

- The prevalence of IBS after infectious gastroenteritis or enterocolitis is 6–7 times higher than that after no infectious episode [5]. The proportion of PI-IBS among the whole IBS population is estimated at 5–25 % [6–8].

CQ. Is quality of life in IBS patients disturbed?

- Health-related quality of life (QOL) in patients with IBS is greatly disturbed [8].

CQ. Does the severity or psychological disturbance in IBS patients determine health care seeking behaviors?

- The severity of IBS (especially abdominal pain or diarrhea) and psychological disturbance in IBS patients determine health care seeking behaviors [9, 10].

2. Pathophysiology

CQ. Does stress relate to the pathophysiology of IBS?

- Stress relates to the pathophysiology of IBS.

Comment: Stress plays a role in the manifestation of IBS. Clinically, gastrointestinal symptoms in IBS patients worsen at the time of self-perceived stress, and this phenomenon has been confirmed psychometrically. Previous research showed that the correlation coefficient between stress loading and exacerbation of gastrointestinal symptoms is high for IBS patients compared with that for healthy individuals [11]. When psychosocial stress is loaded on IBS patients in an examination room, bowel movement is activated, as determined by measurements of colonic manometry [12]. In IBS patients, stimulation of the gastrointestinal system enhances the response of the central nervous system (CNS), to varying degrees between the sexes, with the activation of brain areas that regulate the stress responses (i.e., the amygdala, anterior cingulate cortex and insula) [13]. The inability of IBS patients to adapt quickly to circumstantial changes and the relatively low level of activation in their right dorsolateral prefrontal cortex are thought to play a role in the stress responses specific to IBS patients [14].

CQ. Do microbiota and mucosal inflammation relate to pathophysiology of IBS?

- Microbiota and mucosal inflammation relate to pathophysiology of IBS.

Comment: Compared with healthy individuals, IBS patients have a higher number of mast cells in the mucosa of the terminal ileum and colon [15]. Furthermore, the numbers of intraepithelial lymphocytes, CD3+ cells and CD25+ cells are increased in the colon mucosa of IBS patients (1.8-, 2- and 6.5-fold, respectively, [15]), indicating that the patients are in an immunostimulatory state and a state with increased mucosal permeability. In some individuals, IBS develops after an insult of acute gastroenteritis (i.e., post-infectious IBS) [16, 17]. Normal flora in the intestine in IBS patients differ from those in healthy individuals, and the profiles of intestinal flora in IBS patients also vary between IBS patients with constipation, diarrhea, and mixed subtypes [18]. In Japan, intestinal flora in IBS patients also differ from those observed in healthy individuals, and organic acid by-products observed in the patients correlated with symptoms [19].

CQ. Do neurotransmitters and endocrine substances relate to the pathophysiology of IBS?

- Neurotransmitters and endocrine substances relate to the pathophysiology of IBS.

Comment: A meta-analysis showed that colorectal distension in IBS patients activates the anterior cingulate cortex, amygdala and midbrain but deactivates the medial and lateral prefrontal cortex, thereby revealing an association between IBS symptoms and functional changes in the neuronal network centering on the amygdala [20]. The leading neurotransmitter responsible for the pathology of IBS is serotonin. Depletion of tryptophan, a serotonin precursor, causes visceral hypersensitivity [21] and elicits fear [22] in IBS patients. The administration of an antidepressant that inhibits the reuptake of serotonin in IBS patients suppresses hyperactivity of the anterior cingulate cortex [23] and improves clinical IBS symptoms [24]. Moreover, hormones, especially the main stress-related peptide corticotropin-releasing hormone (CRH), contribute to the pathological state of IBS patients. Bowel movement is activated when CRH is loaded on IBS patients [25], and CRH antagonists suppress stress-induced colonic motility [26]. The administration of melatonin biosynthesized from serotonin reduces abdominal pain in IBS patients [27]. In addition to the substances mentioned above, several neurotransmitters, including histamine [28] and nitric oxide [29], play a role in the manifestations of IBS. In fact, pregabalin, an $\alpha_2\delta$ ligand that inhibits the release of a number of excitatory neurotransmitters, alleviates visceral pain in IBS patients [30].

CQ. Do psychological disturbances relate to the pathophysiology of IBS?

- Psychological disturbances relate to the pathophysiology of IBS.

Comment: The influence of psychological disorders in the pathology of IBS increases as the severity of IBS increases [31]. Representative psychological conditions in IBS are depression and anxiety, followed by somatization [31]. Although a cohort study revealed that depressive or anxiety disorder is a risk factor for the development of IBS [32], IBS itself is not a risk factor for depressive or anxiety disorder. However, functional gastrointestinal disorders as a whole increases the incidence of depressive or anxiety disorders.

CQ. Do genetics relate to the pathophysiology of IBS?

- Genetics relate to the pathophysiology of IBS.

Comment: A study investigating the concordance rate of IBS in 6,060 twins revealed that the rate was 8.4 % in dizygotic twins but as high as 17.2 % in monozygotic twins [33], indicating the hereditary nature of IBS. However, IBS has not been definitively linked to a particular gene [34], despite previous reports of IBS candidate genes such as α_2A (C-1291G), α_2C (Del 332–325) and GNβ3 (C825T). However, there have been recent reports of the association between serotonin transporter gene polymorphism and visceral hypersensitivity [34], between serotonin transporter gene polymorphism and the activation of the anterior cingulate cortex at the time of visceral stimulation [35], and between 5-HT_3A receptor gene polymorphism and the activation of the amygdala at the time of visceral stimulation [36], which all point to the association of IBS and endophenotypes. In a cohort study of patients with a history of infectious enteritis, two of the four genes that were linked to IBS were toll-like receptor 9 (TLR9) genes that play a role in self/nonself pattern recognition in the innate immune system [37]. The third gene was the E-cadherin-1 (CDH1) gene coding for a cell–cell adhesion molecule, and the fourth gene was the interleukin-6 (IL-6) gene coding for a cytokine. Furthermore, 2 % of IBS patients had the G298S mutation in the SCN5A gene coding for sodium channel $Nav_{1.5}$ [38].

CQ. Do subtypes (C, D, M and U) of IBS have a different pathophysiology?

- Subtypes (C, D, M and U) of IBS have a common and different pathophysiology.

Comment: In a 15-month follow-up study, female IBS patients were initially classified as having the constipation (34 %), diarrhea (36 %) and mixed (31 %) subtypes in accordance with the Rome II diagnostic criteria. However, only about 25 % of the patients had the same subtype over 12 months, while the remaining 75 % of patients made at least one transition into the other subtypes [39]. In a study using an X-ray opaque marker, colonic transit time varied by subtype among the constipation (IBS-C), diarrhea (IBS-D), mixed (IBS-M) and unspecified (IBS-U) subtypes classified in accordance with the Rome III diagnostic criteria [40]. However, only 15 % of those with constipation had delayed transit time, and only 36 % of those with diarrhea had shortened transit time. Furthermore, no significant difference in visceral hypersensitivity, colonic motility in response to colonic distension, or colonic motility in response to food intake was observed among the four subtypes, classified in accordance with the Rome III diagnostic criteria, in a study using a barostat and colonic manometry [41].

3. Diagnosis

CQ. Is Rome III criteria useful for diagnosing IBS?

- Rome III criteria is useful for diagnosing IBS. Strong recommendation, evidence level A, Grade 1, 100 % agreed.

Comment: By using Rome III criteria, we can diagnose relatively fewer heterogenous IBS patients without unnecessary examinations than by using a physician's own criteria [1, 42].

CQ. Is family history, a bloody stool or abdominal pain during sleeping useful for differential diagnosis of IBS from organic diseases?

- A bloody stool as an alarm sign [43] and family history as a risk factor [44] are useful for differential diagnosis of IBS from organic diseases. Weak recommendation, evidence level B, Grade 2, 100 % agreed.

Comment: Abdominal pain during sleep provides less evidence for discriminating IBS from other diseases.

CQ. Is specimen (blood, urine and feces) examination useful for diagnosing IBS?

- Specimen (blood, urine and feces) examination is useful for differential diagnosis of IBS from organic diseases [45]. Weak recommendation, evidence level B, Grade 2, 100 % agreed.

CQ. Is a colonoscopy or barium enema useful for diagnosing IBS?

- A colonoscopy or barium enema is useful for differentiating IBS from organic diseases. Weak recommendation, evidence level B, Grade 2, 100 % agreed.

Comment: Colonoscopy has a diagnostic value, not only for excluding organic diseases, but also for supporting the existence of pathophysiology compatible to IBS due to visceral hypersensitivity to colonoscopic procedures and colonic spasms [46, 47].

CQ. Are gastroenterological imaging examinations besidesother than a colonoscopy or barium enema useful for diagnosing IBS?

- Gastroenterological imaging examinations (upper gastrointestinal endoscopy, abdominal ultrasonography,

abdominal CT scan, abdominal magnetic resonance imaging or plain X-ray of the abdomen) other than a colonoscopy or a barium enema are useful for differentiating IBS from organic diseases in some cases. Weak recommendation, evidence level B, Grade 2, 91 % agreed.

Comment: A small number of epidemiological studies of IBS have investigated the utility of diagnostic imaging modalities other than in the colorectal region, including endoscopy in the digestive tract, and reported that upper gastrointestinal endoscopy or ultrasonography, depending on the abdominal symptoms in IBS patients, was beneficial for excluding other conditions in daily clinical practice [48, 49].

CQ. Is histopathological examination of the gut mucosa useful for diagnosing IBS?

- Histopathological examination of the gut mucosa is useful for diagnosing IBS. Weak recommendation, evidence level B, Grade 2, 100 % agreed.

Comment: Histopathological examination of the gut mucosa provides exclusion of collagenous colitis or Celiac disease and evidence of increased mucosal permeability with increased mast cells, increased enterochromaffin cells and inflammatory cells supporting IBS features [50, 51].

CQ. Are examinations of gastrointestinal function useful for diagnosing IBS?

- Examinations of gastrointestinal function (colonic manometry, anorectal manometry, gastrointestinal transit, colorectal barostat or hydrogen breath test) are useful for diagnosing IBS. Weak recommendation, evidence level B, Grade 2, 100 % agreed.

Comment: Although examinations of gastrointestinal function are not universally available, reports support significant difference in these tests between IBS patients and healthy controls [52]. These tests are also useful for differentiating IBS from anorectal dysfunction or small intestinal bacterial overgrowth [53].

CQ. Are questionnaires useful for diagnosing IBS?

- Questionnaires (gastrointestinal symptoms, psychometry or QOL) are useful for diagnosing IBS. Strong recommendation, evidence level A, Grade 1, 100 % agreed.

Comment: Positive IBS symptoms based on Rome diagnostic questionnaires, anxiety/depression/somatization in psychometry, and disturbed QOL are common in IBS patients [54–59].

CQ. Is evaluation of severity useful for diagnosing IBS?

- Evaluation of severity is useful for diagnosing IBS. Weak recommendation, evidence level A, Grade 2, 100 % agreed.

Comment: Evaluation of severity is useful for detecting the changes in IBS symptoms or therapeutic efficacy [59, 60]. Severe and distinct symptoms support the diagnosis of IBS.

CQ. Are there any objective biomarkers for diagnosing IBS?

- There are no certified objective biomarkers for diagnosing IBS at the present time. Insufficient evidence for determining the net benefits or risks, no Grade.

Comment: Despite a previous report [61], the use of diagnostic indicators (biomarkers) is not an established diagnostic method for IBS yet.

4. Treatment

CQ. Is the aim of IBS therapy improvement of IBS symptoms?

- The aim of IBS therapy is improvement of IBS symptoms. Strong recommendation, evidence level A, Grade 1, 100 % agreed.

Comment: Assessment of patient-reported outcomes is recommended, even though no world-wide consensus has been reached [59]. Future challenges include establishing objective diagnostic indicators (biomarkers) that accurately reflect the pathological manifestation of IBS.

CQ. Is the patient-doctor relationship effective in treating IBS?

- The patient-doctor relationship impacts IBS. Forming a nice patient-doctor relationship is recommended for IBS. Strong recommendation, evidence level A, Grade 1, 100 % agreed.

Comment: In a study investigating placebo effects in IBS patients, symptoms improved to a greater extent in patients who were fully informed of the treatment strategy than in those who were not [62], demonstrating the efficacy of placebo in IBS [63]. Regardless of whether a placebo or real formulation is used, treatment efficacy is high among patients in a good doctor-patient relationship, and the response rate will increase further when a real formulation with proven efficacy is used. In addition, patients who are in a good doctor-patient relationship have fewer hospital visits [64].

CQ. Is diet therapy effective in treating IBS?

- Eliminating foods which aggravate IBS symptoms is effective in treating IBS. Examples are a low fermentable oligo-di-monosaccharide and polyol (FODMAP) diet, eliminating high fat foods and avoiding spicy foods. A high fiber diet is effective for constipation in IBS patients. Diet therapy is recommended for IBS. Weak recommendation, evidence level B, Grade 2, 100 % agreed.

Comment: Although the study was limited by the small number of patients, a recent randomized, controlled trial revealed that compared with a normal diet, a diet low in FODMAP is beneficial for IBS patients [65]. In a meta-analysis, a fiber-rich diet was effective for constipation, but not for abdominal pain, in IBS patients [66]. If IBS symptoms worsen after a meal, individualized guidance may be necessary to eliminate a certain food item or ingredient from the diet or to correct irregular eating habits.

CQ. Is behavioral modification other than a change in diet effective at reducing IBS symptoms?

- Behavioral modification is effective at reducing IBS symptoms. Exercise likely suppresses exacerbation in IBS symptoms. Although there is no clear evidence yet of the efficacy of other behavioral modifications, such as eliminating alcohol and smoking, getting good sleep, and taking rest, at reducing IBS symptoms, a reduction of the potential risk for IBS is a plausible strategy. Behavioral modification is recommended for IBS. Weak recommendation, evidence level C, Grade 2, 100 % agreed.

Comment: The exacerbation of gastrointestinal symptoms in IBS patients was suppressed after 12 weeks of exercise therapy (3–5 times per week, moderate to high physical load), effectively enhancing physical activity [67]. To date, only a small number of clinical studies have systematically investigated the effects of lifestyle modification in IBS patients.

CQ. Are probiotics or prebiotics effective in treating IBS?

- Probiotics are effective in treating IBS. Probiotics are recommended for IBS. Strong recommendation, evidence level A, Grade 1, 100 % agreed.
- Prebiotics may be effective in treating IBS. Prebiotics are recommended for IBS. Weak recommendation, evidence level C, Grade 2, 100 % agreed.

Comment: The utility of probiotics in the treatment of IBS has been investigated in a large number of intervention studies, including many high-quality systematic reviews, meta-analyses and RCTs [68–77]. However, it should be noted that their results were somewhat inconsistent. For example, the efficacy of probiotics was shown in a meta-analysis with an odds ratio of 1.6 as well as in many systematic reviews on various bacterial species. In other investigations, one bifidobacterium species was effective, but other probiotics were not. Overall, however, probiotics are considered beneficial for IBS because of their relatively low cost and safety. With regard to prebiotics, even though their use is recommended, only a few studies are currently investigating the utility of prebiotics in the treatment of IBS [78].

CQ. Are antibiotics effective in treating IBS?

- Currently, at least in Japan, antibiotics are not recommended for IBS. Weak/no recommendation, evidence level C, Grade 2, 91 % agreed.

Comment: In the US and Europe, the utility of non-absorbable, antimicrobial agents in IBS has been investigated in multiple intervention studies, and the efficacy of rifaximin [79–83] and neomycin [83, 84] has been proven in high-quality RCTs. However, in Japan, no antimicrobial agent like rifaximin or neomycin has been approved, and the use of other antimicrobial agents in the treatment of IBS is not currently covered by the national health insurance system, making it impossible to propose the use of any antimicrobial agent in the treatment of IBS. However, because of the efficacy demonstrated by the high-quality studies in the United States and Europe, it is anticipated that studies using antimicrobial agents will be initiated in Japan.

CQ. Are 5-HT_3 receptor antagonists effective in treating IBS-D?

- 5-HT_3 receptor antagonists are effective in treating IBS-D. 5-HT_3 receptor antagonists are recommended for IBS-D. Strong recommendation, evidence level A, Grade 1, 100 % agreed.

Comment: In placebo-controlled studies conducted overseas on female diarrhea-dominant IBS patients, the 5-HT_3 receptor antagonist alosetron significantly improved abdominal pain and discomfort in addition to defecation urgency, defecation frequency and loose stool/diarrhea [85–94]. However, in part because of a small number of registered male patients, the efficacy of the 5-HT_3 receptor antagonist in male diarrhea-dominant IBS patients has not yet been demonstrated. In Japan, the efficacy of the 5-HT_3 receptor antagonist ramosetron to treat male diarrhea-dominant IBS patients was shown in multicenter double-blind RCTs [95, 96], whereas the treatment efficacy in female diarrhea-dominant IBS patients was not fully

proven, even though the efficacy tended to be higher in IBS patients than in those receiving the placebo control.

CQ. Are 5-HT_4 agonists effective in treating IBS-C?

- 5-HT_4 agonists are effective in treating IBS-C. 5-HT_4 agonists are recommended for IBS-C. Weak recommendation, evidence level B, Grade 2, 100 % agreed.

Comment: At present, mosapride is the only 5-HT_4 receptor agonist available for clinical use in Japan. The agonist is used frequently in Asian countries, especially in Japan, but rarely in the US and Europe. In cohort studies of IBS-C patients, mosapride improved abdominal pain and bloating, increased defecation frequency, improved stool consistency, shortened colonic transit time and reduced the amount of gas in the gastrointestinal tract [97, 98]. The national health insurance system covers the use of mosapride for chronic gastritis. Prucalopride has been approved for clinical use in Europe but not in Japan.

CQ. Are mucosal epithelium modifiers effective in treating IBS-C?

- Mucosal epithelium modifiers are effective in treating IBS-C. Mucosal epithelium modifiers are recommended for IBS-C. Strong recommendation, evidence level B, Grade 1, 100 % agreed.

Comment: Lubiprostone is a locally acting agent that activates the type-2 chloride ion channel (ClC-2 chloride channel) expressed in the small intestinal epithelial cells. By activating the chloride channels in the small intestine, lubiprostone increases the secretion of intestinal fluid into the intestinal tract, thereby increasing the amount of water content in the stool and softening it, which subsequently facilitates the speed of colonic transit time and defecation. Compared with a placebo, lubiprostone significantly improves abdominal pain, abdominal discomfort, abdominal bloating, severity of constipation, lumpy stool and straining [99, 100]. The effects of lubiprostone appear in the first week of administration, and symptoms improve significantly after two months. Diarrhea and nausea are listed as side effects of lubiprostone. Linaclotide, a once-daily oral guanylate cyclase C (GC-C) receptor agonist, improves constipation by binding to GC-C receptors on the epithelial cells of the intestinal mucosa, upregulating production of cGMP and facilitating water secretion and transport in the gastrointestinal tract [101, 102]. Compared with a placebo, linaclotide improves IBS-related abdominal symptoms such as pain, discomfort and bloating. The side effect of linaclotide is diarrhea.

CQ. Are bulking polymers or dietary fibers effective in treating IBS?

- Bulking polymers or dietary fibers are effective in treating IBS. Bulking polymers or dietary fibers are recommended for IBS. Strong recommendation, evidence level A, Grade 1, 100 % agreed.

Comment: Dietary fiber (bran, ispaghula and so on) improved the symptoms of IBS effectively compared with a placebo [103]. A study comparing the efficacy of soluble fiber [plantain *Plantago aristata* (psyllium *Plantago psyllium*), ispaghula and polycarbophil calcium] and insoluble fiber (cone and wheat bran) in IBS patients revealed that soluble fiber significantly improved IBS symptoms, but insoluble fiber was ineffective and even worsened IBS symptoms in some patients [66]. Polycarbophil calcium is a polyacrylic resin that is hydrophilic but insoluble in water, and it functions as a soluble fiber by maintaining water in the gastrointestinal tract and by regulating the transport of gastrointestinal contents, thereby potentially reducing/alleviating diarrhea and constipation [104]. The efficacy of polycarbophil calcium has been proven in placebo-controlled RCTs as well as large-scale clinical trials conducted in Japan [105].

CQ. Are gastrointestinal motility modifiers effective in treating IBS?

- Gastrointestinal motility modifiers are effective in treating IBS. Gastrointestinal motility modifiers are recommended for IBS. Weak recommendation, evidence level B, Grade 2, 100 % agreed.

Comment: The efficacy of trimebutine maleate in IBS patients was investigated in several small-scale RCTs and meta-analyses conducted overseas. The agent appears to improve gastrointestinal symptoms, including abdominal pain, in addition to defecation frequency and stool consistency [106]. However, an overall improvement was not observed. The use of trimebutine maleate is generally recommended in some guidelines and reviews [107, 108]. With regard to dopamine D_2 blocking agents, a small-scale RCT and meta-analysis investigated the efficacy of domperidone in IBS patients and showed the beneficial effect of this agent on gastrointestinal symptoms. No studies have yet investigated the utility of metoclopramide and its extrapyramidal side effects have been recognized [108, 109]. Furthermore, no clinical evidence on the efficacy of neostigmine [110] or itopride in IBS patients is available.

CQ. Are anticholinergics effective in treating IBS?

- Anticholinergics are effective for some patients with IBS. Anticholinergics are recommended for some patients IBS. Weak recommendation, evidence level B, Grade 2, 100 % agreed.

Comment: In Japan, tiquizium bromide, butylscopolamine bromide, cimetropium bromide hydrate and mepenzolate bromide have been used as anticholinergic agents for the treatment of abdominal symptoms. In other countries, several ongoing small-scale RCTs and meta-analyses of anticholinergic agents indicate that even though anticholinergic agents are effective at improving defecation frequency, stool consistency and gastrointestinal symptoms such as abdominal pain, they do not appear to improve overall symptoms [106]. Furthermore, research has occasionally provided physiological evidence of anticholinergic agents for inhibiting the motor function of the colon [111]. Despite their side effects, as pointed out by some guidelines and reviews, anticholinergic agents are regarded as practicably useful drugs in many articles [106]. Anticholinergic agents are sometimes used as controls in RCTs [112].

CQ. Are anti-diarrheal agents effective in treating IBS-D?

- Anti-diarrheal agents are effective for some patients with IBS-D. Anti-diarrheal agents are recommended for some patients with IBS-D. Weak recommendation, evidence level D, Grade 2, 100 % agreed.

Comment: Antidiarrheal agents used in Japan include loperamide hydrochloride, albumin tannate and berberine chloride. Unfortunately, studies on antidiarrheal agents other than loperamide hydrochloride for the treatment of IBS are rarely found in the United States or Europe. Several small-scale RCTs have been conducted overseas to investigate the efficacy of loperamide hydrochloride in IBS patients [113–115] and the agent was found effective at improving defecation frequency and stool consistency. However, due to inconsistent study results, consensus has not been reached on whether loperamide hydrochloride improves gastrointestinal symptoms such as abdominal pain. Abdominal pain and other side effects develop when it is used for general purposes, indicating that long-term use of the agent is unfavorable. However, it may be useful for special occasions such as traveling, long drives, meals and stressful events [116]. Furthermore, a systematic review reported a high incidence of bile acid malabsorption among IBS patients, and although cholestyramine is used for treatment thereof, the outcome difference between treatment with and without cholestyramine has not been investigated in a RCT involving patients with IBS only [116].

CQ. Are laxatives effective in treating IBS-C?

- Laxatives are effective for some patients with IBS-C. Laxatives are recommended for some patients with IBS-C. Weak recommendation, evidence level D, Grade 2, 100 % agreed.

Comment: No RCTs have investigated the effects of laxatives in patients with IBS only. Representative laxatives are osmotic laxatives and stimulant laxatives, and the former are used worldwide in the treatment of IBS-C patients [117]. Although osmotic laxatives clearly improve stool consistency and defecation frequency, their effects on abdominal pain and bloating as well as the QOL of IBS patients are currently unclear [118]. Magnesium oxide is used frequently in Japan. Although polyethylene glycol (PEG), lactulose and sorbitol are also used in the United States and Europe, they are not indicated for constipation in adults in Japan. With regard to stimulant laxatives, the utility of sodium picosulfate in patients with chronic constipation has been shown in RCTs [119, 120]. Caution should be exercised in the use, especially long-term use, of anthraquinone derivatives like senna because of its negative aspects, such as electrolyte abnormalities, development of tolerance, colon pigmentation known as (pseudo-)melanosis coli and abuse [118].

CQ. Are enemas effective in treating IBS-C?

- Enemas as rescue medication are effective for some patients with IBS-C. Enemas are recommended for some patients with IBS-C. Weak recommendation, evidence level D, Grade 2, 100 % agreed.

Comment: Academic studies have seldom investigated the efficacy of enemas in IBS patients; only expert opinions are available [121]. In relatively well-established procedures, an enema is effective in inducing bowel movement and relatively inexpensive enema products are now available. However, the use of an enema, unquestionably, depends on patient preference.

CQ. Are antidepressants effective in treating IBS?

- Antidepressants are effective in treating IBS. Tricyclic antidepressants or selective serotonin reuptake inhibitors are recommended for some patients with IBS, bearing in mind the side effects. Weak recommendation, evidence level A, Grade 2, 100 % agreed.
- There is no clear evidence of serotonin noradrenaline reuptake inhibitors and noradrenergic and specific serotonergic antidepressant at the present time.

Insufficient evidence to determine the net benefits or risks, no Grade.

Comment: In a meta-analysis of 15 placebo-controlled trials, tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) significantly improved abdominal pain, general physical condition and IBS severity score [106]. In the subgroup analysis, SSRIs improved general physical condition, while tricyclic antidepressants improved abdominal pain and IBS severity score. According to systematic reviews on the effect of antidepressants on IBS, although antidepressants are effective especially in IBS-D patients, tricyclic antidepressants often cause sleepiness, constipation and dry mouth, causing many patients to withdraw from treatment [106]. In addition, tricyclic antidepressants and SSRIs are reportedly no more effective in IBS than bulking agents or antispasmodics [106]; therefore antidepressants should be used with great care. Although no RCTs have been conducted to investigate the effects of serotonin/noradrenaline reuptake inhibitor (SNRI) on IBS, duloxetine was used to treat 15 IBS patients in an open-label study [122]. Duloxetine significantly improved the severity of abdominal pain, QOL, stool consistency, inconvenience at work or home, and anxiety. However, because 7 of the 15 patients withdrew from the trial, the results must be interpreted with caution. According to an RCT involving patients with functional gastrointestinal disorders (IBS and non-ulcer dyspepsia), the administration of the tetracyclic antidepressant mianserin significantly improved abdominal symptoms and social dysfunction, compared with a placebo [123]. Although antidepressants are effective for IBS, they likely have various side effects. Antidepressants should be used in patients who fail to benefit from standard drug therapy, after considering the advantages and disadvantages of antidepressants in individual patients.

CQ. Are anxiolytics effective in treating IBS?

- Anxiolytics are effective in treating IBS. Anxiolytics are recommended only for high anxious patients with IBS for a short period of time. Weak recommendation, evidence level C, Grade 2, 100 % agreed.

Comment: Flutazolam was more effective for IBS than a placebo in a double-blind study [124]. In addition, the rates of improvement of abdominal bloating, diarrhea, anxiety and tension were higher with flutazolam than with diazepam [125]. In another double-blind study, the combined use of chlordiazepoxide and amitriptyline was more effective than antispasmodics, dietary fiber or a placebo [126]. Maximum effect was obtained when the two drugs were used with an antispasmodic and dietary fiber. In a multicenter double-blind study, the combined use of the antispasmodic octatropine and diazepam significantly improved abdominal pain and discomfort [127]. However, the efficacy of a single anxiolytic has seldom been investigated worldwide. Because of issues associated with drug dependency at the recommended dose, benzodiazepine anxiolytics should be indicated only for patients with intense fear over the short term.

CQ. Are anti-psychotics or mood stabilizers effective in treating IBS?

- There is no enough evidence that anti-psychotics or mood stabilizers are effective in treating IBS. Insufficient evidence to determine net benefits or risks, no Grade.

Comment: In clinical practice, these drugs are used occasionally to control abdominal pain or mood in patients with intractable IBS [128]. The drugs should be administered carefully by professionals of psychopharmacotherapy.

CQ. Is placebo effective in treating IBS?

- Placebo is effective on approximately 40 % patients with IBS. Based on high placebo effect, forming better patient-physician relationship is recommended for IBS treatment. Strong recommendation, evidence level A, Grade 1, 100 % agreed.

Comment: Here, rather than recommending the use of placebos in the treatment of IBS, it is recommended that IBS should be treated with the effects of placebo in mind to achieve a greater treatment outcome. In a meta-analysis of RCTs comparing placebo effects with the effects of dietary fiber, antispasmodics, drugs that regulate gastrointestinal motility, and antidepressants, the response rate was 54.1 % in the real-drug group and 40.2 % in the placebo group [129]. The latter rate is particularly high when compared with the response rate of 19–30 % in the placebo control group for IBD. In another meta-analysis of RCTs investigating drug agents and food products, overall improvement and the alleviation of abdominal pain were 52 and 38 %, respectively, in the placebo group [130]. The high overall improvement rate in the placebo group might be attributable to the high number of hospital visits, trial duration and treatment efficacy in the real drug group.

CQ. Are psychotherapies effective in treating IBS?

- Psychotherapies are effective for some patients with IBS. Psychotherapy is recommended for IBS patients who do not respond to pharmacotherapy. Weak recommendation, evidence level B, Grade 2, 100 % agreed.

Comment: Psychotherapy includes group therapy, cognitive behavioral therapy, interpersonal psychotherapy, hypnotherapy, stress management and relaxation. A meta-analysis conducted in 2009 in accordance with the definitions of the Cochrane Collaboration revealed that improvement of symptoms including abdominal pain in patients undergoing group therapy was better than the improvement observed in patients undergoing regular therapy or waiting for treatment initiation, but was no better than the improvement observed in patients undergoing placebo treatment [131]. A similar outcome was observed in patients undergoing cognitive behavioral therapy whose overall symptoms and QOL three months after treatment were better than those in patients undergoing regular therapy or waiting for treatment initiation, but were hardly different from those in patients undergoing placebo treatment. On the other hand, adequate relief, overall symptoms and QOL at three months post treatment in patients undergoing interpersonal psychotherapy as well as overall symptoms including abdominal pain and QOL at two months post treatment in patients undergoing stress management and relaxation were better than those in patients undergoing regular therapy or waiting for treatment to start. In addition, another meta-analysis showed that the alleviation of abdominal pain and other IBS-related gastrointestinal symptoms was better in patients undergoing hypnotherapy than those undergoing regular therapy or waiting for treatment to start [132]. In 83 % of the patients who benefitted from hypnotherapy, the improvement of IBS symptoms continued over 5 years [133, 134].

CQ. Is comprehensive alternative medicine effective in treating IBS?

- Peppermint oil is effective in treating IBS. Peppermint oil is recommended for IBS. Weak recommendation, evidence level A, Grade 2, 100 % agreed.
- Comprehensive alternative medicine, except for peppermint oil, is almost entirely non-effective in treating IBS. Comprehensive alternative medicine is not recommended for IBS. Strong no recommendation, evidence level C, Grade 1, 100 % agreed.

Comment: Peppermint oil is thought to alleviate IBS symptoms by relaxing smooth muscles via calcium channels. Its efficacy for IBS has been shown in several RCTs, and in a meta-analysis, treatment outcome in patients treated with peppermint oil was overall superior to the outcome in the placebo group [103, 135]. Many studies have investigated the effects of acupuncture on IBS; in fact, studies on acupuncture effects account for the largest number of related articles [136]. According to another meta-analysis, however, acupuncture did not improve the symptoms or QOL of IBS patients more than a placebo [137].

CQ. Are kampo agents effective in treating IBS?

- Kampo agents (traditional Japanese medicine) are effective in treating IBS. Kampo agents are recommended for IBS. Weak recommendation, evidence level C, Grade 2, 100 % agreed.

Comment: The results of a meta-analysis showed an overall relative risk (RR) of 1.35 (1.21–1.50), which was considered effective, but the overall quality of the study was poor [138]. Only abdominal pain was improved in a group of 232 IBS patients treated with herbal medicine containing keishi-ka-shakuyaku-to for 4 weeks [139]. However, the use of herbal medicine is not highly recommended because of the overall low quality of the studies, the questionable manufacturing process of herbal medicines and the lack of long-term follow ups. Because some studies have reported benefits, high-level RCTs are needed to further investigate the efficacy of herbal medicine [140].

CQ. Is exercise effective in treating IBS?

- Exercise is effective in treating IBS. Exercise is recommended for IBS. Weak recommendation, evidence level B, Grade 2, 100 % agreed.

Comment: Twelve weeks of exercise significantly improved the symptoms and extraintestinal manifestations of IBS in 102 patients [67]. In addition, 1 h of yoga every day for 4 weeks significantly improved symptoms in 25 teenage IBS patients [141]. On the other hand, 12-week exercise therapy significantly improved only constipation, not other IBS symptoms in an RCT of 56 IBS patients [142], suggesting the potential efficacy of exercise in IBS-C. Despite time constraints and patient preferences, exercise appears to be beneficial for IBS.

CQ. Are major therapies for IBD effective in treating IBS?

- Major therapies for IBD are not effective in treating IBS. No major therapies for IBD are recommended for IBS. Strong no recommendation, evidence level D, Grade 1, 100 % agreed.

Comment: Although 30 mg of prednisolone was administered to 29 PI-IBS patients for 3 weeks in an RCT, IBS symptoms did not improve [143]. Similarly, IBS symptoms did not improve in 18 PI-IBS patients treated with mesalazine for 6 weeks [144] or in 12 IBS-D patients treated with

mesalazine for 4 weeks [145]. Despite a reduction in mast cells, 8 weeks of mesalazine administration did not improve the symptoms of 20 IBS patients in an RCT [146]. Even though symptoms were improved significantly in 18 PI-IBS patients and 43 IBS-D patients after the administration of mesalazine for 30 days, the contribution of the placebo effect to the improvement cannot be ruled out [147]. Due to the lack of treatment efficacy and the side effects that develop after long-term administration, the use of mesalazine as a treatment for IBS-D is not recommended.

CQ. Are anti-allergics effective in treating IBS?

- Anti-allergics are effective in treating IBS. Anti-allergics are recommended for IBS. Moreover, diet therapy with allergic foods elimination after the identification of allergic foods is also effective in treating IBS. Strong recommendation, evidence level B, Grade 1, 100 % agreed.

Comment: After the determination of causal allergens, 150 IBS patients were placed on an elimination diet from which all the allergens were eliminated. Compared with the control group, IBS symptoms were significantly improved in patients on the elimination diet for 12 weeks [148]. In a study of 409 IBS-D patients who had positive skin prick tests, IBS symptoms improved significantly in both the elimination diet group and the cromolyn (anti-allergy medication) group [149]. Furthermore, 8 weeks' administration of the anti-allergy medication ketotifen improved IBS symptoms significantly in 60 IBS patients [150].

CQ. Are narcotics and allied agents effective on abdominal pain in IBS?

- Narcotics are not effective at treating abdominal pain in IBS. Narcotics are not recommended for abdominal pain in IBS. Strong no recommendation, evidence level C, Grade 1, 100 % agreed.
- There is no enough evidence that allied agents of narcotics (κ-opioid agonists) are effective at treating abdominal pain in IBS. Insufficient evidence to determine net benefits or risks, no Grade.

Comment: The efficacy of narcotic agents such as morphine on IBS has not been reported. In fact, increasing dosages of narcotics often cause chronic and recurrent abdominal pain (narcotic bowel syndrome). Despite no significant difference in an intention-to-treat analysis, the 12-week administration of the κ-opioid receptor agonist asimadoline significantly improved symptoms in 596 IBS-D patients in an RCT [151]. Pain was improved in female IBS patients in a study using a barostat [152]. On the other hand, asimadoline was not effective in 155 IBS patients who had been administered the drug as needed for 4 weeks in a population-based study, although the follow-up rate was low at 62.6 % [153]. In an RCT, 6-week administration of fedotozine improved the symptoms of 238 IBS patients [154], and in another RCT, 8-week administration of the opioid receptor antagonist naloxone improved, albeit not significantly, the symptoms of 28 IBS patients [155]. No consensus has been drawn from these findings.

CQ. Are severity-dependent treatments more effective in treating IBS?

- Severity-dependent treatments (e.g., antidepressants or psychotherapy) are more effective in treating IBS. Severity-dependent treatments are recommended for IBS. Weak recommendation, evidence level B, Grade 2, 100 % agreed.

Comment: A cohort study of 350 IBS patients reported a correlation between the severity of IBS and patient satisfaction with treatment in a binary assessment (high satisfaction in patients with mild IBS, and low satisfaction in patients with severe IBS) [156]; however, no consensus was reached. A meta-analysis involving 10,066 IBS patients was conducted to investigate whether the improvement of symptoms depends on their severity. No correlation was observed between the severity of IBS and the improvement of symptoms in a binary assessment, and the difference in abdominal pain at the 50 % improvement rate was small, although significant [59]. Only a few RCTs have investigated treatment efficacy according to severity [157]. In patients with severe IBS, a significant difference was observed in number of hospital visits and improvement in QOL measured with SF-36 scores after the treatment with antidepressants or psychotherapy rather than regular therapy [158].

CQ. Is treatment response different between PI-IBS and non-PI-IBS?

- Treatment response may not be different between PI-IBS and non-PI-IBS. No differential treatment between PI-IBS and non-PI-IBS is recommended. Weak recommendation, evidence level B, Grade 2, 100 % agreed.

Comment: When PI-IBS patients and ordinary IBS patients were administered mesalazine, a drug used for the treatment of inflammatory bowel disease, for 30 days, IBS symptoms improved significantly in both groups, with no significant difference between the groups [147]. No studies have compared treatment outcome between patients with and without post-infectious enteritis in routine IBS treatment.

CQ. Can examinations of gastrointestinal function predict treatment response?

- There is no distinct evidence that examinations of gastrointestinal function can predict treatment response in IBS. Insufficient evidence to determine net benefits or risks, no Grade.

Comment: Examinations of gastrointestinal function is useful for differential diagnosis and clarifying underlining pathophysiology of each patients with IBS [159].

CQ. Is treatment response different among IBS subtypes?

- Treatment response may be different among IBS subtypes but there is no clear evidence to support this notion. Insufficient evidence to determine net benefits or risks, no Grade.

Comment: It is natural to think that certain drugs are beneficial for certain subtypes of IBS (-C, -D, -M and -U) when taking into account the mechanisms underlying drug function and the pathophysiology of the different IBS subtypes [66]. However, treatment outcome of the same treatment for the different IBS subtypes has not been compared in considerable number of patients.

5. Prognosis and Complications

(Prognosis)

CQ. Do symptoms of IBS change with age?

- Symptoms of IBS are likely to decline after the 50s.

Comment: In a meta-analysis of 81 epidemiological studies investigating approximately 260,000 individuals, the prevalence of IBS in individuals aged <30 years and individuals in their 30s, 40s, 50s and 60s was 11.0, 11.0, 9.6, 7.8 and 7.3 %, respectively, with a lower prevalence in individuals aged 50 years or older [160]. Another study also supports a decline of IBS prevalence with age [161].

CQ. Do the subtypes (D, C, M, U) of IBS show transition over time?

- Subtypes of IBS show transition over time [161, 162].

CQ. Is the prognosis of IBS changed by treatment?

- It is unknown whether the prognosis (especially life expectancy or occurrence of serious diseases) of IBS is changed by treatment or not.

(Complications)

CQ. Does IBS show high co-morbidity with functional dyspepsia?

- IBS patients show two times or more higher co-morbidity with functional dyspepsia than non-IBS patients [162].

Comment: In Japan, routine workplace health examinations revealed that the prevalence of functional dyspepsia in individuals with IBS was estimated at more than two-fold that in individuals without IBS [163].

CQ. Does IBS show high co-morbidity with gastro-esophageal reflux disease (GERD)?

- IBS patients show two times or more higher co-morbidity with GERD than non-IBS patients [163, 164].

Comment: The rate of co-morbidity depends on diagnostic criteria of IBS and GERD. Although data on patients who visit practitioners are lacking, data from a mass work place health-screening survey indicated that IBS patients show two times or more higher co-morbidity with GERD than non-IBS patients [163, 164].

CQ. Do IBS and IBD show high co-morbidity and transition with each other?

- In patients with ulcerative colitis, the odds ratio of comorbidity with IBS is 5.7 compared with controls [165]. The relative risk of transition from IBS to IBD considers high values as approximating 16.3 [166].

CQ. Does IBS show high co-morbidity with extra-intestinal disorders?

- IBS shows high co-morbidity with extra-intestinal disorders, especially fibromyalgia [167]. Other disorders like chronic fatigue syndrome, chronic pelvic pain and tempolo-mandubular joint disease require more data.

CQ. Does IBS show high co-morbidity with psychological disturbance?

- IBS patients show a high co-morbidity with psychological disturbance, especially anxiety and depression.

Comment: Almost all IBS patients who visit a clinic or hospital, or 18 % of IBS subjects in the general population, have at least one psychological disturbance [167]. There is no specific psychological disturbance that is co-morbid

with IBS, but anxiety and depression are a common co-morbidity with IBS.

CQ. Do co-morbid disorders with IBS affect QOL or the prognosis of IBS?

- FD and GERD as co-morbid disorders with IBS impair QOL [163]. Other extra-intestinal disorders or psychological co-morbidities with IBS may also impair QOL, but they require further research. Psychological co-morbidities with IBS are a possible risk factor for a bad prognosis [168].

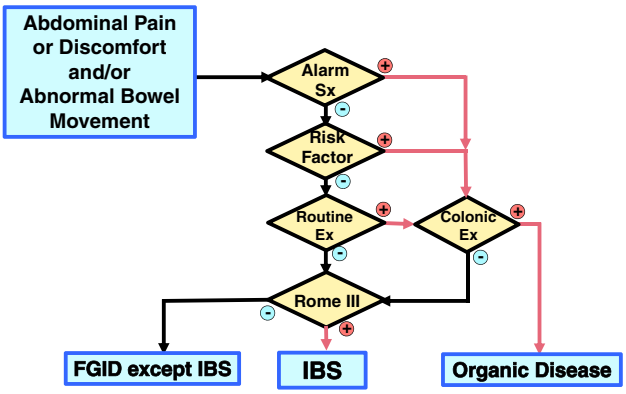

Fig. 1 Diagnostic algorithm for IBS. Check whether the answer is positive (yes) or negative (no) at the diamond. Alarm symptoms (Sx) are fever, arthralgia, bloody stool or unexpected weight loss more than 3 kg within six months. Alarm signs are palpable abdominal mass, abdominal fluctuation, or palpable mass or adhered blood in the rectal digital examination. Risk factors are age more than 50, past or family history of organic diseases of the colorectum, and patient's requirement to have colonic examination. Routine examinations (Ex) are blood chemical analyses, including plasma glucose and thyroid stimulating hormone, complete blood count, inflammatory reaction such as (high-sensitive) C-reactive protein, urinalysis, fecal occult blood test and plain abdominal X-ray. Colonic examination (Ex) will be indicated if these factors are positive. Note that positive fecal occult blood, anemia, hypoproteinemia or positive inflammatory reaction especially requires colonic examination. Colonic examination is either via colonoscopy or Ba enema, but colonoscopy is preferable. It is the clinician's responsibility to perform adequate examination to have an accurate diagnosis in patients. This guideline does not guarantee 100 % exclusion of unexpected organic diseases. Depending on the clinical situation, the following detailed examination *asterisk* may be indicated; gastrointestinal mucosal biopsy, upper GI endoscopy, upper GI series, abdominal ultrasonography, fecal ova test, stool bacterial culture, abdominal computed tomography, abdominal magnetic resonance imaging, small intestinal endoscopy, small intestinal fluoroscopy, lactose tolerance test, hydrogen breath test and so on. If negative clinical examinations and positive Rome III criteria are found, a diagnosis of IBS is made. If Rome III for IBS is negative, patients may be classified into other functional gastrointestinal disorders (FGIDs), including functional abdominal pain, functional bloating, functional constipation, functional diarrhea or unspecified functional bowel disorder. Because Rome III will be revised to Rome IV in 2016, Rome IV will be applicable after 2016. From the JSGE, Japanese IBS Guideline 2014, Nankodo, Tokyo, with permission

6. Diagnostic Algorithm in the Japanese IBS Guideline

Based on the statements above, the diagnostic algorithm for IBS in Japan (Fig. 1) is as follows. Targets are patients with chronic abdominal pain or abdominal discomfort and/or abnormal bowel movement [42]. If more than one of the alarm symptoms/signs, risk factors and routine examinations is positive, colonoscopy is indicated [46]. If all of them or colonoscopy are/is negative, Rome III criteria is applied [1]. As a result, diagnosis will be IBS or an other functional gastrointestinal disorder like functional abdominal pain syndrome, functional constipation, functional diarrhea, functional bloating, unspecified functional bowel disorder and so on. The diagnostic algorithm is well indicated for patients with lower GI symptoms for three - months or more. This guideline is not intended to manage patients with acute GI symptoms.

7. Therapeutic Algorithm in Japanese IBS Guideline

After the diagnosis of IBS, IBS patients proceed to step 1 therapy (Fig. 2). It consists of diet therapy and behavioral modification [56, 58, 64, 65, 67, 148]. Probiotics [68–77], bulking polymer [104, 105] and GI motility modifiers [103, 106–108] are independent subtype treatments. 5-HT_3 antagonist should be used for IBS-D [85–96] or diarrhea as the main feature and antidiarrheal agents, including loperamide [113–115] and cholestyramine [116], are next in line for IBS-D. GI epithelium modifier [99–102] may be used for IBS-C or constipation as the main feature and laxatives [117–121], except anthraquinones, are next in

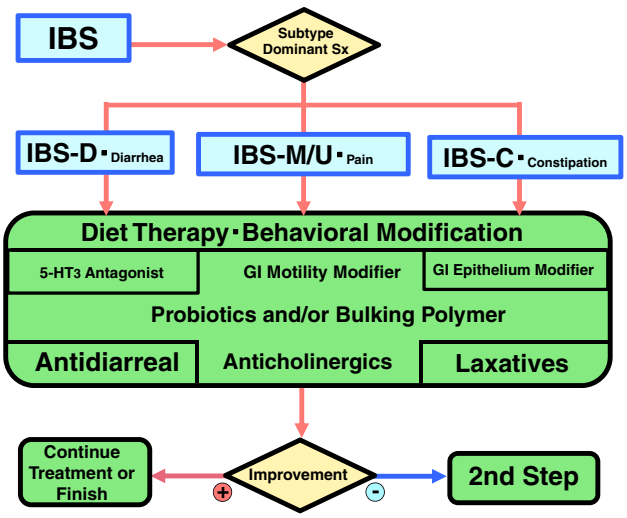

Fig. 2 The first step of the IBS therapeutic algorithm. Subtyping of IBS is necessary at the time of treatment. Based on Rome III criteria, patients are classified into IBS with diarrhea (IBS-D), mixed IBS (IBS-M), unsubtyped IBS (IBS-U) or IBS with constipation (IBS-C). Moreover, the most bothersome symptoms (Sx), including diarrhea, abdominal pain, or constipation, may be targeted. See further details in the main text. From the JSGE, Japanese IBS Guideline 2014, Nankodo, Tokyo, with permission

line for IBS-C. Anticholinergic agents may be added in IBS-M, IBS-U or in abdominal pain-dominant cases [106, 111]. After step 1 therapy for four weeks, unsatisfactory cases proceed to the second step.

Step 2 therapy begins by evaluating the role of psychosocial stress on each IBS patient (Fig. 3). A majority of IBS patients require a co-morbid psychiatric diagnosis, especially anxiety and depression [9–11, 31, 32, 167]. For IBS patients with depression, antidepressants [106, 122, 123] are indicated. For IBS patients with anxiety, antidepressants with anxiolytic action are indicated and anti-anxiety drugs [124–127] for a short duration may be helpful for relieving anxiety. In some cases, simple psychotherapy [129–131] will be added to manage psychosocial stress and negative emotion. In patients with less influence of psychosocial factors, further examination of the digestive system or other organs [48–53] is indicated to rule out organic GI or systemic diseases depending on the clinical demand. If the IBS diagnosis is accurate, prokinetics [97, 98, 159] for constipation, anti-diarrheal agents for diarrhea, antidepressants for abdominal pain, kampo medicine [138–140] and/or anti-allergic agents [149, 150] is/are used. After step 2 therapy for four weeks, unsatisfactory cases proceed to the third step.

Step 3 therapy begins by evaluating the role of psychosocial stress or psychopathology on each IBS patient

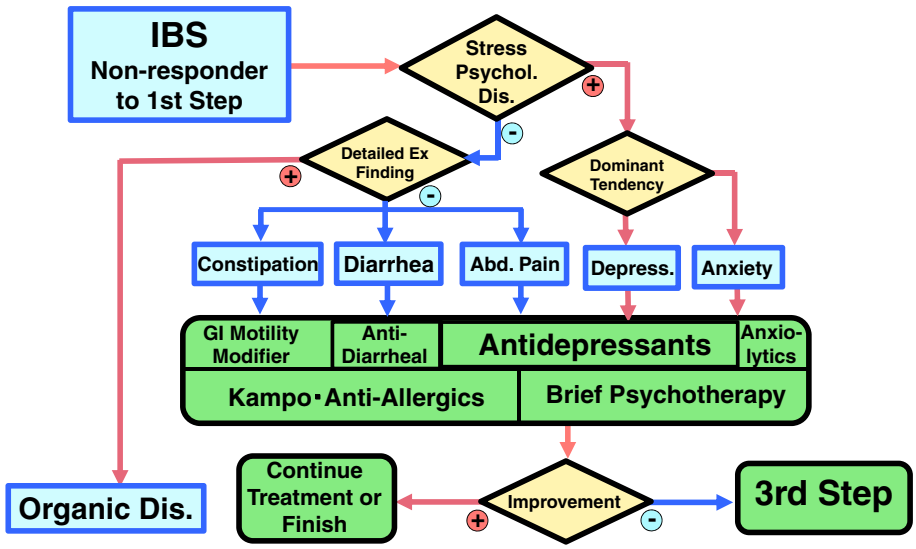

Fig. 3 The second step of the IBS therapeutic algorithm. IBS patients with moderate severity who do not respond to gut-targeted pharmacotherapy are indicative of this step. *Psychol. Dis.* psychological disturbance, *Abd. Pain* abdominal pain, *Depress.* depression. See further detail in the main text. Detailed examination (Ex) *asterisk* in Fig. 1 may be a part of this step depending on the clinical demand. *Organic Dis.* organic disease. From the JSGE, Japanese IBS Guideline 2014, Nankodo, Tokyo, with permission

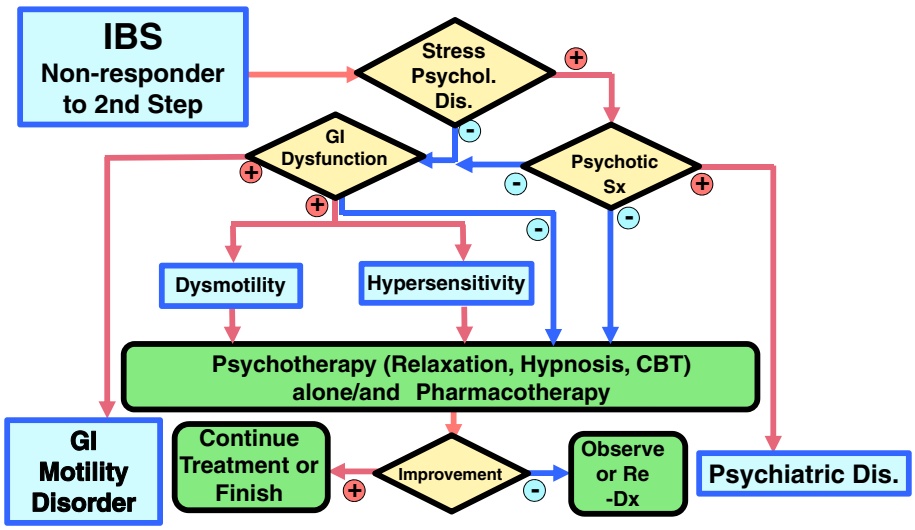

Fig. 4 The third step of the IBS therapeutic algorithm. Severe IBS patients who do not respond to usual pharmacotherapy are indicative of this step. See further detail in the main text. GI dysfunction can be judged via a GI transit study, anorectal manometry, colonic manometry or colorectal barostat examination. *Psychol. Dis.* psychological disturbance, *Psychotic Sx* psychotic symptoms, *Psychiatric Dis.* psychiatric disease, *GI Dysfunction* gastrointestinal dysfunction, *CBT* cognitive behavioral therapy, *Re-Dx* re-diagnosis. From the JSGE, Japanese IBS Guideline 2014, Nankodo, Tokyo, with permission

again. If either factor is positive, psychotic features like delusion, hallucination and personality disorders should be ruled out. Some patients require careful clinical observation for a certain duration to detect a profound psychopathology. In some cases, GI motility examination of the digestive system [12, 41, 52] is indicated to judge compatible pathophysiology of IBS, such as mild dysmotility of the lower GI tract or visceral hypersensitivity and/or to rule out severe GI motility disorders depending on the clinical situation. A majority of IBS patients usually have stress-related pathophysiology [9–14]. A combination of GI agents, psychopharmacological treatments [106, 122–128] and/or specific psychotherapy, including relaxation, hypnotherapy and cognitive behavioral therapy [131–134], will be helpful in these severe cases (Fig. 4).

Conclusion

Evidence-based clinical practice guidelines for IBS have been presented by the JSGE. Several strategies permitted for the care of IBS patients in Japan are capable of being expanded globally in the future. Clinical guidelines and consensus are the best approaches for IBS patients in Japan and they may provide great insight for IBS treatment around the world.

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Appendix

Members of the Working Committee who created and evaluated the "Evidence-based clinical guidelines for irritable bowel syndrome," JSGE.

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The Japanese Society of Gastroenterology

President: Tooru Shimosegawa (Division of Gastroenterology, Tohoku University Graduate School of Medicine)

Former President: Kentaro Sugano (Jichi Medical University)

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