CLINICAL PRACTICE GUIDELINE

Irritable Bowel Syndrome—The Main Recommendations

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SUMMARY

Background: Irritable bowel syndrome is characterized by chronic abdominal symptoms and irregular bowel movements without any cause than can be revealed by routine diagnostic assessment. In recent years, its pathophysiology has come to be much better understood, and new therapeutic approaches have been developed. These advances were taken into consideration and assessed for their relevance to clinical practice in the framework of a new interdisciplinary S3 guideline.

Methods: A systematic search of the literature retrieved a total 5573 articles, from which 243 were selected on the basis of criteria relating to their form and content, individually assessed, and summarized in evidence tables. The recommendations formulated in this way were discussed in a Delphi procedure and a consensus conference, then accordingly modified and finalized.

Results: Variable symptom constellations are caused by disturbances of gastrointestinal regulation at multiple levels. The diagnosis of irritable bowel syndrome requires both chronic bowel symptoms that interfere with everyday life and the exclusion of relevant differential diagnoses. Its treatment is based on general therapeutic principles, dietary recommendations, psychological components, and symptomatic medication. Bulking agents, laxatives, spasmolytics, loperamide, and probiotic agents are recommended (with variable recommendation strengths), as are—for selected patients— antidepressants, 5-HT4 agonists, 5-HT3 antagonists, and topical antibiotics.

Conclusion: The first German S3 guideline on irritable bowel syndrome translates up-to-date scientific knowledge as represented in current publications into concrete recommendations for diagnosis and treatment in clinical practice. In the future, it is likely that further causative pathophysiological mechanisms will be discovered; this should lead, in turn, to the development of new, causally directed treatments, which will supplement or replace the traditional, purely symptomatic treatments that are still in use today.

► Cite this as:
Andresen V, Keller J, Pehl C, Schemann M, Preiss J, Layer P: Clinical practice guideline: Irritable bowel syndrome—the main recommendations. Dtsch Arztebl Int 2011; 108(44): 751–60.
DOI: 10.3238/arztebl.2011.0751

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With the increasing knowledge on the pathogenesis, pathophysiology, and rational management of irritable bowel syndrome, the time has come to implement them in pragmatic recommendations adapted to our health care system. This was the aim of an interdisciplinary S3 guideline under the aegis of the German Society for Digestive and Metabolic Diseases (DGVS, Deutsche Gesellschaft für Verdauungs- und Stoffwechselkrankheiten) and the German Society for Neurogastroenterology and Motility (DGNM, Deutsche Gesellschaft für Neurogastroenterologie und Motilität) (*eBox 1*) (1), the main practice-relevant statements of which are presented in this article. For details of the recommendations and commentary on them, especially in relation to pediatric patients, the reader is referred to the full text of the guideline ([1], in German).

Methods

The DGVS and DGNM formed a coordination committee, which in January 2008, in consultation with the Association of Scientific Medical Societies in Germany (AWMF, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften), laid down the methodology for the guideline. The guideline group was made up of 69 representatives of various medical specialties, 26 of whom were named as authors (*eBox 1*). After the consensus conference (September 2009), a manuscript was produced, which with the agreement of all the participating medical societies was published in February 2011. For the clinical questions, a systematic literature search up to September 2008 was carried out on MedLine, PreMedLine, Psycinfo, cambase, and the Cochrane Central Register of Controlled Trials.

For this, a basic search was defined to capture all relevant publications in the field (*eBox 2*). To answer the questions specific to each working group, the working groups defined further search terms and exclusion criteria that were linked to the basic search and special methodological filters (*eBox 2*). Publications included were controlled studies and observational studies with a study time of at least 4 weeks, but not case series (formal selection). The identified literature was further selected by evaluating each publication on the basis of its title, abstract, and, if necessary, the full text for whether it was suitable to answer key questions (content selection). If questions were answered by evidence level 1 publications, it was unnecessary to draw on publications of a lower evidence level.

TABLE 1

Recommendation strengths

Strength of recommendation	Formulation	Meaning for physicians	Meaning for patients	Symbol
Strongly for	Virtually always	Most patients should receive the recommended intervention	Almost all patients would decide in favor of the recommended intervention; only a small minority would not	↑↑
Weakly for	In most/some patients	Different decisions are appropriate for different patients, depending on the patient's situation but also on personal opinions and preferences	The majority of patients (>50%) would decide in favor of the intervention, but many would not	↑
Weakly against	Rather not	Probably don't do it	The majority of patients (>50%) would decide against the intervention, but many would not	↓
Strongly against	Virtually never	Definitely don't do it	Almost all patients would decide against the recommended intervention; only a small minority would not	↓↓
Unclear	No recommendation should remain an exception to be justified. In clinical practice, a decision often has to be made despite the absence of data.			↔

Out of 5573 identified publications, 243 were selected, individually evaluated, summarized in evidence tables, and the tables made available to all participants as part of the consensus process. In the present short version of the guideline, selected publications are cited that form the basis of central recommendations; more recent studies that were not published at the time the guideline was being compiled are marked accordingly.

After iterative processing in a modified Delphi procedure, the recommendations were modified and agreed at a consensus conference. The formulation of each recommendation strength followed a defined scheme (*Table 1*)**.** Recommendations for which no consensus was reached were readdressed in a further, online Delphi round.

As an aid to comprehension, some of the statements are reproduced in this article in paraphrased and commented form. Evidence level, recommendation strength, and consensus strength are given in general form in the text and more specifically in the tables in the specific treatment sections.

The guideline was exclusively financed through the DGVS and was developed under conditions of editorial independence. All participants were required to declare potential conflicts of interest. The details of the methodology are provided in a comprehensive methods report (2).

Definition

Irritable bowel syndrome (IBS) is present when all three of the following are fulfilled:

- The patient has chronic symptoms, i.e. lasting longer than 3 months (e.g., abdominal pain, bloating), that are ascribed by both patient and physician to the gut and that are usually accompanied by altered bowel habit.
- The symptoms are the reason why the patient has consulted the physician for help and/or is worried, and are so strong that the patient's quality of life is significantly impaired by them.
- It is a precondition that no changes are present which are characteristic of other diseases that are likely to be the cause of the symptoms (strong consensus).

This new definition thus differs from all its predecessors including the Rome III consensus (e1): The hitherto obligatory symptom combination of abdominal pain and altered bowel habit has been dropped; on the other hand, the typical and often particularly distressing symptom complex of bloating and flatulence is included. For the first time the severity of the symptoms, which distinguishes them from ordinary "digestive symptoms," is mandatory for the diagnosis: Only significant impairments of quality of life indicate systematic diagnostic and therapeutic management.

Pathogenesis

In IBS, gastrointestinal motility, secretion, and perception are disturbed. Consistently, although always only in subpopulations, molecular and cellular alterations at the mucosal level, changes in gut flora, disturbances of superordinated regulatory systems, and increased prevalence of psychological co-morbidities are demonstrated. Interactions/interrelationships between causal and secondary alterations are unclear. These changes have been demonstrated in separate studies and are not IBS-specific, and therefore they do not allow a specific diagnosis to be made. However, they do contribute to an understanding of the causative pathological

TABLE 2

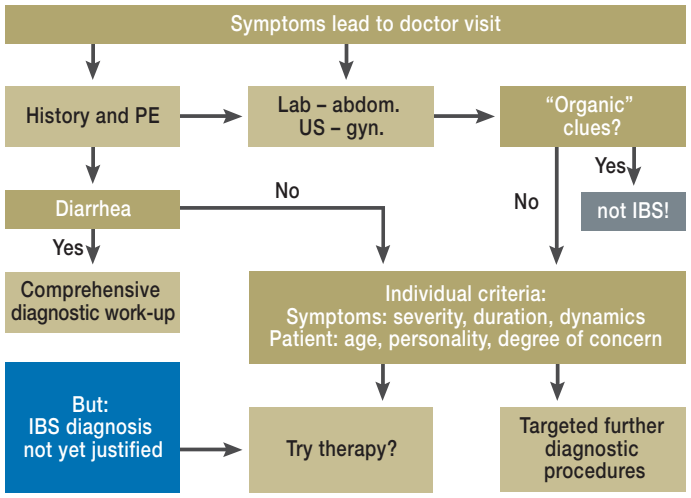
Pathogenic factors and proven changes in Irritable Bowel Syndrome*[1]

A) Pathogenetic factors	Comments
Development of IBS from bacterial enteritis ("postinfectious IBS")	– The risk of IBS is 8 to 15 times higher after bacterial enteritis– The more severe the acute illness, the higher the risk – Up to 30% of those who have acute bacterial enteritis may develop IBS that persists for years
Altered intestinal flora	– Alteration of gut flora has been shown (not yet known is whether this is a cause or a consequence of disturbed function) – IBS developing after bacterial infection of the gut (see above) – IBS developing after antibiotic therapy – Gut flora are important for barrier function and mucosal immune system (see below) – IBS symptoms are improved by probiotics or topical antibiotics
Personal predisposition	– Probable mechanisms: genetic factors; learned behavioral patterns
Psychological factors	– Traumatic events (incl. abuse), psychological co-morbidity (e.g., depression, anxiety disorder), and stress may cause exacerbation; in some subgroups they may even be causative
B) Proven changes	**Comments**
Altered motility	– Increased transit time in constipation-dominant IBS – Reduced transit time in diarrhea-dominant IBS – Disturbed gas transit, mainly through the small intestine, but also in the colon (in addition to increased gas production)
Altered sensitivity	– Reduced pain threshold during rectal balloon distension (barostat) – Altered cerebral processing of visceral stimuli
Mucosal permeability	– Reduced tissue resistance – Reduced barrier function – Reduced expression of tight junction protein ZO-1
Immune cells in mucosal biopsies – Intraepithelial T cells – Mast cells – Nerve–mast cell association	 – Increased number of CD3+ lymphocytes – Increased number and reactivity of c-kit-positive and tryptase-positive cells – Stronger local association between nerves and mast cells
Immune mediators in mucosal biopsies – Tryptase and other proteases – Histamine – Proteases – Cytokines – Defensins	 – Increased release – Increased release – Increased released in diarrhea-dominant IBS – Increased release of IL1β in postinfectious IBS – Increased release of human β-defensin 2
Nerves in mucosal biopsies – Nerve fibers – Visceral afferents	 – Increased number of PGP 9.5-positive nerve fibers, increased expression of substance P – Increased expression of TRPV1
Supernatants of mucosal biopsies – Neural sensitization	– Activation of enteric nervous system by histamine, serotonin, and proteases – Activation of visceral afferents
Immune mediators in the blood – Cytokines – HPA axis – Antibodies	 – Raised Th2 cytokine concentration, raised IL6, IL8, TNFα, and IL1β concentrations – Raised ACTH and cortisol concentrations – Antibodies against bacterial flagellin
Serotonin metabolism – Serotonin concentration – Enterochromaffin cells – Serotonin reuptake transporters (SERTs)	 – Raised plasma serotonin concentration in diarrhea-dominant IBS – Increased number in mucosal biopsies – Altered SERT expression and function
Gene expression – Mucosa	 – Increased expression of DKFZP564O0823 (presumed function: mucus production)
Stool – Mediators originating from <<please confirm>> immune cells or microbiota – Microbiota	 – Increased concentration of human α-defensin, proteases, S100A12, lactoferrin – Unstable microbiota

*[1] Changes shown in separate studies and each time only in subpopulations of the IBS patients; they are not IBS-specific and therefore do not allow a positive diagnosis

ACTH, adrenocorticotropic hormone; HPA axis, hypothalamic-pituitary-adrenal axis; IL, interleukin; ZO-1, zonula occludens 1; PGP, protein gene product (pan-neuronal marker); TRPV1, transient receptor potential vanniloid receptor 1 (visceral afferent marker)

FIGURE 1



Diagnostic work-up in first-time investigation of chronic abdominal symptoms that could point to irritable bowel syndrome

PE, physical examination (including rectal); abdom. US, abdominal ultrasonography; gyn., gynecological examination; IBS, irritable bowel syndrome

BOX 1

Laboratory investigations in patients with unexplained chronic abdominal symptoms

- **Generally recommended laboratory tests**
  - Full blood count
  - Erythrocyte sedimentation rate (ESR)/C-reactive protein (CRP)
  - Urine analysis
- **Optional laboratory tests on an individual basis**
  - Serum electrolytes, renal retention values, hepatic and pancreatic enzymes
  - TSH
  - Blood glucose/HbA_{1c}
  - Fecal microbiology (especially in patients with diarrhea)
  - Celiac disease antibodies (anti-transglutaminase antibodies)
  - Calprotectin A/lactoferrin

mechanisms (*Table 2*), and thus form the foundation for research into new treatment options (3).

Diagnosis

IBS is basically a clinical diagnosis. Careful history taking to record and classify the complex of symptoms is key. The diagnosis can be made on this basis so long as other differential diagnoses can be reliably ruled out.

Thus, confirmation of the diagnosis requires two components:

- The history and pattern of symptoms suggest IBS.
- Other relevant candidate diagnoses can be specifically ruled out on the basis of symptoms, especially when red flag symptoms are present (evidence level B, recommendation strength ↑↑, strong consensus).

Once a reliable initial diagnosis has been made, so long as no new aspects occur, no repeat diagnostic procedure should be undertaken (evidence level A, recommendation strength ↑↑, strong consensus)

Early confirmed diagnosis is important to avoid delayed diagnosis of other, more serious possible causes of the symptoms; this is particularly the case when the symptoms have not been present for very long (4) (evidence level A, recommendation strength ↑↑, strong consensus). If diarrhea is the main symptom, an irritable bowel is usually not the cause (5). However, in more than 10% of cases other constellations of symptoms without alarm symptoms or signs of inflammation are caused by an "organic" disease.

On the other hand, celiac disease (6, 7, e2), chronic inflammatory bowel disease (4, 8), and also colon and ovarian carcinoma (4, 9–11, e3, e4) and chronic

BOX 2

Recommendations relating to nutrition in IBS

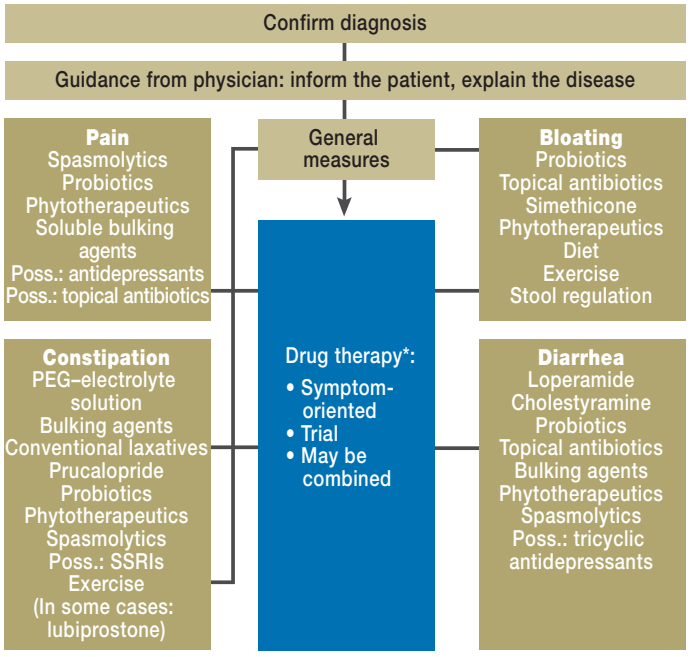
- Investigate for carbohydrate malabsorption syndrome (e.g., lactose fructose, sorbitol), and, if evidence is shown, trial avoidance of the relevant sugar
- Investigate for other food intolerances and trial avoidance of any foods indicated, after extensive dietary advice
- Trial of a reduced-gluten diet is a possibility in some adults with IBS without signs of celiac disease
- During elimination dieting, regular monitoring is essential to prevent malnutrition; the diet should be permanently continued only if the patient shows response to treatment
- Consider the use of bulking agents in patients with constipation
- Consider the use of probiotics; choose strains according to symptoms

TABLE 3

Important differential diagnoses of IBS in patients with chronic abdominal IBS-like symptoms

Main symptom	Important differential diagnoses (among others)
Diarrhea	Chronic infectious enterocolitis, e.g., bacterial, parasitic, or viral (e.g., cytomegalovirus [CMV] with or without immunosuppression) pathogens; fungal infections (e.g., histoplasmosis in HIV)
	Crohn's disease
	Ulcerative colitis
	Celiac disease/sprue
	Bacterial infection of the small intestine
	Symptomatic carbohydrate malabsorption (e.g., lactose or fructose malabsorption)
	Microscopic colitis
	Bile acid malabsorption
	Clostridium difficile colitis
	Motility disorders of the small intestine
	Exocrine pancreatic insufficiency
	Autonomic neuropathy (diabetes)
	Drug intolerance
	Food allergy
	Hyperthyroidism
	Incontinence
	Functionally active neuroendocrine tumor
	Colorectal carcinoma (paradoxical diarrhea)
Pain	Crohn's disease
	Ulcer
	Gastrointestinal tumor
	Mesenteric ischemia
	Porphyria
	Endometriosis
	Ovarian tumor
	Small-bowel stenoses (e.g., radiogenic, adhesions)
	Postoperative functional impairment (e.g., adhesions)
	C1-esterase inhibitor deficiency
	Intestinal motility disorders (e.g., chronic intestinal pseudo-obstruction)
Constipation	Adverse drug effect
	Hypothyroidism
	Colorectal carcinoma (alternating with paradoxical diarrhea in patients with symptoms of stenosis)
	Chronic diverticulitis
	Motility disorders, e.g., neuropathic colonic paresis (slow-transit constipation)
	Functional or structural defecation disorders
Bloating, distension	Bacterial infection (small-intestinal bacterial overgrowth; often secondary, e.g., in small-bowel diverticula, motility disorders, etc.)
	Carbohydrate malabsorption (e.g., symptomatic lactose and/or fructose malabsorption)
	Postoperative functional disorders (e.g., adhesions)

FIGURE 2



The management of IBS involves reliable confirmation of the diagnosis, patient guidance, including explanation of the disease, general measures, and symptom-oriented medical therapy. *It must be borne in mind that many new drugs whose effectiveness has been confirmed are only licensed outside Germany, or are not licensed in Germany for this indication (off-label). Poss., possibly

gastrointestinal motility disorders (12) often show typical "irritable bowel symptoms" as the dominant—often the first or only—clinical manifestation in 40% to 85% of those affected.

A confirmed diagnosis that convinces both the patient and the physician (*Figure 1*) also has significance for treatment and the economics of health: a better relationship of trust and the reassurance conveyed by it makes an essential contribution to the success of treatment. The consequence is a reduction in "doctor shopping" and subsequent diagnostic procedures. Given the chronic nature of the disease, this effect is of great importance in the long-term management.

In an unknown patient, a basic diagnostic procedure must always be carried out (evidence level D, recommendation strength ↑↑, strong consensus) and, depending on the history and pattern of symptoms, be supplemented by individually tailored further diagnostic steps in a carefully targeted manner (evidence level D, recommendation strength ↑, strong consensus). Overdiagnosis and the indiscriminate use of resources should be avoided.

The focus is on a careful history (evidence level A, recommendation strength ↑↑, strong consensus) and the physical examination (evidence level D, recommendation strength ↑↑, strong consensus), supplemented by basic laboratory testing (evidence

TABLE 4

Recommendations for treatment of pain in IBS

Therapy	Try therapy	
Peripheral analgesics	Rather not	[Evidence level B (paracetamol), evidence level D for other drugs, recommendation strength ↓, strong consensus]
Opiates and opiate agonists	Virtually never	[Evidence level A for kappa agonists, evidence level D for μ- agonists and classical opiates, evidence level A for opiate antagonists, recommendation strength ↓↓, strong consensus]
Spasmolytics	In most patients	[Evidence level A, recommendation strength ↑, strong consensus]
Soluble fiber	In some patients	[Evidence level A, recommendation strength ↑, strong consensus]
Tricyclic antidepressants	In some patients	[Evidence level A, recommendation strength ↑, strong consensus]
SSRIs	In some patients	[Evidence level A, recommendation strength ↑, strong consensus]
5-HT3 antagonists	In few selected patients	[Evidence level A, recommendation strength ↑, consensus]
Probiotics	In some patients	[Evidence level A, recommendation strength ↑, strong consensus]
Antibiotics	Rather not	[Evidence level A, recommendation strength ↓, consensus]
Pregabalin/gabapentin	Rather not	[Evidence level B , recommendation strength ↓, strong consensus]
Phytotherapeutics	In some patients	[Evidence level A, recommendation strength ↑, strong consensus]
Aloe vera	Rather not	[Evidence level A, recommendation strength ↓, strong consensus]
Pancreatic enzymes	Virtually never	[Evidence level D, recommendation strength ↓↓, strong consensus]

level B, recommendation strength ↑↑, strong consensus) (*Box 1*), abdominal ultrasound (evidence level D, recommendation strength ↑, consensus), and, in women, gynecological examination (evidence level B, recommendation strength ↑↑, strong consensus).

After these have been carried out, if results are normal, treatment may be started on a trial basis even without a confirmed diagnosis (see below) (evidence level D, recommendation strength ↑, consensus). This should be decided on an individual basis and is justified particularly in patients with mild, non-progressive symptoms, but does not allow a diagnosis of IBS to be made (*Figure 1*).

In patients with chronic diarrhea as an important symptom, detailed diagnostic work-up including pathogen identification in the stool and endoscopic and functional diagnostic examinations (with staged biopsies) are indicated (evidence level A, recommendation strength ↑↑, strong consensus) (*Figure 1*).

Confirmation of IBS in an adult requires an ileocolonoscopy (evidence level D, recommendation strength ↑, consensus).

The diagnostic procedure should be supplemented on an individual basis by endoscopic, imaging, functional diagnostic, and, if relevant, other procedures in order to rule out other candidate diagnoses (see *Table 3*) that can cause symptoms typical of IBS (evidence level B, recommendation strength ↑↑, strong consensus). The criteria for this are the intensity and pattern of symptoms, patient age, duration of symptoms, symptom dynamics, and a psychological assessment of the patient. Food intolerances can be tested by trialing targeted elimination diets (evidence level D, recommendation strength ↑, consensus); testing of immunoglobulin-G titers for food allergens (evidence level D, recommendation strength ↓, consensus) and determination of quantitative parameters of stool flora (e.g., "intestinal ecograms") should not be carried out (evidence level D, recommendation strength ↓↓, consensus).

Treatment

General principles of management

It is important to provide the patient with a comprehensible pathophysiological model of the disease and the management plan. Ruling out possible more threatening differential diagnoses and establishing a relationship of trust between physician and patient will both promote treatment success (13). Individual triggering factors should be identified and taken into account (evidence level D, recommendation strength ↑↑, strong consensus).

The measure of any treatment plan is how far symptoms improve and how well the patient tolerates it, and all treatments are trial treatments at first because it is impossible to predict the response to treatment in any particular case. This should be discussed with the patient beforehand. Any treatment regime that is successful can be continued, changed to a long-term or as-needed regimen, or interrupted for a trial withdrawal. If treatment success is inadequate, various drugs (and non-drug treatments) may be used in succession or in combination. Ineffective drugs should be terminated after 3 months at the latest (evidence level D, recommendation strength ↑, strong consensus).

After careful individualized weighing up of the risks and benefits, in some cases, especially in patients with severe symptoms that are refractory to treatment, off-label therapies may be worthwhile, if current scientific knowledge suggests there is reason to expect relevant therapeutic utility. The same applies to active substances that to date are only licensed abroad, although in this case consultation with a specialized center is advisable (evidence level D, recommendation strength ↑, consensus).

As to nutrition and lifestyle there are no general prescriptions. However, nutritional and behavioral advice should be given to eliminate individual symptom triggers (e.g., stressors, defined foods, lack of exercise or sleep, and so on). Likewise, psychological influential factors and co-morbidities (e.g., depressive disorders) and extraintestinal symptoms (tendency to somatization!) should be ascertained.

Alternative therapies cannot be recommended at present because of a lack of data; complementary therapies may be considered in individual cases (evidence level A* for acupuncture, otherwise C/D; recommendation strength ↓; strong consensus). *A meta-analysis of several acupuncture studies found no acupuncture-specific effect on irritable bowel syndrome (e5).

Nutritional recommendations

Although no general dietetic measures are recommended, individualized advice orientated to the existing symptoms and individual intolerances should be given (*Box 2*) (evidence level B, recommendation strength ↑, strong consensus).

Psychological co-morbidities

To register the psychological co-morbidities that are often present in patients with IBS, it is often enough simply to ask about anxiety disorders and depressive symptoms, and (careful!) exploration of trauma and abuse. If appropriate, the patient should be referred for professional psychiatric/psychological/psychosomatic examination and/or care (evidence level D, recommendation strength ↑, strong consensus). Any signs of relevant psychosocial stress also indicate psychological diagnostic steps and possibly psychotherapy. At the same time, general medical care should be continued (evidence level A, recommendation strength ↑↑, consensus).

At the general and specialist medical level, basic psychotherapeutic intervention can often be carried out to favorable effect, e.g., using self-help strategies (evidence level A, recommendation strength ↑, strong consensus). Pure relaxation therapies (autogenic training, etc.) should not be carried out as monotherapy, but should be combined with other measures (evidence level B, recommendation strength ↓, consensus). More costly and time-consuming psychological techniques (gut-directed hypnosis, cognitive behavioral therapy, psychodynamic therapy) are effective and should be integrated in an interdisciplinary therapy plan (evidence level A, recommendation strength ↑, strong consensus). Antidepressants may be indicated in the presence of psychological co-morbidities (anxiety disorder, depression) (evidence level A, recommendation strength ↑, strong consensus). Tricyclic antidepressants to treat the irritable bowel symptoms (diarrhea, pain; beware of constipation) should be given at doses lower than the usual (evidence level A, recommendation strength ↑, strong consensus); selective serotonin reuptake inhibitors (SSRIs) in particular can also be given in constipation-dominant IBS (evidence level B, recommendation strength ↑, consensus). However, irritable bowel symptoms seem not to respond to antidepressants in the absence of psychological co-morbidities.

Targeted symptom-orientated therapy

General treatment measures including confirmation of the diagnosis and patient information about the disease can be supplemented with symptom-orientated drug treatment (evidence level D, recommendation strength ↑↑, strong consensus) (*Figure 2*).

TABLE 5

Recommendations for the treatment of diarrhea in IBS

Therapy	Try therapy	
Loperamide	In some patients	[Evidence level A, recommendation strength ↑, strong consensus]
Racecadotril	Cannot be recommended	[Evidence level D, recommendation strength ↔, strong consensus]
Bulking agents (soluble fiber)	In some patients	[Evidence level B, recommendation strength ↑, strong consensus]
5-HT3 antagonists	In few selected patients	[Evidence level A, recommendation strength ↑, consensus]
Cholestyramine	In some patients	[Evidence level C, recommendation strength ↑, strong consensus]
Probiotics	In some patients	[Evidence level A, recommendation strength ↑, strong consensus]
Antibiotics	Rather not	[Evidence level C, recommendation strength ↓, strong consensus]
Phytotherapeutics	In some patients	[Evidence level A, recommendation strength ↑, consensus]
Aloe vera	Rather not	[Evidence level A, recommendation strength ↓, strong consensus]
Spasmolytics	In some patients	[Evidence level A, recommendation strength ↑, consensus]
Traditional Chinese medicine/herbal medicine	Rather not	[Evidence level B, recommendation strength ↓, consensus]

In this guideline a conscious decision was made not to give effect sizes for individual therapies, since these would reflect neither the scientific evidence nor practical reality:

- For many therapies insufficient study quality means that no adequate data exist.
- There is a general inhomogeneity of study populations and of the criteria of treatment response (pain, irregular bowel habit, bloating, etc.), which is due to the multiplicity of symptoms, their variability, and differences in pathological mechanisms.
- The typically fluctuating course of symptoms often suggests falsely high rates of response to placebo; on the other hand, all therapies show variable rates of non-responders. For this reason, even for therapies that are highly effective in subgroups, only moderate response rates are documented in the overall patient population. In most cases, however, the relevant subgroup analyses were not carried out. Thus, the moderate response rates do not allow meaningful conclusions to be drawn about the possible success of treatment in any individual patient.

Typical examples of the distribution of the published effect sizes of individual therapies compared to placebo exist for, among others:

TABLE 6

Recommendations for the treatment of constipation in IBS

Therapy	Try therapy	
Bulking agents in the form of soluble gel-forming agents (e.g., psyllium)	In most patients	[Evidence level A, recommendation strength ↑, strong consensus]
Osmotis laxatives of the macrogol type	In some patients	[Evidence level B, recommendation strength ↑, strong consensus].
Other osmotic or stimulating laxatives	In some patients	[Evidence level C, recommendation strength ↑, strong consensus]
Prucalopride	In some patients in cases (refractory to other treatment)	[Evidence level B, recommendation strength ↑, consensus]
Domperidone	Rather not	[Evidence level B, recommendation strength ↓, strong consensus]
Lubiprostone	In some patients (if available)	[Evidence level A, recommendation strength ↑, consensus]
Antibiotics	Rather not	[Evidence level A, recommendation strength ↓, consensus]
Probiotics	In some patients	[Evidence level A, recommendation strength ↑, strong consensus]
Phytotherapeutic STW 5	In some patients	[Evidence level B, recommendation strength ↑, strong consensus]
Other phytotherapeutics	Rather not	[Evidence level B, recommendation strength ↓, strong consensus]
Spasmolytics	In some patients	[Evidence level A, recommendation strength ↑, strong consensus]
SSRIs	In some patients in IBS-C that is refractory to treatment, esp. with pain ± psychol. co-morbidity	[Evidence level B, recommendation strength ↑, consensus]

IBS-C, constipation-dominant IBS; SSRIs, selective serotonin reuptake inhibitors

TABLE 7

Recommendations for the treatment of bloating/abdominal distension/meteorism/flatulence

Therapy	Try therapy	
Probiotics	In some patients	[Evidence level B, recommendation strength ↑, strong consensus]
Rifaximin	In some patients	[Evidence level A, recommendation strength ↑, consensus]
Phytopharmaceuticals	In some patients	Evidence level B, recommendation strength ↑, strong consensus]
Cholinergics/Parasympathomimetics	Rather not	[Evidence level A, recommendation strength ↓, strong consensus]
Antifoaming agents	In some patients	[Evidence level C, recommendation strength ↑, strong consensus]
Pankreatic enzymes	Virtually never	[Evidence level D, recommendation strength ↓↓, strong consensus]
Analgesics	Rather not	[Evidence level B, recommendation strength ↓, strong consensus]
Tricyclic antidepressants and SSRIs	Rather not	[Evidence level B, recommendation strength ↓, consensus]

SSRIs, selective serotonin reuptake inhibitors

- Probiotics, with moderate (!) rates of symptom improvement between 0% and 88%, not only in dependence on the study preparation and end points, but also within fixed study protocols (14, 15).
- Antidepressants, about the fundamental effectiveness of which for irritable bowel symptoms there are completely contradictory assessments: calculated overall effects range from ineffective (tending to poorer) to significantly effective (16, 17).

The most important therapy recommendations in relation to main symptom are summarized below; details of formulations, recommendation strengths, evidence levels, and strength of consensus are given in the accompanying tables.

Pain (*Table 4*): Pain often responds to spasmolytics (butylscopolamine, mebeverine, peppermint oil) (18, e6) or probiotics (14, 15) as a basic therapy; in regard to the latter it is still unclear which preparations ameliorate which symptoms, so failures of treatment attempts are to be expected at the outset. Soluble bulking agents may also trigger symptom exacerbations in some cases. In some cases antidepressants may be tried (especially in patients with psychological co-morbidity) (17), or phytotherapeutics (e.g., STW 5), or, especially in patients with diarrhea, 5-HT_3 antagonists (19).

Classical "analgesics" (acetylsalicylic acid, paracetamol, non-steroidal anti-inflammatories, etc.) are generally unsuitable, as are opioids and opioid agonists (e7). Topical antibiotic therapy (rifaximin) is not yet recommended in the guideline, but randomized studies that have now been published indicate that they can effect lasting amelioration of symptoms in non-constipated patients with IBS (20).

Diarrhea (*Table 5*): In addition to classical antidiarrhetics (such as loperamide [e8]), cholestyramine, soluble bulking agents, or probiotics can be helpful. It can also be worth trying phytotherapeutics (e.g., STW 5) or spasmolytics (e.g., mebeverine, butylscopolamine, peppermint oil) or, especially where there is psychological co-morbidity, tricyclic antidepressants. Where symptoms are severe and refractory to treatment, a selective 5-HT_3 antagonist (e.g., alosetron [19]) may be used, but only after careful weighing of the risks versus the benefits, because of its very rare adverse effects (ischemic colitis, severe constipation) (21). A subgroup of patients respond well to rifaximin (20) (see above), although this is not yet recommended in the guideline.

Constipation (*Table 6*): In patients with constipation, the pathological mechanism should be identified as a first step; in particular, secondary forms of constipation (drug effects, underlying diseases) and impaired anorectal function (defecation disorders) should be ruled out.

Osmotic laxatives of the macrogol type are the most effective and best tolerated (e9). Water-soluble bulking agents are also suitable, but a watch must be kept for increased pain and/or bloating (e6). Other laxatives can

also be tried, according to how effective they are and how well they are tolerated. If adverse effects are experienced or symptoms increase, the new prokinetic prucalopride should be used (22, 23).

Other therapeutic approaches to try include probiotics, phytotherapeutics (STW 5), spasmolytics, and SSRIs; tricyclic antidepressants should be avoided in patients with constipation. In some cases lubiprostone, a chloride channel activator, may be tried, bearing in mind any contraindications and its restricted availability (it is licensed in Switzerland and the USA). The guanylate cyclase-C agonist linaclotide, which has been shown to be effective in constipation-dominant IBS (24), is expected to be licensed soon.

Bloating/abdominal distension/meteorism/flatulence (*Table 7*): Most patients also suffer from considerable—often predominant—symptoms in the form of bloating, meteorism, and flatulence, the treatment of which is therefore very important.

Improving constipation or diarrhea often also improves gas problems (evidence level A, recommendation strength ↑, strong consensus). An effective measure is modulation of the intestinal flora with probiotics (14, 25) or the topical antibiotic refaximin (20). Less well proven are phytopharmaceuticals or antifoaming agents (simethicone, dimethicone).

Conflict of interest statement

Dr. Preiss has received consultancy fees from Essex, authorship, co-authorship, and reviewing fees from Medac, and reimbursement of travel and accommodation costs together with lecture fees from Falk.

Professor Schemann has received consultancy and lecture fees from Shire and Steigerwald. He has also received research funding into a third-party account from Steigerwald.

Dr. Pehl has received consultancy fees from Movetis/Shire. He has had attendance fees at educational events and conferences and travel costs reimbursed by Falk, Lilly, Shire, Merckle-Recordati, Abbott, Essex, Sanofi-Aventis, Novo Nordisk, and Astra Seneca. He has received lecture fees from Buck Elektromedizin, Falk, Lilly, Movetis, and Shire. He has received research funding into a third-party account from Fresenius and Medtronic.

Professor Layer has received consultancy fees from Abbott, Solvay, Shire, and Norgine. He has had travel and accommodation costs reimbursed by Shire and Norgine. He has also received lecture fees from Falk, Movetis/Shire, Abbott/Solvay, Axcan, Boehringer, and Novartis. He has received fees for commissioned clinical studies by Axcan and Solvay.

Dr. Andresen has received consultancy and lecture fees and reimbursement of travel and accommodation costs and attendance fees at educational events and conferences from Norgine, Falk, Axcan, Abbott/Solvay and Shire/Movetis.

Dr. Keller has had attendance fees and travel and accommodation costs relating to lectures reimbursed by Aptalis Pharma and Shire. She has also received lecture fees from these companies.

Manuscript received on 1 July 2011, revised version accepted on 1 August 2011.

Translated from the original German by Kersti Wagstaff MA.

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CLINICAL PRACTICE GUIDELINE

Irritable Bowel Syndrome—The Main Recommendations

Viola Andresen, Jutta Keller, Christian Pehl, Michael Schemann, Jan Preiss, Peter Layer

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CLINICAL PRACTICE GUIDELINE

Irritable Bowel Syndrome—The Main Recommendations

Viola Andresen, Jutta Keller, Christian Pehl, Michael Schemann, Jan Preiss, Peter Layer

eBOX 1

Members of the guideline group

- **Participating medical specialist societies**

Coordination

– German Society for Digestive and Metabolic Diseases (DGVS, Deutsche Gesellschaft für Verdauungs- und Stoffwechselkrankheiten)

in coordination with

– German Society for Neurogastroenterology and Motility (DGNM, Deutsche Gesellschaft für Neurogastroenterologie & Motilität

In collaboration with

– German Society for Internal Medicine (DGIM, Deutsche Gesellschaft für Innere Medizin)
– Association of German Gastroenterologists in Private Practice (bng, Berufsverband Niedergelassener Gastroenterologen)
– Society for Pediatric Gastroenterology and Nutrition (GPGE, Gesellschaft für Pädiatrische Gastroenterologie und Ernährung)
– German Society for Nutritional Medicine (DGEM, Deutsche Gesellschaft für Ernährungsmedizin)
– German Society for General and Visceral Surgery (DGAV, Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie)
– German College of General Practitioners and Family Physicians (Deutsche Gesellschaft für Allgemein- und Familienmedizin)
– German Society for the Study of Pain (DGSS, Deutsche Gesellschaft zum Studium des Schmerzes)
– German Society for Behavioral Medicine and Behavior Modification (DGVM, Deutsche Gesellschaft für Verhaltensmedizin und Verhaltensmodifikation)
– German Society of Psychosomatic Medicine and Medical Psychotherapy (DGPM, Deutsche Gesellschaft für Psychosomatische Medizin und Ärztliche Psychotherapie)
– German Society for Tropical Medicine and International Health (DTG, Deutsche Gesellschaft für Tropenmedizin und Internationale Gesundheit)
– German Society for Naturopathy (Deutsche Gesellschaft für Naturheilkunde)
– German Irritable Bowel Self-Help (Deutsche Reizdarmselbsthilfe e. V.) (patient organization)

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eBOX 2

Example of a literature search (working group on treatment of constipation and bloating in IBS)

- **Basic search**

((“Colonic Diseases, Functional”[MeSH] NOT “Colonic Pseudo-Obstruction”[MeSH]) OR “functional bowel” OR (“functional gastrointestinal” NOT “dyspepsia”[MeSH]) OR bloat* OR flatulence OR “irritable bowel” OR “functional constipation” OR “functional abdominal pain” OR “functional diarrhoea” OR “functional diarrhea”)(((((OR dyspepsia))))) {working groups 4, 6 and 9} AND ((German[LA] OR English[LA]) NOT (letter[PT] OR editorial[PT] OR historical article[PT] OR comment[PT] OR case reports[PT]) NOT (animals[MeSH] NOT humans[MeSH])) AND 1 : 2008/09/30[PDAT])) AND (systematic[SB] OR (randomized controlled trial[PT] OR controlled clinical trial[PT] OR (clinical trial[PT] OR randomized[TIAB] OR placebo[TIAB] OR dt[SH] OR randomly[TIAB] OR trial[TI] OR groups[TIAB]OR (epidemiologic studies[MeSH] OR “case control studies”[MeSH] OR “cohort studies”[MeSH] OR case control[TW] OR (cohort[TW] AND (study[TW] OR studies[TW])) OR Cohort analy*[TW] OR (follow up[TW] AND (study[TW] OR studies[TW])) OR (observational[TW] AND (study[TW] OR studies[TW])) OR longitudinal[TW] OR retrospective[TW] OR cross sectional[TW] OR “cross sectional studies”[MeSH]) OR ((economic[TIAB] AND (evaluation* OR analys*)) OR pharmacoeconomi* OR health economi* OR cost benefit* OR cost containment* OR cost effective* OR cost minimi* OR cost utilit* OR “costs and cost analysis”[MeSH] OR “economics”[MeSH]))

- **Sample specific search strategy (working group 8, treatment of constipation and bloating in IBS) linked to the above basic search**

“Complementary Therapies”[Mesh] OR “Neurotransmitter Agents”[Mesh] OR “Serotonin Antagonists”[Mesh] OR “Receptors, Serotonin, 5-HT4”[Mesh] OR “ATI 7505 “[Substance Name] OR “Receptors, Adrenergic, alpha-2”[Mesh] OR “Clonidine”[Mesh] OR “Somatostatin”[Mesh] OR “Octreotide”[Mesh] OR “alvimopan” [Substance Name] OR “Receptors, Opioid”[Mesh] OR “Receptors, Corticotropin-Releasing Hormone”[Mesh] OR “lubiprostone” [Substance Name] OR “Cholecystokinin”[Mesh] OR “MEN 11420” [Substance Name] OR “SR 48968” [Substance Name] OR “dexloxiglumide” [Substance Name] OR “Cholinergic Antagonists” [Mesh] OR “Muscarinic Antagonists”[Mesh] OR “Antidiarrheals”[Mesh] OR “Loperamide”[Mesh] OR “Loperamide”[Mesh] OR “Benzodiazepines”[Mesh] OR “Anti-Bacterial Agents”[Mesh] OR “Neomycin”[Mesh])OR “Probiotics”[Mesh] OR “Parasympatholytics”[Mesh] OR “Dicyclomine”[Mesh] OR “Trimebutine”[Mesh] OR “Dicyclomine”[Mesh] OR “mebeverine” [Substance Name] OR “DA 3177” [Substance Name] OR “octylonium” [Substance Name] OR “pinaverium” [Substance Name] OR “Desipramine”[Mesh] OR “Amitriptyline”[Mesh] OR “Doxepin”[Mesh] OR “Trimipramine”[Mesh])OR “Mianserin”[Mesh] OR “Paroxetine”[Mesh] OR “Citalopram”[Mesh] OR “Antidepressive Agents”[Mesh] OR “Dietary Fiber”[Mesh] OR “Psyllium”[Mesh] OR “Enema/therapy”[Mesh] OR “Laxatives”[Mesh]

- **Number of publications**

Basic search: 5573
Linked to the working group 8 strategy: 1103
After selection according to content and method: 62