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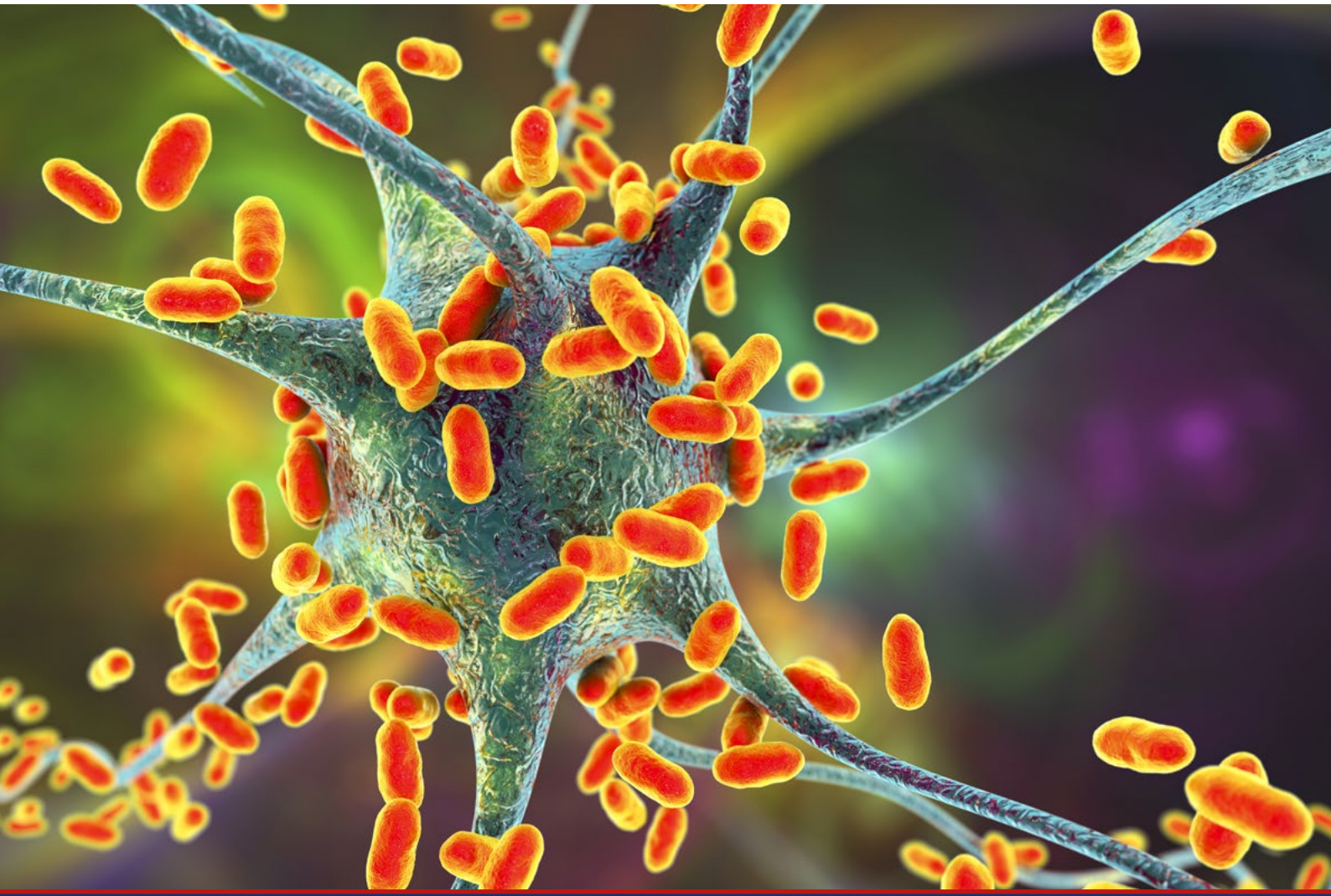
Irritable Bowel Syndrome (IBS)



Causes and approaches to individualized therapy

Prof. Dr. Burkhard Schütz

Irritable Bowel Syndrome (IBS)

Causes and approaches to individualized therapy

Irritable bowel syndrome (IBS) is probably the most common disease of the gastrointestinal tract. It is diagnosed in about 50% of patients who consult a doctor because of gastrointestinal complaints [1].

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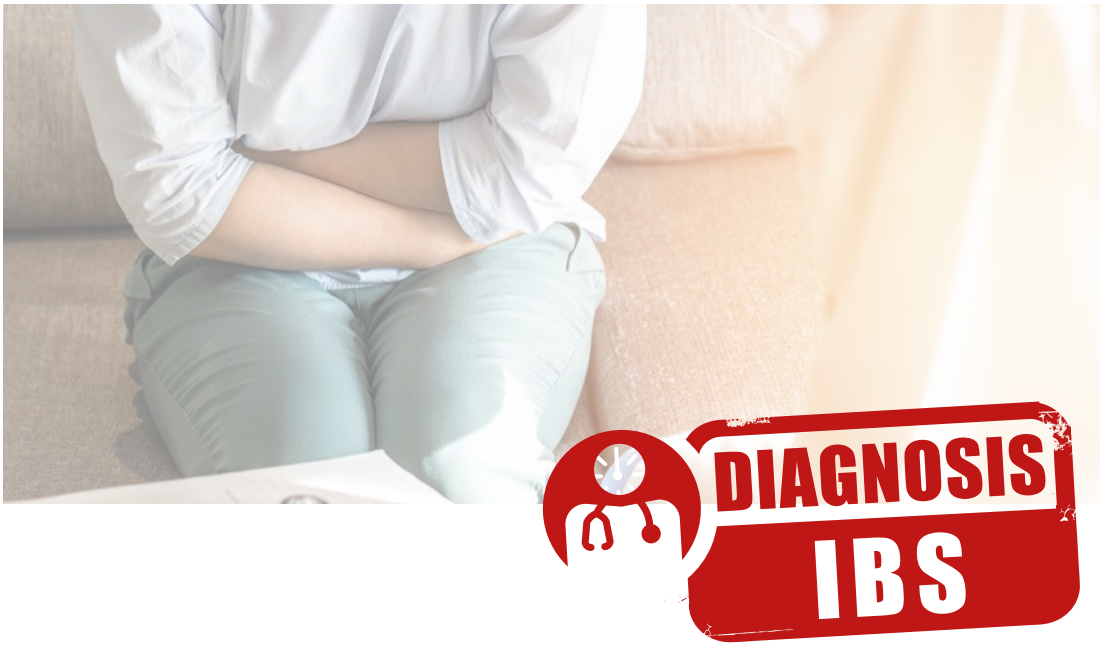


Typical signs of IBS are chronic abdominal pain, which may occur in combination with constipation, diarrhea, and flatulence [2]. It is estimated that around 10 - 15% of the population worldwide suffers from IBS, with women being more frequently affected [3].

Chronic stress promotes the development of an irritable bowel syndrome [4]. It can disrupt the regulation of central pain pathways and alter motility and permeability throughout the gastrointestinal tract [5]. In the presence of stress-related disorders the risk of developing IBS is even twice as high [6, 7] (see Fig. 1).

IBS considerably impairs the quality of life of those affected. It is frequently associated with psychological-psychiatric disorders such as anxiety disorders and depression [8-10]. According to studies, 50-60% of IBS patients suffer from severe psychiatric problems such as anxiety disorders, panic states, social phobias, or depression [11-13].

In current medical practice the treatment of IBS is mostly based on symptomatic measures with limited efficacy [8, 11, 13]. Time and again, studies have been conducted to find better treatment strategies, so far with little success.

With this information brochure, we aim to use molecular mechanisms to explain how intestinal bacteria are involved in the pathogenesis of IBS. Once the etiology has been understood, causal therapeutic approaches can be derived.

Psychological symptoms
↑ Anxiety disorders
↑ Panic disorder
↑ Social phobias
↑ Depression

Gut-brain axis - the center of irritable bowel syndrome

Intestinal Symptoms
↑ Constipation
↑ Diarrhea
↑ Flatulence
↑ Visceral pain

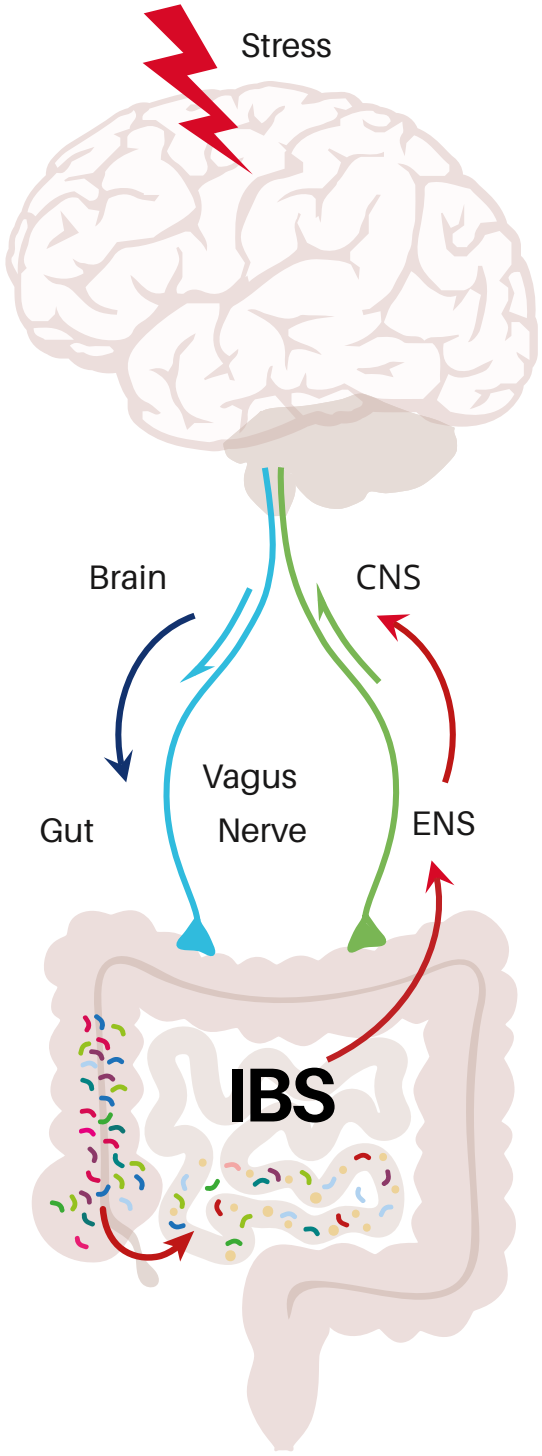
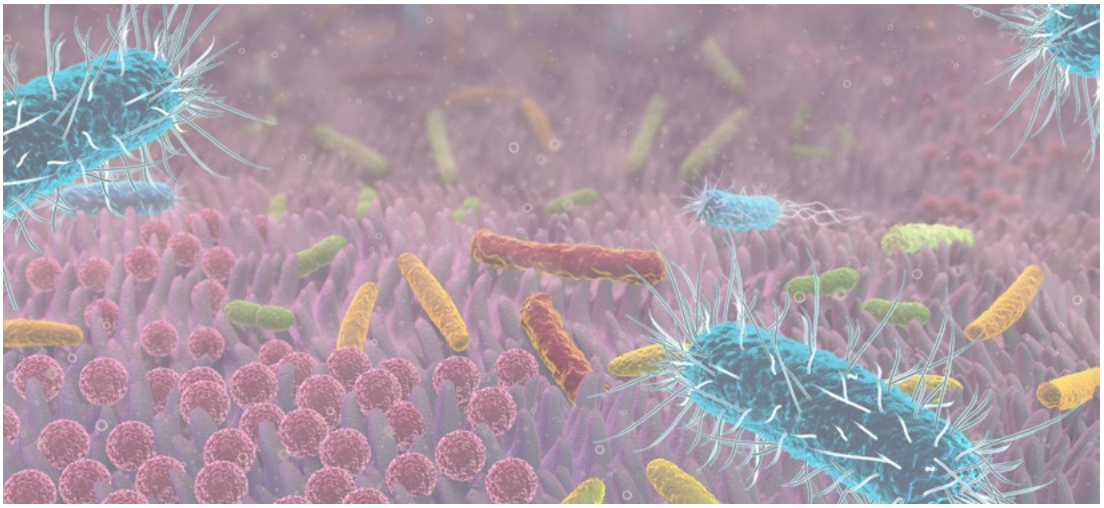


Fig. ***1***
Gut-brain axis at the center of irritable bowel syndrome
(Bron: Own representation based on Martin et al., 2018 [14]).



Role of intestinal microbiota in the pathogenesis of irritable bowel syndrome

The human gastrointestinal tract is home to trillions of microorganisms, the gut microbiome. The largest proportion of intestinal bacteria, the commensals, live in symbiosis with the body and therefore play an important role not only in maintaining the intestinal balance (homeostasis), but also for the general human health. However, if there is an overgrowth of pathogens and thus an imbalance between beneficial (symbionts) and harmful bacteria (pathogens), a so-called dysbiosis is present, which can cause diseases [15, 16].

An intact gut microbiome produces important metabolites and enzymes that are crucial for the supply and absorption of essential nutrients and vitamins [17]. They play an active role in the development and function of the mucosal immune system (MIS). The MIS protects against pathogens [18, 19], while remaining tolerant to harmless food antigens or commensal microorganisms [20, 21].

Dysbiosis is found in a variety of intestinal diseases, including IBS [22, 23]. It is often associated with a decrease in the biodiversity of bacteria [24, 25]. Some studies also point to an increased Firmicutes/Bacteroidetes ratio, a rough indicator for a change in the microbial composition, especially when patients complain of bloating symptoms [26, 27]. A meta-analysis in stool samples eventually demonstrated low levels of Lactobacilli, Bifidobacteria and Faecalibacterium prausnitzii, together with elevated levels of Escherichia coli and Enterobacteria [28, 29] (s. Fig. 2).

IBS patients often show a **bacterial overgrowth of the small intestine** (*Small Intestinal Bacterial Overgrowth*, or **SIBO**) by colon germs, including Klebsiella, *Escherichia coli*, or Clostridia [30, 31]. This overgrowth has its consequences: It leads to increased intestinal permeability, low grade inflammation, disruption of intestinal motility as well as reabsorption of bile acids. Archaea species such as *Methano brevibacter smithii* can also overgrow the small intestine. They produce methane gas in the small intestine, which inhibits intestinal motility and thus delays the passage of the intestinal contents.

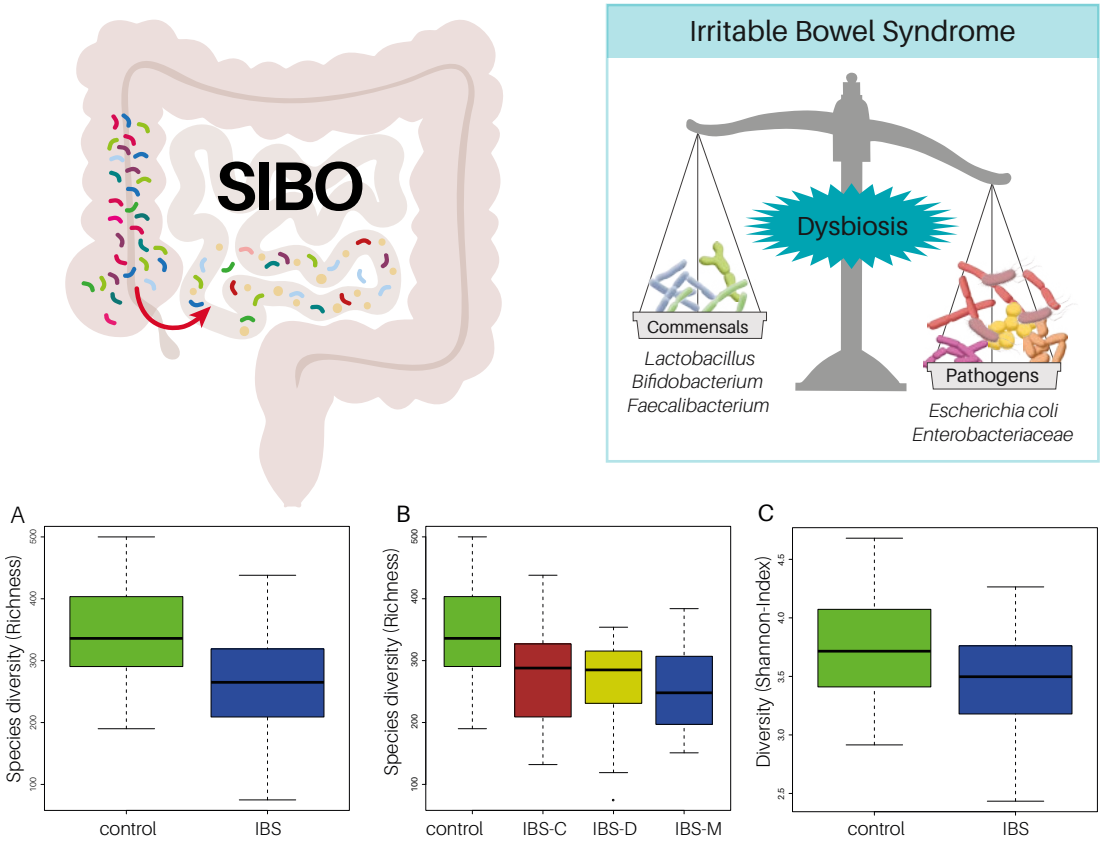
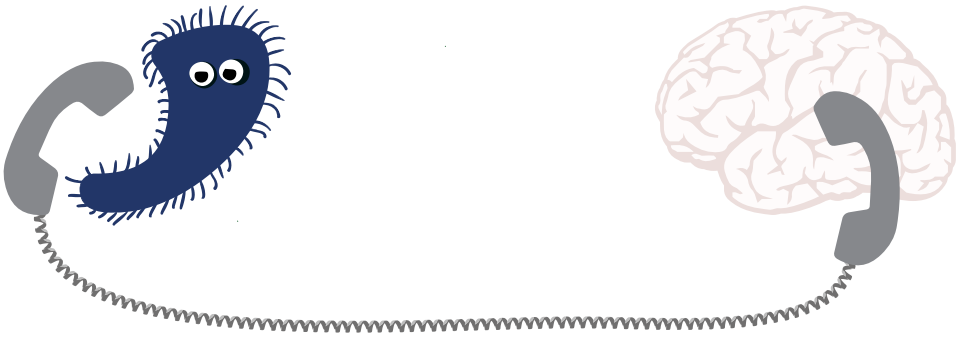


Fig. 2

Microbiota changes in the stool of irritable bowel syndrome (IBS)

IBS patients have a reduced bacterial species diversity (diversity [28,29]), an increased dysbiosis [22,23], and small intestinal bacterial overgrowth (SIBO) [30,31]. (Bron: (left) Jeffery et al., 2020 [32]; (right) Own representation based on Pittayanon et al., 2019 [29])



How does the microbiota influence intestinal homeostasis and IBS pathogenesis?

Increasing evidence suggests a bidirectional communication between the gut microbiota and the enteric (ENS: enteral nervous system) and central nervous system (CNS), referred to as the "brain-gut-microbiome axis" (gut-brain axis for short) [14, 33, 34]. This tight communication suggests that gut bacteria can influence human brain activity indirectly or directly via the ENS. Whether the brain function is positively or negatively influenced is depending on the microbiota composition of symbiotic or pathogenic bacteria [14]. Each bacterial strain metabolizes the available food components in different ways. Therefore, the composition of the bacteria determines the number and variety of bacterial neurotransmitters, metabolites, enzymes, and endocrine factors produced that are beneficial or harmful to human health. In dysbiosis, the overgrowth of pathogens leads to an increased release of harmful rather than beneficial bacterial metabolites. As a result of dysbiosis-related changes, the permeability of the intestinal mucosa increases, allowing microbial products (TLR ligands, etc.) or antigens to enter submucosal areas and activate immune cells. Inflammation is the consequence, resulting in the release of further pro-inflammatory substances, such as cytokines. Like bacterial metabolites and neurotransmitters, these proteins can affect ENS as well as CNS functions and increase or inhibit intestinal motility (see Fig. 3).

Any change in the composition of these factors may be involved in the pathogenesis of IBS and cause one of the major IBS subtypes assigned on the basis of the leading symptoms: Predominantly diarrhea (IBS-D), predominantly constipation (IBS-C), mixed (IBS-M)/alternating (IBS-A) diarrhea and constipation, as well as other undefined symptomatology, such as flatulence and visceral pain (IBS-U) [35].

Therefore, the diagnosis of the microbial groups, producing various neurotransmitters, metabolites, and vitamins, is a valuable approach for establishing appropriate therapeutic options for the treatment of IBS based on different causes.

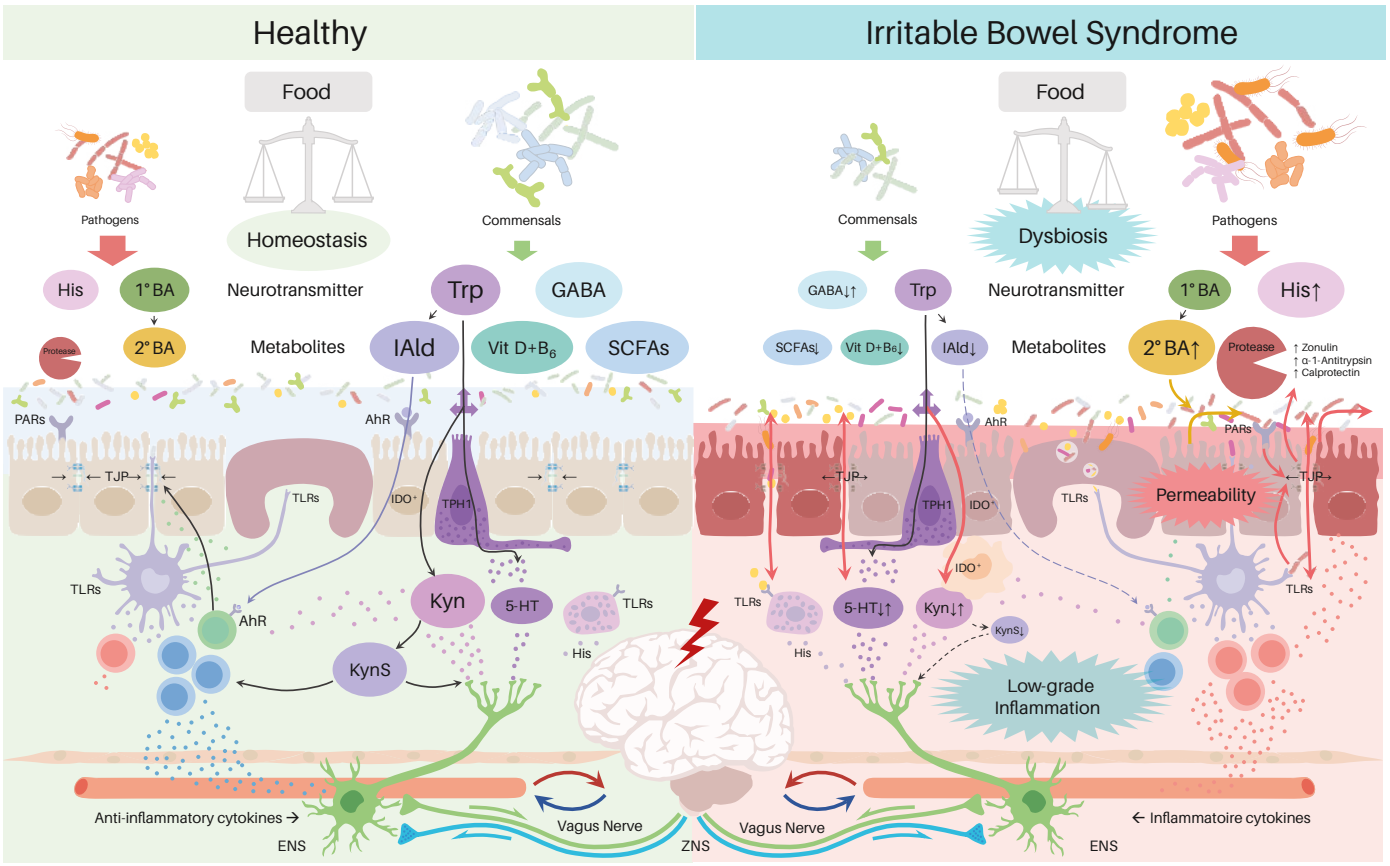


Fig. 3

Intestinal dysbiosis as a cause of irritable bowel syndrome

In a dysbiosis (bacterial imbalance), the ratio of commensals to pathogens tilts, together with the type and amount of microbially produced metabolites in the gut. Studies revealed the ***causal relationship between IBS symptomatology*** *and* ***dysbiosis-altered*** *levels of* ***microbial neurotransmitters*** *(Histamine, GABA, serotonin),* ***metabolites*** *(short-chain fatty acids (SCFAs), vitamins, tryptophan and its Stoffwechsel products), bile acids, TLR ligands, and proteases.*

(Bron: Own representation based on Mishima et al., 2020 [36])

Explanation: *BA, bile acids (1°primary, 2°secondary); His, Histamine; Trp, tryptophan; 5-HT, serotonin; IAld, indole-3-alde- hyd; Kyn, kynurenine; KynS, kynurenic acid; GABA, γ-aminobutyric acid; SCFA, short chain fatty acids. short chain fatty acids; Vit D+B6, vitamin D+B6; AhR, aryl hydrocarbon receptor; PARs, protease-activated receptors; TJP, tight junction proteins; TLRs, toll-like receptors; EC cells, enterochromaffin cells (purple); TPH1, tryptophan hydroxylase; IDO, indoleamine 2,3-dioxygenase; ENS, enteric nervous system; CNS, central nervous system.*

Microbial neurotransmitters

Neurotransmitters produced by microbiota play an important role in the development of irritable bowel symptoms, especially visceral pain, but also flatulence, diarrhea and constipation [37, 38].

Histamine

Neurotransmitters produced by microbiota play an important role in the development of irritable bowel symptoms, especially visceral pain, but also flatulence, diarrhea and constipation ?

Histamine is a biogenic amine responsible for important physiological functions [37] like cell proliferation, cell differentiation and hematopoiesis [39]. However, it also promotes immune responses associated with allergies and inflammation. Histamine additionally has an influence on the motility in the gastrointestinal tract. It increases mucosal permeability in the intestine and affects ion secretion at the mucosa as well [40, 41].

Besides host cells (mast cells, basophils), intestinal bacteria can also synthesize Histamine. These include, for example, E. coli, some Klebsial species and *Morganella morganii*, [42]. Other bacteria carry genes for the synthesis of the enzyme histidine decarboxylase (HDC), which converts the amino acid histidine to Histamine [43]. The increasing Histamine concentration inside the gut, induces an inflammatory cascade via the activation of Histamine-1 receptors (H1HR). Consequently, frequently described complaints of IBS patients with Histamine excess are diarrhea, abdominal pain, cramps, or flatulence. But beware, elevated Histamine levels do not always have to be caused by a dysbiosis. They can also be triggered by stress, a Histamine-rich diet or a reduced Histamine degradation by the enzyme diaminooxidase (DAO) (see. Fig. 4).

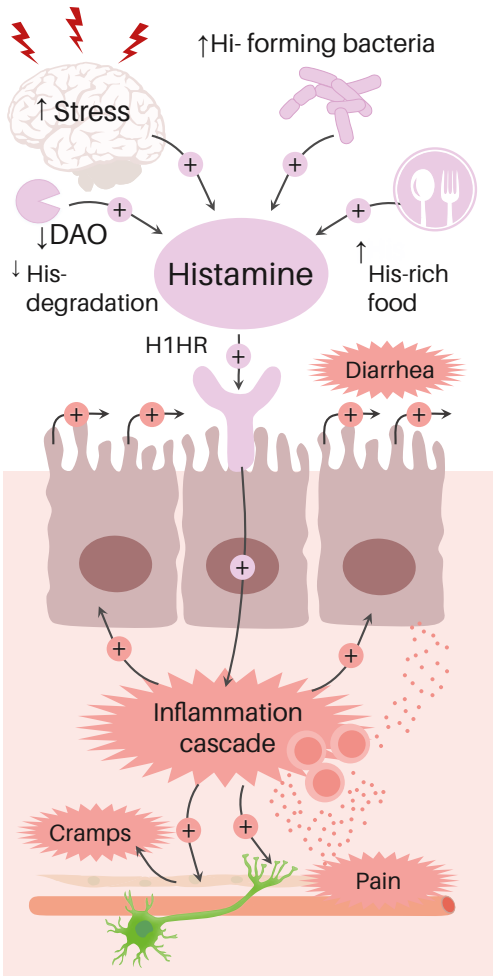


Fig. 4
Histamine in IBS pathogenesis
(Bron: Own representation)

Serotonine

Serotonin (5-hydroxytryptamine, 5-HT) is a multifunctional neurotransmitter, predominantly produced in enterochromaffin cells in the small intestine. The starting substance is tryptophan [44, 45]. Additionally, some intestinal bacteria are also capable of synthesizing serotonin [46]. These include Corynebacteria, Streptococci, Enterococci or Enterobacteriaceae [47, 48]. Some probiotic strains are capable of this as well. It has been described for *Lactobacillus plantarum* - [49] or *Lactococcus lactis strains* [50]. Spore-forming bacteria are not able to synthesize of serotonin, but they can affect serotonin formation by the host [51].

Enteric serotonin appears to be one of the key molecules in the pathogenesis of irritable bowel syndrome, as elevated levels trigger the typical IBS symptoms. These include increased permeability of the intestinal mucosa, visceral hypersensitivity, activation of immune cells, and acceleration of intestinal transit. In some patients with IBS a decreased expression of the serotonin transporter (SERT) can be found, which also results in an increased serotonin level [52, 53].

But IBS patients do not always show high serotonin levels. A lack thereof can also promote the occurrence of pain or constipation via insufficient activation of 5-HT3 or 5-HT4 receptors [54] (see. Fig. 5).

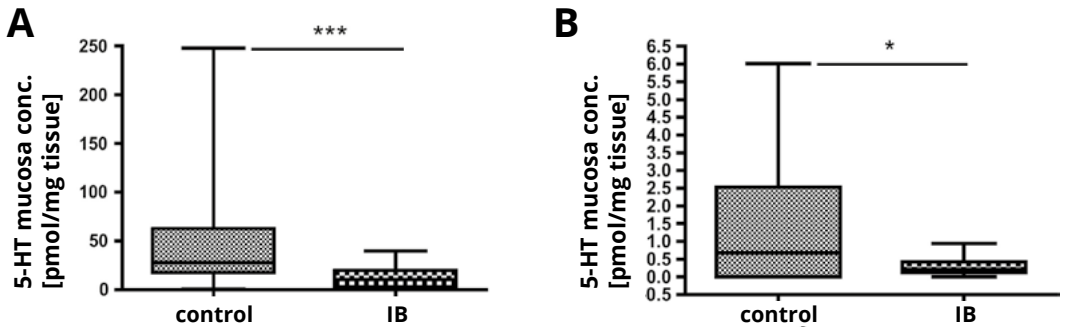


Fig. 5 Increased pain sensitivity in IBS patients with low serotonin (5-HT) and kynurenic acid (KynA) levels in the intestinal mucosa
(Bron: Keszthelyi, D. et al., 2013 [54])

γ-Aminobutyric acid

GABA is an inhibitory neurotransmitter regulating the perception of visceral pain [55]. GABA is formed from glutamate primarily in the central nervous system via the enzyme glutamate decarboxylase (GAD). However, some bacterial strains, such as *Lactobacillus brevis* and *Bifidobacterium dentium*, are also able to synthesize GABA in the intestine [56]. In the context of IBS, Aggarwal et al. (2020) demonstrated that a reduced GABA concentration and an altered GABA signaling system contribute to the pathogenesis of IBS [57]. Supplementing GABA-producing probiotics (*Bifidobacterium dentium*) often has a favorable effect on hypersensitivity. The same applies to visceral pain symptoms associated with GABA deficiency [58].

Microbial metabolites

Microbiota produced metabolites influence a variety of physiological factors in the intestine and body [59]. An altered enteric metabolic profile of intestinal bacteria is another common cause of IBS [60]. The most important microbial metabolites include tryptophan, short-chain fatty acids (SCFAs), bile acids and vitamins. They are briefly described below.

Tryptophan

Tryptophan is an essential amino acid with significant functions in the brain-gut-microbiome axis based on its three main metabolic pathways. A distinction can be made between the serotonin, kynurenine and indole-aryl hydrocarbon receptor (AhR) metabolism. The latter in particular can be strongly influenced by intestinal bacteria [61].

In the human body, only 2% of the ingested tryptophan is converted to serotonin, while the majority is further converted to kynurenic acid (KynS) and quinolinic acid (QS) by the TDO or IDO1 enzymes [62]. Therefore, alterations within the tryptophan metabolism also represent an important reason for development of irritable bowel syndrome [63].

An important metabolite within the kynurenine pathway is kynurenic acid (KynS). It has a regulatory function in both the CNS and the gastrointestinal tract. Via binding to the G-protein receptor GPR35, kynurenic acid has analgesic and anti-inflammatory properties [64]. Decreased levels of this metabolite are frequently found in the intestinal mucosa of IBS patients [54] and are often accompanied by pain symptoms [54] (see Fig. 3 und 5).

Intestinal bacteria such as *E. coli, Achromobacter spp.* or *Bacteroides spp.* metabolize tryptophan to indole aldehyde (IAld), which shows positive effects on intestinal functions via the aryl hydrocarbon receptor (AhR) [65]. AhR-mediated signaling promotes gut health through multiple pathways: It improves the mucosal defense barrier, activates Th17 cells and neutrophils, and promotes the production of interleukin 22. IL-22 enhances biodiversity, promotes mucosal regeneration, and improves the epithelial barrier through the formation of tight junction proteins (TJP) [66, 67]. Not only the just mentioned intestinal bacteria can activate the AhR signaling pathway. Some probiotic strains are also capable of doing so, especially *Lactobacillus reuteri* and *Lactobacillus bulgaricus*. They are an important option to counteract inflammation and dysbiosis [68] to successfully treat IBS

Short-chain fatty acids (SCFAs)

Short-chain fatty acids, mainly produced by microbial degradation of dietary fiber in the large intestine, are of great importance for intestinal health. They are significant for the energy supply of colon epithelia, to strengthen barrier function, to promote wound healing, to contribute to training and maturation of the immune system, and to reduce the sensitivity to pain [69]. Decreased SCFA levels facilitate the occurrence of irritable bowel syndrome [69, 70]. Butyrate, one of the major SCFAs, has mucosal protective and anti-inflammatory effects by inducing regulatory immune cells and controlling proliferation and apoptosis of colonocytes [71]. Therefore, to treat IBS effetively an adequate supply of SCFAs is mandatory.

Vitamins

Vitamin D

Vitamin D plays a crucial role in intestinal health by strengthening the mucosal barrier, regulating immune responses, and acting as an antimicrobial itself [72, 73]. Vitamin D deficiency instead induces the release of proinflammatory cytokines, such as TNF-α and IFN-α, damaging mucosal barrier function and downregulating the formation of tight junction proteins (TJP) [74]. Additionally, the vitamin can interact directly with intestinal bacteria and improve an already existing dysbiosis by strengthening useful bacteria and inhibiting pathogenic or potentially pathogenic ones [74]. By promoting the secretion of anti-microbial peptides, such as α-defensin-2 and lysozyme, vitamin D also has an antimicrobial effect [75]. On the contrary, vitamin D deficiency weakens the host defense system. Patients with IBS often have low vitamin D levels. In summary, this illustrates why supplementation often leads to a decrease in disease activity [76].

Vitamin B6

Vitamin B6 is a water-soluble vitamin that occurs in various forms. The bioactive form, pyridoxal 5-phosphate, serves as a coenzyme in numerous processes [77]. Bacteria or their enzymes are able to influence the vitamin B6 metabolism [77, 78].

A deficiency of vitamin B6 often leads to inflammatory reactions [79], whereby it may be involved in the development of IBS. The low vitamin B6 levels can also aggravate IBS symptoms. substitution of vitamin B6 instead has an alleviating effect on the symptoms [80].

Bile acids

Primary bile acids are synthesized in the liver from cholesterol and coupled to the amino acids taurine or glycine. After intermediate storage in the gallbladder, the conjugated bile acids enter the intestine, where bacteria partially dissolve the amino acid coupling again. Free primary bile acids can be further converted into secondary bile acids by other intestinal bacteria (e.g., eubacteria, clostridia) [81]. Only a small fraction of bile acids is eliminated in the stool. A large proportion is reabsorbed in the terminal ileum and re-enters the liver via the portal vein (entero-hepatic circulation) [82]. Dysbiosis or disorders of the bile acid transporter can cause increased amounts of bile acid in the colon. As a consequence, fluid and electrolyte secretion is enhanced [83, 84]. These processes can lead to an irritable bowel syndrome of the diarrhea type (IBS-D) [85]. In support of this, bile acid malabsorption can be observed in about 30% of IBS-D patients. Additionally, the administration of cholestyramine (adsorbent) has a beneficial effect [86] (see Fig. 3)

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Diagnostic approaches to irritable bowel syndrome

The previous sections discussed how intestinal bacteria are directly or indirectly involved in the pathogenesis of IBS. In order to understand the possible causes leading to IBS in a patient, the factors mentioned above should be investigated (see Fig. 3).

Microbiome analysis

Microbiome analysis are suitable for identifying dysbiosis in IBS patients. The microbiome mini already shows all frequently occurring changes. Moreover, Histamine-forming bacteria or a deficiency of butyrate-forming bacteria can also be detected.

Complementary profile to exclude digestive disorders

It is always strongly advisable to check supplementary parameters, such as digestive residues, pancreatic elastase, α1-antitrypsin, calprotectin and secretory immunoglobulin A. This allows diseases associated with digestive disorders, for example malabsorption or maldigestion, to be detected or ruled out. The supplementary parameters include **quantitative detection** of **bile acids**, which can be used to determine increased amounts of bile acids in the colon as well as bile acid deficiency.

Irritable Bowel Profil:

Detection of Neurotransmitters and significant Tryptophan Metabolites

A new addition to the biovis range of analyses is the **irritable bowel** profile for detecting pathogenetically relevant neurotransmitters and metabolites in stabilized stool, thus offering opportunities for targeted causal therapy approaches. Histamine, tryptophan, serotonin and GABA measurements are included. The profile is based on the results of a pilot study in which samples from 45 IBS patients were examined [Schütz et al., 2019] (see FIG. 6). As many as 81% of the patients showed abnormalities in one or more parameters. 31% of the patients had increased Histamine levels, 57% sufferd from decreased tryptophan and 47% had insufficient serotonin levels. GABA was absent in 48% of the patients. The consequences of the described findings were described for each parameter in the introduction. Changes in neurotransmitters or metabolites enable targeted therapeutic strategies. Some of these are summarized in Table 1. In addition to dietary measures or the substitution of tryptophan, 5-HTP, GABA or missing cofactors, individualized probiotics offer a chance to compensate existing deficiencies or to block the Histamine effect. So far, only a few probiotics are currently available for this purpose, but this is about to change rapidly. Which probiotic strains are able to block the Histamine effect and which ones should better be avoided in patients with Histamine intolerance, is presented in Table 2.

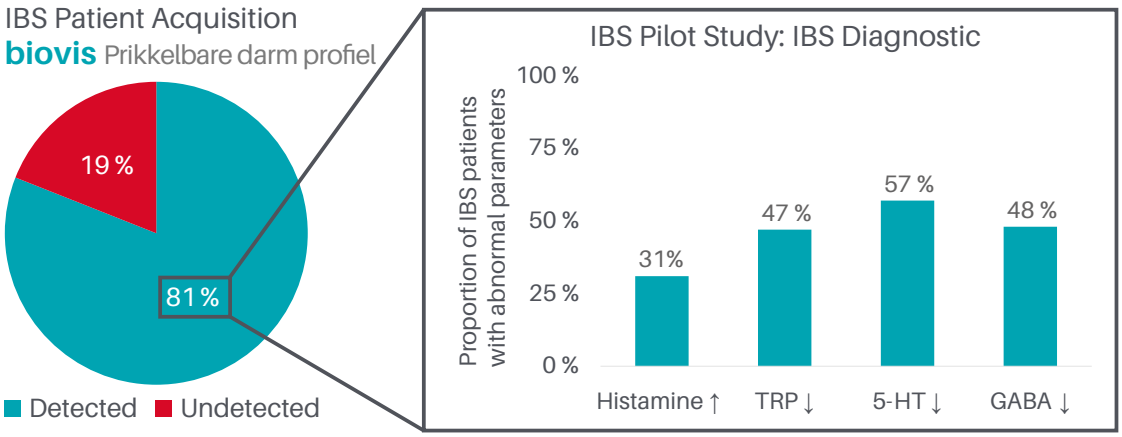

Fig. 6

Pilot study with 45 IBS patients verificates valuable diagnostic parameters

(Source: Own representation based on Schütz et al., 2019)

IBS Diagnostic	Histamine excess	Serotonine excess	Tryptophan deficienc	GABA-deficiency
Parameter	**↑ His [>900 ng/g]**	**↑ 5-HT [>2500 ng/g]**	**↓ Trp [<20 µg/g]** **↓ 5-HT [<500 ng/g]**	**↓ GABA [<13,6 µg/g]**
Frequent symptoms	▪ Diarrhea ▪ Abdominal cramps ▪ Flatulence	▪ Diarrhea ▪ Visceral hypersensitivity	▪ Constipation ▪ Abdominal pain	▪ Pain sensitivity
Physiologische oorzaken	↑ Stress ↑ His-rich food ↑ His-producing bacteria ↓ His degradation by DAO (Histamine intolerance)	→ Reaction to Infection	→ Malabsorption → AT, CP → Fructose-Malabsorption/ overconsumption → ↓**Trp**-uptake → Inflammation ↑**IDO-Activity**	↑ Stress ↓ GABA-forming bacteria
Effect	**Histamine-1 receptor** → Induktion Entzündungskas-kade	**5-HT$_4$ receptor** ▪ Diarrhea	**5-HT$_4$ receptor** → Constipation **5-HT$_3$ receptor** → Pain	**GABA-receptor** → Pain
Therapy	▪ Histamine free diet ▪ DAO-substitution, cofactors(DAO) ▪ „Histamine-blocking probiotics“ [*L. reuteri*⁎, *B. infantis*⁎, *B. longum*] ▪ Classically: AntiHistamine therapy	▪ Classically: 5-HT$_4$ receptor antagonist	▪ Trp of 5-HTP administration ▪ Trp or 5-HTP-probiotics [*L. plantarum*⁎, *L. brevis*, *L. reuteri*⁎] ▪ Classically: 5-HT$_4$ receptor agonisten	▪ GABA-substitution, ▪ GABA-forming [*L. plantarum*⁎, *L. brevis*, *L. lactis*⁎, *B. dentium*]

Tab. ***1***
Therapy approaches to IBS *(⁎ = strain dependent)*

	Histamine-lowering probioticsa	Histamine-neutral probiotics	Histamine-forming probiotics
Probiotics for histamine intolerance	↓ *B. infantis* ↓ *B. longum* ↓ *L. reuteri*∗	→ *Bifidobakterien* → *L. gasseri* → *L. rhamnosus* → *L. salivarius*	↑ *L. delbrueckii* ↑ *L. casei* ↑ *L. fermentum* ↑ *L. plantarum*∗ ↑ *L. reuteri*∗ ↑ *L. lactis*∗ ↑ *E. faecialis* ↑ *E. coli*

Tab. 2
Differentiated use of probiotics in histamine intolerance *(∗=strain dependent)*

SIBO Breath Test Analysis

IBS patients frequently show a bacterial overgrowth of the small intestine (SIBO) with colon germs. This has the following consequences: increased intestinal permeability, low grade inflammation, motility disturbances and/ or impaired reabsorption of bile acids. The SIBO breath test reliably detects an overgrowth syndrome and therefore provides the possibility for a targeted therapy.

Vitamins

Vitamin D and vitamin B6 are of particular significance in patients with an irritable bowel syndrome. Therefore, serum levels should always be examined and, in the event of a deficiency, the vitamins should be substituted. A considerable clinical effect will be achieved.

Conclusie

Irritable bowel syndrome (IBS) is probably the most common disease of the gastrointestinal tract. Worldwide, 10-15% of the population is affected, and significantly more in the course of a crisis or chronic stress. Unclear gastrointestinal complaints can have many causes. Thus, a profound differential diagnosis is essential.

Clearly, a maldigestion or malabsorption should be ruled out first. A severely decreased pancreatic elastase may suggest exocrine pancreatic insufficiency, whereas an increased bile acid excretion may indicate a bile acidosis syndrome. A malabsorption is indicated by abnormal inflammatory markers. High calprotectin levels may be due to invasive mucosal diseases. Slightly raised α-1-antitrypsin or calprotectin levels, on the other hand, are often due to food intolerances or carbohydrate malabsorption.

In addition to maldigestion or malabsorption, intestinal bacteria can also be responsible for a variety of gastrointestinal complaints. Understanding how they influence the pathogenesis of IBS will help derive causal therapeutic approaches for better treatment strategies to offer better help to the patients. The new irritable bowel profiles (Basis A670 & Complete A671), offer a targeted analysis of important neurotransmitters and metabolites. Together with the already known microbiome, breath test and vitamin analyses, a clear picture of the causative factors of IBS can be provided. A causal therapy becomes possible.

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Do you have further questions?

Please, contact us! We are happy to help you!

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