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The Rome IV: Irritable bowel syndrome - A functional disorder

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ABSTRACT

Functional gastrointestinal disorders are the most common disorders encountered in the clinical gastroenterology setting. Over the years the Rome process has generated consensus definitions of functional gastrointestinal disorders, and given diagnostic criteria, based on various symptom patterns, that have evolved over the years. The latest Rome IV consensus was presented in May 2016. This summary points out some of the important changes made from the Rome III 2006 consensus including evaluation of symptoms from the stand-point of basal normative values and disorders of gut-brain interaction, as well as additions of the importance of the microflora. However, we are all aware of the fact that there are limitations, and the Rome consensus does not pick up all patients with functional gastrointestinal disorders. Out of those that seek medical help for their functional gastrointestinal symptoms additional outlines of disease have to be considered and judgements made on the patients' actual symptoms, or rather presentation of their symptoms. The Rome IV consensus is a robust standard for a clinical and research approach to functional gastrointestinal disorders, but might be improved by use of exclusion criteria and additional biochemical biomarkers in order to accurately diagnose those patients who may achieve relief by an extended treatment approach in the clinical setting of gastroenterology. A biopsychosocial approach to the patient is recommended to improve compliance and optimize treatment and outcomes.

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Introduction

Functional gastrointestinal (GI) disorders relate to the patient's reported symptoms against the background of an absence of organic or morphological disease that can be detected by conventional clinical investigations, including biochemical and microbiology tests, be it at the macro- or micropathological level. Instead, a functional disorder is classified in terms of an organ dysfunction which might be related either to the afferent or the efferent neuronal link of the affected organ, against a background of endocrine and paracrine mechanisms. In view of this approach functional GI disorders have mostly been defined in terms of dysmotility and/or visceral sensitivity disturbances, even if secretory and vascular components of GI disease could as well be involved in the pathogenesis.

The foundation for making a diagnosis is the patient's medical history. From this, any medical doctor has to interpret the reported

symptoms and form a likely working hypothesis that should evolve into a diagnosis and form the basis for further medical treatment. As an off-spring from the Manning criteria from 1978 [1], pre-Rome discussions were held over which diagnostic principles that should apply for certain functional GI disorders already in 1988. By using a Delphi approach (Fig. 1) the Rome group of eligible researchers and practicing clinicians arrived at certain diagnostic criteria for the irritable bowel syndrome (IBS) which were consolidated by a consensus process.

Background

The first diagnostic Rome criteria for IBS based on a consensus were published in 1989 [2]. In line with this, a decision was taken for further discussion for a classification system for all functional GI disorders. This should include the five anatomical regions: esophagus, gastroduodenal, bowel, biliary and anorectal and should outline common disorders and their typical features as well as proper diagnosis and treatment [3].

The Rome I consensus appeared 1994 [4–8] and in addition to diagnostic criteria and suggested treatments of the disorders, it also presented guidelines for clinical trials of functional disorders. The

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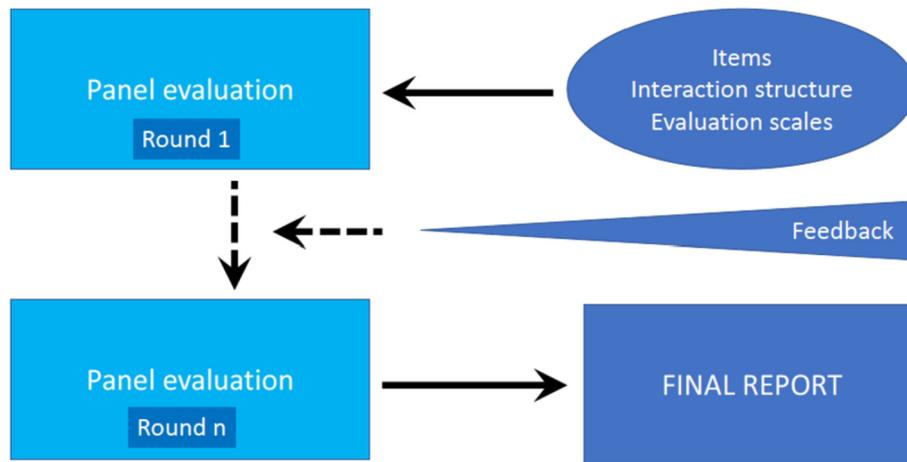


Fig. 1. The principle of a Delphi process where defined questions are individually and anonymously answered by eligible experts. Then, the answers are sent out to the same experts which now can re-consider their responses and adhere to a common standpoint as consensus.

Rome II criteria were published in 1999 [9] at which time general authorities, such as the Food and Drug Administration, decided to recommend the Rome IBS criteria to be used in order to identify eligible patients for clinical trials of drugs directed against functional GI disorders. The Rome III criteria emerged in 2006 [10] with new chapters added and recruited experts representing 18 different countries. As compared to the Rome I and II, the Rome III now used more evidence-based rather than consensus-based data as prolific work and clinical studies using the Rome criteria were published along the way. Hence, experts could draw new conclusions and expand their knowledge in the field as the patient selection in published papers became more precise. This would further permit more strict definitions of eligible patients for studies, necessary in order to disentangle the brocade of symptoms that characterizes the personal features of patients with a functional disorder.

The new

With the Rome IV classification that emerged in May 2016 [11], the Rome Foundation has become an authoritative body with diagnostic criteria for research and clinical trials. Notwithstanding, the Rome Foundation provides educational programs for clinicians and investigators in the field. The Rome foundation update on recent diagnostic features of IBS is presented in Table 1 [12].

Aside from the common functional GI diagnoses of unknown etiology, the Rome IV has added a few diagnoses with known etiology, such as the narcotic bowel syndrome (opioid-induced GI hyperalgesia), opioid-induced constipation and the cannabinoid hyperemesis syndrome. Even though these conditions have a clear etiology and are not merely functional, they still fit the definition of gut-brain interactions as characterized by an altered function of the central nervous system or enteric nervous system. The Rome IV collaboration strives to remove the word “functional” as it carries a

risk for being non-specific and stigmatizing. Instead, the use of the term “disorder” is increasingly recommended with the intention to delimit the weaknesses inherent with the adjective “functional”. In this way many functional diagnoses should lose their psychometric component and stand out as somatic illnesses to be evaluated against a background of normal physiological functions. In Rome IV the microenvironment of the gut, including the microbiota as well as foods and nutrition, have been forwarded in order to improve our understanding of the luminal aspects of the functional disorders. Furthermore, factors such as age, and gender-specific factors, women’s health and multicultural aspects of functional GI disorders have been taken into account. Rome IV also uses thresholds for diagnostic criteria as determined from a normative symptom study [13]. In this way evidence-based thresholds of normality are exercised, and the occurrence and frequencies of symptoms of a functional disorder are assessed against background data from healthy controls.

With the Rome IV, IBS is categorized into the following four subtypes based on the predominant bowel habit: IBS with predominant constipation (IBS-C), IBS with predominant diarrhoea (IBS-D), IBS with mixed bowel habits (IBS-M), and unclassified IBS (IBS-U) [12] which should be considered as a spectrum of symptoms linked to the quantity, intensity and severity of GI symptoms. The overlap between different types of IBS is obvious and symptoms often swap over between different subcategories of IBS. Based on the normative symptom study [13] the criteria of the IBS disease spectrum and subcategories have been adapted to the proportion of pain attacks and symptomatic bowel habits. This step aims to reduce the group of IBS-U which has been considered more as a theoretical construction of an IBS subgroup with no real implication in the clinic. In order to further sharpen the diagnostic criteria of IBS, the term discomfort is now dismissed for the benefit of pain as a symptom to stand out as the main diagnostic criterion (Table 1). Since pain is a clearly distinct symptom, this should exclude cultural differences for the interpretation and expression of the term discomfort which is hampered by its less distinctive character.

Narration

There are several diseases and disorders with a similar symptom pattern as IBS. Even with improvements with the intention to fine-tune the diagnostic features of IBS there are certain shortcomings of the Rome criteria that should be pointed out in order to accurately incorporate patients with a true IBS within this framework. The

Table 1
The current Rome IV diagnostic criteria of irritable bowel syndrome.

Recurrent abdominal pain, on average, at least 1 day per week in the last 3 months, associated with two or more of the following criteria:
<ul style="list-style-type: none"> • Related to defecation • Associated with a change in frequency of stool • Associated with a change in form (appearance) of stool.
Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

diagnosis of IBS according the Rome IV is solely based on positive inclusion criteria. No exclusion criteria have been established other than obvious abnormalities in a routine blood chemistry panel, radiology, or endoscopy with histopathology. Thus, there is an obvious risk to overlook specific diagnoses such as *Helicobacter*-induced dyspepsia [14] and exocrine pancreatic insufficiency [15], both of which treatable disorders with obvious symptoms from the upper gut. In *Helicobacter*-induced dyspepsia we today have sharp diagnostic tools that should reveal a shrouded *Helicobacter* infection, but the final diagnosis cannot be made earlier than one year after successful eradication treatment along with resolution of symptoms. Pancreatic insufficiency is detected in 6% of patients fulfilling the IBS-D criteria [15]. In exocrine pancreatic insufficiency, the diagnostic performance of faecal pancreatic elastase-1 [16] will allow for a 14-day test period with pancreatic enzyme supplementation in order to confirm diagnosis. Similar to what is described for functional diarrhoea [12], commonly accepted biomarkers of inflammation such as serum C-reactive protein and faecal calprotectin can be used for exclusion of inflammatory bowel disease. At a C-reactive protein level of ≤ 0.5 mg/L or calprotectin level of ≤ 40 μ g/g, the probability of overlooking inflammatory bowel disease has been reported to be $\leq 1\%$ [17]. However, in their Rome IV review of IBS [12] diagnostic biomarkers of bile acid malabsorption are reviewed in depth, including analyses even outside of routine clinical practice, such as fibroblast growth factor 19, and 7α -hydroxy-4-cholesten-3-one [12]. To this end, in clinical practice often stool samples are analysed for bacteria, *Clostridium difficile* toxins, parasites and ova as an exclusion measure for IBS, as recommended for functional diarrhoea.

A major problem to the concept of functional GI disorders is the patients' adaptation to their symptoms. Commonly patients with IBS affirm: "I feel best when I don't eat", suggesting that they tend to reduce or chose their digestive load depending on the capacity of GI tract in order to comply with their symptoms. Hence, for a true diagnosis a full standard diet is required in order to correctly assess symptomatic deviations and test results. This is apparent in cases of gastroparesis where even the standard 260 kcal meal for the scintigraphic gastric emptying test [18] by many is regarded as a *too big* meal. Without full compliance to the diagnostic test concept there is an obvious risk for a false negative result. Similarly, for a correct interpretation of faecal fat testing in maldigestion or malabsorption syndromes, the patient is required to follow a high-fat diet of 100 grams of fat each day for three days in a row before taking the faecal fat test. In order to employ normative values [13] we need to have an appropriate background for our assessment of the patient's symptoms, based on a standardized nutritional intake. This is what we usually request in order to perform a standard work-up for celiac disease. As we usually request a standard diet before testing various functional aberrations of the GI tract and judging them as pathological or not, such an approach is yet to be seen for IBS.

There is a number of conditions where patients experience food intolerance without any firm diagnostic signs or tests. One of those is the non-celiac gluten sensitivity where the enzymatic digestion of the visco-elastic gluten proteins requires an appropriate acid secretion and digestive pepsin activity at low pH to be degraded. Fermentable oligosaccharides, disaccharides, monosaccharides, and polyols, the so-called FODMAP, are short-chain carbohydrates that are not readily absorbed in the small intestine. Instead, these are converted to short-chain fatty acids by the anaerobic metabolism in the colon, and can stimulate motility of the ileum inducing abdominal pain, cramps and urge to defecate [19]. The polysaccharide inulin is widely distributed for storage of carbohydrates in plants. Inulin is a general term applied for a heterogenous mixture of repeat fructose polymers ending with a glucose

molecule. Oligofructose, sometimes also called fructooligosaccharides, is a subgroup of inulin with a similar structure. Neither of these polysaccharides are digested in the upper GI tract and therefore have no caloric value and does not increase plasma glucose or stimulate insulin secretion. Inulin is catalyzed by a bacterial exo-inulinase which releases fructose from inulin at a pH optimum of 4.5–5.4, as commonly seen in the cecum, and stimulates the growth of colonic bifidobacteria. On a physiological basis, inulin intake even in relatively small amounts of 40 grams per day may lead to intestinal gas production, bloating and pain. Thus, a careful case history of IBS with eating habits and food preferences is mandatory not to confound a diagnostic situation from a physiological condition. Currently, dietary restriction of FODMAP as treatment for IBS has achieved a certain level of therapeutic efficacy and improvement of quality of life. Comparison of low-FODMAP to a standard IBS diet with regular FODMAP content suggests both regular and low-FODMAP diets proved to be effective in IBS, but post-diet estimates of IBS were significantly lower with low-FODMAP diet [20].

With the Rome IV, the gut-brain interaction axis is recognized as a basis for functional GI disorders. The biopsychosocial aspects on previous exposures, experience and stressors can influence the susceptibility to GI dysfunction with reciprocal influences between the gut and the brain. This comprises earlier GI infections as well as psychological and physical trauma where maladaptive coping might aggravate any disorder. The neural wiring between the gut and the brain communicates information between various parts of the GI tract and emotional and cognitive centres of the brain with direct connections to the myenteric plexus conveying signals to GI end-organs. These systems operate via neurotransmitters to regulate GI functions and pain sensations with secondary influences of mental functioning entangling anxiety disorders and depression. The designation of the bidirectional gut-brain axis calls attention to the gut as the originating point for interactions via this communication linkage. As an example, disordered GI motility generates symptoms such as nausea, vomiting and abdominal pain, whereas reciprocally, strong emotions and stressors can lead to motility disturbances in sensitive people [21,22], but with weak correlation to symptoms that may not always explain the suffering from chronic or recurrent pain.

Water transport in the gut is usually regulated by similar mechanisms as motility and may therefore cause diarrhoea and incontinence as a consequence of increased neuronal activity. The concept of visceral hypersensitivity involves an association of pain to motility by way of a lower pain threshold upon luminal balloon distension. The described hypersensitivity includes not only pain itself, but also a whole range of symptoms from "first sensation" signifying the mere presence of the balloon, over feelings of distension, discomfort and finally pain upon step-wise increasing volumes and pressures. This suggests that patients have an overall hypersensitivity to common events and normal GI functions, i.e. allodynia. This further indicates that the disturbance involved with visceral hypersensitivity covers the whole function of neuronal somatic sensory fibres. Whether this malfunction is generated at a peripheral or central level is not known at this time, but sensory signalling can be facilitated and enhanced at various levels on its way up to the brain. A theoretical concept for visceral hypersensitivity is a weakened GI barrier function. This is clearly outspoken in cases of *Helicobacter* dyspepsia as well as in post-infectious IBS [23,24]. Alterations of the microflora leading to leakage over tight junctions may change the mucosal immune functions as a basis for the hypersensitivity. Access of luminal antigens to the submucosa can, even in minute amounts activate mast cells and stimulate a cytokine release, along with gastritis precipitating symptoms [25–29]. The recent highlighting of the importance of the gut

microbiome has resulted in a cascade of research where genetics, nutrients and microbiota are intermingled in the microbiome-gut-brain axis concept [30,31] pointing out serotonergic and kynureninic mechanisms for elaboration of neurotoxic and neuroprotective metabolites [31]. The notification of increased Firmicutes and decreased Bacteroidetes at the phylum level, as well as increased Clostridia and Clostridiales, in addition to decreased Bacteroidia and Bacteroidales at lower taxonomic levels seems relatively consistent [32,33]. In a review, IBS was summarized to show significantly less Lactobacilli, Bifidobacteria and *Faecalibacterium prausnitzii*, but not of the Bacteroides-Prevotella group, *Escherichia coli* or other genera or species compared to healthy controls. Specifically, in IBS-D little expression of Lactobacilli and Bifidobacteria was found [34]. In IBS-C the numbers of *Bacteroides thetaiotamicron*, *Pseudomonas aeruginosa*, and *Veilonella spp.* were higher than in healthy controls [35]. In line with this, various nutrients have great impact on IBS symptoms. Our diet provides substrates for the microbial fermentation providing gases such as hydrogen and carbon dioxide from which also methane is produced. Patients' attribution to the effect of different foods is well-known, but little taken account for in clinical practice. Prevalence of food allergies is estimated to be about 2% [36], which might be an underestimation as methods used currently to detect food allergies are still debatable and hampered by low sensitivity and specificity [37]. If a food allergy is recognized, an exclusion diet may be of benefit and a therapeutic trial with sodium chromoglycate might be of value, but with limited evidence of efficacy [38]. However, no single diet is the cure and treatment must be personalized and customized to each single individual.

Lately we have encountered a new entity of functional GI disorder related to specific foods and eating habits, the so-called avoidant/restrictive food intake disorder (ARFID). This concept was introduced in the Feeding and Eating Disorders section of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-5.1)* in 2013 [39]. It has become apparent that there are adolescents and young adults who display feeding issues with ensuing malnutrition and weight loss that do not fit into the diagnostic categories of anorexia nervosa or bulimia nervosa. These patients do not fear weight gain, are not displeased with their body weight, shape or figure, and do not present any cognitive symptoms associated with psychiatric disease. Often these patients are given varying diagnoses involving unspecified eating disorder. Such patients often require a gastroenterological approach to provide nutrition and medical management, as well as psychological treatment. In brief, ARFID can be diagnosed in patients whose eating behaviour is avoidant or restrictive to the point where the eating behaviour results in marked abdominal meal-related pain and weight loss with requirement of nutritional supplementation to meet daily energy needs. The diagnosis ARFID requires that concurrent medical or mental disorders are ruled out, why visits to a gastroenterologist is common [40]. The diagnosis is exclusively dependent on the patient's symptoms and as GI symptoms are involved a functional GI disorder has to be excluded before a psychiatric referral is done. ARFID is yet to be discussed within the Rome framework.

Conclusion

The Rome IV defines functional GI disorders as follows: "Functional GI disorders are disorders of gut-brain interaction. It is a group of disorders classified by GI symptoms related to any combination of the following: motility disturbance, visceral hypersensitivity, altered mucosal and immune function, altered composition and function of the gut microbiota, and altered central nervous system processing." This means that different body processes can lead to a functional GI disorder. The Rome IV consensus emphasizes

that the best management for functional GI disorders requires a biopsychosocial approach and includes a section to provide physicians with guidance on partnering with patients to improve treatment and outcomes.

Conflicts of interest

None of the authors have any disclosures as regards conflict of interest to make.

Practice points:

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- Irritable bowel syndrome shall today be look upon as a gastrointestinal disorder.
 - Irritable bowel syndrome is defined by a positive gastrointestinal symptom complex.
 - Even if defined by positive criteria, improved diagnostics might be attained by adding exclusion criteria.
 - Considering irritable bowel syndrome as a primary care assignment, several biomarkers can be added to optimize accuracy of the diagnosis according to Rome IV.
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Research agenda:

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- Optimize diagnostic criteria for irritable bowel syndrome in order to correctly make diagnosis.
 - Validate the influence of standardized meal intake on triggering of characteristic symptoms.
 - Evaluate the importance of gastrointestinal microbiota dysbiosis for development of irritable bowel syndrome.
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