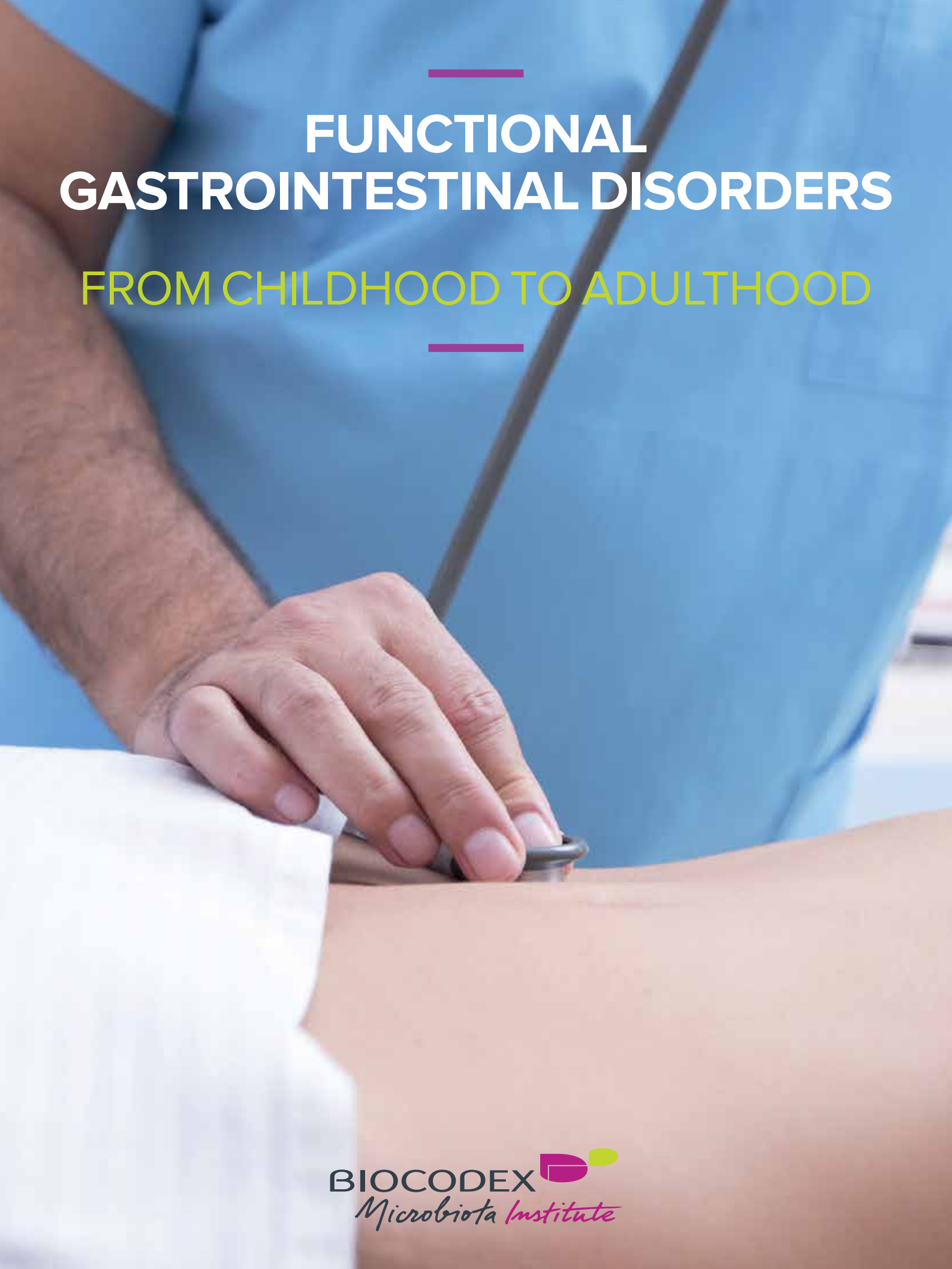

FUNCTIONAL GASTROINTESTINAL DISORDERS

FROM CHILDHOOD TO ADULTHOOD

BIOCODEX
Microbiota Institute

Functional gastrointestinal disorders (FGIDs) have long remained underacknowledged, by health professionals as well as patients.

They include a range of pathologies diagnosed only based on symptomatic criteria detailed in the Rome classification[1]. Its recent update (Rome IV) puts forward etiological and pathophysiological studies as well as the identification of biological markers guiding the development of new therapies and personalized patient care. In that respect, intestinal bacterial populations represent an active research field, whose results–sometimes controversial– are discussed hereafter.

[1] The Rome Foundation is an independent not-for-profit organization designed to produce and spread scientific data regarding FGIDs and classify its symptoms (theromefoundation.org)

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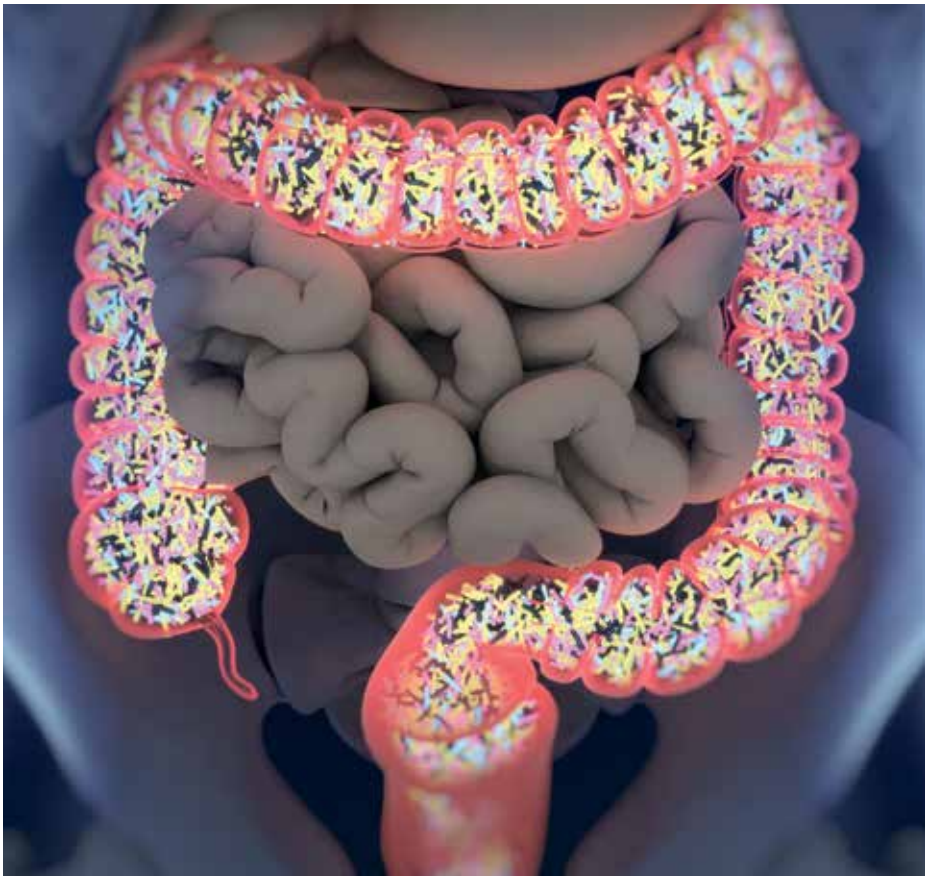
1
PATHOPHYSIOLOGY

The intestinal microbiota: etiologic factor or avenue of therapeutic response for FGIDs? Both assumptions are progressively confirmed and completed as scientific advances are made. Nevertheless, the use of diagnostic classification is met with limits in clinical practice and leads to frequent delays in diagnosis. Mechanisms involved in the microbiota-FGID relation still need to be specified, including neuroendocrine processes involving the gut-brain axis.

Functional gastrointestinal disorders: a set of diseases defined in correlation with the intestinal microbiota



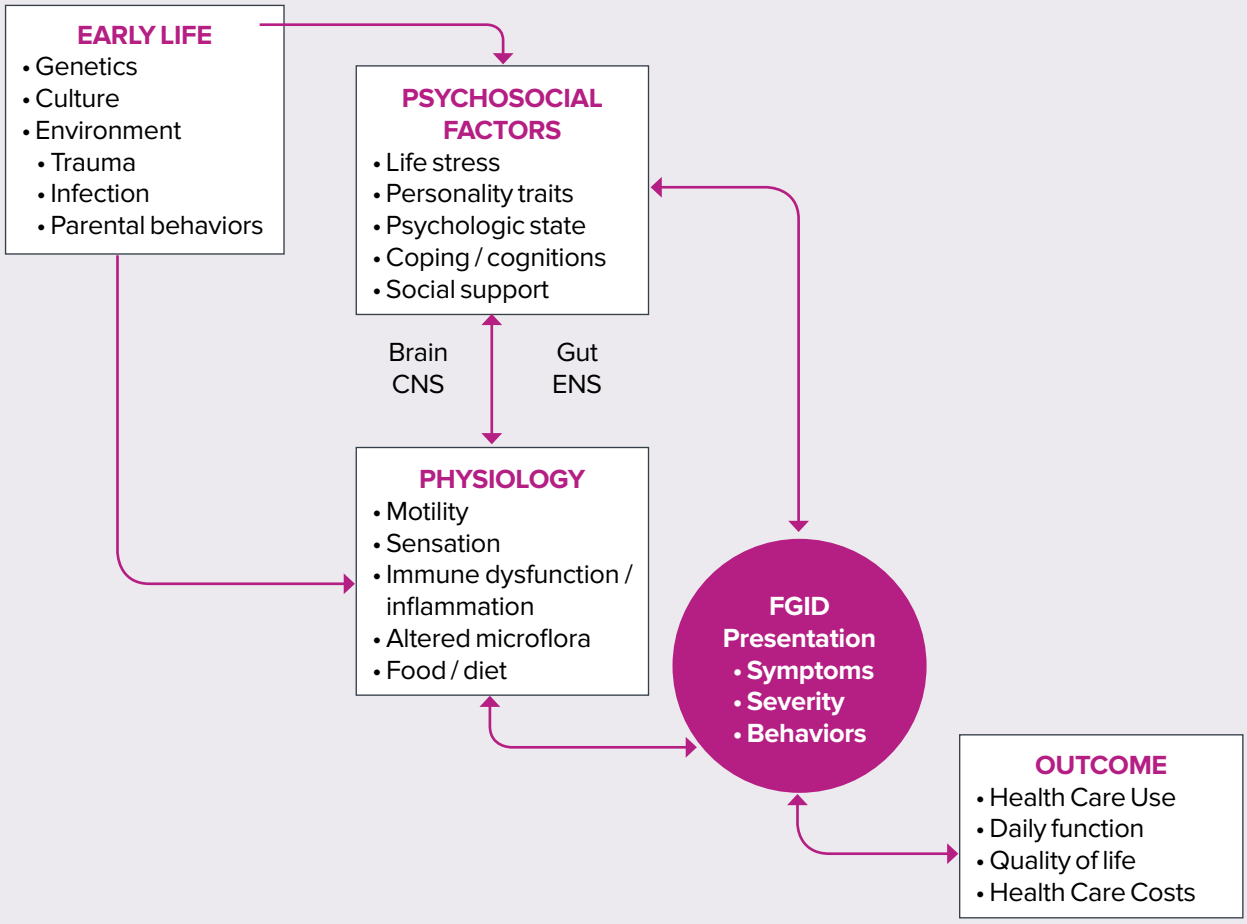
CHANGE IN STATUS

Viewed as shameful in many cultures, functional GI disorders were long regarded as a private matter and related to stress and feelings rather than an easily identifiable organic trouble. The perception changed in the years 1960's thanks to technical and scientific advances: works on etiology and pathophysiology provided a foundation for an organic understanding of FGIDs. In the following decades, the "all physiological" vision was gradually abandoned and the related psychosocial processes were deepened, before the standard modern biopsychological model was ultimately reached.

ROME, CRADLE OF CLASSIFICATION

In the fourth edition of its work of reference (Rome IV), the Rome Foundation proposes a definition of FGIDs collaboratively designed by a panel of experts: they include disorders of the gut-brain axis, i.e. a "group of disorders classified based on gastrointestinal symptoms, related to a combination of the following: motility disturbance, visceral hypersensitivity, deterioration of the mucosa and immune functions, change in intestinal microbiota and alteration of central nervous system functions". The result of that review is

FIGURE 1 :
BIOPSYCHOSOCIAL CONCEPTUAL MODEL OF THE PATHOGENESIS, CLINICAL EXPERIENCE AND EFFECTS OF FGIDS: A MODEL COMBINING NEURO-GASTROENTEROLOGICAL DISRUPTIONS AND GUT-BRAIN INTERACTIONS[2]



a precise categorization of FGIDs as well as a rationale for their study and treatment.

53 DIFFERENT TYPES OF FGID

The Rome IV classification is based on symptomatic criteria grouped by anatomic region (esophageal, gastroduodenal, intestinal, biliary and anorectal). However, symptom location by itself is not enough, especially regarding irritable bowel syndrome (IBS), functional dyspepsia, or abdominal pain syndrome (hard to place and influenced by global effects resulting from deregulation of signaling pathways between central and enteric nervous systems) mediated by the central nervous system. Its 33 items for adults and 20 for newborns, children and teenagers ensure a precise diagnosis and facilitate the implementation of targeted patient care. In this regard, the Rome Foundation insisted on the importance of not limiting therapeutic approaches to medication alone and recommends a biopsychosocial approach to face the variability of cases and individual expectations of patients suffering from FGIDs.

[2] Drossman D. *Functional Gastrointestinal Disorders: History, Pathophysiology, Clinical Features and Rome IV.* Gastroenterology. 2016 Feb 19

FIGURE 2: FGIDS ACCORDING TO ROME IV[2]

A. Esophageal Disorders

A1. Functional chest pain
A2. Functional heartburn
A3. Reflux hypersensitivity
A4. Globus
A5. Functional dysphagia

B. Gastroduodenal Disorders

B1. Functional dyspepsia
- B1a. Postprandial distress syndrome (PDS)
- B1b. Epigastric pain syndrome (EPS)

B2. Belching disorders
- B2a. Excessive supragastric belching
- B2b. Excessive gastric belching

B3. Nausea and vomiting disorders
- B3a. Chronic nausea vomiting syndrome (CNVS)
- B3b. Cyclic vomiting syndrome (CVS)
- B3c. Cannabinoid hyperemesis syndrome (CHS)

B4. Rumination syndrome

C. Bowel Disorders

C1. Irritable bowel syndrome (IBS)
- IBS with predominant constipation (IBS-C)
- IBS with predominant diarrhea (IBS-D)
- IBS with mixed bowel habits (IBS-M)
- IBS unclassified (IBS-U)

C2. Functional constipation
C3. Functional diarrhea
C4. Functional abdominal bloating/distension
C5. Unspecified functional bowel disorder
C6. Opioid-induced constipation

D. Centrally Mediated Disorders of Gastrointestinal Pain

D1. Centrally mediated abdominal pain syndrome (CAPS)
D2. Narcotic bowel syndrome (NBS) / Opioid-induced GI hyperalgesia

E. Gallbladder and Sphincter of Oddi (SO) Disorders

E1. Biliary pain
- E1a. Functional gallbladder disorder
- E1b. Functional biliary SO disorder

E2. Functional pancreatic SO disorder

F. Anorectal Disorders

F1. Fecal incontinence
F2. Functional anorectal pain
- F2a. Levator ani syndrome
- F2b. Unspecified functional anorectal pain
- F2c. Proctalgia fugax

F3. Functional defecation disorders
- F3a. Inadequate defecatory propulsion
- F3b. Dyssynergic defecation

G. Childhood Functional GI Disorders: Neonate/Toddler

G1. Infant regurgitation
G2. Rumination syndrome
G3. Cyclic vomiting syndrome (CVS)
G4. Infant colic
G5. Functional diarrhea
G6. Infant dyschezia
G7. Functional constipation

H. Childhood Functional GI Disorders: Child/Adolescent

H1. Functional nausea and vomiting disorders
- H1a. Cyclic vomiting syndrome (CVS)
- H1b. Functional nausea and functional vomiting
  - H1b1. Functional nausea
  - H1b2. Functional vomiting
- H1c. Rumination syndrome
- H1d. Aerophagia

H2. Functional abdominal pain disorders
- H2a. Functional dyspepsia
  - H2a1. Postprandial distress syndrome
  - H2a2. Epigastric pain syndrome
- H2b. Irritable bowel syndrome (IBS)
- H2c. Abdominal migraine
- H2d. Functional abdominal pain - NOS

H3. Functional defecation disorders
- H3a. Functional constipation
- H3b. Nonretentive fecal incontinence

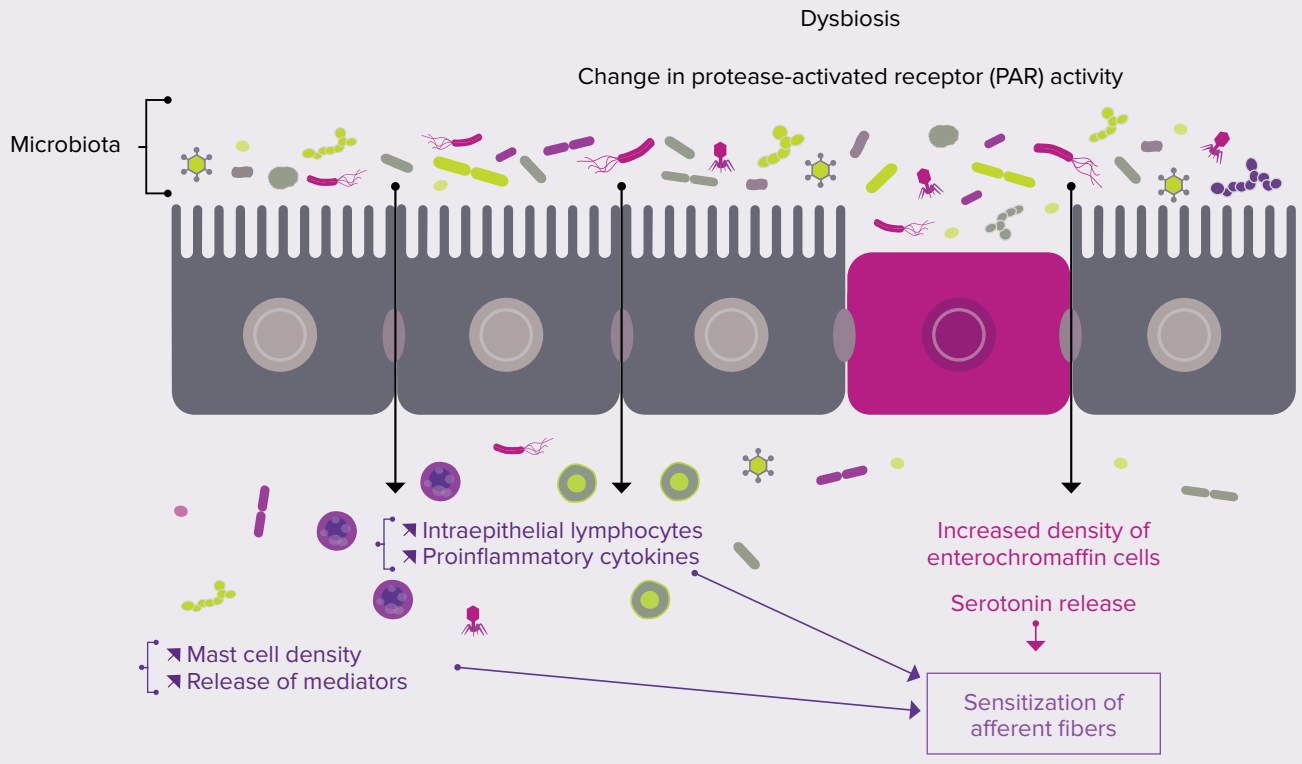
MICROBIOTA: A MAJOR INTESTINAL PLAYER [3,4]

The intestinal microbiota has a complex influence on the metabolism, nutrition and immune functions of the host. Its alteration plays a central role in FGIDs. Dysbiosis has been specifically studied regarding IBS and studies in animals have shown that this imbalance might be involved in the observed visceral hypersensitivity (via endoluminal bile acids), as well as in gastrointestinal dysmotility through the expression of enzymes involved in the synthesis of neuromodulators (gamma-aminobutyric acid [GABA], for instance) and products of colonic fermentation (gas or short-chain fatty acids, SCFA). Finally, dysbiosis seems to promote the disruption of the intestinal barrier: increased intestinal permeability would thus improve the crossing of bacterial antigens responsible for low-grade inflammation leading to sensitization of sensory afferent fibers of the enteric nervous system.

PROMISING APPROACH

Heterogeneity of FGIDs and contradictory results in terms of bacterial composition depending on studies and methods do not allow microbiota and its metabolites to be used as relevant markers for diagnosis, monitoring of the progression of the disease, or treatment response. Literature confirms however the importance of diversity and composition of the intestinal microbiota in the pathophysiology of FGIDs, and consequently the potential impact of approaches related to modulations of intestinal bacterial populations.

FIGURE 3:
PATHOPHYSIOLOGICAL LINKS BETWEEN DYSBIOSIS, INCREASED INTESTINAL PERMEABILITY AND HYPERSENSIBILITY4[4]



[3] Ringel Y. *The Gut Microbiome in Irritable Bowel Syndrome and Other Functional Bowel Disorders*. Gastroenterol Clin North Am. 2017 Mar.
[4] Marteau P, Doré J. *Le microbiote intestinal, un organe à part entière*. John Libbey Eurotext. 2017

Focus on the gut-brain axis[4, 5, 6]

Psychic disorders influence the development of FGIDs, and conversely, through the gut-brain axis. In this regard, the intestinal microbiota could have an impact on the expression of psychiatric symptoms.

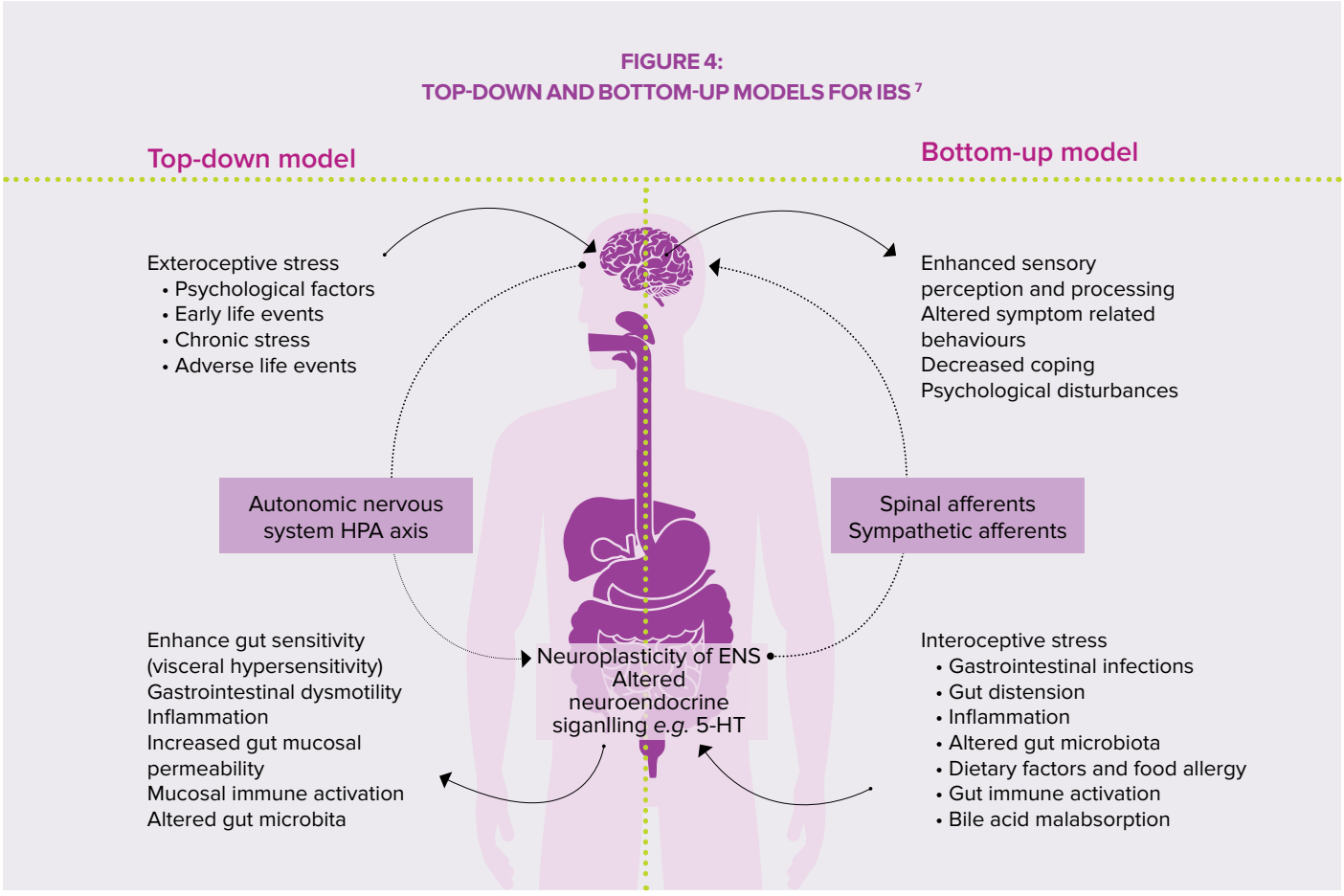
GUT-BRAIN: BIDIRECTIONAL COMMUNICATION

Psychological and psychosocial factors are key to understanding the pathophysiology of FGIDs. Psychic disorders (anxiety, depression, neurosis...) are frequent comorbidities in patients with FGIDs. It is however difficult to determine whether the former generate the latter, or if it is the opposite. Recent studies clearly concluded that bidirectionality is at play, i.e. a reciprocal influence. At a visceral level, exchanges are based on the enteric nervous system and substances produced by intestinal bacteria (SCFA, metabolites...). At a central level, the involved structures are those of the emotional motor system (anterior cingulate cortex, hippocampus, hypothalamus...).

ROLE OF THE GUT-BRAIN AXIS IN IBS

Animal models have revealed that bidirectional communication was disrupted in patients with IBS, although mechanisms ensuring communication between microbiota and brain have not been elucidated. However, several elements that appear to contribute to this mechanism have been identified: the microbiota sends signals to the CNS through enteroendocrine cells (release of serotonin), dendritic cells and B-cells (release of cytokines), products of bacterial metabolism (SCFA, GABA...) and stimulation of vagal afferent fibers. In the other direction, stress and feelings affect the composition of the microbiota through stress hormones and sympathetic nervous system.

FIGURE 4:
TOP-DOWN AND BOTTOM-UP MODELS FOR IBS [7]



[5] G. De Palma, S. Collins, P. Bercik. *The microbiota-gut-brain axis in functional gastrointestinal disorders*. Gut Microbes. 2014 May-Jun
[6] Fukui H, Xu X, Miwa H. *Role of Gut Microbiota-Gut Hormone Axis in the Pathophysiology of Functional Gastrointestinal Disorders*. J Neurogastroenterol Motil. 2018 Jul 30
[7] Devanarayana NM, Rajindrajith S. *Irritable bowel syndrome in children: Current knowledge, challenges and opportunities*. World J Gastroenterol. 2018 Jun 7

2

FGIDS: FROM INFANTS TO ADULTS

Functional gastrointestinal disorders are liable to manifest themselves from the first moments of life. The predominating pathologies vary according to age, but are accompanied by extensive involvement of the intestinal microbiota.

In newborns

The main FGID in infants is colic. This disorder, whose pathophysiology is poorly understood, could originate in the microbiota and is thought to warrant new therapeutic approaches, as the efficacy of standard treatments has proven variable from one individual to another.

A DISEASE WITH IMPRECISE BOUNDARIES

Baby colic has an estimated prevalence of 5% to 28% depending on the study, and is a benign syndrome characterized by recurring bouts of crying, often accompanied by physical symptoms: clenched fists, straightened legs, facial redness. Appearing classically at around two weeks old, it reaches peak severity between 5 to 8 weeks and resolves spontaneously at around the age of 4 months. Its pathogenesis is still unclear, and diagnosis is currently based on Rome IV criteria. Organic causes are thought to represent only a small proportion of causes involved (5%). Additional factors such as an allergy to cow's milk protein, family tensions and anxiety, etc. are likely to play a part.

CURRENT TREATMENTS

The diversity of causes makes patient care complex and encourages the diversification of treatment options, rendering treatment non-specific. What are the main current approaches? Drugs (mucosal protective agents, antispasmodics...), diet (modified diets, especially formulas based on casein hydrolysate, whey or soy milk...), behavioral techniques (chiropractic, reduced stimulation of the child...) and some probiotics.

INNOVATIVE ETIOLOGICAL HYPOTHESES INVOLVING THE MICROBIOTA[8]

An international team has proposed three etiological hypotheses which could lead to new therapeutic approaches: first of all, immaturity of the enterohepatic circulation and of the action of bile acids leading to malabsorption of fats and other nutrients, as well as possible side effects on the intestinal microbiota. Secondly, intestinal dysbiosis, triggering an increase in nutrient fermentation and reduced levels of dehydroxylated bile acids in the colon. Finally, immaturity of the enteric nervous system resulting in abnormal sensorimotor function in the intestines and colon. The future characterization of these three mechanisms, which display numerous potential interactions, could lead to a more specific diagnosis and personalized management based on targeted biomarkers.

[8] Camilleri M, Park S, Scarpato E, et al. Exploring hypotheses and rationale for causes of infantile colic. Neurogastroenterol Motil. 2017 Feb

TABLE 1:
MAIN FGIDS AND RELATED DYSBIOSIS

PATHOLOGIES AND RELATED SYMPTOMS	DYSBIOSIS OBSERVED	
	PHYLUM/CLASS/ORDER/FAMILY	GENUS
Baby colic[8] Recurrent or sustained crying, restlessness or irritability, with no specific cause	*Proteobacteria* ▲ *Bacteroidetes* ▼ *Firmicutes* ▼	*Lactobacillus* ▼* *Bifidobacterium* ▼ Butyrate-producing bacteria ▼ Coliform bacteria ▲ *Klebsiella* ▲ *Serratia* ▲ *Vibrio* ▲ *Escherichia* ▲ *Enterobacter aerogenes* ▲ *Yersinia* ▲ *Pseudomonas* ▲
IBS in children[7] Abdominal pain, relieved by bowel movements, and associated with changes in stool consistency (either diarrhea or constipation, or a combination of both) and stool frequency	Ratio *Firmicutes/Bacteroidetes* ▲ *Enterobacteriaceae* ▲ *Clostridiales* ▼	*Veillonella* ▲ *Dorea* ▲ *Bifidobacterium* ▼ *Collinsella* ▼ *Haemophilus parainfluenzae* ▲
IBS in adults[9] Combination of chronic abdominal pain or abdominal discomfort, bloating and transit disorders (either diarrhea or constipation, or a combination of both)	*Enterobacteriaceae* ▲ *Lactobacillales* ▲ Ratio *Firmicutes/Bacteroidetes* ▼ or ▲** *Ruminococcaceae* ▲	*Lactobacillus* ▼ or ▲** *Bifidobacterium* ▼ *Ruminococcus* ▲ Methanogens▼ *Veillonella* ▲ *Faecalibacterium* ▼
Chronic constipation in adults[10] Unsatisfactory bowel movements, due to infrequent stools or difficulty evacuating stool, or both		*Bacteroides* ▲ *Bifidobacterium* ▲ *Clostridium difficile* ▲ *Lactobacillus* ▼ *Faecalibacterium prausnitzii* ▼

* It should be noted that there are some specificities: some lactobacilli are only found in healthy children (*L. acidophilus*) and other only in colicky children (*L. brevis and L. lactis*)
** Depending on studies

[9] Cited in Rodiño-Janeiro BK, Vicario M, Alonso-Cotoner C, Pascua-García R, Santos J. A *Review of Microbiota and Irritable Bowel Syndrome: Future in Therapies*. Adv Ther. 2018 Mar
[10] Zhao Y, Yu YB. *Intestinal microbiota and chronic constipation*. Springerplus. 2016 Jul 19;5(1):1130. doi: 10.1186/s40064-016-2821-1. eCollection 2016. Review
Parthasarathy G, Chen J, Chen X, Chia N, O'Connor HM, Wolf PG, Gaskins HR, Bharucha AE. Relationship Between Microbiota of the Colonic Mucosa vs Feces and Symptoms, Colonic Transit, and Methane Production in Female Patients With Chronic Constipation. Gastroenterology. 2016 Feb;150(2):367-79.e1. doi: 10.1053/j.gastro.2015.10.005. Epub 2015 Oct 13.
Cited in Cao H, Liu X, An Y. *Dysbiosis contributes to chronic constipation development via regulation of serotonin transporter in the intestine*. Sci Rep. 2017 Sep 4

In children and adolescents[7]

Functional abdominal pain associated with pediatric FGIDs may assume various forms which should be clearly identified for correct management. In many cases it is triggered by irritable bowel syndrome.

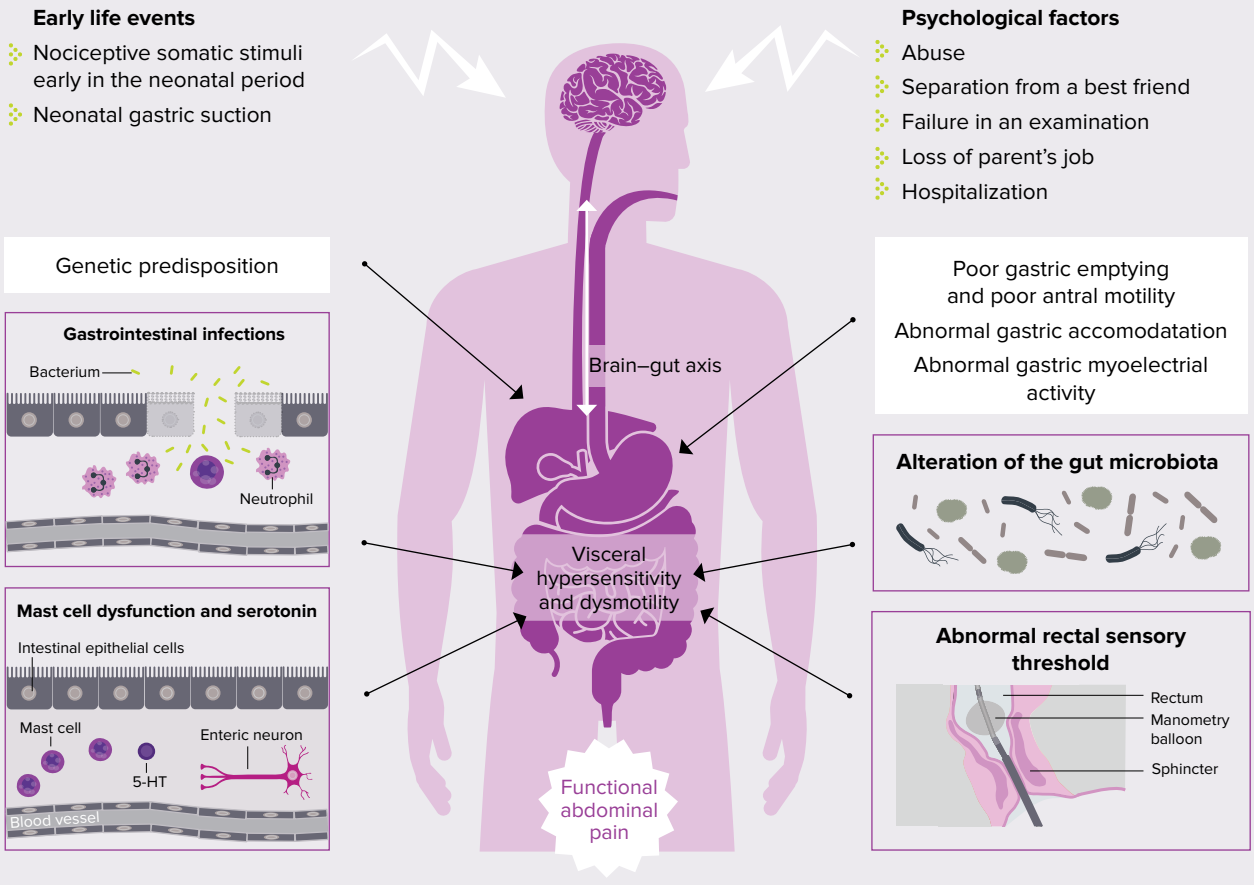
PATHOPHYSIOLOGY OF FUNCTIONAL ABDOMINAL PAIN[11]

Functional abdominal pain is one of the most common syndromes in children, with an estimated global prevalence of 13.5% in 2014. Most causes are functional and involve changes in visceral sensation (hyperalgesia) and impaired gastrointestinal motility. The former are expressed as discomfort and pain, the latter as diarrhea or constipation, nausea, bloating, distension... The diversity of symptoms observed led the Rome Foundation to distinguish four broad categories of functional abdominal pain in children: irritable bowel syndrome, functional dyspepsia, abdominal migraine and functional abdominal pain not belonging to any of the above-mentioned categories.

IBS: A CULTURAL PERCEPTION?

Even though irritable bowel syndrome is the most common FGID in children and a real public health issue at global

FIGURE 5:
PATHOGENESIS OF FUNCTIONAL ABDOMINAL PAIN IN CHILDREN [12]



[11] Korterink JJ, Diederen K, Benninga MA, Tabbers MM. *Epidemiology of pediatric functional abdominal pain disorders: a meta-analysis*. PLoS One. 2015 May 20;10(5):e0126982. doi: 10.1371/journal.pone.0126982. eCollection 2015

[12] Korterink J, Devanarayana NM, Rajindrajith S, Vlieger A, Benninga MA. *Childhood functional abdominal pain: mechanisms and management*. Nat Rev Gastroenterol Hepatol. 2015 Mar

level, it remains overlooked. The very perception of this condition seems to vary significantly between countries and studies, since its prevalence varies from 5.1% in the United States to 22.6% in Turkey, and ranges from 2.8% to 25.7% in some Asian countries. Such differences could possibly be ascribed to local particularities, but are more probably due to interpretations of the Rome IV diagnostic criteria that vary depending on culture, relationship to pain and what is considered a true disease–and not a simple change in bowel movements.

IBS IN CHILDREN: HOLISTIC MANAGEMENT

Characterized by a less diverse gastrointestinal microbiota (especially in contact with the mucosa), increased levels of some *Clostridia* and *Firmicutes* (*Veillonella*) and reduced levels of bifidobacteria (Table 1), IBS represents 40 to 45% of FGIDs in children. The therapeutic education of the parents occupies a central place in its treatment, as their anxiety can have a significant impact on the severity of symptoms and the efficacy of treatment, whether it is pharmacological or not. Standard drugs are those used to treat IBS in adults: gastrointestinal motility stimulants, antispasmodic agents, antacids, antihistamines, antireflux agents... whose efficacy has not been evaluated. A literature review suggests that among non-pharmacological treatments, some psychological approaches (mental imagery, hypnosis, cognitive behavioral therapy, yoga) could help improve the child's health. In view of the disruptions of the microbiota identified in young IBS patients, the use of probiotics is also a promising therapeutic option.

PREDISPOSITION AND PREVENTION

A multitude of factors predispose to the development of IBS: gender, age, psychological factors, neonatal trauma, gastrointestinal infections, asthma, atopic disorders, diet, socioeconomic, familial and environmental factors... Some of these may represent potential areas for the implementation of preventive actions which would aim to reduce the prevalence of disorders in children and adults weakened during their childhood, as well as decrease individual and societal healthcare costs. It is the responsibility of the different healthcare systems to prioritize their approaches and actions according to risks, needs, and possibilities.

In adults[13, 14, 15]

The FGIDs encountered in adults are functional diarrhea, functional bloating, and especially IBS and functional constipation. As in children, their etiology is poorly understood.

IBS SUBTYPES ACCORDING TO ROME IV

IBS-D (associated with diarrhea)
IBS-C (associated with constipation)
IBS-M (mixed subtype)
IBS-U (unclassified)

The pathophysiological mechanisms that fall under one subtype rather than another remain obscure, but the clinical differences foreshadow the existence of specific biological markers capable of guiding diagnosis and management.

A MICROBIAL SIGNATURE

An Italian team has suggested the hypothesis that bacterial and biological markers (SCFA) could be used to discriminate between the different subtypes of IBS, a disorder that affects between 7% to 21% of the general population depending on the countries under consideration. Characterization of the fecal samples of 40 patients suffering from IBS (5 samples collected at 4 week intervals) demonstrated that certain bacterial species enabled the different IBS subtypes to be discriminated: in particular, greater abundance of bacteria belonging to the *Ruminococcaceae* and *Lachnospiraceae* families were observed in the IBS C subtype compared to the IBS-D subtype. Fecal concentrations of SCFA would also seem to be effective markers for discrimination of the different subtypes: among others, fecal concentrations of acetate, butyrate, propionate and valerate are significantly higher in patients with IBS-D compared to patients with IBS-C. Finally, for each pathological subtype, the bacterial signatures identified could be correlated with a specific fecal concentration of SCFAs, fecal cytokine levels as well as stool consistency.

CHRONIC CONSTIPATION: THE SEROTONIN PATHWAY (5-HT)

Although chronic constipation in adults is less often mentioned, it does impact quality of life. The disorder affects between 2% and 20% of the population depending on the study; it is frequently accompanied by intestinal dysbiosis and could involve hormone-mediated interactions. An international team has investigated serotonin, a key neurotransmitter of the gut-brain axis, which is thought to be involved in gastrointestinal motility. The concentration of serotonin, 95% of which is secreted by enterochromaffin cells, could be regulated by the intestinal microbiota via the expression of the serotonin transporter (SERT). This hypothesis was tested through fecal transplants from human subjects with chronic constipation and healthy individuals to mice whose microbiota was weakened by antibiotic therapy. The mice that received a transplant quickly displayed reduced gut peristalsis, abnormal defecation parameters, overexpression of SERT in the colon and reduced serotonin concentrations. Characterization of bacterial populations in these mice showed a depletion of *Clostridium*, *Lactobacillus*, *Desulfovibrio* and *Methylobacterium* genera and an enrichment of Bacteroides and Akkermansia genera. This reflects a marked dysbiosis, which, according to the researchers, could trigger positive regulation of SERT expression, and consequently increase the reuptake of the serotonin responsible for a reduction in intestinal motility.

[13] Cao H, Liu X, An Y. *Dysbiosis contributes to chronic constipation development via regulation of serotonin transporter in the intestine*. Sci Rep. 2017 Sep 4
[14] Gargari G, Taverniti V, Gardana C. *Fecal Clostridiales distribution and short-chain fatty acids reflect bowel habits in irritable bowel syndrome*. Environ Microbiol. 2018 May 11
[15] Chey WD, Kurlander J, Eswaran S. *Irritable bowel syndrome: a clinical review*. JAMA. 2015 Mar 3;313(9):949-58. doi: 10.1001/jama.2015.0954

3

WHAT COULD BE THE ROLE OF MICROBIOTA MODULATION?

Fecal transplant, targeted diets, probiotic supplementation…: although the prospects are promising, the conclusions of some publications point not only to the complexity of the subject but also to its limitations.

Modulation of the microbiota by FMT: controversial results[16, 17]

The efficacy of fecal transplant in the treatment of dysbiosis seems proven, but its impact on FGIDs is more questionable.

REAL EFFICACY AGAINST DYSBIOSIS

A Danish study conducted in 2016 highlighted the efficacy of fecal transplant in cases of dysbiosis in IBS patients and revealed a significant improvement in the diversity of their gastrointestinal microbiota. The collection of fecal samples at each visit (enrolment, 1, 3 and 6 months) allowed the characterization of bacterial populations by sequencing. Analysis of the microbiota of the transplanted patients at 3 months revealed the presence of 11 species of interest. Two species displayed weak negative correlations with the IBS-SSS–or *Irritable Bowel Syndrome Severity Scoring System*–(both belonging to the *Blautia* genus which is associated with a healthy gastrointestinal microbiome) and three moderately positive (two belonging to the *Bacteroides* genus and one to the *Ruminoccocaceae* family). As of now, fecal transplant therefore appears to represent a technique for the treatment of dysbiosis in IBS patients, and potentially all FGIDs, although larger scale studies are required to define its clinical efficacy.

[16] Halkjær S, Christensen A, Lo B, et al. *Faecal microbiota transplantation alters gut microbiota in patients with irritable bowel syndrome: results from a randomised, double-blind placebo-controlled study*. Gut. 2018 Jul 6

[17] Johnsen J, Hilpüsch F, Cavanagh J et al. *Faecal microbiota transplantation versus placebo for moderate-to-severe irritable bowel syndrome: a double-blind, randomised, placebo-controlled, parallel-group, single-centre trial.* Lancet Gastroenterol Hepatol. 2018 Jan; 2017 Nov 1

IBS-SSS SCORE

Functioning

The IBS-SSS score is comprised of 5 parameters quantified on a 100-point analog scale.
The five items added together give a severity score between 0 and 500.

- 0-75 > control or patient in remission
- 75-175 > benign form
- 175-300 > moderate
- 300 and over > severe

Criteria

- Severity of abdominal pain;
- Frequency of abdominal pain;
- Severity of bloating;
- Relief after defecation;
- Interference with quality of life

DIVERGENT RESULTS

The question is however raised: is fecal transplant also able to correct the pathological phenomena associated with dysbiosis? It is difficult to give a final answer regarding FGIDs, mainly because of the scarce number of randomized clinical studies. The few trials available in the scientific literature deal with IBS and do not yet allow a judgment to be made because of divergent conclusions.

PROS AND CONS

In Norway in 2015, 83 participants aged between 18 and 75 took part in a study: after an enema 2/3 of them received a fecal transplant and 1/3 a placebo (their own feces) in both cases via the colon. The reduction of symptoms at three months was evaluated using the IBS-SSS score. The difference was significantly in favor of transplant: 65% improvement against 43% for the placebo–a difference which was not confirmed at 12 months. The "loss of efficacy" could be explained by a powerful effect of the transplanted microbiota right after the administration, but a difficulty in grafting durably in its host due to the effect of exogenous and/or endogenous factors. One year later in 2016, another study disproved the benefit of fecal transplant: after an enema, 52 patients with moderate or severe disease received a graft (orally) from healthy donors (n=26) or a placebo (n=26). The IBS-SSS score and quality of life were then evaluated. At 3 months, a significantly greater improvement in symptoms and quality of life was observed... in the placebo arm. Suggested hypotheses: the fecal transplant could counteract a positive effect of the enema; some pathogenic microorganisms could be removed by the enema then reintroduced by transplant; the duration of treatment or the quantity of re-implanted fecal bacteria might be insufficient.

FODMAP-free diet: not for all patients[18, 19]

Its use remains questionable in FGIDs, but a possible correlation between bacterial populations and response to the FODMAP-free diet could help refine the therapeutic choice.

TREATMENT OF IBS

The FODMAP-free diet (*Fermentable Oligosaccharides Disaccharides Monosaccharides and Polyols*) seems to represent an appropriate therapeutic response to IBS. The incriminated foods in fact cause intestinal disruption when they are fermented by bacteria via the production of gas and short-chain fatty acids. Restricting their intake provides benefits that are confirmed by the literature, but which must be weighed against potential negative effects to confirm the value of this type of diet as a first- line therapeutic option. The absence of FODMAPs can in fact cause eating disorders, deficiencies and biological disruption, directly or following dysbiosis of the intestinal microbiota. They should also not be used as a diagnostic test for IBS in

[18] Hill P, Muir J, Gibson P. *Controversies and Recent Developments of the Low-FODMAP Diet*. Gastroenterol Hepatol (N Y). 2017 Jan
[19] Valeur J, Småstuen M, Knudsen T, et al. *Exploring Gut Microbiota Composition as an Indicator of Clinical Response to Dietary FODMAP Restriction in Patients with Irritable Bowel Syndrome*. Dig Dis Sci. 2018 Feb

place of recognized symptomatic criteria (those of Rome IV), note the experts, who also recall the importance of the gradual reintroduction of excluded foods, after checking that the organism will tolerate them.

THERAPEUTIC EFFICACY AND BACTERIAL PROFILE

A FODMAP-free diet could therefore be appropriate for some types of disorders or individuals, but not for others. This research area has been explored by a Norwegian team, who compared the composition of the intestinal microbiota of IBS patients with response to treatment. In this study, a patient was judged responsive if they showed a reduction of symptoms of at least 50% at 4 weeks on an IBS-SSS score. Out of 61 subjects, 32 (29 women, 3 men) were considered as respondents and 29 (25 women, 4 men) as non-respondents. The analysis of 54 bacterial markers by means of a specific test demonstrated significant differences between the two groups for 10 of these markers. From the data collected, a response index (RI) graduated from 0 to 10 and based on the median values of 10 bacterial markers of the responsive patients was created. Result: subjects with an RI higher than 3 were five times more likely to respond to treatment. A possible innovative therapeutic approach for the treatment of FGIDs.

AN ALTERNATIVE THERAPY, AMONG OTHERS

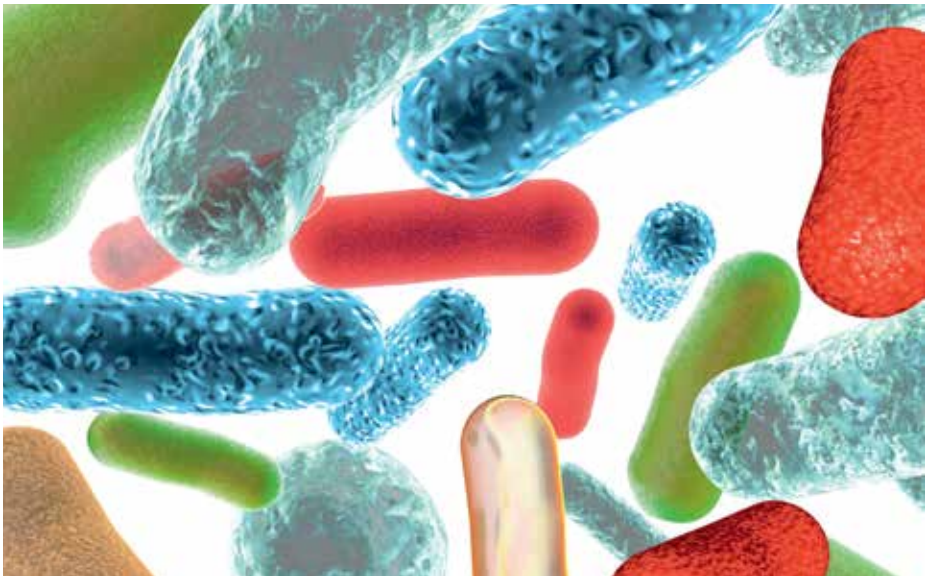
These reservations have led to the study of other non-pharmacological alternatives in FGIDs (hypnotherapy, gluten-free diet etc..). The literature tends to demonstrate that the conventional dietary advice given by health professionals provides less benefit: list of products to be avoided (fatty or spicy foods, coffee, alcohol, onions...) and eating habits to be adopted (eating at regular intervals, in reasonable quantities, chewing thoroughly...). On the contrary, hypnotherapy might offer the same physiological advantages as the low-FODMAP diet and a better psychological impact in patients suffering from IBS. Regarding the gluten-free diet, there is no comparative study with the low-FODMAP diet, but drawing comparisons between similar studies holds out the prospect of similar results.

Probiotics: what are the benefits?

Probiotics are intended to modulate the intestinal microbiota. However, their efficacy has yet to be defined, even though available data encourage continued research to identify the most effective strains in the treatment of FGIDs.

ACTION IN IBS

The definition of probiotics, namely "a living microorganism which, when administered in sufficient quantity, exerts a beneficial effect on the health of the host[20]", refers, in practice, to three large families used in the health and food industries for over-the-counter products: *lactobacillus*, *bifidobacterium* and yeasts. The effect of probiotics on FGID symptoms has been the subject of a limited number of publications[21] and it is difficult to identify commensal bacteria of particular value in FGIDs. In IBS, a positive effect is however observed; and results in animals suggest that the efficacy of probiotics is linked to effects that impact the pathways acting on visceral motility and hypersensitivity, inflammation and local immune activity, the integrity of the intestinal barrier, the composition of the microbiota and the gut-brain axis.



A PROBIOTIC FOR EACH SYMPTOM

The controversy remains regarding rhythm, urgency, rumbling, and the feeling of incomplete evacuation: inefficacy of probiotics in some studies, partial efficacy in others (no action on rhythm). However, in infantile colic, the use of probiotics based on bifidobacteria could help restore the balance of the gastrointestinal microbiota and exert a beneficial effect on immune defenses. Some studies[22, 23] have shown that supplementation with *Lactobacillus reuteri* could reduce colic. Other microorganisms such as *Bifidobacterium breve*, a dominant species found in children fed on mother's milk, might also represent approaches to be investigated[24]. In children suffering from IBS, *L. rhamnosus* and *L. reuteri* would seem to reduce the frequency and severity of abdominal pain[25, 26]. A meta-analysis[27] confirms the efficacy of probiotics in adults on symptoms associated with IBS (more for IBS-D than IBS-C), without naming any strain in particular. The World Gastroenterology Organisation[28] recommends the use of *B. infantis* to reduce abdominal pain, bloating, and normalize bowel movements. Functional constipation is thought to be improved by means of an Artichoke-*L paracasei*[29] combination. These observations open the way to detailed research into intake of synbiotics (combination of pre- and probiotics).

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[20] Joint FAO/WHO Expert Consultation on Evaluation of Health and Nutritional Properties of Probiotics in Food including Powder Milk with Live Acid Bacteria, 1-4 October 2001

[21] Lee H, Choi J, Ryu H, et al. *Therapeutic Modulation of Gut Microbiota in Functional Bowel Disorders*. J Neurogastroenterol Motil. 2017 Jan

[22] Indrio F et al. *Prophylactic use of a probiotic in the prevention of colic, regurgitation, and functional constipation: a randomized clinical trial*. JAMA Pediatr. 2014 ; 168(3) : 228-33

[23] Savino F et al. *Lactobacillus reuteri DSM 17938 in infantile colic: a randomised, double blind, placebo-controlled trial*. Pediatrics 2010 ; 126 : e526-e533

[24] Giglione E, Prodam F, Bellone S, Monticone S, Beux S, Marolda A, Pagani A, Di Gioia D, Del Piano M, Mogna G, Bona G. *The Association of Bifidobacterium breve BR03 and B632 is Effective to Prevent Colics in Bottle-fed Infants: A Pilot, Controlled, Randomized, and Double-Blind Study.* Proceedings from the 8th Probiotics, Prebiotics & New Foods for Microbiota and Human Health meeting held in Rome, Italy on September 13-15, 2015: S164-S167. J Clin Gastroenterol. 2016 Nov/Dec;50 Suppl 2.

[25] Pediatrics. 2010 Dec; A randomized controlled trial of Lactobacillus GG in children with functional abdominal pain. Francavilla R1, Miniello V, Magistà AM, De Canio A, Bucci N, Gagliardi F, Lionetti E, Castellaneta S, Polimeno L, Peccarisi L, Indrio F, Cavallo L.

[26] Jadrešin O, Hojsak I, Mišak Z, Kekez AJ, Trbojević T, Ivković L, Kolaček S. *Lactobacillus reuteri DSM 17938 in the Treatment of Functional Abdominal Pain in Children: RCT Study*. J Pediatr Gastroenterol Nutr. 2017 Jun.

[27] Ford, A. C. et al. *Efficacy of prebiotics, probiotics, and synbiotics in irritable bowel syndrome and chronic idiopathic constipation: systematic review and meta-analysis*. Am. J. Gastroenterol. 109, 1547–1561; quiz 1546 (2014).
Cited in Simrén M, Tack J. New treatments and therapeutic targets for IBS and other functional bowel disorders. Nat Rev Gastroenterol Hepatol. 2018 Jun 21

[28] http://www.worldgastroenterology.org/guidelines/global-guidelines/irritable-bowel-syndrome-ibs/irritable-bowel-syndrome-ibs-french

[29] Riezzo G, Orlando A, D'Attoma B, Guerra V, Valerio F, Lavermicocca P, De Candia S, Russo F. *Randomised clinical trial: efficacy of Lactobacillus paracasei-enriched artichokes in the treatment of patients with functional constipation--a double-blind, controlled, crossover study.* Aliment Pharmacol Ther. 2012 Feb.
Cited in Lee H, Choi J, Ryu H, et al. Therapeutic Modulation of Gut Microbiota in Functional Bowel Disorders. J Neurogastroenterol Motil. 2017 Jan

DR MARC BELLAICHE

Dr. Marc Bellaiche is a Pediatric Gastroenterologist at the Teaching Hospital Robert Debré for Mothers and Children (Paris, France). His expertise on FGIDs in children help us underline the diagnostic complexity and raise avenues for treating the disorders under investigation (targeted pro and pre-biotics), especially in the first two years of life.

MANAGING FGIDs IN CHILDREN

What diagnostic difficulties do health professionals face?

As a reminder, Rome IV criteria include seven broad types of symptoms in newborns: regurgitation, cyclic vomiting, rumination, functional diarrhea, functional constipation, dyschezia, and colic (which is the most frequent FGID between 1 and 4 months of age). All health professionals are aware of the impact of FGIDs on the welfare of children and that of their parents, but general practitioners are less informed regarding Rome IV classification. Summarizing, clarifying, and spreading the criteria from the Rome Foundation would make it easier to implement current diagnostic tools, especially regarding treatment (be it medical or medico-psychological) of young children. After the age of two, childhood FGIDs look more like that of adults and are better addressed by practitioners.

Has the increasing awareness of the intestinal microbiota changed the situation?

I believe so. For instance, the definition of infant colic has been widened: etiological hypotheses are now based on the composition of the intestinal microbiota and not exclusively on standard clinical data. But treatment for FGDIs remains complicated in young children: there is more often a combination of disorders rather than a single one, as shown by a recent cohort study of 2,700 newborn children[30]. Abundance of disorders explains the distress of some parents and increases difficulties to establish a diagnosis. For physicians, it is key to systematically refer to Rome IV criteria.

"It is key to systematically refer to Rome IV criteria."

[30] Bellaiche M, Oozer R, Gerardi-Temporel G, et al. *Multiple functional gastrointestinal disorders are frequent in formula-fed infants and decrease their quality of life*. Acta Paediatr. 2018 Jul;107(7):1276-1282. doi: 10.1111/apa.14348. Epub 2018 Apr 26

“Probiotics are a promising therapeutic avenue.”

What are the priority therapeutic areas?

Beyond pain management, dysbiosis regulation with probiotics, is a promising therapeutic avenue. Swedish researchers were the first to work on the addition of specific strains of *Lactobacillus* (*L. reuteri*) and several studies and meta-analyses agree that these lactobacilli have proven their efficacy. According to a recent clinical study, the combination of two strains of *Bifidobacterium* breve could present a potential interest and decrease duration of crying in newborns with colic and fed with formula milk. Another novel concept: formulas that combine bifidogenic prebiotics (fructo-oligosaccharids and galacto-oligosaccharides) and that seem to reduce the duration of crying. ●

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