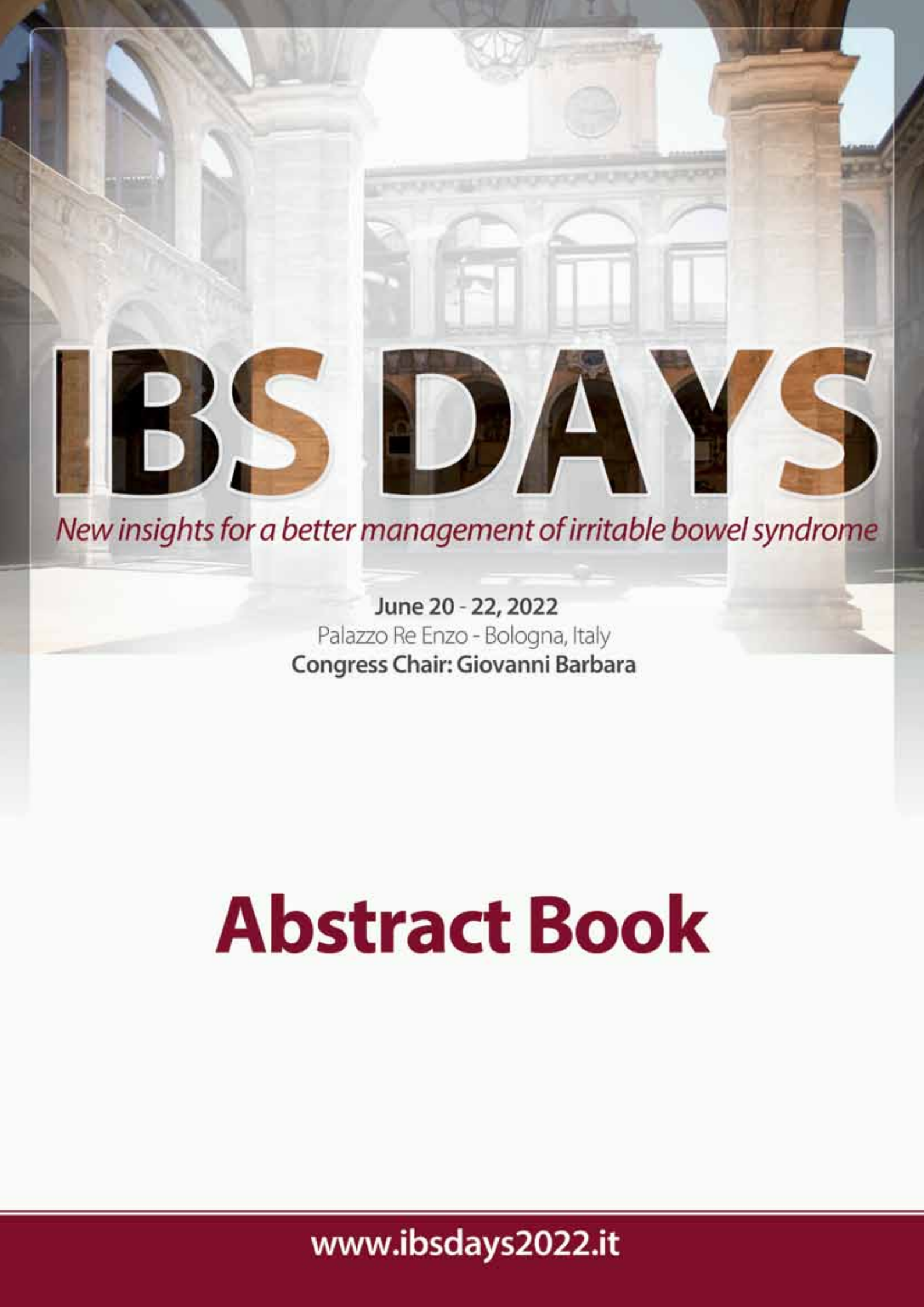




IBS DAYS

New insights for a better management of irritable bowel syndrome

June 20 - 22, 2022

Palazzo Re Enzo - Bologna, Italy

Congress Chair: Giovanni Barbara

Abstract Book

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ENDORSEMENTS



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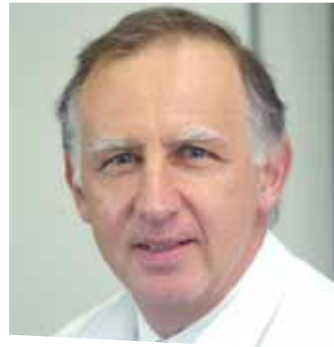
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Opening Ceremony - Monday - June 20th

Palazzo Re Enzo

18.00 **Welcome**

Giovanni Barbara, Congress Chair, *University of Bologna*

Vincenzo Stanghellini, Scientific Committee Chair, *University of Bologna*

Giovanni Molari, Rector, *University of Bologna*

Pierluigi Viale, Director, Department of Medical
and Surgical Sciences, *University of Bologna*

Francesco Saverio Violante, President, School of Medicine, *University of Bologna*

Chiara Gibertoni, General Director, IRCCS Policlinico St. Orsola, Bologna

Gilberto Poggioli, Director, Medical and Surgical Department of Digestive Hepatic
and Endocrine Metabolic Diseases, IRCCS Policlinico St. Orsola, Bologna

18.30 **Lecture**

**Under The Porticos. Tales of Art and Mystery
in Bologna**

Marco Riccomini (Italy)

19.30 **Welcome Cocktail**

Program - Tuesday - June 21st

Plenary Session - Palazzo Re Enzo

07.00 **Registration**

08.00 **Program Overview**

Giovanni Barbara (Italy)

Session I - Rome Foundation Symposium

Chairs: Jan Tack (USA), Vincenzo Stanghellini (Italy)

08.30 **The Global Burden of DGBI**

Magnus Simren (Sweden)

08.55 **Chronic Abdominal Pain**

Douglas Drossman (USA)

09.20 **Extra-Intestinal Comorbidities**

Lin Chang (USA)

10.05 **Coffee Break**

Session II - Clinical Entities and Diagnostic Process

Chairs: Lin Chang (USA), Enrico Corazziari (Italy)

10.30 **The Diagnostic Process in the Difficult Patient:
How Much in Depth Should We Go?**

Brian Lacy (USA)

10.55 **Is IBS a Micro-Organic Disease?**

Giovanni Barbara (Italy)

11.20 **Boundaries Between IBS and Intestinal Organic
Disease**

Eamonn Quigley (USA)

Session III - Brain to Gut - Gut to Brain

Chairs: Magnus Simren (Sweden),
Giovanni Barbara (Italy)

- 11.45 **Influence of Psychological Factors in IBS**
Laurie Keefer (USA)
- 12.10 **The Multi-Dimensional Pain Experience in Patients with IBS**
Qasim Aziz (United Kingdom)
- 12.35 **Bile Acid Malabsorption in IBS-D**
Michael Camilleri (USA)
- 13.00 ***Lunch Break and Poster session***
- Poster session**
- Moderators**
Gabrio Bassotti (Italy)
Gabriele Bazzocchi (Italy)
Francesca Galeazzi (Italy)
Paola Iovino (Italy)

Program - Tuesday - June 21st

Workshop I – Oratorio di San Giovanni Battista dei Fiorentini

Chairs: Qasim Aziz (United Kingdom), Roberto De Giorgio (Italy)

- 14.30 **SPONSORED LECTURE - GE Healthcare The Added Value of SeHCAT Test in the Work Up of Patients with BAD. The Spanish Experience**
Jordi Guardiola Capon (Spain)
- 15.00 **Cannabinoids and DGBI**
Giovanni Sarnelli (Italy)
- 15.25 **Motility: What are We Learning with HRM?**
Maura Corsetti (United Kingdom)
- 15.50 **Effect of Dietary Fibre on the Small and Large Intestine: Novel Insights from MRI**
Robin Spiller (United Kingdom)
- 16.15 **Update on H2020 DISCOVERIE Project**
Development, Diagnostic and Prevention of
Gender-Related Somatic and Mental
Comorbidities in IBS in Europe
Javier Santos (Spain)

- 16.40 : **Coffee Break**
- : **Free Paper Session**
- : Chairs: Robin Spiller (United Kingdom),
- : Maura Corsetti (United Kingdom)
- 17.00 : **Effect of Transplant Route of Administration on the Outcome of Fecal Microbiota Transplantation for Patients with IBS**
- : Magdy El-Salhy (Norway)
- 17.15 : **Microbial Histamine Induces Visceral Hyperalgesia Through H4 Receptor Dependent Mechanisms**
- : Giada De Palma et al. (Canada)
- 17.30 : **Diagnostic Methods for Idiopathic Bile Acid Diarrhea**
- : Greger Lindberg et al. (Sweden)
- 17.45 : **The DOMINO Trial: Therapeutic Outcome and Predictors of a New FODMAP Lowering Diet Smartphone Application Vs. Medication in Primary Care IBS**
- : Florencia Carbone et al. (Belgium)
- 18.00 : **Adjourn**
- 20.00 : **Gala Dinner**

Program - Tuesday - June 21st

Workshop II – Palazzo Re Enzo

Chairs: Mauro D'Amato (Italy), Cesare Cremon (Italy)

- 14.30 : **SPONSORED LECTURE - Schwabe Pharma Italia Herbal Medicinal Treatment Options in DGBI**
- : Ahmed Madisch (Germany)
- 15.00 : **SPONSORED LECTURE - Diadema Farmaceutici Effect of dietary geraniol in irritable bowel syndrome**
- : Giovanni Barbara (Italy)
- 15.25 : **Wheat Immunogenic Proteins: Myths, Reality and Misconceptions**
- : Elena Verdù (Canada)

- 15.50 : **FODMAPs: Choosing Wisely**
Enrico Corazziari (Italy)
- 16.15 : **Probiotics: Current Evidence and Future Perspectives**
Francisco Guarner Aguilar (Spain)
- 16.40 : **Coffee Break**
- 16.40 : **Free Paper Session**
Chairs: Brian Lacy (USA),
Maria Raffaella Barbaro (Italy)
- 17.00 : **A Pilot Nutrigenetic Study of Response to Dietary Intervention in Irritable Bowel Syndrome**
Andreea Zamfir Taranu et al. (Spain)
- 17.15 : **A Randomized Controlled Clinical Trial Comparing Two Different Carbohydrate Restrictive Diets and Optimized Medical Treatment in Irritable Bowel Syndrome (IBS): The CARIBS Study**
Sanna Nybacka et al. (Sweden)
- 17.30 : **The Faecal Abundance of Collinsella Aerofaciens and Other Potential Pathobionts May Predict the Clinical Efficacy of the Probiotic Lactobacillus Paracasei DG in Non-Constipated IBS Patients**
Simone Guglielmetti et al. (Italy)
- 17.45 : **Large-scale GWAS Meta-analyses of Stool Frequency and Consistency Identify Actionable Pathways Relevant to Gut Dysmotility and Irritable Bowel Syndrome**
Isotta Bozzarelli et al. (Spain)
- 18.00 : **Adjour**
- 20.00 : **Gala Dinner**

Program - Tuesday - June 21st

Workshop III – Auditorium Enzo Biagi - Sala Borsa

Chairs: Lin Chang (USA), Massimo Bellini (Italy)

14.30 : **Communication Skills Workshop**

: Douglas Drossman (USA)

16.00 : **Breath Testing in IBS**

: Daniel Pohl (Switzerland)

16.25 : **UEG / ESNM Guidelines on Functional Bowel Disorders with Diarrhea**

: Edoardo Savarino (Italy), Giovanni Barbara (Italy)

16.50 : **Break (Coffee and refreshment available throughout)**

: **Free Paper Session**

: Chairs: Daniel Pohl (Switzerland),

: Guido Basilisco (Italy)

17.10 : **Environmental Factors and Irritable Bowel Syndrome, New Prospective by
Pandemic Restrictive Measures: the “Cocoon Effect”**

: Stefano Kayali et al. (Italy)

17.25 : **A Possible Gut Microbiota Signature in Patients With Bloating:
Results from Real Life**

: Stefania Piccirelli et al. (Italy)

17.40 : **Anxiety, Depression, and Somatic Symptoms Overlap: Implications for The
Presentation of Disorders of Gut-Brain Interaction in a Global Epidemiologic
Sample**

: Ines A. Trindade et al. (Sweden)

17.55 : **Irritable Bowel Syndrome, Depression and Anxiety:
Genetic Overlap and Causality**

: Amanda Rodriguez Urrutia (Spain)

18.10 : **Adjourn**

20.00 : **Gala Dinner**

Program - Wednesday - June 22nd

Plenary Session – Palazzo Re Enzo

Session IV - Infection

Chairs: Francisco Guarner Aguilar (Spain),
Marco Ventura (Italy)

08.00 **Highlights from Tuesday's Free Paper Sessions**

Robin Spiller (United Kingdom), Brian Lacy (USA),
Daniel Pohl (Switzerland)

08.30 **Long COVID and DGBI**

Giovanni Marasco (Italy)

08.55 **Post-C. Difficile Gut Dysfunction: A Variant of PI-IBS**

Stephen Collins (Canada)

Session V - Genetics and Barriers

Chairs: Javier Santos (Spain),
Robin Spiller (United Kingdom)

09.20 **Genetic Factors**

Mauro D'Amato (Italy)

09.45 **Leaky Gut: Triggers and Therapeutic Modulation**

Antonio Gasbarrini (Italy)

10.10 **The Vascular Barrier: New Player in the Gut-Brain Axis**

Maria Rescigno (Italy)

10.35 **Coffee Break**

Session VI - Microbiota

Chairs: Nathalie Vergnolle (France), Patrizia Brigidi (Italy)

11.00 **The Microbiota-Brain Axis**

Premysl Bercik (Canada)

11.25 **Gut Microbiome, Diet and Symptoms**

Francisco Guarner Aguilar (Spain)

- 11.50 **FMT: State-of-the-Art and Future Indications**
Colleen Kelly (USA)
- Session VII - Management**
Chairs: Eamonn Quigley (USA),
Peter Malfertheiner (Germany)
- 12.15 **Current and Future Management of IBS-C**
Carmelo Scarpignato (Malta)
- 12.40 **Current and Future Management of IBS-D**
Jan Tack (Belgium)
- 13.05 **Concluding Remarks and Awards
for Best Abstracts**
Giovanni Barbara (Italy)
- 13.15 ***Lunch***

Lectures



The Multi-Dimensional Pain Experience in Patients with IBS

Qasim Aziz

Professor of Neurogastroenterology, Centre for Neuroscience, Surgery and Trauma, Blizard Institute, Wingate Institute of Neurogastroenterology, Barts and the London School of Medicine and Dentistry, Queen Mary University of London

Biosketch

Professor Aziz after completing his undergraduate medical training in his native Pakistan he came to the UK in 1988 for higher medical training. After completing core medical training in Manchester, he started his research career at the University of Manchester as a Digestive Disorders Foundation (currently CORE) clinical research fellow and obtained his PhD in 1996. He held posts of Lecturer, Senior Lecturer, and Professor of Gastroenterology at the University of Manchester, and is now Professor of Neurogastroenterology and Director of The Wingate Institute of Neurogastroenterology at Barts and The London School of Medicine and Dentistry at Queen Mary, University of London.

Professor Aziz has obtained national and international awards for his research the two most important being the British Society of Gastroenterology Research Gold Medal and the American Gastroenterology Association, Janssen Award for Basic and Clinical Research. He has published numerous original articles in reputed medical journals such as Nature Medicine, Nature Neuroscience, Lancet and Gastroenterology. He has held the position of Chairman, Neurogastroenterology and Motility Section of the British Society of Gastroenterology, executive committee member of the European Society of Neurogastroenterology and Motility and member of the United European Gastroenterology Federation Education Committee. He is currently co-lead for World Health Organisations ICD-11 coding for visceral pain and past Chair of the Abdominal and Pelvic Pain Special Interest Group of the International Society for the Study of Pain. He has been a member of Rome III and Rome IV Committees for criteria for Functional Gastrointestinal Disorders. He is also a member of the Association of Physicians and Surgeons of UK and Ireland. He is currently gastroenterology speciality lead for North Thames Clinical Research Network.

Abstract

Pain is a multidimensional experience and involves sensory discriminative, cognitive and emotional components. The contribution that each component makes to the pain experience may vary between individuals and thus contributes to the inter-individual differences often seen in patients including those with IBS. Variation in the cognitive and emotional response to pain in particular is dependent on a range of psychophysiological factors such as personality, early life experiences, co-existing anxiety and depression, autonomic, immune, genetic and epigenetic factors. However other coexisting clinical factors can also influence the way in which patients with IBS experience and report pain.

In IBS patients, abdominal pain is typically associated with bowel movements. However, in many patients these typical features are confounded by other factors which leads to an evolution of pain into more complex and multi-dimensional features. For instance, an IBS patient may develop abdominal wall pain after abdominal trauma or surgery and this requires treatment which is very different from that of IBS. Similarly, other conditions such as abdominal migraine may also overlap. Contributions from small intestinal bacterial overgrowth and food intolerance / allergy may also be prominent in some patients. Rarely, abdominal vascular entrapment syndromes may also be identified in a patient who typically presented with IBS symptoms but overtime there is an evolution of symptoms into a more post prandial pattern which may be confused with functional dyspepsia. Therefore, it is important for the physician to be aware of the multitude of possibilities that may contribute to the experience of chronic abdominal pain in a patient who has a primary diagnosis of IBS.



Is IBS a Micro-Organic Disease?

Giovanni Barbara

Professor of Internal Medicine and Gastroenterology

Chief, Division of Internal Medicine, neuovascular, hepatic and metabolic disease

Acting Chief, Division of Gastroenterology

Biosketch

Giovanni Barbara is Full Professor of Internal Medicine and Gastroenterology, Chief of the Internal Medicine Neurovascular and Hepatic-Metabolic Division and Chief of the Gastroenterology Division at the University of Bologna, Italy.

He graduated summa cum laude in Medicine at the University of Bologna. He subsequently qualified in internal medicine and then in gastroenterology at the same University. He was trained partly in London, UK and completed a 3-year post-doctoral research fellowship in neuro-immunology at McMaster University, Canada.

Professor Barbara's main research interests relate to basic and clinical aspects of Disorders of Gut-Brain Interaction and Neurogastroenterology, and he has authored more than 250 indexed peer-reviewed articles and reviews on these topics, published in various biomedical journals, including Gastroenterology, Gut, Journal of Clinical Investigation, PNAS and Trends in Pharmacological Sciences. He is, or has been, a member of the Editorial Boards of Gut, the American Journal of Gastroenterology, Neurogastroenterology and Motility, the American Journal of Physiology, Clinical Gastroenterology and Hepatology.

Professor Barbara has received national and international awards including those from the American Gastroenterological Association (1996), the Functional Brain Gut Research Group (1997), the European Society of Neurogastroenterology and Motility (2000) and the Master Award in Gastroenterology from the American Gastroenterological Association (2007).

He is currently member of the Board of Directors of the Rome Foundation, Past-President of the European Society of Neurogastroenterology and Motility (ESNM) and currently Chair of the Gut Microbiota and Health Section of ESNM.

Abstract

Is IBS a Micro-Organic Disease? Irritable bowel syndrome (IBS) is one of the most common conditions diagnosed in gastroenterology practice. The prevalence of IBS is around 4% worldwide according to a recent international survey conducted by the Rome Foundation. Although the etiology of IBS is still obscure, its pathophysiology is dominated by a combination of both psychological factors and gastrointestinal dysfunction. Recent efforts have allowed identification of several peripheral

microorganic abnormalities. These include changes in gut microbiota, low-grade mucosal inflammation, and epithelial dysfunction. Additionally, genetic polymorphisms and environmental factors, including dietary factors and enteric infections, have been shown to play a role. The identification of these factors and their interaction with the brain has opened an entirely new era in the understanding, recognition, and legitimization of IBS and functional gastrointestinal disorders (FGID). As a consequence, there has been agreement among experts to eliminate the term functional from Rome IV criteria and redefine these conditions as disorders of gut-brain interactions (DGBI).

Effect of Dietary Geraniol in IBS

Giovanni Barbara

Abstract

Geraniol is an acyclic monoterpene alcohol with well-known anti-inflammatory and antimicrobial properties. Geraniol has demonstrated eubiotic activity on the gut microbiota both in preclinical models of colitis and in patients with IBS. We recently evaluated microbiota modulation and symptoms improvements in patients with Rome III IBS treated with geraniol in a double-blind, placebo-controlled, randomized multicenter trial involving 56 patients. There was some significant difference in microbiota composition after geraniol administration. Symptoms as assessed by IBS-SSS score after geraniol administration were significantly reduced compared to placebo (IBS-SSS score 195 vs 265, $p=0.001$). We found a significant difference in the rate of responders according to IBS-SS score (geraniol 52% vs placebo 16.7%), mainly due to the rate of responders in IBS-M subtype (geraniol 53.9% vs placebo 7.7%, $p=0.011$). Adverse events were comparable between the treatment groups and geraniol therapy was well tolerated.



The Microbiota-Gut-Brain Axis

Premysl Bercik

Professor, McMaster University Hamilton, ON, Canada

Biosketch

Dr. Bercik received an MD degree from Charles University, Prague, Czechoslovakia, and a doctoral degree from the University of Lausanne, Switzerland. He completed a residency in internal medicine at General University Hospital, Prague followed by post-doctoral research training and gastroenterology fellowship at McMaster University, Canada. Dr. Bercik has been on the faculty at McMaster University since 2007, currently at the rank of Professor.

Dr. Bercik is a clinician-scientist, with research interests including both clinical and basic research in the microbiota-gut-brain axis, functional bowel disorders, neuro-immune interactions and celiac disease. He published over 130 peer-reviewed papers; his current Google Scholar h-index is 62, with more than 17,000 citations. He was awarded the 2021 Research Excellence Award from Canadian Association of Gastroenterology.

Dr. Bercik's research in microbiome spans over 25 years, originating with studies on the role of *H. pylori* in acid secretion, followed by the role of commensal bacteria on gut motility and visceral sensitivity, and finally exploring interactions between the microbiota and brain function. He strongly believes that while associations have been established between the microbiome and many gastrointestinal conditions, the future of microbiome research in gastroenterology resides in proving causality and increasing mechanistic understanding that will lead to therapies.

Abstract

Accumulating data suggests that gut microbiota affects brain structure and function, likely through multiple mechanisms, including immune, metabolic and neural pathways. This is well illustrated by animal studies, mainly in gnotobiotic mice. Compared with conventional mice,

germ-free mice display anxiolytic and altered social behavior, impairment of blood brain barrier, altered hypothalamic-pituitary-adrenal axis and microglia function. Interestingly, most of these abnormalities normalize after bacterial colonization. Maternal microbiota serves as the major inoculum for initial colonization, and its disruption may alter mouse brain maturation, leading to impaired behavior in adulthood. Indeed, antibiotic treatment during infancy increases risk of development of mental illness in children, suggesting that perturbation of the host-microbial cross-talk in early life may have long-term consequences. Our latest data suggest that innate immune system plays a key role in the first critical steps that initiate microbial-host interaction and mechanisms, which lead to establishment of normal behavior. Gut microbiota affects the brain function also in later stages in life, as antibiotic treatment in adulthood may transiently alter behavior and brain chemistry. Microbiota composition seem to differ between patients with psychiatric and neurodegenerative disorders, and transferring these microbiota profiles into germ-free mice induces abnormal behavioral phenotype. Microbiota may also have beneficial effects on the host, as several probiotic strains were shown to improve anxiety and depressive-like behavior in animal models. We have shown that a specific probiotic can improve depression scores and abnormal brain activity in patients with IBS, likely due to production of bioactive metabolites.



Bile Acid Malabsorption in IBS-D

Michael Camilleri

Professor of Medicine, Pharmacology, and Physiology at Mayo Clinic College of Medicine and Science, Consultant in the Division of Gastroenterology and Hepatology at Mayo Clinic in Rochester, Minnesota USA

Biosketch

Michael Camilleri is Professor of Medicine, Pharmacology, and Physiology at Mayo Clinic College of Medicine and Science and is Consultant in the Division of Gastroenterology and Hepatology at Mayo Clinic in Rochester, Minnesota. His research interests include clinical enteric neurosciences, gut neurohormonal control, obesity, irritable bowel syndrome, and pharmacology and pharmacogenomics; his work is funded by National Institutes of Health. He has received numerous awards and honors including the 2012 Ismar Boas Medal from the German Society of Digestive and Metabolic Disease, the 2012 American Gastroenterological Association (AGA) Distinguished Mentor Award, the Janssen Research Award, the AGA Joseph B. Kirsner Award, the AGA Julius Friedenwald Medal in 2021, as well as honorary doctorates from the University of Antwerp (Belgium) and the University of Malta, and he was elected to the membership of the prestigious Association of American Physicians. Dr. Camilleri participates in educational and mentorship activities at Mayo Clinic and has mentored more than 80 national and international postdoctoral fellows and scientists. He maintains an active clinical practice in gastroenterology at Mayo Clinic, specializing in gastrointestinal motility disorders, gastroparesis, and functional GI disorders. He is Past-President of the American Neurogastroenterology and Motility Society and the American Gastroenterological Association, former editor of *Clinical Gastroenterology and Hepatology* and *Neurogastroenterology and Motility*.

Abstract

Support: NIH R01-DK115950

The objective of the talk is to review what is known about idiopathic bile acid diarrhea (BAD) and to review recent studies comparing BAD with IBS-diarrhea without altered bile acid metabolism,

with specific focus on diagnosis, impact (symptoms, QOL), colonic transit, permeability, bile acid metabolism, fecal short chain fatty acids, ileal and colonic mucosal mRNA expression, and fecal microbiota.

Prevalence: An SRMA of the literature on BAD in IBS-D or functional diarrhea demonstrates that about 25% of patients have evidence of BAD. It is estimated that 1% of the general population has BAD.

Diagnosis: The most widely used diagnostic tests are ⁷⁵SeHCAT retention, fasting serum 7αC4 and FGF-19, 48h fecal bile acids, and combined serum 7αC4 and percent primary fecal bile acids in a random stool sample.

Putative Mechanisms: Primary BAD has been associated with reduced functional expression of FGF-19 in ileal biopsies in response to stimulation by bile acids or by protein expression on immunohistochemistry.

1. There are five pivotal genes that may play a role in the absorption (SLC10A2) and feedback regulation of bile acid synthesis [NR1H4 (gene for the nuclear farnesoid X receptor of ileal enterocyte that determines FGF-19 levels in portal blood); klotho β (KLB) and FGF-4 (FGF-R4) which together determine the FGF-19 feedback regulation of hepatocyte synthesis of bile acids]. The fifth gene, TGR5, is the gene for the receptor mediating effects of bile acids in target organs, e.g., colonic motility and transit.
2. Fecal bile acids may be impacted by colonic transit and microbiota. The microbiota impacts the deconjugation, dehydroxylation, and sulfation of conjugated bile acids in the colon and their biological effects. Increased proportions of chenodeoxycholic acid (CDCA) and cholic acid (CA) were demonstrated in IBS-D patients with elevated total fecal bile acid excretion over 48 hours.

Overview of Recent Original Research: In patients with Rome III criteria of IBS-D, we compared impact (symptoms, QOL), biochemical features, colonic transit, rectal sensation, deep genotype of 5 bile acid-related genes, ileal and colonic mucosal mRNA [differential expression (DE) analysis], and stool dysbiosis (including functional analysis of microbiome). Results in BAD were compared to IBS-D without abnormal bile acid metabolism. Among 219 patients (79% female) with IBS-D, 44 had BAD; the BAD group were significantly older and had higher body mass index (BMI) than those without BAD. Patients with BAD had more severe bowel dysfunction and impact on IBS-QOL (need of toilet proximity) and were more likely to receive antidiarrheals, bile acid binders, and antacid secretory agents compared to IBS-D without BAD. Severity of diarrhea and need of toilet proximity were predictors of BAD in IBS-D ($P < 0.01$). Patients with BAD were more likely to have depression score > 8 on HAD inventory. Compared to 161 patients with IBS-D without abnormal bile acid metabolism, 44 patients with BAD had significantly faster colonic transit, increased intestinal permeability, lower microbial alpha diversity, different compositional profile (beta diversity), and higher Firmicutes to Bacteroidetes ratio, with evidence of decreased expression of bile acid thiol ligase (involved in transformation of primary to secondary bile acids) and decreased sulfatases. In BAD (compared to IBS-D without abnormal bile acid metabolism), terminal ileal biopsies showed downregulation of SLC44A5 (a bile acid transporter), and ascending colon biopsies showed upregulation in barrier-weakening genes (CLDN2), serine protease inhibitors, immune activation, cellular differentiation, and a cellular transporter, FABP6, (BA binding). No differential expression of genes was documented

in descending colon biopsies. The two groups had similar rectal sensation.

Conclusion: Though sharing clinical symptoms with IBS-D, BAD is associated with biological differences and mechanisms having potential to enhance diagnosis and treatment (e.g., barrier function, inflammatory and microbial changes).

References

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3. BouSaba J, et al. Impact of bile acid diarrhea in patients with diarrhea-predominant irritable bowel syndrome on symptoms and quality of life. *Clin Gastroenterol Hepatol* 2021 Dec 4:S1542-3565(21)01273-8
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Extraintestinal Comorbidities

Lin Chang

Professor of Medicine and Vice-Chief of the Vatche and Tamar Manoukian Division of Digestive Diseases, Department of Medicine at the David Geffen School of Medicine at UCLA, USA

Biosketch

Lin Chang, MD is a Professor of Medicine and Vice-Chief of the Vatche and Tamar Manoukian Division of Digestive Diseases, Department of Medicine at the David Geffen School of Medicine at UCLA. She serves as the Co-Director of the G. Oppenheimer Center for Neurobiology of Stress and Resilience at UCLA. She is also Program Director of the UCLA Gastroenterology Fellowship Program. Dr. Chang's clinical expertise is in disorders of gut-brain interaction (also known as functional gastrointestinal disorders). Her research focuses on brain-gut interactions underlying irritable bowel syndrome (IBS), specifically, the pathophysiology of IBS related to stress, early life adversity, sex differences, genetic and epigenetic factors, and gut microbiome and the treatment of IBS. She has recently served as the Clinical Research Councilor of the AGA Governing Board. She previously served as President of the American Neurogastroenterology and Motility Society (ANMS) and is a member of the Rome Foundation Board of Directors.

Abstract

Irritable bowel syndrome (IBS) and other disorders of gut-brain interaction (DGBI) coexist with extraintestinal symptoms and disorders more frequently than would occur by chance. Some have referred to these disorders collectively as functional somatic syndromes. Functional somatic syndromes are characterized by the presence of one or more chronic symptoms that cannot be attributed to an identifiable organic cause. These include temporomandibular joint disorder (TMD), interstitial cystitis/chronic pelvic pain, tension headache, fibromyalgia, and chronic fatigue syndrome (CFS). They are complex disorders associated with significant impact on health-related quality of life (HRQOL) and be managed using an integrated biopsychosocial approach.

Somatic disorders that occur more frequently in DGBI are not limited to other chronic pain disorders, such as fibromyalgia, but also include many disorders common in the general population. Increased somatic symptoms (e.g., fatigue, headache, backaches) and/or increased somatization scores are associated with DGBI. Many studies have also demonstrated that sleep disturbance (i.e., poor sleep quality, insomnia) is associated with DGBI. Comorbid somatic disorders have been found to be more common among IBS patients with psychiatric disorders, but comorbidity was increased even in IBS patients without psychiatric diagnoses. It has been hypothesized that the comorbidity does not result from any specific disease associations, but rather from “hypervigilance for noticing somatic sensations and a lower threshold for consulting a physician”. However, studies have suggested shared pathophysiologic mechanisms between IBS and other somatic pain disorders. The presence of an IBS-related comorbidity such as dyspepsia, interstitial cystitis, GERD, dyspareunia, migraine headaches, fibromyalgia, and sleep disturbances increases health care utilization. Predictors of impaired work productivity among IBS patients includes the presence of comorbid extra-intestinal diagnoses such as fibromyalgia or interstitial cystitis and GI-specific anxiety.

Psychiatric disorders have also been shown to be more common in IBS, including generalized anxiety panic attacks, stress reaction, somatization disorder, depression, and substance abuse. Depression and anxiety are more prevalent in the pain-predominant DGBI in the majority of studies, but data is stronger for an association with anxiety than depression. Psychiatric comorbidity in treatment-seeking populations is as high as 58%; however, the relationship between psychiatric comorbidity and DGBIs could be bi-directional. Anxiety and depression symptoms are associated with increased GI symptom severity, alterations in autonomic tone and visceral sensitivity as measured by lactulose challenge. Anxiety about health has also been commonly associated with DGBI and appears to be a risk factor distinct from depression and anxiety.

Management of DGBI, particularly in patients with moderate to severe symptoms, is best approached by addressing not only GI symptoms but extraintestinal symptoms and/or disorders. However, the coexistence of extraintestinal symptoms and disorders in patients with DGBI can be more challenging to diagnose and treat since patients are often seen by multiple health care providers of different specialties and undergo multiple diagnostic tests. Nonetheless, establishing a positive diagnosis of DGBI, developing an effective provider-patient relationship, recommending treatments for DGBI that can also be efficacious for other somatic or psychologic disorders, such as brain-gut behavior therapies and central neuromodulators, and providing an integrated care approach can help to successfully manage symptoms and improve HRQOL.

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Gut Dysfunction Following Clostridium Difficile Infection; A New Form of Post-Infectious “IBS”?

Stephen Collins

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Biosketch

Dr. Stephen M Collins obtained his medical training at University College, London and at The Westminster Hospital Medical School, London UK. He trained in gastroenterology at McMaster University in Canada before completing 3 years of research training in cell biology at the Digestive Diseases Branch of the National Institutes of Health (NIH) in Bethesda, Maryland USA. He has been a faculty member at McMaster University since 1981, becoming Director of the Intestinal Diseases Research Unit from 1983-1993, and Head of the Division of Gastroenterology since 1993-2006. His research has focused on the role of pathogenic and commensal microbes in the pathogenesis of functional intestinal disorders. His work has generated over 250 peer-reviewed publications including papers in Nature Medicine, Science Translational Medicine, Lancet, PNAS, Gastroenterology and Gut. He is past president of the Canadian Association of Gastroenterology and has served on advisory committees for Crohn's and Colitis Foundations of America and of Canada. He has served on review panels for the Gairdner Award for Biomedical Research and the Canada Wightman Award. Dr. Collins established and directs The Farncombe Family Digestive Health Research Institute at McMaster University where he is also the Associate Dean for Research in the Faculty of Health Sciences. He is a Fellow of the Royal Society of Canada.

Abstract

Recurrent Clostridium Difficile Infection (RCDI) is a common problem in hospital and community-based patients and often requires protracted antibiotic therapy for eradication¹.

Studies have demonstrated that up to 25% of patients recovered from RCDI the chronic GI symptomatology reminiscent of post-infectious IBS¹⁻⁴. Within this group we have found several

patients who present with severe colonic inertia and refractory constipation. Our observation is that this problem occurs in those treated only with antibiotics as opposed to FMT, raising the hypothesis that the microbiota may play a role in the development of post-RCDI colonic failure, although toxin-induced damage of glial cells has been implicated⁵. To address this, we investigated the ability of microbiota from 2 such patients to influence colonic function when transferred into germ free mice.

Our results show reduced diversity and compositional change in the microbiota of post-RCDI patients compared to controls. Colonization of mice with post RCDI microbiota, but not that of healthy controls, resulted in slow colonic transit. This was accompanied by degeneration of the Interstitial Cell of Cajal (ICC) network and macrophage activation and infiltration of the colonic neuromuscular layers. Clodronate depletion of macrophages restored normal transit. Administration of fecal microbial transfer (FMT) to mice colonized with RCDI microbiota reversed the slow transit, disruption of the ICC network and macrophage activation, confirming the role of the microbiota in this condition. We next attempted to improve the condition using diet-induced changes in the microbiota and found that 15% psyllium improved microbiota composition, normalized transit and improved ICC damage and macrophage infiltration and this was accompanied by increased fatty acid production. The benefit of psyllium did not persist after stopping the fiber.

Together these results identify a dysbiotic microbiota as a likely contributor to colonic inertia post-RCDI. Thus, we predict that this subgroup occurs only in antibiotic-, but not FMT-treated RCDI patients. The underlying mechanism involves macrophage activation and destruction of the ICC network and can be reversed with FMT or psyllium. Further studies are required to determine the prevalence of slow transit constipation in antibiotic-treated patients with RCDI and to evaluate the clinical efficacy of FMT and psyllium in the prevention and treatment of colonic dysfunction post RCDI.

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FODMAPs: Choosing Wisely

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Biosketch

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Abstract

The term FODMAP (Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols) identifies those substances that once ingested and fermented by the intestinal microbiota attract water, release hydrogen and methane, and reduce histamine release. These effects do not cause any disturbance in healthy people; however, in subjects with predisposing factors, such as increased intestinal permeability and visceral hypersensitivity, the resulting distension of the intestinal loops may cause abdominal discomfort such as pain, bloating and abdominal distension and diarrhea.

A diet that reduces the intake of FODMAP (Low FODMAP diet) is highly effective in reducing symptoms in a subgroup of the numerous patients suffering from irritable bowel syndrome (IBS) both in the short and long term. Regrettably there is no general consensus and no markers to identify responders to the Low-FODMAP diet.

The Low-FODMAP diet includes three phases: the first of FODMAP restriction, the second of trial

and error gradual reintroduction of FODMAP containing foods , and a third of customization of the long-term diet. Excessive restrictions, calorie and nutrient inadequacies should be avoided. Clinical experience and several studies indicate that the success of a Low-FODMAP diet requires that it should be managed by an expert nutritionist and be tailored to the individual's habitual diet. NICE guidelines for IBS indicates the low FODMAP diet as a second-line therapy following general lifestyle and dietary advice that, nonetheless, suggests to reduce some foods containing FODMAPs and. as expected , it is less effective than a Low-FODMAP diet .

The Low-FODMAP diet has proven to be effective in IBS, but it has been attempted in other pathological conditions with increased intestinal epithelial permeability and hypersensitivity.

A non-pathological condition of increased intestinal permeability occurs during physical activity and the Low-FODMAP diet has been shown to improve the performance of endurance sport.

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Motility: What are We Learning with High-Resolution Manometry?

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Biosketch

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Abstract

Irritable bowel syndrome (IBS) is a functional disorder characterized by the presence of recurrent abdominal pain or discomfort in association with abnormalities in the frequency and shape of stool (1). The prevalence of IBS is around 10% in Western countries, and due to its chronic relapsing course, up to 50% of patients see a doctor for these symptoms (2). Several mechanisms have been implicated in the pathophysiology of IBS symptoms, including impaired gastrointestinal motility. The presence of impaired motility of the gastrointestinal tract has been described in studies since the early 1960s, and proposed as a diagnostic feature of IBS (3). However, motility abnormalities have been reported to correlate imperfectly with symptomatic intestinal disorders in IBS (4). It is unclear whether this is related to the fact that conventional manometry has not been able to identify subtle motor abnormalities.

The introduction of high-resolution manometry has improved the clinical accuracy of esophageal manometry, which has been shown to be predictive of treatment response in patients with achalasia (5, 6). This did not happen for the manometry of the small intestine and colon.

The literature will be critically reviewed to evaluate the most recent studies applying high-resolution manometry to study upper and lower gastrointestinal motility to demonstrate what we are learning about the role of motility in health and disease.

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Genetic Factors

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Biosketch

Mauro D'Amato investigates how genetic variations predispose to gastrointestinal (GI) disease. Through computational and genetic approaches, his team strive to identify causative genes and the mechanisms by which they affect risk to inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), and other GI conditions. They also study how human genes influence gut microbiota composition, and the dysregulation of this interaction in human disease. Their ultimate goal is a translational application for improved therapeutic precision in gastroenterology. Mauro D'Amato is an IKERBASQUE Research Professor, and Head of the Gastrointestinal Genetics Unit at the BioDonostia Health Research Institute in San Sebastian, Spain. He formed in Rome at the University "La Sapienza" and the National Research Council. Later, first as a postdoctoral fellow and then as senior researcher, Mauro worked at the Wellcome Trust Center for Human Genetics in Oxford UK, and the Karolinska Institutet in Stockholm Sweden, where he currently holds a Visiting Professor chair in Gastrointestinal Genetics. Mauro has published more than 130 articles in the area, conceived and coordinates the bellygenes initiative on the genetics of IBS (www.bellygenes.org), and has established large international collaboration that constitutes an excellent platform for the development of junior scientists and clinical researchers.

Abstract

Genetic research in IBS has been generally scarce and characterized by small underpowered studies, mostly leading to inconclusive results. As proposed already ten years ago, population-based approaches for powered IBS genetic studies recently became a tangible opportunity thanks to the availability of a wealth of genomic and health-related data from large international cohorts and biobanks. At the same time, these data have allowed the study of gut motility and other endophenotypes by looking at their proxies (ie stool frequency and consistency) in questionnaire-based analyses of unprecedented sample size. A few large-scale genetic

surveys, including four powered genome-wide association studies (GWAS), have thus led to the discovery of genes, cell types and molecular pathways associated with credible genetic effects on IBS risk and/or intestinal transit time (whose heritability was demonstrated for the first time). Compelling evidence links now IBS and gut (dys)motility to DNA sequence variation in genes involved in the digestion of carbohydrates, ion channel function, neurotransmitters and their receptors, motor neurons and neuronal pathways, mood and anxiety disorders, and bidirectional communication along the gut-brain axis. In particular from GWAS studies of stool frequency, polygenic scores summarizing the genetic make-up of individuals were shown to allow the identification of those more likely (up to 5 times) to suffer from IBS with diarrhea than the rest of the population. Altogether, recent findings represent important breakthroughs in the long-lasting quest for IBS genes, and warrant additional studies that may ultimately and collectively contribute to the delineation of personalised risk predictive models and therapeutic interventions.



Chronic Abdominal Pain

Douglas A. Drossman

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Biosketch

Dr. Drossman received his M.D. degree at Albert Einstein College of Medicine and specialized in biopsychosocial (psychosomatic) medicine and Gastroenterology. He received gastroenterology training at the University of North Carolina, where he founded the UNC Center for Functional GI and Motility Disorders. Currently, he is a Professor Emeritus of Medicine and Psychiatry in Gastroenterology at UNC. He is a Fellow of the American College of Physicians, a Master of the American College of Gastroenterology, Past-President of the American Psychosomatic Society (1997).

Dr. Drossman has established multiple organizations to advance patient-centered education and treatment of Disorders of Gut-Brain Interaction (DGBI). He founded the Rome Foundation, served as president until 2019, and is currently the President Emeritus and Chief of Operations. He has served as Senior Editor of Rome I, II, III, IV and is co-senior editor of Rome V to be released in 2026. He edited the Multi-Dimensional Clinical Profile (MDCP) for DGBI (3rd edition 2021), the Rome IV Clinical algorithms (2nd edition), the Rome IV slide sets, and the Rome IV GI Genius, an intelligent software application.

As a gastroenterologist, Dr. Drossman consults or manages the care of difficult-to-diagnose and -treat patients with DGBIs. He receives faculty and trainees to visit his practice as part of the Clinical Scholar Program

As Founder and President of DrossmanCare (Center for Education and Practice of Biopsychosocial Care) Dr. Drossman produces educational materials to teach communication skills and patient-centered care. He has published peer-reviewed articles and videotapes on medical interviewing

and the patient-doctor relationship. As an educator and practitioner, he also facilitates workshops and communication skills training programs and has received numerous awards. He collaborates with the Rome Foundation to produce a curriculum for training clinicians that includes the Communication 101, 101.5 and 202 video series, Train the Trainer programs, and workshops and symposia globally. Most recently he co-authored a book with a patient advocate: Gut Feelings: Disorders of Gut-Brain Interaction and the Patient-Doctor Relationship for patients and clinicians.

Dr. Drossman has written over 500 articles and book chapters serves on six editorial and advisory boards, was Associate Editor of the journal Gastroenterology and was the Gastroenterology Section Editor of the Merck Manual for 17 years.

His research relates to the clinical, epidemiological, psychosocial and treatment aspects of gastrointestinal disorders, and he has been a principal investigator in several NIH-funded epidemiological, outcomes, clinical trials and abuse grants in DGBI and has done brain imaging in IBS.

Abstract

This presentation will focus on the biopsychosocial understanding and care of a patient with chronic and severe abdominal pain. We will begin with a brief video showing an initial clinical visit where the patient presents in extreme distress, reporting unremitting abdominal pain. She meets Rome IV criteria for Centrally Medicated Abdominal Pain (CAPS) from a diagnostic standpoint. Unlike other Disorders of Gut-Brain Interaction (DGBI), there is a more significant contribution of the central nervous system (CNS) in producing pain symptoms relative to gut afferent activity acting peripherally. The Rome IV criteria are at least three months of 1) continuous or nearly continuous abdominal pain, 2) no or only occasional relationship of the pain with physiological events like eating, defecation or menses, 3) the pain limits daily functioning 4) the pain is not feigned and 5) no other structural or functional GI disorder or medical condition explains the pain¹.

It becomes evident early in the interview that several other factors need consideration. These include an initial history of post-infection IBS that changed from IBS-D to IBS-C progression to CAPS, opioid-induced constipation², and narcotic bowel syndrome¹. From a psychosocial perspective, the patient also has a history of early sexual and physical trauma and current symptoms of illness anxiety (visceral anxiety) and somatic symptom disorder based on DSM5 criteria. She displays agitation and symptom-related behaviors, demanding to be hospitalized and receive narcotics for the pain. The doctor is in a dilemma. How can he address the patient's requests in a safe, therapeutic fashion and in a manner that optimizes a patient-provider relationship³?

The presentation will then highlight some of the key features of the interview,³ briefly discuss some of the pathophysiological features of the patient's chronic pain and associated comorbidities. Following this he discusses possible treatment options, including central neuromodulators⁴. Finally, a video at the end of the clinic visit demonstrates how the provider

attempts to offer education on the patient's medical problems and possible treatments within the context of effective interview methods.

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Leaky Gut: Triggers and Therapeutic Modulation

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Biosketch

ANTONIO GASBARRINI, born in Bologna the October 11th 1963, is Full Professor of Internal Medicine at the Università Cattolica of Rome. He is also the Director of Postgraduated School in Internal Medicine in the same institution. Chairman of Medical and Surgical Sciences Department and Director of Internal Medicine and Gastroenterology Unit at the Fondazione Policlinico Universitario Gemelli IRCCS. He obtained his Medical Degree at the University of Bologna and specialties in Internal Medicine and Gastroenterology in the same institution. He completed his training in the University of Bologna and in the University of Pittsburgh in Pittsburgh (USA). His fields of interests are: Irritable Bowel Syndrome and Inflammatory Bowel Disease, Gut Microbiome and Metabolome, acute and chronic Liver insufficiency, viral hepatitis, hepatocellular carcinoma and Liver transplantation, celiac disease and intestinal malabsorption. He is the winner of over 30 national and international prizes or awards, member of numerous international associations and of over 15 journal editorial boards, and author of more than 1000 scientific publications (h-index = 87) and over 35.000 citations. He gained international recognition for his pioneering work in the field of microbiota related disorders, microbiota signature of diseases, microbiota modulation and fecal microbiota transplantation.

Abstract

The intestinal barrier protects the host against gut microbes, food antigens, and toxins present in the gastrointestinal tract. However, gut barrier integrity can be affected by intrinsic and extrinsic factors, including genetic predisposition, the Western diet, antibiotics, alcohol, circadian rhythm disruption, psychological stress, and aging. Chronic disruption of the gut barrier can lead to translocation of microbial components into the body, producing systemic, low-grade inflammation. While the association between gut barrier integrity and inflammation in intestinal diseases is well established, new evidence suggest that the mucosal barrier and microbiota dysbiosis may contribute to the development of metabolic, autoimmune, and aging-related disorders. Emerging interventions to improve gut barrier integrity and microbiota composition become then crucial to restore gut homeostasis.



The Added Value of SehCAT Test in the Work up of Patients with BAD. The Spanish Experience

Jordi Guardiola Copon

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Biosketch

Dr. Jordi Guardiola is Head of the Digestive Diseases Department of the Hospital Universitari de Bellvitge (Barcelona) and Associate Professor at the University of Barcelona medical school. He is the past President of the "Catalan Society of Gastroenterology". Dr. Guardiola is an expert advisor for the "Spanish Working Group for Crohn's Disease and Ulcerative Colitis" and past member of the Steering Committee of this organization. His main research interests include inflammatory bowel diseases and colorectal cancer.

Abstract

Bile acid diarrhoea (BAD) is increasingly recognized as a common cause of chronic diarrhoea overlapping with irritable bowel syndrome with diarrhoea (IBS-D) and functional diarrhoea but it is still frequently misdiagnosed or underdiagnosed. Importantly, delay in diagnosis and treatment of BAD greatly affects patient's quality of life and may increase the overall cost of diagnosis.

Idiopathic, primary BAD occurs in 25%–33% of patients presenting with chronic diarrhoea, and its prevalence is estimated at around 1% of the adult Western population. Up to 30% of patients with IBS-D have evidence of BAD as determined by 75SeHCAT testing. In addition, BAD is also frequent following cholecystectomy, in patients with Crohn's disease or microscopic colitis, as well as in patients having metformin. Another under recognized group are those with cancer especially those receiving pelvic chemoradiotherapy or those treated by right hemicolectomy where the terminal ileum is resected.

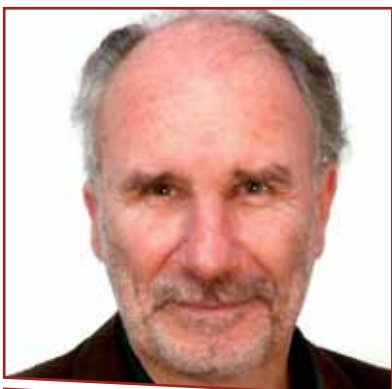
The underlying mechanism of primary BAD relates to a disruption in the negative feedback

mechanism in bile acid (BA) production due to impaired FGF19 signaling leading to increased hepatic BA synthesis that exceeds the reabsorptive capacity of the active transport mechanisms in the ileum.

BAD can be diagnosed by the $^{75}\text{SeHCA}$ T retention test, by measurement of faecal BA, by biomarkers such as $7\alpha\text{C4}$ or FGF-19 or by therapeutic response.

Most of the patients with BAD according to a $< 10\%$ SeHCA T retention test have partial or complete response to BA sequestrants although they are often discontinued because of poor tolerance.

The objective of this review is to give an overview of BAD.



Gut Microbiome, Diet and Symptoms

Francisco Guarner Aguilar

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Biosketch

Dr. Francisco Guarner graduated in Medicine at the University of Barcelona in 1973, trained Gastroenterology and Hepatology at Hospital Clinic (Barcelona); obtained PhD degree at University of Navarra (Spain). He was Research Fellow at Royal Free Hospital (London, UK), King's College Hospital (London, UK), and Wellcome Research Laboratories (Beckenham, UK). He is Consultant of Gastroenterology at the Teknon Medical Centre (Barcelona, Spain). Member of the Steering Committee of the International Human Microbiome Consortium (www.human-microbiome.org), member of the Scientific Committee of Gut Microbiota for Health Section of the European Society of Neurogastroenterology and Motility (www.gutmicrobiotaforhealth.com), and past member of the Board of Directors on the International Scientific Association for Probiotics and Prebiotics (isappscience.org). Co-author of 335 publications on original research or reviews (Web of Science), holds an h-index of 65.

<https://publons.com/researcher/4053457/francisco-guarner/>

Abstract

A healthy diet rich in vegetables and legumes has been shown to increase microbial production of butyrate and species diversity. Butyrate is associated with improved mucosal barrier function and immunoregulation. However, diets rich in vegetables may induce abdominal discomfort. In some individuals, symptoms include abdominal bloating, pain, and excessive evacuation of gas per anus. We investigated the relationships among diet, abdominal sensations, gas evacuation and colonic microbiota in healthy individuals and in patients complaining of flatulence. In patients, meal-induced symptoms such as bloating, distention and pain, were found to be linked with microbial instability. The diet rich in fermentable vegetables induced abdominal symptoms, and patients' gut microbiotas developed instability in composition, exhibiting variation in abundance of the dominant genera and reduction of microbial diversity.

In contrast, healthy subjects showed minor or no symptoms and their gut microbiotas were stable. In patients, but not in healthy individuals, the volume of gas evacuated correlated with abundance of *Bilophila wadsworthia* in fecal samples. This species is bile-tolerant and generates hydrogen sulfide, which is an irritating gas that might induce symptoms. The study suggested that symptomatic responses may be due to insufficient adaptation of gut microbial metabolic networks for processing food substrates.

A common therapeutical approach to manage functional abdominal symptoms is the avoidance of foods that contain fermentable oligosaccharides, disaccharides, monosaccharides and polyols, called low “FODMAP” diet. The approach is successful in reducing symptoms, but does not provide permanent relief. We compared the effects of a prebiotic supplement plus a placebo diet (Mediterranean-type diet) to a placebo supplement plus a diet low in FODMAPs in patients with IBS. The intervention had opposite effects on fecal microbiota composition in the two groups. *Bifidobacterium* spp. increased in the prebiotic group and decreased in the low-FODMAP group, whereas *Bilophila wadsworthia* (a sulfide producing species) decreased in the prebiotic group and increased in the low-FODMAP group. The prebiotic option may provide better opportunities for adaptation of the microbiome to process food substrates.



Influence of Psychological Factors in IBS

Laurie Keefer

GI Health Psychologist and Professor of Medicine and Psychiatry at the Icahn School of Medicine at Mount Sinai in New York City, USA

Biosketch

Dr Laurie Keefer, PhD is a GI Health Psychologist and Professor of Medicine and Psychiatry at the Icahn School of Medicine at Mount Sinai in New York City. She has a more than 20 years of experience in the development and implementation of behavioral therapies for chronic digestive disorders, including Inflammatory Bowel Disease (IBD). She currently directs the GRITT Program, an integrated care model for Crohn's and ulcerative colitis patients within the IBD Center at Mount Sinai Hospital. She maintains a clinical practice focused on psychosocial concerns among medically complex IBD.

Her research focuses on the application of positive psychology principles, particularly resilience and acceptance to the management of chronic digestive conditions. She has sustained NIH funding since 2008, including holding the first ever T32 Training grant for young investigators at the intersection of physiology and psychology. She continues to focus on the development of precision-based, scalable GI self-management interventions and recently co-founded Trellus Health, Inc, a digital care solution for the chronic conditions based on her GRITT Methodology.

Dr Keefer is Founder and Chair of the Rome Foundation's GastroPsych group and serves on the Board of Directors of the Rome Foundation. She has more than 200 peer-reviewed publications and recently co-edited the Handbook of Psychogastroenterology for Mental Health Professionals. Dr Keefer is a sought-after speaker, mentor and collaborator.

Dr Keefer received her PhD in clinical psychology from the University of Albany in New York and completed a residency and fellowship in health psychology at Rush University Medical Center in Chicago. She has been a champion for integrated behavioral care in gastroenterology and has trained many in this model around the world. She lives in Northern NJ with her husband, two teens and dog.

Abstract

Irritable bowel syndrome has long been understood from the framework of the biopsychosocial model. Advances in cognitive neuroscience, behavioral intervention science and psychophysiology have enabled a more comprehensive understanding of the psychological factors driving symptom perception and outcomes and how these may be leveraged towards treatment, including brain-gut behavior therapies. In this presentation, Dr Keefer will discuss advances in the field of psychogastroenterology, including the benefits of integrated care. She will also provide clinical behavioral assessment and intervention pearls that can be used by the gastroenterology provider as part of routine IBS care.



FMT: State-of-the-Art and Future Indications

Colleen R. Kelly

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Biosketch

The focus of Dr. Kelly's research and clinical practice is *Clostridioides difficile* infection (CDI) and fecal microbiota transplantation (FMT). She was the principal investigator (PI) for the first placebo-controlled trial of FMT for treatment of recurrent CDI and one of the first investigators to sponsor of an investigational new drug (IND) application for FMT with the United States Food and Drug Administration. She has since served on several working groups focusing on regulatory issues related to FMT. Dr. Kelly has been involved in industry funded trials of live microbiota for treatment of recurrent CDI as well as investigator-initiated clinical trials assessing conventional FMT for CDI treatment. Dr. Kelly is interested in the long-term effects around manipulation of gut microbiota and serves as one of the PIs for the FMT National Patient Registry which is funded by the National Institutes of Health to answer important questions around the real-world effectiveness and safety of FMT. She has collaborated on several studies investigating the impact of FMT on patients with Inflammatory Bowel Disease. In addition to coauthoring current FMT guidelines and participating in drafting the European Consensus Conference on Fecal Microbiota Transplant in Clinical Practice, she was the lead author for the recently published American College of Gastroenterology (ACG) 2021 *C. difficile* treatment guidelines. Dr. Kelly is a Fellow in the ACG and is a Fellow and past member of the scientific advisory board for Gut Microbiome Research and Education of the American Gastroenterological Association (AGA) and is a current member of the AGA Counsel.

Link to Dr. Kelly's bibliography:

<https://www.ncbi.nlm.nih.gov/myncbi/browse/collection/44192192/?sort=date&direction=ascending>

Abstract

Randomized controlled trials (RCT) have shown fecal microbiota transplant (FMT) to be over 90% effective at resolving *Clostridioides difficile* infection (CDI)¹ and it appears remarkably safe, with few related serious adverse events reported. FMT is now widely performed and recommended by current treatment guidelines² after conventional antibiotics fail to resolve the infection.

Microbial transplant is believed to work by restoring gut microbiota diversity, beneficial anaerobes and normal bile acid metabolism in patients with dysbiosis resulting from repeated courses of antibiotics. There is hope that therapeutic manipulation of gut microbiota through FMT or more refined microbial consortia will prove effective for other diseases associated with perturbations in gut microbiota, such as inflammatory bowel diseases and hepatic encephalopathy. Several randomized controlled trials have shown FMT to be effective in inducing remission in patients with mild to moderate ulcerative colitis³. Unlike in CDI, multiple treatment doses may need to be administered and there are areas of uncertainty including donor microbiota characteristics, need for ongoing maintenance therapy and long-term safety. There are currently more than 200 clinical trials worldwide investigating FMT, and, in the future, therapeutic manipulation of gut microbiota may be utilized for treatment of diseases outside the gastrointestinal tract⁴.

There are many questions about the best methods for performing FMT, though donor identification and screening are important steps to ensure patient safety. Regulatory issues present challenges and emerging pathogens, such as SARS-CoV-2 have recently limited patient access. Given concerns over safety and the logistics of donor identification and screening, commercial formulations of intestinal microbiota, known as live biotherapeutic products (LBPs) have been developed for CDI. Late stage clinical trials have completed⁵⁻⁷, and the US Food and Drug Administration is expected to approve one or more formulations within the next year. LBPs with compositions ranging from a single strain to a defined consortium of organisms to a full spectrum community found in human feces will expand treatment options and may reduce concerns about donor screening and infection transmission.

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The Diagnostic Process in the Difficult Patient: How Much in Depth Should We Go?

Brian E. Lacy

Consultant and Professor of Medicine at Mayo Clinic Jacksonville, USA

Biosketch

Brian E. Lacy, Ph.D., M.D., FACP is currently Consultant and Professor of Medicine at Mayo Clinic Jacksonville. He previously worked at the Dartmouth-Hitchcock Medical Center where he was Section Chief of Gastroenterology and Hepatology and Professor of Medicine at the Geisel School of Medicine at Dartmouth.

Dr. Lacy's clinical and basic science research interests focus on disorders of gastrointestinal motility, with an emphasis on irritable bowel syndrome, achalasia, dyspepsia, gastroparesis, acid reflux disease, constipation, intestinal pseudo-obstruction and visceral pain. He is the author of over 215 peer-reviewed articles on gastrointestinal motility disorders and functional bowel disorders, in addition to multiple textbook chapters. Dr. Lacy is a reviewer for many scientific journals, and is a member of a number of different scientific organizations, including the American College of Gastroenterology, the American Gastroenterology Association, and the American Neurogastroenterology & Motility Society. Dr. Lacy is the co-author of a book for the general public on acid reflux disease, "Healing Heartburn", is the author of "Making Sense of IBS", a book for the general public on irritable bowel syndrome, and he edited and authored the books "Curbside Consultations in IBS", "Functional and Motility Disorders of the Gastrointestinal Tract" and "Essential Disorders of the Stomach and Small Intestine" for health care providers. Dr. Lacy recently finished a 6-year tenure as co-Editor in Chief of the American Journal of Gastroenterology. He is the former Editor in Chief of Clinical and Translational Gastroenterology. Dr. Lacy was the co-Chairman for the Rome IV Committee on Functional Bowel Disorders. He is on the Board of Trustees for the Rome Committee.

Dr. Lacy received his doctorate in cell biology from Georgetown University in Washington, DC, and his medical degree from the University of Maryland in Baltimore. Dr. Lacy was a resident in Internal Medicine at the Dartmouth-Hitchcock Medical Center in Lebanon, NH, where he continued his training as Chief Resident and as a Fellow in Gastroenterology. He is board certified in Gastroenterology and Hepatology.

Abstract

The cardinal symptom of IBS is the presence of recurrent abdominal pain. Abdominal pain should be present at least one day per week (on average) and associated with two or more of the following per Rome IV criteria: related to defecation; associated with a change in stool frequency; associated with a change in stool form. Like other Rome diagnoses, symptoms should have developed at least 6 months earlier and be present for the past 3 months. Although gas and bloating are common symptoms, they are not required to fulfill the diagnosis of IBS.

IBS can be subtyped into three major categories based on predominant bowel habits – constipation (IBS-C), diarrhea (IBS-D), and mixed constipation and diarrhea (IBS-M). Stool form can be categorized using the Bristol Stool Form Scale (BSFS) and should be based on the predominant bowel habit on the days with abnormal bowel movements.

The diagnosis of IBS is based on a careful history (medical, surgical, dietary, psychological, family), a thoughtful physical examination, an evaluation for potential warning signs (also called “red flags”), limited testing and the use of the Rome IV criteria. While the presence of “red flags” or alarm signs and symptoms may indicate a need for further diagnostic workup, most patients with red-flag symptoms have not been found to have an organic disorder to explain their IBS symptoms. According to the American College of Gastroenterology (ACG) Task Force on IBS, alarm features include rectal bleeding; weight loss; iron-deficiency anemia; nocturnal symptoms; and a family history of colon cancer, IBD, or celiac disease.

In contrast to the Rome III criteria, the Rome IV criteria note that limited laboratory testing is appropriate. A complete blood count, and C-reactive protein (CRP) should be performed. Serologic tests for celiac disease should be performed in patients with suspected IBS and diarrhea symptoms. Fecal calprotectin (and CRP, as noted above) should be checked in patients in patients with suspected IBS and diarrhea without alarm features to rule out inflammatory bowel disease. Routine thyroid tests are not helpful. Routine colonoscopy does not need to be performed in all patients with IBS, especially those under the age of 45 without warning signs, given the low pretest probability of detecting Crohn’s disease, ulcerative colitis, and colonic neoplasia in this group.

The question of whether further testing should be performed in patients with difficult symptoms, or persistent symptoms of IBS, often arises. My lecture will review the merits of making a positive diagnosis of IBS, discuss recommended diagnostic tests, define the difficult patient, and review additional diagnostic testing for the patient with difficult/persistent symptoms.

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Herbal Medicinal Treatment Options in Disorders of Gut-Brain Interaction (DGBI)

Ahmed Madisch

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Biosketch

Specialist and Professor of internal medicine and Gastroenterology

12 years Head of Department of the Clinic for Gastroenterology

Since 2021 Senior Consultant and Partner of the largest gastroenterological practice clinics in Frankfurt, Germany

The scientific focus includes amongst other functional gastrointestinal disease, inflammatory bowel disease including microscopic colitis and gastroesophageal reflux disease

Author and Co-author of several national treatment guidelines (chronic constipation, irritable bowel syndrome, diverticulitis, *Helicobacter pylori* and reflux disease).

Abstract

Functional gastrointestinal disorders are also known as disorders of gut-brain interaction (DGBI). Functional dyspepsia (FD) and irritable bowel syndrome (IBS) are the most common functional gastrointestinal disorders.

The "Rome IV Diagnostic Consensus" defines FD as postprandial distress syndrome with postprandial fullness and early satiety, and epigastric pain syndrome with epigastric pain or burning. In addition, nausea, bloating, and belching are associated symptoms. IBS is characterized by abdominal pain associated with bowel movements. Subgroups of IBS include IBS with predominant constipation, diarrhoea, mixed bowel movements, abdominal pain and/or distension/bloating. The pathomechanisms of functional gastrointestinal disorders are heterogeneous, multifactorial and partly unclear. The diagnosis and treatment of both FD and

IBS is symptom-based and largely depends on the patient's perception. International guidelines do not identify 'first choice' medications for FD and IBS and their related symptoms.

As these are mostly chronic and recurrent conditions, the safety and tolerability of long-term medication use is of great importance, in addition to the efficacy of treatment.

Herbal medicines, with their good safety profile, are therefore a very good option for treating the gastrointestinal symptoms related to FD and IBS.

One herbal medicinal product for the treatment of gastrointestinal symptoms is Menthacarin®. Menthacarin® is the proprietary combination of 90 mg essential oil of *Mentha x piperita* L. (peppermint oil) and 50 mg essential oil of *Carum carvi* (caraway oil) (and is the active ingredient in Carmenthin® and Gaspan®, manufactured by Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany). Both ingredients have a long tradition in medicine for treating various gastrointestinal complaints and could be a good way to satisfy gastroenterologists' patients. Randomized controlled trials have shown clinically relevant treatment effects on abdominal pain, flatulence and/or bloating. Because of its favorable safety profile, Menthacarin® is suitable for the chronic recurrent nature of this health problem. Thus, Menthacarin® is a valuable and well-established therapeutic option in primary care for complaints due to various gastrointestinal symptoms.



Long COVID and DGBI

Giovanni Marasco

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Biosketch

Prof. Giovanni Marasco is Assistant Professor of Internal Medicine at the Department of Medical and Surgical Sciences of the University of Bologna and as Consultant at the Internal Medicine and Digestive Pathophysiology Unit of the IRCC Sant'Orsola Malpighi University Hospital of Bologna in Italy. He is also part of the Young Member Committee of the Italian Society of Gastroenterology and Digestive Endoscopy and the Treasure of the Italian Society of Young Gastroenterologist and Endoscopists.

Prof. Marasco got the Medical Degree in 2014 at the University of Bologna, where he also started his research career in 2013 focusing on gut microbiota of celiac disease patients and diverticular disease. Thereafter, he continued his research career starting the PhD program in Gastroenterology and Hepatology. He completed his specialist training in Gastroenterology, Hepatology and Endoscopy in 2019. Currently, his research focus is the study of gut microbiota in gastrointestinal and internal medicine disease and its modulation with fecal microbiota transplantation.

Abstract

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) global pandemic, known as COVID-19, has spread across the world with more 5.9 million deaths. An emerging pathological entity in COVID-19 survivors is the so-called long-COVID-19, consisting of residual effects after SARS-CoV-2 infection as fatigue, dyspnea, chest pain, cognitive disturbances, arthralgia and decline in quality of life. Ancillary studies also reported long-term and post-acute digestive symptoms in COVID-19 survivors such as abdominal pain, anorexia, diarrhea, and vomiting. The

hypothetical mechanisms responsible for gastrointestinal COVID-19 symptoms and their long-term presence underlie cellular damage and inflammation, dysbiosis, enteric nervous systems dysfunction and a pro-coagulant state induced by the virus. Therefore, SARS-CoV-2 infection may lead to persistent gastrointestinal dysfunction resembling aspects of post-infection disorders of gut-brain interaction (DGBI). Besides, it is extensively known that acute infection gastro-enteritis represents the strongest known risk factor for irritable bowel syndrome (IBS) development. Preliminary reports suggested increased rates of DGBI in COVID-19 patients, although these data need to be confirmed in larger studies.

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Breath Testing in IBS

Daniel Pohl

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Biosketch

Professor Dr. med. Daniel Pohl is a board-certified Internist and Gastroenterologist at the Department of Gastroenterology and Hepatology at the University Hospital Zurich, Switzerland. He started his career as a fellow of the GI Functional Diagnostic Center in 2005, Zurich, emphasizing clinics and research on upper gut motility and later, disorders of brain-gut interaction. Daniel Pohl was a research fellow at the Esophageal Disorders Clinic with Prof. Castell, Medical University of South Carolina, USA. Daniel is currently Head of the Gastroenterology Unit at the University Hospital Branch at Zurich Airport "The Circle", as well as Head of Neurogastroenterology and Motility. He is founding member and Past-President of the Swiss Society of Neurogastroenterology and Motility (SwissNGM) and member of the Executive Committee in his position as treasurer of the European Society of Neurogastroenterology and Motility (ESNM) as well as the European Foregut Society (EFS).

Abstract

Hydrogen-based breath tests are a simple, non-invasive, inexpensive and widely available technique to study conditions like carbohydrate intolerances, small intestinal bacterial overgrowth and intestinal transit. They are based on the repetitive quantification of hydrogen (H₂), optionally methane (CH₄), in the exhalate after oral provocation with the chosen substrate; symptoms can be monitored at the same time.

Where this technique is very appealing for the reasons stated above, the use of breath tests and their interpretation has long been hindered by lack of standardization and appropriate comparative gold standards. The significant intra- and interindividual variations in fermentation that relies on mostly bacterial processing is an inherent weakness of the test. Gut motility, location of substrate and fermentative capacity of the individual microbiome, as well as concomitant fermentative substrates consumed prior to testing also make interpretation of tests challenging.

Breath testing in FGID, specifically in IBS, received a renewed spark of interest with the publication of the FODMAP-hypothesis that described effects of fermentable sugars on the gastrointestinal tract and since then has been further developed into dietary approaches significantly reduced of fermentable carbohydrates. This diet has shown great promise in controlling cardinal symptoms of IBS such as bloating, diarrhea and abdominal pain. Incorporating symptom documentation based on carbohydrate intolerance as tested by a breath test, rather than mere malabsorption may be the way to go in the future, more trials are needed in this regard. Data also suggest that IBS and non-IBS patients can be differentiated based on adapted breath tests also including a nutrient challenge in addition to a single carbohydrate. The growing interest in the gut microbiome and pathologic, if poorly understood, conditions such as SIBO (small intestinal bacterial overgrowth) has also led to more use of hydrogen-breath tests. In this role, the test is most criticized, with both, glucose and lactulose test, having shortcomings, possibly reduced by concomitant scintigraphy to control for intestinal transit.

Two reviews on the methodology, performance and use of hydrogen breath tests, are currently the most updated and meaningful references, the American and the more recent European consensus papers. This presentation “breath tests in IBS” during the IBS-days in Bologna will highlight the international consensus on breath tests based especially on the European consensus paper.

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Boundaries between IBS and Organic Disease

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Biosketch

Eamonn M M Quigley MD FRCP FACP MACG FRCPI MWGO is David M Underwood Chair of Medicine in Digestive Disorders and Chief of the Division of Gastroenterology and Hepatology at Houston Methodist Hospital. A native of Cork, Ireland, he graduated in medicine from University College Cork. He trained in internal medicine in Glasgow, completed a two-year research fellowship at the Mayo Clinic and training in gastroenterology in Manchester, UK. He joined the University of Nebraska Medical Center in 1986 where he rose to become Chief of Gastroenterology and Hepatology. Returning to Cork in 1998 he served as Dean of the Medical School and a PI at the Alimentary Pharmabiotic Center. He served as president of the American College of Gastroenterology and the WGO and as editor-in-chief of the American Journal of Gastroenterology. Interests include IBS, gastrointestinal motility and the role of gut microbiota in health and disease. He has authored over 1000 publications and has received awards and honorary titles world-wide. Married for over 40 years to Dr Una O'Sullivan they have 4 children and three grandchildren. Interests outside of medicine include literature, music and sport and rugby, in particular; Dr Quigley remains a passionate supporter of Munster and Irish rugby.

Abstract

The first challenge that this topic presents is definition – what is the difference between a functional and an organic disorder? The term functional is perceived by many as negative and even dismissive while the clinician's focus on "organic" can lead to an excessive emphasis on investigation and the pursuit of therapies that target pathogenetic mechanisms that may not be relevant. Reflecting the manner in which we have been taught and trained, most clinicians feel more "comfortable" in the organic than the functional realms. But the twain can and do meet in a number of scenarios.

First, it is well recognized that persistent or recurrent symptoms in individuals with well-

defined inflammatory disorders may not be explained by disease activity, as defined by all available methods. This phenomenon has been most thoroughly investigated in the context of inflammatory bowel disease but has also been reported in relation to celiac disease and diverticulitis. These are intriguing observations and have led to the exploration of a number of factors that might contribute to why such symptoms persist.

Second, there are those instances of IBS, as conventionally defined, where a clear initiating or perpetuating factor can be identified. Post-infection IBS is a clear example. Similar scenarios have been described elsewhere such as post-viral gastroparesis, post-infection FD, FD related to infection with *Helicobacter pylori* and non-erosive reflux disease. More examples are coming to light, and we are now encouraged to look for disaccharidase deficiency, small intestinal bacterial overgrowth and exocrine pancreatic insufficiency among our IBS subjects. If one of these entities is uncovered, does it cease to be IBS?

Finally, there is an emerging and expanding literature on relationships between “new entities” and IBS: including, but not limited to, Ehlers Danlos Syndrome Type III, joint hypermobility syndrome, mast cell activation syndrome, POTS, “brain fog”, dysbiosis, non-celiac gluten (or wheat) intolerance and enteric eosinophilia. Several of these relationships remain to be defined and their final position on one or other side of the organic-functional boundary clarified.

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The Vascular Barrier: New Player in the Gut-Brain Axis

Maria Rescigno

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Biosketch

Maria Rescigno (H-index 65) is full professor, vice-rector and delegate to research at Humanitas University and group leader at Humanitas Research hospital, Milan. She graduated in Biology in the University of Milan and received her PhD in Pharmacology and toxicology. She worked at the University of Cambridge, UK, as a visiting scholar. From 2001 to 2017 she has been the director of the Dendritic cell biology and immunotherapy Unit at the Department of Experimental Oncology at the European Institute of oncology. She was the first to show that dendritic cells actively participate to bacterial uptake in the gut and the existence of a gut vascular barrier that resembles the blood brain barrier. She authored more than 160 publications in high impact journals. She was nominated EMBO young investigator in 2007. In 2008-2013 she was visiting professor at the University of Oslo. In 2011 Maria Rescigno was elected EMBO member. She has been the recipient of three ERC grants (starting, proof-of-concept and consolidator). From 2019 she is member of the EMBO council. In 2016 Maria Rescigno founded Postbiotica s.r.l. a spin-off of the University of Milan that exploits microbiota-derived metabolites as new pharmaceutical agents

Abstract

The human gut is home to trillions of microbial cells with over 1,000 diverse microbial species that contribute to the primary functions of the gastrointestinal tract, including nutrition, mucosal immunity and pathogen defence. The gastrointestinal tract mucosa constitutes the major interface that separates the luminal environment from the internal milieu and it is also the body's primary site for interaction with the microbial world living within the gut lumen. The surface of the gastrointestinal mucosa is estimated at up to 4,000 square feet when laid out flat and, most importantly, contains adapted structures allowing bi-directional host-microbe communication. The gut barrier has to guarantee nutrient and metabolite exchange with the microbiota but at the same time also protection against the microbial world. The gut barrier

consists of three major components including a mucus layer, an intact epithelial monolayer and a lamina propria with mucosal immune cells. All three layers contribute to well-functioning of the gut barrier. The epithelial monolayer is not a static structure and the tight junctions that seal spaces between epithelial cells are regulated by the gut microbiota and dietary components. Below the mucosal barrier there is an additional barrier, the gut vascular barrier that controls what enters in the systemic circulation, and avoids bacterial translocation at systemic sites. When the microbiota composition changes due to inflammatory conditions, dietary misbehaviour or antibiotic treatment, there is a change in mucosal barrier permeability. Microbial components can gain access to the systemic circulation and disseminate to other organs including the liver and the brain generating a state of systemic inflammation. This leads to the modulation of a new vascular barrier in the brain that we identified in the choroid plexus.



Update on The DISCOVERIE PROJECT

Javier Santos

on behalf of all the "DISCOVERIE Horizon
2020 Consortium"

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Biosketch

Dr Javier Santos is consultant of Gastroenterology at Vall d'Hebron Hospital, Barcelona, Director and Principal Investigator of the Neuro-Immuno-Gastroenterology Group and Coordinator of the Liver and Digestive Diseases Area, Vall d'Hebron Research Institute (<http://www.vhir.org/portal1/area.asp?t=malalties-digestives-i-hepatiques&s=recerca&contentid=187000>), and member of the Internal Scientific Committee of VHIR.

Dr. Santos graduated in Medicine and Surgery at the University of Navarra (Spain) in 1988. He then completed his degree in Gastroenterology and Hepatology (1989-1993) and obtained the title of Specialist (1994) at the Hospital General Universitari Vall d'Hebron, Barcelona, Spain. In parallel, he completed predoctoral studies in basic and clinical research in neuro-gastroenterology at the Digestive Diseases Research Unit, Department of Gastroenterology, Hospital Vall d'Hebron (1993-1997), and obtained his Ph.D. (1997) from the Autonomous University of Barcelona, Spain. D. (1997), with the lecture of the thesis entitled "Neuro-regulation of digestive functions by thyrotropin-releasing hormone in the central nervous system". Later he started a 3-year postdoctoral stage (1997-1999) in immunology and gastrointestinal physiology, at the Intestinal Disease Research Program, McMaster University, Canada, under the mentorship of Dr. Mary H. Perdue, where he received the CAG/ASTRA fellowship for Meritorious Research, returning in 2000 to the Hospital Vall d'Hebron. Subsequently he carried out two post-doctoral training stays

in centers of international prestige such as the Alimentary Pharmabiotic Centre, Bioscience Institute, University College Cork, Cork, Ireland and the Faircomb Institute, Faculty of Health Sciences, Hamilton, Canada. In 2016 he also became a Rome Foundation Fellow (R.F.F.). Dr. Santos has been awarded by the Association of European and Mediterranean National Societies of Gastroenterology as Rising Star of Gastroenterology 2003, and more recently by the International Foundation for Functional Gastrointestinal Disorders (IFFGD) with the 2009 Research Award for the best Researcher in Clinical Sciences, for his contributions in the field of functional gastrointestinal disorders.

His clinical practice develops mainly in the outpatient setting of the Hospital, integrated in a large referral unit and focuses specifically, but not only, on functional gastrointestinal disorders, food allergies and intolerances and chronic diarrheal processes. Dr Santos is author of over one hundred peer-reviewed publications, hundreds of presentations and lectures and has contributed to the development of clinical guidelines in the field of gastroenterology and to the organization of national and international training courses on aspects related to functional diseases of the digestive system. He also develops various academic and scientific activities, including the tutoring of gastrointestinal fellows during their residency and the direction and mentoring of dozens of predoctoral and postdoctoral research fellows. He is member of several international professional and scientific societies, such as the European Society of Neurogastroenterology and Motility, the International Foundation for Functional Gastrointestinal Disorders, the American Gastroenterological Association or the European Gastroenterological Federation. He also collaborates as an external expert reviewer for regional, national and supranational public and private funding agencies and academic institutions, and for a very large number of scientific journals including some editorial boards.

In addition, he leads the neuro-immuno-gastroenterology research laboratory at Hospital Vall d'Hebron for twenty years. His research in the field of neuro-immuno-gastroenterology remains inherently translational, with special emphasis on the mechanisms linking genetic, molecular, microbial, cellular and environmental determinants to the clinical manifestations of irritable bowel syndrome and other functional gastrointestinal disorders. His research also pursues the identification of sensitive and specific biomarkers potentially useful for the diagnostic and therapeutic management of these disorders. Dr Santos is integrated in the Spanish Network of Hepatic and Digestive Diseases since 2009 (CIBERehd) and his research lab has been acknowledged within the Consolidated Research Groups of Catalonia (2009 SGR 00219), having participated in several European projects, such as the European Training Network in Neural Regulation of Intestinal Function (NeuroGut, <https://cordis.europa.eu/project/id/607652/reporting/es>), two COST actions (BM1007, Mast Cells and Basophils Targets for Innovative Therapies; www.mastcell-basophil.net; BM1106, GENIEUR, The Genes in Irritable Bowel Syndrome Research Network Europe, www.cost.eu/COST_Actions/bmbs/BM1106; <https://genieur.eu/>) and has recently obtained a bid european project as the main Coordinator, for the study of the origin of comorbidities in Irritable Bowel Syndrome, www.discoverie.eu). He is also member of the ROME FOUNDATION (<https://theromefoundation.org/>).

Abstract

Background: DISCOvERIE - Development diagnosis and prevention of gender-related Somatic and mental COMorbiditiEs in iRritable Bowel Syndrome in EU - is a project coordinated by the Vall d'Hebron Research Institute (VHIR) and funded under H2020 Research Programme of the European Commission (Grant Agreement n°: 848228).

Material and methods: The key objective of this 5-year project (2020-2025) is to provide an enhanced understanding on Irritable bowel syndrome (IBS), mental (depression, anxiety) and somatic (fibromyalgia and chronic fatigue) comorbidities and their risk factors. For this, we will recruit up to 800 patients.

In particular, DISCOvERIE is meant to study the existing link between anxiety and depression and irritable bowel syndrome – a brain-gut connection while identifying biomarkers for more accurate and earlier diagnosis, prognosis and monitoring of patients' condition.

DISCOvERIE is a pioneer in Europe in the study of IBS and its comorbidities from an innovative and disruptive approach, hence the findings of this project will directly impact patients' quality of life. The DISCOvERIE consortium includes 19 partners from 10 European countries and United States, collaborating with clinical and research experts and opinion leaders in the field of neuro-gastroenterology, psychiatric disorders and somatic pain disorders to contribute to new directions for clinical research and personalized care.

Results & Conclusions: Methodology, expected outcomes and preliminary results will be presented and discussed with the audience.

References

<https://discoverie.eu/>



Cannabinoids and DGBi

Giovanni Sarnelli

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Biosketch

Present

Associate Professor of Gastroenterology University of Naples Federico II, Department of Clinical Medicine and Surgery

Lecturer in Gastroenterology of the integrated course of Diseases of the Endocrine- Metabolic System and Digestive System, 4th year, Specialist Degree Course in Medicine and Surgery, Federico II University of Naples.

Professor of Gastroenterology of the Integrated Course of Specialized Methodology and Nursing 2, II year, of the Degree Course in Nursing Sciences, Federico II University of Naples.

Professor of Gastroenterology at the School of Specialization in Gastroenterology and Digestive Endoscopy, Federico II University of Naples; secretary of the Specialization School

Lecturer of the PhD in Food and Health: Biotechnologies and Methodologies Applied to digestive physiopathology "Second University of Naples.

Professor of the Master's Degree Course in Human Nutrition Sciences, (Interfaculty with Biotechnological Sciences) Federico II University of Naples. Frontal teaching activity, practical training and supplementary activities.

Leader of the research group team involved in the R&D of next generation probiotics and their application in precision medicine.

Head of the Digestive and Nutritional Pathophysiology unit, University Hospital Federico II
2006-2018

Co-Founder and CEO of Next-Biomics (Biotech company, spin-off of the Federico II University of Naples).

2020 Present

A biotech company involved in the research and development of Next Generation Probiotics for the bacterial production of drugs and healthy molecules for the treatment of highly prevalent diseases and to pave the way to use bacteria as an alternative and green strategy for approaching the gender and precision medicine.

Abstract

The management of symptoms in disorders of gut-brain interaction, including irritable bowel syndrome (IBS) and functional dyspepsia (FD), is very challenging. Given symptoms recurrence and the available treatments options, many patients have turned to cannabis and cannabinoids, as an alternative therapeutic approach given its perceived beneficial properties. Cannabinoids act on the cannabinoid receptors (CB1 and CB2) of the endocannabinoid system (ECS), a lipid endogenous signalling system which is involved in the control of diverse gastrointestinal functions such as motility, barrier function, inflammation and gut-brain signalling. The location of CB1 and CB2 in the central and enteric nervous system and epithelial cells in the gut, and CB2 on immune cells, suggests that the ECS, may influence gastrointestinal motility, visceral sensitivity and intestinal epithelial transport and barrier function. By inhibiting acetylcholine release of from the myenteric plexus, endocannabinoids and phytocannabinoids act via CB1 to reduce contractility and propulsive motility throughout the GI tract. Animals and human studies indicated that that CB1 receptor agonists inhibit the gastric accommodation reflex and delay gastric emptying, while CB1 antagonists/inverse agonists are able to enhance transit. Emerging evidence also supports putative analgesic properties of endocannabinoids, potentially affecting pain that is a key symptom in patients with DGBI. However, recent controlled clinical trials with cannabinoids-targeting drugs failed to find significant effects of over placebo or were limited by their central psychoactive effects. The development of compounds targeting other components of the ECS, without unwanted psychotropic side effects, offers promise for future therapies for the treatment of disorders of gut-brain interaction. There are also early observations of therapeutic potential in DGBIs of PEA, the endogenous fatty acid which acts through PPAR α as well as through activation of endocannabinoid receptors. It has been recently demonstrated that as compared to controls there was an impaired release of endogenous PEA, and that PEA inhibits mast cell mediator and NGF release via PPAR α receptors. If confirmed, such endogenous system for the homeostatic control of mast cell activation, and therefore visceral sensitivity, provides a plausible pathophysiological mechanism to explain the pain experienced functional dyspepsia patients and offer a novel therapeutic approach to treat it, since PEA is available as a food supplement and has been used to treat IBS as demonstrated in a controlled trial in IBS patients. Although the effects of cannabinoids have not been rigorously examined in large clinical trials, which are urgently needed. The development of compounds targeting other components of the ECS, without unwanted psychotropic side effects, offers promise for future therapies for the treatment of disorders of gut-brain interaction.



UEG / ESNM Guidelines on Functional Bowel Disorders with Diarrhea

Edoardo V. Savarino

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Biosketch

Prof. Edoardo Vincenzo Savarino received his Medical and Ph.D. degrees from the University of Genoa, Genoa, Italy. He completed his residency training in internal medicine and gastroenterology at the Department of Internal Medicine, Azienda Ospedaliera-Universitaria San Martino of Genoa, Genoa, Italy. Presently, he is Associate Professor of Gastroenterology at University of Padua, Padua, Italy. He is mainly interested in neurogastroenterology and immune-mediated diseases, including inflammatory bowel diseases and eosinophilic disorders of the gastro-intestinal tract. He has published extensively (h-index 51, published papers n=421) on gastroesophageal reflux disease (GERD), esophageal motility disorders, Barrett's Esophagus, functional GI disorders (functional dyspepsia, irritable bowel syndrome), eosinophilic esophagitis, and inflammatory bowel diseases. He received various prizes for his work from UEG Federation, OESO foundation, ISDE, Società Italiana di Gastroenterologia ed Endoscopia. He is Reviewer for various journals, including The New England Journal of Medicine, American Journal Respiratory and Critical Care Medicine, Gastroenterology, Gut, Alimentary Pharmacology and Therapeutics, Clinical Gastroenterology and Hepatology, American Journal of Gastroenterology, and Neurogastroenterology and Motility (NMO).

Abstract

Irritable bowel syndrome with diarrhoea (IBS-D) and functional diarrhoea (FDr) are the two major functional bowel disorders characterized by diarrhoea. In spite of their high prevalence, IBS-D and FDr are associated with major uncertainties, especially regarding their optimal diagnostic work-up and management. A Delphi consensus was performed during the last two years with experts from 10 European countries who conducted a literature summary and voting process on 31 statements. Quality of evidence was evaluated using the grading of recommendations, assessment, development, and evaluation (GRADE) criteria. Consensus (defined as >80%

agreement) was reached for 30 statements. In terms of diagnosis, the consensus supports a symptom-based approach also with the exclusion of alarm symptoms, recommending the evaluation of full blood count, C-reactive protein, serology for coeliac disease, and faecal calprotectin, and consideration of diagnosing bile acid diarrhoea. Colonoscopy with random biopsies in both the right and left colon is recommended in patients older than 50 years and in presence of alarm features. Regarding treatment, a strong consensus was achieved for the use of a diet low fermentable oligo-, di-, monosaccharides and polyols, loperamide, gut-directed psychological therapies, rifaximin, bile acid sequestrants and eluxadoline. A weak or conditional recommendation was achieved for antispasmodics, probiotics, 5-hydroxytryptamine-3 antagonists (i.e. alosetron, ondansetron, or ramosetron). The Consensus Group voted on various statements that may guide clinicians in the management of functional bowel disorders with diarrhoea in clinical practice, and also provide areas in need of future research to improve the quality of care of such challenging disorders.

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Current and Future Management of IBS-C

Carmelo Scarpignato

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Biosketch

Carmelo Scarpignato graduated in Biochemistry at the University of Messina, and in Medicine and Surgery at the University of Modena in Italy. He is currently Professor of Medicine & Clinical Pharmacology at the Faculty of Health Sciences, LUdeS Lugano Campus, Switzerland & United Campus of Malta, Msida, Malta as well as Associate Professor of Gastroenterology at University of Nantes. He is also Honorary Clinical Professor at Chinese University of Hong Kong and Consultant Clinical Pharmacologist & Gastroenterologist. He has been Visiting Professor at some prestigious European and USA Universities.

Professor Scarpignato's main research interests focus on digestive clinical pharmacology, gastrointestinal motility, and upper GI pathophysiology as well pain medicine. He has authored more than 500 publications (of which 350 are full papers or book chapters) on these topics and has also edited 28 books on clinical evaluation of GI function and on Pharmacology & Therapeutics of Digestive Diseases. He is or has been on the editorial boards of Pharmacology, Gut, Digestion, Digestive Diseases, Current Gastroenterology Reports, Alimentary Pharmacology & Therapeutics, BMC Gastroenterology, BMC Medicine, World Journal of Gastroenterology, American Journal of Pharmacology & Therapeutics, Therapeutic Advances in Drug Safety and Current Clinical Pharmacology, amongst others. He is also a Section Editor (GI and Liver Pharmacology) of Fundamental and Clinical Pharmacology and of Gastroenterology International, and has been co-Editor of two prestigious book series, Frontiers of Gastrointestinal Research and Progress in Basic and Clinical Pharmacology.

Professor Scarpignato is a Fellow of the Royal College of Physicians (London), the American College of Physicians, the American College of Clinical Pharmacology, the American College of Gastroenterology and of the American Gastroenterological Association. In addition, he has been recognized Fellow of the European Board of Gastroenterology & Hepatology, besides being member of several national and international scientific societies, including the New York Academy of Sciences and the EU Academy of Sciences. He has been the Past Governor for Italy of the American College of Gastroenterology (ACG) and is presently the At-large Member, Governing Board of the World Organization for Specialized Studies on Diseases of the Oesophagus (OESO).

Abstract

Irritable bowel syndrome with constipation (IBS-C) occurs more commonly in women than in men, and frequently includes additional symptoms such as abdominal bloating and discomfort, hard stools, straining, and sensation of incomplete evacuation [1]. Although in the past IBS therapy has mostly been driven by the prevailing symptom, the availability of new drugs has recently allowed to target the entire symptom complex. Evaluation of drug efficacy remains however challenging. Indeed, in IBS-C, placebo response rates are high, reaching up to some 35% for some end-points, even in RCTs adhering to current FDA-recommended endpoints [2].

Besides macrogol (an osmotic laxative), which only improves bowel movements but not symptoms and is not recommended by ACG guidelines [3], current treatments rely on intestinal secretagogues (guanylyl cyclase-C agonists, chloride channel activators, and sodium-hydrogen exchanger isoform 3 inhibitors) and prokinetics (tegaserod and prucalopride).

A network meta-analysis of RCTs [4] found all secretagogues to be superior to placebo. As a consequence, they are strongly recommended by ACG guidelines [3]. Linaclotide (290 µg once daily) was ranked first in efficacy based on the FDA-recommended primary end points (abdominal pain and complete spontaneous bowel movements) while tenapanor (50 mg twice daily) was ranked first for decreasing bloating. However, the licensed drugs for IBS-C are all superior to placebo in addressing this symptom [5].

For tegaserod, a partial 5-HT₄-agonist once again approved for use in IBS-C under a more restricted labeling (women under the age of 65 without heart disease or additional cardiovascular risk factors) [6], the odds ratios for clinical response (pooled from 4 RCTs) during the last 4 weeks in the overall and restricted populations were 1.37 (1.18-1.59; $p < 0.001$) and 1.38 (1.18-1.61; $p < 0.001$), respectively [7]. In an updated network meta-analysis including 3 RCTs with tegaserod (6 mg twice daily), this prokinetic ranked third (after linaclotide and tenapanor) when the indirect evidence for failure to achieve the FDA-recommended endpoint was adopted as an outcome [8]. Prucalopride is effective (and approved) for treatment of chronic constipation and is able to reduce abdominal symptoms after intestinal gas challenge in women with functional bowel disorders [9]. It may well be employed in IBS-C. In this connection, a small South American trial [10] found that prucalopride and tegaserod improve similarly all the evaluated symptoms in patients with IBS-C, although the former appeared more effective on abdominal pain.

Although drug therapy is efficacious, dietary intervention should not be overlooked. The AGA Clinical Practice Update and the 2021 ACG Guidelines make a strong recommendation for the use of soluble (but not insoluble) fiber for the treatment and improvement of global symptoms in IBS-C [11, 3].

Despite recent advances in IBS-C treatments, there are still some unmet clinical needs. Indeed, a recent survey found that only one in four individuals was “very satisfied” with FDA-approved prescription therapies [12]. In this connection, several new drugs (new secretagogues and pain-targeted therapies) are under active development. Elobixibat is an ileal bile acid transporter (IBAT) that increases bile acid concentration in the gut and accelerates colonic transit while mizaglifozin is a sodium-glucose co-transporter 1 inhibitor that decreases intestinal fluid absorption thereby increasing colonic fluid secretion. Both compounds are able to increase spontaneous bowel movement frequency. Olorinab, a peripheral highly selective CB₂-agonist,

decreases visceral inflammation and hypersensitivity and improves abdominal pain in patients with IBS-C, an effect shared by ebastine, an H1-receptor antagonist [13]. These new drugs with alternative mechanisms of action will represent additional tools to address the diverse pathophysiology of IBS-C.

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The Global Burden of DGBI

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Biosketch

Doctor Simrén is head of the Neurogastroenterology Unit at Sahlgrenska University Hospital. His main research areas are the pathogenesis and pathophysiology of disorders of gut-brain interaction (DGBI), as well as the treatment of these. He has published more than 350 original articles and written several book chapters on GI motility diseases and DGBI and is currently supervisor for fifteen PhD students and eight post-docs. Doctor Simrén has been the President of the Scandinavian Association for Gastrointestinal Motility (SAGIM), and Scientific Secretary to the Swedish Society of Gastroenterology, and served as council member for several international organizations. He has been the chair of the United European Gastroenterology (UEG) Scientific Committee 2013-2017, the UEG Secretary General (2018-2021), and a member of the UEG council (2013-2021). Professor Simrén has also been working as Deputy Editor and Associate Editor of Gut, and as the Clinical Editor of Neurogastroenterology and Motility. Currently, Professor Simrén is Associate Editor of Gastroenterology (2022-). He is also on the Rome Foundation Board of Directors since 2011 and the Research Director of the Rome Foundation Research Institute (RFRI) 2017-.

Abstract

Disorders of gut-brain interaction (DGBI), formerly known as functional gastrointestinal (GI) disorders, is a group of disorders classified by GI symptoms related to any combination of motility disturbance, visceral hypersensitivity, altered mucosal and immune function, altered

gut microbiota, and altered central nervous system (CNS) processing. These disorders are divided into five anatomic groups in adults (esophageal, gastroduodenal, gallbladder and sphincter of Oddi, bowel, and anorectal disorders) and centrally mediated disorders of GI pain, and two groups in childhood (neonate/toddler and child/adolescent). In the Rome Foundation Global Epidemiology Study, conducted via the Internet in 24 countries, personal interviews in 7 countries, and both in 2 countries (33 countries in total; n=73,076 adult respondents; 49.5% women), at least one DGBI was reported by 40.7% persons who completed the Internet surveys and 20.9% of persons who completed the household surveys. The overall rate for meeting at least one DGBI diagnosis was generally consistent between countries without major regional differences. A DGBI was more common in females than in males (OR 1.4-1.7), and the female predominance was noted for DGBI in all regions of the GI tract, from the esophagus to the rectum. The global burden of DGBI was demonstrated by lower quality of life and more frequent doctor visits among individuals with vs. without a DGBI. Furthermore, having DGBI in multiple anatomic regions was associated with increasing non-GI symptom reporting (somatization), IBS symptom severity, anxiety and depression, concerns and embarrassment about bowel function, doctor visits, medications, and abdominal surgeries. Quality of life decreased with increasing number of DGBI regions. Having meal-related abdominal symptoms is recognized as a cardinal feature across various DGBI, and frequent meal-related abdominal pain was reported by 11% of the global population. This was associated with other GI and non-GI somatic symptoms, psychological distress, healthcare utilization, a poorer quality of life and a high likelihood of fulfilling the diagnostic criteria for a DGBI. To conclude, DGBI constitute a major health care problem across the globe, associated with profound suffering for individuals and high costs for society and the individuals.

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The Effect of Nutrients on the GI Tract and Symptoms Assessed with MRI

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Biosketch

Professor Spiller is Professor of Gastroenterology in the Nottingham Digestive Diseases Centre at the University of Nottingham.

Past Editor of Gut (2003-2009) and member of the Board of the Rome Foundation (2000-2015), he twice edited the British Society of Gastroenterology (BSG) Guidelines for the management of IBS. His main research interest is the pathophysiology of irritable bowel syndrome (IBS), particularly the role of infection, inflammation, diet and alterations in the microbiome. He also has a long standing collaboration with the Sir Peter Mansfield Imaging Centre pioneering the use of MRI to image the underlying mechanisms in functional bowel diseases and how the structure of food alters postprandial small and large intestinal volumes and motility. Author/co-author of more than 414 scientific reviews and original publications, H index 86. Our group has a long track record of collaborative investigator initiated research projects with industry including Norgine, Dr Falk, Ironwood and Zespri most recently Sanofi-Aventis. Current studies include work on the postinfectious IBS, the role of fibre in altering fermentation in the gut and studies of the mode of action of drugs altering gut motility.

Abstract

The aim of the lecture is to briefly describe the digestion of simple sugars and fat and then focus on the impact of dietary fibre and poorly absorbed carbohydrate which significantly alter both bowel function and the microbiota. They also mediate symptoms in a hypersensitive gut typical of patients with the irritable bowel syndrome (IBS).

Simple sugars as well as starch found in bread are rapidly absorbed as they exit the stomach into the upper small intestine so small bowel water content (SBWC) remains low. By contrast poorly absorbed, low molecular weight monosaccharides such as mannitol and fructose exert a

powerful osmotic effect increasing SBWC and distending the small intestine 1,2. Fat stimulates pancreatic secretions which can be detected by a rapid increase in SBWC 3. Plant fibres such as psyllium also increase SBWC but by a different mechanism. This involves trapping water in hygroscopic gels thus restricting convective movement and slowing the absorption of water and dissolved nutrients like glucose 4. Adding bran to a test meal further increases SBWC even though bran is not hygroscopic 1. The mode of action may involve a shearing effect on the mucosa which is known to stimulate both secretion and 5-HT release 5. There has been considerable interest in the effect of fibre on satiation which starts in the mouth and stomach. Whole apples, high in the fibre pectin, increase satiation both immediately by the effect of chewing and distension of the stomach but also after the meal has left the stomach by increasing distension of both the small bowel and colon, an effect which reduces subsequent food intake 6.

One of the most hygroscopic dietary fibres is psyllium. This forms gels which trap substantial amounts of water in the small bowel and delivers this to the colon, whose water content is significantly elevated as assessed by the relaxation time constant T1. This significantly alters the microenvironment and alters the microbiota. Since psyllium is only slowly degraded by colonic microbiota its effect persists during passage through the colon enabling it to increase luminal water content throughout the colon, soften stool and thus relieve one of the main symptoms of constipation 4. It does however not stimulate motility as much as other laxatives and is associated with significantly larger colonic volumes which most likely explains why some patients complain of bloating when taking it as therapy. Kiwifruit also contains a very hygroscopic fibre which exerts similar effects to psyllium and is an effective laxative 7. Some green vegetables stimulate water secretion, possibly by secreting cytotoxins active against herbivorous insects 8. Plant storage polysaccharides such as inulin pass through the small bowel intact and do not alter SBWC but are rapidly fermented within the ascending colon producing gas and distension, which in IBS patients leads to pain, bloating and discomfort 9. Altering the rate of fermentation by restricting access of microbiota to inulin can alter fermentation pathways thus reducing gas production potentially reducing symptoms in IBS patients. This is the subject of ongoing research in Nottingham.

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Current and Future Management of IBS-D

Jan Tack

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Biosketch

Professor Jan Tack is currently a Head of Clinic in the Department of Gastroenterology, a Professor in Internal Medicine and Chairman of the Department of Clinical and Experimental Medicine at the University of Leuven, Belgium, and a principal researcher in TARGID (the Translational Research Center for Gastrointestinal Disorders) at the University of Leuven. He graduated summa cum laude in 1987 from the University of Leuven and specialised in internal medicine and gastroenterology at the same institution. A research fellow at the Department of Physiology at the Ohio State University, Columbus, Ohio, USA, from 1989 to 1990, he has been conducting research at Leuven University since 1990.

Professor Tack's scientific interest focuses on neurogastroenterology and motility, and includes diverse topics such as the pathophysiology and management of gastrointestinal functional and motor disorders, the physiology and pharmacology of the enteric nervous system, gastrointestinal hormones and the control of satiation and food intake. He has published more than 580 articles and 40 book chapters on various aspects of scientific and clinical gastroenterology.

Abstract

Irritable bowel syndrome with diarrhoea (IBS-D), is a common and sometimes challenging condition in clinical practice. The diagnosis requires a thorough history and clinical examination, and carefully selected cost-effective additional technical examinations. Once the diagnosis is made, several treatment options are available for the management of IBS-D, including

pharmaceutical and non-pharmaceutical interventions. A number of national and international societies have produced guidelines for the management of IBS. Through a recent Delphi consensus with experts several European countries, the UEG and ESNM guidelines for IBS-D were generated.

In terms of diagnosis, a symptom-based approach with the exclusion of alarm symptoms is recommended, in association with evaluation of full blood count, C-reactive protein, serology for coeliac disease, and faecal calprotectin, and consideration of testing for bile acid diarrhoea. Colonoscopy with random biopsies is recommended in patients older than 50 years or with alarm features.

Regarding pharmacotherapy, the European consensus achieved strong support for rifaximin, bile acid sequestrants and eluxadoline, although many of these are not readily available for use in IBS-D in Europe. Weak or conditional recommendation for current treatment options such as antispasmodics, loperamide, probiotics and 5-hydroxytryptamine-3 receptor antagonists. Behavioral or psychological therapies can be considered for refractory patients.

Emerging novel therapies include the locally acting “medical device” containing xyloglucan, pea protein reticulated with tannins and xylo-oligosaccharides, evaluated in recent controlled and open studies, and rifamycin MMX, evaluated in a recent European phase 2 study.

The most intense research focus has been on the use of dietary interventions for IBS-D. The efficacy a diet low fermentable oligo-, di-, monosaccharides and polyols (FODMAPs) is well-accepted, but the diet with elimination and stepwise reintroduction of FODMAPs remains complex for large-scale applications. A recent study blinded FODMAP reintroduction revealed a personalized pattern of symptom recurrence, with fructans and mannitol as the most prevalent triggers, but exclusion of just these 2 would not sufficiently control symptoms. Studies are evaluating enzymatic approach to digestion of FODMAP to gain easier symptom control. Less intense dietary approaches, such as the NICE diet, may also be efficacious. A controlled trial in primary care IBS demonstrated that a simple FODMAP-lowering diet app was superior to medical therapy for symptom relief, making dietary treatment accessible for large patient groups. The most recent wave is the use of confocal laser endomicroscopy (CLE) to unravel atypical protein food allergic reactions, that have been implicated in IBS-D symptom generation. These CLE studies have identified a multitude of food allergens capable of triggering local mucosal reactions, and the potential of improving symptoms through targeted dietary elimination is currently under investigation.

In conclusion, while the current approach to IBS-D is well-established and supported by international consensus, a large number of recent or ongoing clinical trials are reshaping the clinical arena, with novel pharmacological or “medical device” approaches, as well as novel dietary intervention strategies.

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Wheat Immunogenic Proteins: Myths, Reality and Misconceptions

Elena Verdù

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Biosketch

Dr. Elena Verdù has had a longstanding interest in microbial commensal influence on chronic inflammatory disorders. She obtained a medical degree in Argentina before embarking on a research career with training under the supervision of Prof. Andre Blum in Lausanne, Switzerland where she earned a doctorate in human physiology. The discovery that a bacterium could cause gastric and duodenal ulcers was revolutionary and sparked her interest in the role of gut bacteria in other chronic intestinal conditions. Funded by a UNESCO fellowship, Dr. Verdù pursued a Ph.D. degree under the direction of Prof. Helena Taskalova, in immunology and gnotobiology at the Czech Academy of Science on the effect of commensal bacterial antigens in inflammatory bowel disease and celiac disease. She then trained as a post-doctoral fellow with Prof. Stephen Collins at McMaster University, where her work focused on beneficial (probiotic) bacteria and their effect on gut function and inflammation. In 2006 Dr. Verdù was appointed faculty at McMaster University, where she developed a program to investigate host-microbial and dietary interactions in the gastrointestinal tract. Her research aims at deciphering commensal and opportunistic pathogen metabolism of dietary antigens and how that process affects their inflammatory capacity in the host. In addition to her own research lab, she is director of the Axenic and Gnotobiotic facility and Associate Director of the Farncombe Institute at McMaster. She has been honored by the 2007 New Investigator Award (Canadian Celiac Association; CCA), the 2011 Master's Award in Gastroenterology in Basic Science (American Gastroenterology Association), the 2012 Canadian Association of Gastroenterology (CAG) Young Investigator Award, the 2017 CAG Visiting Research Professor Award, the 2019 CAG Education Excellence Award, the 2020 CAG Research Excellence Award, and the 2020 Crohn's and Colitis of Canada (CCC)-Pfizer Women in IBD: Outstanding Research Achievement Award. Currently she holds the rank of full professor and a Canada Research Chair in Inflammation, Microbiota and Nutrition. She is active in many professional volunteer-based activities including as past Treasurer of the CAG, as founding member and past president of the Society for the Study of Celiac Disease (US), and as a member of committees with the AGA Institute. She also participates

in community activities that support patients' associations, such as the CCC and the CCA. Knowledge translation activities include her leading role as Nutrition specialist in international platforms such as Gut Microbiota for Health.

Abstract

Non-celiac wheat sensitivity (NCWS) is a poorly understood entity, that is diagnosed based on self-reported onset of a wide range of intestinal and extra-intestinal symptoms upon ingestion of wheat containing food, once celiac disease and wheat allergy have been ruled out. While gluten is a likely trigger, several ingredients in a wheat containing diet can induce symptoms in a proportion of individuals. Because there is no known or validated biomarker, diagnosis is difficult and usually based on a positive history of symptoms during a gluten/wheat containing diet, symptom resolution after exclusion of gluten/wheat-containing food, and re-appearance of symptoms with reintroduction of gluten/wheat products. As suggested by the Salerno consensus, this requires a double-blind, placebo controlled, cross-over challenge approach. While these strict criteria can be implemented easily during a research protocol, they are not practical in the clinical setting. Moreover, only 16% those who self-report as gluten-sensitive will fulfil the current consensus criteria for a diagnosis of NCWS. There is urgent need for pathophysiologic understanding and development of biomarkers to first identify these patients in clinical practice, and secondly implement dietary approaches in a personalized manner. The picture is complicated by the fact that symptomatic responses to one wheat component does not rule out reaction to another, and this was suggested in a study where the combination of gluten and wheat amylase trypsin inhibitors (ATI) synergized to induce gut dysfunction in mice. Recently, and like other gastrointestinal conditions such as irritable bowel syndrome (IBS), studies have shown that NCWS may indeed constitute a clinical spectrum. Thus, NCWS is emerging as a complex syndrome in gastroenterology, comprising an heterogeneous population of patients that react to a variety of wheat components, including gluten, and that develop characteristic clinical and immunopathological phenotypes. Research into the triggers and mechanisms of NCWS is critical for the identification of biomarkers that will guide personalized dietary intervention strategies.

Free Papers

Workshop I

Effect of transplant route of administration on the outcome of fecal microbiota transplantation for patients with IBS

M. El-Salhy¹

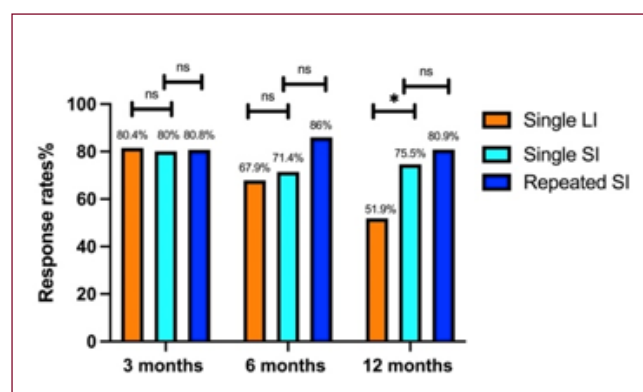
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Objective: Fecal microbiota transplantation (FMT) as an intervention for irritable bowel syndrome (IBS) has been applied in several randomized controlled studies with varied outcome. The present study aimed at evaluating the increasing the dose, the route of administration of fecal transplant as well as repeated FMT on the FMT outcome.

Methods: The study included 186 IBS patients who randomized 1:1:1 into transplant administrated to the colon (single LI), to the duodenum (single SI), or to the distal duodenum twice with a week interval (repeated SI). The fecal transplant dose was 90g. The patients provided a fecal sample and were asked to complete five questionnaires to assess their symptoms, fatigue and quality of life at the baseline, and at 3, 6, and 12 months after FMT. The fecal bacteria composition and dysbiosis index (DI) were analyzed using 16S rRNA gene PCR DNA amplification/probe hybridization covering the V3–V9 regions.

Results: The response rate was significantly higher in single SI than that of single LI at 12 months after FMT (Figure). Symptoms and quality of life improved in all the treated groups at all time intervals after FMT. The abdominal symptoms were significantly lower and quality of live higher in repeated SI group than those of single SI at all observation times after FMT. DI decreased significantly in all the treated groups at all observation times after FMT. The bacterial profiles changed in all groups at all observation intervals. However, these changes differed between single LI on and single SI/repeated SI. Of these bacteria 6 were correlated to abdominal symptoms and 2 were correlated to fatigue. In the first 5 days following FMT, nausea, mild intermittent abdominal pain, diarrhea or constipation were reported. There was no significant difference between single LI, single SI and repeated SI regarding these adverse events.

Conclusions: Increasing the dose of fecal transplant to 90 g did not improve responses. Administrating transplant to the small intestine had a long-term higher response rate than that administrated to the large intestine. Repeating FMT had more effect on symptoms and quality of life than a single FMT.



Microbial histamine induces visceral hyperalgesia through H4 receptor dependent mechanisms

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Gut microbiota has been implicated in chronic pain disorders, including Irritable Bowel Syndrome (IBS), yet specific underlying mechanisms remain unclear. We have previously shown that symptomatic improvement of IBS patients on a low fermentable (FODMAP) diet is associated with changes in gut microbiota and decreased urinary histamine, the latter correlating with improved abdominal pain. However, the sources of urinary histamine and its exact role in IBS pathogenesis are unknown.

Objective: To investigate the putative role of bacterial histamine in visceral hyperalgesia.

Methods: Germ-free mice colonized with the microbiota from IBS patients with high and low urinary histamine, and from healthy controls, were fed either a high or a low fermentable diet. Bowel distension was assessed by CT scan. Visceral sensitivity was assessed by pseudoaffective responses to colorectal distention and by electrophysiological recordings of colonic afferent nerves stimulated mechanically. Intestinal tissues and contents were collected for immunohistochemistry and microbiome analyses. Histamine was measured by ELISA.

Results: Mice colonized with IBS microbiota had greater gas content and bowel distension than mice with healthy control microbiota, but only mice with microbiota from IBS patients with high urinary histamine (IBS-HH mice) displayed visceral hyperalgesia. This was associated with increased density of colonic mast cells, which often co-localized with nerve fibers. In IBS-HH mice, we isolated a Gram-negative bacterium with a special variant of histidine decarboxylase gene that produced very high levels of histamine, when in a proper fermentative milieu, and which induced mast cell hyperplasia in monocolonized mice. While histamine receptor 1 (H1R) and H2R pathways were not affected, H4R was upregulated in the colon and its blockade prevented visceral hyperalgesia and neuroimmune alterations in mice colonized with histamine producing microbiota. Finally, this histamine producing bacterium was present in microbiome of 20-30% of IBS patients and high bacterial histamine levels correlated with episodes of abdominal pain in these patients.

Conclusions: Bacterial histamine through H4R dependent pathways triggers visceral hyperalgesia in a subset of patient with IBS. Identifying these patients may direct dietary or microbiome-directed therapies to manage their chronic abdominal pain.

Diagnostic methods for idiopathic bile acid diarrhea

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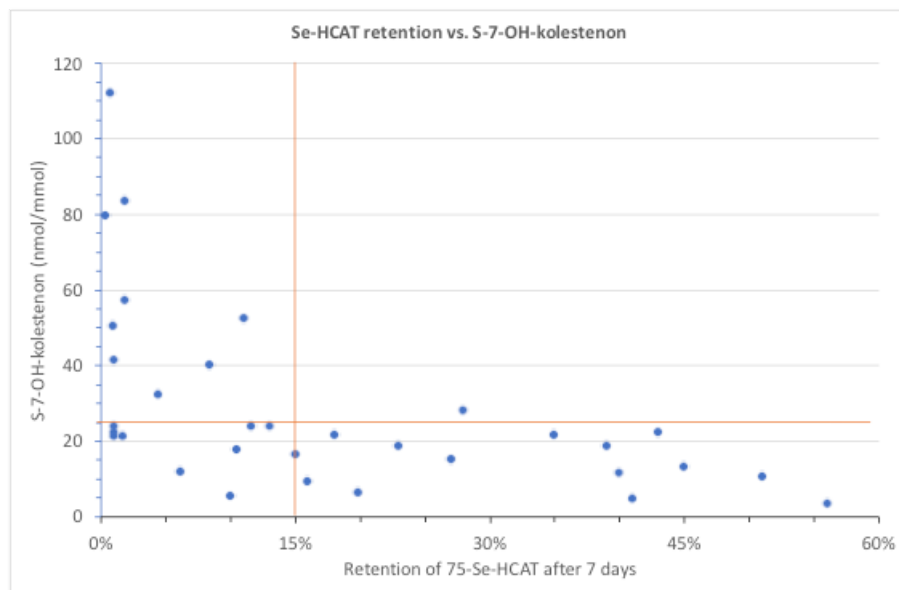
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Objectives: Idiopathic bile acid diarrhoea is the most commonly missed diagnosis in patients with chronic diarrhoea. Treatment with bile acid sequestrants without a firm diagnosis is difficult. 75-Se-HCAT (homocholic acid taurine) has long been used for the assessment of increased bile acid losses. Normal values are >15% retention after 7 days. Low values (<10% retention) signal increased bile acid losses. However, in the range 10%-15% retention the results are unclear. A new method for diagnosing bile acid diarrhoea is to determine the level of 7-OH-kolestenon, an intermediate bile acid metabolite, in serum. Values above 25 nmol/mmol cholesterol indicate increased bile acid turnover (i.e. losses), whereas values below 18 nmol/mmol cholesterol are normal. Again, there is a grey zone between 19-25 nmol/mmol cholesterol where it is difficult to judge the meaning of the result. We undertook this retrospective analysis to compare the two methods in patients that had undergone both tests for bile acid diarrhoea.

Methods: We analysed data for 33 patients who had undergone both Se-HCAT and 7-OH-kolestenon at Karolinska University Hospital 2010-2020. We excluded patients who had undergone bowel resection, patients with Crohn's disease and those in whom one or both investigations had been done under the influence of bile acid sequestrants.

Results: Ten patients had elevated (≥ 25 nmol/mmol) 7-OH-kolestenon and 9 of these had <15% retention of Se-HCAT (8 had <10% retention). Normal levels of 7-OH-kolestenon (2,5-19 nmol/mmol) were found in 14 patients and 11/14 patients had >15% retention of Se-HCAT. Nine patients had 7-OH-kolestenon 19-25 nmol/mmol and 6/9 had Se-HCAT <15%, (see figure). Bile acid sequestrants were given to 19 patients and 14 responded well to treatment. Six patients with Se-HCAT (1.0%-13%) but 7-OH-kolestenon in the range 21.3-23.9 nmol/mmol also responded well to treatment with bile acid sequestrants.

Conclusions: Agreement between the two methods was excellent for extreme values. Both tests can identify patients with bile acid diarrhea. 7-OH-kolestenon-levels between 19-25 nmol/mmol as well as Se-HCAT retention between 10-15% are grey zones with unclear significance with regard to bile acid diarrhea. Using both methods may help clarifying findings in the grey zones.



The DOMINO trial: therapeutic outcome and predictors of a new FODMAP lowering diet smartphone application vs. medication in primary care IBS.

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Spasmolytic agents like otilonium bromide (OB) and also the low FODMAP diet have shown benefit in tertiary care IBS. The low FODMAP diet is laborious and complex and needs thorough guidance of an experience dietitian, excluding it from being standard of care in primary care IBS. The aim of the DOMINO trial was to compare the efficacy and identify response predictors for OB and a new FODMAP lowering self-management smartphone application.

Methods: Primary care IBS patients (n=470, 41±15yo, 76%female, 70% fulfilling IBS Rome IV) were randomized to OB (n=232, 60 mg t.i.d.) or diet app (n=227). Response was defined as ≥50 point improvement on IBS Symptom Severity Score (IBS-SSS) and was evaluated at 8,16&24 weeks. We explored at baseline laboratory and stool biochemical markers (CRP, calprotectin (FC), secretory Immunoglobulin A (sIgA), human beta-defensin 2 (HBD-2), elastase, microbiota composition, and genetic profile as predictors of response and repeated these measures (except genetics) after 8 weeks treatment. The IBS subtype (Bristol stool scale, BSS), quality of life (IBS-QoL), and levels of anxiety (GAD), depression (PHQ9), and somatization (PHQ15) were also evaluated.

Results: The diet showed a higher treatment response than OB after 8 (diet: 71% (155/218) vs. OB: 61% (133/217)) and 16 (74% vs. 57%) (p<0.05), while both had similar response rates at 24 weeks (69% vs. 70%). Improvement from baseline was observed in both treatments for quality of life and psychologic distress levels (all p<0.001) without difference between arms (p>0.05).

Associations to response to OB were the baseline level of somatization and genetic polymorphisms in the genes SLC6A4, TRPA1, CACNA1C. For the diet, predictors were female gender and polymorphisms in the genes IL5RA and CCR3. No associations to treatment response were found for microbiota composition (enterotypes, taxa, genera) or lab and stool biochemical markers. A significant reduction for HBD-2 occurred in both arms (diet p=0.0081; OB p=0.0003) and for sIgA after OB (p=0.048).

Conclusions: In primary care, a FODMAP lowering self-management smartphone app is superior to standard spasmolytic therapy. Microbiota or stool and laboratory tests did not predict treatment response, but genetic markers seem associated with response to diet or medication.

Workshop II

A pilot nutrigenetic study of response to dietary intervention in irritable bowel syndrome

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Background and aim: IBS patients often report dietary triggers, and a lowFODMAP diet is known to be effective to treat some, but not all, patients. We have previously shown that defective (hypomorphic) sucrase-isomaltase variants are associated with increased risk of IBS and a poorer response to the lowFODMAP diet. Similar mechanisms may be detected for other enzymes involved in the digestion of carbohydrates (EDCs).

Methods: We (retrospectively) studied EDC gene single nucleotide variants (SNVs) in relation to a lowFODMAP diet in IBS patients from the DOMINO trial (N=201 in the dietary arm, N=161 in a medication arm with otilonium bromide). An EDC-specific Illumina AmpliSeq panel was designed based on targeted sequencing of relevant genes. Potential EDC hypomorphic variants were identified via computational annotation with CADD and M-CAP clinical pathogenicity classifiers. We used age- and sex-adjusted logistic regression to evaluate the response to treatment in IBS carriers and non-carriers of (any of) these variants.

Results: Targeted sequencing was successful with high coverage (>30x) for 6 EDC genes, namely (AMY2B, LCT, MGAM, MGAM2, SI and TREH). Out of 50 hypomorphic variants detected, 48 were rare (allele frequency, AF<5%) and 2 common (AF>5%). In cumulative analyses (collapsing all relevant variants into a single hypomorphic group), IBS-D hypomorphic carriers were more likely to respond to the lowFODMAP diet than non-carriers (72.4% vs 41.2% response respectively; 1-tail P=0.005; OR=4.9). Additional associations were observed for rare variants in all IBS patients (80.6% vs 65.9% response in carriers and non-carriers, respectively, one-tail P=0.009; OR=2.33). No association was detected when EDC hypomorphic variants were tested versus treatment response in the medication arm (otilonium bromide).

Conclusions: We report initial evidence that hypomorphic variants in genes involved in carbohydrate digestion may be relevant to dietary treatment and the response to a low-FODMAP diet in IBS patients. This warrants additional testing and replication of findings, and further investigation of the specific nutrigenetic mechanisms behind statistical observations. EDC genetic profiling may ultimately contribute to the development of personalized dietary treatment of IBS patients.

A randomized controlled clinical trial comparing two different carbohydrate restrictive diets and optimized medical treatment in irritable bowel syndrome (IBS): the CARIBS study

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Objective: Treatment options in IBS include dietary advice and medications based on the predominant symptoms. No direct comparisons between these treatment strategies exist. We aimed to compare the effects on IBS symptoms, lipid and glucose levels of two different carbohydrate restrictive diets and an optimized medical treatment strategy in a randomized, controlled trial.

Methods: Adults with IBS with at least moderate IBS symptom severity (IBS-SSS ≥ 175) were randomized to one of three treatment options for 4 weeks; 1) diet with low total carbohydrate content (LCD); 2) diet combining low- fermentable oligo-, di-, monosaccharides and polyols (FODMAP) and traditional IBS dietary advice (LFTD); 3) an optimized medical treatment (OMT). The LCD consisted of 10 E% carbohydrates, 67 E% fat, and 23 E% protein, and corresponding numbers were 50 E%, 33 E%, and 17 E% in LFTD. The OMT was based on the predominant IBS symptom. Fasting blood samples were taken at baseline and after the intervention.

Results: We included 407 IBS patients and 302 were randomized. After exclusion of 7 patients, 295 were included in the intention to treat analysis, where 272 completed the intervention period (drop-out; 6 LCD, 7 LFTD, 10 OMT). The severity of IBS symptoms was reduced by all three interventions ($p < 0.001$, within groups), and the mean changes in IBS-SSS were -131, -147, and -76 in LCD, LFTD and OMT, respectively ($p < 0.001$). Fasting levels of lipids, glucose and HbA1c did not differ between groups at baseline and remained unchanged in the OMT arm after intervention. In the LCD, total cholesterol and LDL levels had significantly increased, while levels of triglycerides and HbA1c had decreased. In the LFTD arm, total cholesterol, LDL, HDL, and triglyceride levels had decreased significantly.

Conclusions: Dietary treatments, both an LCD and an LFTD, as well as OMT, offer symptom reduction to patients with IBS, with a larger benefit with the dietary treatment options. However, fasting blood lipids had worsened during the LCD intervention period while most lipids had improved in the LFTD arm (except for HDL). This highlights the importance of monitoring lipid levels if recommending an LCD diet as treatment for IBS.

Table. Characteristics, IBS symptom severity, and blood tests in the CARIBS study.

	Low carbohydrate diet	Low FODMAP + traditional IBS diet	Optimized medical treatment	p-value [#]
N in ITT	97	97	101	
Gender (women), %	78.4	85.6	82.2	0.42
Age, y	39±14	38±13	40±13	0.55
Baseline				
IBS-SSS total	322±69	322±67	320±70	0.95
Weight, kg	73.0±13.8	74.2±14.2	71.8±12.6	0.45
BMI, kg/m ²	25.3±4.2	25.5±3.9	24.8±4.0	0.45
Cholesterol	4.9±1.1	4.9±1.0	5.0±1.0	0.79
HDL cholesterol	1.7±0.5	1.7±0.5	1.7±0.4	0.61
LDL cholesterol	3.1±1.0	3.1±0.9	3.2±0.9	0.89
Triglycerides	1.0±0.7	1.0±0.8	1.1±0.6	0.75
P-glucose	5.3±0.7	5.2±0.5	5.2±0.4	0.71
HbA1c	31.9±3.1	31.7±3.1	31.3±3.0	0.54
After intervention				
IBS-SSS total	191±106	175±113	244±109	<0.001
Weight, kg	71.7±13.4	72.0±13.3	71.1±12.4	0.90
BMI, kg/m ²	25.0±4.1	24.9±3.9	24.5±3.9	0.72
Cholesterol	5.1±1.1	4.6±0.9	5.0±0.9	0.002
HDL cholesterol	1.7±0.5	1.5±0.4	1.7±0.4	0.007
LDL cholesterol	3.4±1.0	3.0±0.9	3.2±0.9	0.009
Triglycerides	0.9±0.5	0.9±0.5	1.0±0.5	0.068
P-glucose	5.2±0.5	5.2±0.6	5.2±0.5	0.60
HbA1c	31.4±3.0	31.7±2.9	31.3±2.9	0.78
Change in IBS-SSS	-131±110	-147±116	-76±94	<0.001
Weight, kg	-1.4±1.7**	-1.3±2.2**	0.1±1.3	<0.001
BMI, kg/m ²	-0.5±0.6**	-0.4±0.7**	0.0±0.5	<0.001
Change in cholesterol	0.2±0.7*	-0.3±0.5**	-0.1±0.6	<0.001
Change in HDL cholesterol	0.0±0.2	-0.1±0.2**	0.0±0.2	<0.001
Change in LDL cholesterol	0.3±0.7**	-0.1±0.4*	-0.0±0.5	<0.001
Change in Triglycerides	-0.1±0.4*	-0.2±0.4**	-0.0±0.3	0.053
Change in P-glucose	-0.1±0.6	-0.0±0.4	-0.1±0.4	0.55
Change in HbA1c	-0.4±1.4*	-0.1±1.5	0.1±1.4	0.13

*p-value <0.05 **p-value <0.001, paired samples t-test, baseline vs. after intervention

[#]p-value indicate between group comparisons using analysis of variance test (ANOVA)

The faecal abundance of *Collinsella aerofaciens* and other potential pathobionts may predict the clinical efficacy of the probiotic *Lactobacillus paracasei* DG in non-constipated IBS patients

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Objective: To assess the effect of *L. casei* DG® (*Lactobacillus paracasei* CNCM11572; DSM34154; Enterolactis® PLUS) on abdominal symptoms and gut microbiota composition in non-constipated IBS patients.

Methods: In a multi-centre, randomized, double-blind, parallel-group, placebo-controlled trial, patients were randomized to receive Enterolactis® PLUS or placebo capsules b.i.d. for 12 weeks. Proportion of patients that had a response in pain and in stool consistencies was assessed for primary outcomes. The faecal microbial ecosystem was characterized by 16S rRNA gene profiling.

Results: To establish whether the patients who benefited from the probiotic treatment (RESPs) had characteristics that distinguished them from the patients who did not experience significant improvements (NRs), the levels of faecal bacteria were compared between the two groups. This analysis found that RESPs were characterized by a significantly greater abundance of different microbial groups that were observed in other studies to be expanded in IBS compared to healthy subjects, such as *Bacteroides plebeius*, *Dorea* spp., *Ruminococcus bromii*, *Ruminococcus* spp., *Blautia* spp., and *Collinsella aerofaciens*. In particular, the most important taxonomic group distinguishing RESPs from NRs was *C. aerofaciens*. The probiotic treatment induced a reduction (trending towards significance, $P=0.068$) of *C. aerofaciens* in RESPs. Conversely, *C. aerofaciens* did not change either in the NRs or in the placebo group. Similar results were also observed re-analysing data from a previous clinical trial conducted with Enterolactis® PLUS in IBS patients. In particular, we found that patients in which *C. aerofaciens* decreased during the probiotic treatment simultaneously had a significant decrease in abdominal pain ($P=0.049$) and a tendency to decrease in faecal type ($P=0.071$).

Conclusions: This study suggests that Enterolactis® PLUS is effective on “dysbiotic” non-constipated IBS patients, i.e. with a greater abundance of potential IBS-associated pathobionts. Among these, the increased abundance of *C. aerofaciens*, a bacterium shown to contribute to pro-inflammatory immune states, emerges as a potential predictor of the efficacy of Enterolactis® PLUS.

The study was registered at ClinicalTrials.gov registry under identifier NCT03449628.

Large-scale GWAS meta-analyses of stool frequency and consistency identify actionable pathways relevant to gut dysmotility and irritable bowel syndrome

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Background and Objective: Gut dysmotility is a hallmark of Irritable Bowel Syndrome (IBS), and genetic studies may reveal novel actionable pathways. We propose the use of endophenotypes for large-scale genetic surveys, using questionnaire-data on stool frequency and consistency as proxies for powered gut motility investigations.

Methods: We performed GWAS (genome-wide association study) meta-analyses of stool frequency (FRQSTL), frequency of hard stool (HDSTL) and frequency of loose stool (LSSTL) in 185,106 individuals from UK Biobank and LifeLines cohorts. GWAS results were annotated using a computational pipeline including fine mapping of causative genes and variants, gene- and pathway-enriched analyses, phenome-wide associations, genetic correlations, and drug target identification. Polygenic scores (PGS) summarizing GWAS outcomes were used to predict IBS risk in the studied cohorts.

Results: We demonstrate gut motility is a heritable trait in humans (SNP heritability range 4.9-6.9% for FRQSTL, HDSTL and LSSTL). In total for the 3 traits, we detected 3815 genome-wide ($p < 5 \times 10^{-8}$) association signals, tagging 27 loci harboring genes primarily involved in olfactory signaling pathway, ion channel activity, synaptic transmission, nervous system and digestive tract development. Some of these regions were linked to gastrointestinal diseases, psychiatric and cardiovascular conditions, and other traits from previous studies. The overall genetic architecture of all traits strongly correlates with that of IBS ($r_g = 0.262-0.487$), and mood and anxiety disorders ($r_g = 0.261-0.34$). We observed inverse genetic correlation between HDSTL and LSSTL endophenotypes ($r_g = -0.143$), suggesting similar genotype-driven mechanisms may act, in opposite directions, in constipation and diarrhea-predominant IBS subtypes. Druggable pathways were also identified, including some already targeted by current IBS medications (lomotilide and Tenapanor). Finally, individuals from the top percentiles of PGS distribution were exposed to markedly increased IBS risk in the studied populations.

Conclusions: Investigating IBS endophenotypes reduces complexity, increasing the chances of discovering genetic factors and mechanisms crucial to IBS pathophysiology. The identification of genes and pathways influencing gut motility offers actionable targets and new routes for therapeutic

exploitation in IBS and other dysmotility syndromes. Finally, novel genetic knowledge may contribute to predicting IBS risk in the general population, and should stimulate new pharmacogenetic studies.

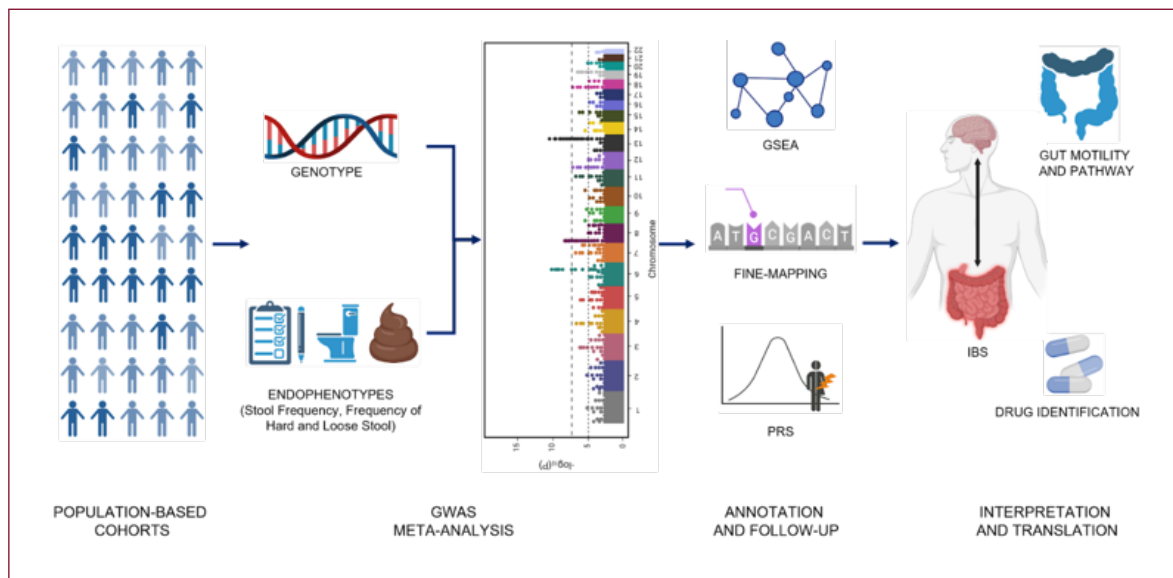


Figure: Graphical summary of the workflow performed in the study.

Workshop III

Environmental factors and irritable bowel syndrome, new prospective by pandemic restrictive measures: the “Cocoon effect”

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Introduction: Irritable Bowel Syndrome (IBS) is a highly prevalent disorder that greatly affects patients' quality of life, causing a significant burden to healthcare systems worldwide. Its pathophysiology is incompletely understood but symptoms seem to be the result of an interplay between environmental and patient-related factors.

This study aimed to analyse the influence of lockdown-forced changes in lifestyle habits and COVID-19 pandemic stress on the development of IBS manifestations.

Aims and Methods: An online survey was sent to groups of people representative of the general population. It contained questions regarding socio-demographic data, dietary habits, alcohol consumption, smoking habits, physical activity, sleeping hours, working activities, stress level and GI symptoms, related to both the pre-pandemic and lockdown period. A P-value<0.05 was considered statistically significant. Uni and Multivariate Cox methods and Wald test were used to evaluate the association between exposure variables and IBS occurrence/resolution.

Results: From April 1st to 30th, 2020, 2735 participants completed the survey (mean age: 39.7±16.1 years, F:M=2:1). During lockdown 122 IBS patients (46.2%) reported improvement of symptoms while 118 negative subjects (4.8%) developed IBS. Age, gender, BMI, employment, teleworking and smoking were not associated with IBS incidence or resolution. Reduced general stress (OR=2.23, 95%CI 1.09-4.56, P=0.029), increased fibers intake (OR=2.83, 95%CI 1.60-5.02, P<0.001) and increased hours of sleep (OR=2.00, 95%CI 1.07-3.76, P=0.031) were associated with a high probability of resolution of IBS, while increased intake of anxiolytic pills (OR=0.14, 95%CI 0.04-0.46, P=0.001) showed a low probability of resolution of IBS. Reduced physical activity (OR=2.04, 95%CI 1.30-3.19, P=0.002), increased anti-inflammatory (OR=2.38, 95%CI 1.39-4.10, P=0.002), anxiolytic pills intake (OR=3.52, 95%CI 2.08-5.95, P<0.001) and increased work related stress (OR=1.81, 95%CI 1.16-2.83, P=0.009) were risk factors for IBS occurrence. Finally, the resolution of IBS did not affect the onset of upper GI functional symptoms (OR=0.18, 95%CI 0.11-0.31, P<0.001).

Conclusions: Lifestyle changes forced by COVID-19 lockdown resulted in a beneficial effect in almost half of IBS patients, whereas they favoured the development of IBS in 5% of healthy subjects, thus confirming that environmental factors play a pivotal role in the pathophysiology of IBS. In particular, stress, fibres and alcohol intake seem to be able to influence IBS occurrence or resolution.

A possible gut microbiota signature in patients with bloating: results from real life

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Background: Abdominal bloating is a bothersome symptom affecting 16-31% of the general population and most of the patients affected by Irritable Bowel Syndrome (IBS). Gut microbiota modulation has recently shown promising results in IBS patients complaining of bloating. Few studies focused solely on the relationship between bloating and specific gut microbial shifts. Recent evidence correlated efficacy of a low FODMAP (Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyols) approach in patients with bloating and increased levels of Firmicutes.

Methods: aim of this study was to analyse the gut microbiota composition of 90 out of 153 patients referred for microbiota evaluation who reported bloating as the main symptom [IBS patients (n=52); functional abdominal bloating (n=24); bloating associated with chronic constipation (n=13) and chronic diarrhea (n=1), respectively]. Gut microbiota analysis of these patients was compared to that of the remaining 63 patients without bloating. Alpha-biodiversity and taxonomy were analyzed using 16S rRNA sequencing. Statistical significance was calculated using the Wilcoxon two-sample test ($p < 0.05$).

Results: Patients with bloating demonstrated an increase in richness ($p < 0.05$, 95% IC), higher levels of Firmicutes (52.06 ± 15.29 vs 44.58 ± 14.26 , $p < 0.003$) and lower levels of Bacteroidetes (42.90 ± 15.22 vs 49.68 ± 15.38 , $p < 0.006$). Firmicutes/Bacteroidetes ratio resulted significantly increased ($p < 0.004$). The most abundant taxa observed in patients with bloating were butyrate- and acetate-producing bacteria (Christensenellaceae R-7 group, Faecalibacterium, Fusicatenibacter, Hydrogenoanaerobacterium, Ruminiclostridium, Ruminococcus, Subdoligranulum) along with taxa belonging to Tenericutes and Lentisphaerae ($p < 0.01$). Conversely, Lachnospirillum, Lactobacillus and Ruminococcus gnavus group resulted decreased ($p < 0.05$) in patients with bloating.

Conclusions: In addition to Firmicutes, also Lentisphaerae and Tenericutes show a positive co-occurrence in patients with bloating. Since Firmicutes and Lentisphaerae are known to be particularly rich in FODMAP-metabolizing enzymes, our results suggest a better-defined microbiota signature that may guide the clinician in choosing an effective therapy in patients complaining of abdominal bloating.

Anxiety, depression, and somatic symptoms overlap: Implications for the presentation of disorders of gut-brain interaction in a global epidemiologic sample

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Objectives: The main aim of this study was to examine how the overlap between anxiety, depression, and somatic symptoms influences the presentation of Disorders of Gut-Brain Interaction (DGBIs) in terms of number of anatomical regions affected with a DGBI. This study also examines how this overlap associates with quality of life (QoL) and healthcare use.

Methods: This study includes nationally representative samples of 54,127 adult participants (49.1% women) from 26 countries. Participants completed the Internet survey of the Rome Foundation Global Epidemiology Study, which included questions regarding healthcare utilization, and self-report measures of anxiety and depressive symptoms (PHQ-4), somatic symptom severity (PHQ-15), DGBI diagnoses (Rome IV Diagnostic Questionnaire), and QoL (PROMIS Global-10). The recommended cut-off scores for the PHQ-4 and PHQ-15 were used to identify clinically meaningful levels of psychological (anxiety and depression) and somatic symptoms. The presence of clinically meaningful anxiety, depressive, and/or somatic symptoms is abbreviated as PS in this study.

Results: 34.1% (95%CI 34.0-34.2) of the sample reported PS. Among these participants, 64.8% (64.7-65.0) also met criteria for at least one DGBI, while only 29.9% of participants without PS reported a DGBI. Participants with PS had 4.49 greater odds of having at least one DGBI than participants without PS. An increasing number of different types of PS was associated with a larger likelihood of having a higher number of anatomical regions affected with a DGBI (Table 1). PS overlap was also associated with lower mental (OR= 0.6; 0.6-0.7) and physical (OR= 0.6; 0.6-0.6) QoL, with a gradual reduction in QoL with higher number of types of PS. Furthermore, participants with higher PS overlap were more likely to be taking medication for pain, anxiety, depression, or sleep (ORs 2.6-5.8), and reported more specialist visits (ORs 2.0-3.9) and alternative medicine use (ORs 2.8-6.3).

Conclusions: A high proportion of participants with PS reported at least one concomitant DGBI diagnosis. Our results suggest that the presence of clinical levels of anxiety, depressive symptoms,

and/or somatic symptoms, especially if overlapping, is linked to a higher number of DGBI-affected anatomical regions and is associated with poorer well-being and higher healthcare use.

Table 1. Comparison of participants by number of PS and number of DGBI by anatomical regions. Odds ratios derived from mixed ordinal regression with country as random intercept.

Number of anatomical regions involved †	Number of PS				OR (95%CI)
	0 (N=35665)	1 (N=9829)	2 (N=5234)	3 (N=3399)	
0	69.2% (68.7-69.7)	39.7% (38.7-40.6)	32.3% (31.0-33.6)	17.1% (15.8-18.4)	Ref.
1	24.2% (23.8-24.7)	36.0% (35.0-36.9)	38.7% (37.3-40.0)	33.3% (31.7-34.9)	3.2 (3-3.3)
2	5.3% (5.1-5.6)	16.0% (15.3-16.7)	18.1% (17.1-19.2)	26.0% (24.5-27.5)	7.2 (6.8-7.6)
3	1.1% (1.0-1.2)	6.2% (5.7-6.7)	7.9% (7.2-8.7)	15.3% (14.1-16.6)	14 (12.9-15.3)
4	0.2% (0.2-0.2)	2.2% (1.9-2.5)	3.0% (2.6-3.5)	8.3% (7.4-9.3)	25 (21.8-28.8)

† Esophageal disorders, Gastroduodenal disorders, Bowel disorders, and/or Anorectal disorders

Irritable bowel syndrome, depression and anxiety: genetic overlap and causality

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Background: We aimed to i) quantify the genetic correlation between IBS depression and anxiety, ii) identify novel genetic risk associations for IBS using cross-trait analyses and iii) investigate causal relationships between IBS depression and anxiety.

Material and Methods: We used publicly available single nucleotide polymorphism (SNP)-level genome-wide association study (GWAS) summary statistics for IBS (N cases=53,400; N controls=433,201), depression (N cases=170,756; N controls=329,443) and anxiety (N cases=16,730; N controls=101,021). Causal relationships between IBS and correlated traits were assessed using causal analysis using summary effect estimates.

Results: We found strong genetic correlations between IBS and both mental disorders ($r_G=0.62$, $s.e.=0.037$ for IBS and depression and $r_G=0.71$, $s.e.=0.078$ for IBS and anxiety). The Multi-trait analysis of GWAS (MTAG) highlighted 21 new genome-wide significant loci for IBS located in, or nearby, genes related with antidepressants response, neuroticism, depression, among others. We also found consistent evidence for a causal effect of the genetic liability of IBS on depression ($P=8.7e-07$) and anxiety ($P=7.6e-05$).

Conclusions: Our results are consistent with a shared common genetic background between IBS, depression and anxiety.

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Posters

Gut microbiome in chronic intestinal failure

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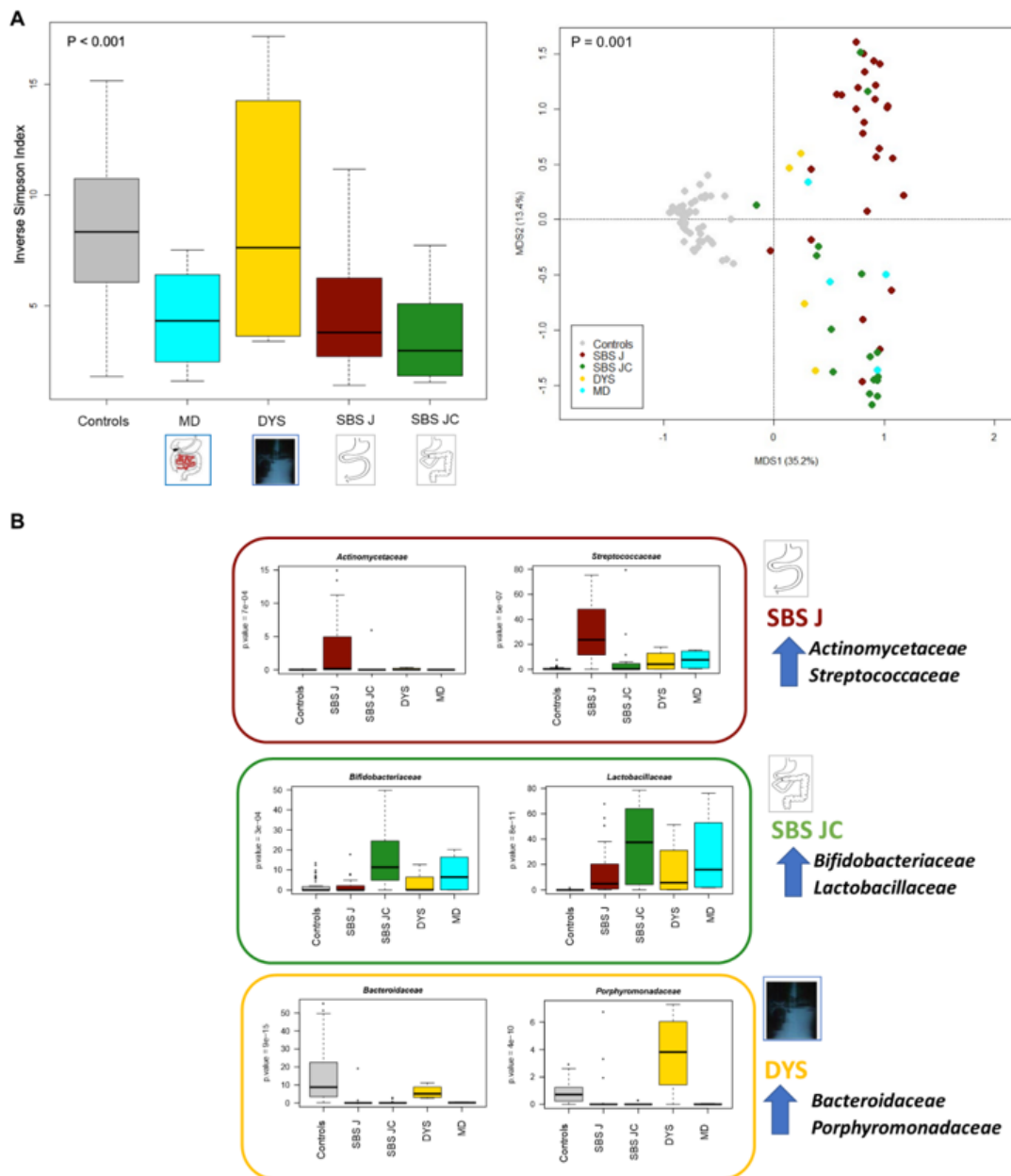
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Objective: Intestinal dysbiosis has been observed in patients with chronic intestinal failure (CIF) due to Short Bowel Syndrome (SBS). Despite the enormous importance of the gut microbiome in several aspects of the host's life including digestive efficiency, vitamin production, xenobiotic metabolism and immune system homeostasis, few data are available on the gut microbiome of CIF patients. The aim of the study was to profile the gut microbiome in the different and unexplored categories of mechanism of CIF.

Methods: Cross-sectional study on adult patients with benign CIF attending scheduled outpatient visits between March 2020 and July 2021. Fecal samples were collected and sequencing of V3-V4 hypervariable regions of the 16S rRNA gene was performed. Microbiome sequences from healthy subjects, matched by sex and age and selected from pre-existing cohorts, were used as the control group. Non-parametric statistical tests were carried out.

Results: Fifty-one patients were enrolled (female, 61%) with different pathophysiological mechanisms of CIF: SBS with end-jejunostomy (SBS J) 53%, SBS with jejunocolic anastomosis (SBS JC) 31%, dysmotility (DYS) 8%, extensive mucosal disease (MD) 8%. According to our results, alpha-diversity (i.e., intra-individual diversity) was reduced in all patients ($p < 0.001$; Kruskal-Wallis test) and inter-individual diversity (i.e., beta-diversity) of CIF patients was significantly different from healthy controls ($p = 0.001$; Adonis) (Figure 1A). From the taxonomic standpoint, increased proportions of Actinomycetaceae ($p = 7 \times 10^{-4}$) and Streptococcaceae ($p = 5 \times 10^{-7}$) characterized SBS J patients, Bifidobacteriaceae ($p = 3 \times 10^{-4}$) and Lactobacillaceae ($p = 8 \times 10^{-11}$) distinguished SBS JC and Bacteroidaceae ($p = 9 \times 10^{-15}$) and Porphyromonadaceae were enriched in DYS ($p = 7 \times 10^{-9}$); no specific gut microbial signatures were highlighted for MD subjects (Figure 1B).

Conclusions: CIF patients showed marked intestinal dysbiosis with microbial family-level signatures specific to the pathophysiological mechanism of CIF. The gut microbiome could be a biomarker and therapeutic target to optimize outcomes and improve the quality of life of patients with CIF.



Gut microbiome signatures of CIF patients.

(A) Left, boxplots showing the distribution of alpha-diversity, estimated with the inverse Simpson index in extensive mucosal disease (MD), dysmotility (DYS), SBS with end-jejunosomy (SBS J), and SBS with jejunocolic anastomosis (SBS JC) patients compared to healthy controls ($p < 0.001$, Kruskal-Wallis test). Right, PCoA based on Bray-Curtis distances between the gut microbiome profiles of CIF patients and controls. Ellipses include 95% confidence area based on the standard error of the weighted average of sample coordinates. Significant separation among groups was found ($p = 0.001$, Adonis).

(B) Boxplots showing the relative abundance distribution of families significantly differentially represented in SBS J, SBS JC and DYS patients compared to healthy controls. No significant signatures were found for the MD group ($p < 0.001$, Kruskal-Wallis test).

GWAS meta-analysis of Rome IBS subtypes in 24,735 patients

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Objective: IBS shows genetic predisposition, and large-scale genome-wide association studies (GWAS) are finally emerging. The genetic architecture of IBS subtypes is under investigation.

Methods: Based on Rome III Criteria from questionnaire data, we identified a total of 24,735 IBS cases (13,132 IBS-M, 6,481 IBS-D and 4,330 IBS-C) and 77,149 asymptomatic controls from two European population-based cohorts (UK Biobank and LifeLines). Individual GWAS were conducted in the two cohorts with SAIGE, adjusting for age, sex, and principal components, followed by meta-analysis using METAL. SNP heritability (h^2) and genetic correlations (r_g) were calculated based on linkage-disequilibrium score regression. Best candidate genes at risk loci were prioritized via computational annotation integrating data from FINEMAP, positional and expression quantitative trait loci from FUMA, Open Targets Genetics, and literature mining.

Results: Significant h^2 was observed for all IBS types ($p < 0.0001$; ranging from 10.4% for IBS to 13.2% for IBS-M). IBS traits showed considerable genetic overlap (with strongest correlation between IBS and IBS-M; $r_g = 0.96$). This included traits at the opposite ends of the stool consistency spectrum ($r_g = 0.47$ for IBS-D vs IBS-C). We detected four association signals ($P < 5 \times 10^{-8}$) in GWAS meta-analyses of IBS (tagged by SNPs rs6899057, rs2035380 and rs9517497) and IBS-M (rs6899057 and rs2048419), with one signal in common between IBS and IBS-M (rs6899057). Functional annotation of GWAS findings narrowed down novel candidate genes with possible roles in the pathophysiology of IBS. Among these are: ADCY2 (from the common locus rs6899057), highly expressed in the brain and skeletal muscle and involved in relevant signalling pathways including chemical synaptic transmission and muscle contraction; and ARNTL (rs2035380), contributing to the control of the circadian clock, expressed on myocytes and epithelial cells, and previously associated to neuroticism and bipolar disorder, peripheral artery disease, and sex hormone levels.

Conclusions: IBS and its subtypes defined according to gold-standard Rome Criteria are (partly) heritable traits, which show similar genetic architecture. Associations detected via population-based large-scale GWAS meta-analyses led to the identification of pathways, genes and variants that warrant further explorative analyses in patients and in in vitro experimental systems.

Regulatory role of peripheral sympathetic innervation on mouse gastrointestinal function and small intestine neuromuscular responses

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Objective: Irritable bowel syndrome (IBS) is a still poorly understood functional disorder and anomalies in gut immune/inflammatory responses and gut-brain communications have been proposed as potential determinant factors. In IBS patients changes in the sympathetic modulation of gut-brain axis of myoelectrical may contribute to the development dysfunctions and altered gastrointestinal transit. Thus, we aimed to assess the impact of pharmacological sympathetic denervation with 6-hydroxydopamine (6-OHDA) on the functional and structural integrity of mouse enteric nervous system (ENS).

Methods: Wild-type (WT) male C57BL/6J mice (8±2 weeks old) were subjected to peripheral sympathectomy by intraperitoneal administration of 6-OHDA (80 mg/kg/day) on three consecutive days. To maintain sympathectomy, mice were injected with 6-OHDA (80 mg/kg) every 10 days thereafter until day 20. Changes in ileal muscle tension were isometrically recorded following: cumulative addition of carbachol (CCh; 0.001–100 µM); electrical field stimulation (EFS, 0–40 Hz); EFS 10 Hz in non-adrenergic, non-cholinergic (NANC) conditions (1 µM atropine, 1 µM guanethidine), with or without 0.1 µM 1400W (inhibitor of inducible nitric oxide synthase, iNOS), or 100 µM L-NAME (pan-NOS inhibitor). The architectural integrity of the myenteric plexus was analyzed by immunofluorescence distribution of the pan-neuronal marker HuC/D, the glial markers S100β, GFAP, and PLP-1. Gastrointestinal transit was measured by assessing the distribution of the nonabsorbable-FITC-labeled dextran.

Results: Peripheral sympathectomy determined a marked decrease of carbachol-mediated contraction ($E_{max} = -55\%$; $P < 0.01$) and EFS-induced excitatory responses ($E_{max} = -45\%$, $P < 0.01$) together with significant increase of NANC-mediated relaxation ($+180\%$, $P < 0.001$) mainly mediated by nNOS-derived NO. In the myenteric plexus of 6-OHDA mice, a higher immunoreactivity of S100β, GFAP and PLP-1 was detected ($+16\%$, $+26\%$ and $+50\%$, respectively; $P < 0.01$) associated to a reduction of HuC/D+ neurons (-15% , $P < 0.001$), suggesting the development of enteric neuronal sufferance. Gastrointestinal transit time increased following sympathetic denervation.

Conclusions: Our study suggests that peripheral sympathetic innervation elicits marked glia activation and impaired cholinergic-mediated neuromuscular response, conceivably due to higher NO-mediated relaxation. These neuroglial plastic changes with dysmotility are highly suggestive of the important regulatory role of catecholamines in ensuring the integrity of gut neuroimmune crosstalk.

Anxiety, depression and quality of life in functional and organic GI patients: results from the Bologna COMparison - RETrospective - (CORE) preliminary study

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Aim: Mental health is a neglected domain for patients suffering because gastrointestinal (GI) disorders. Psychiatric interventions ameliorate clinical outcomes as well as treatment satisfaction and quality of life among patients with GI disorders. A huge debate is still running within the scientific community to identify GI patients who are at higher need of psychiatric care. In order to develop a clinical and research intervention, we aimed to retrospectively compare anxiety/depression severity and quality of life between patients with IBD and IBS disorders collected at the S. Orsola Hospital, Bologna.

Methods: GI diagnoses have been formulated by expert gastroenterologists. HADS and SF-36 were administered to evaluate depression/anxiety and quality of life. 12 IBD patients consecutively evaluated were compared with 24 age and sex matched - IBS patients from the same hospital.

Results: IBD patients scored lower on both physical (37.5 ± 13.5 vs 51.2 ± 8.7 , $p=0.006$) and mental (34.9 ± 7.2 vs 46.4 ± 10.8 , $p=0.001$) SF-36 sub-scores and achieved higher score on HADS depression severity (9.7 ± 3.8 vs 5.9 vs 3.4 $p=0.008$). No significantly statistical difference has been found for HADS anxiety severity between IBD and IBS patients.

Conclusions: Psychiatric evaluation and care seem to be useful for both "organic" as well as for "functional" GI patients.

Bile acid malabsorption in IBS-D and FD: an overlooked diagnosis?

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Introduction: Bile acid malabsorption (BAM) may be due to gastrointestinal diseases, surgery, drugs, or it can be a primary idiopathic condition. About 30% of patients with irritable bowel syndrome with diarrhea (IBS-D) and functional diarrhea (FD) seem to suffer from BAM, but studies on prevalence are lacking in Italy. Our aims were to evaluate: the prevalence of BAM among IBS-D and FD patients in a tertiary gastroenterological center in Italy; the correlation between BAM severity, symptom severity and quality of life; the correlation between cholestyramine (CH) and BAM severity.

Methods: 89 patients were enrolled (35 IBS-D and 54 FD). Bristol Stool Chart (BSC), IBS-SSS, SF-36 and a questionnaire about bowel habits were administered before entering the study (T0). Subjects were evaluated for BAM by retention values of 75-selenium homocholic acid taurine (SeHCAT) (mild: $\leq 15\%$, moderate: $\leq 10\%$ and severe: $\leq 5\%$). Patients with BAM were given CH (2 gr/day), increasing the dosage by 2 gr/week until normal fecal consistency (Bristol 3-5) or the maximum tolerated dose. After 8 weeks (T1) they were re-assessed using the same questionnaires.

Results: Forty-two patients (47%) (16 IBS-D, 26 FD) showed BAM: 19 (45%) mild BAM, 6 (14%) moderate and 17 (40%) severe. The severe BAM group reported a higher frequency of bowel movements, lower bowel satisfaction ($p < 0.05$) and SF36 ($p < 0.01$). Twenty-eight patients accepted treatment with CH, but 6 discontinued before T1. At T1 mild BAM patients improved in BSC ($p < 0.01$), IBS-SSS, pain and health change ($p < 0.05$), whereas severe BAM subjects improved in BSC, IBS-SSS ($p < 0.01$), fecal incontinence, urgency, daily bowel movements and most domains of SF36 ($p < 0.05$). At T2 mild BAM results improved also in daily bowel movements, energy, emotional problems and well-being ($p < 0.01$), while severe BAM patients slightly worsened (compared to T1 but not to T0) in energy, emotional well-being, social functioning, pain and general health, while they improved in BSC, fecal incontinence and daily bowel movements ($p < 0.01$).

Conclusions: BAM is frequent in a tertiary gastroenterological center. SeHCAT evaluates BAM severity, which relates to symptom severity, QoL and response to CH. A positive diagnosis could lead to a more rational use of CH, which can induce adverse events and is poorly palatable.

Bowel habits variability in irritable bowel syndrome

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Objective: The aim of our study was to describe bowel habits and its variability in irritable bowel syndrome (IBS) using a stool diary and to compare this with healthy volunteers (HV).

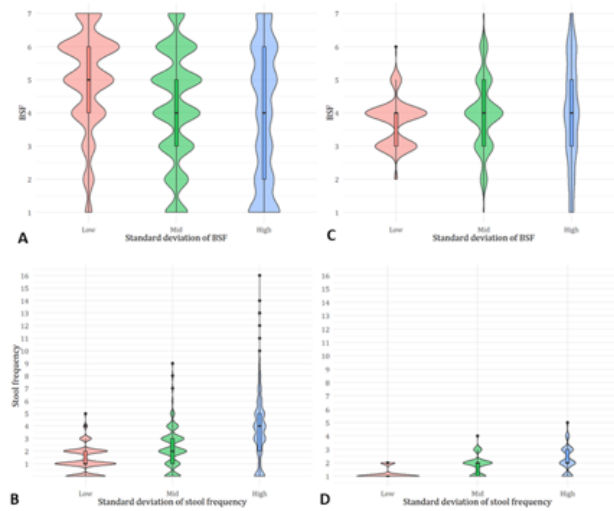
Methods: We included IBS patients and HV, who prospectively completed a one- or two-week stool diary based on the Bristol Stool Form scale (BSF). The average stool frequency and consistency and IBS subtype (Rome IV) were assessed. The results are presented with number and percentage for qualitative data and median [Q1;Q3] for quantitative data. For analysis of variability of the bowel habits, the patients and HV were grouped according to the standard deviation (SD) of the stool consistency and frequency (low (SD<25%), medium (SD=25-75%) and high (SD>75%) variability).

Results: We included 80 HV and 783 IBS patients (43.9% IBS-D, 35.8% IBS-C, 13.9% IBS-M, 6.4% IBS-U). IBS patients had higher stool frequency (1.6 [1.1;2.4] vs 1.3 [1.1;1.6] stools/day, $p<0.001$) but similar stool consistency (4.1 [3.2;5.1] vs 4.0 [3.6;4.3], $p=0.096$) compared to HV.

SD of the stool consistency and frequency were higher in patients compared to HV. In IBS patients, a low variability in stool consistency was associated with looser stools (higher BSF) when compared to the medium and high variability groups (figure A), while a high variability in stool frequency was associated with higher stool frequency (figure B). In HV, the stool consistency was similar in the variability groups, (figure C), while group differences in stool frequency were similar as in the IBS group, but less pronounced (figure D). In IBS patients, stool consistency was positively associated with stool frequency, without clear differences based on stool frequency variability, but the link was stronger in patients with low variability in stool consistency vs. medium or high variability.

Conclusions: There is a stronger, but inconsistent, impact of bowel habit variability on stool consistency and frequency in IBS compared to health. Bowel habit variability can be a relevant outcome parameter in studies of a disturbed bowel habit and should be considered in future subtyping and clinical characterization of IBS patients.

Figure: Stool consistency and frequency according to their distribution



The figure represented violin/blopplot displaying the distribution of stool consistency (BSF) according to “low” (<25%), “mid” (25-75%), and “high” (>75%) variability in IBS patients (A) and HV (C); and the distribution of stool frequency according to “low” (<25%), “mid” (25-75%), and “high” (>75%) variability in IBS patients (B) and HV (D). BSF: Bristol stool form

Poster no. 007

Celiac disease prevalence in irritable bowel syndrome patients in Isfahan, Iran (2019-20)

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Background and Objective: Irritable bowel syndrome (IBS) is the most prevalent gastrointestinal disorder and is one the common conditions seen by gastroenterologists in their daily practice. This study was done to determine the prevalence of celiac disease in patients with irritable bowel syndrome in Isfahan-Iran.

Materials and Methods: This descriptive study was conducted on 105 patients with IBS whom referred to the gastroenterology unit in Isfahan-Iran during 2019-20. Serum IgA anti tTG were measured all patients with positive for antibodies against tTG were candidate for upper endoscopy and biopsy. Data were analyzed using SPSS-16, t-test, Chi-Square and Fisher's exact tests.

Results: The average age of IBS subjects were 31.4 ± 10.14 years (range 16-63 years). Celiac disease was diagnosed in 14 subjects (13.5%). The celiac patient age were 22-55 years with mean of 34.93 ± 9.47 . Among celiac afflicted patients IBS type D and M observed among 10 and 4 patients, respectively. Celiac affected female constituted 12 (85.7%) of all patients ($P < 0.05$). 10 of these patients were IBS-D and 4 with IBS-M. From 14 celiac patient 4 (28.57%) were family related, but this rate among IBS patient was 3.3%, this difference was significant ($P < 0.05$).

Conclusions: This study showed that the prevalence of celiac in patients with IBS is found to be 13.5% which seem is more than there studies in other parts of Iran.

Keywords: Celiac disease, Irritable bowel syndrome, Isfahan.

Comparison of the habitual dietary intake in patients with irritable bowel syndrome and the general population

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Objectives: Food hypersensitivity is of importance in the pathophysiology of IBS. To improve gastrointestinal symptoms, patients with IBS tend to avoid triggering foods, which might be associated with a change in habitual dietary intakes. Therefore, we aimed to determine and compare the habitual dietary intake of IBS patients and controls.

Methods: We used baseline data of patients with IBS who were recruited for a dietary intervention study or a study investigating pathophysiological factors. For the age and gender-matched control sample, we used data from a Swedish population-based study that collected data during the same period, the Riksmaten study (2010-2015). The habitual dietary intake was assessed with consecutive 4-day food diaries, during Wednesday-Saturday in the patient cohort, and with an equal distribution of weekdays and weekend days in the matched control group. A dedicated software (DIETIST XP V.3.1) was used to calculate the mean daily energy and macronutrient intake. The food group categorization was based on a classification used by the Swedish National Food Administration.

Results: We included 197 patients with IBS and 197 controls (both cohorts: 77% female, age: 37±14 years, BMI: 24±4 kg/m²). In both patients and controls the intake of fat was higher than the recommendations, i.e. 25-35 %E (Table). The intake of other macronutrients adhered to the Swedish national nutrition recommendations. Total energy intake was higher in patients, including a higher intake of fat and protein, but less carbohydrates. Patients also had a higher cereal, egg, fish, meat, nuts and seeds intake, and a lower coffee, and mixed dishes intake compared with controls. Reported intake of alcohol, dairy, fruits, and vegetables did not differ between patients and controls.

Conclusions: The reported habitual dietary intake in patients with IBS included a higher energy intake with slight differences in macronutrient composition, i.e. a higher fat, and protein intake, and a lower carbohydrate intake, compared with a population-based control group. Habitual dietary intakes should be monitored in clinical practice to assure healthy eating habits.

Table. Habitual dietary intake in IBS vs. controls based on the Swedish Nutrition Guidelines and Recommendations*

	IBS (n=197)	Controls (n=197)	p-value
Demographics & GI-symptoms			
Gender (% female)	77	77	>0.99
Age (years)	37 ± 14	37 ± 14	0.98
BMI (kg/m ²)	24 ± 4	24 ± 4	0.14
IBS subtypes (% IBS-C/D/nonCnonD)	25/38/37	-	NA
IBS-SSS (score)	307 ± 80	-	NA
Macronutrients			
Energy (Kcal)	2127 ± 550	1858 ± 616	<0.001
Protein (%E)	17 ± 4	16 ± 4	0.007
Fat (%E)	38 ± 8	36 ± 7	0.003
Carbohydrates (%E)	40 ± 8	43 ± 7	0.002
Alcohol (%E)	3 ± 4	3 ± 5	0.87
Food groups (g/d)			
Alcohol	75 [233]	50 [175]	0.08
Bread	75 [64]	74 [74]	0.39
Cereal	89 [98]	71 [88]	0.03
Coffee	175 [350]	250 [488]	0.007
Dairy	238 [241]	218 [238]	0.35
Drinks	50 [175]	50 [175]	0.73
Eggs	14 [50]	4 [26]	0.002
Fast food	0 [67]	3 [88]	0.23
Fish	25 [57]	18 [44]	<0.001
Fruit	106 [145]	83 [141]	0.06
Juice	0 [100]	0 [75]	0.48
Legumes	0 [8]	0 [0]	0.07
Meat	101 [89]	71 [74]	<0.001
Mixed dishes	109 [137]	182 [162]	<0.001
Nuts and seeds	1 [16]	0 [5]	<0.001
Potatoes	10 [50]	11 [53]	0.75
Salty snacks	0 [11]	0 [3]	0.08
Sweet dishes and desserts	59 [69]	57 [78]	0.91
Tea	50 [200]	25 [175]	0.13
Vegetables	104 [106]	91 [113]	0.16

*NOTE: GI; Gastrointestinal, IBS; Irritable Bowel Syndrome, BMI; Body Mass Index, IBS-C; IBS with predominant constipation, IBS-D; IBS with predominant diarrhea, IBS-nonCnonD; IBS-non-constipation, non-diarrhea, Data are presented as mean ± standard deviation or median [interquartile rage]. P-values<0.05 were considered as statistically significant.

Functional dyspepsia and irritable bowel syndrome in fibromyalgia patients: a prospective study

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Objective: It is well known that Fibromyalgia (FM), an extraintestinal chronic pain disorder characterized by widespread pain, is frequently associated with Irritable Bowel Syndrome (IBS) with higher severity of illness. Only one study described the association between FM and Functional Dyspepsia (FD). However, there are no data about the relationship between FM and Disorders of Gut-Brain Interaction (DGBI), using Rome IV criteria. This study aimed to evaluate the prevalence of FM in patients with IBS and/or (FD) and the prevalence of IBS and FD in FM patients using Rome IV criteria.

Methods: FD and IBS patients diagnosed accordingly Rome IV criteria and FM patients were recruited from two outpatient clinics devoted to DGBI and FM, respectively. All patients underwent a standardized gastrointestinal symptoms questionnaire. FM symptoms in DGBI patients were assessed through Fibromyalgia Rapid Screening Tool (FiRST) and Fibromyalgia Impact Questionnaire. Thereafter, the rheumatologists evaluated them.

Results: 49.0% (24/49) of FM patients fulfilled the diagnostic criteria for IBS, 81.6% (40/49) for FD with an overlap for both IBS/FD in 44.9% (22/49). IBS-C was the most prevalent IBS-subtype in DGBI patients, whereas IBS-M was the most prevalent in FM patients ($p=0.01$).

45.3% (24/53) of DGBI patients reported pathological FiRST scores. Among these patients 30.2% (16/53) had IBS, 37.7% (20/53) had FD and 22.6% (12/53) had an overlap for both IBS/FD. A significant difference in the frequency-intensity scores of upper abdominal symptoms such as epigastric fullness, pain and burning, upper abdominal bloating and distension was found among all groups with graduated scores. DGBI patients with FM showed the highest score followed by FM patients with DGBI and DGBI without FM. A significant difference was found among the lower abdominal symptoms only in abdominal pain and DGBI without FM had the highest score. Moreover, the frequency-intensity scores of the GI symptoms did not significantly differ between primary and secondary FM patients ($p > 0.05$).

Conclusions: DGBI are common in FM patients and vice-versa. For the first time we demonstrated that the presence of FD is extremely frequent in FM patients. A multidisciplinary approach should be routinely used for the management of these patients.

Gut-brain interaction disorders (DGBIs), disgust and body image in anorexia nervosa: a pilot study

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Objective: Gastrointestinal complaints are common in Anorexia Nervosa (AN) and are often related with Body Image Disturbance (BID). Disgust is a primary emotion and some of its characteristics and complex derivatives (for example, shame) may play a role in Eating Disorders (EDs), for example inducing vomiting even in the absence of stimuli. This pilot study aimed to (a) investigate the prevalence of DGBIs in AN patients, (b) explore AN psychological aspects that might impact on DGBI.

Methods: Thirty female patients (mean age=19.3±5.9; mean BMI=17.5±2.4) with newly-diagnosed AN were consecutively recruited in a devoted outpatient clinic. The presence of DGBIs were assessed according to Rome IV criteria and gastrointestinal symptoms were evaluated by a standardized questionnaire. Several psychological aspects were verified through clinical screening tests: Eating Disorder Inventory – 3(EDI-3), Hospital Anxiety and Depression Scale(HADS), Social Physique Anxiety Scale(SPAS) as well as Body Uneasiness Test(BUT), which measures body image concern (cut-off value>1.2) and Disgust Scale (cut-off value>26).

Results: Eighty-three% AN patients fulfilled criteria for Postprandial Distress Syndrome (PDS), 57% for Functional Heartburn (FH), 47% for Irritable Bowel Syndrome predominant Constipation (IBS-C) and 43% as Epigastric Pain Syndrome (EPS). We observed a mean score on disgust scale $m=67.9$ ($SD=12.9$) for IBS-C, $m=66.6$ ($SD=13.5$) for PDS, $m=65.7$ ($SD=12.0$) for EPS and $m=63.7$ ($SD=10.9$) for FH. Mean Global Severity Index (GSI) of BUT was $m=3.2$ ($SD=0.8$) for PDS, $m=3.1$ ($SD=0.9$) for IBS-C, $m=2.9$ ($SD=0.7$) for FH and, $m=2.9$ ($SD=0.8$) for EPS.

A significant correlation ($p<0.05$) was found between disgust and postprandial nausea ($r=.399$) and between early satiety and BUT subscales Weight Phobia ($r=.439$), Compulsive Self-Monitoring ($r=.434$) and BIC ($r=.439$). Moreover, as expected, Body Image Concern (BIC) significantly correlated both with EDs risk scale ($r=.716$) and Global Psychological Maladjustment ($r=.798$).

Conclusions: AN is a multifactorial disorder. Consequently, the presence of numerous contributing factors and variables can affect the outcomes of treatment and even the specific diagnosis. It is necessary to implement studies with an integrated approach taking into account DGBIs, as well as to monitor the emotional-cognitive structure that acts as a factor in maintaining the disorder.

Hypercontractile esophagus: role of upper esophageal sphincter on pathogenesis and clinical manifestations. A high resolution manometry study

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Objective: UES manometric parameters study and their impact on pathogenesis and clinical presentation of patients affected by "hyper-contractile" esophagus (formerly Jackhamer) according to the criteria of Chicago Classification v4.0.

Methods: Manometric tracings, epidemiological and clinical data of patients with a diagnosis of "hyper-contractile" esophagus in our departments between 07 / 2019-07 / 2021 were analyzed. Manometric parameters of UES function (mean contraction pressure, mean resting pressure, resting time, recovery time) as well as other manometric parameters were analyzed and correlated through multifactor statistic analysis (MFA) with clinical and epidemiological data.

Results: Data from 26 patients (12 M, mean age 65 years) were analyzed. 46.1% presented dysphagia, 34.6% GERD related symptoms and 19.3% cough as main clinical presentation at the time of HRM examination. Mean contractile pressure of the lower esophageal sphincter (LES) was 36.8 mmHg (R16-86.9), mean integrated relaxation pressure (IRP) was 13.33 mmHg (R 9-33.1), mean Distal Contractile Integral (DCI) 10.031 (mmHg -cm-s) (R 5783-30867), mean Distal Latency 6.4 (R 4-10.2), mean UES contractile pressure 83.5 mmHg (R32.3-301), mean UES resting pressure 8.17 mmHg (R 0.3 -42.2), mean UES resting time 793.6 ms (R348-1047), mean recovery time 560.4 (R 441-715). 9 patients (34.6%) had abnormal UES manometric parameters. Multifactorial statistic analysis revealed a statistically significant correlation of the pathological UES resting time with abnormal LES resting pressure ($p = 0.038$) as well as a marginal statistical correlation of the abnormal UES resting pressure with their main clinical symptom $p = 0.049$.

Conclusions: UES motility has not been extensively studied on HRM in patients with disorders of esophageal peristalsis. It seems that in hyper-contractile esophagus a significant number of patients presented abnormal UES function. UES motility abnormalities is combined with abnormal LES function in patients with hypercontractile esophagus and particularly characterize patients with predominant dysphagia.

Individual temporal relationships between somatic and psychological complaints in patients with IBS – A time series approach

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Objective: Irritable bowel syndrome is a disease of the (microbiota)-gut-brain axis, often associated to psychological distress. The aim of the study was to investigate precisely the temporal relationships between somatic and psychological variables in patients with IBS.

Methods: In this longitudinal study, using daily diary data over 3 months, eight patients filled in questionnaires regarding somatic and psychological variables, e.g. abdominal pain or nervousness. The time series were analyzed using vector-autoregressive (VAR) models.

Results: Positive same-day correlations between somatic and psychological time series were observed during a day for all patients. Identifying temporal relationships, the picture was mixed. 26 significant lagged relationships were identified. 17 (65%) relationships indicated that somatic values were predictive of psychological complaints on the following days, 9 (35%) indicated the other way round. In all patients the patterns were different. In five patients somatic complaints predicted psychological complaints more often, in one patient the opposite was true. Furthermore, all patients showed mixed pictures regarding somatic and psychological temporal relationships.

Conclusions: Temporal relationships between somatic and psychological complaints in patients with IBS are complex and should be studied on an individual level. Identifying temporal relationships can help to form explanatory models and treatment concepts in the future.

Post-infection irritable bowel syndrome in SARS-CoV-2 patients: the GI-COVID19 Study

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Objectives: The long-term consequences of COVID-19 infection on the gastrointestinal tract remain unclear. We aimed to evaluate the prevalence of gastrointestinal symptoms and post-infection disorders of gut-brain interaction (DGBI) up to 12 months after hospitalization, and factors associated with their presence.

Methods: The GI-COVID19 is a prospective, multicenter, controlled study. Patients with and without COVID-19 diagnosis were assessed at hospital admission and followed-up after 1, 6 and 12 months to assess gastrointestinal symptoms using the Gastrointestinal Symptoms Rating Scale, the Rome IV Diagnostic Questionnaire for Functional Gastrointestinal Disorders in Adults and the hospital anxiety and depression scale. ClinicalTrials.gov number, NCT04691895.

Results: The study included 2183 hospitalized patients. A total of 883 patients (614 COVID-19 and 269 controls) were included for the primary analysis. At enrollment, gastrointestinal symptoms occurred more frequently in COVID-19 patients than in the control group (59.3% vs. 39.7%, $P<0.001$). Symptoms more frequently complained by COVID-19 patients at enrollment were nausea, diarrhea, loose stool and urgency. Constipation and hard stools were significantly less prevalent in COVID-19 patients than in the control group at 12 months follow-up (9.6% vs. 16%, $P=0.019$ and 10.9% vs. 17.7%, $P=0.011$, respectively). COVID-19 patients reported higher rates of DGBI during follow-up compared to controls (Figure 1), namely irritable bowel syndrome (IBS) according to Rome III criteria (4.4% vs 1.1%, $P=0.036$) and Rome IV criteria (3.2% vs 0.5%, $P=0.045$). The rate of COVID-19 patients depressed at 6 months and with anxiety at 12 months was higher compared to controls. Factors significantly associated with IBS diagnosis were anamnestic allergies, chronic intake of proton pump inhibitors and the presence dyspnea.

Conclusions: Hospitalized COVID-19 patients complain less constipation and hard stools than control at 12 months after acute infection. COVID-19 patients are also more likely to develop IBS.

Figure 1. DGBI, anxiety and depression occurrence at 6 and 12 months follow-up in patients of the GI-COVID19 study selected for primary aim analysis.

	6 Months follow-up			12 Months follow-up		
	Controls n (%) n=224	COVID-19 n (%) n=548	P	Controls n (%) n=188	COVID-19 n (%) n=435	P
DGBI						
Epigastric pain syndrome	0	3 (0.6)	0.267	2 (1.1)	8 (1.8)	0.480
Post-prandial distress syndrome	3 (1.3)	9 (1.6)	0.757	3 (1.6)	17 (3.9)	0.134
Functional dyspepsia	3 (1.3)	11 (2)	0.528	4 (2.1)	16 (3.7)	0.314
Chronic nausea and vomiting Syndrome	3 (1.3)	6 (1.1)	0.774	3 (1.6)	2 (0.5)	0.145
Cyclic vomiting syndrome	1 (0.5)	0	0.118	-	-	-
Functional diarrhea	0	1 (0.2)	0.522	0	1 (0.2)	0.511
Irritable bowel syndrome (Rome IV)	2 (0.9)	3 (0.6)	0.587	1 (0.3)	14 (3.2)	0.045
Irritable bowel syndrome (Rome III)	3 (1.3)	9 (1.6)	0.757	2 (1.1)	19 (4.4)	0.036
HADS						
Depression			0.014			0.1
Normal	209 (93.3)	471 (86)		176 (93.6)	384 (88.3)	
Borderline abnormal	9 (4)	54 (9.9)		7 (3.7)	36 (8.3)	
Abnormal	6 (2.7)	23 (4.1)		5 (2.7)	15 (3.4)	
Anxiety			0.914			0.088
Normal	196 (90.7)	445 (89.7)		174 (92.5)	390 (89.7)	
Borderline abnormal	12 (5.6)	31 (6.3)		12 (6.4)	25 (5.8)	
Abnormal	8 (3.7)	20 (4)		2 (1.1)	20 (4.5)	

Abbreviations: COVID-19: coronavirus 19 associated disease; n: number; DGBI: Disorders of Gut-Brain Interaction; HADS: Hospital Anxiety and Depression Scale.

Prevalence of disorders of gut-brain interaction in obese patients followed up two years after treatment

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Objectives: Obesity has a negative impact on many health outcomes. We aimed to identify the burden of gastrointestinal symptoms compatible with one or more of the specified disorders of gut-brain interaction (DGBI) among patients with obesity, and to study the effect of obesity treatment on these.

Methods: We used baseline and two-year follow-up data from a prospective non-randomized cohort study including 1121 patients with BMI ≥ 35 kg/m² referred for treatment of obesity in Region Västra Götaland, Sweden, between May 2015 and November 2017, the BAriatic surgery SUBstitution and Nutrition (BASUN) study. Patients completed the Rome III diagnostic questionnaire before being treated with Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy (SG), or medical treatment (MT) including a period with very low energy diet according to clinical guidelines and the patient's preference. Additional measures used to characterize the cohort included validated questionnaires assessing anxiety (BAI), depression (PHQ-9), and quality of life (QoL) (EQ-5D). Data are presented as mean $\pm$ SD, median [inter quartile range] or percentage (95%CI).

Results: In total, 911 patients (75% female, 44 $\pm$ 13 years, 42 $\pm$ 5 kg/m², 40% RYGB, 21% SG 39%, MT) completed the Rome III questionnaire at baseline and 660 patients (32 $\pm$ 6 kg/m²) at follow-up. The proportion of obese patients fulfilling diagnostic criteria for one or more DGBI at baseline and at follow-up was 61.8% (58.7%, 64.8%) and 55.3% (51.5%, 59.1%), respectively. Details about the prevalence of the different DGBI diagnoses at baseline and follow-up are given in the Table. When patients with vs. without a DGBI were compared in regards to, BMI (42.1 $\pm$ 5.1 kg/m² vs. 42.0 $\pm$ 4.5 kg/m², p=0.77), anxiety (BAI: 10.0 [13.0] vs. 5.0 [8.0], p<0.001), depression (PHQ-9: 7.0 [9.0] vs. 4.0 [6.0], p<0.001), and QoL (EQ5D-VAS: 51.8 $\pm$ 20.2 vs. 56.5 $\pm$ 19.1, p=0.002) at baseline, significant differences were found between the groups.

Conclusions: The majority of patients suffering from obesity fulfil criteria for one or more DGBI, which is associated with psychological distress and reduced QoL. After treatment to reduce weight, the proportion of patients having a DGBI has mostly decreased, but for some DGBI, such as functional dysphagia, rumination, and functional constipation, the proportion has increased.

Table. Proportion of patients fulfilling Rome III criteria for disorders of gut-brain interaction*

<i>Diagnosis</i>	Baseline	2-year follow-up	Change
<i>Esophageal disorders</i>	23.4 (20.8, 26.2)	15.3 (12.7, 18.3)	↓
Functional chest pain	5.4 (4.1, 7.0)	4.3 (2.8, 6.1)	↓
Functional heartburn	13.8 (11.7, 16.1)	6.9 (5.0, 9.1)	↓
Globus	2.5 (1.6, 3.7)	0.6 (0.2, 0.7)	↓
Functional dysphagia	4.3 (3.1, 5.7)	5.2 (3.6, 7.2)	↔
<i>Gastroduodenal disorders</i>	26.2 (23.5, 29.1)	25.3 (22.0, 28.8)	↓
Functional dyspepsia	9.2 (7.4, 11.2)	8.8 (6.7, 11.2)	↓
Belching disorder	7.7 (6.1, 9.5)	7.7 (5.8, 10.1)	-
Nausea and vomiting disorders	16.2 (13.9, 18.6)	15.2 (12.6, 18.2)	↓
Rumination syndrome	0.6 (0.2, 1.3)	0.8 (0.2, 1.8)	↔
<i>Bowel disorders</i>	37.4 (34.4, 40.5)	33.6 (30.1, 37.3)	↓
Irritable bowel syndrome	20.9 (18.4, 23.5)	14.6 (12.0, 17.5)	↓
IBS-C	2.8 (1.9, 4.0)	4.0 (2.6, 5.8)	↔
IBS-D	5.7 (4.3, 7.4)	3.4 (2.1, 5.1)	↓
IBS-M	10.9 (9.0, 13.0)	6.2 (4.4, 8.3)	↓
IBS-U	1.3 (0.7, 2.3)	1.4 (0.6, 2.6)	↔
Functional constipation	10.3 (8.4, 12.3)	16.4 (13.7, 19.4)	↔
Functional diarrhea	4.1 (2.9, 5.5)	0.0 (0.0, 0.5)	↓
Functional abdominal bloating/distention	5.4 (3.7, 7.6)	3.3 (2.0, 5.2)	↓
<i>Anorectal disorders</i>	9.3 (7.6, 11.3)	8.2 (6.2, 10.5)	↓
Fecal incontinence	8.9 (7.2, 10.9)	6.9 (5.0, 9.1)	↓
Functional anorectal pain	0.6 (0.2, 1.0)	1.7 (0.8, 3.0)	↔

*NOTE: IBS; irritable bowel syndrome, IBS-C; irritable bowel syndrome with predominant constipation, IBS-D; irritable bowel syndrome with predominant diarrhea, IBS-M; irritable bowel syndrome with mixed bowel habits, IBS-U; irritable bowel syndrome unsubtyped. Data are presented as percentages (95%CI).

Poster no. 015

Real-world evidence data from a pharmacy-based patient survey - comparing conventional spasmolytics with a phytotherapeutic drug in the treatment of crampy abdominal pain a leading symptom in irritable bowel syndrome (IBS)

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Introduction: Spasmolytic drugs and phytotherapeutics are commonly used to treat abdominal cramps, which are a leading symptom in IBS. However, there are little data on how patients perceive the effectiveness and tolerability of those interventions on their abdominal symptoms in a real-world setting.

Objective: A pharmacy-based patient survey was performed to compare Peppermint oil 182mg (PO) and hyoscine-N-butylbromide 10mg (HBB) in patients' perception.

Patients & Methods: Patients purchasing either PO or HBB were offered to participate in a survey to evaluate among others the perceived onset of action, effectiveness, and tolerability. Severity of complaints was assessed on a 10-point numeric rating scale, 0 representing no pain/discomfort and 10 representing very severe pain/discomfort.

Results: 1045 patients aged between 18 to 92 years (average 42 years) participated in the survey of whom 75% were females and 25% males. Notably, HBB (86%) was most frequently used for treatment of "abdominal cramps and pain in the gastrointestinal tract", PO (63%) most frequently due to "bloated/distended abdomen".

Almost 92% of PO users stated onset of action within 4 hours, while 94% of HBB users reported onset of action within 1 hour. On average, the severity of complaints improved by -3.5 for PO, 4 hours after the first dose, and by -4.0 (HBB) 1 hour after the first dose.

The effectiveness of HBB was rated as either very satisfactory or satisfactory by 97% of the users, this percentage was slightly lower for PO (86%), but generally leading to a high recommendation rate of the respective preparation to others (HBB: 97%, PO: 87%).

Conclusions: Comparison of the spasmolytic HBB with the phytotherapeutic PO in the treatment of patients with different abdominal discomforts, revealed that users felt HBB to act faster and more efficient in comparison to PO in a real-world setting. This indicates that HBB could be useful in acute treatment of crampy abdominal pain, while PO might be more suitable in the treatment of persisting symptoms.

The study was sponsored by Sanofi

Significance of upper esophageal sphincter (UES) abnormalities in patients with extra-esophageal GERD underwent pH-impedance and high resolution manometry (HRM)

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Objective: To investigate UES function in patients underwent esophageal testing with pH-impedance and HRM for suspected GERD

Methods: GERD is a complex condition with a typical (heartburn, regurgitation or epigastric pain) and an atypical presentation with symptoms such as chronic cough, hoarseness, globus, dysphagia or throat clearing caused by the retrograde movement of gastric contents above the UES into the laryngopharynx. The association between GERD and UES abnormalities is not clearly known. HRM has allowed accurate measurement and evaluation of UES and esophageal function. We evaluate UES function of the HRM exams in patients underwent pH-impedance for suspected GERD with typical or atypical symptoms.

Results: HRM tracings of 60 patients (35F, median age 53,08 R23-74), 35 with typical (20F, m.a 51,42 R24-74) and 25 with atypical (15F, m.a 51,73 R29-74) symptoms who underwent Ph-impedance for suspected typical and atypical GERD were evaluated. 40% of those with typical presentation had a positive pH-impedance for GERD versus 8% of those with atypical symptoms. Patients with typical symptoms presented in 42,85% UES abnormalities versus 60% of the patients with atypical presentation. From those patients with typical GERD symptoms that had a positive pH-impedance the 40% had a concomitant UES abnormality versus 100% of the patients with atypical presentation and a confirmed GERD diagnosis. Statistical analysis revealed a significant association between positive pH-impedance result and LES residual pressure in patients with typical ($p=0,045$) and atypical ($p=0,038$) symptoms.

Conclusions: UES abnormalities is the prevalent diagnostic finding in patients with atypical GERD underwent pH-impedance. UES dysfunction characterize all patients diagnosticated with atypical GERD by Ph-impedance.

The brain gut axis and the gender: evidence for a serotonergic treatment option in women

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The term brain-gut axis describes an anatomic and functional substrate in which the brain and psychosocial factors influence the GI tract and vice versa. The clinical phenotype that we understand as functional gastrointestinal disorders (FGIDs) emerges from the interactions of multiple systems in the periphery and in the brain interacting with each other in bidirectional ways that lead to the FGID phenotype. Pain and other symptoms seen in FGIDs may generate in women more than in men a feeling of anger, shame, or silence. These symptoms are often considered typical traits of FGIDs. A large body of evidence suggests a sex-related activity of several pathophysiological factors involved in irritable bowel syndrome (IBS) symptom generation. Interestingly, female patients with IBS showed an enhanced mast cell activity compared to male IBS patients. Recent findings indicate an increased permeability of female patients with IBS. According to some studies women with FGID appear to respond well to psychological treatment and the newer serotonergic agents, such as 5-HT₃ antagonists and 5-HT₄ agonists. However, more recent reviews suggest the differences in the response to treatment could be biased by the prevalence of female patients in the pharmacologic and behavioral trials.

Prevalence of irritable bowel syndrome in health workers exposed to occupational stress

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Objective: Occupational stress is a precipitant factor for different diseases, although its role in Irritable Bowel Syndrome (IBS) needs to be clarified. The aim of this study was to investigate the prevalence of IBS diagnosis among health workers and explore its possible relationship with work-related stress levels and work ability.

Methods: 653 health workers (238 m; 18-65 yrs), undergoing periodical health surveillance at the Occupational Health Department of a University Hospital in central Italy, were consecutively recruited and screened for an IBS diagnosis, according to the Rome IV criteria. The IBS-SSS, DCSQ and WAI were used to assess IBS severity, occupational stress and work ability levels. Information on sleep quality, anxiety and depression were collected from electronic health records regarding the previous year.

Results: IBS prevalence was 16.8% and it was higher in women (86 f, 24 m; $p<0.01$). No differences were found according to participants' jobs (313 nurses, 191 doctors, 83 health operators, 59 health technicians, 7 psychologists).

IBS patients (IBS+) had a lower BMI than non-IBS subjects (IBS-) (22.5 vs 23.7; $p=0.02$). IBS+ had an increased prevalence of anxiety or depression compared to IBS- (9.9% vs 4.4%; $p<0.04$). IBS+ with anxiety or depression showed higher IBS-SSS scores compared to those without (median IBS-SSS scores: 265 vs 175 respectively; $p<0.03$). The prevalence of sleep disturbances among the IBS+ group was higher than among the IBS- (15.3% vs 4.6%; $p<0.001$). IBS+ workers showed lower work ability levels, lower social support and control at work and higher levels of job demands when compared to IBS-. The IBS-SSS score correlated negatively with work ability ($p<0.001$) and positively with levels of job demands ($p<0.001$).

Conclusions: This is the first time that IBS prevalence and its correlation with work ability have been evaluated among Italian health workers exposed to occupational stress. Health workers showed a higher prevalence of IBS when compared to the Italian population. Furthermore, IBS symptom severity was positively correlated with occupational stress and negatively with work ability. These conclusions encourage the pressing need for preventive strategies in the workplace aimed at protecting the health, well-being, and productivity of health workers.

Case-based evaluation shows highly varied approach to IBS-D treatment by European experts

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Objective: To highlight differences in the management of IBS-D based on individual patient profiles as exemplified by differing predominant complaints.

Methods: 24 European experts, part of the UEG working group for the European guidelines on IBS management completed a case-based online survey. 10 IBS-D case vignettes were presented and experts indicated their management approach for each case. Each vignette consisted of three consecutive lines of diagnosis and treatment. Here four cases of differing predominant complaint are illustrated (pain predominance, urgency and anxiety, bloating predominance and a “simple case” without specific characteristics).

Results: At least 88% conducted initial diagnostic workup. In second and third line 29%-58% and 17%-54% did not conduct diagnostic workup respectively. Initially, most experts chose celiac serology, c-reactive protein and complete blood count (79%-96%) as well as stool calprotectin (70-92%) irrespective of predominant symptom.

Treatment choices are summarized in the figure.

Simple case: In first line, dietary intervention (38%) or antispasmodics (29%) were preferred. Experts chose antibiotics most often in second line (25%) followed by antispasmodics or dietary intervention (17% each). In third line ondansetron was most often chosen (25%), favored over antibiotics and neuromodulators (mainly tricyclic) (17% each).

Urgency and anxiety: Initially, 38% chose antispasmodics and 21% antidiarrheals. Second line were neuromodulators (25%) and antibiotics (17%). Neuromodulators were dominant in third line (42%), ondansetron and dietary intervention were chosen by 13% each.

Bloating: In first approach, dietary intervention was preferred (42%) followed by antispasmodics (21%). In second line, pre- or probiotics and diet were favored (21% each) followed by antibiotics and neuromodulators (13% each). In third line antibiotics (29%) were most often chosen, followed by dietary intervention (17%), bile acid sequestrant or neuromodulators (13% each)

Pain: Antispasmodics were chosen by 54% in first line. In second line, neuromodulators (33%) were most often chosen, followed by antispasmodics or diet (21% each). Neuromodulators were also most often chosen as a third approach (38%), followed by ondansetron (13%).

Conclusions: This case-based survey among European experts shows individualized management of patients with IBS-D depending on symptom profile and impact. The low rates of agreement highlight the complexity of tailored management.

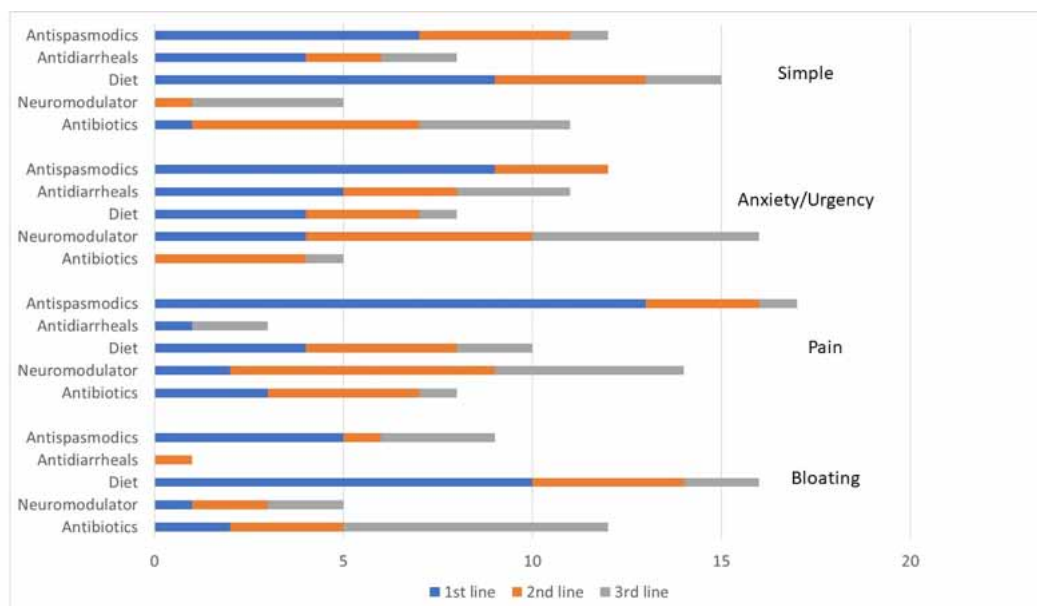


Figure 1: Number of experts that chose the respective treatment option in simple IBS-D, IBS-D with predominant anxiety/urgency, predominant pain or predominant bloating in first, second and third line

Diagnosis of disordered defecation in IBS-C patients by minimally invasive diagnostic tests

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Introduction: Irritable Bowel Syndrome Type C (IBS-C) can be associated with dyssynergic defecation (DD). It is relevant to identify IBS-C patients with DD for they may respond to biofeedback. DD diagnosis is based on anorectal physiology testing not widely available.

Aim of this study was to evaluate the accuracy and Odds Ratio (OR) of a straining questionnaire (Q) plus digital rectal examination (DRE) on predicting DD diagnosis in IBS-C patients.

Methods: 36 IBS-C patients (Rome III) were drawn from a larger pool of subjects with functional constipation enrolled for a prospective study of marginally invasive DD diagnosis according to Rome III criteria.

A Q (Which muscles do you mainly/predominantly use to strain to defecate?) was administered to patients before (T0) and after a 30-day fiber trial (T30). There were four possible answers: "belly"; "anal"; "both"; "don't know/no answer".

DRE was performed at T0.

At T30, patients underwent ARM and BET.

OR, sensitivity, specificity, positive and negative predictive values (PPV, NPV) were calculated for Q and DRE in predicting DD.

60 volunteers were enrolled as healthy controls (HC).

Results: 19 patients out of 36 (53%) had features of DD at ARM and failed BET.

The most significant response to Q in predicting DD was "anal" (Q+). At T30, the OR of this response in predicting DD is 27.4 ($p=0.0035$). This response has: sensitivity of 63.16%, specificity of 94.12%, PPV of 92.31%, and NPV of 69.57% in diagnosing DD.

The most significant DRE pattern in predicting DD was: failure of anal relaxation during push (DRE+). The OR of this pattern in predicting DD is 5.13 ($P=0.02$). This pattern has: sensitivity of 73.68%, specificity of 64.71%, PPV of 70%, and NPV of 68.75% in diagnosing DD.

All 60 HC had a normal BET. 1.67% of HC had Q+.

Conclusions: In our sample of 36 IBS-C patients 53% showed features of DD according to Rome III criteria. Our data support screening for DD by Q and DRE in refractory IBS-C patients to improve management and facilitate referral to anorectal physiology.

Easing abdominal discomfort and indigestion with kiwifruit - a systematic scoping review

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Objective: Kiwifruit have positive effects on protein digestion and constipation. Clinical intervention trials often also report an ease of symptoms such as abdominal discomfort and pain, indigestion, and reflux. We aimed to assess whether kiwifruit are able to reduce other gastrointestinal symptoms in clinical trials on healthy participants and participants with chronic constipation and to determine which symptoms are affected by habitual kiwifruit consumption.

Methods: We searched three electronic databases from 1947 to January 2021 to identify clinical trials describing effects of kiwifruit supplements or green or gold kiwifruit on other gastrointestinal symptoms as secondary outcomes in healthy participants or participants with chronic constipation to complete a systematic scoping review. Studies utilizing the Gastrointestinal Symptom Rating Score (GSRS) were separated from those who did not. Non-GSRS outcomes were described, and GSRS results were pooled and statistically analysed.

Results: A total of 661 participants taking part in 12 clinical trials (124 control, 537 receiving intervention) provided information for additional symptom relief with kiwifruit consumption. The GSRS was used in five clinical trials.

The data shows that green kiwifruit may ease abdominal discomfort and pain, and that habitual kiwifruit intake may positively affect indigestion.

We observed an average reduction of -0.85 (95% CI [-1.1, -0.57], $Z = 6.1$) in abdominal discomfort and pain scores and -0.33 (95% CI [-0.52, -0.15], $Z = -3.5$) in indigestion scores with a pooled GSRS outcome analysis.

Conclusions: The number of clinical trials documenting effects of habitual kiwifruit consumption on symptoms other than constipation is small. However, the evidence that kiwifruit may ease abdominal discomfort and pain, and indigestion is consistent. More research is needed to fortify the data.

Rifaximin prevents intestinal fermentation and improves irritable bowel symptoms induced by high fermentable oligo-di- and mono-saccharides and polyols dietary challenge

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Objective: The low fermentable oligo-, di-, mono-saccharides and polyol (FODMAP) diet is now indicated as a first-line treatment in irritable bowel syndrome (IBS). However, concerns have been raised as restricting fermentable carbohydrates might result in nutritional deficits or alter composition and function of the gut microbiome in the long term. Rifaximin was proven to be efficacious in a subset of IBS patients, likely by reducing intestinal fermentation. Whether rifaximin is able to prevent intestinal fermentation and to improve IBS symptoms' induced by a High-FODMAP diet is not known.

Methods: Ten healthy volunteers were studied in order to verify the effect on intestinal fermentation of a 2 days diet with low (LF, 15 g/day) and high (HF, 50 g/day) FODMAPs content, respectively. In 10 patients with Rome IV-based diagnosis of predominant-diarrhea IBS the HF challenge was also performed at the end of a 7-days pre-treatment with 800 mg/day of rifaximin. The effect of LF, HF and rifaximin on daily intestinal fermentation was evaluated for 10 hours by a portable H₂-breath test device, with each measurement being performed every 90 min. After each treatment the severity of abdominal symptoms (visual analogue scale, VAS) and the stool form (Bristol Charts) were assessed.

Results: As compared to LF, the HF diet caused a significantly higher total H₂ hydrogen excretion, than LF, in both patients and controls (88±11 vs. 48 ±9 and 93±17 vs. 55±15 ppm, p<0.05 and 0.01, respectively). In IBS patient's pretreatment with rifaximin significantly prevent HF-induced intestinal fermentation (55±7 ppm, p<0.05 vs HF) and improved overall symptoms severity (71±27 vs. 164±27 mm, p<0.05), abdominal pain (14±4 vs. 20±6 and 42±7 mm, for LF and HF p<0.05 and 0.01, respectively) and bloating (15±4 vs. 30±9 and 42±7 mm, for LF and HF, p<0.05 vs. HF). No significant effects were observed in the stool form.

Conclusions: We showed that pretreatment with Rifaximin significantly reduced the intestinal fermentation induced by a short HF dietary challenge and this is associated with a significant improvement of IBS severity. Controlled trials are needed to propose rifaximin as an alternative treatment to LF in the management of IBS patients.

Translational gap between guidelines and clinical medicine: the viewpoint of Italian general practitioners in the management of IBS

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Introduction: Guidelines on Irritable Bowel Syndrome (IBS) are usually developed by specialists, with a possible translational gap in primary care. The aim of our study was to assess the awareness and the use of criteria for the diagnosis and management of IBS in a group of Italian general practitioners (GPs).

Methods: For this purpose, a survey was carried out involving 235 GPs randomly selected from those working in three cities of Northern, Central and Southern Italy. The participants were divided into two groups according to their years of activity: "junior GPs" (JGPs) (≤ 10 years) and 170 "senior GPs" (SGPs) (> 10 years). They were asked to rate their IBS knowledge (satisfactory or unsatisfactory) and if they needed specific updating on this topic. Moreover, the GPs answered regarding their knowledge and clinical use of the Rome IV Criteria (RC IV) and of the Bristol Scale (BS), the essential symptoms for IBS diagnosis, the possible causes of IBS, the reasons for a referral to a gastroenterologist, and to rate the satisfactory management of their IBS patients.

Results: JGPs were more familiar with the RC IV and BS than SGPs. Abdominal pain, bowel movement frequency and bloating were the most frequent symptoms used to make a diagnosis. The most probable causes of IBS were reported to be abnormal gastrointestinal motility and psychological triggers. SGPs report more frequently than JGPs that challenging management and a patient's request were motivations for a gastroenterological consultation.

Conclusions: There is still a gap regarding expert guidance, i.e. between national and international guidelines, and primary care. Abdominal pain related to defecation and changes in bowel frequency are considered to be the most important symptoms for IBS diagnosis, but most GPs, both JGPs and SGPs, would like to consider abdominal bloating as another useful symptom. Developing shared guidelines, involving both gastroenterologists and GPs, would be highly desirable in order to improve IBS management strategies in everyday clinical practice.

Poster no. 024

Alterations of gut microbiota in functional diarrhea - a retrospective single-center study

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Functional diarrhea is an invalidant condition affecting many patients referred to Gastroenterology clinics. Available evidences suggest a link between functional diarrhea and dysbiosis.

Aim of this study was to analyze the gut microbiota composition of 40 out of 153 patients referred for microbiota evaluation who reported diarrhea as the main symptom (30 IBS-D patients and 10 patients with functional diarrhea). Gut microbiota analysis of these patients was compared to that of the remaining 113 patients without diarrhea. Alpha-biodiversity and taxonomy were analyzed using 16S rRNA sequencing. Statistical significance was calculated using Wilcoxon two-sample test ($p < 0.05$).

Alpha-biodiversity demonstrated lower values for patients with diarrhea compared to patients without diarrhea. Bacteroidetes were significantly higher in the diarrhea group (p -value 0.0101), while Firmicutes were lower (p -value 0.0082).

Furthermore, our analysis confirmed a gram negativity gut microbiota composition in patients with chronic diarrhea, with a decreased gram +/- ratio (p -value 0.00191).

Regarding taxa analysis, a reduction in butyrate-acetate producer bacteria was observed. *Eubacterium hallii*, *Eubacterium xylanophilum*, *Lachnospira*, *Ruminococcus* and *Blautia* were decreased, while *R. torques* and *Lachoclostridium* were increased.

These results suggest as possible marker of functional diarrhea a reduction of rarefaction curve, Firmicutes and grams +/- ratio, and a corresponding increase in *R. torques* and *Lachnolostrium*.

Evaluation of abdominal gas by plain abdominal radiographs

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Purpose: Our aim was to determine the reliability of plain abdominal radiographs for the evaluation of abdominal gas content in patients with functional digestive symptoms.

Methods: Abdominal CT scan scout views, mimicking a conventional plain abdominal radiograph, were obtained from 30 patients both during episodes of abdominal distension and basal conditions. Physicians (n=48) were instructed to rate the estimated volume of gas in the 60 images presented in random sequence using a scale graded from 0 to >600 mL.

Results: The gas volumes estimated in the scout views differed from those measured by CT by a median of 90 (95% CI 70-102) mL. The accuracy was independent of the order of the images. Gas volume measured by CT in the images obtained during episodes of distension differed by a median of 39 (95% CI 29-66) mL from those during basal conditions, and this difference was misestimated by a median of 107 (95 % CI 94-119) mL. The accuracy of these estimations was not related to the absolute gas volumes ($R = -0.352$; $p < 0.001$) or the magnitude of the differences.

Conclusions: Plain abdominal radiographs have limited value for the evaluation of abdominal gas volume in patients with functional gut disorders

Mechanism of abdominal distension in patients with functional gut disorders

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Objective: Background. Episodic abdominal distension is a frequent and bothersome complaint in patients with functional gut disorders, which has been attributed to distorted interpretation (subjective sensation without objective counterpart), intestinal gas accumulation and abdominophrenic dyssynergia (paradoxical contraction of the diaphragm and downwards displacement of abdominal contents coupled with relaxation and protrusion of the anterior abdominal wall).

Aim: Determine the relative contribution of these mechanisms to abdominal distension in clinical practice.

Methods: Consecutive patients with functional gut disorders whose primary complaint was episodes of visible abdominal distension (130 women, 9 men; age range: 19-79 years), were included in a series of studies following the same protocol: patients were evaluated under basal conditions (without or minimal distension) and during an episode of abdominal distension; under each condition, static abdominal CT images (during a breath-hold) were taken in 104 patients, and continuous EMG recordings of the abdominal walls in 76 patients, with diaphragmatic activity valid for analysis in 35 (owing to patient intolerance or refusal of intubation on one of the study days).

Methods: Only patients with discrete episodes of abdominal distension were included in these studies after ruling out organic disease. Patients were evaluated during basal conditions (without or minimum abdominal distension) and during episodes of severe abdominal distension by abdominal (n=68) or abdomino-thoracic (n=43). CT scans; hence, abdominal data of 101 patients and thoracic data of 43 of them were available.

Results: During episodes of self perceived abdominal distention all patients but one exhibited an increase in girth. Distention was associated with a descent of the diaphragm with relatively modest increase in intestinal gas (66 ± 9 ml) and total abdominal contents (520 ± 210 ml). Of the 43 patients with thoracic evaluation, 38 of them exhibited thoracic insufflation (by 342 ± 184 ml volume increment) with increased anteroposterior diameter of the thorax (8 ± 3 mm).

Conclusions: Abdominal distention is a somatic expression produced by the walls rather than by its content.

Risk factors for abdominal pain severity in patients with constipation-prevalent irritable bowel syndrome

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Objective: Symptoms of irritable bowel syndrome (IBS) have been associated to altered colonic motility and sensation. Smoking affects pain perception and it has been recognized an important risk factor in the development of post infectious IBS, but the effect of smoking on abdominal pain and colonic transit remains to be elucidated in IBS.

Methods: 40 patients with IBS-C and 28 with IBS-M were selected based on the Rome IV criteria. Colonic transit time (CTT) was studied and smoking habit was recorded. Presence of mild or severe abdominal pain was scored, as well as the prevalent pain characteristics, defined as diffuse or localized, chronic or acute, with cramps or gradually distending. Data were analysed by univariate and stepwise multiple logistic regression analysis was also used to verify the risk association between pain and all other variables.

Results: IBS-C patients had a longer transit time in the right colon and scored more chronic pain than IBS-M patients. When severity of abdominal pain was used as discriminating factor, a significant number of subjects reporting severe pain were males (16/30 vs 4/38, $p < 0.001$) and smokers (20/30 vs 4/38, $p < 0.001$). Multivariate analysis confirmed that only smoking was an independent factor associated with severe abdominal pain (OR 14.3, CI 2-99, $p = 0.007$). Smoking was not associated with colonic transit times and, in turn, colonic transit was not associated with IBS symptoms' severity (both $p = \text{N.S.}$).

Conclusions: Smoking was the only factor independently associated with severe abdominal pain. As smoking does not seem to affect colonic transit time, we suggest that smoking may influence visceral perception and symptoms severity in IBS patients.

The effects of Escherichia Coli Nissle 1917 on the gut microbiota composition in ulcerative colitis patients

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Background: Escherichia coli Nissle (ECN) 1917 is a Gram-negative bacterium that belongs to the family of Enterobacteriaceae and it is currently used as probiotic drug in the management of infectious gastroenteritis and in maintenance of remission in ulcerative colitis (UC) patients.

Objective: To evaluate the effect of administration of ECN on the composition of the gut microbiota in patients affected by UC.

Methods: Five patients affected by UC were treated with ECN for 30 days. Fecal samples were collected at baseline (T0), after ten days (T1) and after one month of treatment (T2). 16S rRNA was amplified and analyzed on a 454-Junior Genome Sequencer. Reads were analyzed by Quantitative Insights into Microbial Ecology (QIIME, v.1.8.0), grouped into operational taxonomic units (OTUs) by sequence matching against Greengenes database. The α and β diversity and the Kruskal Wallis test were performed by QIIME software.

Results: The T test on good's coverage index revealed that the qualitative composition of the gut microbiota between the T0 and T2 conditions resulted significantly different. Box plot of Shannon and Chao1 indices revealed a growth in the OTUs total number at the time point T1. Post hoc analysis at phylum taxonomic level revealed that Firmicutes were significantly reduced at T1 in comparison to T0. Indeed, at family taxonomic level the post hoc analysis revealed that Clostridiaceae relative abundance had a T1 median value higher than the T0 and T2. At genus level, the T test confirms the variability in the two conditions (T0 and T2), with significant differences for Actinomyces, Anaerostipes, Bacteroides, Bulleidia, Corynebacterium, Dialister, Enterobacteriaceae, Erysipelotrichaceae, Finegoldia, Granulicatella, Lactobacillaceae, Peptoniphilus, Phascolarctobacterium, Roseburia, Serratia, Veillonellaceae, Veillonella dispar, belonging to Firmicutes, Bacteroidetes and Proteobacteria phyla. Furthermore, the administration of ECN improved intestinal permeability of treated patients.

Conclusions: ECN leads to an improvement of the composition of the gut microbiota in patients with UC. These effects are stronger at the end of treatment in terms of wealth, with a stable variability between the genera after 1 month of treatment. Further studies should be performed to investigate the effects of ECN on gut microbiota modulation in patients affected by UC.

Biallelic variants in *LIG3* cause a novel mitochondrial neurogastrointestinal encephalomyopathy

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Objectives: Chronic intestinal pseudo-obstruction (CIPO) is a gut dysmotility characterized by recurrent non-mechanical, sub-occlusive episodes and highly disabling digestive symptoms. Seven patients (M=5; age range: 2–38 yrs) born from healthy unrelated parents (three families) presented CIPO, leukoencephalopathy, epilepsy, stroke-like episodes, neurogenic bladder. We aimed to identify the genetic cause underlying this disorder.

Methods: Exome sequencing, morpholino, genome-editing studies, immunofluorescence and western blotting were performed.

Results: The affected sibs of each family shared biallelic damaging variants in *LIG3*, encoding the ligase for mitochondrial DNA (mtDNA) maintenance. *lig3* disruption in zebrafish reproduced brain and gut transit abnormalities. Patient-derived fibroblasts showed a severe decrease in *LIG3* protein and ligase activity, leading to mtDNA depletion and mitochondrial dysfunction. Patients' fibroblasts increased their growth when treated with high glutamine [6mM], compared to the standard one. Glutamine supplementation to the three affected sibs (one family) improved their gastrointestinal (GI) symptoms, as evaluated by the Gastrointestinal Symptom Rating Scale.

Conclusions: We identified a new recessive disorder caused by *LIG3* mutations, with a clinical phenotype characterized by CIPO and neurologic abnormalities related to defective mtDNA maintenance. Although preliminary, data on glutamine, showing beneficial effects on GI symptoms, suggest this amino acid as a promising supplementation for *LIG3*-mutant CIPO patients.

How long-term proton pump inhibitor therapy affects the gut microbiota - a single-center experience

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Objective: Proton Pump Inhibitors (PPI) are clinically used to treat gastroesophageal reflux disease and peptic ulcers. 4-8 weeks usage of PPI can be defined as PPI-long term use. Patients with PPI-long term use show hypochlorhydria and small intestine bacterial overgrowth (SIBO), reporting bloating as the main symptom. The aim was to characterize the gut microbiota of patients under long-term PPI treatment and to assess if there was a signature of SIBO.

Methods: The gut microbiota of 152 patients referred to Gastroenterology outpatient clinic was stratified based on PPI treatment [n=43 PPI-on, n=109 PPI-off]. A sub-analysis was performed considering only patients without probiotics-intake at the time or 3 months before stool sample [n=31 PPI-on, n=82 PPI-off]. Phyla and taxa were analyzed using 16S ribosomal RNA (rRNA) sequencing. Comparisons between two groups were made using the normal approximation for the Wilcoxon two-sample test and statistical significance was defined as a p-value < 0.05.

Results: Compared to PPI-off patients, PPI users demonstrated a lower richness (p<0.05, 95% CI) and significant increased abundances for some taxa either frequently observed in oral microbiota or belonging to Proteobacteria like *Lactobacillus* (p<0.005), *Lactococcus* (p<0.05), *Streptococcus* (p< 0.005), *U. m. of Coriobacteriaceae* (p<0.005) *Hafnia* (p<0.05) and *Butyricimonas* (p< 0,005). Other taxa demonstrated significant lower values (Table 1). Out of 43 patients treated with PPI, 29 reported bloating as the main symptom. Moving to the analysis on probiotic-free patients, a statistically significant increase of the same taxa was confirmed.

Conclusions: Long-term PPI treatment has an important impact on patients' gut microbiota and might worsen bloating symptoms. As already reported, PPI users show an increase in oral bacteria especially *Lactobacillales*. Due to the possible link existing between bloating, dysbiosis, and PPI use, intercepting subjects with this signature can lead to a PPI reduction, if possible, and/or the administration of antibiotics to reduce SIBO related symptoms.

	Taxa	Mean +/- SD PPI off	Mean +/- SD PPI on	p value
DECREASE	Desulfovibrio	0,0014146 +/- 0,0025685	0,0009511 +/- 0,0021916	0,0314
	Lachnospira	0,0157966 +/- 0,0245135	0,0063728 +/- 0,0093963	0,0194
	Sutturella	0,011324 +/- 0,0134658	0,0057433 +/- 0,0073252	0,0209
	Turicibacter	0,0006922 +/- 0,0023865	0,0003446 +/- 0,0009684	0,0471

Effect of *Pedococcus acidilactici* CECT7483, *Lactopantibacillus plantarum* CECT7484 and *Lactopantibacillus plantarum* CECT7485 on in vitro intestinal permeability: implications for irritable bowel syndrome

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Objective: Irritable bowel syndrome (IBS) is characterized by alteration in intestinal permeability. The mucosal soluble mediators from a subgroup of IBS patients are able to increase paracellular permeability in an in vitro model based on Caco-2 cells (1). The aim of this work was to evaluate the ability of a blend consisting of three bacterial strains (*Pedococcus acidilactici* CECT7483, *Lactopantibacillus plantarum* CECT7484, and *Lactopantibacillus plantarum* CECT7485) to reduce the permeability increase produced by mucosal soluble mediators from IBS patients.

Methods: Mucosal mediators spontaneously released (SUP) by 11 IBS-D, 10 IBS-M and 7 asymptomatic controls (AC) were collected and incubated on Caco-2 monolayer with or without the bacterial blend (104 and 106 cfu/well). Paracellular permeability was evaluated by quantifying the flow of sulfonic acid conjugated to fluorescein through the epithelial cells layer. In addition, gene expression in Caco-2 cells after SUP and/or bacterial strains incubation was assessed. Namely, tight junctions (TJs) proteins zonula occludens (ZO)-1 and occludin, and β -actin were quantified.

Results: Compared to Caco2 cells incubated with medium alone, the probiotic blend significantly reduced the paracellular permeability after three hours of incubation ($p < 0.05$). The three bacterial strains induced a significant recovery of permeability compared to IBS SUP alone ($p < 0.05$). When analysing separately the IBS-D and IBS-M subgroups, a trend of permeability decrease is observed after three hours of probiotics incubation. The qPCR results displayed the enhancement of mRNA transcription of ZO-1 and β -actin after bacterial incubation.

Conclusions: The blend of three bacterial strains is able to enhance the barrier function of the epithelial monolayer and prevent the paracellular permeability increase induced by IBS SUP.

These findings suggest the potential therapeutic role that *Pedococcus acidilactici* CECT7483, *Lactopantibacillus plantarum* CECT7484, and *Lactopantibacillus plantarum* CECT7485 may have in IBS.

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Poster no. 032

Increased intestinal permeability correlates with abdominal symptoms, psychological comorbidity and quality of life in IBS-D patients

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Objective: Irritable bowel syndrome (IBS) is a multifactorial condition including alterations in intestinal permeability which can contribute to symptom generation. The present study aimed to assess: intestinal permeability of the gastrointestinal tract in a well-characterized IBS-D cohort and asymptomatic controls (AC); the correlations between intestinal permeability alterations and abdominal symptoms, psychological functioning and general health; the diagnostic accuracy of sugar test in discriminating between IBS-D and AC.

Methods: Thirty patients with IBS-D and 18 AC have been enrolled. Rome IV criteria, Bowel disease questionnaire, Short Form 36, Hospital Anxiety Depression Scale were used to phenotype patients. Mannitol, lactulose, sucralose, and sucrose urinary excretion was assessed by HPLC-MS. The lactulose/mannitol ratio (L/M ratio) was calculated. Correlation analyses were performed between demographic and experimental data. The accuracy of sugar test in discriminating between IBS-D and AC was evaluated by the receiver operating characteristic curves.

Results: Compared to AC, lactulose ($P<0.05$), sucralose ($P<0.01$), sucrose ($P<0.01$) excretion and the L/M ratio ($P<0.01$) were significantly increased in IBS-D patients. Abdominal pain and bloating scores correlated with the excretion of all sugars. Anxiety score correlated with sucrose ($P=0.026$; $rs:0.324$) and lactulose ($P=0.022$; $rs:0.333$) excretion and with L/M ratio ($P=0.001$; $rs:0.462$). Depression score correlated with L/M ratio ($P<0.0001$; $rs:0.552$), sucrose ($P=0.033$; $rs:0.311$), lactulose ($P=0.003$; $rs:0.420$) and sucralose ($P=0.039$; $rs:0.303$) excretion. Physical and mental health-related quality of life inversely correlated with L/M ratio, sucrose, lactulose and sucralose excretion. The highest diagnostic accuracy in discriminating IBS-D from AC was associated to L/M ratio.

Conclusions: Intestinal permeability is increased along the gastrointestinal tract and correlates with abdominal and psychological symptoms in IBS-D patients. The highest diagnostic accuracy in discriminating IBS-D from AC is associated to L/M ratio.

Intestinal permeability and dysbiosis in female patients with recurrent cystitis: a pilot study

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Introduction: Recurrent cystitis (RC) is a common disease, especially in female population. Anatomical, behavioral and genetic predisposing factors are associated with ascending retrograde route, which often causes bladder infections. RC seems to be mainly caused by agents deriving from the intestinal microbiota and most frequently by *Escherichia coli*. Intestinal contiguity contributes to the etiopathogenesis of RC and an alteration of intestinal permeability could have a major role in RC.

Aim of the study: The aim of this pilot study is to assess gut microbiome dysbiosis and intestinal permeability in patients with RC.

Materials and Methods: We recruited 16 female patients with at least two episodes of acute uncomplicated cystitis in the last 6 months or three episodes in the last year (I cohort) and compared with 15 healthy female subjects (II cohort). We calculated Acute Cystitis Symptom Score/ Urinary Tract Infection Symptom Assessment (ACSS/UTISA) and Gastrointestinal Symptom Rating Scale (GSRS) scores. Subsequently we evaluated intestinal permeability through the new H2 Lactulose/ Mannitol Breath Test and analyzed the fecal microbiome with the metagenomic 16S ribosomal RNA (rRNA) analysis. Cohort III, composed by 238 patients with gastrointestinal (GI) symptoms, was enrolled to evaluate the incidence of urinary symptoms.

Results: Patients with RC showed an increased prevalence of urological and GI symptoms compared with healthy controls and among patients in cohort I, 11 (68%) had a final diagnosis of gastrointestinal disease. More than 90% of patients with RC showed an increased intestinal permeability and a reduced biodiversity of gut microbiota than healthy controls. Particularly the potential markers of dysbiosis during RC seem to belong all to the phylum of Firmicutes, such as *Ruminococcus*, *Blautia*, *Veillonella*, *Streptococcus* spp. Similarly, among cohort III, patients reported higher incidence of urinary symptoms with a diagnosis of RC in 20%.

Conclusions: These results constitute the rationale for further studies to evaluate the potential clinical effects of active gut microbiota modulation on recurrency of cystitis. Surely this pilot study laid the foundations for further investigations, aimed to understand in greater depth the role of intestinal barrier integrity and the role of microbiota in the development of urinary tract infection

Prevalence of antigliadin IgG antibodies (AGA IgG) and the association with symptoms in irritable bowel syndrome (IBS)

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Objective: Antibody reactivity to gluten has been suggested to be linked to symptoms of IBS patients (Uhde et al. Gastroenterology, 2020). We therefore aimed to assess the prevalence of serum antigliadin (AGA) specific Immunoglobulin-G (IgG) antibodies, and to identify associations between AGA IgG, including subclasses, and symptoms in IBS.

Methods: IBS patients (n=506; 78% females; all with negative transglutaminase IgA) provided serum samples as well as recordings of gastrointestinal symptoms (IBS-SSS) and psychological distress (HADS). Demographics included sex, age, and body mass index (BMI). Levels of total AGA IgG and subclasses (IgG1-4) were assessed by Gliadin IgG ELISA (IBL International Hamburg, Germany). IgG subclass profiles were only assessed in those deemed with a positive AGA IgG test (>14.0 U/mL). Associations between AGA IgG, IgG1-4 and demographics/IBS symptoms /psychological distress were assessed with binary logistic and linear regression analyses. All variables were tested in univariate regression models, followed by multiple regression models. Associations are presented as β -coefficients with standard error.

Results: In total, 11% of the IBS patients had a positive AGA IgG test (>14.0 U/mL). Demographics, IBS symptoms or psychological distress did not differ between patients with a positive vs. negative AGA IgG test, except for BMI and abdominal distension. A multiple logistic regression model showed that a positive AGA IgG test was associated with lower BMI (-0.070 (.035), $P=.044$) and less abdominal distension (-0.013 (.005), $P=.007$).

Among IgG subclasses, IgG1 was associated with more abdominal pain (.002 (.001), $P=.044$) in a univariate linear regression model. IgG2 was associated with more abdominal distension (.005 (.002), $P=.005$) and less psychological distress (-0.020 (.008), $P=.016$) in a multiple linear regression model. Further, IgG4 was associated with sex and daily life interference scores where a multiple linear regression model was only able to confirm the association for male sex (-0.358 (.178), $P=.048$). No associations were observed between IgG3 and the examined variables.

Conclusions: A positive AGA IgG test does not have a clear association to common IBS symptoms. Follow-up studies are needed to understand the relevance of IgG antibody responses to gliadin for symptom generation in IBS.

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IBS DAYS

New insights for a better management of irritable bowel syndrome