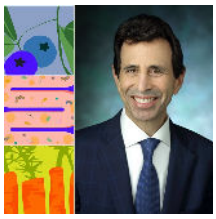
Microbiome, Gut and Systemic Health: New Frontiers in Personalised Nutrition



Keynote Speaker

Dr. Gerard Mullin, MD

Nutritional Modulation of Irritable Bowel Syndrome

9:45-10:30am

An event by: Nutritional Medicine Institute

Platinum sponsors: regenerus labs VIRIDIAN pure encapsulations

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Nutritional Modulation of the Irritable Bowel Syndrome

Gerard E. Mullin, MD
Associate Professor of Medicine
Johns Hopkins University School of Medicine

NMI SUMMIT 2023
Microbiome, Gut and Systemic Health:
New Frontiers in Personalised Nutrition

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Objectives

1. To discuss the natural history and pathophysiology of the irritable bowel syndrome (IBS).
2. To understand the strategies used to evaluate and effectively manage IBS.
3. To become familiar with the evidence-based nutritional considerations for IBS.

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Case Presentation

- 44-year-old female with IBS-D which was diagnosed after undergoing a cholecystectomy in 2008 for gallstones.
- She now presents with worsening of her post-prandial diarrhea but notes bloating, fatigue and flushing after meals.
- Past medical history is otherwise non-contributory except for episodic arthralgias and eczema since the worsening of her diarrhea.
- Her physical exam in notable for dermatographism.
- She notes no recent antibiotic exposure but heavy use as teenager for acne.

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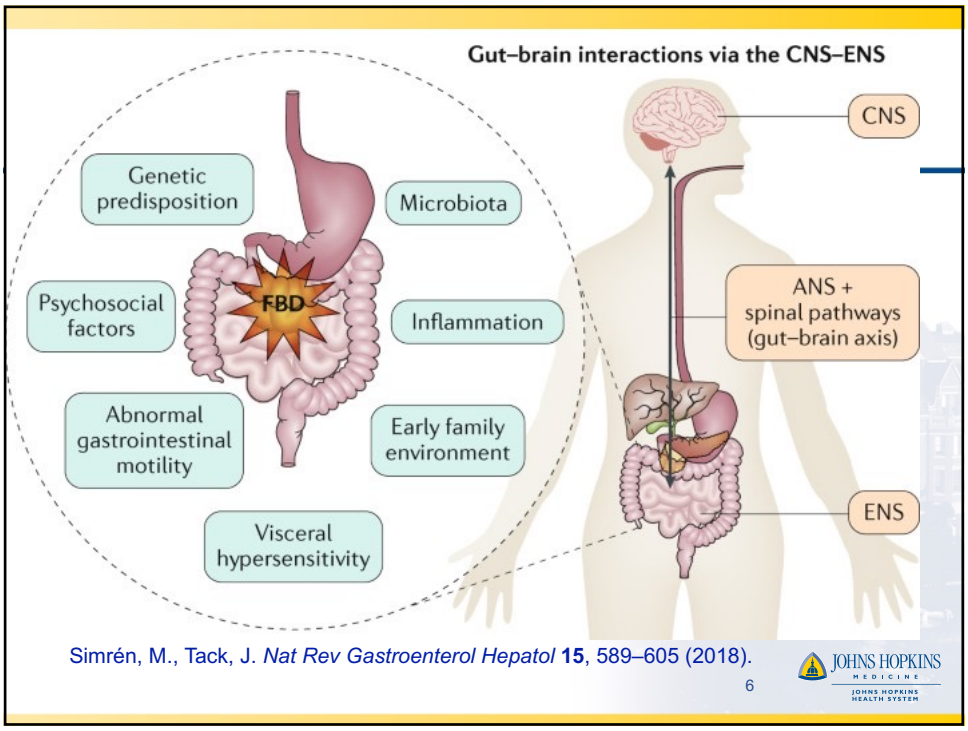

Simrén, M., Tack, J. *Nat Rev Gastroenterol Hepatol* **15**, 589–605 (2018).

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The Irritable Bowel Syndrome (IBS)

- 2nd most commonly diagnosed GI disorder that generates a significant health care burden estimated to be $30B annually in the US.
- Symptoms can occur as a result of a combination of factors, including visceral hypersensitivity, altered bowel motility, neurotransmitter imbalance, infection and psychosocial factors.
- The walls of the intestines are lined with layers of muscle that contract and relax, helping move food through the digestive system. With IBS, these muscles may function abnormally, including causing painful muscle spasms.

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Defining and characterizing IBS

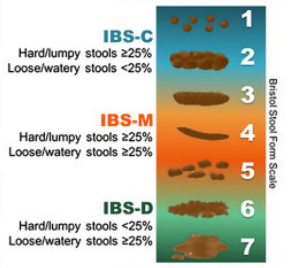
1A. Rome IV Criteria for IBS

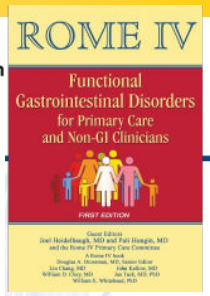
Recurrent abdominal pain, on average, ≥1 day per week in the last 3 months, associated with ≥ 2 of the following:

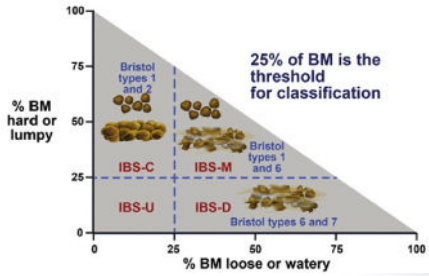
- Related to defecation
- Change in frequency of stool
- Change in form (appearance) of stool

Criteria should be fulfilled for the last 3 months with symptom onset ≥ 6 months before diagnosis

1B. IBS Subtypes Based on Bristol Stool Forms







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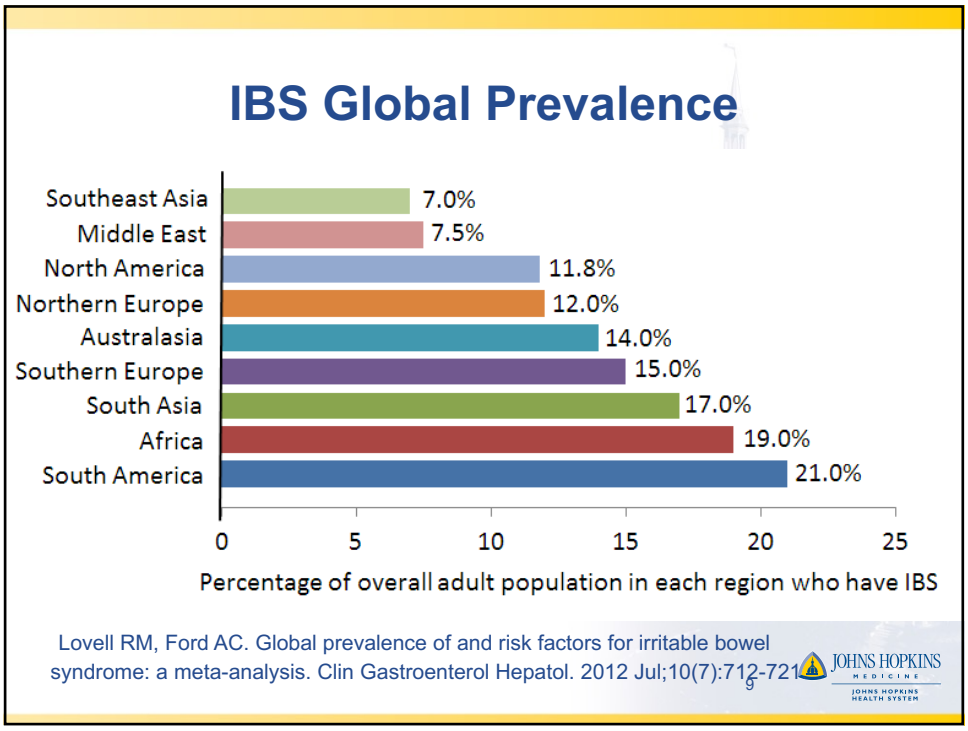
IBS Global Prevalence
Southeast Asia
Middle East
North America
Northern Europe
Australasia
Southern Europe
South Asia
Africa
South America
7.0%
7.5%
11.8%
12.0%
14.0%
15.0%
17.0%
19.0%
21.0%
0
5
10
15
20
25
Percentage of overall adult population in each region who have IBS
Lovell RM, Ford AC. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. Clin Gastroenterol Hepatol. 2012 Jul;10(7):712-721
9
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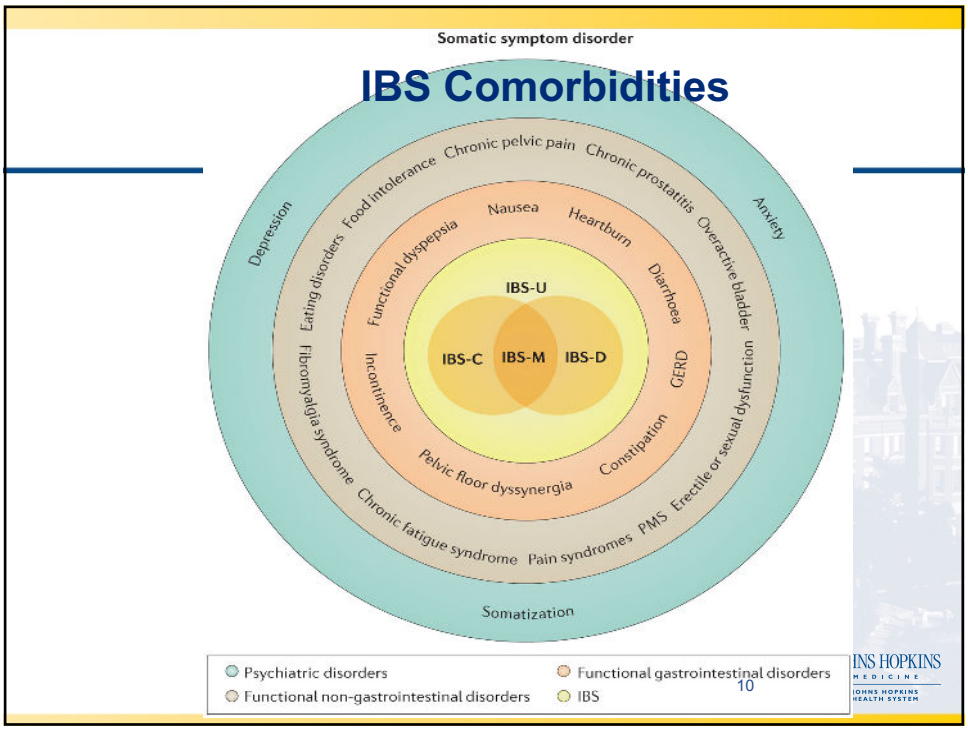
Somatic symptom disorder
IBS Comorbidities
Depression
Food intolerance
Chronic pelvic pain
Chronic prostatitis
Anxiety
Eating disorders
Nausea
Heartburn
Overactive bladder
Functional dyspepsia
Diarrhoea
Fibromyalgia syndrome
IBS-U
IBS-C
IBS-M
IBS-D
Incontinence
GERD
Pelvic floor dyssynergia
Constipation
Chronic fatigue syndrome
Pain syndromes
PMS
Erectile or sexual dysfunction
Somatization
Psychiatric disorders
Functional gastrointestinal disorders
Functional non-gastrointestinal disorders
IBS
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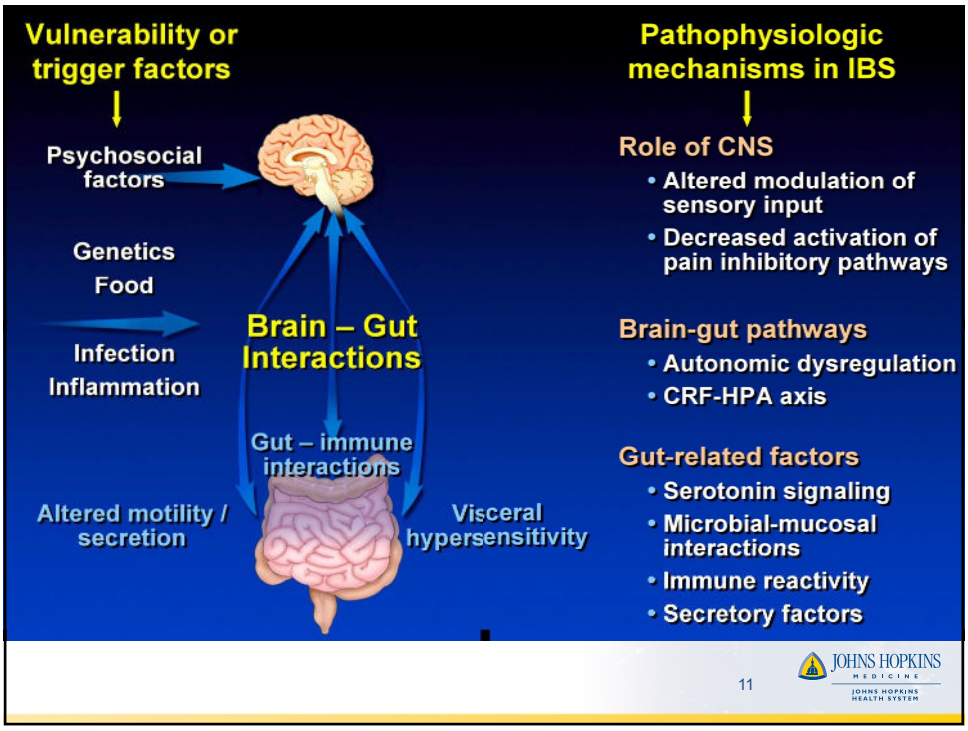
Vulnerability or trigger factors
Psychosocial factors
Genetics
Food
Infection
Inflammation
Brain – Gut Interactions
Gut – immune interactions
Altered motility / secretion
Visceral hypersensitivity
Pathophysiologic mechanisms in IBS
Role of CNS
• Altered modulation of sensory input
• Decreased activation of pain inhibitory pathways
Brain-gut pathways
• Autonomic dysregulation
• CRF-HPA axis
Gut-related factors
• Serotonin signaling
• Microbial-mucosal interactions
• Immune reactivity
• Secretory factors
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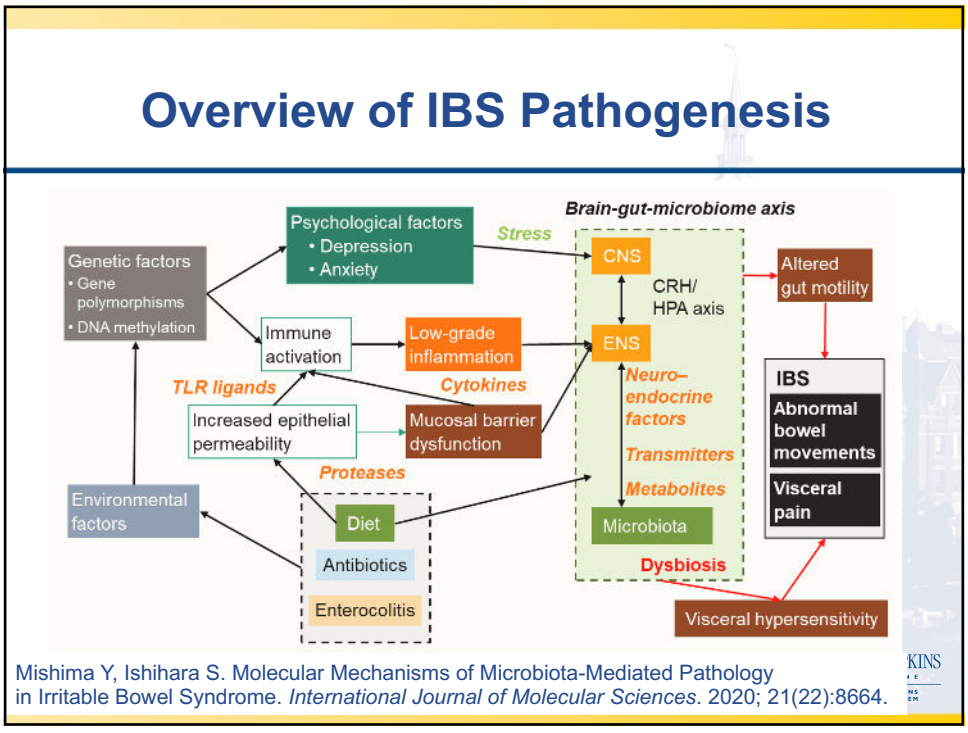
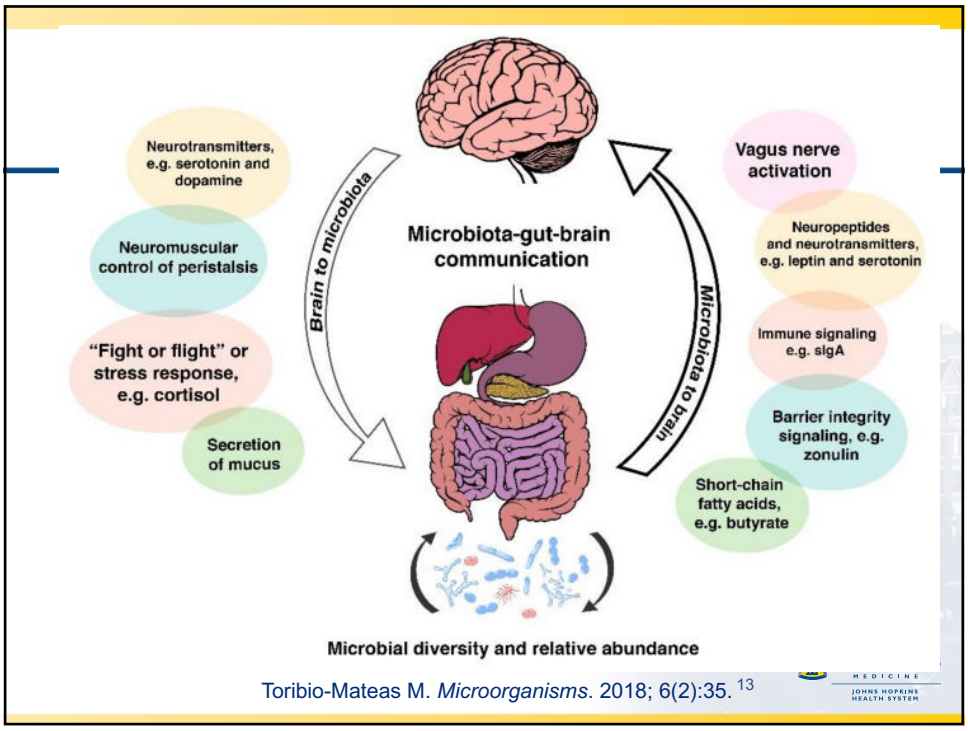
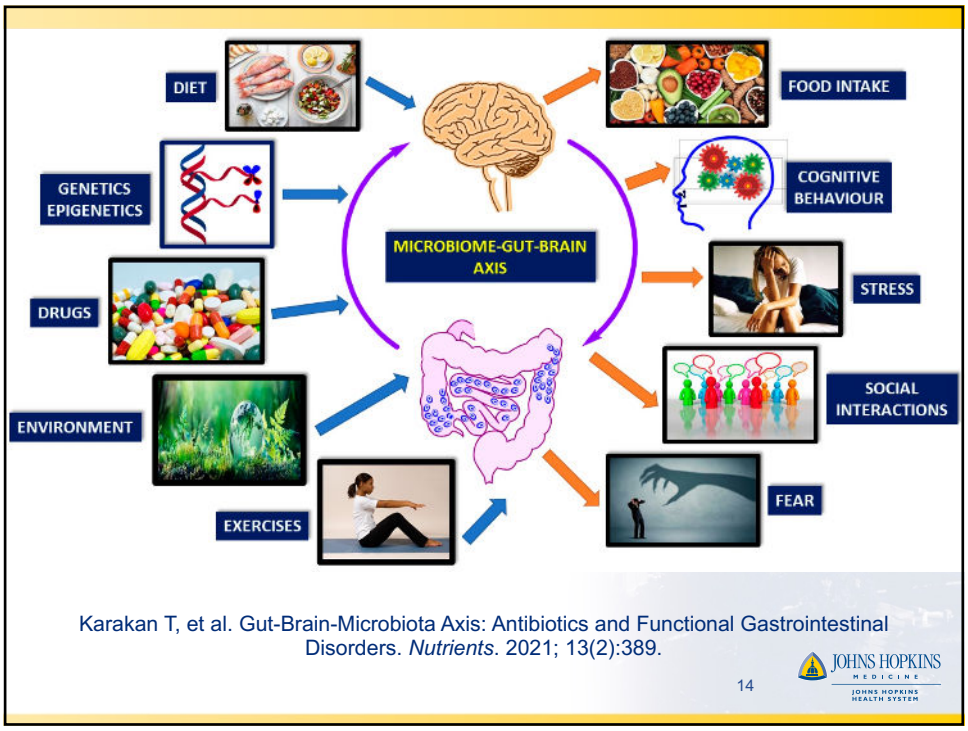

Overview of IBS Pathogenesis
Brain-gut-microbiome axis
Psychological factors
• Depression
• Anxiety
Stress
Genetic factors
• Gene polymorphisms
• DNA methylation
Immune activation
Low-grade inflammation
TLR ligands
Cytokines
Increased epithelial permeability
Mucosal barrier dysfunction
Proteases
Environmental factors
Diet
Antibiotics
Enterocolitis
CNS
CRH/ HPA axis
ENS
Neuro–endocrine factors
Transmitters
Metabolites
Microbiota
Dysbiosis
Altered gut motility
IBS
Abnormal bowel movements
Visceral pain
Visceral hypersensitivity
Mishima Y, Ishihara S. Molecular Mechanisms of Microbiota-Mediated Pathology in Irritable Bowel Syndrome. International Journal of Molecular Sciences. 2020; 21(22):8664.

12



Toribio-Mateas M. *Microorganisms*. 2018; 6(2):35. [13]

13



Karakan T, et al. Gut-Brain-Microbiota Axis: Antibiotics and Functional Gastrointestinal Disorders. *Nutrients*. 2021; 13(2):389.

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Evidence to Support a Pivotal Role of Gut Microbiome in IBS

- Post-infectious IBS-D
- Altered Colonic Microbiome
- Probiotics
- Antibiotics
- Small Intestine Bacterial Overgrowth (SIBO)

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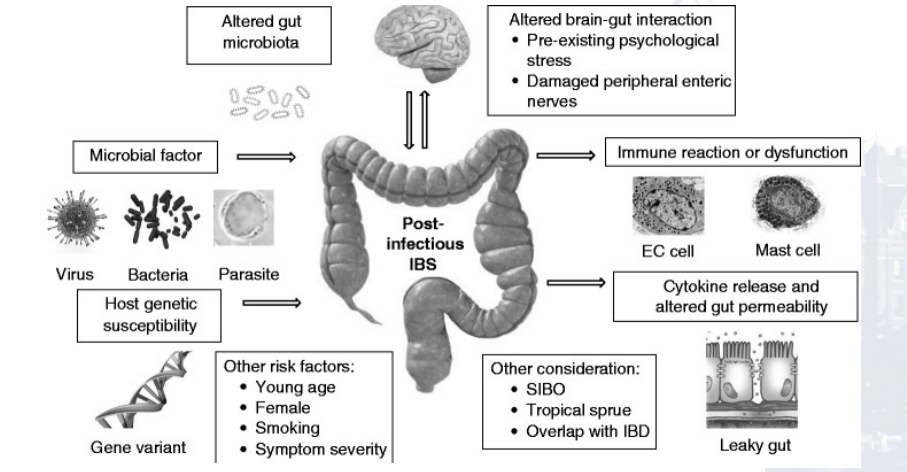
Post-Infectious IBS-D



Lee, Y.Y., Annamalai, C. & Rao, S.S.C. Curr Gastroenterol Rep (2017) 19: 56.

16

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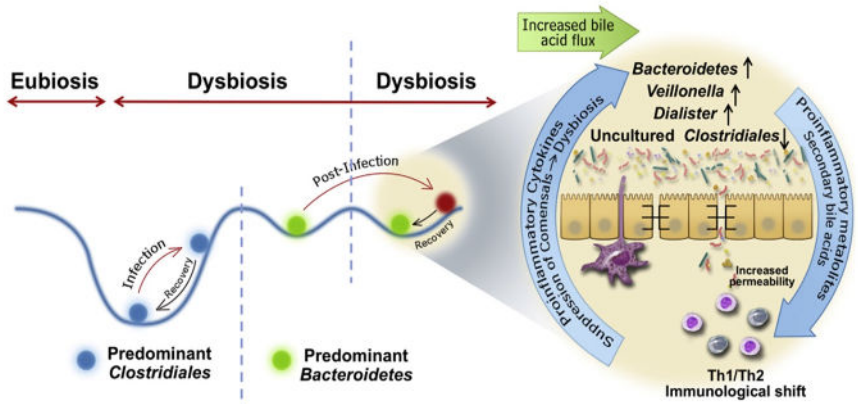
Role of Infection-associated Shifts in Microbiota in Pi-IBS



Barbara G, Grover M, Bercik P, Corsetti M, Ghoshal UC, Ohman L, et al. Rome Foundation Working Team Report on Post-Infection Irritable Bowel Syndrome. Gastroenterology 2019;156:46–58.

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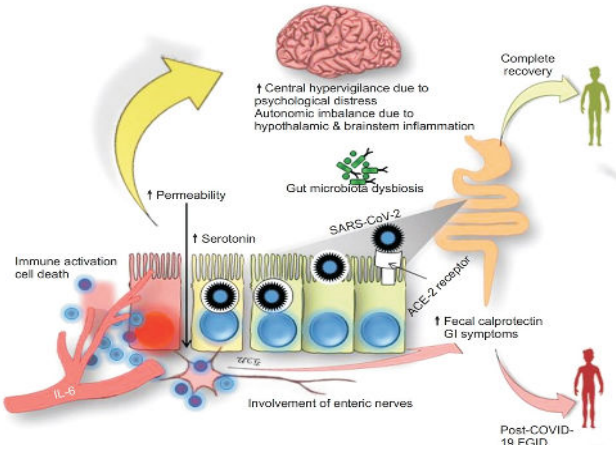
Long COVID-19 and Pi-IBS-D



Ghosal US. Post-infectious Irritable Bowel Syndrome. Gut Liver 2022;16(3):331-34

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Evidence to Support a Pivotal Role of Gut Microbiome in IBS

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- Antibiotics
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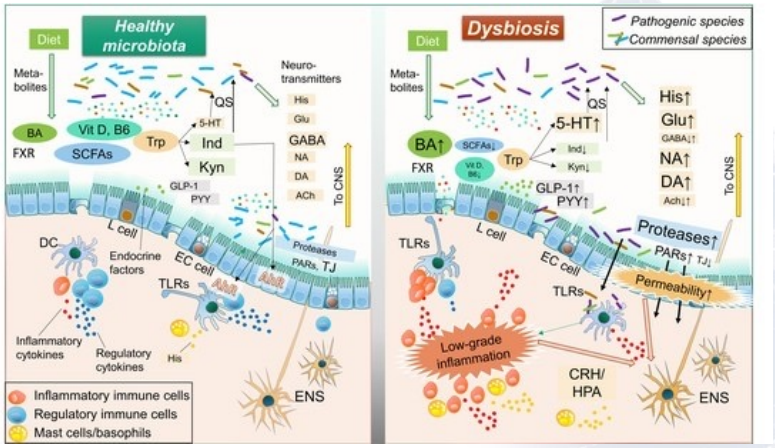
Molecular Mechanisms of Microbiota-mediated Pathology in Irritable Bowel Syndrome.



Mishima Y, Ishihara S. Molecular Mechanisms of Microbiota-Mediated Pathology in Irritable Bowel Syndrome. *International Journal of Molecular Sciences*. 2020; 21(22):8664.

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Gut Microbial Products in IBS

Microbial Products	Visceral Pain	GI Motility	Mucosal Permeability	Mucosal Inflammation	Influencing Dysbiosis
Neurotransmitters					
Histamine	↑↑	↑	↑	↑	
Serotonin	↑	↑	↑	↑	++
Glutamate	↑↑		↓?	↑	+
γ-aminobutyric acid	↓	↓		↓	
Noradrenalin	↑	↑	↑	↑↓	
Dopamine	↓	↑↓	↑?	↓?	+
Acetylcholine		↑		↓	
Compounds					
Toll-like receptor ligands	↑↓	↑↓	↑↓	↑↓	
Cytokines	↑↓	↑↓	↑↓	↑↓	
Pore-forming toxins, N-formylated peptides	↑		↑	↑	
Metabolites					
Tryptophan (aryl hydrocarbon receptor, kynurenine pathways)	↓↑		↓	↓	+
Short-chain fatty acids	↑↓	↑	↓	↓	
Bile acids	↓	↑		↑	+
Vitamin D and B6	↓		↓	↓	+
Endocrine factors					
Glucagon-like peptide-1	↓	↓		↓	
Peptide YY	↓	↓			
Enzymes					
Proteases	↑	↑↓	↑↑↑	↑	

Mishima Y, Ishihara S. Molecular Mechanisms of Microbiota-Mediated Pathology in Irritable Bowel Syndrome. *International Journal of Molecular Sciences*. 2020; 21(22):8664.

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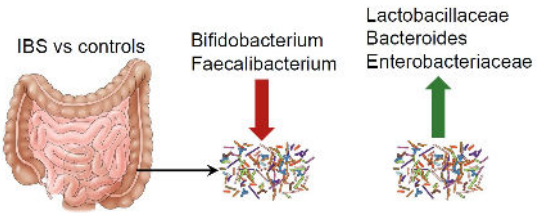
Gut Microbiome Meta-analyses for the Irritable Bowel Syndrome

eat right.

RESEARCH
Review

Gut Microbial Dysbiosis in the Irritable Bowel Syndrome: A Systematic Review and Meta-Analysis of Case-Control Studies

Lin Wang, MSc, MD*; Nuha Alammar, MD*; Rajdeep Singh, MBBS; Julie Nanavati, MLS, MA; Yiran Song, MBBS; Rahul Chaudhary, MD; Gerard E. Mullin, MD



Wang L, Alammar N, Singh R, Nanavati J, Song Y, Chaudhary R, Mullin GE. Gut Microbial Dysbiosis in the Irritable Bowel Syndrome: A Systematic Review and Meta-Analysis of Case-Control Studies. J Acad Nutr Diet. 2020 Apr;120(4):565-586.

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Evidence to Support a Pivotal Role of Gut Microbiome in IBS

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- Probiotics
- Antibiotics
- Small Intestine Bacterial Overgrowth

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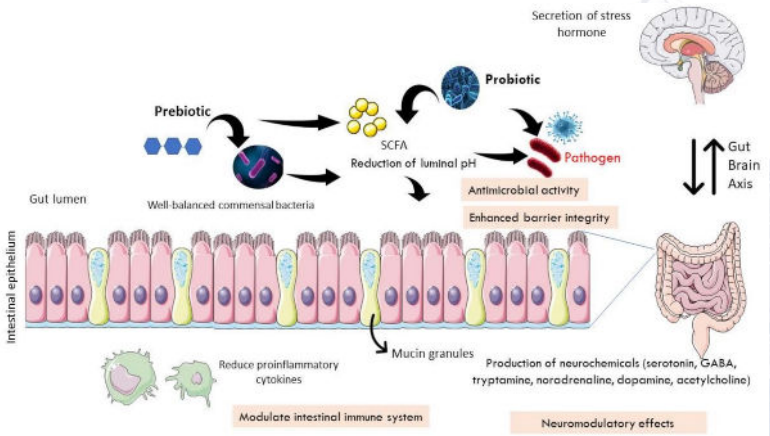
Mechanisms of Prebiotic and Probiotic Action in Modulating Bidirectional Gut−brain Axis.



Aziz MNM, Kumar J, Muhammad Nawawi KN, Raja Ali RA, Mokhtar NM. Irritable Bowel Syndrome, Depression, and Neurodegeneration: A Bidirectional Communication from Gut to Brain. *Nutrients*. 2021; 13(9):3061

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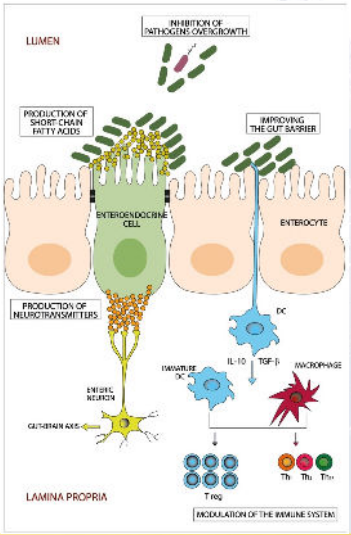
Potential Beneficiary Effects of Probiotics on the Gut

Mazzawi T. Gut Microbiota Manipulation in Irritable Bowel Syndrome. *Microorganisms*. 2022; 10(7):1332.



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Efficacy of Probiotics in Irritable Bowel Syndrome: Systematic Review and Meta-analysis

Supplementary Table 7. Efficacy of Probiotics in Terms of Effect on Global Symptom Scores in Irritable Bowel Syndrome.

	Number of trials	Number of patients	SMD for persistence of global symptoms (95% CI)	*p* value for the difference	I^2 (*p* value for χ^2)
Combination	20	1685	-0.36 (-0.52 – -0.20)	<0.001	53% (0.003)
Lactobacillus	8	542	-0.01 (-0.18 – 0.16)	0.89	0% (0.44)
Bifidobacterium	4	666	-0.27 (-0.72 – 0.18)	0.24	74% (0.004)
Bacillus	2	148	-1.43 (-2.47 – -0.39)	0.007	85% (0.009)
Clostridium	1	166	-0.34 (-0.64 – -0.03)	0.03	N/A
Saccharomyces	1	67	-0.12 (-0.60 – 0.36)	0.61	N/A

N/A; not applicable

Goodoory VC, Khasawneh M, Black CJ, Quigley EM, Moayyedi P, Ford AC, Efficacy of Probiotics in Irritable Bowel Syndrome: Systematic Review and Meta-analysis, Gastroenterology (2023), doi: https://doi.org/10.1053/j.gastro.2023.07.018.

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Efficacy of Probiotics in Irritable Bowel Syndrome: Systematic Review and Meta-analysis

Supplementary Table 13. Efficacy of Probiotics in Terms of Effect on Abdominal Pain Scores in Irritable Bowel Syndrome.

	Number of trials	Number of patients	RR of persistence of abdominal pain (95% CI)	p value for the difference	I2 (p value for χ2)
Combination	25	2043	-0.30 (-0.45 -0.14)	<0.001	61% (<0.001)
Lactobacillus	7	888	-0.32 (-0.52 – -0.13)	0.001	51% (0.05)
Saccharomyces	6	510	-0.47 (-1.13 – 0.20)	0.17	92% (<0.001)
Bifidobacterium	4	539	-0.35 (-0.70 0.00)	0.05	63% (0.04)
Bacillus	3	177	-1.62 (-2.36 -0.87)	<0.001	73% (0.02)
Clostridium	1	166	-0.26 (-0.56 – 0.05)	0.10	N/A

N/A; not applicable

Goodoory VC, Khasawneh M, Black CJ, Quigley EM, Moayyedi P, Ford AC, Efficacy of Probiotics in Irritable Bowel Syndrome: Systematic Review and Meta-analysis, Gastroenterology (2023), doi: https://doi.org/10.1053/j.gastro.2023.07.018.

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Efficacy of Probiotics in Irritable Bowel Syndrome: Systematic Review and Meta-analysis

Supplementary Table 20. Efficacy of Probiotics in Terms of Effect on Abdominal Bloating or Distension Scores in Irritable Bowel Syndrome.

	Number of trials	Number of patients	RR of persistence of abdominal bloating or distension (95% CI)	*p* value for the difference	I^2 (*p* value for χ^2)
Combination	25	1976	-0.23 (-0.39 – -0.07)	<0.001	63% (<0.001)
Lactobacillus	5	606	-0.13 (-0.30 – 0.04)	0.14	17% (0.30)
Saccharomyces	4	239	-0.92 (-2.00 – 0.17)	0.10	93% (<0.001)
Bifidobacterium	3	501	-0.30 (-0.68 – 0.09)	0.13	68% (0.04)
Bacillus	3	177	-1.26 (-2.27 -0.25)	0.01	87% (<0.001)
Clostridium	1	166	-0.05 (-0.35 – 0.26)	0.75	N/A

N/A; not applicable

Goodoory VC, Khasawneh M, Black CJ, Quigley EM, Moayyedi P, Ford AC, Efficacy of Probiotics in Irritable Bowel Syndrome: Systematic Review and Meta-analysis, Gastroenterology (2023), doi: https://doi.org/10.1053/j.gastro.2023.07.018.

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Evidence to Support a Pivotal Role of Gut Microbiome in IBS

- Post-infectious IBS-D
- Altered Colonic Microbiome in IBS
- Probiotics
- Antibiotics
- Small Intestine Bacterial Overgrowth

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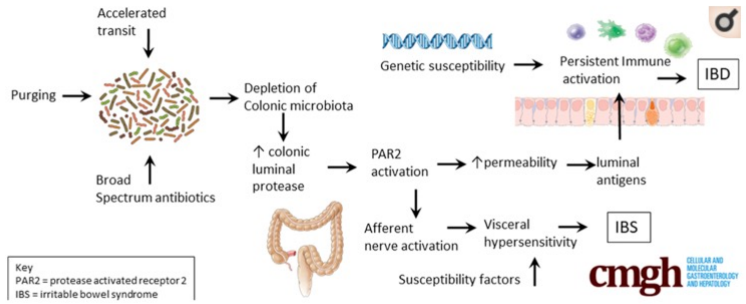
Antibiotics Increase the Risk of IBS-D

Supplemental Graphical Summary



Spiller RC. Hidden Dangers of Antibiotic Use: Increased Gut Permeability Mediated by Increased Pancreatic Proteases Reaching the Colon. Cell Mol Gastroenterol Hepatol. 2018 Jul 11;6(3):347-348.e1.

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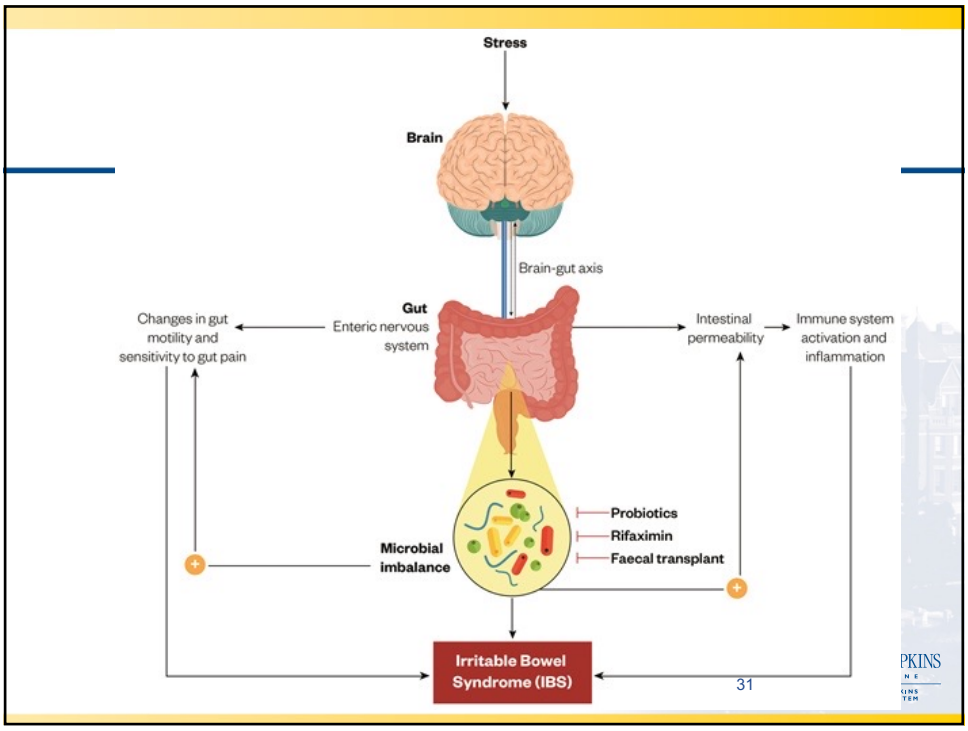

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Evidence to Support a Pivotal Role of Gut Microbiome in IBS

- Post-infectious IBS
- Altered Colonic Microbiome in IBS
- Probiotics
- Antibiotics
- Small Intestine Bacterial Overgrowth

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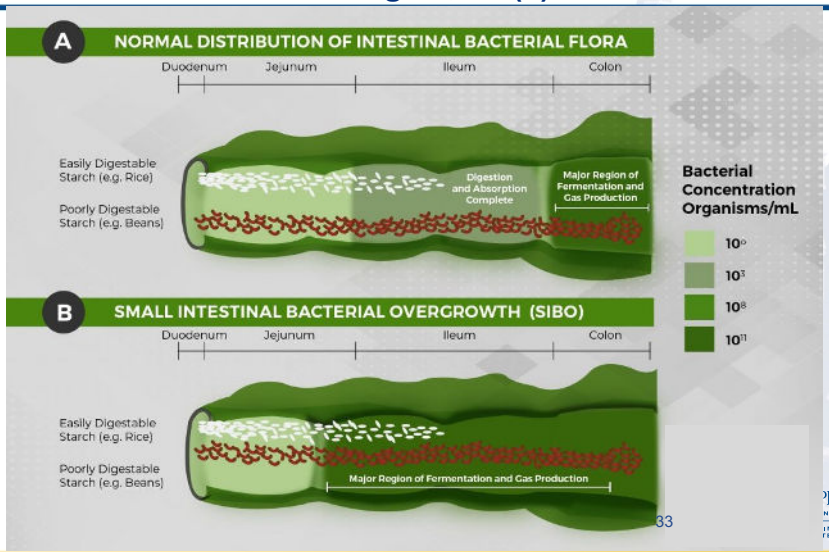
Lin HC. Small intestinal bacterial overgrowth: a framework for understanding irritable bowel syndrome. JAMA. 2004 Aug 18;292(7):852-8.



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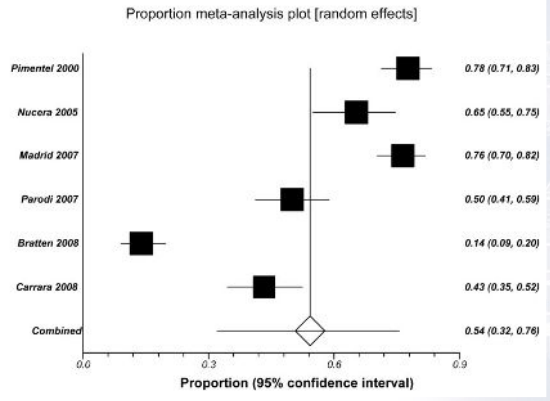
Relationship of SIBO to IBS



Pooled odds ratio for any positive LBHT test was 3–5-fold times greater in IBS than controls

Ford AC, Spiegel BM, Talley NJ, Moayyedi P. Small intestinal bacterial overgrowth in irritable bowel syndrome: systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2009 Dec;7(12):1279-86.

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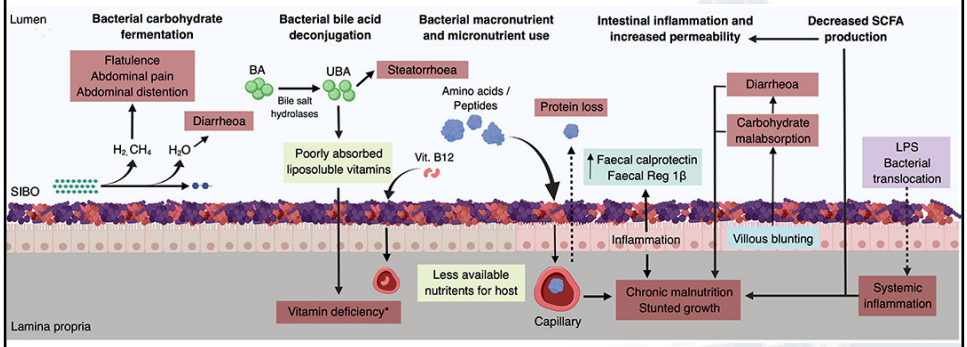
SIBO and IBS-D Pathophysiology



Avelar Rodriguez D, Ryan PM, Toro Monjaraz EM, Ramirez Mayans JA, Quigley EM. Small Intestinal Bacterial Overgrowth in Children: A State-Of-The-Art Review. Front Pediatr. 2019 Sep 4;7:363.

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Conditions Associated with Small Intestine Bacterial Overgrowth

Category	Specific Condition
Mechanical Issues	Intussusception Postsurgical changes Small bowel tumor Volvulus
Systemic Disease	Amyloidosis Collagen Vascular Disease Diabetes Hypothyroidism Scleroderma
Motility Disorders	Irritable Bowel Syndrome Mitochondrial diseases Pseudoobstruction Visceral Myopathies
Medications	Opiates Potent anti-acid secretory medications
Malabsorptive	Pancreatic insufficiency Liver cirrhosis (bile acid alterations)
Immune	Agammaglobulinemia Common Variable Immunodeficiency HIV IgA deficiency
Other	Aging Small Bowel Diverticulosis

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Treatment Options for SIBO

The goal is to treat the underlying cause(s), contain the bacterial overgrowth, and provide nutritional support.

- Diet *(low FODMAPs)*
- Antibiotic therapy *(Weeding)*
- Prokinetic agents
- Herbs for weeding* *(berberine, oregano oil, wormwood)*
- Probiotics *(multiple mechanisms)*
- Serum Bovine-derived Immunoglubulins *(SBIs)*
- Enzymes/HCl
- Other (*Antrantil, SYN-001:)*

*Mullin, G et al. **Herbal Therapy Is Equivalent to Rifaximin for the Treatment of Small Intestinal Bacterial Overgrowth**. *Global Advances in Health and Medicine.* 2014;3(3):16-24.

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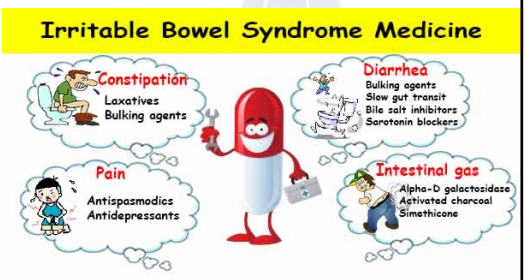
Nutritional Therapies for IBS

- Gut Microbiome
- Elimination Diets
- Herbals
- Nutraceuticals
- Enzymes



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Food: The Forgotten Factor in the Irritable Bowel Syndrome

Shanti Eswaran, MD[a], Jan Tack, MD, PhD[b], William D. Chey, MD, AGAF[a,*]

KEYWORDS
• Carbohydrate • Lactose • Fructose • FODMAP
• Gluten • Lipid • Diet

Between 7% and 20% of adults exp
bowel syndrome (IBS), a disorder de
abdominal pain in association with alte
or easily identifiable biochemical abn
Several factors have been suggested
including disturbed motility, the brain
function, immunologic dysregulation,
More recently, there has been increas
have long associated their IBS symptoms with the ingestion of certain foods, combi-

•> 60% IBS patients report worsening symptoms after meals, 28% within 15 minutes, 93% within 3 hours

Eswaran S, Tack J & Chey W. Food: The Forgotten Factor in the Irritable Bowel Syndrome. Gastroenterol Clin N Am 40 (2011) 141–162

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for IBS. This lack of enthusiasm for dietary counseling has increasingly caused

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Therapy	Description	Level of Evidence	Quality of Evidence Strength of Recommendation
Targeted Elimination Diets	Remove suspected food groups then gradual reintroduction 1 food group at a time to confirm provocative foods to avoid. Suspect foods not limited to but include alcohol, caffeinated products, spicy foods, dairy, wheat, gluten, known food allergens, suspected food allergens.	IIB	3, Moderate.
Elimination Diets based upon IgG4 serum testing	Remove foods showing IgG4 antibody reactivity.	IIB	2, Low.
Generalized Elimination Diets	Remove top 8 allergenic food groups then reintroduce one at a time.	IV	1, Low.
FODMAPs Elimination Diet	Remove Fermentable Oligo-, Di-, Mono-saccharides-And Polyols	IA	4, High.
Fiber	Ispaghula	IA	3, Moderate.
Fiber	Wheat Bran	IA	2, Low.

Singh R, Salem A, Nanavati J, Mullin GE. The Role of Diet in the Treatment of the Irritable Bowel Syndrome–A Systematic Review. GI Clinics of North America. Feb 2018.

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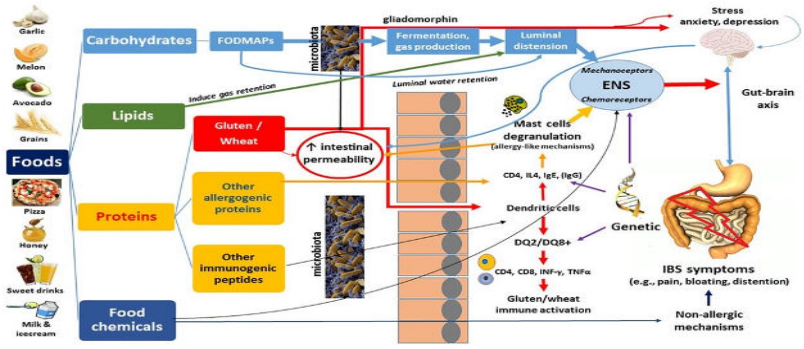
Mechanisms of Action of FODMAPs in Triggering IBS Symptoms



De Giorgio R, Volta U, Gibson PR. Sensitivity to wheat, gluten and FODMAPs in IBS: facts or fiction? *Gut* 2016;**65:**169-178.

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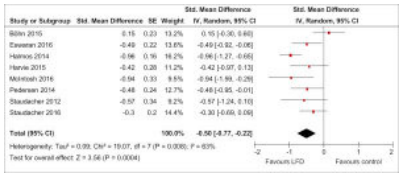
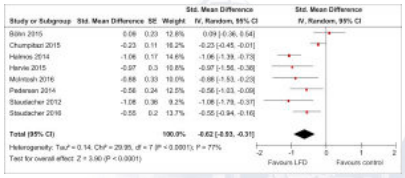
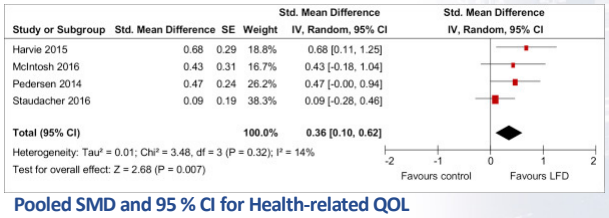
Low FODMAPs Diet in the Treatment of IBS: A Systematic Review and Meta-analysis



Pooled SMD and 95 % CI for severity of abdominal pain obtained from RCTs



Pooled SMD and 95 % CI for overall symptom severity score



Pooled SMD and 95 % CI for Health-related QOL

Schumann D, Klose P, Lauche R, Dobos G, Langhorst J, Cramer H. Low FODMPAs diet in the treatment of irritable bowel syndrome: A systematic review and meta-analysis. Nutrition. 2018 Jan;45:24-31.

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RCTs on the Effect of Low FODMAPs Diet on Gut microbiota and Metabolites

Authors, Years	Study Design and Duration	Diagnostic Criteria and Materials	Gut Microbiota: Microbial Analysis	Gut Microbiota: Findings	Microbiota Metabolites: Methods	Microbiota Metabolites: Findings
Halmos EP et al., 2015 [44]	RCT, crossover (single blind), 3 weeks	Rome III IBS and healthy controls; LFD vs. ordinary diet; IBS n = 27, Healthy controls n = 6	qPCR	Lower absolute abundances of Bifidobacteria, *F. prausnitzii* and Clostridium Cluster IV and lower relative abundance *Akkermansia muciniphila* in LFD than ordinary diet. Lower total bacteria in LFD at baseline. Greater diversity Clostridium Cluster XIVa in LFD than ordinary diet at baseline	Gas liquid chromatography	No difference in total or individual stool SCFAs in LFD compared to ordinary diet, baseline.
McIntosh K. et al., 2017 [53]	RCT (single blind), 3 weeks	Rome III IBS, LFD n = 19, HFD n = 16	16S rRNA sequencing (Illumina)	Higher richness of Actinobacteria, Firmicutes, Clostridiales in LFD than HFD. No difference in α- or β-diversity after LFD vs. baseline. Higher richness in LFD than HFD. Higher abundance of Clostridiales family XIII *Incertae sedis* spp. and Peptoniphilaceae spp. in LFD than baseline. Lower abundance of Propionibacteriaceae, Bifidobacteria in LFD than baseline.	Mass spectroscopy	Urinary metabolomic profile at baseline in LFD vs. HFD showed no difference but separated after intervention. Three metabolites (histamine, p-hydroxybenzoic acid and sebacic acid) discriminated groups. Correlations between metabolite concentrations and abundance of various taxa.
Staudacher HM et al., 2012 [54]	RCT (unblind), 4 weeks	Rome III IBS, LFD n = 19, Habitual diet n = 22	Fluorescence in situ hybridization	Lower abundance of Bifidobacteria in LFD than habitual diet. No difference in total abundance of other groups (*F. prausnitzii*)	Gas liquid chromatography	No difference in total or individual stool SCFAs in LFD compared to habitual diet
Staudacher HM et al., 2017 [52]	RCT (single blind), 4 weeks	Rome III IBS, LFD n = 61, Sham n = 53	qPCR	Lower abundance of Bifidobacteria in LFD compared to sham	Gas liquid chromatography	Lower stool acetate concentration in LFD compared to control

IBS: irritable bowel syndrome; RCT: randomized controlled trial; LFD: low FODMAP diet; HFD, high FODMAP diet; SCFA, short chain fatty acid; qPCR, quantitative polymerase chain reaction. All differences reported are significant ($p < 0.05$).

Mazzawi T. Gut Microbiota Manipulation in Irritable Bowel Syndrome. *Microorganisms*. 2022; 10(7):1332.

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Controversial Features of Low FODMAP Approach

- Short- and long-term limitations (a high level of restriction.
- The need for monitoring by an expert dietitian.
- Potential nutritional deficiencies.
- Significant eubiotic gut microbiota reduction.
- Lack of predictors of response*Aliment Pharmacol Ther. 2015 Aug;42(4):418-27.
- People improve IBS symptoms with just a gluten-free diet or even traditional dietary advice! Gastroenterology. 2015 Nov;149(6):1399-1407, Gut. 2016 Jan;65(1):169-78
- The potential lack of advantage over alternative dietary, pharmacological and psychological interventions for IBS.

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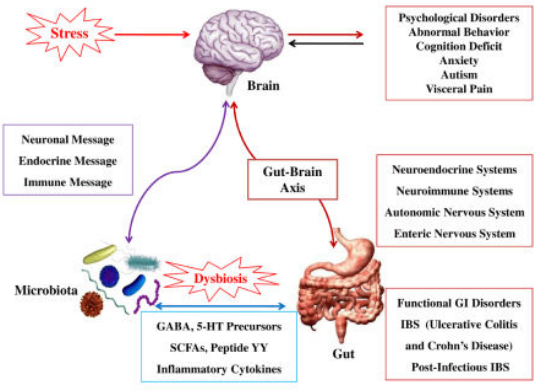
Integrative Therapies for IBS

- *Stress-reduction*
- Diet-Microbiome
- Medical Foods
- Herbal
- Enzymes



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Clinical Gastroenterology and Hepatology 2021;19:1538–1553

SYSTEMATIC REVIEWS AND META-ANALYSES

Potential Benefit With Complementary and Alternative Medicine in Irritable Bowel Syndrome: A Systematic Review and Meta-analysis

- 2825 articles identified, 66 were included.
- Herbal therapy demonstrated significant benefit over placebo for abdominal pain.
- Benefit with mind-body based therapy for abdominal pain was of borderline significance.
- Herbal therapy, dietary supplements and mind-body based therapy showed benefit for overall response compared to placebo.
- Body-based and energy healing therapies demonstrated no significant benefit over placebo or sham for abdominal pain for overall response.

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Mind-Body Studies in IBS

- Meditation
- Hypnotherapy
- Behavioral Therapy
- Psychological Therapy
- Multi-Component Therapy

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Nutritional Tools for Your IBS Patient

- Anti-anxiety Herbs
- Anti-microbials for SIBO
- Artichoke leaf extract
- Elimination Diet
- Fiber
- Enzymes
- FODMAP-restricted diet
- Melatonin
- Peppermint Oil
- Probiotics
- Turmeric
- Glutamine
- Zinc-L-carnosine

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Lab Assessment

Digestion

- CBC/diff nl
- CMP-lipids nl
- 25-OH D: 32 ng/mL
- Thyroid hormone
  - TSH 4.20 abnl
- Stool analysis: low fecal elastase
- Solid Liquid Phase Gastric Emptying:
  (+) Gastroparesis

Immune/Inflammation

- Celiac panel (-)
- ANA 1:640, Anti-DNA (-),
- RF (-), Anti Sm

Gut Microbiome

- Stool analysis: Dysbiosis, Candida
- Breath Test: SIBO (H2)
- Stool O&P:
  - (+) *B. hominis*

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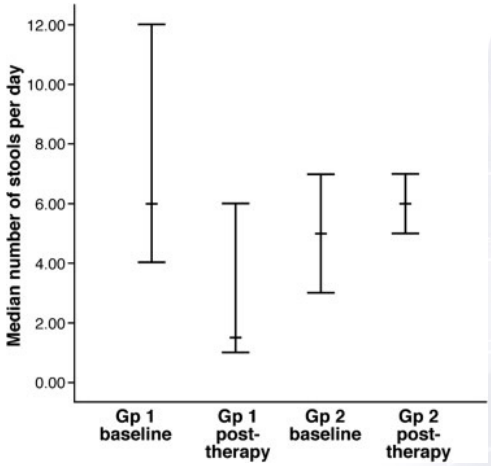
Median Daily Stool Frequency Before and After Enzyme Supplementation In Patients with IBS-D



Leeds JS, Hopper AD, Sidhu R, Simmonette A, Azadbakht N, Hoggard N, Morley S, Sanders DS. Some patients with irritable bowel syndrome may have exocrine pancreatic insufficiency. Clin Gastroenterol Hepatol. 2010 May;8(5):433-8.

Gp 1=enzyme
Gp2=placebo

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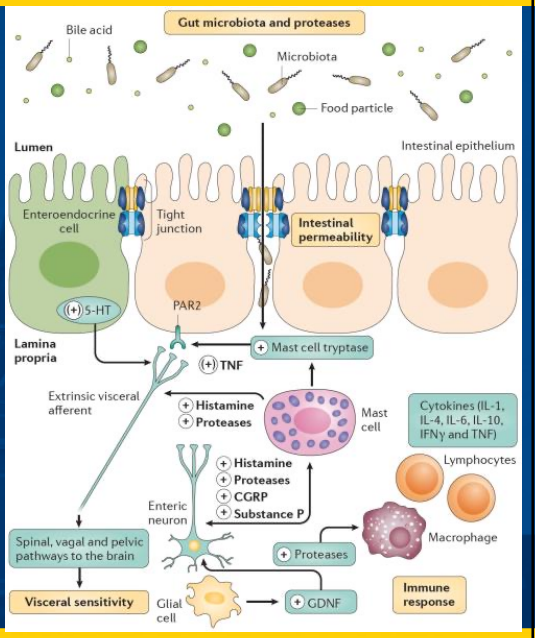
Possible Role of Mast Cells in the Pathophysiology of IBS

Enck P, Aziz Q, Barbara G, et al. Irritable bowel syndrome. Nature reviews Disease primers. 2016;2:16014. doi:10.1038/nrdp.2016.14.



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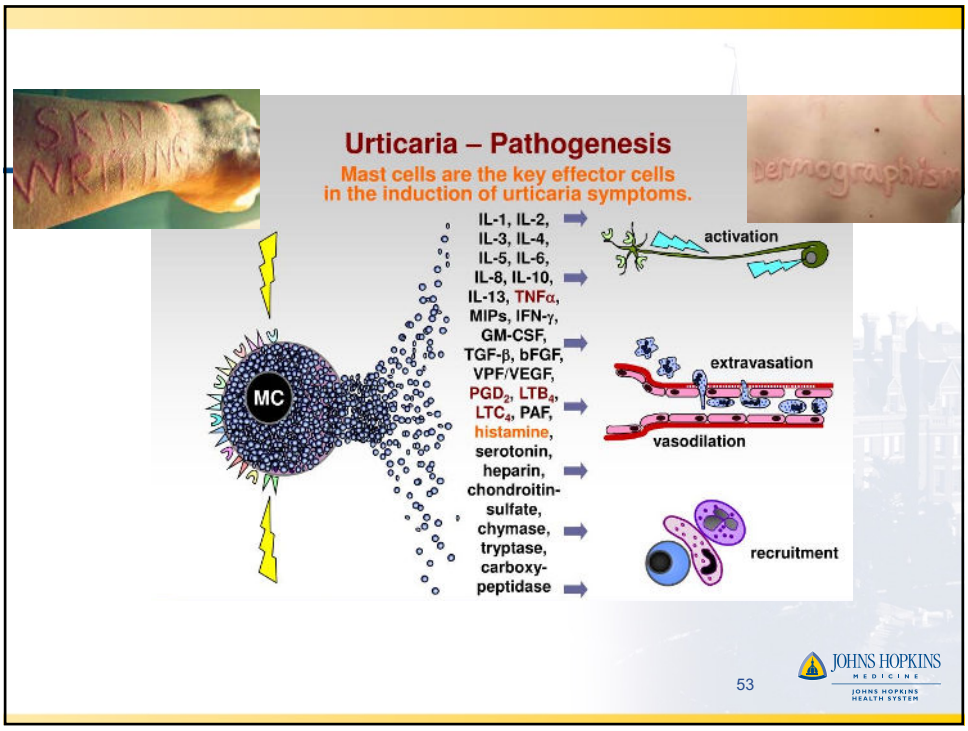
Urticaria – Pathogenesis
Mast cells are the key effector cells in the induction of urticaria symptoms.
MC
IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, IL-13, TNFα, MIPs, IFN-γ, GM-CSF, TGF-β, bFGF, VPF/VEGF, PGD2, LTB4, LTC4, PAF, histamine, serotonin, heparin, chondroitin-sulfate, chymase, tryptase, carboxy-peptidase
activation
extravasation
vasodilation
recruitment
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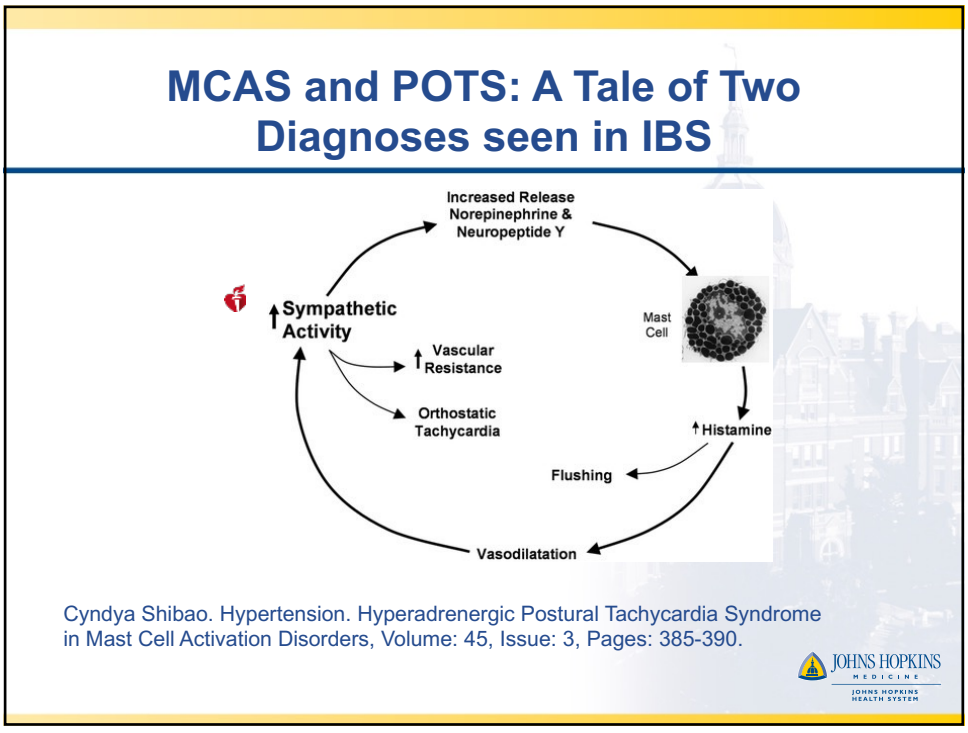
MCAS and POTS: A Tale of Two Diagnoses seen in IBS
Increased Release Norepinephrine & Neuropeptide Y
Sympathetic Activity
Vascular Resistance
Orthostatic Tachycardia
Mast Cell
Histamine
Flushing
Vasodilatation
Cyndya Shibao. Hypertension. Hyperadrenergic Postural Tachycardia Syndrome in Mast Cell Activation Disorders, Volume: 45, Issue: 3, Pages: 385-390.
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Bile Acid-Induced Diarrhea

Type 1

Ileal dysfunction/resection (**secondary** bile acid malabsorption):
Bile acid spillover into the colon.

Type 2

Idiopathic (**primary** bile acid malabsorption):
Impaired feedback leading to excessive bile acid synthesis

Type 3

Miscellaneous conditions-bile acid cycling, motility, etc.
Chronic pancreatitis
Microscopic colitis
Postcholecystectomy
Radiation enteritis
SIBO
Vagotomy, post-gastric surgery

Type 4

Congenital transport defect
Ileal bile acid transporter/apical sodium-dependent bile salt transporter

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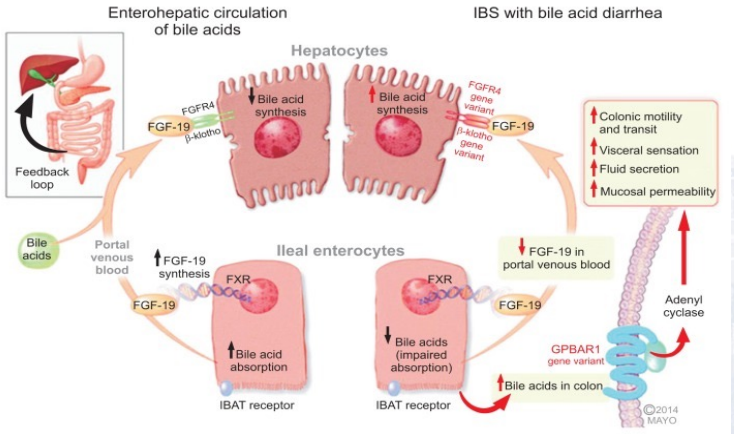
Enterohepatic Circulation and Bile Acid Diarrhea



Oduyebo I, Camilleri M. Bile acids: the emerging epidemic. Current Opinion in Gastroenterology, 01 May 2017, 33(3):189-195

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Tests for Bile Acid Malabsorption

- Quantitative fecal bile acid measurement
  - 48-hour stool collection, Mayo Clinic Labs
- Serum C4 (7 α-hydroxy-4-cholesten-3-one)(higher in Bile Acid Malabsorption) Mayo Clinic Labs
- Serum fibroblast growth factor-19 (lower in Bile Acid Malabsorption) Mayo Clinic Labs.

Schiller LR, Sellin JH. Chapter 16 Diarrhea. In Sleisenger & Fordtran's Gastrointestinal and Liver Disease : Pathophysiology, Diagnosis, Management. 11th Edition. Feldman M, Friedman FS, Brandt LJ Editors. Philadelphia :Elsevier, 2022.

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Summary of Findings

- Gastroparesis
- Dysbiosis (SIBO, parasite, etc.)
- Hypothyroidism
- Abnormal pancreatic function
- Mast cell activation syndrome
- Post-cholecystectomy bile acid diarrhea.

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What is Your Treatment Plan?

The 5 Rs

- Remove
- Replace
- Reinoculate
- Repair
- Rebalance

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Treatment Plan

- Acupuncture, Ginger for gastroparesis.
- Low FODMAP diet avoid high histamine foods.
- Herbs for dysbiosis [bacterial, parasitic].
- Glutamine short-term for gut repair.
- Enzymes for pancreatic insufficiency.
- Re-check thyroid after dysbiosis resolves.
- Bile acid binders.
- Multicomponent probiotic.

Patient improved on treatment!!

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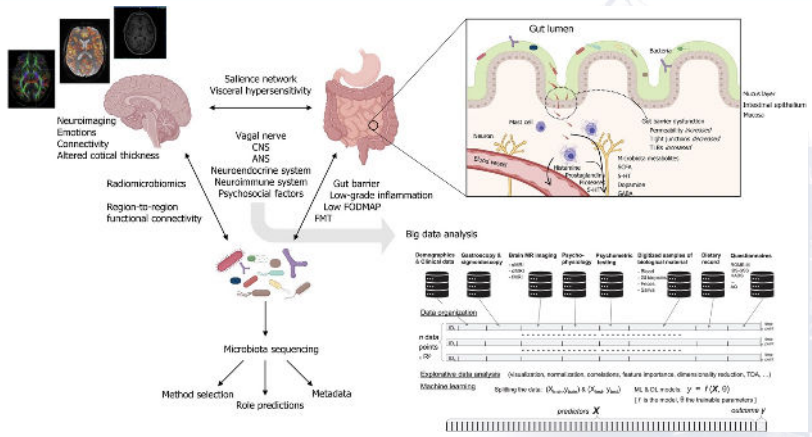
Integration of Multimodal and Interdisciplinary Approaches for Big Data Analysis in Irritable Bowel Syndrome



Hillestad EMR, van der Meeren A, Nagaraja BH, Bjørsvik BR, Haleem N, Benitez-Paez A, Sanz Y, Hausken T, Lied GA, Lundervold A, Berentsen B. Gut bless you: The microbiota-gut-brain axis in irritable bowel syndrome. *World J Gastroenterol* 2022; 28(4): 412-431.

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When Traveling Though the Tube……..

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Thank you!

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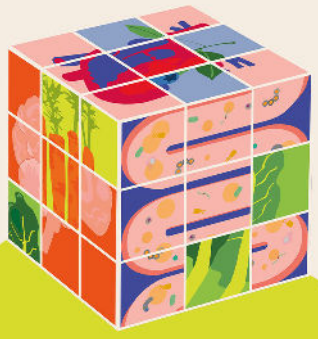
Microbiome, Gut & Systemic Health:

New Frontiers in Personalised Nutrition

NMI SUMMIT 2023

Friday 13th October

Featuring Dr. Gerard Mullin, Professor Glenn Gibson, Dr. Amrita Vijay, Justine Bold, Dr. Indra Barathan and Dr. Miguel Toribio-Mateas



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