The Role of SIBO and SIFO in the Irritable Bowel Syndrome (IBS) and Inflammatory Bowel Disease (IBD)

A4M METABOLIC INSTITUTE MODULE IV GASTROENTEROLOGY

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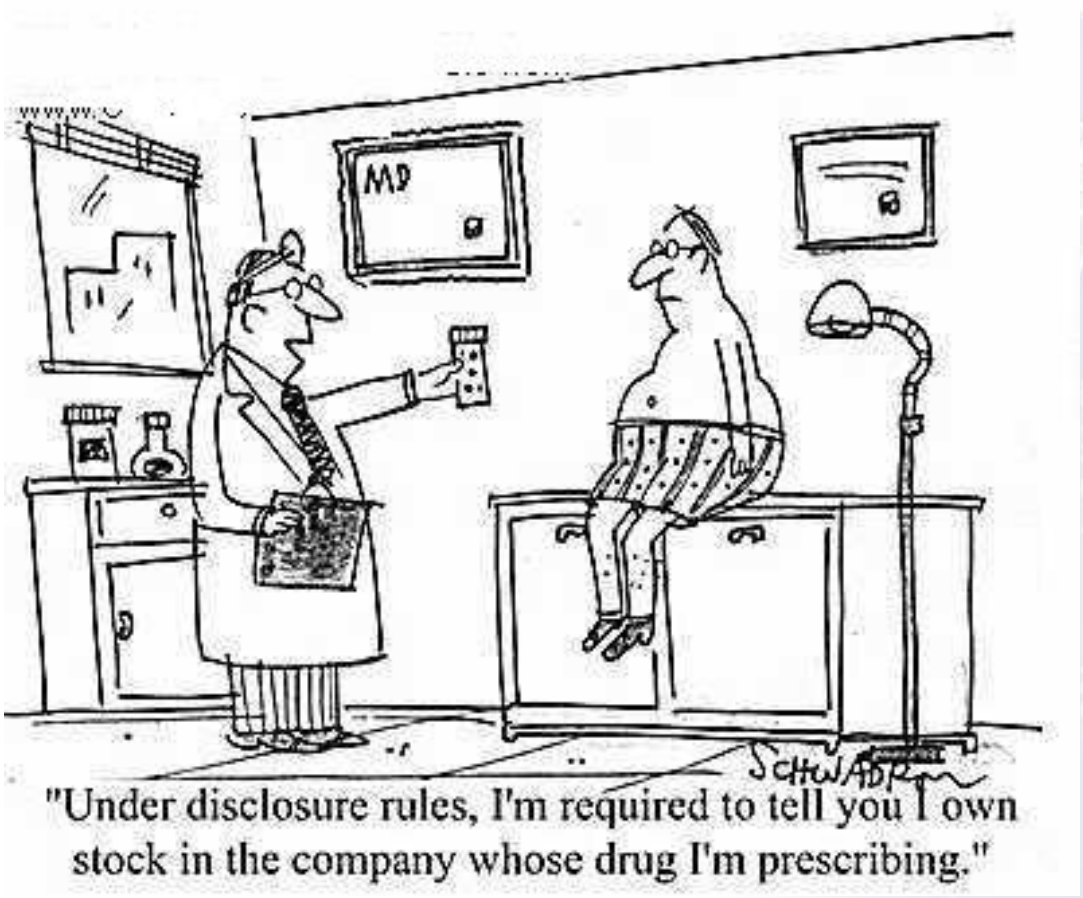

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Objectives

1. To discuss the pathophysiology of SIBO and SIFO in context to chronic disease.
2. To understand the dietary strategies used to evaluate and effectively manage SIBO and SIFO.
3. To become familiar with the evidence-based nutritional considerations for SIBO and SIFO.

Case Presentation

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

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 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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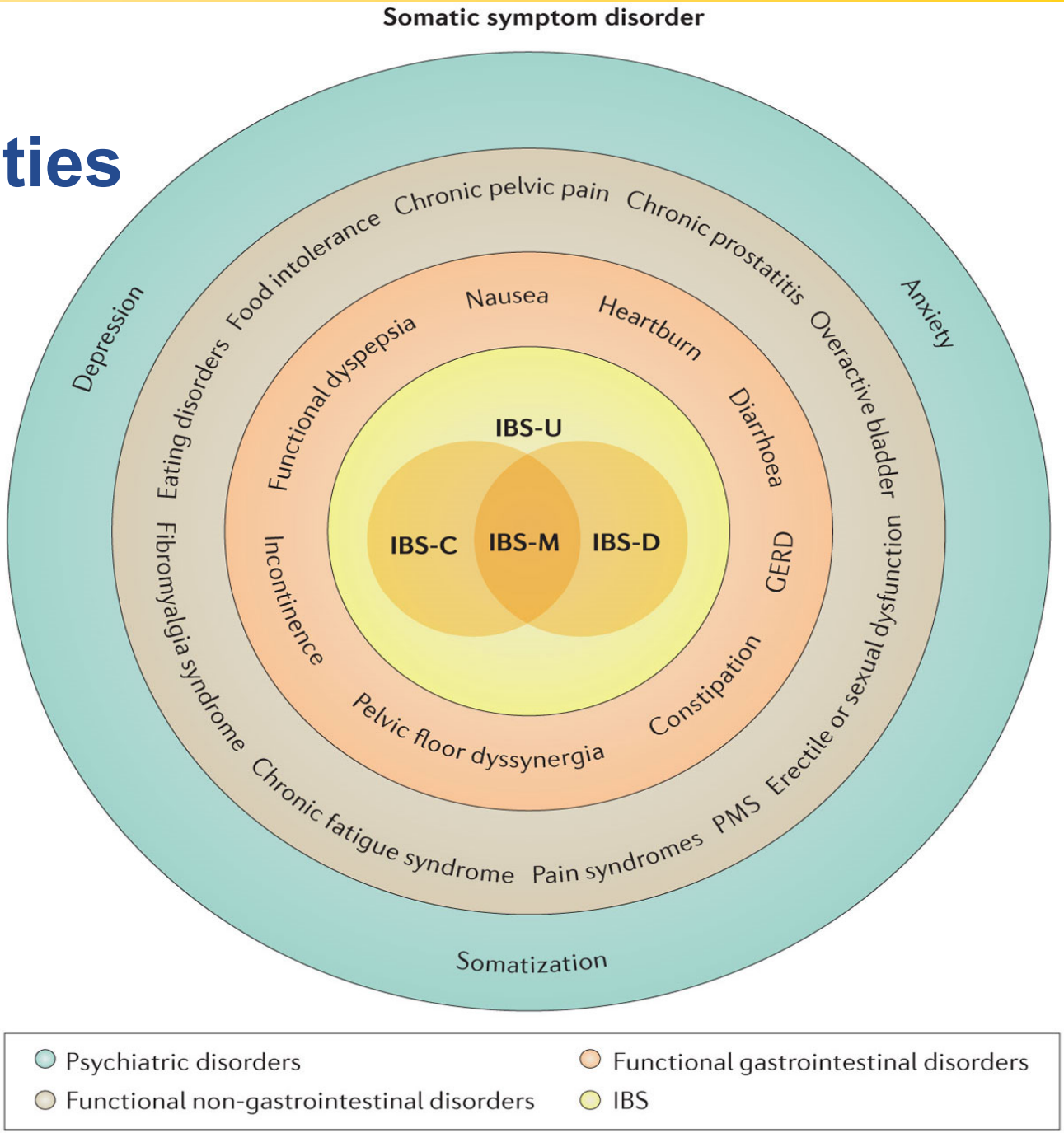
IBS-comorbidities



Nature Reviews | Disease Primers

Vulnerability or trigger factors

Psychosocial factors

Genetics

Food

Infection

Inflammation

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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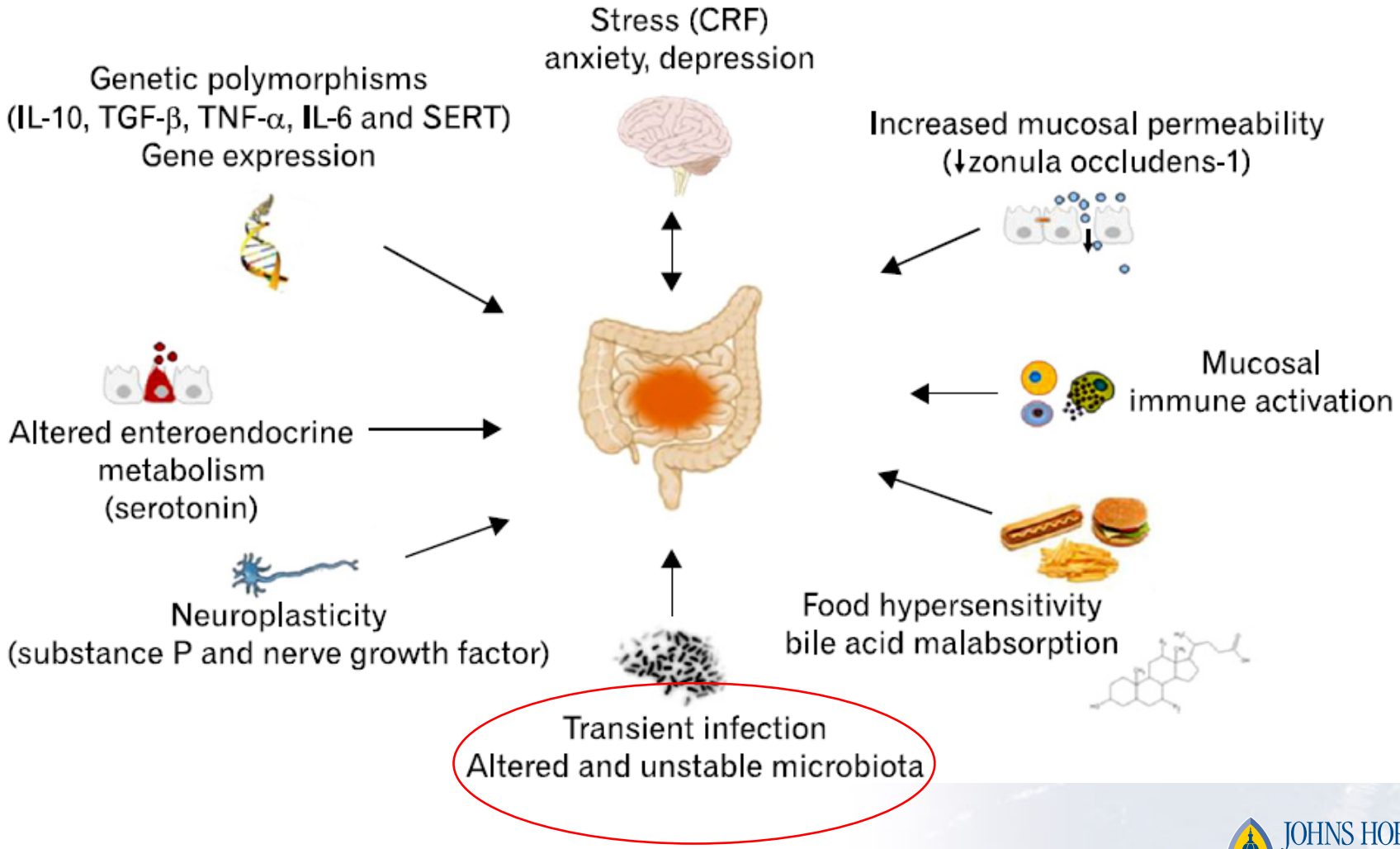
Pathophysiology of IBS



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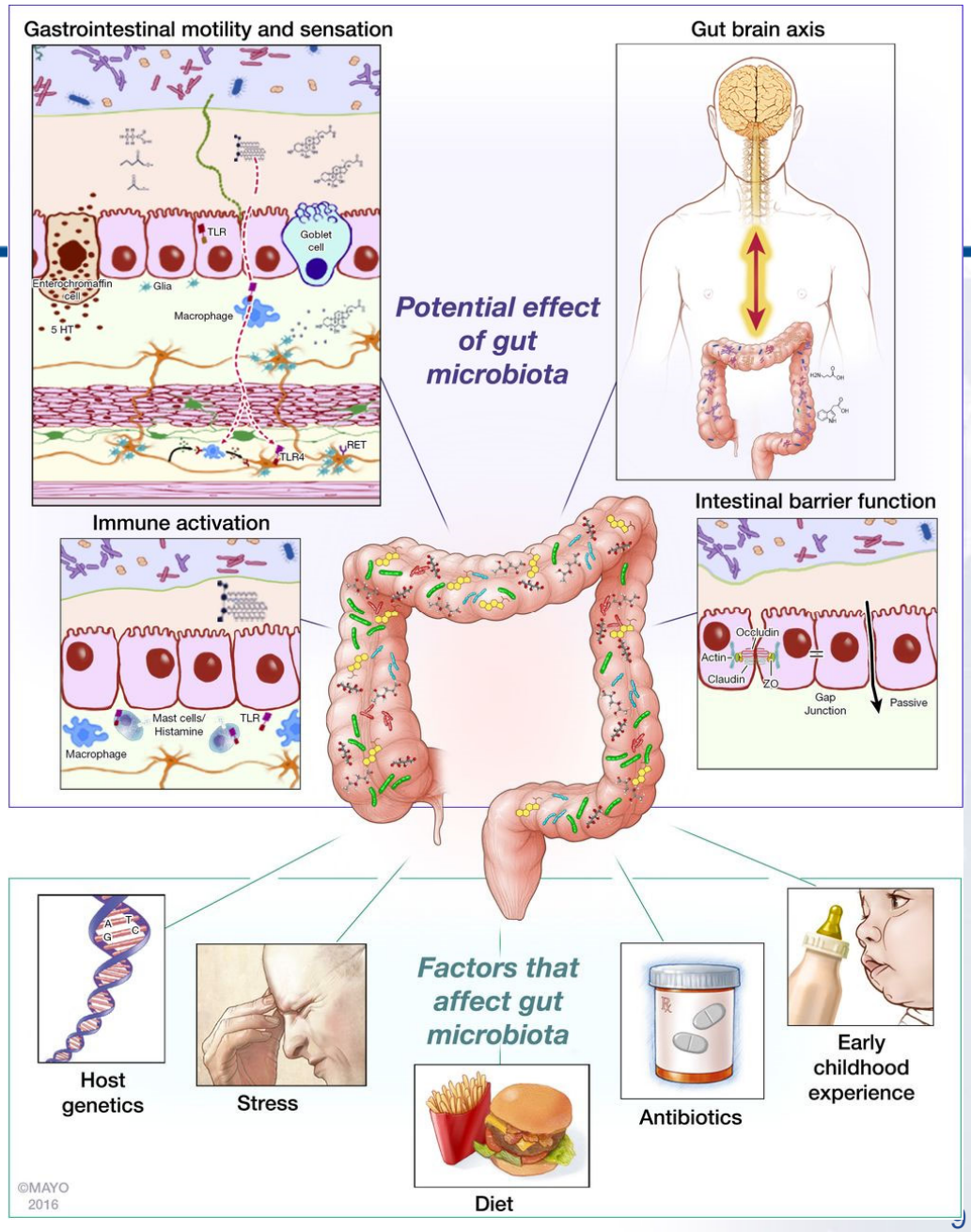

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Evidence to Support a Pivotal Role of Gut Microbiome in IBS

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

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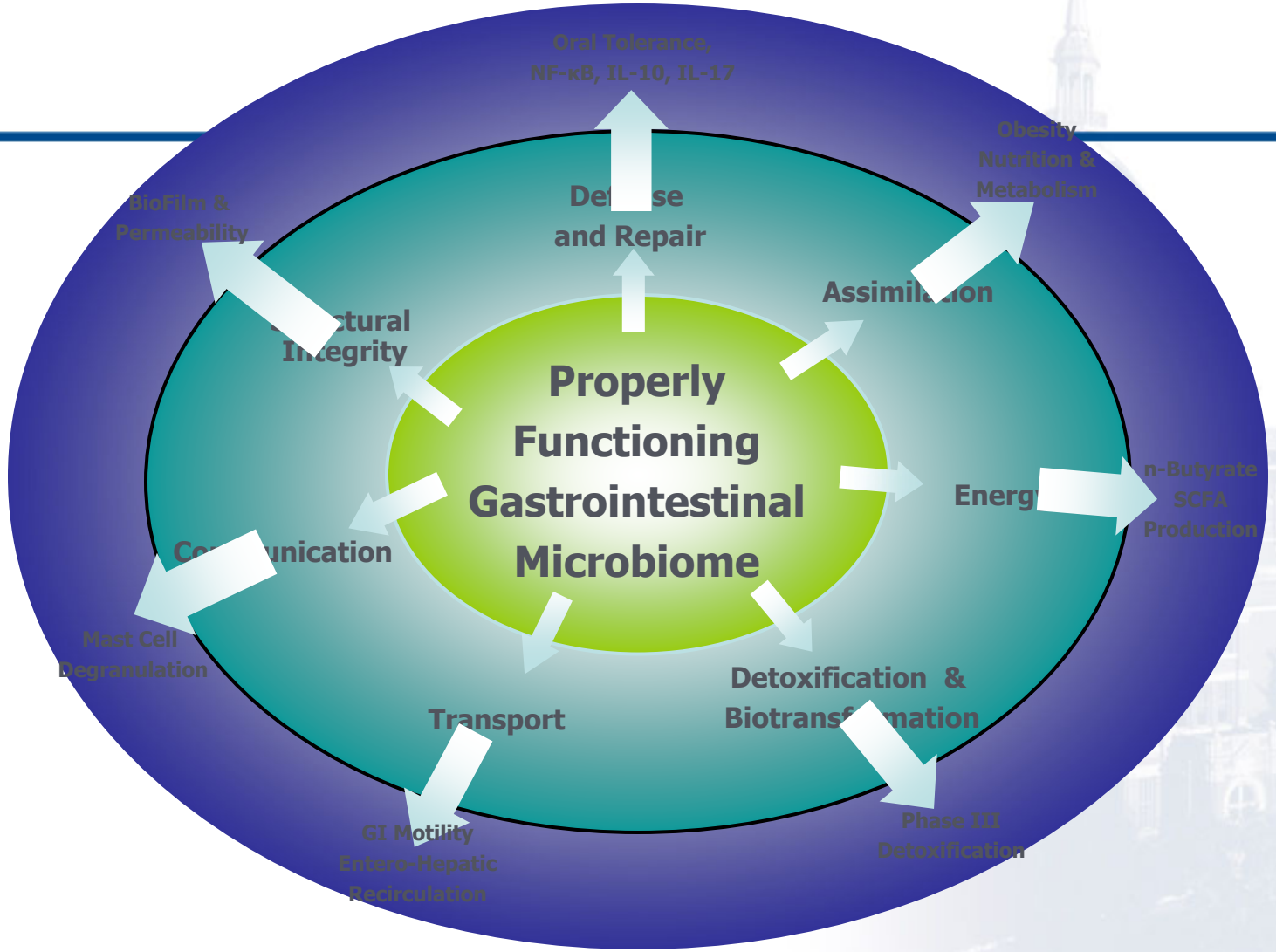

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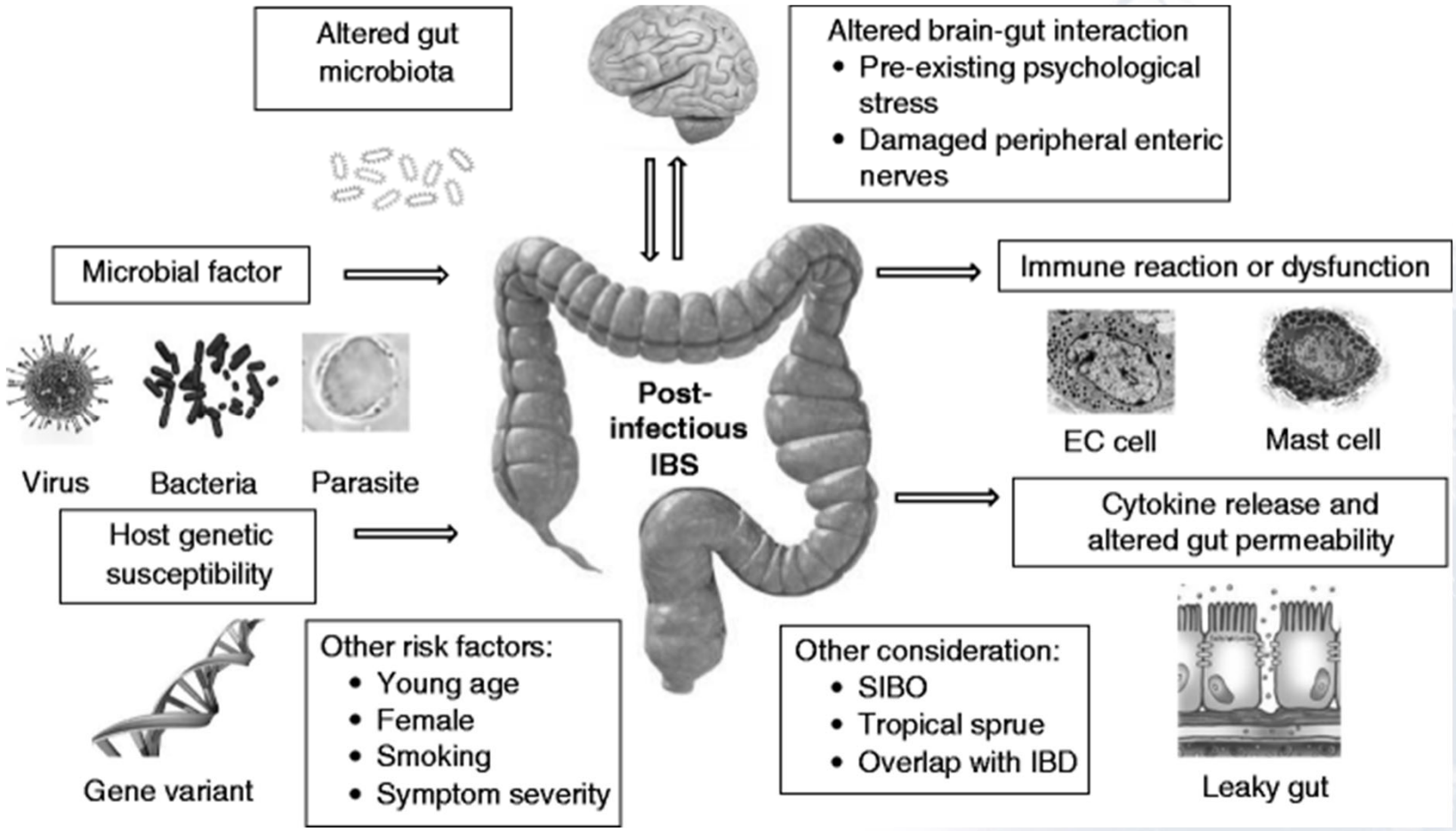
Post-Infectious IBS-D



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

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Evidence to Support a Pivotal Role of Gut Microbiome in IBS

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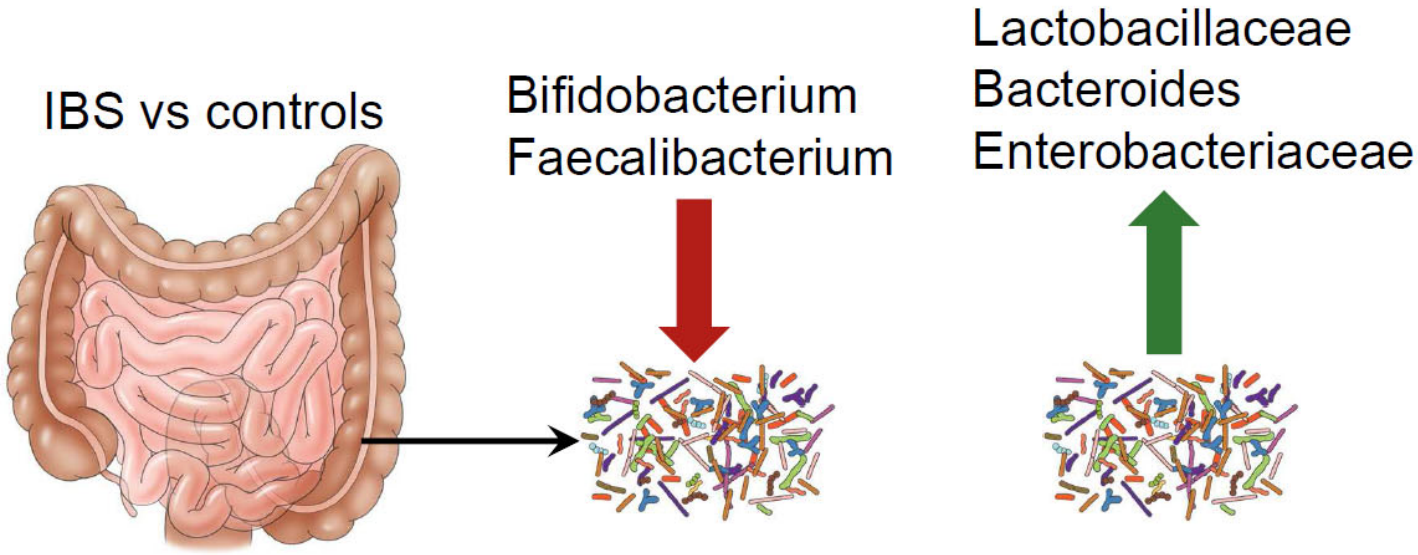
Microbial Dysbiosis in IBS



Gastroenterology

Gastroenterology. 2019 Mar 30. pii: S0016 5085(19)34649-9

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RESEARCH
Review

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

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*Authors share co-first authorship.

ABSTRACT

Background Irritable bowel syndrome (IBS) is the most common functional digestive condition in the industrialized world. The gut microbiota plays a key role in disease pathogenesis.

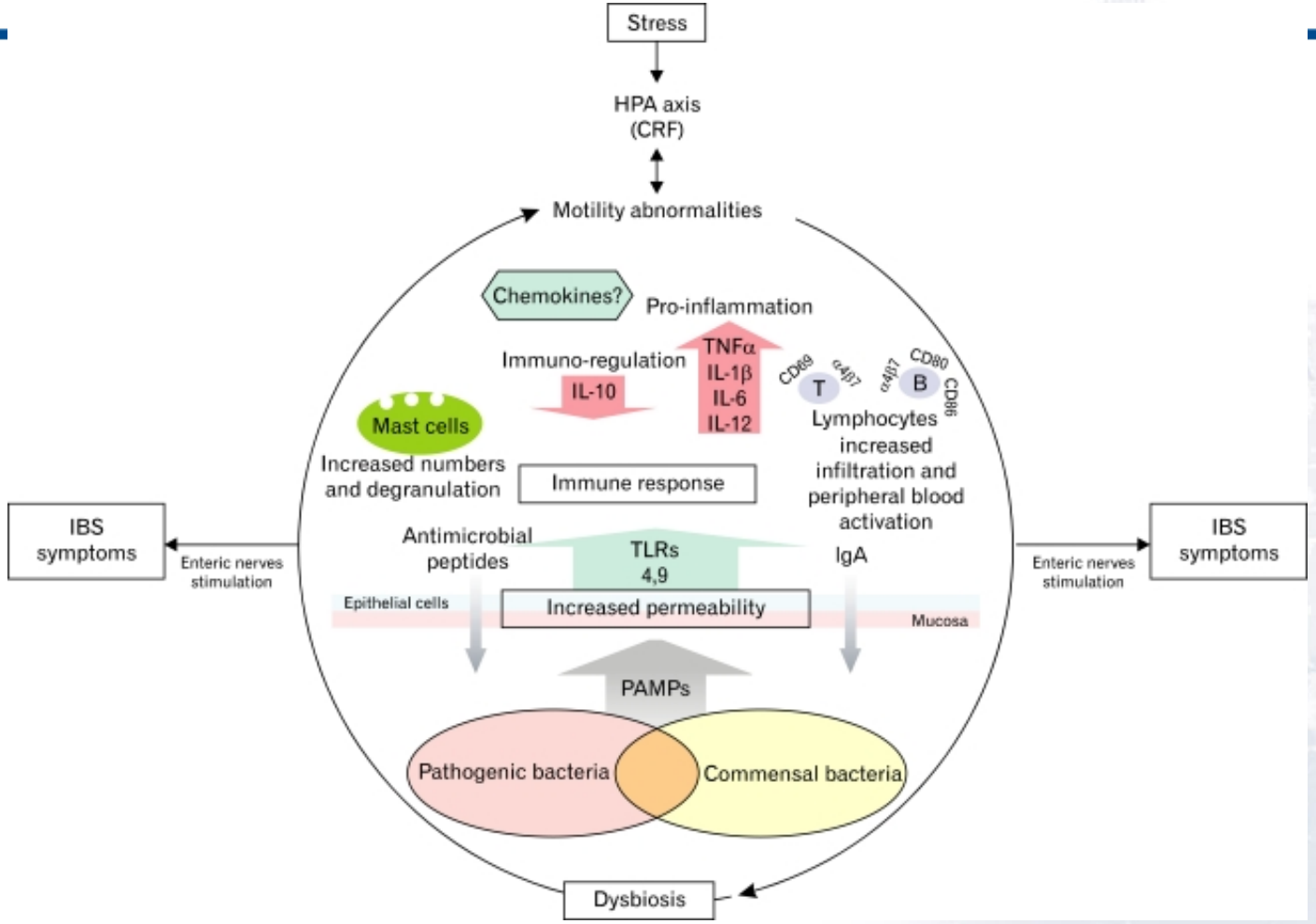
Objective A systematic review and meta-analysis on case–control studies was conducted to determine whether there is gut microbial dysbiosis in participants with IBS in comparison with healthy controls and, if so, whether the dysbiosis pattern differs among IBS subtypes and geographic regions.

Methods This review was conducted and reported according to the MOOSE (Meta-Analysis of Observational Studies in Epidemiology) 2000 and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2009 guidelines. Research articles published up to May 9, 2018 were identified through MEDLINE (PubMed), Cochrane Central Register of Controlled Trials (Cochrane Library), ClinicalTrials.gov, EMBASE, and Web of Science. Study quality was assessed using the Newcastle-Ottawa Scale. Case–control studies of participants with IBS who had undergone quantitative gut microbial stool analysis were included. The primary exposure measure of interest is $\log_{10}$ bacterial counts per gram of stool. Meta-analyses were performed to estimate the mean difference (MD) in gut microbiota between participants with IBS and healthy controls using the random-effects model with inverse variance in Revman 5.3 and R 3.5.1. Publication bias was assessed with funnel plots and Egger's test. Between-study heterogeneity was analyzed using Higgins I^2 statistic with 95% CIs.

Results There were 6,333 unique articles identified; 52 qualified for full-text screening. Of these, 23 studies were included for analysis (n=1,340 participants from North America, Europe, and Asia). Overall, the studies were moderate in quality. Comparing participants with IBS to healthy controls, lower fecal *Lactobacillus* (MD=−0.57 $\log_{10}$ colony-forming unit [CFU]/g; $P<0.01$) and *Bifidobacterium* (MD=−1.04 $\log_{10}$CFU/g; $P<0.01$), higher *Escherichia coli* (MD=0.60 $\log_{10}$CFU/g; $P<0.01$), and marginally higher *Enterobacter* (MD=0.74 $\log_{10}$CFU/g; $P=0.05$). No difference was found between participants with IBS and healthy controls in fecal *Bacteroides* and *Enterococcus* ($P=0.18$ and 0.68, respectively). Publication bias was not observed except in *Bifidobacterium* ($P=0.015$). Subgroup analyses on participants with diarrhea-predominant and constipation-predominant IBS showed consistent results with the primary results. A subgroup analysis of Chinese studies was consistent with the primary results, except for fecal *Bacteroides*, which was increased in participants with IBS vs healthy controls (MD=0.29; 95% CI 0.13 to 0.46; $P<0.01$). Although substantial heterogeneity was detected ($I^2>75\%$) in most comparisons, the direction of the effect estimates is relatively consistent across studies.

Conclusions IBS is characterized by gut microbial dysbiosis. Prospective, large-scale studies are needed to delineate how gut microbial profiles can be used to guide tar-

Summary: Dysbiosis in IBS



Journal of Neurogastroenterology and Motility. 16. 363-73. 10.5056/jnm.2010.16.4.363.

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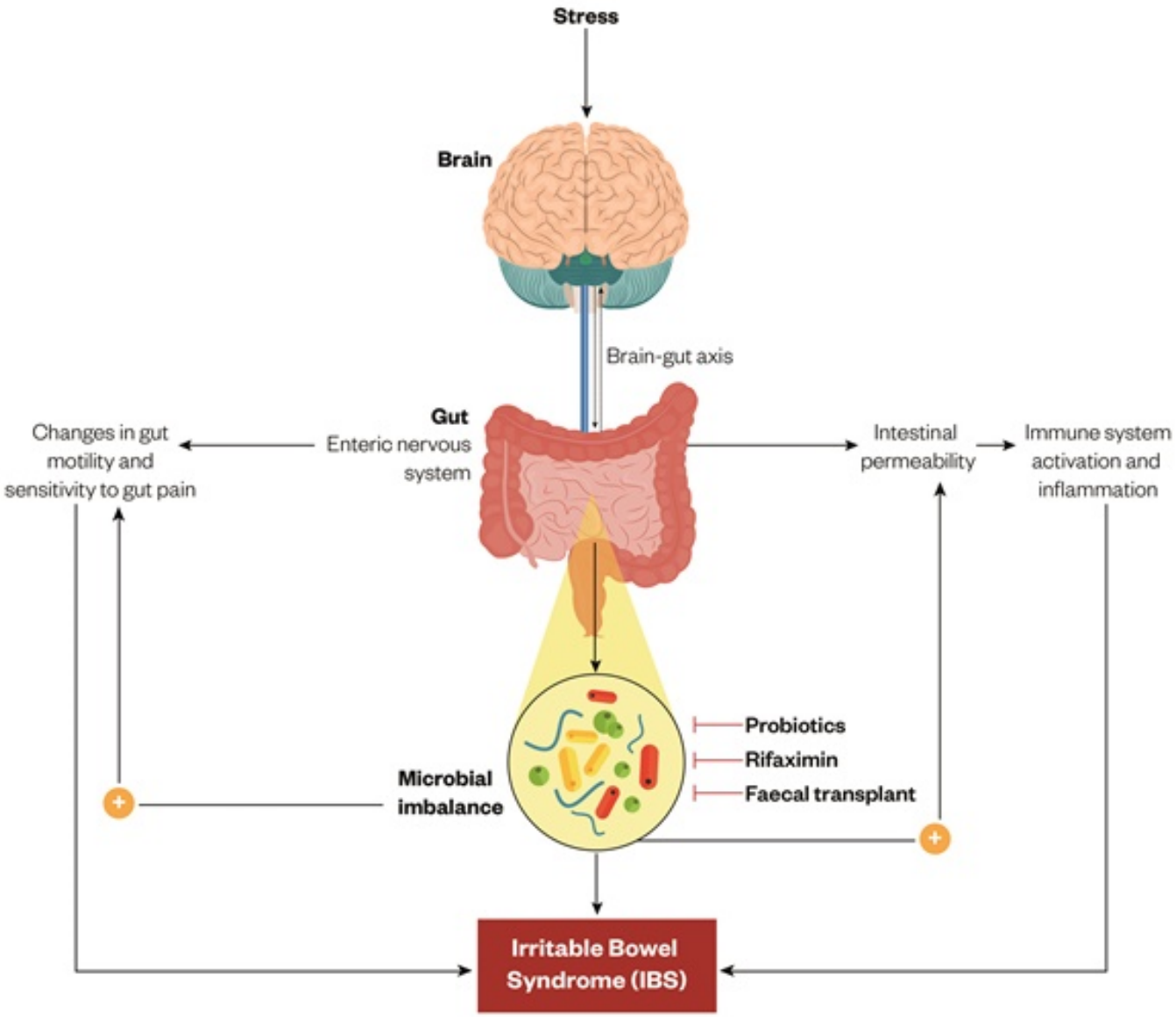

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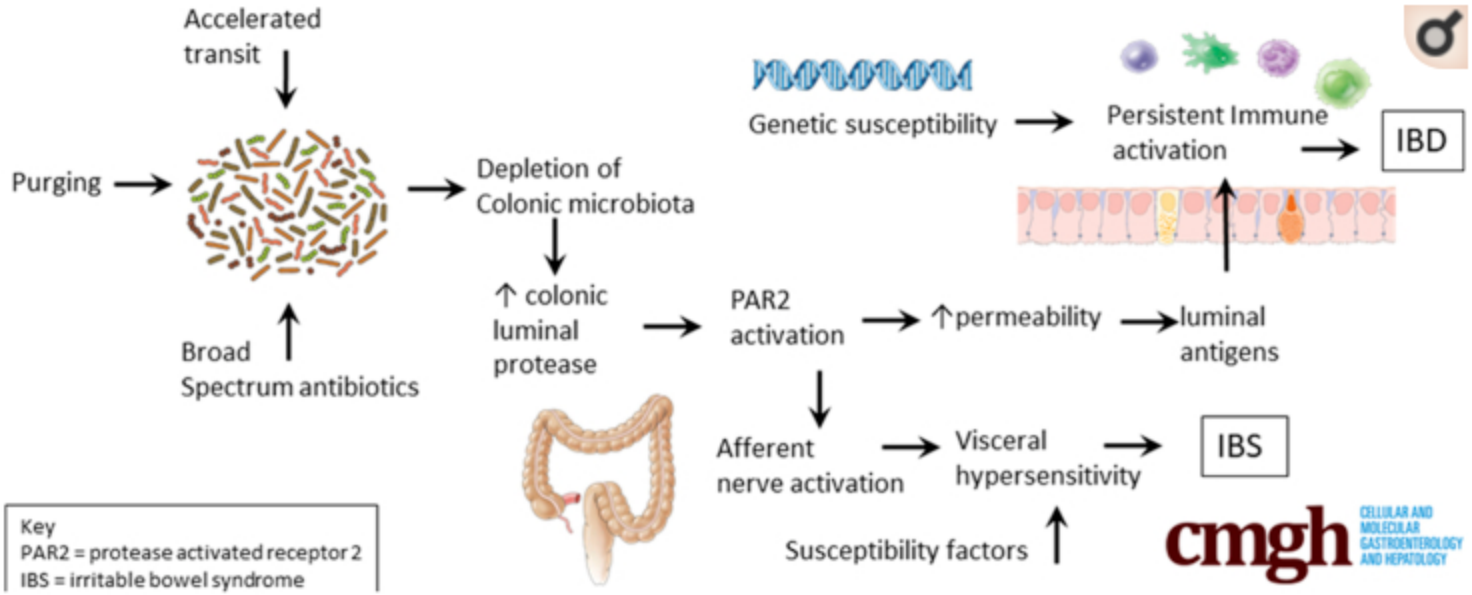
Antibiotics increase the risk of IBS-D

Supplemental Graphical Summary



Cell Mol Gastroenterol Hepatol. 2018; 6(3): 347–348.e1.
Published online 2018 Jul 11. doi: 10.1016/j.jcmgh.2018.06.005

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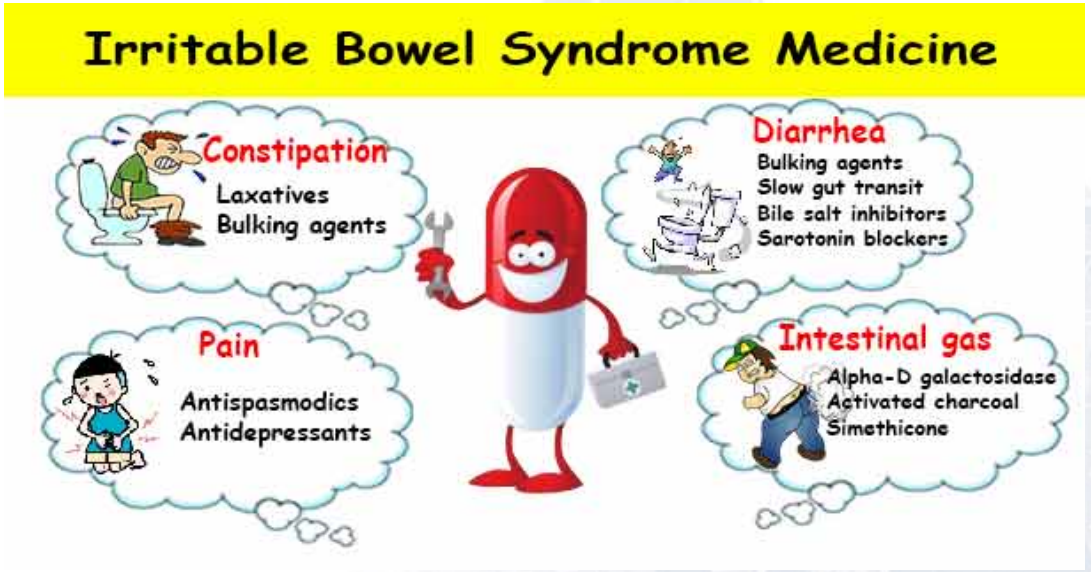
Therapies for IBS

- Stress-reduction
- *Diet-Microbiome*
- Medical Foods
- Herbals
- Nutraceuticals
- Enzymes



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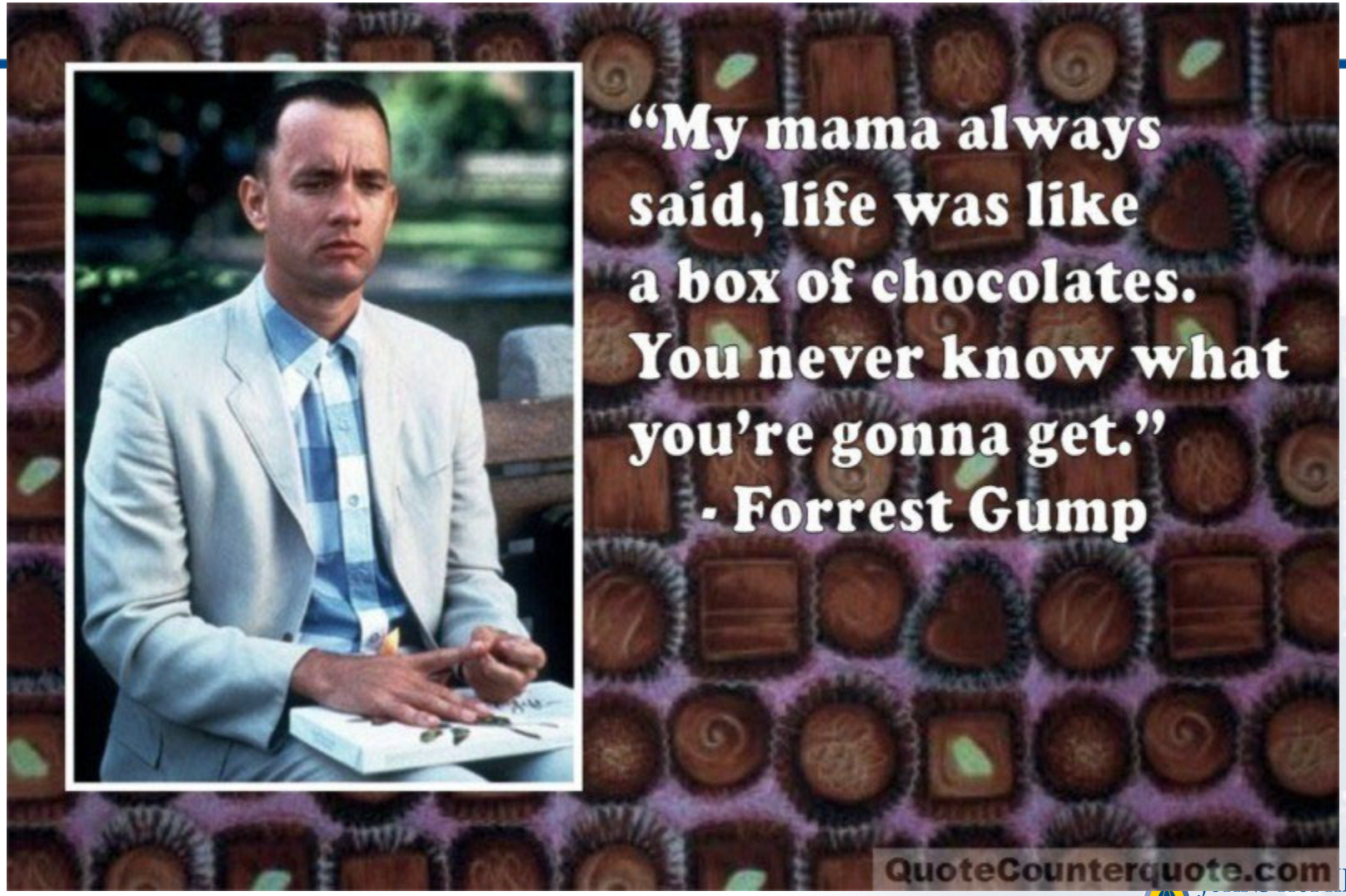
Probiotics in IBS



Systematic review with meta-analysis: the efficacy of prebiotics, probiotics, synbiotics and antibiotics in irritable bowel syndrome

Results: The search identified 4017 citations. Data for prebiotics and synbiotics were sparse. Fifty-three RCTs of probiotics, involving 5545 patients, were eligible. Particular combinations of probiotics, or specific species and strains, appeared to have beneficial effects on global IBS symptoms and abdominal pain, but it was not possible to draw definitive conclusions about their efficacy. There were five trials of similar design that used rifaximin in non-constipated IBS patients, which was more effective than placebo (RR of symptoms persisting = 0.84; 95% CI 0.79-0.90). Adverse events were no more common with probiotics or antibiotics.

Conclusions: Which particular combination, species or strains of probiotics are effective for IBS remains, for the most part, unclear. Rifaximin has modest efficacy in improving symptoms in non-constipated IBS.

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Conclusions from Ford et al. Study

- Combination probiotics reduces risk of persistent IBS symptoms, improves global IBS symptoms, abdominal pain, flatulence and a strong trend towards improving bloating.
- *L. plantarum* DSM 9843, *E. coli* DSM17252, and *S. faecium* improved global symptoms.
- Rifaximin decrease the risk of persistent IBS symptoms (NNT=11) but not in those w/ prior response.

Ford AJ et al. Am J Gastroenterol (2018) 113:1–18.

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Sept. 26, 2018

AGA's interpretation of the latest probiotics research

The AGA Center for Gut Microbiome Research and Education responds to new probiotics research.

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- Post-infectious IBS
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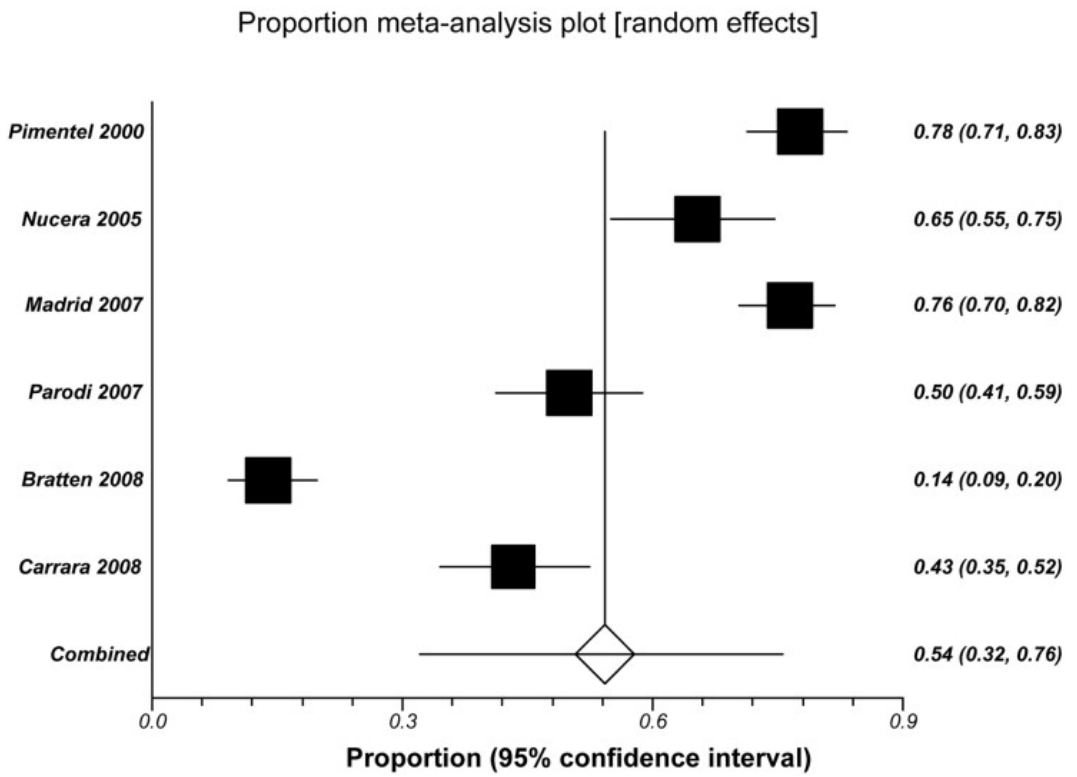
Relationship of SIBO to IBS



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. doi: 10.1016/j.cgh.2009.06.031. Epub 2009 Aug 12.

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What is SIBO?

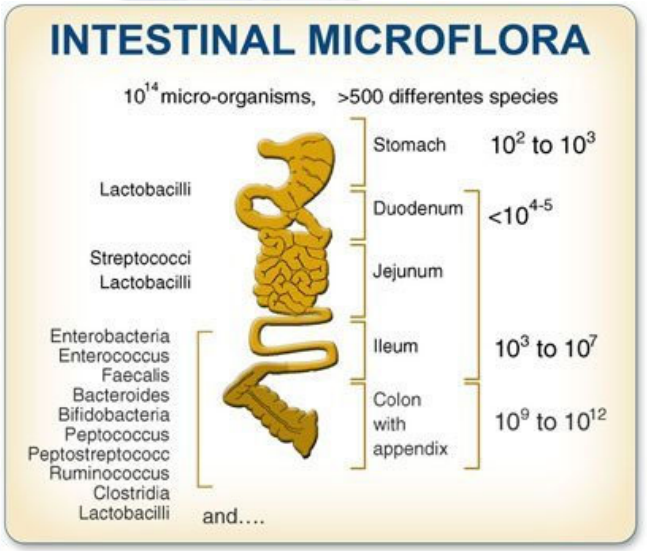
SMALL INTESTINAL BACTERIAL OVERGROWTH (SIBO)

SIBO refers to a condition in which:

- Abnormally **large numbers of bacteria** (at least 10,000 bacteria per ml of duodenal aspirate) are present **in the small intestine**

- AND -

- Decreased Biodiversity



1. Quigley, E.M.M. The Spectrum of Small Intestinal Bacterial Overgrowth (SIBO). Curr Gastroenterol Rep 21, 3 (2019). https://doi.org/10.1007/s11894-019-0671-z
2. Pimentel M, Saad RJ, Long MD, Rao SSC. ACG Clinical Guideline: Small Intestinal Bacterial Overgrowth. *Am J Gastroenterol*. 2020;115(2):165-178. doi:10.14309/ajg.0000000000000501

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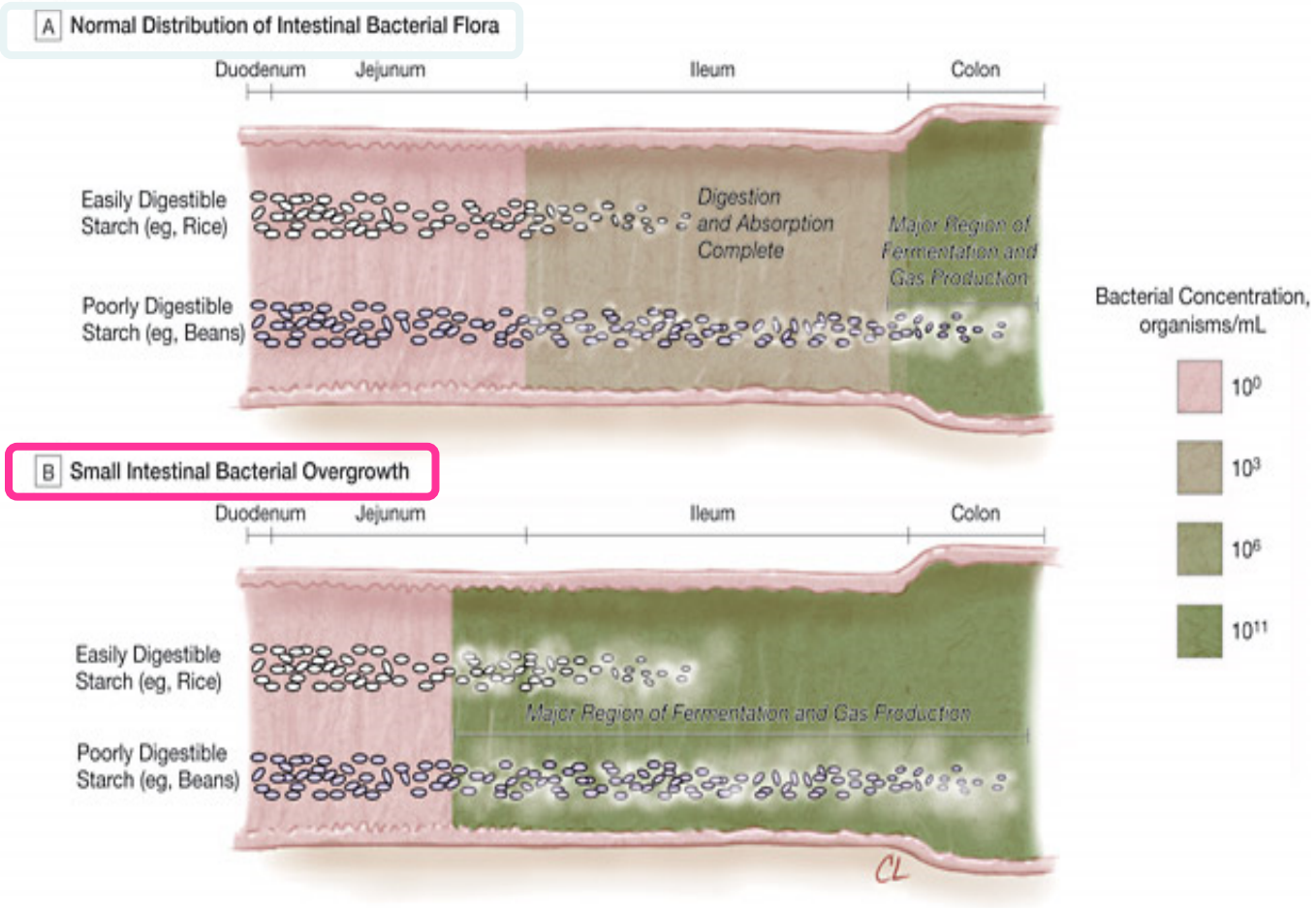
Distribution of Intestinal Bacterial Flora in Normal Gut and in SIBO



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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Clinical Features of SIBO

SIBO can lead to small intestinal inflammation, maldigestion, malabsorption, and other extraintestinal symptoms:

- Gas-bloat
- Flatulence
- Abdominal discomfort
- Diarrhea
- Steatorrhea
- Weight loss
- Symptoms from micronutrient deficiencies
  - Vitamins B12, A, D, E, K, iron, thiamine, niacin

1. Quigley, E.M.M. The Spectrum of Small Intestinal Bacterial Overgrowth (SIBO). Curr Gastroenterol Rep 21, 3 (2019). https://doi.org/10.1007/s11894-019-0671-z
2. Rasmussen, Jamie MS; Duriancik, David M. PhD Management of Small Intestinal Bacterial Overgrowth in Adult Patients, Gastroenterology Nursing: May/June 2019 - Volume 42 - Issue 3 - p 269-276 doi: 10.1097/SGA.0000000000000369

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SIBO: An Overlooked Contributor to Some Common Disorders

IBS

- **78%** of patients tested positive
- 48% of successfully treated patients no longer met Rome criteria for IBS

Fibromyalgia and CFIDS

- **78% and 77%** of subjects, respectively, have SIBO
- Both disorders overlap

Pimentel M, Chow EJ, Lin HC: Eradication of small intestinal bacterial overgrowth reduces symptoms of irritable bowel syndrome. *Am J Gastroenterol* 95:3503-3506, 2000)

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Pathogenesis of SIBO

- Abnormalities in the following:
  - Salivary IgA
  - Gastric acid
  - Duodenal bile
  - Abnormal GI motility
  - Secretory IgA
  - Paneth cell & defensing
  - Ileocecal valve

- Factors associated with SIBO:
  - Female gender
  - Old age
  - IBS-D
  - Marked bloating & flatulence
  - PPI & narcotic intake
  - Low hemoglobin

Ghoshal UC, Shukla R, Ghoshal U. Small Intestinal Bacterial Overgrowth and Irritable Bowel Syndrome: A Bridge between Functional Organic Disorders. Gut Liver. 2017;11(2):196-208. doi:10.5009/gnl16126.

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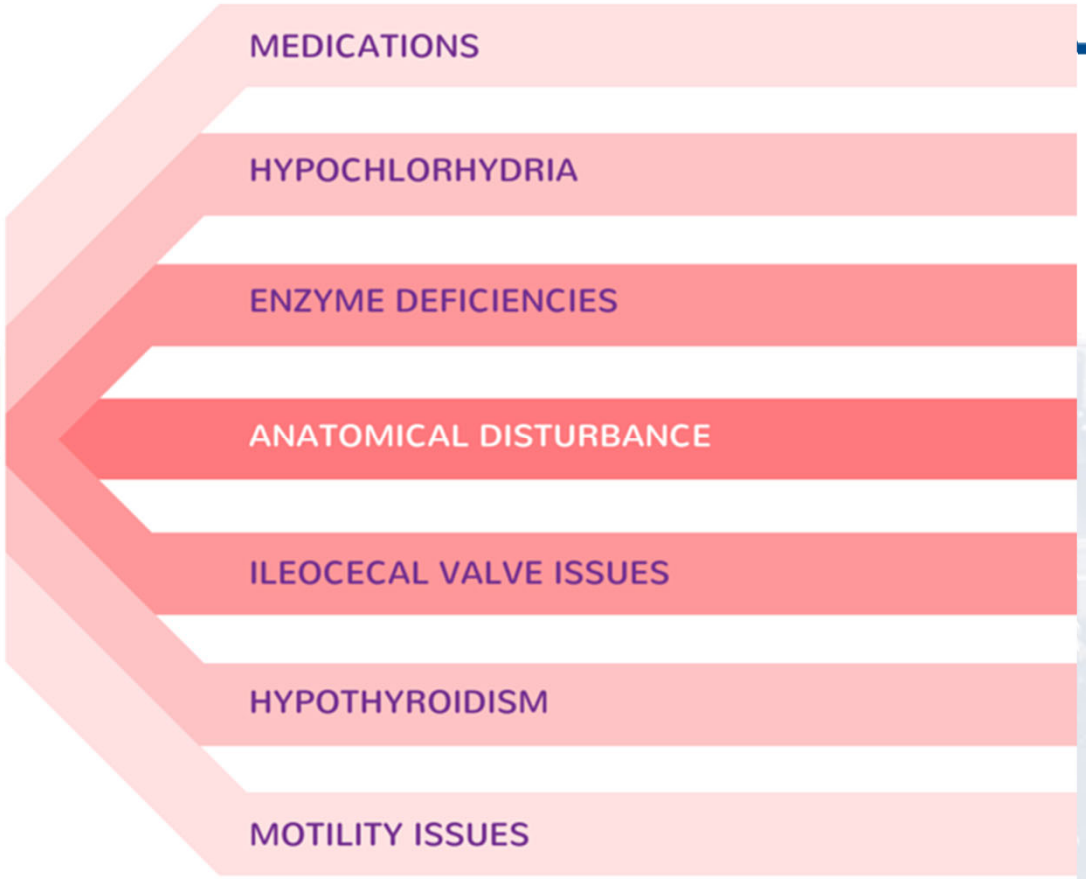
SIBO CAUSES



http://endsibo.com/what-causes-sibo/

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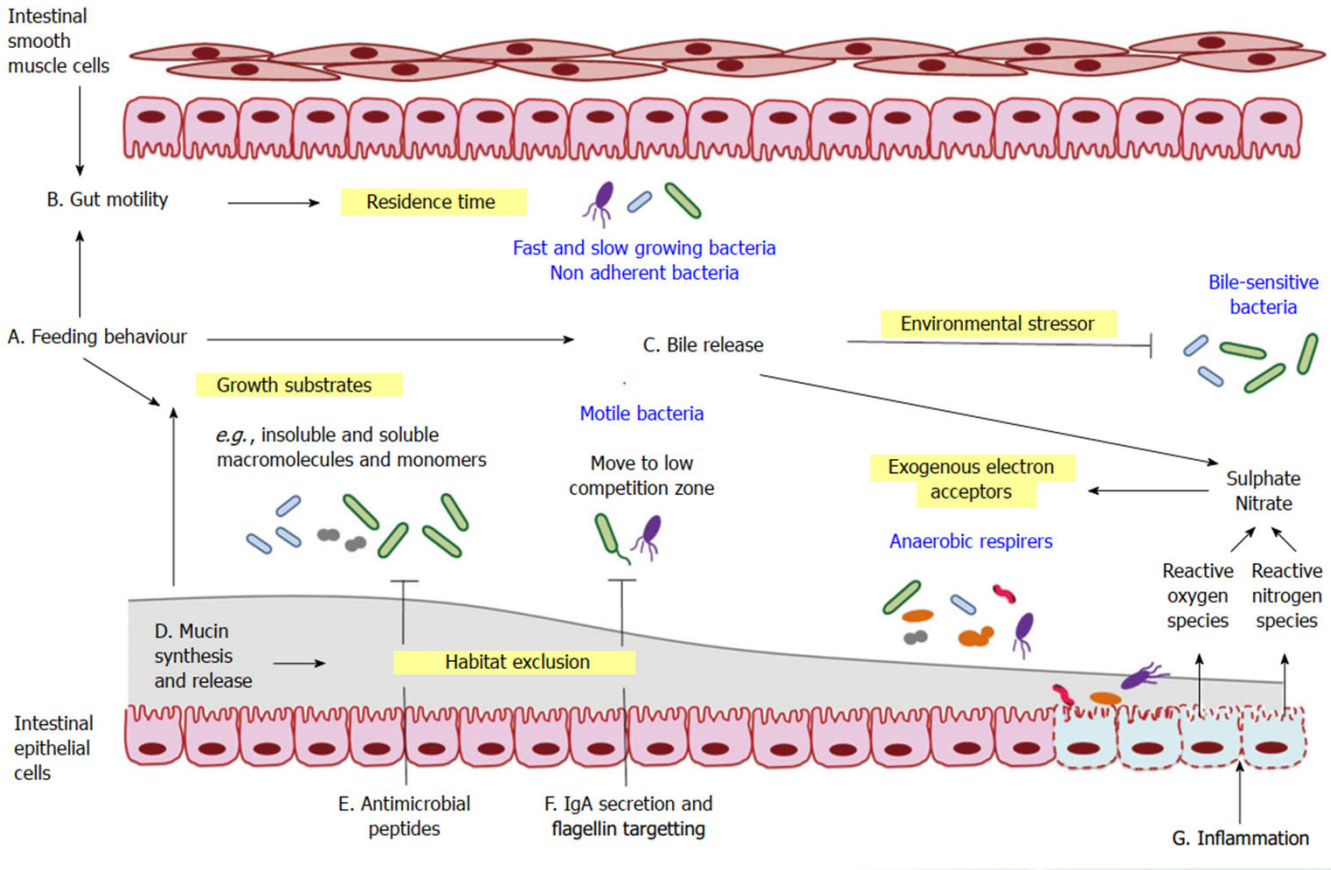
Multiple host-mediated mechanisms regulate bacterial growth and their activities.



World J Gastroenterol 2014 November 28; 20(44): 16498-16517

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What can we learn about SIBO using a wireless motility capsule (WMC)?

Studied consecutive patients referred for wireless motility capsule (WMC) and lactulose hydrogen breath testing (LBT) at the Johns Hopkins Center for Neurogastroenterology:

- All patients had symptoms suggestive of SIBO including:
  - Abdominal pain
  - Abdominal bloating & distention
  - Nausea/vomiting
  - Flatulence
  - Weight loss
- 34 patients identified who underwent both tests

Chander Roland et al, **Low Ileocecal Valve Pressure Associated with SIBO**, Dig Dis Sci. 2014 Jun; 59(6)
Chander Roland et al, **Small intestinal transit time is Prolonged in Small Intestinal Bacterial Overgrowth**, J Clin Gastroenterol. 2015

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Measurements and Methods

- Motility parameters calculated per standard WMC criteria:
  - Small bowel transit time (SBTT)
  - Additional transit times: Gastric emptying time (GET), colonic transit time (CTT), whole gut transit time (WGTT)
  - Gastric and small bowel pH

- Novel WMC metric: Ileocecal junctional pressures (ICJP)
  - Surrogate marker for ileocecal valve function

- Normative data developed using results of WMC testing in healthy controls, as previously published (2007)
- Patients on chronic acid suppressive therapy *excluded* from pH analyses
- All WMC studies interpreted by a single, blinded reader

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Small Bowel Transit Time (SBTT) is Prolonged in SIBO

- SBTT significantly longer in LBT-positive vs. LBT-negative patients [6.59 vs. 4.19 hr, p=0.04]
- SBTT significantly longer in LBT-positive vs. healthy controls [6.59 vs. 4.23 hr, p=0.03]
- Using manufacturer's recommended cut-off (6 hours), significantly lower percentage of LBT- positive patients (52.3%, p=0.02) fell within normal SBTT vs. LBT-negative patients (95.3%, p<0.01) and healthy controls (89.13%; p<0.01)

Chander Roland et al, **Small intestinal transit time is Prolonged in Small Intestinal Bacterial Overgrowth (SIBO)**; J Clin Gastroenterol. 2015

Higher Intestinal pH is associated with SIBO

- Gastric pH significantly higher in LBT-positive vs LBT-negative [2.76 vs. 1.63, p=0.01]
- Gastric pH significantly higher in LBT-positive vs healthy controls [2.76 vs. 1.18, p<0.01]
- Small bowel pH higher in LBT-positive vs LBT-negative individuals [7.19 vs. 6.65, *p=0.08**

Chander Roland et al, **Small intestinal transit time is Prolonged in Small Intestinal Bacterial Overgrowth (SIBO)**; J Clin Gastroenterol. 2015

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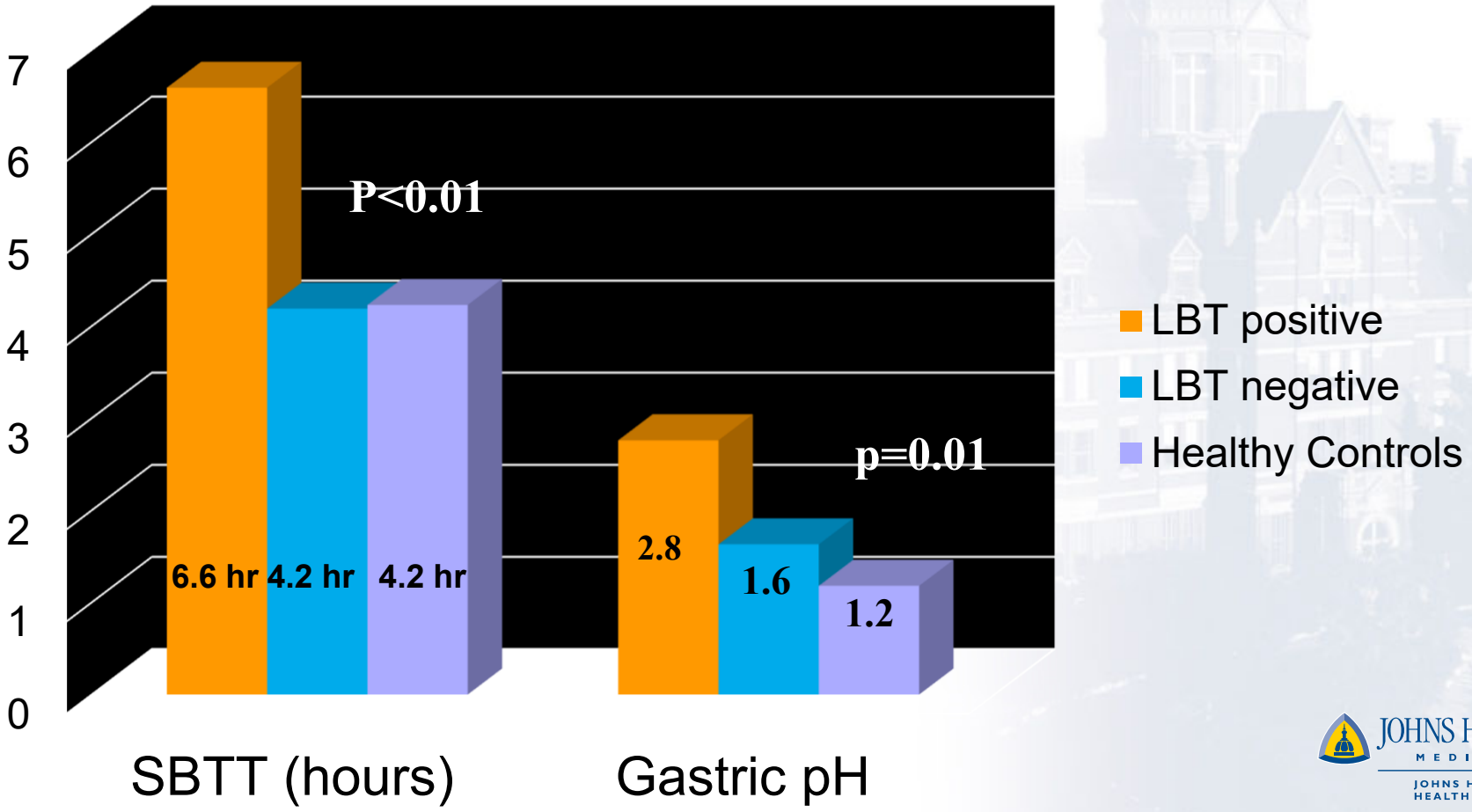
Prolonged SBTT and higher gastric pH in SIBO



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Novel parameter: Ileocecal valve

- Relatively unexplored sphincter in the GI tract
- Hypothesized to protect against SIBO development
- Prior attempts to study valve constrained by technical issues associated with manometry & sedation
- Subjects underwent colonoscopy with manometric ICV measurements after cecal distention: LBT + patients failed to increase ICV pressure but appropriate increase observed in LBT - subjects

Chander Roland et al, **Low Ileocecal Valve Pressure Associated with SIBO**, Dig Dis Sci. 2014 Jun; 59(6)

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Novel parameter: IC valve

- New WMC metric: Ileocecal junctional pressures (ICJP)
- Novel method to measure ICJP, a surrogate marker for ICV pressure
  - Based on time stamping characteristic pH drop as capsule exits the ileum into the cecum with identification of highest peak pressure during a 4-min window prior to the pH drop
  - Offers a simple and non-invasive method

Chander Roland et al, **Low Ileocecal Valve Pressure Associated with SIBO**, Dig Dis Sci. 2014 Jun; 59(6)

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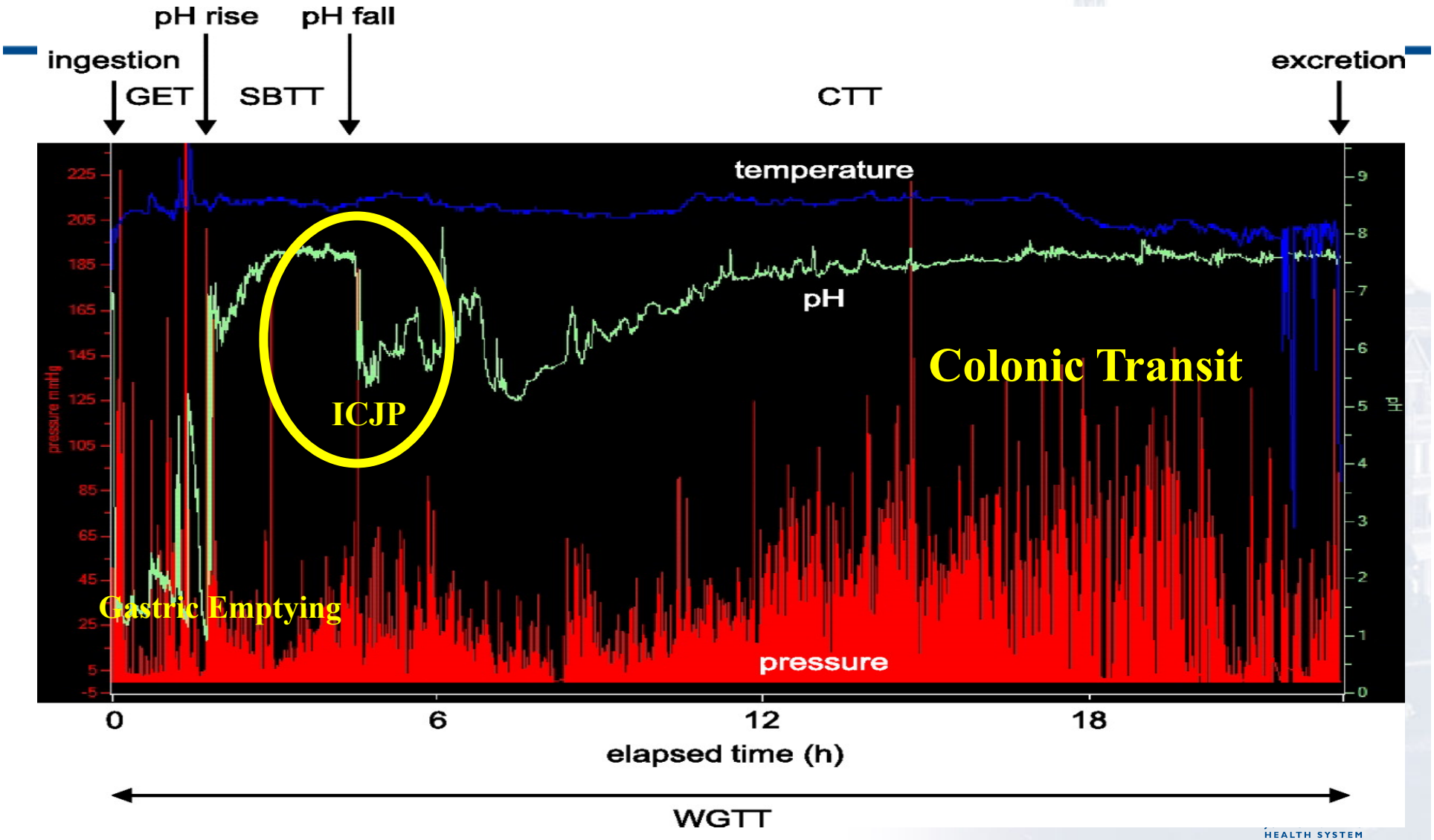
Wireless Motility Capsule Analysis



Ileocecal-junctional Pressures (ICJP) are Hypotensive in SIBO

- ICJP significantly lower in LBT positive vs negative patients [45.07 vs 79.88 mmHg, p<0.01]
- ICJP significantly lower in LBT positive vs historical healthy controls [45.07 vs. 61.47 mmHg, p=0.02]
- After calculating normal cutoffs based on healthy control data, 66.7% of LBT positive had ICJP below the lower limit of normal cutoff vs 0% in LBT negative (p<0.01)

Chander Roland et al, **Low Ileocecal Valve Pressure Associated with SIBO**, Dig Dis Sci. 2014 Jun; 59(6)

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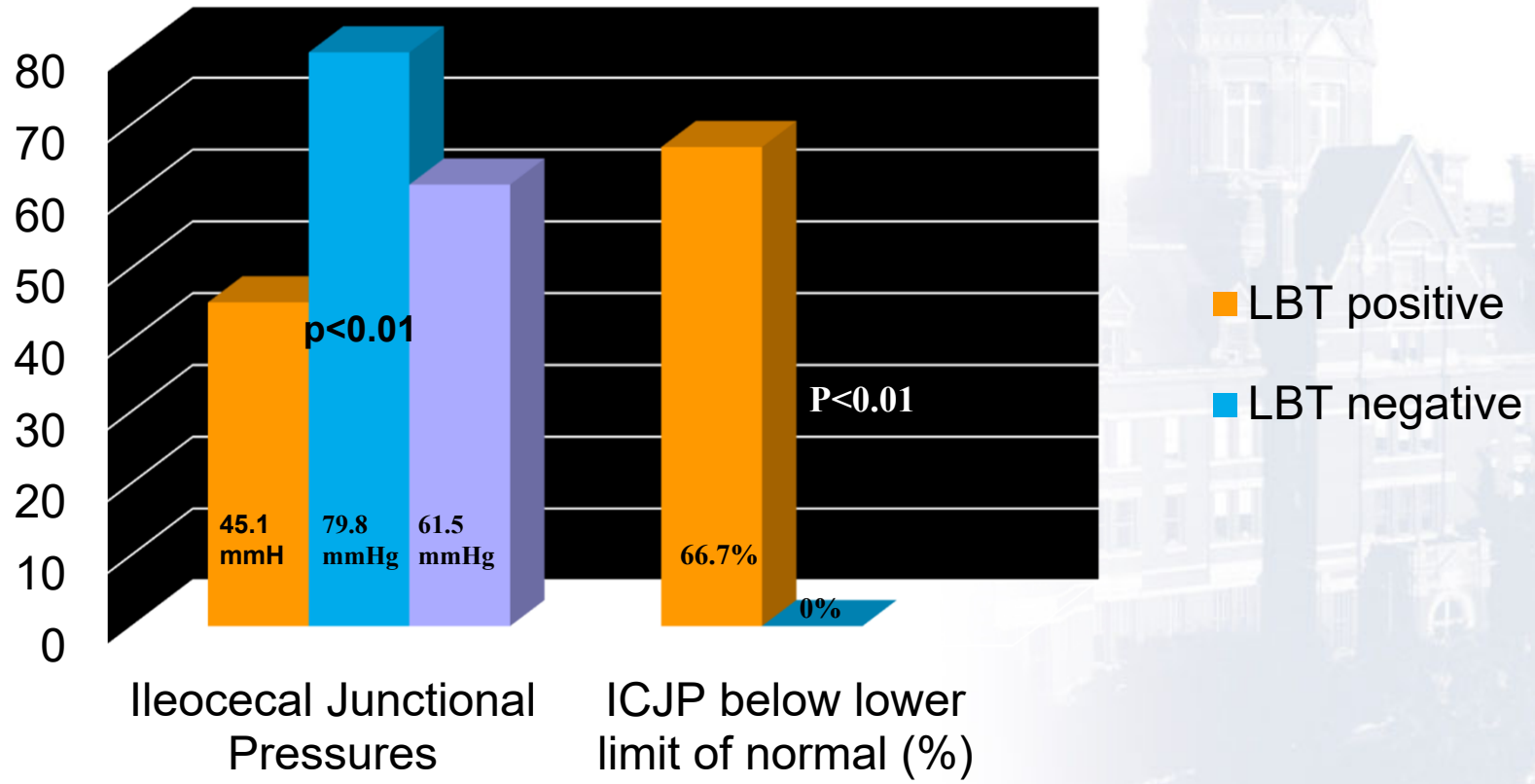
Ileocecal Junctional Pressures (ICJP) Lower in LBT Positive subjects



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Univariate Logistic Regression Modeling Positive LBT

- Univariate logistic regression analyses showed a significant association between LBT-positivity, ICJ pressure and SB mean pH and a trend with SBTT

Independent Variable	OR (95% CI)	P-value
SBTT	1.43 (0.97, 2.12)	0.06
ICJ pressure	0.93 (0.87, 0.98)	0.01
Gastric pH*	1.40 (0.848, 2.314)	0.19
SB pH *	40.39 (0.784, *undefined*)	0.04

*OR for a 0.1-unit change in pH

Using ICJP alone to model positive LBT showed that increase in ICJP by 1 unit reduces the odds of having a positive LBT by 7%

Chander Roland et al, **Low Ileocecal Valve Pressure Associated with SIBO**, Dig Dis Sci. 2014 Jun; 59(6)

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Poor Correlation of Pathophysiologic Abnormalities Among LBT Positive Subjects

- We found poor correlation between ICJP and SBTT (r= -0.132, p-value = 0.548)
- Poor correlation between ICJP and gastric mean pH (r= -0.239, p-value = 0.271) and with small bowel mean pH (-0.187, p-value = 0.392)
- Poor correlation of SBTT with gastric pH and small bowel pH
- Findings suggest *distinct* pathophysiologic mechanisms independently contribute to the development of SIBO

Chander Roland et al, **Low Ileocecal Valve Pressure Associated with SIBO**, Dig Dis Sci. 2014 Jun; 59(6)

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Summary of Findings

- Subjects with SIBO have significant delays in SBTT, hypotensive ICJP, and higher gastric pH
- These mechanisms appear to be independent, suggesting that there are sub-sets of patients with SIBO
- Association between prolonged SBTT and low ICJP with positive LBT may be useful to:
  - Identify patients with SIBO
  - Target therapeutic options in refractory subjects
- Future, large scale studies are needed to further characterize intestinal dysmotility and other contributing pathophysiological mechanisms in SIBO

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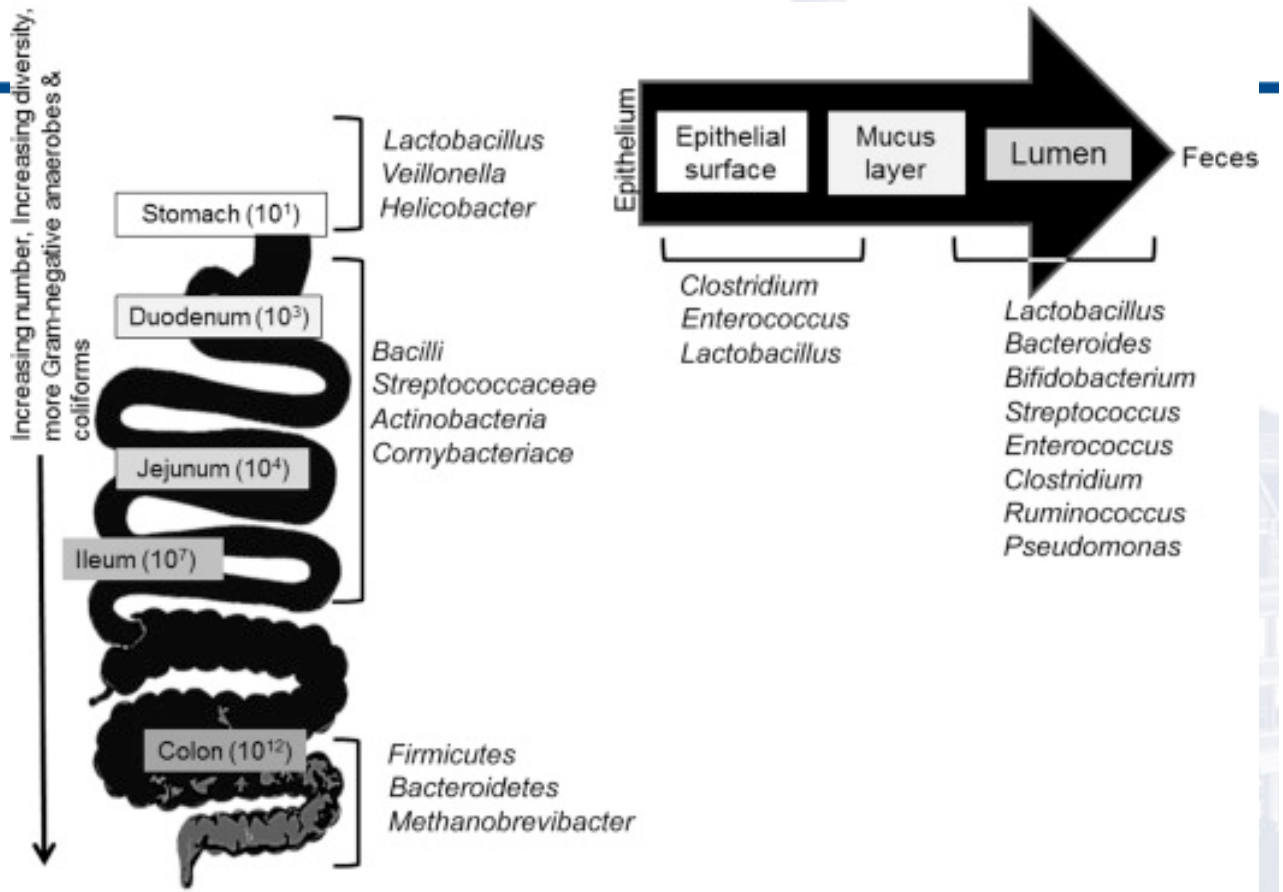
Distribution of Normal Human Gut Flora



Ghoshal UC, Ghoshal U. Small Intestinal Bacterial Overgrowth and Other Intestinal Disorders. Gastroenterol Clin North Am. 2017 Mar;46(1):103-120. doi: 10.1016/j.gtc.2016.09.008.

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The Flora in SIBO is Dysbiotic

- The small intestine normally contains few bacterial populations.
- **SIBO bacteria are mainly of the colonic type**: predominantly gram-negative aerobes and anaerobic species
  - The most common bacteria found in SIBO include *Escherichia coli, Streptococcus, Lactobacillus, Bacteroides*, and *Enterococcus* species (polymicrobial).

Patients with underlying SIBO tend to have significant delays in small bowel transit time as compared with those without.

important role in the manifestation of signs and symptoms of overgrowth *(bile acid diarrhea, bloating, mucosal damage, etc.)*

- **Concentrations always higher than normal (>10^4/mL)**

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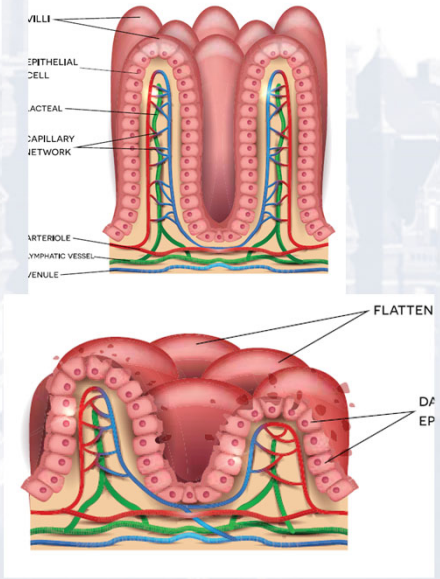
SIBO can also affect Morphology of Small Bowel

Bacteria that are normal in the colon may produce deleterious effects within the delicate environment of the small intestine …

- Analysis of small bowel biopsies in elderly patients with bacterial overgrowth revealed **blunting of the intestinal villi, thinning of the mucosa and crypts, and increased intraepithelial lymphocytes.**[1]
- **Microscopic inflammatory changes** (especially in the lamina propria) and villous atrophy are found regularly.[2]
  - Villous atrophy in SIBO must be distinguished from that of celiac disease.



1. Haboubi NY, Lee GS, Montgomery RD. Duodenal mucosal morphometry of elderly patients with small intestinal bacterial overgrowth: Response to antibiotics treatment. Age Ageing. 1991;20:29–32.
2. Bures J, Cyrany J, Kohoutova D, et al. Small intestinal bacterial overgrowth syndrome. World Journal of Gastroenterology : WJG. 2010;16(24):2978-2990. doi:10.3748/wjg.v16.i24.2978.

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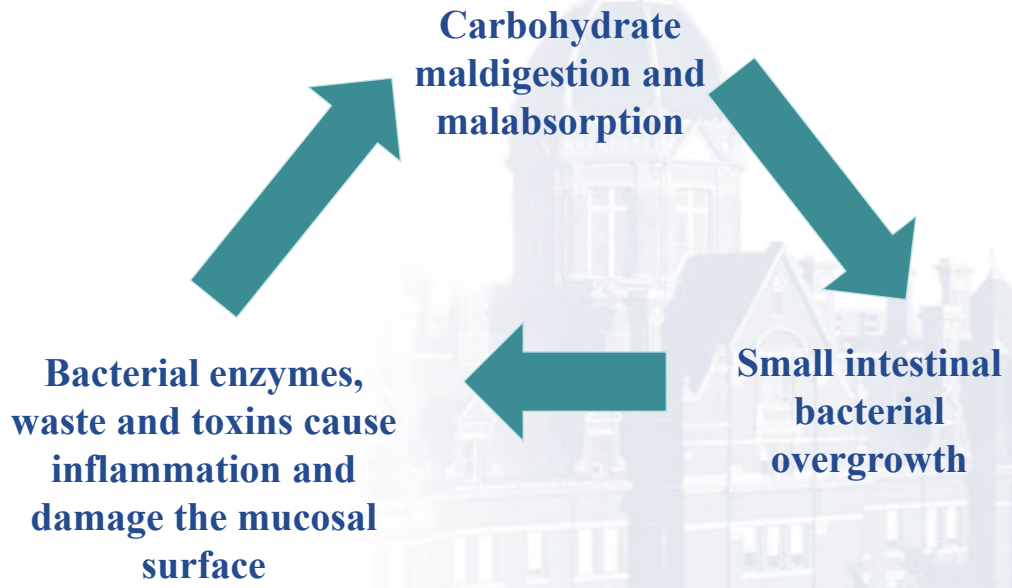
Analysis of small bowel biopsies in elderly patients with bacterial overgrowth revealed **blunting of the intestinal villi, thinning of the mucosa and crypts, and increased intraepithelial lymphocytes.**



Haboubi NY, Lee GS, Montgomery RD. Duodenal mucosal morphometry of elderly patients with small intestinal bacterial overgrowth: Response to antibiotics treatment. Age Ageing. 1991;20:29–32.

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Malabsorption of Fat in SIBO

1. **Bacteria can deconjugate bile salts to free bile acids.**
   - Low bile salts leads to impaired micelle formation → fat malabsorption and steatorrhea

2. **Pseudomembrane → mechanical interference with absorption of fats**
   - N.B. Mucosal damage → malabsorption of proteins and sugars (disaccharidase and peptidase deficiencies)

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Malnutrition in SIBO

- **Unabsorbed fatty acids may form insoluble soaps with minerals** such as Ca and Mg, leading to:
  - Osteomalacia, night blindness, hypocalcemic tetany, and possibly metabolic bone disease
- **Vitamin B_{12} deficiency**
  - Bacteria utilize B_{12} and detach B_{12} from intrinsic factor
  - Serum folate usually normal or elevated
- **Hypoproteinemia**
  - Protein-losing enteropathy or protein malabsorption
  - Bacterial metabolism of proteins to ammonia and fatty acids
- **Iron deficiency anemia** (rare)

1. Johnson E, Vu L, Matarese LE. Bacteria, Bones, and Stones: Managing Complications of Short Bowel Syndrome. Nutr Clin Pract. 2018;33(4):454-466. doi:10.1002/ncp.10113
2. Losurdo G, Salvatore D'Abramo F, Indellicati G, Lillo C, Ierardi E, Di Leo A. The Influence of Small Intestinal Bacterial Overgrowth in Digestive and Extra-Intestinal Disorders. Int J Mol Sci. 2020;21(10):3531. Published 2020 May 16. doi:10.3390/ijms21103531
3. Bures J, Cyrany J, Kohoutova D, et al. Small intestinal bacterial overgrowth syndrome. World J Gastroenterol. 2010;16(24):2978-2990. doi:10.3748/wjg.v16.i24.2978
4. Adike A, DiBaise JK. Small Intestinal Bacterial Overgrowth: Nutritional Implications, Diagnosis, and Management. Gastroenterol Clin North Am. 2018;47(1):193-208. doi:10.1016/j.gtc.2017.09.008

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Pathophysiologic Mechanisms and Specific Disorders Associated With SIBO

Stomach-Small Bowel Etiologies

- Atrophic gastritis
- PPIs
- Advanced age
- Vagotomy
- Gastrectomy
- Gastric Bypass
- Myopathies
- CTD, Amyloid Chagas, RT
- Medications (i.e., opioids)

Others

- SB diverticulosis
- Fistula, strictures
- Ileo-cecal valve resection
- Common Variable Immunodeficiency
- Hypogammaglobulinemia
- T cell Deficiency
- Celiac Disease
- Cirrhosis
- Chronic pancreatitis

Bohm M, Siwiec RM, Wo JM. Diagnosis and management of small intestinal bacterial overgrowth. Nutr Clin Pract. 2013 Jun;28(3):289-99. doi: 10.1177/0884533613485882.

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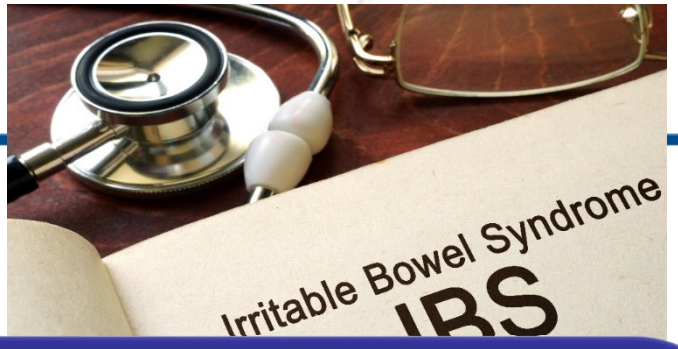
Prevalence and predictors of small intestinal bacterial overgrowth in irritable bowel syndrome: a systematic review and meta-analysis



More than 1/3 of IBS patients tested positive for SIBO, **and the odds of SIBO in IBS were increased by nearly fivefold.**

The prevalence of SIBO varied according to the diagnostic modality performed. **Female gender, older age, and IBS-diarrhea, but not PPI use, were associated with SIBO among individuals with IBS.**

Chen B, Kim JJ, Z… …alysis.
J Gastroenterol. 2018 Jul;53(7):807-818. doi: 10.1007/s00535-018-1476-9.

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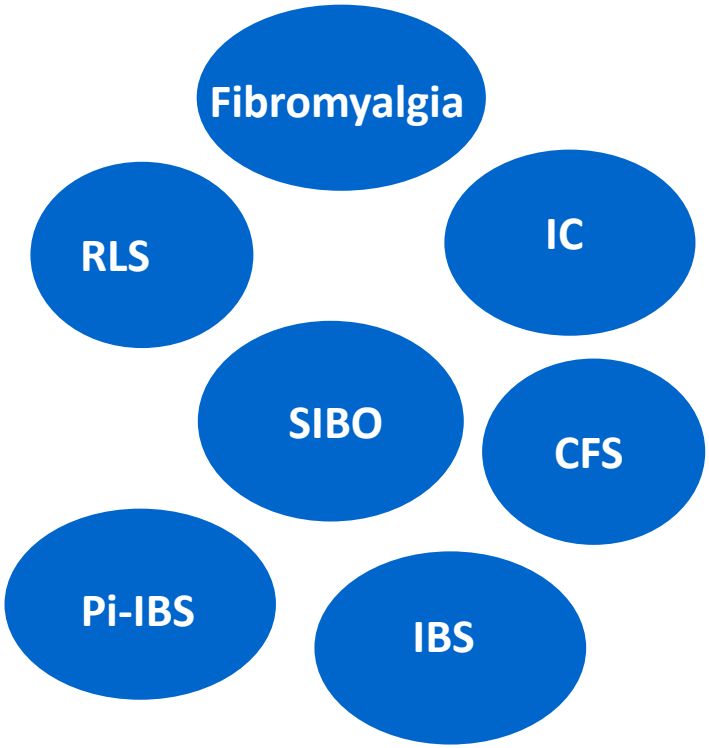
Current Thought Process

Individual Conditions



Future Outlook

SIBO Overlap

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Causes/Associated Conditions 2017-2019 Literature

- **Atherosclerosis:** PMID 28275304
- **Deep Venous Thrombosis**: PMID 27044499
- **Coronary Artery Disease:** PMID 29110161
- **Hyperlipidemia:** PMID 31055549
- **Osteopenia:** PMID 14571751
- **Smoking:** PMID 28223728
- **Rosacea:** PMID 27501017
- **PPI use (meta-analysis):** PMID 28770351
- **Pancreatitis:** PMID 29358867, PMID 31008737
- **Multiple Sclerosis:** PMID 27890460
- **T1D:** PMID 30155878
- **Cystic Fibrosis:** PMID 30232597
- **Obesity:** PMID 28480652, PMID 28940740
- **High visceral fat:** PMID 27282099
- **Celiac Disease (meta-analysis):** PMID 28191721
- **Crohn's Disease:** PMID 28134633
- **RYGBP vs. Gastric Banding:** PMID 27576576
- **Appendectomy, Cholecystectomy:** PMID 28223728
- **Gallstone Disease:** PMID 29392773
- **Gender, Age:** PMID 27073800
- **Chronic Liver Disease:** PMID 28988228
- **NAFLD:** PMID 31050979, PMID 30915401

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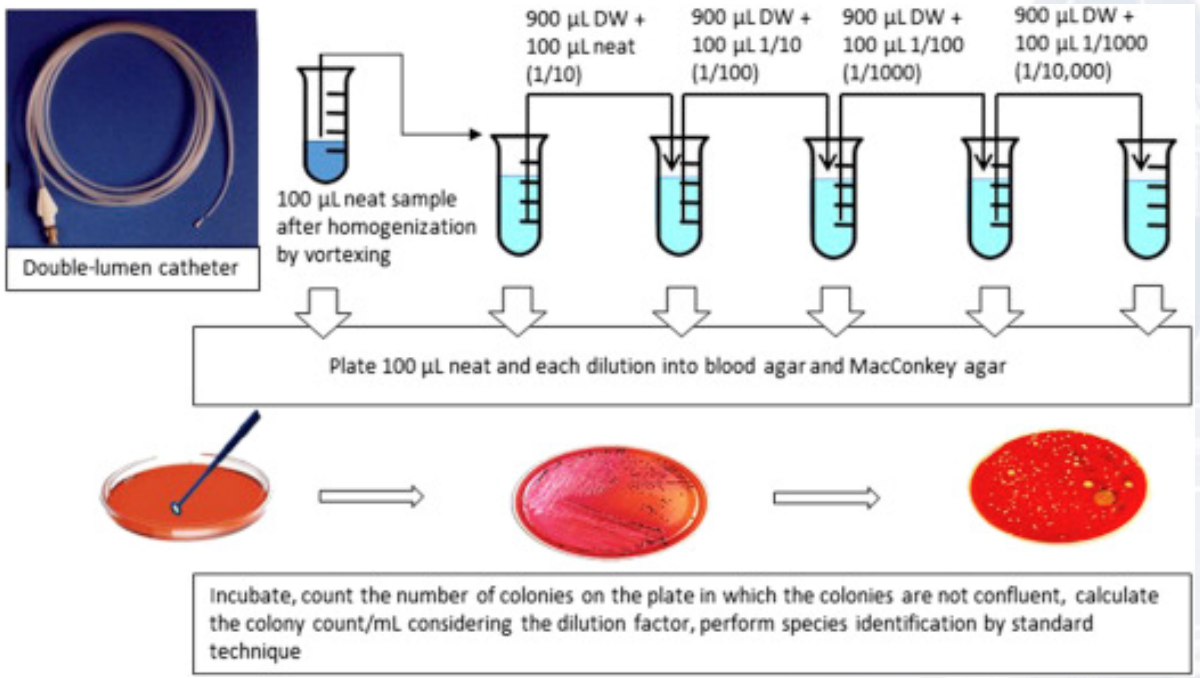
Diagnosis of SIBO

Diagnostic Tool	Specific Tests
Physical Exam	Abdominal distension, Nonspecific findings: abdominal distension, small intestinal succession splash [Taylor *et al.* 1991], scarring associated with prior surgeries, severe cases may have latent tetany, polyneuropathy and skin manifestations (rosacea)
Labs	Anemia, low vitamin B12, signs of malnutrition (lymphopenia, low serum pre-albumin and transferrin), elevated serum folate and vitamin K levels (bacteria produce these)
Direct Tests	Quantitative culture of luminal contents
Indirect Tests	Breath tests: ^{14}C d-xylose, hydrogen
Other diagnostic tests	Urinary tests, serum test
Imaging	Barium studies, CT enterography to identify mechanical causes of SIBO

Small Bowel Cultures to Diagnose SIBO



Technique of fluid aspiration from the third or fourth portions of the duodenum during an upper endoscopy with a sterile double lumen catheter

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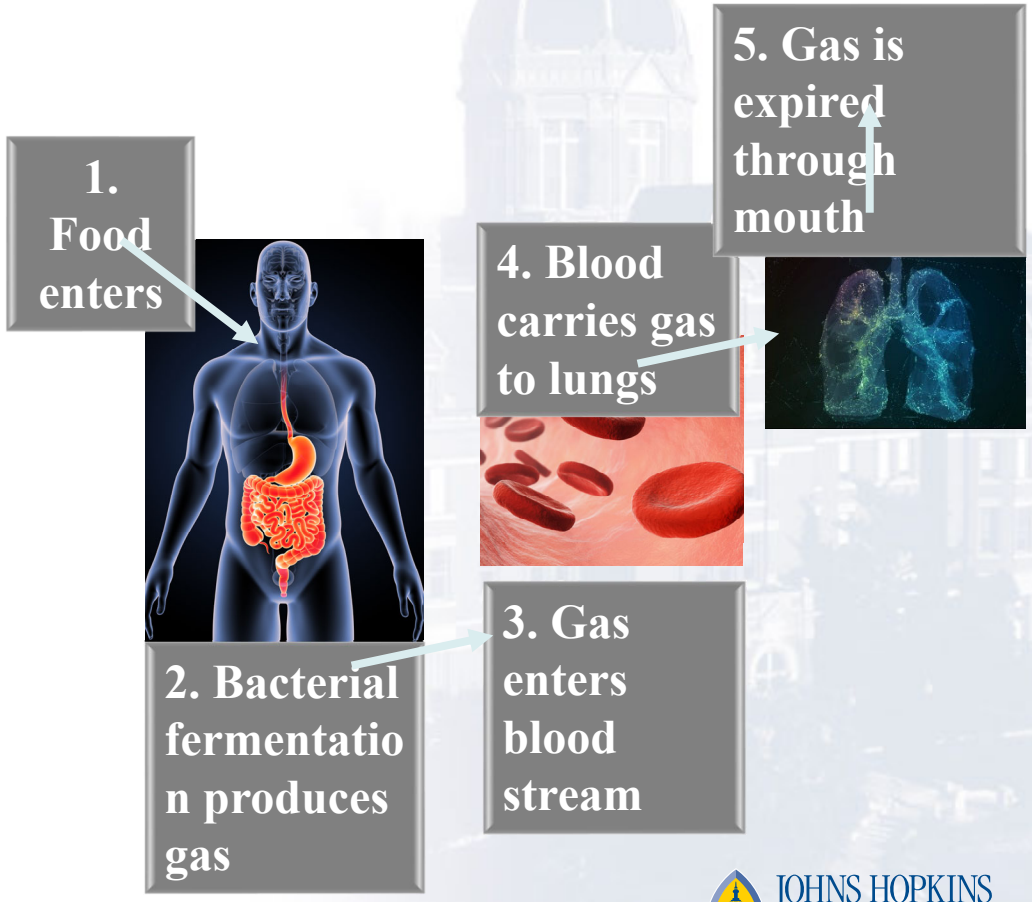
Principles Behind SIBO Breath Test

- **Hydrogen breath testing (HBT) after ingestion of lactulose or glucose** is the most commonly used method, based on the principle that exhaled hydrogen and methane are solely produced by bacterial fermentation of carbohydrates.
- The **measurement of methane** in addition to hydrogen may improve the diagnostic yield of breath testing. *(20% to 30% of the general population produces methane as the main by-product of carbohydrate fermentation)*



Choi CH, Chang SK. Role of Small Intestinal Bacterial Overgrowth in Functional Gastrointestinal Disorders. Journal of Neurogastroenterology and Motility. 2016;22(1):3-5. doi:10.5056/jnm15196.

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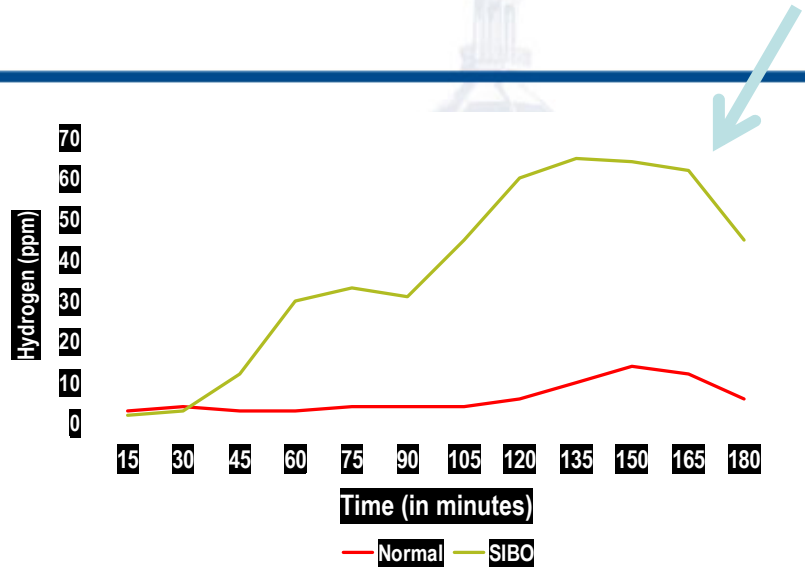
SIBO Diagnosis: Breath Testing

- Indirect test: can be done in person of at home with a kit
- **Measures fermentation: H_2 and CH_4**
- Transit: too fast gives false positive
- Substrate:
  - Glucose spec > sens
  - Lactulose sens > spec



Rezaie A, Buresi M, Lembo A, et al. Hydrogen and Methane-Based Breath Testing in Gastrointestinal Disorders: The North American Consensus. Am J Gastroenterol. 2017;112(5):775-784. doi:10.1038/ajg.2017.46

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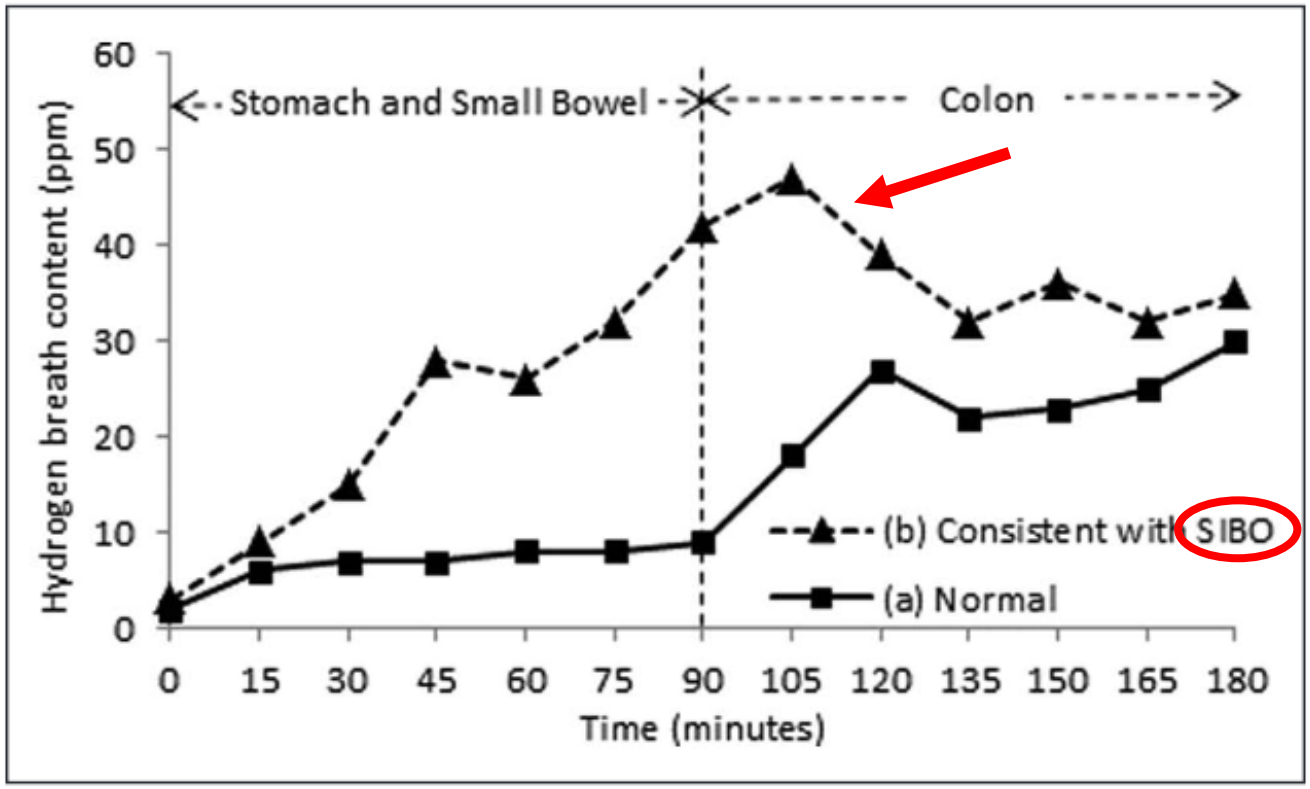
Example of hydrogen breath test



Bohm M, Siwiec RM, Wo JM. Diagnosis and management of small intestinal bacterial overgrowth. Nutr Clin Pract. 2013 Jun;28(3):289-99. doi: 10.1177/0884533613485882.

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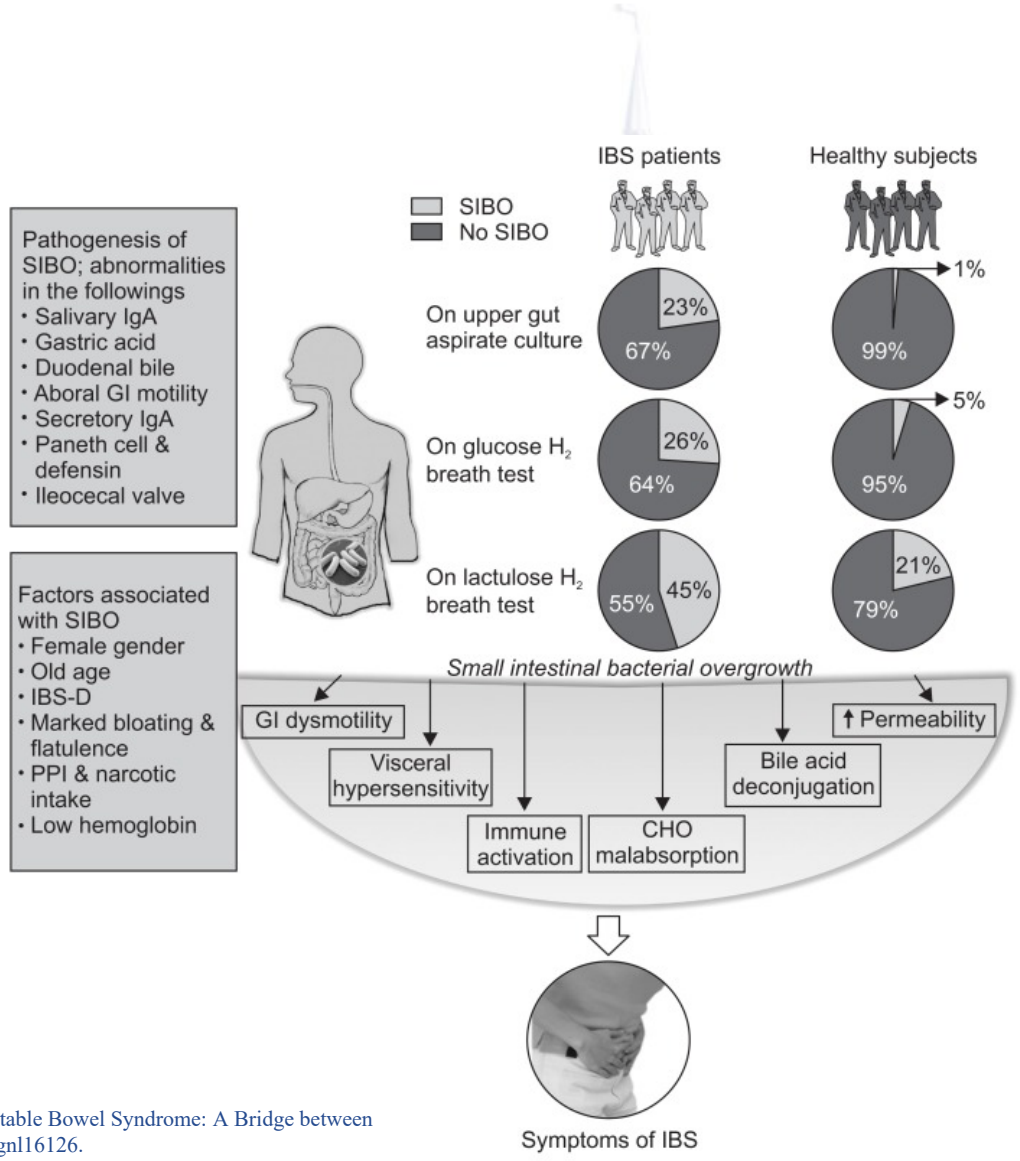
Schematic diagram showing the frequency of small intestinal bacterial overgrowth (SIBO) using quantitative jejunal aspirate culture, glucose and lactulose hydrogen breath tests (GHBT and LHBT, respectively) among patients with irritable bowel syndrome



Ghoshal UC, Shukla R, Ghoshal U. Small Intestinal Bacterial Overgrowth and Irritable Bowel Syndrome: A Bridge between Functional Organic Dichotomy. Gut and Liver. 2017;11(2):196-208. doi:10.5009/gnl16126.

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Hydrogen & Methane Production: The Basics

- Normal, healthy gut:
  - The site of hydrogen production by bacterial fermentation is limited to the distal gut. For fermentation to begin, food must reach these distal gut bacteria.
  - Proximal jejunum < 10^4 bacteria/mL per mL
  - In the ileum, enteric bacterial populations increase in amount (including coliforms) up to 10^9 CFU/mL in the terminal ileum.
- Abnormal fermentation: **Bacteria translocation to the site of food assimilation must be occurring for fermentation and gas production to take place.**

A potentially important consequence of bacterial translocation is immune activation.

Studies of confirmed bacterial translocation have observed an increase in the number of intraepithelial lymphocytes as mucosal evidence of this immune response.

1. Bures J, Cyrany J, Kohoutova D, et al. Small intestinal bacterial overgrowth syndrome. World Journal of Gastroenterology : WJG. 2010;16(24):2978-2990. doi:10.3748/wjg.v16.i24.2978.
2. Lin HC. Small Intestinal Bacterial Overgrowth: A Framework for Understanding Irritable Bowel Syndrome. JAMA. 2004;292(7):852-858. doi:10.1001/jama.292.7.852

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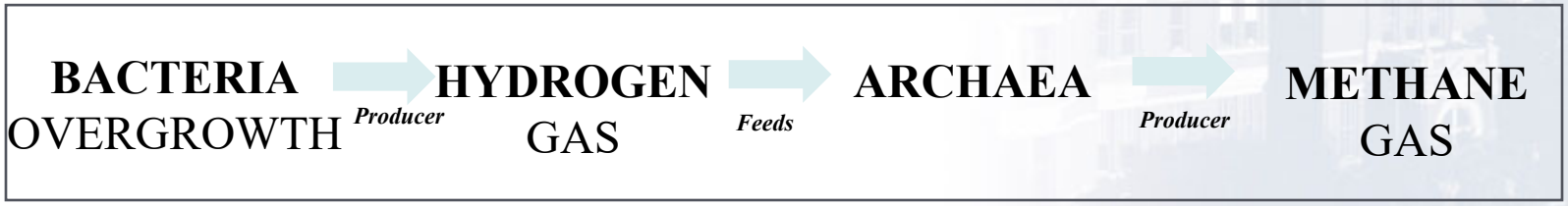
Hydrogen & Methane Production: The Basics

- Anaerobic fermentation of undigested polysaccharide fraction of carbohydrates by bacteria produces **hydrogen.**
- ***Hydrogen* is the substrate for intestinal methanogens.**
  - Methanogens are primitive "bugs" belonging to the Kingdom ***Archaea.***
  - Intestinal methanogens in humans: *Methaninobrevibacter smithii* most predominant, followed by *Methanospaera stadmagnae.*
- Certain *Clostridium* and *Bacteroides* species can also produce CH4.
- **20%-50% of the methane produced is excreted in the exhaled breath.**



Triantafyllou K, Chang C, Pimentel M. Methanogens, Methane and Gastrointestinal Motility. Journal of Neurogastroenterology and Motility. 2014;20(1):31-40. doi:10.5056/jnm.2014.20.1.31.

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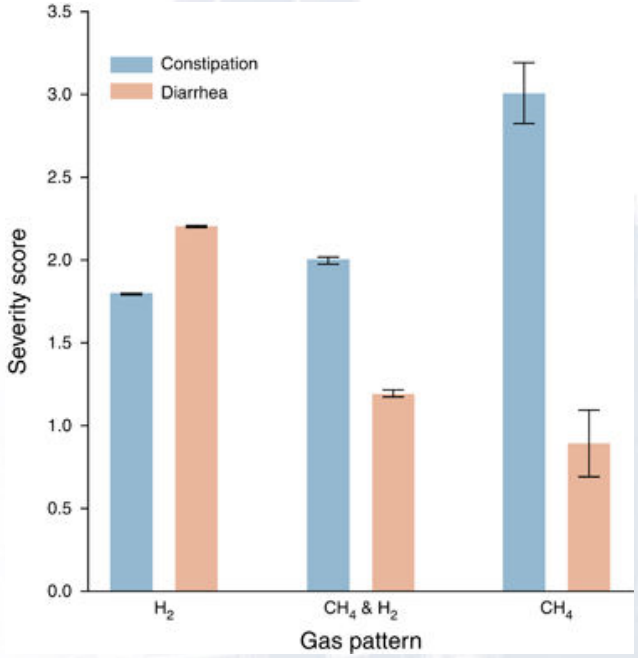
SIBO dominant forms: Hydrogen & Methane

- SIBO can be predominantly methane-producing, hydrogen-producing, or both.
- Association with symptoms:
  - **Hydrogen-dominant SIBO** – associated with diarrhea
  - **Methane-dominant SIBO** – associated with constipation (methane delays intestinal transit, possibly acting as a neuromuscular transmitter)



Mean diarrhea and constipation severity scores of subjects with small intestinal bacterial overgrowth (SIBO; N=551) as a function of the type of gas pattern produced on lactulose breath testing. P<0.00001 for trend in reduction of diarrhea with the presence of methane; P<0.05 for the trend toward increasing constipation with the presence of methane.

Pimentel M et al. Methanogens in Human Health and Disease. Am J Gastroenterol Suppl (2012) 1:28–33; doi:10.1038/ajgsup.2012.6

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SIBO Subtypes

Breath Testing	Severity
Hydrogen	Mild-easily correct with diet or one course antimicrobials
Methane	Moderate-needs diet and antimicrobials for extended period
Hydrogen and Methane	Recurrent-returns after 4 weeks of Rx
Hydrogen Sulfide	Refractory-fails multiple rounds of therapy

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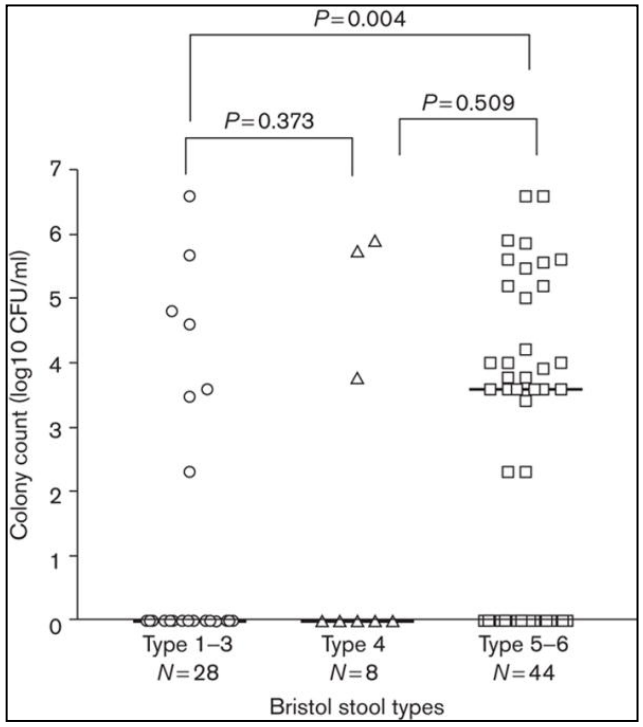
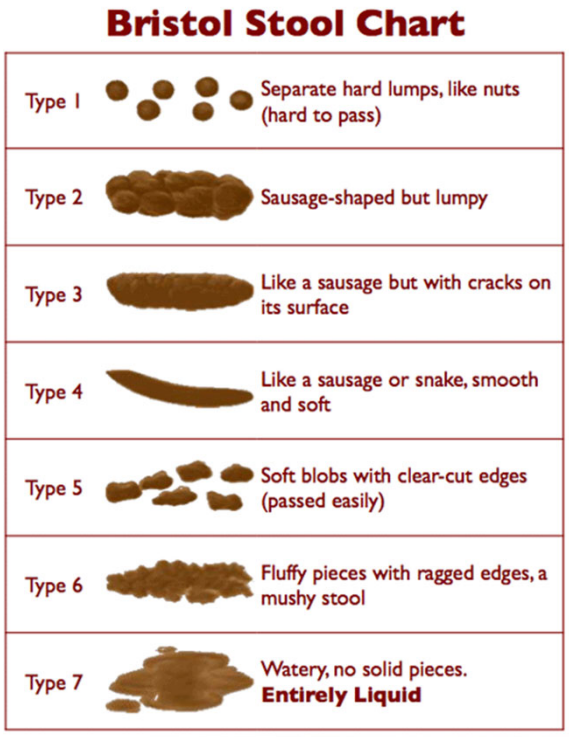
Slide 66

KR263 Added clinical experience icon as this used to be noted in the references section
Kirsten Ramsdell, 9/11/2020

Scatter plot of the relationship between small bowel bacterial colony count and stool form of IBS patients.





Ghoshal UC, Srivastava D, Ghoshal U, Misra A. Breath tests in the diagnosis of small intestinal bacterial overgrowth in patients with irritable bowel syndrome in comparison with quantitative upper gut aspirate culture. Eur J Gastroenterol Hepatol. 2014 Jul;26(7):753-60. doi: 10.1097/MEG.0000000000000122.

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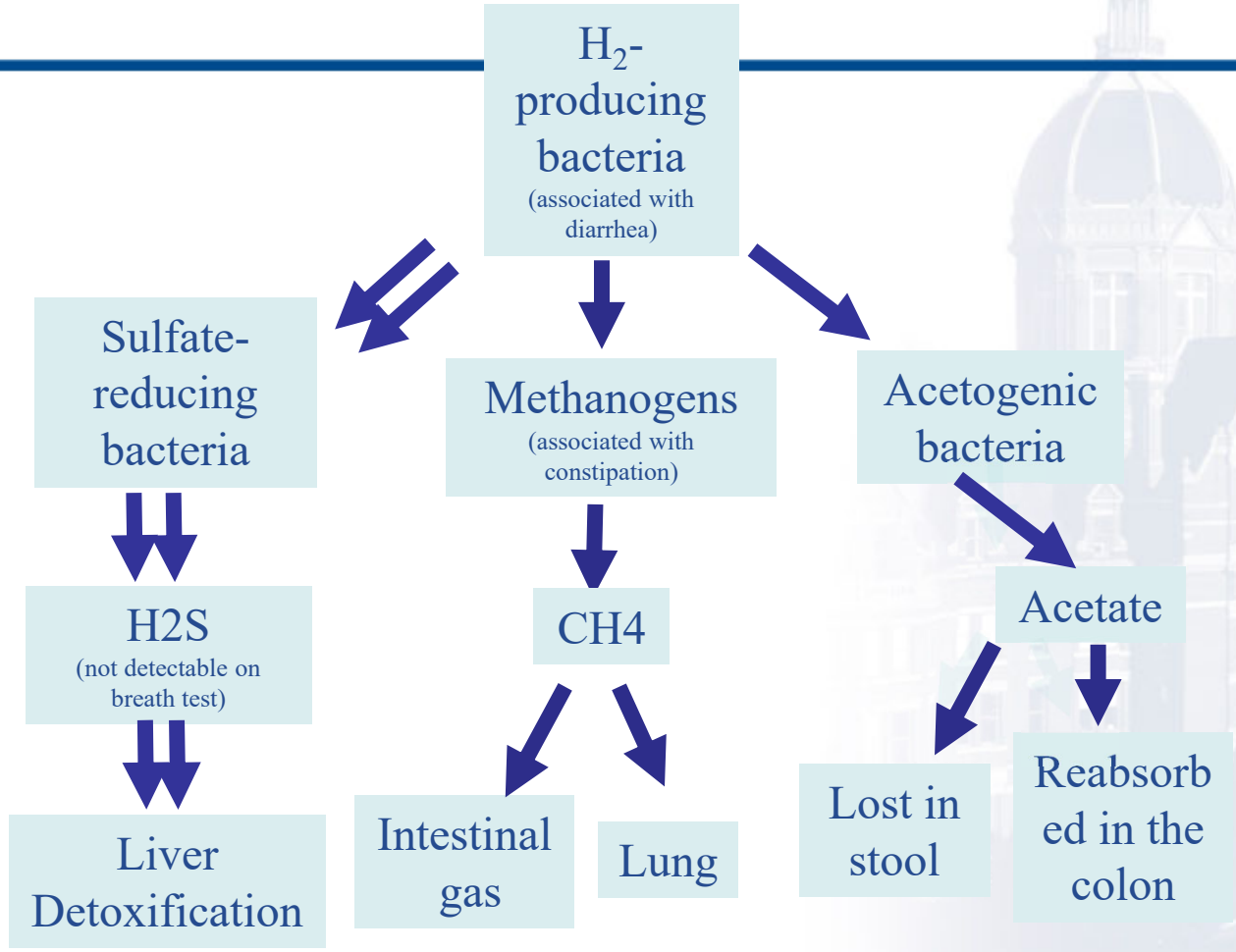
Breath Testing Linkage to Transit



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Triantafyllou K, Chang C, Pimentel M. Methanogens, methane and gastrointestinal motility. J Neurogastroenterol Motil. 2014;20(1):31–40. doi:10.5056/jnm.2014.20.1.31

Hydrogen Sulfide Pattern on Breath Test

Samples	H2	CH4	CO2
BASELINE	1	3	4.1
15 min	3	3	4.1
30 min	3	3	3.4
45 min	1	3	3.9
60 min	1	4	4.2
75 min	1	3	4.1
90 min	4	4	4.3
105 min	4	4	4
120 min	3	4	4.2
135 min	3	3	3.8
150 min	3	3	4
165 min	4	4	4.1
180 min	3	4	3.9

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SIFO Case Report & Review of Literature


Wasting Syndrome and Malnutrition Caused by Small Intestine Fungal Overgrowth: Case Report and Review of the Literature

Adding proper nutrients and slowly eradicating the dysbiotic fungi in the small intestine can help in resolution of GI symptoms and return to functional status.

Rajdeep S, Mullin, GE. A Wasting Syndrome and Malnutrition Caused by Small Intestine Fungal Overgrowth: Case Report and Review of the Literature. Integrative Medicine. Jun/Jul 2017; 16.3: 48-51.

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The patient presented to the clinic with a wasting syndrome consisting of watery diarrhea and a 40-pound (18.14 kg) weight loss in the course of 5 months prompting admission to the hospital.

Thin fragile, female with wasting in the subscapular and sternocleidomastoid area. Nontender, nondistended abdomen with colostomy bag present without surrounding erythema.

Upper endoscopy-showed duodenal scalloping with unremarkable biopsies. Small bowel fluid aspirate-positive for overgrowth of *Candida tropicallis* and also found to have anti-*Candida* IgA 2.7 times the upper limit of normal.

Dx: SIFO (based on the above findings)

10/13/2009

10/14/2009

11/17/2009

2/26/2010

Chief Complaint:

48-year old female with medical history of Sjorgren's syndrome and stage II cervical cancer complicated by a rectovaginal fistulae postradiation therapy requiring a colectomy and ileostomy.

The patient was begun on central parenteral nutrition and she completed a 3-wk course of fluconazole. Her symptoms slowly improved and she started gaining weight.

She was gradually weaned off of total parenteral nutrition during the next 3 months, with slow reintroduction of healthy whole foods.

She returned to work by the 4-month postdischarge with appropriate weight gain.

Patient's weight was up to 111 pounds (50.35 kg) with resolutions of her malnourishment, diarrhea, and weight loss.

Rajdeep S, Mullin, GE. A Wasting Syndrome and Malnutrition Caused by Small Intestine Fungal Overgrowth: Case Report and Review of the Literature. Integrative Medicine. Jun/Jul 2017; 16.3: 48-51.

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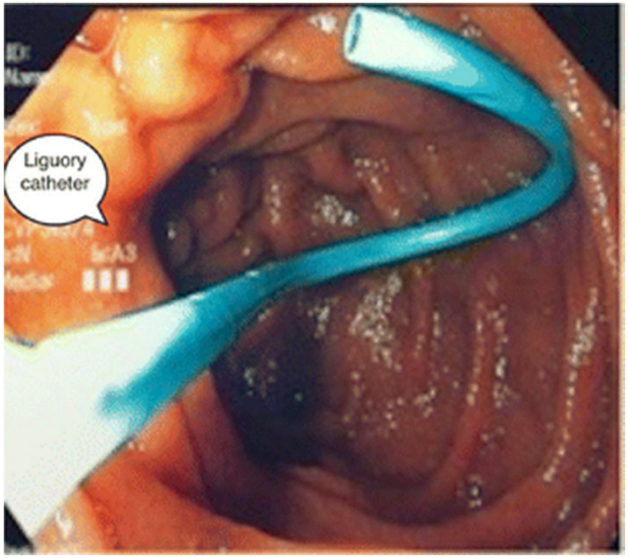
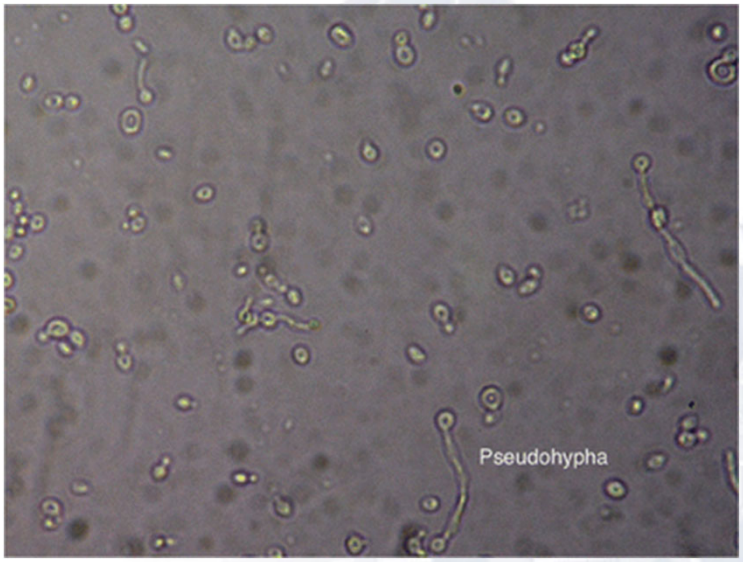
Small Intestinal Fungal Overgrowth (SIFO)



Technique of fluid aspiration from the third or fourth portions of the duodenum during an upper endoscopy with a sterile Liguory catheter



Pseudohypha budding patterns of *Candida* under direct microscopic view with ×400 magnification in a patient with SIFO

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Small Intestinal Fungal Overgrowth

Two recent studies showed that **26% and 25.3% of a series of patients with unexplained GI symptoms had SIFO**.

Small intestinal dysmotility and use of PPIs has been implicated.

A 2–3 week course of antifungal therapy is recommended and may be effective in improving symptoms, but evidence for eradication is lacking.

Erdogan A, Rao SSC. Small intestinal fungal Overgrowth. *Current Gastroenterology Reports*. 2015;17(4). doi:10.1007/s11894-015-0436-2.

Definition of Intestinal Fungal Overgrowth

- A condition where abnormally large numbers of fungi/yeast are found in the small bowel, also called SIFO
- Generally defined as >1,000 fungi per ml of small intestinal aspirate
- This can also occur in the large intestine (LIFO).
- SIFO/LIFO are commonly used together as it is difficult to ascertain where the overgrowth is located in a clinical setting.

Rao SSC, et al. Does colectomy predispose to small intestinal bacterial (SIBO) and fungal overgrowth (SIFO)?. Clin Transl Gastroenterol. 2018;9(4):146. doi:10.1038/s41424-018-0011-x

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Relationship between SIBO and SIFO/LIFO

- In those who have SIBO, is estimated that 30% have SIBO alone
- 55% have both SIBO and SIFO/LIFO
- 25% have SIFO/LIFO alone

Erdogan A, Rao SS. Small intestinal fungal overgrowth. Curr Gastroenterol Rep. 2015 Apr;17(4):16. doi: 10.1007/s11894-015-0436-2.

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Dysmotility and/or PPI use: Independent Significant Risk Factors for SIBO or SIFO

- Bacterial growth ≥10^3 CFU/mL or fungal growth was considered evidence for SIBO/SIFO.
- 150 subjects with unexplained GI symptoms and negative endoscopy/radiology tests were evaluated.
  - 63% overall had microbial overgrowth on culture
  - 40% had SIBO
  - 26% had SIFO
  - 34% had mixed SIBO/SIFO

*SIBO was predominately due to *Streptococcus, Enterococcus, Klebsiella,* and *E. coli.*

*SIFO was due to *Candida*.

*53% patients had dysmotility and 43% used PPI.

Jacobs C, Coss Adame E, Attaluri A, Valestin J, Rao SS. Dysmotility and proton pump inhibitor use are independent risk factors for small intestinal bacterial and/or fungal overgrowth. Aliment Pharmacol Ther. 2013;37(11):1103–1111. doi:10.1111/apt.12304

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SIBO and/or SIFO after colectomy

- **RESULTS:**

Compared to controls, patients with colectomy had…

  - significantly higher prevalence of SIBO
  - significantly higher prevalence of mixed SIBO/SIFO
  - higher prevalence of aerobic organisms together with decreased anaerobic and mixed organisms
  - significantly greater severity of diarrhea, vomiting, and abdominal pain at baseline

- **CONCLUSION:** Colectomy is a risk factor for SIBO/SIFO.

Rao SSC, Tan G, Abdulla H, Yu S, Larion S, Leelasinjaroen P. Does colectomy predispose to small intestinal bacterial (SIBO) and fungal overgrowth (SIFO)? Clin Transl Gastroenterol. 2018 Apr 25;9(4):146. doi: 10.1038/s41424-018-0011-x.

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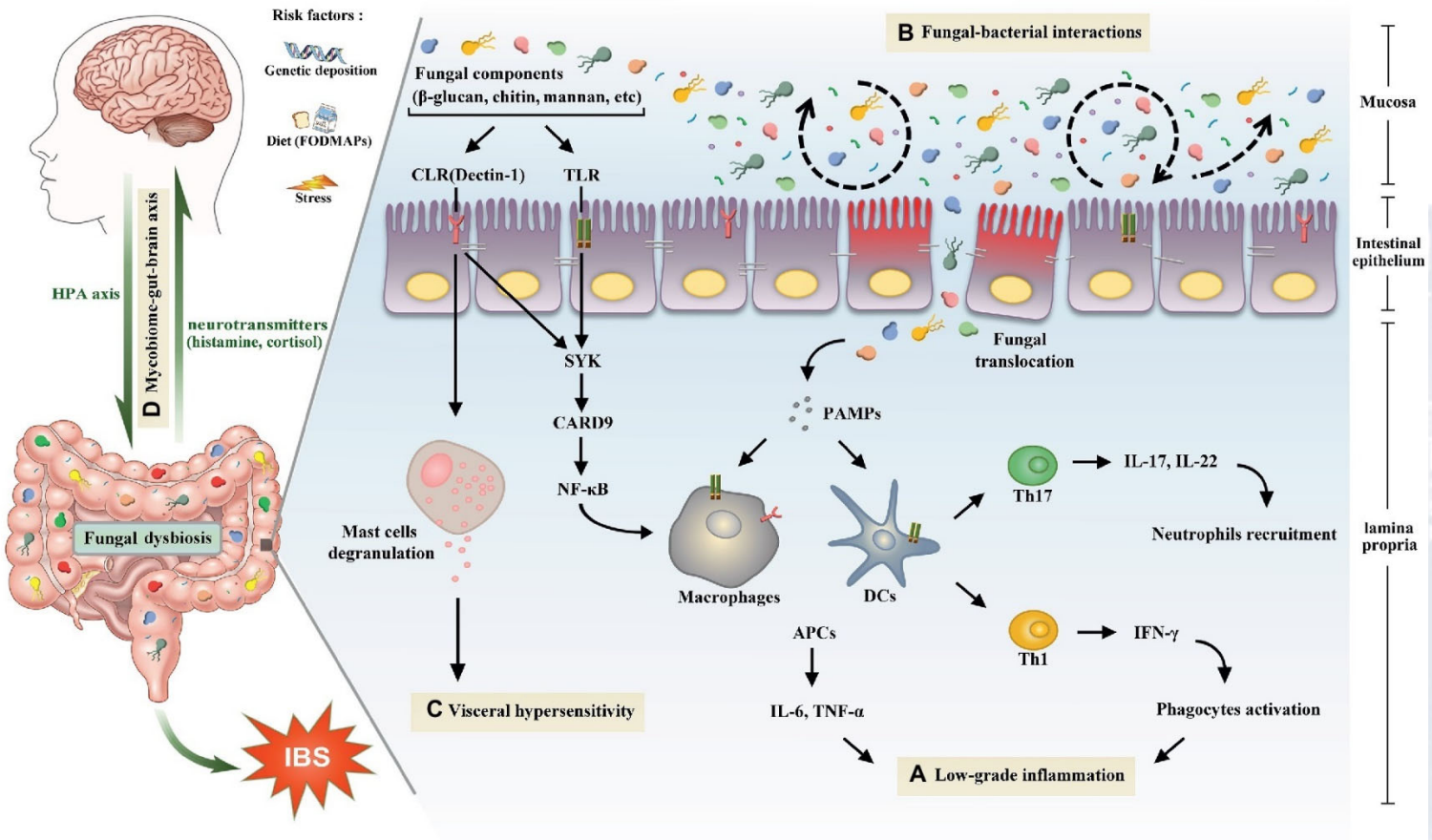
The potential role of gut mycobiome in the pathogenesis of irritable bowel syndrome.



Front. Microbiol., 21 August 2019 | https://doi.org/10.3389/fmicb.2019.01894

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Summary: CAUSES AND CONSEQUENCES OF SIBO/SIFO

Etiologies:

- Achlorhydria
- Hypochlorhydria
- PPIs, opioids, (possible: levothyroxine)
- Stasis: dysmotility
- Malnutrition
- Collagen vascular disease
- Immune deficiency
- Surgery (loops, vagotomy)
- Advancing Age, Female
- Smoking
- Celiac disease, Crohn's disease
- Pancreatitis (moderate to severe)

Consequences:

- Carbohydrate/Fiber intolerance
- Bloating after meals
- Iron, Vitamin D, & B_{12} deficiencies
- Fat malabsorption
- Enteropathy
- Food allergies
- Systemic inflammation
- Autonomic dysfunction
- Chronic Fatigue, Restless legs syndrome (RLS)
- Atherosclerosis
- Depression
- Rosacea

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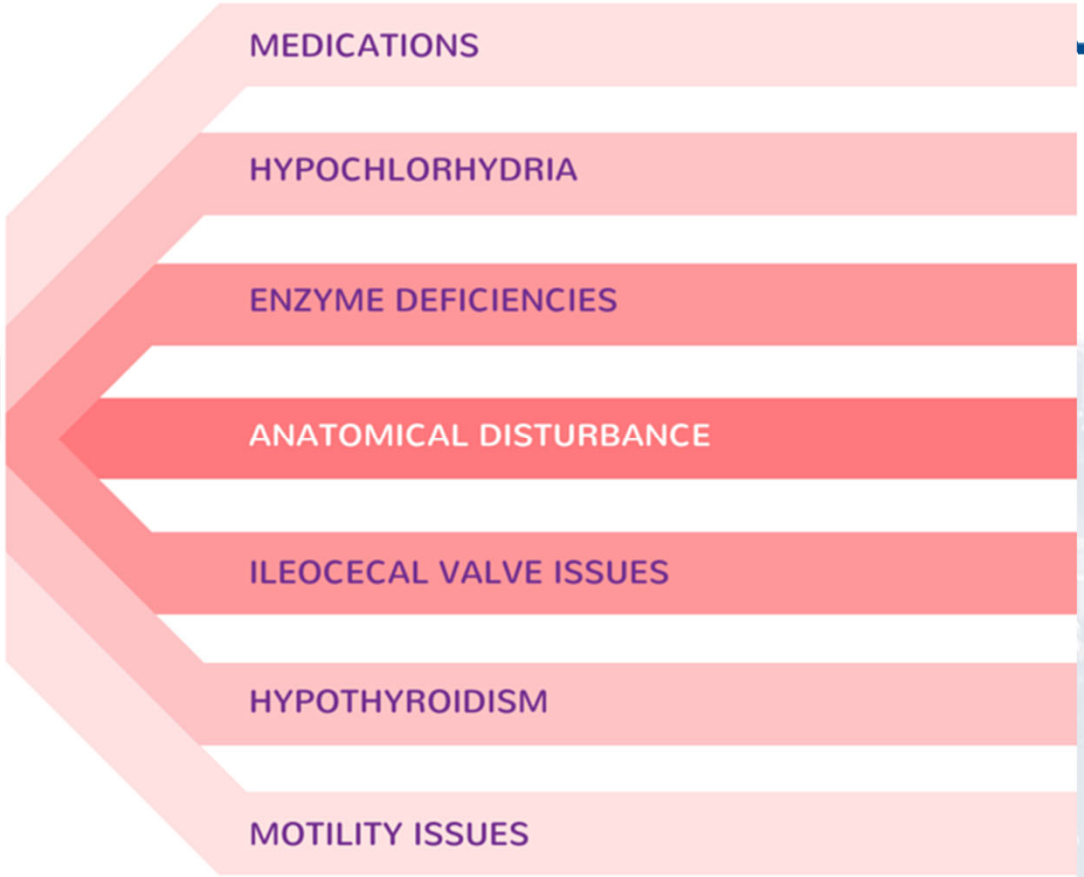
SIBO CAUSES



http://endsibo.com/what-causes-sibo/

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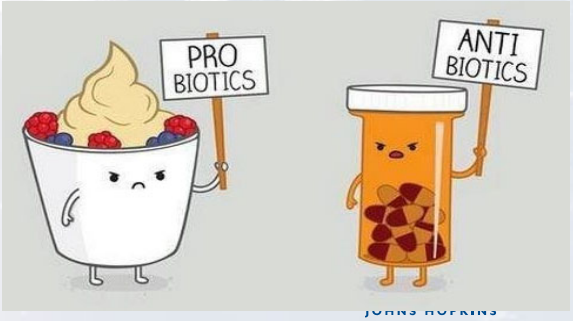
Treatment Options for SIBO

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

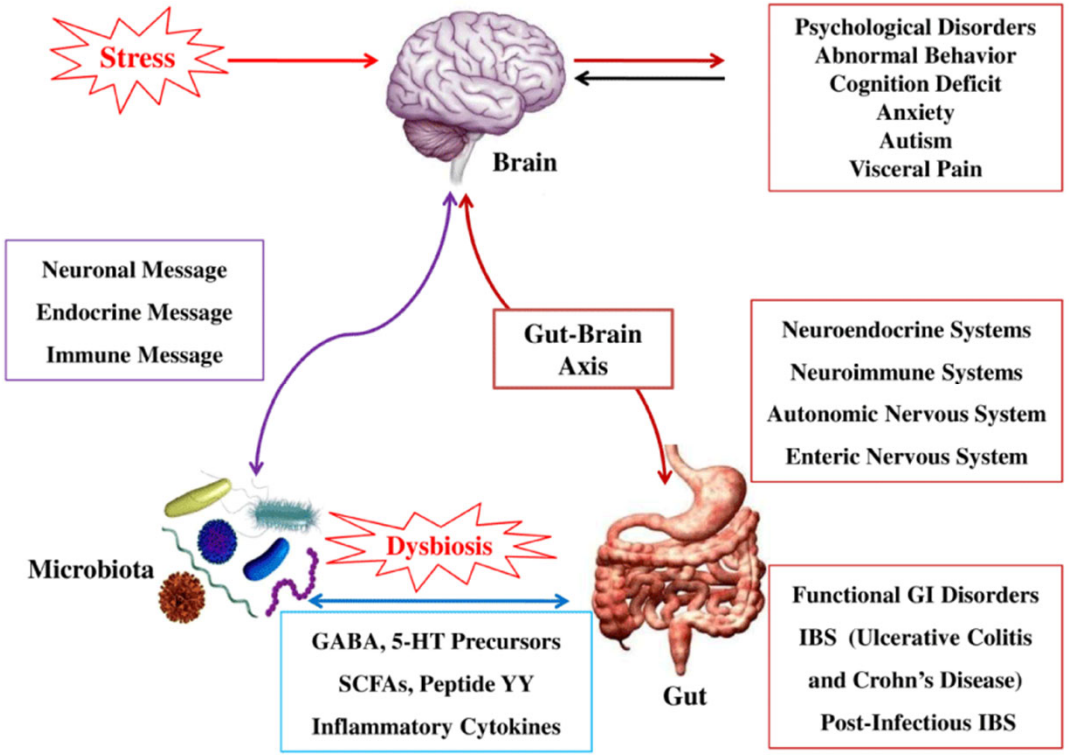
- **Diet** *(low FODMAPs)*
- **Antibiotic therapy** *(Weeding)*
- **Prokinetic agents**
- **Herbs for weeding*** *(berberine, oregano oil, wormwood)*
- **Probiotics** *(multiple mechanisms)*
- **Serum Bovine-derived Immunoglubulins** *(SBIs)*
- **Enzymes/HCl**
- **Other** (*Antrantil, SYN-001:)*



*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. doi:10.7453/gahmj.2014.019.

Therapies for IBS

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



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Mind-Body Studies in IBS

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

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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

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

Exclusion-Based Diets

- Based on Food Hypersensitivity Testing Dairy (IgG4, ALCAT, etc)
- Top Food Allergens
- Carbs, Lactose, Fructose, FODMAPs, Gluten (all improve IBS symptoms).
- Caffeine, Additives, Amines.
- Elimination Diet (suspected vs. restrictive)

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The Role of Diet in the Treatment of Irritable Bowel Syndrome: A Systematic Review

Rajdeep Singh, MD[a], Ahmed Salem, MD[b], Julie Nanavati, MLS, MA[c], Gerard E. Mullin, MD[d,*]

KEYWORDS

• Nutrition • Diet • Irritable bowel syndrome • FODMAPs • Gluten • Food sensitivities • Fiber • Elimination diets

KEY POINTS

- Irritable bowel syndrome (IBS) is characterized by recurrent abdominal pain and altered stool frequency and form, which is diagnosed according to the updated Rome IV criteria.
- Food may induce symptoms that have a range of effects in the human body, including in-

Singh R et al GI Clin North America Feb 2018.

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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. In Press.

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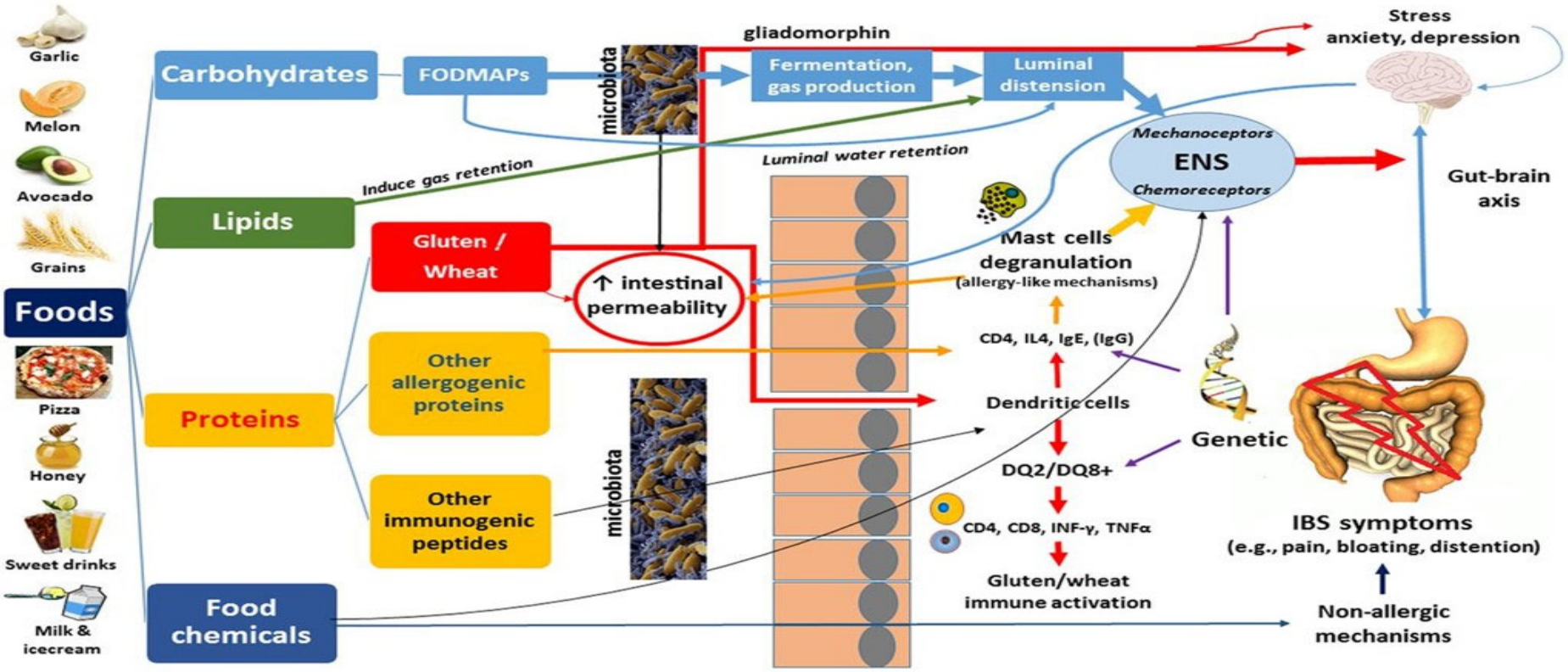
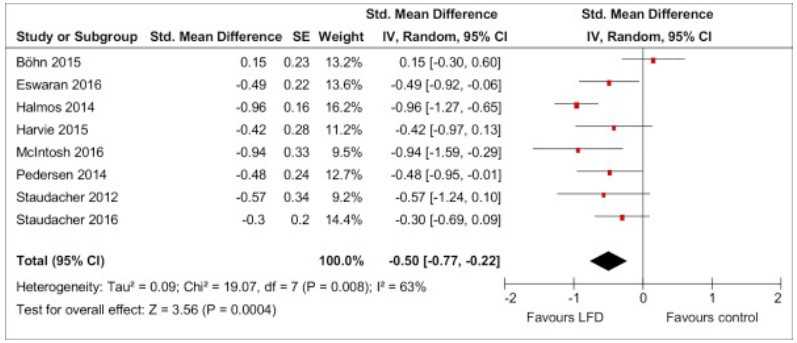
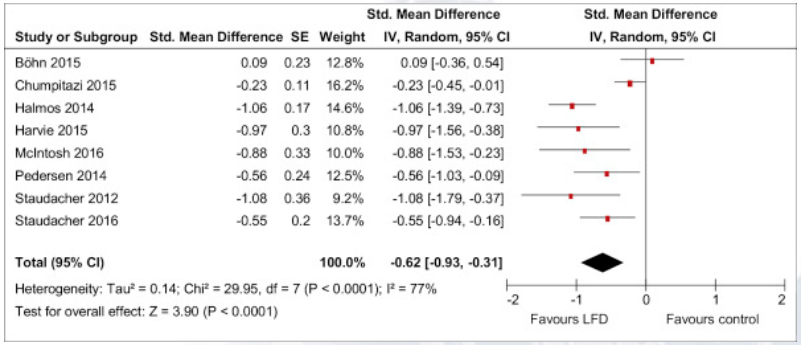
Mechanisms of Action of FODMAPs in Triggering IBS Symptoms



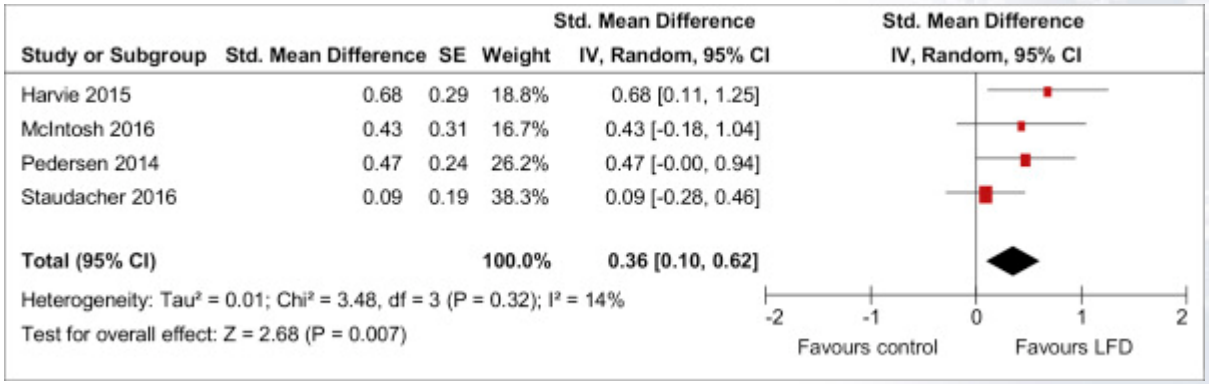
Low FODMAPs Diet in the treatment of IBS: A systematic review and meta-analysis



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. et al Nutr. Volume 45, January 2018, Pages 24-31

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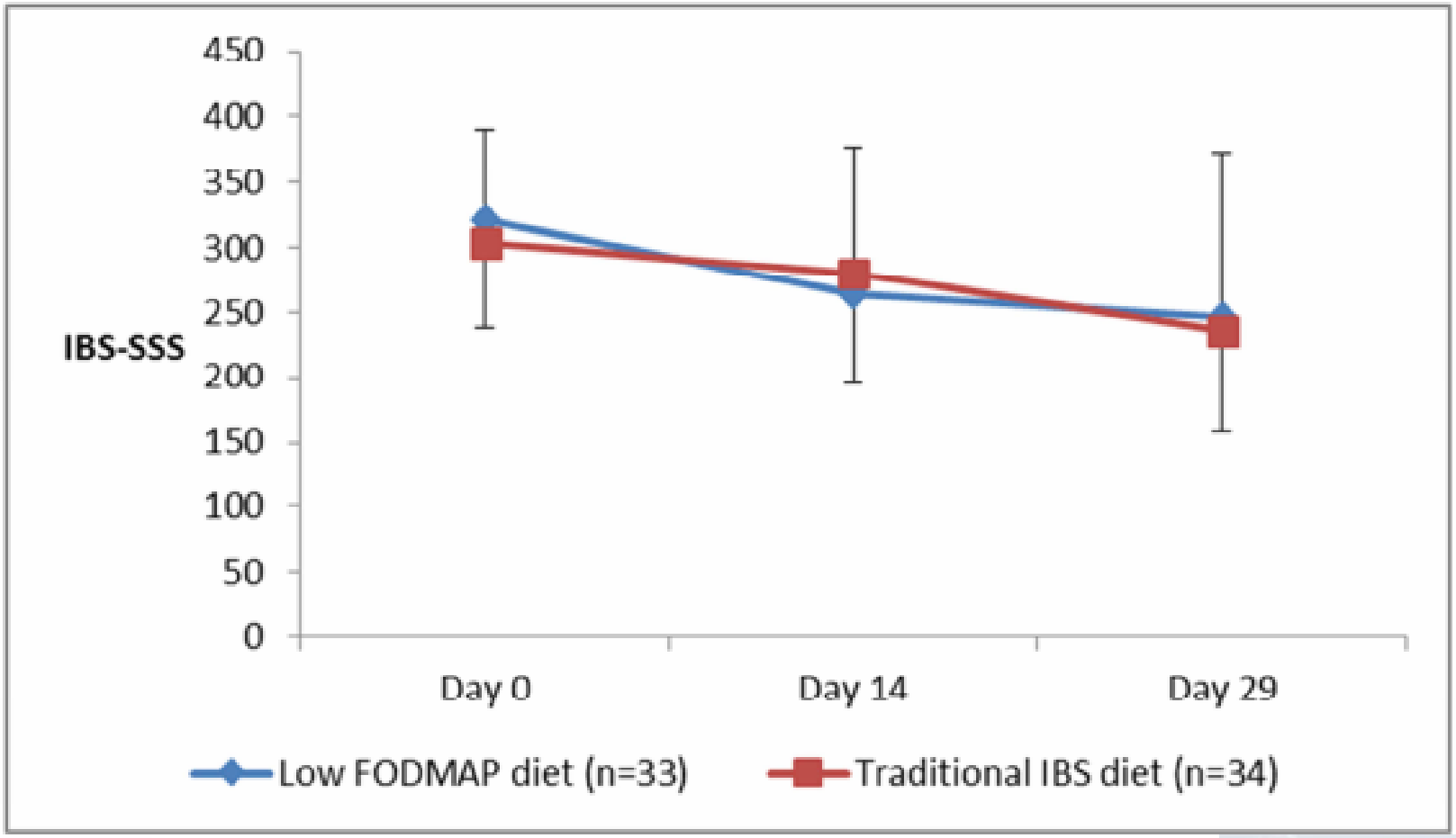
Diet low in FODMAPs Reduces Symptoms of Irritable Bowel Syndrome as Well as Traditional Dietary Advice: A Randomized Controlled Trial

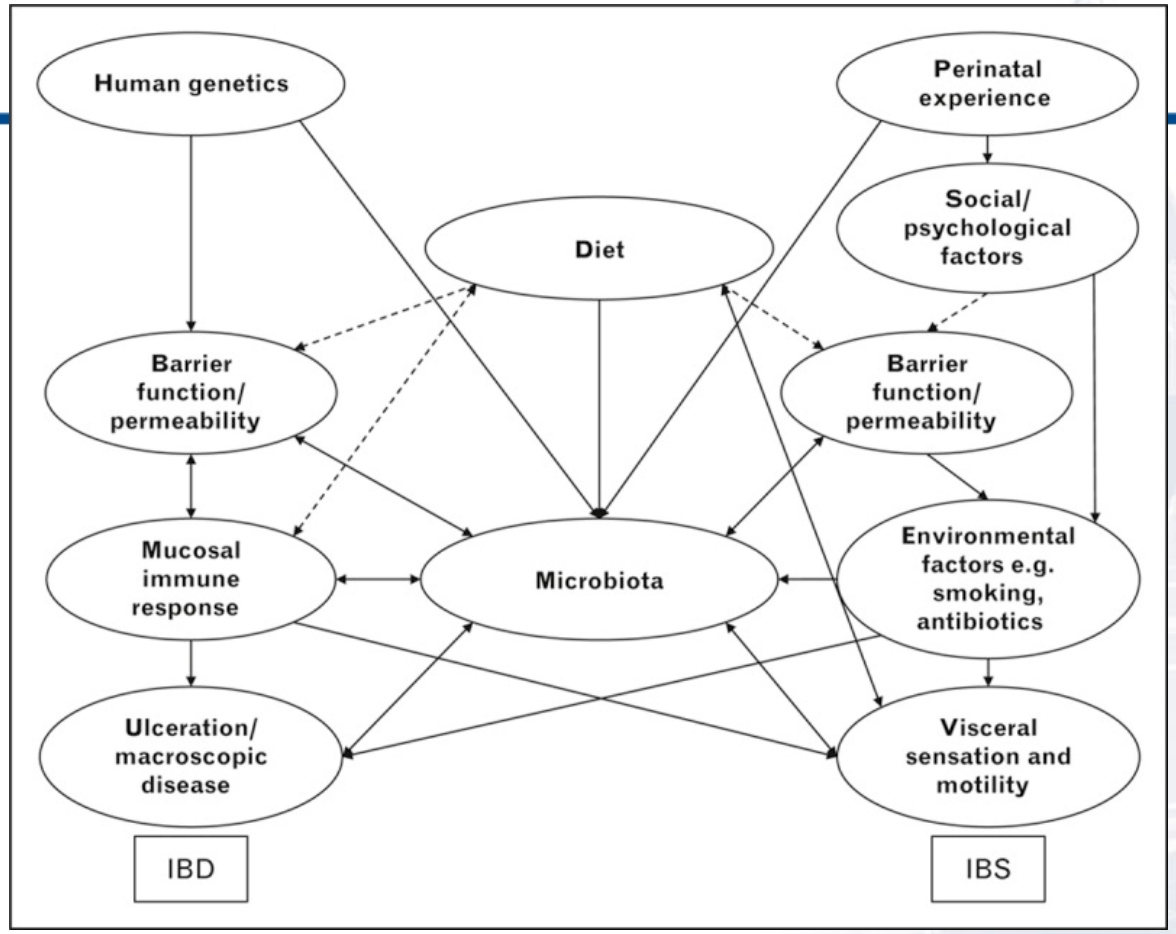
Lena Böhn, RD[1,2]; Stine Störsrud, RD, PhD [1,2]; Therese Liljebo, RD[3]; Lena Collin, RD[4]; Perjohan Lindfors, MD, PhD[4,5]; Hans Törnblom, MD, PhD [1,2]; Magnus Simrén, MD, PhD [1,2].

Fig 3 Böhn et al



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 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.



Major G, Spiller R. Irritable bowel syndrome, inflammatory bowel disease and the microbiome. *Current Opinion in Endocrinology, Diabetes, and Obesity*. 2014;21(1):15-21. doi:10.1097/MED.0000000000000032.

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IBD and Low-FODMAP Diet: 2020 Single-Blind Trial

- **Study:** n = 52 patients with quiescent Crohn's disease or ulcerative colitis and persistent gut symptoms.
- **Intervention:** Low-FODMAP diet (n = 27) or a control diet (n = 25), with dietary advice, for 4 weeks.
- **Results:** A higher proportion of patients reported adequate relief of gut symptoms following the low FODMAP diet **(14/27, 52%)** than the control diet (4/25, 16%, P=.007).
- **Conclusions:** While there were no significant difference after 4 weeks in change in IBS severity scores**, there were significant improvements in specific symptom scores and numbers reporting adequate symptom relief.**

Cox SR, Lindsay JO, Fromentin S, et al. Effects of Low FODMAP Diet on Symptoms, Fecal Microbiome, and Markers of Inflammation in Patients W
Inflammatory Bowel Disease in a Randomized Trial. *Gastroenterology*. 2020;158(1):176-188.e7. doi:10.1053/j.gastro.2019.09.024

Balance Between Fungi and the Host

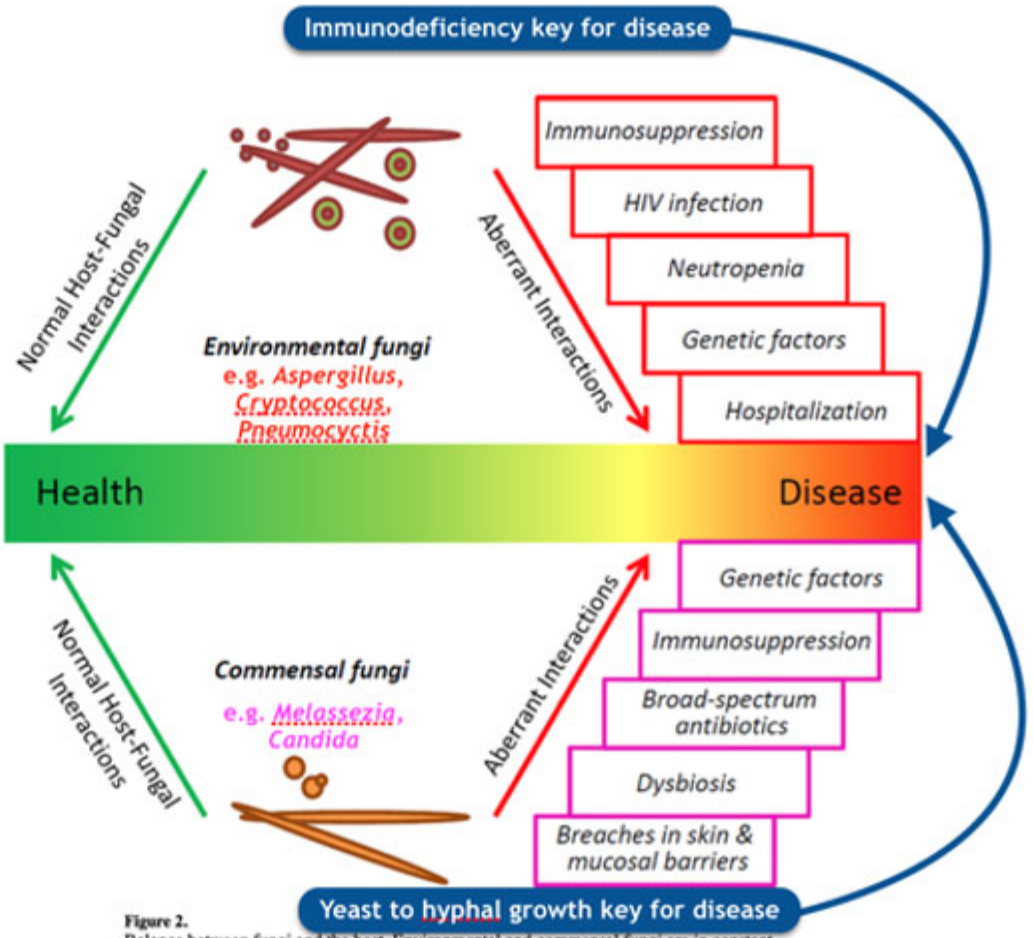

Figure 2.
Balance between fungi and the host. Environmental and commensal fungi are in constant contact with the host providing myriads of fungal antigens with which to interact. During homeostatic conditions commensal fungi are kept at the mucosal surfaces and the skin, while environmental fungi are either killed or tolerated upon contact with the host. Under aberrant conditions when mucosal and immune barriers are compromised, fungi invade tissues leading to dissemination, inflammation and disease.

Suhr M, Hallen-Adams H. The human gut mycobiome: Pitfalls and potentials–a mycologist's perspective. *Mycologia*. 2015;107(6):1057–73.

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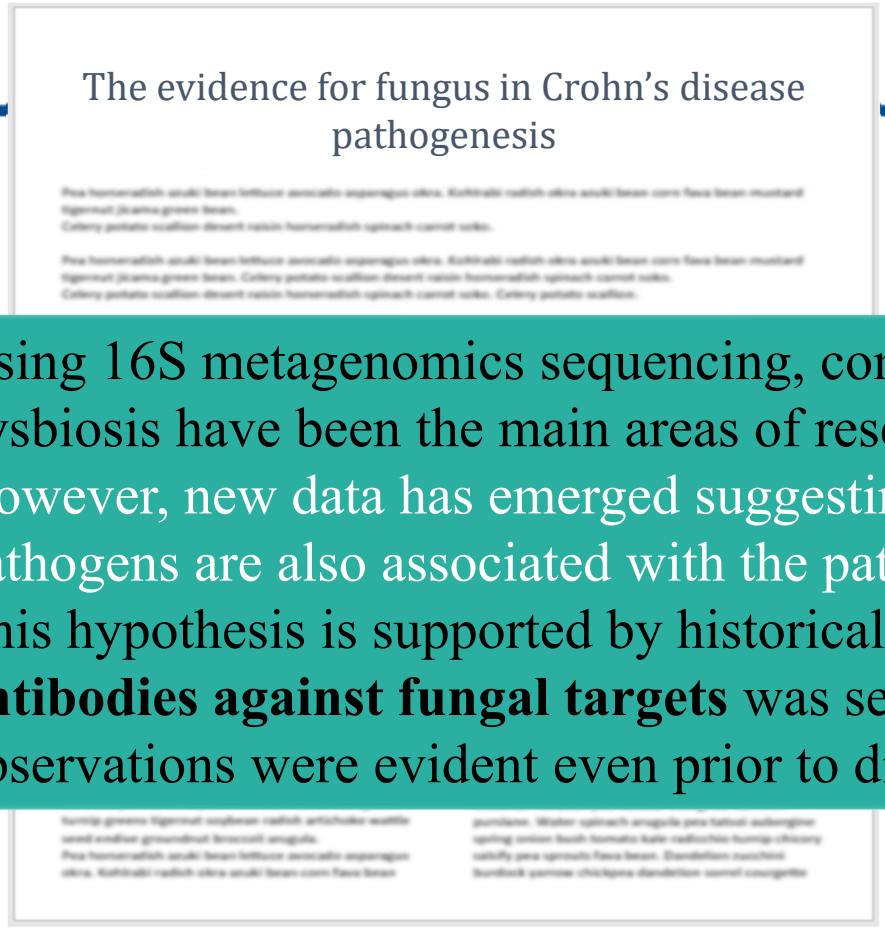
CK [2]1

The evidence for fungus in Crohn's disease pathogenesis



Using 16S metagenomics sequencing, complex bacterial communities and dysbiosis have been the main areas of research focus in patients with CD. However, new data has emerged suggesting that fungal opportunistic pathogens are also associated with the pathogenesis and chronicity of IBD. This hypothesis is supported by historical observations, where elevated **antibodies against fungal targets** was seen in CD patients. These observations were evident even prior to disease diagnosis.

Miyoshi J, Sofia MA, Pierre JF. The evidence for fungus in Crohn's disease pathogenesis. Clin J Gastroenterol. 2018 Dec;11(6):449-456. doi: 10.1007/s12328-018-0886-9.

CK [2]1 paraphrased
Carey Kunz, 9/8/2020

Table 1. Major contributors of non-bacterial microbiota changes in IBD.

		IBD Type	Change	Reference
Mycobiome		CD + UC	↑ *Basidiomycota/Ascomycota* ratio	[53]
		CD + UC	↑ *Candida albicans*	[53]
		CD	↑ *Candida tropicalis*	[54]
		CD	↑ *Candida glabrata*	[55]
		CD	↑ *Gibberella moniliformis*	[55]
		CD	↑ *Alternaria brassicola*	[55]
		CD	↑ *Aspregillus clavatus*	[55]
		CD	↑ *Cystofilobasidiaceae* family	[55]
		CD + UC	↓ *Saccharomyces cerevisiae*	[53]
		CD + UC	↓ *Malassezia sympodialis*	[53]
		UC	↓ Fungal diversity	[53]
		CD + UC	↑ Fungal burden	[55,56]
		UC	↑ Fungal–bacteria interactions	[53]
		CD	↓ Fungal–bacteria interactions	[53]
Virome	**Phageome**	CD	↑ Phages infecting bacterial orders *Alteronomoadales* and *Clostridiales*	[87]
		CD	↓ *Microviridae* family	[89]
		CD + UC	↑ *Caudovirales* order	[88,90]
		CD + UC	↓ Phage diversity	[88,90]
	Eukaryotic virome	CD	↑ *Retroviridae* family	[87]
		UC	↑ *Pneumoviridae* family	[90]
		UC	↓ *Anelloviridae* family	[90]
		CD + UC	↑ *Herpesviridae* family	[97,98]
		CD + UC	↑ *Hepadnaviridae* family	[99]
		CD + UC	↑ *Hepeviridae* family	[99]
		UC	↓ *Polydnaviridae* family	[99]
		UC	↓ *Tymoviridae* family	[99]
		CD	↓ *Virgaviridae* family	[99]
Archaeome		CD + UC	↓ *Methanobrevibacter smithii*	[138,140]
		CD + UC	↑ *Methanosphaera stadtmanae*	[138]
Eukaryotic parasites		UC	↑ *Blastocystis hominis*	[157,158]
		UC	↓ *Blastocystis hominis*	[161–165]

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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

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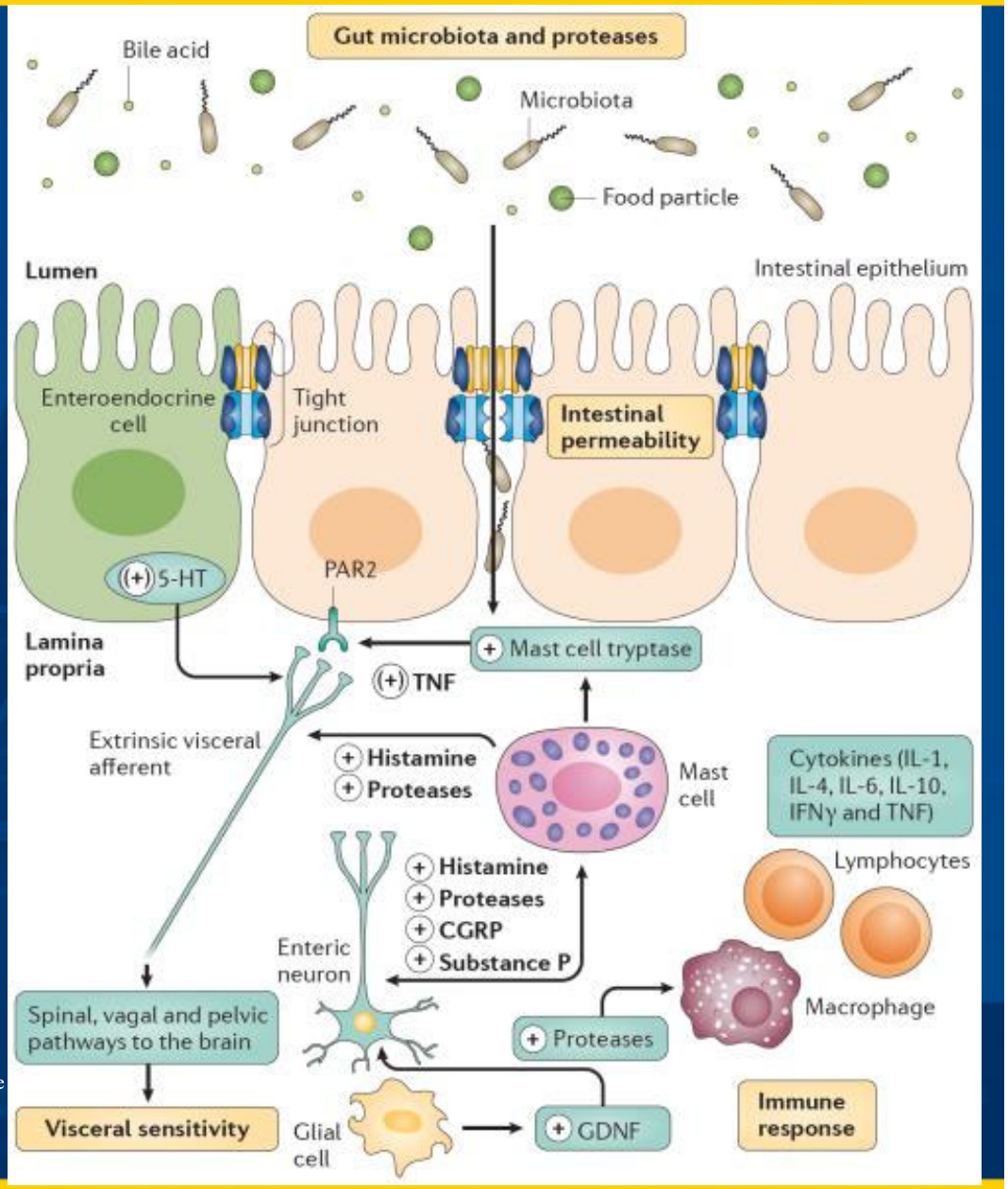
Overview of the Pathophysiology of IBS



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

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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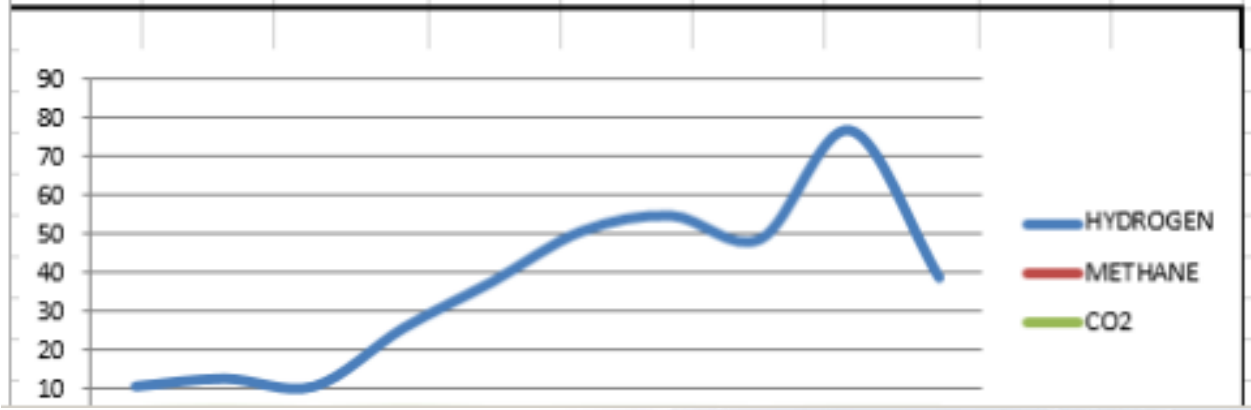
SIBO

Samples	H2	CH4	CO2
BASELINE	11	0	3.9
20min	13	0	4.7
40min	11	0	3.9
60min	26	0	4.7
80min	38	0	4
100min	51	0	4.2
120min	55	0	4.3
140min	49	0	3.9
160min	77	0	4.3
180mn	39	0	4.2



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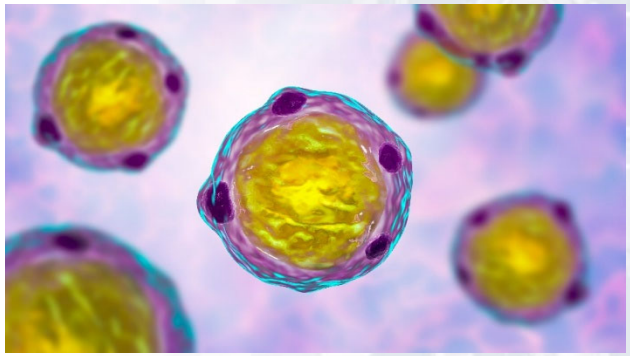
Protozoal Prevalence is Higher then Expected

Statistics from one commercial lab revealed **23.5 % of clinical samples tested positive for at least one parasite** (3,223/13,857).

- *Blastocystis hominis* (12.5%)
- *Dientamoeba fragilis* (3.8%)
- *Entamoeba* spp. (3.4%)
- *Endolimax nana* (2.2%)
- *Giardia lamblia* (0.7%)



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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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Interplay between bile acid metabolism and microbiota in irritable bowel syndrome

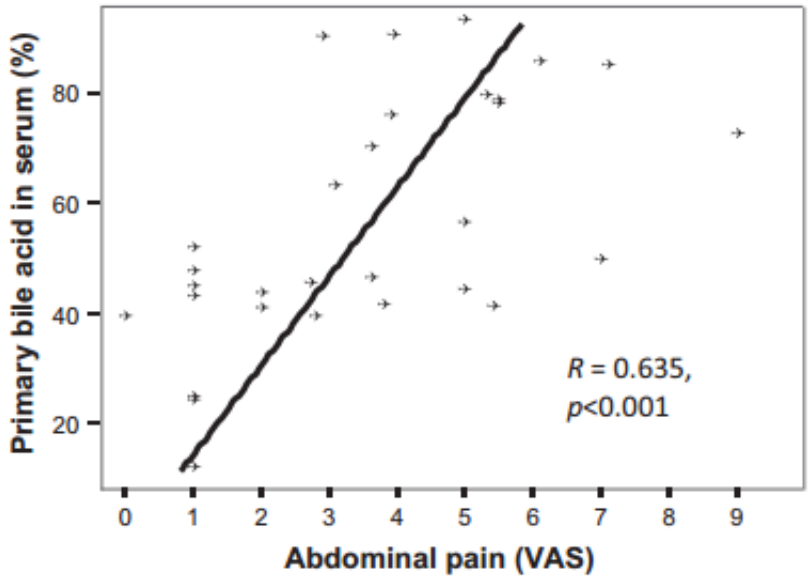

Figure 4 Correlation between primary bile acids in serum and abdominal pain.

Dior, M et al. (2016), Interplay between bile acid metabolism and microbiota in irritable bowel syndrome. *Neurogastroenterol. Motil.,* 28: 1330–1340. doi:10.1111/nmo.12829

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Treatment Plan

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

Patient improved on treatment!!

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Thank you!

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