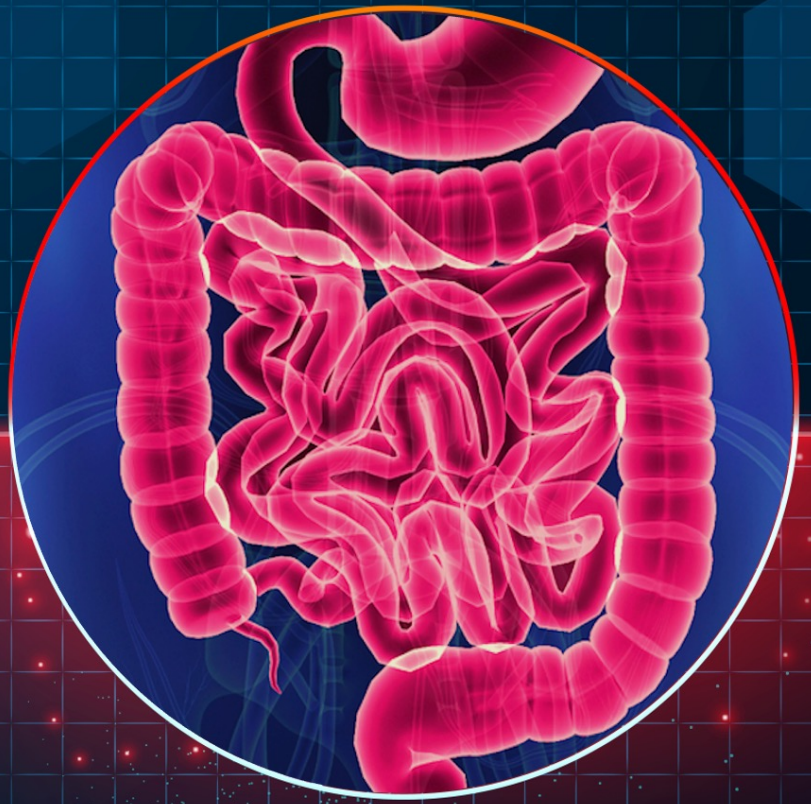
Diagnostic Solutions laboratory

GI-MAP® *Advanced Practice Series*

Assessing Patients with IBS & SIBO Symptoms



Presented by Thomas Fabian, PhD

Irritable Bowel Syndrome

- Diagnosis based on symptoms (Rome IV criteria): frequent abdominal pain, altered motility (IBS-C, IBS-D, IBS-M, IBS-U)
- Bloating & distension are common (90% of IBS-C, lower in IBS-D) but not included in Rome IV criteria
- No widely-accepted test(s) for diagnosis
- **Emerging paradigm:** testing, diagnosis, & treatment will be guided by evidence-based pathophysiological mechanisms (especially ***microbiome & neuro-immune interactions***)

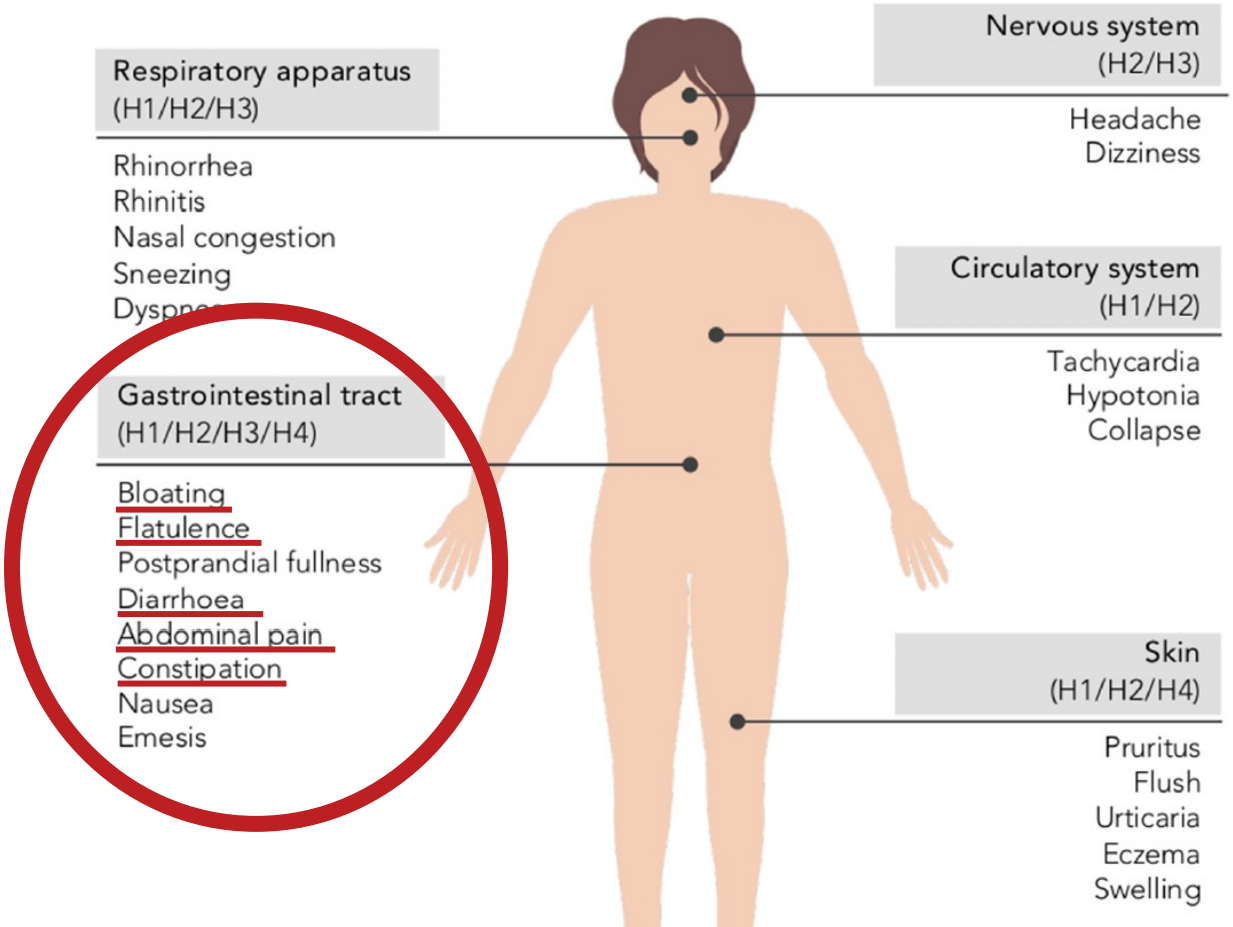
Table 1 Common symptoms of overlapping gastrointestinal disorders in inflammatory bowel disease patients

Disease	Symptoms
Bile-acid malabsorption	Diarrhea, urgency
Exocrine pancreatic insufficiency	Abdominal discomfort, bloating, diarrhea, greasy stools
Carbohydrates intolerance	Abdominal discomfort, bloating, diarrhea
Small intestinal bacterial overgrowth	Abdominal discomfort, bloating, constipation, diarrhea, distention, sensation of incomplete evacuation, urgency
Small intestinal fungal overgrowth	Abdominal discomfort, bloating, diarrhea, distention, urgency
Dyssynergic defecation	Abdominal discomfort, bloating, constipation, diarrhea, distention, sensation of incomplete evacuation, straining, urgency
Ehlers-Danlos syndromes-hypermobility type	Abdominal pain, bloating, constipation, distention, sensation of incomplete evacuation, straining, pelvic floor dysfunction
Mast cell activation syndrome	Abdominal discomfort, bloating, dynamic allergies, diarrhea, distention, sensation of incomplete evacuation, urgency
Eosinophilic gastroenteritis	Abdominal pain, bloating, diarrhea
Intra-abdominal adhesions	Abdominal pain, bloating, distention
Irritable bowel syndrome	Abdominal discomfort, bloating, diarrhea /constipation, distention, sensation of incomplete evacuation, urgency
Celiac disease	Abdominal discomfort, bloating, diarrhea
Giardiasis	Abdominal discomfort, bloating, diarrhea

World J Gastroenterol. 2019 Aug 21;25(31):4414-4426.

Review > Biomolecules. 2020 Aug 14;10(8):1181. doi: 10.3390/biom10081181.

Histamine Intolerance: The Current State of the Art



Gut. 2022 Oct 28;gutjnl-2022-328515.

Original research

Irritable bowel syndrome: treatment based on pathophysiology and biomarkers

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[2]Center of Intestinal Neuroimmune Interaction, Division of Gastroenterology, Translational Research Center for GI Disorders (TARGID), Leuven University, Leuven, Belgium

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ABSTRACT

Objective To appraise the evidence that pathophysiological mechanisms and individualised treatment directed at those mechanisms provide an alternative approach to the treatment of patients with irritable bowel syndrome (IBS).

Design A PubMED-based literature review of mechanisms and treatment of IBS was conducted independently by the two authors, and any differences of perspective or interpretation of the literature were resolved following discussion.

Results The availability of several noninvasive clinical tests can appraise the mechanisms responsible for symptom generation in IBS, including rectal evacuation disorders, abnormal transit, visceral hypersensitivity or hypervigilance, bile acid diarrhoea, sugar intolerances, barrier dysfunction, the microbiome, immune activation and chemicals released by the latter mechanism. The basic molecular mechanisms contributing to these pathophysiologies are increasingly recognised, offering opportunities to intervene with medications directed specifically to food components, receptors and potentially the microbiome. Although the evidence supporting

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The current guidelines suggest algorithms regarding the sequence of choice of medications based on predominant symptoms particularly bowel dysfunction in patients with irritable bowel syndrome (IBS).

WHAT THIS STUDY ADDS

⇒ This review documents the evidence that pathophysiological mechanisms and individualised treatment directed at those mechanisms provide an alternative approach to the management of patients with IBS.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This review focuses the attention of researchers to the translational and basic molecular mechanisms that deserve further studies to enhance the diagnosis and management of IBS, and it informs policy makers and those involved in developing guidelines for clinical practice

Gut. 2022 Oct 28;gutjnl-2022-328515.

"The widespread availability of noninvasive clinical tests that can appraise the mechanisms responsible for symptom generation in IBS provides the opportunity to advance the practice from treatment based on symptoms to ***individualisation of treatment guided by pathophysiology & clinically identified biomarkers****."*

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Review > Gut. 2023 Jan 19;gutjnl-2020-320633.

BMJ Open Access Full Text

OPEN ACCESS

Understanding neuroimmune interactions in disorders of gut–brain interaction: from functional to immune-mediated disorders

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Correspondence to
Professor Guy Boeckxstaens, Translational Research Center for Gastrointestinal Disorders (TARGID), Department of Chronic Diseases and Metabolism (ChroMeta),

ABSTRACT

Functional gastrointestinal disorders—recently renamed into disorders of gut–brain interaction—such as irritable bowel syndrome and functional dyspepsia are highly prevalent conditions with bothersome abdominal symptoms in the absence of structural abnormalities. While traditionally considered as motility disorders or even psychosomatic conditions, our understanding of the pathophysiology has evolved significantly over the last two decades. Initial observations of subtle mucosal infiltration with immune cells, especially mast cells and eosinophils, are since recently being backed up by mechanistic evidence demonstrating increased release of nociceptive mediators by immune cells and the intestinal epithelium. These mediators can activate sensitised neurons leading to visceral hypersensitivity with bothersome symptoms. The interaction between immune activation and an impaired barrier function of the gut

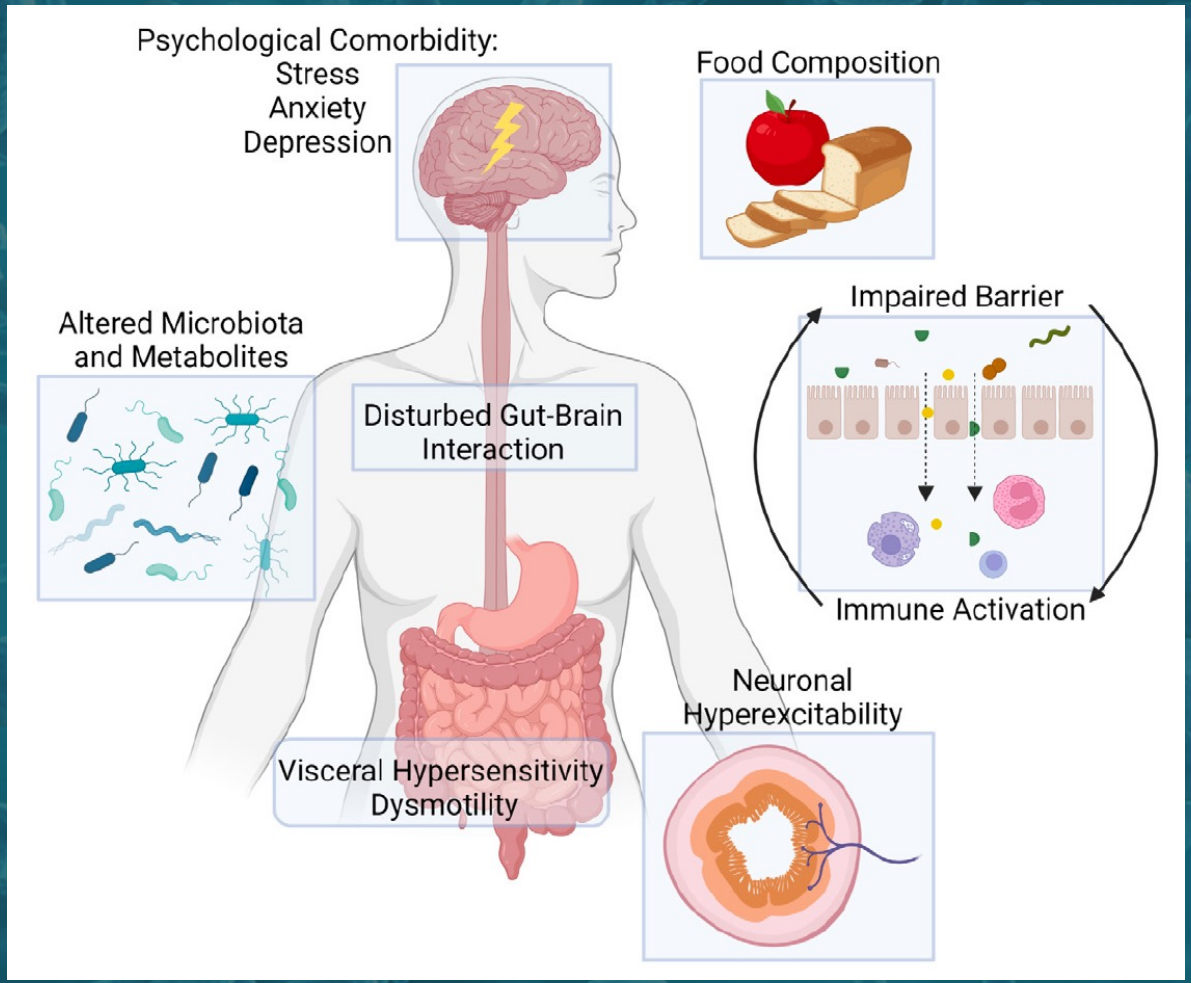
KEY MESSAGES

⇒ Functional gastrointestinal disorders—or disorders of gut–brain interaction—are highly prevalent conditions with limited effective treatment options.
⇒ Mucosal sensory neurons in irritable bowel syndrome patients are sensitised through an increased release of nociceptive mediators from immune cells and the epithelium.
⇒ Subtle infiltration and activation of mast cells and eosinophils, both a source of nociceptive mediators, have been demonstrated in irritable bowel syndrome and functional dyspepsia.
⇒ Psychological stress, food components, microbiota and an impaired barrier function may all contribute to immune activation in functional gastrointestinal disorders.
⇒ Novel treatment options, specifically targeting

ABSTRACT

Functional gastrointestinal disorders—recently renamed into disorders of gut–brain interaction—such as irritable bowel syndrome and functional dyspepsia are highly prevalent conditions with bothersome abdominal symptoms in the absence of structural abnormalities. While traditionally considered as motility disorders or even psychosomatic conditions, our understanding of the pathophysiology has evolved significantly over the last two decades. Initial observations of subtle mucosal infiltration with immune cells, especially mast cells and eosinophils, are since recently being backed up by mechanistic evidence demonstrating increased release of nociceptive mediators by immune cells and the intestinal epithelium. These mediators can activate sensitised neurons leading to visceral hypersensitivity with bothersome symptoms. The interaction between immune activation and an impaired barrier function of the gut is most likely a bidirectional one with alterations in the microbiota, psychological stress and food components as upstream players in the pathophysiology. Only few

Figure 2 Pathophysiological mechanisms in disorders of gut–brain interaction.

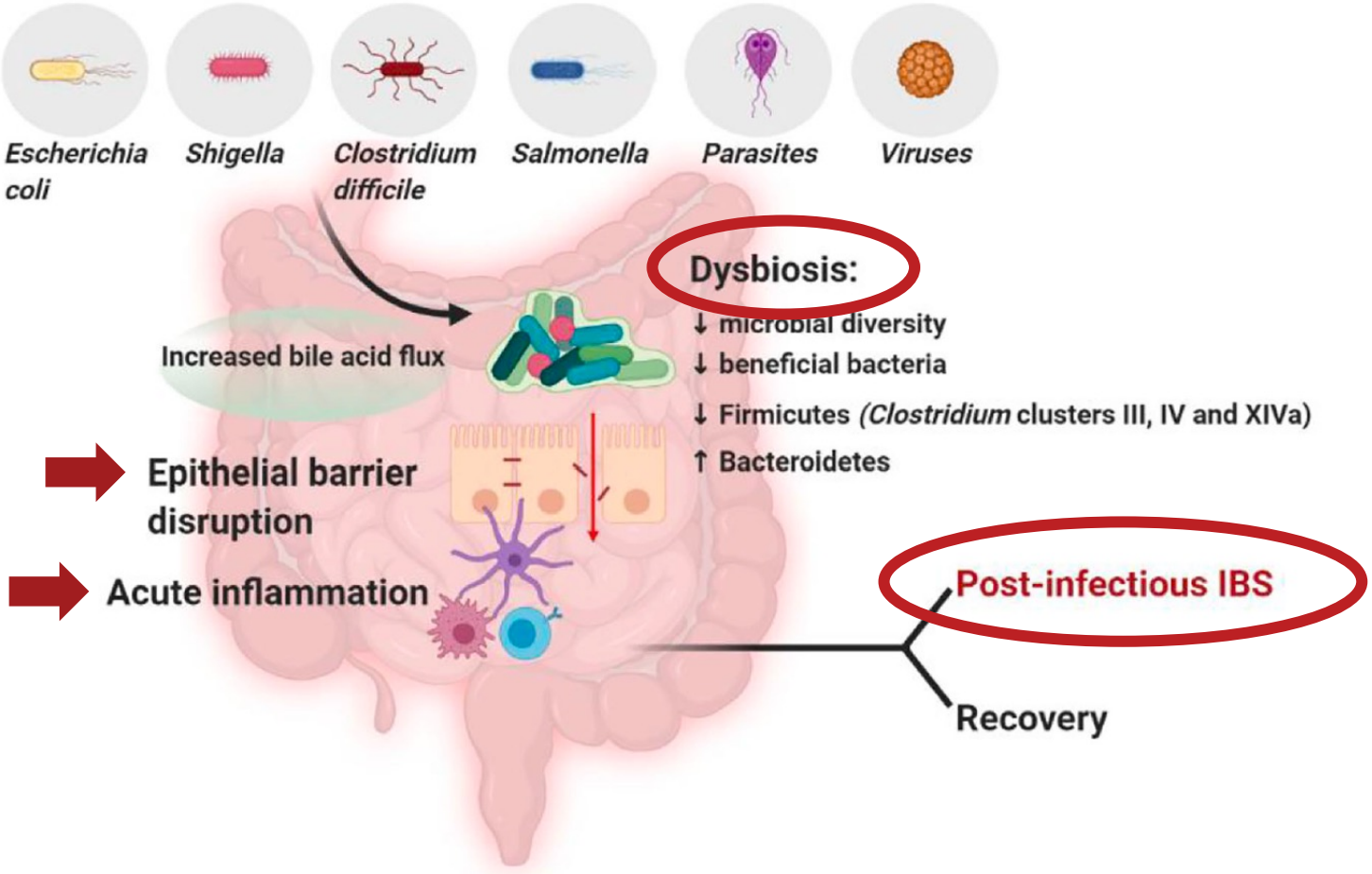


Review > Nat Rev Gastroenterol Hepatol. 2019 Dec;16(12):733-747.
doi: 10.1038/s41575-019-0193-z. Epub 2019 Sep 13.

Intestinal gases: influence on gut disorders and the role of dietary manipulations

"Abdominal ***bloating*** with or without abdominal pain is, in general, ***not associated with excessive gas production***, but rather is a manifestation of ***altered visceral sensitivity***."

"The administration of lactulose (an undigestible disaccharide) has been associated with ***colonic gas production*** (as shown by a marked increase in H_2 levels in the breath) and abdominal ***distension in healthy individuals and patients with IBS***, but ***only patients with IBS experience symptoms of pain and bloating***."



Review > Front Cell Infect Microbiol. 2020 Sep 9;10:468. doi: 10.3389/fcimb.2020.00468.

Nat Rev Gastroenterol Hepatol. 2021 Mar;18(3):149.

IBS

Understanding the immune drivers of food-induced abdominal pain

> After clearance of the infection, repeated exposure to ovalbumin resulted in diarrhoea and gut pain in the mice

A new paper published in *Nature* explores the underlying mechanisms and links between infection, irritable bowel syndrome (IBS) symptoms and food intake. The research reveals that bacterial gastrointestinal infection can trigger a break in oral tolerance and localized immune responses that react to food antigens, leading to meal-induced abdominal pain.

IBS can develop after gastrointestinal infection, and individuals with IBS often report symptoms (including abdominal pain) after food ingestion. Previous work had linked histamine release as a result of mast cell activation to hyper-responsiveness to TRP agonists and increased pain responses in patients with IBS. After clearance of the infection, repeated exposure to ovalbumin resulted in diarrhoea and gut pain in the mice. This bacterial infection led to a local immune response that was limited to the intestine in the mice, with the production of dietary antigen-specific IgE antibodies. Moreover, re-exposure to ovalbumin after infection induced increased visceral hypersensitivity (increased pain responses to colorectal distension). This visceral hypersensitivity was associated with increased mucosal permeability and was dependent on IgE production and mast cell activation (increased mast cell degranulation and histamine release). Notably, the development of increased

individuals as controls. Importantly, none of the study participants were allergic to these antigens (as confirmed by allergy testing, including skin prick testing and checking IgE antibodies in serum). All 12 patients with IBS had mucosal reactions to at least one of the food antigens tested, compared with only two of the healthy individuals. Moreover, food antigens induced local mucosal oedema and mast cell activation in patients with IBS. Although there was no difference in total number of mast cells or IgE^+ mast cells between patients with IBS and healthy individuals, those with IBS had more IgE^+ mast cells in close proximity to nerve fibres. The distance between IgE^+

Nat Rev Gastroenterol Hepatol. 2021 Mar;18(3):149

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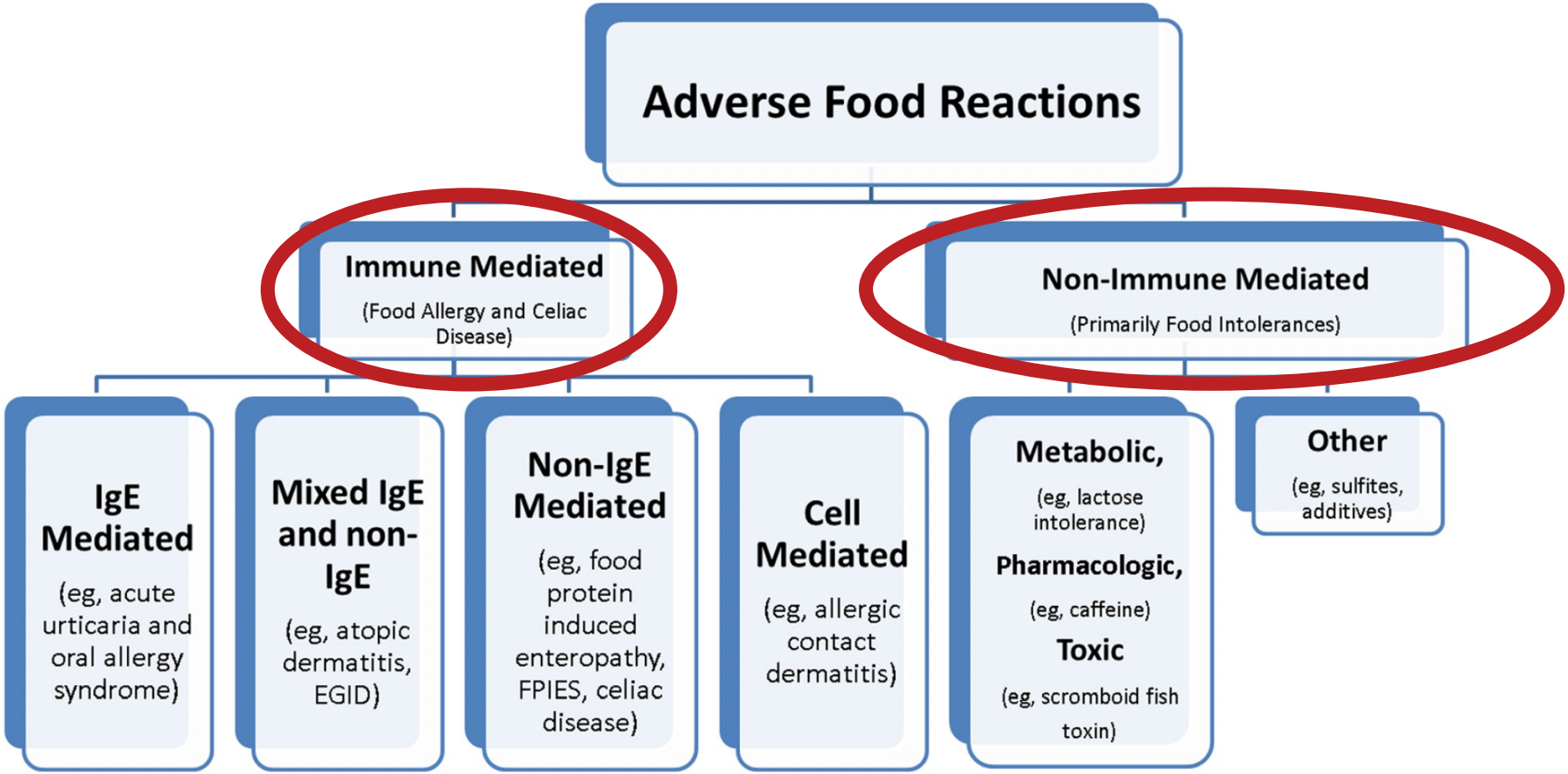


Clinic Rev Allerg Immunol (2019) 57:244–260

› Dig Dis Sci. 2020 Feb;65(2):534-540. doi: 10.1007/s10620-019-05780-7. Epub 2019 Sep 6.

Sucrase–Isomaltase Deficiency as a Potential Masquerader in Irritable Bowel Syndrome

"SID [sucrase-isomaltase deficiency] was found in ***35% of patients with presumed IBS-D/M*** and should be considered in the differential diagnosis of patients presenting with abdominal pain, diarrhea, or bloating."

Review > Front Cell Infect Microbiol. 2020 Sep 9;10:468. doi: 10.3389/fcimb.2020.00468.

frontiers in Cellular and Infection Microbiology

REVIEW
published: 09 September 2020
doi: 10.3389/fcimb.2020.00468

Increasing Evidence That Irritable Bowel Syndrome and Functional Gastrointestinal Disorders Have a Microbial Pathogenesis

Caterina Carco[1,2,3,4], *Wayne Young*[2,3,4], *Richard B. Gearry*[4,5], *Nicholas J. Talley*[6], *Warren C. McNabb*[2,4] *and Nicole C. Roy*[2,4,7,8*]

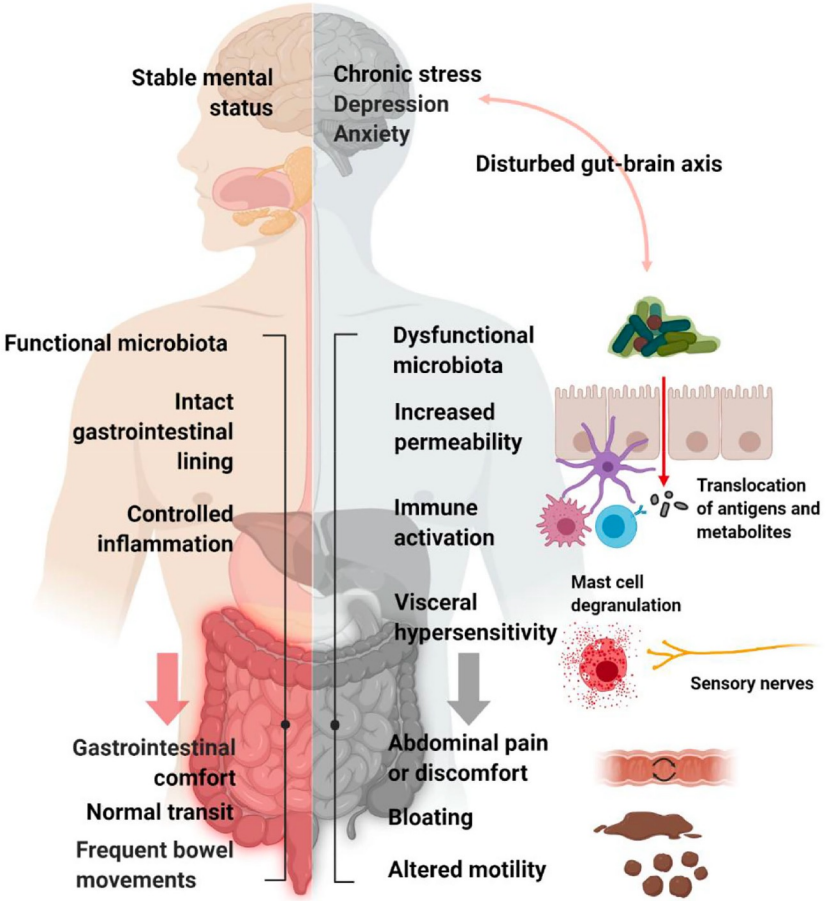
[1] School of Food and Advanced Technology, Massey University, Palmerston North, New Zealand, [2] Riddet Institute, Massey University, Palmerston North, New Zealand, [3] Food Nutrition and Health Team, AgResearch Grasslands, Palmerston North, New Zealand, [4] The High-Value Nutrition National Science Challenge, Auckland, New Zealand, [5] Department of Medicine, University of Otago, Christchurch, New Zealand, [6] Faculty of Health and Medicine, University of Newcastle, Callaghan, NSW, Australia, [7] Liggins Institute, University of Auckland, Auckland, New Zealand, [8] Department of Human Nutrition, University of Otago, Dunedin, New Zealand

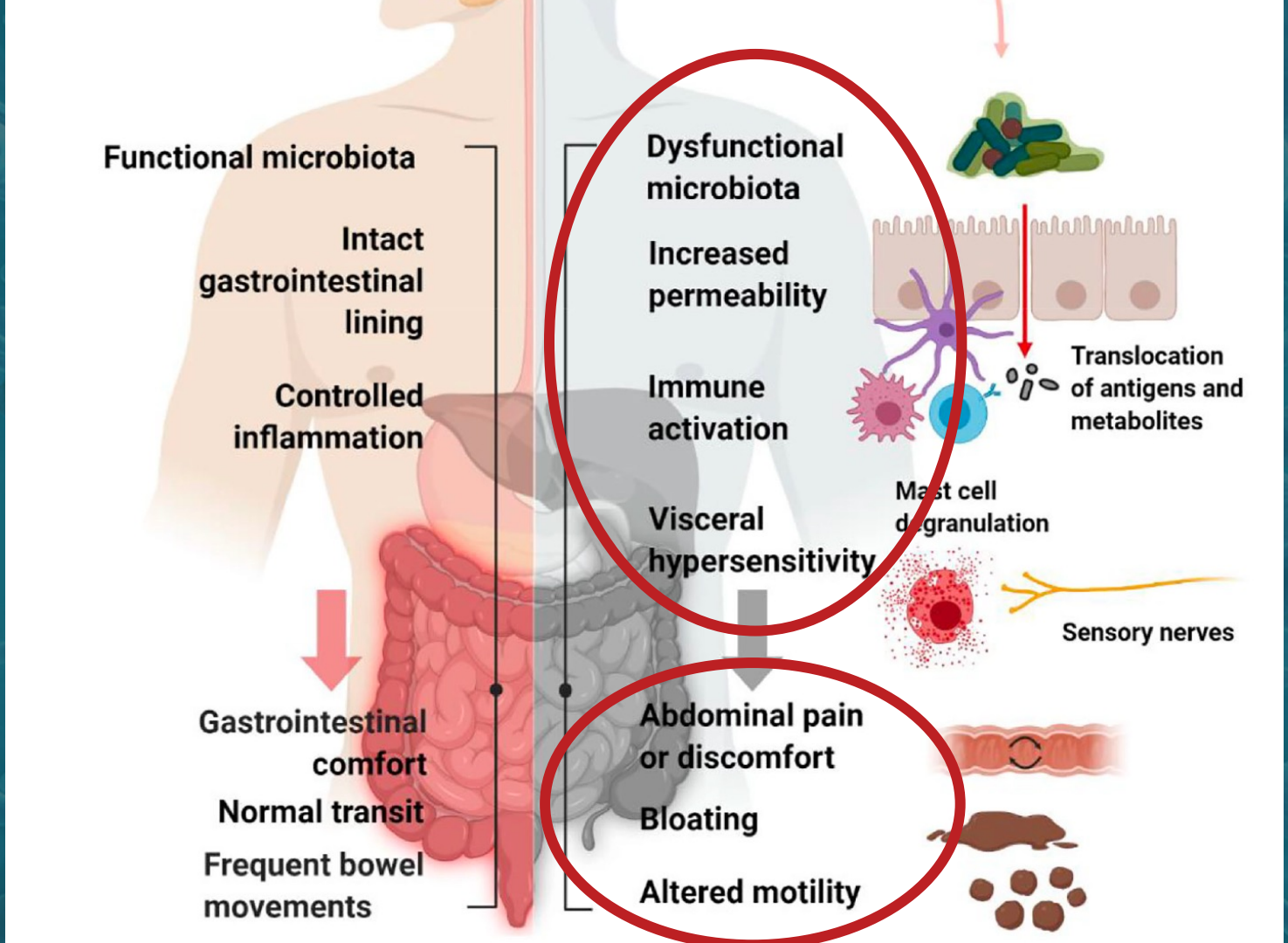
The human gastrointestinal tract harbors most of the microbial cells inhabiting the body, collectively known as the microbiota. These microbes have several implications for the maintenance of structural integrity of the gastrointestinal mucosal barrier, immunomodulation, metabolism of nutrients, and protection against pathogens.

OPEN ACCESS

Edited by:

FIGURE 1 | Schematic representation of IBS pathophysiology.




Functional microbiota
Intact gastrointestinal lining
Controlled inflammation
Gastrointestinal comfort
Normal transit
Frequent bowel movements
Dysfunctional microbiota
Increased permeability
Immune activation
Visceral hypersensitivity
Abdominal pain or discomfort
Bloating
Altered motility
Translocation of antigens and metabolites
Mast cell degranulation
Sensory nerves

IBS – Key Pathophysiological Mechanisms

- ***Microbial involvement:*** infections and dysbiosis, including specific microbes & their products
- ***Immune activation:*** mast cells, eosinophils, etc. induced by foods and/or microbes
- ***Visceral hypersensitivity & altered motility:*** induced by microbial products and/or immune activation
- ***Intestinal barrier dysfunction:*** caused by dysbiosis and immune activation

Microbes Implicated in IBS Pathophysiology

Klebsiella spp.

Staphylococcus aureus

Escherichia coli

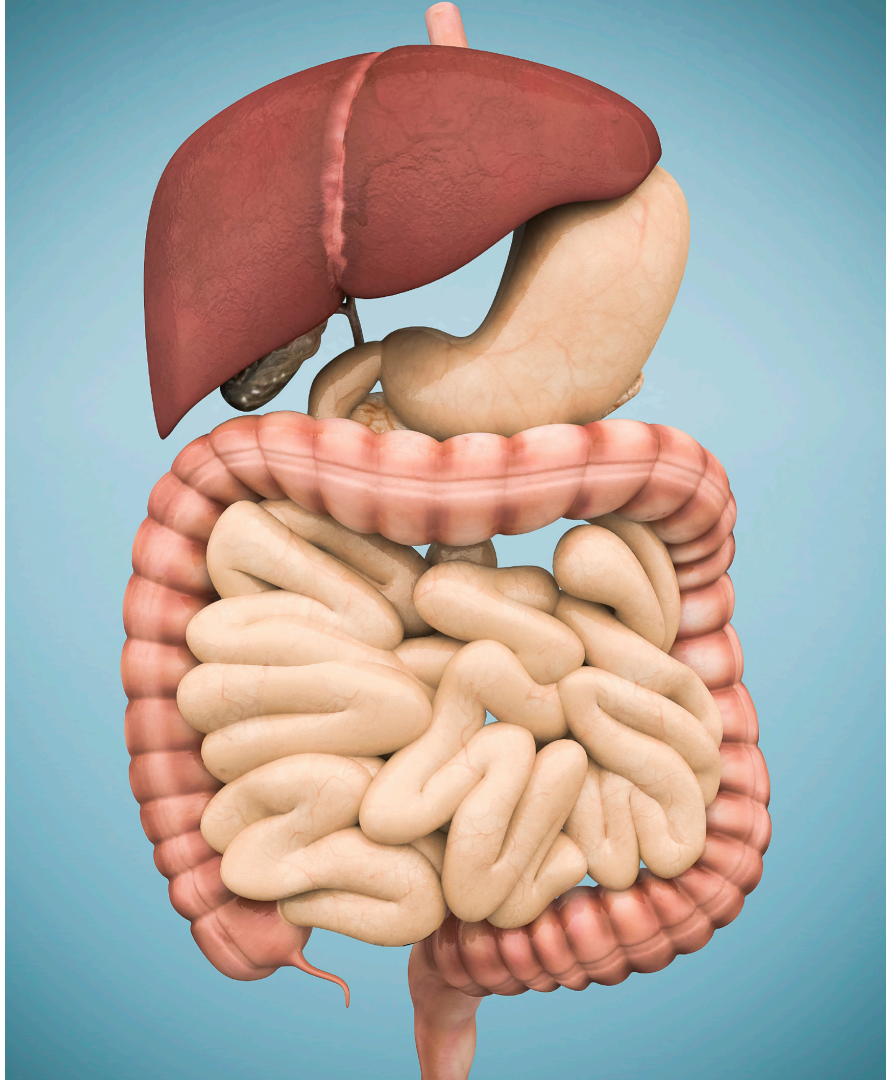
Pseudomonas aeruginosa

Enterococcus spp.

Streptococcus spp.

Firmicutes (H_2)

Methanobacteriaceae (CH_4)



Proc R Soc Med. 1966 Dec;59(12):1244-6.

Influence of abnormal bacterial flora on small intestinal function

Table 2

Percentage incidence of different types of organism cultures from jejunal fluid

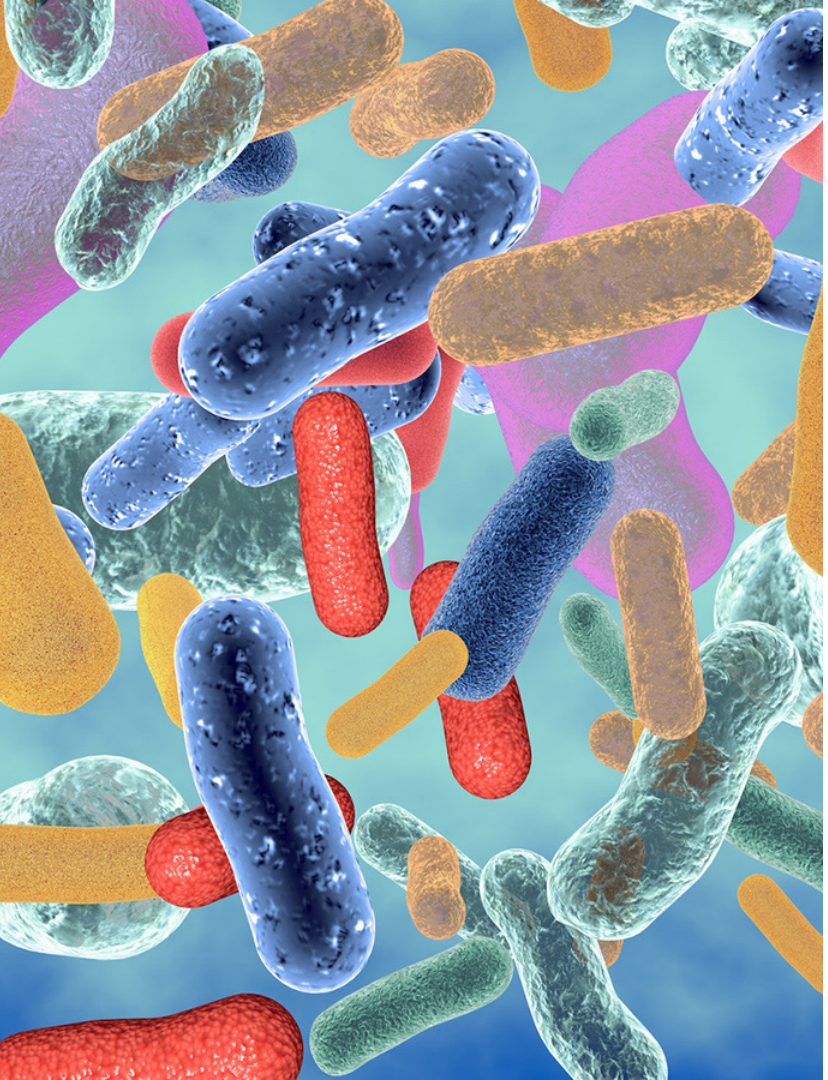
Organism	*Percentage incidence*
E. coli	72
Strep. fæcalis	20
Proteus	10
Klebsiella	8
Strep. viridans	12
Bacteroides and lactobacilli	8
α-hæmolytic streptococci	4
paracolon	

Am J Gastroenterol. 1999 May;94(5):1327-31. doi: 10.1111/j.1572-0241.1999.01016.x.

Bacterial populations contaminating the upper gut in patients with small intestinal bacterial overgrowth syndrome

Table 1. Prevalence of the Main Bacterial Genus Isolated From 55 SIBOS Patients

Bacteria	No. of Viable Organisms (mean ± log CFU/ml)	Prevalence (%)
Microaerophilic	7.4 ± 0.9	100
Streptococcus	6.2 ± 0.8	71
Staphylococcus	6.2 ± 0.6	25
Micrococcus	6.0 ± 0.7	22
Escherichia coli	7.2 ± 0.9	69
Klebsiella	7.1 ± 0.8	20
Proteus	6.1 ± 0.8	11
Acinetobacter	8.0 ± 2.2	9
Enterobacter	7.3 ± 0.2	7
Neisseiria	6.5 ± 0.4	16



Microbial Products Implicated in IBS Pathophysiology

Histamine

Serotonin

Tryptamine

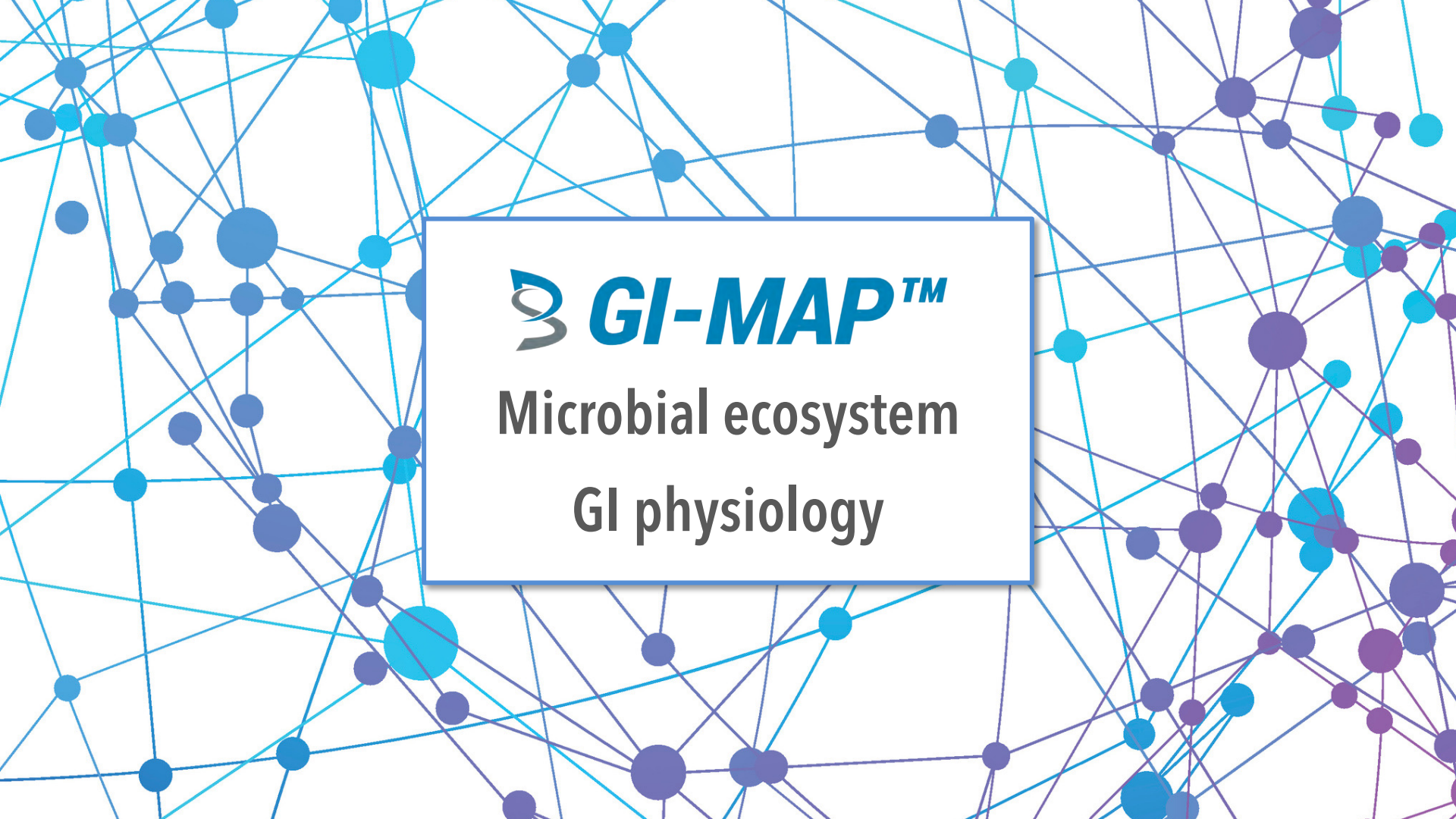
Lipopolysaccharide (LPS)

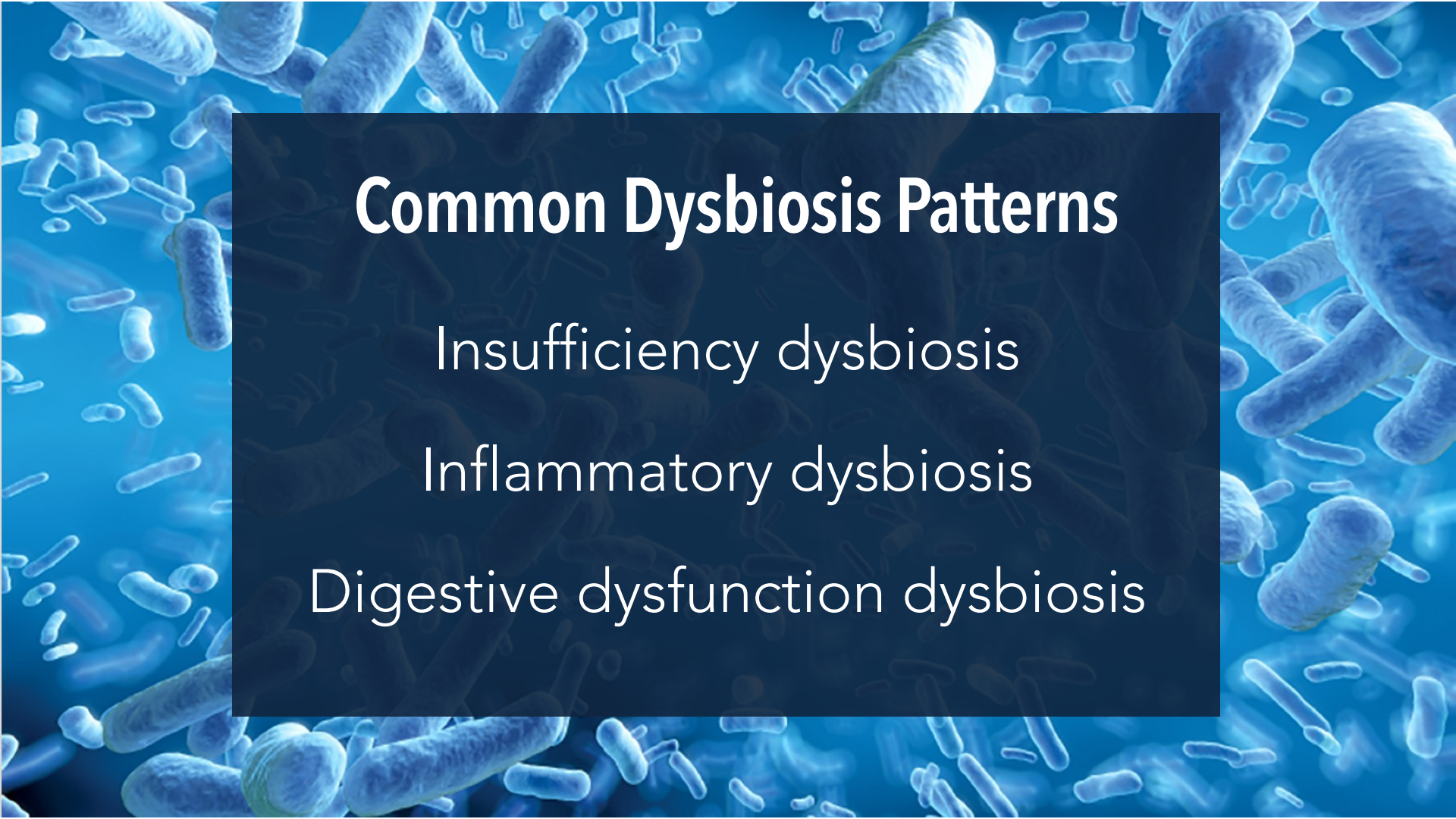
Bile acids

Short-chain fatty acids

Enzymes (proteases, etc.)

Gases (H_2, CH_4, H_2S)


GI-MAP™
Microbial ecosystem
GI physiology


Common Dysbiosis Patterns
Insufficiency dysbiosis
Inflammatory dysbiosis
Digestive dysfunction dysbiosis

GI-MAP PATTERNS

UNDERSTANDING COMMON DYSBIOSIS PATTERNS WITH GI-MAP

INSUFFICIENCY DYSBIOSIS

Insufficiency dysbiosis is characterized by low levels of beneficial bacteria that provide critical support for healthy intestinal and immune function. Insufficient levels of beneficial bacteria may result in an elevated risk of intestinal infections, increased intestinal barrier permeability, decreased protective factors such as secretory IgA, and increased inflammation. Lack of keystone bacteria is common in autoimmune, allergic, and chronic inflammatory conditions.

Table 9.

Markers Characterizing Insufficiency Dysbiosis	
	Bacteroides fragilis
	Bifidobacterium **spp.**
	Enterococcus **spp.**

Gut Barrier Permeability ("Leaky Gut") Pattern			
Intestinal Permeability	Any Pathogen	High	*Pathogens (page 1)*
	Lactobacillus spp.	Low	*Normal Flora (page 2)*
	Akkermansia muciniphila	Low; <dl	
	Candida albicans	High	*Fungi/Yeast (page 3)*
	Anti-gliadin IgA	High	*Intestinal Health Markers (Page 4)*
	Zonulin	High	
Low Butyrate/SCFA Production	*Clostridia (class)*	Low; <dl	*Normal Flora (page 2)*
	Faecalibacterium prausnitzii	Low	
	Firmicutes phylum	Low	
Poor Mucosal Health	*Bifidobacterium* spp.	Low; <dl	*Normal Flora (page 2)*
	Escherichia spp.	Low	
	Lactobacillus spp.	Low	
	Akkermansia muciniphila	Low; <dl	
	Bacteroidetes phylum	Low	

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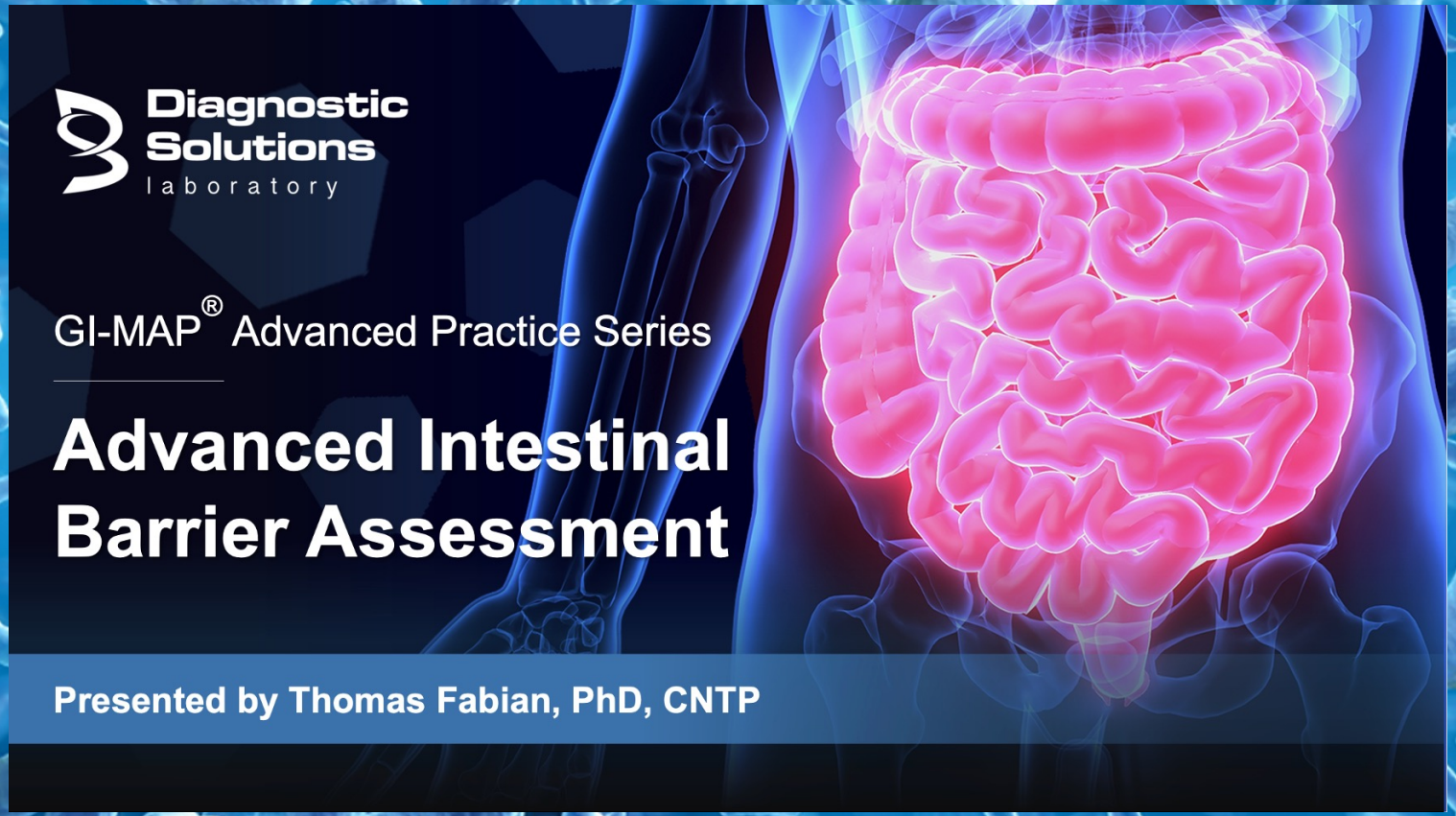
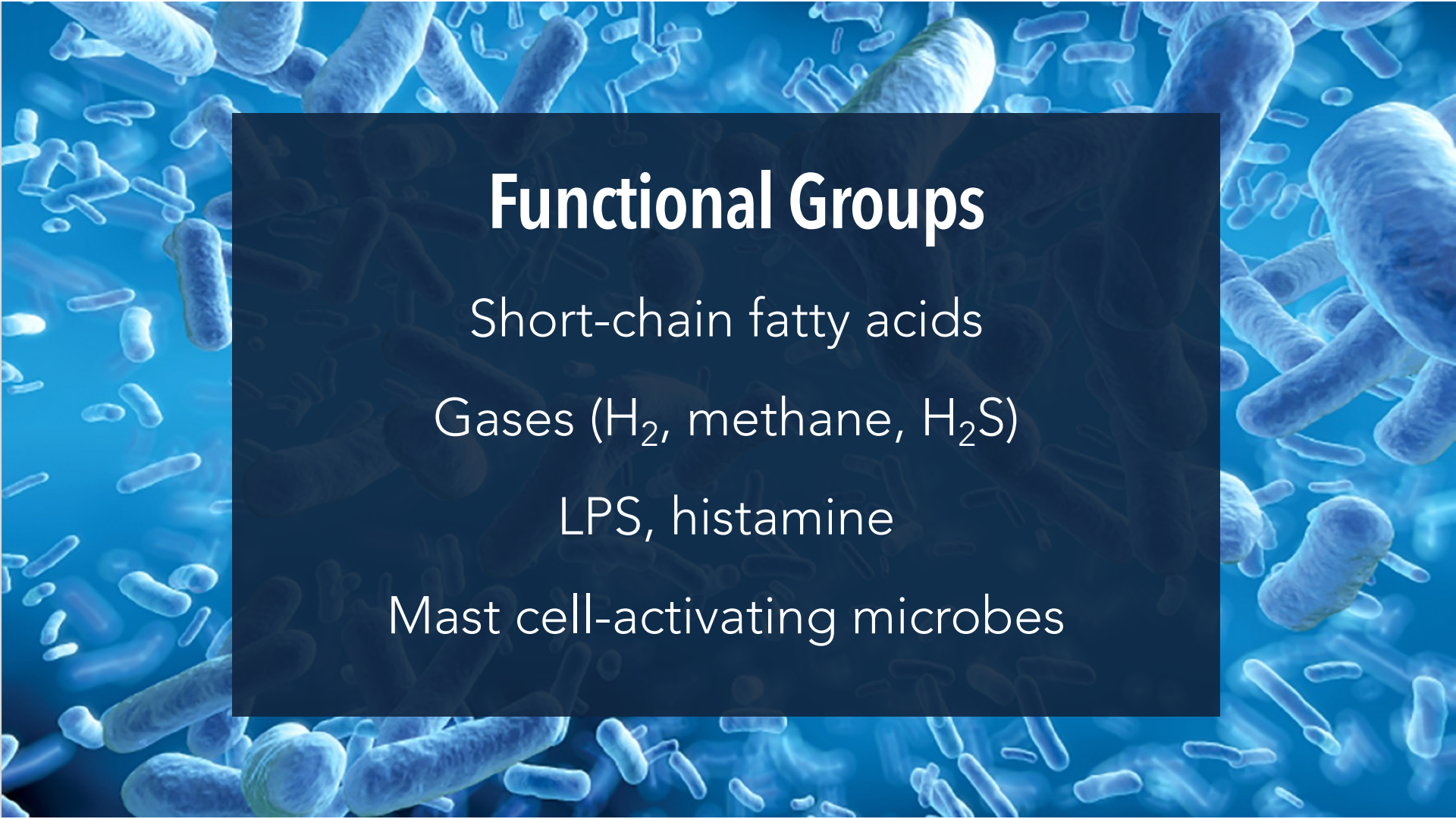
GI-MAP® Advanced Practice Series

Advanced Intestinal Barrier Assessment



Presented by Thomas Fabian, PhD, CNTP


Functional Groups
Short-chain fatty acids
Gases (H_2, methane, H_2S)
LPS, histamine
Mast cell-activating microbes

Diagnostic Solutions laboratory

RESEARCH. TECHNOLOGY. RESULTS.

Microbe Categories and GI-MAP® Patterns Associated with IBS & SIBO

Primary Hydrogen Producers
Faecalibacterium prausnitzii
Roseburia spp.
Bacteroidetes phyla
Firmicutes phyla

Primary Methane Producers
Methanobacteriaceae (family)

Primary Hydrogen Sulfide Producers
Bacteroides fragilis
Escherichia spp.
Enterobacter spp.
Desulfovibrio spp.
Morganella spp.
Pseudomonas aeruginosa
Staphylococcus aureus
Citrobacter spp.
Citrobacter freundii
Klebsiella spp.
Klebsiella pneumoniae
Proteus spp.
Proteus mirabilis
Fusobacterium spp.

Histamine Producing Bacteria
Lactobacillus spp.
Morganella spp.
Pseudomonas

Mast Cell-Activating Microbes
H. pylori
Enterococcus faecalis
Pseudomonas aeruginosa
Staphylococcus aureus
Streptococcus spp.
Candida spp.
Candida albicans
Lipopolysaccharide producers *(see LPS list)*

Lipopolysaccharide (LPS) Producing Bacteria
Escherichia spp.
Enterobacter spp.
Morganella spp.
Pseudomonas spp.
Pseudomonas aeruginosa
Citrobacter spp.
Citrobacter freundii
Klebsiella spp.
Klebsiella pneumoniae
Proteus
Proteus mirabilis

GI-MAP®

GI Microbial Assay Plus

Review > Am J Gastroenterol. 2022 Jun 1;117(6):937-946.
doi: 10.14309/ajg.0000000000001812. Epub 2022 May 4.

Mechanisms Underlying Food-Triggered Symptoms in Disorders of Gut-Brain Interactions

"Diet-microbiota interactions are a critical source of neuroactive mediators that significantly modulate intestinal nociceptive signaling and ***cause visceral hypersensitivity***. Multiple bacterial mediators have been implicated, including ***histamine, proteases, tryptamine, 5-HT [serotonin], and lipopolysaccharide.***"

Review > Gut. 2022 Sep 28;gutjnl-2022-328166. doi: 10.1136/gutjnl-2022-328166.
Online ahead of print.

Advancing human gut microbiota research by considering gut transit time

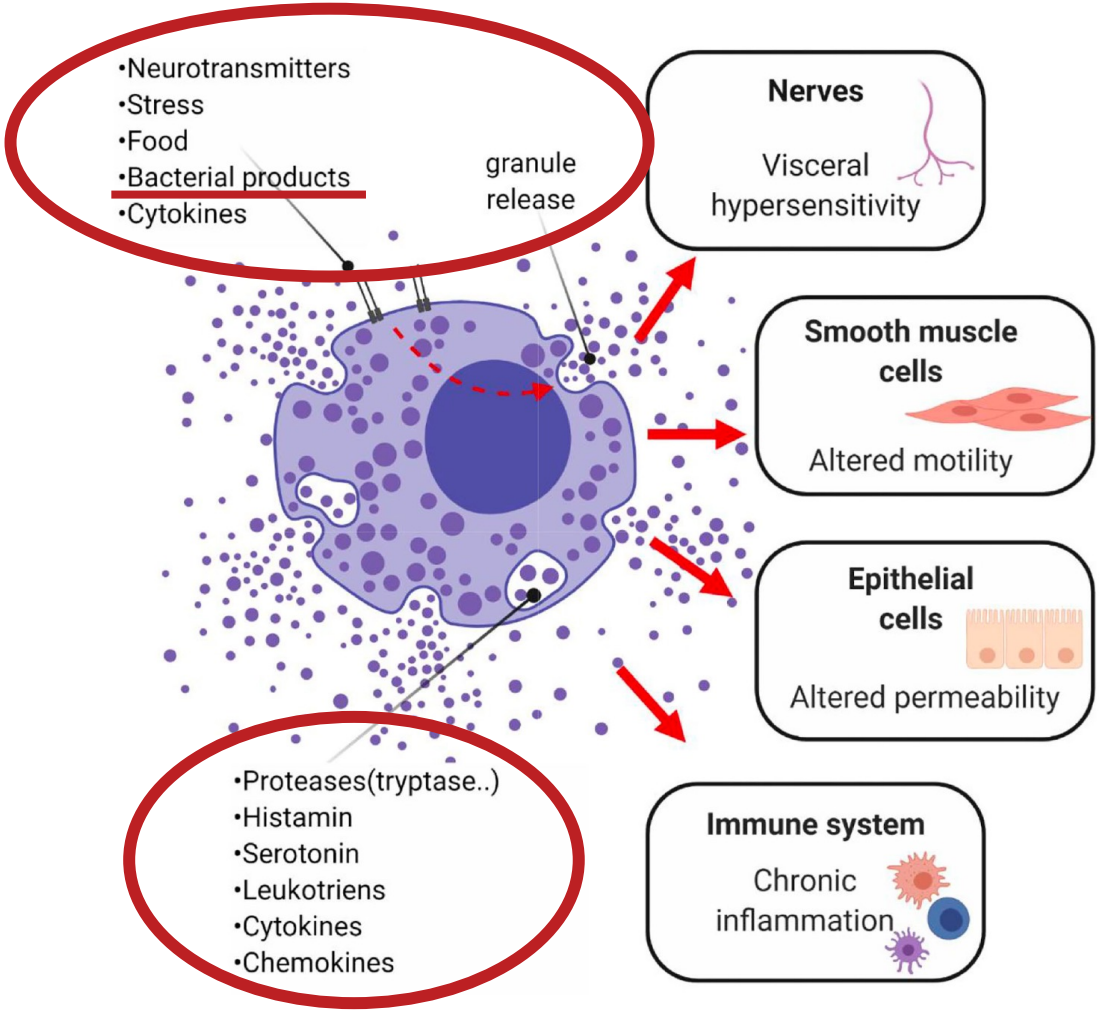
"The gut microbiota produces metabolites such as ***short-chain fatty acids (SCFA), secondary bile acids, tryptamine, histamine, H_2 or CH_4***. These microbial-derived metabolites can influence gastrointestinal motility and thereby impact gut transit time."

Review > Front Immunol. 2021 Jun 15;12:685865. doi: 10.3389/fimmu.2021.685865. eCollection 2021.

Responses of Mast Cells to Pathogens: Beneficial and Detrimental Roles

Microbes that can stimulate mast cell responses:

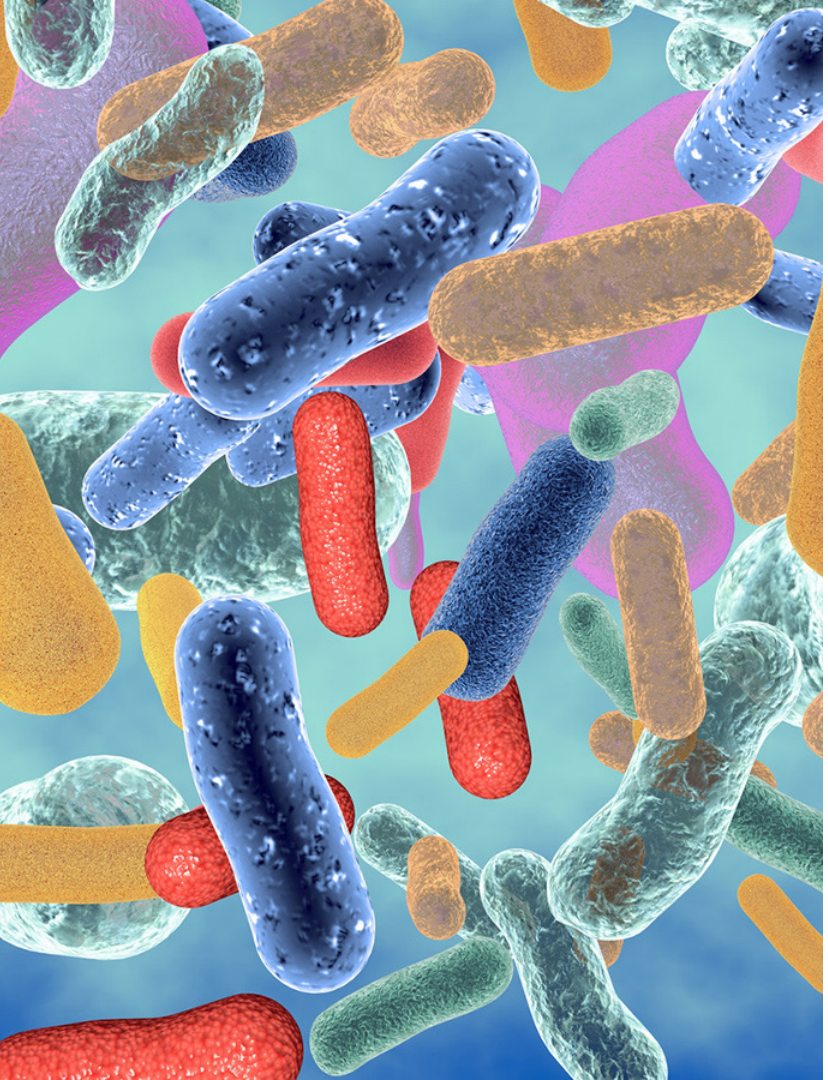
- Staphylococcus aureus
- Streptococcus spp.
- Pseudomonas aeruginosa
- Enterococcus faecalis
- Candida
- H. pylori
- Klebsiella & other LPS and histamine producers



Review > Front Cell Infect Microbiol. 2020 Sep 9;10:468. doi: 10.3389/fcimb.2020.00468.

GI-MAP™

Case Example



Case Example

59 y/o female

Dx with IBS-C

Lower abdominal pain, especially with fatty foods

BACTERIAL PATHOGENS	Result	Reference
Campylobacter	<dl	< 1.00e3
C. difficile Toxin A	<dl	< 1.00e3
C. difficile Toxin B	<dl	< 1.00e3
Enterohemorrhagic E. coli	<dl	< 1.00e3
E. coli O157	<dl	< 1.00e3
Enteroinvasive *E. coli/Shigella*	<dl	< 1.00e3
Enterotoxigenic *E. coli* LT/ST	<dl	< 1.00e3
Shiga-like Toxin *E. coli* stx1	<dl	< 1.00e3
Shiga-like Toxin *E. coli* stx2	<dl	< 1.00e3
Salmonella	<dl	< 1.00e4
Vibrio cholerae	<dl	< 1.00e5
Yersinia enterocolitica	<dl	< 1.00e5
PARASITIC PATHOGENS		
Cryptosporidium	<dl	< 1.00e6
Entamoeba histolytica	<dl	< 1.00e4
Giardia	<dl	< 5.00e3
VIRAL PATHOGENS		
Adenovirus 40/41	<dl	< 1.00e10
Norovirus GI/II	<dl	< 1.00e7

HELICOBACTER PYLORI

H. PYLORI & VIRULENCE FACTORS	Result	Reference
Helicobacter pylori	1.33e2	< 1.00e3
Virulence Factor, babA	N/A	Negative
Virulence Factor, cagA	N/A	Negative
Virulence Factor, dupA	N/A	Negative
Virulence Factor, iceA	N/A	Negative
Virulence Factor, oipA	N/A	Negative
Virulence Factor, vacA	N/A	Negative
Virulence Factor, virB	N/A	Negative
Virulence Factor, virD	N/A	Negative

COMMENSAL/KEYSTONE BACTERIA

COMMENSAL BACTERIA	Result	Reference
Bacteroides fragilis	3.48e9	1.6e9 - 2.5e11
Bifidobacterium spp.	4.36e9	> 6.7e7
Enterococcus spp.	2.43e5	1.9e5 - 2.0e8
Escherichia spp.	3.15e5 L	3.7e6 - 3.8e9
Lactobacillus spp.	2.47e6	8.6e5 - 6.2e8
Enterobacter spp.	1.53e6	1.0e6 - 5.0e7
Akkermansia muciniphila	<dl L	1.0e1 - 8.2e6
Faecalibacterium prausnitzii	9.80e6	1.0e3 - 5.0e8
Roseburia spp.	3.98e7 L	5.0e7 - 2.0e10

BACTERIAL PHYLA		
Bacteroidetes	3.05e11 L	8.6e11 - 3.3e12
Firmicutes	3.17e10 L	5.7e10 - 3.0e11
Firmicutes:Bacteroidetes Ratio	0.10	< 1.0

DYSBIOTIC & OVERGROWTH BACTERIA	Result		Reference
Bacillus spp.	1.68e5		< 1.76e6
Enterococcus faecalis	**7.42e5**	**High ↑**	< 1.00e4
Enterococcus faecium	2.39e3		< 1.00e4
Morganella spp.	<dl		< 1.00e3
Pseudomonas spp.	**4.53e8**	**High ↑**	< 1.00e4
Pseudomonas aeruginosa	**9.19e3**	**High ↑**	< 5.00e2
Staphylococcus spp.	<dl		< 1.00e4
Staphylococcus aureus	<dl		< 5.00e2
Streptococcus spp.	**4.53e4**	**High ↑**	< 1.00e3
COMMENSAL OVERGROWTH MICROBES			
Desulfovibrio spp.	6.54e5		< 7.98e8
Methanobacteriaceae (family)	2.43e6		< 3.38e8

INFLAMMATORY & AUTOIMMUNE-RELATED BACTERIA			
Citrobacter spp.	1.67e4		< 5.00e6
Citrobacter freundii	4.69e5		< 5.00e5
Klebsiella spp.	**1.66e5**	**High ↑**	< 5.00e3
Klebsiella pneumoniae	**4.16e5**	**High ↑**	< 5.00e4
M. avium subsp. paratuberculosis	<dl		< 5.00e3
Proteus spp.	<dl		< 5.00e4
Proteus mirabilis	<dl		< 1.00e3
COMMENSAL INFLAMMATORY & AUTOIMMUNE-RELATED BACTERIA			
Enterobacter spp.	1.53e6		< 5.00e7
Escherichia spp.	3.15e5		< 3.80e9
Fusobacterium spp.	3.20e5		< 1.00e8
Prevotella spp.	3.25e6		< 1.00e8

FUNGI/YEAST

FUNGI/YEAST	Result	Reference
Candida spp.	<dl	< 5.00e3
Candida albicans	<dl	< 5.00e2
Geotrichum spp.	<dl	< 3.00e2
Microsporidium spp.	<dl	< 5.00e3
Rhodotorula spp.	<dl	< 1.00e3

VIRUSES

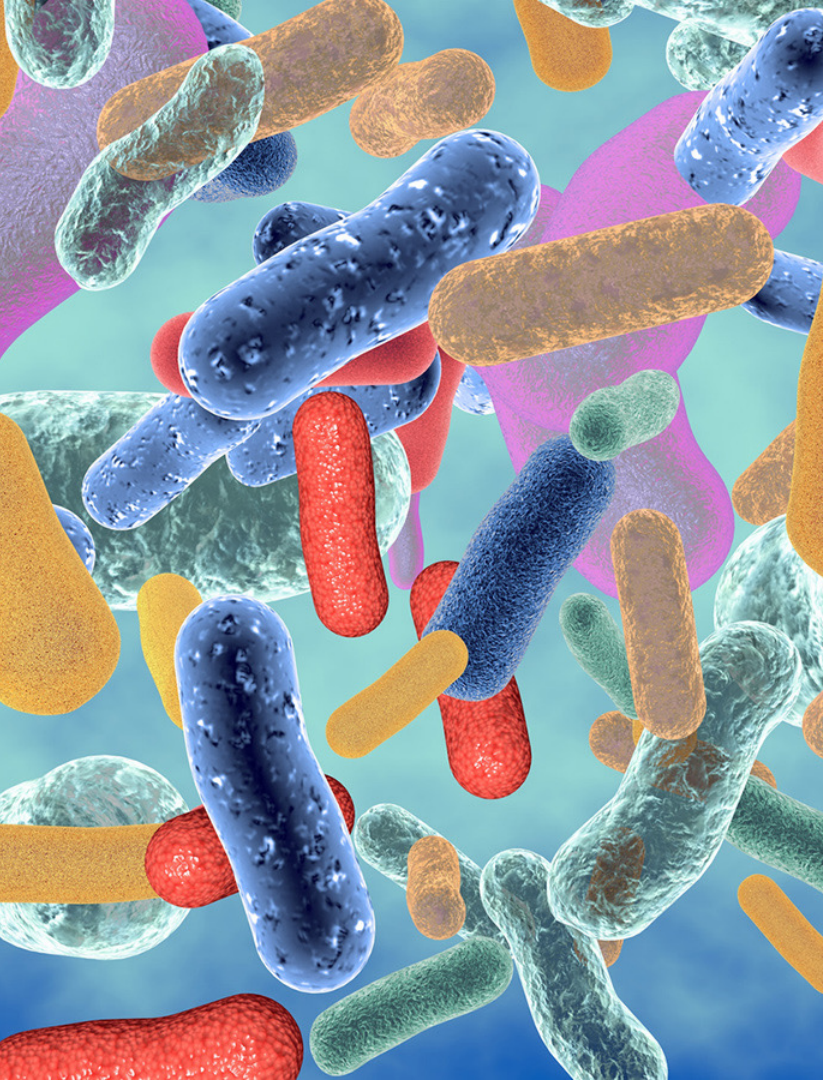
VIRUSES	Result	Reference
Cytomegalovirus	<dl	< 1.00e5
Epstein-Barr Virus	<dl	< 1.00e7

PARASITES

PROTOZOA	Result	Reference
Blastocystis hominis	<dl	< 2.00e3
Chilomastix mesnili	<dl	< 1.00e5
Cyclospora spp.	<dl	< 5.00e4
Dientamoeba fragilis	<dl	< 1.00e5
Endolimax nana	<dl	< 1.00e4
Entamoeba coli	<dl	< 5.00e6
Pentatrichomonas hominis	<dl	< 1.00e2
WORMS		
Ancylostoma duodenale	Not Detected	Not Detected
Ascaris lumbricoides	Not Detected	Not Detected
Necator americanus	Not Detected	Not Detected
Trichuris trichiura	Not Detected	Not Detected
Taenia spp.	Not Detected	Not Detected

INTESTINAL HEALTH MARKERS

DIGESTION	Result	Reference
Steatocrit	8	< 15 %
Elastase-1	601	> 200 ug/g
GI MARKERS		
β-Glucuronidase	883	< 2486 U/mL
Occult Blood - FIT	<dl	< 10 ug/g
IMMUNE RESPONSE		
Secretory IgA	439 L	510 - 2010 ug/g
Anti-gliadin IgA	133	< 175 U/L
Eosinophil Activation Protein (EDN, EPX)	0.94	< 2.34 ug/g
INFLAMMATION		
Calprotectin	26	< 173 ug/g



Case Summary

Low commensal & keystone species

Opportunistic overgrowth, including Klebsiella and Pseudomonas

Low secretory IgA, elevated steatocrit

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Bacillus spp.	1.68e5		< 1.76e6
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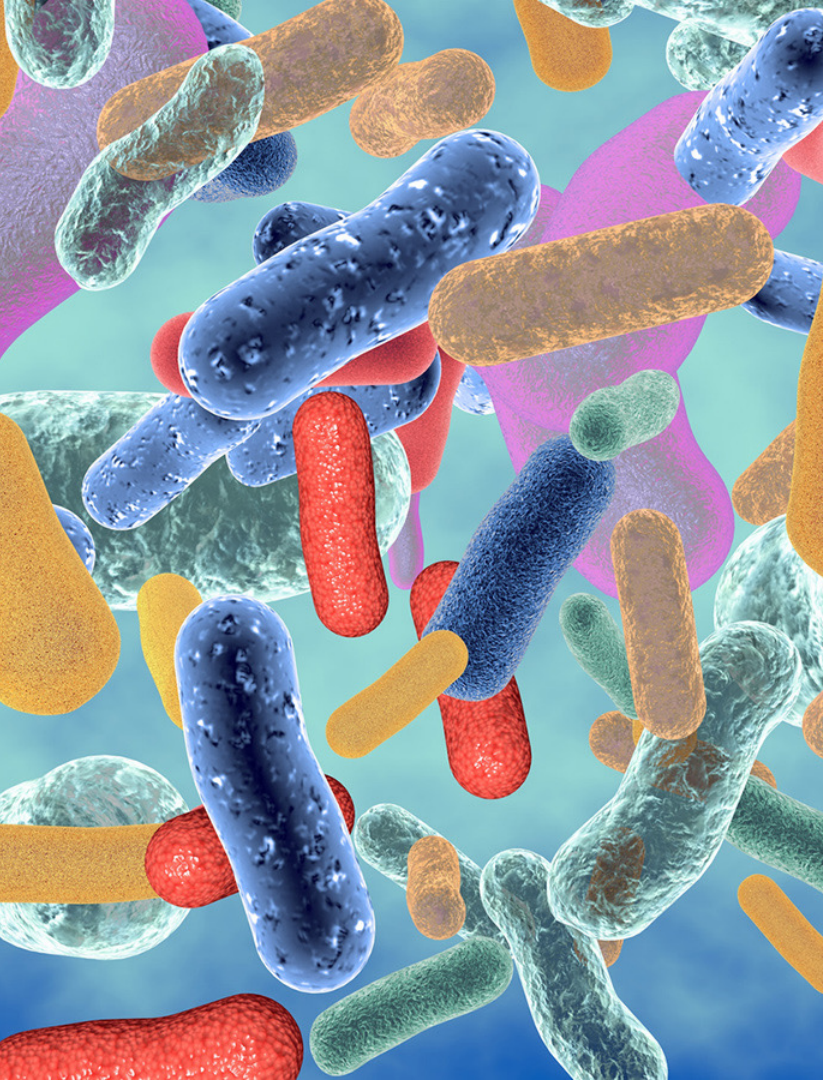

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Opportunistic overgrowth, including Klebsiella and Pseudomonas

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COMMENSAL/KEYSTONE BACTERIA

COMMENSAL BACTERIA	Result	Reference
Bacteroides fragilis	3.48e9	1.6e9 - 2.5e11
Bifidobacterium spp.	4.36e9	> 6.7e7
Enterococcus spp.	2.43e5	1.9e5 - 2.0e8
Escherichia spp.	3.15e5 L	3.7e6 - 3.8e9
Lactobacillus spp.	2.47e6	8.6e5 - 6.2e8
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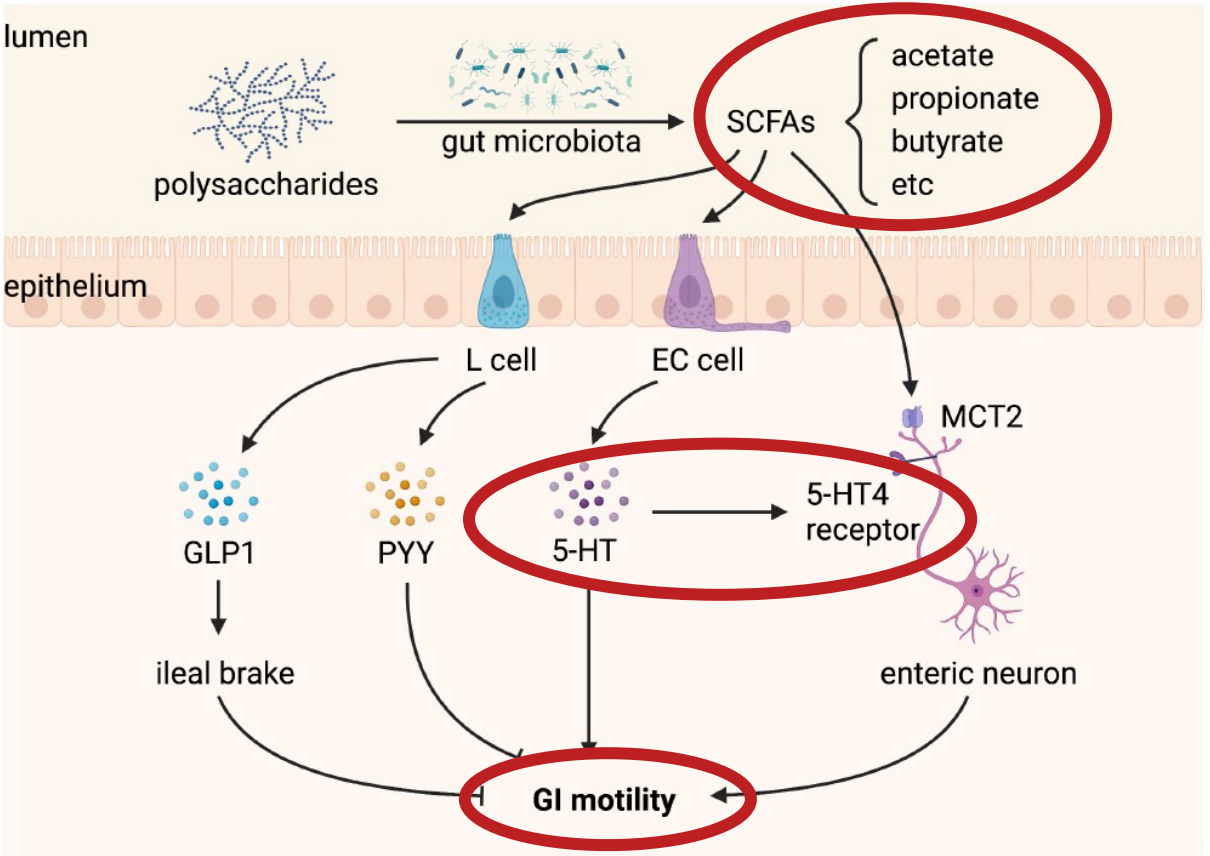
Review > Gut. 2022 Sep 28;gutjnl-2022-328166. doi: 10.1136/gutjnl-2022-328166.
Online ahead of print.

Advancing human gut microbiota research by considering gut transit time

"The gut microbiota produces metabolites such as ***short-chain fatty acids (SCFA), secondary bile acids, tryptamine, histamine, H_2 or CH_4***. These microbial-derived metabolites can influence gastrointestinal motility and thereby impact gut transit time."

FIGURE 5

Short-chain fatty acids (SCFAs) produced by gut microbiota regulate gastrointestinal (GI) motility.



Front Med (Lausanne). 2022 Jul 22;9:961703.

Allergy. 2020 Aug;75(8):1966-1978.

Received: 8 October 2019 | Revised: 24 January 2020 | Accepted: 6 February 2020

DOI: 10.1111/all.14254

ORIGINAL ARTICLE

Basic and Translational Allergy Immunology

Butyrate inhibits human mast cell activation via epigenetic regulation of FcεRI-mediated signaling

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[2]Department of Pulmonary Medicine, Erasmus MC Rotterdam, Rotterdam, The Netherlands

[3]Department of Pathology, Stanford University School of Medicine, Stanford, CA, USA

[4]Dermatological Allergology, Dermatology and Allergy, Charité – Universitätsmedizin Berlin, Berlin, Germany

[5]Department of Molecular Pharmacology, Faculty of Science and Engineering, University of Groningen, Groningen, The

Abstract

Background: Short-chain fatty acids (SCFAs) are fermented dietary components that regulate immune responses, promote colonic health, and suppress mast cell–mediated diseases. However, the effects of SCFAs on human mast cell function, including the underlying mechanisms, remain unclear. Here, we investigated the effects of the SCFAs (acetate, propionate, and butyrate) on mast cell–mediated pathology and human mast cell activation, including the molecular mechanisms involved.

Method: Precision-cut lung slices (PCLS) of allergen-exposed guinea pigs were used to assess the effects of butyrate on allergic airway contraction. Human and mouse mast cells were co-cultured with SCFAs and assessed for degranulation after IgE- or non–IgE-mediated stimulation. The underlying mechanisms involved were investi-

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Review > Front Med (Lausanne). 2022 Jul 22;9:961703. doi: 10.3389/fmed.2022.961703. eCollection 2022.

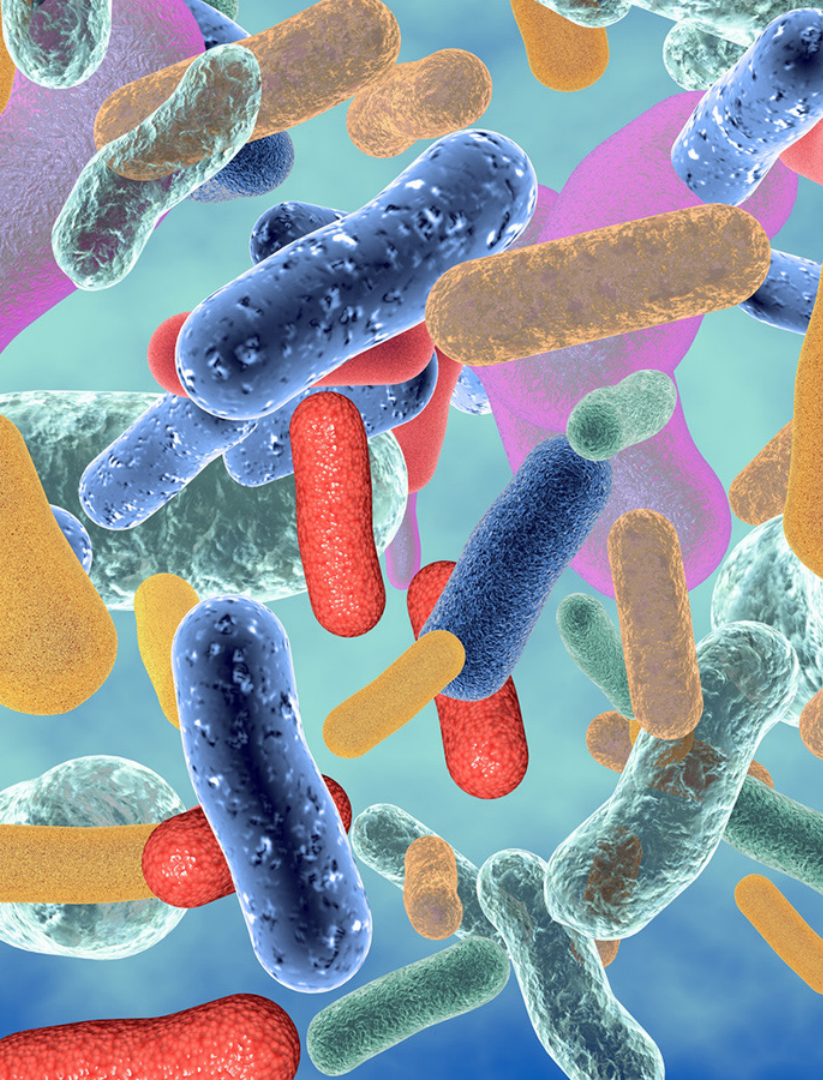
Role of gut microbiota-derived signals in the regulation of gastrointestinal motility

Other specific cell wall components of commensal bacteria can also directly interact with TLR2. Amuc_1100, an outer membrane protein of *Akkermansia muciniphila* (*A. mucinphila*), promotes the intestinal biosynthesis of serotonin (5-HT) and further improves the function of GI motility through TLR2 signaling (41). *Clostridium butyricum* (*C. butyricum*), a probiotic strain, increase the secretion of ghrelin and SP and may promote GI motility by inducing the cell viability of ICCs

Review > Int J Mol Sci. 2021 Sep 23;22(19):10235. doi: 10.3390/ijms221910235.

Enteric Microbiota-Mediated Serotonergic Signaling in Pathogenesis of Irritable Bowel Syndrome

"One of the most important neurotransmitters in the pathology of IBS is serotonin (5-HT), as it influences gastrointestinal motility, pain sensation, mucosal inflammation, immune responses, and brain activity, all of which shape IBS features."



Case Summary

Low commensal & keystone species

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Citrobacter spp.	1.67e4		< 5.00e6
Citrobacter freundii	4.69e5		< 5.00e5
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Prevotella spp.	3.25e6		< 1.00e8

Comment > Nat Rev Gastroenterol Hepatol. 2022 Oct;19(10):623.
doi: 10.1038/s41575-022-00681-z.

Bacterial histamine and abdominal pain in IBS

"***Bacterium-produced histamine induces abdominal pain sensitivity*** via histamine H4 receptor signalling, leading to the ***accumulation and activation of mast cells in the colon***. The study pinpoints ***Klebsiella aerogenes as a major producer of histamine*** and a potential therapeutic target in the management of pain in irritable bowel syndrome (IBS)."

Review > Biomolecules. 2020 Aug 14;10(8):1181. doi: 10.3390/biom10081181.

Histamine Intolerance: The Current State of the Art

"Specifically, the Enterobacteriaceae species Hafnai aluei, Morganella morganii and ***Klebsiella pneumoniae*** have been identified as some of the most ***prolific histamine-forming bacteria***. "

DYSBIOTIC & OVERGROWTH BACTERIA	Result		Reference
Bacillus spp.	1.68e5		< 1.76e6
Enterococcus faecalis	**7.42e5**	**High ↑**	< 1.00e4
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Staphylococcus spp.	<dl		< 1.00e4
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COMMENSAL OVERGROWTH MICROBES			
Desulfovibrio spp.	6.54e5		< 7.98e8
Methanobacteriaceae (family)	2.43e6		< 3.38e8

Journal of Medical Microbiology (2011), **60**, 236–245 DOI 10.1099/jmm.0.022848-0

Molecular analysis of faecal and duodenal samples reveals significantly higher prevalence and numbers of *Pseudomonas aeruginosa* in irritable bowel syndrome

Angèle P. M. Kerckhoffs,[1] Kaouther Ben-Amor,[2] Melvin Samsom,[1] Michel E. van der Rest,[3] Joris de Vogel,[3] Jan Knol[2] and Louis M. A. Akkermans[1]

Correspondence
Angèle P. M. Kerckhoffs
AngeleKerckhoffs@hotmail.com

[1]Gastrointestinal Research Unit, Departments of Gastroenterology and Surgery, University Medical Center Utrecht, Utrecht, The Netherlands

[2]Danone Research – Centre for Specialised Nutrition, Wageningen, The Netherlands

[3]BioVisible BV, Groningen, The Netherlands

Intestinal microbiota may play a role in the pathophysiology of irritable bowel syndrome (IBS). In this case–control study, mucosa-associated small intestinal and faecal microbiota of IBS patients and healthy subjects were analysed using molecular-based methods. Duodenal mucosal brush and faecal samples were collected from 37 IBS patients and 20 healthy subjects. The bacterial 16S rRNA gene was amplified and analysed using PCR denaturing gradient gel electrophoresis (DGGE). Pooled average DGGE profiles of all IBS patients and all healthy subjects from both sampling sites were generated and fingerprints of both groups were compared. The DGGE band fragments which were confined to one group were further characterized by sequence analysis. Quantitative real-time PCR (q-PCR) was used to quantify the disease-associated microbiota. Averaged DGGE profiles of both groups were identical for 78.2 % in the small intestinal samples and for 86.25 % in the faecal samples. Cloning and sequencing of the specific bands isolated from small intestinal and faecal DGGE patterns of IBS patients showed that 45.8 % of the clones belonged to the genus *Pseudomonas*, of which *Pseudomonas aeruginosa* was the predominant species. q-PCR analysis revealed higher levels ($P<0.001$) of *P. aeruginosa* in the small intestine of IBS patients (8.3 % ± 0.950) than in the small

> Nat Commun. 2019 Mar 13;10(1):1198. doi: 10.1038/s41467-019-09037-9.

Duodenal bacterial proteolytic activity determines sensitivity to dietary antigen through protease-activated receptor-2

"These results demonstrate that ***proteases expressed by opportunistic pathogens*** impact host immune responses that are relevant to the development of food sensitivities, independently of the trigger antigen."

Comment Immunity. 2022 May 10;55(5):824-826. doi: 10.1016/j.immuni.2022.04.011.

Virulence triggered allergies: Pseudomonas gets the Las laugh

Justin L McCarville [1], Janelle S Ayres [2]

Affiliations

PMID: 35545032 DOI: 10.1016/j.immuni.2022.04.011

Abstract

The mechanisms of how infectious diseases contribute to allergy remain unanswered. In this issue of Immunity, Agaronyan et al. (2022) show that Pseudomonas aeruginosa drives immune deviation through induction of type 2 immune responses, resulting in niche remodeling that incites allergic responses to innocuous antigens.

Review > Am J Gastroenterol. 2022 Jun 1;117(6):937-946.
doi: 10.14309/ajg.0000000000001812. Epub 2022 May 4.

Mechanisms Underlying Food-Triggered Symptoms in Disorders of Gut-Brain Interactions

"Diet-microbiota interactions are a critical source of neuroactive mediators that significantly modulate intestinal nociceptive signaling and ***cause visceral hypersensitivity***. Multiple bacterial mediators have been implicated, including ***histamine, proteases, tryptamine, 5-HT [serotonin], and lipopolysaccharide.***"

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Review > Front Immunol. 2021 Jun 15;12:685865. doi: 10.3389/fimmu.2021.685865. eCollection 2021.

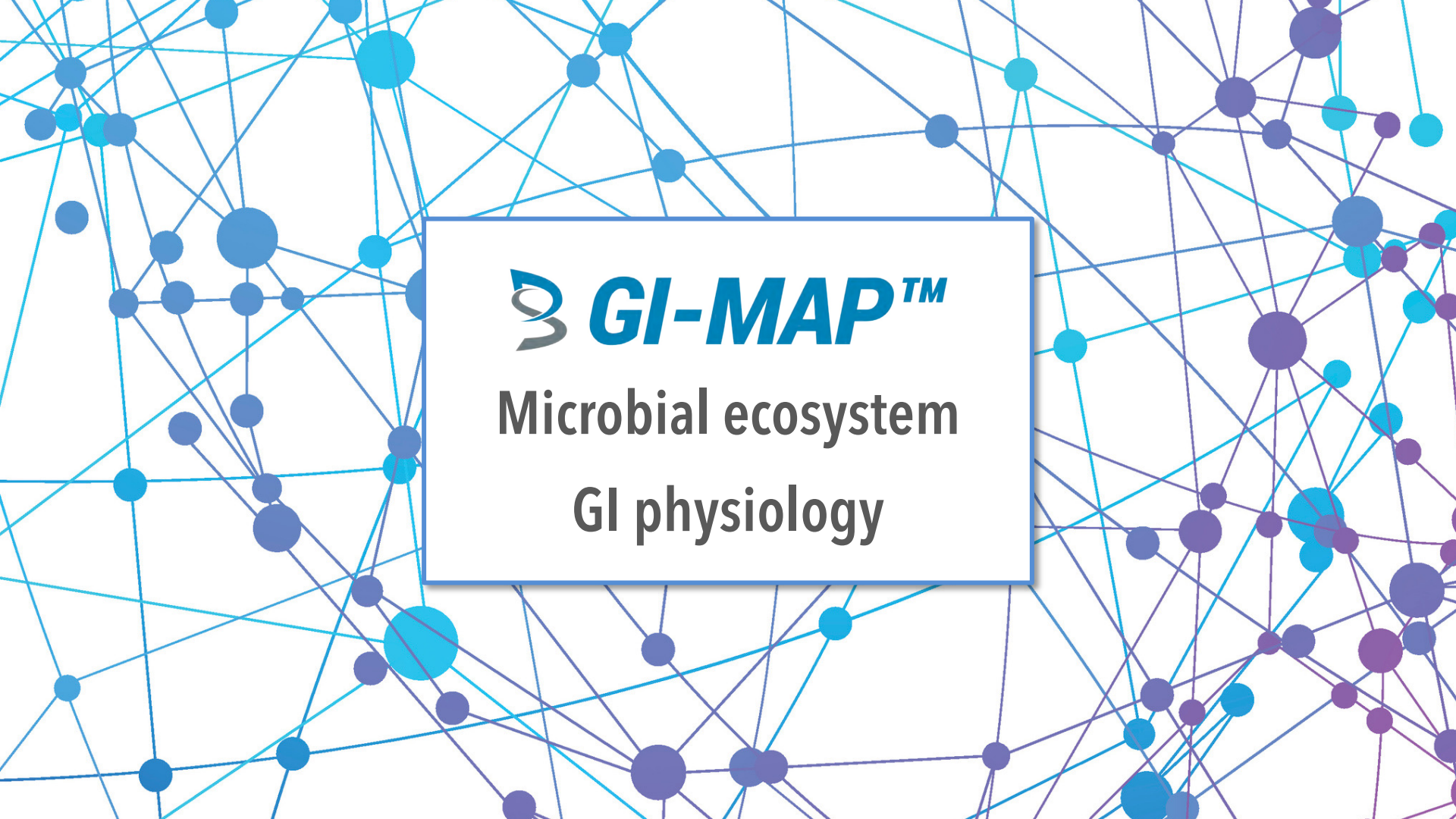
Responses of Mast Cells to Pathogens: Beneficial and Detrimental Roles

Microbes that can stimulate mast cell responses:

- Staphylococcus aureus
- Streptococcus spp.
- Pseudomonas aeruginosa
- Enterococcus faecalis
- Candida
- H. pylori
- Klebsiella & other LPS and histamine producers

Case Example: Treatment Options

1. Increase beneficial commensals with fiber, polyphenols, probiotics, butyrate
2. Consider antimicrobial herbs for dysbiotic overgrowth bacteria (especially Morganella & Klebsiella). Standard herbal formulas tend to work well.
3. Consider possible role for hypochlorhydria (common cause of opportunistic overgrowth) & low bile production, and supplement accordingly
4. Increase sIgA by supporting commensals, supplementing with S. boulardii, glutamine, immunoglobulins (colostrum or non-dairy serum bovine)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GI physiology