

Microbiome ◀ ▶ GI Disorders

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Key Points

- Our gut microbiota
- Where to find them?
- Symbiosis or Why do we need them?
- Dysbiosis or when things go wrong
- How to modulate microbiota?
- Does it help?
- The future



Who Are Them

- 100 Trillions of microbial organisms
- Microbiota: Bacteria, viruses, fungi, and protozoa
- Bacteria: Main 4 phyla (99% of total)

Firmicutes
Bacteroidetes

	Firmicutes
	Bacteroidetes
	Actinobacteria
	Proteobacteria
	Verrucomicrobia
	Fusobacteria
	Cyanobacteria
	Elusimicrobia
	Others

Stomach and Duodenum

$10^1 - 10^2$ CFU/mL

Lactobacilli
Streptococci
Yeasts

Colon

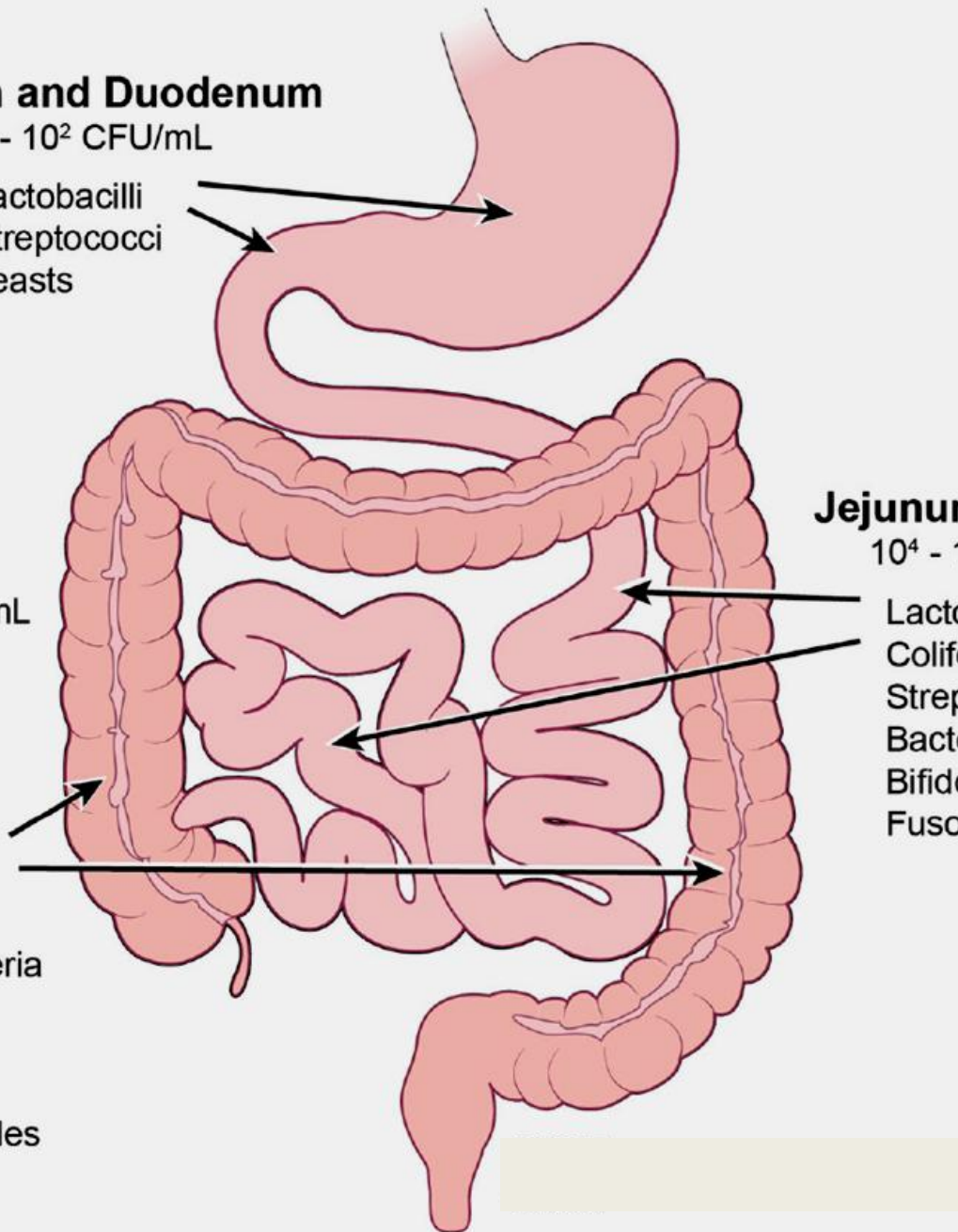
$10^{10} - 10^{12}$ CFU/mL

Bacteroides
Bifidobacteria
Streptococci
Eubacteria
Fusobacteria
Clostridia
Veilonella
Coliform bacteria
Lactobacilli
Proteus
Staphylococci
Pseudomonades
Yeasts
Protozoa

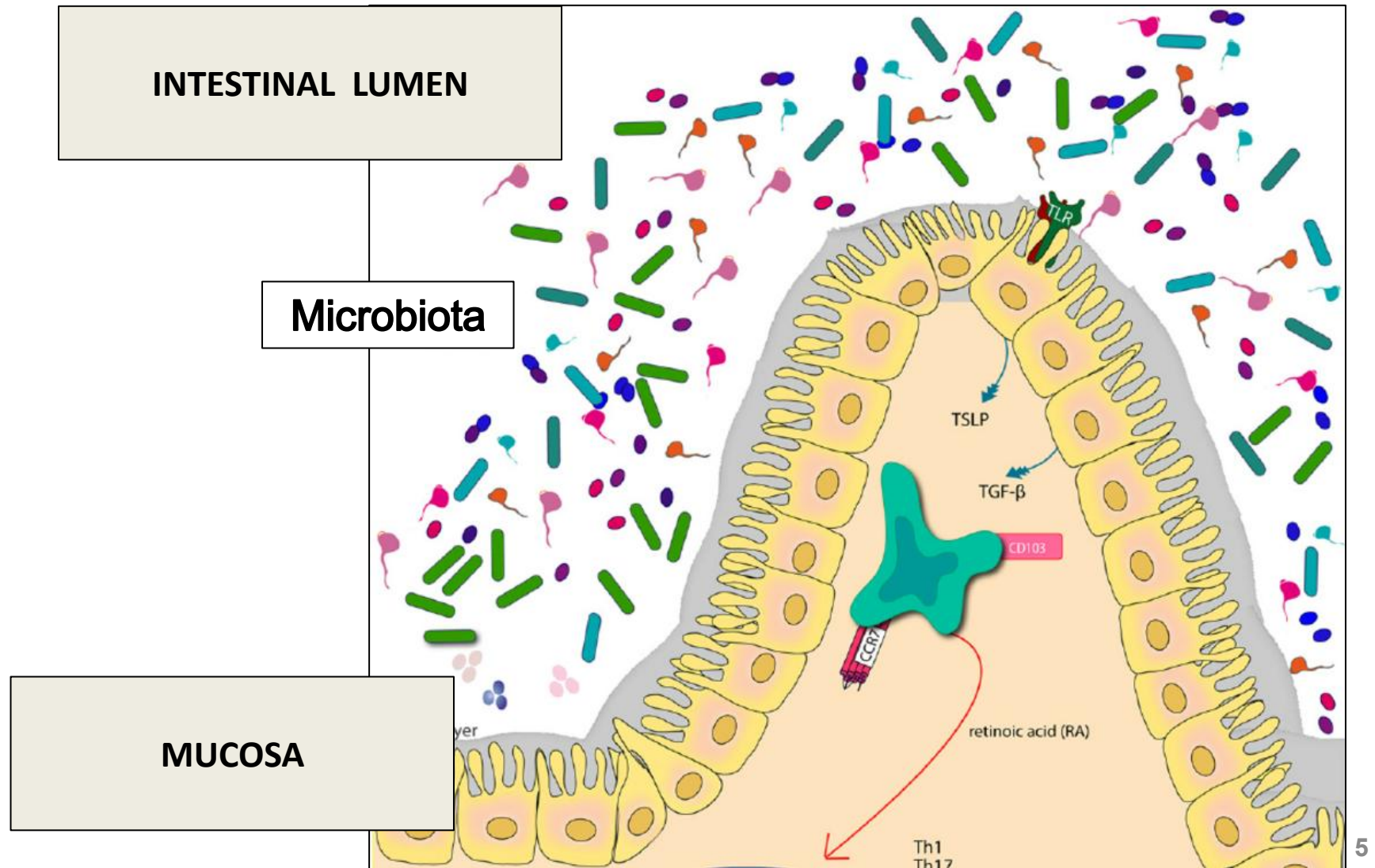
Jejunum and Ileum

$10^4 - 10^8$ CFU/mL

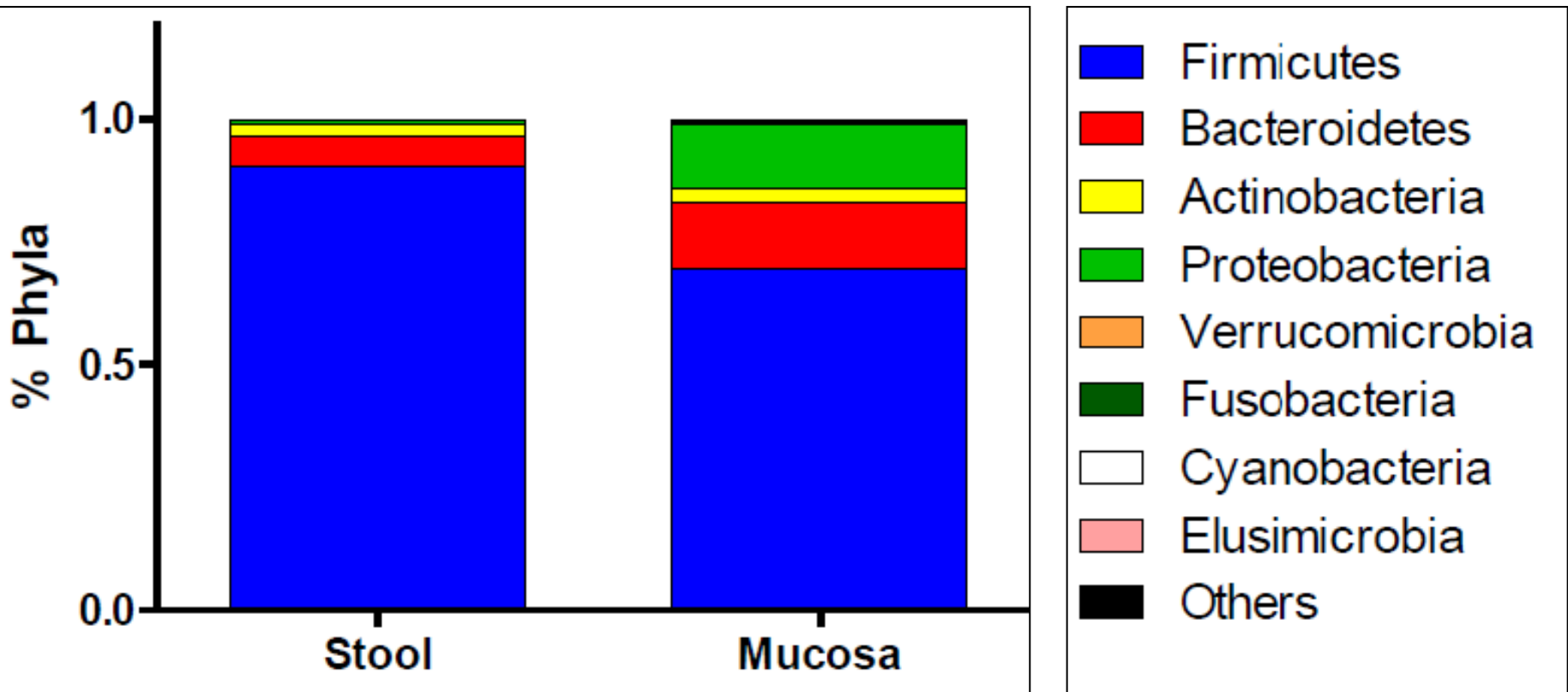
Lactobacilli
Coliform bacteria
Streptococci
Bacteroides
Bifidobacteria
Fusobacteria



Where to Find Them

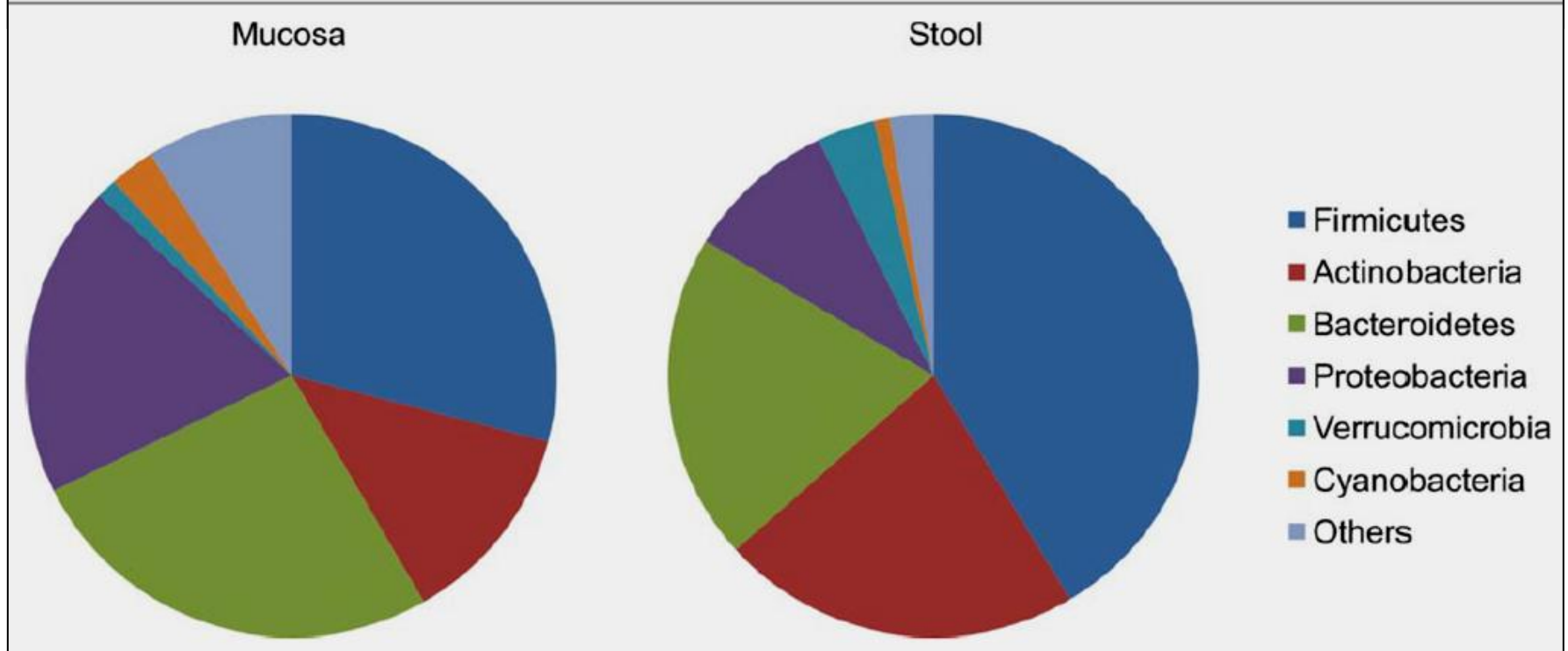


Mucosa vs. Lumen



High throughput sequencing reveals distinct microbial populations within the mucosal and luminal niches in healthy individuals

Yehuda Ringel^{1,*†}, Nitsan Maharshak^{1,2,†}, Tamar Ringel-Kulka³, Elizabeth Ashley Wolber¹, R Balfour Sartor¹, and Ian M Carroll¹



Gut Microbes 2015;6: 173–81.

Summary: Microbiota Along the GI Tract

- Mapping is improved
- Limited information due to:
 - Culturing anaerobic bacteria
 - Limited accessibility (...small intestine)
 - Stool samples vs. Mucosal biopsies
 - Regional differences and similarities
 - Bowel preparation for colonoscopy

- Psychosomatic Medicine, 2017, 857-867
- Aliment Pharmacol Ther 2015;42:1211–21.

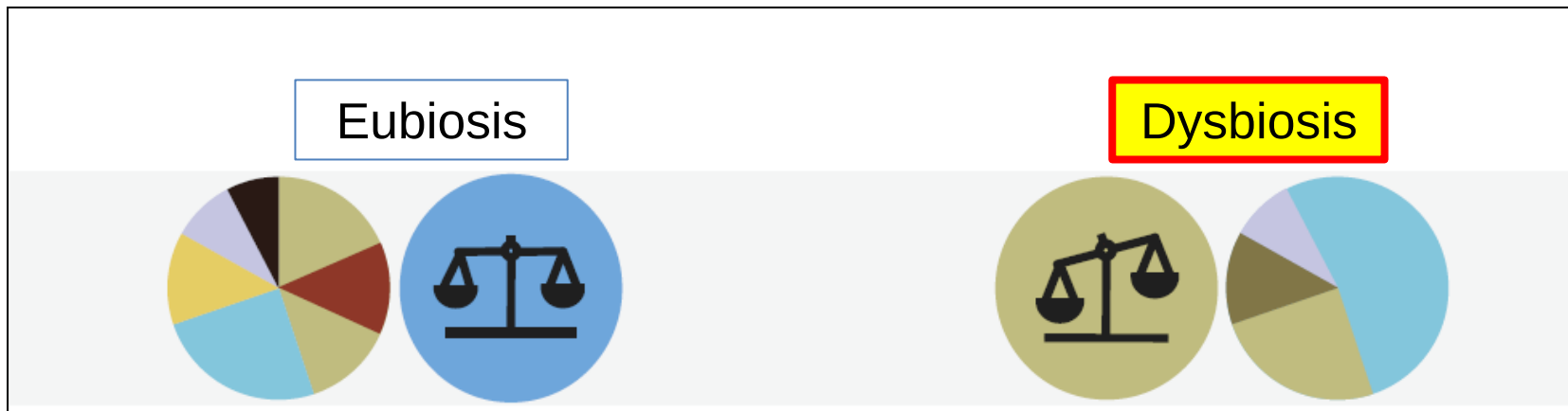
Why Do We Need Microbiota?

- Nutrient & Energy
 - Bifidobacterium ► Vitamin K & B
 - Bacteroidetes and Firmicutes ► Butyrate
- Immune training & control
 - IgA production
 - T helper (Th1/Th2) balance
 - Regulatory T cells ► Suppress inflammation
 - Barrier function
- Defense
 - Colonization resistance
 - Production of antimicrobial factors

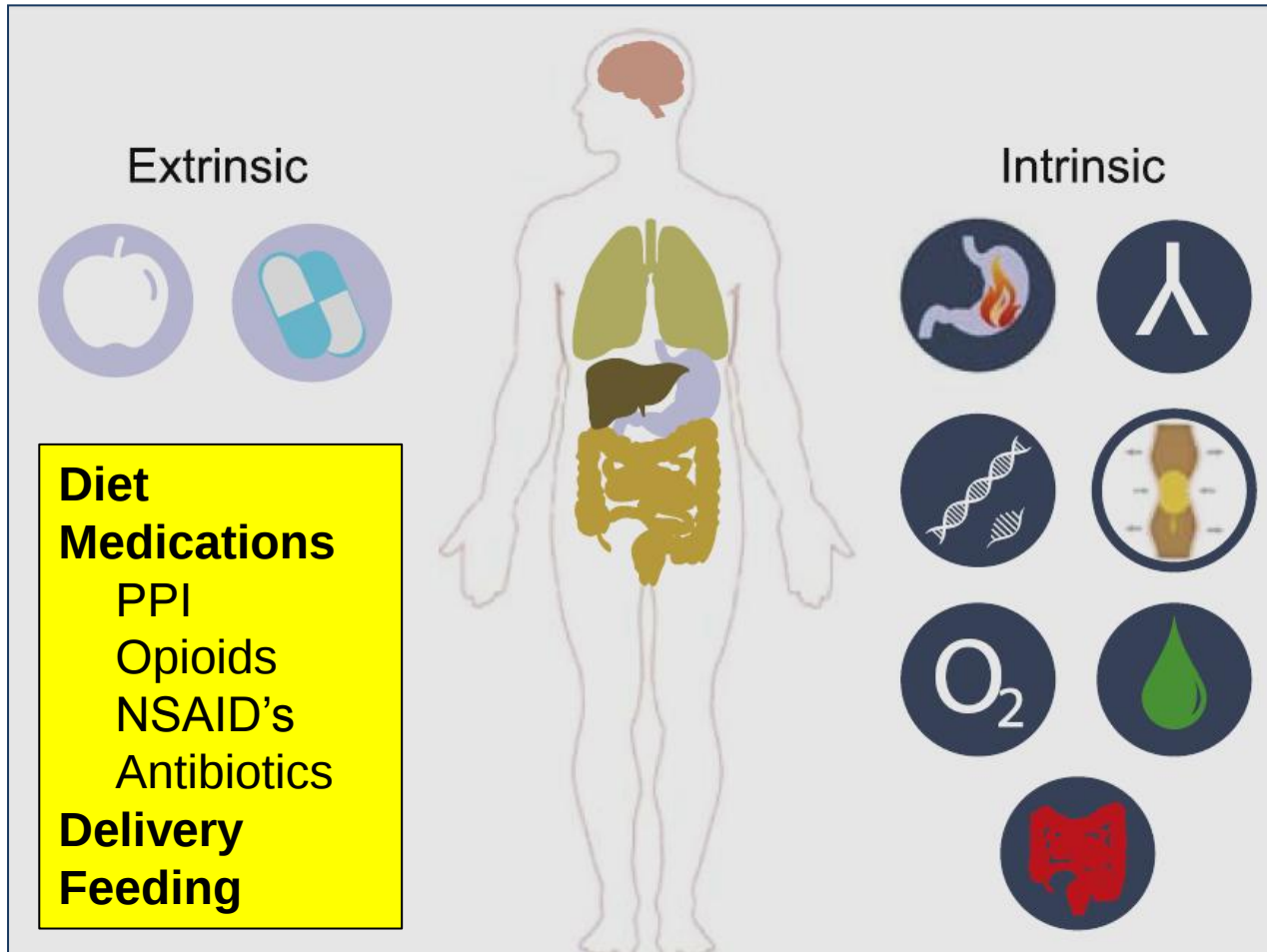
What Can Go Wrong



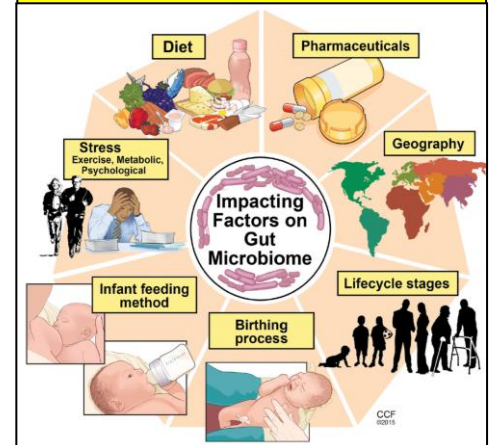
- Eubiosis vs. Dysbiosis
- High vs. Reduced **Stability & Diversity**



Who Affects Stability and Diversity



Acid secretion
O₂ production
Genetics
Immune system
Motility
Stress



Why Dysbiosis Is important?

- Association with GI diseases?
 - Inflammatory Bowel Disease (IBD)
 - Irritable Bowel Syndrome (IBS)
 - Obesity
- Alteration of gut microbiota were identified!
- Questions:
 - What is the relevance?
 - Manipulating microbiota = Therapy for IBS and IBD?

- Cell Host Microbe 2014;15:382–92
- Inflamm Bowel Dis 2009;15:1183–9
- Cell 2015;160:447–60
- Aliment Pharmacol Ther 51–41:342;2015
- PLoS One 2012;7:e39242
- Am J Gastroenterol 2015;110:921–30
- Gut 2012;61:997–1006

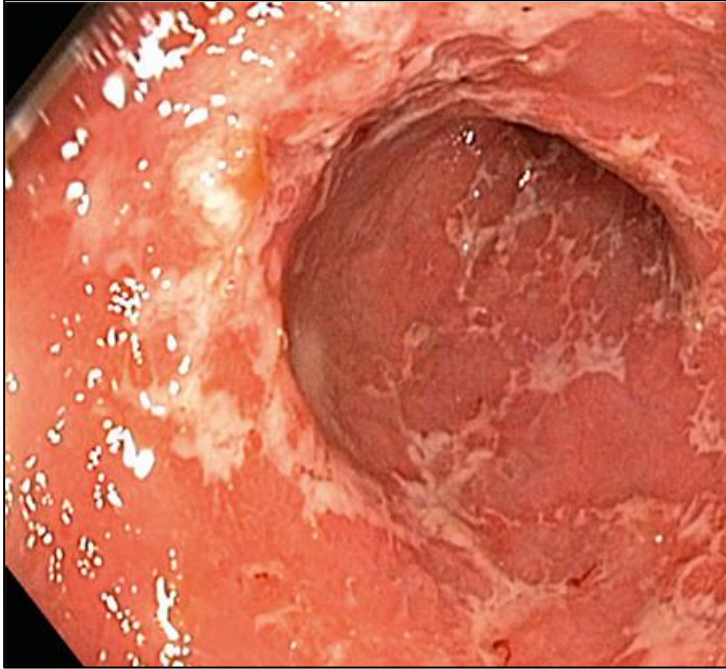
Inflammatory Bowel Diseases (IBD)

- Ulcerative Colitis (UC) & Crohn's Disease (CD)
- Chronic, Remitting, and Relapsing
- Prevalence approaches 1%
- Diagnosis: Before the age of 40 years
- Poor quality of life and social functioning
- Genetic and environmental factors

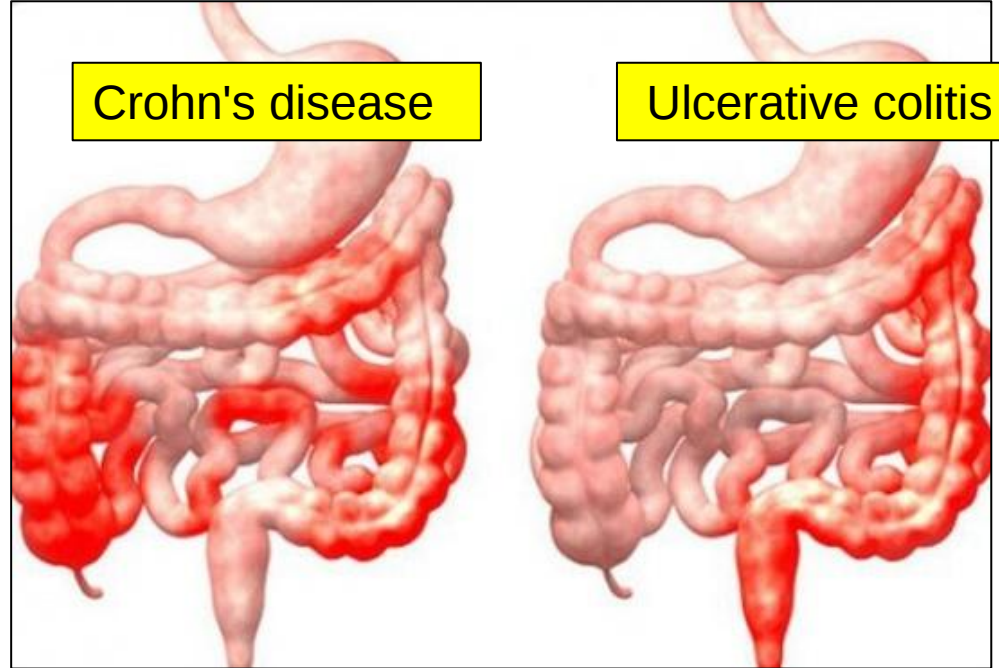
Gastroenterology 2012;142:46–54



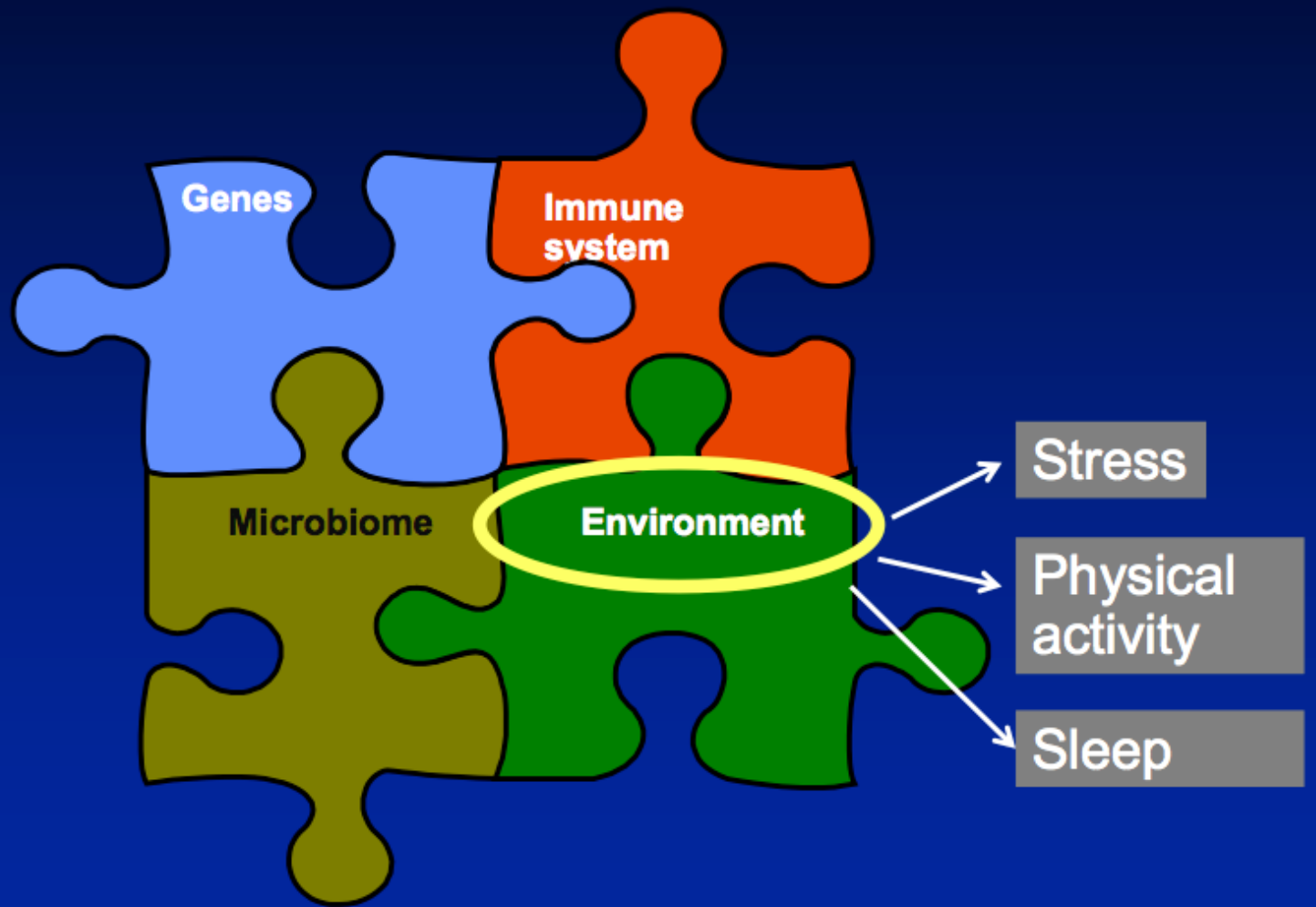
Pathophysiology - IBD



Etiology?



Immune response + Genetics + Environment

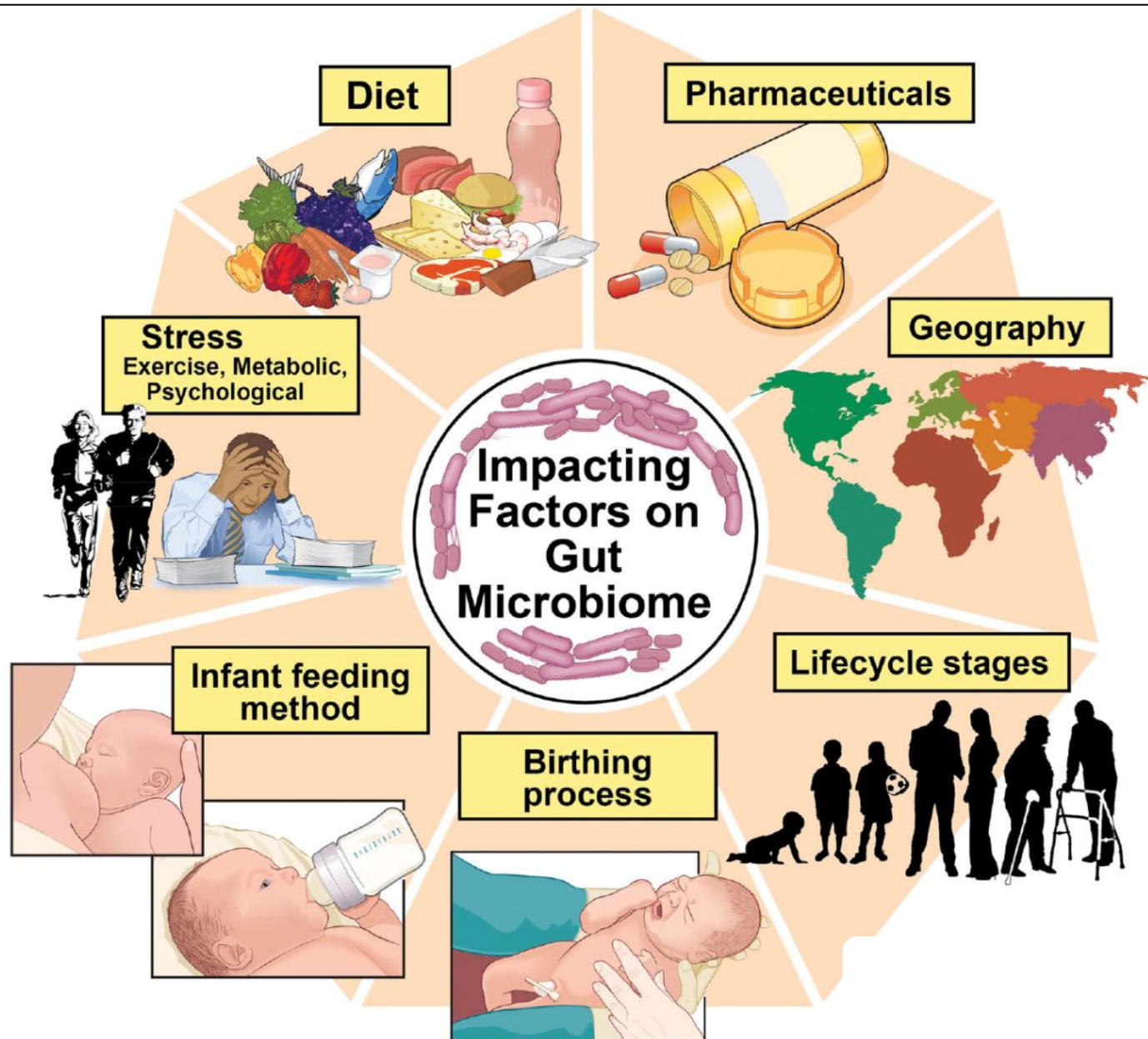




Environmental risk factors for inflammatory bowel diseases: Evidence based literature review

Ayokunle T Abegunde, Bashir H Muhammad, Owais Bhatti, Tauseef Ali

“Genetically susceptible individuals develop intolerance to **dysregulated gut microflora (dysbiosis)** and chronic inflammation develops ...”



Gut Microbiota in IBD

- Fecal samples:

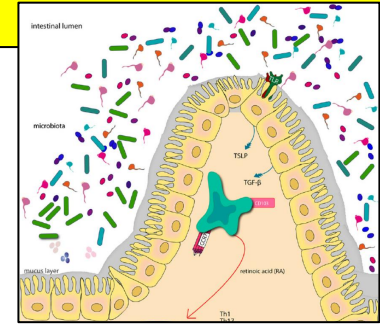
↓ – Less: Firmicutes and Bacteroides
Bacterial Diversity

↑ – More: Proteobacteria and Actinobacteria

- Mucosal biopsies

↓ – Less: Firmicutes
Bacterial Diversity

↑ – More: Proteobacteria Bacteroides

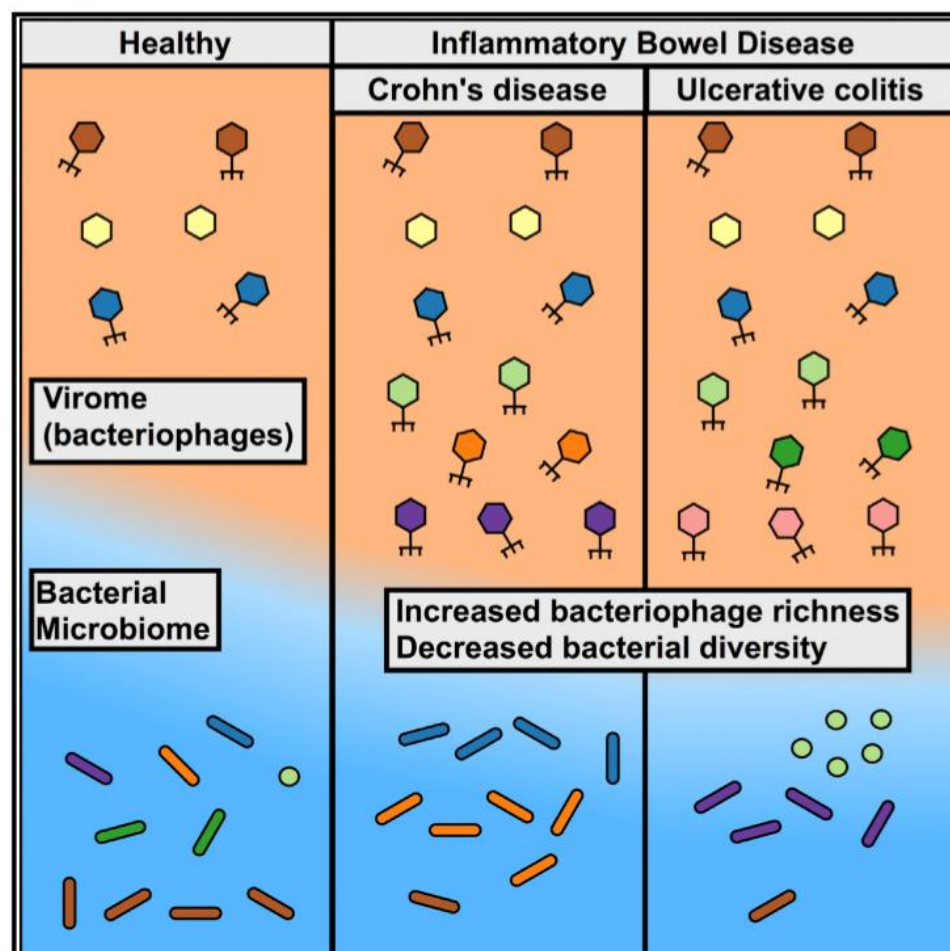


Characterization of Gut Microbiota in IBD

- Observational studies
- Children and adults with IBD:
 - ↓ – Abundance of
 - Erysipelotrichales (order)
 - Clostridiales (order)
 - **Butyrate producers**
 - Gram-negative Clostridia
 - ↓ – Fecal bacterial diversity and fungal diversity
 - ↓ – Mucosal Firmicutes
 - ↑ – Fecal Candida
 - ↑ – Bacteriophages and Eukaryotic viruses

Disease-Specific Alterations in the Enteric Virome in Inflammatory Bowel Disease

Graphical Abstract



Authors

Jason M. Norman, Scott A. Handley, ..., Miles Parkes, Herbert W. Virgin

Correspondence

virgin@wustl.edu

In Brief

The enteric virome is abnormal in multiple cohorts of inflammatory bowel disease patients, exhibiting disease-specific features that are not explained by changes in bacterial diversity and richness.

Clinical Evidence

- What is the link?
 - Abnormal immune response to a normal microbiota?
 - Normal immune response to an abnormal microbiota?
- Trigger Flare or Complications:
 - Pediatric: Lower diversity and abundance of *Rothia Mucilaginosa*
 - Adults: lower Firmicutes/Bacteroidetes ratio
- Maintain Active Inflammation ► Complications
 - Pediatric: Lower diversity
- Maintain Remission and Block Flares:
 - High abundance of *Faecalibacterium Prausnitzii*
- Good Response to Therapy
 - High abundance of *Faecalibacterium Prausnitzii*

- Psychosomatic Medicine, 2017, 857-867
- Cell Host Microbe 2014;15:382–92

Links: Gut Microbiota - IBD

- Conclusions:
 - Evidence is growing
 - Links are still... too weak!
 - More studies are needed on
 - Composition
 - **Association with natural course**
- Psychosomatic Medicine, 2017, 857-867
- Aliment Pharmacol Ther 2015;42:1211–21.

Irritable Bowel Syndrome (IBS)

- Chronic, Recurrent condition
- Abdominal pain + Altered bowel movements
- Normal clinical investigations
- Young age
- Prevalence approaches 11%
- Low QOL and Work productivity
- Low Social functioning
- Rome IV Criteria



IBS Subtypes

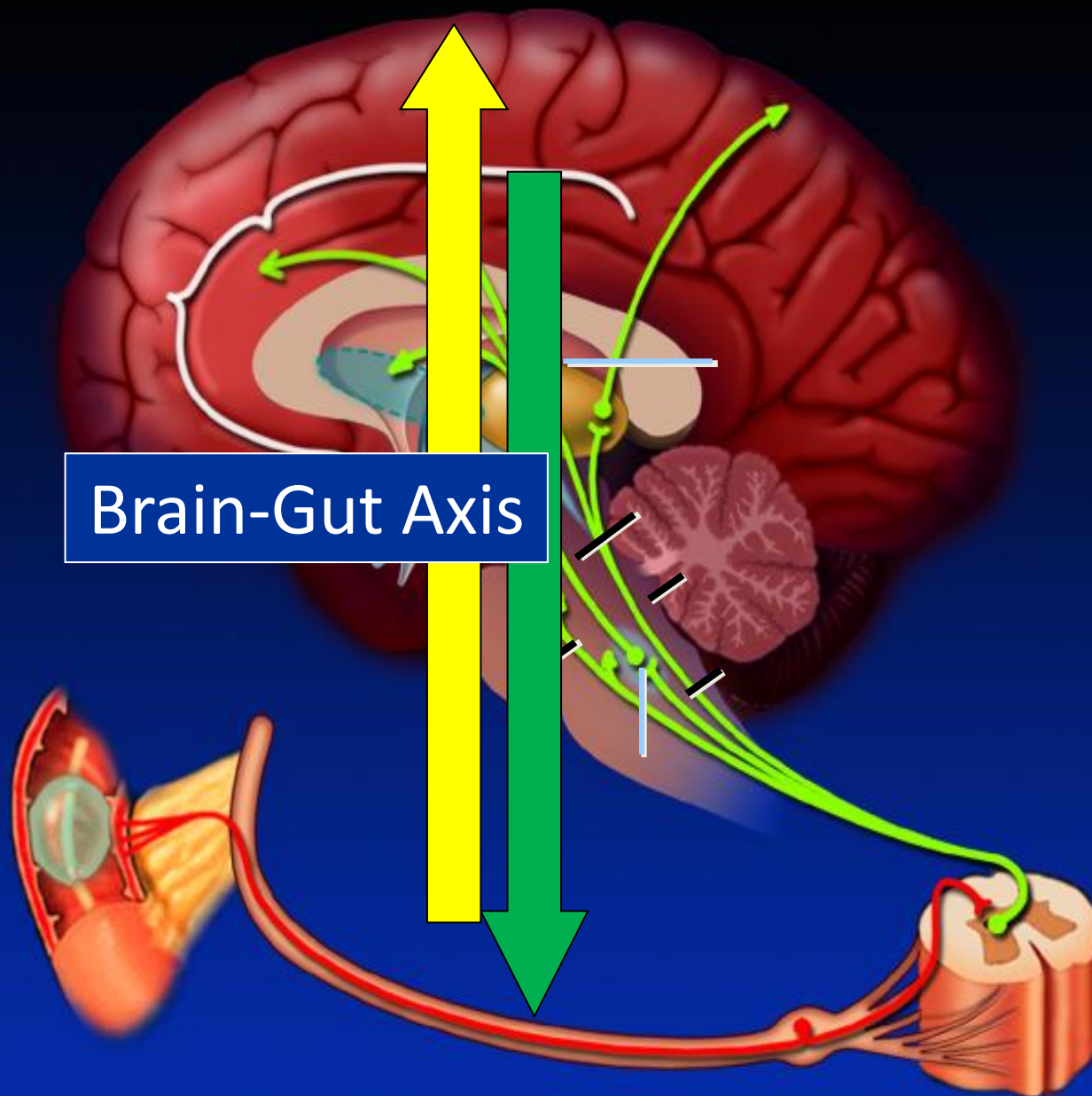
- Diarrhea-predominant IBS (IBS-D)
- Constipation-predominant (IBS-C)
- Mixed IBS (IBS-M)
- Post Infectious IBS (10%)

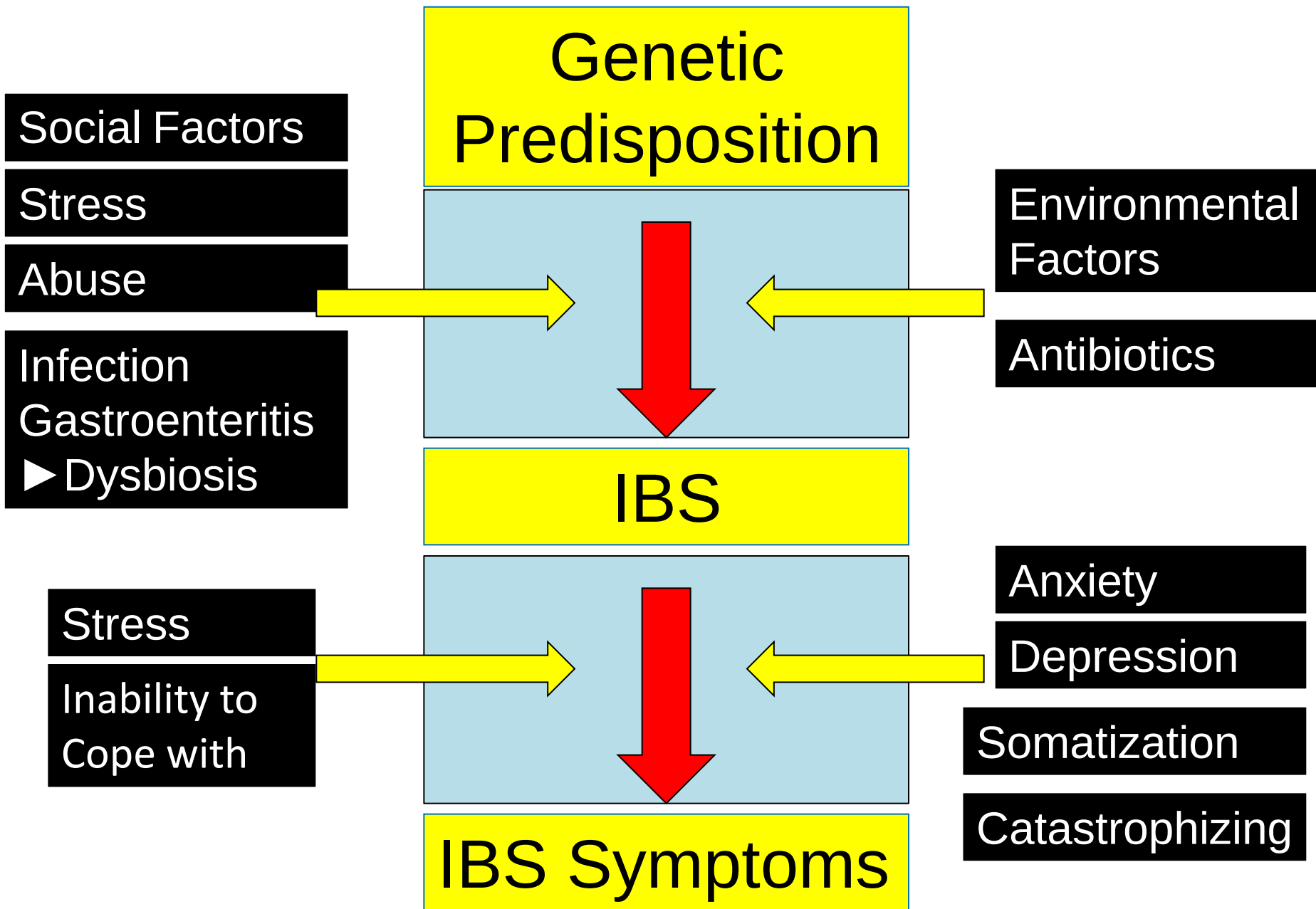
Pathophysiology of IBS



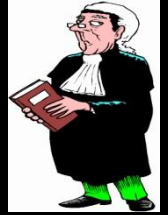
- Etiology?
 - Abnormal Brain-Gut Interactions
 - Visceral Hypersensitivity
 - Gut Dysmotility and Secretion
 - Psychosocial Factors
 - Gut Microbiota Composition
 - Gut Permeability
 - Low Grade Immune Activity

Brain-Gut Axis





Biopsychosocial Model



- Bio
- Psycho
- Social



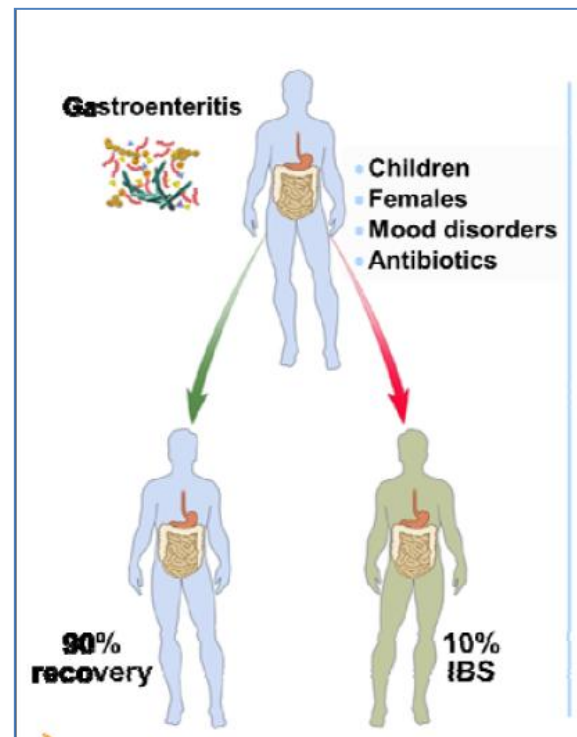
Pathophysiology of IBS

The Role of Microbiota

- Bacterial Gastroenteritis ► Post-Infection IBS
- Small Intestinal Bacterial Overgrowth (**SIBO**)
- Microbiota in IBS is different?
- Efficacy of Antibiotics and Probiotics

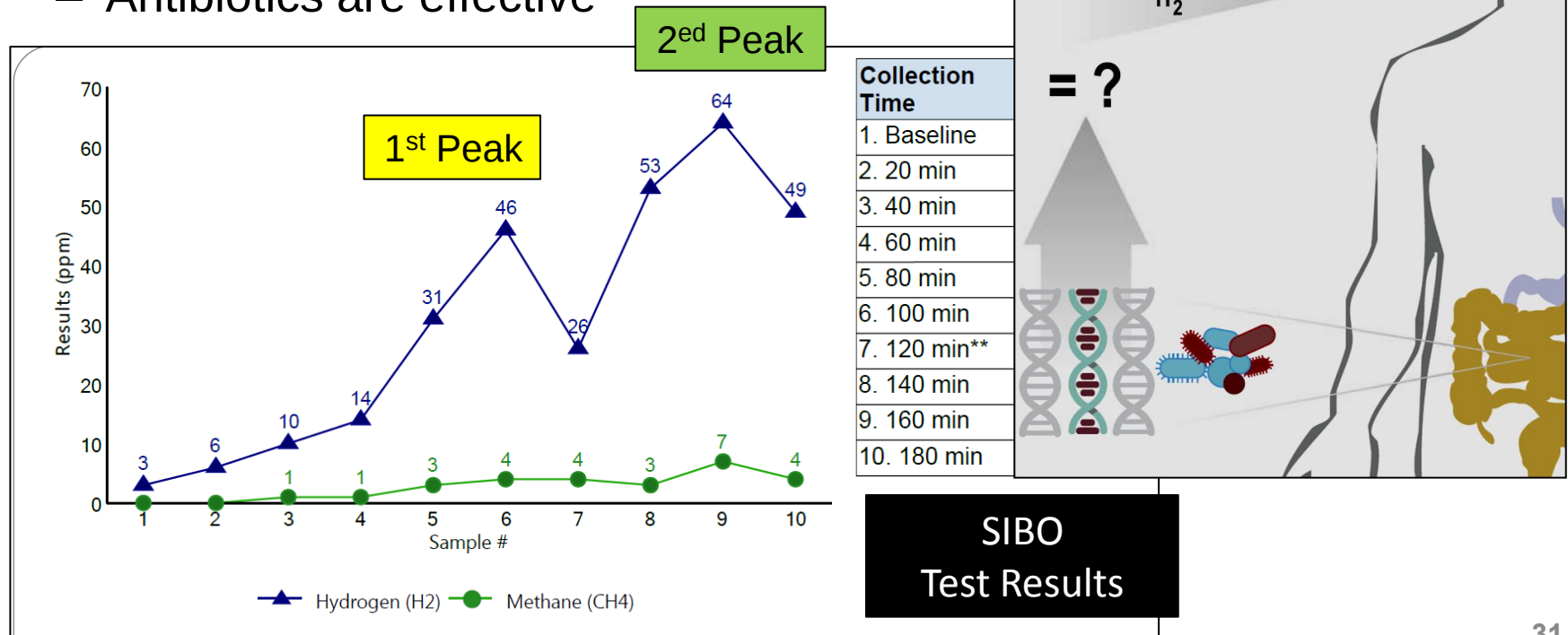
Post Infectious IBS

- 10% of all IBS cases
- Infection ► 7-10 times risk ► IBS
- Risk factors
 - Females
 - Children
 - Mood disorders
 - Antibiotics



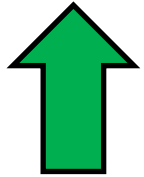
Small Intestinal Bacterial Overgrowth (SIBO)

- Biopsies are impractical
- Breath tests = Practical alternative
- Metaanalysis:
 - IBS patients have more SIBO
 - Symptoms overlap
 - Antibiotics are effective

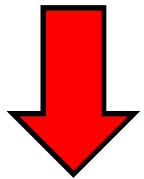


Gut Microbiota in IBS

- Different Microbiota Compositions:

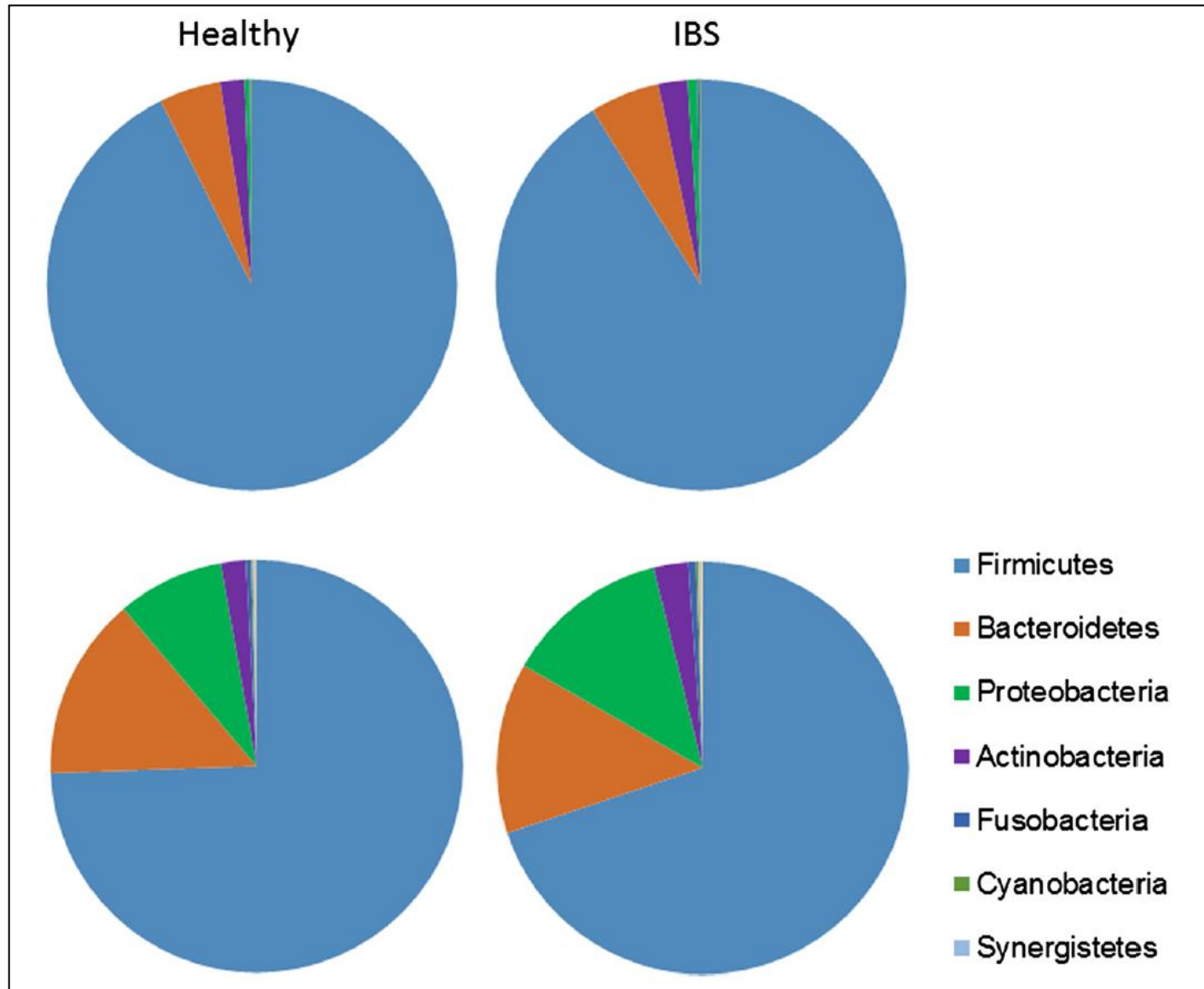


- Increased **Firmicutes**/Bacteroidetes Ratio
- More Fecal **Ruminococcus Torques**



-
- Reduced Fecal **Lactobacilli**
 - Reduced Fecal and Mucosal **Diversity**

Fecal and Mucosa-Associated Intestinal Microbiota in Patients with Diarrhea-Predominant Irritable Bowel Syndrome

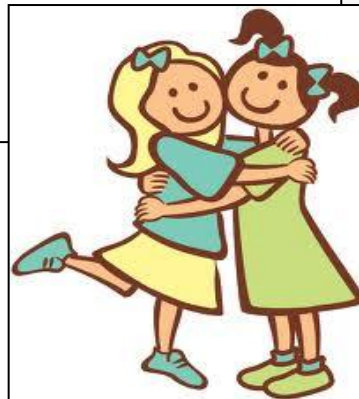


Clinical Evidence

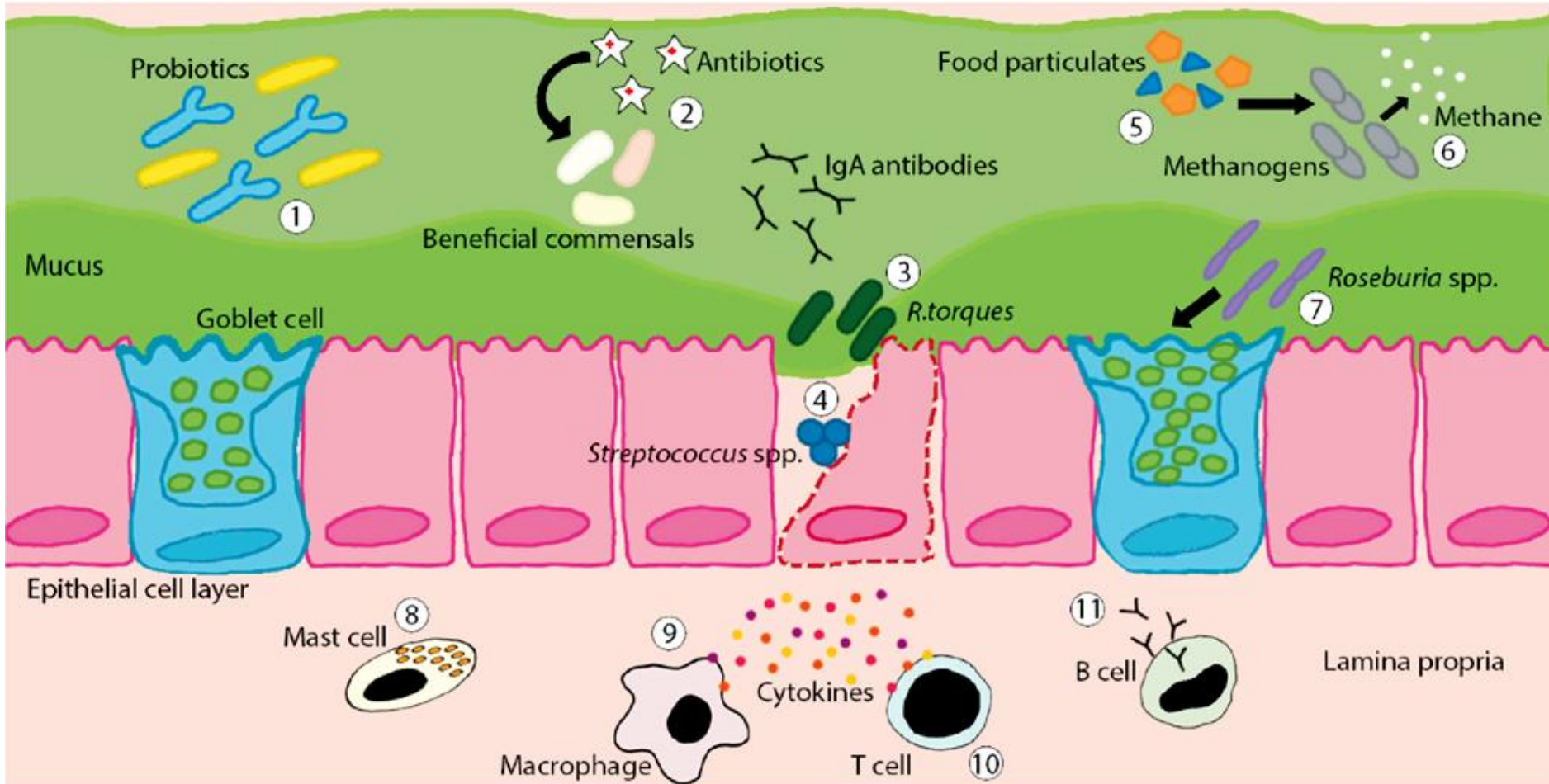
- Symptoms ◀ microbiota?
- IBS+Constipation: More Bifidobacteria?
- Overlap with Controls
- **Non**-Microbiota factors count!
- Evidence is growing

Psychosomatic Medicine, 2017, 857-867
Gut 2012;61:997–1006

Infection
SIBO
Food
Intolerance
Diet
Dysbiosis?



Very Few Clear Targets ► Therapy?



Therapeutic Approaches for Dysbiosis

Diet & Prebiotics



Probiotics



FMT



Antibiotics

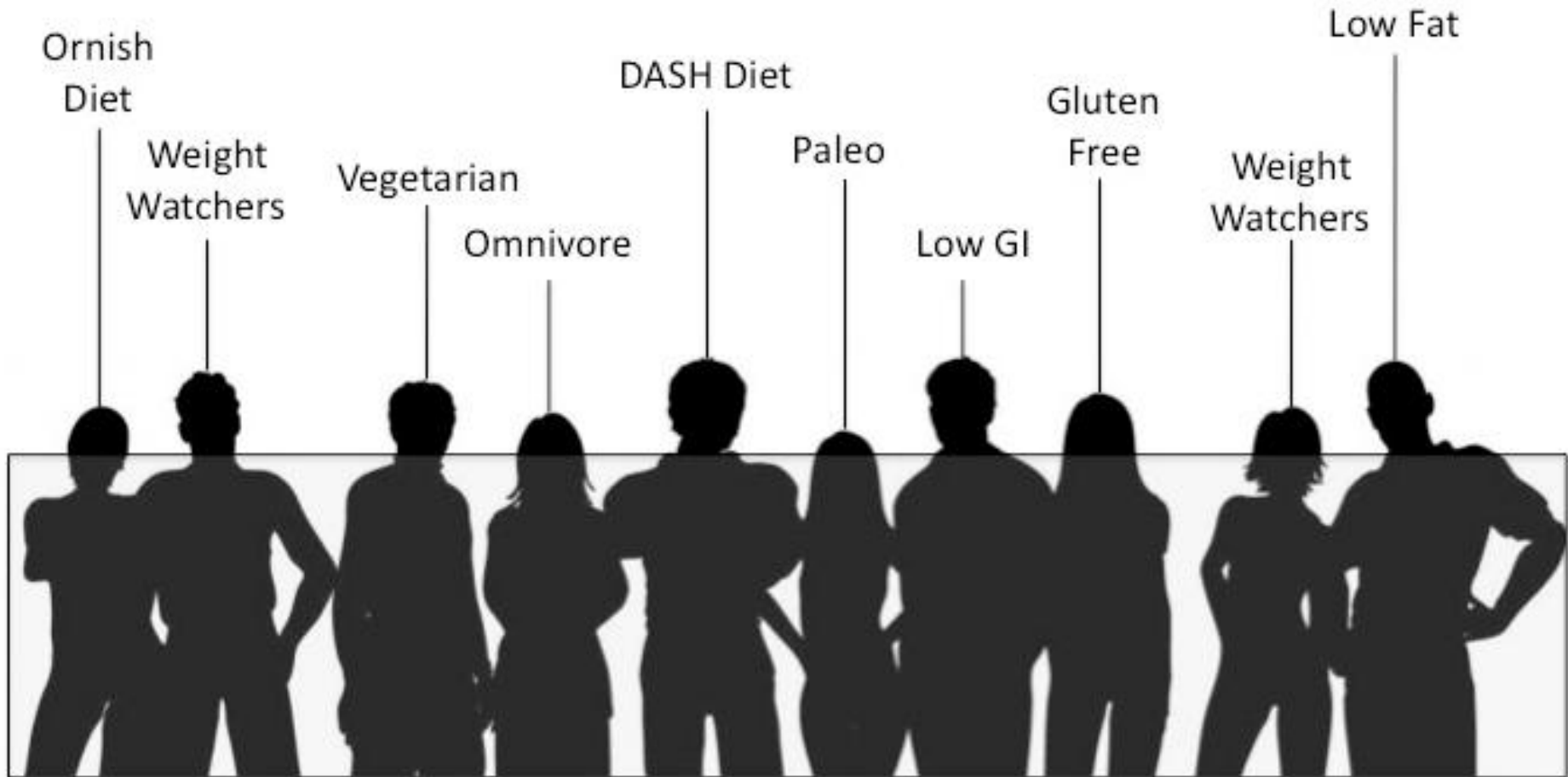


DYSBIOSIS

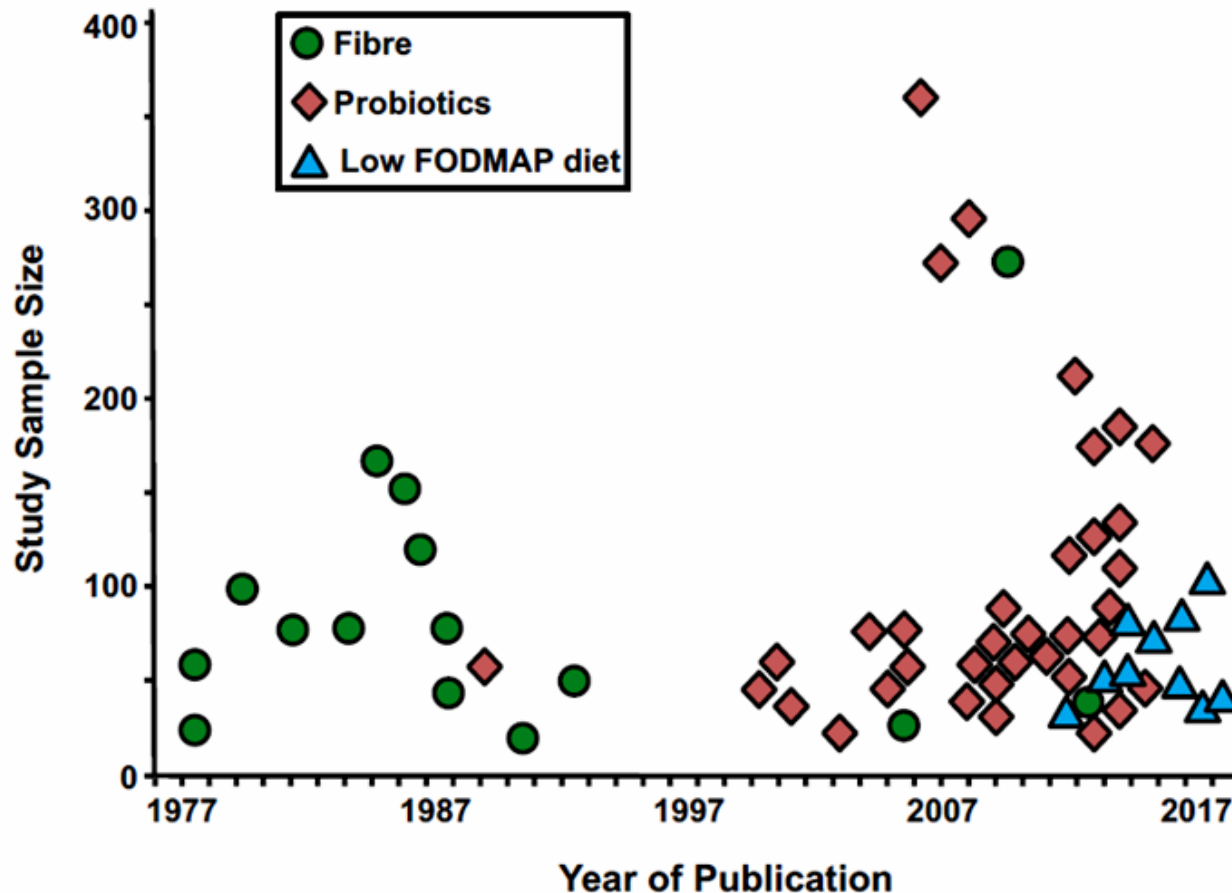
Very few targets ► Empirical treatment

- Diet
- Prebiotics
- Probiotics
- Fecal Microbial Transplantation (FMT)
- Antibiotics
 - Rifaximin, Metronidazole

On What Diet Are You?



Trends in Diet Interventions in IBS

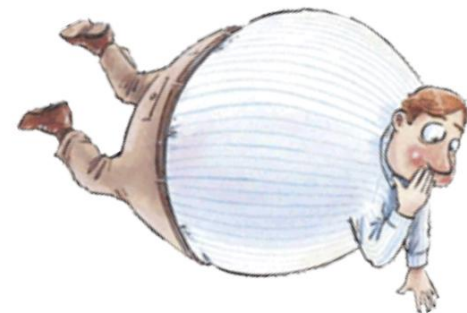


Dimidi E et al., Curr Opin Clin Nutr Metab Care 2017

No. 1 Empirical Diet Intervention

- Low FODMAP Diet
 - **F**ermentable...
 - **O**ligosaccharides
 - **D**isaccharides
 - **M**onosaccharides
 - **A**nd **P**olyols

Healthy food, for many but not for all!

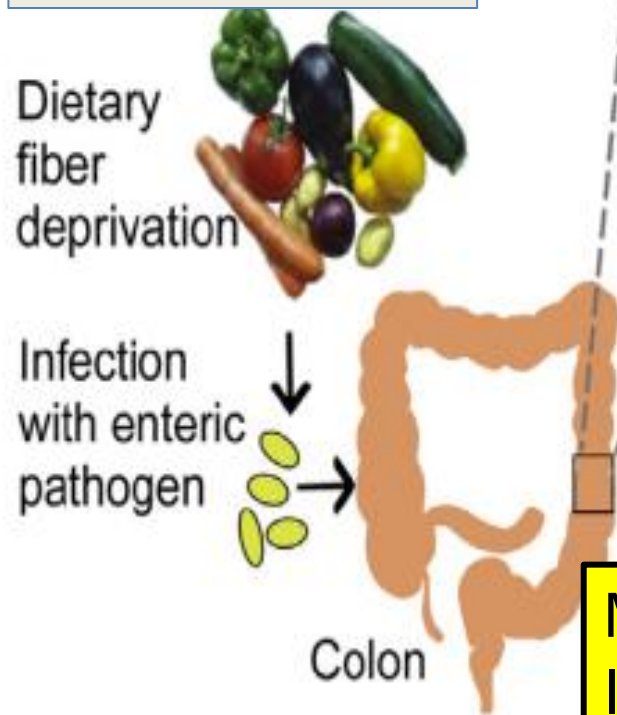


Diet Interventions in IBS

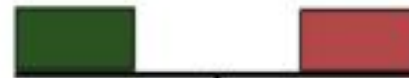
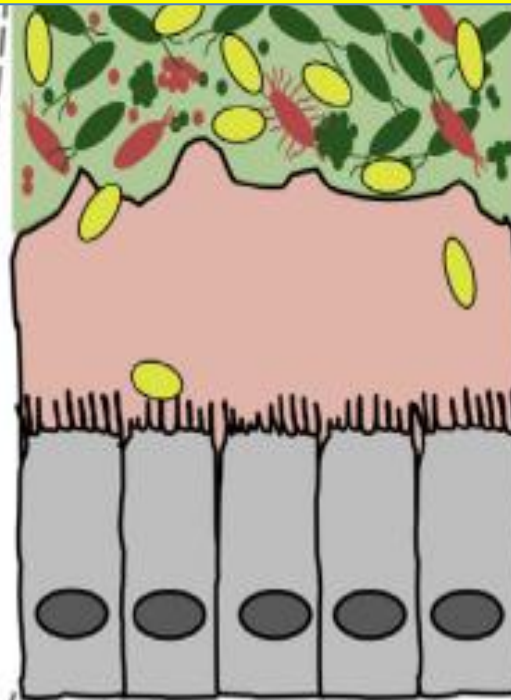
- Common practice
- The Low FODMAP Diet reduces symptoms
- Effect on gut microbiota ?
- Side effect - May reduce microbiota diversity!

Halmos EP, et al. Gut 2015;64:93–100

The Role of FIBER

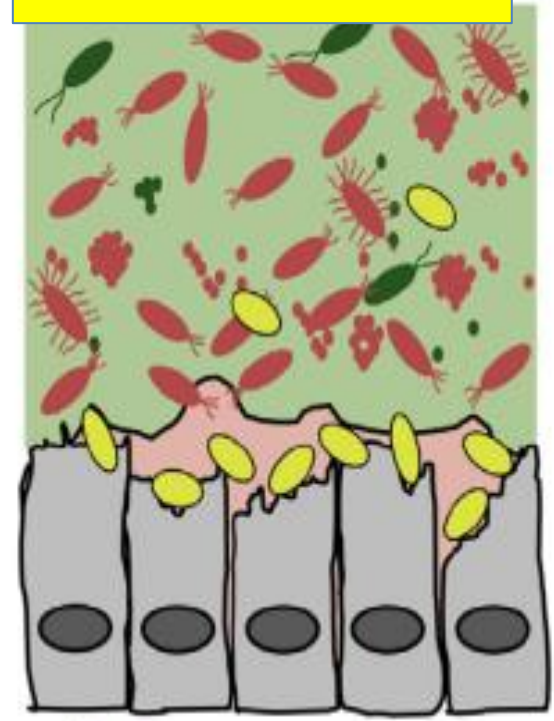


Fiber Rich Diet



Mature Mucus
Intact Barrier Function!

No Fiber



Eroded Mucus
Barrier Damage

Probiotics

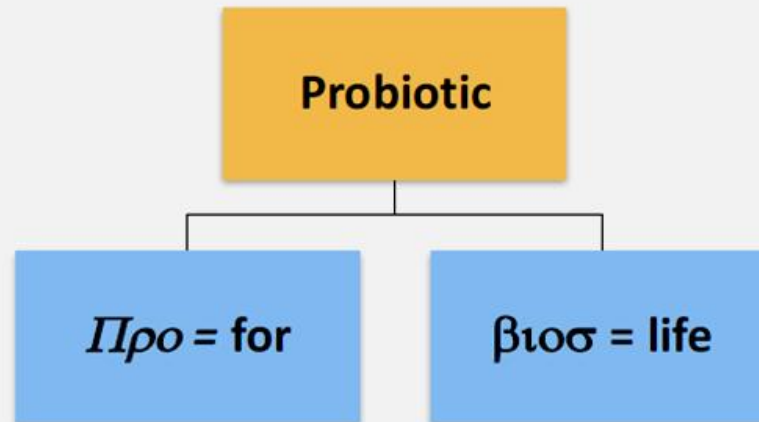


CONSENSUS STATEMENTS

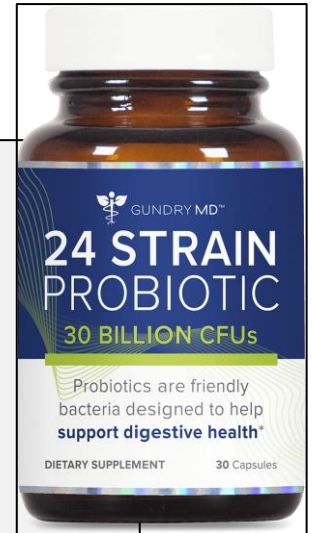
EXPERT CONSENSUS DOCUMENT

The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic

Colin Hill, Francisco Guarner, Gregor Reid, Glenn R. Gibson, Daniel J. Merenstein, Bruno Pot, Lorenzo Morelli, Roberto Berni Canani, Harry J. Flint, Seppo Salminen, Phillip C. Calder and Mary Ellen Sanders



Live organisms, which when administered in adequate amounts, confer a health benefit on the host



Probiotics in Health

RESEARCH

Open Access



Alterations in fecal microbiota composition by probiotic supplementation in healthy adults: a systematic review of randomized controlled trials

Nadja B. Kristensen*, Thomas Bryrup, Kristine H. Allin, Trine Nielsen, Tue H. Hansen and Oluf Pedersen

- Systemic review
- 7 Randomized control trials
- Healthy adults
- **No effect on microbiota parameters**

Kristensen NB et al., Genome Med 2016;8:52

Probiotics in Disease

Ritchie ML, PLoS ONE 2012;7:e34938

A Meta-Analysis of Probiotic Efficacy for Gastrointestinal Diseases

Marina L. Ritchie*, Tamara N. Romanuk

- **74 studies**
- **84 trials**
- **10,351 patients**

Disorder	Positive Effect	Risk reduction
Infectious Diarrhea	Yes	0.5
Antibiotic ► Diarrhea	Yes	0.5
Traveler Diarrhea	No	
IBS	Yes	0.5
IBD - Paucities	Yes	0.5
Helicobacter pylori	Yes	0.5
Clostridium Colitis	Yes	0.5
Necrotizing Ent.Colitis	No	

Probiotics - Recommendations

American College of Gastroenterology Monograph on Management of Irritable Bowel Syndrome



INTERVENTIONS THAT MODIFY THE MICROBIOTA: PROBIOTICS

- 53 RCTs involving 5'545 patients
- Probiotics superior to placebo (RR of IBS not improving = 0.81)
- NNT: 7
- Adverse events not higher with probiotics (RR 1.09)
- Significant heterogeneity between studies ($I^2 = 71\%$, $P < 0.001$)

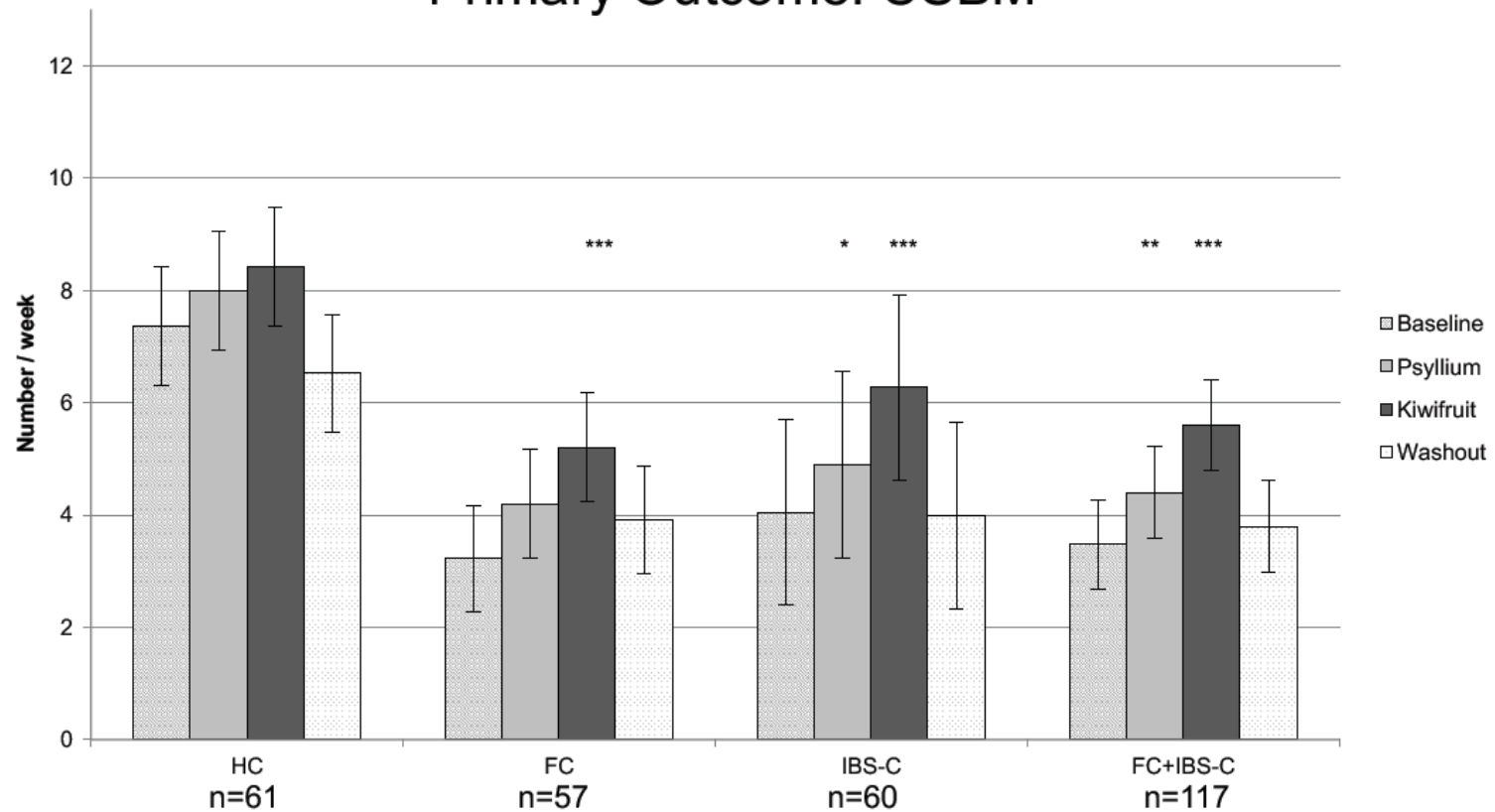
We suggest probiotics, taken as a group, to improve global symptoms, as well as bloating and flatulence in IBS patients

Recommendation: weak; **Quality of evidence:** low

Ford AC et al., Am J Gastroenterol 2018;113:1-18

Effect of Green Kiwifruit in Functional Constipation and IBS-C

Primary Outcome: CSBM



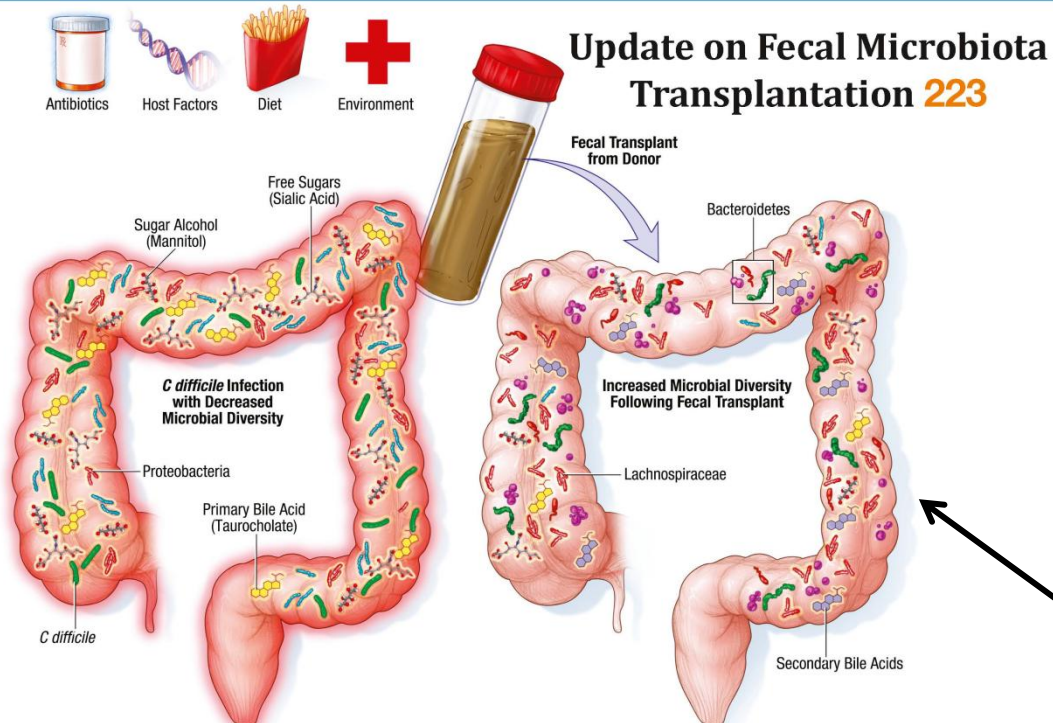
Barbara G et al. DDW 2018

Fecal Microbial Transplantation (FMT)

Gastroenterology

www.gastrojournal.org

Volume 149 Number 1 July 2015



Colleen R et al, et al Gastroenterology 2015;149:223–37

Clinical Practice

- *C. Difficile* Infection
 - Relapsing/Recurrent
 - Resistant

Research

- IBD
- IBS
- Obesity/Metabolic Synd.
- Diabetes Mellitus Type 2
- Fatty Liver
- Hepatic Encephalopathy
- Pediatric Allergy Synd.

Following FMT ►
Increased Microbial Diversity!

Fecal Microbial Transplantation: Preparation and Delivery Modalities



Fresh



Frozen



Dry Capsule

Preparation



Nasogastric tube



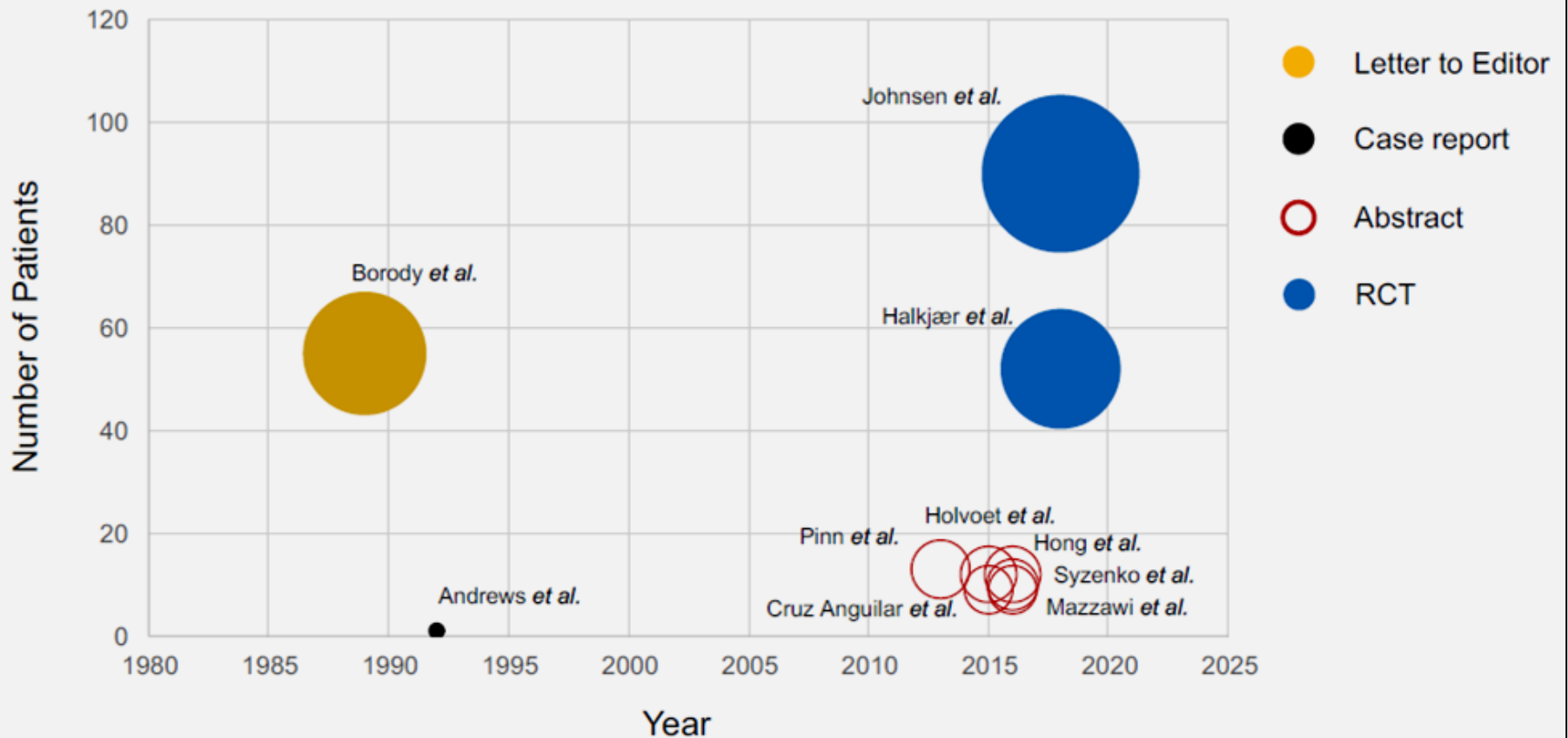
Enema



Colonoscopy

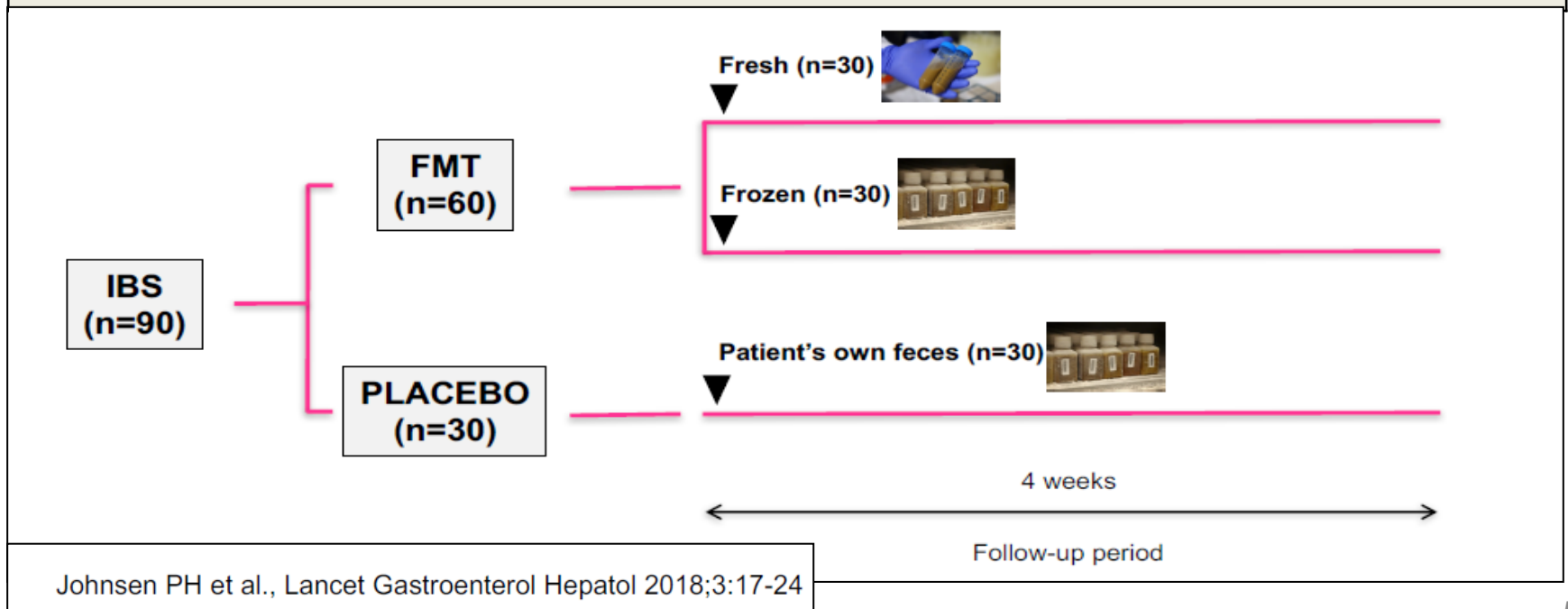
Delivery

Trials of FMT in IBS



Trials of FMT in IBS

Trial	No. of Patients	Symptoms	Side effects
Johnsen 2018	90	Improved	No Serious

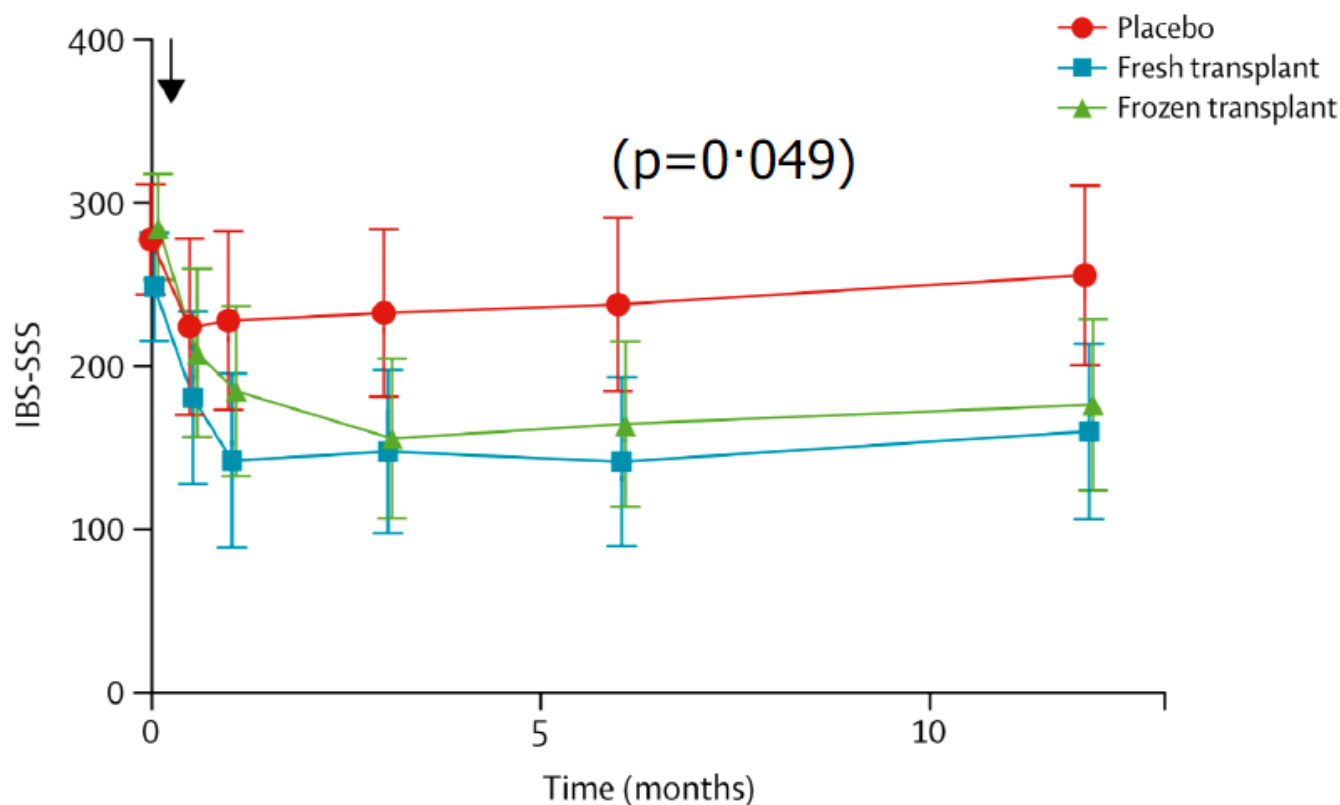


FMT in IBS: STUDY 1



FMT for IBS Primary endpoint

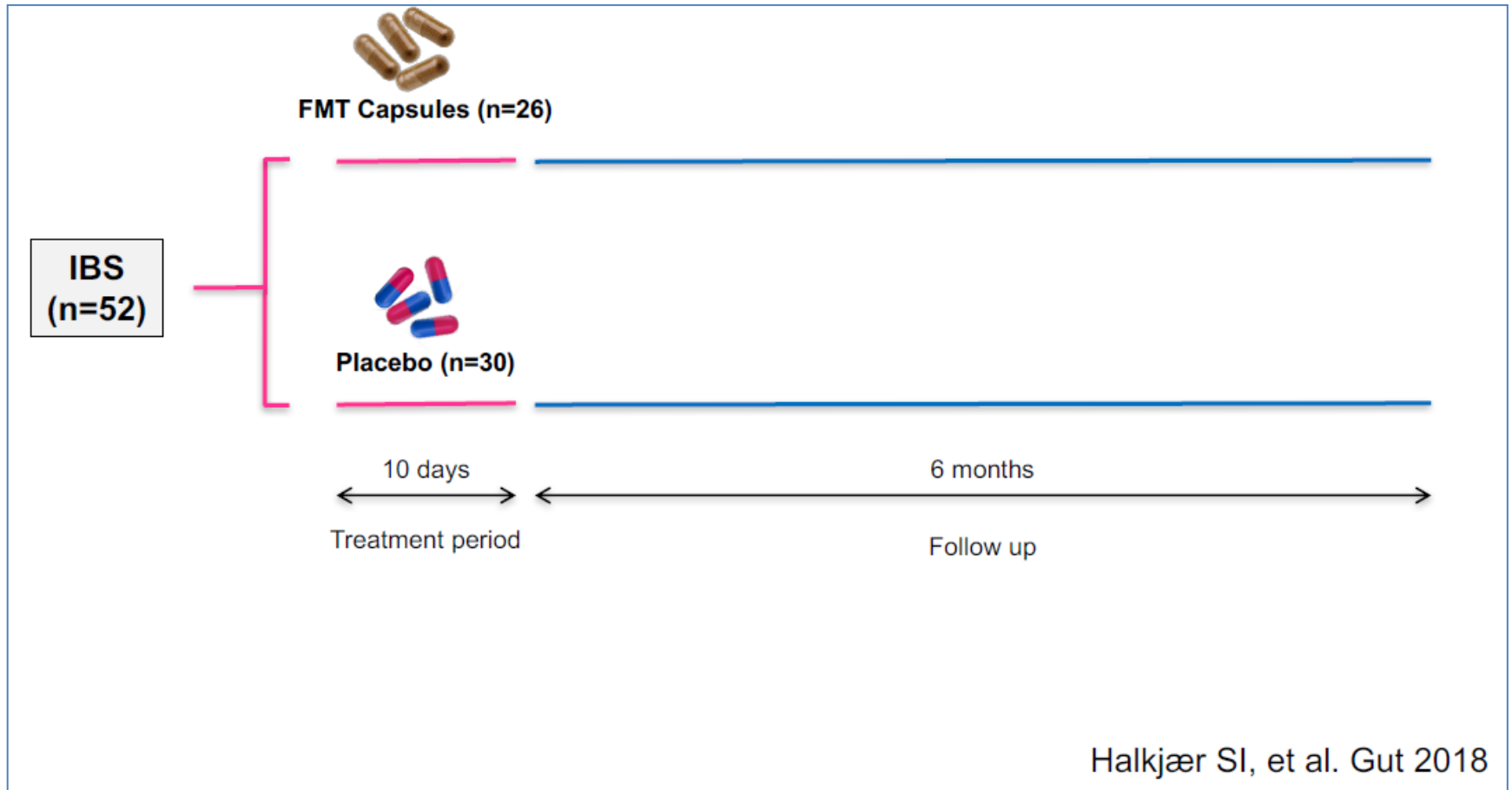
Symptom relief of more than 75 points on the IBS-SSS



- No serious adverse events

Johnsen PH et al., Lancet Gastroenterol Hepatol 2018;3:17-24

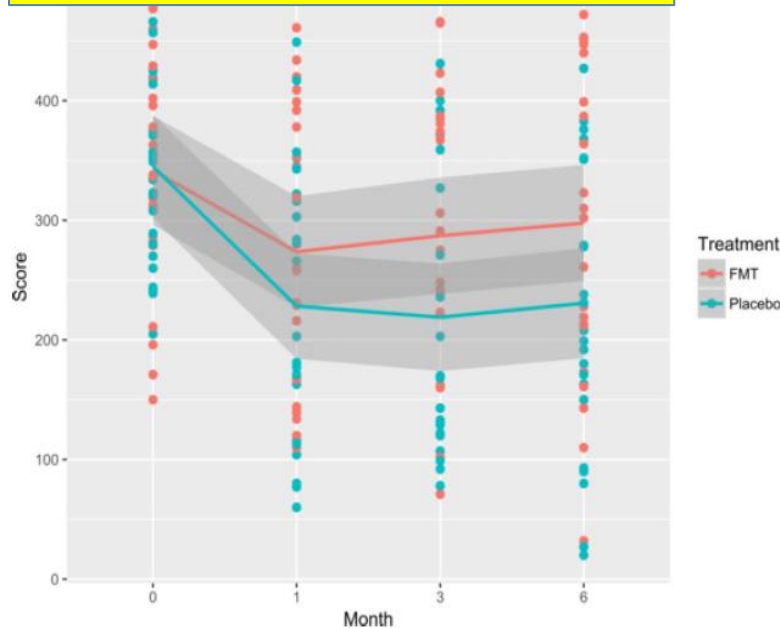
FMT in IBS: STUDY 2



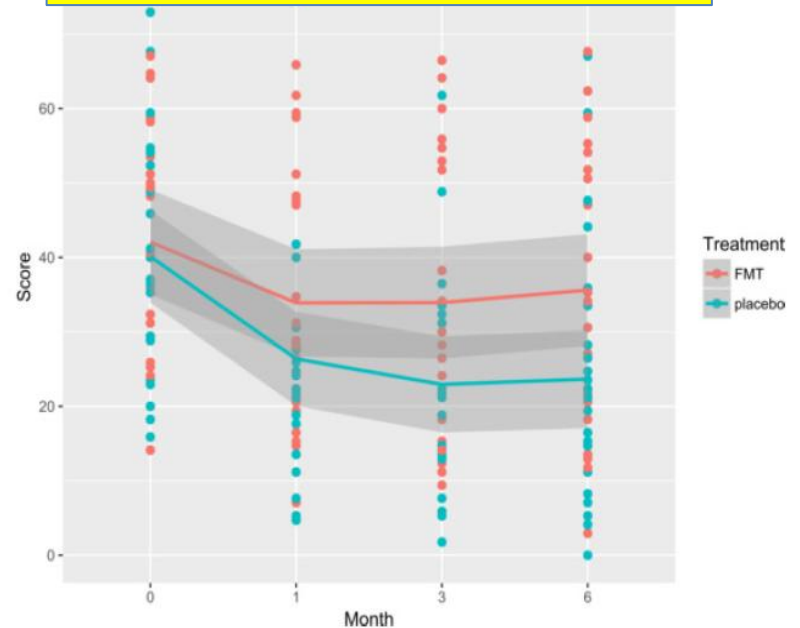
FMT in IBS: STUDY 2

- FMT increased biodiversity (First study)
- Symptoms and quality of life improved with placebo

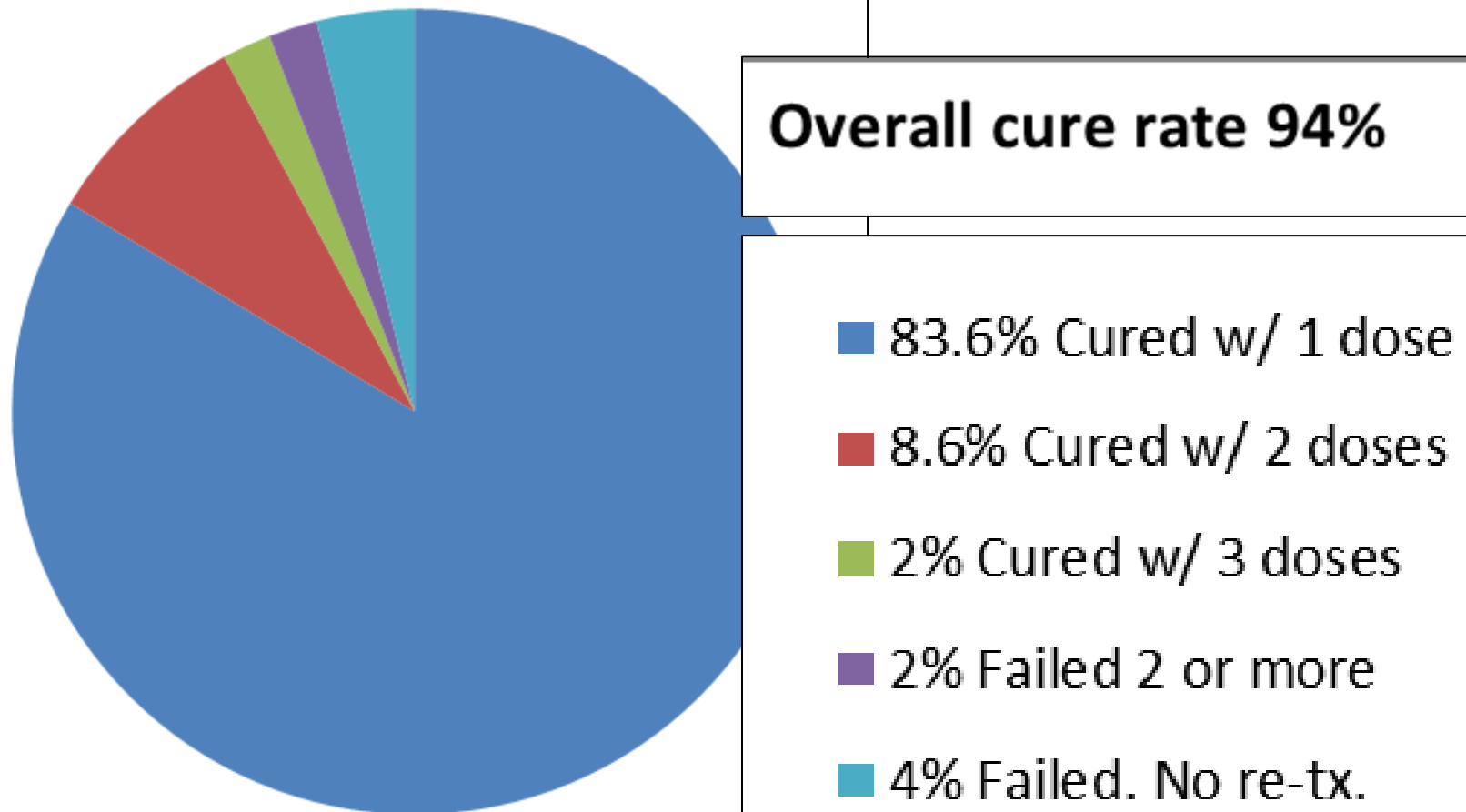
Change in Symptom Severity



Change in Quality of Life



Oral FMT for Recurrent CDI



Randomized FMT Trials in Adult UC Patients

Fecal Microbiota Transplantation Induces Remission in Patients With Active Ulcerative Colitis in a Randomized Controlled Trial

Paul Moayyedi,¹ Michael G. Surette,¹ Peter T. Kim,^{2,3} Josie Libertucci,¹ Melanie Wolfe,¹ Catherine Onischi,³ David Armstrong,¹ John K. Marshall,¹ Zain Kassam,⁴ Walter Reinisch,¹ and Christine H. Lee³

Findings From a Randomized Controlled Trial of Fecal Transplantation for Patients With Ulcerative Colitis

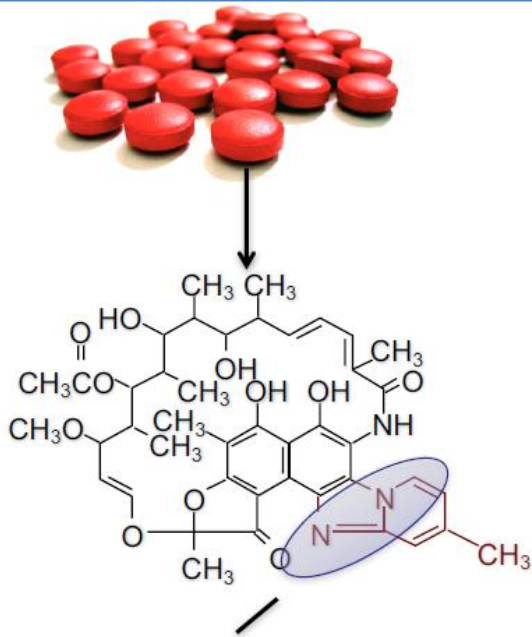


Noortje G. Rossen,¹ Susana Fuentes,² Mirjam J. van der Spek,¹ Jan G. Tijssen,³ Jorn H. A. Hartman,² Ann Duflou,¹ Mark Löwenberg,¹ Gijs R. van den Brink,¹ Elisabeth M. H. Mathus-Vliegen,¹ Willem M. de Vos,^{2,4} Erwin G. Zoetendal,² Geert R. D'Haens,¹ and Cyriel Y. Ponsioen¹

Multi-Donor FMT for Active Ulcerative Colitis

- Multicenter, double-blind, randomized, placebo-controlled trial
- Mild-moderate active UC to either FMT or placebo colonoscopic infusion, followed by enemas 5 days per week for 8 weeks
- FMT enemas were from between 3-7 unrelated donors
- **Primary outcome: steroid-free clinical remission with endoscopic remission or response at week 8**
- Performed 16S rRNA stool analysis to assess associated microbial changes

Antibiotics in IBS: Rifaximin

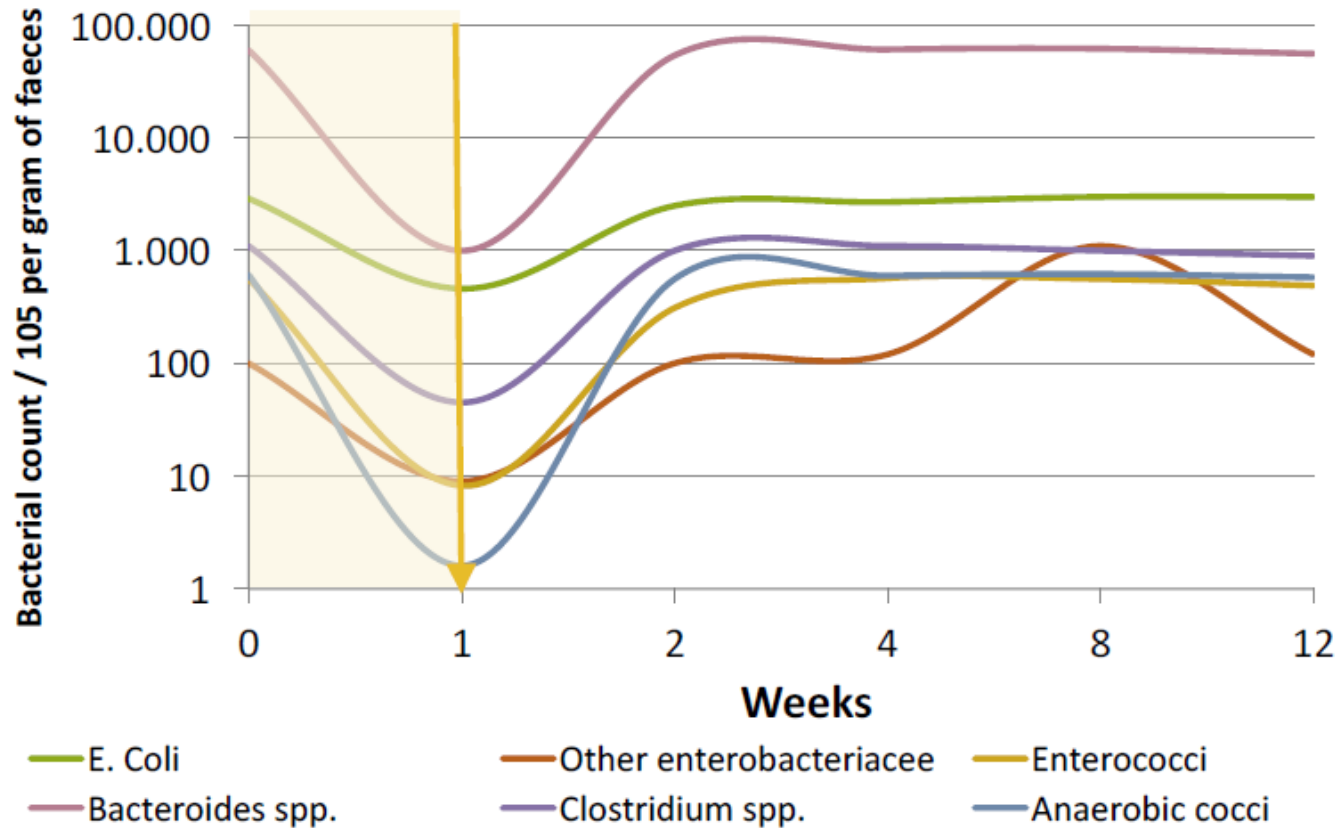


The presence of two opposite charged nitrogens prevents its absorption by passive diffusion

- Poorly absorbed, broad spectrum antibiotic
- Structural analogue of rifampin
- Inhibits bacterial RNA synthesis by binding to the β -subunit of bacterial DNA-dependent RNA polymerase
- Five polymorphic forms of rifaximin have been identified so far, i.e. rifaximin- α , - β , - γ , - δ , - ϵ
- Rifaximin- α has negligible absorption: <1%

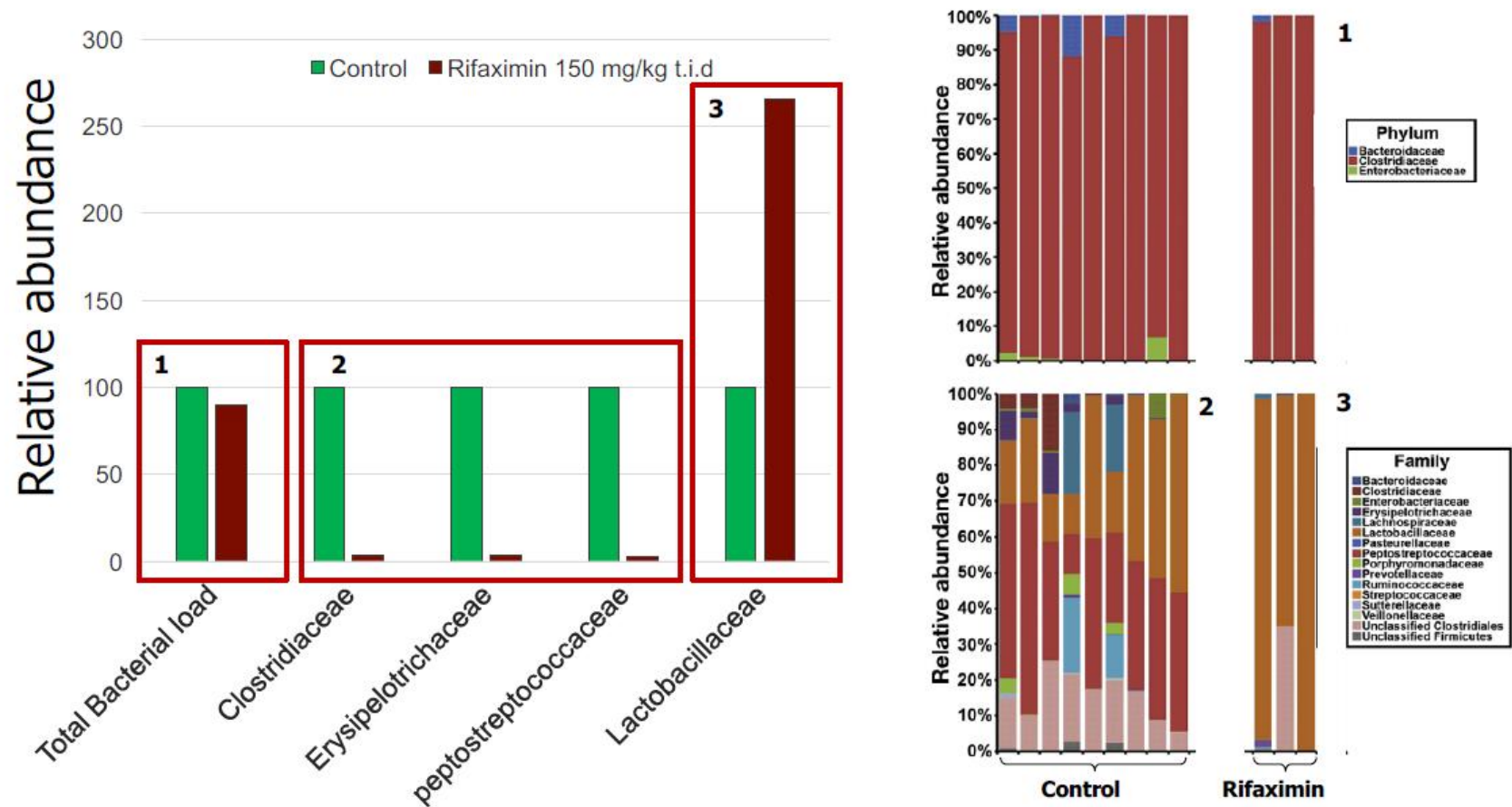
Effect of Rifaximin on Gut Microbiota

5-days Rifaximin (800 mg / day) in 10 healthy volunteers)



Gillis Drugs 1995; DeLeo Drug Exptl Clin Res 1986

The Eubiotic Effect of Rifaximin



Xu D et al., Gastroenterology 2014;146:484-96

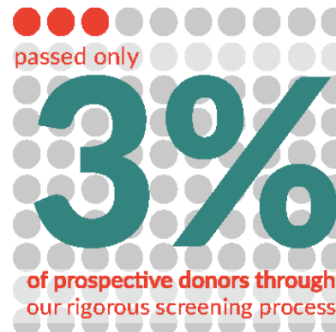
Multi-Donor FMT for Active Ulcerative Colitis

OPENBIOME

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Processed over
4000 pounds
of stool
that's **2 tons** of stool!



Primary Outcomes

- 6-month UC related hospitalizations
- 6-month cumulative incidence of infection
- UC Remission at week 12



Study: Fecal Microbiota in Small Intestinal Bacterial Overgrowth (SIBO)

- **Breath tests:**
 - 60 patients with SIBO
 - 20 patients without SIBO
 - 20 Healthy controls
- **Results**

Conclusions & The future

- GI symptom generation is linked to gut microbiome
- In some patients with IBS gut microbiota is different
- Treatment options:
 - Restriction diets ► Reduce biodiversity
 - Probiotics, Antibiotics ► Beneficial but limited
 - FMT ► Conflicting results
- Future: More studies:
 - Diet-Microbiota interactions-GI symptoms
 - Host-Microbiota interactions
 - Treatment studies-Symptom generation

Thank you!

SAVE LIVES.



EARN MONEY.



DONATE YOUR STOOL.

