

**GI ON DEMAND**  
ACG GastroGut

Access GI Expertise, Educational Resources and Support  
for You and Your Patients

Registered Dietitians   GI Psychologists   GI Sub-Specialists   APP Patient GI   Genetic Testing   Telehealth Features   Education Resources

A Free ACG Member Benefit Designed to Help You and Your Patients!  
Learn More and Join Today at  
[GIONDEMAND.COM](http://GIONDEMAND.COM)

1

*Special Issue:*  
**WELL-BEING**

JOY AND WELL-BEING IN THE PRACTICE  
OF MEDICINE - THE IMPORTANCE OF THE  
HUMAN CONNECTION

**ACG MAGAZINE**  
[BIT.LY/ACG-MAG-WELLBEING](http://BIT.LY/ACG-MAG-WELLBEING)

2



**2024** ACG'S HEPATOLOGY SCHOOL  
& MIDWEST REGIONAL  
POSTGRADUATE COURSE

**AUGUST 23-25, 2024** | RADISSON BLU MALL OF AMERICA  
MINNEAPOLIS, MINNESOTA



Register online: [meetings.gi.org](https://meetings.gi.org)



3



ACG Virtual Grand Rounds universe.gi.org

*AJG Special Issue*

**INFLAMMATION  
IN DIGESTIVE DISEASES**

*Submit your clinically relevant manuscript*

SUBMISSION WINDOW  
**FEBRUARY 1, 2024**  
through  
**JULY 1, 2024**

**LEARN MORE >**

4

ACG  
JUNE 7-9, 2024  
THE CAPITAL HILTON  
WASHINGTON, DC

# 2024 ACG IBD SCHOOL & EASTERN REGIONAL POSTGRADUATE COURSE

> ACG'S IBD SCHOOL | > EASTERN REGIONAL POSTGRADUATE COURSE

EARN UP TO 7.5 CME CREDITS | EARN UP TO 7.5 MOC POINTS | EARN UP TO 11.5 CME CREDITS | EARN UP TO 11.5 MOC POINTS

The poster features a large blue and purple arch at the top. On the right, there is a circular inset image of the US Capitol building. The ACG logo is in the top right corner.

5

Virtual Grand Rounds | universe.gi.org

## Participating in the Webinar

All attendees will be muted and will remain in "Listen Only Mode"

Type your questions here so that the moderator can see them. Not all questions will be answered but we will get to as many as possible.

A handout with the slides and room to take notes can be downloaded from your control panel.

Moderator:  
Neil H. Stollman, MD, FACG

Control panel icons: Mute, Hand, Chat, Download, Info, Exit

The slide has a blue background. It includes a photo of the moderator, Neil H. Stollman, MD, FACG. Three yellow boxes with arrows point to the mute icon, the chat icon, and the download icon in the control panel on the right side of the slide.

6

ACG Virtual Grand Rounds universe.gi.org

## ACG Virtual Grand Rounds

Join us for upcoming Virtual Grand Rounds!



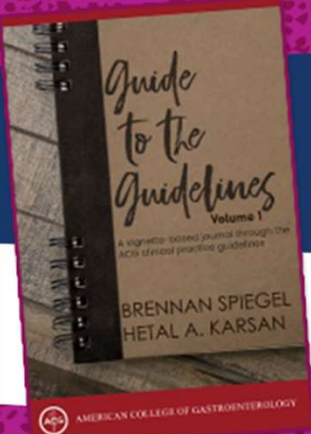
**Week 16 – Thursday, April 18, 2024**  
 A Practical Approach to Pouch Disorders  
 Faculty: Laura E. Raffals, MD, MS, FACG  
 Moderator: Shannon Chang, MD, MBA  
 At Noon and 8pm Eastern




**Week 17 – Thursday, April 25, 2024**  
 Best of ACG 2023! Outstanding Science, Expert Discussions  
 Faculty: Laith Jamil, MD, Jean Chalhoub, MD, Alyssa Choi, MD, Adam Bucholtz, MD, and Amer AlSamman, MD  
 Moderators: Vladimir Kushnir, MD, FACP, and Daniela Guerrero Vinsard, MD  
 At Noon and 8pm Eastern

[Visit gi.org/ACGVGR](https://gi.org/ACGVGR) to Register


7





## ACG ANNOUNCES a New Book Series

Now Available!



Visit [gi.org](https://gi.org) to purchase your copy!

8

AJG The American Journal of GASTROENTEROLOGY

**ACG MONOGRAPH ON MICROBIOME THERAPEUTICS**

→ Currently available online and in print

Wolters Kluwer

ACG INSTITUTE FOR CLINICAL RESEARCH AND EDUCATION

Unrestricted educational grants to support the monograph have been provided to the ACG Institute for Clinical Research and Education from Nestlé Health Science and Seres Therapeutics and Ferring Pharmaceuticals Inc.

9

ACG Virtual Grand Rounds universe.gi.org

## Disclosures



Ari Grinspan, MD, FACG : Seres Therapeutics: consultant; Ferring Therapeutics: consultant.



Olga Aroniadis, MD, MSc, FACG: No relationships with ACCME defined commercial interests.



Neil H. Stollman, MD, FACG:  
Amsurg: Advisory Board; Doximity: Stockholder; Ferring Pharma: Consultant; Nestle Health Sciences: Speakers Bureau; Phathom Pharmaceuticals: Speakers Bureau; Provation Medical: Advisory Board; UpToDate: Royalties

*\*All of the relevant financial relationships listed for these individuals have been mitigated*

10



## An Introduction to the Microbiome

**Ari Grinspan, MD**

Associate Professor of Medicine  
Director, Microbial Therapeutics Program  
The Dr. Henry D. Janowitz Division of Gastroenterology  
Icahn School of Medicine at Mount Sinai

**Olga C. Aroniadis, MD, MSc**

Svetlana Koroleva Endowed Professor in Gastroenterology  
Associate Professor of Medicine  
Chief, Division of Gastroenterology and Hepatology  
Stony Brook University Hospital

11



## Outline

- Characterization of microbial communities
- The role of dysbiosis
  - *C. difficile* infection
  - Inflammatory Bowel Disease (IBD)
  - Irritable Bowel Syndrome (IBS)
- Introduction to manipulation of the microbiome

12



## Characterization of Microbial Communities

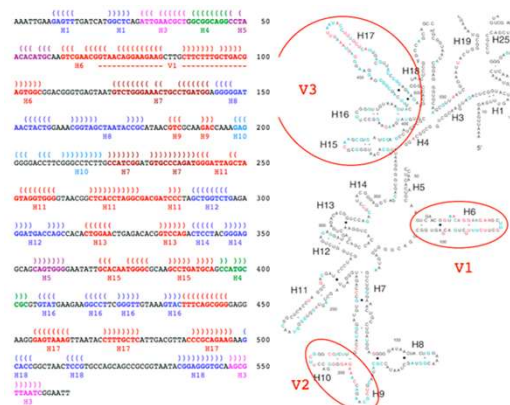
13



## Definitions

### Microbiota

The *microorganisms* inhabiting a particular environment



### Microbiome

The collective *genomes* of all the microorganisms inhabiting a particular environment

14

ACG Virtual Grand Rounds universe.gi.org

## Microbial Hierarchy

Kingdom

Domain

Phylum

Class

Order

Family

Genus

Species

4 predominant phyla of the GI tract:

- 1) Bacteroidetes
- 2) Firmicutes
- 3) Actinobacteria
- 4) Proteobacteria

15

ACG Virtual Grand Rounds universe.gi.org

20%  
Cultured

80%  
Uncultured

↓

**Microbe gene sequencing**  
 $3.9 \times 10^{13}$  bacteria/person  
 200-400 bacterial species/person  
 # bacteria = # human cells

Sender, et al. PLOS, 2016

16

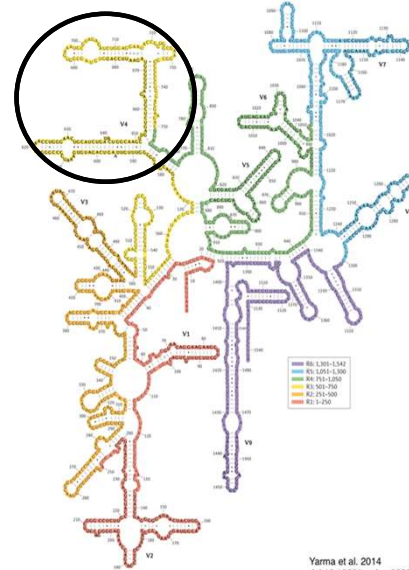




## 16s DNA Sequencing

### 16S gene

- Part of *all* bacteria
- Found *only* in bacteria
- Conserved and variable regions (V1-V9)
- Closely-related bacteria have more similar variable regions
- Amplicon sequencing of a section of the 16S gene
- Sequence similarity distinguishes microbes from each other
  - OTUs – fundamental unit used in 16s sequencing



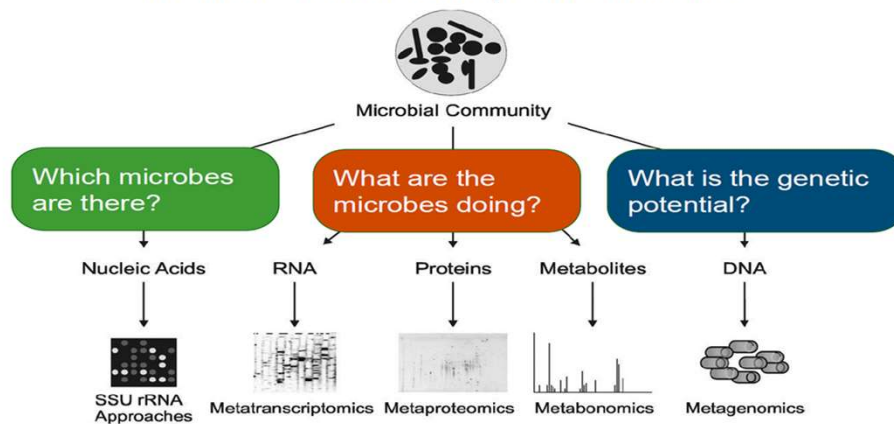
Yama et al. 2014  
doi:10.1038/nrmicro3330  
Nature Reviews Microbiology

17



## Intestinal Microenvironment

No universal method that provide all answers



18

ACG Virtual Grand Rounds universe.gi.org

## Intestinal Microenvironment

19

ACG Virtual Grand Rounds universe.gi.org

## Our microbes matter

**Metabolism:**

- Deconjugate bile acids
- Degrade fiber → SCFA
- Folate, B vitamins, Vit K
- Regulate fat/cholesterol
- Drugs

**Colonization Resistance:**

- Defend against pathogens
- Bacteriocins

**Immunity:**

- GALT development
- Pro and Anti inflammatory cascades
  - Treg, Th17, Il-10, Il-22, NOD2
- Tolerance to luminal flora and antigens

**Immune responses**

- Development
- Inflammatory responses (V/I)

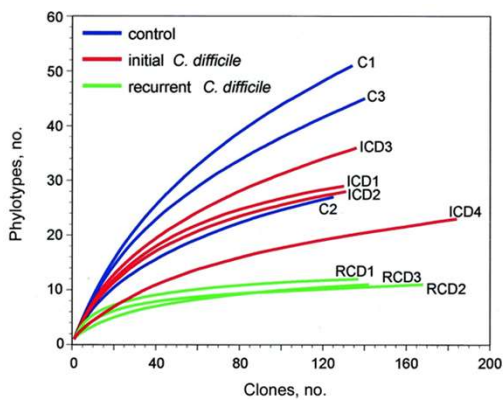
Vincent B Young BMJ 2017;356:bmj.j831

20

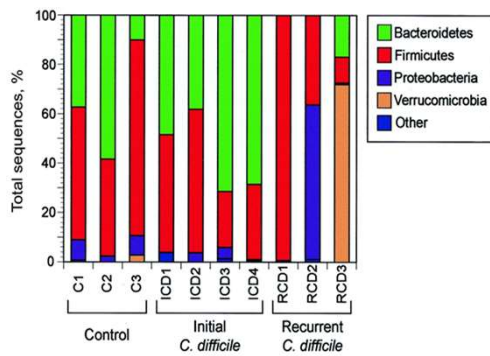
# C. difficile infection

21

## Recurrent C. difficile infection is characterized by dysbiosis

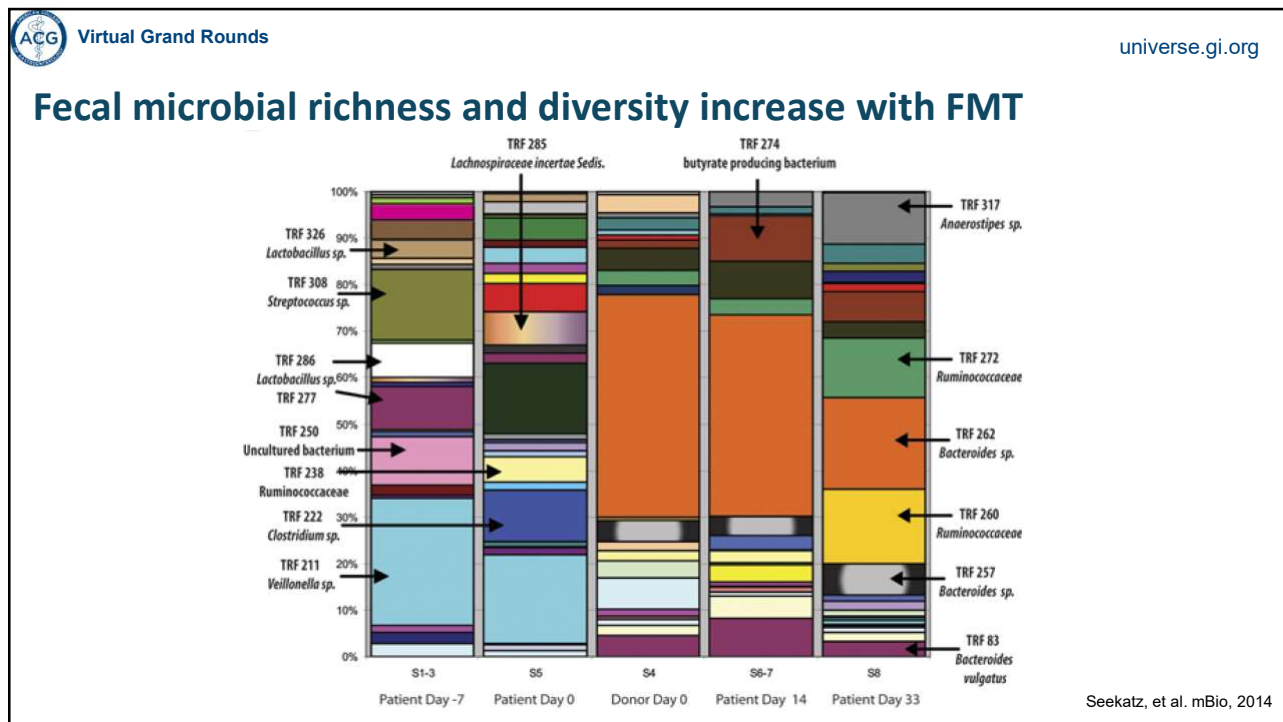


Patients with recurrent *C. difficile* have decreased phylogenetic richness

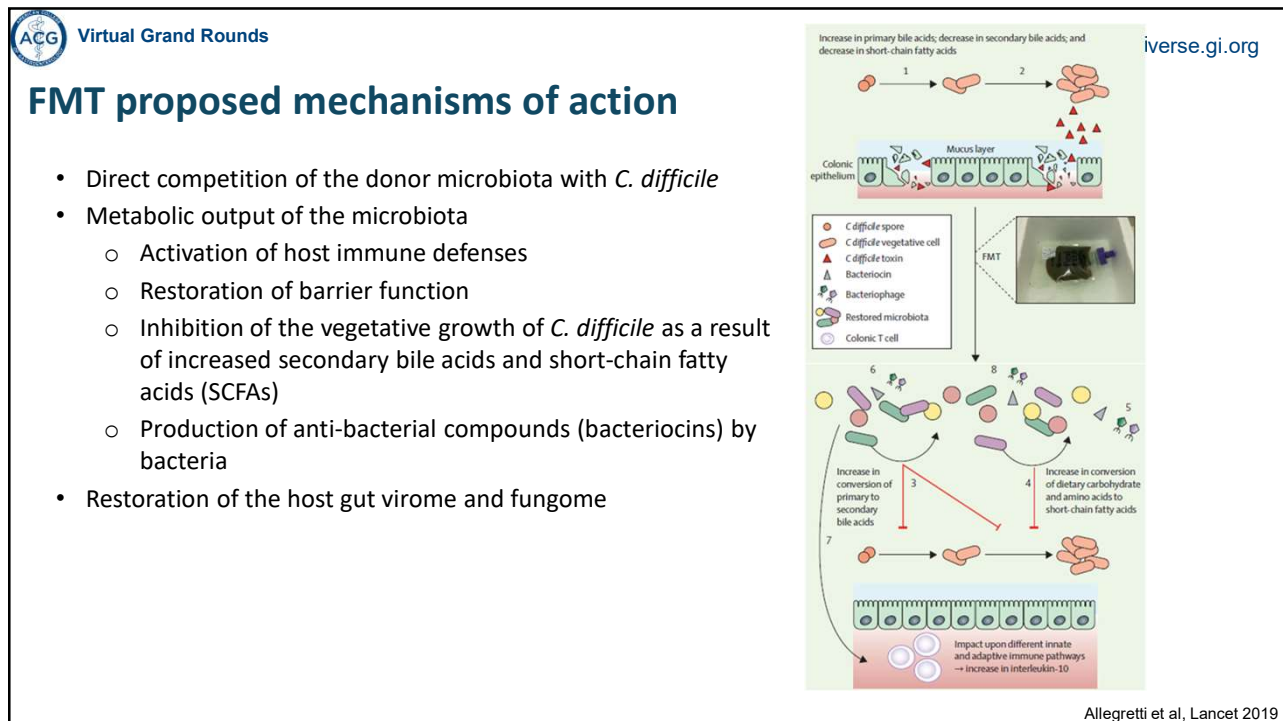


*Bacteroidetes* and *Firmicutes* are reduced in patients with recurrent *C. difficile* but not in patients with just one episode of *C. difficile* infection

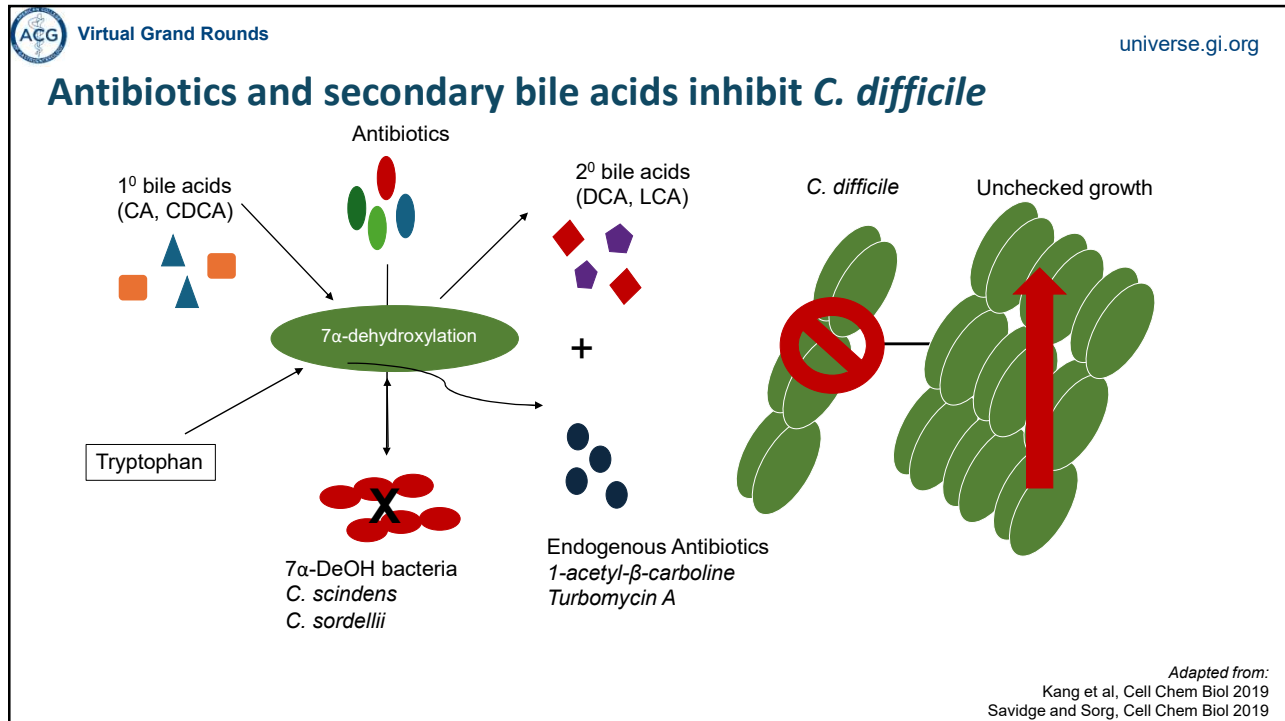
22



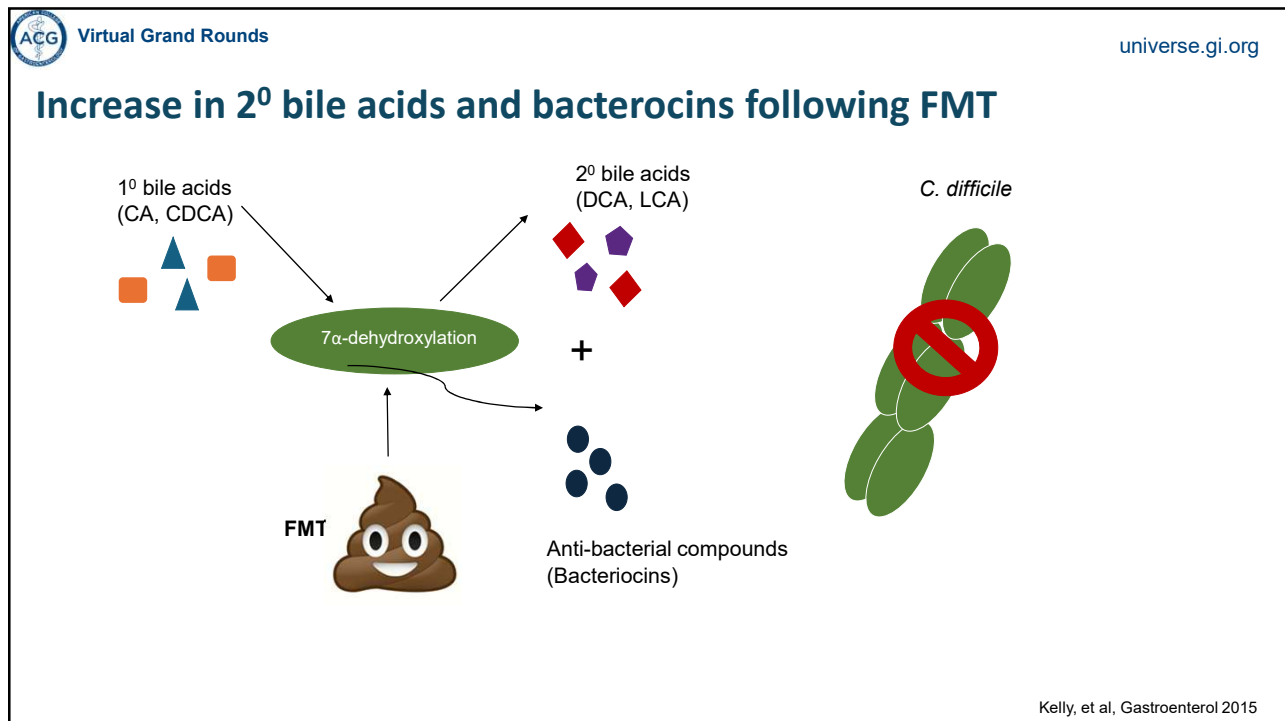
23



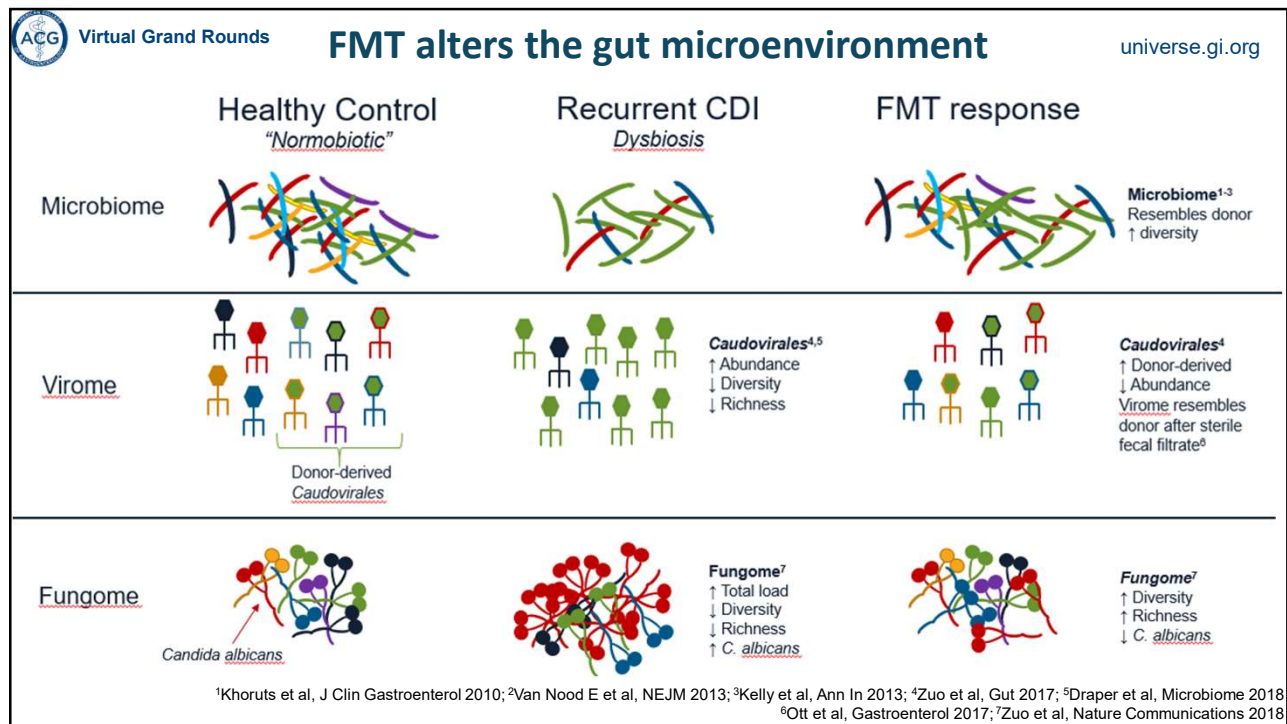
24



25



26



27


ACG Virtual Grand Rounds **FMT efficacy for recurrent CDI (RCDI)** universe.gi.org

- Multiple case-reports and case-series
- Meta-analyses & systematic reviews
- >10 clinical trials

**Bottom-line:** FMT has been shown to be an effective treatment for halting the RCDI cycle

van Nood, et al. NEJM, 2013  
Kao, et al. JAMA, 2017  
Kelly, et al. Ann Int Med, 2015  
Tariq, et al. CID, 2019  
Ianiro, et al. United European Gastroenterol J, 2018  
Quraishi, et al. Aliment Pharmacol Ther, 2017

28

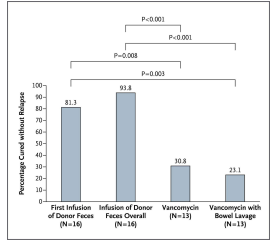


Virtual Grand Rounds

universe.gi.org

## FMT is successful for RCDI


### FMT vs vancomycin - via duodenal infusion



**80%**

Van Nood 2013

### Fresh vs Frozen FMT- via enema

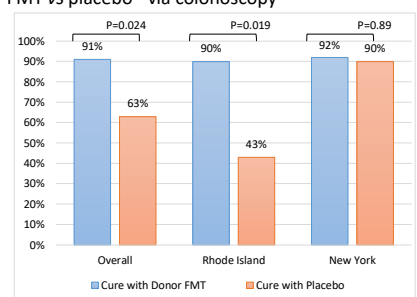


No. of FMTs	Per-Protocol Population	
	Frozen (n = 91)	Fresh (n = 87)
1	57 (62.7)	54 (62.1)
2	19 (83.5)	20 (85.1)
3-5	9 (93.4)	9 (95.4)
>5	2 (95.6)	1 (96.6)
<b>Total</b>	<b>87/91 (95.6)</b>	<b>84/87 (96.6)</b>

**60%**

Lee 2016


### FMT vs placebo - via colonoscopy



**90%**

Kelly 2016


### Encapsulated FMT



- Fresh (Louie 2013)
- Frozen (Youngster 2014, Kao 2017)
- Microbial Emulsion Matrix (Fischer/Openbiome 2015)
- Freeze-dried (Khoruts 2017)

**70-90%**

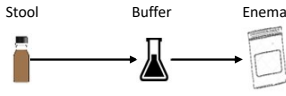
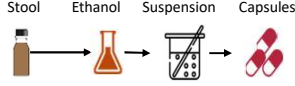
29



Virtual Grand Rounds

universe.gi.org

## FDA-approved Microbiome Products

	Product Overview	Composition	Bowel Prep	Dosing	Delivery	Efficacy vs Placebo
<b>Fecal microbiota live-jslm</b>		Full-Spectrum	✗	1 dose	Enema	70.6% vs 57.5%
<b>Fecal microbiota spores live-brpk</b>		Fractionated	✓	4 capsules daily for 3 consecutive days	Capsule	87.6% vs 60.2%

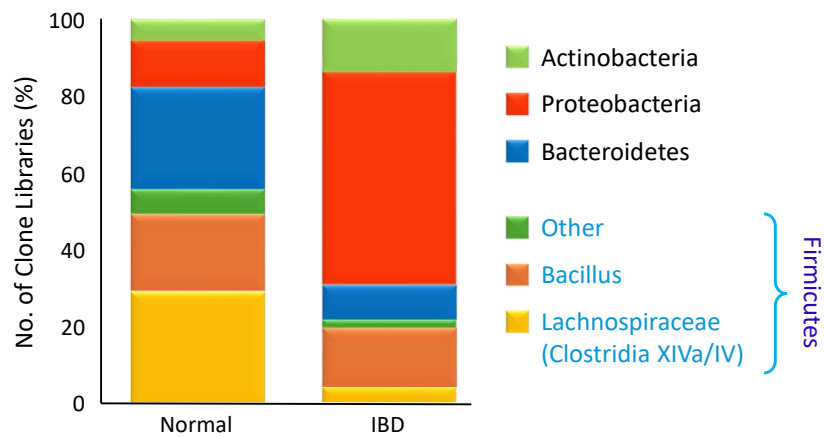
30



## Inflammatory Bowel Disease (IBD)

31

### IBD is characterized by “Dysbiosis”



Frank DN, et al. Proc Natl Acad Sci U S A. 2007;104(34):13780-13785.

32

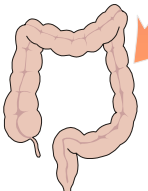


ACG Virtual Grand Rounds universe.gi.org

## Enteric bacteria are essential in pathogenesis of intestinal inflammation

**No bacteria**

No immune activation



**No colitis**

Mice

IL-2 KO (↓)  
IL-10 KO  
TCRa KO  
CD3e26TG  
MDR1 KO  
SAMP1/Yit (↓)  
CD45RB<sup>hi</sup> SCID

Rats

HLA-B27 TG  
Indomethacin

Guinea pigs


Carrageenan

Primate

Cotton-top tamarin

**Resident bacteria**

Macrophage and TH<sub>1</sub>/TH<sub>17</sub> immune activation



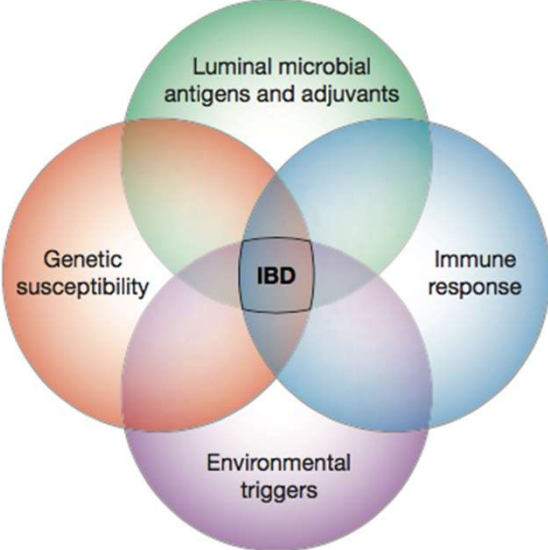
**Colitis**

KO = knock out; HLA = human leukocyte antigen; TG = transgenic.  
Adapted from Sartor AGA Teaching Slides.

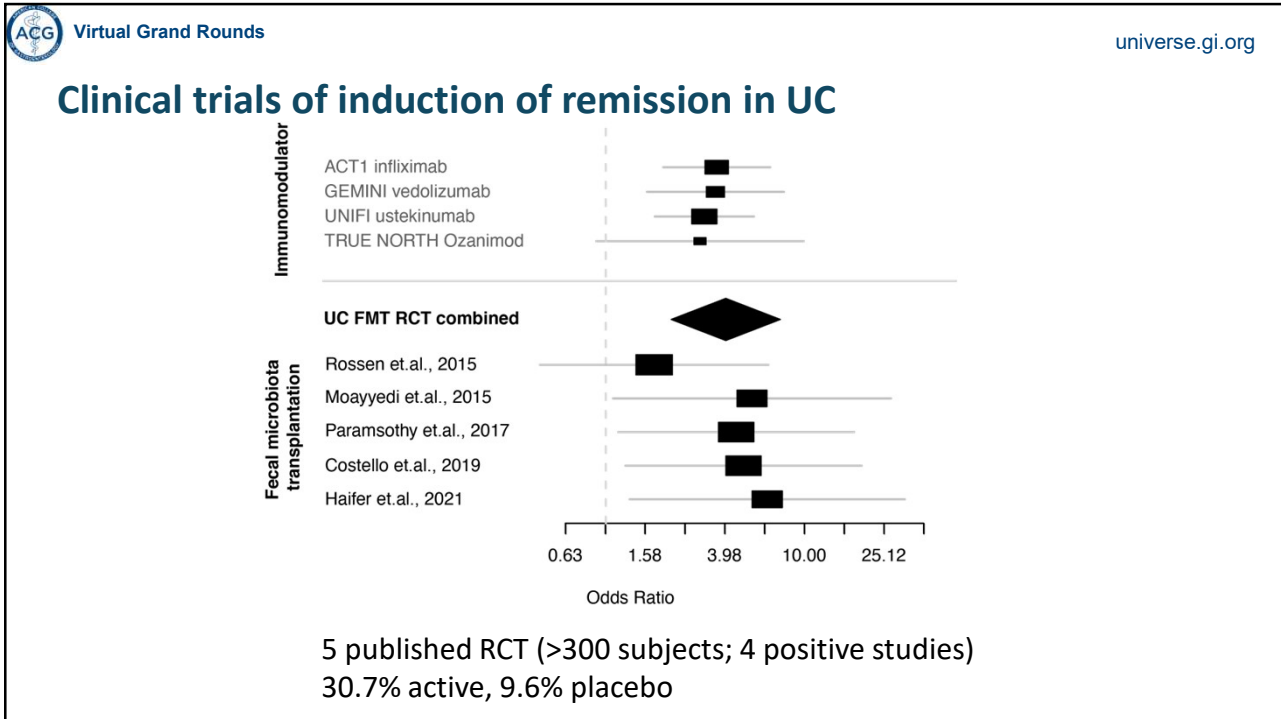
33

ACG Virtual Grand Rounds universe.gi.org

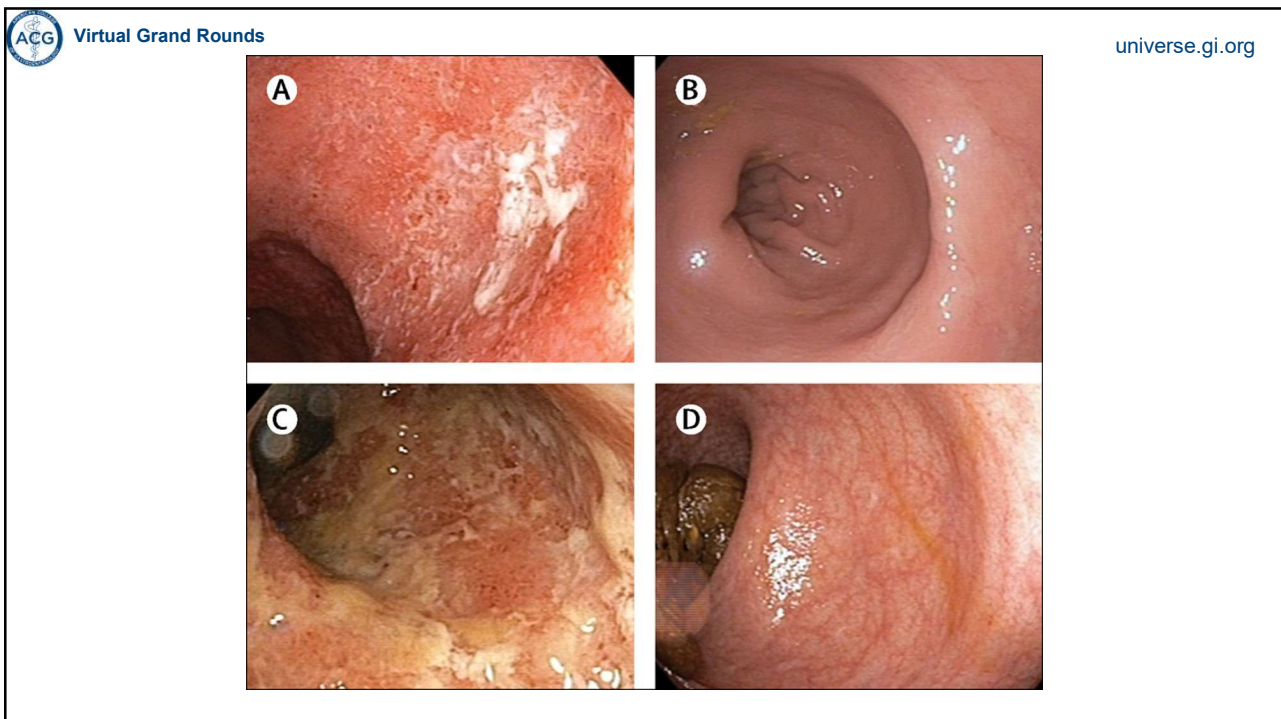
## IBD = Multifactorial pathogenesis



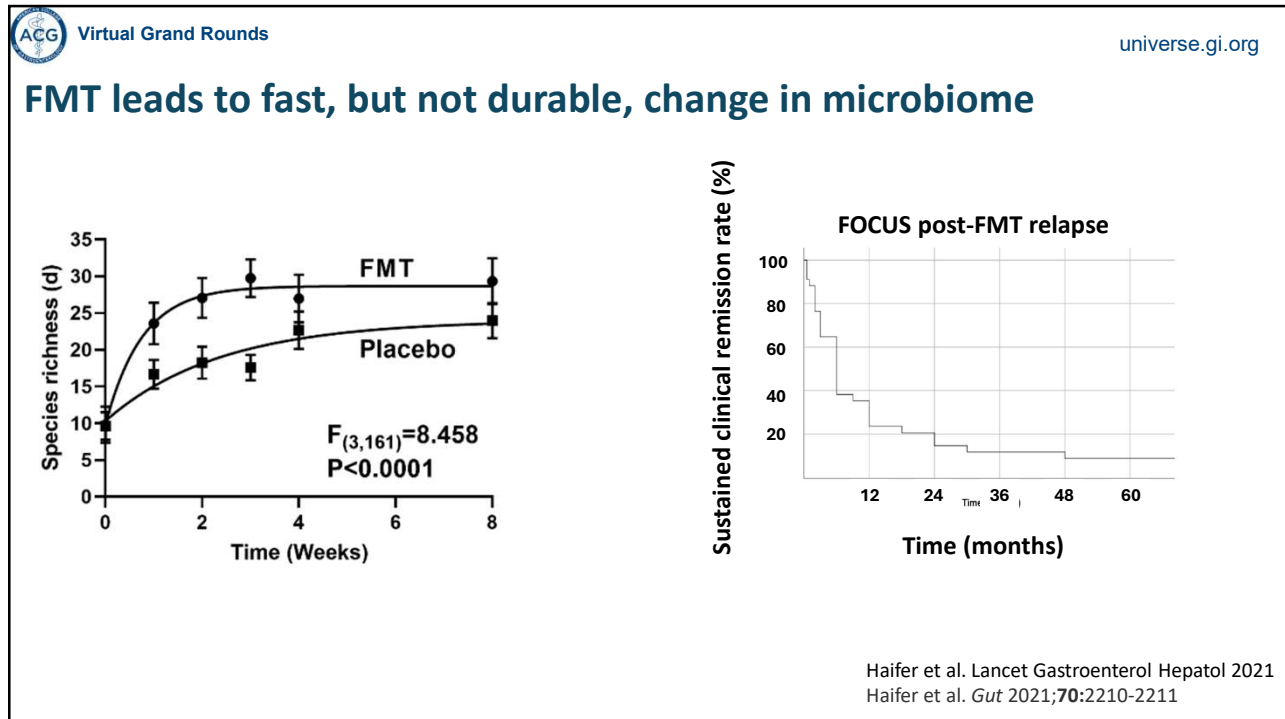
34



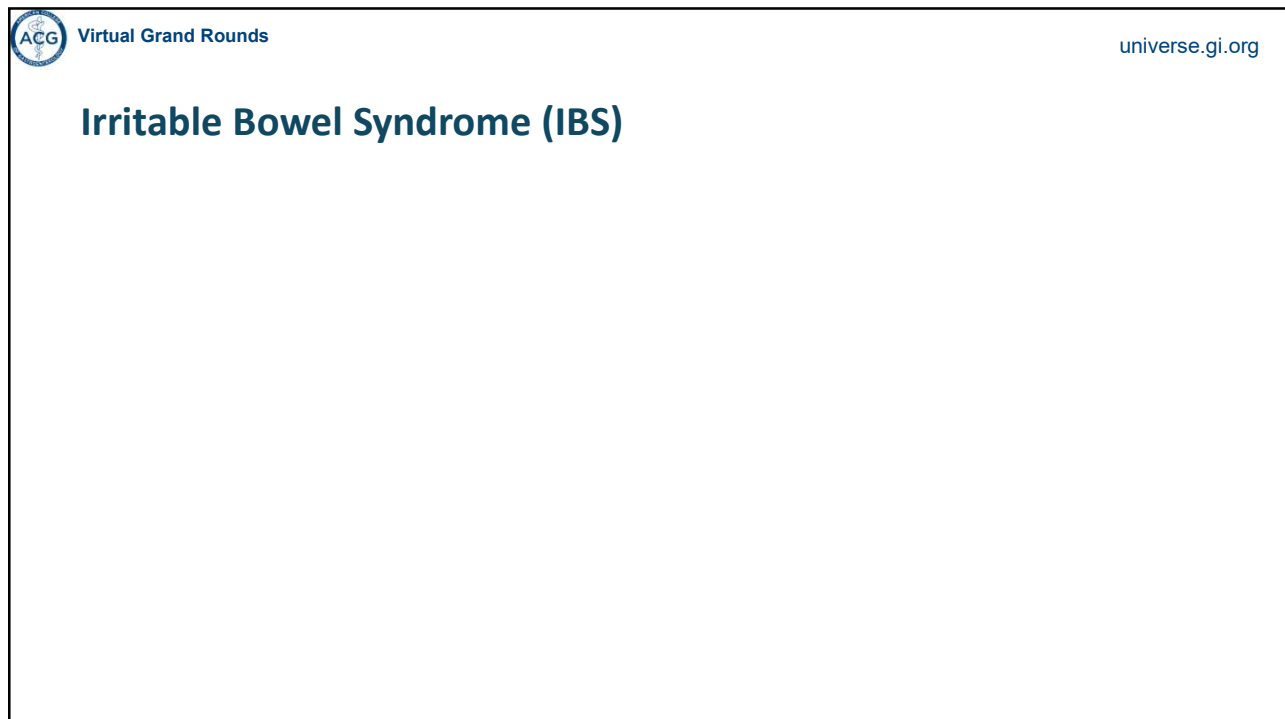
35



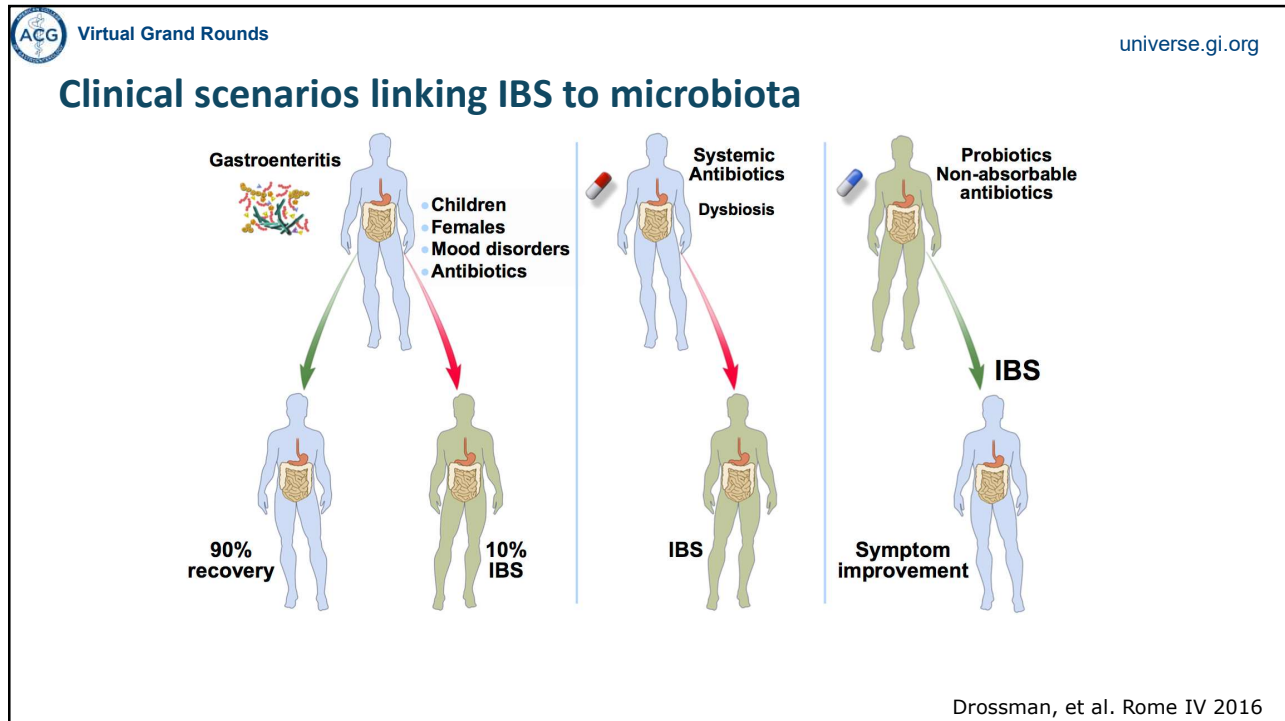
36



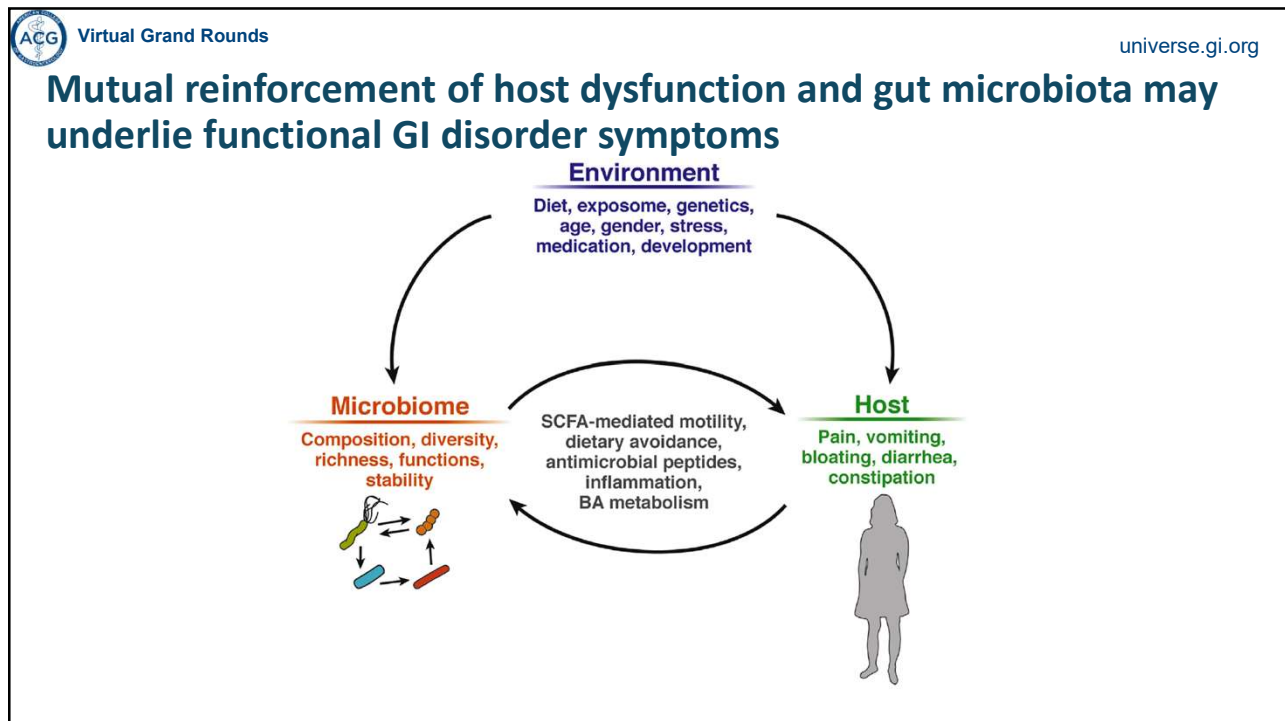
37



38



39



40

ACG Virtual Grand Rounds universe.gi.org

## Common microbiome and metabolomic profiles have not been clearly identified in IBS

IBS vs controls

Bifidobacterium  
Faecalibacterium

Lactobacillaceae  
Bacteroides  
Enterobacteriaceae

- Marked heterogeneity with no 2 studies reporting exactly the same differences<sup>1</sup>
  - Different methods were used to assess the microbiota
  - Statistical methodological flaws
- No common metabolomic profile identified in IBS patients compared with controls<sup>2</sup>
- IBS patients displayed differences in SCFA production when compared with controls<sup>3</sup>

<sup>1</sup>Pittayanon, et al. *Gastroenterol* 2019  
<sup>2</sup>Bennet, et al. *Neurogastroenterol Motil* 2020  
<sup>3</sup>Sun, et al. *Medicine* 2019

41

ACG Virtual Grand Rounds universe.gi.org

## Although no consistent microbial or metabolomic signatures have been identified in IBS patients, phenotype can be transferred by fecal microbiota

Conventional Mouse

Healthy Volunteer

Germfree Mouse

Healthy Mouse Model

IBS, colonic hypersensitivity

Germfree Mouse

IBS Mouse Model

Visceral hypersensitivity of IBS patients can be transferred to recipient mice

Crouzet, et al. *Neurogastroenterol Motil* 2013

42

ACG Virtual Grand Rounds universe.gi.org

## IBS supernatant increases permeability and visceral pain

**Permeability (Caco cells)**

Group	ZO-1 mRNA level
Healthy subjects	~23
IBS	~3*

*Piche et al. Gut 2009*

**Activation of visceral afferents**

*Barbara et al. 2007*

**Visceromotor response to distention**

*Cinac et al. JCI 2007*

Drossman, et al. Rome IV 2016

43

ACG Virtual Grand Rounds universe.gi.org

## Probiotic Bifidobacterium longum reduces depression scores and alters brain activity in IBS

**Before treatment**

- All brain regions
- ROI - Amygdala

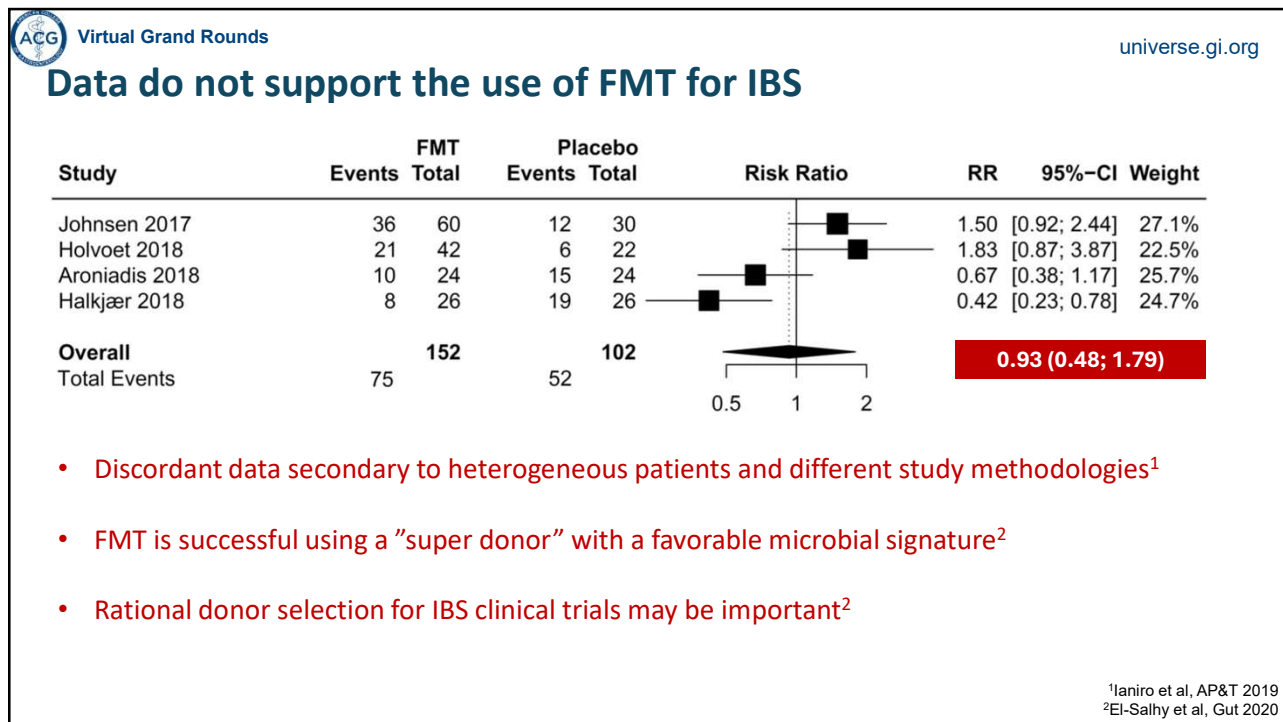
**After treatment**

- All brain regions
- ROI - Amygdala

**After treatment**  
 Lesser engagement of the amygdala  
 (involved in mood and anxiety regulation)

Pinto-Sanchez, et al. Gastroenterology, 2017

44



45

ACG Virtual Grand Rounds universe.gi.org


## Conclusions

- The human gut harbors a diverse array of microbiota
  - Important biological functions
  - Diversity is good!
- Alterations in gut bacteria are associated with disease
  - But association does NOT mean causation
- *Clostridioides difficile* infection
  - FMT works
  - Fecal microbiota live-jslm
  - Fecal microbiota spores live-brpk
- Therapeutic manipulation of gut microbiota is promising
  - Insufficient data to recommend FMT for conditions other than *C difficile*


46

ACG Virtual Grand Rounds universe.gi.org


## Questions



Ari Grinspan, MD, FACP



Neil H. Stollman, MD, FACP



Olga Aroniadis, MD, MSc, FACP

47

# CONNECT AND COLLABORATE IN GI



**ACG GI Circle**  
Connect and collaborate within GI



**IBD Circle**  
A Partnership of the American College of Gastroenterology and the Crohn's & Colitis Foundation



**ACG Hepatology Circle**



**ACG Functional GI  
Health and Nutrition Circle**

ACG's Online Professional Networking Communities  
LOGIN OR SIGN-UP NOW AT: [acg-gi-circle.within3.com](http://acg-gi-circle.within3.com)



48