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Gastrointestinal Manifestations of COVID-19
Latest Data on Symptoms, Stool Testing, and Clinical Outcomes

Monday, May 18, 2020 at 8pm Eastern

Brennan Spiegel, MD, MSHS, FACG
Professor of Medicine and Public Health
Director of Health Services Research, Cedars-Sinai
Co-Editor-in-Chief, American Journal of Gastroenterology

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ACG & CCF IBD Circle

IBD in the COVID-19 Era: Update for the Busy Clinician
Tuesday, May 12, 2020 at 8 pm EDT

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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.

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Week 9: Positioning of Old and New Therapies in IBD
David T. Rubin, MD, FACP
May 21, 2020 at Noon EDT

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Disclosures:

Moderator:
Brooks D. Cash, MD, FACG
Consultant: Allergan, QOL Medical, Salix, Takeda
Speakers Bureau: Allergan, QOL Medical, Salix, Takeda

Speaker:
Neil Stollman, MD, FACG
Advisory Board: OpenBiome
Consultant: Assembly Biopharma
Research Grant: Assembly Biopharma
Royalties: UpToDate
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None

C. difficile and Fecal Microbiota Transplant (FMT):
The Beginnings of ‘Microbiome Management’

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University of California San Francisco
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OUTLINE

• Biome 101
  – What’s a good biome?
  – Biomes Gone Bad (dysbiosis)
• *C. difficile*: the ‘opportunist’
• FMT: the ‘fixer’
• The Future: can we target biome interventions to cure disease?

Credit: Antoine Doré for Nature Outlook

“MICROBIOMANIA” (J. Eisen PhD UCD)

The Microbiome Solution
a radical new way to heal your body from the inside out

Feel better from the inside out.
We’ll detect the nutrients and toxins in your gut and personally recommend foods and nutrients to keep your microbiome balanced.

Credit: Robynne Chutkan, author of OUTLIER

American College of Gastroenterology
It’s also the new new (research) thing.....

>80% of all human biome research has occurred since 2017

We are not alone!

- Living inside each of us are trillions of bacteria, viruses, and fungi collectively known as the microbiome.
- There are multiple human organ biomes Firmicutes and Bacteroidetes make up 90% of the gut biome.
- 1.5x bacteria in/on us per 1 human cell
- 100x bacterial genes per every human gene
• Humans emit $10^6$ biological particles/hour
• Studied in ‘sanitized climate chamber’ for 2-4 hours
• “….individuals occupying a space emit their own distinct personal microbial cloud”


And it’s not just IN us (and another case for social distancing....)

It’s not just about the vast numbers of bugs: Consistently Decreased Microbial Diversity in rCDI

...speaking of diversity

Major American Cities (pop>400k) Ranked by Diversity

Hornfndahl-Hirschman Index

Percentage of the city population that is:
- White *
- Black *
- Hispanic/Latino *
- Asian *
- Other *

1. Oakland, California (HHI = 0.233542)
2. Atlanta, Georgia
3. New York, New York (0.260098)
4. Chicago, Illinois (0.289780)
5. Long Beach, California (0.289253)
6. San Jose, California (0.295186)
7. Boston, Massachusetts (0.307096)
8. San Diego, California (0.309732)
9. San Francisco, California (0.311676)
10. Houston, Texas (0.314006)
11. Milwaukee, Wisconsin (0.315346)
12. Dallas, Texas (0.321295)
13. Fort Worth, Texas (0.322432)
14. Philadelphia, Pennsylvania (0.327408)
15. Las Vegas, Nevada (0.332481)
16. Fresno, California (0.334839)
17. Charlotte, North Carolina (0.335335)
18. Los Angeles, California (0.387181)
19. Austin, Texas (0.388040)
20. Oklahoma, Oklahoma (0.372218)
21. Washington, District of Columbia (0.391355)


And it’s not one organism → one outcome
Complex communities sharing similar ‘niches’

Nope!!

Co-dependency rules, with symbiotic metabolic support from multiple community members to each other (and to the host)

Bacteria: help digest nutrients, prevent colonization by pathogens, aid immune system development

Host: provides nutrients and a mobile home with a view

Yep!!
Yeah, it’s all just that simple.....

When do we acquire our biome?

- GI tract colonized in the first few years and remains stable, leading to a ‘unique lifelong microbiome signature’
- Birth / peripartum period is the major first exposure for humans
  - Vaginal and skin-to-skin contact
  - Maternal blood and breast milk contain microbial DNA of organisms found in infants’ stool; unclear role in colonizing infant
  - C-sections may predispose to increased allergies, obesity, infections
  - Vaginal gauze (incubated 1 hour) rubbed over infant mouth and skin immediately after birth leads to colonization and improved diversity (improved clinical outcomes)
It's not just mom... early life environmental exposures matter

- The “Biome of the Built Environment”
- Pet ownership and livestock exposure: ↓ risk asthma
- rCDI patients who own pets: ↓ recurrence (OR=0.86)
- Antibiotics in early life may ↑ later obesity, asthma, IBD
- Farmers have a different microbiome than city workers; sailors’ oral microbiome changes while at sea
- Exercise, stress, sleep deprivation correlate with biome changes
- The gut microbiome is influenced by circadian rhythm... and can itself affect the host’s circadian rhythm

Redding LE et al. Op For Inf Dis 2020; 7:541

Diet effects on our gut microbiome

- Modern urban populations have far less biome diversity than indigenous populations (who typically eat 10x more fiber)
- The effects of the same dietary ingredient on glucose metabolism can vary in individuals based on their microbiome profile
- The microbiome can influence leptin; ? appetite or diet preferences
- Immigrant’s biomes rapidly ‘westernize,’ starting within 9 months
  - Lower diversity and increased obesity
  - Lose plant fiber degrading enzymes
  - Bacteroides strains displace Prevotella
Oh, and grapes are food, right?

- Evaluated in 3 independent population-based cohorts
- **Red wine consumption positively associated with α-diversity**
- Even rare consumption had effect
- White wine a lesser but suggestive association with α-diversity
- No associations with other alcohol categories.


#intimacymatters (marriage is healthy...could biome mediate?)

- We think that gut microbiota remains stable after age 3-5 (unless perturbed) so siblings should be more alike than spouses?
  - Wisconsin Longitudinal Study (>10K HS grads 1957)
  - Living with spouse \(\rightarrow\) greater diversity and richness than living alone
  - Spouses have more similar microbiota than siblings and the longer married and closer the marriage, the more similar the biome
So, what IS a ‘good’ or ‘healthy’ gut biome?

- 500-1000 different species (and many subspecies) of bacteria, viruses, fungi, phages
- Currently have a catalogue (‘field guide’) but know little about interactions or consequences
- Diversity is better
- Immune responses affect changes in the microbiome and the biome markedly affects the immune system

Credit: Antoine Doré for Nature Outlook

MY BIOME

This is a picture of your Gut microbiome sample(s): 🌟

- **All My Bacteria**
  - 1. Firmicutes: 74.78%
  - 2. Bacteroidetes: 21.04%
  - 3. Actinobacteria: 2.09%
  - 4. Proteobacteria: 2.02%
  - 5. Cyanobacteria: 0.05%

- **Most Unique**
  - 1. Lentisphaerae: 0.0139%
  - 2. Cyanobacteria: 0.0487%
  - 3. Actinobacteria: 2.0932%
  - 4. Bacteroidetes: 21.0431%
  - 5. Proteobacteria: 2.0167%

- **Most Enriched**
  - 1. Firmicutes: 1.26X
  - 2. Bacteroidetes: 0.93X
  - 3. Actinobacteria: 0.84X
  - 4. Proteobacteria: 0.62X

- **Most Depleted**
  - 1. Proteobacteria: 1.61X
  - 2. Actinobacteria: 1.19X
  - 3. Bacteroidetes: 1.07X
  - 4. Firmicutes: 0.79X

American College of Gastroenterology
When bugs go bad: Types of ‘dysbiosis’

– OUTGROWTH OF PATHOBIONTS: commensal microbiota usually present in small amounts but can ‘bloom’ with changes in the ecosystem.

– LOSS OF COMMENSALS: reduction / loss of normal microbiota due to microbial killing or decreased proliferation. Restoration of commensals underlies success of FMT.

– LOSS OF DIVERSITY (richness): by diet, drugs, illness (also improved by FMT)

– Cause or consequence?
– And changes not necessarily pathological:
  • “Varibiosis” (a biome change without known mechanistic role)

Dysbiosis: Disease associations

***Patients with C. diff have radically less diverse biomes and are cured by instillation of healthy stool*** (our proof-of-concept)

• Other observations:
  – Gut biome can classify people as lean or obese with >90% accuracy
  – The abundance of Christensenella within the human are negatively correlated with BMI, and can induce weight loss when fed to mice
  – Autism Spectrum Disorder: animal models demonstrating the role(s) of bacterial metabolites in mediating autism-like behaviors, and ? role FMT
  – Modern increase in allergic / immune diseases likely due to biome perturbation (rather than genetics)
C. difficile: Epidemiology

- Anaerobic gram-positive spore-forming bacillus
  - Found in >50% of healthy infants and 5-10% of healthy adults
  - Colonizes 20-40% of inpatients >2d and >50% of pts in LTCFs
  - Increase in peripartum, IBD, cirrhosis, organ transplant, chemoRx
- Leading cause of nosocomial diarrhea
- >10% mortality in elderly
- NAP1/BI/027 strain: epidemics, increased toxin production, lower cure and higher recurrence rates
A bit of good news.....24% decrease CDI burden 2011-17
Due to ↓ health-care associated infections; no change in community-acquired infections

C. difficile: Why do we get it?

• Infection requires both:
  1. alteration of the microbiome  (usually due to Abx)
  2. exposure to the organism  (usually in a health care facility)

• Transmission: fecal → oral, person to person

• Spores can survive in environment for days / months and are resistant to common hospital disinfectants.

• Once ingested, germinate in small bowel, multiply in colon and cause inflammation.

• Bile salts important in spore germination, to common hospital disinfectants.
**CDI: Clinical Manifestations**

- Asymptomatic colonization (60-65%)  
  - 6x higher risk of CDI if colonized at admission (>20% vs 3%)
- Diarrhea, mild to severe
- Fulminant colitis / toxic megacolon (2-3%)
- Recurrent infection (20-30%)
  - 20% after 1st dx, 40% after 1st recurrence, 60% after 2nd
  - Common and impactful ($$, well-being)

**Testing, Prevention and Treatment: Current Major Society Guidelines**

- American College of Gastroenterology - 2013
  
  *Am J Gastroenterol* 2013;108:478-498
  (update in progress)

- IDSA / SHEA Guidelines - 2018
  
  *Clin Inf Dis* 2018; 66: e1–e48
FMT currently recommended solely for rCDI

- ACG Guidelines 2013: “If there is a 3rd recurrence after a pulsed vancomycin regimen, FMT should be considered.” (conditional recommendation, moderate-quality evidence)
- IDSA Guidelines 2018: “FMT recommended for patients with multiple recurrences of CDI who have failed appropriate antibiotic treatments” (strong recommendation, moderate-quality evidence)
- ACG Guidelines 2020: in draft but likely to recommend FMT after 2nd or further recurrence.

Fecal Microbiota Transplantation (FMT)

- Administration of feces (typically containing the entire gut microbial community) from a human donor to another, with intent to favorably affect the recipient’s microbiota
- Described in 4th C. Chinese medicine texts
- ‘Transfaunation’ in veterinary literature
- Eiseman (1958): fecal enemas show ‘dramatic’ resolution in 4 cases of ‘pseudomembranous colitis’ (presumed CDI)
- ? “Intestinal Microbiota Transplant” (IMT)?
FMT: HOW to do it? “The 5 D Approach”

- Decision
- Discussion
- Delivery
- Donor
- Discharge

FMT Delivery

- **Nasogastric or nasoduodenal tube**
  - Uncomfortable, increased risk
  - X-ray or EGD placement
- **Retention enemas**
  - Variable patient ability to tolerate
- **Lower endoscopy**
  - Enables examination of mucosa
  - Likely more effective (90% vs 75%)
  - $$$, sedation risks
- **Encapsulation**
  - Likely decreased risk and cost, if equal efficacy
FMT: WHY IT WORKS? ENGRAFTMENT

*Khoruts A. J Clin Gastroenterol 2010*

Engraftment is durable (3 months)

*Li SS, et al Science 2016; 352:586-9*
FMT for rCDI (open label case series, colonoscopy)

- 77 (of 94 eligible) followed 3-68 months (mean 17)
  - Primary Cure rate: 91%
  - Secondary Cure rate: 98%
- All late recurrences occurred w/ subsequent antibiotics
- No overt AEs, although 4 patients developed auto-immune diseases subsequently (ITP, Sjogren’s, RA)


First RCT: FMT (nasoduodenal) for rCDI

43 Dutch centers, patients with >1 recurrence
A) Vanco 500mg QID x 14d
B) Vanco 500mg QID plus bowel lavage
C) Vanco 500mg QID x5 days, plus lavage and then nasoduodenal infusion (donor pool);

2nd infusion (different donor) offered if failed (3)

First Infusion Donor Feces (n=16)
Infusion of Donor Feces Overall (n=16)
Vancomycin (n=13)
Vancomycin plus lavage (n=13)

Cured without relapse

81.3 93.8 30.8 23.1


First US RDBPCT FMT (colonoscopy)

Cochrane Review 2013
- 11 studies
- 273 CDI patients
- Overall cure 90%
  - Upper: 82%
  - Lower: 91%
  - No reported AEs

Systematic Review 2015
- 12 case-series, 2 RCTs
- 516 patients (rCDI)
- Overall cure 85%
  - Upper: 77%
  - Lower: 90%
  - Enema: 78%
  - ‘Few short term AEs’

Systematic Review 2017
- 37 studies, 7 RCTs
- 1973 patients
- Overall cure 92%
  - Upper: 88%
  - Lower: 95%
  - Fresh 92% vs frozen 93%
  - ‘safe and generally well tolerated’

Overall cure: 85-92%
Lower: 90-95%
Upper: 77-88%


After FMT......

- Do **not** resume vancomycin (or other abx)
- Do **not** “test for cure.”
  - Repeat stool testing only if suggestive symptoms.
  - Toxin assay, NOT PCR ALONE
FMT for rCDI: special populations

- Immunocompromised
  - Safe but avoid neutropenic patients, consider CMV, EBV status?
  - Retrospective data: 78% success rate with no increase in AEs (but recent death was an immunosuppressed patient)

- Pediatric
  - Seems safe, but somewhat limited data. Often use mother as donor.

- Pregnant
  - Limited experience

- Patients on long-term antibiotics
  - Increased likelihood of failure and recurrence. ? Role of ‘prophylactic’ vanco

- Patients with limited life expectancy
  - Long-term low-dose vancomycin maintenance reasonable

Some cautions about FMT for rCDI....

- Is it as simple as giving the ‘right’ bacteria?
  - Open label, 5 pts with rCDI, fecal filtrates depleted of bacteria, via NJ tubes
  - 5/5 Symptom free for > 6months (CDI status?)
  - Did show increased diversity and changes in the virome, ? cause vs effect?
  - If confirmed, suggests that the nonmicrobial contents of stool (bacteriophages, dead bacteria, viruses, debris, metabolites) may be the active Rx

- Be wary of PI-IBS overlap in the non-vanco responsive patient
  - PCR (+) / toxin (−) patients have outcomes similar to PCR (-) / toxin (-) patients
  - 25% of FMT referrals have alternative diagnoses, maintain high suspicion as patients and providers often get focused on CDI when it’s often a bystander.
Safety: still TBD.....

- Risk of infection from infusate
  - Norovirus, CMV following home FMT
  - Two recent cases (1 fatal) of MDRO in immunocompromised adults (ESBL E coli, found in same donor)
- Risk of infection with yet-unrecognized pathogen?
- Risks related to administration itself
  - Perforation, sedation-related complications, aspiration
- Can biome alteration → autoimmune illness?
  - Case reports RA, ITP, obesity, Sjogren’s, lymphoma
  - Can cause IBD flares, ? from antigenic/immune stimulation

"FMT in the time of COVID..."

- OpenBiome – non-profit stool bank in Boston. Over 50K treatments provided to date.
- Still ‘open’ and shipping material to clinicians (far less Rx's now)
- All material being used and shipped was collected prior to 12/1/19
- Additional screening protocols for future donors and testing TBD
- There have been no reports of no reports of SARS-CoV-2 transmission by FMT.
Do-it-Yourself FMT??

- Online survey 2018-2019
- 84 respondents (71% female, 92% white, mostly US west coast)
- 80% did it on themselves (12% a child, 2% a spouse)
- 87% used the internet for guidance
- 64% done ‘because other Rxs didn’t work’
- 92% knew their stool donor, 65% screened the donor in some way
- 95% via enema, 43% had ‘performed >10 FMTs’
- Indications: IBD 35%, food allergies 30%, IBS 29%, SIBO 11%, ASD 2%
- 12% AEs (abd pain, gas/bloat, mood changes)
- 82% improved, 96% ‘would do it again’ but 57% would ‘prefer a clinical setting’


FMT for other diagnoses: ongoing trials (>200)

- *C. difficile* infection
- Crohn’s
- Ulcerative Colitis
- Pouchitis
- IBS
- Constipation
- NAFLD/NASH
- PSC
- Intestinal pseudo-obstruction
- CNS diseases (and SDAT)
- Graft vs host disease
- Obesity/metabolic syndrome
- HIV
- DM-II
- Pancreatitis
- Hepatitis / cirrhosis
- MRSA enterocolitis
- MDROs
- Hepatic encephalopathy
- Post-stem cell transplant
- Autologous FMT (preventative)
- Autism spectrum disorders
FMT for OTHER INDICATIONS

- **IBD** – data in UC, inconsistent, 20-30% response ranges, likely takes repeated Rxs and probable ‘donor effect’
- **IBS** – data largely negative, including early terminated studies; may show benefit when we can select for dysbiotic etiology
- **HE** – open label data, n=20, but positive
- **MDROs** – DDW 2020, n=20, open label upper x1, favorable
- **ASDs** – also favorable open label data, trials underway

### Microbiome therapeutics in development

<table>
<thead>
<tr>
<th>Product Overview</th>
<th>Composition</th>
<th>Bowel Prep</th>
<th>Dosing</th>
<th>Delivery</th>
<th>Clinical Trial</th>
<th>Mean Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rebiotix RBX-2660</td>
<td>Broad-Spectrum</td>
<td>x</td>
<td>Similar to FMT</td>
<td>Enema</td>
<td>Ph. II (Complete)</td>
<td>61-67% (PUNCH-CD2)</td>
</tr>
<tr>
<td>Seres SER-109</td>
<td>Narrow-Spectrum</td>
<td>✔</td>
<td>1000-fold lower dose than FMT</td>
<td>Capsule</td>
<td>Ph. II (Complete)</td>
<td>56% (ECOSPOR)</td>
</tr>
<tr>
<td>Finch CP101</td>
<td>Broad-Spectrum</td>
<td>x</td>
<td>Similar to FMT</td>
<td>Capsule</td>
<td>Ph. II (P0103)</td>
<td>88% (Staley et al. 2017)</td>
</tr>
</tbody>
</table>

Courtesy of Zain Kassam
FMT: unanswered questions, future directions

• Route: NG/ND vs F/S vs colonoscopy vs oral pills
• Random healthy donors vs ‘rational’ or ‘super-donors’
• Full-spectrum stool vs narrow consortia ‘synthetic’ stool
• Non-bacterial FMT? Role of virome, fungome, metabolome
• FDA currently exercising ‘enforcement discretion’
• Indications beyond C. difficile still TBD
• FMT will be a template for future bacteriotherapy and targeted biome restoration Rxs

Thank you!!

Neil@Stollman.com
@DrStollman
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