

Fecal Microbiota Transplantation

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Disclosures

- None

What & Why?

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FMT @Penn

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Applications
in Oncology

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Applications
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Fecal Microbiota Transplantation (FMT)

- Transplant fecal microbiota from healthy donor to colon of recipient
- Methods: frozen oral capsules, solution via enteric tube, enema, colonoscopy
- Indications:
 - *C. difficile* infection (CDI) = driving force behind development
 - MDRO colonization
 - inflammatory bowel disease (IBD)
 - oncology: auto-FMT post allo-SCT; immune checkpoint inhibitors; GVHD

Clostridiooides difficile Infection

- Infectious colitis that occurs after antibiotic treatment ("antibiotic-associated")
- Depletion of protective taxa (abx & PPI) → altered bile acid metabolism → germination of resident or recently ingested *C. difficile* spores → expansion of vegetative *C. difficile* → toxin production → colonic inflammation → CDI
- Treatment with anti-CDI antibiotics (vancomycin, fidaxomicin) contributes to persistent depletion of protective taxa → risk for recurrent CDI
- **FMT restores colonization resistance by restoring protective taxa**
- Note: treatment with anti-CDI antibiotics is prerequisite

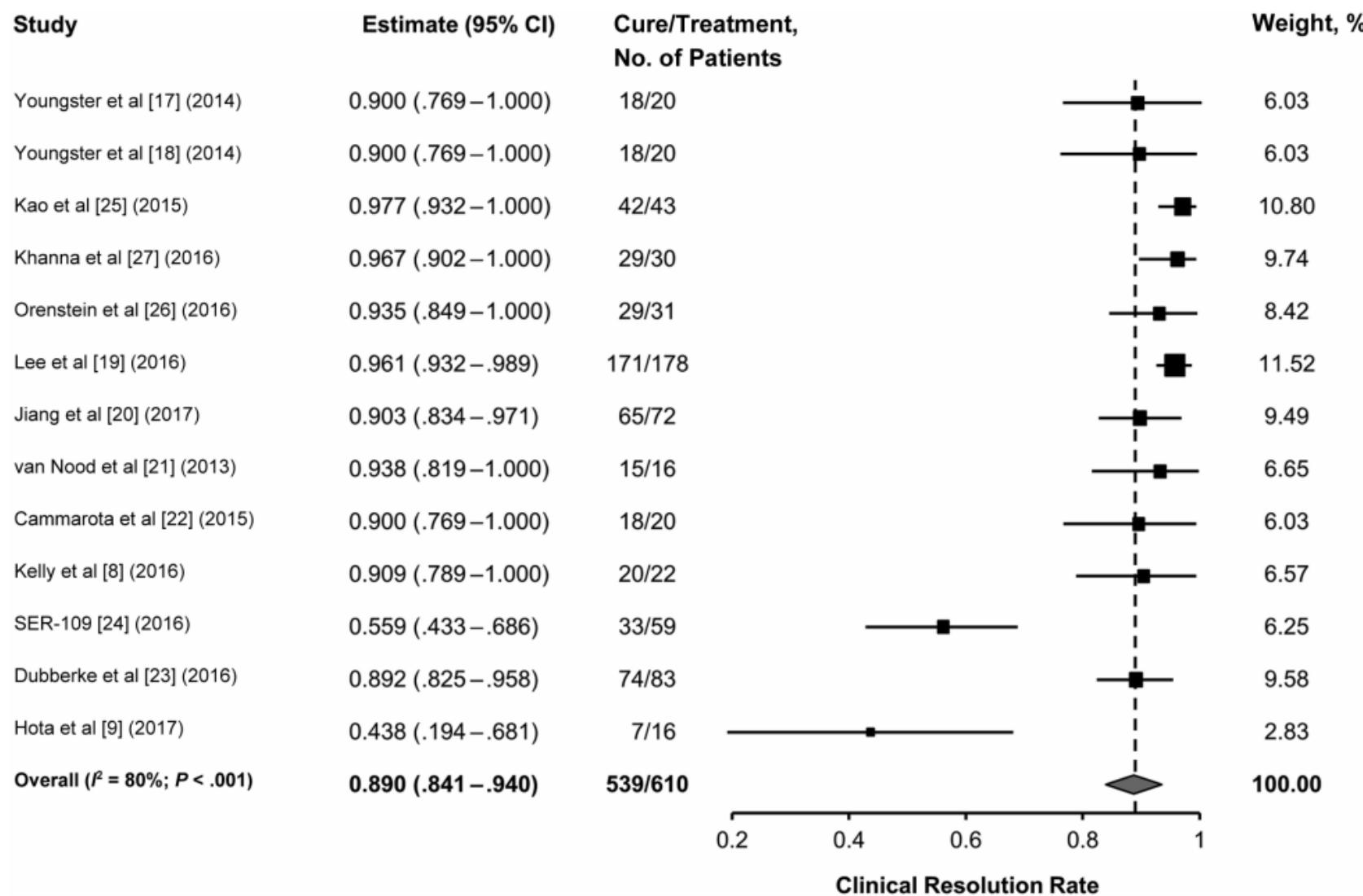


Table 1. Recommendations for the Treatment of *Clostridium difficile* Infection in Adults

Clinical Definition	Supportive Clinical Data	Recommended Treatment ^a	Strength of Recommendation/ Quality of Evidence
Initial episode, non-severe	Leukocytosis with a white blood cell count of $\leq 15\,000$ cells/mL and a serum creati- nine level < 1.5 mg/dL	<ul style="list-style-type: none">• VAN 125 mg given 4 times daily for 10 days, OR• FDX 200 mg given twice daily for 10 days• Alternate if above agents are unavailable: metronidazole, 500 mg 3 times per day by mouth for 10 days	Strong/High Strong/High Weak/High
Initial episode, severe ^b	Leukocytosis with a white blood cell count of $\geq 15\,000$ cells/mL or a serum creati- nine level > 1.5 mg/dL	<ul style="list-style-type: none">• VAN, 125 mg 4 times per day by mouth for 10 days, OR• FDX 200 mg given twice daily for 10 days	Strong/High Strong/High
Initial episode, fulminant	Hypotension or shock, ileus, megacolon	<ul style="list-style-type: none">• VAN, 500 mg 4 times per day by mouth or by nasogastric tube. If ileus, consider adding rectal instillation of VAN. Intravenously administered metronidazole (500 mg every 8 hours) should be administered together with oral or rectal VAN, particularly if ileus is present.	Strong/Moderate (oral VAN); Weak/Low (rectal VAN); Strong/Moderate (intrave- nous metronidazole)
First recurrence	...	<ul style="list-style-type: none">• VAN 125 mg given 4 times daily for 10 days if metronidazole was used for the initial episode, OR• Use a prolonged tapered and pulsed VAN regimen if a standard regimen was used for the initial episode (eg, 125 mg 4 times per day for 10–14 days, 2 times per day for a week, once per day for a week, and then every 2 or 3 days for 2–8 weeks), OR• FDX 200 mg given twice daily for 10 days if VAN was used for the initial episode	Weak/Low Weak/Low Weak/Moderate
Second or subsequent recurrence	...	<ul style="list-style-type: none">• VAN in a tapered and pulsed regimen, OR• VAN, 125 mg 4 times per day by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days, OR• FDX 200 mg given twice daily for 10 days, OR• Fecal microbiota transplantation^c	Weak/Low Weak/Low Weak/Low Strong/Moderate

Abbreviations: FDX, fidaxomicin; VAN, vancomycin.

IDSA/SHEA Guidelines: McDonald LC et al *Clin Inf Dis* 2018

Efficacy Despite Product Heterogeneity?

- FMT contains multitudes:
 - bacteria, fungi, archaea... bacteriophage, eukaryotic viruses (e.g., TTVs) ...
 - ... human colonocytes, metabolites
- Causal models for efficacy versus *C. difficile* infection:
 - Direct bacterial interaction? Bile acid metabolism-mediated interaction?
 - Bile acid metabolism & Th17 regulatory cells?
- **We do it because it works, but we don't know why!**

Bojanova & Bordenstein *PLoS Biology* 2016; Ott et al *Gastroenterology* 2017; Hang et al *Nature* 2019

FMT Regulation & Commercial Alternatives

- Guideline-recommended for CDI but no FDA-approved product:
 - IND required for non-CDI indications
 - for CDI, FDA exercises "enforcement discretion"
 - concern that product availability (e.g., OpenBiome) limiting RCT enrollment
- Multiple companies with "ecobiotic" FMT alternatives in phase 2/3 trials:
 - Finch, Rebiotix, Seres, Vedanta
 - May 2020: "Rebiotix and Ferring are the first to announce positive preliminary results on primary efficacy endpoint from ongoing pivotal Phase 3 clinical trial"

What & Why?

FMT @Penn

Applications
in Oncology

FMT Program Development at Penn

- 2014-2016: ID Division Stool Bank
 - FDA enforcement discretion (no IND)
 - 67 FMTs: 82% aggregate cure rate
- 2016-2018: OpenBiome partnership
- 2019-present: "Penn Microbiome Therapy (PMT)"
 - IND for 3 products: capsule, upper GI liquid, enema
 - 3 protocols: R-CDI, SC-CDI, postpartum incontinence (OB-GYN: Uduak Andy, PI)
(compassionate use for MDRO colonization)

Impact of COVID-19 on FMT at Penn

- **FDA partial hold:** all doses manufactured after December 1, 2019
- Adequate donor/dose screening:
 - challenges with stool testing for SARS-CoV-2 (high LOD)
 - donor screening with serology? NP NAAT?
- Ongoing COVID-19 activity slows (already slow) clinical trial enrollment
- **Recent resumption of enrollment for all protocols**

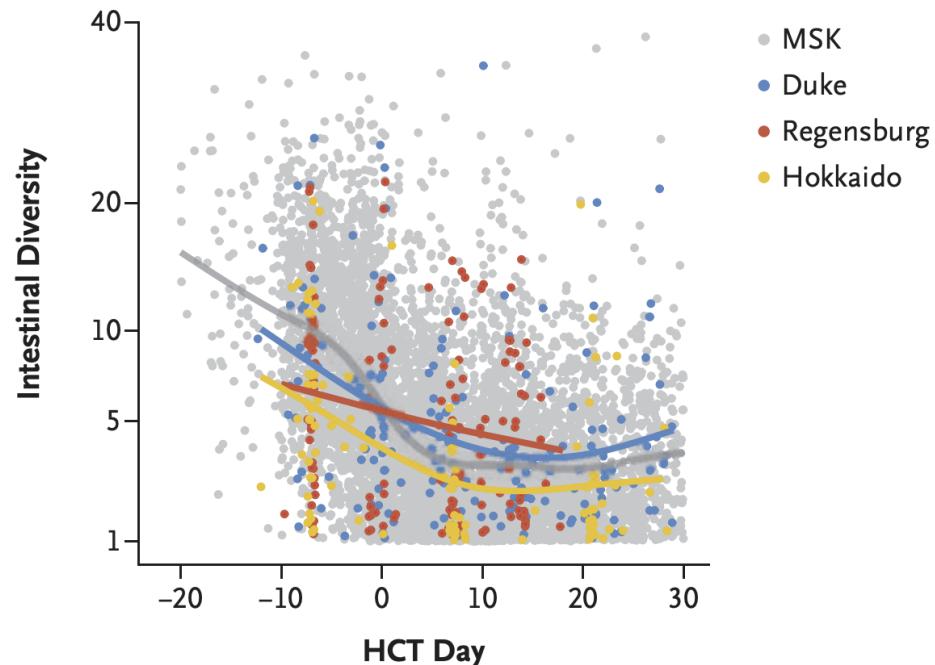
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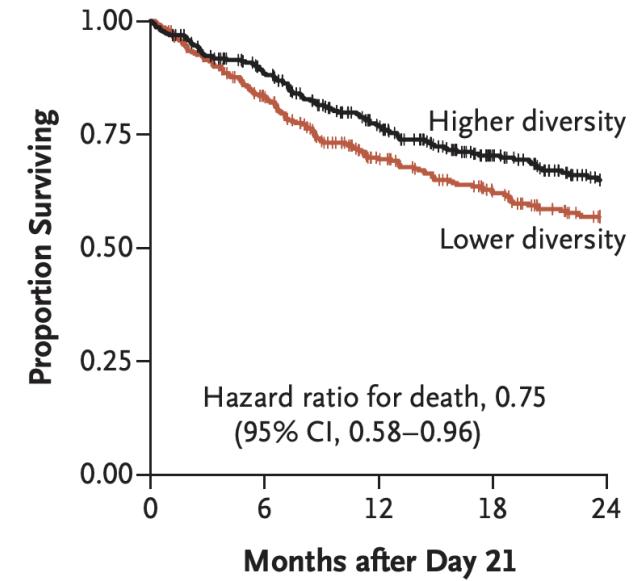
Applications
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Dysbiosis & Death

A Change in Diversity of Intestinal Microbiota during HCT Period



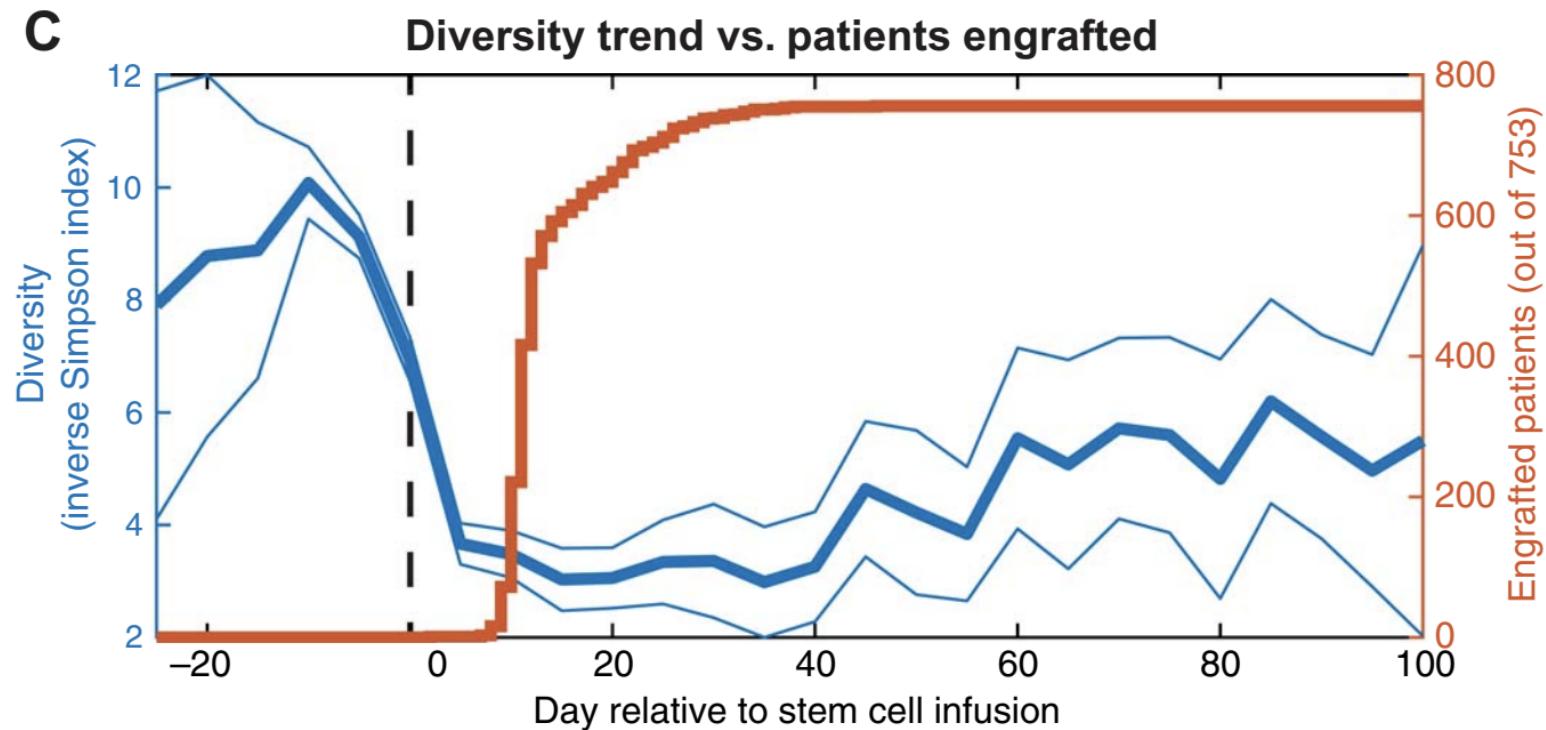
B Overall Survival — Cohort 1

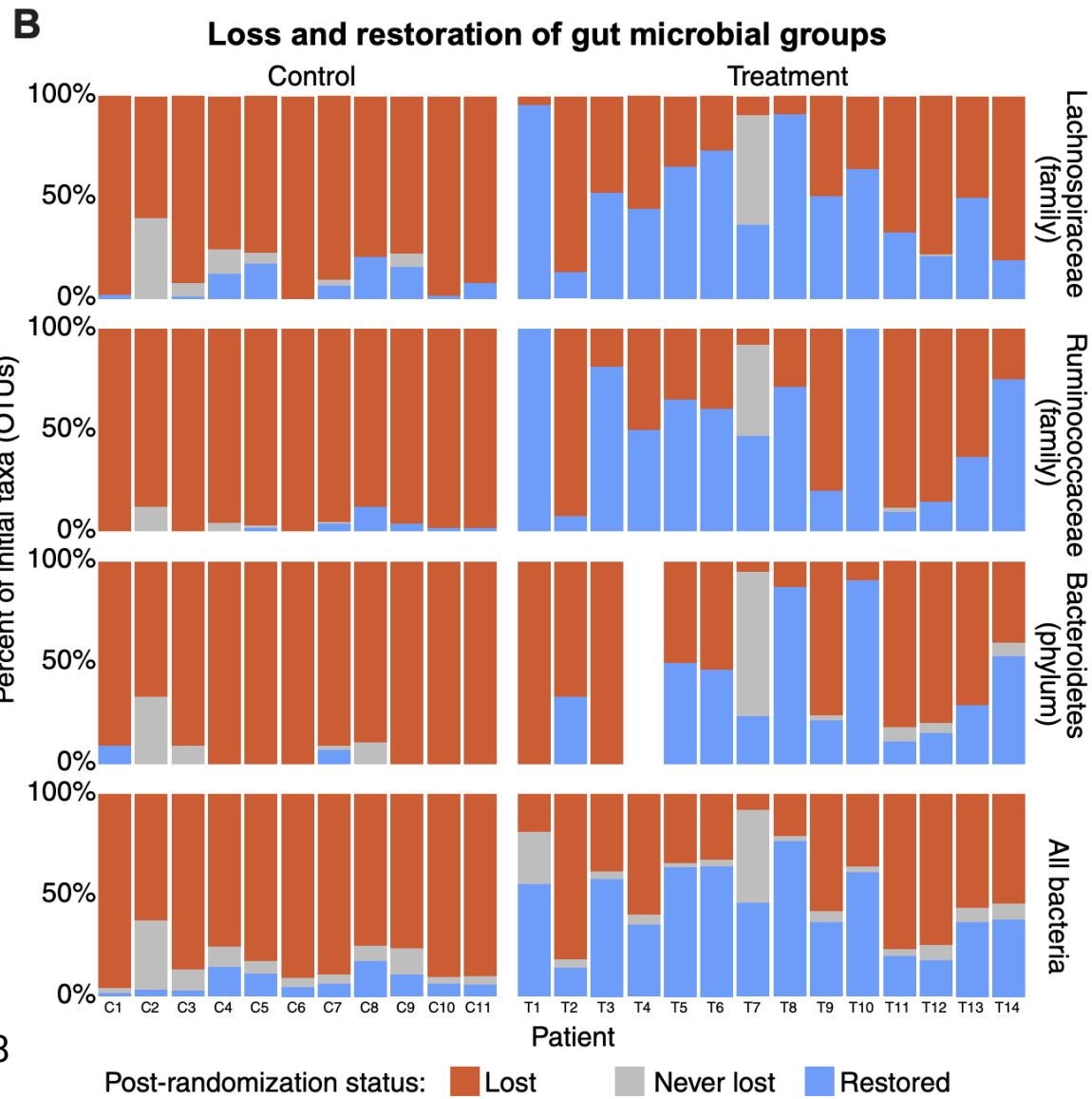


No. at Risk

Higher	354	289	220	159	116
Lower	350	281	204	164	129

Auto-FMT Post Allo-SCT





FMT & Immune Checkpoint Inhibitors

- Differential bacterial signatures of ICI responders versus non-responders
- Modulation of the gut microbiome via FMT from patients alters antitumor immunity and response to ICI therapy in gnotobiotic mice
- FMT also applied to & resolves ICI-related colitis:
 - variable (donor-dependent) effects on microbiome
 - increase proportion of regulatory T-cells in colonic mucosa

Routy et al *Science* 2018; Gopalakrishnan et al *Science* 2018; Matson et al *Science* 2018; Wang et al *Nat Med* 2018

FMT & GVHD

- Disruption of intestinal microbiota associated with GVHD
- Recent prospective single-arm study:
 - 15 post-allo-HCT with steroid-dependent, acute or late-onset acute intestinal GvHD
 - effect of donor FMT on GVHD symptoms and biomarkers
 - 10 of 15 study participants with complete clinical response observed within 1 month after FMT, without additional interventions to alleviate GVHD symptoms
 - associated increase in gut microbial alpha-diversity, a partial engraftment of donor bacterial species, and increased abundance of butyrate-producing bacteria, including *Clostridiales* and *Blautia* species

Risks of FMT in Oncology Patients

- Disseminated bacterial infection:
 - ESBL *E. coli* sepsis and death*
- CMV & EBV:
 - CMV colitis post-FMT has been reported
 - risk of CMV listed on informed consent for our PMT products
(donors are screened for CMV/EBV but not restricted)
- GVHD: given heterogeneity of FMT, potential for exacerbation?

*DeFilipp et al *NEJM* 2019



Questions?