Getting to the Bottom of Fecal Transplants

By Ricki Lewis, PhD
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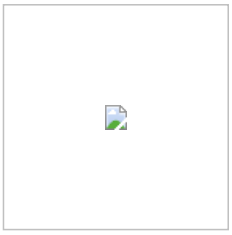
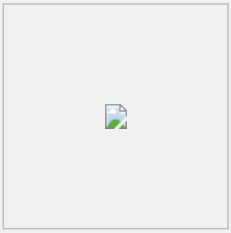
Imagine that you are a bacterium, comfortably living inside a human bowel movement.



Suddenly, a chemical attack kills most of your neighbors. As other types of microorganisms arrive and begin to take over the vacated niches, they alter the milieu so that you're washed out in a sudden stream propelled by a blast of gas. How can your few surviving colleagues back in the colon re-establish the peaceful old community?

An infusion of feces from another body can reboot a healthy microbiome in the large intestine (colon), in a biological gentrification of sorts that's been well studied and much discussed. Now, Vincent B. Young and his team from the University of Michigan and the Essentia Institute of Rural Health in Duluth report in the May/June issue of mBio the biological functions that "fecal microbiota transplantation" (FMT) alters to restore the neighborhood of the colon.

A NOT-SO-NEW APPROACH



Clostridium difficile can take over when antibiotics cleanse the intestines (NHGRI)

FMT delivers other peoples' excrement to treat recalcitrant infections of *Clostridium difficile*, a painful and sometimes lethal condition that sweeps in after antibiotics have altered the gut microbiome. In recent years "*C. diff*" infection incidence and severity have been on the rise.

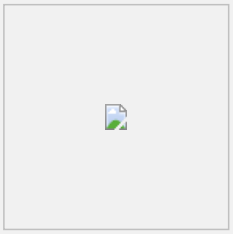
Fecal transplants have been done in cattle (via enema) for a century, and on people, in various settings, since the late 1950s. Marie Myung-Ok Lee's "Why I Donated My Stool," in the *The New York Times* a year ago, traces the approach even farther back. She recounts a DIY experience, doctor-guided, that indeed helped her friend with ulcerative colitis. And the New England Journal of Medicine published the straight poop last year demonstrating efficacy.

Feces are a very accessible research material chock full of bacteria. Along the 5 feet of loops of the colon live some 6,800 bacterial species. In one of the first microbiome studies (the subject of one of my very first blog posts and the classic example I use in my textbook), researchers chronicled the establishment of the gut bacterial community by tracking the contents of soiled diapers from 14 healthy babies for the first year, one the child of the chief investigator.

David Relman, Patrick Brown and their colleagues at Stanford University, today a powerhouse of microbiome

research, found that the babies' bacteria were quite different at the outset, but by the end of the year, their communities resembled those in the adult digestive tract. And it was published right here at PLOS.

(I ventured briefly into the realm of the microbiome for Medscape, reporting on distinctions between the circumcised and uncircumcised penile ecosystems.)



Studies aren't necessary to demonstrate microbiome differences between breast vs bottle fed infants — it's obvious.

THE EXPERIMENT

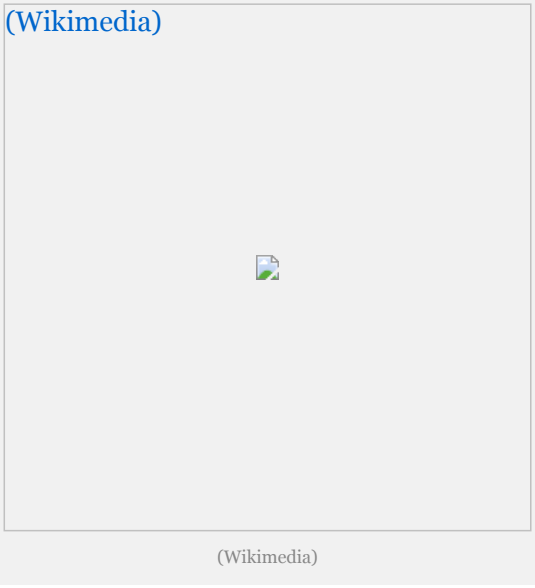
In the new study, 14 people who'd suffered at least two *C. difficile* infections received FMT. And it was, as metagenomic studies tend to be, a tremendously data-rich endeavour.

But before I get to the results, let's address the product and its delivery system. I usually skim, skip, or read last the *Methods* section of a paper, but in this case I read it first. Just out of curiosity. And it instantly convinced me that my recent decision to switch from the drip coffee method to a French press was wise.

"Donor stool ... was collected 6 hours prior to the procedure and then brought to the clinic for preparation of the stool suspension by laboratory staff. The stool was then combined with 90 ml sterile saline and processed in a blender until a smooth consistency is reached. The suspension was then filtered using a coffee filter twice, yielding 40 to 60 ml of stool suspension to be used for transplantation."

The product, delivered through a nasogastric tube, looks like a melted frozen coffee drink.

(Wikimedia)



(Wikimedia)

The processing destroys the distinctive morphology of feces as depicted so colorfully in the Bristol Stool Chart, a medical tool that I will readily admit I had not heard of. (You can order a coffee mug festooned with the chart.) Ken Heaton, from the University of Bristol, invented it in 1997. Apparently the presentations of human turds hold clues to digestive health.

The researchers identified the bacterial residents in feces from the 14 participants, before and after treatment, from ribosomal RNA sequences, a tried-and-true way to tell eukaryotes (us) from prokaryotes (them). (No fancy genome sequencing required.) Overall, *Bacteroidetes* become more abundant while *Proteobacteria* become less so as new feces take up residence.

But the new investigation also imputed what was going on metabolically – presumably so that one day these exact effects can be mimicked by some more palatable approach. "If we can understand the functions that are missing, we can identify supplemental bacteria or chemicals that could be given therapeutically to help restore proper gut function," Dr. Young said. It reminds me a little of developing infant formula by trying to recreate human milk.

The analytical tools used offer quite a data dump. Software called "mothur" identifies "operational taxonomic units" (OTUs), which I assume are something akin to species. Then to get at what these microbes are doing rather than simply what they are, the researchers used HUMAnN (HMP Unified Metabolic Analysis Network), which taps into such resources as the KEGG (Kyoto Encyclopedia of Genes and Genomes). Then something called PICRUSt (Phylogenetic Investigation of Communities by Reconstruction of Unobserved States) provides the "metagenomics contribution," the acronym evoking the image of a "meadow muffin," one of my favorite scatological synonyms.

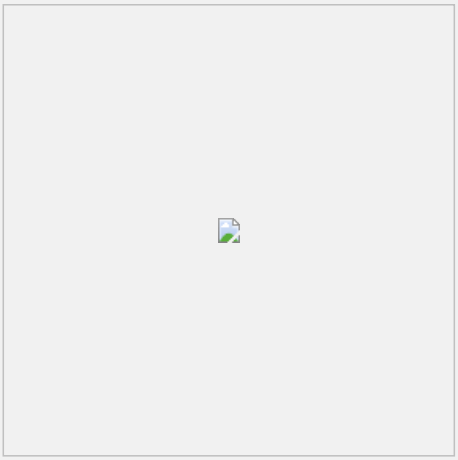
Enterococcus faecalis, a normal resident of the human colon. (USDA)

Put another way, what, exactly, does the new crap do?

The analysis found 75 "gene modules" of 5 to 20 genes each. And their functions at first conjured up bad memories of graduate school courses in biochemistry. Things that change as new bacteria move in include:

amino acid synthesis and degradation
pace of the citric acid cycle
function of amino acyl tRNA synthetases (key enzymes in protein synthesis)
vitamin and nucleic acid metabolism

Many altered activities were classed as "environmental information processing," which I deduced from the details referred to a lot of schlepping of amino acids and sugars.



Spermidine contributes some odor to stools. (Wikimedia)

Also altered pre- and post-transplant were levels of spermidine and putrescine," "foul-smelling organic compounds" initially isolated from rotting meat and semen, respectively. They produce odors reminiscent of rotting flesh, halitosis, and, despite the name, the piscine-like scent of a vaginal bacterial infection.

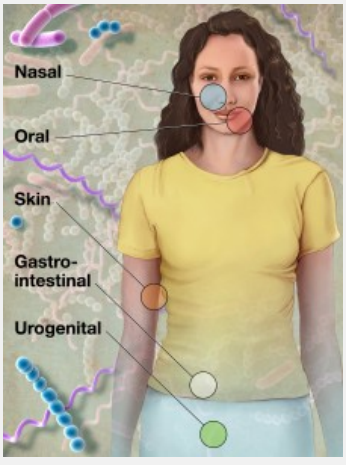
Some biochemical pathways that didn't work well in the throes of a bout with *C. diff* recovered after the treatment. Other pathways revved up after treatment, such as changes in glutamate and gamma amino butyric acid (GABA) metabolism that indicate stressed bacteria.

But remembering biochem isn't necessary to follow the terrific *mBio* paper, because a beautifully clear figure lists the pathways on the left, and color-coded sets of three horizontal bars on the right: red for "pre-FMT," green for "post-FMT," and blue for the donor material. The green bars inch along from red to blue as the microbial community recovers.

The study confirmed efficacy. Five of the 14 participants still tested positive for *C. diff* after treatment, but 3 of them were clinically okay, the fourth improved on vancomycin, and the fifth was lost to follow up when the study ended at 6 months. That's a 12/14 or 86% success rate.

"The bottom line is fecal transplants work, and not by just supplying a missing bug but a missing function being carried out by multiple organisms in the transplanted feces," Young said. "By restoring this function, *C. difficile* isn't allowed to grow unchecked, and the whole ecosystem is able to recover."

The treatment brings back "colonization resistance," which is the ability to fend off pathogens that comes with the natural gut microbiome. All of this confirms my long-held hypothesis that bowel-cleansing regimens make little biological sense. Leave nature be.



Perhaps one shouldn't mess with a functioning microbiome. (NHGRI)

CAVEATS AND CAUTIONS

In May 2013 the Food and Drug Administration announced that it would regulate FMT as an investigational new drug, but a public hearing led to loosening of that requirement.

Discussion continues about whether human feces for transplant should be regulated as a drug or as a tissue. Meanwhile, stool banks have been established, procedures are being performed in hospitals to treat *C. difficile* infections, and I'm sure companies are exploring the potential new market. I

ventured into a health food supermarket today just to be sure they aren't jumping the gun, and to my relief, among the gas suppressors and bowel cleansers, I didn't find anything resembling stool replacement. I suspect the approach may have a bit of a PR problem, a little like comandeering HIV to deliver gene therapy.

Dr. Young and colleagues call for further research to better define the risks of fecal transplants: viral or bacterial infection or inflammatory bowel disease exacerbation in the short-term, and the effects of replacing the gut microbiome with a "non-self" set of microbes in the long term.

I hope we won't be seeing excrement elixirs as dinnertime infomercials just yet.

(opening photo courtesy of University of Minnesota, via Wikimedia)

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