Fecal Transplantation

From Theory to Practice in Ridge Meadows

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13 January 2016
The Human Genome

• How many different chromosomes do humans have?
• 46 chromosomes – 23 pairs
The Human Genome

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  - 46 chromosomes – 23 pairs

- Mitochondrial chromosomes
  - Bacterial DNA inside human cells: related to Rickettsiae or SAR11 bacteria
The Human Genome

• How many different chromosomes do humans have?

• Thousands!
The Royal “We”

• Bacterial cells amongst human cells: The Human Microbiome

• We are a complex ecosystem (“holobiont”)

• The microbiome is “an acquired organ with plasticity”
Our Microbial Component

• C&S vs DNA analysis
  – 100 billion vs 100 trillion microbes
  – Compared to 20 billion human cells

• Human/microbiome/diet/disease interaction
  – “wheat belly”
Functions of the Microbiome

- Colonization resistance
- Production of vit K, folate, biotin
- Aid in breakdown of plant cell walls, digestion of fiber to SCFAs, absorption and storage of lipids
- Control of immune tolerance and inflammation (eg ↓ IgE, ↓ peanut antigen uptake)
- Endocrine and neurological effects
- Cause vs effect
When Our “Microbiome” Goes Bad

• Mitochondrial
  – Parkinson’s, Alzheimers, Type 2 diabetes, Aging

• Bacteria and other organisms
  – Clostridium difficile infection
  – Other diseases?
    • Diet vs microbiome vs disease state
Clostridium Difficile Infection

• Scope of the problem
  – Increasing in frequency and severity
  – 700-800 inpatient cases per year in FHA
CDI Severity

- 2.3% unadjusted mortality
- 24% mortality in ICU patients
Recurrent CDI

- recurrence rates after the first episode are 15–35%. Patients who have one recurrence have up to a 40% chance of a second recurrence, and after their second recurrence, up to 65% of patients will suffer a third
- most relapses occur within 7–10 days i.e. recurrence
- As many as 26 relapses in a single patient
Current Therapies for Recurrent CDI

- Vancomycin (Gm +ves) and Flagyl (anaerobes) affect normal gut flora, and might therefore impair colonization resistance
- Fidaxomicin more selective
- None kill spores
- Failure after treatment of 2\(^{nd}\) recurrence: vancomycin 35% fidaxomicin 20%
- Colectomy
- Colectomy in ICU for CDI had 36% mortality in ICU, and 56% at 1 year
Rationale for Microbial Therapy in CDI

- Up to 25% of nurses carry C. dif
- Persistence of C. dif spores
- Loss of “colonization resistance”
  - ? “reverse colonization resistance”
\[ \forall \geq 6-8 \text{ weeks to establish normal flora} \]
Probiotics

• Conflicting interpretations of data

• For treatment: McFarland (JAMA 1994)
  – Vanco ± Florastor 35% vs 65% recurrence
  – Not confirmed (Clin ID 2000) except ? With vanco 2,000 mg/day

• For prevention: Cochrane review (May 2013):
  – 64% decrease
  – Mostly lactobacillus
Terminology

• Fecal transplant
• Fecal microbiota transplantation
• Fecal bacteriotherapy
• Fecal Flora Reconstitution

• This is a transplant in the true sense of the word
Evidence for Fecal Transplantation for CDI

• Ge Hong (4<sup>th</sup> century): human fecal suspension by mouth for food poisoning or severe diarrhea.
• Li Shizhen (16<sup>th</sup> century): variety of fecal preparations called “yellow soup” for diarrhea, abdominal pain, vomiting, and constipation.
• Paulini 1697 “Heilsame Dreck-Apotheke
• Eiseman Surgery 1958: first published use of fecal transplant in “western medical literature” (case series of four patients)
Case Series in FMT

- At least 11 series, max 87 patients, approx 800 total
  - Typically 86-98% cure (average around 92%)
  - May need >1 transplant ± antibiotics
  - Most lower GI

- Thomas Borody >3,000 patients (multiple diseases). Few published
Randomized Trial

- Van Nood et al, NEJM Jan 2013
  - 50 gm via ND tube
  - Stopped early
  - 94% cure after 1 or 2 transplants
  - vs 23-41% with vanco ± lavage
    - Most had ≥ 4 relapses
  - Of 16 transplant patients had 5 cramps, 15 diarrhea (!)
Another Randomised Trial

• Cammarota et al Aliment Pharmacol Ther May 2015
• Fecal transplant vs vancomycin for >3 weeks for recurrent C dif
• 90% vs 26% clinical cure
Current Trials

• At least 30 underway in clinicaltrials.gov
Current Regulations

• FDA May 2013 declared feces “an unapproved new drug”
  – July 2013 issued “enforcement discretion” in cases of recurrent CDI if informed consent obtained
Health Canada

• Food and Drugs Act
  – “drug” includes any substance or mixture of substances manufactured, sold or represented for use in...restoring, correcting or modifying organic functions in human beings or animals...”
Health Canada

• Natural Health Products Regulations
  – “natural health product” means a substance or combination of substances…that is manufactured, sold or represented for use in…restoring or correcting organic functions in humans; or modifying organic functions in humans …”
  • (limits on permitted ingredients)
Health Canada Guidance

• FMT is an investigational new biological drug
• Strict adherence is not mandatory, but must be supported by adequate justification
• Only for recurrent C dif not responsive to conventional therapy
• Cultured bacteria are excluded (“Repoopulate”)

Health Canada Guidance

- Informed consent
- Donor known to patient or provider
- No high-risk donors
- Thorough screening
- Recorded follow up of patient and donor
- Submission of Notification of the Use of Fecal Microbiota Therapy for the Treatment of C. difficile Infections Form to the BGTD
Indications/cautions

- At least two recurrences of C dif despite appropriate therapy
- No absolute age restriction
- Informed consent needed
- Recommended not pregnant/breastfeeding
- No severe immunocompromise
- No imminent antibiotics
- Critically ill, acute abdomen
Donor Screening

• Canadian Blood Services Questionnaire (modified)

• Recent travel, infection, IBD, IBS, GI malignancy, autoimmune disease (except thyroid), severe mental health issues, morbid obesity antibiotics in last 3 months
Donor Screening

- HIV, Hep A, B, C, HTLV
- Syphilis
- Tryps and Strongyloides
- CBC, dif, LFTs
- Stool C dif, C&S, O&P x2, Giardia, Cryptosporidium, AFB for Microspora, Norovirus, Rotavirus, VRE, CPO, ESBL
Donors

• Non-patient-contact healthy volunteers
  – Less “yucky”
  – Multiple donations per donor, therefore:
    • Cheaper
    • quicker
Process of Transplantation

• Fresh stool 25 - 50 gm in non-bacteriostatic saline or water, shaken, filtered in gauze

• Inpatients: enema or ND tube  BGH and RMH

• Outpatients: enema  RMH
Concerns with Fecal Transplant

- Contamination
  - Patient by donor
    - Stool borne “pathogens”
    - Transmigration of bowel flora into peritoneum
  - Hospital by donor
  - Of transplant material by hospital
Non-Infectious Complications

- ???
Esthetic Concerns

- Patients usually prefer anonymous screened donors
- Brandt regarding his 77 patients, “97% of these patients stated they would have another FMT if they were to develop CDI again, and 58% said they would choose to have FMT rather than antibiotics”
COSTS

• Approximately $400 q6 months *per donor*
• “Disposables” approx $50-100

• Vanco: $240-360 inpt, $360-540 outpt
• Fidaxomicin $2310
• Hospital stays, colectomy, disability
  – Approx $12,000 in Massachusetts
POSSIBLE Future Directions

Role of fecal transplant in....
POSSIBLE Future Directions

Inflammatory bowel disease
  Diet vs microbiome vs disease state

  Case series: ?best in Crohns and paeds?
  2 randomized trials in UC published (Gastroenterology July 2015) “Not Just Yet”
    2 Rx by NG: 30 vs 20% improvement
    6 Rx by enema: 24 vs 5% improvement     ??superdonor??

  Trials in clinicaltrials.gov: UC: 15, Crohns: 5, IBD: 7
POSSIBLE Future Directions

IBS: 4 trials
Chronic constipation: 3 trials
Hepatic encephalopathy: 2 trials
Eradicating MROs: 4 trials
POSSIBLE Future Directions

Obesity and Metabolic Syndrome

The microbiome may affect caloric extraction, gut nutrition/permeability, inflammation, hepatic lipogenesis and glucogenesis, insulin sensitivity, and satiety (serotonin)

Randomized clinical trial
Vrieze et al Gastroenterology 2012
Doubled peripheral insulin sensitivity

5 trials registered
Case report
Microbiome and Mental Illness

- Bowel flora make dopamine, serotonin and GABA
- Patients with *active* depression have altered bowel flora
- Norepinephrine promotes growth of bacteria
- Reduced stress response in mice fed Lactobacillus (produces GABA), or raised sterile
- Abnormal bacteria associated with mental illnesses

- No human trials registered
WHAT WE KNOW FOR SURE
WHAT WE KNOW FOR SURE

Prevention is best

No C dif acquired in RMH for 2 ½ months!
  Isolation
  Bleach
  Vernacare

Antibiotic stewardship
PPIs