Fecal Microbiota Transplantation and Emerging Applications

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Thomas Borody MD PhD FRACP FACG AGAF
Director
Centre for Digestive Diseases
Sydney

“All disease begins in the gut”

Hippocrates 460 BC – c. 370 BC
Objectives

• Short Review of FMT – eg History
• Use of FMT in CDI
• How to carry out a FMT
• Likely mechanisms of action
• Application outside CDI - IBD; IBS; Autism; Diabetes etc.
• Refining FMT ‘Transplant Material’
GI Bacteria Influence Life

- Obesity / Metabolic Syndrome (*Ley et al*)
- Fatty liver (*Dumas et al*)
- Insulin Sensitivity, Type II diabetes (*Vrieze et al; Larsen et al*)
- Kidney stones (*Sidhu et al*)
- Constipation/Bloat (*Andrews et al*)
- Colorectal cancer (*Uronis et al*)
- Neurologic – Botulism; Autism; CFS; some MS; PD
- Immunologic – ITP; RA; Sacro/Ileitis; S Cholangitis
Fecal Microbiota Transplantation (FMT)

- **Definition:** Instillation of distal stool microbiota from a healthy person into a sick person to cure a certain disease.
- **Rationale:** A perturbed imbalance in our intestinal microbiota (dysbiosis) is associated with, or causes, disease and can be corrected by re-introduction of donor GI microbiota.
History of FMT

- C4th China - Ge Hong fecal suspension for food poisoning
- C16th China – Li Shizhen, “yellow soup” (fresh/fermented fecal suspension) - diarrhea
- First described in animal use as “transfaunation” – 17th Century; currently used in ruminal acidosis
- 1958 – Eiseman – 4 cases of antibiotic ‘colitis’. All cured after faecal enema. Retrospectively CDI
- 1958 - 1989 20 more cases described by 4 authors
- Since 1989 rapid growth of FMT particularly in Australia and Scandinavian countries > 500 reported
- At CDD > 3000 FMT carried out from 1988
- US CDI epidemic – many clinics practice FMT
- FDA - IND required for all FMT treatments
Mechanisms of Action of FMT

- Patients with relapsing CDI many have deficient *Bacteroidetes* and *Firmicutes* components.
- FMT implants *Bacteroidetes* and *Firmicutes*
- Grehan: 10 FMT patients, showed 60-80% of donor-derived flora **durably colonized** the GI tract of recipients (Grehan MJ, Borody TJ et al 2010)
FIGURE 1. A, Dendrogram of the 16S-based T-RFLPs obtained from fecal material from the patient and the donor before and after fecal transplantation. B, Distribution of bacterial species in feces of the donor and the patient before and after fecal transplantation. The bacterial species represented by TRFs are color coded and are valid across columns. The purgative wash-out occurred on day 0, shortly before fecal transplantation.

Current Use of FMT in CDI

- Use of FMT steeply increasing in North America
- Est. 200 clinics in N. America have carried out CDI FMT
- Increasing number of reports published (eg Kelly, Brandt, Surawicz, Mellow) > 500 cases
- CDI cure rate varies 92-100% - mean 96%
- Clinical drive for greater use of FMT in CDI
- Encouragement for *early FMT* in CDI to prevent moribund stages
- “Transcolonoscopic FMT should be first line treatment of severe CDI” - Brandt.JCG 2011–
Protocol for FMT in Recurrent CDI

- **Choose donor**
  - we avoid spouse/intimate partner
  - 1st degree relative
  - other (friend, stranger)
  - universal donor

- **Donor exclusions**
  - antibiotic use within 3 months
  - diarrhea, constipation, IBS, IBD, colorectal CA, immunocompromise, anti-neoplastic drugs, obesity, metabolic syndrome, atopy, high-risk behaviors

- **Donor testing**
  - **stool:** culture, Listeria, vibrios O & P, *C. difficile*, *H. pylori* Ag, Giardia Ag, cryptosporidium Ag, *acid-fast stain (cyclospora, isospora)*, Rotavirus
  - **blood:** hepatitis A, B, C, syphilis, HIV
How To Carry Out FMT:

Transcolonoscopic infusion of 100-300cc liquid filtered flora
## FMT in Recurrent *C. difficile*

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|                | 434  | 81   | 6    | 347  | ~ 93   |
FMT in IBD

- First FMT was in pseudomembranous colitis (Eisenman et al. 1958, Surgery)
- Bennet et al. 1989 Lancet letter – Self treated with FMT clinical and histological normality
- 2003 – We reported 6 cases – remained ‘cured’ 1-15 years
- 2011 – Repeated enema infusions – key to IBD resolution (ACG poster 2012)
FMT and UC: Case 1

- 33 y M. 8 wk abdominal pain, diarrhoea, mucus + blood. *First diagnosis of UC*
- FMT via trans-colonoscopic infusion then daily, twice-weekly, weekly. After 80 FMT he was re-colonoscoped on 14/9/12.
- He was passing normal stool once per day and was off all drugs then for 7 months.
53yo M, severe distal colitis on immune-suppressants, 5ASA antibiotics facing surgery. Chose recurrent FMT, *C. difficile toxin positive*

9/12/2011 underwent first FMT. Severe distal inflammation. For CDI - had single trans-colonoscopic FMT followed by enema. 7 weeks later he felt “fantastic”. No urgency, no blood, one motion per day.

Colonoscopy 10/1/2013 - tubular adenoma removed but mucosa normal. Histology - small numbers of neutrophils within lamina propria - focal mild cryptitis The patient was passing normal formed stools daily.
FMT and Proctitis: Case 3

- 57 y F, nine year history of refractory proctitis: failed 5-ASA, steroids, antibiotics, probiotics, acetarsol and immunosuppressants
- FMT commenced Dec 2007 (69 sessions of infusions)
- 10 days into FMT, immediate clinical response: diarrhoea ceased.
- Colonoscopy at 3y showed no visible or histological inflammation. Now asymptomatic, >5 yrs and off all meds without relapse – normal histology. Back at 5 years. Still cured
FMT and Crohn’s + CDI: Case 4


- Terminal ileum CD - 17/1/2012, FMT 17/4/2012. Instead of doing 2 infusions mother continued home infusions with marked improvement. Total of 60 infusions. No antibiotics. Able to stop Imuran. *Acne healed by 7 days.* Stools: 1-2 formed per day with all inflammatory parameters normal.

- Colonoscopy 15/11/2012 - *terminal ileum was totally normal*, not even aphthoid erosions, no cobblestoming, no inflammation. Donor was 15 year old cousin.

Well off all therapy May 2013. CRP normal.
Applications of FMT outside CDI

- Constipation - Andrews et al
- IBS - Borody et al
- Colitis - Borody et al
- Other - Arthritis, sacro-ileitis, ITP, CFS, Parkinson’s, MS, Metabolic S; Autism
FECAL MICROBIOTA TRANSPLANTATION (FMT) IN MULTIPLE SCLEROSIS (MS)

Thomas J Borody, Sharyn Leis, Jordana Campbell, Margaux Torres, Anna Nowak
CENTRE FOR DIGESTIVE DISEASES, Sydney, Australia

Introduction

Whilst the cause of Multiple Sclerosis remains unknown, the prevailing theory holds that MS occurs as a result of autoimmune responses to myelin antigens, resulting in chronic inflammatory demyelination of the central nervous system (CNS) white matter. Treatment therefore primarily consists of immunosuppressive therapy aimed at ameliorating disease symptoms and delaying disease progression. Recent studies however have shown that MS drugs do not slow disease progression, are largely ineffective, and are in most cases outweighed by costs and side effects experienced.

The prevalence of constipation in MS patients is significantly high compared to the general population, with Hinds et al. reporting that up to 68% of MS patients experience constipation and/or fecal incontinence. Despite this, constipation in this patient population has often been dismissed as related to nervous system dysfunction, immobility and the use of constipating medications. An infectious etiology in this disease has long been recognized, but a definitive pathogen is currently lacking. Research thus far has primarily focused on infections within the CNS, however infections originating outside of the CNS, in the gastrointestinal microbiota, are capable of inducing neurological dysfunction via various pathways. Considered the largest virtual organ of the body, this highly populated microbiota can be the source of toxic molecule production or harbor organisms with the capacity for neuronal damage e.g. Clostridium botulinum and Clostridium tetani. We report on three patients with long-standing MS who achieved durable symptom reversal following FMT treatment for constipation.

Case Series

Case 1: A 30yr old man presented with constipation and a recent history of MS. MS symptoms of vertigo, impaired concentration and mood alterations developed suddenly post-surgery in 1993, leading to optic neuritis and trigeminal neuralgia, resulting in an MS diagnosis, confirmed on MRI. Previous treatments, including interferons, had all failed. FMT was administered in 1994 for constipation, resulting in complete resolution. Interestingly his MS symptoms progressively improved, regaining the ability to walk and facilitating catheter removal. The patient remains asymptomatic 15 yrs post-FMT without relapse. Follow-up MRI 15 years post-FMT reported no halting of disease progression and no evidence of active disease.

Case 2: A 29yr old male presented with severe, chronic constipation, and atypical MS. Bilateral leg paralysis and urinary incontinence had left him wheelchair-bound with an indwelling urinary catheter. FMT was performed in 1999 for constipation, which resulted in dramatic resolution-defecating daily with ease. The patient also reported a rapid and progressive improvement in MS symptoms, eventually regaining the ability to walk, defecate and urinate normally, facilitating urinary catheter removal. The patient remains asymptomatic 7yrs post-FMT.

Case 3: An 80 yr old female presented with severe chronic constipation, and an x year history of atypical MS manifesting as severe muscular weakness, leaving the patient wheelchair-bound. FMT resulted in rapid improvement of constipation and increased energy levels. At eight months she reported complete resolution of bowel symptoms and neurological improvement, now walking long distances unassisted. Two years post-FMT, the patient remains asymptomatic.

Discussion

We report on three wheelchair-bound MS patients with concomitant constipation successfully treated with FMT. Resolution of their primary symptom of constipation achieved a unique response and dramatic improvement in their neurological symptoms, including regaining their previously static motor skills and eventually the ability to walk unassisted. Two of the patients with prior indwelling urinary catheters experienced restoration of urinary function following FMT, facilitating catheter removal.

To date, a large amount of factual data points to an infectious etiology in MS. Whilst gastrointestinal dysfunction is a well-documented feature in patients with neurological diseases such as Multiple Sclerosis and Parkinson’s Disease, it has rarely been analysed in an etiological context. Current research into an infectious etiology in MS has predominantly focused on pathogen detection within the CNS, however we know of a number of pathogen, particularly Clostridium species, which have the ability to exert their neurological effects remotely from the gastrointestinal tract. The benefits derived from elucidating an infectious pathogen in this disease could be enormous if arresting MS progression or microbial cure were achieved. Following these recent findings, it is instructive to re-examine a number of other neurological diseases including Parkinson’s Disease, Alzheimer’s disease and Autism which may hold the key to unlocking their etiology.

Conclusion

- FMT is capable of reversing MS symptoms.
- The response of MS to FMT, which targets the GI microbiota, is suggestive of an infectious etiology in this disease.
- GI symptoms in neurological conditions may be etiologically significant.

References


American College of Gastroenterology
Annual Scientific Meeting and Postgraduate Course 2011
WASHINGTON D.C.
October 28-November 02, 2011
Postulated FMT Benefit in Regressive Autism

- Restoration of depleted or missing gut microbiota
- Inhibition of rouge ? Clostridia / Desulfovibrios
- Probiotic use – few in number and fail to implant
- FMT diversity and large numbers of microbes
- Implantation - seeking improvement of autism symptoms to permit training by abolishing presumed toxins
- Future therapy – in liquid or powdered form
- Efficacious & safe procedure of CDI – may take centre stage in treatment of autism
Antibiotic therapy in regressive autism

- Vancomycin has short term benefits in improving autism symptoms
  - Sandler et al. (2000) reported improvement in 8/10 children on oral vancomycin (500mg/day) although effect wore off on average 2 weeks after discontinuation
  - CDD experience – Borody treated in clinical practice 9 children with 6 weeks of oral vancomycin followed by bid 3-9 months select, cultured flora [non-pathogenic Clost. Bacteroides and E coli] – Response -

Refining and Future FMT Transplant Material

- Currently raw stool homogenised with saline
  - Filtered and infused
  - No shelf life, no standardisation
- Improved minimally-modified stool
  - Highly filtered to remove non-bacterial components
  - Freeze with cryoprotectant to -80°C
  - Long shelf life, transportable
  - Equipotent to raw stool
- Highly filtered material further modified
  - Lyophilised, enteric coated capsules,
  - Long term application possible
  - Applicable in children – yoghurt; drinks; capsules
Experience in IBS

- First reported 55 cases 1989 – most IBS
- CDD - most common indication is D-IBS
- Constipation-IBS more difficult to reverse – requires repeated enema infusions
- Several ‘chronic nausea’ patients treated
- Several ‘abdominal pain’ only treated

Borody et al 1989; MJA 150: 604
• FMT in Relapsing CDI is becoming mainstream
• In IBD FMT shows promise - but need for repeated infusions is a barrier
• Many unanswered questions in IBD – e.g. treat actively inflamed mucosa or heal first with conventional therapies then FMT; Donor differences etc
• Oral enteric-coated FMT may be the ultimate therapy
• Given the response to FMT the mechanisms underlying IBD may need to be re-examined
• With availability of oral preparations IBS ? a target
“All disease begins in the gut”

*Hippocrates 460 BC – c. 370 BC*

“Health is determined by the microbiota in our gut”

*Hippocrates, 2012*
THANK YOU FOR YOUR TIME
From the Team

- Dr Antony Wettstein  - GI
- Dr Robert Kim  - GI
- Dr Simon Benstock  - GI
- Sharyn Leis RN  FMT Lab Manager
- Sarah Finlayson  Research Manager
- Anna Nowak  Research Assistant