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Fecal Microbiota Transplant as an Emerging Therapy

George Hylands Russell, MD, MS
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I have had no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in this CME activity.



Plan

- Background
- **F**ecal **M**icrobiota **T**ransplant (FMT) for recurrent *Clostridium difficile* infection
- FMT for treatment of IBD
- FMT for other disease processes
- Safety, Regulation, Handling

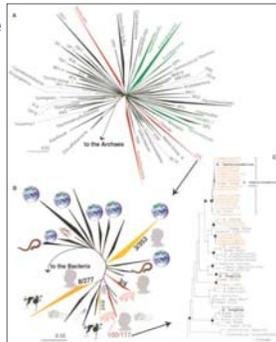


• Background



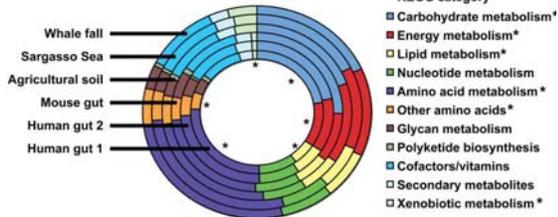
The gut microbiome

- > 100 trillion cells
- 10 x greater number than human germ/somatic cells
- 100 x the genes
- Mutualistic
- Self-replicates/self-repairs
- >5600 taxa but even more serotypes



Backhol F, Ley R, Sonnenburg I et al. Host-Bacterial Mutualism in the Human Intestine. Science. The Gut: Inner Tube of Life. 307(5717):1915-1920, March 25, 2005





Turnbaugh, et al. Human Microbiome Project. Nature: 2007: 449, 807



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Dosed up: could excessive prescription of antibiotics be hampering children's ability to fight disease?

Stop the killing of beneficial bacteria

Concerns about antibiotics focus on bacterial resistance – but permanent changes to our protective flora could have more serious consequences, says **Martin Blaser**.

Nature Volume:476, Pages:393–394 Date published:25 August 2011

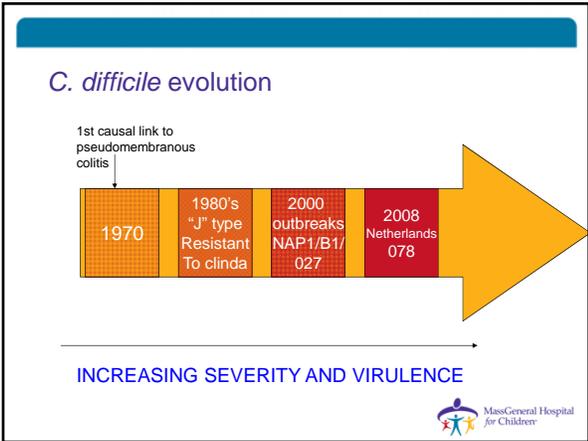
Multiple hits to the microbiome

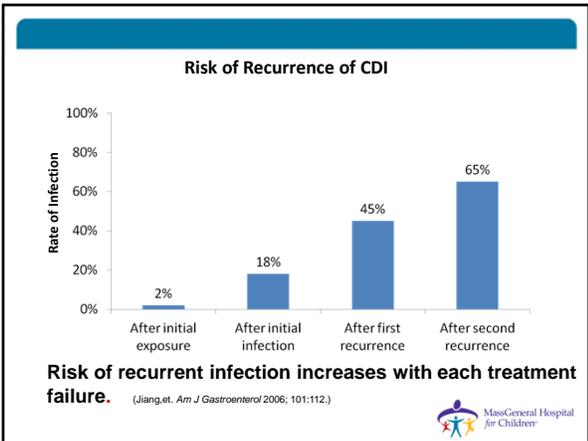
- Studies have shown:
 - Gut flora changes dramatically with antibiotic use
 - It takes a long time for the microbiome to return to baseline
 - In some cases, the microbiome does not return to “steady state”
 - Repeated hits can be catastrophic to the ecosystem of the gut

Loeffl et al, PNAS 2012; Robinson & Young, Gut Microbes 2010; Jakobson et al, PLoSOne, 2010; Antopolous, et al Infect Immunol 2009; Dehelefe, et al Plos Biol, 2008.

• FMT for recurrent *Clostridium difficile* infection







Fecal Microbiota Transplant

- The perfect probiotic
- Khoruts shows that pre-FMT, the RCDI patient lacks *Bacteroides* predominance that was present after FMT (Khoruts A, et al. *J Clin Gastroenterology*. 2010; 44:354-360.)
- Grehan shows that transplanted microflora remain similar to donor even 24 weeks after FMT (Grehan, et al. *J Clin Gastroenterology*. 2010; 55: 541-561.)
- Up until 1989 - fecal retention enema was used. Now NGT and colonoscopy also used.



FMT (continued)



- Russell, et al. report index case of child with recurrent NAP1/B1/027 CDI tx by FMT (*Pediatrics*. 2010; 146: e239-42.)
- Review of experience from literature from 1958-2010: 275 cases, 89% success rate (Brandt L, et al. *J Clin Gastroenterology*. 2011; 45: S159-67.)
- In adult medicine, now routinely used after three recurrences (Bakken JS, et al. Treatment of RCDI with FMT. *Clin Gastroenterol Hep*; 2011:1044-9.)
- Recent prospective American case series of 70 pts with RCDI (Mattila, et al. *Gastroenterology* 2012; 142:490-6
 - 100% of non NAP1/B1/027 cured
 - 89% of NAP1/B1/027 (4 failures had pre-existing serious conditions)
 - FAILURES: 4 patients who initially cured relapsed within 1 year and 50% successfully re-transplanted



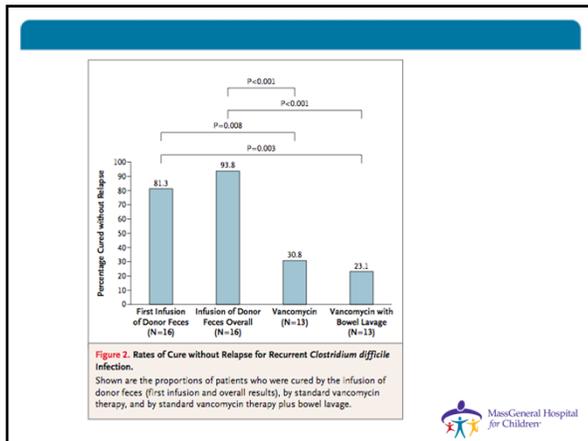
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 31, 2013 VOL. 368 NO. 5

Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

Els van Nood, M.D., Anne Vrieze, M.D., Max Nieuwdorp, M.D., Ph.D., Susana Fuentes, Ph.D., Erwin G. Zoetendal, Ph.D., Willem M. de Vos, Ph.D., Caroline E. Visser, M.D., Ph.D., Ed J. Kuijper, M.D., Ph.D., Joep F.W.M. Bartelsman, M.D., Jan G.P. Tijssen, Ph.D., Peter Speelman, M.D., Ph.D., Marcel G.W. Dijkgraaf, Ph.D., and Jobbert J. Keller, M.D., Ph.D.





Our single center FMT experience for treatment of Recurrent *C. difficile* Infection

- 11 children, ages 18 mos – 19 years
- 2 delivered by NGtube, 9 by colonoscopy
- 8 otherwise healthy patients/ 3 with IBD
 - 2 Crohn's/ 1 UC
- All patients who returned to baseline health when treated with antibiotics, had sustained “cure” of RCDI
- 2/3 IBD patients had sustained “cure” of RCDI but the FMT did not sustainably change IBD disease activity
- Overall success rate 91%



FMT for relapsing *C. difficile* infection in Adults and Children Using a Frozen Inoculum

- Clinicaltrials.gov NCT 01704937
- 19 pts recruited
- Ngtube delivery appears to be as effective as colonoscopic delivery of the FMT inoculum
- Overall success rate of 91.6%
- No short term safety concerns



• FMT for treatment of IBD



AP, T Alimentary Pharmacology and Therapeutics

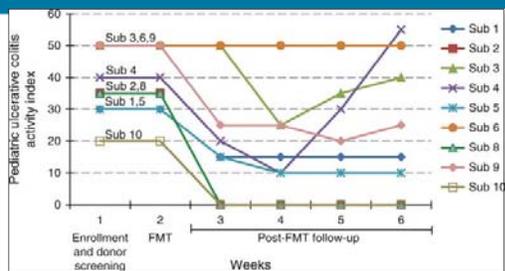
Systematic review: faecal microbiota transplantation in the management of inflammatory bowel disease

J. L. Anderson, R. J. Edney & K. Whelan

- Meta-analysis of 17 articles and 41 patients
- 27 UC, 12 CD, and 2 IC
- Summary of findings
 - 15/15 had resolution of RCDI
 - 19/25 reduction of IBD symptoms
 - 13/17 had cessation of meds
 - 15/24 disease remission



Alimentary Pharmacol & Ther, 2012.



Kunde, Sachin; Pham, Angela; Bonczyk, Sarah; Crumb, Teri; Duba, Meg; Conrad, Harold; Cloney, Deborah; Kugathasan, Subra
Safety, Tolerability, and Clinical Response After Fecal Transplantation in Children and Young Adults With Ulcerative Colitis.
Journal of Pediatric Gastroenterology & Nutrition. 56(6):597-601, June 2013.
 DOI: 10.1097/MPG.0b013e318292f6d4



Why not race forward?

- Aesthetically displeasing
- Logistically challenging
- Almost no prospective evidence



Safety concerns



- Who is healthy?
- What about the virome?
- What about transference of the resistome?
- What about unknown pathogens?
- What about FMT matching?
- Long-term safety questions?



How do we manage our source?

- Safe
- Reproducible
- Deliverable when needed
- Available
- Controllable
- Trackable
- Testable
- Standardized



AGA Confirms IND is Required for Fecal Microbiota Transplantation

- FDA strongly suggests but does not currently require IND for the use of FMT for recurrent *C. difficile* infection that has failed standard medical therapies
- FDA requires IND for the use of FMT for any other therapeutic modality other than recurrent *C. difficile* infection
- FDA requires IND for any research project using FMT for all therapeutic modalities