Using Feces to Cure Disease: Current and Future State

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DISCLOSURES

• Microbiome Processing, LLC - equity and IP

• Sub-Investigator (Emory site), Ecospor™ trial, Seres Therapeutics
Outline

• Dysbiosis and the use of fecal microbiota transplant as a therapeutic agent
• Current state of FMT-like biologics
• Future state of microbiome therapy
Intestinal dysbiosis is bad

Lawley, 2012, PLOS Pathogens
Evaluating what makes a keystone species

Antibiotic Use

Anti *C. difficile* antibiotics kill the bacteria but do not replant the garden.

What if we did not need all of the seeds, but if just planting a few kinds replaced the garden?
The worsening threat of *C. difficile* infection (CDI)

- Incident *C. difficile* infections in the United States was 453,000
  - Estimated number of first recurrences of *C. difficile* infection was 83,000
  - Estimated deaths were 29,300
- Up to $4.8 billion in excess healthcare costs in US acute care hospitals in 2008

Lessa et al, 2014, NEJM; Dubberke et al, 2012, CID
Fecal microbiota transplantation (FMT) has become mainstream

- A.K.A. Stool transplant
  - Intestinal microbiota transplantation (IMT)
  - Fecal bacteriotherapy
  - Microbial ecosystems therapeutics
- Transfer of intestinal microorganisms from a healthy donor via an infusion of a liquid suspension of stool
- Restore the normal micro-environment in a persons with altered gut microbiota
The microbiome of the most antibiotic experienced patients

- Long term acute care hospital
  - Patients with complex medical problems
  - Often transferred from ICU
  - Ventilator weaning
- Extended stay (20-30 days)
- Antibiotic use extremely high
Evaluated microbiome of 12 individuals

N=2

N=10

C. difficile MDROs

DNA Extraction

- Age
- Gender
- Antibiotics
- C. difficile
- PPI
Vancomycin-resistant *Enterococcus* domination of intestinal microbiota is enabled by antibiotic treatment in mice and precedes bloodstream invasion in humans

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Changes in the Composition of the Human Fecal Microbiome After Bacteriotherapy for Recurrent Clostridium difficile-associated Diarrhea

Alexander Khoruts, MD,* Johan Dicksved, PhD, † Janet K. Jansson, PhD, ‡ and Michael J. Sadowsky, PhD §
“Quick, inexpensive, and a 90% cure” – Mayo clinic website

- 2013: Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

- 2014: Fecal Microbiota Transplant for Relapsing *Clostridium difficile* Infection Using a Frozen Inoculum From Unrelated Donors: A Randomized, Open-Label, Controlled Pilot Study

- 2015: Randomised clinical trial: faecal microbiota transplantation by colonoscopy vs. vancomycin for the treatment of recurrent *Clostridium difficile* infection

van Nood et al, 2013, NEJM; Youngster et al, 2014, CID; Cammarota, 2015, Aliment Pharmacol Ther
Luminal as compared to the adherent microbiota

- Enrolled 10 patients who were undergoing FMT for recurrent *C. difficile*
- Collect stool and mucosal biopsies at time of FMT, 2 weeks and 10 weeks later
Outline

• Dysbiosis and the use of fecal microbiota transplant as a therapeutic agent
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FDA regulates FMT

• May 2-3, 2013
  – Because fecal microbiota transplantation (FMT) is not approved for any therapeutic purposes, an investigational new drug (IND) application is needed for the use of FMT to treat any disease including *C. difficile* infection.

• June 19, 2013
  – The agency acknowledges these concerns and intends to exercise *enforcement discretion* regarding the IND requirements for the use of FMT to treat *C. difficile* infection not responding to standard therapies provided the treating physician obtains adequate informed consent from the patient.
FDA concerned about long-term effects

• “There are possible risks of transferring one person’s stool bacteria to another that are not related to infection. These include the possibility that inflammatory, allergic or metabolic conditions or weight/obesity could be related to or changed by a specific combination of stool bacteria. You will be getting stool bacteria from a health person.”

Weight Gain After Fecal Microbiota Transplantation

Neha Alang¹ and Colleen R. Kelly²

¹Department of Internal Medicine, Newport Hospital, and ²Division of Gastroenterology, Center for Women’s Gastrointestinal Medicine at the Women’s Medicine Collaborative, The Miriam Hospital, Warren Alpert School of Brown University, Providence, Rhode Island
A new class of “Biologics”

• NCT01868373: Defined Fecal Microbiota Transplantation for *Clostridium difficile* Diarrhea

(Baylor College of Medicine)
Rebiotix®

- NCT02299570: Microbiota Restoration Therapy for Recurrent *Clostridium difficile* Infection -PUNCH CD 2

**WHAT IS RBX2660?**

RBX2660 contains a suspension of live human-derived microbes. Each 50g/150 mL dose is supplied in a ready-to-use enema format.

In this study, the microbes were derived from the stool of four donors who were screened for pathogens on a regular basis. The product was manufactured in donor-specific batches that could be tracked to individual patients.
Seres Therapeutics™

• NCT02437487: SER-109 Versus Placebo to Prevent Recurrent *Clostridium difficile* Infection (RCDI) (ECOSPOR)

• SER-109 is an ecology of bacterial spores enriched and purified from healthy, screened human donors
FMT trials related to gastrointestinal indications

- Inflammatory Bowel Disease (32 trials)
  - 2 for pouchitis
- Irritable Bowel Syndrome (5 trials)
- Slow Transit Constipation (3 trials)
- Pancreatitis (2 trials)
- Hepatic encephalopathy (1 trial)
- Primary sclerosing cholangitis (1 trial)
- Nonalcoholic Fatty Liver disease (1 trial)
Outline

• Dysbiosis and the use of fecal microbiota transplant as a therapeutic agent
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• Future state of microbiome therapy
Clinical trials for FMT for non-gastrointestinal indications

- HIV (NCT02256592) - UCSF
- Metabolic Syndrome (NCT02050607) - Catholic University of the Sacred Heart
- Obesity (NCT02336789) - Kaplan Medical Center
The new frontier: MDRO elimination?

Loss of Vancomycin-Resistant *Enterococcus* Fecal Dominance in an Organ Transplant Patient With *Clostridium difficile* Colitis After Fecal Microbiota Transplant

Joshua Stripling,1 Ranjit Kumar,2 John W. Baddley,1 Anoma Nellore,1 Paula Dixon,1 Donna Howard,3 Travis Ptacek,4 Elliot J. Lefkowitz,2,4 Jose A. Tallaj,5 William H. Benjamin Jr,3 Casey D. Morrow,6 and J. Martin Rodriguez1

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The new frontier: MDRO elimination?
Fecal Microbiota Transplantation and Successful Resolution of Multidrug-Resistant-Organism Colonization

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(A)

Admitted to hospital

6/8/2012

FMT

9/21/2012

- CRE K. pneumoniae2
- MDR A. baumannii4
- MDR A. baumannii4
- MDR A. baumannii4
- MDR A. baumannii4
- MDR A. baumannii4
- MDR A. baumannii4
- MDR A. baumannii4
- MDR A. baumannii4
- MDR A. baumannii4

15 weeks post FMT

1/11/2013

(B)

15 weeks post FMT

1/11/2013

Death

10/30/2014
FMT trials for MDRO elimination

- Autologous Fecal Microbiota Transplantation (Auto-FMT) for Prophylaxis of *Clostridium difficile* Infection in Recipients of Allogeneic Hematopoietic Stem Cell Transplantation (Sloan-Kettering)
- Stool Transplantation to Reduce Antibiotic Resistance Transmission (Medical University of Warsaw)
- FMT for Multidrug Resistant Organism Reversal (Washington University)
- Biotherapy for MRSA Enterocolitis (Jinling Hospital, China)
Summary

• Fecal microbiota transplant has established itself as a method for restoration of the diversity of microbiota
• Current research is trying to determine what is the most important species and methods to restore microbiota
• Lessons learned from *C. difficile* are being applied in other disease states
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