



Using Feces to Cure Disease: Current and Future State

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DISCLOSURES

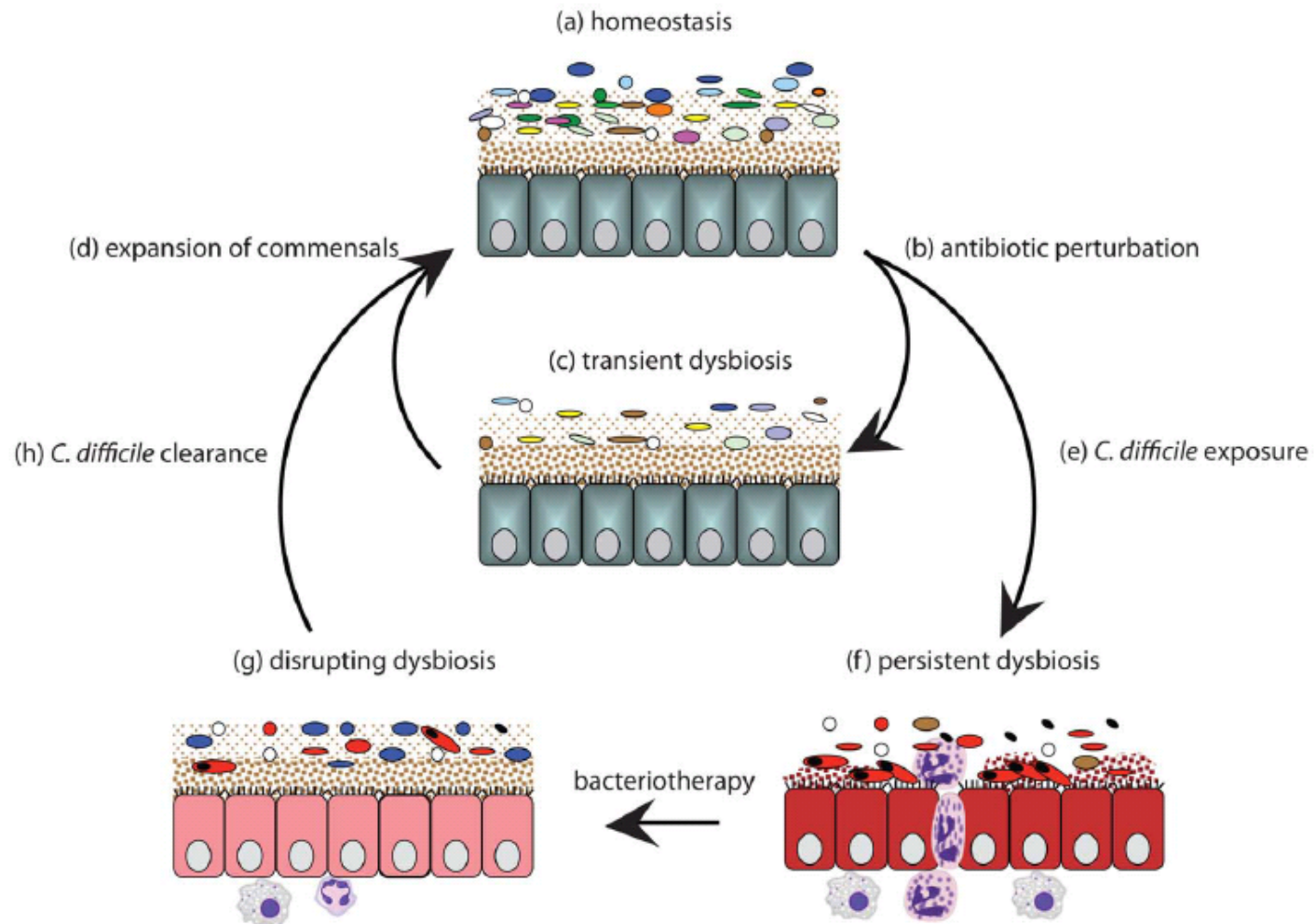
- Microbiome Processing, LLC - equity and IP
- Sub-Investigator (Emory site), Ecospor™ trial, Seres Therapeutics



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





Evaluating what makes a keystone species

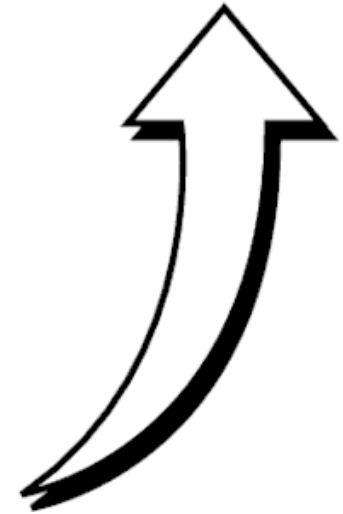


What if we did not need all of the seeds, but if just planting a few kinds replaced the garden?

Antibiotic Use



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





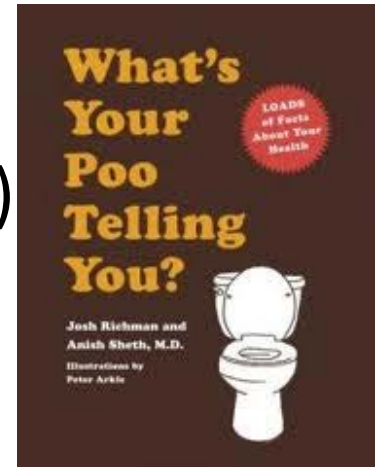
The worsening threat of *C. difficile* infection (CDI)

- 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



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

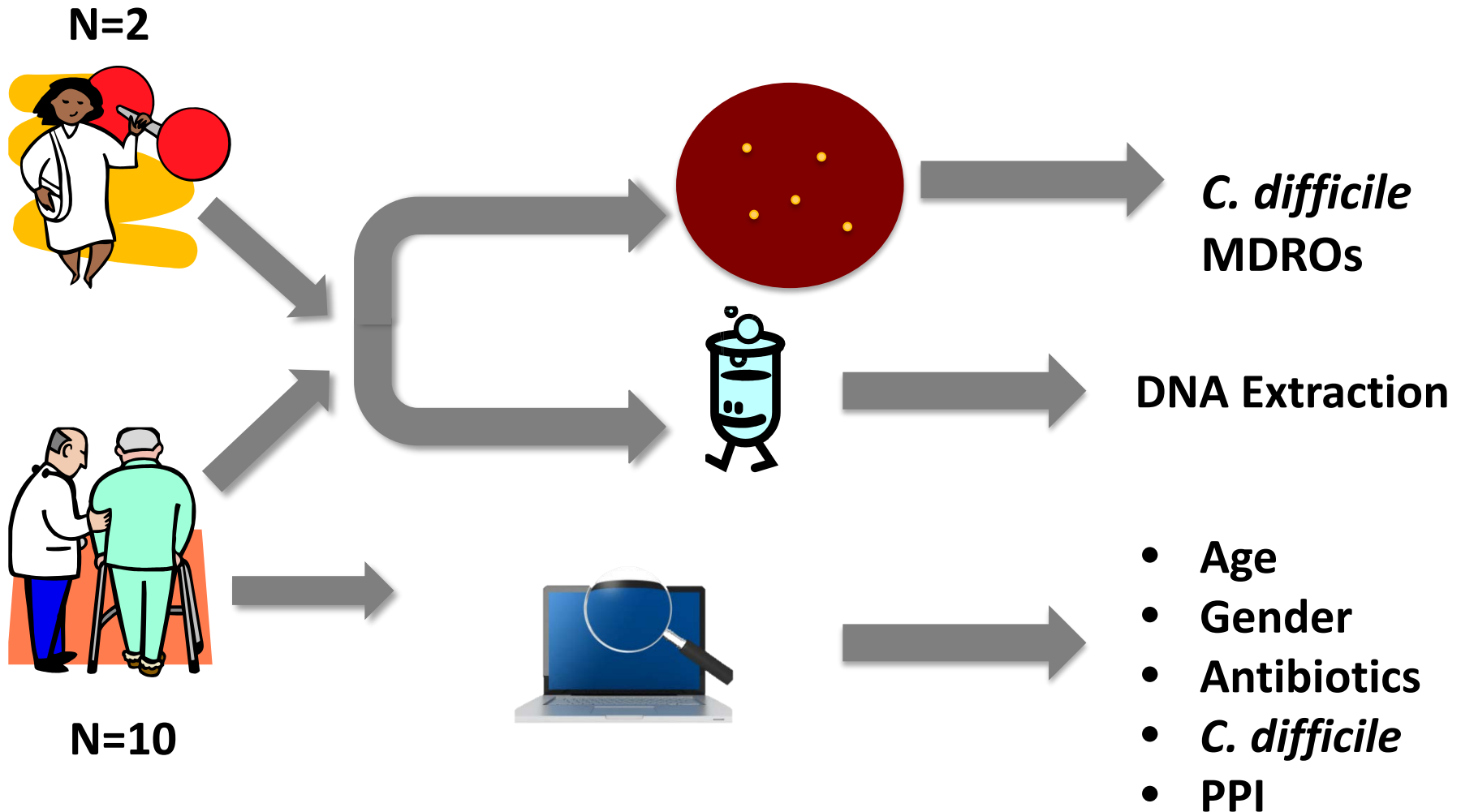




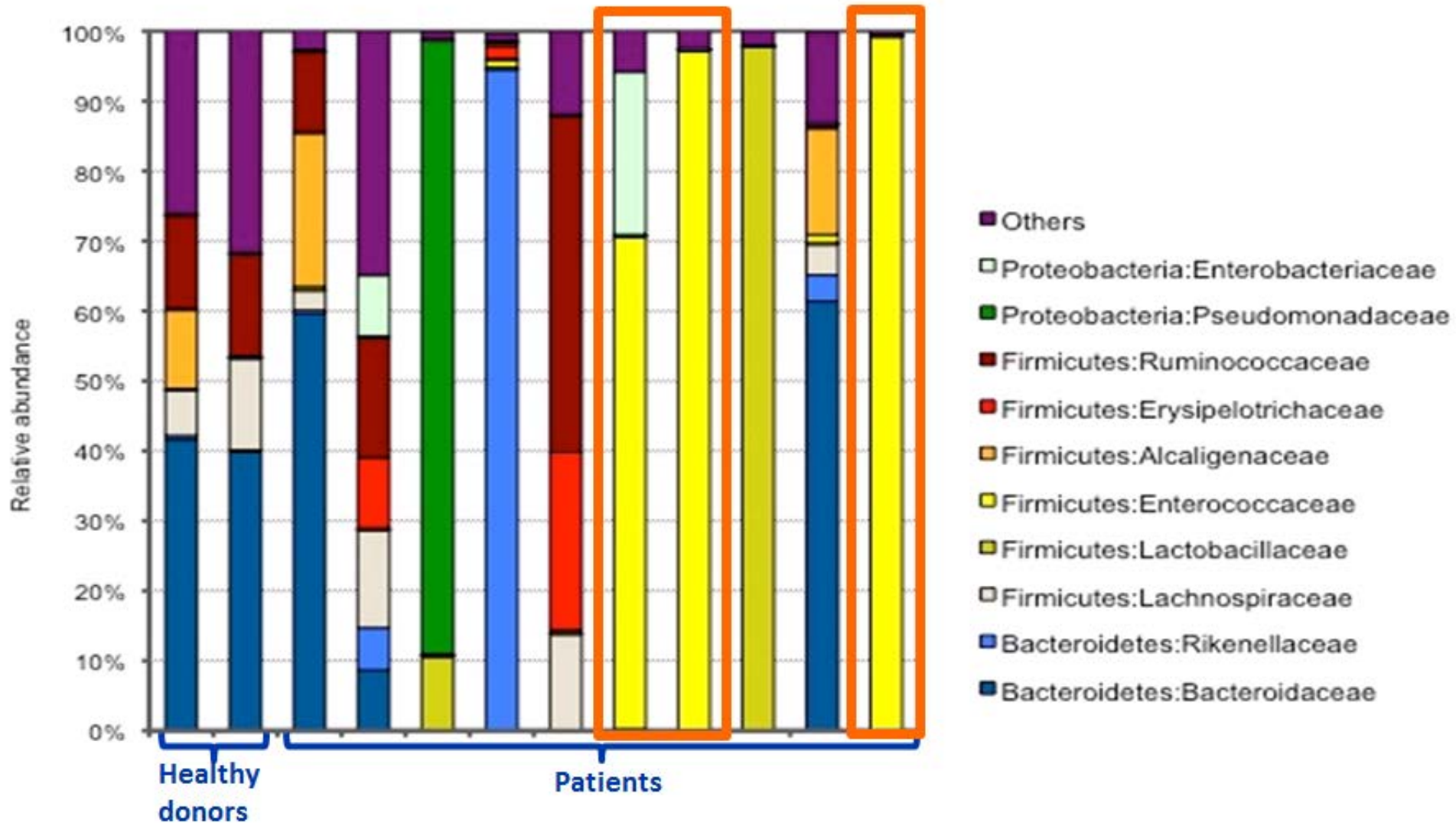
The microbiome of the most antibiotic experienced patients

- 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



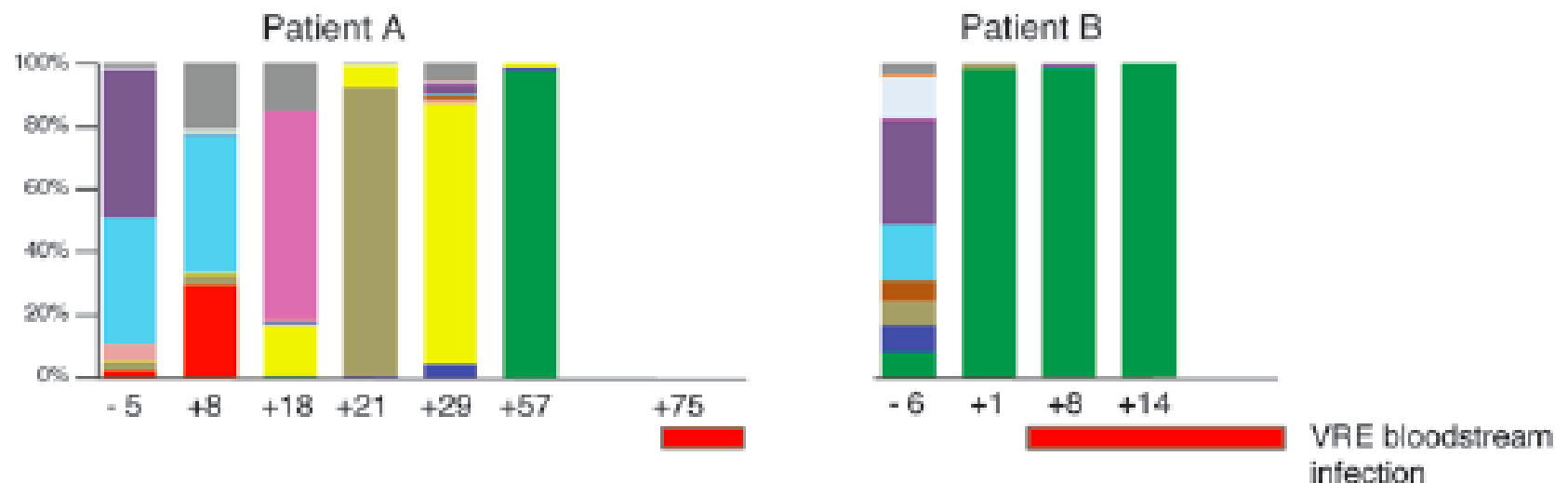
Microbial Community Composition



Vancomycin-resistant *Enterococcus* domination of intestinal microbiota is enabled by antibiotic treatment in mice and precedes bloodstream invasion in humans

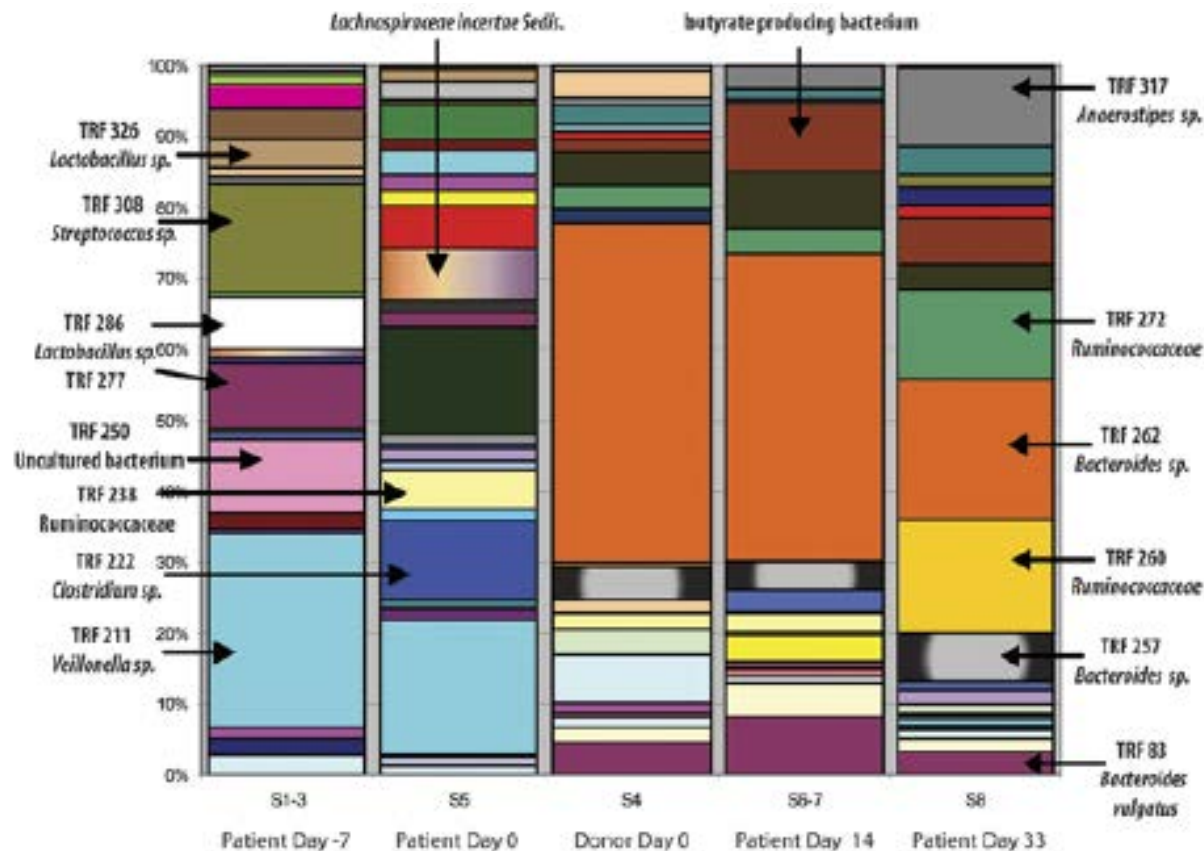
Carles Ubeda,^{1,2} Ying Taur,¹ Robert R. Jenq,³ Michele J. Equinda,^{1,2} Tammy Son,³ Miriam Samstein,^{1,2} Agnes Viale,⁴ Nicholas D. Socci,⁵ Marcel R.M. van den Brink,^{2,3} Mini Kamboj,¹ and Eric G. Pamer^{1,2}

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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§





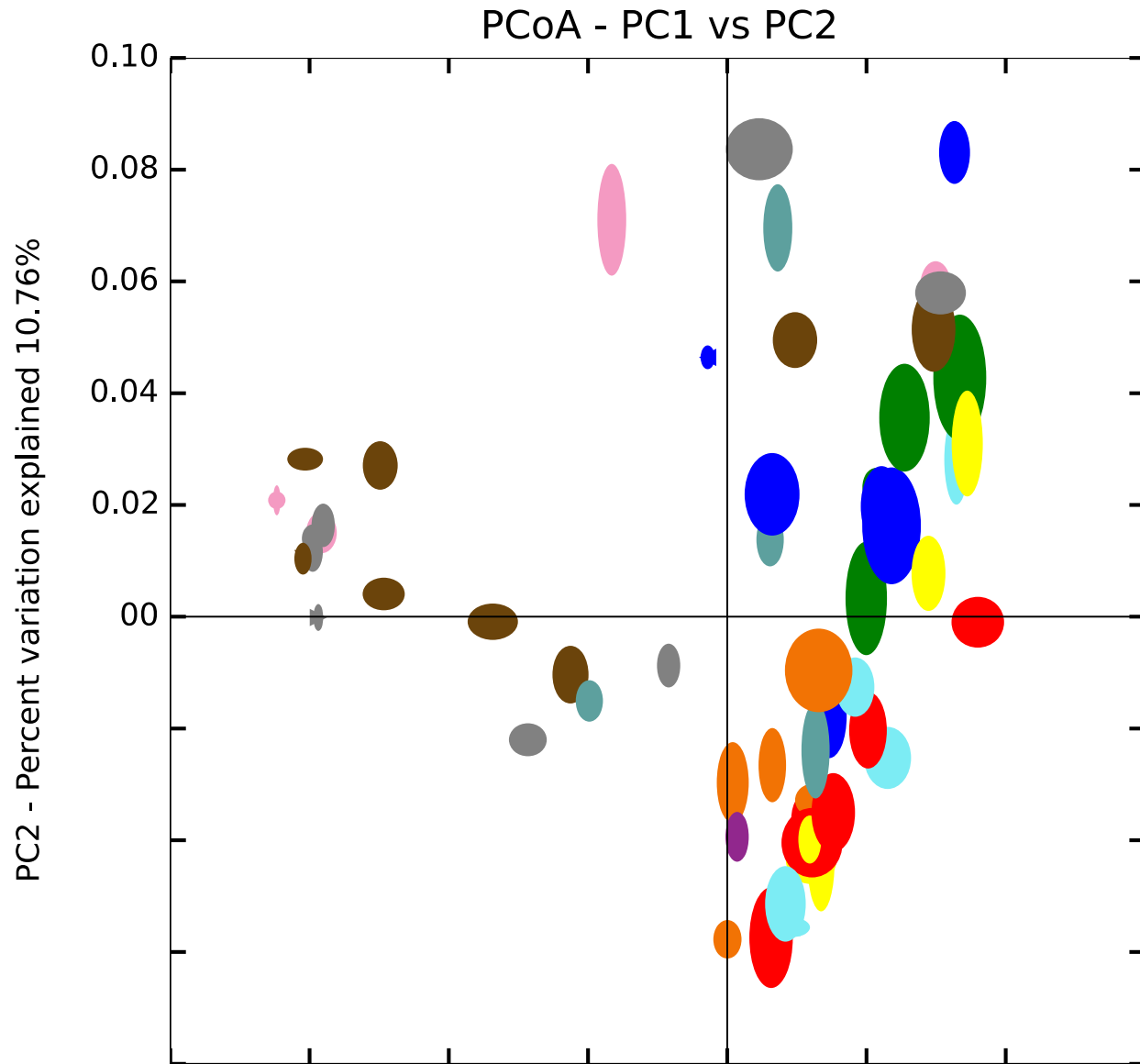
“Quick, inexpensive, and a 90% cure” – Mayo clinic website

- **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**



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





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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)

THE LANCET, MAY 27, 1989

BACTERIOTHERAPY FOR CHRONIC RELAPSING CLOSTRIDIUM DIFFICILE DIARRHOEA IN SIX PATIENTS

M. TVEDE¹

J. RASK-MADSEN²

Department of Clinical Microbiology, Rigshospitalet, Statens Seruminstitut;¹ and Section of Gastroenterology, Department of Medicine G, Bispebjerg Hospital, University of Copenhagen, Denmark²

TABLE II—EFFECT OF BACTERIAL STRAINS USED FOR BACTERIOTHERAPY ON GROWTH OF CL DIFFICILE STRAINS ISOLATED FROM PATIENTS AND VICE VERSA

Bacterial strain (registration number)	Patient					
	1	2	3	4	5	6
<i>S faecalis</i> (1108-2)	0	0	0	0	0	0
<i>Cl innocuum</i> (A27-24)	0	0	0	0	0	0
<i>Cl ramosum</i> (A31-3)	0	0	0	0	0	0
<i>Bact ovatus</i> (A40-4)	×	×	×	×	×	×
<i>Bact vulgatus</i> (A33-14)	×	×	×	×	×	×
<i>Bact thetaiotaomicron</i> (A33-12)	×	×	×	×	×	×
<i>E coli</i> (1109)	0	0	0	0	0	0
<i>E coli</i> (1108-1)	+	+	+	+	+	+
<i>Cl bifermentans</i> (A27-6)	+	+	+	+	+	+
<i>P productus</i> (1108-2)	+	+	+	+	+	+

0 denotes “no inhibition”

× denotes “test strain inhibited by *Cl difficile*”

+ denotes “*Cl difficile* inhibited by test strain.”



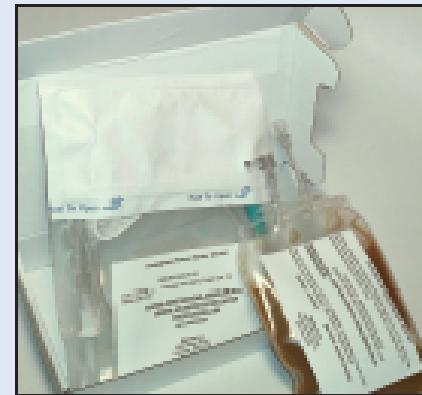
Rebiotix[®]

- 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)



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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

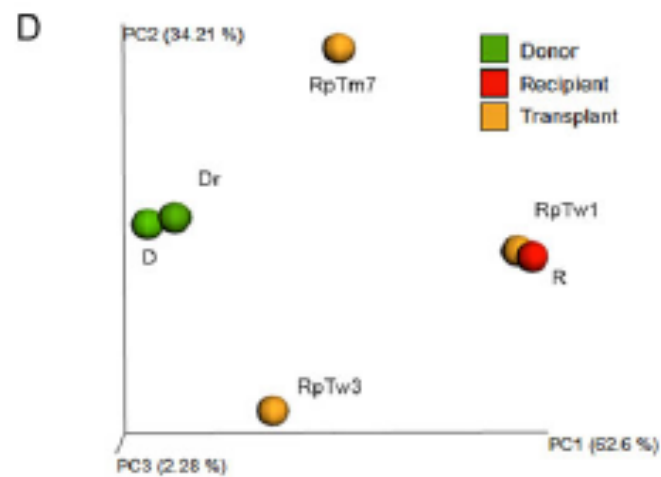
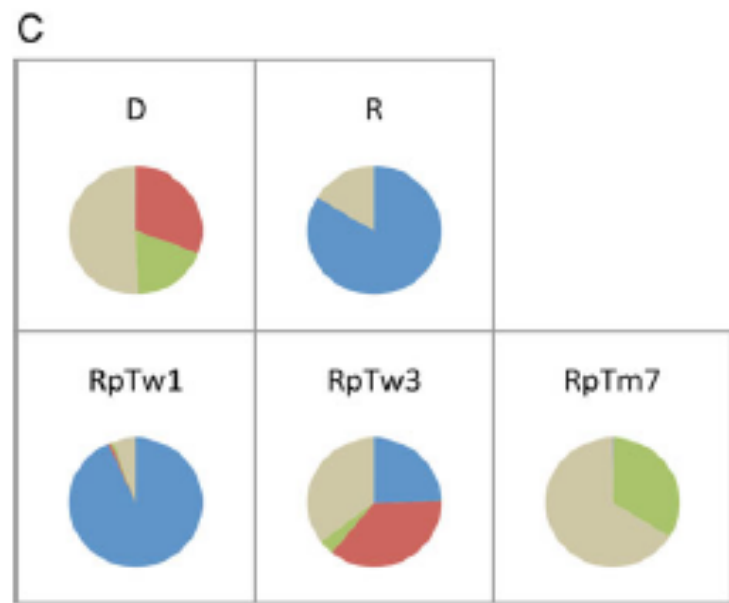
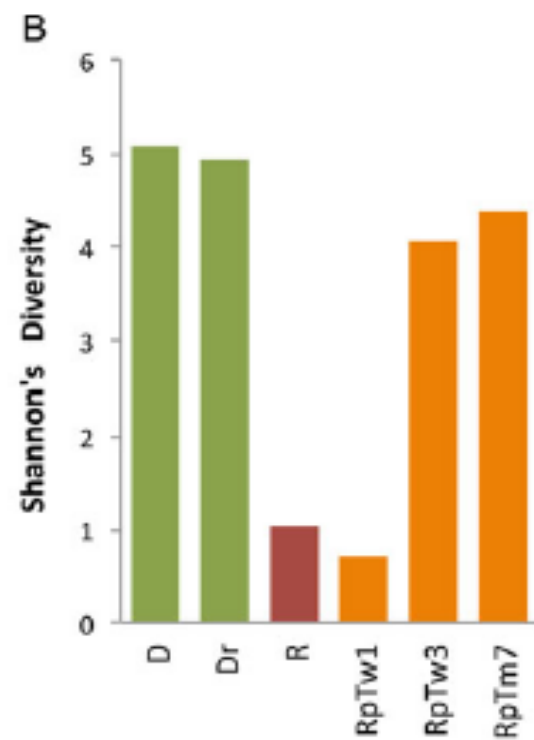
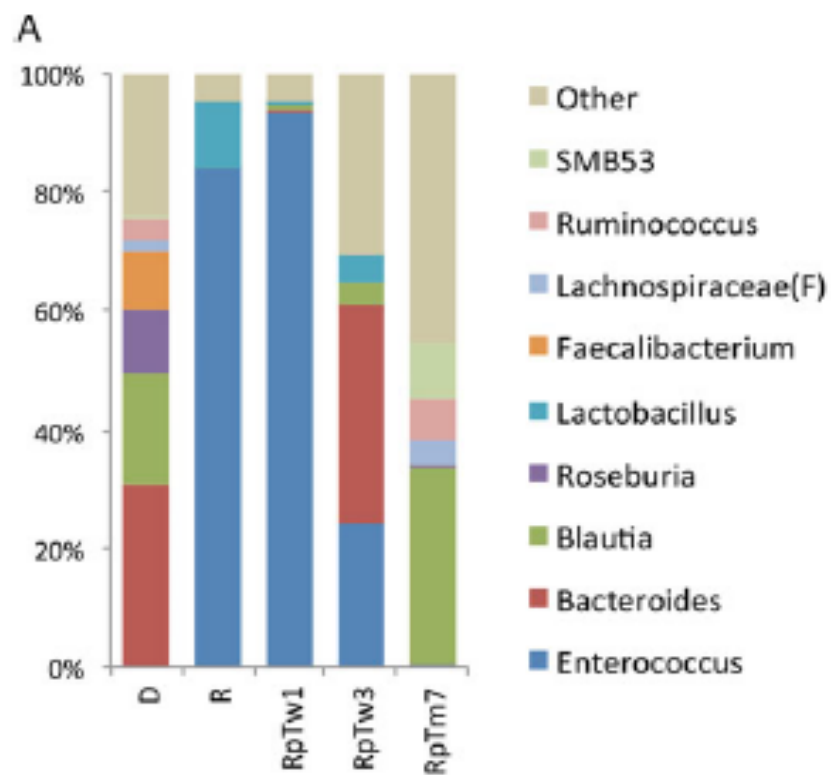


The new frontier: MDRO elimination?

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**

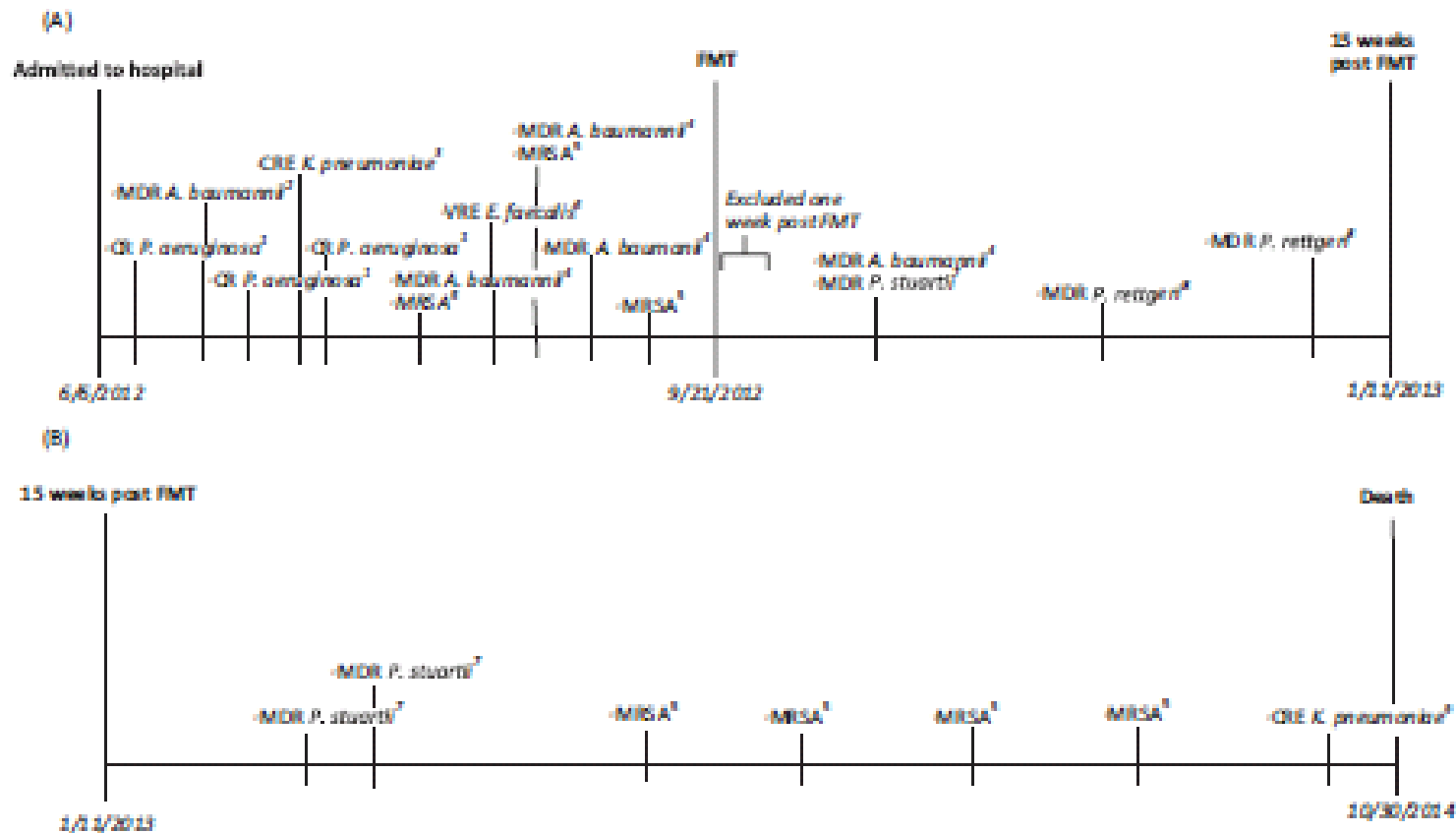
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Fecal Microbiota Transplantation and Successful Resolution of Multidrug-Resistant-Organism Colonization

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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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