



RECENT ADVANCES IN FECAL MICROBIOTA TRANSFORMATION in Inflammatory Bowel Disease



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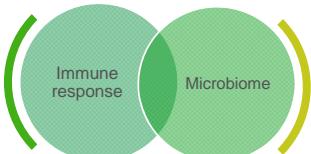


Objectives

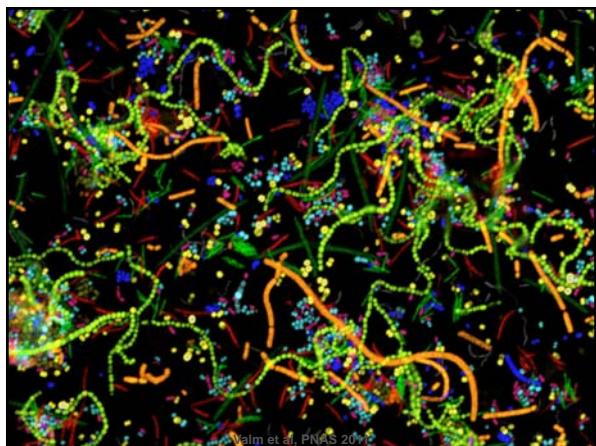
- Review of the fecal microbiome
- Dysbiosis and Inflammatory bowel disease
- Modulate the fecal microbiome
 - Fecal Microbial Transplants (FMT)
 - Diet



IBD Paradigm: Immune dysregulation

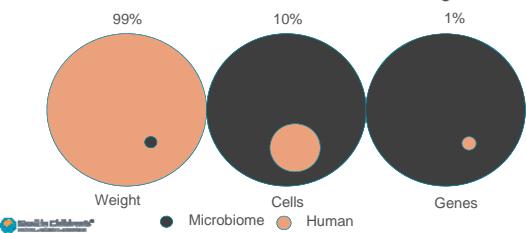


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Human Microbiome

- 100 trillion microorganisms
- Human gut - 2lbs of bacteria
- Outnumber human cells by a factor of ten
 - Genomes encode around 3 million different genes



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Fecal microbiome

Who's there?
What are they doing?

Who's they are varies: your microbiota is
plastic and personalized.

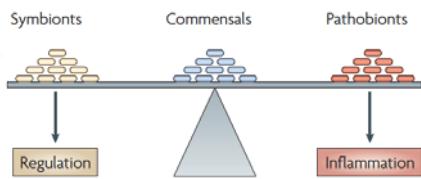
What they're doing is *adapting to
their environment:*
you, your body, and your environment.



Savage, DC. Annu Rev Microbiol 1977; 31:107-133

Backhed, F. et al Science. 2005; 307: 1915-1920.

Microbiome and Human disease



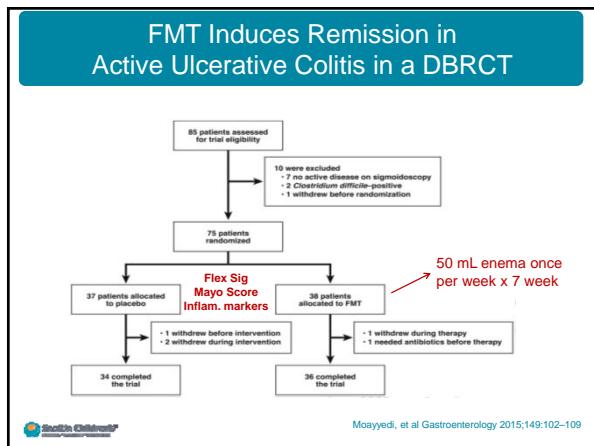
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Round JL. Nature Reviews Immunology 2009.

Flipping the Paradigm

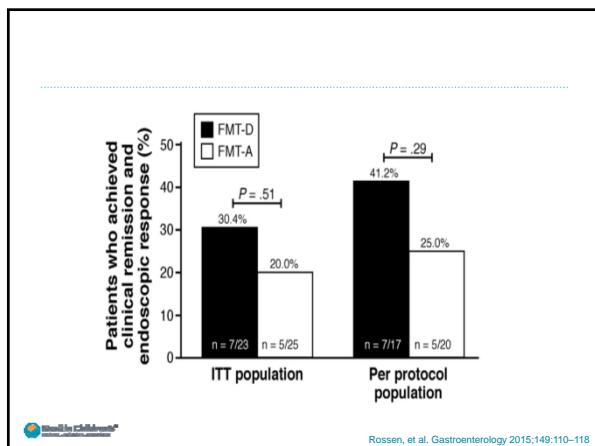
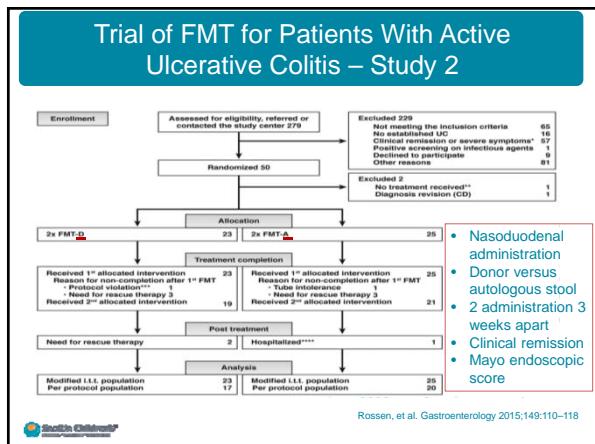
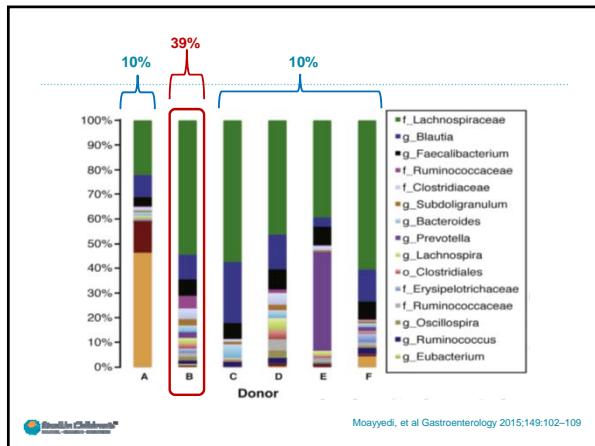


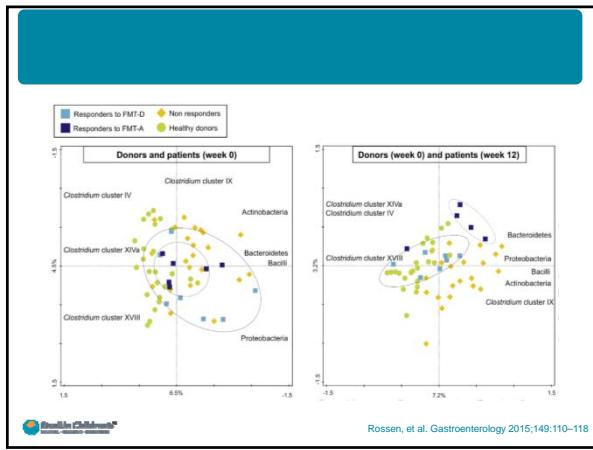
Study	#IBD pts	IBD Type	IBD Severity	FMT Dosage	FMT Delivery	Pre-Abs/ Leaveage	Frequency	Donor	Follow-Up
Borody et al. (1998)	2	UC, CD	Active	NR	NR	NR	NR	NR	1-12 months
Borody et al. (2001)	3	UC	Quiescent	Suspended in 200ml saline	Enema	NR	Daily x 5 days	Healthy Adults	8-28 months
Borody et al. (2003)	6	UC	Severe	200-300g (diluted to 200-300ml)	Enema	Vancomycin, Metronidazole and rifampicin	Daily x 5 days	Family or Close Relation	1-13 years
Borody et al. (2011)	3	IBD	Isevere	NR	Enema (self)	NR	Daily/Weekly X34-70	Clinic donor, family, partner	1-4 years
Kellermayer et al. (2013)	4(1 ⁺)	UC	IM/anti-TNF Dependent	NR	Colonoscopy	NR	Serial	?	>5 months
Suskind et al. (2014)	3	UC	Mild-Moderate	60ml	NG	Rifaximin	X 1	Parent	12 weeks
Vermeire et al. (2012) ¹	4	CD	Medically-refractory	200g feces	NI infusion	NR	3x in 36 hours	Healthy Donor	2 months
Kunde et al. (2013)	10(1 ⁺)	UC	Mild-moderate	90-113g/250ml	Enema up to 440ml/day	NR	x5 days	Parents	6 weeks
Kung et al. (2013)	6	UC	Therapy-refractory	150g/ 200 saline	Colonoscopy	Usage of donor	x1	Nonrelatives,	1 year
Angelberger et al. (2013)	5	UC	Severe	6-22g/100ml	NI + Enema	Metronidazole	x3 days	No Family/ Hospital Staff	>1 year
Suskind et al. (2014)	9	CD	Mild-moderate	60ml	NG	Rifaximin	x1	Parents	12 weeks
Landy et al. (2013)	5	UC	refractory pouchitis	30g/250ml Saline	Nasogastric	NR	x1	Nominated by participating pts	4 weeks
Zhang et al. (2013)	16	CD	Refractory (HB [±])	NR	Gastroscopic	NR	x1	NR	1 month
Dammann et al. (2014)	8(1 ⁺)	UC	Mild-moderate (UCDA 3-10)	NR	Colonoscopic	Standard colon prep	x1	Chosen by Recipient	12 weeks
Vaughn et al. (2014)	9	CD	Active CD (HB [±])	50g in 250ml Saline	Colonoscopic	Standard colon prep	x1	Healthy Unrelated	12 weeks



Outcome	Placebo (n = 37)	FMT (n = 38)	P value
Clinical remission, n (%)	2 (5)	9 (24)	.03
Clinical response, n (%)	9 (24)	15 (39)	.16
Full Mayo score	6.34	6.09	.42
CRP, mg/L (n = 17 placebo, n = 15 FMT)	3.3 ± 3.4	4.9 ± 5.9	.38
ESR, mm/h (n = 17 placebo, n = 15 FMT)	13.1 ± 11.2	15.9 ± 17.0	.59
Patients with serious adverse events n (%)	2 (5)	3 (8)	1.0

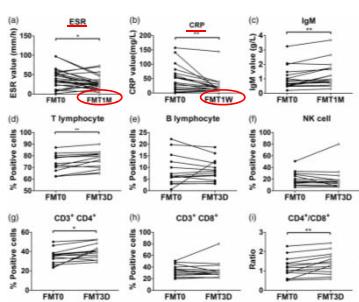
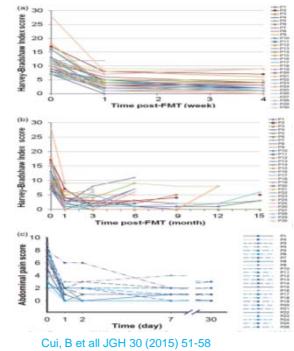
Moayedi, et al Gastroenterology 2015;149:102-109





FMT in Crohn's Disease: Study One

- Active disease
- Mid gut via enteroscopy.
- Mesalamine and dietary changes.
- Day 1-3, week 1, month 1, then every 3 months.



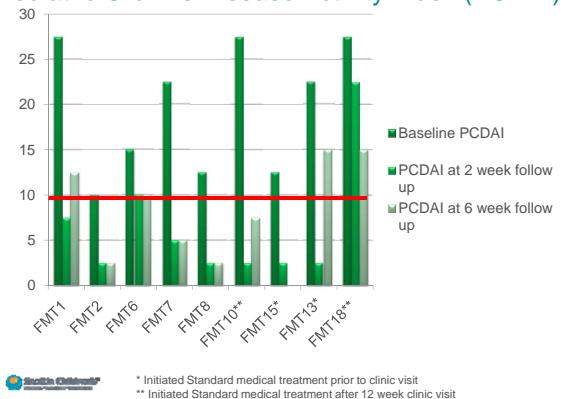
FMT in Crohn's disease: Study 2

- Mild to moderate active disease
 - 9 Patients
 - 12-19 years of age
 - Medication therapy continued
- Pre-FMT antibiotics
- Nasogastric tube
- Disease activity and microbiome
 - Follow up 2, 6, and 12 weeks

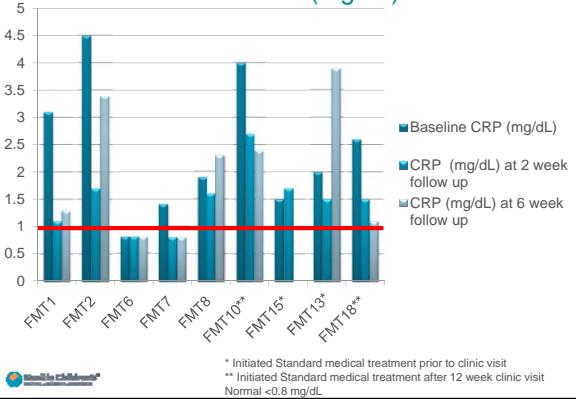


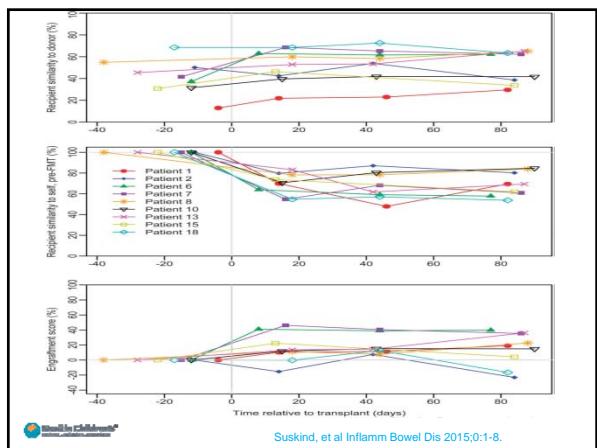
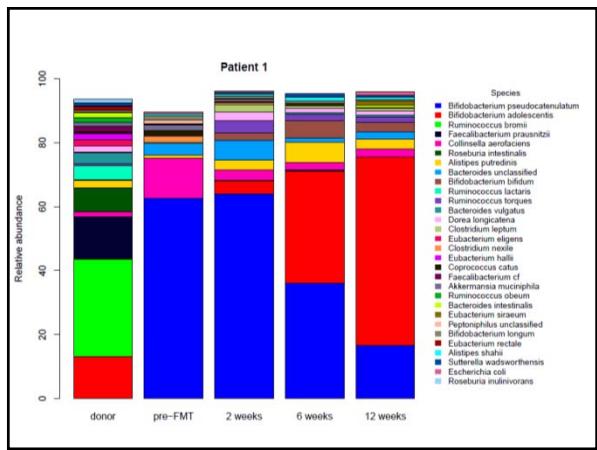
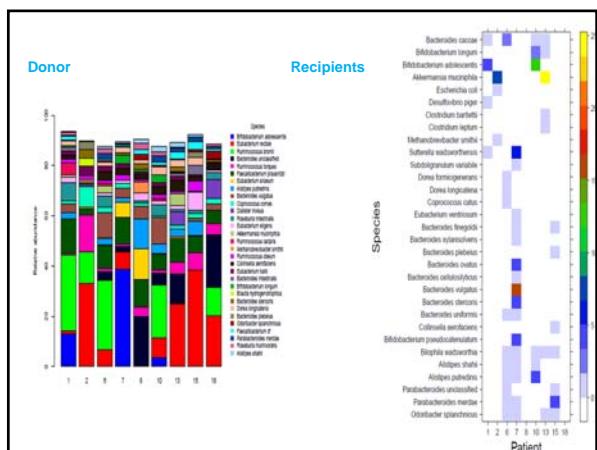
Suskind, et al Inflamm Bowel Dis 2015;0:1-8.

Pediatric Crohn's Disease Activity Index (PCDAI)



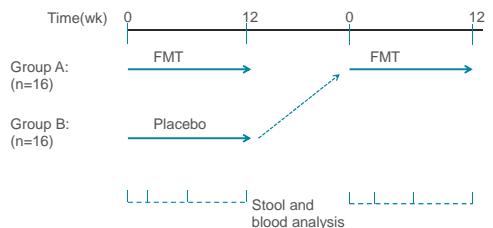
C-Reactive Protein (mg/dL)



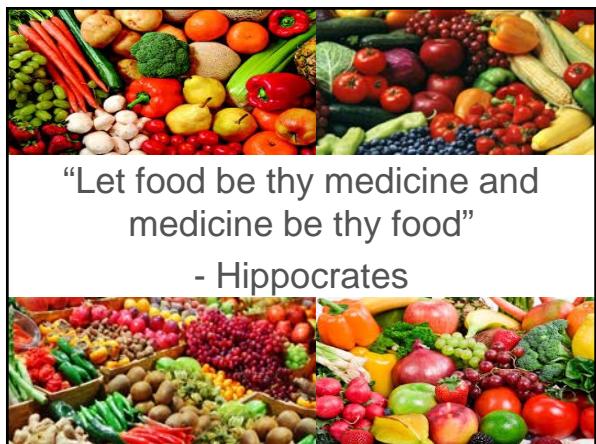


Double Blind Placebo Control trial of FMT in active Crohn's disease

- Results Pending

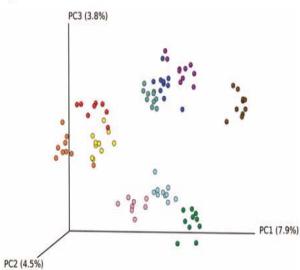


ClinicalTrials.gov Identifier: NCT02272868

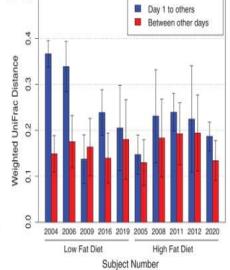


Effects of Modifying the Diet on Microbiome

A



B



Wu, G, Science 334, 105 (2011); 105-108

Specific Carbohydrate Diet(SCD)

- Removes
 - Removes all grains
 - milk products except for yogurt fermented greater than 24 hours
 - Sugars except honey
- Sidney Haas MD
 - Early 1930s used to treat celiac disease
- Popularized by Elaine Gottschall
 - Breaking the Vicious Cycle



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Haas, S, Haas M, Am J Gastroenterol 1955 Apr;23(4):344-60

SCD at SCH

- Retrospective study
 - Children with Crohn's disease
 - Tried dietary therapies as sole medical treatment for their Crohn's disease
- Seattle Children's Hospital
 - January 2005 to December 2012

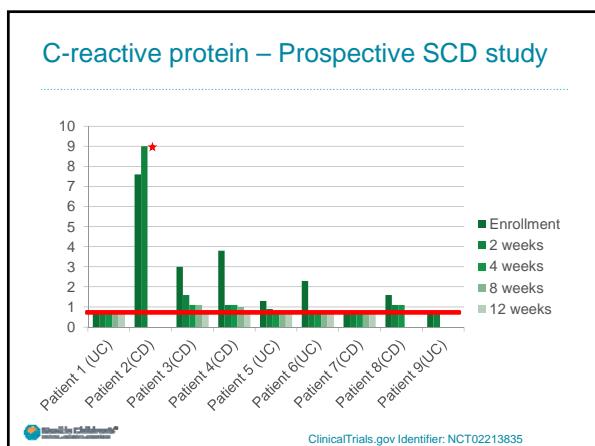
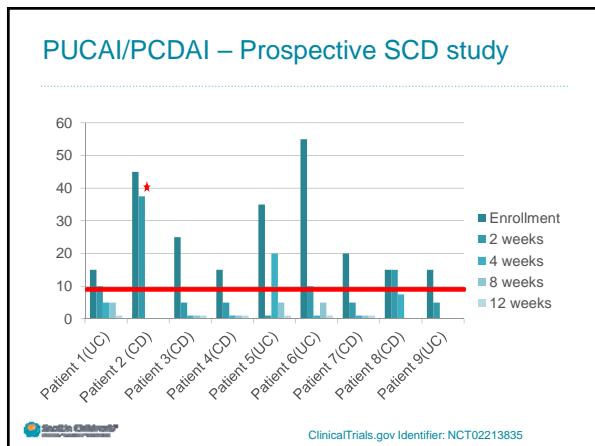
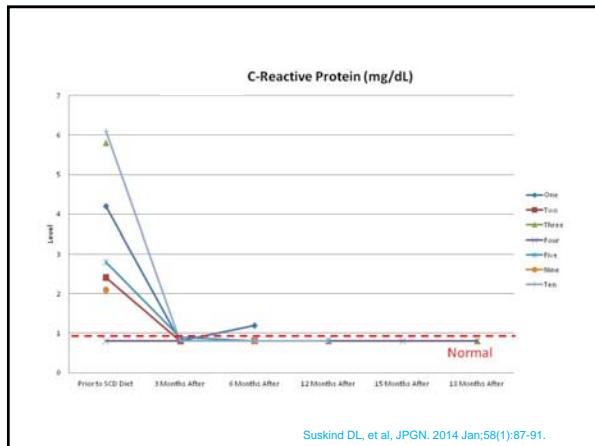
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Suskind DL, et al, JPGN. 2014 Jan;58(1):87-91.

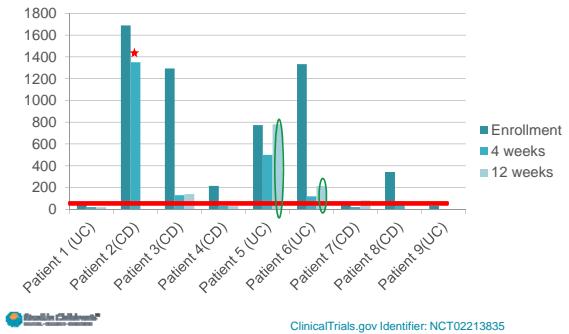
Pediatric Crohn's Disease Activity Index						
Study ID	Prior to Diet Intervention	3 Months After	6 Months After	12 Months After	15 Months After	18 Months After
		After	After	After	After	After
One	20	0	0			
Two	30	0	0			
Three	30	0	0	0		0
Four	10	0	0	0	0	0
Five	15	0	0	0		
Nine	25	0	0			
Ten	10	0	0	0		

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Suskind DL, et al, JPGN. 2014 Jan;58(1):87-91.



Calprotectin – Prospective SCD study



Microbiome Analysis

Species	Baseline	Week 2	Week 6	Week 12
Escherichia coli	12.3	0.3	1.8	0.2
Ruminococcus gnavus	15.0	4.7	4.4	1.9
Bacteroides fragilis	8.2	1.3	12.1	1.1
Bacteroides ovatus	8.4	3.0	1.1	1.6
Akkermansia Muciniphila	0.114	5.663	0.583	20.115
Bacteroides stercoris	6.7	4.6	1.0	2.9

Conclusion

- Fecal Microbiome is complex and biologically important in Health and Disease
- Fecal Microbiome modulates us
- We modulate our Fecal Microbiome





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