Fecal Microbial Transplant Effect on Clinical Outcomes and Fecal Microbiome in Active Crohn's Disease

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Original Clinical Articles

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Background

- 4 Mio People worldwide are affected by IBD
- Hypothesis that Crohn's disease is a result of immune response to the fecal microbiota in genetically susceptible individuals
- The dysbiosis in CD has been characterized by depletion of commensal bacteria (Firmicutes and Bacteroidetes) and a decreased abundance of Clostridia as well as an increase in Proteobacteria
- Numerous clinical studies have attempted to modulate the fecal microbiome to decrease the inflammatory immune response using prebiotic, probiotic, and antimicrobial therapies. The results of these trials have been mixed

Background

- dysbiosis in Crohn's patients has been better defined with nonculturable techniques, such as 16s RNA sequencing for identification of species within the fecal microbiota.
- It's posslible to modify the human microbiome through fecal microbial transplant (FMT) since in since 1958 for treatment of Clostridium difficile colitis
- There is little data for treatment of Crohn's patients dysbiosis with FMT

materials and methods

- Prospective single-center open-label study
- tolerability, safety, potential efficacy of FMT in pediatric patients with CD with mild-to-moderate disease

Patients

- Age 12 to 21 years
- Diagnose of CD by a primary gastroenterologyst based on history, physcal examination, laboratory/radiological studies and histology.
- Mild-to-moderate symptoms (PCDAI 10-29)
- Medication without change for at least 1 month (none TNF inhibitor)
- **Exlusion criteria**
- History of or active abscess
- Fistula
- Stricturing CD
- Serios systemic diseases

Initial Evaluation

- Laboratory tests
- Stool studies for C. Difficile, bacterial culture, ova, parasite
- **Donors (one of the patients parents)**
- Questionnaire of American Association of Blood Banks Donor
- Hepatitis A,B,C,HIV,EBV,CMV
- No antibiotics 3 month before

Stool Transplantation

- Premedication: Rifaximin 200mg 1-1-1 (3x), Omeprazol
- Nasogastric tube
- 30g of donor stool (mixed with 100-200ml normal saline blended with commercial blender at low speed for 2-4min, filtered twice, administered over 3 min)

Posttransplantation Follow-up

- Call after 2 days
- Clinical follow-up at 2,6,12 weeks
  - Standardized questionnaires + PCDAI
- Diary cards to assess possible side effects

Method Section for Microbiome

DNA Extraction

- Total genomic DNA was extracted from stool using PowerSoil DNA Isolation Kit
- **Metagenomic Sequencing**
- Illumina HiSeq 2000 or MiSeq platform
- **Bioinformatics Analysis**
- Human DNA sequence was identified and removed using BMTagger19
- **....**

Results

Patients

- 14 families were screend
- 5 families exluded (exlusion criteria incl. no suitable donor)
- Age 16.2 +- 2.9 years (5 boys, 4 girls)
- Average disease duration 3.9 +-1.8 years
- Therapie:4 Methotrexate,1 azathiprine, 1 Mercaptopurine, 3 mesalacine, 1 no medication

Patient	Gender	Age, yr	Disease Duration, yr	Modified Paris Classification	Disease Location	Concomitant IBD Medications
1	Male	19	5	A2, L3, B1, G0	Colon, terminal ileum	Methotrexate, folic acid
2	Male	16	3	A1b, L1/4a, B1, G0	Duodenum, terminal ileum	Mesalamine
6	Female	18	5	A2, L1/4a, B1, G0	Stomach, duodenum, terminal ileum	6-mercaptopurine
7	Female	12	4	A1b, L2/4a, B1, G0	Duodenum, colon	Methotrexate, folic acid
8	Male	17	7	A2, L3/4ab, B1, G0	Esophagus, duodenum, colon, terminal ileum	Mesalamine
10	Female	19	2	A2, L3, B1, G0	Colon, terminal ileum	Methotrexate, folic acid, mesalamine
13	Male	13	4	A1b, L3/4b, B1, G0	Duodenum, colon, terminal ileum	Azathioprine
15	Male	19	4	A2, L2/4a, B1, G0	Duodenum, colon	Methotrexate, folic acid
18	Female	13	<1	A1b, L2, B1, G0	Colon	None

Patient	Sample	PCDAI	CRP, mg/dL	Calprotectin, μg/g	Clinical Remission at 2 wk	Engraftment Score at 2 wk, %	Engraftment Type	Pre-FMT Similarity to Donor, %
1	Baseline	27.5	3.1	1380	Yes	10	Gradual	13
	2 wk	7.5	1.1	1287				
	6 wk	12.5	1.3	729				
	12 wk	10	<0.8	827				
2	Baseline	10	4.5	544	Yes	−15	Failure	50
	2 wk	2.5	1.7	353				
	6 wk	2.5	3.4	718				
	12 wk	10	7.4	791				
6	Baseline	15	<0.8	<16	No	41	Immediate	37
	2 wk	10	<0.8	<16				
	6 wk	10	<0.8	<16				
	12 wk	5	<0.8	<16				
7	Baseline	22.5	1.4	23	Yes	46	Immediate	42
	2 wk	5	<0.8	<16				
	6 wk	5	<0.8	<16				
	12 wk	2.5	1.5	<16				
8	Baseline	12.5	1.9	1456	Yes	11	Gradual	55
	2 wk	2.5	1.6	899				
	6 wk	2.5	2.3	672				
	12 wk	7.5	1.1	1186				
10	Baseline	27.5	4	1074	Yes	12	Gradual	32
	2 wk	2.5	2.7	799				
	6 wk	7.5	2.4	1349				
	12 wk	20	2.3	1320				
13	Baseline	22.5	2	596	Yes	14	Gradual	46
	2 wk	2.5	1.5	532				
	6 wk	15	3.9	1318				
	12 wk[a]	2.5[a]	<0.8[a]	434[a]				
15	Baseline	12.5	1.5	>2500	Yes	22	Immediate	31
	2 wk	2.5	1.7	1231				
	6 wk[a]	7.5[a]	1[a]	>2500[a]				
	12 wk[a]	0[a]	<0.8[a]	22[a]				
18	Baseline	27.5	2.6	839	No	0	Failure	69
	2 wk	22.5	1.5	906				
	6 wk	15	1.1	1224				
	12 wk	22.5	2.1	1172				

[a]Received additional standard treatment before visit.

Reportet adverse events

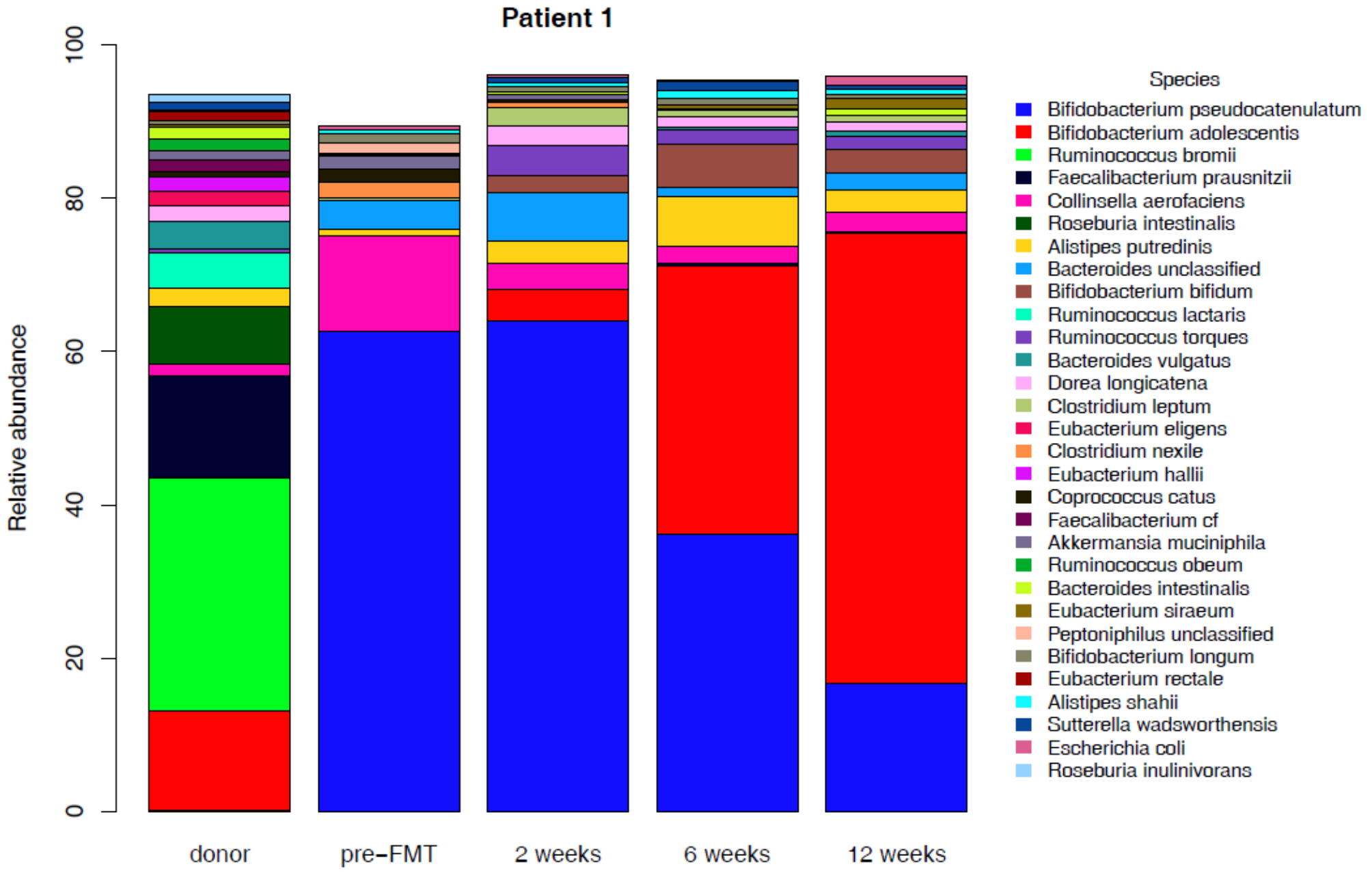
- 1x moderate abdominal pain
- 5x mild abdominal pain
- 5x bloating
- 4x diarrhea
- 3x side effects related to NG tube
- All symptoms returned to baseline wihin 48 hours

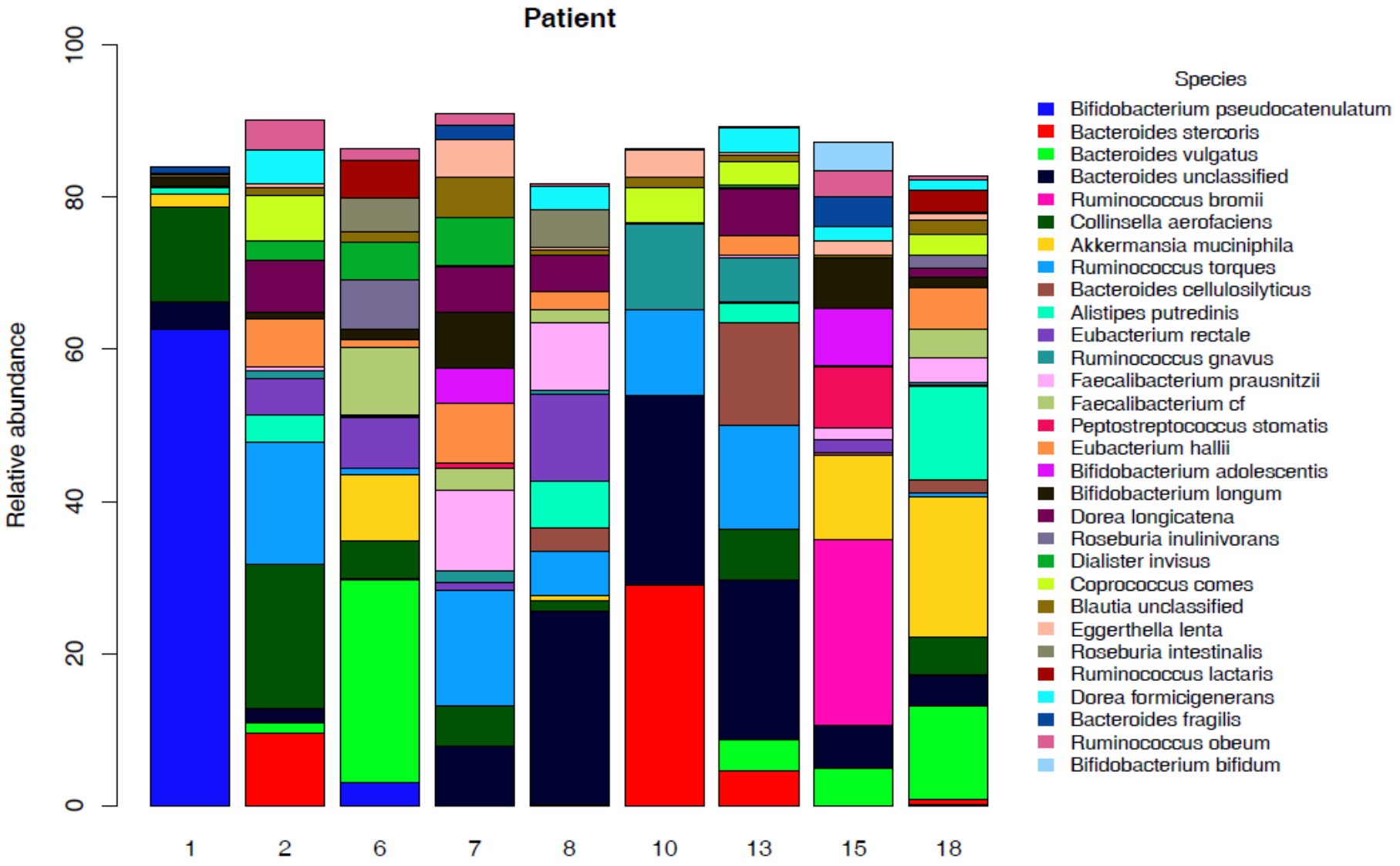
Clinical course

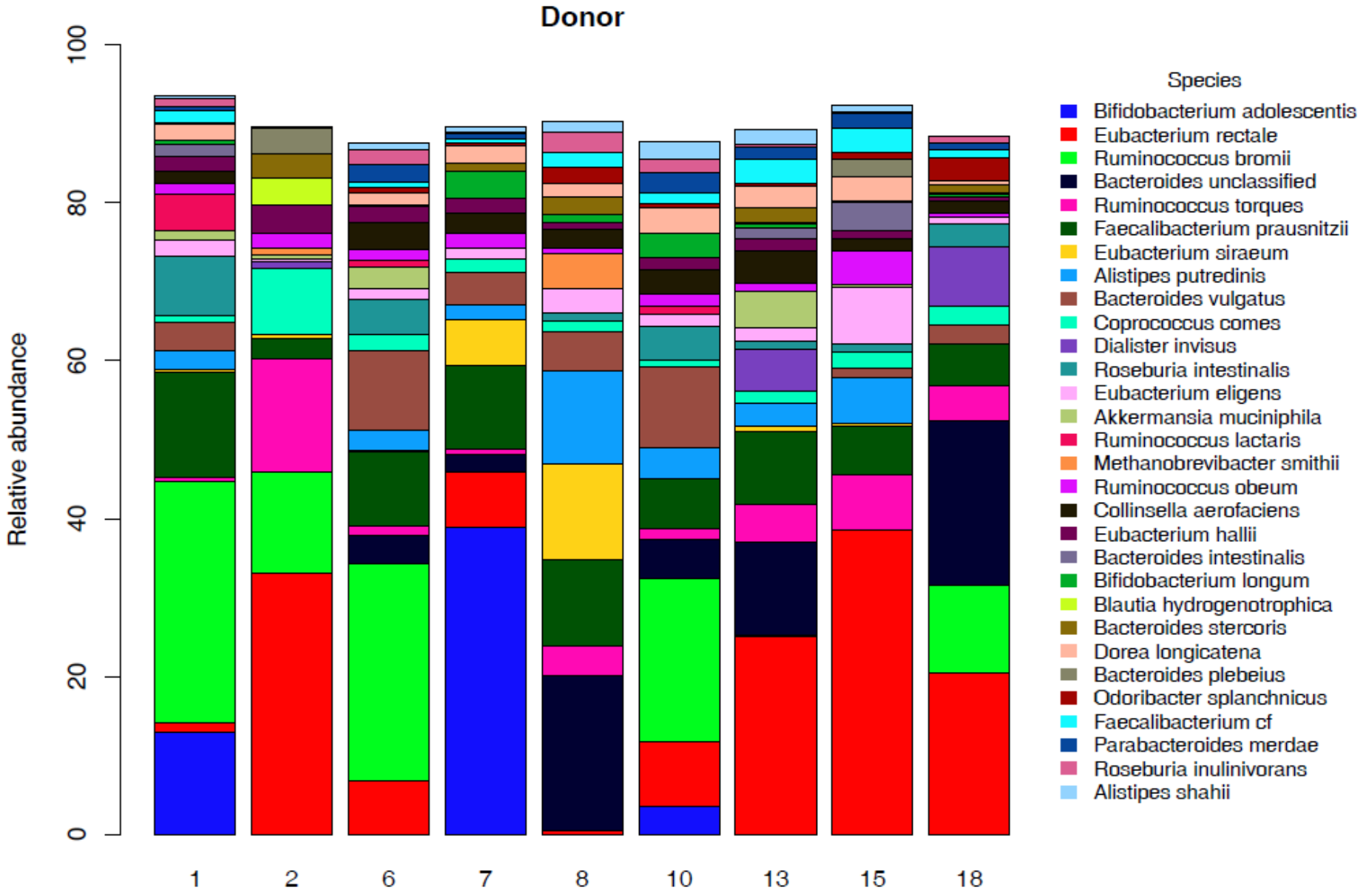
- Two weeks after FMT:
  - 7/9 patients in clinical remission
- 6 + 12 weeks after FMT
  - 5/9 patients who did not recieve additional therapy were still in remission
  - 2 received additional standart medical therapies
- Calprotectin
  - Decreased or remained unchanged
  - 936 -+782 to 671-+474 (week 2)

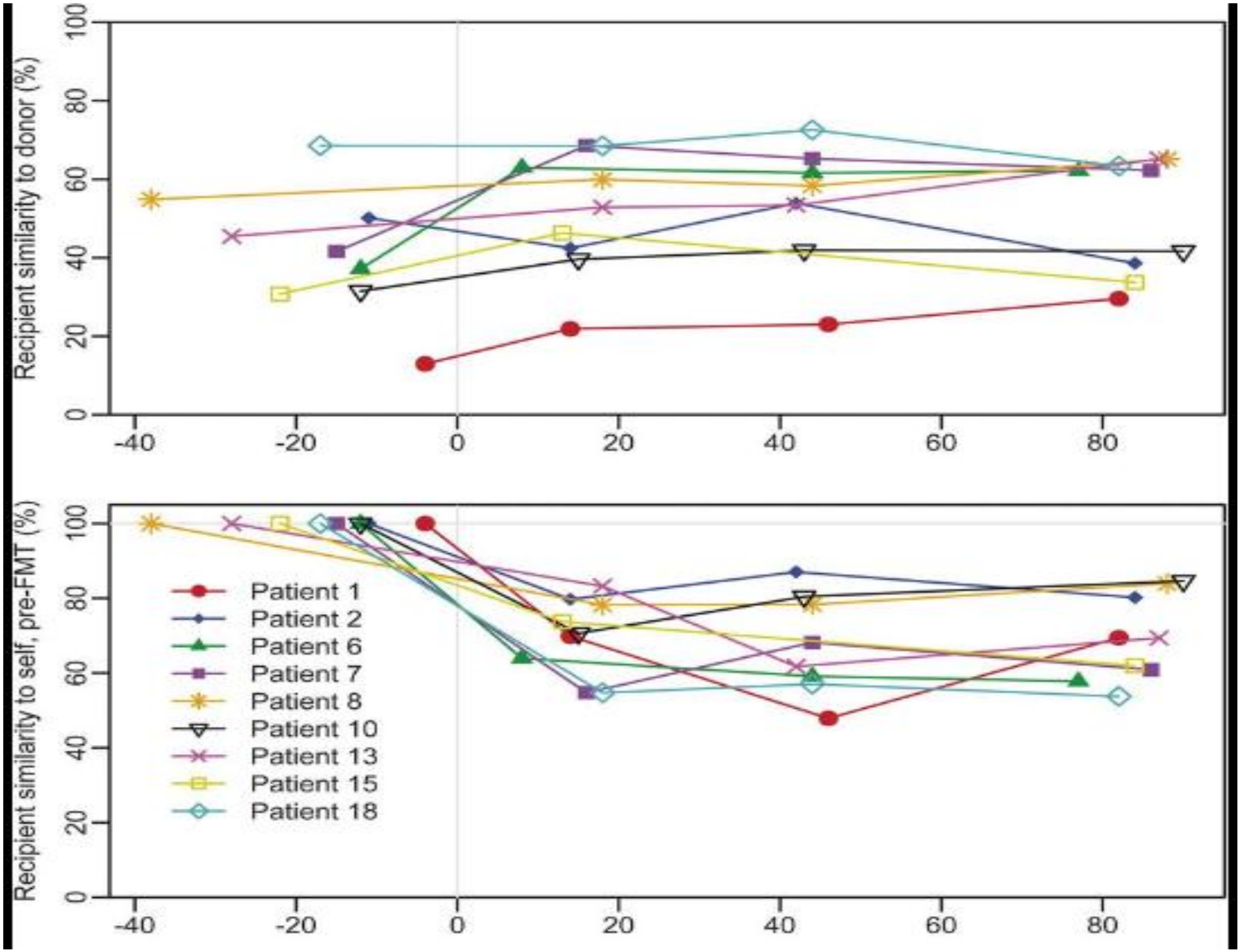
Microbiome

- Fecal microbiome similarity to donor, **pre-FM**T had a mean of 41.7% ± 16.1%
- relative change in similarity to donor ranged from -15% to 46%
  - 2 pat: no similarity
  - 4 pat: gradual similarity
  - 3 pat: immediate similaritiy (very quick by the 2 week)
- total 116 species were identified
  - 92% were found in the donors
  - 11 of the 30 most abundant species in the donors were found in all 9 donors
  - Greater homogeneity for donors in relation to patients for the most abundant species


Patient 1
Relative abundance
0
20
40
60
80
100
donor
pre−FMT
2 weeks
6 weeks
12 weeks
Species
Bifidobacterium pseudocatenulatum
Bifidobacterium adolescentis
Ruminococcus bromii
Faecalibacterium prausnitzii
Collinsella aerofaciens
Roseburia intestinalis
Alistipes putredinis
Bacteroides unclassified
Bifidobacterium bifidum
Ruminococcus lactaris
Ruminococcus torques
Bacteroides vulgatus
Dorea longicatena
Clostridium leptum
Eubacterium eligens
Clostridium nexile
Eubacterium hallii
Coprococcus catus
Faecalibacterium cf
Akkermansia muciniphila
Ruminococcus obeum
Bacteroides intestinalis
Eubacterium siraeum
Peptoniphilus unclassified
Bifidobacterium longum
Eubacterium rectale
Alistipes shahii
Sutterella wadsworthensis
Escherichia coli
Roseburia inulinivorans


Patient
Relative abundance
0
20
40
60
80
100
1
2
6
7
8
10
13
15
18
Species
Bifidobacterium pseudocatenulatum
Bacteroides stercoris
Bacteroides vulgatus
Bacteroides unclassified
Ruminococcus bromii
Collinsella aerofaciens
Akkermansia muciniphila
Ruminococcus torques
Bacteroides cellulosilyticus
Alistipes putredinis
Eubacterium rectale
Ruminococcus gnavus
Faecalibacterium prausnitzii
Faecalibacterium cf
Peptostreptococcus stomatis
Eubacterium hallii
Bifidobacterium adolescentis
Bifidobacterium longum
Dorea longicatena
Roseburia inulinivorans
Dialister invisus
Coprococcus comes
Blautia unclassified
Eggerthella lenta
Roseburia intestinalis
Ruminococcus lactaris
Dorea formicigenerans
Bacteroides fragilis
Ruminococcus obeum
Bifidobacterium bifidum


Donor
Relative abundance
0
20
40
60
80
100
1
2
6
7
8
10
13
15
18
Species
Bifidobacterium adolescentis
Eubacterium rectale
Ruminococcus bromii
Bacteroides unclassified
Ruminococcus torques
Faecalibacterium prausnitzii
Eubacterium siraeum
Alistipes putredinis
Bacteroides vulgatus
Coprococcus comes
Dialister invisus
Roseburia intestinalis
Eubacterium eligens
Akkermansia muciniphila
Ruminococcus lactaris
Methanobrevibacter smithii
Ruminococcus obeum
Collinsella aerofaciens
Eubacterium hallii
Bacteroides intestinalis
Bifidobacterium longum
Blautia hydrogenotrophica
Bacteroides stercoris
Dorea longicatena
Bacteroides plebeius
Odoribacter splanchnicus
Faecalibacterium cf
Parabacteroides merdae
Roseburia inulinivorans
Alistipes shahii


Recipient similarity to donor (%)
0
20
40
60
80
100
-40
-20
0
20
40
60
80
Recipient similarity to self, pre-FMT (%)
Patient 1
Patient 2
Patient 6
Patient 7
Patient 8
Patient 10
Patient 13
Patient 15
Patient 18

clinical course

- Pat 1:
  - pre-FMT micorbiom was least similar to donor (13%)
  - PCDAI: 27.5 to 7.5 (best)
- Pat 18:
  - Pre-MFT mibrobiom wasmost similar to donor (69%)
  - PCDAI: 27.5 tp 22.5
- 2 Pat with deterioration: dramatic increase of relative abundance of E.coli during flare.

Discussion

- Published experience of FMT for active CD is limitade (only 2 retrospective case reports)
- FMT was safe in this small cohort of pediatric pat.
- Clinical and labortory improvements were seen in the most of pat.
- Current therapies focus on suppressin the immune system. FMT focuses on possible trivgger of immune dysregulation.
- Goal of FMT in CD is to alter fecal microbiome to less „dysbiotic, less proinflammatory.
- Intresting: bloom of E.coli during flare

Limitations

- Study design (open-labeled, single-center)
- Small population
- Strong personal belief of pat and parents that FMT would improve symptoms
- Relative effect of pretreatment of patients with rifaximin