

Fecal Microbiota Transplantation for Severe sepsis and Diarrhea : a Case Report

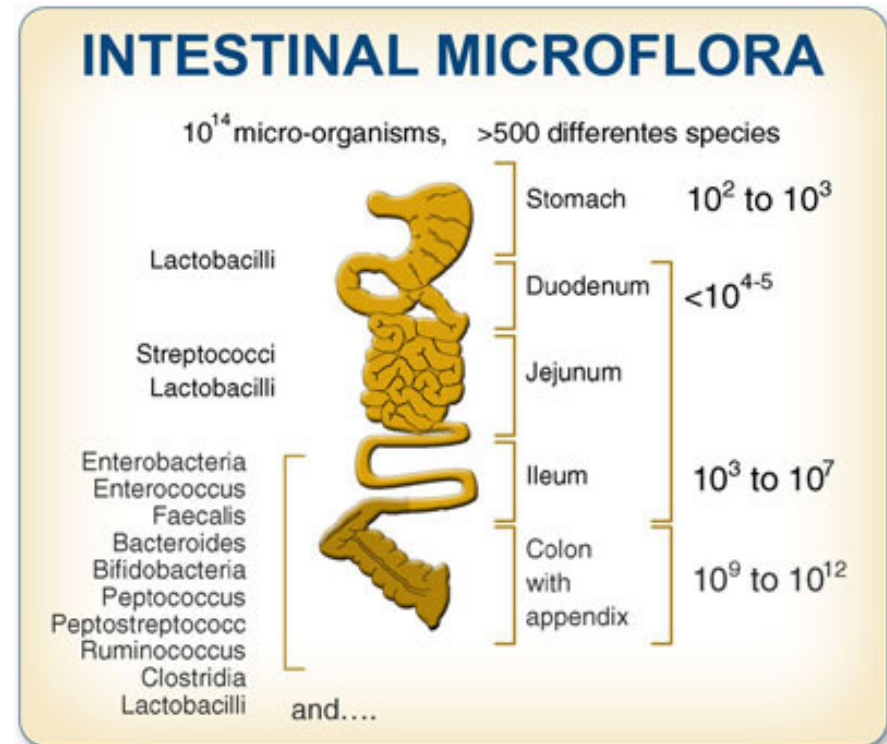
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Gut Microbiota

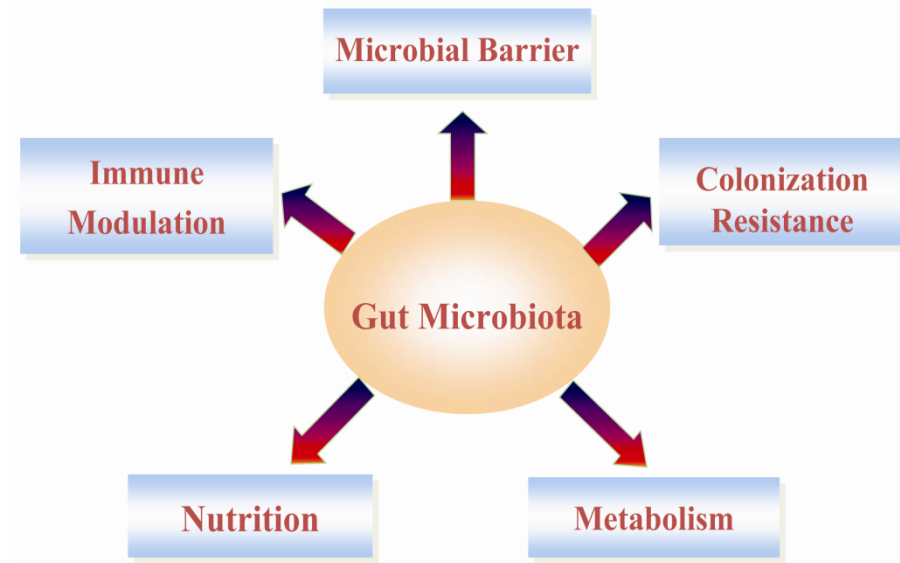
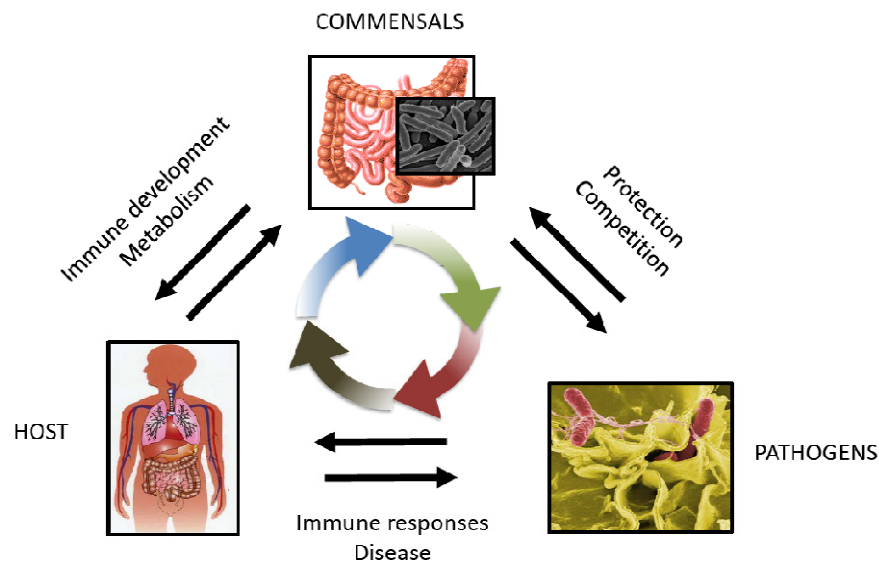
- 100 trillion cells
- 10-fold of the human cell number
- > 200 genera, >500 microbial species
- gastrointestinal tract harbors >80% of total microbes in human body
- is a major component of intestinal barrier



Vital Roles of Gut Microbiota

Gut microbiota

- is recently considered as an important “organ”
- carries out vital processes for human physiology and nutrition
- the microbiota dysbiosis is closely involved in infection, colitis, and metabolic disorders

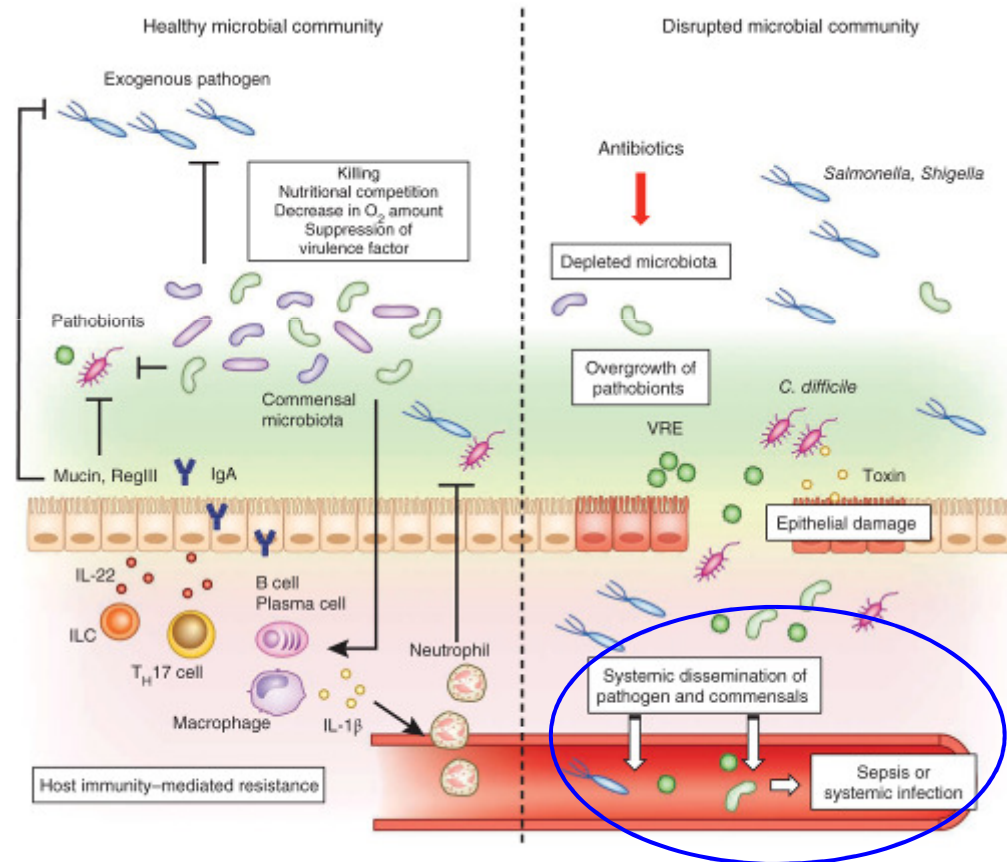


Sepsis and Intestinal Dysbiosis

As shown in the right image,

- in the healthy gut, commensal microbiota suppresses the proliferation and colonization of enteric pathogens.
- conversely, the disruption of gut microbial community could allow enteric bacteria to translocate the circulation, leading to systemic infection and septic shock.
- The dysbiosis of gut microbiota are often seen in sepsis patients.

Therefore, **dysbiosis of gut microbiota is probably relevant for the etiology of sepsis.**



Cited from: Nature Immuno. 2013; 14: 685-690.

Therapeutic Value of Microbiota-targeted Modulation

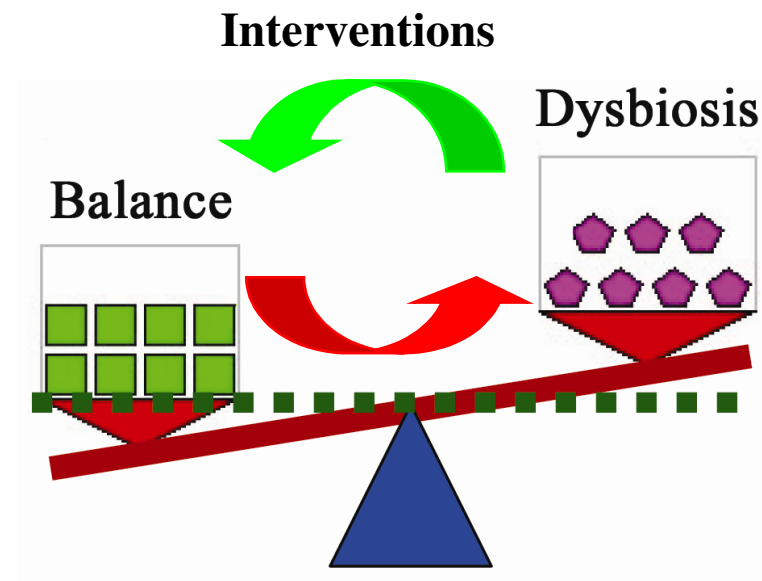
Recent studies have showed:

- modulation of gut microbiota can promote the eradication of enteric pathogens, such as *Clostridium difficile*, EPEC and EHEC
- the gut microbiota can enhance mucosal immunity to defend against enteric infection
- providing an interesting possibility

of harnessing the gut microbiota

to clearing bacterial pathogens

and to restore host immune balance in sepsis

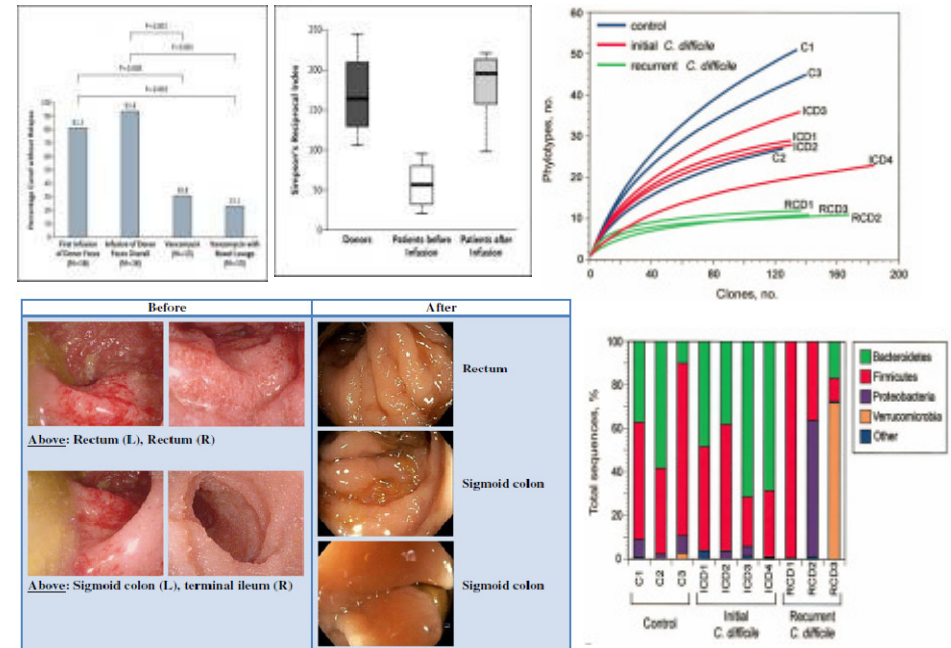


Fecal Microbiota Transplantation (FMT)

- also named as fecal transplant,
fecal bacteriotherapy
- used primarily to treat *Clostridium Difficile*-associated infection (CDI) and IBD
- its cure rate is up to 90% in CDI
- the mechanism underlying the procedure is to correct the intestinal dysbiosis by introducing donor-fecal microbiota
- indicating it's potential in treatment of other microbiota-associated diseases, such as sepsis.



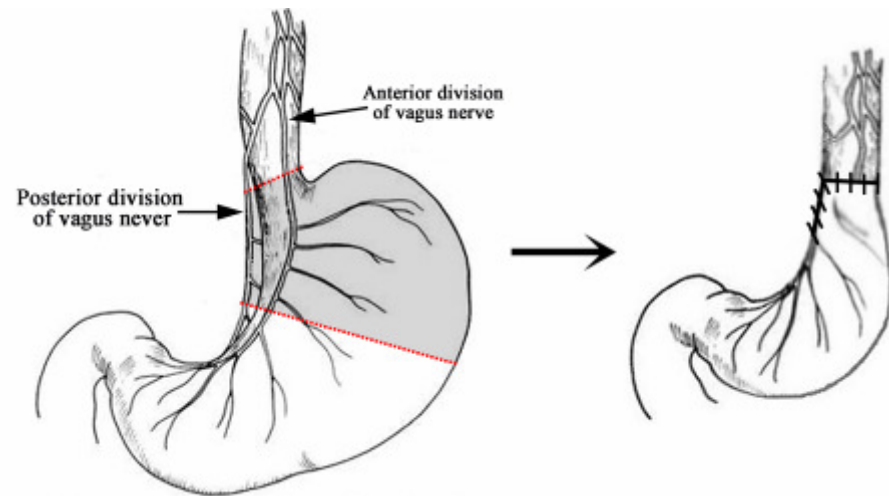
Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*



Case Presentation

The patient:

- a 44-year old woman
- hospitalized for gastric aches
- was then diagnosed with gastric neuroendocrine tumor
- underwent a proximal gastrectomy and bilateral truncal vagotomy at April, 2013
- The operation was successful, and no surgical complication



Interventions

The treatment mainly included:

- **supportive strategies**

trachea intubated

vasopressor drugs

corticosteroids

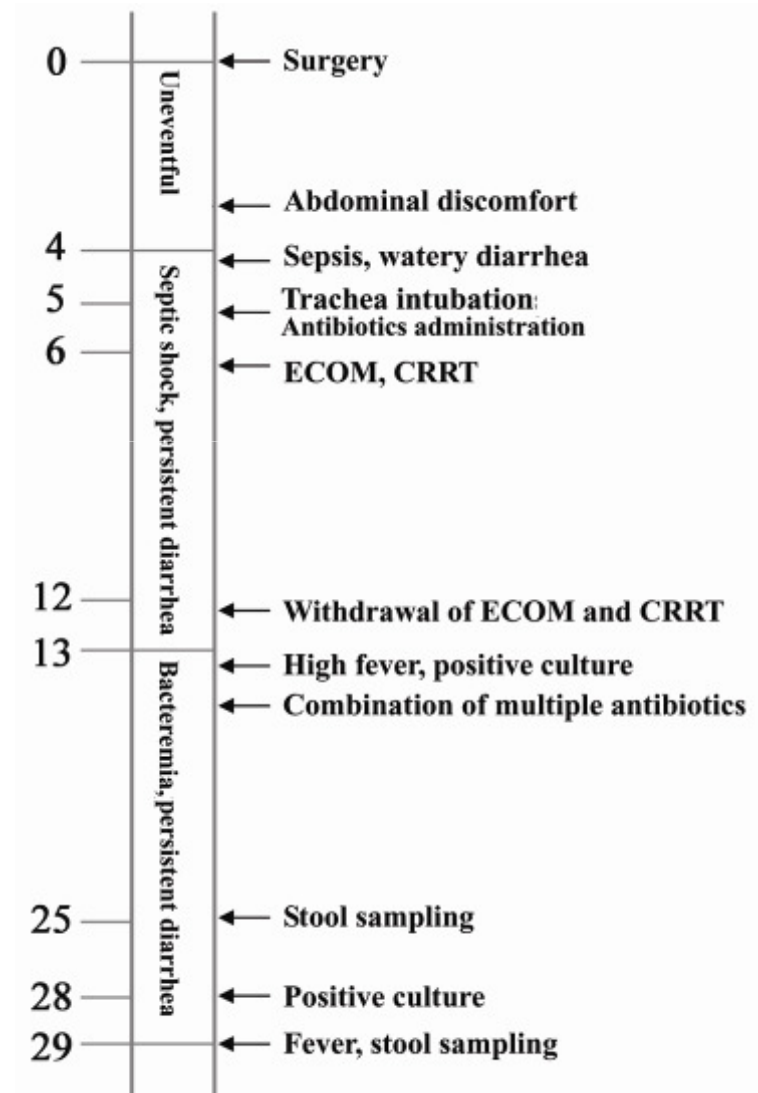
intensive intravenous fluids

ECMO and CRRT (6 days)

- **antibiotic administration**

multiple antibiotics were intravenously given

- **probiotic supplement**



Outcomes

After treated for about 1 month,

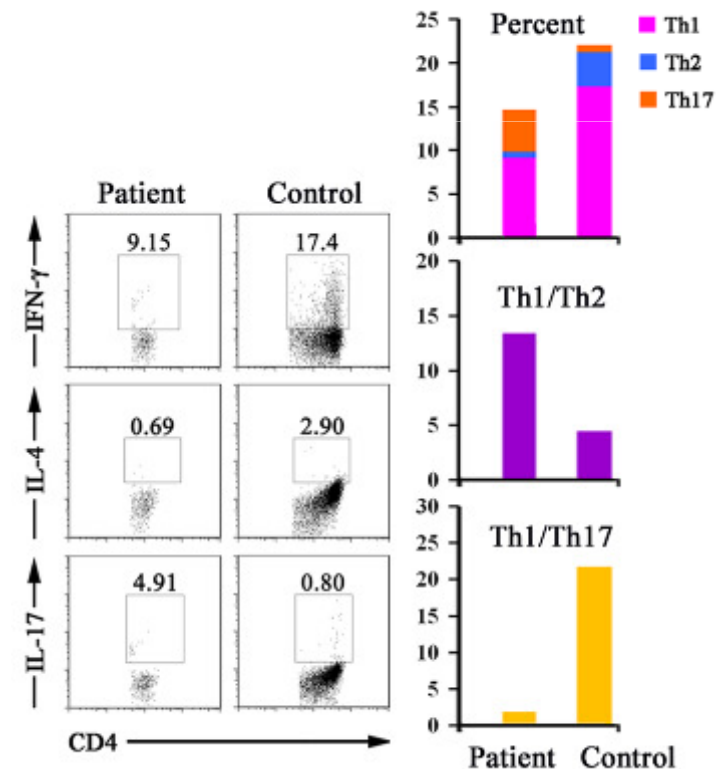
- the patient's vital symptoms became stabilized

Unfortunately,

- the fevers were remained (38.3°C)
- watery diarrhea was persistent and didn't improve (>2000mT/d)

In addition,

- blood cultures were continuously positive
- elevated inflammatory mediators, including **TNF- α , IL-1 β , IL-6, IL-10, IL-18, IFN- γ , HMGB-1**
- dysregulation of innate immune cells, especially imbalance of Th cells (Th1/2/17)
- It is required to **search for novel therapeutic strategies** to restore immune balance and clear the inflammatory response.



Assessment of Gut Microbiota

Considering the possibility of intestinal dysbiosis, we evaluated the fecal microbiota in the patient.

We showed that the patient's microbiota was extensively perturbed, characterized by

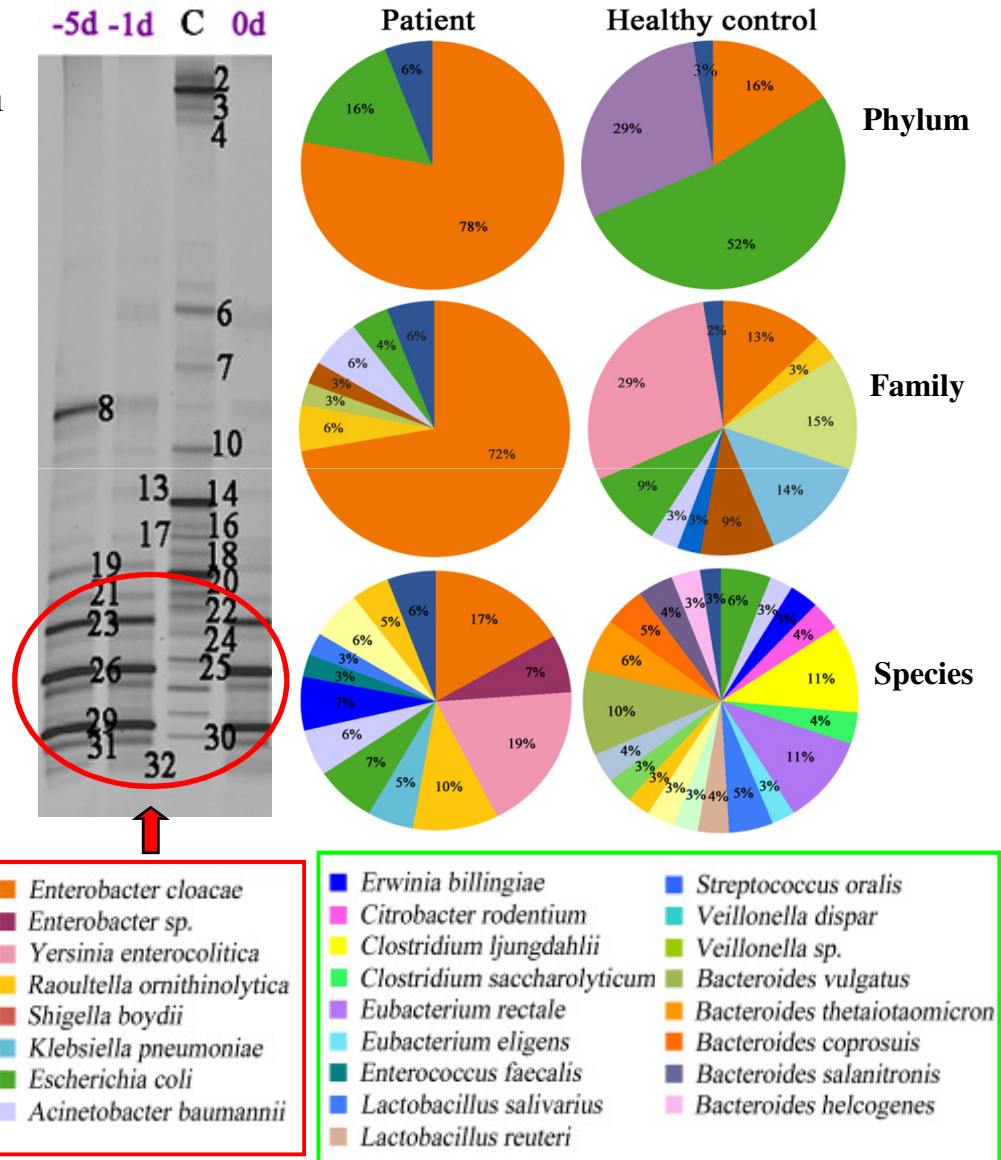
- very low similarity (<10%) comparing to the healthy control
- biodiversity also decreased
- significant depletion in the commensal organisms of Firmicutes and Bacteroidetes
- overgrowth of the pathobionts in

Proteobacteria, especially

Enterobacter cloacae,

Yersinia enterocolitica,

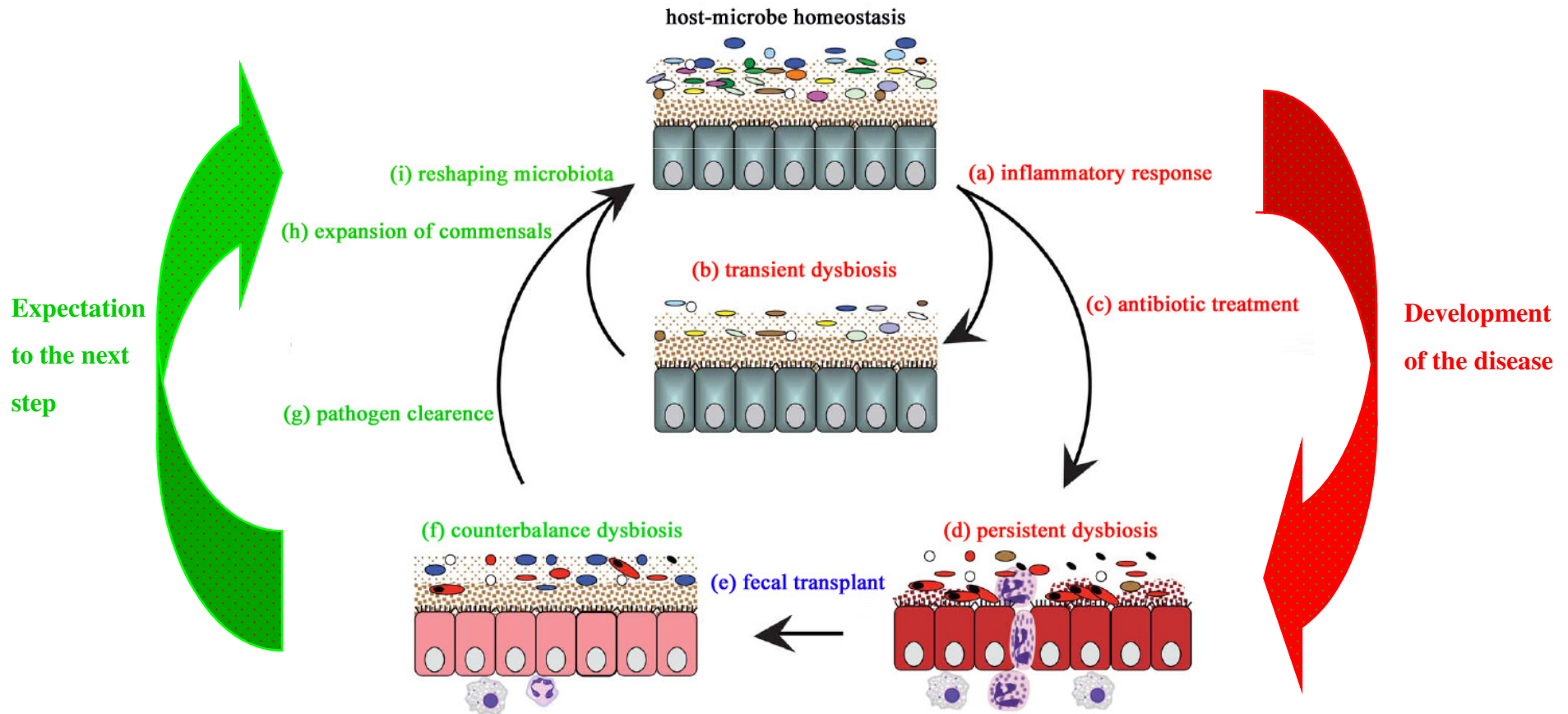
Raoultella ornithinolytica



Our Hypothesis

Based on the data above, we speculated that

- correction of the microbiota dysbiosis is probably a vital step for the treatment of the patient
- fecal transplantation may be an ideal therapeutic option especially for the extensive disturbance



Infusion of Donor-feces

Donor:

- the patient's brother
- screened to exclude bloodborne communicable diseases
- validated negative for common stool pathogens

Transfer of fecal suspension:

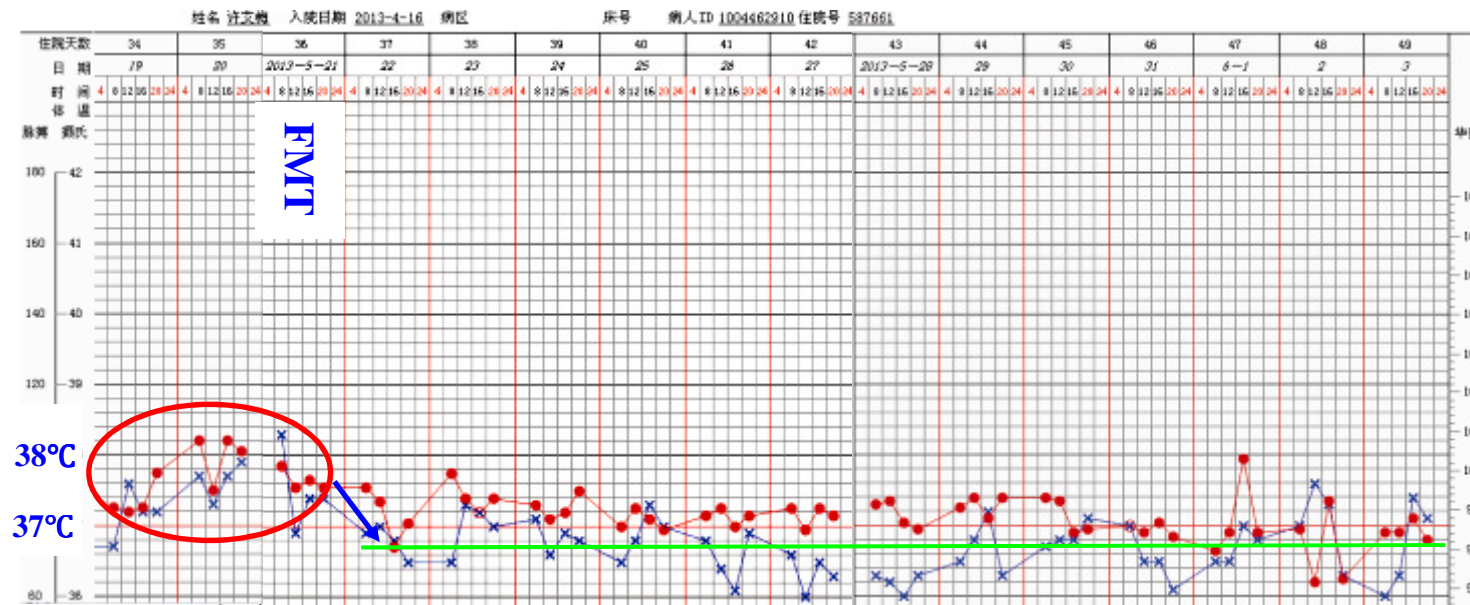
- 70 grams of donor feces freshly collected was used to make a slurry
- the slurry was then filtered to remove particulate matter
- 120 mL of the filtrates were infused via the nasogastric tube



Clinical Improvement

After infusion of donor-feces,

- the fevers went down in the next day
- there was no recurrence in septic symptoms in the following days
- more importantly, cultures of the blood became sterile.



The Second FMT

Within the 4 days,

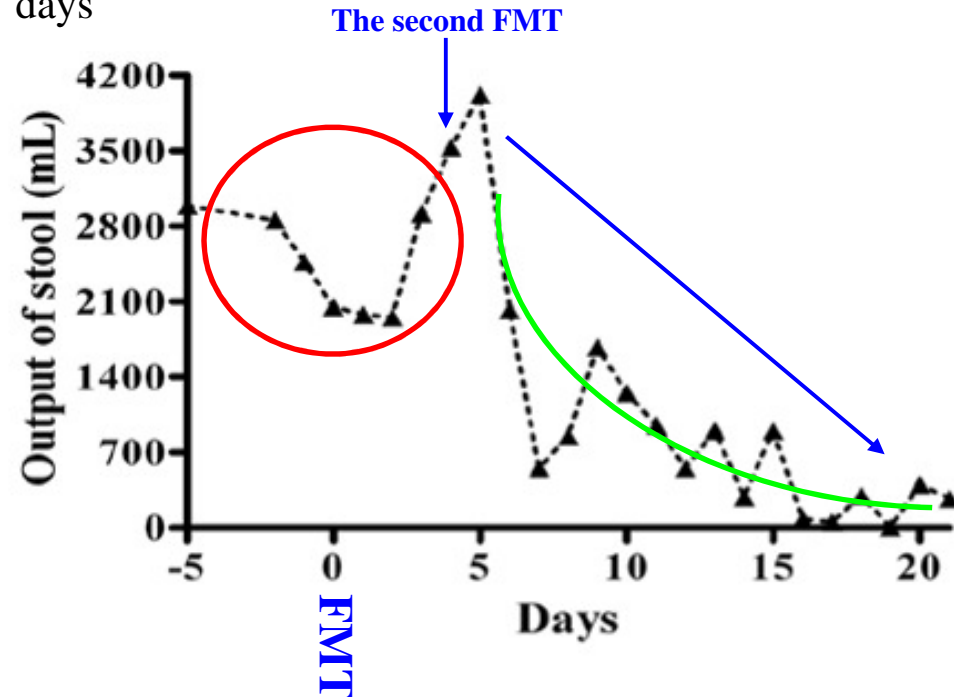
- no significant improvement in watery diarrhea was seen

Thereby,

we conducted the second FMT on the 4th day

Subsequently,

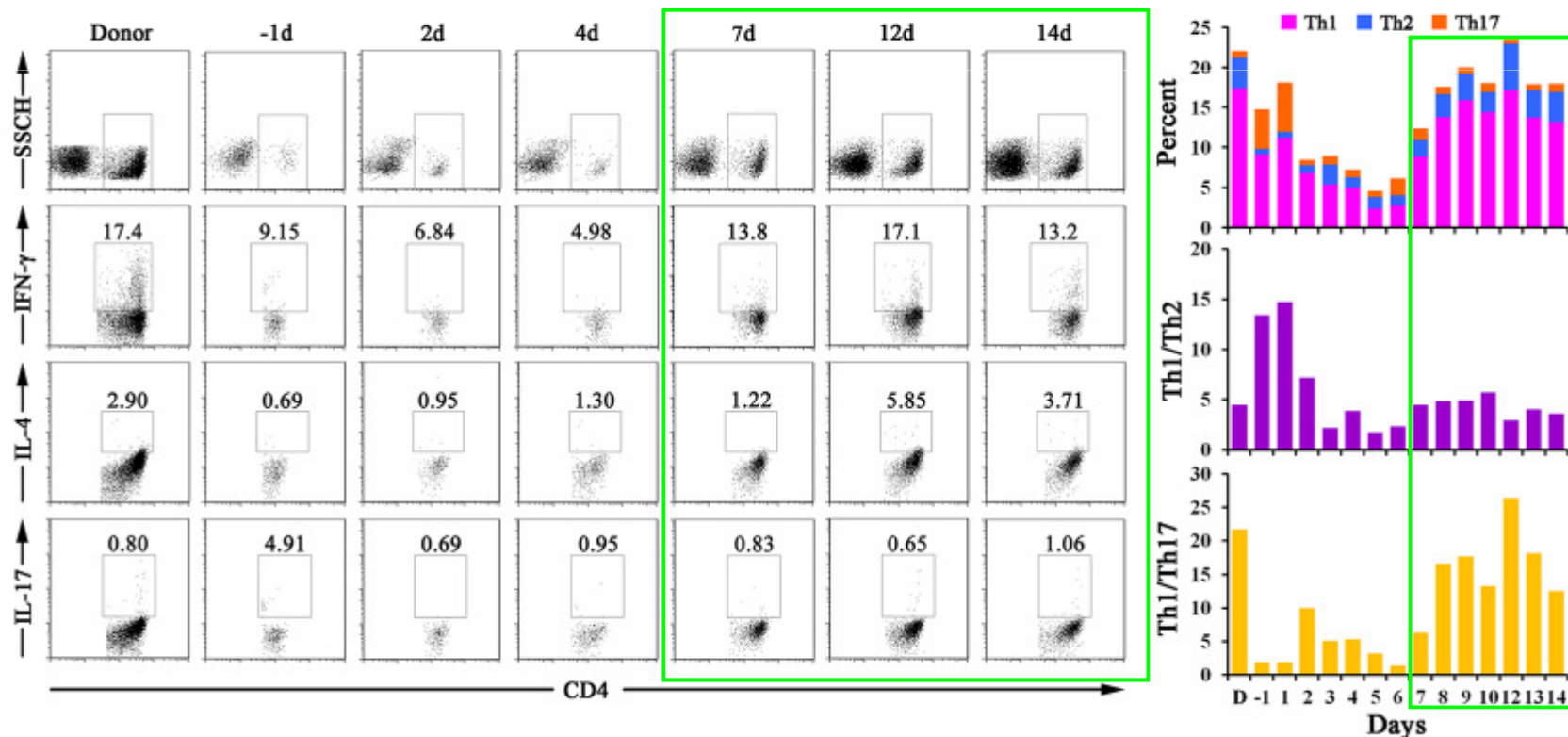
- the frequency and output of stools began to reduce
- diarrhea was completely controlled at 17 days



Response of Th cells to FMT

Following the FMT,

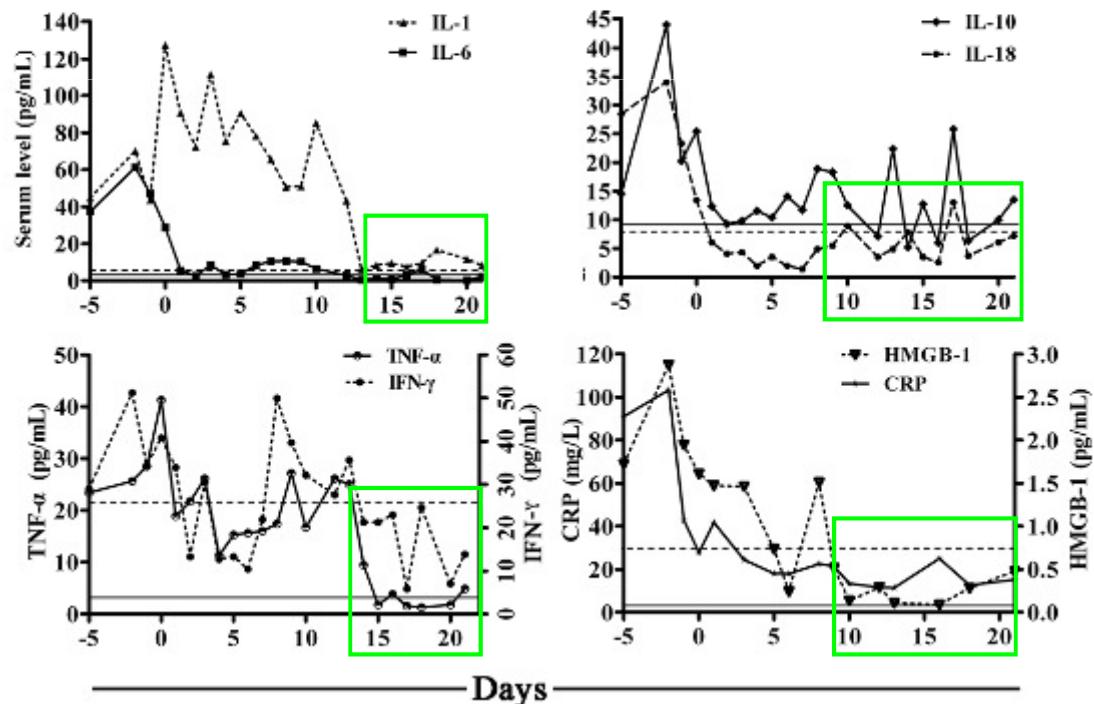
- Th-cell population (Th 1, Th2, Th17) shifted towards normal composition
- the balance of the innate immune cells restored 7 days later
- indicated that FMT may feedback to influence host immunity



Alleviation of Systemic Inflammatory Response

Interestingly,

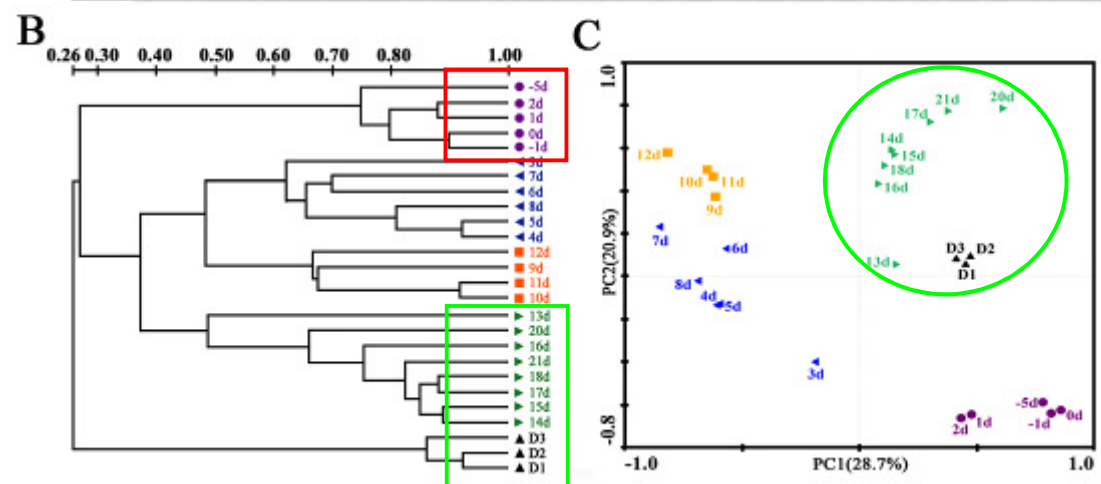
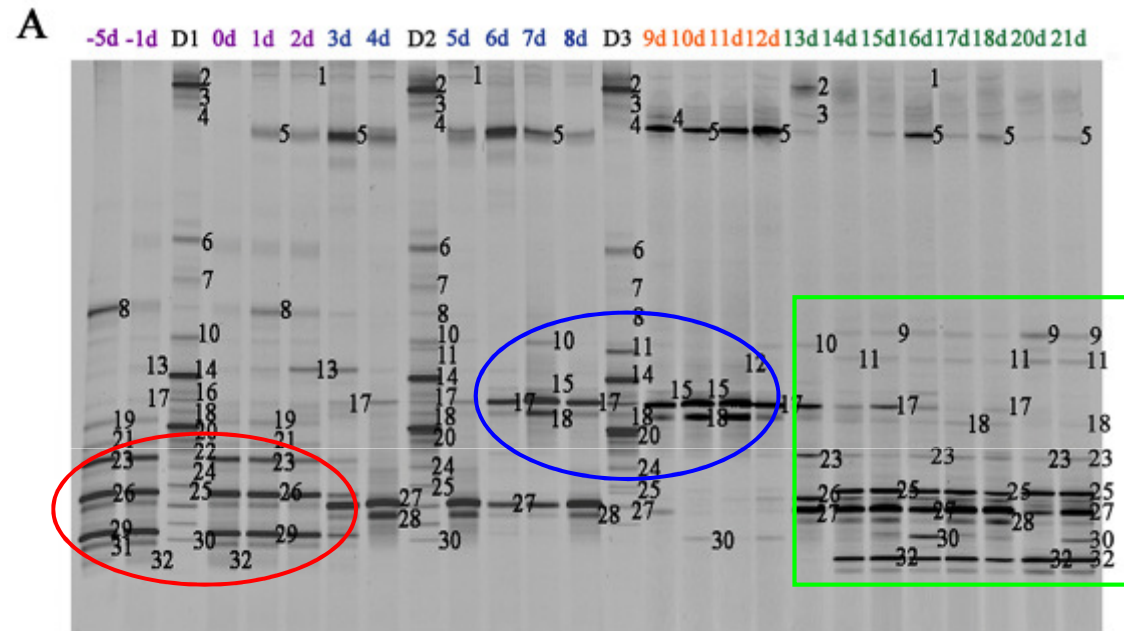
- Serum levels of multiple cytokines, including IL-1, IL-6, TNF- α and IFN- γ , decreased to be normalized after 12 days.
- the excessive inflammatory response was well controlled



Modification of Gut Microbiota following FMT

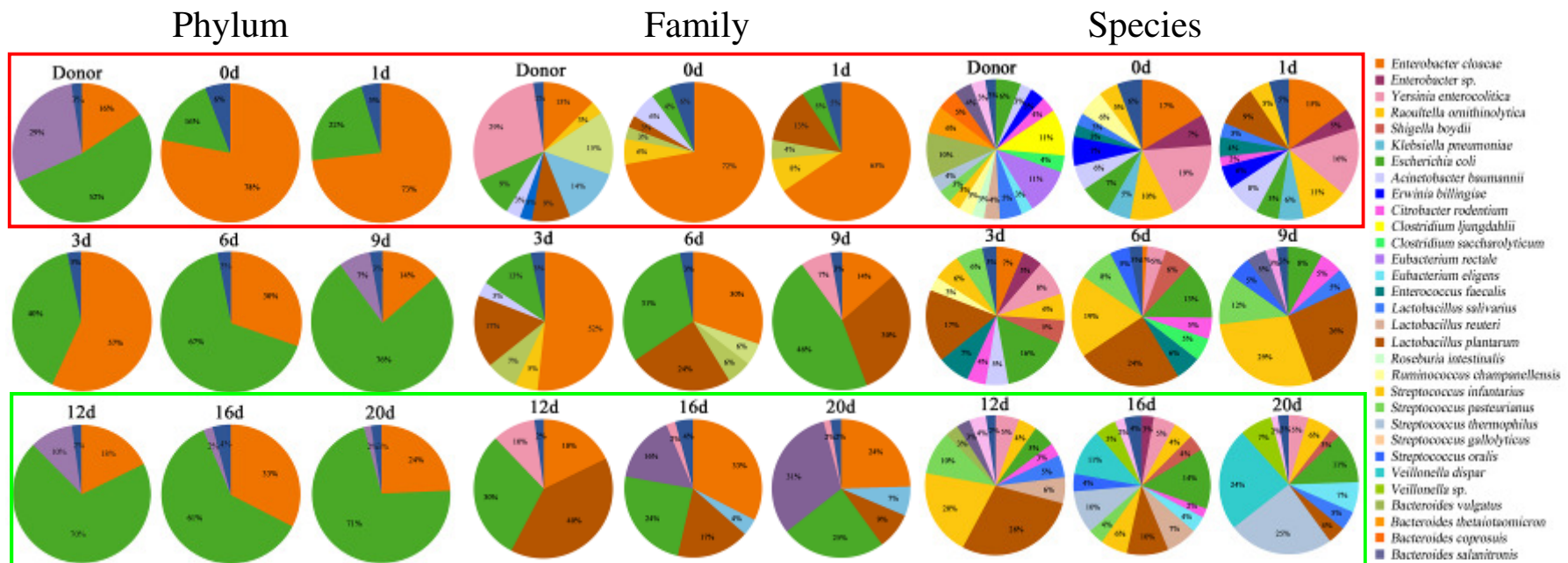
In attempt to explore the mechanism underlying the clinical improvements, we further evaluated the shifts of the fecal microbiota composition after the treatment.

- The structure of intestinal microbiota significantly changed, especially 6 days later
- The community structures trended to be stable after 14 days
- The structure similarities increased to 40-50% compared to the donor
- Principal component analysis also supported the results

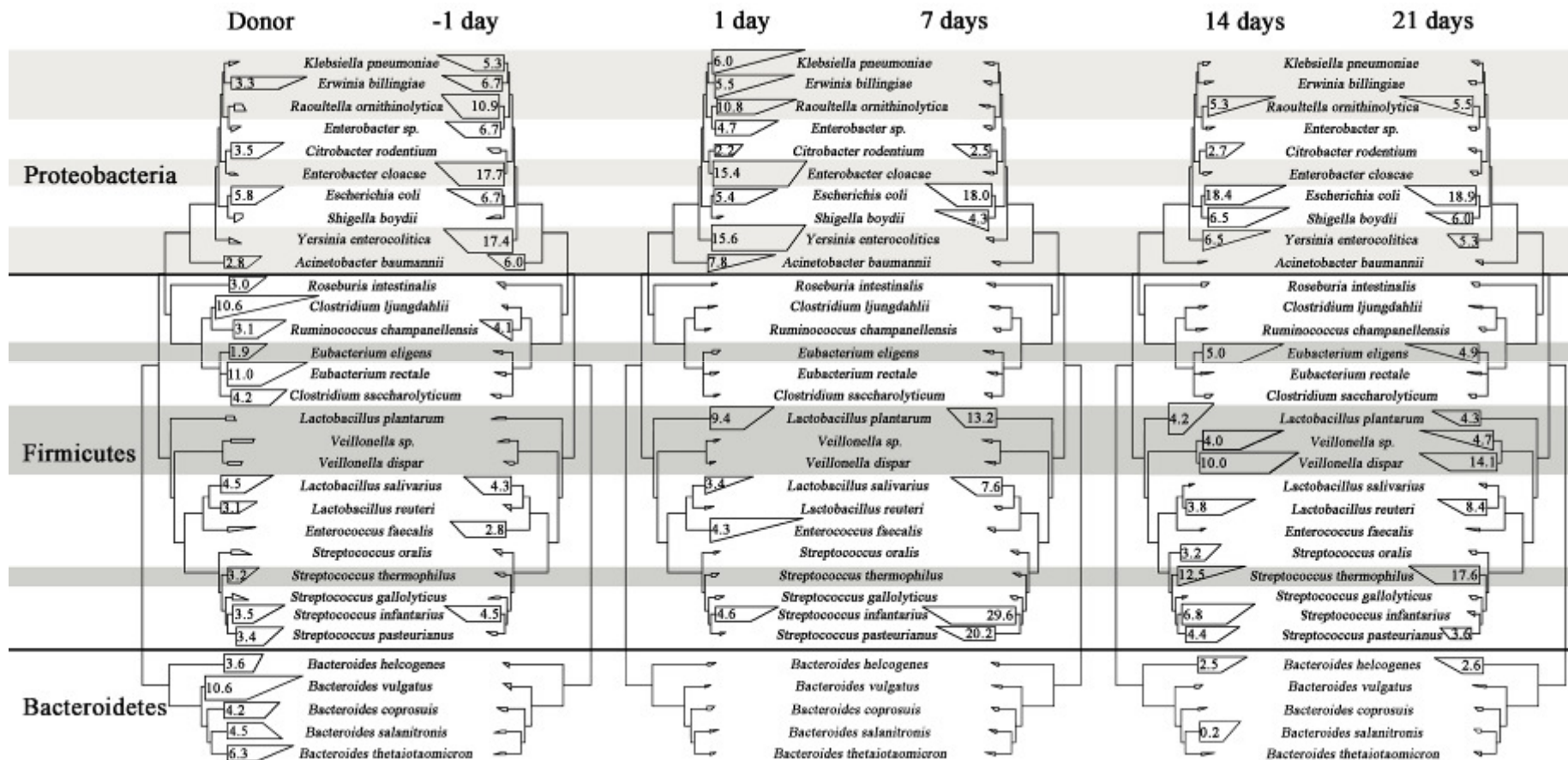


Compositional Changes of Gut microbiota

- The microbiota composition shifted towards normalized following FMT
- The most significant shifts in the microbiota were a profound expansion in Firmicutes and a striking reduction in Proteobacteria
- the commensal organisms, including *Lactobacillus plantarum*, *Eubacterium eligens* and *Veillonella dispar*, largely colonized and dominated in the microbiotas.
- the pathobionts of the family Enterobacteriaceae, were significantly depleted.
- FMT may induce a significant modification in gut microbiota, reshaping a microecologically defense barrier in the patient.



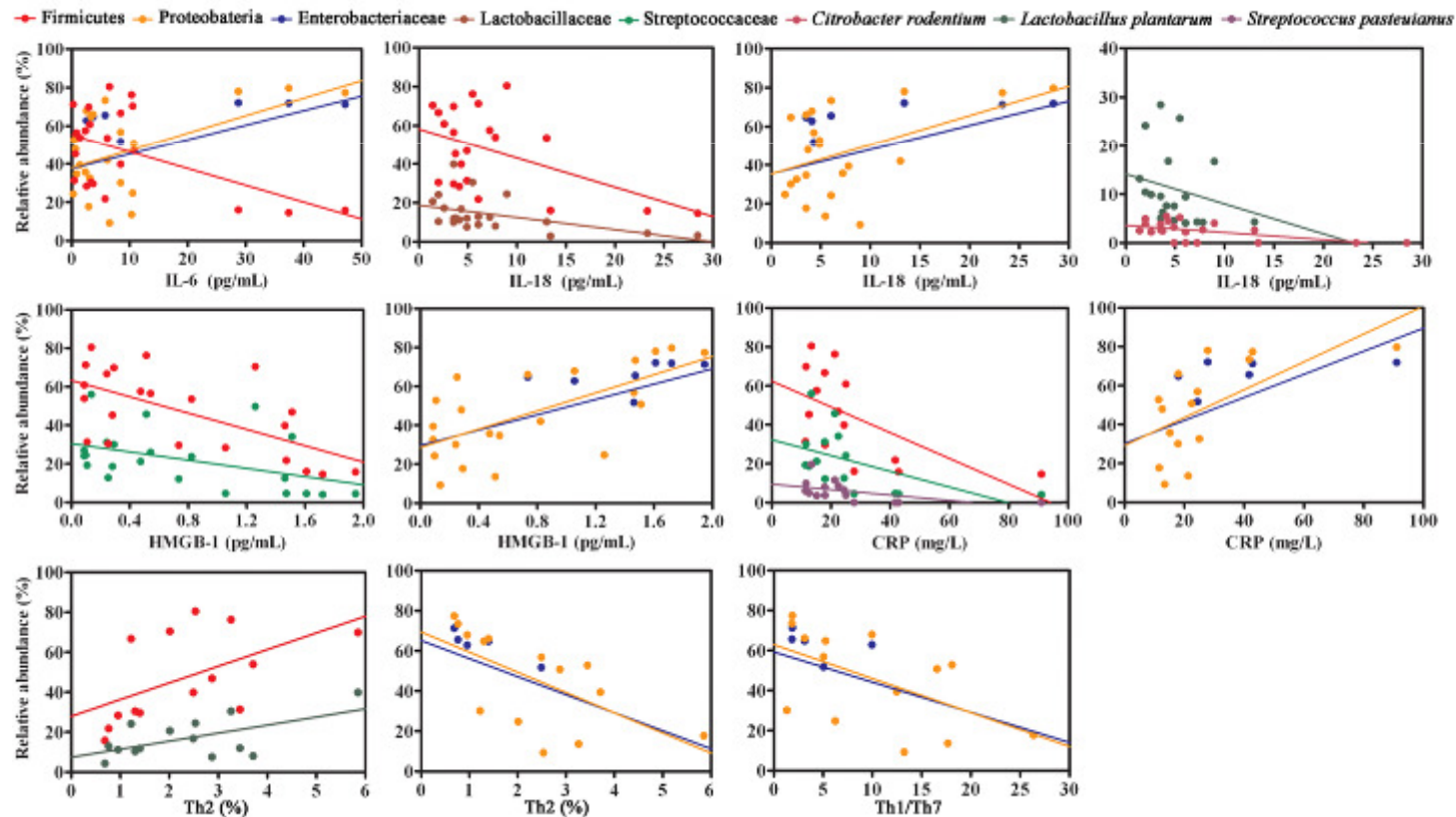
Phylogenetic Analysis



It provided further evidence indicating the shifts in microbial composition.

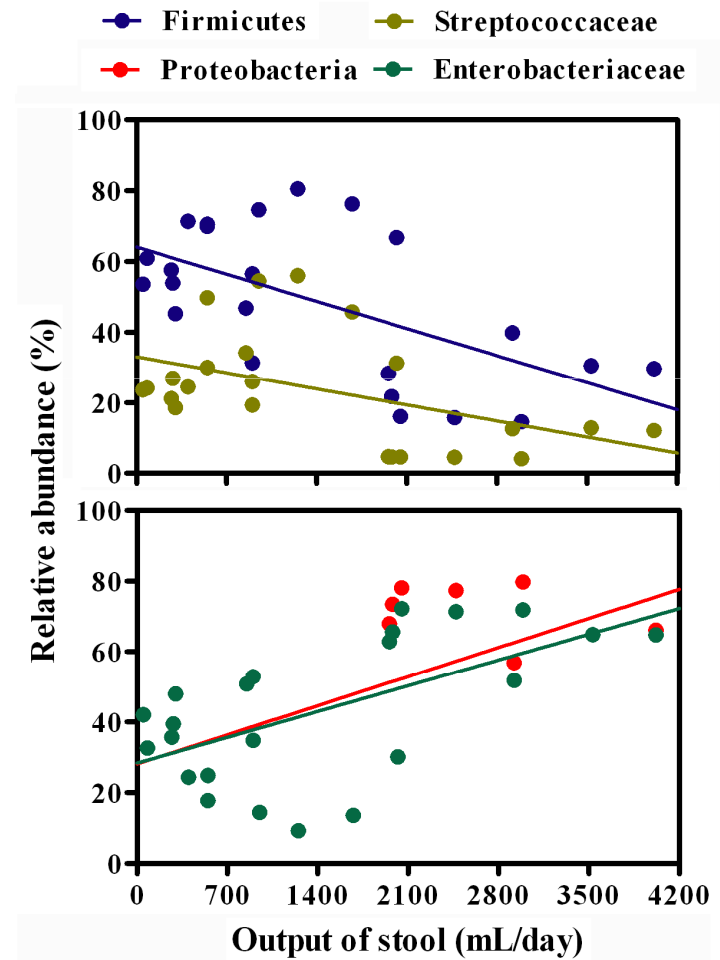
Associations between Clinical Benefits and Gut Microbiota

- The Firmicutes and the families Streptococcaceae, Lactobacillaceae were negatively correlated with inflammatory markers, such as IL-6, IL-18, HMGB-1, or CRP, or Th 2 cell.
- The Proteobacteria and Enterobacteriaceae were positively correlated with them.
- indicated that the clinical improvements may be attributed to the modulation of the microbiotas.



Alterations of Gut Microbiota and Diarrhea

- Correlative analyses also suggested a close link between gut microbiota changes and stool output.
- The taxon abundance of Firmicutes and Streptococcaceae was negatively associated with the output of stools.
- The Proteobacteria and Enterobacteriaceae positively correlated with it.
- As a result, effective control of watery diarrhea might benefit from reconstruction of the gut microbiota by FMT.



Conclusions

On the basis of the data, we demonstrate:

- FMT is probably effective in treating sepsis and severe diarrhea.
- The clinical benefits from the unconventional approach is, at least in part, due to FMT being able to facilitate the reestablishment of normal microbiota.
- FMT might also elicit immunological mechanism to restore intestinal homeostasis and protect the patient.
- Lastly, but the most important, is that, FMT may provide an ideal therapeutic alternative for sepsis, which might be especially suitable for the patients without improvement from conventional strategies.

Questions?

Thanks a lot