

IL TRAPIANTO DI MICROBIOTA FECALE COME STRATEGIA TERAPEUTICA PER LA GVHD INTESTINALE REFRATTARIA AL TRATTAMENTO STEROIDEO: STUDIO RETROSPETTIVO DI SICUREZZA, TOLLERABILITÀ ED EFFICACIA

R. Masetti, E. Muratore, F. Venturelli, G. Marasco, C. Cremon, D. Leardini, F. Baccelli, T. Belotti, A. Marangoni, M. Djusse, T. Lazzarotto, A. Prete, M. Cefalo, G. Angelino, F. Quagliarella, F. Galaverna, M. Gabelli, E. Savarino, A. Biffi, M. Zecca, M. Faraci, P. Brigidi, G. Barbara, L. Putignani, F. Locatelli, P. Merli

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Disclosures of Pietro Merli

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Trajectories of microbiota diversity during HSCT

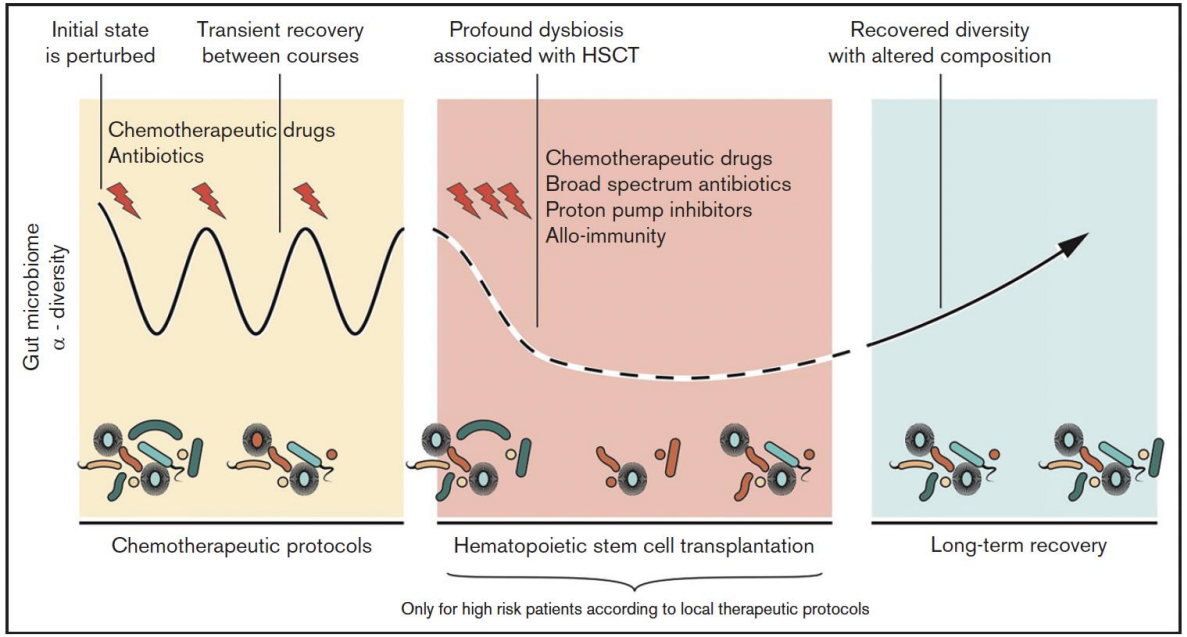


Figure 2. The trajectory of the GM during the therapeutic course of AL. The initial microbial state is perturbed by chemotherapeutic cycles with partial recovery between them. HSCT exerts a strong dysbiotic effect on the GM. Reconstitution after HSCT resembles the pre-HSCT state, but dysbiotic features often persist.

The initial microbial state is perturbed by chemotherapeutic cycles with partial recovery between them. HSCT exerts a strong dysbiotic effect on the GM (predominance of **Gram- bacteria** (E. coli, Klebsiella, Enterobacter spec.) and **Gram+ Lactobacillales** (Lactobacillus, Enterococcus e Streptococcus spec.). Reconstitution after HSCT resembles the pre-HSCT state (after 2-3 months), but dysbiotic features often persist.

Masetti R et al., 2021, *Blood Adv*

Fecal

- Medical
  transferri
  donor to
- Currently
  of *Clostr*
- Possible
  - Acu
  - Dec

haematologica
Open access journal of the Ferrata-Storti Foundation, a non-profit organization

Vol. 110 No. 12 (2025): December, 2025 > Fecal microbiota transplantation for decolonization from...

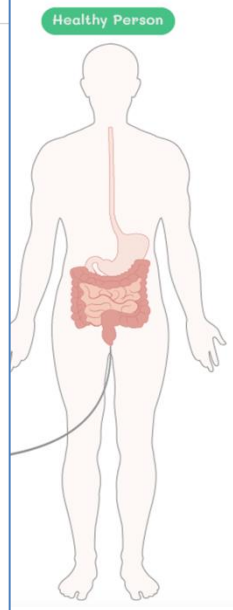
LETTERS TO THE EDITOR

Fecal microbiota transplantation for decolonization from multidrug-resistant bacteria in pediatric allogeneic hematopoietic stem cell transplantation recipients: a retrospective real-world data study

Footnotes
References

Riccardo Masetti , Giovanni Barbara , Edoardo Muratore , Giovanni Marasco , Cesare Cremon , Antonella Marangoni , Patrizia Brigidi , Lorenza Putignani , Giulia Angelino , Francesco Quagliarella , Federica Galaverna , Davide Leardini , Tiziana Lazzarotto , Maria Gabelli , Edoardo Savarino , Marco Zecca , Maura Faraci , Arcangelo Prete , Alessandra Biffi , Franco Locatelli , Pietro Merli

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sl Res. 2020

Fecal Microbiota Transplantation for GVHD

Regulation of intestinal
by microbiota following
bone marrow transplant

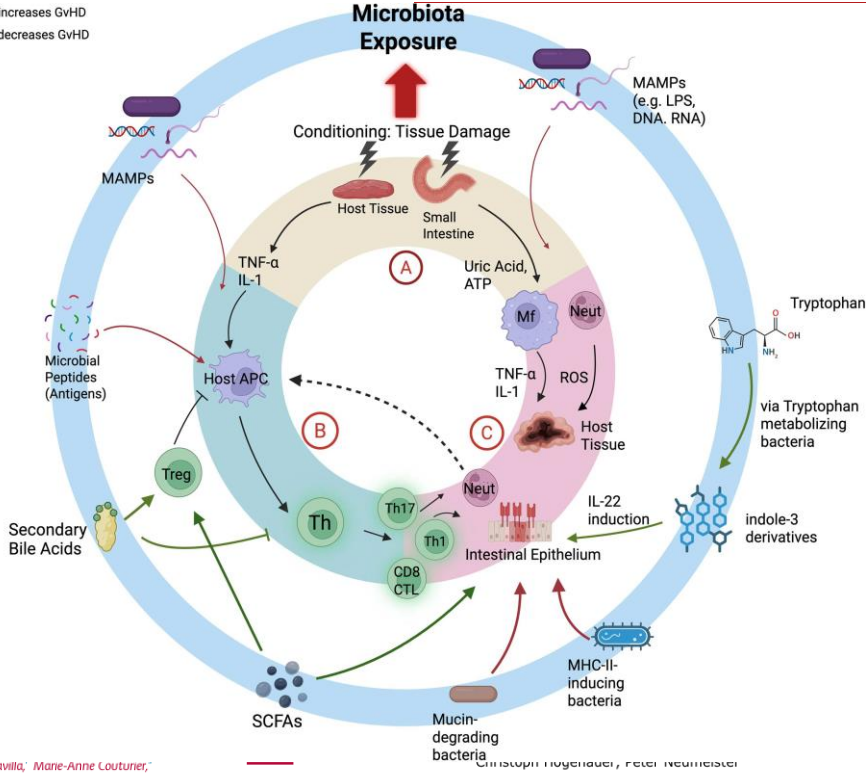
Robert R. Jenq,[1,6] Carles Ubeda,[3,4] Yin
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Jenna D. Goldberg,[1,6] Kazutoshi Aoyam
Eric G. Pamer,[2,3,4,6,7] and Marcel R.M.

Journal of Experimental Medicine (2012)

EClinicalMedicine 2023

Pooled allogeneic faecal microl
resistant gastrointestinal acute
single-arm, multicentre phase

Florent Malard,[a,] Michael Laschi,[b] Anne Huynh,[c] Thomas Cluzeau,[b] San
Amandine Charbonnier,[g] Marta Panz-Klapuch,[h] Deborah Desmier,[i] Jean-I
Karin Bilger,[h] Maria J. G. T. Vehreschild,[e] Patrice Chevallier,[f] Hélène Labussière-Wallet,[n] Clemence Medaville,[c] Marie-Anne Couturier,[c]
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Cyrielle Gasc,[z] Emilie Plantamura,[z] and Mohamad Mohty[a]



blood

patients with steroid-resistant acute

ıo Najima,[1] Go Kuwata,[6] Satoshi Sasajima,[7] Iyo Mimura,[8]
Masahira Hattori,[4,9] Yutaro Hino,[1] Shuntaro Ikegawa,[1]
ımi,[6] Kenya Honda,[5,7,11] and Kazuteru Ohashi[1]

(*Blood.* 2016;128(16):2083-2088)

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lantations Attenuate Diarrhea And
Fecal Microbiota In Acute, Refractory
t-Disease

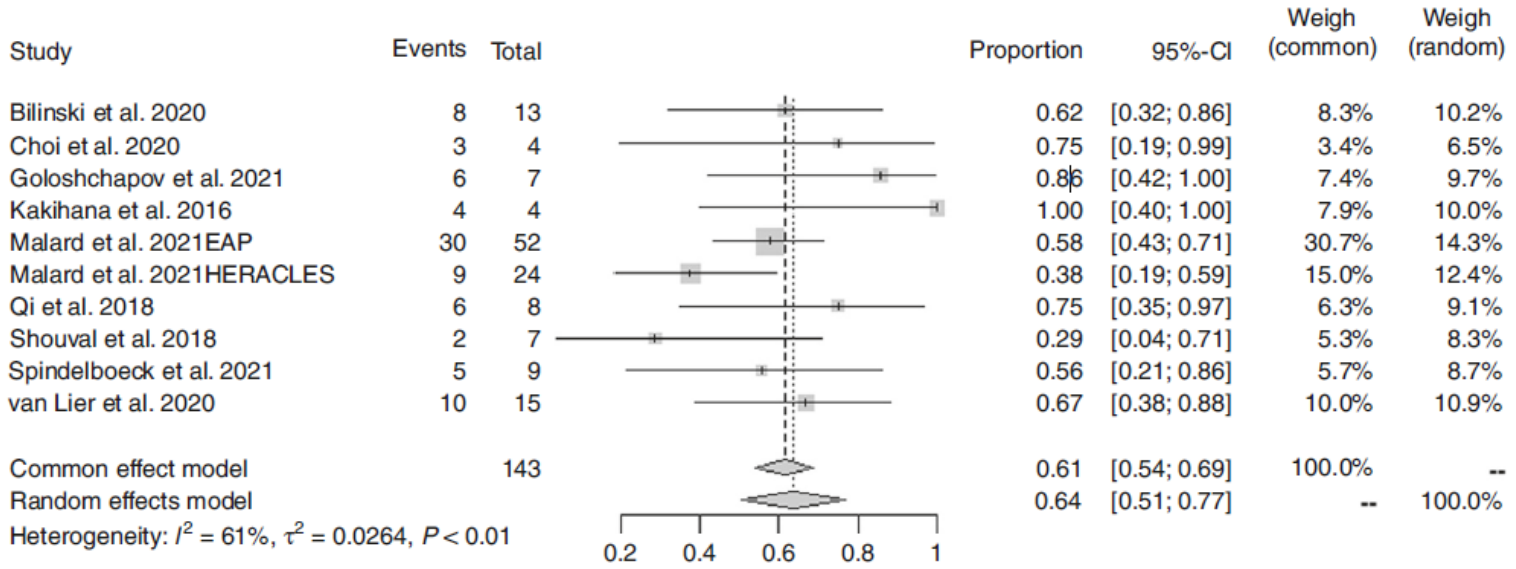
hofer, Ariane Aigelsreiter, Wilma Zinke-Cerwenka,
Gregor Gorkiewicz, Heinz Sill, Hildegard Greinix,

Haematologica May 2017 102: e210-e213; **Doi:**10.3324/haematol.2016.154351

Fecal Microbiota Transplantation for SR-aGVHD

Meta-analysis of 242 patients with steroid-resistant or steroid-dependent GVHD treated with FMT.

The estimate of clinical remission odds ratio was 5.51 (95% CI 1.49–20.35) in cohort studies, and the pooled clinical remission rate is 64% (51–77%) in prospective single arm studies and 81% (62–95%) in retrospective studies, case series and case reports.



Qiao et al., Bone Marrow Transplant 2023

FMT for SR-GvHD: the retrospective Bologna-Roma-Padova experience

Retrospective evaluation of the safety, tolerability, and efficacy of FMT used under compassionate-use conditions in patients with SR intestinal GvHD, treated in Bologna, Padua, and Rome between 2018 and 2025, with concomitant analysis of the gut microbiome in selected cases.



Masetti R and Merli P 2025 unpublished data

	Patients n=10/ infusions n=23	% - range
Center Rome/Bologna/Padova	3/6/1	30/60/10
Age, median	4.0	(0.8-18.6)
Transplant indication		
AML/ALL	4	40
ALL	2	20
JMML	1	10
Thalassemia	1	10
LAD	1	10
SCID	1	10
Donor		
MUD	5	50
Haplo	3	30
UCBT	2	20
Conditioning		
Myeoloablative	9	90
TBI-based	2	20
RIC	1	10

	Patients n=10/ infusions n=23	% - range
Time from HCT to GvHD, median days	45	18-97
MAX grade aGvHD (MAGIC grading)		
III	3	30
IV	7	70
N.° previous lines GvHD therapy, median	4.5	3-7
Steroids	10	100
Ruxolitinib	7	70
TNFa-inhibitor	3	30
ECP	5	50
MMF	3	30
MSC	1	10
Vedolizumab	1	10
Ustekinumab	3	30
Begelomab	2	20
Abatacept	1	10
Ibrutinib	1	10
Time from HCT to FMT, median days	271	64-527

All had gut involvement

	Patients n=10/ infusions n=23	% - range
Time from HCT to FMT, median days	271	64-527
Number of administrations, median	2	1-4
FMT donor		
Unrelated	9	90
Related	1	10
Preparation		
Frozen	9	90
Fresh	1	10
Route of administration		
Upper GI	10	100
NJT	5	50
PEJ	3	30
Endoscopy	2	20
Antibiotic preparation (pre)		
No	2	20
Yes	8	80
Volume administered, ml, median	150	150-250

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Drug-Resistant *E. coli* Bacteremia Transmitted by Fecal Microbiota Transplant

A Antimicrobial Resistance Patterns of ESBL-Producing *E. coli*

	Donor (stool)		Patient 1 (blood)		Patient 2 (blood)	
	Minimal Inhibitory Concentration μg/ml	Interpretive Category	Minimal Inhibitory Concentration μg/ml	Interpretive Category	Minimal Inhibitory Concentration μg/ml	Interpretive Category
Ampicillin	≥32.00	Resistant	≥32.00	Resistant	≥32.00	Resistant
Amoxicillin–clavulanic acid	8.00	Susceptible	16.00	Intermediate	8.00	Susceptible
Ampicillin–sulbactam	16.00	Intermediate	≥32.00	Resistant	16.00	Intermediate
Piperacillin–tazobactam	≤4.00	Susceptible	8.00	Susceptible	≤4.00	Susceptible
Cefazolin	≥64.00	Resistant	≥64.00	Resistant	≥64.00	Resistant
Ceftriaxone	32.00	Resistant	≥64.00	Resistant	≥64.00	Resistant
Cefepime	2.00	Susceptible	2.00	Susceptible	8.00	Susceptible dose dependent
Aztreonam	16.00	Resistant	16.00	Resistant	16.00	Resistant
Ertapenem	≤0.50	Susceptible	≤0.50	Susceptible	≤0.50	Susceptible
Imipenem	≤0.25	Susceptible	≤0.25	Susceptible	≤0.25	Susceptible
Meropenem	≤0.25	Susceptible	≤0.25	Susceptible	≤0.25	Susceptible
Amikacin	≤2.00	Susceptible	8.00	Susceptible	≤2.00	Susceptible
Gentamicin	≥16.00	Resistant	≥16.00	Resistant	≥16.00	Resistant
Ciprofloxacin	≥4.00	Resistant	≥4.00	Resistant	≥4.00	Resistant
Levofloxacin	≥8.00	Resistant	≥8.00	Resistant	≥8.00	Resistant
Tetracycline	≥16.00	Resistant	≥16.00	Resistant	≥16.00	Resistant
Nitrofurantoin	128.00	Resistant	128.00	Resistant	128.00	Resistant
Trimethoprim–sulfamethoxazole	≤20.00	Susceptible	≤20.00	Susceptible	≤20.00	Susceptible

B Sequence Variant Analysis Based on Whole-Genome Sequencing

Sample ID	Donor	Patient 1 — HE Trial	Patient 2 — HCT Trial	Control
Donor	0	1	0	121
Patient 1 — HE trial	1	0	1	124
Patient 2 — HCT trial	0	1	0	123
Control	121	124	123	0

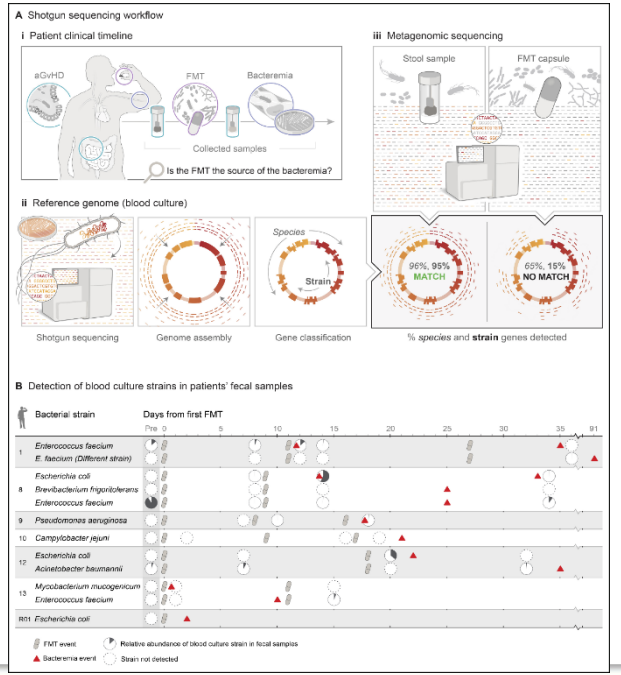
Figure 1. ESBL-Producing *E. coli* Antimicrobial Resistance Patterns and Sequence Variant Analysis Based on Whole-Genome Sequencing.
Panel A shows antimicrobial resistance patterns of extended-spectrum beta-lactamase (ESBL)–producing *Escherichia coli*. The testing method and interpretive categories were based on the recommendations of the Clinical and Laboratory Standards Institute.[17] Panel B shows sequence variant analysis based on whole-genome sequencing. Patient 1 was enrolled in an open-label trial of fecal microbiota transplantation (FMT) oral capsules for the treatment of refractory hepatic encephalopathy (HE) (ClinicalTrials.gov number, NCT03420482). Patient 2 was enrolled in a phase 2 trial to preemptively administer FMT oral capsules before and after allogeneic hematopoietic-cell transplantation (HCT) (NCT03720392). Numbers denote single-nucleotide polymorphism distances between pairs of isolates, as computed by counting the number of variable sites. The yellow-tinted boxes indicate clonal isolates.

STIMULUS REPORT
blood advances
Check for updates

Origins of bloodstream infections following fecal microbiota transplantation: a strain-level analysis

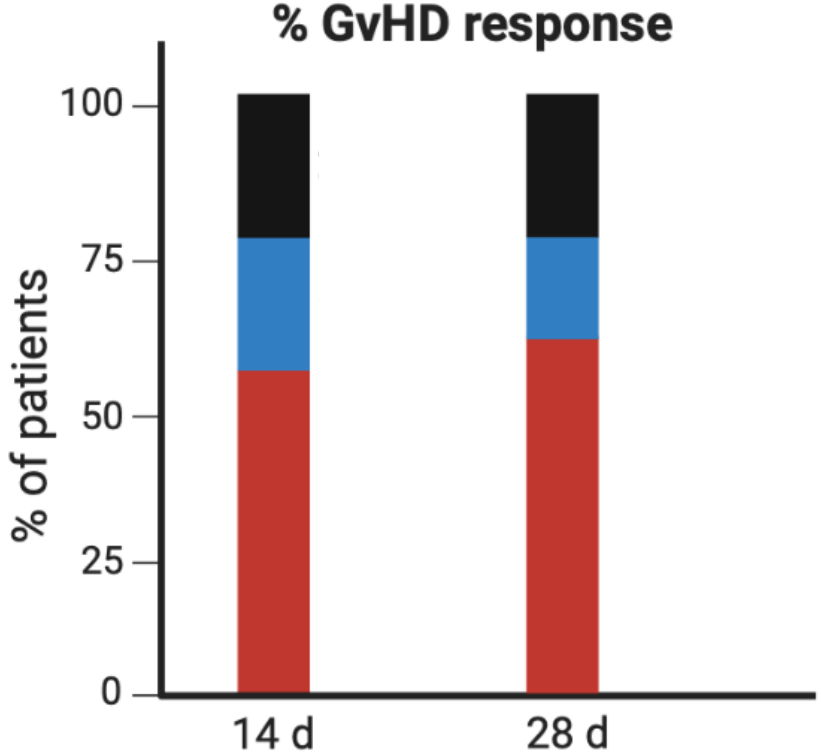
Adi Eshel,[1,*] Itai Sharon,[2,3,*] Arnon Nagler,[4,5,*] David Bomze,[4,5] Ivetta Danylesko,[4,5] Joshua A. Fein,[6] Mika Geva,[4,5] Israel Henig,[7] Avichai Shimoni,[4,5] Tsila Zuckerman,[7,8] Ilan Youngster,[9,10,*] Omry Koren,[1,*] and Roni Shouval[4,5,11,12]

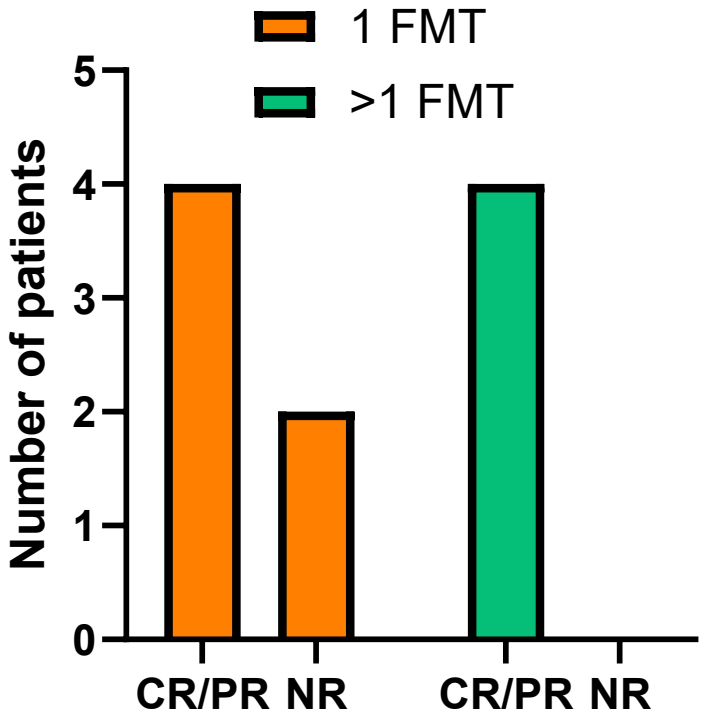
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	Patients n=10/ infusions n=23	% - range
SAE related to FMT, n	0	
AE related to FMT, n	4	40
Grade		
I	2	20
II	2	20
III-IV	0	
Response day +14		
CR	5	50
PR	3	30
NR	2	20
Response day +28		
CR	7	
PR	1	
NR	2	
Steroid tapering	7	70
Relapse	2	20


% GvHD response
% of patients
100
75
50
25
0
14 d
28 d


1 FMT
>1 FMT
Number of patients
5
4
3
2
1
0
CR/PR
NR
CR/PR
NR

FMT for SR-GvHD: single patient analysis

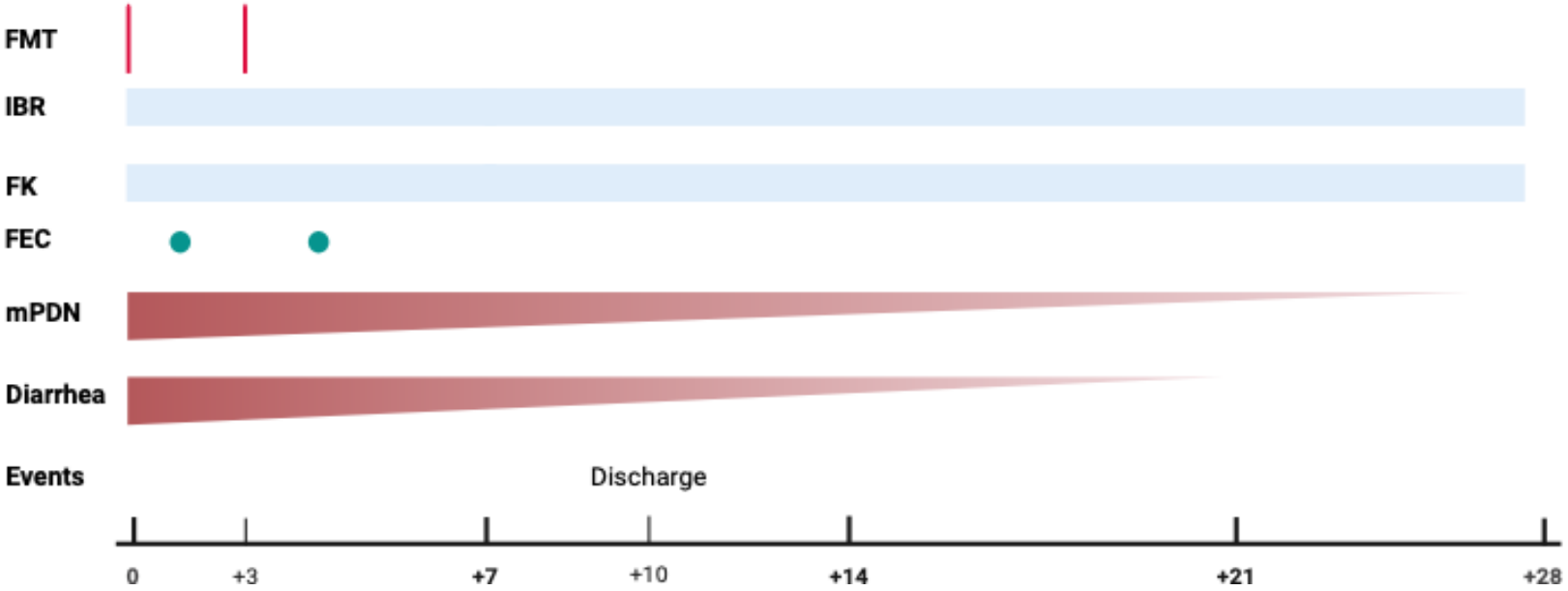
- 3 years-old boy with AML M7 with complex caryotype in CR1

- HCT: - Donor: Haploindentical (mother)
  - Stem cell source: Bone marrow (4,17x10^6 CD34+/kg)
  - Conditioning regimen: Busulfan-Fludarabine-Thiotepa
  - GvHD prophylaxis: post transplant cyclophosphamide, cyclosporine A and mofetil mycophenolate
  - Neutrophil engraftment: day +14

- GvHD: - Onset at day +97 Grade III (skin ++, gut +++) non responder to corticosteroids, ruxolitinib, abatacept and extracorporeal photoapheresis.
  - 3 months after disease onset, worsening of gut symptoms occurred, with bloody diarrhea, abdominal pain and fever (Grade IV, gut ++++). Ruxolitinib and abatacept were suspended, and the patient started tacrolimus and later ibrutinib.
  - Blood in the stool resolved, but diarrhea and abdominal pain persisted

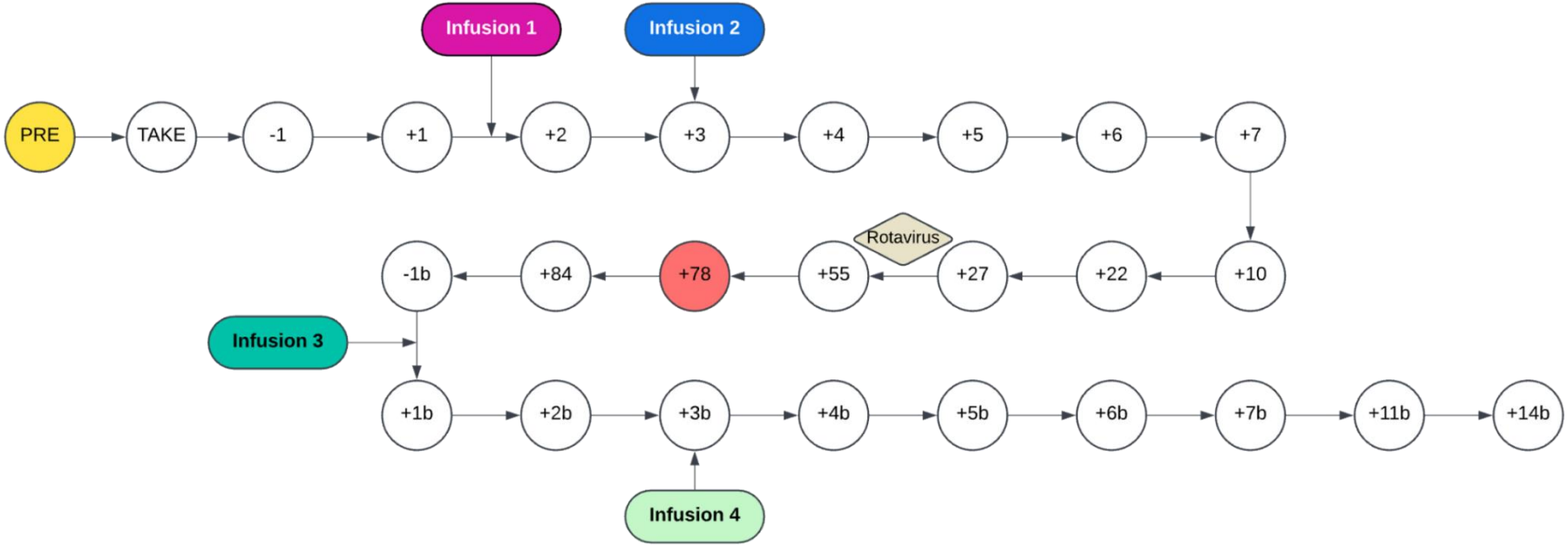
FMT for SR-GvHD: single patient analysis

Infused 150 ml of frozen material from an unrelated donor via naso-jejunal tube on day +224 after HCT and repeated on day +227



Muratore et al, Scientific Reports 2026

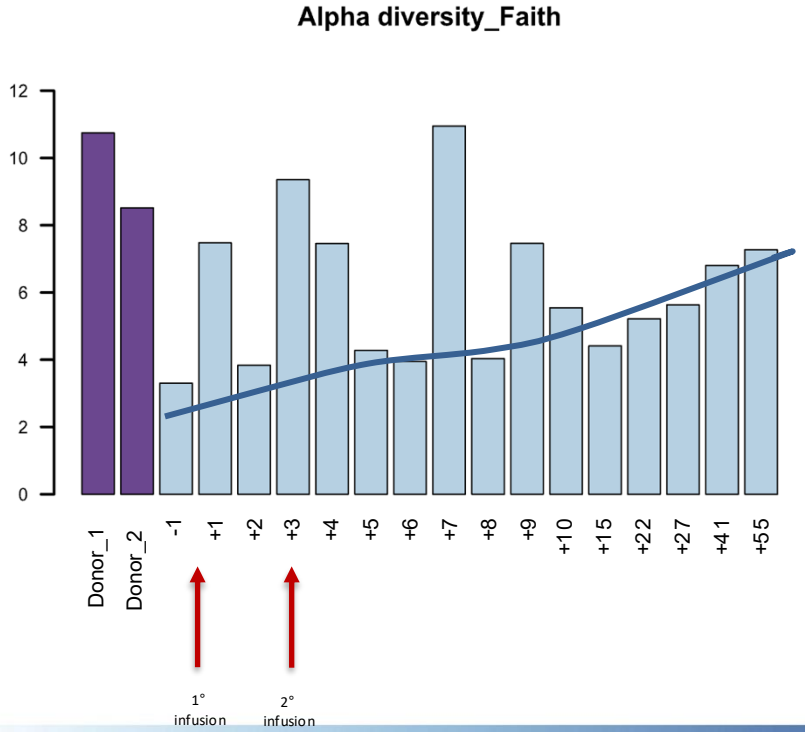
FMT for SR-GvHD: single patient analysis - Longitudinal sampling

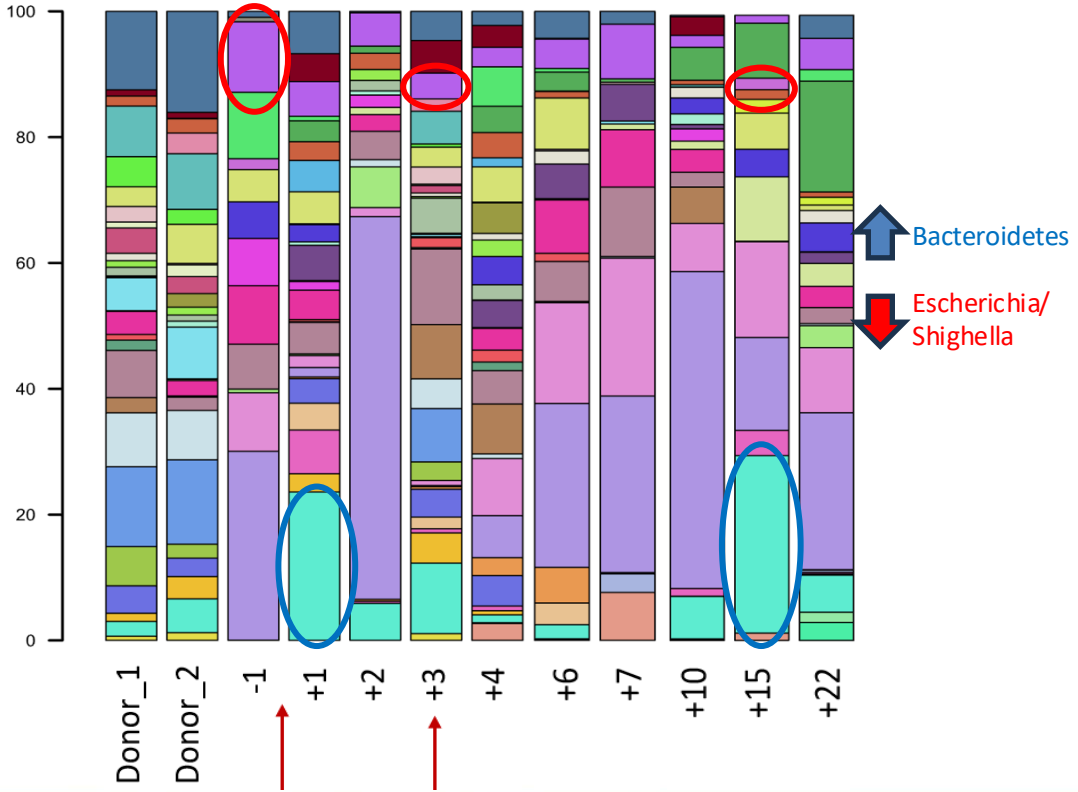


- Prime-boost NG FMT
- Rotavirus infection day +28
- *E. coli* BSI day +78

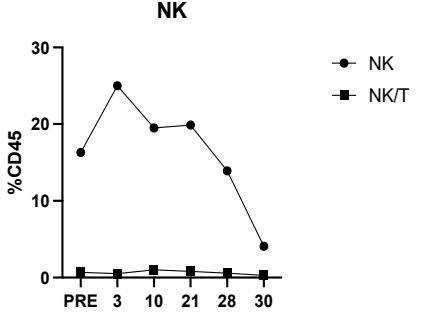
- Second prime-boost NG FMT for recurrence of GI-GvHD
- FUP up to ~ +110 days

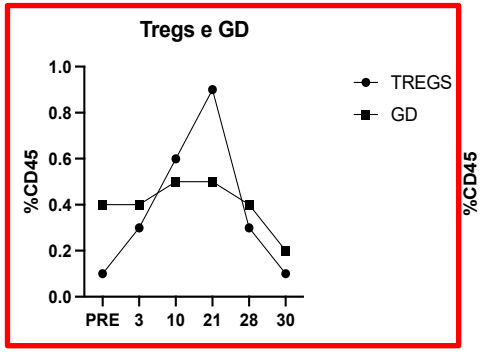
Alpha diversity slowly and progressively increased after the two infusion. At the same time, enrichment of commensals and loss of pathobionts was observed

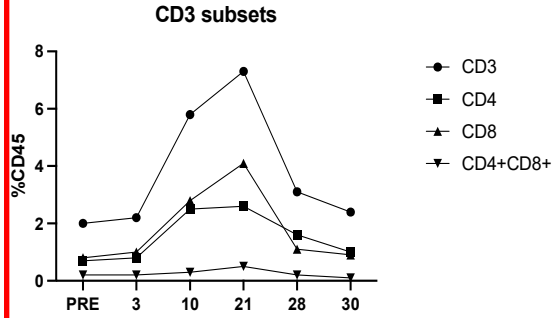


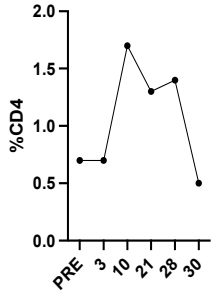


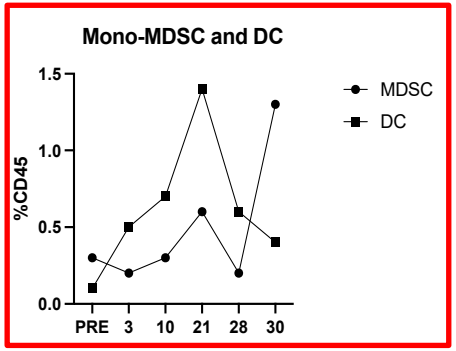
T-regolatory, Monocytic Myeloid-derived suppressor and dendritic cells expansion up to day +21 from FMT, markers of increased immuno-tolerance

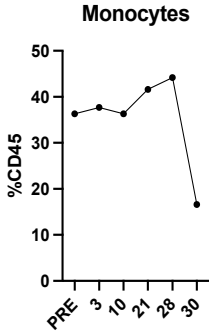


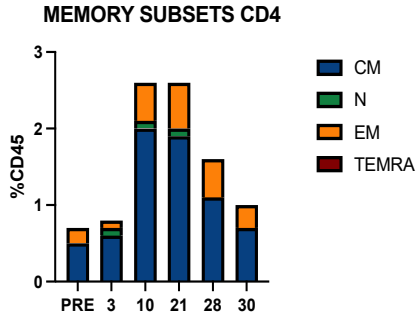


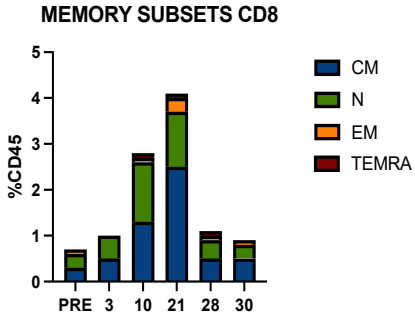






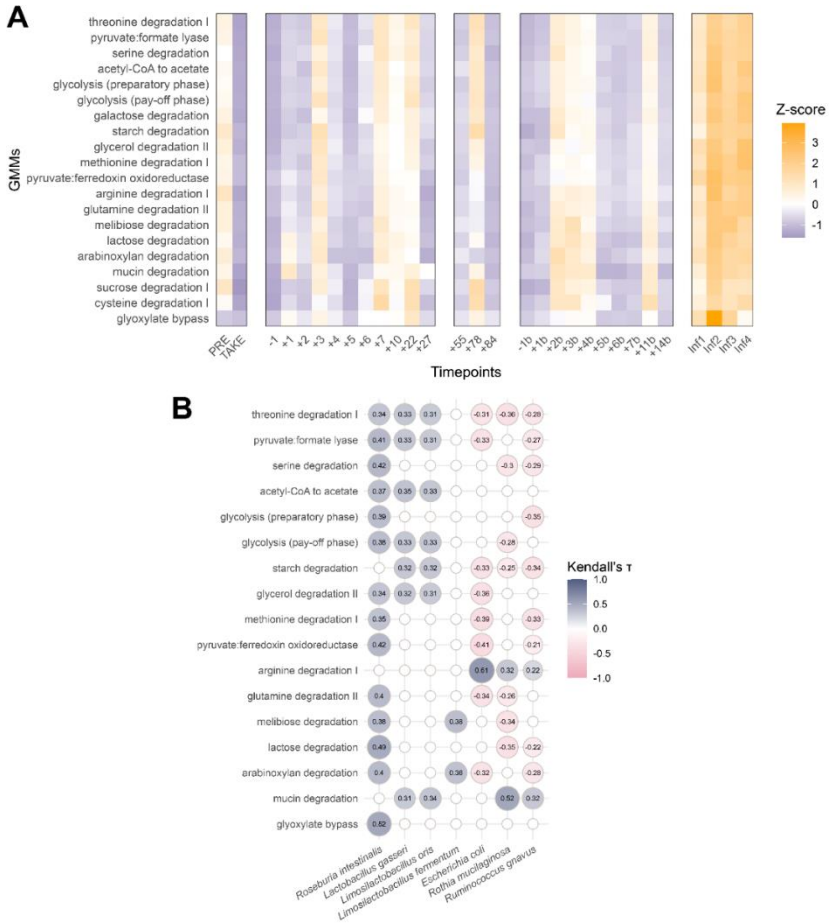






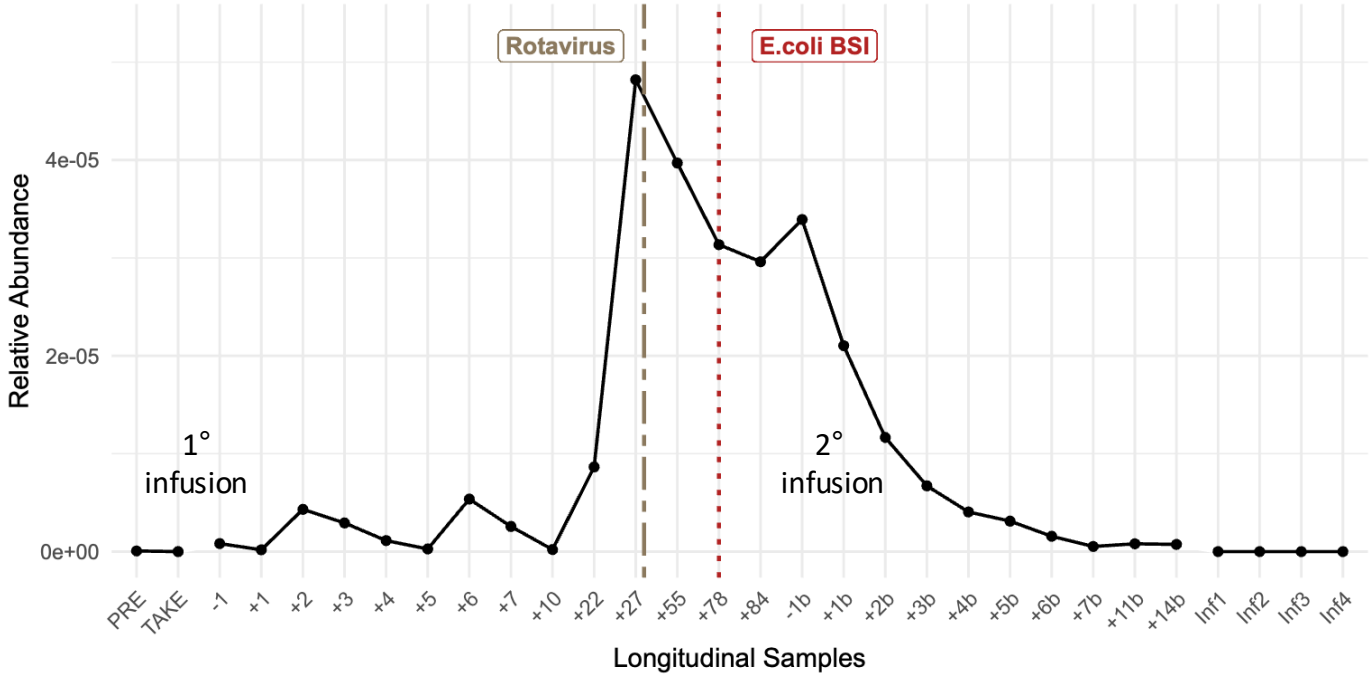
FMT: Metagenomic analysis

- Following FMT, the recipient showed significant increases in donor associated pathways, indicating successful transfer of metabolic functionality.
- *R. intestinalis* was strongly correlated with the majority of such asset of gut metabolic models, with *L. gasseri*, *L. oris* and *L. fermentum* showing significant associations with several GMMs as well.
- On the other hand, *E. coli*, *R. mucilaginosa* and *R. gnavus* negatively correlated with the presence of such GMMs and positively correlated with the GMMs of arginine degradation I and mucin degradation.



FMT for GvHD: a case study of bacteremia after FMT

Mapping the *E. coli* genome revealed how the source of bacteremia was endogenous, as the same strain of *E.Coli* was present in the patient prior to the first FMT and absent in the infused material. A bloom in E.coli abundance in the stools is observed prior to BSI, that was reduced after the second FMT.



New Protocol OPBG2023

CENTRO NAZIONALE TRAPIANTI

Alla Cortese attenzione

Dott. Pietro Merli
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Dipartimento di Oncoematologia
Pediatrica, Terapia Cellulare e Genica
IRCCS Ospedale Pediatrico Bambino Gesù
Roma

E, p.c.

Dott.ssa Chiara Mennini
Segreteria Tecnico-Scientifica (Direzione Generale)
Ospedale Pediatrico Bambino Gesù

Oggetto: protocollo sperimentale "Trapianto di microbiota intestinale per il trattamento della malattia del trapianto contro l'ospite steroido-resistente".

NCT07602751

- **2 patients enrolled (3-yr with TM and 11-yr with T-ALL)**
- Both transplanted from **10/10 matched unrelated donor (MUD)**.
- Developed **severe gastrointestinal acute GvHD**, resistant to **steroids, ruxolitinib (and, in 1 patient, to infliximab)**
- Received **3 and 2 infusionsof FMT, respectively, using thawed fecal material from an unrelated donor**, administered through a **nasojejunal tube (NJT)**.
- **Adverse events**: Grade I and II abdominal pain.
- **Response**: at 14 days → both PR
  at 28 days →

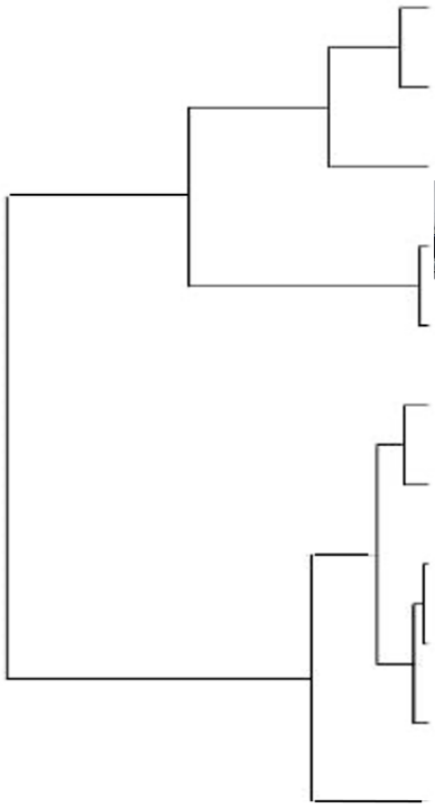
Conclusions

- FMT is an emerging new player in the treatment of SR-GI-GVHD

- FMT can be considered safe and effective also in pediatric patients, but high-quality evidence are lacking. Enrollment in clinical studies is currently under way to further address its safety and efficacy.

- FMT is able to change the gut microbiome architecture towards a protective configuration, being able to transfer commensal species and metabolic potential, while reducing the overgrowth of pathobionts

Thanks



ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

Bambino Gesù
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GASLINI

Fondazione IRCCS
Policlinico San Matteo