Il trapianto di microbiota umano

Pietro Merli

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Bologna, 04/10/2023

XLVIII CONGRESSO NAZIONALE AIEOP

Bologna
2-4 Ottobre 2023

Il sottoscritto Pietro Merli

ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,

dichiara

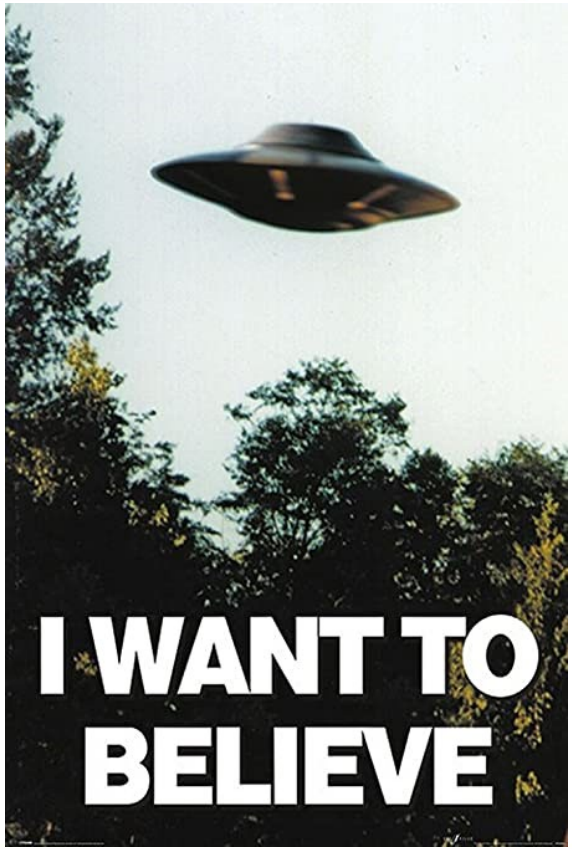
❑ *che negli ultimi due anni ha avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:*

- *SOBI*
- *AMGEN*
- *JAZZ*
- *MEDAC*

Believers ⟷ Deniers

↓

DATA



A brief historical perspective

- First records of FMT traced back to the 4th century in China, where human fecal material called **yellow soup** was used inpatients with severe diarrhea;
- Until China Ming Dynasty in the 16th century, there were descriptions of fresh or fermented fecal suspensions applied in patients with GI conditions, including diarrhea, constipation and abdominal pain;
- Eiseman and colleagues successfully treated patients with FMT for pseudomembranous colitis in 1958, the first report in the medical literature;
- Italian surgeon Acquapendente created the term "**transfaunation**", which means transference of gastrointestinal content from a healthy to a sick animal, and applied extensively in the field of veterinary medicine;
- van Nood et al. carried out the first randomized controlled trial in **2013** for CDI.

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JANUARY 31, 2013 VOL. 368 NO. 5

Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

Els van Nood, M.D., Anne Vrieze, M.D., Max Nieuwdorp, M.D., Ph.D., Susana Fuentes, Ph.D., Erwin G. Zoetendal, Ph.D., Willem M. de Vos, Ph.D., Caroline E. Visser, M.D., Ph.D., Ed J. Kuijper, M.D., Ph.D., Joep F.W.M. Bartelsman, M.D., Jan G.P. Tijssen, Ph.D., Peter Speelman, M.D., Ph.D., Marcel G.W. Dijkgraaf, Ph.D., and Josbert J. Keller, M.D., Ph.D.

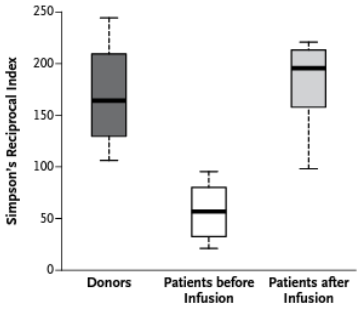


Figure 3. Microbiota Diversity in Patients before and after Infusion of Donor Feces, as Compared with Diversity in Healthy Donors.

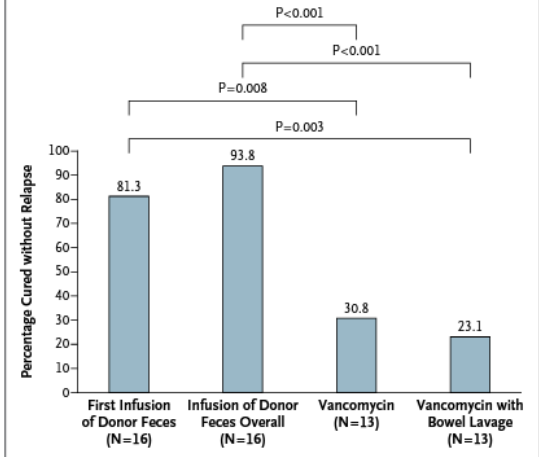


Figure 2. Rates of Cure without Relapse for Recurrent *Clostridium difficile* Infection.

Shown are the proportions of patients who were cured by the infusion of donor feces (first infusion and overall results), by standard vancomycin therapy, and by standard vancomycin therapy plus bowel lavage.

Table 2. Adverse Events in 16 Patients in the Infusion Group.*

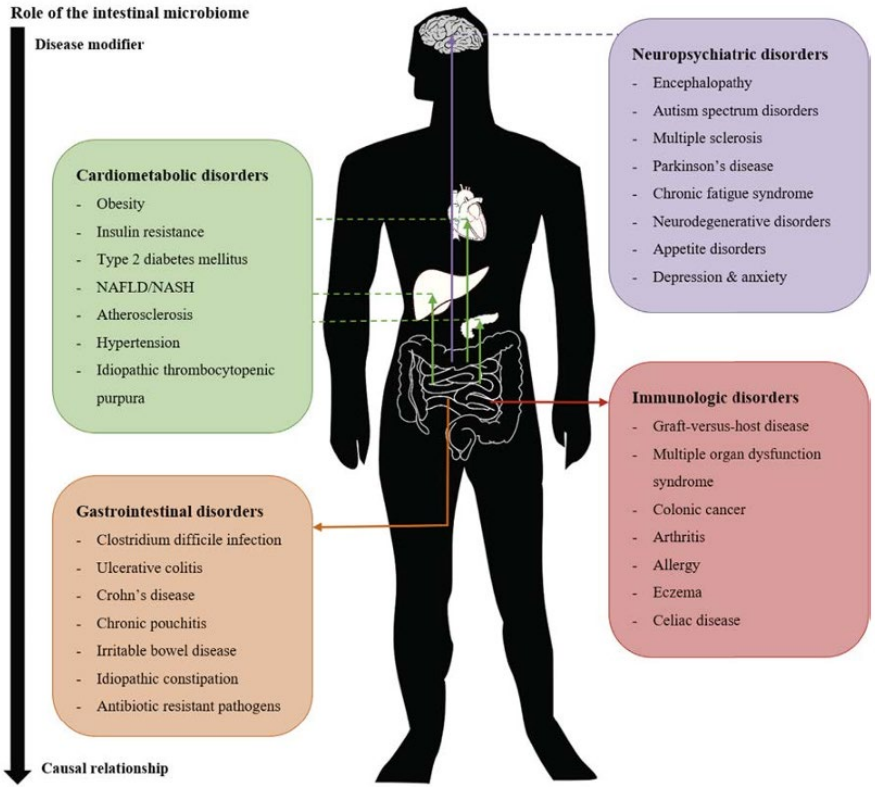
Adverse Event	On Day of Infusion of Donor Feces	During Follow-up
	no. of events	
Belching	3	0
Nausea	1	0
Vomiting	0	0
Abdominal cramps	5	0
Diarrhea	15	0
Constipation	0	3
Abdominal pain	2 (associated with cramping)	0
Infection	0	2†
Hospital admission	NA	1‡
Death	0	0
Other adverse event	1§	1‡

* Adverse events that were reported on the day of donor-feces infusion and those that were reported during follow-up are listed separately. NA denotes not applicable.
† During follow-up, one patient with recurrent urinary tract infections had a urinary tract infection for which antibiotics were prescribed. Another patient had fever during hemodialysis for which antibiotics were prescribed; cultures remained negative.
‡ On day 56, one patient was hospitalized for symptomatic choledocholithiasis, for which endoscopic retrograde

van Nood E, et al, *N Engl J Med*. 2013

FMT - Variables

- Indications
- Preparation
- Donor: auto, “allo”-related, “allo”-third party (±pool)
- Fresh/frozen
- Route of administration
- Number (and interval) (and quantity)
- Aftercare
- Monitoring


Role of the intestinal microbiome
Disease modifier
Causal relationship
Cardiometabolic disorders
- Obesity
- Insulin resistance
- Type 2 diabetes mellitus
- NAFLD/NASH
- Atherosclerosis
- Hypertension
- Idiopathic thrombocytopenic purpura
Gastrointestinal disorders
- Clostridium difficile infection
- Ulcerative colitis
- Crohn's disease
- Chronic pouchitis
- Irritable bowel disease
- Idiopathic constipation
- Antibiotic resistant pathogens
Neuropsychiatric disorders
- Encephalopathy
- Autism spectrum disorders
- Multiple sclerosis
- Parkinson's disease
- Chronic fatigue syndrome
- Neurodegenerative disorders
- Appetite disorders
- Depression & anxiety
Immunologic disorders
- Graft-versus-host disease
- Multiple organ dysfunction syndrome
- Colonic cancer
- Arthritis
- Allergy
- Eczema
- Celiac disease

Hematology/Oncology

- (CDI)
- MDR decontamination
- GvHD treatment
- Improve response to therapy (including HSCT)

Table 1 | FMT studies in HSCT recipients for the treatment of CDI.

Study	Indication/ Population	Number of Patients	Administration Route	Study Type	Donor Relation	Total Number of FMTs	Adverse Events	Response
Neeman *et al.*[68]	Severe fulminant CDI/ allo-HSCT	1	Naso-jejunal	Case report	Husband	1	No serious AEs	1/1 resolution of CDI
de Castro *et al.*[69]	Recurrent CDI/ allo-HSCT	1	Push enteroscopy	Case report	Unrelated	1	No serious AEs	1/1 no recurrence of CDI
Mittal *et al.*[67]	Recurrent CDI/ auto-HSCT	1	Enema	Case report	Unrelated	2	No serious AEs	1/1 no recurrence of CDI
Webb *et al.*[62]	Recurrent CDI allo-HSCT	7	Naso-jejunal tube/-colonoscopy	Retrospective, case series	Unrelated	8	No serious AEs	6/7 no recurrence of CDI
Moss *et al.*[64]	Recurrent CDI allo/auto HSCT	8	Oral capsules	Retrospective, case series	Unrelated	8	No serious AEs	8/8 no recurrence of CDI
Bluestone *et al.*[66]	Recurrent CDI	3	Gastric tube/-colonoscopy	Retrospective, case series	Relative/ unrelated	3	No serious AEs	1/3 no recurrence of CDI

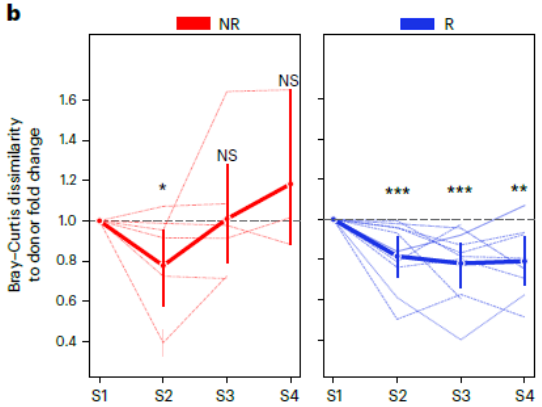
Abbreviation: FMT: Fecal microbiota transplantation, HSCT, Hematopoietic stem cell transplantation, CDI: Clostridioides difficile infection, Allo: Allogenic, Auto: Autologous, AE: Adverse event.

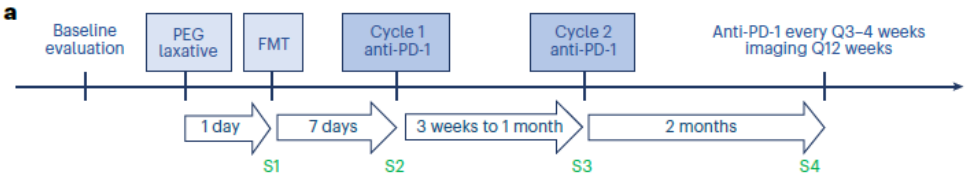
nature medicine

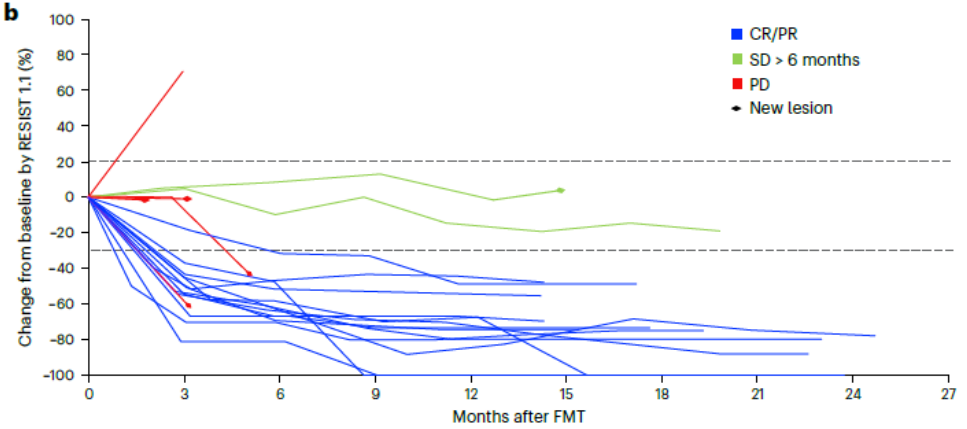
Article

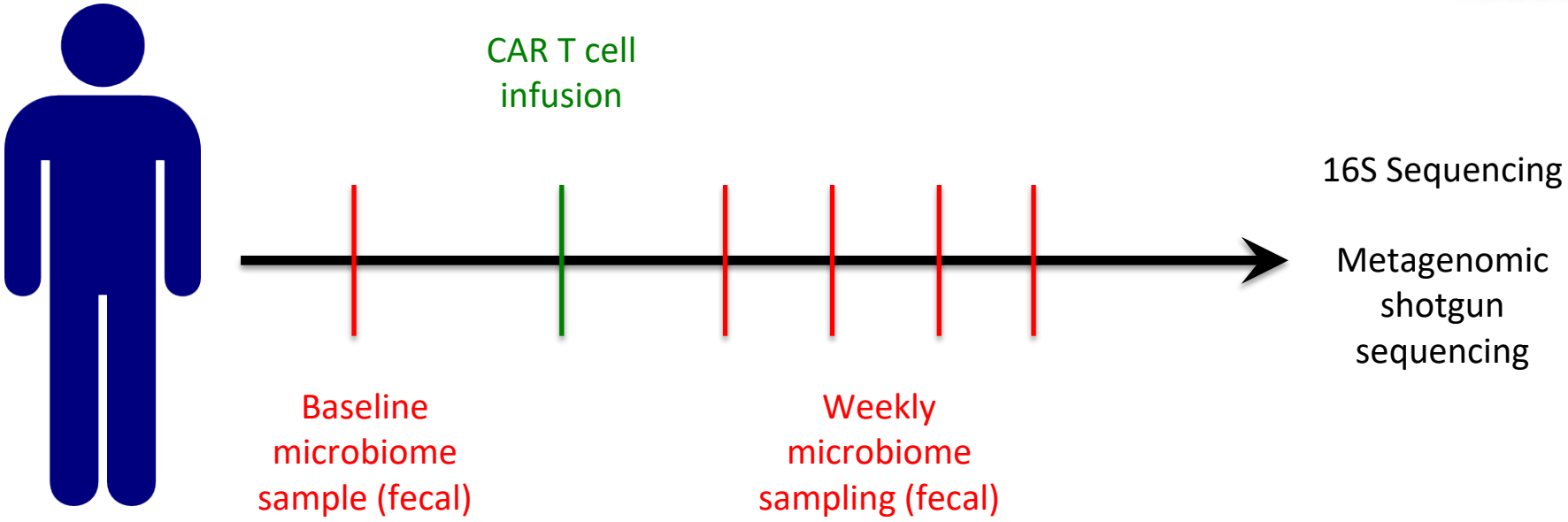
https://doi.org/10.1038/s41591-023-02453-x

Fecal microbiota transplantation plus anti-PD-1 immunotherapy in advanced melanoma: a phase I trial

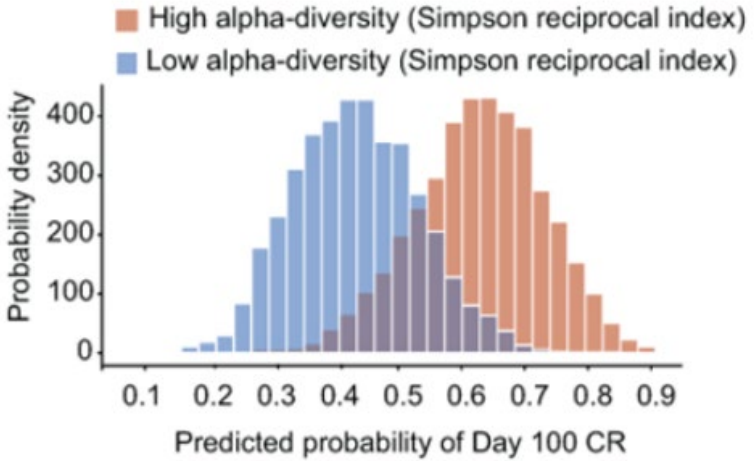


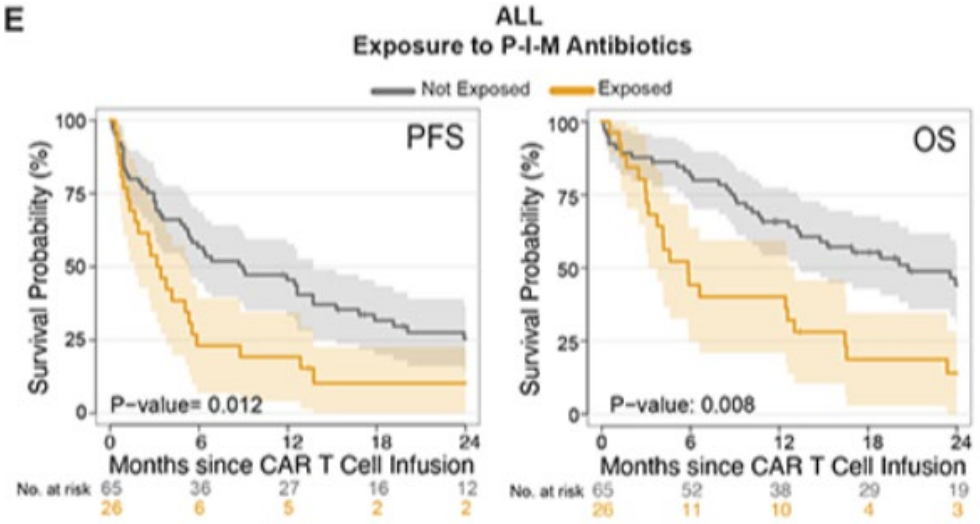






Patients received CARs targeting MUC16, BCMA or CD19





Smith M, et al. *Nat Med*. 2022

Gut decontamination using broad-spectrum antibiotics

Mitigation of Secondary Disease of Allogeneic Mouse Radiation Chimeras by Modification of the Intestinal Microflora

D. W. van Bekkum, J. Roodenburg, P. J. Heidt, D. van der Waaij

JNCI: Journal of the National Cancer Institute, Volume 52, Issue 2, February 1974, Pages 401–404, https://doi.org/10.1093/jnci/52.2.401
Published: 01 February 1974 **Article history** ▾

Summary

Conventional CBA mice subjected to lethal whole-body irradiation and allogeneic bone-marrow transplantation developed delayed secondary disease, which caused 95% mortality within 100 days. Symptoms of secondary disease as well as mortality were virtually absent in similarly treated mice kept in the germfree state or given a colonization-resistant (CR) flora. Conventionalization of these mice as early as 40 days after transplantation did not induce a significant degree of secondary disease except in 1 group of CR mice derived from conventional mice by antibiotic treatment. The acute form of secondary disease occurring after transplantation of allogeneic spleen cells was much less influenced by the gnotobiotic conditions, which confirmed the concept that the mortality was caused primarily by severe graft-versus-host reactions. The implications of these findings for the treatment of patients receiving bone-marrow grafts are discussed.

AIEOP
ASSOCIAZIONE ITALIANA EMATOLOGIA ONCOLOGIA PEDIATRICA
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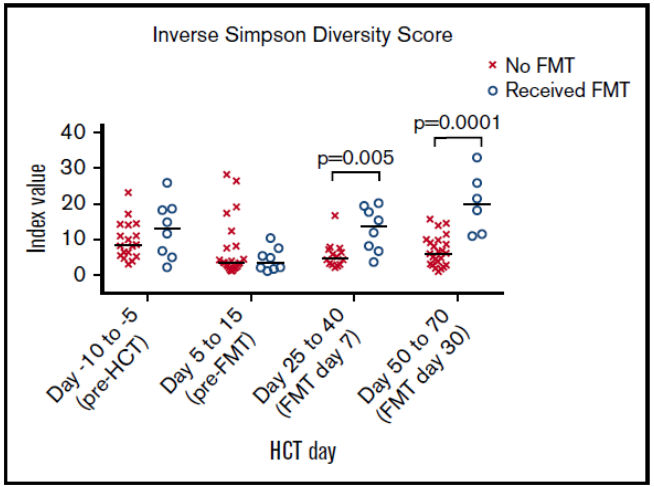
Bologna
2-4 Ottobre 2023

REGULAR ARTICLE

blood advances

Third-party fecal microbiota transplantation following allo-HCT reconstitutes microbiome diversity

Zachariah DeFilipp,[1] Jonathan U. Peled,[2,3] Shuli Li,[4] Jasmin Mahabamunuge,[5] Zeina Dagher,[5] Ann E. Slingerland,[2,3] Candice Del Rio,[1] Betsy Valles,[1] Maria E. Kempner,[1] Melissa Smith,[1] Jami Brown,[1] Bimalangshu R. Dey,[1] Areej El-Jawahri,[1] Steven L. McAfee,[1] Thomas R. Spitzer,[1] Karen K. Ballen,[6] Anthony D. Sung,[7] Tara E. Dalton,[7] Julia A. Messina,[8] Katja Dettmer,[9] Gerhard Liebisch,[10] Peter Oefner,[9] Ying Taur,[3,11] Eric G. Pamer,[3,11] Ernst Holler,[12] Michael K. Mansour,[5] Marcel R. M. van den Brink,[2,3] Elizabeth Hohmann,[5] Robert R. Jenq,[13,14,*] and Yi-Bin Chen[1,*]

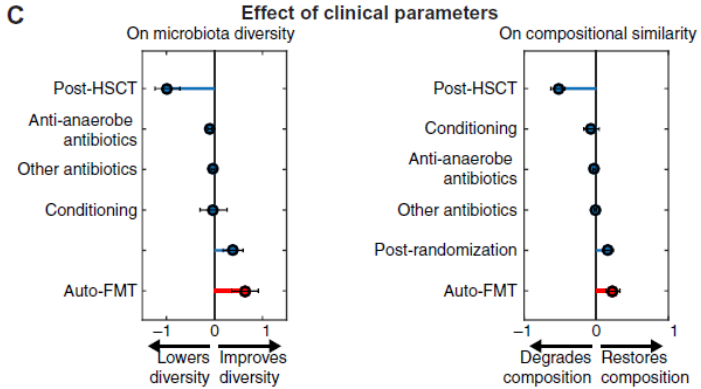


SCIENCE TRANSLATIONAL MEDICINE | REPORT

GUT MICROBIOTA

Reconstitution of the gut microbiota of antibiotic-treated patients by autologous fecal microbiota transplant

Ying Taur[1], Katharine Coyte[1,2,3], Jonas Schluter[1], Elizabeth Robilotti[1], Cesar Figueroa[1], Mergim Gjonbalaj[1], Eric R. Littmann[1], Lilan Ling[1], Liza Miller[1,4], Yangtsho Gyaltshen[1,5], Emily Fontana[1], Sejal Morjaria[1], Boglarka Gyurkocza[1], Miguel-Angel Perales[1], Hugo Castro-Malaspina[1], Roni Tamari[1], Doris Ponce[1], Guenther Koehne[1], Juliet Barker[1], Ann Jakubowski[1], Esperanza Papadopoulos[1], Parastoo Dahi[1], Craig Sauter[1], Brian Shaffer[1], James W. Young[1,6,7], Jonathan Peled[1], Richard C. Meagher[1], Robert R. Jenq[8], Marcel R. M. van den Brink[1,6], Sergio A. Giralt[1], Eric G. Pamer[1]*, Joao B. Xavier[1]*



Brief Report
blood

TRANSPLANTATION

CME Article

Fecal microbiota transplantation for patients with steroid-resistant acute graft-versus-host disease of the gut

Kazuhiko Kakihana,[1,*] Yuki Fujioka,[2,3,*] Wataru Suda,[4,5,*] Yuho Najima,[1] Go Kuwata,[6] Satoshi Sasajima,[7] Iyo Mimura,[8] Hidetoshi Morita,[8] Daisuke Sugiyama,[2] Hiroyoshi Nishikawa,[2] Masahira Hattori,[4,9] Yutaro Hino,[1] Shuntaro Ikegawa,[1] Keita Yamamoto,[1] Takashi Toya,[10] Noriko Doki,[1] Koichi Koizumi,[6] Kenya Honda,[5,7,11] and Kazuteru Ohashi[1]

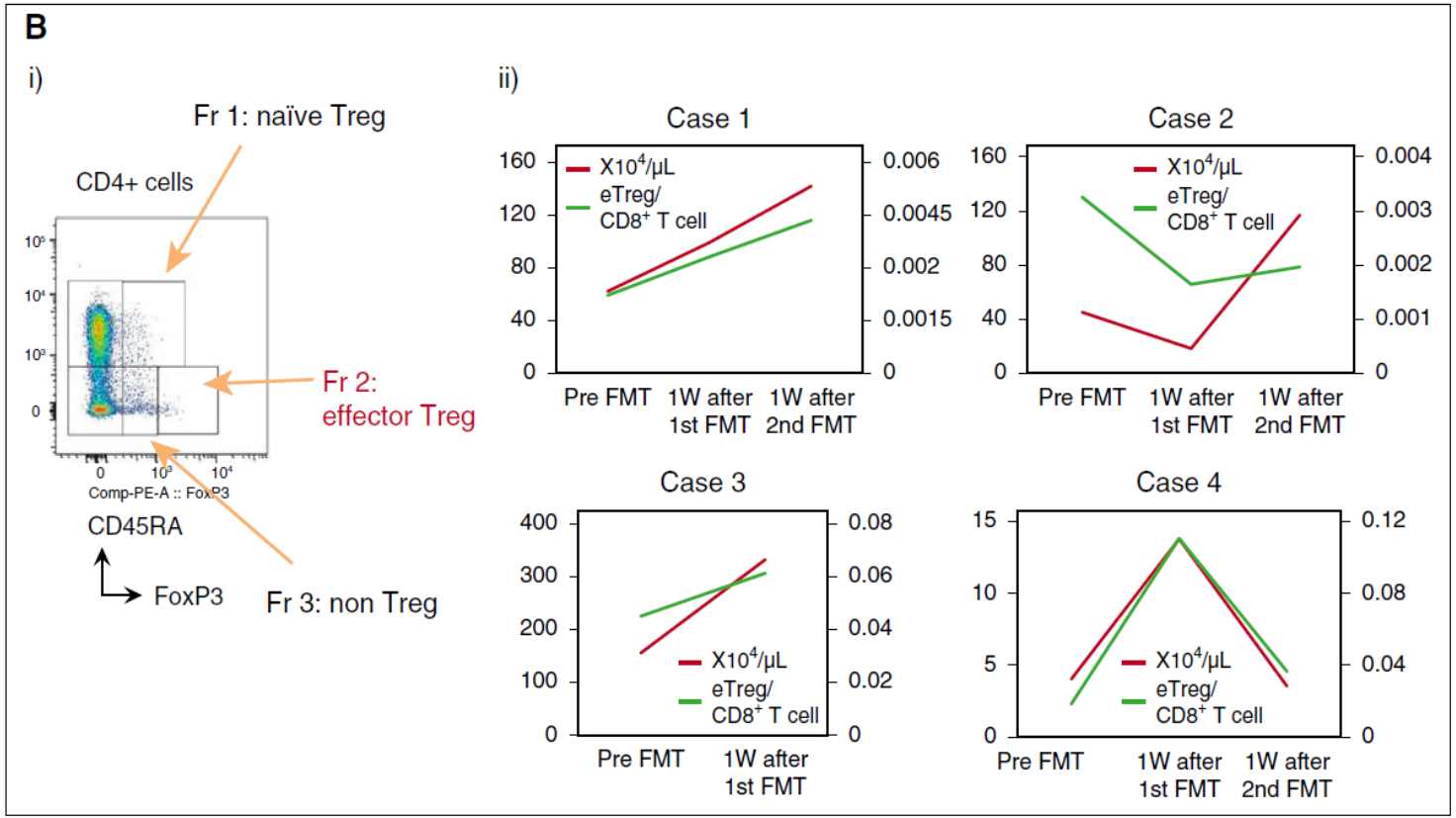
(*Blood*. 2016;128(16):2083-2088)

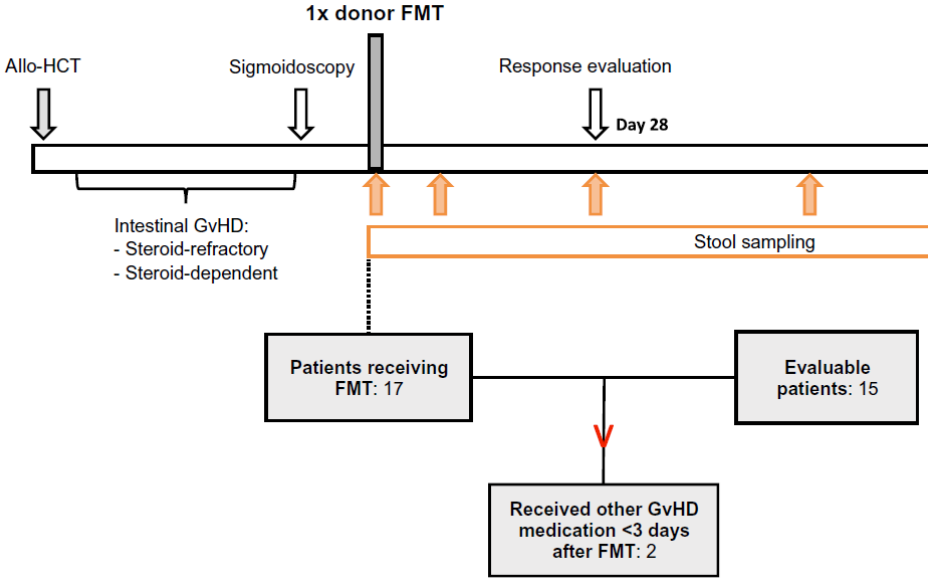
haematologica

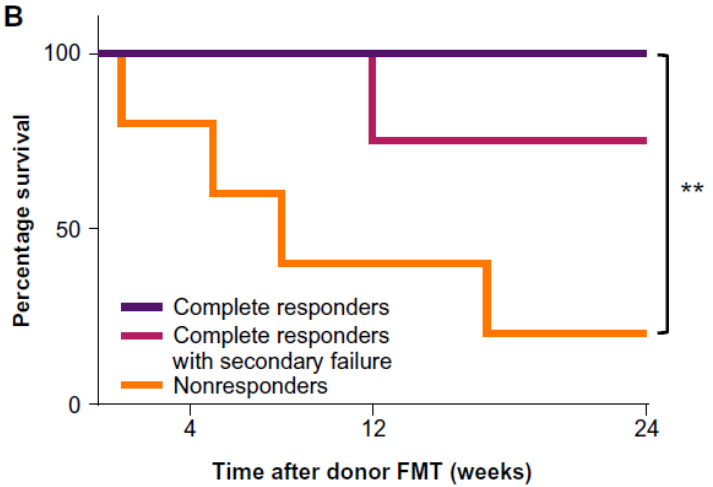
Repeated Fecal Microbiota Transplantations Attenuate Diarrhea And Lead To Sustained Changes In The Fecal Microbiota In Acute, Refractory Gastrointestinal Graft-*Versus*-Host-Disease

Walter Spindelboeck, Eduard Schulz, Barbara Uhl, Karl Kashofer, Ariane Aigelsreiter, Wilma Zinke-Cerwenka, Adnan Mulabecirovic, Patrizia K. Kump, Bettina Halwachs, Gregor Gorkiewicz, Heinz Sill, Hildegard Greinix, Christoph Högenauer, Peter Neumeister

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


B
i)
Fr 1: naïve Treg
CD4+ cells
Fr 2:
effector Treg
Comp-PE-A :: FoxP3
CD45RA
FoxP3
Fr 3: non Treg
ii)
Case 1
Case 2
Case 3
Case 4
X10⁴/μL
eTreg/
CD8⁺ T cell
Pre FMT
1W after
1st FMT
1W after
2nd FMT





Van Lier YF et al, *Sci Transl Med* 2020

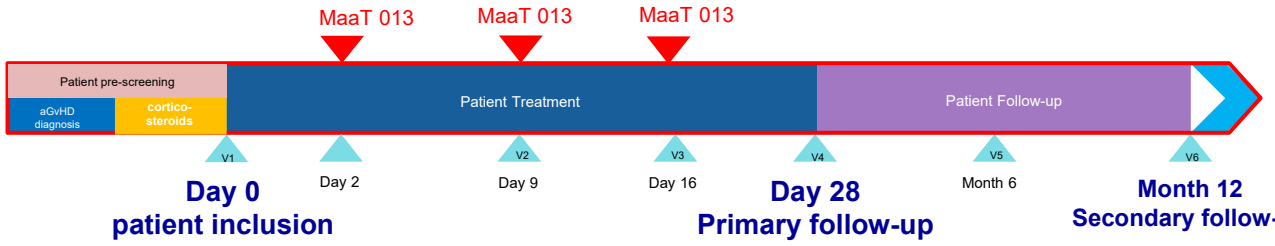
AIEOP ASSOCIAZIONE ITALIANA EMATOLOGIA ONCOLOGIA PEDIATRICA
XLVIII CONGRESSO NAZIONALE AIEOP
Bologna 2-4 Ottobre 2023

Pooled allogeneic faecal microbiota MaaT013 for steroid-resistant gastrointestinal acute graft-versus-host disease: a single-arm, multicentre phase 2 trial

Florent Malard,[a,*] Michael Loschi,[b] Anne Huynh,[c] Thomas Cluzeau,[b] Sarah Guenounou,[c] Faezeh Legrand,[d] Leonardo Magro,[e] Corentin Orvain,[f] Amandine Charbonnier,[g] Marta Panz-Klapuch,[h] Deborah Desmier,[i] Jean-Baptiste Mear,[j] Jérôme Cornillon,[k] Christine Robin,[l] Etienne Daguindau,[m] Karin Bilger,[n] Maria J. G. T. Vehreschild,[o] Patrice Chevallier,[p] Hélène Labussière-Wallet,[q] Clémence Mediavilla,[r] Marie-Anne Couturier,[s] Claude-Eric Bulabois,[t] Vincent Camus,[u] Sylvain Chantepie,[v] Patrice Ceballos,[w] Béatrice Gaugler,[a] Ernst Holler,[x] Joël Doré,[y] Emmanuel Prestat,[z] Cyrielle Gasc,[z] Emilie Plantamura,[z] and Mohamad Mohty[a]

MaaT013

- ✓ Enema
- ✓ > 10^{11} CFU
- ✓ Stability 24 months at -80°C
- ✓ 455 OTU

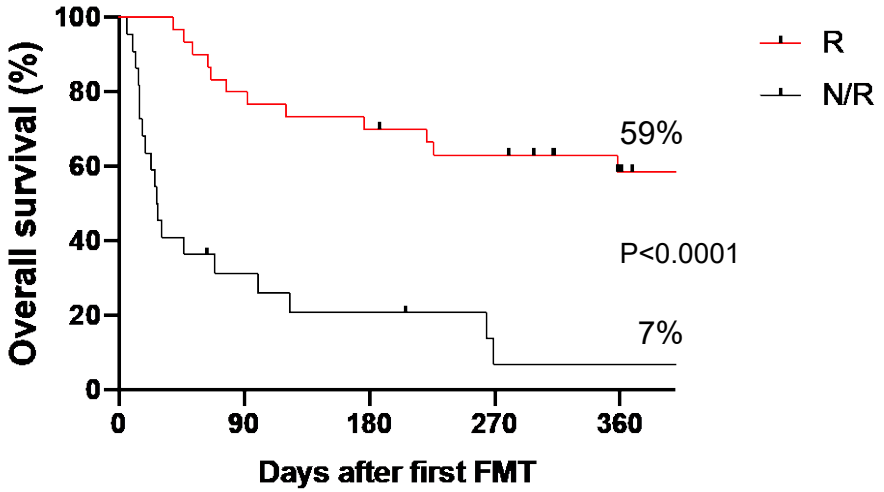


N=24 patients with steroid refractory gastrointestinal acute GVH

Compassionate Use and Expanded Access Program: GI SR aGVHD response

CUP: N=52 steroid-resistant GI-aGVHD (resistance n=22, dependance n=7)
Median 3 previous line of treatment (range, 1-6), 40 (77%) received ruxolitinib

Response	Patients (N=52) N (%)
• **GI aGVHD response at D28**	**30 (58%)**
○ Complete response	17 (33%)
○ Very good partial response	9 (17%)
○ Partial response	4 (8%)
• **Best GI aGVHD response before D28**	**35 (67%)**
○ Complete response	21 (40%)
○ Very good partial response	10 (19%)
○ Partial response	4 (8%)



Courtesy of Dr. Malard (ASH oral abstract 262)

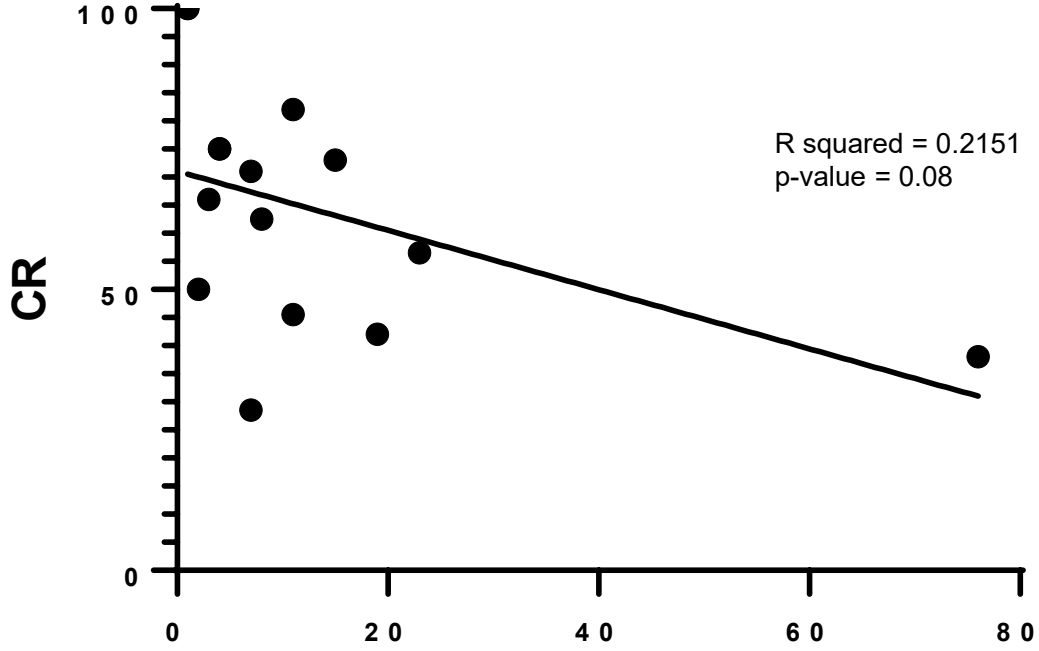
Study	Indication/ Population	Number of Patients	Administration Route	Study Type	Donor Relation	Total Number of FMTs	Serious Adverse Events	Response
Kakihana et al. [99]	Steroid-resistant/dependent gut GvHD	4	Nasogastric tube	Prospective	Spouse/ relative	7	1 lower GI bleeding, hypoxemia (probably not related)	$n = 3$, CR; $n = 1$, PR
Spindelboeck et al. [100]	Steroid-resistant grade IV gut GvHD	3	Colonoscopy	Retrospective, case series	Unrelated/ sibling	9	No serious AEs	$n = 2$, CR; $n = 1$, PR
Qi et al. [101]	Steroid-resistant GvHD	8	Nasoduodenal tube	Prospective	Unrelated	12	No serious AEs	$n = 5$, CR; $n = 1$, PR
Shouval et al. [102]	Steroid-resistant/ dependent GvHD	7	Oral capsules	Prospective	Unrelated	15	2 bacteremia (deemed unrelated)	$n = 2$, CR
van Lier et al. [103]	Steroid-resistant/ dependent GvHD	15	Nasoduodenal tube	Prospective	Unrelated	15	No serious AEs	$n = 11$, CR
Kaito et al. [104]	Steroid-resistant grade IV gut GvHD	1	Oral capsules	Prospective	Unrelated	2	No serious AEs	$n = 1$, PR
Zhong et al. [105]	Steroid-resistant grade III gut GvHD	1	Nasoduodenal tube	Retrospective	Unrelated	2	No serious AEs	$n = 1$, CR
Biernat et al. [106]	Steroid-resistant grade IV gut GvHD	2	Nasoduodenal tube	Retrospective	Unrelated	7	No serious AEs	$n = 1$, CR
Mao et al. [107]	Steroid-resistant grade IV gut GvHD	1	Oral capsules	Retrospective, case report	Unrelated	2	No serious AEs	$n = 1$, CR
Goloshchapov et al. [108]	Steroid-resistant GvHD/4-overlap GvHD	19	3 gastroscopy, 3 nasointestinal tube, 13 oral capsules	Prospective	15 unrelated, 4 related	19	No data	$n = 8$, CR; $n = 8$, PR
Goloshchapov et al. [109]	Steroid-resistant GvHD/2-overlap GvHD	7	2 gastroscopy, 2 nasoduodenal tube, 3 oral capsules	Prospective pediatric	4 unrelated, 3 related. All were also [illegible] donors	7	No serious AEs	$n = 5$, CR; $n = 1$, PR
Goeser et al. [110]	Steroid-resistant GvHD	11	9 oral capsules, 2 nasojejunal tube	Retrospective, case series	Unrelated	11	No serious AEs	$n = 9$, CR; $n = 2$, PR
Zhao et al. [111]	Steroid-resistant GvHD	23	Nasoduodenal nasogastric tube	Prospective	Unrelated	43	2 thrombocytopenia and cardiac events	$n = 13$, CR; $n = 3$, PR
Biliński et al. [23]	Steroid-resistant GvHD	11	Nasoduodenal tube	Prospective	Unrelated	14	2 sepsis and septic shock	$n = 5$, CR; $n = 1$, PR
Biliński et al. [21]	Steroid-resistant GvHD	4	Nasoduodenal tube	Prospective	Unrelated	15	No serious AEs	$n = 3$, CR
Malard et al. [24]	Steroid-resistant grade III–IV gut aGvHD $n = 24$, Steroid-dependent or Steroid-resistant gut aGvHD (classical $n = 41$, late onset $n = 3$, overlap syndrome $n = 8$) for Expanded Access Program	76	[illegible] tube, 74 enema	Prospective	Pooled unrelated	192	5 serious AEs in 2 patients	$n = 29$, CR; $n = 14$, VGPR $n = 5$, PR
TOTAL		193				372	12 (4.8%)	ORR (CR + VGPR + PR) = 74%

Route: up down

Donor: related unrelated

Bilinski J. et al., *Biomedicines* 2022

FMT studies for SR-aGVHD



OPBG Case 1

- 4 year-old boy; AML FAB6 in 1st CR
- UCBT (8/8); GVHD prophylaxis ATLG, CsA, low-dose steroids
- Acute GVHD 30 days after SCT: skin stage 2, gut stage 4; overall grade IV
- Therapy:
  - Full-dose methylprednisolone
  - ECP
  - Infliximab
  - Begelomab (anti-CD26)

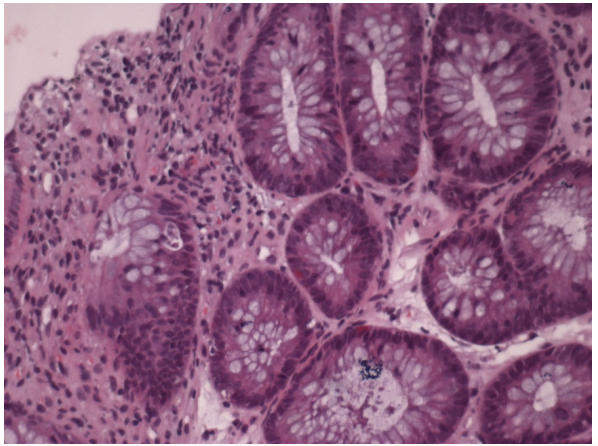
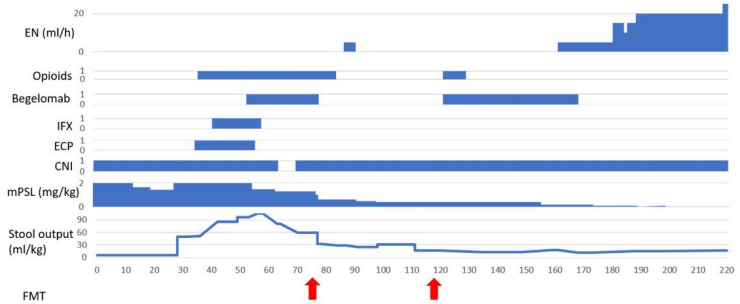


Fig 1A


EN (ml/h)
Opioids
Begelomab
IFX
ECP
CNI
mPSL (mg/kg)
Stool output (ml/kg)
FMT

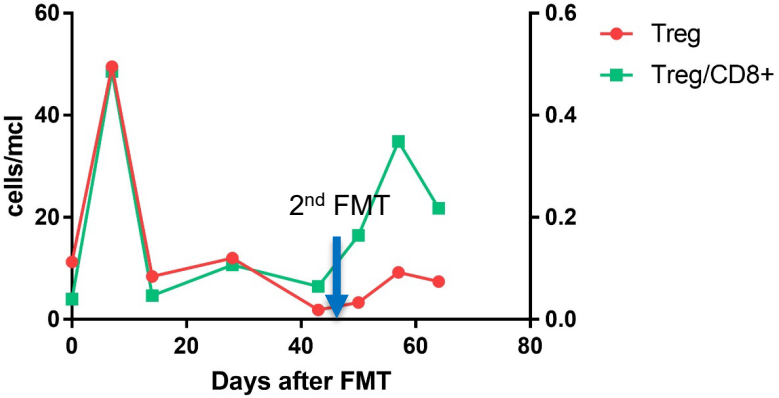
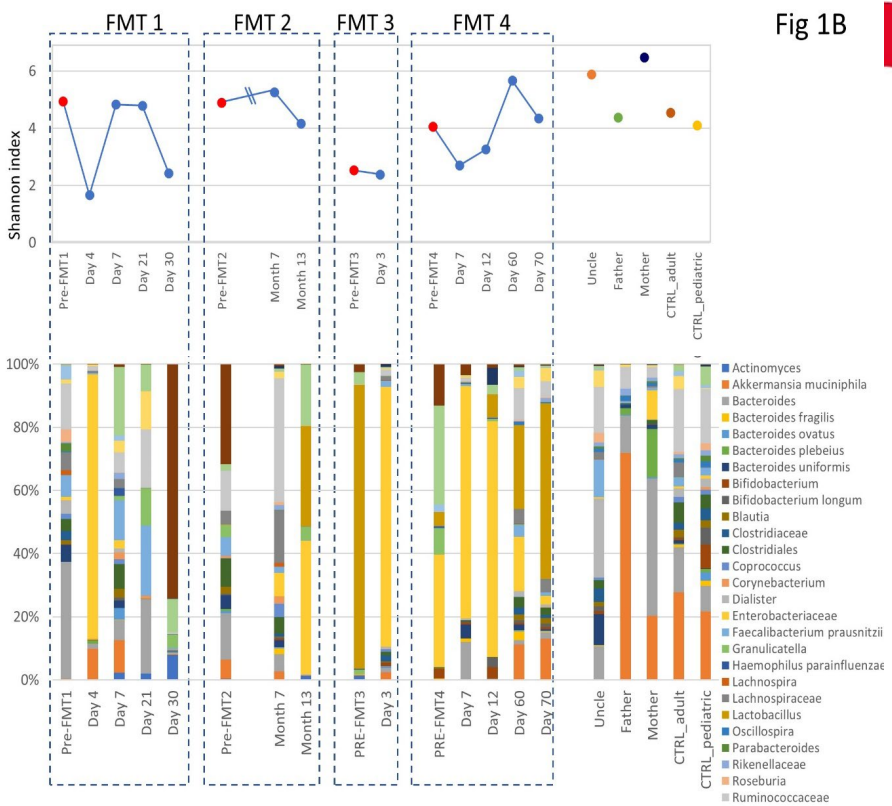

cells/mcl
2nd FMT
Treg
Treg/CD8+
Days after FMT

Fig 1B


FMT 1
FMT 2
FMT 3
FMT 4
Shannon index
Pre-FMT1
Day 4
Day 7
Day 21
Day 30
Pre-FMT2
Month 7
Month 13
Pre-FMT3
Day 3
Pre-FMT4
Day 12
Day 60
Day 70
Uncle
Father
Mother
CTRL_adult
CTRL_pediatric
Actinomyces
Akkermansia muciniphila
Bacteroides
Bacteroides fragilis
Bacteroides ovatus
Bacteroides plebeius
Bacteroides uniformis
Bifidobacterium
Bifidobacterium longum
Blautia
Clostridiaceae
Clostridiales
Coprococcus
Corynebacterium
Dialister
Enterobacteriaceae
Faecalibacterium prausnitzii
Granulicatella
Haemophilus parainfluenzae
Lachnospira
Lachnospiraceae
Lactobacillus
Oscillospira
Parabacteroides
Rikenellaceae
Roseburia
Ruminococcaceae

FMT for decolonization of MDR bacteria

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America
hivma hiv medicine association
OXFORD

Fecal Microbiota Transplantation in Patients With Blood Disorders Inhibits Gut Colonization With Antibiotic-Resistant Bacteria: Results of a Prospective, Single-Center Study

Jaroslaw Bilinski,[1] Pawel Grzesiowski,[2] Nikolaj Sorensen,[3] Krzysztof Madry,[1] Jacek Muszynski,[4] Katarzyna Robak,[1] Marta Wroblewska,[5,6] Tomasz Dzieciatkowski,[5] Grazyna Dulny,[7] Jadwiga Dwilewicz-Trojaczek,[1] Wieslaw Wiktor-Jedrzejczak,[1] and Grzegorz W. Basak[1]

Table 3. Decolonization of Particular Strains of Antibiotic-Resistant Bacteria in All Participants and Those Without Antibiotics Use During the First Week After Fecal Microbiota Transplantation

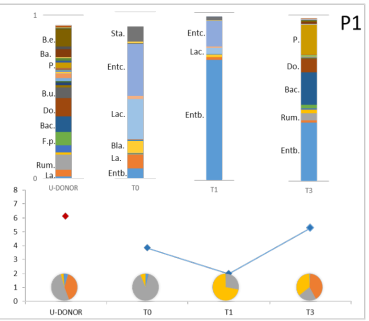
	Negative Rectal Swab at 1 Week				Decolonization at 1 Month			
	All		Without Antibiotics		All		Without Antibiotics	
Pathogen	No.	%	No.	%	No.	%	No.	%
Klebsiella pneumoniae								
New Delhi metallo-β-lactamase 1	8/14	57	6/6	100	6/10	60[a]	5/6	83[a]
Other, carbapenem-resistant	2/3	67	2/2	100	3/3	100	2/2	100
ESBL+	1/2	50	0/1	0	1/2	50	1/1	100
Escherichia coli								
ESBL+	11/11	100	3/3	100	11/11	100	3/3	100
OXA-48 – extended-spectrum oxacillinase-48	1/1	100	1/1	100	1/1	100	1/1	100
Pseudomonas aeruginosa								
MBL+	2/2	100	2/2	100	2/2	100	2/2	100[a]
Other, carbapenem resistant	1/2	50	1/2	50	2/2	100	2/2	100
Carbapenem-resistant *Enterobacter cloacae*	1/2	50	1/2	50	2/2	100	2/2	100
Vancomycin-resistant enterococci	2/2	100	1/1	100	2/2	100	1/1	100
Acinetobacter ursingii MBL+	1/1	100	1/1	100	1/1	100[a]	1/1	100[a]
Stenotrophomonas maltophilia	1/1	100	1/1	100	1/1	100	1/1	100

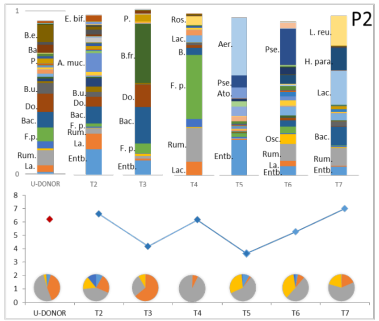
Table 2 | FMT studies in HSCT recipients for restoring gut microbiota and eradication of antibiotic-resistant bacteria.

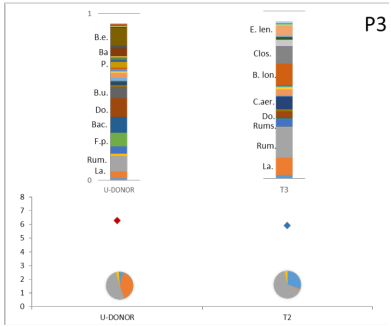
Study	Indication	Number of Patients	Administration Route	Study Type	Donor Relation	Total Number of FMTs	Adverse Events	Response/ Endpoint
Bilinski *et al.*[74]	Multidrug-resistant bacteria decolonization	20 (n = 8 allo-HSCT recipient; n = 12 other hematologic conditions)	Nasoduodenal tube	Prospective	Unrelated	25	No serious AEs	15/20 decolonization of multidrug-resistant bacteria
DeFilipp *et al.*[72]	Gut microbiota reconstitution following allo-HSCT	13	Oral capsules	Prospective	Unrelated	13	1 abdominal pain	Improved microbiome diversity
Taur *et al.*[73]	Gut microbiota reconstitution following allo-HSCT	25 (n = 14 received auto FMT; n = 11 no intervention)	Enema	Randomized controlled trial	Autologous FMT	25	No serious AEs	Restored gut microbiota to pre allo-HSCT state
Battipaglia *et al.*[75]	Multidrug-resistant bacteria decolonization	10 (n = 6 after allo-HSCT; n = 4 before allo-HSCT)	Enema/ nasogastric tube	Retrospective	Unrelated/ relative	13 (n = 9 after allo-HSCT)	No serious AEs	7/10 decolonization of multidrug-resistant bacteria

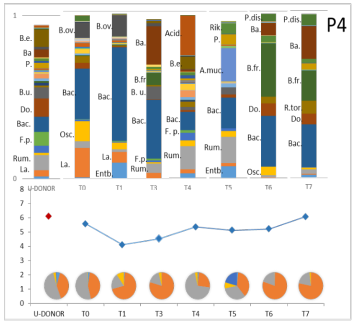
Abbreviation: FMT: Fecal microbiota transplantation, HSCT: Hematopoietic stem cell transplantation, Allo: Allogenic, GVHD: Fraft-*versus*-host disease, AE: Adverse event.

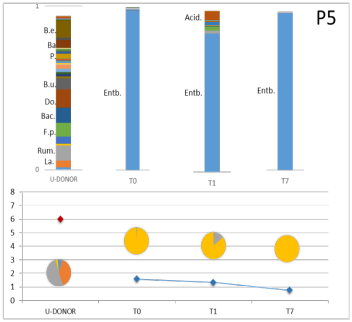
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Age (years) at FMT / Gender	18/M	17/M	11/M	9/M	2/F	11/M	11 (months)/M	6/F	2 + 10/12 /M
Haematological disease	AML	AML	AML	ALL	SCID	AML	HLH (GS)	AML	CGD
MDR pathogen	PA	CF, KOr, EntCl	KP, EC	EC	EC, KO	PA	KO	PA	KP
AMR gene	VIM	VIM	VIM	OXA 48-181-232	NDM	VIM	VIM	VIM	NDM
Relevant infections pre FMT	Sepsis by Carb-R-PA	Sepsis by Carb-R-EC	None	None	Multiple sepsis and meningoence phalitis by Carb-R-EC	Multiple Sepsis by Carb-R-PA	None	Multiple Sepsis by Carb-R-PA	None
Donor	Third party	Third party	Third party	Third party	Third party	Third party	Third party	Third party	Third party
Stool	fresh	frozen	frozen	frozen	frozen	frozen	frozen	frozen	frozen
N. of FMT	1	1	1	1	1	1	1	1	1
Preparation with oral antibiotic	N	Y	Y	Y	Y	Y	Y	Y	Y
Quantity infused	3,2 ml/kg	3,4 ml/kg	2,9 ml/kg	5,1 ml/kg	12,5 ml/kg	3.4 ml/kg	6.3 ml/kg	7.2 ml/kg	6.6 ml/kg
HSCT post FMT	Y (Day 12)	Y (Day 14)	Y (Day 13)	Y (Day 16)	Y (Day 16)	Y (Day 20)	Y (Day 10)	Y (Day 45)	Y (Day 14)
Decolonization 1 week after FMT	Yes	Yes	No	Yes	Yes	Yes	Yes (also urine)	Yes	Yes
Decolonization 4 weeks after FMT	No	No	Yes	No	No	No	Yes	No	Yes


P1
U-DONOR
T0
T1
T3


P2
U-DONOR
T2
T3
T4
T5
T6
T7

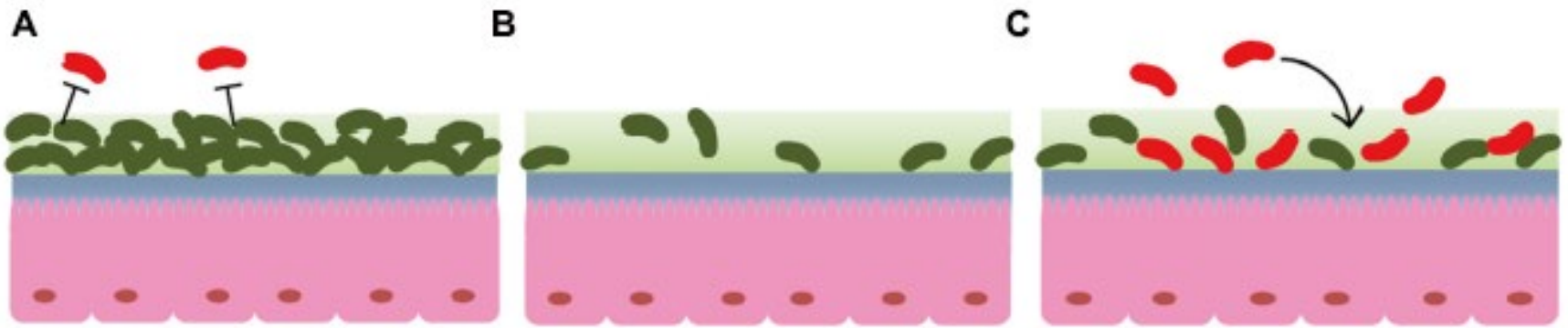

P3
U-DONOR
T2


P4
U-DONOR
T0
T1
T3
T4
T5
T6
T7


P5
U-DONOR
T0
T1
T7


Actinobacteria
Bacteroidetes
Firmicutes
Proteobacteria
Verrucomicrobia

Conditioning before FMT?



Ji et al., Front Microbiol 2017

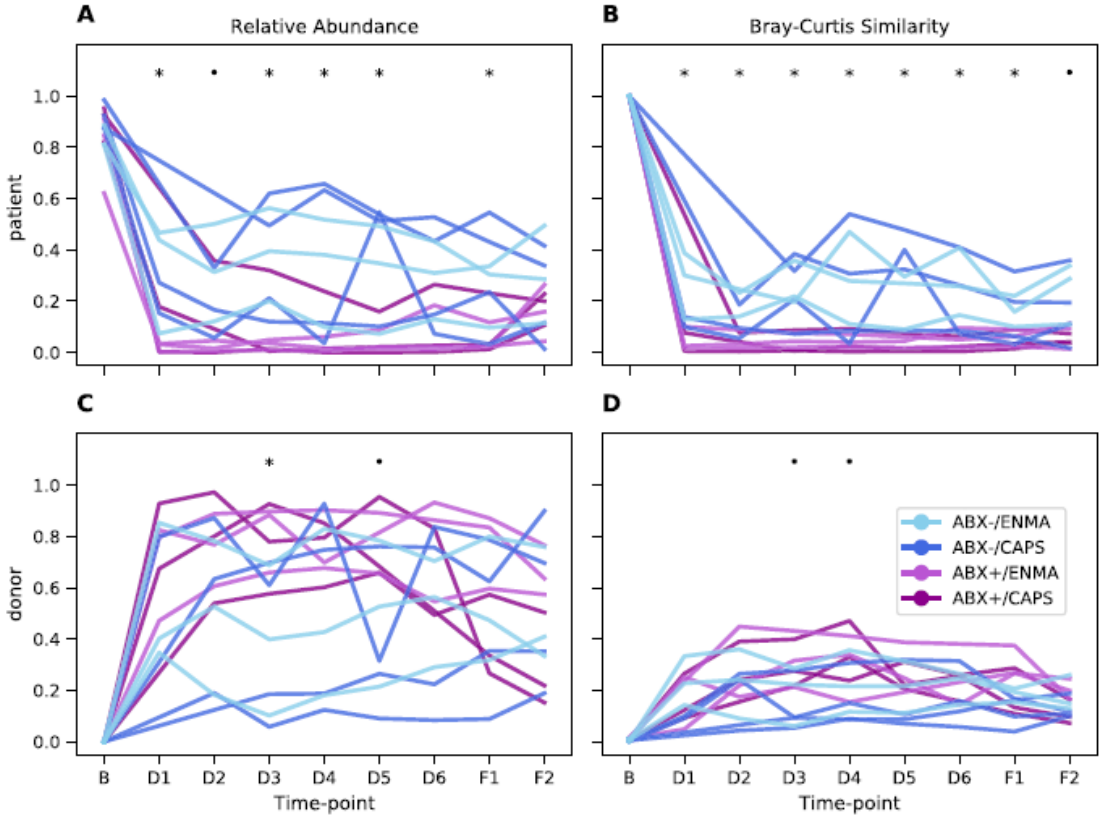
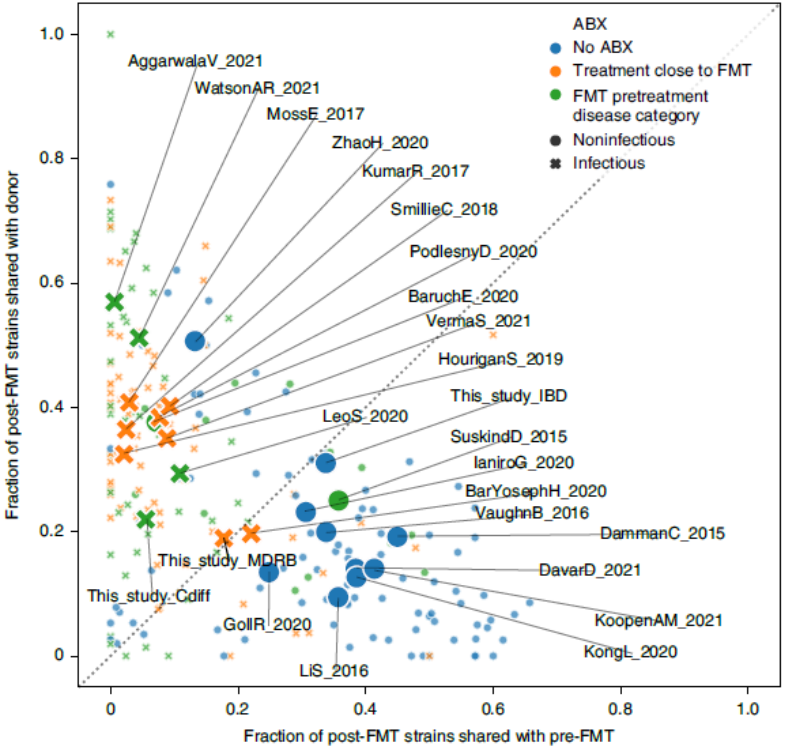

A
Relative Abundance
B
Bray-Curtis Similarity
C
D
patient
donor
1.0
0.8
0.6
0.4
0.2
0.0
B
D1
D2
D3
D4
D5
D6
F1
F2
Time-point
ABX-/ENMA
ABX-/CAPS
ABX+/ENMA
ABX+/CAPS

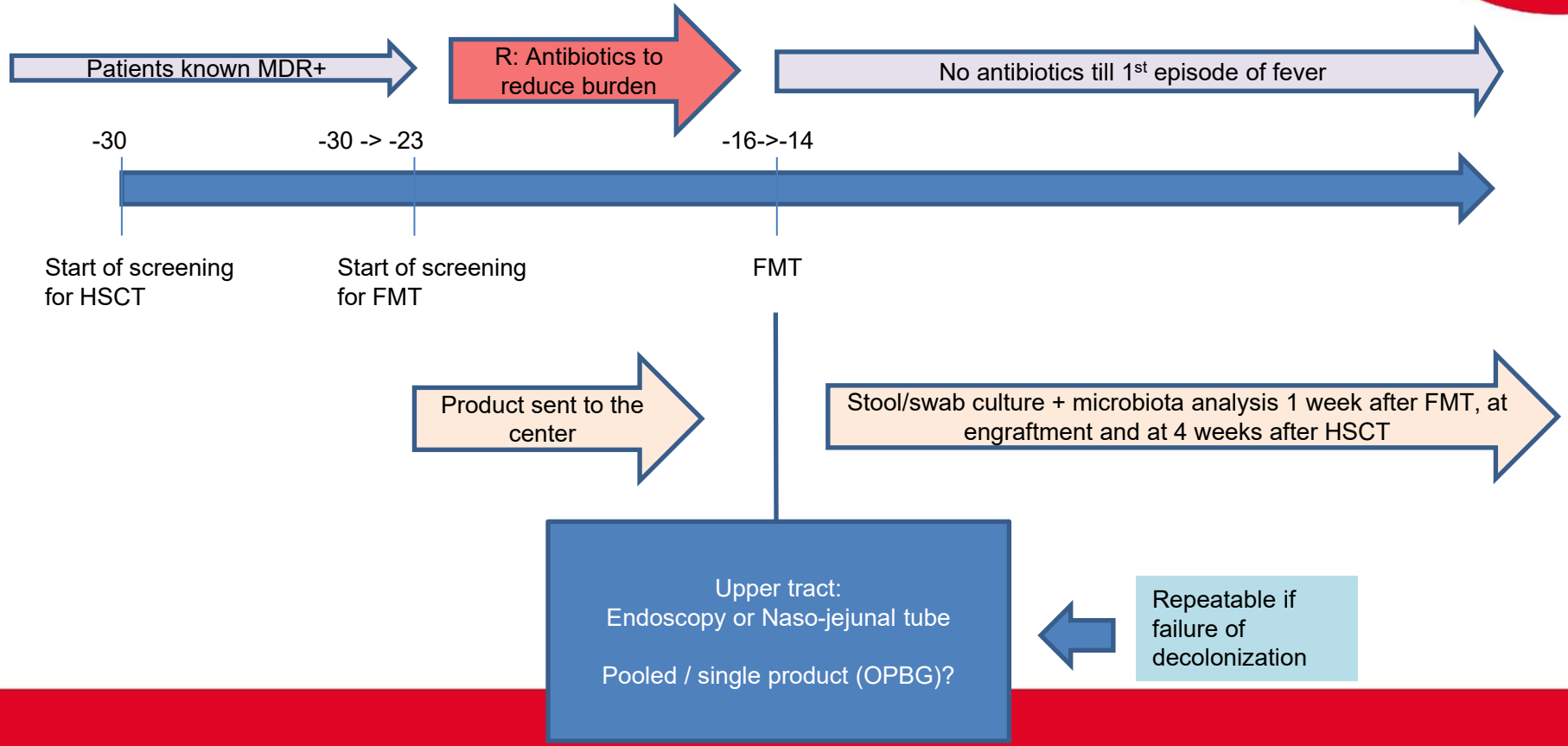
Table 1 | Summary and main characteristics of the FMT datasets included in this meta-analysis

Disease	No. of datasets (new datasets)	No. of recipients (new recipients)	No. of samples (new samples)	Median no. of post-FMT samples [IQR]	Disease category
Clostridioides difficile infection	9 (1)	96 (16)	529 (94)	2.0 [3.0]	Infectious
Inflammatory bowel disease	5 (1)	38 (2)	188 (8)	2.0 [1.0]	Chronic
Multidrug-resistant bacteria colonization	3 (1)	21 (5)	109 (13)	1.0 [2.0]	Infectious
Melanoma	2	24	248	4 [7]	Oncological
Tourette syndrome	1	5	25	2.0 [0.0]	Chronic
Metabolic syndrome	2	16	154	3 [0.2]	Chronic
Irritable bowel syndrome	1	20	91	2.0 [0.0]	Chronic
Tyrosine kinase inhibitor-dependent diarrhea	1	6	27	2.0 [1.5]	Oncological
Total	**24 (3)**	**226 (23)**	**1,371 (116)**	**2 [2]**	



Ianiro G. et al., Nat Med 2022

FATTI IN CASA: Fecal microbiota transplantation in Italian centers for pediatrics hematology/oncology



Key inclusion criteria

- 6 months to 30 years of age.
- Patient in need of an allograft or a cycle/procedure known to cause profound cytopenia (including treatment with CAR T cells).
- Colonized by *multidrug-resistent organisms* (MDROs): only carbapenemase-producing bacteria.
- Signed informed consent (patient/parents/legal guardian).

Key exclusion criteria

- Uncontrolled active infection(s) (bacterial, viral or fungal).
- Patient affected by inflammatory bowel diseases or any other condition with altered mucosal barrier.

Primary endpoint

Decolonization rate at 4 weeks after HSCT

Secondary endpoints

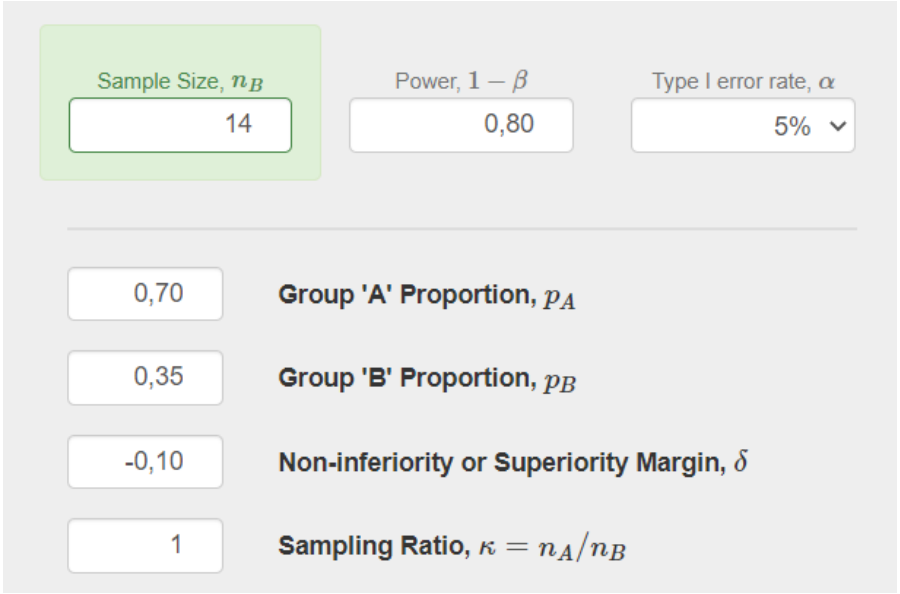
- Safety (CTC-AE)
- Decolonization rate at 1 week
- Incidence of BSI
- Changes of Shannon Index (or other metrics)
- Description of microbiota trajectories
- TRM
- Cumulative incidence of GvHD
- OS/DFS
- ….

Italian centers who agreed to participate/interested in the study

- Rome (Bambino Gesù)
- Padova
- Bologna
- Pavia
- Monza?
- Genova?

Statistics for a randomized question

Proportion of patients still colonized at 4 weeks at OPBG



Safety

- serious adverse events (SAEs) are rare
- Sistematic review (Wang et al.): adverse event (AE) incidence of 28.5%, with the majority of these deemed to be mild to moderate; including abdominal discomfort, bloating, diarrhea, constipation and transient fever.
- Among children, a multicenter retrospective cohort study of 335 pediatric patients receiving FMT for CDI (Nicholson et al.) demonstrated SAEs in 4.7% of individuals in the 3-month period following FMT
- 2 episodes of SIRS at OPBG

Safety

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.

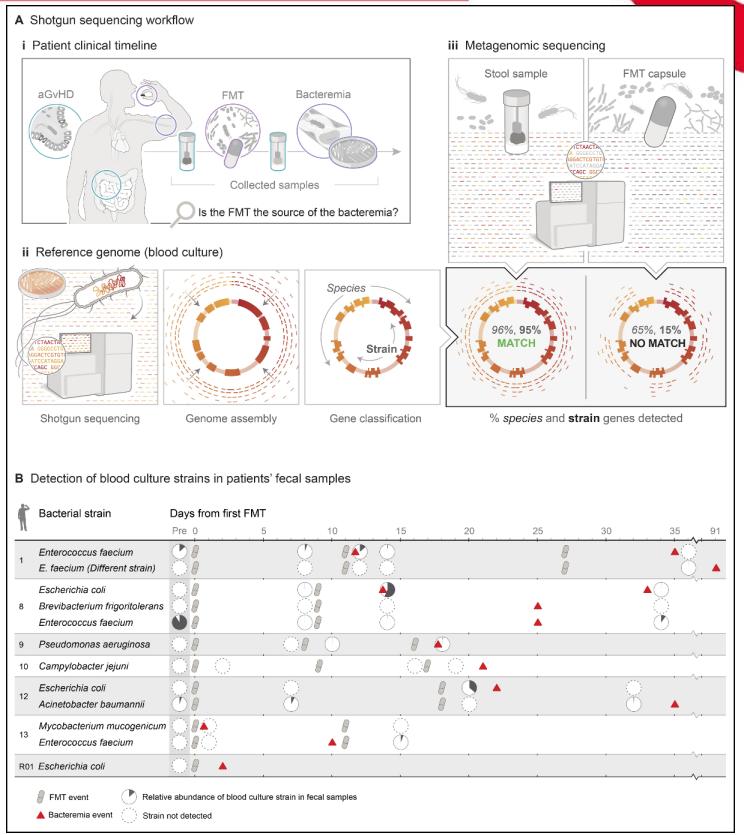
DeFilipp Z et al., New Engl J Med 2020

STIMULUS REPORT
blood advances
Check for updates

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

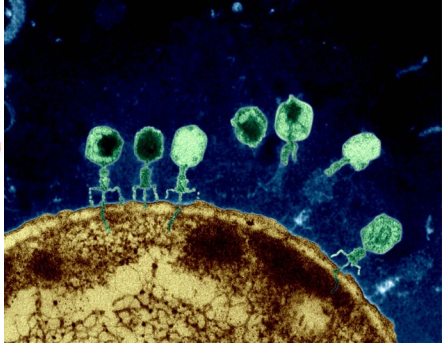
Adi Eshel,[1,*] Itai Sharon,[2,3,*] Arnon Nagler,[4,5,*] David Bomze,[4,5] Ivetta Danylesko,[4,5] Joshua A. Fein,[6] Mika Geva,[4,5] Israel Henig,[7] Avichai Shimoni,[4,5] Tsila Zuckerman,[7,8] Ilan Youngster,[9,10,*] Omry Koren,[1,*] and Roni Shouval[4,5,11,12]

[1]Azrieli Faculty of Medicine, Bar Ilan University, Safed, Israel; [2]Department of Computer Science, Tel-Hai Academic College, Qiryat Shemona, Israel; [3]Migal Galilee Research Institute, Qiryat Shemona, Israel; [4]Hematology and Bone Marrow Transplantation Division, Chaim Sheba Medical Center, Tel Hashomer, Israel; [5]Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel; [6]Department of Internal Medicine, University of Connecticut, Farmington, CT; [7]Department of Hematology and Bone Marrow Transplantation, Rambam Health Care Campus, Haifa, Israel; [8]Ruth and Bruce Rappaport Faculty of Medicine, Technion, Haifa, Israel; [9]Shamir Medical Center, Tel Aviv, Israel; [10]Department of Pediatrics, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel; [11]Adult BMT Service, Memorial Sloan Kettering Cancer Center, New York, NY; and [12]Weill Cornell Medical College, New York, NY

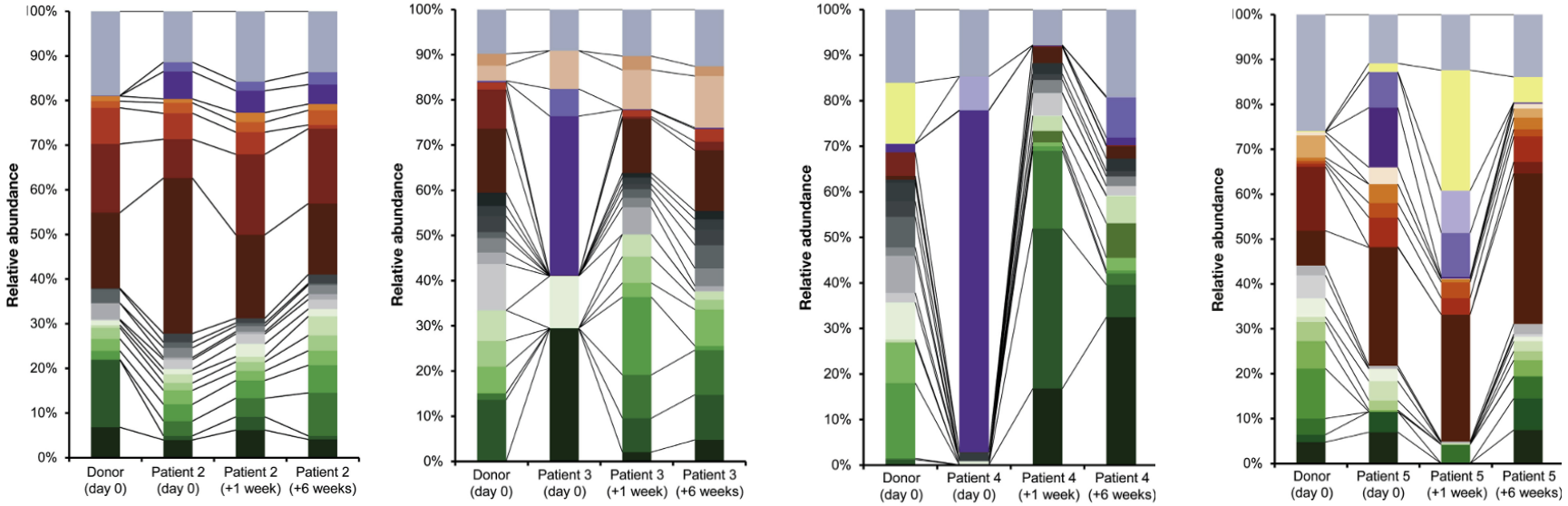


"We observed high rates of bloodstream infections (BSIs) following fecal microbiota transplantation (FMT) for graft-versus-host-disease (33 events in 22 patients). "

"Our findings support FMT safety in immunocompromised patients but do not rule out FMT as an inducer of bacterial translocation"



Efficacy of Sterile Fecal Filtrate Transfer for Treating Patients With *Clostridium difficile* Infection



Ott SJ et al., Gastroenterology 2017

Conclusions

- Indications are increasing
- Still limited data (some very promising) with no RCT
- Safety profile, with some notable exceptions
- Best donor/donors?
- Type of product
- Standards?

MINISTERO DELLA SALUTE
Istituto Superiore di Sanità
Centro Nazionale Trapianti

WHO Collaborating Centre
On Vigilance and Surveillance for
Human Cells, Tissues and Organs

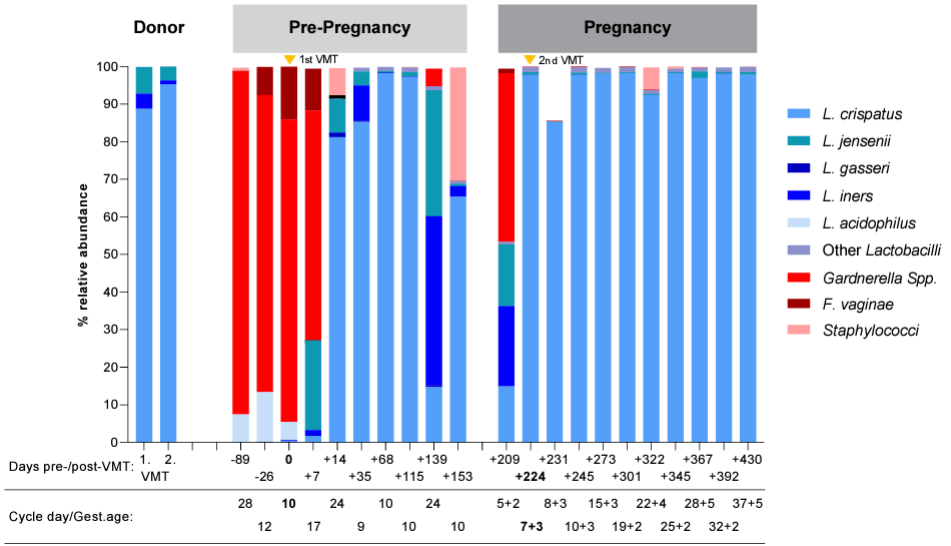
Programma Nazionale sul Trapianto di Microbiota Fecale umano (FMT) – aspetti regolatori, clinici e organizzativi. (Revisione 04.08.2020)

- ***La medicina consiste nell'introdurre medicamenti che non si conoscono in un corpo che si conosce ancora meno per guarire delle malattie di cui non sa niente.***
  (Voltaire)

AIEOP
ASSOCIAZIONE ITALIANA EMATOLOGIA ONCOLOGIA PEDIATRICA
XLVIII CONGRESSO NAZIONALE AIEOP
Bologna
2-4 Ottobre 2023

Antibiotic-free vaginal microbiota transplant with donor engraftment, dysbiosis resolution and live birth after recurrent pregnancy loss: a proof of concept case study

Tine Wrønding,[a] Kilian Vomstein,[a] Elleke F. Bosma,[b] Brynjulf Mortensen,[b] Henrik Westh,[c,k] Julie Elm Heintz,[c] Sarah Mollerup,[c] Andreas Munk Petersen,[c,d,k] Laura M. Ensign,[e,f,g,h,i,j] Kevin DeLong,[b] Johan E. T. van Hylckama Vlieg,[b] Anne Bloch Thomsen,[b] and Henriette Svarre Nielsen[a,k,*]



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Department of Hematology -Oncology , IRCCS "Bambino Gesù" Children's Hospital, Rome

Director: Franco Locatelli

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Elia Girolami
Simone Biagini
Gian Pietro Conflitti
David Malaspina

Giovanna Leone
Giovanna Del Principe
Stefania Lazzaro
Antonella Meschini

Transplant Immunogenetics

Marco Andreani
Maria Troiano
Mariarosa Battarra
Tiziana Galluccio
Paola Giustiniani

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Stefania Pane
Alessandra Russo

Endoscopy Unit

Luigi Dall'Oglio
Francesca Rea
Erminia Romeo
Simona Faraci
Filippo Torroni

Policlinico Gemelli
Luca Masucci

Bambino Gesù
OSPEDALE PEDIATRICO