Effect of FMT on antimicrobial resistance clearance

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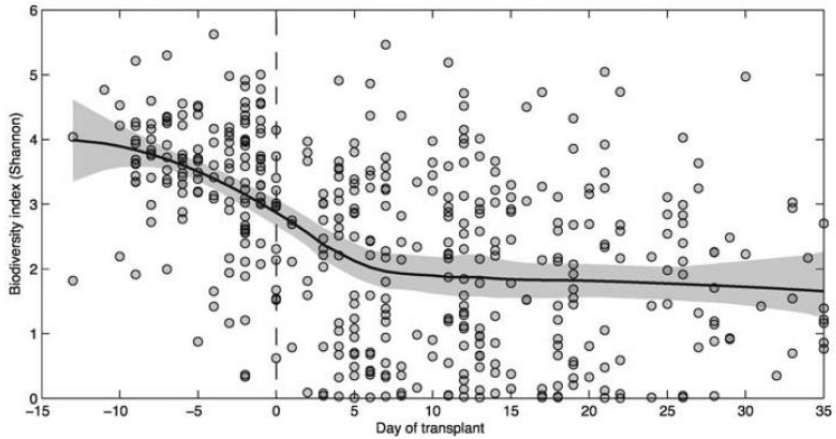
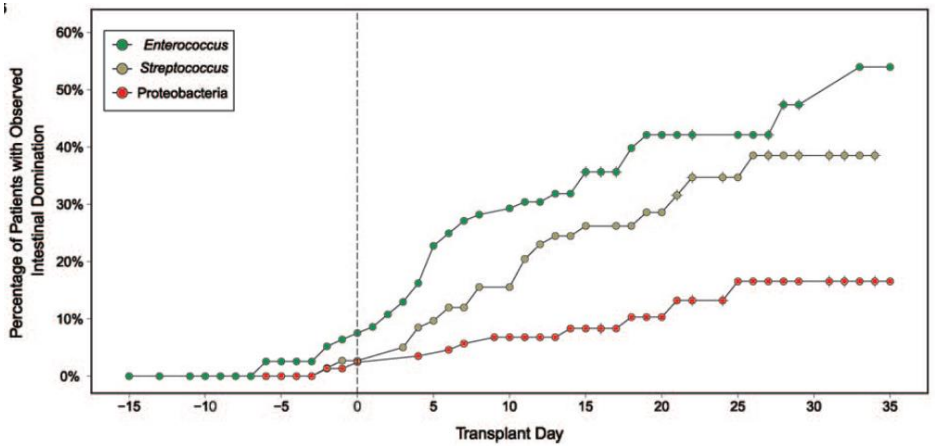
Barcelona, 2019

AlloHCT results in decreased heterogeneity of gut flora, which contributes to gut domination by single taxons



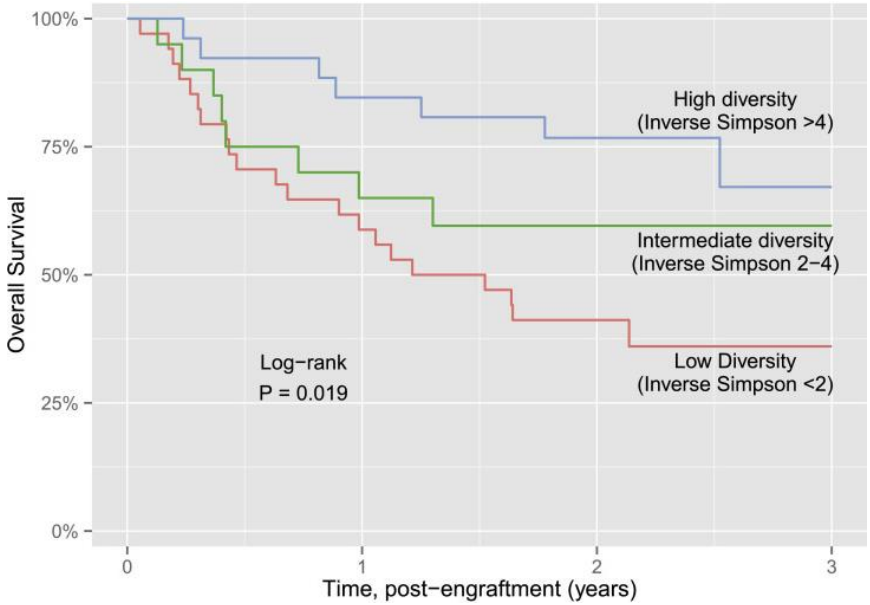


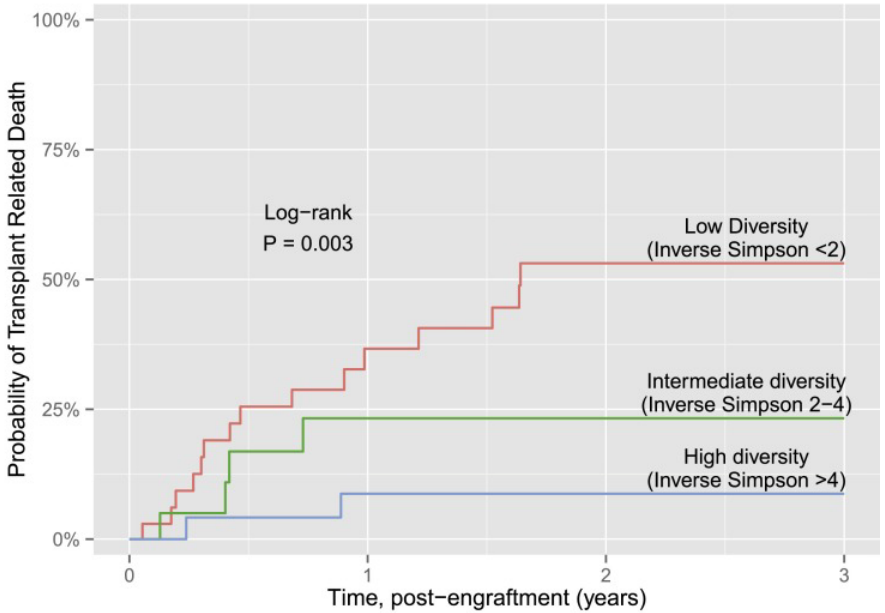
Dominance of gut by single taxons

	VRE Bacteremia		Gram-negative Bacteremia	
Dominating Taxon[b]	HR (95% CI)	*P*	HR (95% CI)	*P*
Enterococcus	9.35 (2.43–45.44)	.001	1.35 (.25–5.08)	.690
Streptococcus	0.21 (.00–1.75)	.184	0.82 (.09–3.65)	.823
Proteobacteria	0.75 (.01–6.14)	.837	5.46 (1.03–19.91)	.047

Taur et al. Clin Infect Dis 2012;55:905

Impact of gut flora diversity on the outcomes of allogeneic stem cell transplantation





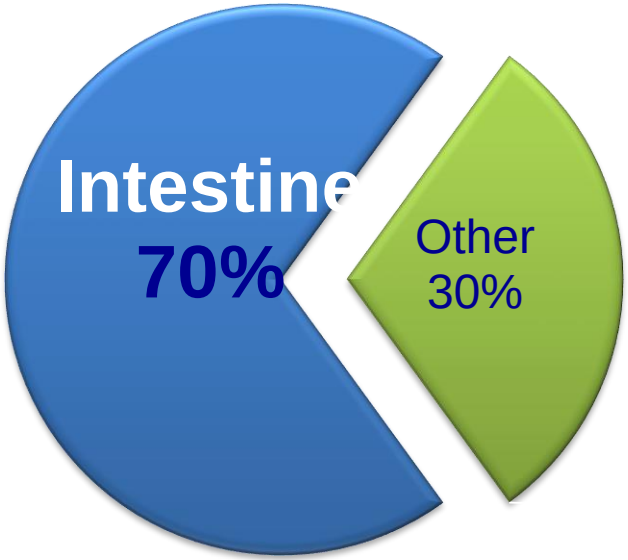
Taur et al. Blood, 2014

Dominating causes of death after allogeneic HSCT

1. Relapse
2. Infection
3. Graft versus host disease

The source of the bacteremia in AML patients

The origin of E. coli bacteremia in hematooncology group of patients



Other 30%:
- Wounds
- Respiratory tract
- Genito-urinary system
- Catheters
- Not known

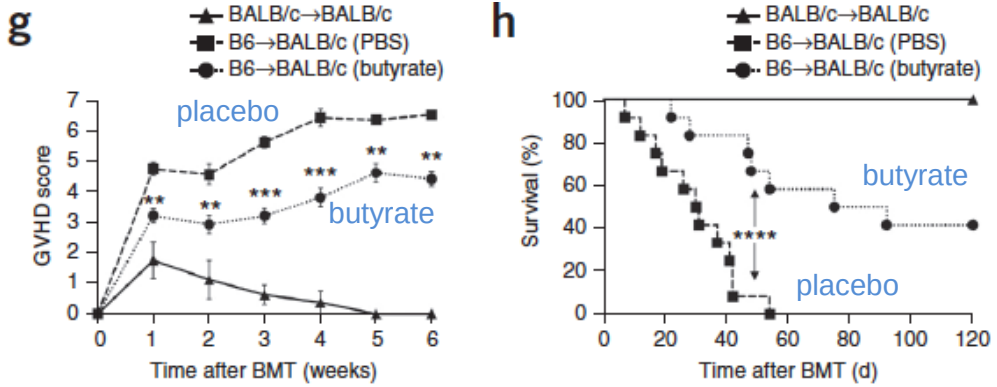
Samet A. Eur J Clin Microbiol Infect Dis. 2013; 32(11): 1393–1400

nature immunology

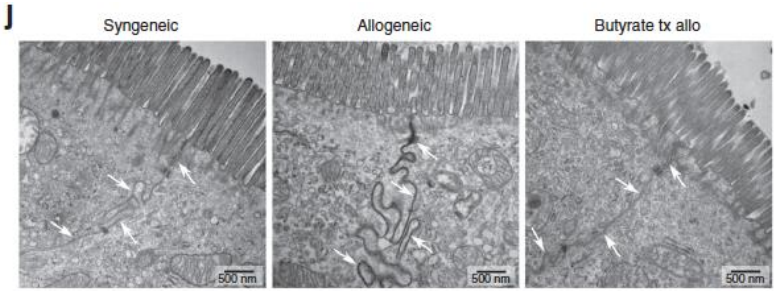
Gut microbiome–derived metabolites modulate intestinal epithelial cell damage and mitigate graft-versus-host disease

Nathan D Mathewson[1,2,7], Robert Jenq[3,7], Anna V Mathew[4,7], Mark Koenigsknecht[5,7], Alan Hanash[3,7], Tomomi Toubai[1], Katherine Oravecz-Wilson[1], Shin-Rong Wu[1,2], Yaping Sun[1], Corinne Rossi[1], Hideaki Fujiwara[1], Jaeman Byun[4], Yusuke Shono[3], Caroline Lindemans[3], Marco Calafiore[3], Thomas C Schmidt[5], Kenya Honda[6], Vincent B Young[5,7], Subramaniam Pennathur[4,7], Marcel van den Brink[3,7] & Pavan Reddy[1]

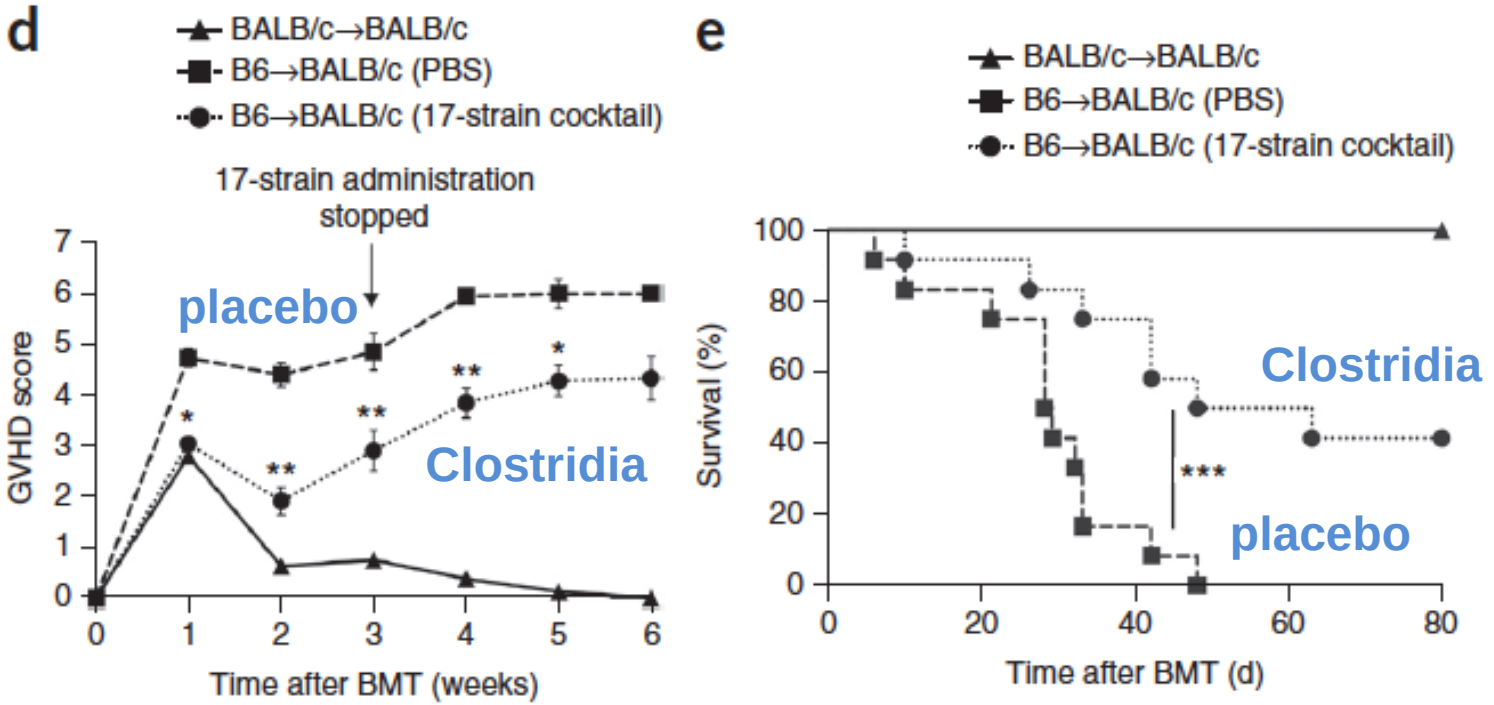
- After alloHCT the loss of butyrate in the enterocytes have epigenetic results – decreasing histone acetylation;
- This reduces the thightness between enterocytes



Exogenous butyrate supplementation decreases apoptosis of the enterocytes, improves junctional integrity and mitigates GvHD increasing OS



Similar effect was reached after administration of cocktail of 17 Clostridial species



Mathewson et al. Nat. Immunology 2016

Colonization resistance

THE FATAL ENTERIC CHOLERA INFECTION IN THE GUINEA PIG, ACHIEVED BY INHIBITION OF NORMAL ENTERIC FLORA

ROLF FRETER*
From the Department of Microbiology, The University of Chicago, Chicago 37, Illinois

RESISTANCE OF THE MOUSE'S INTESTINAL TRACT TO EXPERIMENTAL SALMONELLA INFECTION

II. Factors Responsible for Its Loss Following Streptomycin Treatment*

By MARJORIE BOHNHOFF, C. PHILLIP MILLER, M.D., and WILLIAM R. MARTIN,‡ Ph.D.

(*From the Departments of Medicine and Microbiology, University of Chicago, Chicago*)

(Received for publication, July 2, 1964)

TABLE VI

Growth of Salmonella in Colon Content of Streptomycin-Treated and Untreated Mice

Colon content* obtained:	Increase (log 2) in No. of *Salmonella*							
	pH 6.0		pH 6.1		pH 6.2		pH 6.4	
	6 hrs.	24 hrs.	6 hrs.	24 hrs.	6 hrs.	24 hrs.	6 hrs.	24 hrs.
1 day after treatment‡	4.3	17.6 (5)	5.4	18.0 (15)	5.7	18.2 (5)	5.9	19.0 (5)
3 " " "	2.7	15.4 (6)	3.7	17.6 (14)	5.1	18.0 (4)		
5 " " "	1.5	12.3 (4)	3.0	17.0 (14)	4.8	17.6 (6)		
Untreated controls	−0.4	1.1 (12)	0.3	7.2 (15)	1.4	11.1 (11)		

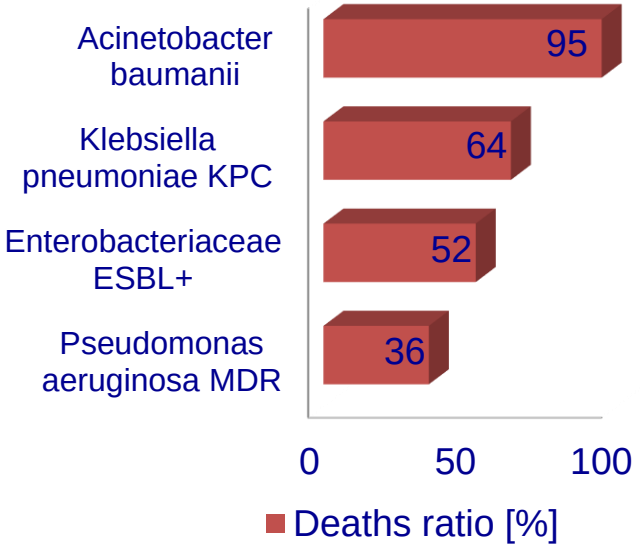
Results given as means of the number of observations shown in parenthesis.

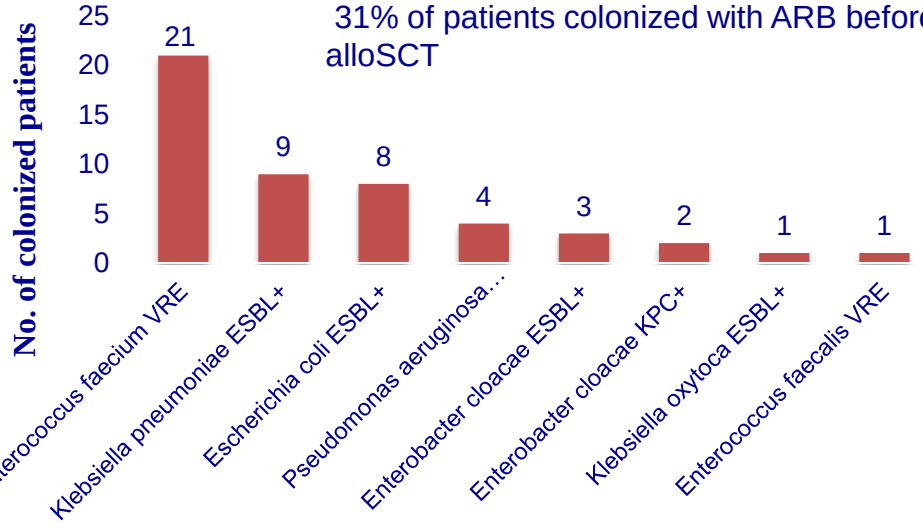
* Heat-Killed supernatants of buffered suspensions of pooled content of cecum and transverse colon from 15 to 20 mice.

‡ 50 mg streptomycin *per os*.

Freter R. J Infect Dis 1955; 97: 57–65; Bohnhoff MJ. Exp Med 1964;120: 817–828.

Death incidence in patients previously colonized with antibiotic resistant bacteria (ARB) – hematology population



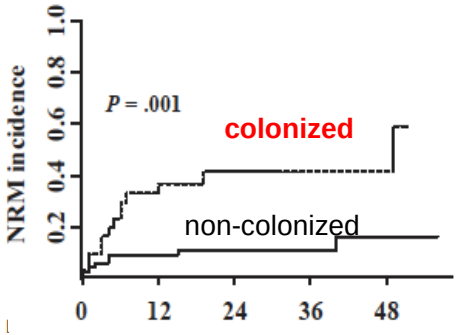


Girmenia C. Bone Marrow Transplant. 2015; 50**,** 282–288; Kim SB. Scand J Infect Dis 2014; 46(2):81–8; Pagano L. 2014;20(7):1235-1236; Tumbarello M. Antimicrobial Agents and Chemotherapy. 2006;50(2):498-504; Caselli D. Haematologica. 2010;95(9):1612-1615

Biliński J. Biol Blood Marrow Transplant 2016; 22(6):1087-93

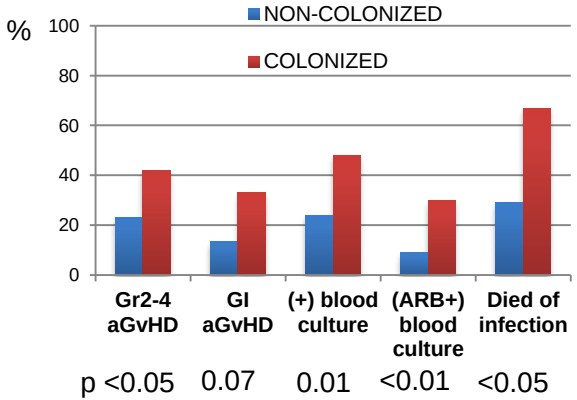
Gut microbiota affect outcomes of patients after allogeneic hematopoietic cell transplantation (alloHCT)

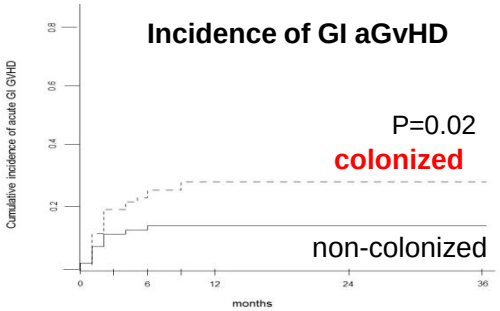
- **Gut colonization by antibiotic-resistant bacteria (ARB) before alloHCT contributes to decreased OS and increased NRM after transplantation**



Risk factor	HR	p
Colonized patient	**3.53**	**0.0006**
Age of recipient > 50 years	1.21	NS
High-risk disease	2.00	0.07
Unrelated donor	1.56	NS
Myeloablative conditioning	0.59	NS

- **due to increased rate of infections, gr. 2-4 aGvHD and gut aGvHD**





Biliński…and Basak. Biol Blood Marrow Transplant 2016

Peric Z et al. (Biol Blood Marrow Transplant 2017)

Restoration/regeneration of healthy gut microbiome by FECAL MICROBIOTA TRANSPLANTATION (FMT) cures resistant Clostridium difficile colitis

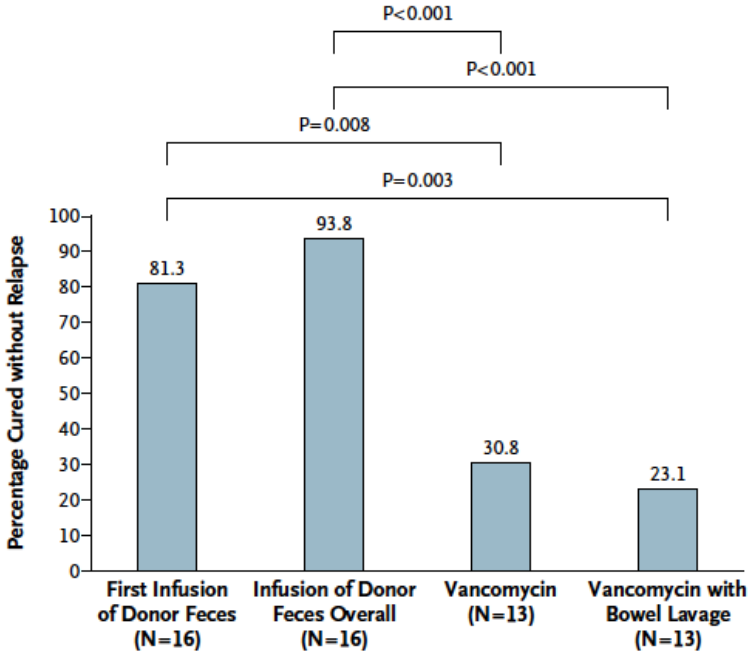
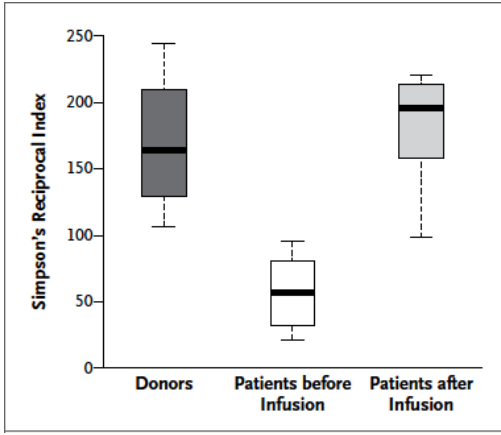


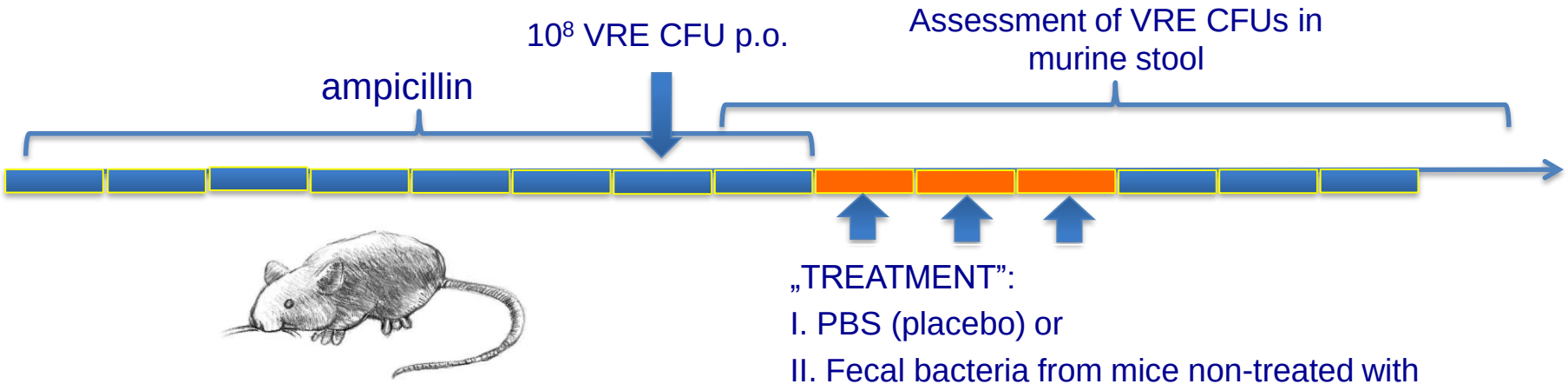
Table 2. Adverse Events in 16 Patients in the Infusion Group.*

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‡



Van Nood et al. NEJM 2013

Colonization resistance – FMT inhibits the VRE colonization in mice treated with ampicillin



„TREATMENT”:

I. PBS (placebo) or

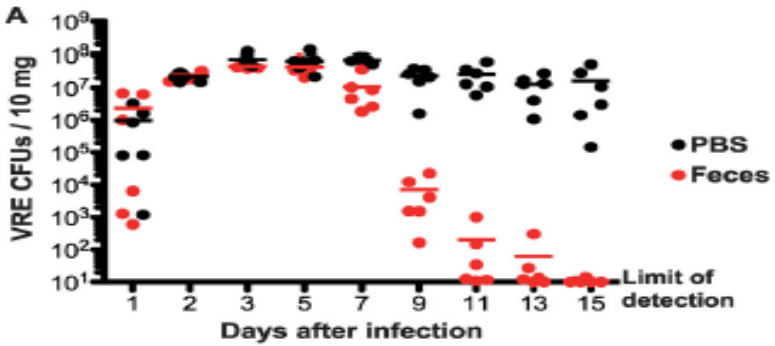
II. Fecal bacteria from mice non-treated with ampicillin, cultured in aerobic conditions (aero) or

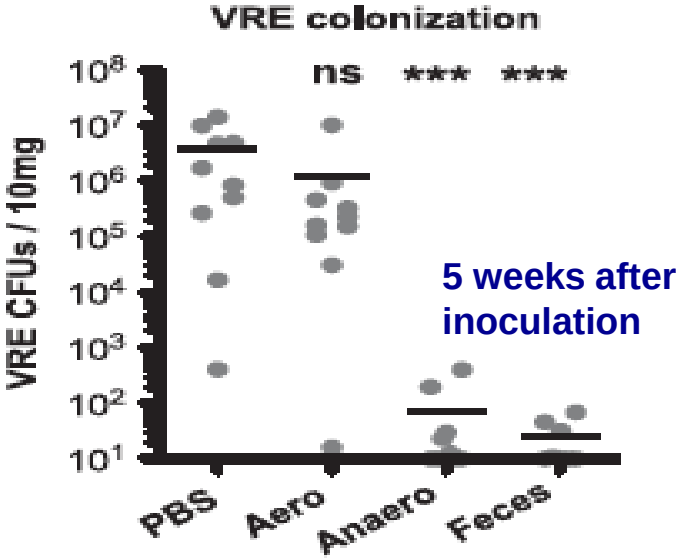
III. Fecal bacteria from mice non-treated with ampicillin, cultured in anaerobic conditions (anaero) or

IV. Feces solution from mice non-treated with ampicillin (feces)

Ubeda C. Inf Immunity 2013;81:965

Colonization resistance – FMT inhibits the VRE colonization in mice treated with ampicillin



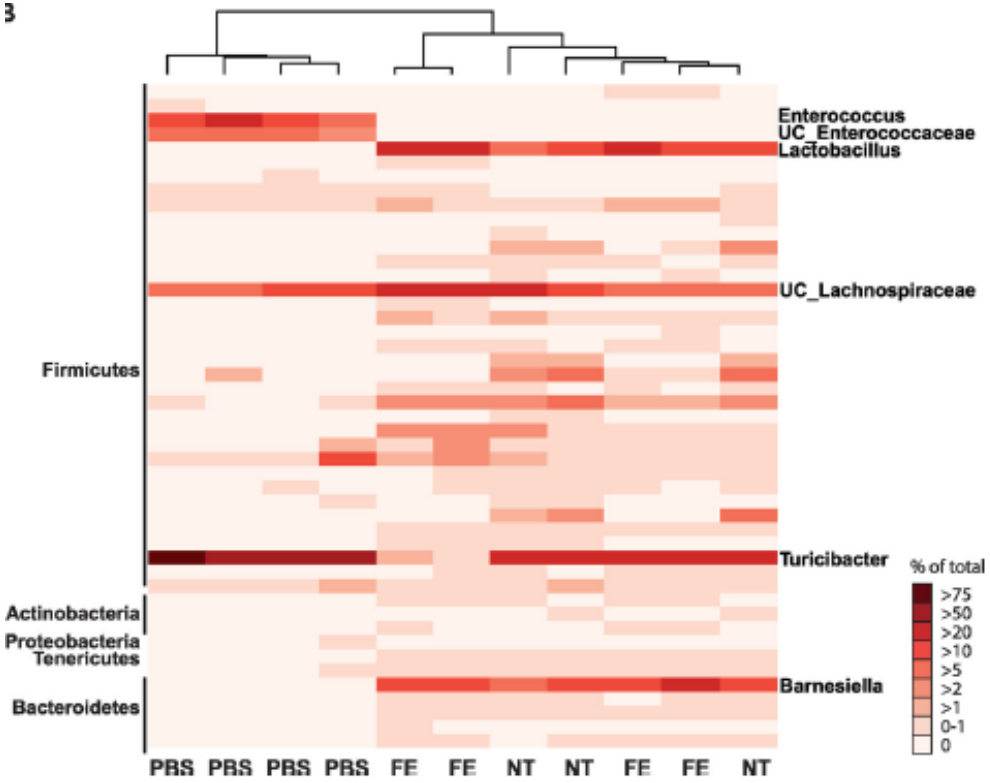


Day 15 – VRE density per 1g of feces under the detection limit

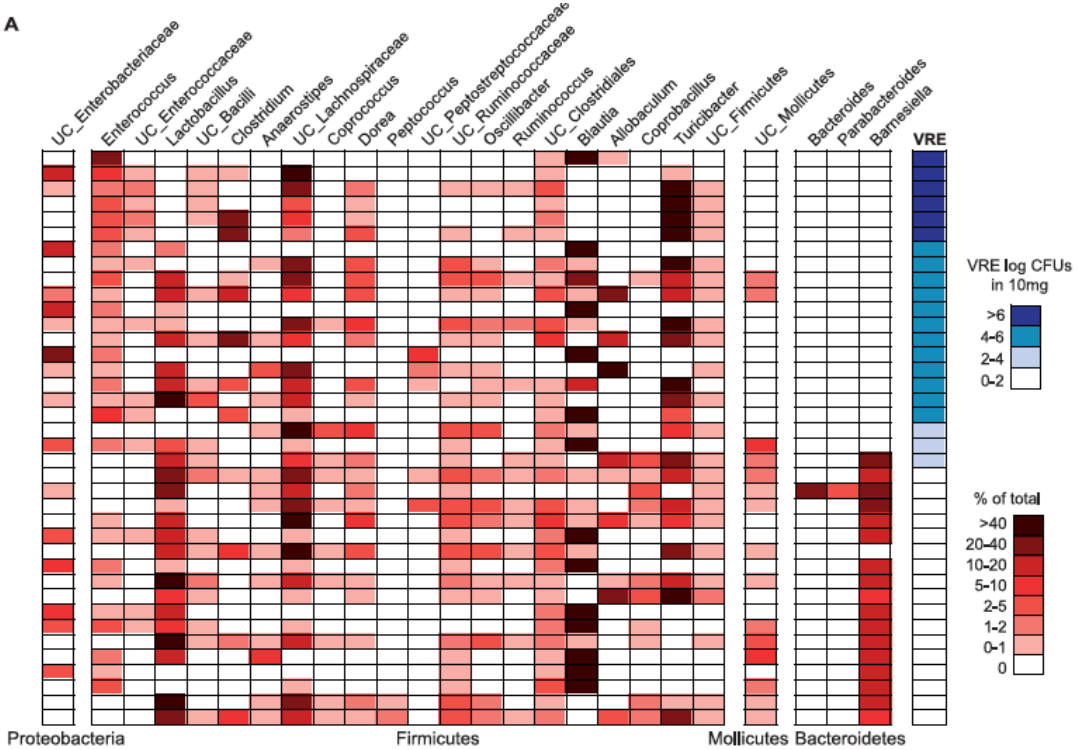
Ubeda C. Inf Immunity 2013;81:965

Commensal anaerobic bacteria suppress VRE colonization in antibiotic-treated mice

- Composition of the microbiotas of PBS and fecal transplant (FE) mice was analyzed 15 days following infection and compared with that of the microbiotas of untreated mice (NT).
- Hierarchical clustering was used to cluster samples by their microbiota composition at the genus level.
- Each column represents one mouse. Each row represents one genus. The most predominant phyla (left) and genera (right) are indicated.



Reconstitution with Barnesiella correlates with VRE clearance.



While reconstitution of mice with bacterial taxa varied from mouse to mouse irrespective of VRE density, clearance of VRE was markedly enhanced in mice recolonized with bacteria belonging to the Barnesiella genus

Similar observations in murine model have been made according to eradication of Gram (–) bacteria from the gut

- Administration of a diverse microbiota to chronically infected mice can lead to clearance of **Salmonella typhimurium** from the gut lumen, suggesting that some components of the normal flora either displace S. typhimurium or create an inhospitable environment */Endt et al. PLoS Pathog 2010; 6:e1001097./.*
- Recent studies using the murine Salmonella typhimurium model of intestinal infection demonstrated that bacteria belonging to the **Porphyromonadaceae** family are associated with resistance to intestinal infection, suggesting that this subset of obligately anaerobic bacteria belonging to the **Bacteroidetes phylum** provides colonization resistance against at least some pathogenic Gram-negative bacteria */Ferreira et al. PLoS One 2011; 6:e20338./.*

Cell Host Microbe. 2018 Aug 8;24(2):296-307.e7. doi: 10.1016/j.chom.2018.07.002. Epub 2018 Jul 26.

A Gut Commensal-Produced Metabolite Mediates Colonization Resistance to Salmonella Infection.

Jacobson A[1], Lam L[1], Rajendram M[2], Tamburini F[3], Honeycutt J[1], Pham T[1], Van Treuren W[1], Pruss K[1], Stabler SR[4], Lugo K[1], Bouley DM[5], Vilches-Moure JG[5], Smith M[4], Sonnenburg JL[6], Bhatt AS[7], Huang KC[8], Monack D[9].

⊕ Author information

Abstract

The intestinal microbiota provides colonization resistance against pathogens, limiting pathogen expansion and transmission. These microbiota-mediated mechanisms were previously identified by observing loss of colonization resistance after antibiotic treatment or dietary changes, which severely disrupt microbiota communities. We identify a microbiota-mediated mechanism of colonization resistance against Salmonella enterica serovar Typhimurium (S. Typhimurium) by comparing high-complexity commensal communities with different levels of colonization resistance. Using inbred mouse strains with different infection dynamics and S. Typhimurium intestinal burdens, we demonstrate that Bacteroides species mediate colonization resistance against S. Typhimurium by producing the short-chain fatty acid propionate. Propionate directly inhibits pathogen growth in vitro by disrupting intracellular pH homeostasis, and chemically increasing intestinal propionate levels protects mice from S. Typhimurium. In addition, administering susceptible mice Bacteroides, but not a propionate-production mutant, confers resistance to S. Typhimurium. This work provides mechanistic understanding into the role of individualized microbial communities in host-to-host variability of pathogen transmission.

Hypothesis:

Reintroduction of commensal flora by fecal microbiota transplantation (FMT) could be used to eradicate antibiotic-resistant bacteria (ARB) from the gut in order to improve outcomes of alloHCT in the future

METHODS (1)

Design: Prospective interventional study */ClinicalTrials.gov ID: NCT02461199/*

Inclusion criteria:

Colonization of the GI tract with ARB: **CPE**, **ESBL+ *Enterobacteriaceae***, **VRE** and **other bacteria with documented resistance to at least two classes of antibiotics** (documented by at least two positive cultures of material from rectal swabs taken within 2 weeks before FMT).

ANC on the day of FMT ≥0.5 G/L.

Age≥18y

Exclusion criteria:

Planned use of strong myelosuppressive **chemotherapy within 2 days after FMT**,

First 30 days after HCT,

Mucositis (excluding symptoms of graft-versus-host disease),

Requirement for intensive antimicrobial therapy.

Bilinski… and Basak. Clin Infect Dis. 2017

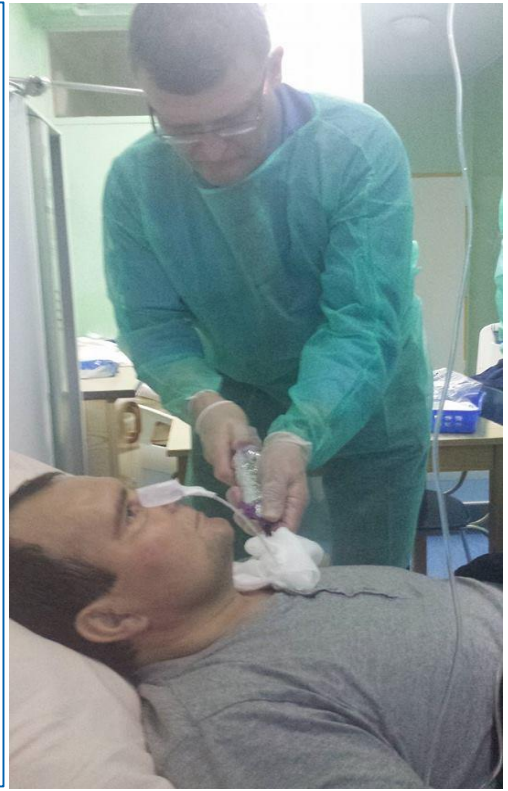
METHODS (2)

Fecal donors: 3 **unrelated donors** thoroughly evaluated according to universal recommendations

Fecal material: fresh sample homogenized in saline, filtered and diluted (100g/200 ml)

FMT procedure:

From day -1: proton pump inhibitors, standard bowel cleansing with macrogols, strict diet from late afternoon;
Day 0: PPI, insertion of **nasoduodenal tube**, infusion of 200 ml of fecal sample;
Day 1: PPI, repeated infusion of 200 ml of fecal sample;



- Bilinski… and Basak. Clin Infect Dis. 2017

METHODS (3)

Evaluation of results:

Continuous monitoring of side effects

Basic biochemistry, CRP, procalcitonin

Time points: 1 week, 1 month, 6 months: >2 x rectal swabs for bacterial culture and PCR

Definitions:

Decolonization: negative result for ≥2 consecutive rectal swab cultures. ***/when CPE, a negative result of a qPCR also required/.***

Complete ARB decolonization: decolonization of all the strains of ARB,

Partial ARB decolonization: decolonization of at least one strain of ARB.

- **Primary endpoint:** complete ARB decolonization at one month after FMT;
- **Secondary endpoints:** safety assessments and partial ARB decolonization.

Bilinski… and Basak. Clin Infect Dis. 2017

PATIENTS' CHARACTERISTICS

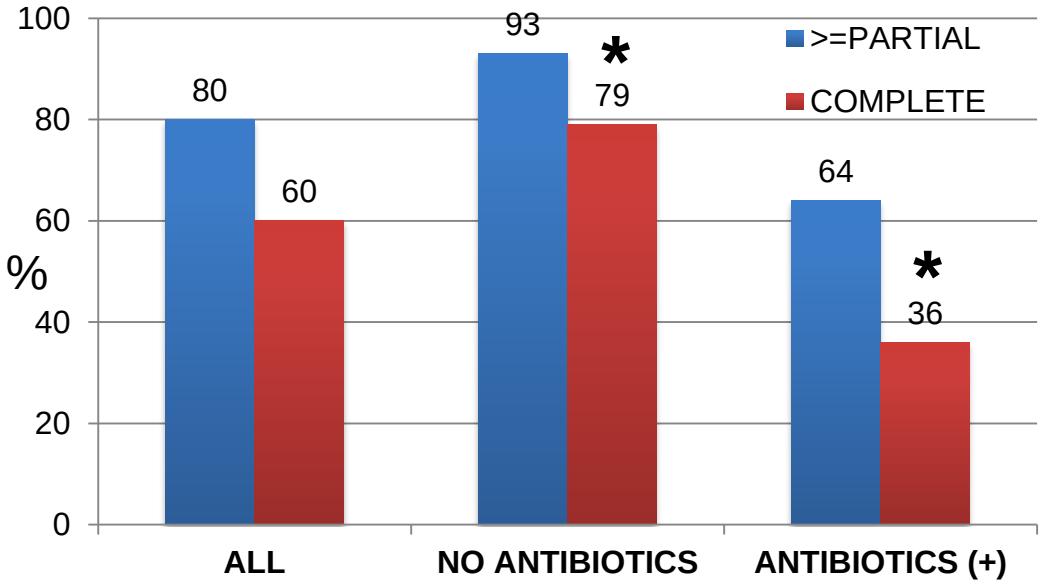
Characteristic	
Participants	20
FMTs	25
Participants who underwent 2/3 FMTs	3/1
Male sex	14 (56%)
Age at FMT (years, median, range)	51 (22-77)
ANC at FMT (x10^9/L, median, range)	2.1 (0.5-16.5)
Diagnosis	
AML	5
aGvHD	4
cGvHD	2
MM	3
DLBCL	2
MDS	1
Lung cancer	1
TTP	1
Kidney transplant recipient	1

GUT-COLONIZING ARB	
Strains of colonizing ARB (median, range)	2 (1-4)
Klebsiella pneumoniae	N
NDM1+	14
Other, carbapenem-resistant	3
ESBL+	2
Escherichia coli	
ESBL+	11
OXA-48+	1
Pseudomonas aeruginosa	
MBL+	2
Other, carbapenem-resistant	2
Carbapenem-resistant *Enterobacter cloacae*	2
Vancomycin-resistant enterococci (VRE)	2
Acinetobacter ursingii MBL+	1
Stenotrophomonas maltophilia	1

Bilinski… and Basak. Clin Infect Dis. 2017

RESULTS:

Decolonization rate **at 1 month** after FMT (as % of the procedures)



* p<0.05

Bilinski… and Basak. Clin Infect Dis. 2017

- **Complete ARB decolonization was achieved in 15/20 (75%) of the participants (including repeated FMTs).**

- Decolonization could be investigated by PCR in 17 individuals:
- 53% negative at 1 month
- 89% negative at 6 months.

Eradication rate of specific ARB bacteria:

- *Klebsiella pneumoniae* **53%**
- *E. coli* **100%**

RESULTS: adverse events after FMT

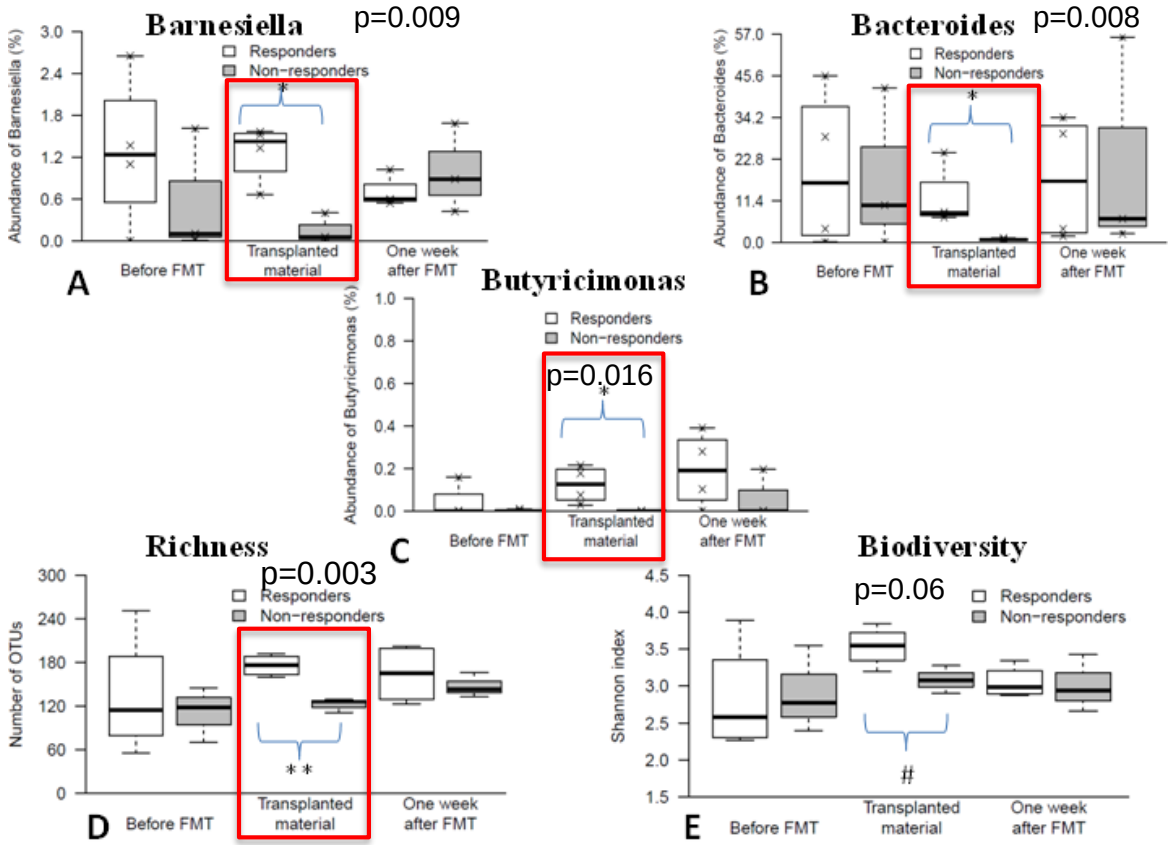
40% of patients in neutropenia at FMT (NEU 0.5-1.8 G/L)

Event	No.	%	Comment
Vomiting	1	4	Immediately after infusion
Diarrhea within 3 days after FMT	25	100	Grade 1, transient
Abdominal pain	2	8	Grade 3, present already before FMT
Ileus	2	8	Grade 2, present already before FMT

Grading according to the CTCAE v. 4.0

Bilinski… and Basak. Clin Infect Dis. 2017

RESULTS: NGS sequencing of stool samples from donors and patients (taken before and after FMT) colonized with *Klebsiella pneumoniae* NDM1+



white bars: responders (n=4)
gray bars: non-responders (n=3)

Next-generation sequencing of 16S rRNA revealed **correlation between high richness of the transplanted fecal material as well as higher abundance of**

- ***Barnesiella***
- ***Bacteroides***
- ***Butyrycimonas***

and eradication of *K. pneumoniae*

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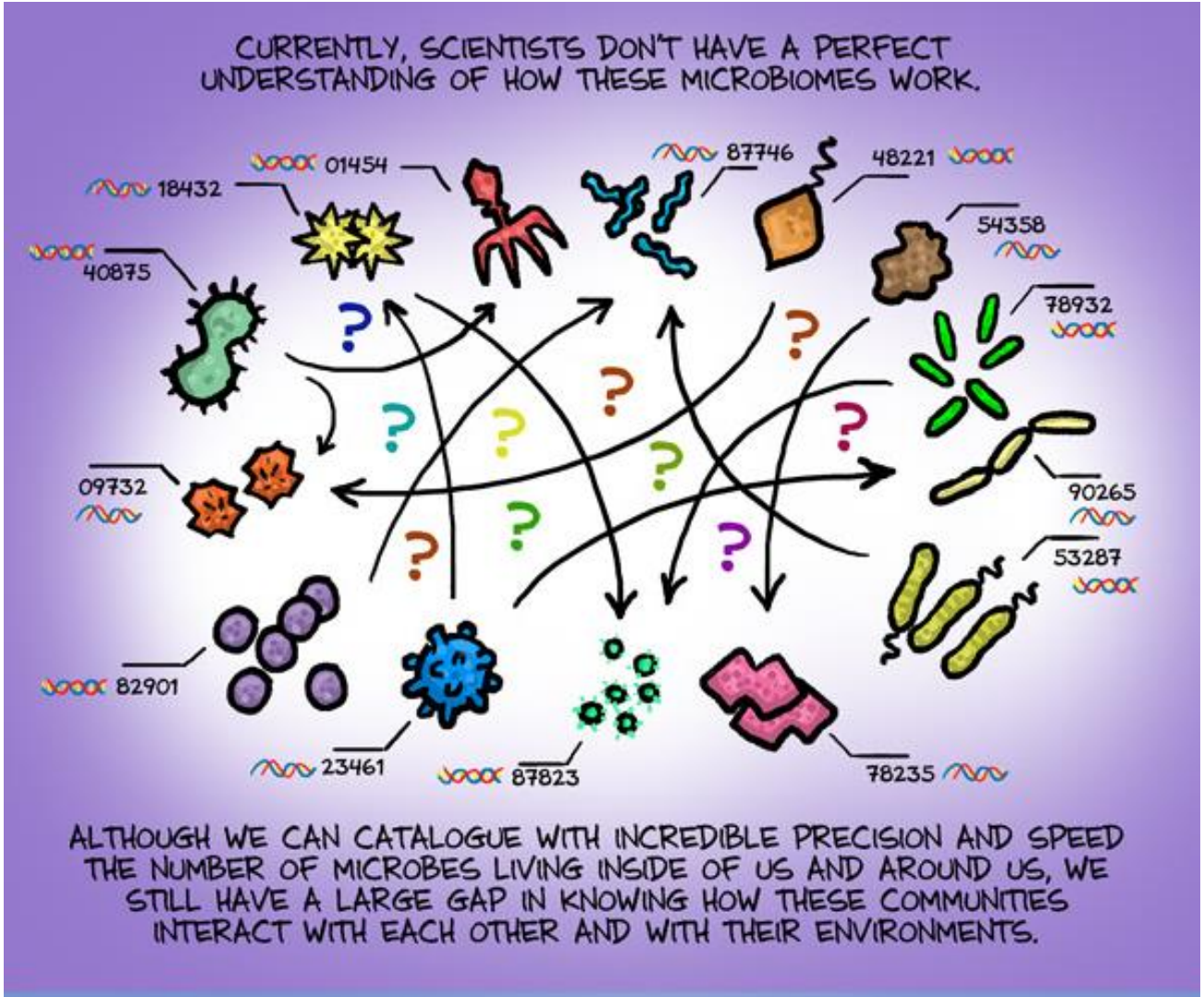

CURRENTLY, SCIENTISTS DON'T HAVE A PERFECT UNDERSTANDING OF HOW THESE MICROBIOMES WORK.
01454
18432
87746
48221
54358
40875
78932
09732
90265
53287
82901
23461
87823
78235
ALTHOUGH WE CAN CATALOGUE WITH INCREDIBLE PRECISION AND SPEED THE NUMBER OF MICROBES LIVING INSIDE OF US AND AROUND US, WE STILL HAVE A LARGE GAP IN KNOWING HOW THESE COMMUNITIES INTERACT WITH EACH OTHER AND WITH THEIR ENVIRONMENTS.

FMT before or after alloHCT

5 patients with gut aGvHD and ARB colonization/*Clostridium difficile* inf.

2 patients: clinical improvement after transient exacerbation of diarrhoea, relapse of aGvHD in 1 patient after 6 months, responded to 2nd FMT, immunosuppression-free one month after 1st FMT and at LFU

1 patient: stabilisation of symptoms, rise in CRP and fever

2 patients: no response, severe condition at the procedure time, required antibiotics just after FMT due to severe infections; died of GvHD and sepsis 1 month after FMT

2 patients with cGvHD: no objective impact on cGvHD symptoms

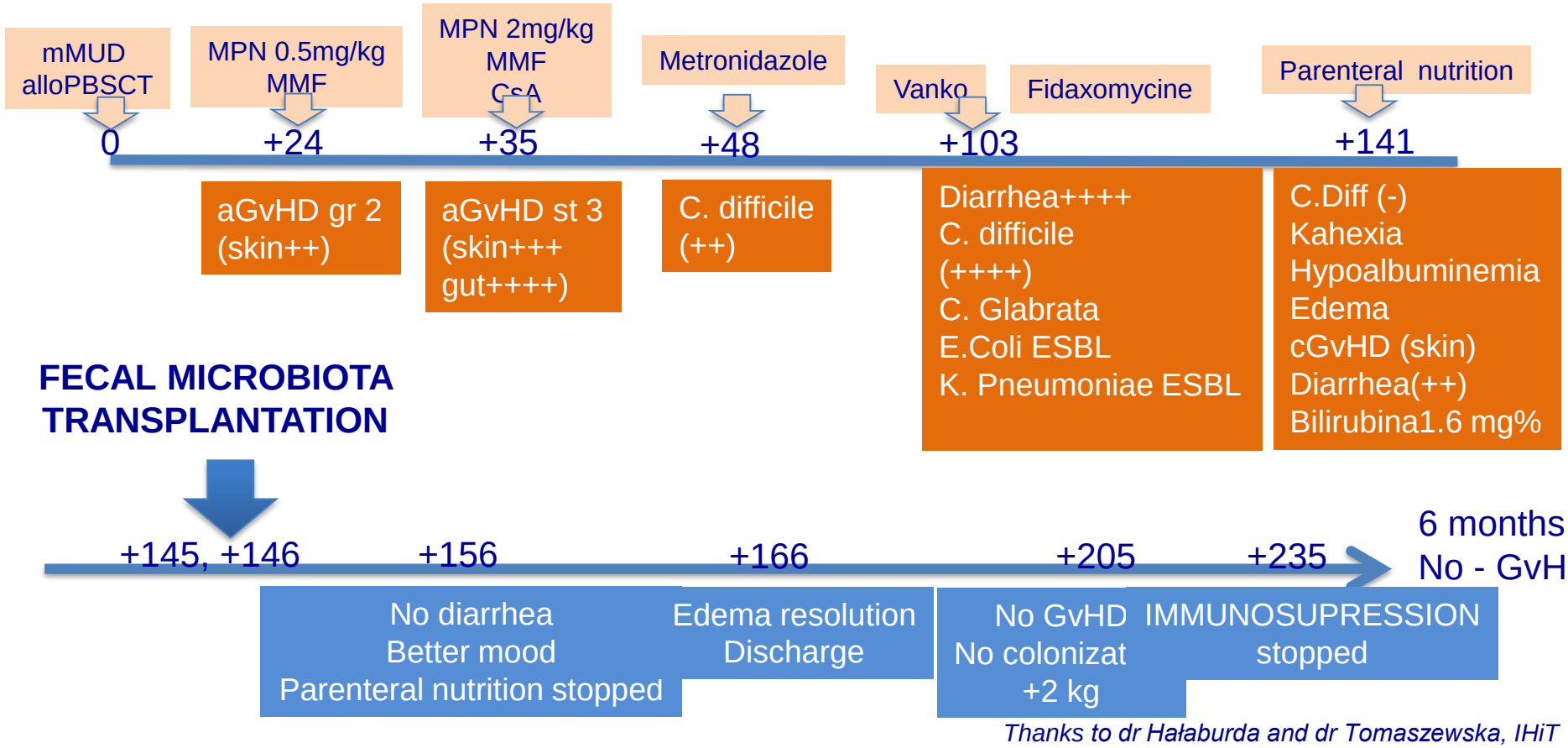
5 patients - FMT before alloHCT:

No septic episodes;

No acute or chronic GvHD after alloHCT;

2 deaths due to disease relapse

FMT after alloHCT in patient with severe aGvHD



Thanks to dr Hałaburda and dr Tomaszewska, IHiT

BMC Res Notes. 2018 Mar 22;11(1):190. doi: 10.1186/s13104-018-3293-x.

Fecal microbiota transplantation against intestinal colonization by extended spectrum beta-lactamase producing Enterobacteriaceae: a proof of principle study.

Singh R[1,2], de Groot PF[3], Geerlings SE[4], Hodiamont CJ[5], Belzer C[6], Berge IJMT[7], de Vos WM[6], Bemelman FJ[7], Nieuwdorp M[8,9,10,11].

Author information

Abstract

OBJECTIVE: Infections with multidrug-resistant microorganisms are associated with increased hospitalization, medication costs and mortality. Based on our fecal microbiota transplantation (FMT) experience for Clostridium difficile infection, we treated 15 patients carrying ESBL-producing Enterobacteriaceae (ESBL-EB) with FMT. Seven patients underwent a second FMT after 4 weeks when ESBL-EB remained, amounting to a total number of 22 transplants. The objective was decolonization of ESBL-EB.

RESULTS: Three out of fifteen (20%) patients were ESBL-negative at 1, 2 and 4 weeks after the first transplant, while six out of 15 (40%) were negative after the second transplant. Comparison of fecal microbiota at baseline and 4 weeks after FMT revealed restoration of microbial diversity after FMT and a microbial shift towards donor composition. Finally, we suggest several possible factors of response to therapy, such as donor-recipient microbiota match and number of FMTs. Therefore, FMT can be an effective treatment in patients carrying ESBL-EB. Response may be determined by microbiota composition and number of FMT procedures. Trial registration ISRCTN ISRCTN48328635 Registered 11 October 2017, retrospectively registered.

KEYWORDS: ESBL; Fecal microbiota transplantation; Microbiota; Multidrug resistance microorganisms

BMC Res Notes. 2018 Mar 22;11(1):190. doi: 10.1186/s13104-018-3293-x.

Fecal microbiota transplantation against intestinal colonization by extended spectrum beta-lactamase producing Enterobacteriaceae: a proof of principle study.

Singh R[1,2], de Groot PF[3], Geerlings SE[4], Hodiamont CJ[5], Belzer C[6], Berge IJMT[7], de Vos WM[6], Bemelman FJ[7], Nieuwdorp M[8,9,10,11].

Author information

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Médecine et maladies infectieuses

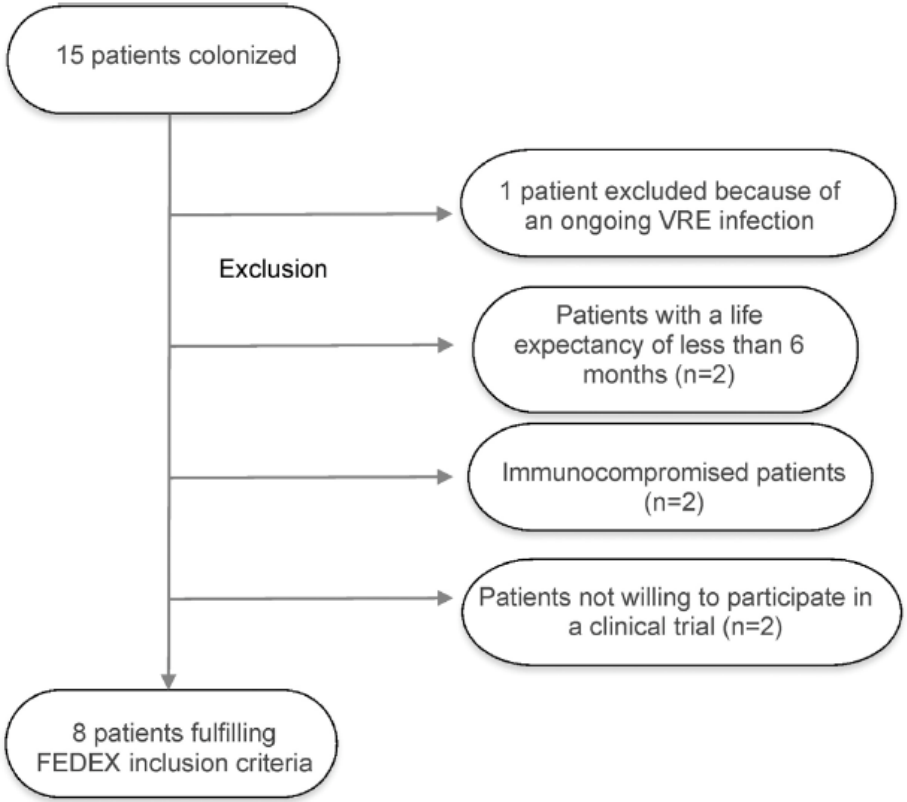
Médecine et maladies infectieuses xxx (2018) xxx–xxx

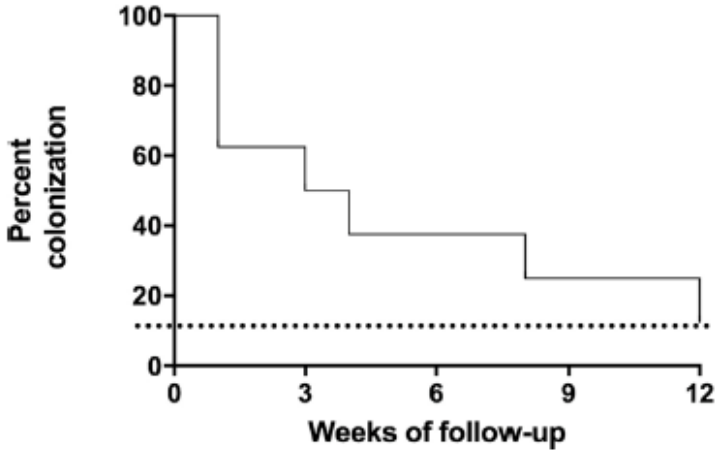
Short communication

Fecal microbiota transplantation to eradicate vancomycin-resistant enterococci colonization in case of an outbreak

Impact de la transplantation de microbiote fécal sur la colonisation à entérocoque résistant à la vancomycine dans le cadre d'une épidémie

B. Davido [a,*], R. Batista [b], H. Fessi [c], H. Michelon [d], L. Escaut [e], C. Lawrence [f], M. Denis [g], C. Perronne [a], J. Salomon [a], A. Dinh [a]


15 patients colonized
1 patient excluded because of an ongoing VRE infection
Exclusion
Patients with a life expectancy of less than 6 months (n=2)
Immunocompromised patients (n=2)
Patients not willing to participate in a clinical trial (n=2)
8 patients fulfilling FEDEX inclusion criteria


Percent colonization
100
80
60
40
20
0
0
3
6
9
12
Weeks of follow-up

IDCases 13 (2018) e00432

Contents lists available at ScienceDirect

IDCases

journal homepage: www.elsevier.com/locate/idcr

Case report

Fecal microbiota transplantation as a potential way to eradicate multiresistant microorganisms

Cátia Dias*, Sara Pipa, Filipa Duarte-Ribeiro, Margarida Mota

Department of Internal Medicine, Centro Hospitalar de Vila Nova de Gaia/Espinho, Portugal

FDA In Brief: FDA warns about potential risk of serious infections caused by multi-drug resistant organisms related to the investigational use of Fecal Microbiota for Transplantation

FDA In Brief

June 13, 2019

Media Inquiries

Content current as of:
06/19/2019

CONCLUSIONS

- FMT is a **safe** procedure for patients with blood disorders, including those before and after alloHCT;
- FMT promoted decolonization of most participants, although administration of antibiotics shortly after FMT decreased the success rate;
- Eradication of *K. pneumoniae NDM1+* may depend on the higher abundance of *Barnesiella* spp., *Bacteroides* and/or *Butyricimonas* in the transplanted fecal material;
- **FMT appears to constitute a valid tool to tackle colonization of the gut by ARB in patients with blood disorders and for potential modulation of gut microbiome in the context of alloHCT.**

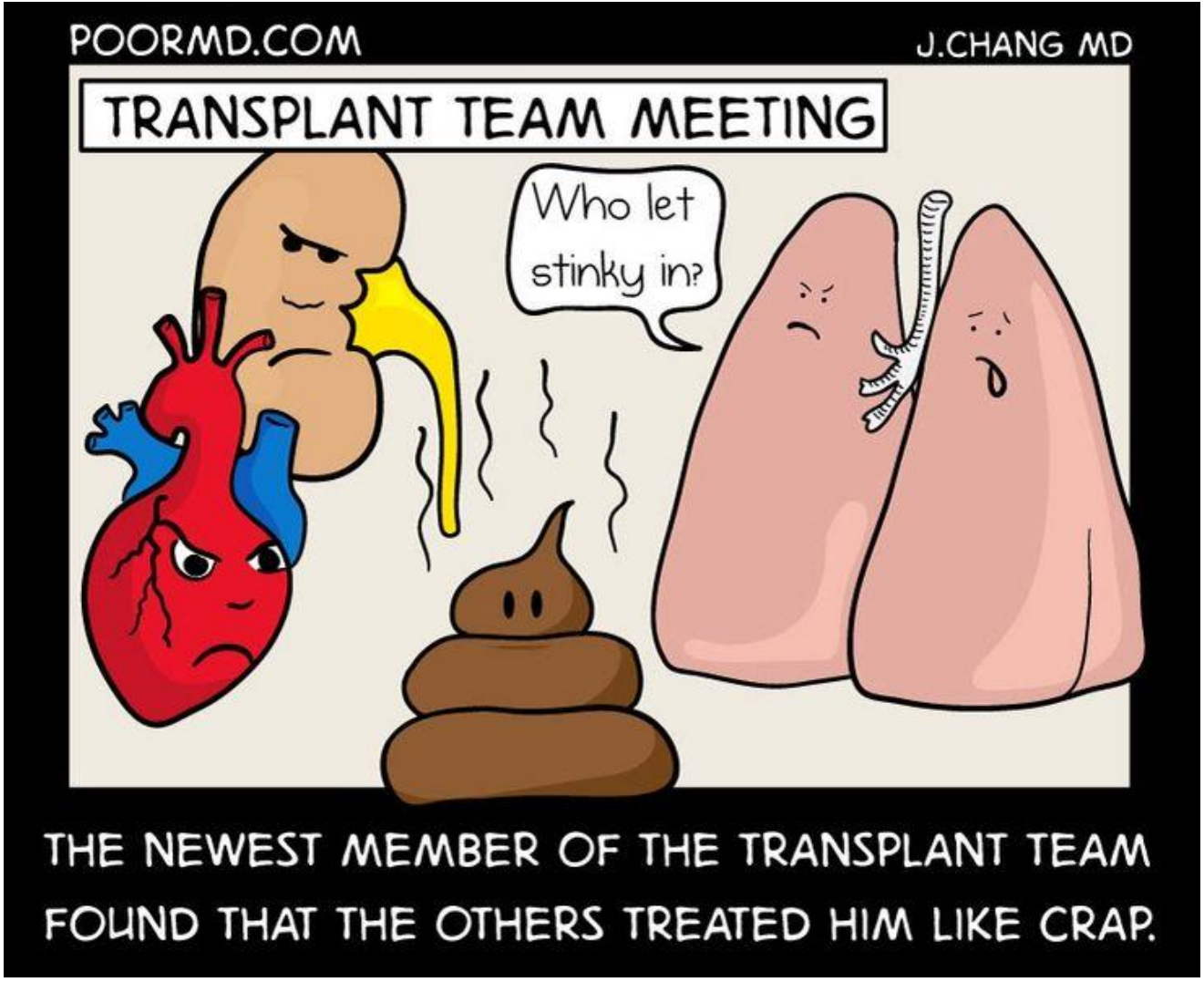
Acknowledgements

Dr. Jarosław Biliński

Dr. Paweł Grzesiowski

Prof. Wiesław Wiktor-Jędrzejczak

… and all the collaborators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THE NEWEST MEMBER OF THE TRANSPLANT TEAM FOUND THAT THE OTHERS TREATED HIM LIKE CRAP.