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Fondazione Policlinico Universitario A. Gemelli
Università Cattolica del Sacro Cuore

AMCLI associazione microbiologi clinici italiani
Ente del Terzo Settore

CATANZARO - 12 APRILE 2024

GASTROENTERITI INFETTIVE:
NUOVI PERCORSI DIAGNOSTICI

Hotel Marechiaro
Viale Stazione ss 18
88040 Gizzeria Lido /Lamezia Terme (CZ)

The Microbiome Collapse: implicazioni cliniche e possibili soluzioni terapeutiche

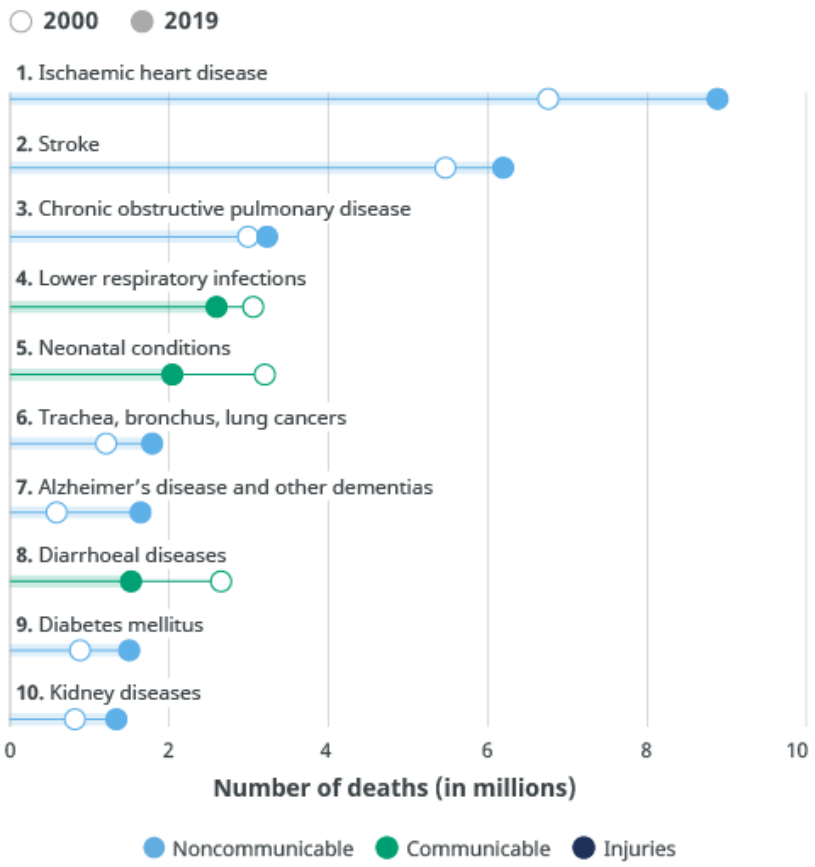
Maurizio Sanguinetti

Department of Laboratory Sciences and Hematology

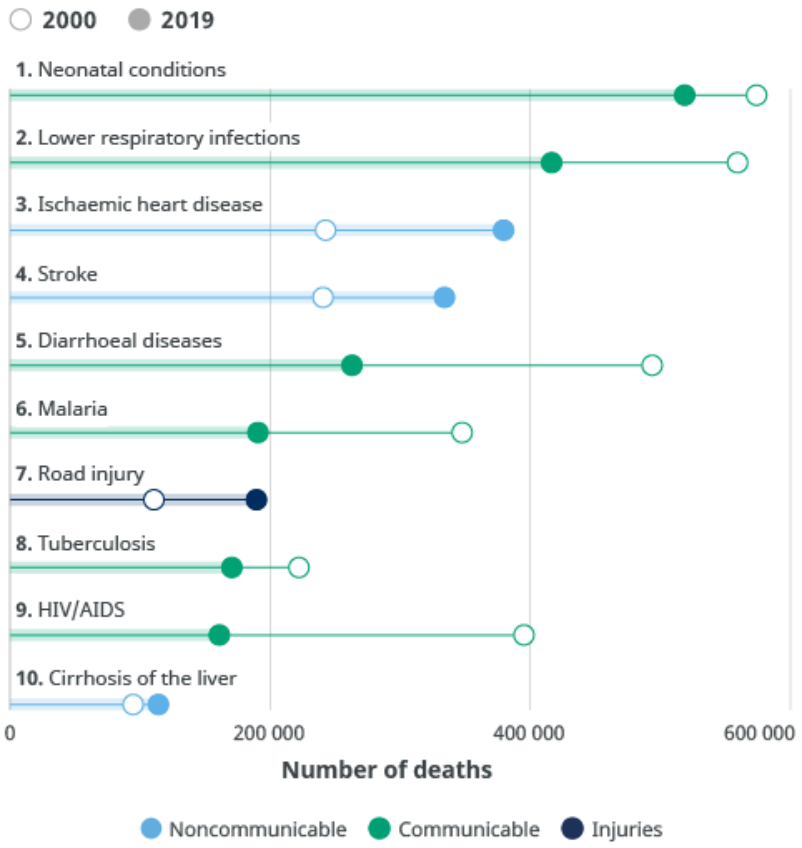
Fondazione Policlinico Universitario «A. Gemelli» IRCCS

The top 10 causes of death - Source WHO

Global



LMIC

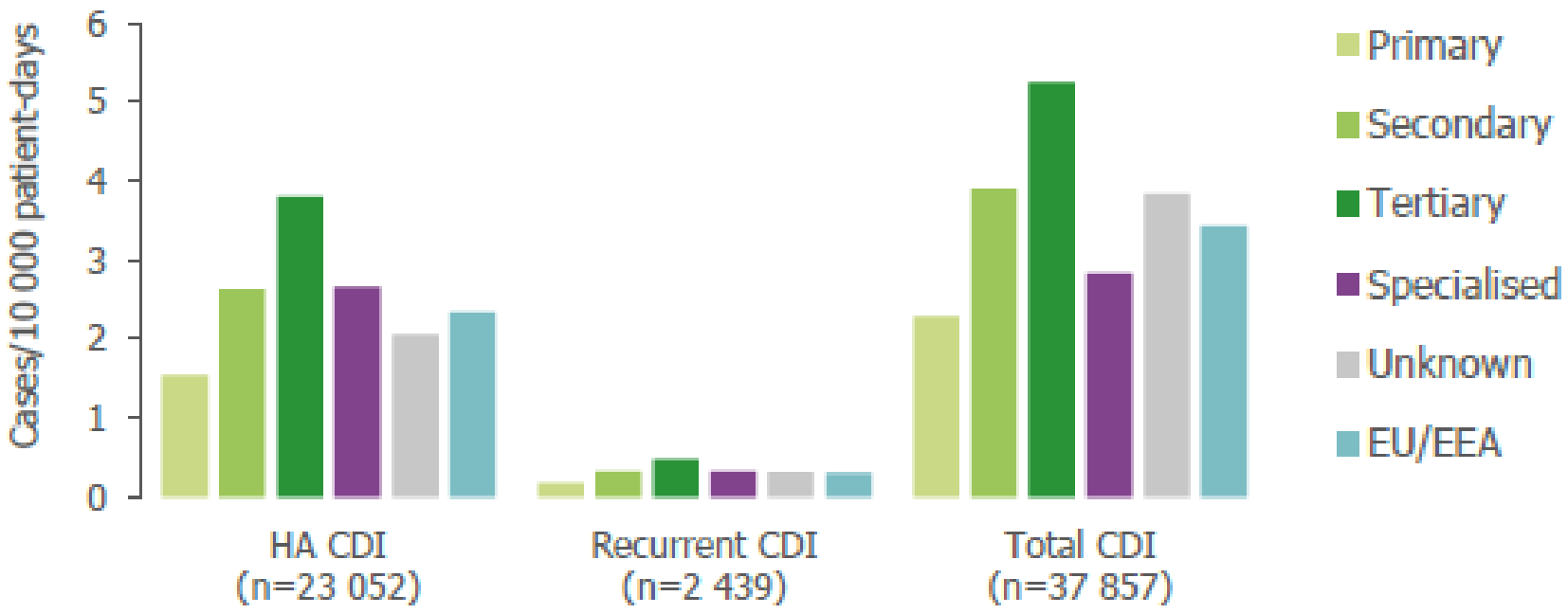


A global comparison of CDI burden and epidemiology in different regions of the world

Nation/Region	Incidence of CDI	Reference
United States	Incidence of 101.3 [CA (51.2) and HA (50.1)] cases per 100,000 persons in 2020; incidence of 148.55 [CA (65.81) and HA (82.74)] cases per 100,000 persons in 2015	CDC 2020 [28]
Canada	National rate of HA-CDI decreased from 5.9 to 4.3 per 10,000 patient days from 2009 to 2015	Katz et al. [38]
Europe	Mean incidence of CDI was 3.48 cases per 10,000 patient days in 2016–2017; 60.9% HA, 32.7% CA, and 6.7 rCDI	ECDC 2022 [46]
Australia	HA-CDI 3.94 per 10,000 patient bed days in 2013 and 4.05 per 10,000 patient bed days in 2018	ACSQHC 2020 [55]
Asia	Pooled incidence rate at 5.3 per 10,000 patient days	Collins et al. [81]

From: Liu et al., Antibiotics, 2023

Mean incidence density in hospital surveillance periods in 2016–2017, by type of hospital and origin of CDI, EU/EEA



ECDC 2022. *Clostridioides* (*Clostridium*) *difficile* Infections—Annual Epidemiological Report for 2016–2017

frontiers in Public Health

ORIGINAL RESEARCH
published: 26 November 2020
doi: 10.3389/fpubh.2020.562957

The Economic Burden of *Clostridioides difficile* in Denmark: A Retrospective Cohort Study

Uffe Christian Braae[1], Frederik Trier Møller[1], Rikke Ibsen[2], Steen Ethelberg[1,3], Jakob Kjellberg[4] and Kåre Mølbak[1,5]*

- The study included 12,768 CDI patients and 23,272 matched controls.
- The total health care cost was significantly larger for CDI cases than controls throughout all periods.
- During the index admission period, cost was 12,867 euro per CDI case compared to 4,522 euro ($p < 0.001$) for controls, which increased to an average of 31,388 and 19,512 euro ($p < 0.001$) in Year 1 for the two groups, respectively.
- Excess costs were found both among infections with onset in hospitals and in the community.
- Diagnosis compatible with complications increased costs to on average >91,000 euro per case. The regression analysis showed that CDI adds a substantial economic burden, but only explains about 1/3 of the crude difference observed in the matched analysis

Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis

*Antimicrobial Resistance Collaborators**

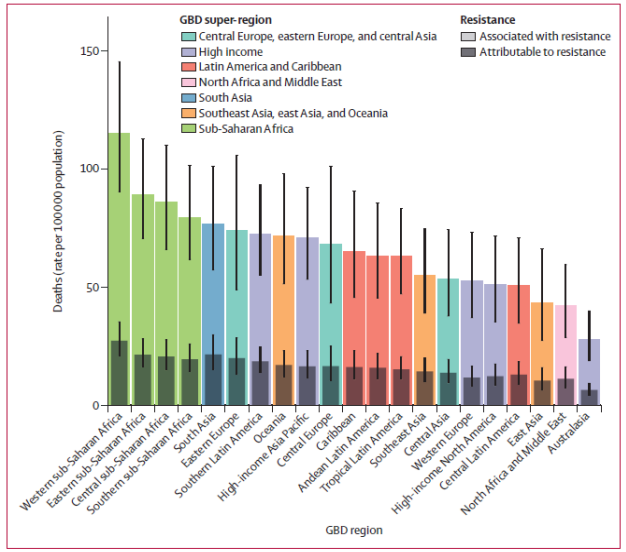


Figure 2: All-age rate of deaths attributable to and associated with bacterial antimicrobial resistance by GBD region, 2019

12, 2022

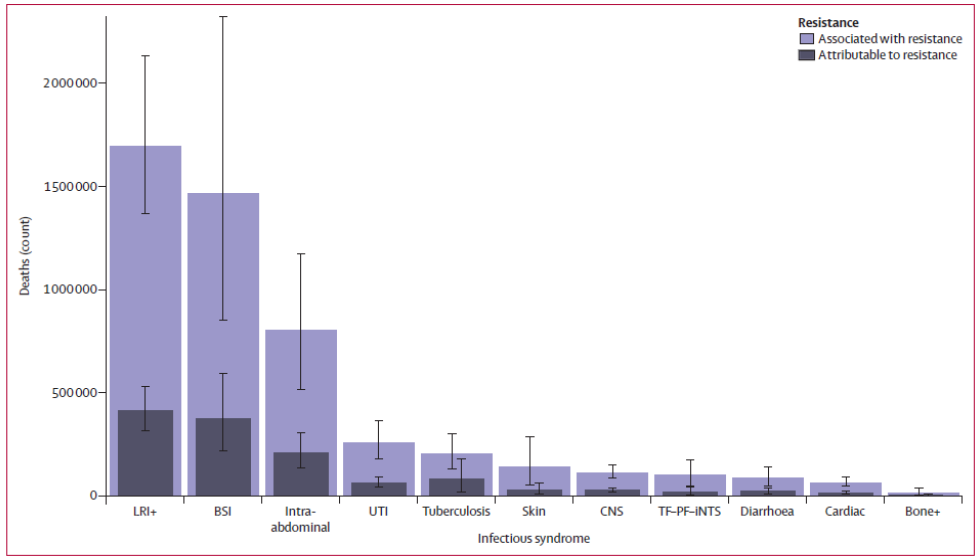


Figure 3: Global deaths (counts) attributable to and associated with bacterial antimicrobial resistance by infectious syndrome, 2019

"On the basis of our predictive statistical models, there were an estimated 4.95 million (3.62-6.57) deaths associated with bacterial AMR in 2019, including 1.27 million (95% UI 0.911-1.71) deaths attributable to bacterial AMR"

Anaerobe 61 (2020) 102136

Contents lists available at ScienceDirect

Anaerobe

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

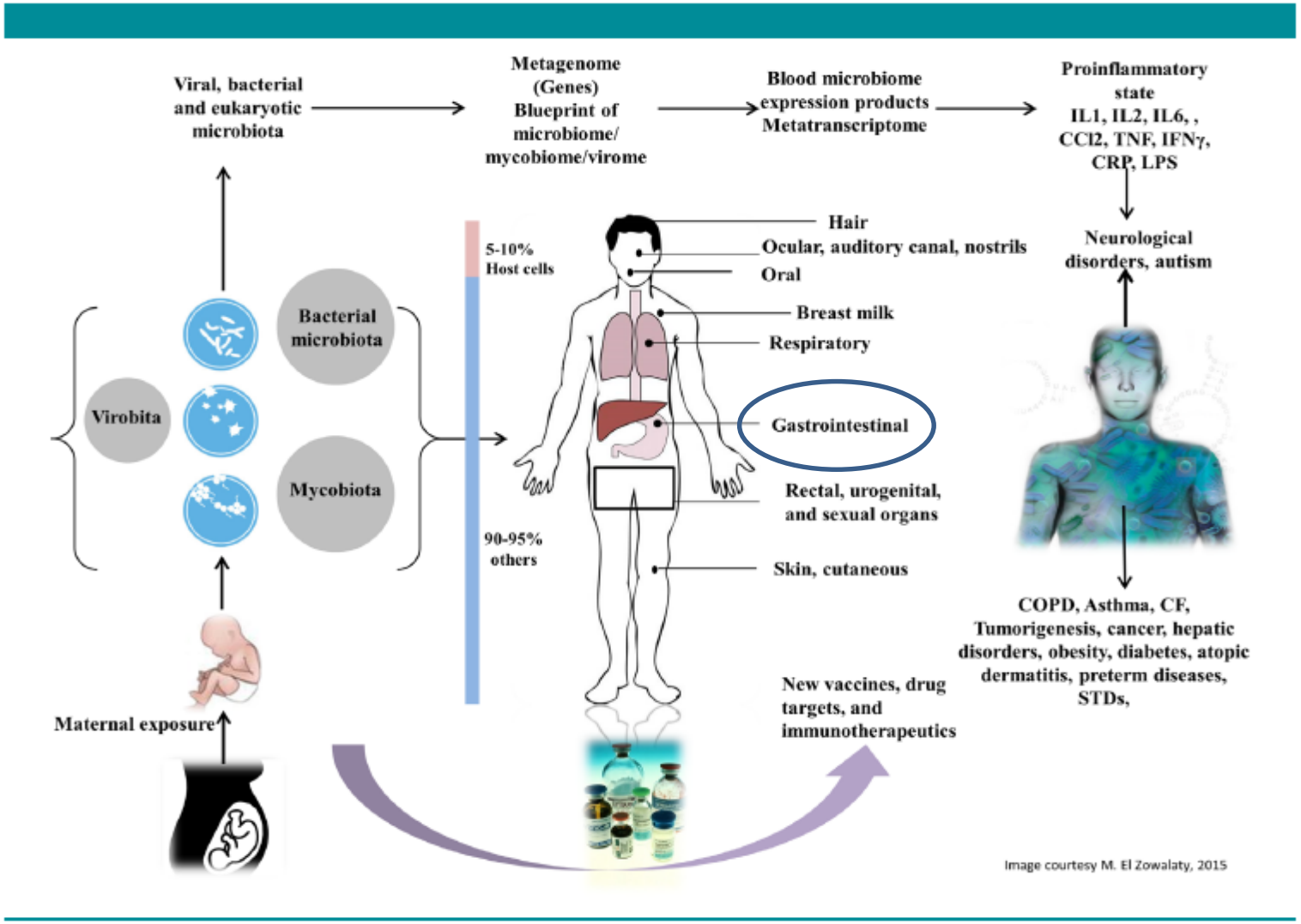
Clostridioides (Clostridium) difficile (including epidemiology)

Microbiological characteristics of human and animal isolates of *Clostridioides difficile* in Italy: Results of the Istituto Superiore di Sanità in the years 2006–2016

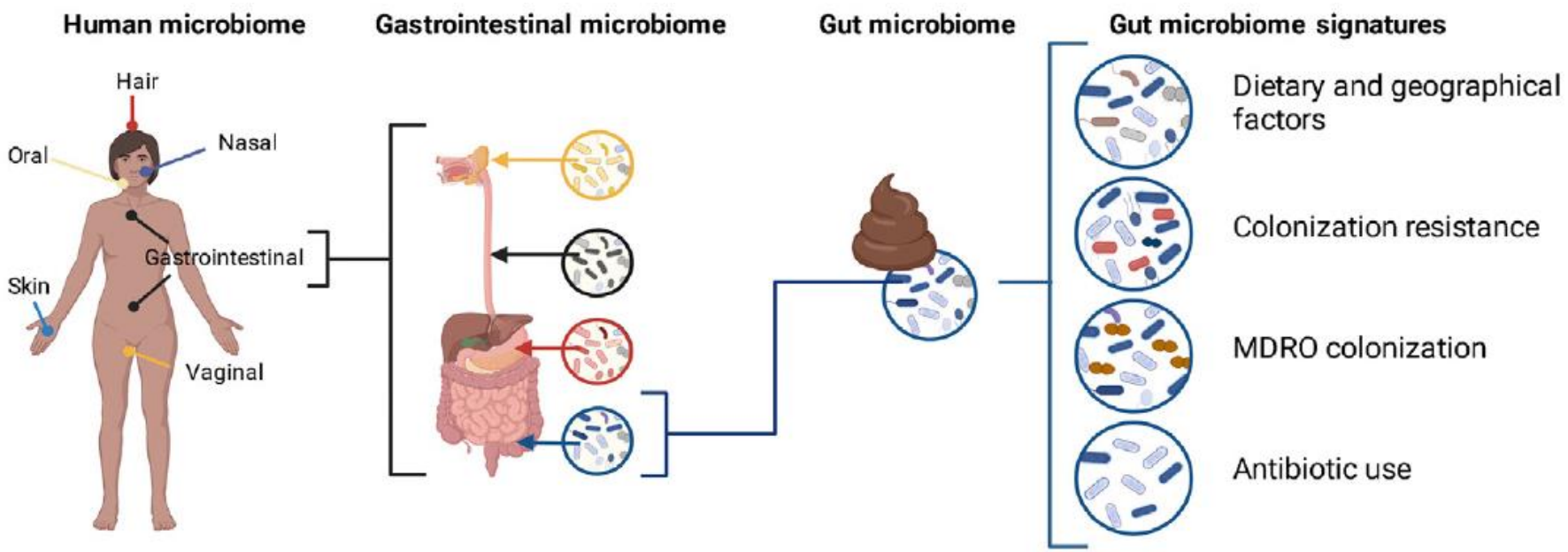
Fabrizio Barbanti, Patrizia Spigaglia*

Department of Infectious Diseases, Istituto Superiore di Sanità, Rome, Italy

- Antibiotic susceptibility analysis showed that 78% (652/831) of isolates were resistant to almost one class of the antibiotics tested, while 62% (517/831) were resistant to three or four classes and therefore considered MDR
- MICs distribution indicated that resistance to ERY, CLI, MXF and RIF was widespread among human isolates, while all isolates were susceptible to MTZ and VAN, except one isolate RT 010 that showed a MIC = 4 mg/L for MTZ
- Almost 90% (460/517) of MDR isolates detected in this study belonged to the three prevalent lineages identified in humans
- In particular, MDR isolates represented 97%, 87% and 55% of the isolates belonging to the RT 018- lineage, RT 027-lineage and RT 078-lineage, respectively



The human microbiota and their interplay with different body sites. The figure shows that virome translocates, circulates, stimulates immune system and infects cellular bacterial, fungal, and eukaryotic cells. Bottom part shows the interplay between microbiome and medicine and highlighting the advances in microbiome will help decipher new targets and discover new therapeutics.



- A major role of the gut microbiome is to provide a barrier against invasion and expansion of potentially pathogenic microorganisms, termed colonization resistance.
- Loss of colonization resistance can lead to the expansion of multidrug-resistant organisms (MDROs) in the gut.
- Such expansion of MDROs, for instance, vancomycin-resistant Enterococci and *Clostridioides difficile*, has been associated with higher morbidity and mortality, including increased risk of septicemia, as organisms are easily able to cross the gut barrier.

From: Isles *et al*, Trends Microbiol., 2022

nature microbiology

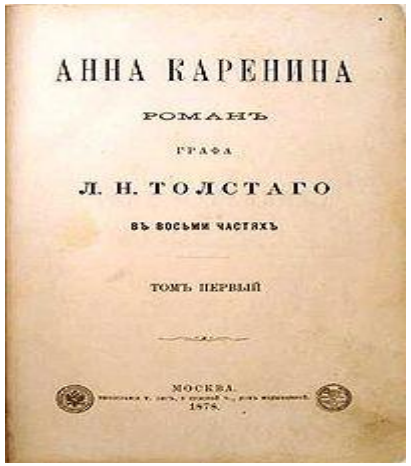
PERSPECTIVE

PUBLISHED: 24 AUGUST 2017 | VOLUME: 2 | ARTICLE NUMBER: 17121

Stress and stability: applying the Anna Karenina principle to animal microbiomes

Jesse R. Zaneveld[1]*, Ryan McMinds[2] and Rebecca Vega Thurber[2]*

“all happy families look alike; each unhappy family is unhappy in its own way”


АННА КАРЕНИНА

РОМАНЪ

ГРАФА

Л. Н. ТОЛСТАГО

ВЪ ВОСЬМИ ЧАСТЯХЪ

ТОМЪ ПЕРВЫЙ

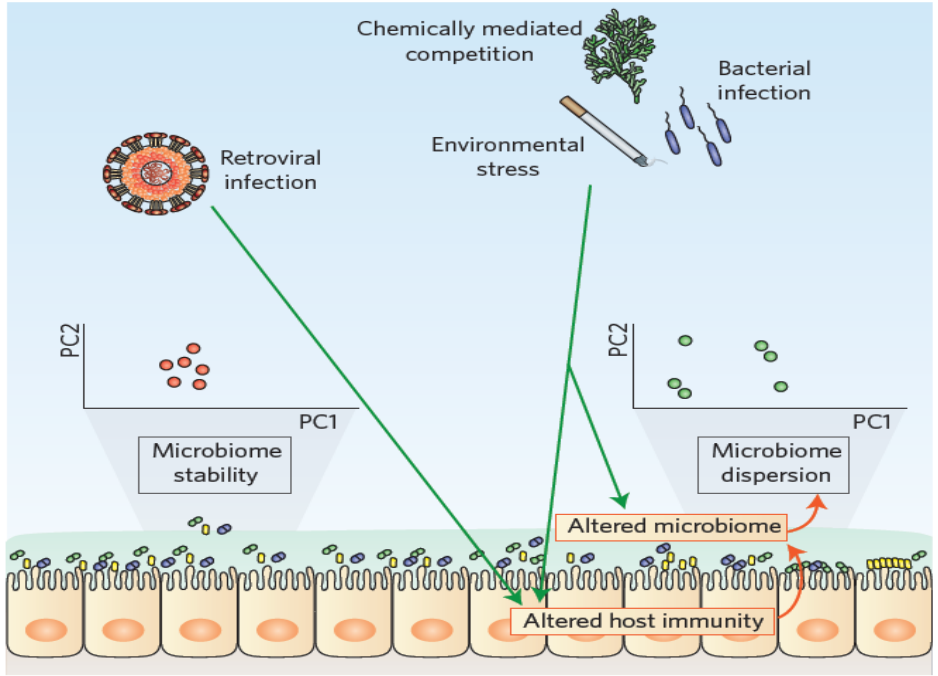
МОСКВА.

1878.

“all healthy microbiomes are similar; each dysbiotic microbiome is dysbiotic in its own way”

- Typically, healthy hosts possess relatively stable microbiomes that form tight clusters in ordination space.
- In contrast to movement of these clusters to a new place in ordination space a variety of external stressors have been shown to disrupt this stability, resulting in more dispersed microbiomes.
- More dispersed microbiomes have been associated with a variety of negative outcomes for the host, including increased invasibility and altered clinical parameters (for example, endotoxaemia in alcoholics).
- In principle, these disruptions may act indirectly by affecting host immunity (as in HIV and SIVcpz), indirectly by altering the microbiome (for example, by displacing protective mutualists like antibiotic producers), or through a combination of both mechanisms.

Anna Karenina principle of perturbations inducing microbiome destabilization



From: Zaneveld *et al*, Nat. Microbiol., 2017

Collapse of the Microbiome, Emergence of the Pathobiome, and the Immunopathology of Sepsis

John C. Alverdy, MD, FACS, Monika A. Krezalek, MD

Crit Care Med 2017; 45:337–347

- *We propose a new vision of the pathophysiology of sepsis that includes the invariable loss of the host's microbiome with the emergence of a pathobiome consisting of both "healthcare-acquired and healthcare-adapted pathobiota."*
- *Under this framework, the critically ill patient is viewed as a host colonized by pathobiota dynamically expressing emergent properties which drive, and are driven by, a pathoadaptive immune response*.

De Maio et al. Gut Pathog (2021) 13:62
https://doi.org/10.1186/s13099-021-00459-9

Gut Pathogens

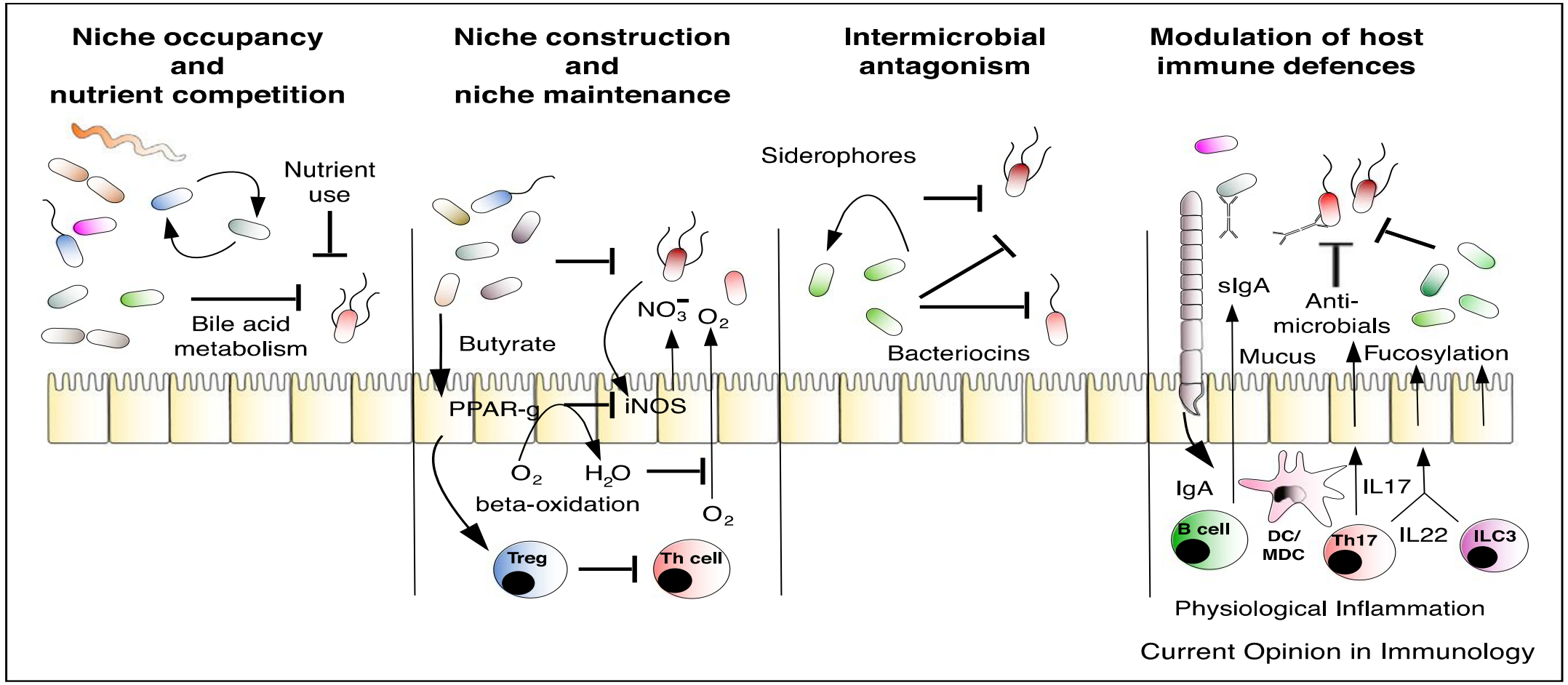
LETTER TO THE EDITOR Open Access

Improved gut microbiota features after the resolution of SARS-CoV-2 infection

Flavio De Maio[1,2], Gianluca Ianiro[3,4], Gaetano Coppola[4], Francesco Santopaolo[4], Valeria Abbate[4], Delia Mercedes Bianco[1,2], Fabio Del Zompo[4], Giuseppe De Matteis[5], Massimo Leo[4], Antonio Nesci[5], Alberto Nicoletti[4], Maurizio Pompili[3,4], Giovanni Cammarota[3,4], Brunella Posteraro[6,2], Maurizio Sanguinetti[1,2], Antonio Gasbarrini[3,4] and Francesca Romana Ponziani[3,4,7*]

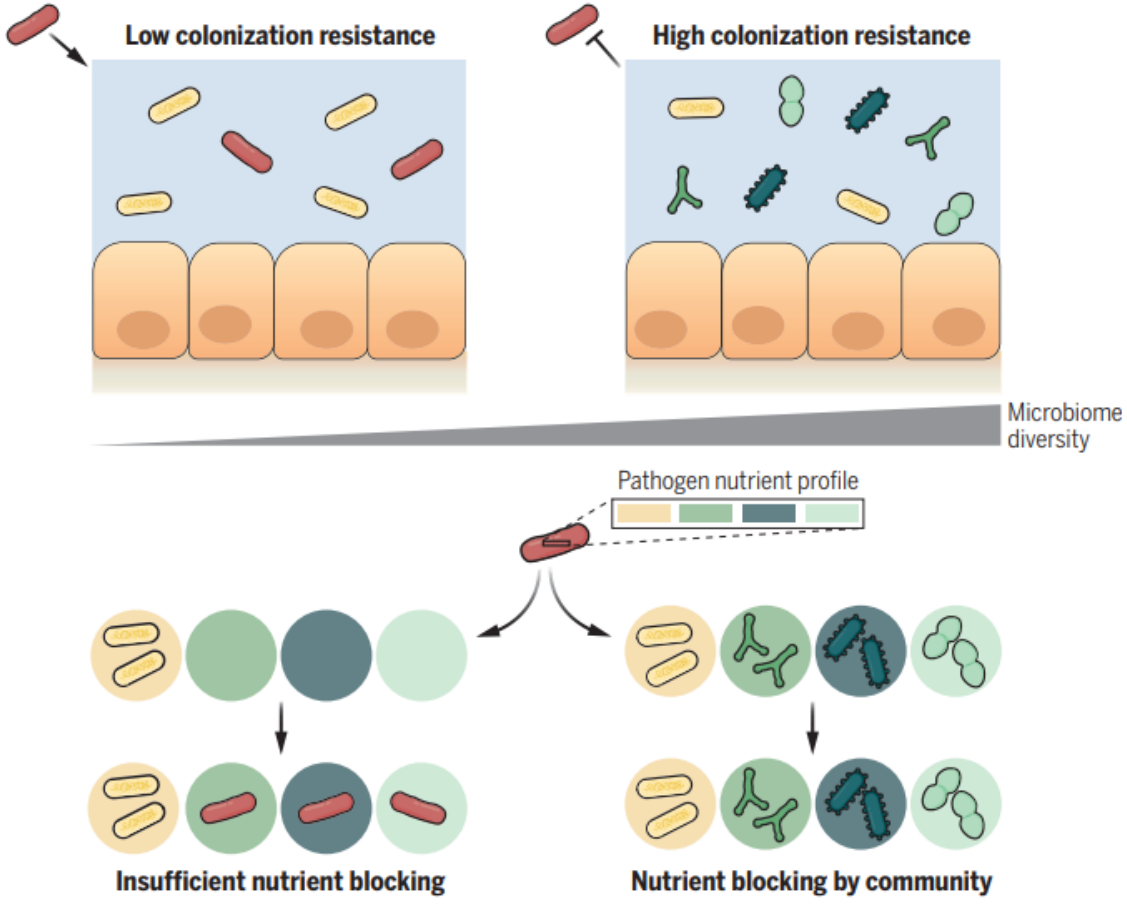
- We enrolled 30 patients hospitalized for SARS-CoV-2-related pneumonia.
- Their gut microbiota was analyzed within 48 h from the admission and compared with:
  - that of other patients admitted for suspected bacterial pneumonia (control group)
  - that obtained from the same subject 6 months after nasopharyngeal swab negativization.
- Gut microbiota alpha-diversity increased 6 months after the resolution of SARS-CoV-2 infection. Bacteroidetes relative abundance was higher (≈ 36.8%) in patients with SARS-CoV-2 and declined to 18.7% when SARS-CoV-2 infection resolved ($p = 0.004$).
- Conversely, Firmicutes were prevalent (≈ 75%) in controls and in samples collected after SARS-CoV-2 infection resolution ($p = 0.001$).
- Ruminococcaceae, Lachnospiraceae and *Blautia* increased after SARS-CoV-2 infection resolution, rebalancing the gut microbiota composition.
- SARS-CoV-2 infection is associated with changes in the gut microbiome, which tend to be reversed in long-term period.

Mechanisms involved in gut microbiota-mediated resistance against enteropathogen infection



Schnupf P et al., Curr Op Immunol, 2018

Microbiome diversity protects against pathogens by nutrient blocking. Pathogens (red) fail to colonize when they overlap with the community (yellow and green bacteria) in nutrient-utilization profiles (nutrient niches are indicated by colored circles). As microbiome diversity increases, the probability that different nutrients are consumed increases, which helps to block pathogen growth and improve colonization resistance

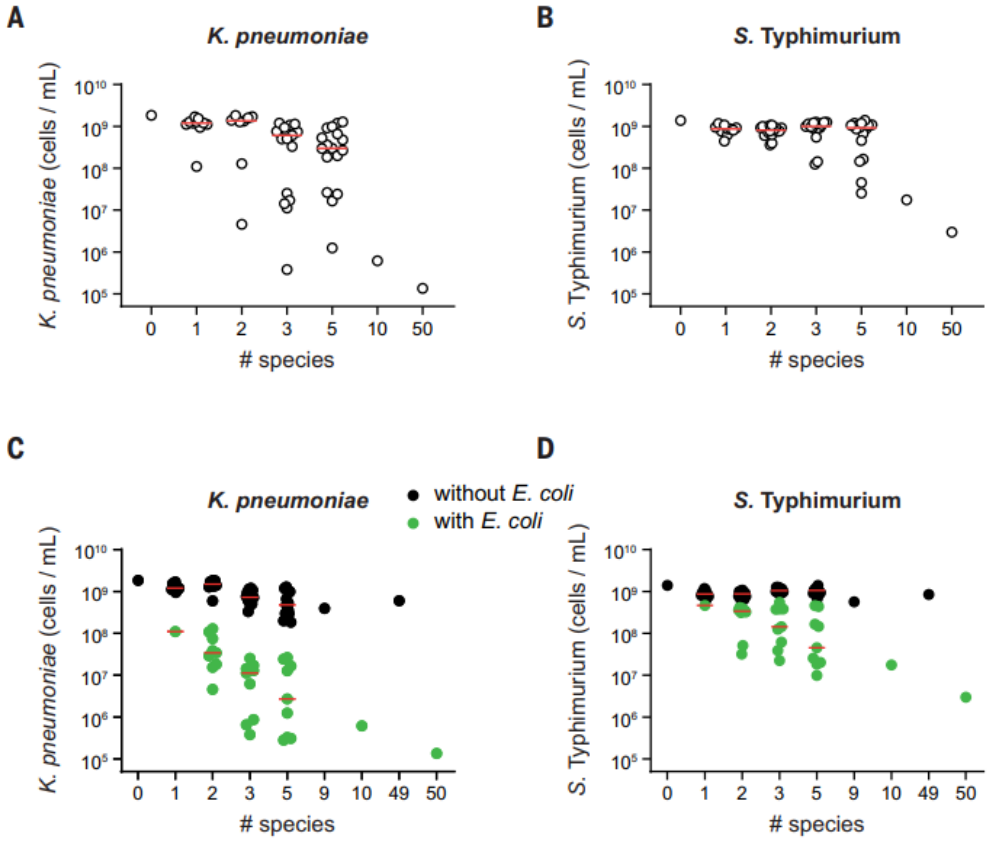


MICROBIOTA

Microbiome diversity protects against pathogens by nutrient blocking

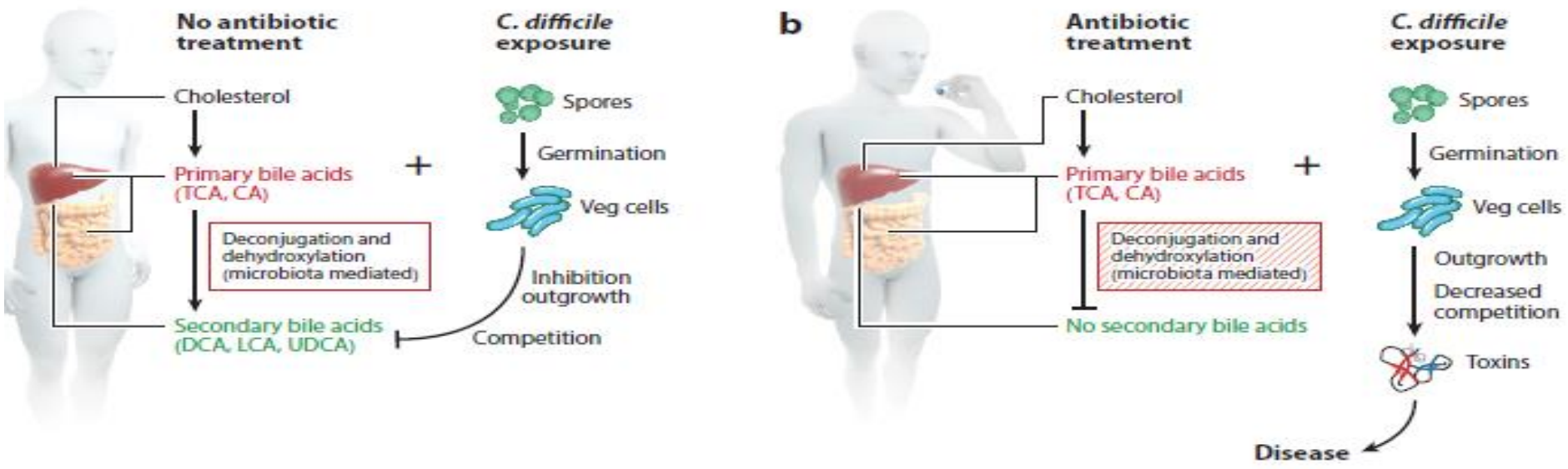
Frances Spragge†, Erik Bakkeren†, Martin T. Jahn, Elizete B. N. Araujo, Claire F. Pearson, Xuedan Wang, Louise Pankhurst, Olivier Cunrath*, Kevin R. Foster*

Science **382**, 1259 (2023) 15 December 2023



Ecological diversity and key members are needed for efficient colonization resistance in vitro

Antibiotic-induced alterations in gut microbial metabolism decrease colonization resistance against *C. difficile*



Antibiotic treatment alters the gut microbiota structure, specifically decreasing bacteria that can deconjugate and dehydroxylate primary bile acids into secondary bile acids. The loss of secondary bile acid metabolism and competition from the gut microbiota allow for *C. difficile* outgrowth, toxin production, and disease.

Antibiotic-induced gut metabolome and microbiome alterations increase the susceptibility to *Candida albicans* colonization in the gastrointestinal tract

Daniel Gutierrez,[a] Anthony Weinstock,[b] Vijay C. Antharam[c], Haiwei Gu,[d] Paniz Jasbi,[d] Xiaojian Shi,[d] Blake Dirks,[e] Rosa Krajmalnik-Brown,[e,f,g] Juan Maldonado,[g] Jack Guinan[a], Shankar Thangamani[h*]

FEMS MICROBIOLOGY ECOLOGY

Published: 26 November 2019

- Mice treated with the broad-spectrum antibiotic cefoperazone promoted the growth, morphogenesis and gastrointestinal (GI) colonization of *C. albicans*.
- Levels of carbohydrates, sugar alcohols, and primary bile acids increased, whereas carboxylic acids and secondary bile acids decreased in antibiotic treated mice susceptible to *C. albicans*.
- Further, *in vitro* assays showed that carbohydrates, sugar alcohols and primary bile acids promote, whereas carboxylic acids and secondary bile acids inhibit the growth and morphogenesis of *C. albicans*.
- Taken together, our *in-vivo* and *in-vitro* results indicate that cefoperazone-induced metabolome and microbiome alterations favor the growth and morphogenesis of *C. albicans,* and potentially play an important role in the gastrointestinal colonization of *C. albicans.*

Microbial Pathogenesis 154 (2021) 104826

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Microbial Pathogenesis

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

Alterations in the gut microbiota and metabolic profiles coincide with intestinal damage in mice with a bloodborne Candida albicans infection

Wanchao Hu [1], Dan Xu [1], Ziyang Zhou, Junfeng Zhu, Dan Wang, Jianguo Tang *

Department of Trauma-Emergency & Critical Care Medicine, Shanghai Fifth People's Hospital, Fudan University, Shanghai, 200240, China

Table 3
Differential fecal metabolites and pathways.

Number	Metabolites	KEGG ID	VIP[a]	Relative concentration		Model VS Control		Metabolic pathway	Classification
				Model	Control	FC[b]	P-value[c]		
1	Succinic acid	C00042	1.54	203.95 ± 82.3	82.76 ± 15.44	2.46	0.0053**	Central carbon metabolism in cancer	Fatty Acyls
2	L-Phenylalanine	C00079	3.8	2366.03 ± 345.5	1746.8 ± 315.08	1.35	0.0088**	Central carbon metabolism in cancer/ Protein digestion and absorption	Organic acids and derivatives
3	L-Proline	C00148	2.44	1185.16 ± 134.49	925 ± 77.14	1.28	0.0021**	Central carbon metabolism in cancer/ Protein digestion and absorption	Organic acids and derivatives
4	L-Isoleucine	C00407	4.17	3654.85 ± 349.38	2867.65 ± 329.65	1.27	0.0025**	Central carbon metabolism in cancer/ Protein digestion and absorption	Organic acids and derivatives
5	L-Valine	C00183	2.03	1146.78 ± 192.31	911.47 ± 129.86	1.26	0.0323*	Central carbon metabolism in cancer/ Protein digestion and absorption	Organic acids and derivatives
6	L-Glutamine	C00064	1.1	112.32 ± 36.29	59.94 ± 7.14	1.87	0.006**	Central carbon metabolism in cancer/ Protein digestion and absorption	Organic acids and derivatives
7	Crotonoyl-CoA	C00877	1.27	136.99 ± [illegible]	65.77 ± [illegible]	2.08	0.0217*	carbon metabolism/Fatty acid metabolism	Fatty Acyls
8	Deoxycholic acid	C04483	9.2	11242.01 ± 3119	15765.4 ± 3129.24	0.71	0.031*	Bile secretion	Secondary bile acids
9	Lithocholic acid	C03990	5.67	1333.54 ± [illegible]	2813.37 ± [illegible]	0.47	0.0039**	Bile secretion	Secondary bile acids
10	Taurolithocholate sulfate	C03642	1.1	37.38 ± 47.25	103.99 ± 51.91	0.36	0.0424*	Bile secretion	Steroid conjugates
11	Deoxycholic acid 3-glucuronide	C03033	11.4	7084.4 ± 5338.59	1625.77 ± 531.14	4.36	0.0319*	Bile secretion/Pentose and glucuronate interconversions	Steroid conjugates
12	Lithocholate 3-O-glucuronide	C03033	1.69	682.97 ± 119.94	554.96 ± 53.29	1.23	0.038*	Bile secretion/Pentose and glucuronate interconversions	Steroidal glycosides
13	Cholic acid	C00695	4.96	2284.16 ± 1156.42	1002.15 ± 198.18	2.28	0.0232*	Bile secretion/Primary bile acid biosynthesis	Primary bile acid
14	Quinine	C06526	1.18	245.95 ± 83.25	159.89 ± 37.41	1.54	0.0435*	Bile secretion	Unclassified
15	LTC4	C02166	1.54	373.84 ± 93.18	241.26 ± 72.02	1.55	0.0202*	Bile secretion/Arachidonic acid metabolism	Fatty Acyls
16	15-deoxy-delta-12,14-PGJ2	C14717	1.23	132.2 ± 99.75	34.89 ± 9.54	3.79	0.0387*	Arachidonic acid metabolism	Fatty Acyls
17	19S-HETE	C14749	2.86	797.87 ± 566.51	208.25 ± 270.64	3.83	0.0442*	Arachidonic acid metabolism	Fatty Acyls
18	LTE4	C05952	1.39	208.16 ± 96.65	106.2 ± 21.93	1.96	0.0304*	Arachidonic acid metabolism	Fatty Acyls
19	PGJ2	C05957	1.58	210.7 ± 158.55	53.21 ± 12.3	3.96	0.0357*	Arachidonic acid metabolism	Fatty Acyls

[a] VIP was obtained from the OPLS-DA model. [b] FC was calculated based on a binary logarithm for model vs. control. Data are presented as means ± S.E.M. (n = 6). [c] *p*-value was calculated by *t*-test analysis, $*P < 0.05$, $**P < 0.01$.

Microbiota destruction and antibiotic-resistant infections

- Recommendations to combat the progression of antibiotic resistance included barrier and hygiene approaches to reduce transmission, limits on antibiotic use, and development of new and more effective antibiotics.
- A concern with these approaches, however, is that antibiotic resistance has grown despite their implementation.
- Recently, the White House provided a national action plan for combating antibiotic-resistant bacteria, which included specific milestones that introduced the potential role of the microbiome and the microbiota in combating antibiotic resistance (www.whitehouse.gov/sites/default/files/docs/national_action_plan_for_combating_antibotic-resistant_bacteria.pdf).

Examples of microbial signatures associated with acquisition of MDROs in the human gut

Organism(s)	Microbiota associated with increased risk of MDRO acquisition	Microbiota associated with protection against MDRO acquisition	Patients cohort
VRE	*Enterobacterales*	-	Patients with rCDI undergoing FMT
Either VRE or resistant Gram-negative bacteria	*Enterococcus*		Nursing home patients
ESBL *Enterobacterales*	*Prevotella*	*Desulfovibrio, Oscillospira, Parabacteroides, Coprococcus*	
Third-generation cephalosporin-resistant *Enterobacterales*	*Enterobacterales*, Proteobacteria	Pseudomonadaceae, *Prevotella massiliensis*	Healthy adult population
Multiple MDROs	*Enterococcus*, *Klebsiella*, *Enterobacterales*	*Bacteroides, Faecalibacterium, Lachnospira, Blautia*	Patients undergoing liver transplantation

From: Isles *et al*, Trends Microbiol., 2022, modified

Clinical Infectious Diseases

MAJOR ARTICLE

Compositional Flux Within the Intestinal Microbiota and Risk for Bloodstream Infection With Gram-negative Bacteria

Igor Stoma,[1,2] Eric R. Littmann,[1] Jonathan U. Peled,[3,4] Sergio Giralt,[3,4] Marcel R. M. van den Brink,[3,4] Eric G. Pamer,[1,4,5] and Ying Taur[1,4,5]

[1]Center for Microbes, Inflammation and Cancer, Sloan Kettering Institute, Memorial Sloan Kettering Cancer Center, New York, New York, USA; [2]Department of Infectious Diseases, Belarusian State Medical University, Minsk, Belarus; [3]Adult Bone Marrow Transplantation Service, Memorial Hospital, Memorial Sloan Kettering Cancer Center, New York, New York, USA; [4]Weill Cornell Medical College, New York, New York, USA; and [5]Infectious Diseases Service, Memorial Hospital, Memorial Sloan Kettering Cancer Center, New York, New York, USA

Table 3. Predictors of Gram-negative Bloodstream Infections

	Univariate		Multivariate	
Predictor	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age (>50 y)	2.48 (1.29–5.31)	.005	2.83 (1.46–6.13)	.002
Sex (female)	0.52 (.27–.94)	.031	0.57 (.29–1.03)	.063
Race (nonwhite)	1.32 (.67–2.41)	.404	…	
Underlying disease (leukemia vs other)	0.90 (.52–1.54)	.693	…	
Risk (high vs other)	1.27 (.70–2.22)	.413	…	
Intensity (MA vs other)	1.20 (.70–2.08)	.498	…	
Cord source	1.36 (.70–2.48)	.345	…	
HLA matched source	0.93 (.54–1.65)	.795	…	
T-cell depleted graft	2.27 (1.31–4.02)	.004	1.95 (1.09–3.56)	.024
Prior GNR BSI (60 d)	2.68 (.74–6.87)	.120	2.26 (.61–5.95)	.194
Fluoroquinolone administration[a]	0.44 (.25–.78)	.006	0.45 (.26–.81)	.009
TMP-SMX administration[a]	0.64 (.33–1.17)	.150	0.66 (.33–1.24)	.207
Vancomycin (IV) administration[a]	2.83 (.62–30.20)	.212	…	
Initial Proteobacteria colonization	2.01 (1.05–4.32)	.035	1.73 (.87–3.80)	.120
Proteobacteria domination[a,b]	9.66 (5.44–16.75)	.000	7.52 (4.14–13.39)	.000

Abbreviations: BSI, bloodstream infection; CI, confidence interval; GNR, xxx; HLA, human leukocyte antigen; HR, hazard ratio; IV, intravenous; MA, xxx; TMP-SMX, trimethoprim-sulfamethoxazole.

[a]Time-dependent predictor.

[b]Intestinal domination: >30% relative abundance.

Clinical Infectious Diseases
MAJOR ARTICLE

Increased Relative Abundance of *Klebsiella pneumoniae* Carbapenemase-producing *Klebsiella pneumoniae* Within the Gut Microbiota Is Associated With Risk of Bloodstream Infection in Long-term Acute Care Hospital Patients

Teppei Shimasaki,[1] Anna Seekatz,[2] Christine Bassis,[2] Yoona Rhee,[1] Rachel D. Yelin,[1] Louis Fogg,[3] Thelma Dangana,[1] Enrique Cornejo Cisneros,[1,4] Robert A. Weinstein[1], Koh Okamoto,[1,5] Karen Lolans,[1] Michael Schoeny,[3] Michael Y. Lin,[1] Nicholas M. Moore,[1] Vincent B. Young,[2] and Mary K. Hayden[1]; for the Centers for Disease Control and Prevention Epicenters Program

- In this study were collected 2319 samples from 562 admissions (506 patients); KPC-Kp colonization was detected in 255 (45.4%) admissions and KPC-Kp bacteremia in 11 (4.3%).
- A relative abundance cutoff of 22% predicted KPC-Kp bacteremia with sensitivity 73%, specificity 72%, and relative risk 4.2 (P = .01).
- In a multivariable Cox regression model adjusted for age, Charlson comorbidity index, and medical devices, carbapenem receipt was associated with achieving the 22% relative abundance threshold (P = .044).
- Carbapenem receipt was associated with increased hazard for high relative abundance of KPC-Kp in the gut microbiota. Increased relative abundance of KPC-Kp was associated with KPC-Kp bacteremia.

nature COMMUNICATIONS

ARTICLE

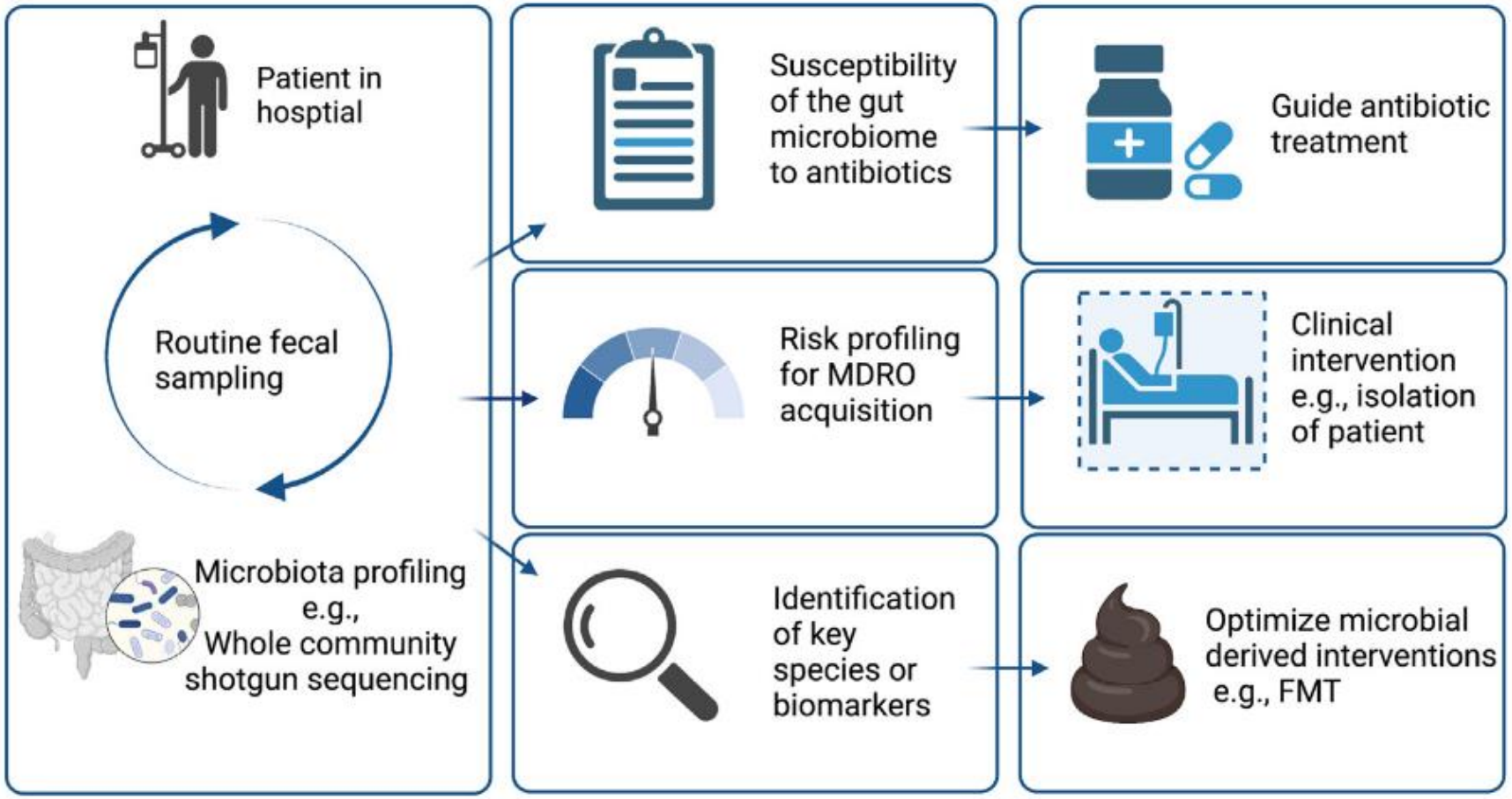
https://doi.org/10.1038/s41467-019-12633-4 OPEN

Colonizing multidrug-resistant bacteria and the longitudinal evolution of the intestinal microbiome after liver transplantation

Medini K. Annavajhala[1,2], Angela Gomez-Simmonds[1], Nenad Macesic[1,3], Sean B. Sullivan[1,2], Anna Kress[1], Sabrina D. Khan[1,2], Marla J. Giddins[1,2], Stephania Stump[1,2], Grace I. Kim[4], Ryan Narain[4], Elizabeth C. Verna[4] & Anne-Catrin Uhlemann[1,2*]

- Gut dysbiosis characteristic of end-stage liver disease may predispose patients to intestinal multi-drug resistant bacteria (MDRB) colonization and infection, in turn exacerbating dysbiosis.
- In multivariate linear mixed-effect models, MDRB colonization predicts reduced Shannon α-diversity, after controlling for underlying liver disease, antibiotic exposures, and clinical complications.
- Importantly, pre-liver transplantation microbial markers predict subsequent colonization by MDRB.
- Patients who never developed MDRB colonization were significantly enriched before liver transplantation in *Faecalibacterium prausnitzii*, *Bacteroides,* and *Bifidobacterium*, as well as *Parabacteroides distasonis*, *Prevotella stercorea*, and *Lachnospira*

Microbial signatures of the human gut to inform interventions for improved outcomes



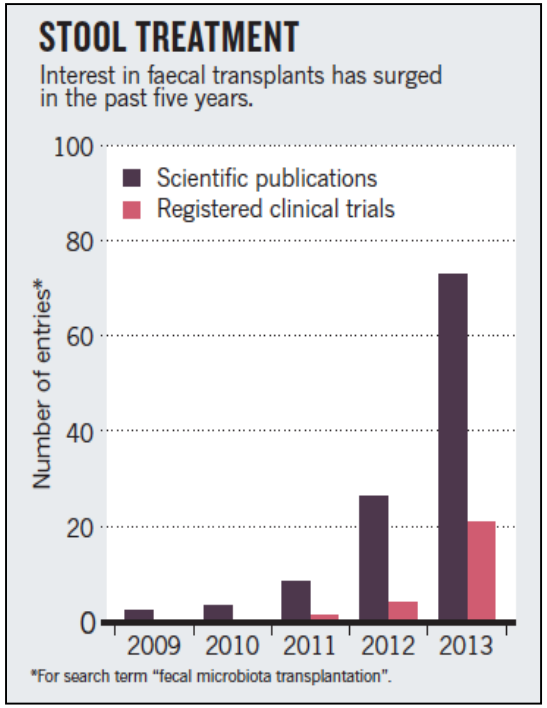
From: Isles *et al*, Trends Microbiol., 2022

FMT: a success story

First reported application of FMT for pseudomembranous colitis

1958 — 2010s

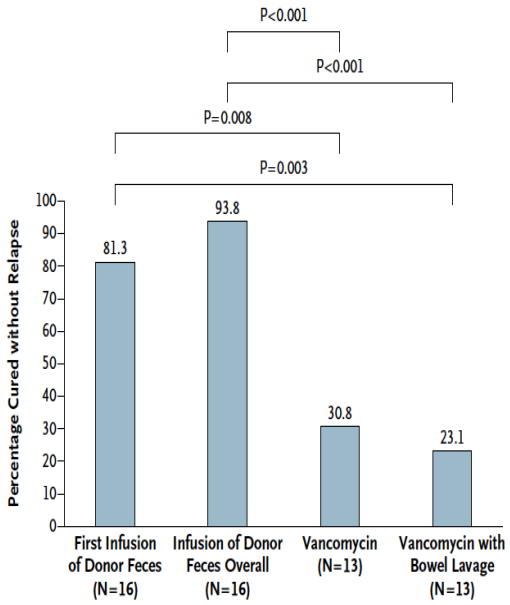
- First RCT on FMT for MetS **2012**
- First RCT on FMT for CDI **2013**
- FMT in American CDI guidelines **2013**
- First capsule FMT study **2014**
- First RCT on FMT for UC **2015**
- First synthetic microbiota consortium **2016**
- First Consensus Conference on FMT **2016**



Eiseman B, et al. Surgery 1958; Surawicz C, et al. Am J Gastroenterol 2013; van Nood E, et al. N Engl J Med 2013, Youngster I, et al. JAMA 2014; Orenstein et al – Clin Infect Dis 2016; Cammarota G, et al. Gut 2017

FMT for recurrent CDI: Randomized Clinical Trials

- Short vanco+FMT vs Short vanco+bowel prep vs Standard vanco
- Study stopped after an interim analysis
- Resolution of CDAD
  - FMT group (n=16): 81%1 FMT, **94% >1 FMT**
  - Vancomycin group (n=13): 31%
  - Bowel prep (n=13): 23%
- No significant adverse events



Van Nood et al – NEJM 2013

Randomised clinical trial: faecal microbiota transplantation by colonoscopy vs. vancomycin for the treatment of recurrent *Clostridium difficile* infection

G. Cammarota*, L. Masucci†, G. Ianiro*, S. Bibbò*, G. Dinoi*, G. Costamagna‡, M. Sanguinetti† & A. Gasbarrini*

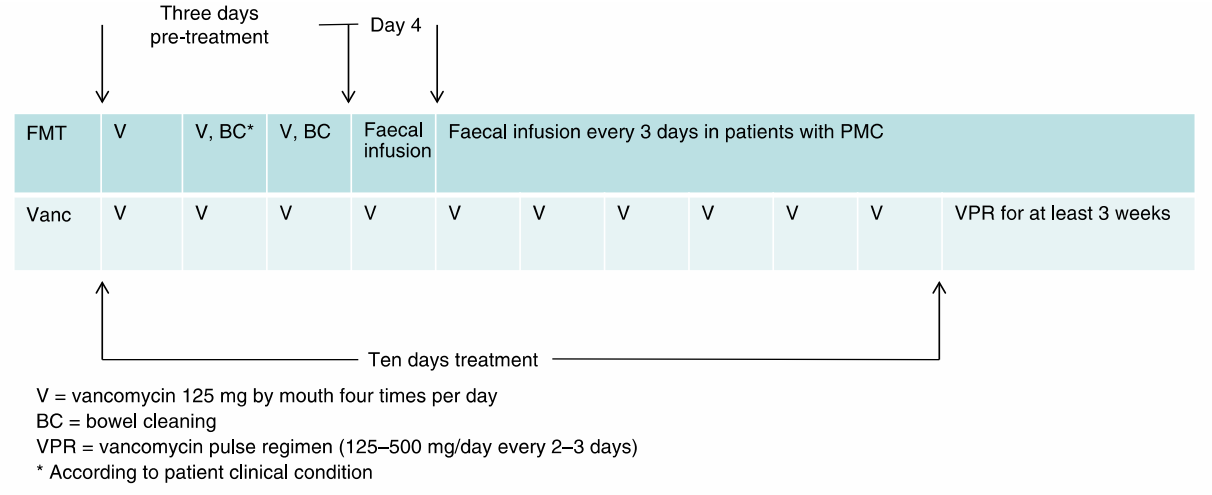


Figure 1 | Timeline of scheduled treatments after patient randomisation.

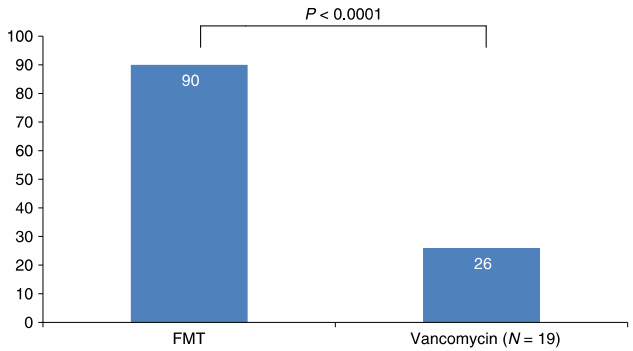


Figure 2 | Percentage of patients cured.

Randomized Controlled Trial > Lancet Gastroenterol Hepatol. 2022 Dec;7(12):1083-1091.
doi: 10.1016/S2468-1253(22)00276-X. Epub 2022 Sep 22.

Faecal microbiota transplantation for first or second Clostridioides difficile infection (EarlyFMT): a randomised, double-blind, placebo-controlled trial

Simon Mark Dahl Baunwall [1], Sara Ellegaard Andreasen [2], Mette Mejlby Hansen [3], Jens Kelsen [3], Katrine Lundby Høyer [2], Nina Rågård [3], Lotte Lindgreen Eriksen [2], Sidsel Støy [3], Tone Rubak [4], Else Marie Skjøde Damsgaard [4], Susan Mikkelsen [5], Christian Erikstrup [6], Jens Frederik Dahlerup [2], Christian Lodberg Hvas [2]

- Between June 21, 2021, and April 1, 2022, we consecutively screened 86 patients, of whom 42 were randomly assigned to faecal microbiota transplantation (n=21) or placebo (n=21)
- The trial was stopped after the interim analysis done on April 7, 2022 for ethical reasons because a significantly lower rate of resolution was identified in the placebo group compared with the faecal microbiota transplantation group (Haybittle-Peto boundary limit p<0·001)
- 19 (90%; 95% CI 70-99) of 21 patients in the faecal microbiota transplantation group and seven (33%, 95% CI 15-57) of 21 patients in the placebo group had resolution of CDAD at week 8 (p=0.0003)
- In patients with first or second *C. difficile* infection, first-line faecal microbiota transplantation is highly effective and superior to the standard of care vancomycin alone in achieving sustained resolution from *C. difficile*

Evidence for different indications of FMT

	Metanalyses	RCTs	Open label trials	Case series/reports	Efficacy data
C. difficile infection	+++	+++	++++	++++	Outstanding
Ulcerative colitis	+	+	++	+++	Promising
Hepatic encefalopathy		+		+	Quite promising
Metabolic syndrome		+		+	Quite promising
Crohn's disease			+	+	Poor
IBS		+	+	+	Poor
Multi-resistant infections			+	+	Poor/promising
Autism			+	+	Poor
GVHD				+	Poor

Courtesy Gianluca Ianiro

Classification of fecal microbiota transplantation across countries

Country	FMT classification
USA, Canada	investigational drug used in context of clinical trial or to treat rCDI
France	investigational drug used in context of clinical trial or use in hospital setting
Italy, Netherlands, and Belgium	considered as a tissue transplant. (European Commission has identified stools as a SoHO and his regulation will be under the EUTCD)
United Kingdom	FMT is regulated as a medicinal product
Australia, Germany	FMT is regulated as a practice of medicine

FMT, fecal microbiota transplantation; rCDI, recurrent *Clostridioides difficile* infection; SoHO, substance of human origin; EUTCD, European Union Tissues and Cells Directive.

From: Porcari et al., Cell Host Microb., 2023

Trapianti di microbiota inseriti nell'applicativo del Centro Nazionale Trapianti al 30/09/2023

Centro FMT	N trapianti
Alessandria, A.O. SS Antonio e Biagio e Cesare Arrigo	17
Bologna, S. Orsola - Malpighi	5
Firenze, A.O.U. Careggi	1
Padova, Azienda Ospedaliera Universitaria	10
Roma, Policlinico Gemelli	134
San Govanni Rotondo (FG), Ospedale Casa Sollievo della Sofferenza - IRCCS	2
	169

From: Report ISS – CNT, 2023

Fecal Microbiota Transplantation at the "A. Gemelli" Hospital - Overall Data (years 2013–2019)

- **190 patients treated** (mean age, 73 years; range, 29–94 years)
- Mean number of recurrences of *Clostridium difficile* infection (rCDI) = **3 (range = 2–11)**
- Mean Charlson Comorbidity Index score = 3
- Inpatients/Outpatients = 100/50
- **Overall, 283 infusion procedures** (91 patients received one infusion, 79 multiple infusions)
- Fresh material/Frozen material= 166/117

FMT procedures/year

- June–December 2013 = 9 (7 pts)
- 2014 = 24 (15 pts)
- 2015 = 36 (25 pts)
- 2016 = 49 (30 pts)
- 2017 = 58 (40 pts)
- 2018 = 57 (43 pts)
- 2019 = 59 (37 pts)

RESULTS:

- Severe colitis (PMC) in 65 patients
- Follow-up range = 1–60 months
- **Resolution of rCDI in 186/190 treated patients (98%)**
- **No patients experienced further FMT recurrences**
- **No more surgery for CDI in our hospital since 2014**

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Contents lists available at ScienceDirect

Journal of Autoimmunity

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

Fecal microbiota transplantation for recurrent *Clostridioides difficile* infection in patients with concurrent ulcerative colitis

Serena Porcari [a,b], Andrea Severino [a,b], Debora Rondinella [a,b], Stefano Bibbò [a,b], Gianluca Quaranta [c], Luca Masucci [c], Marcello Maida [d], Franco Scaldaferri [a,b], Maurizio Sanguinetti [c], Antonio Gasbarrini [a,b], Giovanni Cammarota [a,b,1], Gianluca Ianiro [a,b,*,1]

- *Clostridioides difficile* infection (CDI) is a major challenge for healthcare systems. Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease, is a risk factor for primary and recurrent CDI (rCDI). Moreover, CDI itself often worsens the clinical picture of IBD, increasing the risk of complications.
- Fecal microbiota transplantation (FMT) is a highly effective treatment for rCDI, but data from patients with IBD and CDI are limited and often referred to mixed cohorts.
- We aimed to report outcomes from a cohort of patients with UC treated with FMT for rCDI superinfection.
- In a retrospective, single-centre cohort study we evaluated characteristics and outcomes of patients with UC who received FMT for rCDI. The primary outcome was negative *C. difficile* toxin 8 weeks after FMT.
- Thirty-five patients were included in the analysis.
- Sixteen patients were cured after single FMT, while 19 patients received repeat FMT.
- Overall, FMT cured rCDI in 32 patients (91%), and repeat FMT was significantly associated with sustained cure of CDI compared with single FMT (84% vs 50%, $p = 0.018$). Twenty-four patients (69%) experienced remission or an amelioration of UC activity.

Multidrug-resistant pathogens

Successful case series/case reports on:

- Methicillin-resistant *Staphylococcus aureus* (MRSA) Enterocolitis
- Vancomycin-resistant *Enterococcus* (VRE)
- *Klebsiella pneumoniae* MBL(+)
- *Escherichia coli* ESBL(+)

Wei et al – BMC Infect Dis 2015
Stripling et al – Open Forum Infect Dis 2015
Bilinsky et al- Arch Immunol Ther Exp 2016

One open-label trial:

- 20 participants, median of 2 strains of ARB
- FMT by nasoduodenal tube
- Complete ARB decolonization in 15 of 20 patients (75%)
- No severe adverse events

From: Bilinsky et al, Clin Infect Dis, 2017

International Journal of Antimicrobial Agents 53 (2019) 355–361

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

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

Faecal microbiota transplantation shortens the colonisation period and allows re-entry of patients carrying carbapenamase-producing bacteria into medical care facilities

Nadia Saïdani[a], Jean-Christophe Lagier[a,b,*], Nadim Cassir[a], Matthieu Million[a,b], Sophie Baron[a,c], Grégory Dubourg[a,b], Carole Eldin[a,b], Jad Kerbaj[a], Camille Valles[b], Didier Raoult[a,b], Philippe Brouqui[a,b]

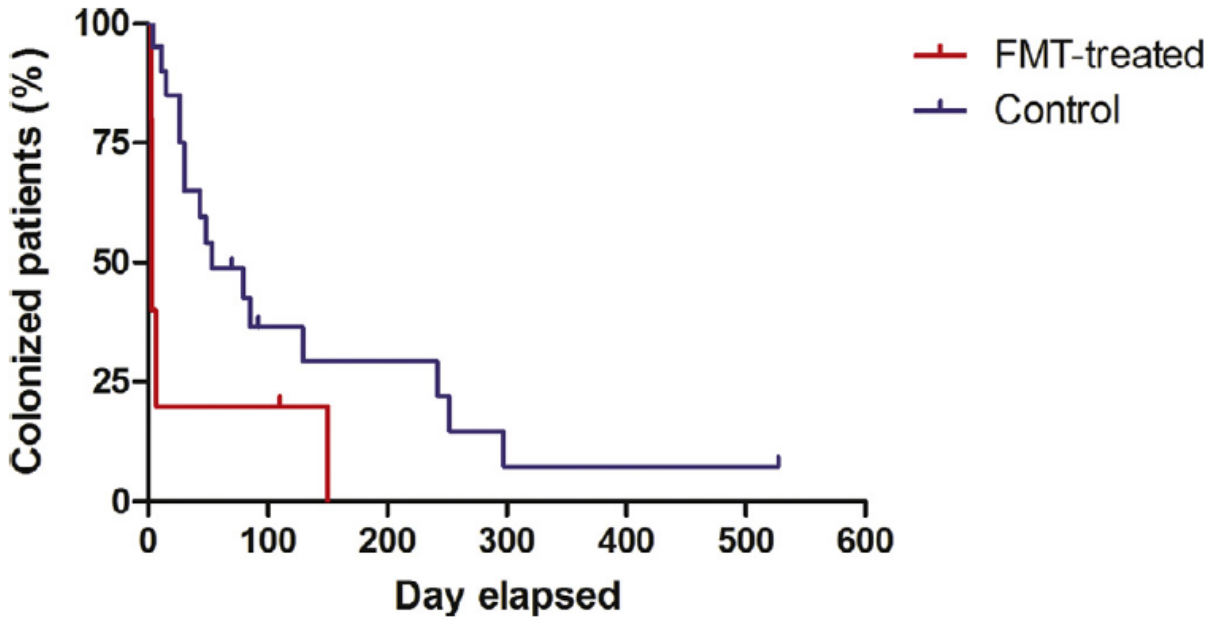


Fig. 2. Effect of faecal microbiota transplantation on carbapenemase-producing Enterobacteriacea/Acinetobacter carriage.

- Fecal microbiota transplantation led patients to reduce the delay in decolonization (median 3 days post FMT for treated patients vs. 50.5 days after the first documentation of digestive carriage for control patients) and discharge from hospital (median 19.5 days post FMT for treated patients vs. 41 for control patients)

Table 1: List of bacterial strains isolated by culturomics and relative concentrations in BC and MIC values obtained by Epsilon tests performed in triplicate. MER: meropenem; CLI: clindamycin; MRD: metronidazole; TZP: piperacillin-tazobactam; not applicable: there are no EUCAST clinical breakpoints for these strains.

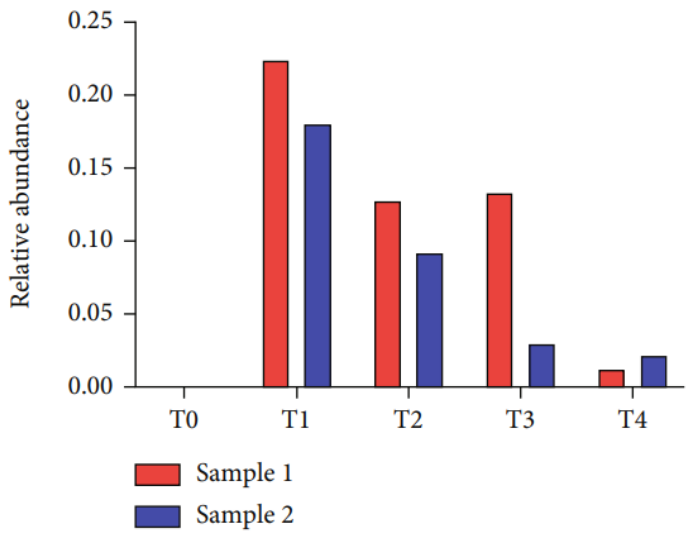
Bacterial strain	Concentration (CFU/mL)	MIC values
Acidaminococcus intestini	5×10^8	Not applicable
Bacteroides fragilis	5×10^8	MER 1 S CLI 64 R MRD 1 S TZP 4 S
Bacteroides ovatus	5×10^8	MER 0.25 S CLI 4 S MRD 8 R TZP 4 S
Bacteroides uniformis	5×10^8	MER 0.25 S CLI 2 S MRD 4 S TZP 4 S
Bifidobacterium longum	5×10^8	Not applicable
Clostridium scindens	5×10^8	Not applicable
Lactobacillus casei	5×10^8	Not applicable
Lactobacillus gasseri	5×10^8	Not applicable
Lactobacillus rhamnosus	5×10^8	Not applicable
Lactobacillus parabuchneri	5×10^8	Not applicable
Parabacteroides distasonis	5×10^8	Not applicable
Propionibacterium avidum	5×10^8	Not applicable
Ruminococcus gnavus	5×10^8	Not applicable

Hindawi
BioMed Research International
Volume 2022, Article ID 5787373, 9 pages
https://doi.org/10.1155/2022/5787373

Research Article

"Bacterial Consortium": A Potential Evolution of Fecal Microbiota Transplantation for the Treatment of *Clostridioides difficile* Infection

Gianluca Quaranta,[1] Gianluca Ianiro,[2] Flavio De Maio,[1] Alessandra Guarnaccia,[1] Giovanni Fancello,[1] Chiara Agrillo,[1] Federica Iannarelli,[1] Stefano Bibbo,[2] Amedeo Amedei,[3] Maurizio Sanguinetti,[1,4] Giovanni Cammarota,[2] and Luca Masucci[1,4]



T0: Time of FMT

T1: 7 days

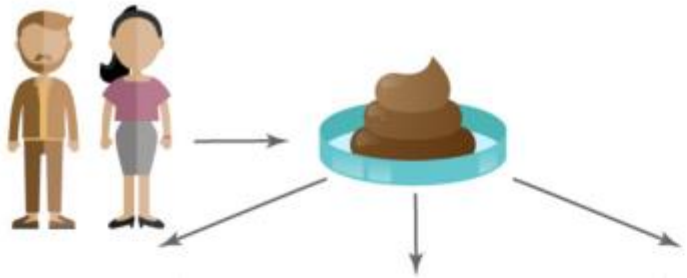
T2: 14 days

T3: 30 days

T4: 90 days

Figure 5: Relative abundance of *Akkermansia muciniphila* in PZ1 (sample 1) and PZ 2 (sample 2).

Comparison of specificities, safety and efficacy of microbiota-derived therapies in recurrent *Clostridioides difficile* infection (rCDI)



PRODUCT NAME	RBX2660	SER-109	VE303
PRODUCT TYPE	FMT-DERIVED		BACTERIAL CONSORTIA
STOOL PROCESSING	Dilution (0.9% saline/polyethylene glycol)	Spore enrichment (50 – 70% v/v EtOH 2-hrs treatment)	Bacterial culture (8 strains of Clostridiales)
FORM OF DELIVERY	Liquid enema	4x Oral capsules	2x / 10x Oral capsules Low dose / High dose
REDUCTION OF rCDI	13.1%	28.0%	8.5% / 31.7%
BATCH-TO-BATCH VARIATION	YES	YES	NO
CHARACTERIZATION OF COMPOSITION	NO	NO	YES
RISK OF PATHOGEN (AMR) TRANSMISSION	POSSIBLE	POSSIBLE	LIMITED

From: Benech et al, Clin. Microbiol. Infect., 2023

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OPEN

Variability of strain engraftment and predictability of microbiome composition after fecal microbiota transplantation across different diseases

Gianluca Ianiro[1,2,8], Michal Punčochář[3,8], Nicolai Karcher[3,8], Serena Porcari[1,2], Federica Armanini[3], Francesco Asnicar[3], Francesco Beghini[3], Aitor Blanco-Míguez[3], Fabio Cumbo[3], Paolo Manghi[3], Federica Pinto[3], Luca Masucci[4,5], Gianluca Quaranta[4,5], Silvia De Giorgi[1,2], Giusi Desirè Sciumè[1,2], Stefano Bibbò[1,2], Federica Del Chierico[6], Lorenza Putignani[6], Maurizio Sanguinetti[4,5], Antonio Gasbarrini[1,2], Mireia Valles-Colomer[3,9], Giovanni Cammarota[1,2,9] and Nicola Segata[3,7,9]

- An integrated shotgun metagenomic systematic meta-analysis of new and publicly available stool microbiomes collected from 226 triads of donors, pre-FMT recipients and post-FMT recipients across eight different disease types was performed
- Recipients with higher donor strain engraftment were more likely to experience clinical success after FMT (P = 0.017) when evaluated across studies
- Increased engraftment was associated with:
  - receiving FMT from multiple routes (for example, both via capsules and colonoscopy during the same treatment)
  - Receiving an antibiotic treatment with infectious diseases compared with antibiotic-naïve patients with noncommunicable diseases
  - Bacteroidetes and Actinobacteria species (including Bifidobacteria) displayed higher engraftment than Firmicutes except for six under-characterized Firmicutes species.
- Cross-dataset machine learning predicted the presence or absence of species in the post-FMT recipient at 0.77 average AUROC proposing a model able to predict donors that might optimize post-FMT specific microbiome characteristics for disease-targeted FMT protocols.

Conclusions

- Human microbiota study is one of the most intriguing and exciting research topics in the last years
- The dramatic modifications occurring after significant microbiota stresses (e.g., prolonged antibiotic therapies) can lead to the selection of a potentially dangerous “Pathobiota”
- The assessment of the microbiota composition, and in particular the detection of an “intestinal domination”, will permit to tailor therapeutic procedures
- The use of FMT is supported by promising evidences derived from basic science and needs to be tested more extensively in randomized clinical trials, in particular for decolonization purposes

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