
# IL MICROBIOTA

## Microbiota: non solo intestino

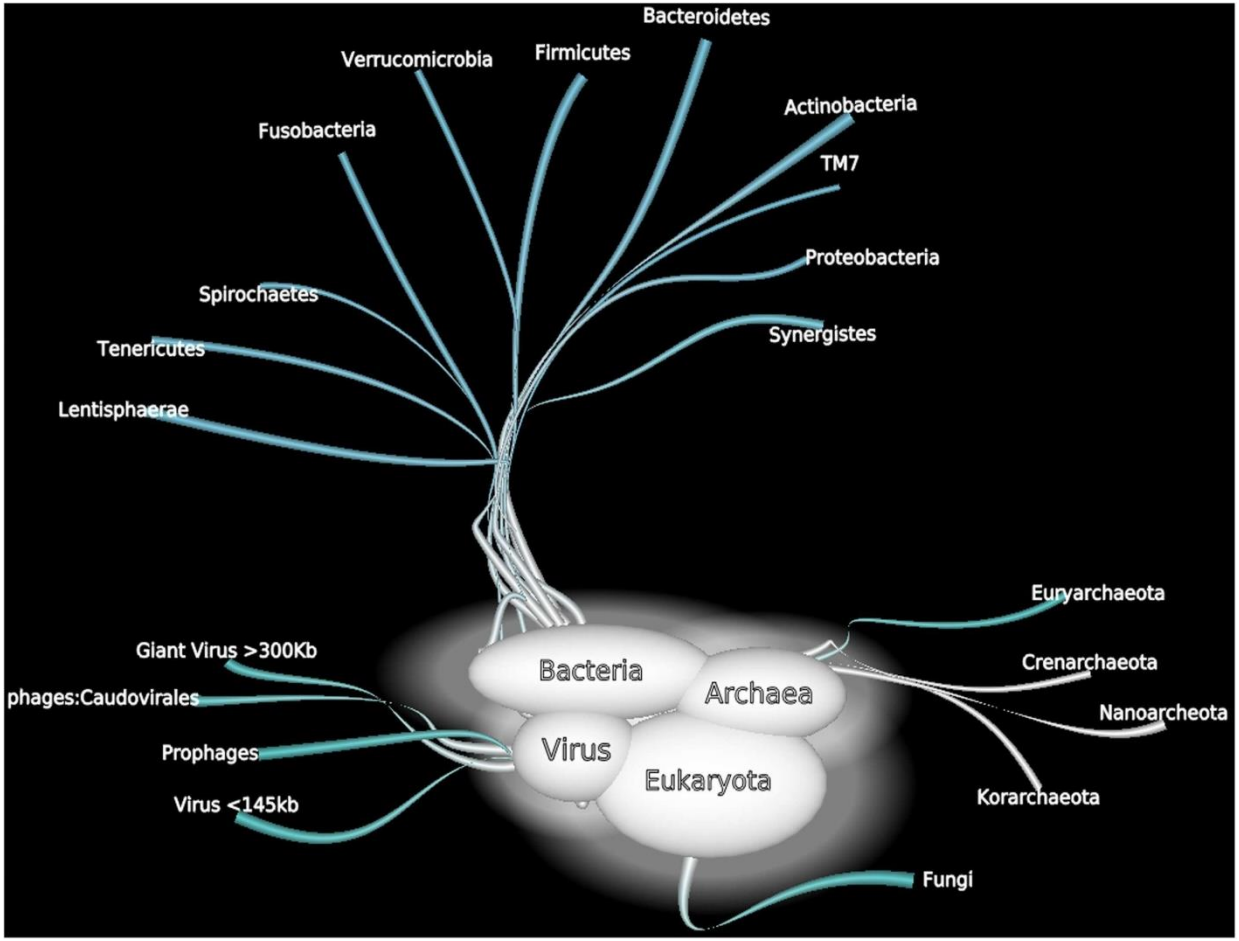
Maurizio Sanguinetti

# Glossary of terms

| Definition | Explanation |
|---|---|
| Microbiota | All the microbes that are found in a particular region or habitat; the term “microflora” is no longer used |
| Microbiome | The totality of the microbes with their genes that are harbored by the microbiota and the milieu in which they interact |
| Operational taxonomic unit (OTU) | Specific sequences based on sequence similarity (typically threshold is 97%) to reference genes. This is taken as a proxy for species-level |
| Taxon | A group of phylogenetically related microbes that belong to the same taxonomic group, such as order, family, or genus |
| Richness | Number of different taxa within a single population |
| $\alpha$ Diversity | How many types of sequences in a sample |
| $\beta$ Diversity | How many different types of sequences are shared among samples |

- Humans are viewed as composites of human and microbial cells.
- Human microbiota are complex and dynamic microbial communities composed mainly of bacteria, but also includes protozoa, archaea, viruses, and fungi that resides in and on different body niches (oral cavity, throat, esophagus, stomach, colon, urogenital tract, respiratory tract, and skin).
- The colonic microbiota constitutes the most abundant microbial domain within the human body, with the vast majority belonging to the bacterial phyla of *Firmicutes* and *Bacteroidetes*.

# A non-exhaustive overview of human gut microorganisms among bacterial, *Archaea*, viral, and *Eukaryota* domains




From: Lagier *et al*, Front Cell Infect Microbiol, 2012

# Microbiota influencers

- **Sanitation**
- **Mode of delivery, breast-feeding..**
- **Diet**
  - ***Composition (calories, fat, fibres, vegetable, meat..)***
  - ***Cooking***
  - ***Natural food additives (safrol..)***
  - ***Artificial chemical food additives:***
    - ***Preservatives (benzoic acid, sodium benzoate, nitrite/nitrate, sulfur dioxide/sulfite..)***
    - ***Sweeteners, emulsifiers and stabilizers, flavors, thickeners, antifoaming, anticaking, bulking, antioxidants..)***
    - ***Others (titanium dioxide..)***
- **Exercise**
- **Sleep**
- **Stress**
- **Violence**
- **Drugs**

# How to define an EUBIOTIC enterotype?

***EU= good*** ***BIOS= life***

- **Composition:** ***Diversity***
  ***Richness***
  ***Relative Abundance***

***Our gut is a sophisticated ecosystem that is regulated by the logic of RELATIONAL HARMONY***

***Microbiota and Host live in a COOPERATIVE SYSTEMIC AGGREGATION MODEL***

# EUBIOSIS

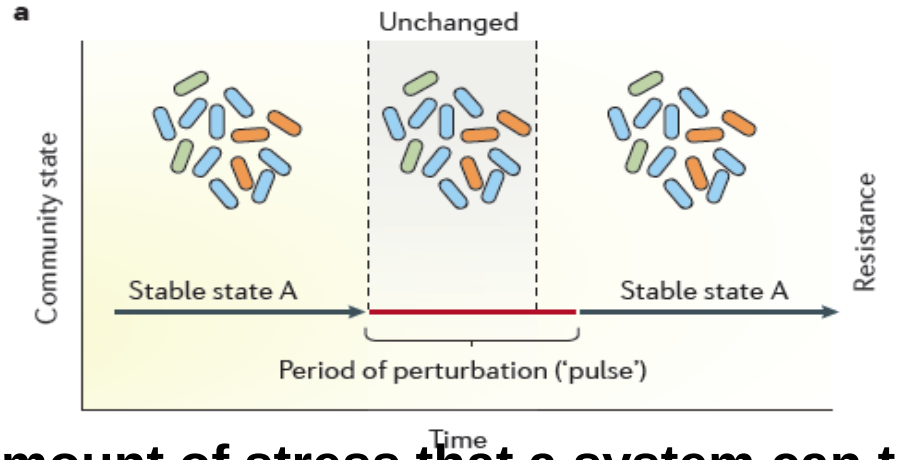
***Failure of HOST-MICROBIOTA equilibrium***

***Quali-quantitative alterations of oral, esophageal, gastric, small bowel and/or colonic microbiota***

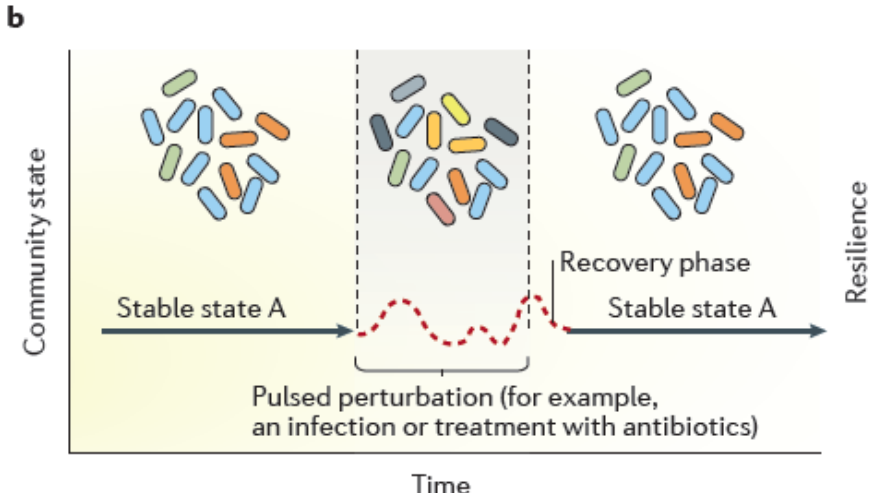
# DYSBIOSIS

# *From EUBIOSIS to DYSBIOSIS*

**RESISTANCE:** **a given ecosystem to stand unchanged in the face of a disturbance**



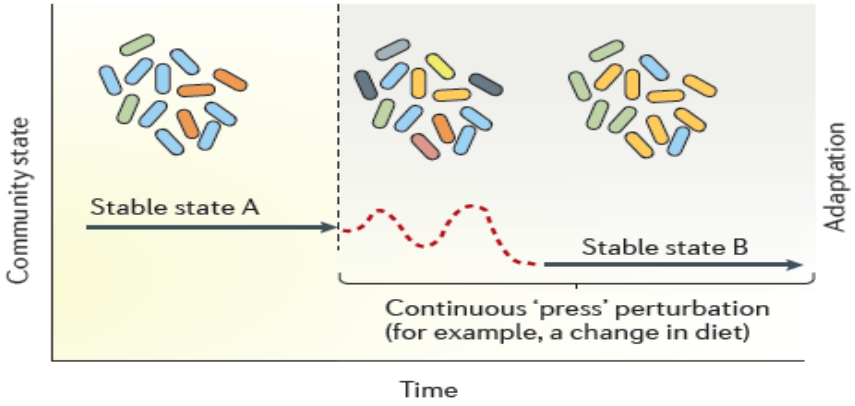

**RESILIENCE:** **amount of stress that a system can tolerate before its homeostatic state shifts towards a new equilibrium with different functions and services**



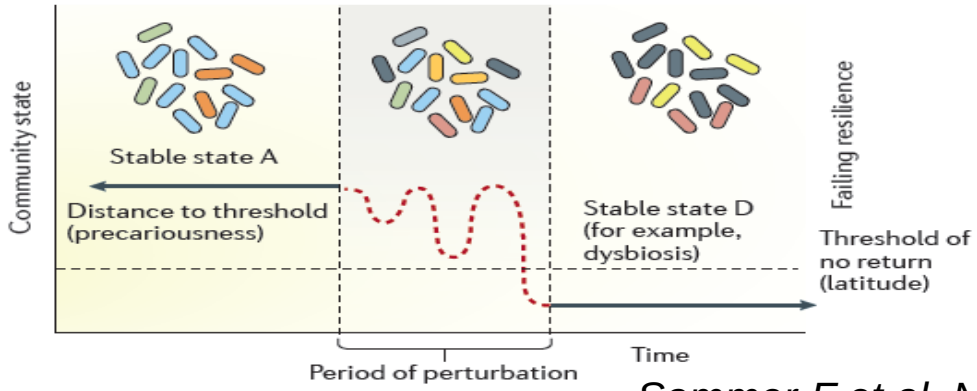

*Sommer F et al.*
*Nat Rev Microbiol 2017*

# *From EUBIOSIS to DYSBIOSIS*

**Facing a continuous perturbation, the composition of the microbiota may adopt a new beneficial or detrimental state: ADAPTATION**




**Acquisition of an unhealthy and dysbiotic microbiota with high resilience potential may contribute to chronicity of human microbiota-associated diseases**




*Sommer F et al. Nat Rev Microbiol 2017*

nature microbiology

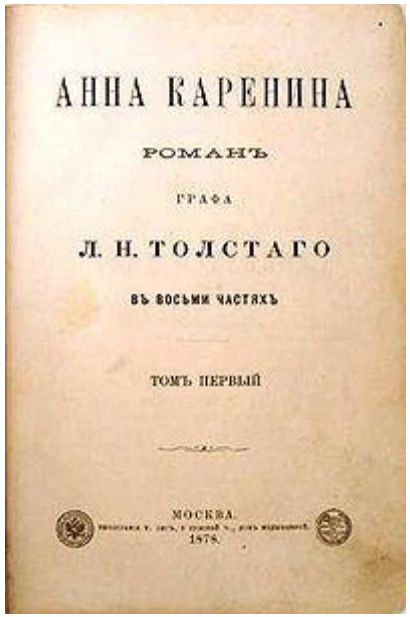
PERSPECTIVE

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”**
- **“Tutte le famiglie felici sono simili le une alle altre; ogni famiglia infelice è infelice a modo suo”**


АННА КАРЕНИНА

РОМАНЪ

ГРАФА

Л. Н. ТОЛСТАГО

ВЪ ВОСЬМИ ЧАСТЯХЪ

ТОМЪ ПЕРВЫЙ

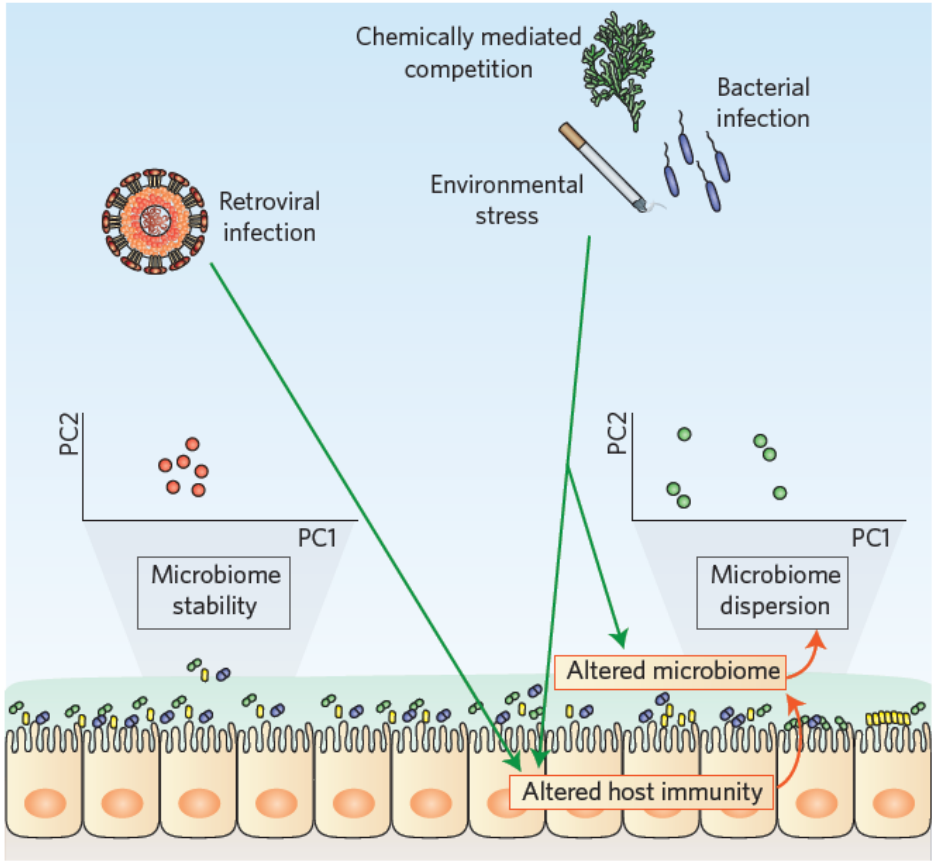
МОСКВА.

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

# EFFECTS OF GUT MICROBIOTA ON HOST HEALTH

- Barrier effect
- **Immunocompetence/Tolerance**
- **Protection against infections**
- Synthesis
- Metabolic/Trophic function
- Drug metabolism
- Behavior conditioning

# *Gut microbiome precision medicine*

***Moving to a Microbiota signature for any disease or pathological status?***

Gut Online First, published on February 7, 2017 as 10.1136/gutjnl-2016-313235


OPEN ACCESS

ORIGINAL ARTICLE

# A microbial signature for Crohn's disease

## How might it impact on clinical practice in the foreseeable future?

- Considering CD and UC as two distinct subtypes of IBD at the microbiome level could help designing specific therapeutic targets.
- The microbial signature specific to CD combined with either imaging techniques or calprotectin data could help decision-making when the diagnosis is initially uncertain among CD, UC and IBS.

## What are the new findings?

- Dysbiosis is greater in CD than in UC, with a lower microbial diversity, a more altered microbiome composition and a more unstable microbial community.
- Different microbial groups are associated with smoking habit and localisation of the disease in CD and UC.
- Eight groups of microorganisms including *Faecalibacterium*, an unknown Peptostreptococcaceae, *Anaerostipes*, *Methanobrevibacter*, an unknown Christensenellaceae, *Collinsella* and *Fusobacterium*, *Escherichia* could be used to discriminate CD from non-CD; the six first groups being in lower relative abundance and the last two groups in higher relative abundance in CD.

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ORIGINAL ARTICLE

# A microbial signature for Crohn's disease

Victoria Pascal,[1] Marta Pozuelo,[1] Natalia Borruel,[1,2] Francesc Casellas,[1,2] David Campos,[1] Alba Santiago,[1] Xavier Martinez,[1] Encarna Varela,[1] Guillaume Sarrabayrouse,[1] Kathleen Machiels,[3] Severine Vermeire,[3] Harry Sokol,[4] Francisco Guarner,[1,2] Chaysavanh Manichanh[1,2]

- We analysed a cohort of 2045 non-IBD and IBD faecal samples from four countries (Spain, Belgium, the UK and Germany), applied a 16S rRNA sequencing approach and analysed a total dataset of 115 million sequences.
- In the Spanish cohort, dysbiosis was found significantly greater in patients with CD than with UC, as shown by a more reduced diversity, a less stable microbial community and eight microbial groups were proposed as a specific microbial signature for CD.
- Tested against the whole cohort, the signature achieved an overall sensitivity of 80% and a specificity of 94%, 94%, 89% and 91% for the detection of CD versus healthy controls, patients with anorexia, IBS and UC, respectively.
- Although UC and CD share many epidemiologic, immunologic, therapeutic and clinical features, these results showed that they are two distinct subtypes of IBD at the microbiome level.
- For the first time, microbiomarkers were proposed to discriminate between CD and non-CD independently of geographical regions.

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ORIGINAL ARTICLE

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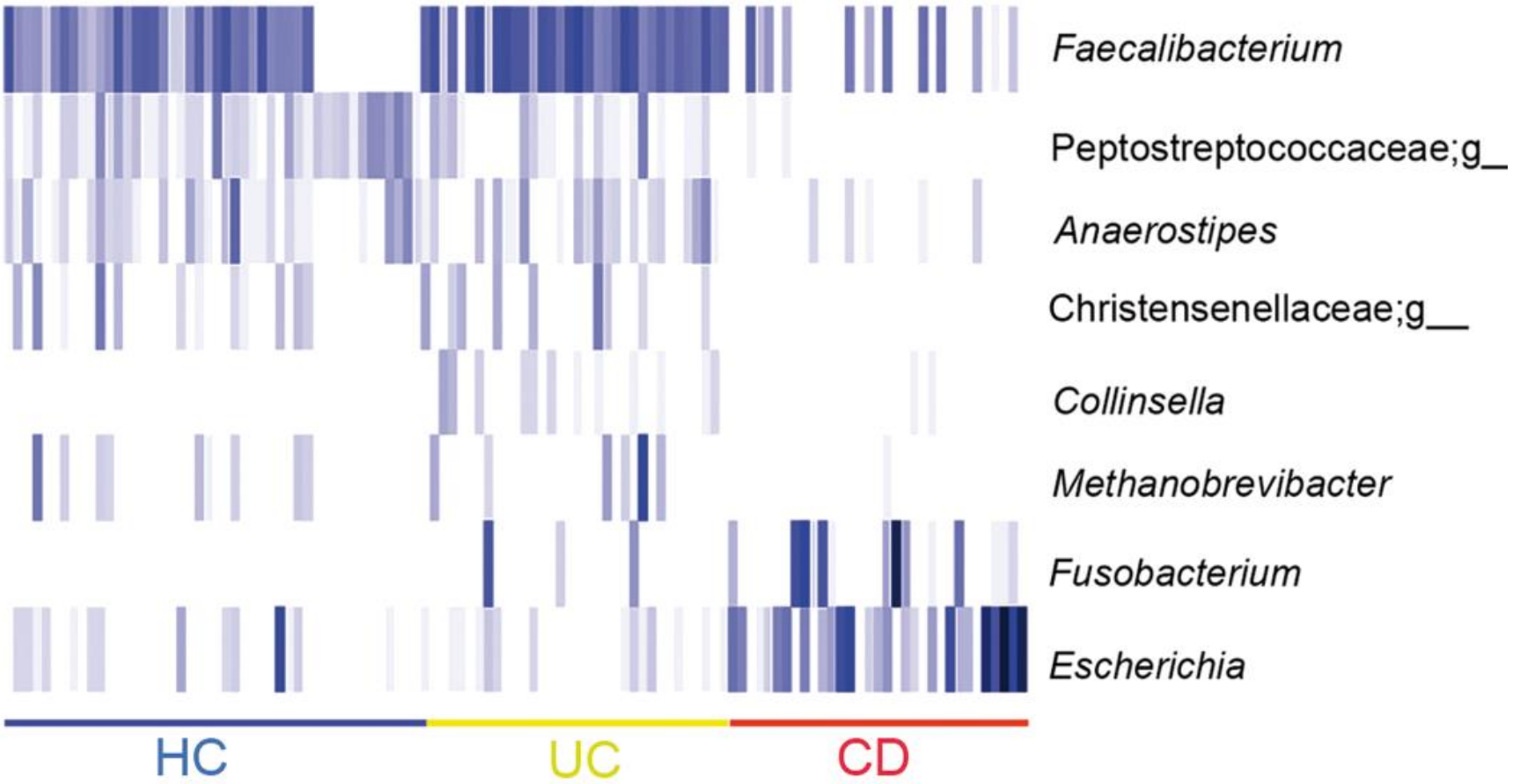
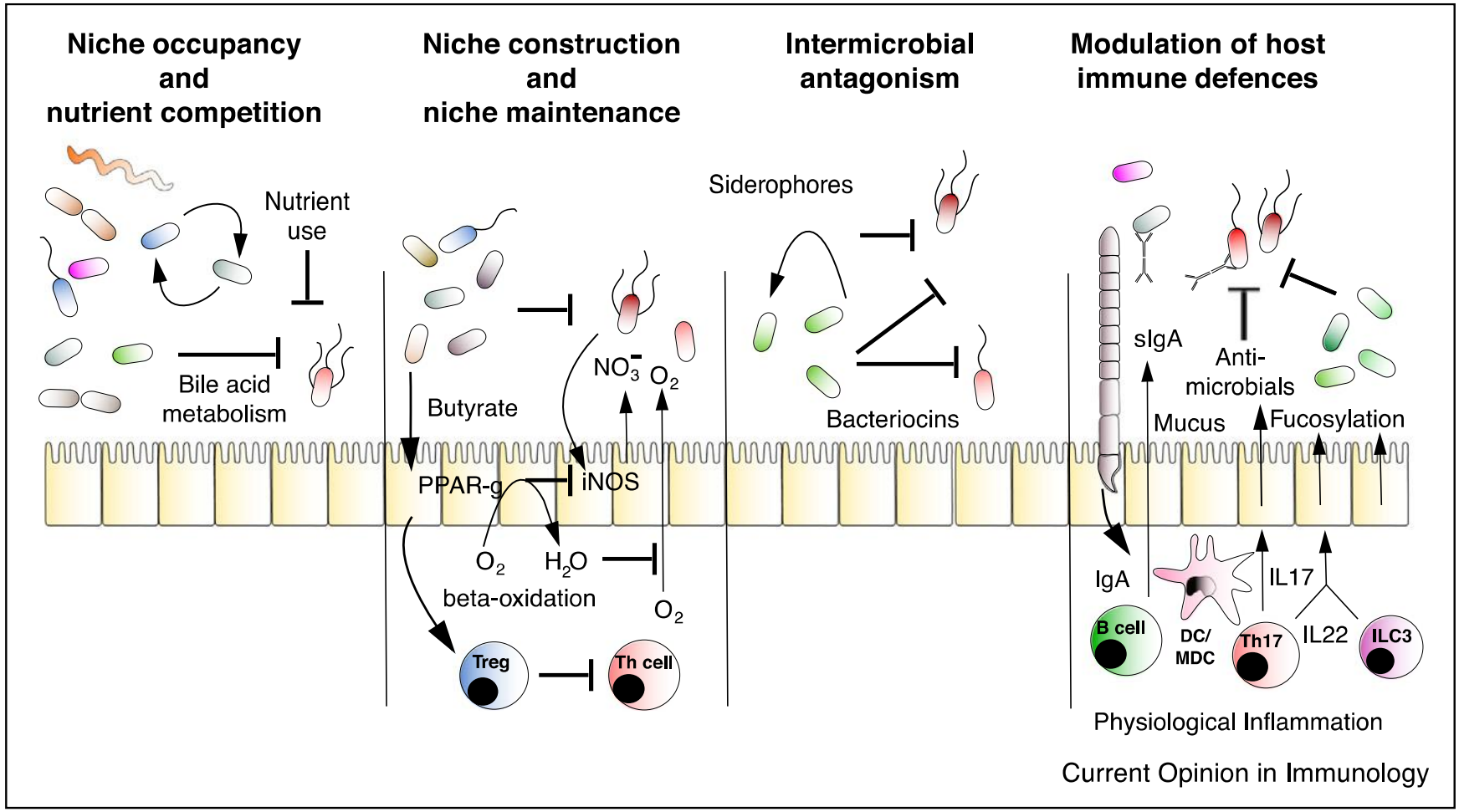
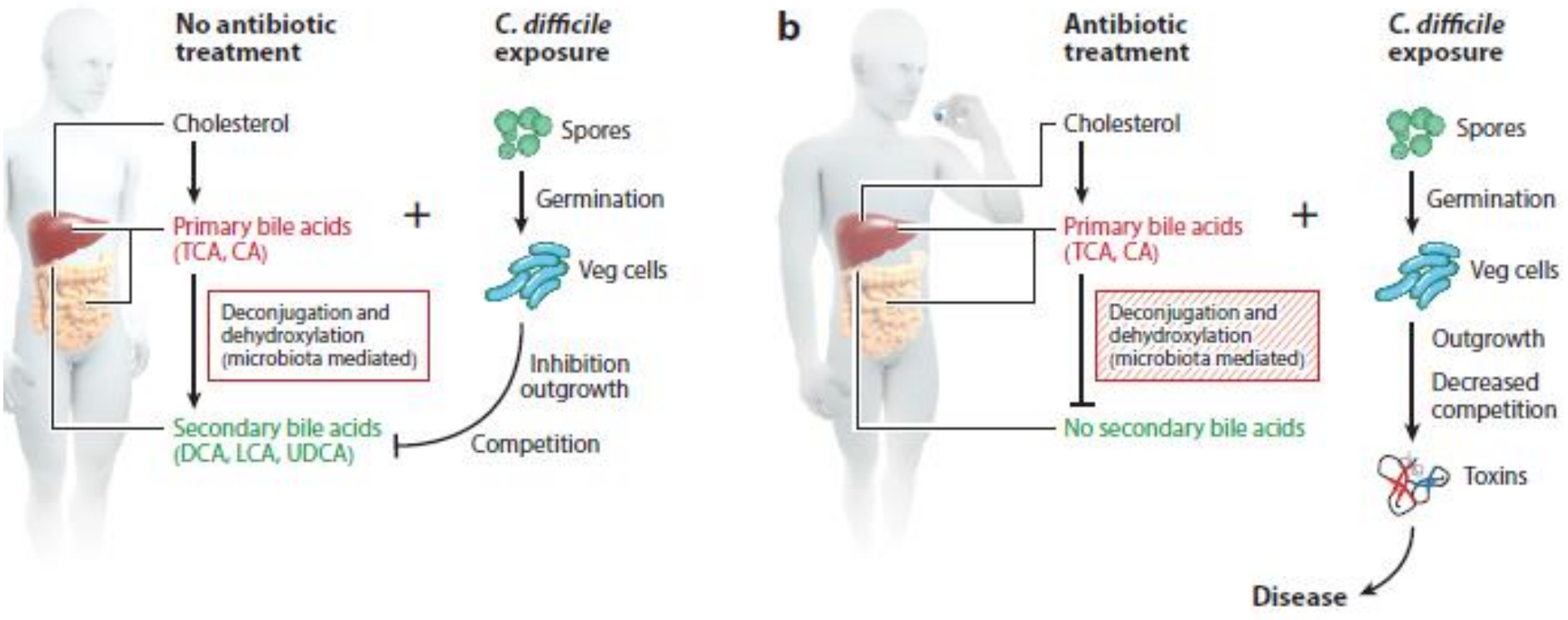


# Mechanisms involved in gut microbiota-mediated resistance against enteropathogen infection




Schnupf P et al.,Curr Op Immunol, 2018

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




Antibiotic treatment alters the gut microbiota structure, specifically decreasing bacteria that are able to 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.

# 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*

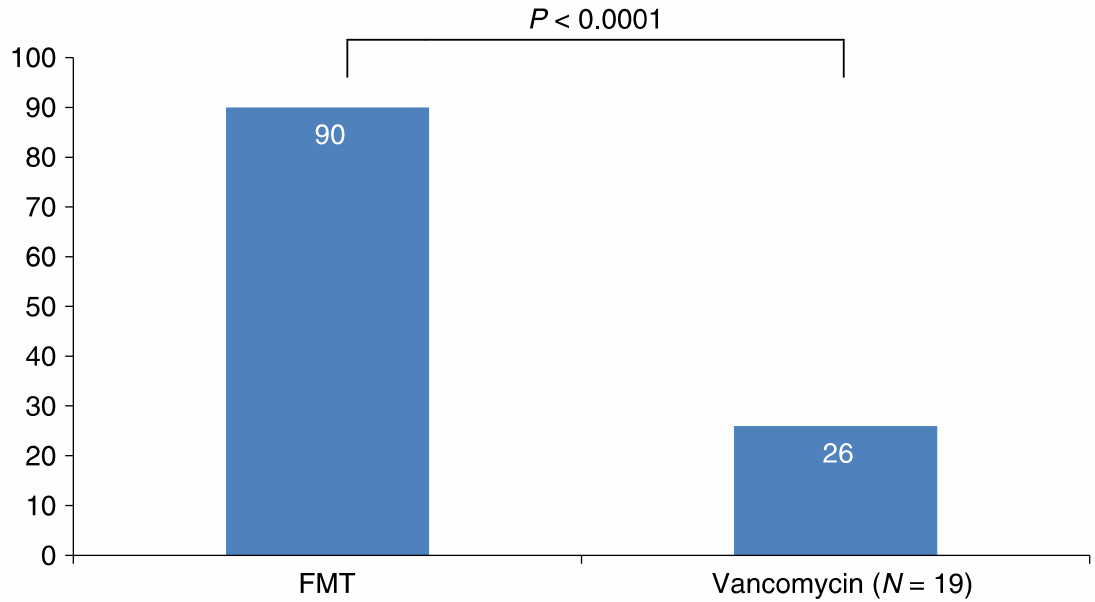


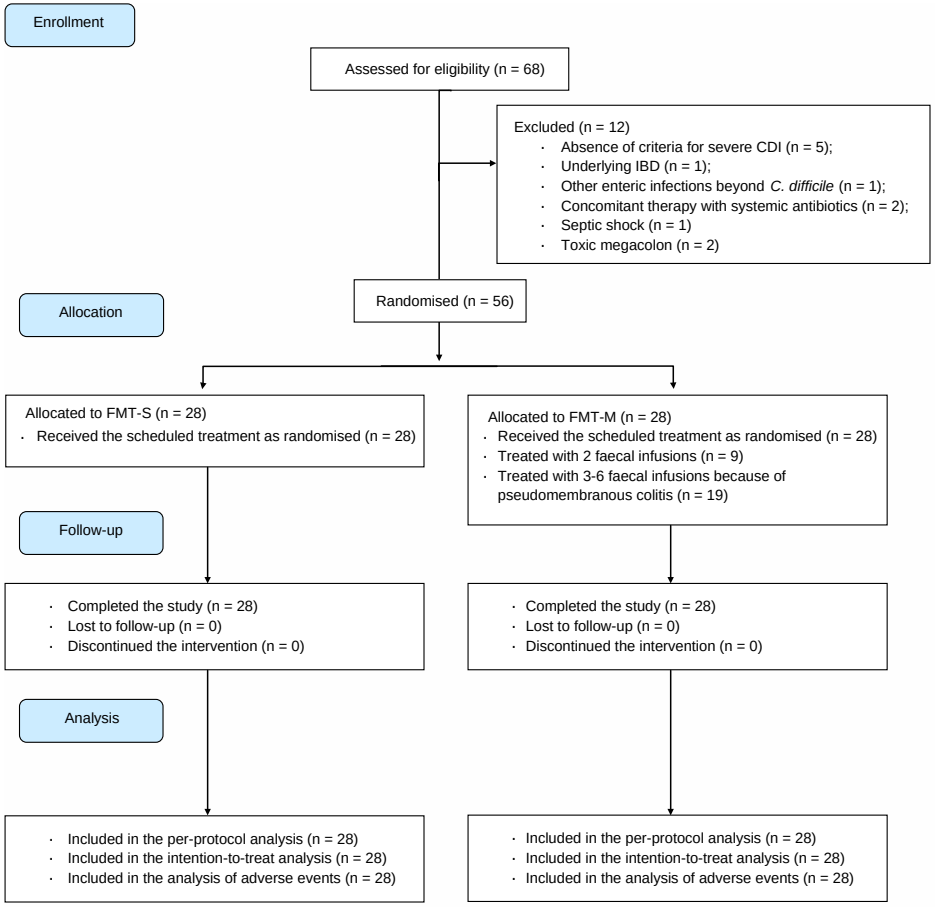

**Figure 2 |** Percentage of patients cured.

Received: 8 February 2018 | First decision: 8 March 2018 | Accepted: 30 April 2018
DOI: 10.1111/apt.14816

WILEY AP&T Alimentary Pharmacology & Therapeutics

# Randomised clinical trial: faecal microbiota transplantation by colonoscopy plus vancomycin for the treatment of severe refractory Clostridium difficile infection—single versus multiple infusions

G. Ianiro[1] | L. Masucci[2] | G. Quaranta[2] | C. Simonelli[1] | L. R. Lopetuso[1] | M. Sanguinetti[2] | A. Gasbarrini[1] | G. Cammarota[1]




- Subjects with severe *Clostridioides difficile* infection refractory to antibiotics were randomly assigned to one of the two following treatment arms:
  - FMT-S, including a single faecal infusion via colonoscopy followed by a 14-day vancomycin course,
  - FMT-M, including multiple faecal infusions plus a 14-day vancomycin course. In the FMT-M group, all subjects received at least two infusions.
- The primary outcome was the cure of refractory severe *Clostridioides difficile* infection.
- Fifty six subjects, 28 in each treatment arm, were enrolled.
- Twenty one patients in the FMT-S group and 28 patients in the FMT-M group were cured (75% vs 100%, respectively, both in per protocol and intention-to-treat analyses; $P = 0.01$).
- No serious adverse events associated with any of the two treatment protocols were observed.

# Fecal Microbiota Transplantation at the "A. Gemelli" Hospital - Overall Data (years 2013–2018)

- **150 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 223 infusion procedures** (91 patients received one infusion, 79 multiple infusions)
- Fresh material/Frozen material= 126/87

**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)
- Jan-Jul 2018= 47 (33 pts)

**RESULTS:**

- Severe colitis (PMC) in 65 patients
- Follow-up range = 1–60 months
- **Resolution of rCDI in 147/150 treated patients (98%)**
- **No patients experienced further FMT recurrences**
- **No more surgery for CDI in our hospital since 2014**

# L'infezione da *Clostridium difficile* è uno dei temi caldi in ospedale

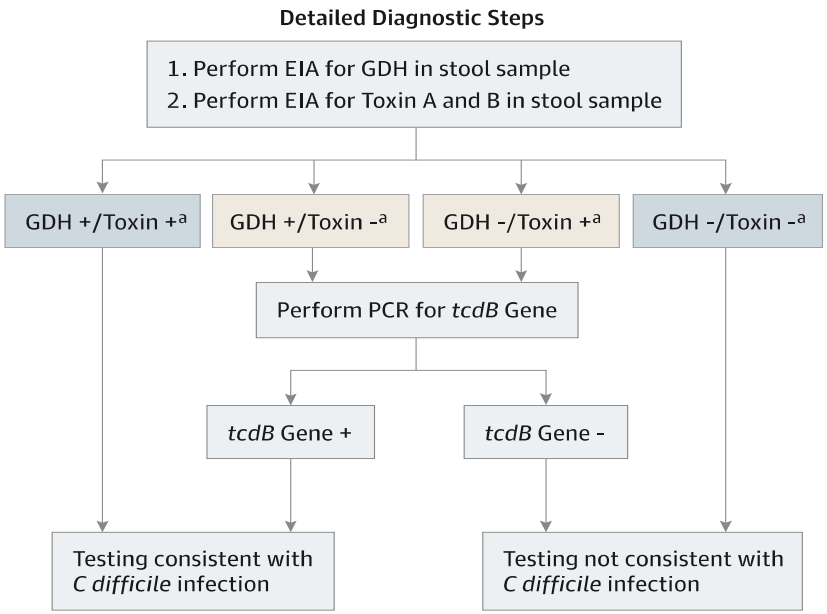
Gemelli
Fondazione Policlinico Universitario A. Gemelli
Università Cattolica del Sacro Cuore

| PROCEDURA<br>PERCORSO CLINICO ASSISTENZIALE DEL PAZIENTE CON INFEZIONE DA CLOSTRIDIUM DIFFICILE (CDI) | Rev.: 0<br>PRO.POL.RMA. 188 |
|---|---|

Procedura
**Percorso Clinico Assistenziale del paziente con Infezione da Clostridium difficile (CDI)**

Adopted procedure for the management of *C. difficile* infection at the "A. Gemelli" Hospital

Questo PCA è stato **attivato nel 2015** per rispondere all'esigenza di tenere sotto controllo il fenomeno dell'infezione da *Clostridium difficile* identificando una procedura standard. Questa procedura prevedeva l'introduzione di algoritmi e test diagnostici innovativi

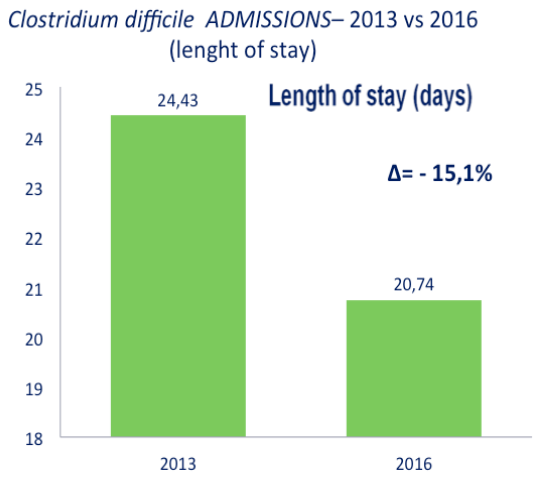



Il PCA prevede tre passi principali già in PS:

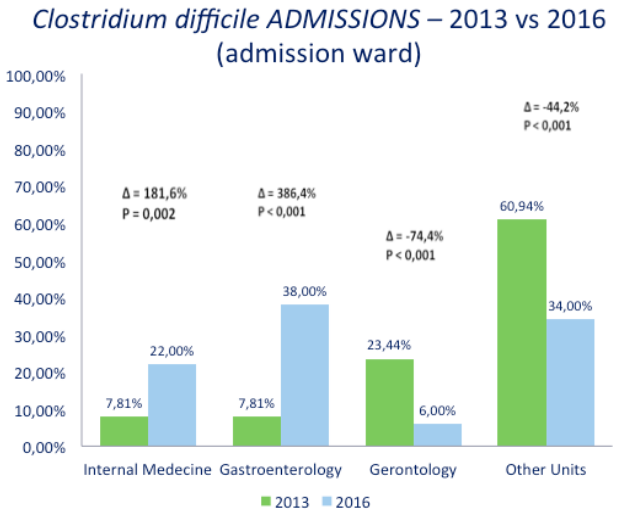
1. Identificazione del paziente con sospetta infezione da *Clostridium difficile*
2. Valutazione microbiologica real-time del paziente
3. Gestione del paziente a seconda dell'esito degli approfondimenti diagnostici (inclusa la possibilità di FMT)

# The pre-post analysis of the procedure implementation revelead impacts on the lenght of stay, on the appropriateness of the treatment and on mortality

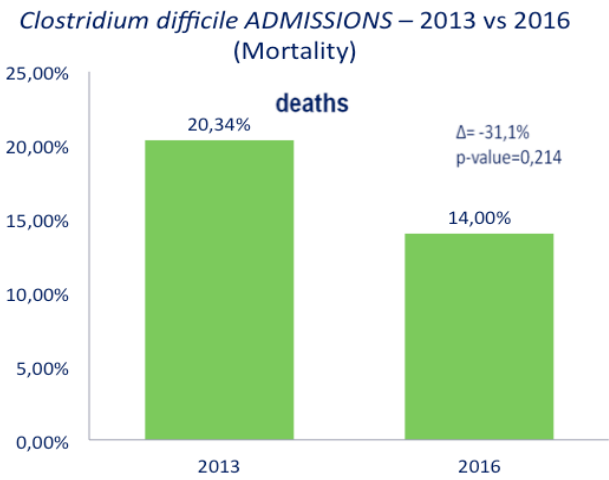
## Lenght of stay (days)

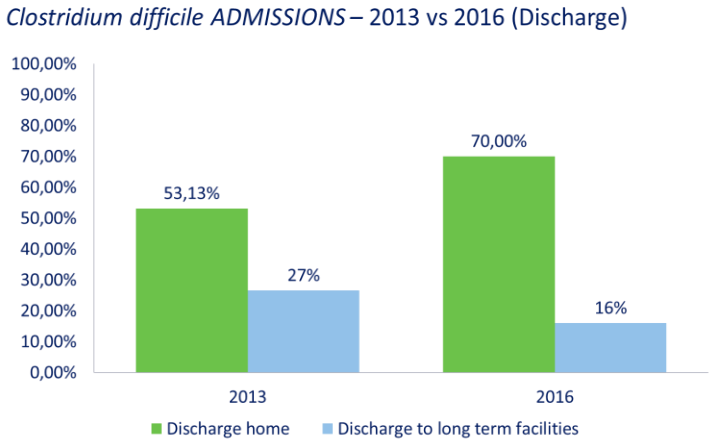



## Ward of treatment



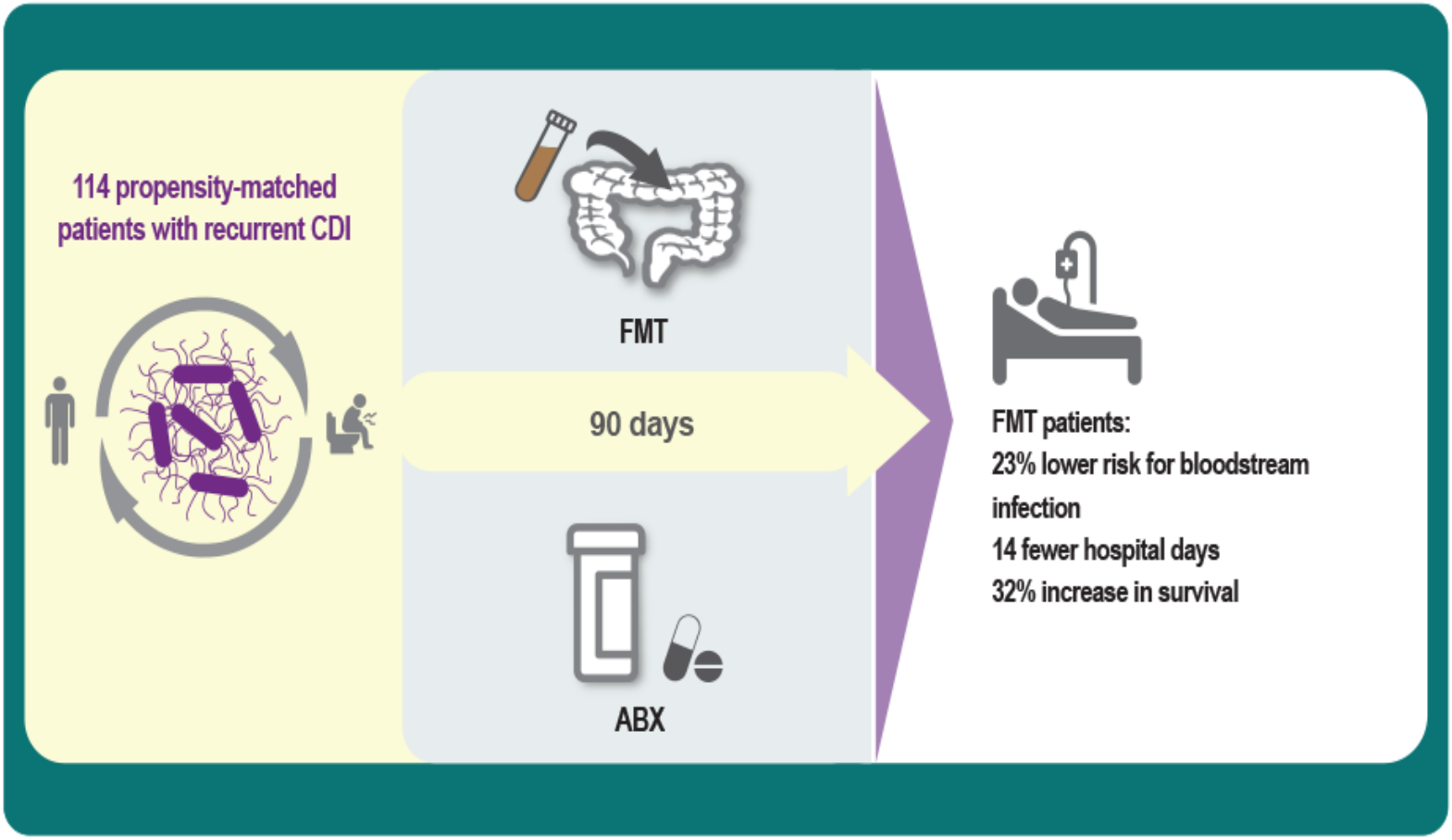

## Hospital mortality (%)




De Belvis et al., IJID, 2019

# Is treatment of recurrent *Clostridiodes difficile* infection (CDI) with fecal microbiota transplantation (FMT) versus antibiotics (ABX) associated with incidence of CDI-associated bloodstream infection?




Annals of Internal Medicine

Ianiro G, Murri R, Sciumè GD, et al. Incidence of bloodstream infections, length of hospital stay, and survival in patients with recurrent Clostridioides difficile infection treated with fecal microbiota transplantation or antibiotics. A prospective cohort study. Ann Intern Med. 29 October 2019. [Epub ahead of print]. doi:10.7326/M18-3635
http://annals.org/aim/article/doi/10.7326/M18-3635

Annals of Internal Medicine ORIGINAL RESEARCH

# Incidence of Bloodstream Infections, Length of Hospital Stay, and Survival in Patients With Recurrent *Clostridioides difficile* Infection Treated With Fecal Microbiota Transplantation or Antibiotics

## A Prospective Cohort Study

Gianluca Ianiro, MD; Rita Murri, MD; Giusi Desirè Sciumè, MD; Michele Impagnatiello, MD; Luca Masucci, MD; Alexander C. Ford, MBChB, MD; Graham R. Law, PhD; Herbert Tilg, MD; Maurizio Sanguinetti, MD; Roberto Cauda, MD, PhD; Antonio Gasbarrini, MD; Massimo Fantoni, MD; and Giovanni Cammarota, MD

*Table 2.* Outcome Data in the Original Cohort and in the Propensity Score–Matched Cohort

| Variable | Original Cohort | | | After Propensity Score Matching | | |
|---|---|---|---|---|---|---|
| | Treated With FMT | Treated With Antibiotics | Difference, % | Treated With FMT | Treated With Antibiotics | Difference (95% CI), % |
| **Patients, *n*** | 109 | 181 | – | 57 | 57 | – |
| **Primary outcomes, *n* (%)** | | | | | | |
| BSI | 5 (5) | 40 (22) | 16 | 2 (4) | 15 (26) | 23 (10–35) |
| Polymicrobial* | 1 (1) | 11 (6) | – | 0 (0) | 0 (0) | – |
| Bacterial | 5 (5) | 28 (15) | – | 2 (4) | 8 (14) | – |
| Fungal | 0 (0) | 12 (7) | – | 0 (0) | 7 (12) | – |
| **Secondary outcomes** | | | | | | |
| Length of hospitalization | – | – | 24 | – | – | 14 (9–20) |
| Mean (SD), *d* | 13.3 (14.8) | 29.7 (22.6) | – | 13.4 (13.7) | 27.8 (17.6) | – |
| Median (interquartile range), *d* | 8 (2–20) | 22 (14–39) | – | 9 (2–21) | 22 (14–40) | – |
| Overall survival at 90 d | – | – | 30 | – | – | 32 (16–47) |
| Alive after 90 d, *n* (%) | 100 (92) | 111 (61) | – | 51 (89) | 33 (58) | – |
| Total deaths within 90 d, *n* (%) | 9 (8) | 70 (39) | – | 6 (11) | 22 (39) | – |
| Deaths in days 0–30, *n* | 5 | 53 | – | 3 | 15 | – |
| Deaths in days 31–90, *n* | 4 | 17 | – | 3 | 7 | – |

BSI = bloodstream infection; FMT = fecal microbiota transplantation.
* 12 of 45 patients developed a polymicrobial BSI (from multiple bacteria in 10 patients and from fungal and bacterial organisms in 2 patients).

# Incidence of Bloodstream Infections, Length of Hospital Stay, and Survival in Patients With Recurrent *Clostridioides difficile* Infection Treated With Fecal Microbiota Transplantation or Antibiotics

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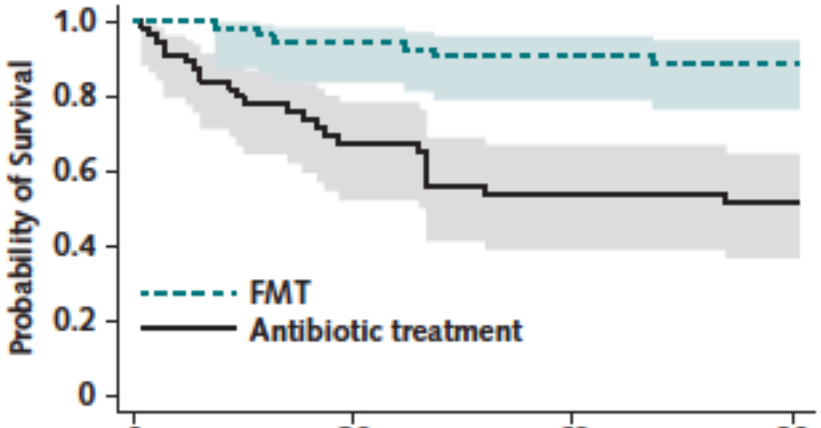
*Figure 2.* Overall survival at 90 d in 57 patients treated with FMT compared with 57 patients treated with antibiotics matched by propensity score.




| At risk, *n* | | | | |
|---|---|---|---|---|
| FMT | 57 | 51 | 46 | 43 |
| Antibiotic treatment | 57 | 31 | 24 | 22 |

Shaded areas are 95% CIs. FMT = fecal microbiota transplantation.

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

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

Zachariah DeFilipp, M.D., Patricia P. Bloom, M.D., Mariam Torres Soto, M.A., Michael K. Mansour, M.D., Ph.D., Mohamad R.A. Sater, Ph.D., Miriam H. Huntley, Ph.D., Sarah Turbett, M.D., Raymond T. Chung, M.D., Yi-Bin Chen, M.D., and Elizabeth L. Hohmann, M.D.

## SUMMARY

Fecal microbiota transplantation (FMT) is an emerging therapy for recurrent or refractory *Clostridioides difficile* infection and is being actively investigated for other conditions. We describe two patients in whom extended-spectrum beta-lactamase (ESBL)–producing *Escherichia coli* bacteremia occurred after they had undergone FMT in two independent clinical trials; both cases were linked to the same stool donor by means of genomic sequencing. One of the patients died. Enhanced donor screening to limit the transmission of microorganisms that could lead to adverse infectious events and continued vigilance to define the benefits and risks of FMT across different patient populations are warranted.

# European consensus conference on faecal microbiota transplantation in clinical practice

Giovanni Cammarota,[1] Gianluca Ianiro,[1] Herbert Tilg,[2] Mirjana Rajilić-Stojanović,[3] Patrizia Kump,[4] Reetta Satokari,[5] Harry Sokol,[6] Perttu Arkkila,[7] Cristina Pintus,[8] Ailsa Hart,[9] Jonathan Segal,[9] Marina Aloi,[10] Luca Masucci,[11] Antonio Molinaro,[12] Franco Scaldaferri,[1] Giovanni Gasbarrini,[1] Antonio Lopez-Sanroman,[13] Alexander Link,[14] Pieter de Groot,[15] Willem M de Vos,[5,16] Christoph Högenauer,[4] Peter Malfertheiner,[14] Eero Mattila,[17] Tomica Milosavljević,[18] Max Nieuwdorp,[12,15,19] Maurizio Sanguinetti,[11] Magnus Simren,[20] Antonio Gasbarrini,[1] The European FMT Working Group

Cammarota G, *et al. Gut* 2017;**66**:569–580.

## Box 3 Blood and stool testing to check donors for any potentially transmittable disease

**GENERAL BLOOD TESTING**

- Cytomegalovirus
- Epstein-Barr virus
- Hepatitis A
- HBV
- HCV
- Hepatitis E virus
- Syphilis
- HIV-1 and HIV-2
- *Entamoeba histolytica*
- Complete blood cell count with differential
- C-reactive protein and erythrocyte sedimentation rate
- Albumin
- Creatinine and electrolytes
- Aminotransferases, bilirubin, gamma-glutamyltransferase, alkaline phosphatase

**BLOOD TESTING IN SPECIFIC SITUATIONS**

- Human T-lymphotropic virus types I and II antibodies
- *Strongyloides stercoralis*

**GENERAL STOOL TESTING**

- Detection of *Clostridium difficile*
- Detection of enteric pathogens, including *Salmonella*, *Shigella*
- *Campylobacter*, *Escherichia coli O157 H7*, *Yersinia*, vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus*, Gram-negative multidrug-resistant bacteria
- Norovirus
- Antigens and/or acid fast staining for *Giardia lamblia* and *Criptosporidium parvum*
- Protozoa (including *Blastocystis hominis*) and helminths
- Faecal occult blood testing

**STOOL TESTING IN SPECIFIC SITUATIONS**

- Detection of *Vibrio cholera* and *Listeria monocytogenes*
- Antigens and/or acid fast staining for *Isospora* and *Microsporidia*
- Calprotectin
- *Helicobacter pylori* faecal antigen
- Rotavirus

# Microbiota destruction and antibiotic-resistant infections

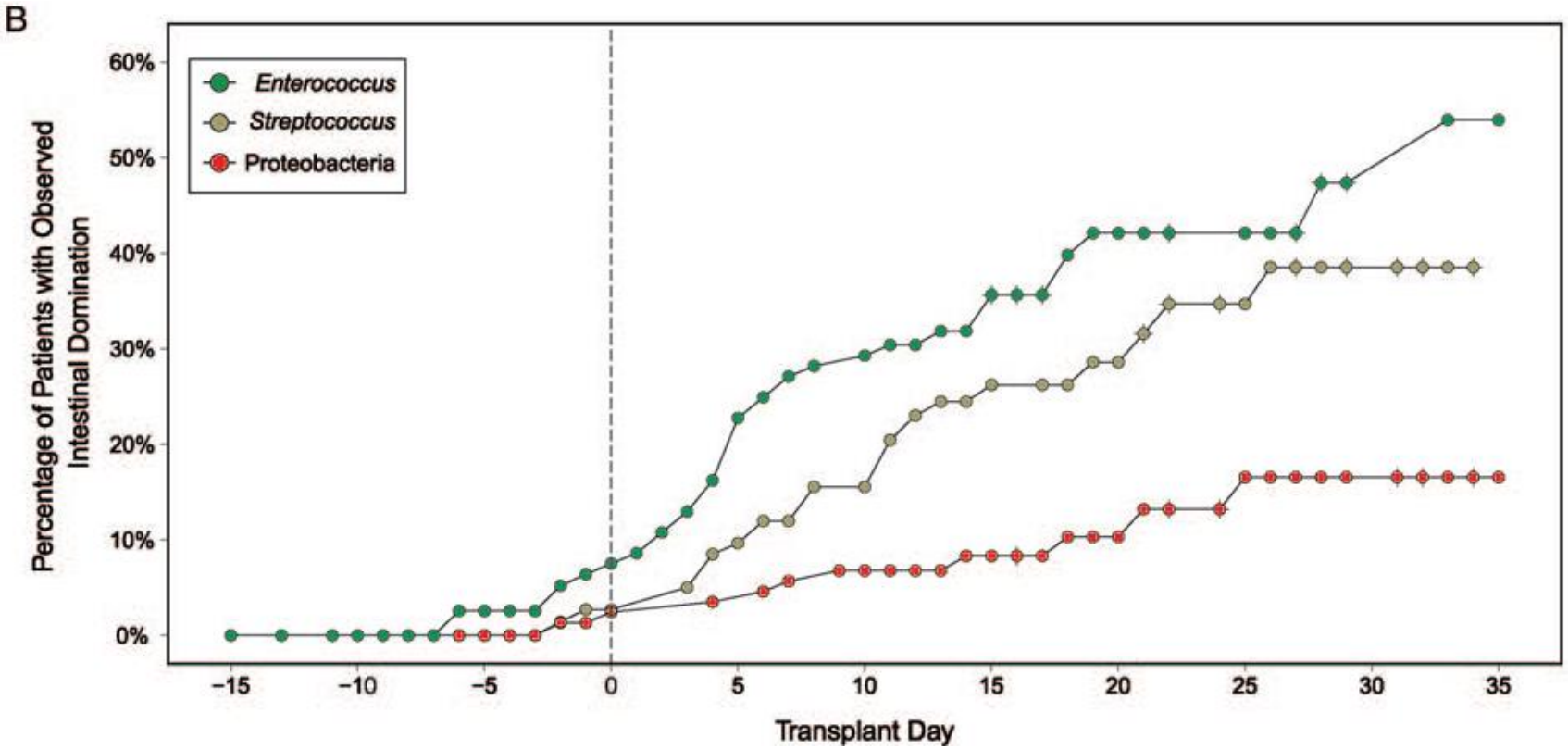
- Recommendations to combat the progression of antibiotic resistance included barrier and hygiene approaches to reduce transmission, limits on antibiotic use, and development of new and more effective antibiotics.
- A concern with these approaches, however, is that antibiotic resistance has grown despite 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).

MAJOR ARTICLE

# Intestinal Domination and the Risk of Bacteremia in Patients Undergoing Allogeneic Hematopoietic Stem Cell Transplantation

Ying Taur,[1,2] Joao B. Xavier,[2,3] Lauren Lipuma,[2] Carles Ubeda,[5] Jenna Goldberg,[4] Asia Gobourne,[2] Yeon Joo Lee,[1] Krista A. Dubin,[2] Nicholas D. Socci,[3] Agnes Viale,[6] Miguel-Angel Perales,[4] Robert R. Jenq,[4] Marcel R. M. van den Brink,[4,5] and Eric G. Pamer[1,2,5]

CID 2012:55 (1 October)




Characterization of the intestinal microbiota during allogeneic hematopoietic stem cell transplantation

# Intestinal Domination and the Risk of Bacteremia in Patients Undergoing Allogeneic Hematopoietic Stem Cell Transplantation

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**Table 3. Association of Intestinal Domination With Bacteremia[a]**

| | 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 |

Abbreviations: CI, confidence interval; HR, hazard ratio; VRE, Vancomycin-resistant *Enterococcus*.

[a] Bacteremia for each organism was defined as at least one positive blood culture within the study period.

[b] Intestinal domination was analyzed as a time-varying predictor.

*Clinical Infectious Diseases*

MAJOR ARTICLE

# Gut Microbiome Composition Predicts Infection Risk During Chemotherapy in Children With Acute Lymphoblastic Leukemia

**Hana Hakim,[1] Ronald Dallas,[1] Joshua Wolf,[1] Li Tang,[2] Stacey Schultz-Cherry,[1] Victoria Darling,[1] Cydney Johnson,[1] Erik A. Karlsson,[1] Ti-Cheng Chang,[3] Sima Jeha,[4] Ching-Hon Pui,[4] Yilun Sun,[2] Stanley Pounds,[2] Randall T. Hayden,[5] Elaine Tuomanen,[1] and Jason W. Rosch[1]**

Departments of [1]Infectious Diseases, [2]Biostatistics, [3]Computational Biology, [4]Oncology, and [5]Pathology, St Jude Children's Research Hospital, Memphis, Tennessee

- After the induction and reinduction I phases of chemotherapy, microbial diversity decreased significantly relative to the prechemotherapy value.
- After chemotherapy, the relative abundance of certain bacterial taxa (eg, *Bacteroidetes*) decreased significantly, whereas that of other taxa (eg, *Clostridiaceae* and *Streptococcaceae*) increased.
- A baseline gut microbiome characterized by *Proteobacteria* predicted febrile neutropenia. Adjusting for the chemotherapy phase and ALL risk level, *Enterococcaceae* dominance (relative abundance ≥30%) predicted significantly greater risk of subsequent febrile neutropenia and diarrheal illness, whereas *Streptococcaceae* dominance predicted significantly greater risk of subsequent diarrheal illness.
- In children undergoing therapy for newly diagnosed ALL, the relative abundance of *Proteobacteria* before chemotherapy initiation predicts development of febrile neutropenia, and domination of the gut microbiota by *Enterococcaceae* or *Streptococcaceae* at any time during chemotherapy predicts infection in subsequent phases of chemotherapy.

*Clinical Infectious Diseases*

MAJOR ARTICLE

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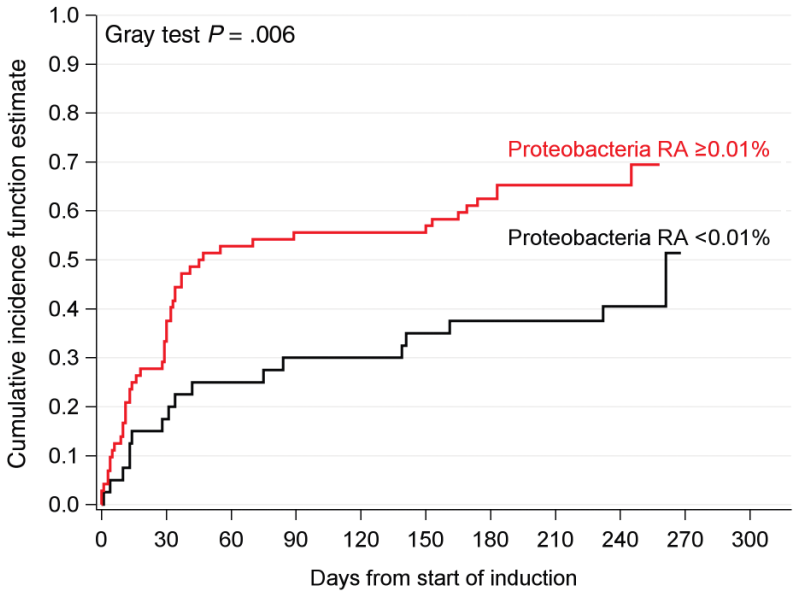


**Figure 3.** The relative abundance (RA) of Proteobacteria in the baseline gut microbiota at acute lymphoblastic leukemia diagnosis is associated with increased cumulative incidence of first episodes of febrile neutropenia. The estimated hazard ratio was 2.12 (95% confidence interval, 1.22–3.69; $P = .008$) for a Proteobacteria RA of ≥0.01 vs an RA of <0.01%, adjusting for gender.

*Clinical Infectious Diseases*

MAJOR ARTICLE

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- Of 14 patients with dominant *Enterococcaceae*, 7 (50%) developed subsequent infection, as did 4 of 5 (80%) patients with dominant *Streptococcaceae*.
- Adjusting for chemotherapy phase and ALL risk level, *Enterococcaceae* dominance was significantly associated with increased risk of subsequent febrile neutropenia (HR, 2.97) and diarrheal illness (HR, 4.23) compared to nondominance of both *Streptococcaceae* and *Enterococcaceae*, while *Streptococcaceae* dominance carried a greater risk (HR, 7.94) of subsequent diarrheal illness.
- Thus, a gut microbiota dominated by *Enterococcaceae* or *Streptococcaceae* is associated with subsequent infections.

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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.

Posteraro *et al. Gut Pathog* _####################_
https://doi.org/10.1186/s13099-019-0325-6

Gut Pathogens

CASE REPORT Open Access

# First bloodstream infection caused by *Prevotella copri* in a heart failure elderly patient with *Prevotella*-dominated gut microbiota: a case report

Patrizia Posteraro[1†], Flavio De Maio[2†], Giulia Menchinelli[2], Ivana Palucci[2], Federica Maria Errico[1], Mariantonietta Carbone[3], Maurizio Sanguinetti[2,4*], Antonio Gasbarrini[5,6*] and Brunella Posteraro[5,6]

- We report the case of a 90-year-old heart failure (HF) patient who was admitted to the hospital for an

**Table 1 Most relatively abundant bacteria on order, family, genus, and species level identified in the patient's fecal sample**

| Taxa | % abundance | Taxa | % abundance |
|---|---|---|---|
| Order | | Genus | |
| *Bacteroidales* | 34.114 | *Prevotella* | 15.253 |
| *Clostridiales* | 27.590 | *Faecalibacterium* | 8.215 |
| *Selenomonadales* | 7.493 | *Dialister* | 6.372 |
| | | *Parabacteroides* | 3.849 |
| | | *Bacteroides* | 3.750 |
| Family | | Species | |
| *Prevotellaceae* | 19.024 | *Prevotella copri* | 6.133 |
| *Ruminococcaceae* | 16.519 | *Dialister succinatiphilus* | 5.869 |
| *Lachnospiraceae* | 9.157 | *Faecalibacterium prausnitzii* | 3.180 |
| *Porphyromonadaceae* | 6.999 | *Parabacteroides distasonis* | 2.488 |
| *Veillonellaceae* | 6.758 | *Prevotella* sp. (DJF RP53) | 2.050 |
| *Bacteroidaceae* | 3.750 | | |

The listed taxa belong to the *Firmicutes* and *Bacteroidetes* phyla, whose relative abundances were 37.054% and 34.664%, respectively. Unlisted species include two other *Prevotella* sp. (BI-42 and DJF B112), whose relative abundances were 1.504% and 0.836%, respectively

*Clinical Infectious Diseases*

MAJOR ARTICLE

# 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]

**Clinical Infectious Diseases® 2017;65(3):364–70**

**Table 2. Impact of Fecal Microbiota Transplantation on Complete and Partial Antibiotic-Resistant Bacteria (ARB) Decolonization, With or Without Antibiotics During the First Week After Transplantation**

| | All FMTs n = 25 | | With Antibiotics, n = 11 | | Without Antibiotics, n = 14 | | |
|---|---|---|---|---|---|---|---|
| Endpoint | No. | % | No. | % | No. | % | *P* Value |
| Effect on all strains of ARB per FMT (complete ARB decolonization) | | | | | | | |
| At 1 month | 15/25 | 60 | 4/11 | 36 | 11/14 | 79 | .039 |
| At 6 months | 13/14 | 93 | 4/5 | 80 | 9/9 | 100 | .037 |
| Effect on at least 1 strain of ARB per FMT (partial ARB decolonization) | | | | | | | |
| At 1 month | 20/25 | 80 | 7/11 | 64 | 13/14 | 93 | NS |
| At 6 months | 13/14 | 93 | 4/5 | 80 | 9/9 | 100 | – |

Abbreviations: ARB, antibiotic-resistant bacteria; FMT, fecal microbiota transplantation.

Clinical Infectious Diseases

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**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 |

Abbreviations: ESBL, extended-spectrum β-lactamase; MBL, metallo-β-lactamase.

[a]Decolonization confirmed by quantitative real-time polymerase chain reaction.

ARTICLE

https://doi.org/10.1038/s41586-018-0616-y

# Pathogen elimination by probiotic *Bacillus* via signalling interference

Pipat Piewngam[1,2], Yue Zheng[1,5], Thuan H. Nguyen[1,5], Seth W. Dickey[1], Hwang-Soo Joo[1,4], Amer E. Villaruz[1], Kyle A. Glose[1], Emilie L. Fisher[1], Rachelle L. Hunt[1], Barry Li[1], Janice Chiou[1], Sujiraphong Pharkjaksu[2], Sunisa Khongthong[3], Gordon Y. C. Cheung[1], Pattarachai Kiratisin[2] & Michael Otto[1]*

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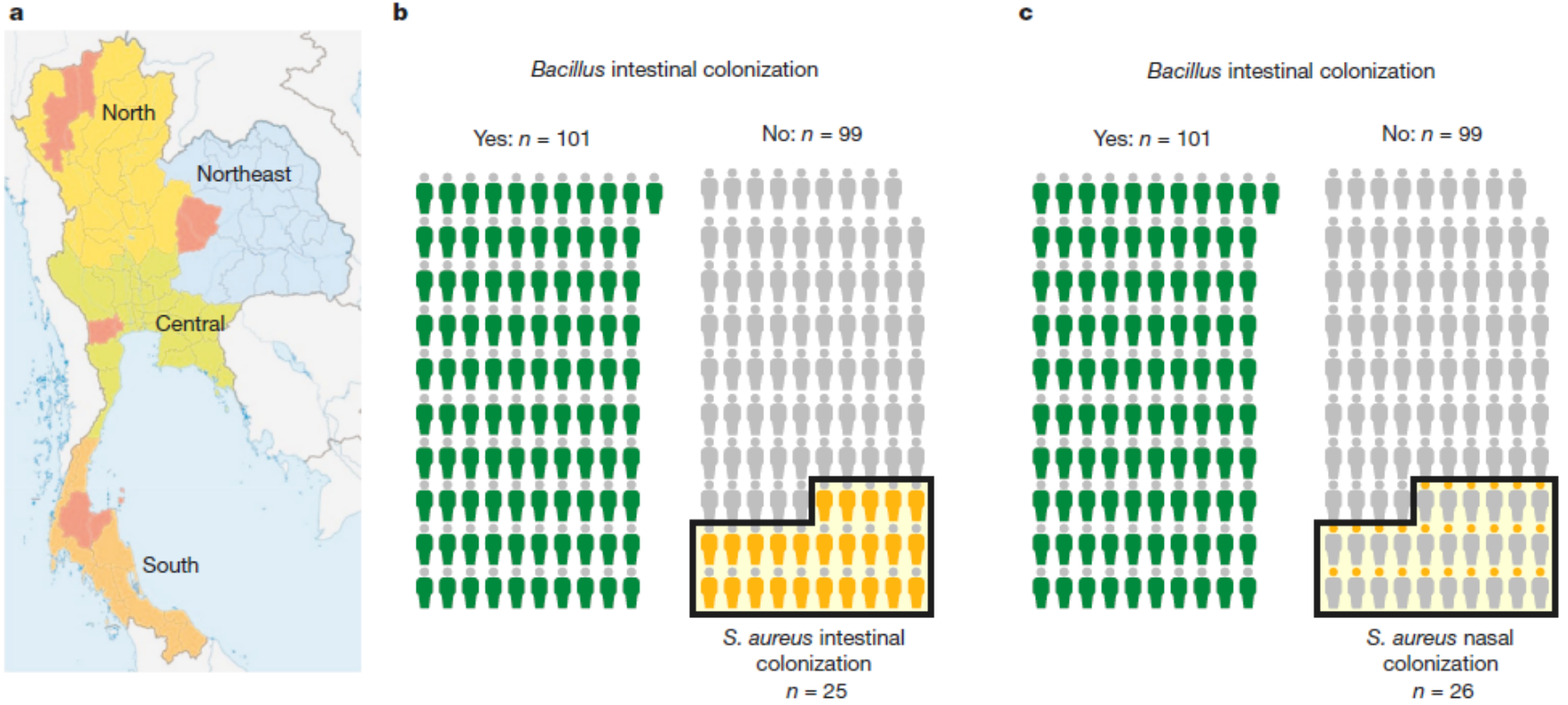


**Fig. 1 | Exclusion of *S. aureus* colonization by dietary *Bacillus* in a human population. a**, Areas (in red) from which faecal samples were collected in rural populations and analysed for the presence of *Bacillus* and *S. aureus*. **b**, **c**, Intestinal (**b**) and nasal (**c**) colonization with *S. aureus* (yellow) in individuals that showed (green) or did not show (grey) intestinal colonization with *Bacillus*.

ARTICLE

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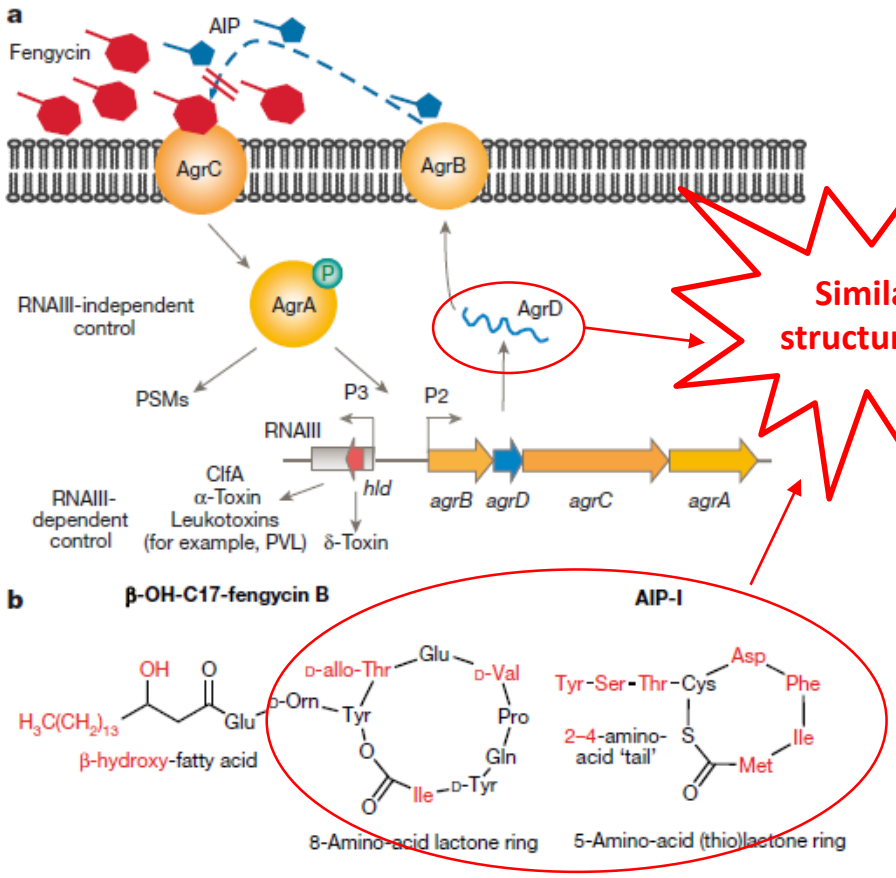
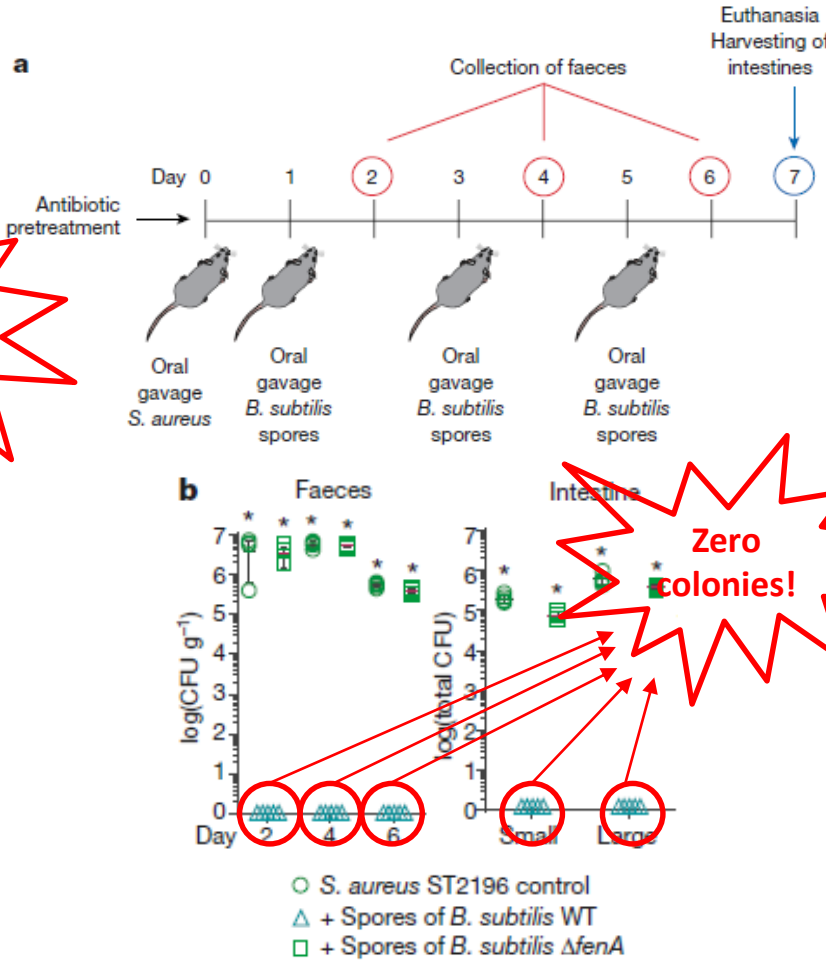
NATURE | VOL 562 | 25 OCTOBER 2018

Competitive inhibition of *S. aureus* AIP activity by fengycins




Similar structure!!!

Inhibition of *S. aureus* colonization by dietary fengycin producing *Bacillus* spores in a mouse model




Zero colonies!

# Conclusions

- Human microbiota study is one of the most intriguing and exciting research topics in the last years
- In the near future the association of specific microbiota types with specific diseases will permit to make treatment able to restore the “good microbiota” modified by therapeutic approaches
- The assessment of the microbiota composition that has to be used for FMT by -omics will permit to patient tailor this therapeutic procedure
- The use of “Bugs as Drugs”, by FMT, probiotics or phages, is supported by promising evidences derived from basic science and needs to be tested more extensively in randomized clinical trials.

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