

Modulation of the microbiome in sepsis

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Div. Infectious Diseases, Amsterdam UMC

Infectious diseases program, Athens, 26 March 2021





The microbiome: a hype or of real importance for the field of infectious diseases?



Surviving sepsis campaign: research priorities for sepsis and septic shock

Craig M. Coopersmith¹, Daniel De Backer^{2*} , Clifford S. Deutschman^{3,4}, Ricard Ferrer^{5,6}, Ishaq Lat⁷, Flavia R. Machado⁸, Greg S. Martin⁹, Ignacio Martin-Loeches¹⁰, Mark E. Nunnally¹¹, Massimo Antonelli¹², Laura E. Evans¹³, Judith Hellman¹⁴, Sameer Jog¹⁵, Jozef Kesecioglu¹⁶, Mitchell M. Levy¹⁷ and Andrew Rhodes¹⁸

Table 1 Top research priorities

Can targeted/personalized/precision medicine approaches determine which therapies will work for which patients at which times?

What are ideal endpoints for volume resuscitation and how should volume resuscitation be titrated?

Should rapid diagnostic tests be implemented in clinical practice?

Should empiric antibiotic combination therapy be used in sepsis or septic shock?

What are the predictors of sepsis long-term morbidity and mortality?

What information identifies organ dysfunction?

How does sepsis (and/or approaches used to manage sepsis) alter phenotypes and interactions in the host microbiome and do alterations in the microbiome effect outcomes



ELSEVIER

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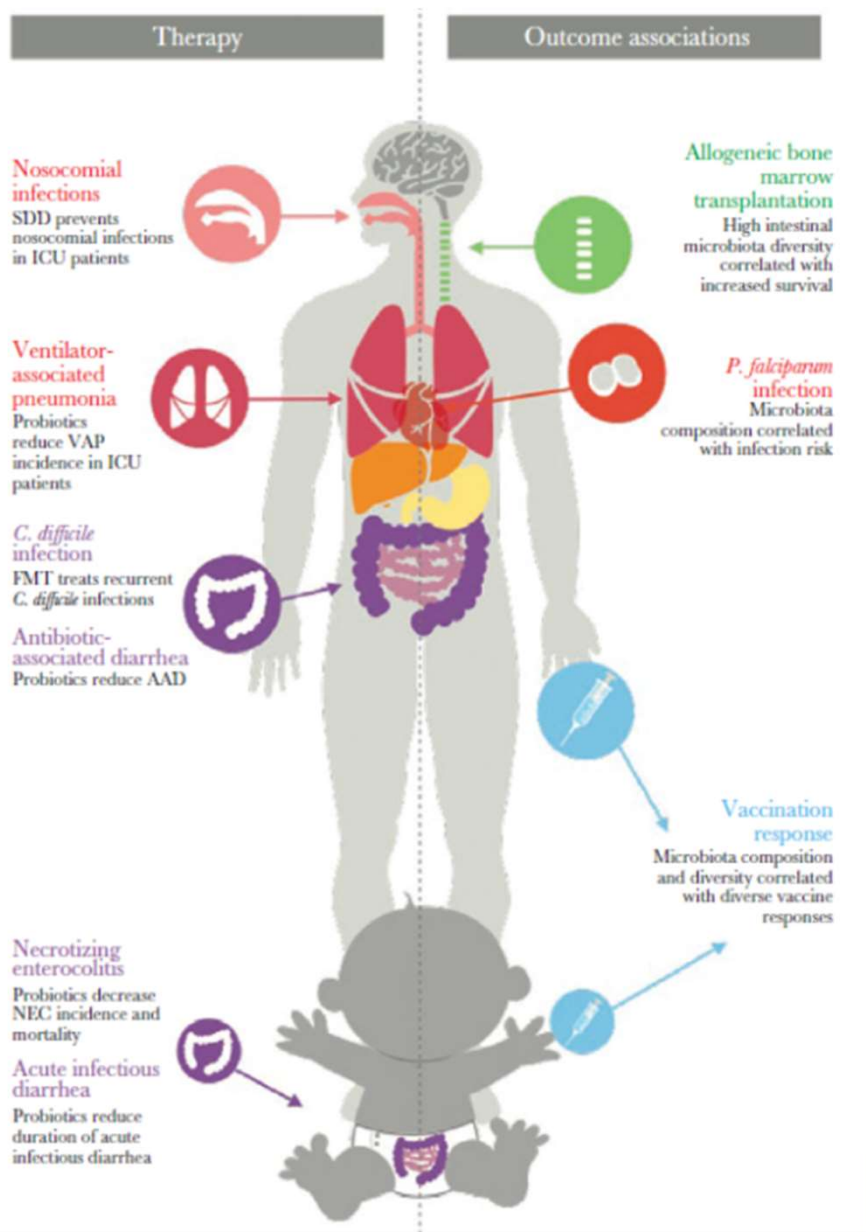
Guidelines

Towards precision medicine in sepsis: a position paper from the European Society of Clinical Microbiology and Infectious Diseases

J. Rello ^{1,*}, †, T.S.R. van Engelen ², †, E. Alp ³, T. Calandra ⁴, V. Cattoir ⁵, W.V. Kern ^{6,13}, M.G. Netea ^{7,12}, S. Nseir ⁸, S.M. Opal ⁹, F.L. van de Veerdonk ⁷, M.H. Wilcox ¹⁰, W.J. Wiersinga ^{2,11,13,**}

“In order to restore the microbiome after antibiotic treatment or to promote a functional microbiome, novel strategies should be evaluated such as FMT and the use of probiotics..”

Is this a hype or of real importance for patients with sepsis?



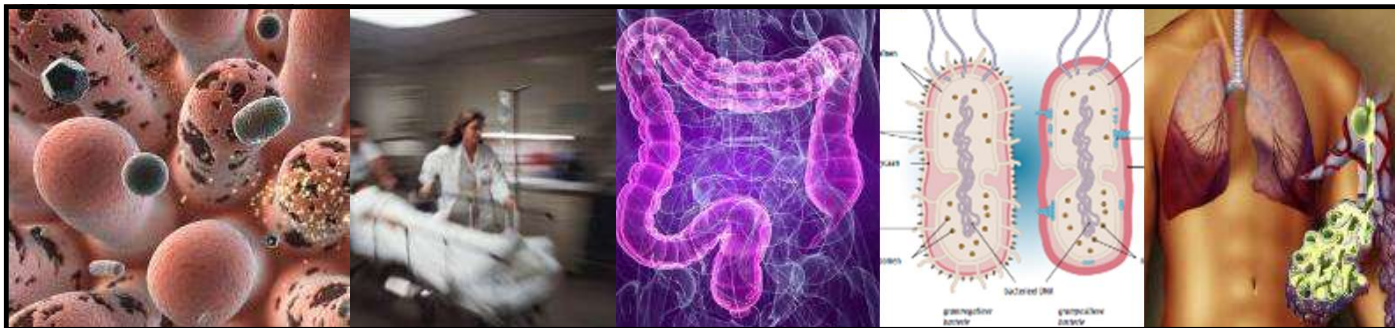
The Intestinal Microbiome in Infectious Diseases: The Clinical Relevance of a Rapidly Emerging Field

Vanessa C. Harris,^{1,2*} Bastiaan W. Haak,^{1,*} Michaël Boele van Hensbroek,^{2,3} and Willem J. Wiersinga¹

¹Department of Medicine, Division of Infectious Diseases and Center for Experimental and Molecular Medicine, Academic Medical Center, Amsterdam, Netherlands; ²Amsterdam Institute for Global Health and Development, Amsterdam, Netherlands; ³Erasmus Children's Hospital, Academic Medical Center, Amsterdam, Netherlands

- Microbiome basics: rapid review
- Composition and function of the microbiome in sepsis
- Therapeutic manipulation of the microbiome in sepsis
- Future perspective

Microbiome basics

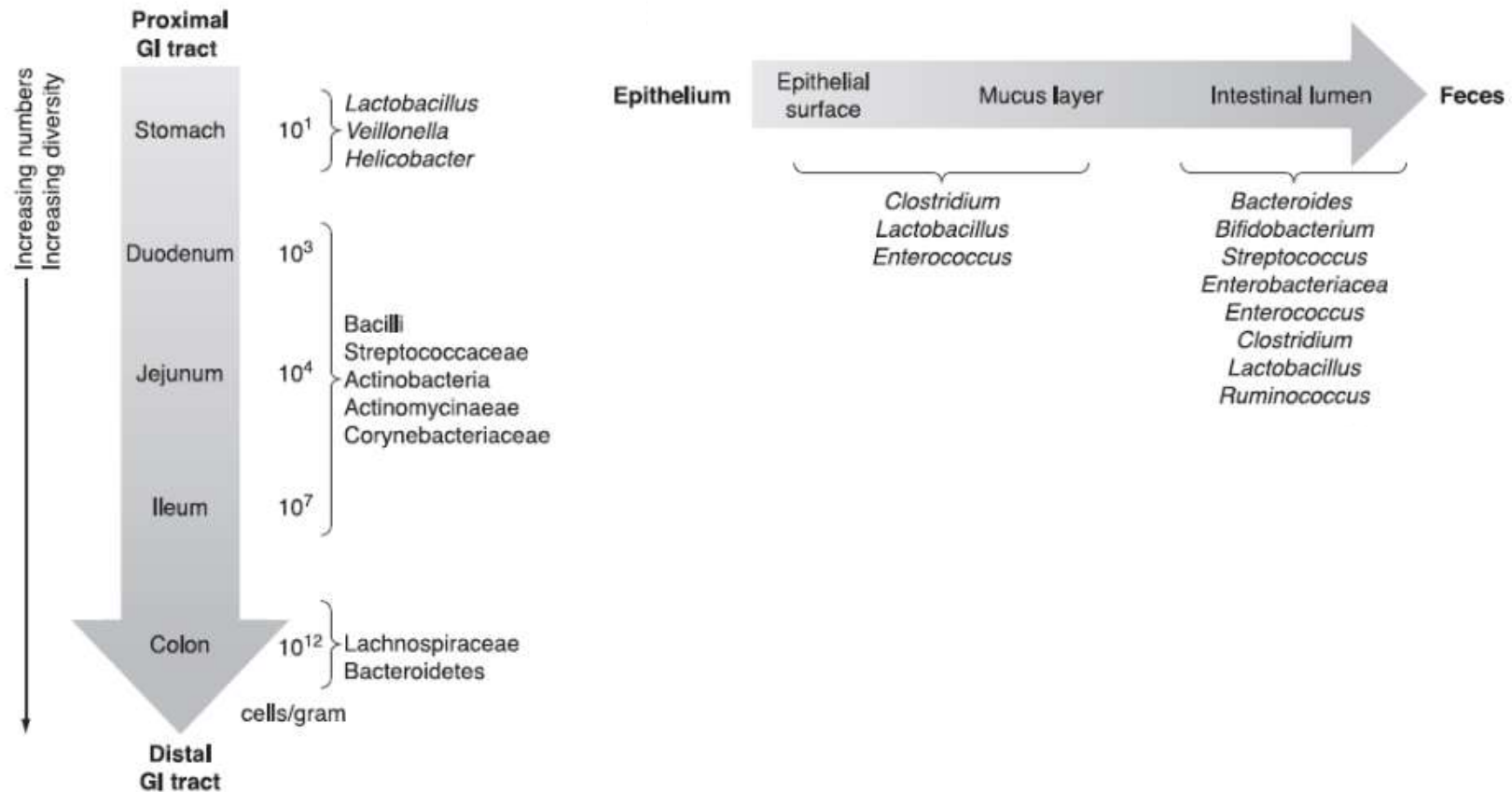


Composition of the gut microbiome

- Fetuses *in utero* sterile, development of fingerprint in first 2 years (40-50% via parents, remainder lifestyle).
- Adults gut microbiota: $\sim 10^{14}$ microorganisms
- ~ 1000 different bacterial species, dominant phyla:

Phylum	Characteristics	Examples
<u>Firmicutes</u>	Gram-positive; diverse in their morphology (rod, coccoid, spiral), physiology (anaerobic, aerobic); include commensal and beneficial bacteria	<i>Lactobacillus</i> , <i>Ruminococcus</i> , <i>Clostridium</i> , <i>Staphylococcus</i> , <i>Enterococcus</i> , <i>Faecalibacterium</i>
<u>Bacteroidetes</u>	Gram-negative; composed of 3 large classes widely distributed in the environment, including soil, seawater, and guts of animals	<i>Bacteroides</i> , <i>Prevotella</i>
Proteobacteria	Gram-negative; include a wide variety of pathogens	<i>Escherichia</i> , <i>Pseudomonas</i>
<u>Actinobacteria</u>	Gram-positive; diverse morphology; major antibiotic producers in the pharmaceutical industry	<i>Bifidobacterium</i> , <i>Streptomyces</i> , <i>Nocardia</i>

Composition of the gut microbiome is dependent on anatomy and age



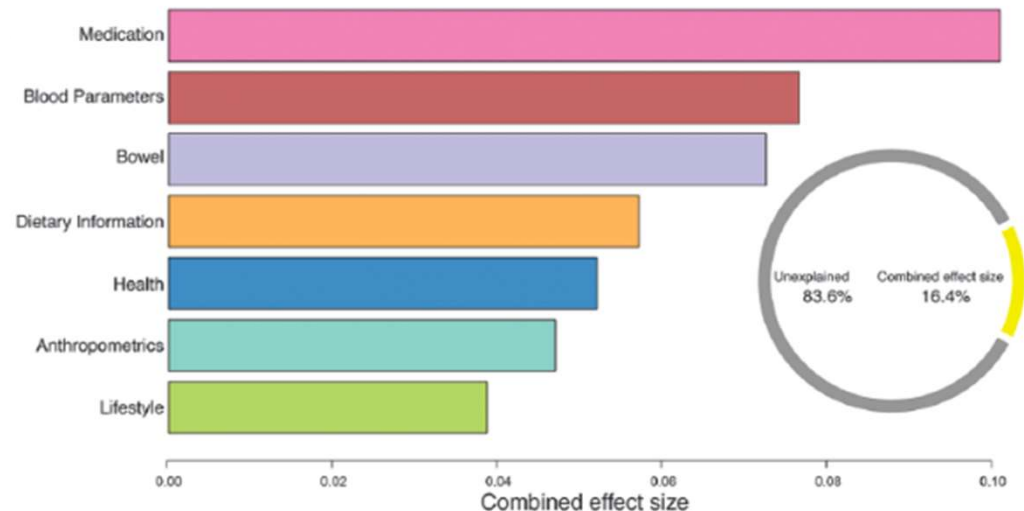
Composition of the normal gut microbiome.. if it exists.. And what does influence its composition?

MICROBIOME

Population-level analysis of gut microbiome variation

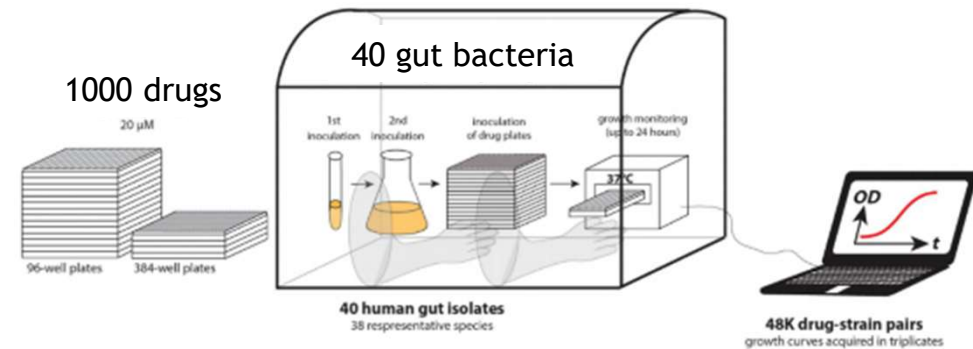
Gwen Falony,^{1,2*} Marie Joossens,^{1,2,3*} Sara Vieira-Silva,^{1,2*} Jun Wang,^{1,2*} Youssef Darzi,^{1,2,3} Karoline Faust,^{1,2,3} Alexander Kurilshikov,^{4,5} Marc Jan Bonder,⁶ Mireia Valles-Colomer,^{1,2} Doris Vandeputte,^{1,2,3} Raul Y. Tito,^{1,2,3} Samuel Chaffron,^{1,2,3} Leen Rymenans,^{1,2,3} Chloë Verspecht,^{1,2} Lise De Sutter,^{1,2,3} Gipsi Lima-Mendez,^{1,2} Kevin D'hoel,^{1,2,3} Karl Jonckheere,^{2,3} Daniel Homola,^{2,3} Roberto Garcia,^{2,3} Ettje F. Tigchelaar,^{6,7} Linda Eeckhaut,^{2,3} Jingyuan Fu,^{6,8} Liesbet Henckaerts,^{1,9} Alexandra Zhernakova,^{6,7} Cisca Wijmenga,⁶ Jeroen Raes^{1,2,3,†}

Fecal microbiome variation in the average, healthy population has remained under-investigated. Here, we analyzed two independent, extensively phenotyped cohorts: the Belgian Flemish Gut Flora Project (FGFP; discovery cohort; $N = 1106$) and the Dutch LifeLines-DEEP study (LLDeep; replication; $N = 1135$). Integration with global data sets (N combined = 3948) revealed a 14-genera core microbiota, but the 664 identified genera still underexplored total gut diversity. Sixty-nine clinical and questionnaire-based covariates were found associated to microbiota compositional variation with a 92% replication rate. Stool consistency showed the largest effect size, whereas medication explained largest total variance and interacted with other covariate-microbiota associations. Early-life events such as birth mode were not reflected in adult microbiota composition. Finally, we found that proposed disease marker genera associated to host covariates, urging inclusion of the latter in study design.



Extensive impact of non-antibiotic drugs on human gut bacteria

Lisa Maier^{1*}, Mihaela Pruteanu^{1†*}, Michael Kuhn^{2*}, Georg Zeller², Anja Telzerow¹, Exene Erin Anderson¹, Ana Rita Brochado¹, Keith Conrad Fernandez¹, Hitomi Dose³, Hirotsada Mori³, Kiran Raosaheb Patil², Peer Bork^{2,4,5,6} & Athanasios Typas^{1,2}



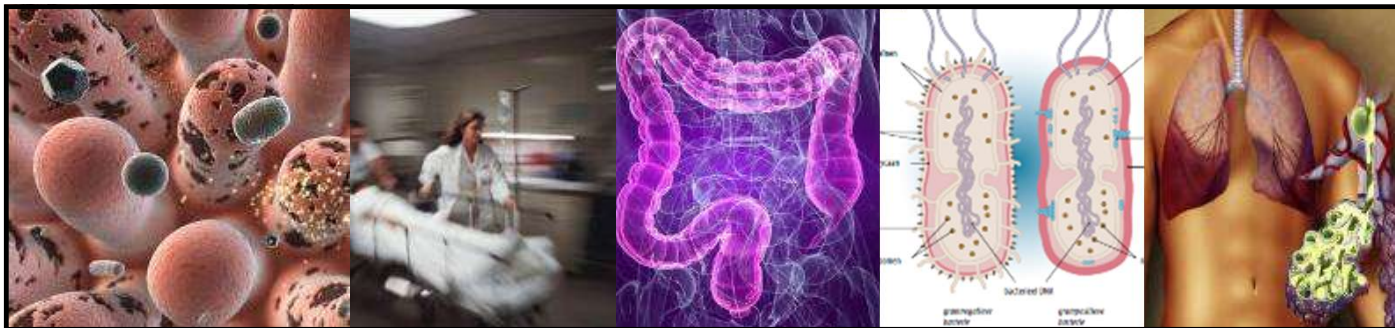
- 24% of non-antibiotic drugs inhibited the growth of ≥ 1 bacterial strain: metformin, PPI and antipsychotics
- Are associations found between a certain disease and gut microbiome composition caused by the drugs used for that disease?
- How does metformin work for diabetes? By changing the gut microbiome?
- Can the use of certain non-antibiotic drugs also induce antibiotic resistance?



The gut microbiota as an organ: functions

- **Metabolism**
 - Fermenting unused energy substrates
 - Synthesis of nutrients, vitamins and metabolites
- **Development of immune system**
- **Defence against pathogens**
 - Competition for nutrients and space with pathogens
 - Production of bacteriocins
 - Induction of antimicrobials and mucus production
 - Systemic effect on distant immune effector cells

Influence of antibiotics?





“Each generation could be beginning life with a smaller endowment of ancient microbes than the last.”



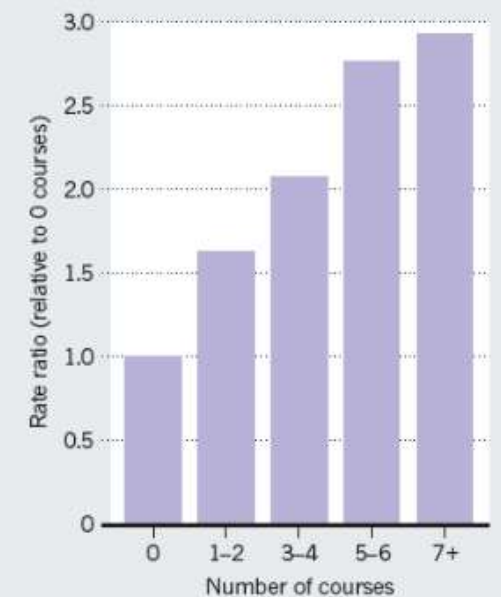
Dosed up: could excessive prescription of antibiotics be hampering children's ability to fight disease?

Stop the killing of beneficial bacteria

Concerns about antibiotics focus on bacterial resistance – but permanent changes to our protective flora could have more serious consequences, says **Martin Blaser**.

TROUBLING CORRELATION

The risk of inflammatory bowel diseases in children rises with the number of courses of antibiotics taken.



Blaser M, Nature, 2012; Blaser, Science, 2016

The influence of antibiotics



Incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation

Les Dethlefsen^a and David A. Relman^{a,b,1}

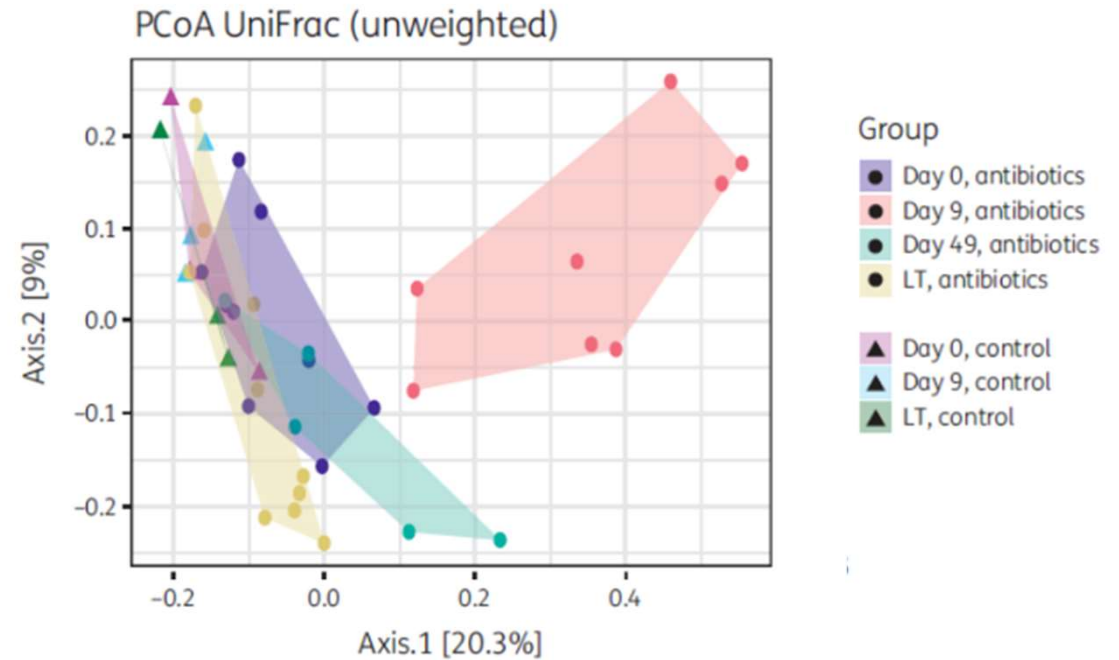
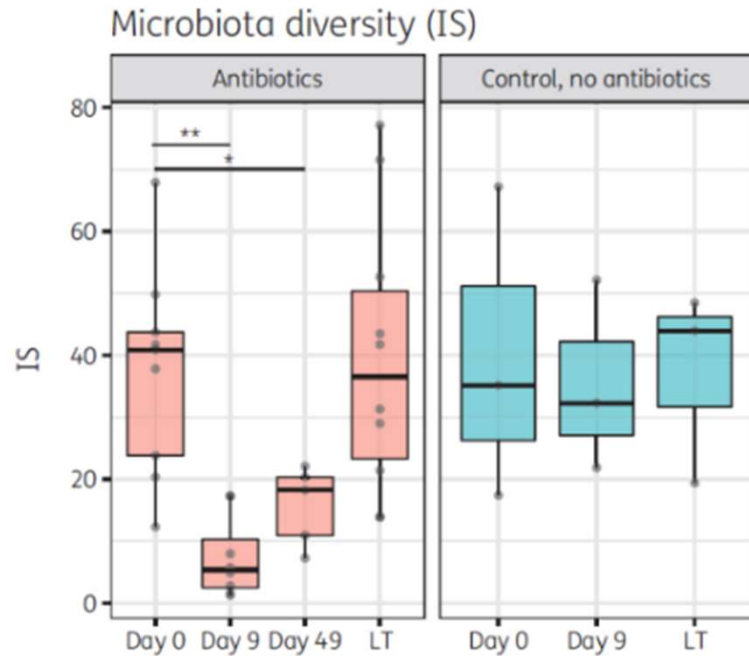
^aDepartment of Microbiology and Immunology and Department of Medicine, Stanford University School of Medicine, Stanford, CA 94305; and ^bVeterans Affairs Palo Alto Health Care System, Palo Alto, CA 94304

Edited by Jeffrey I. Gordon, Washington University School of Medicine, St. Louis, MO, and approved August 17, 2010 (received for review March 15, 2010)

- A simple course of antibiotics can change the composition of the gut microbiome fast and profound.. usually takes months to recover.
- Of note, also bacterial species which are not intrinsically sensitive for a given antibiotic can be wiped out because of many bacterial species depend on each other. For instance vancomycin will also lead to depletion of Gram-negative bacteria.

Long-term impact of oral vancomycin, ciprofloxacin and metronidazole on the gut microbiota in healthy humans

Bastiaan W. Haak ^{1*}, Jacqueline M. Lankelma¹, Floor Hugenholtz¹, Clara Belzer²,
Willem M. de Vos³ and W. Joost Wiersinga^{1,4}



The microbiome in sepsis



Composition of the microbiome in critical illness

Membership and Behavior of Ultra-Low-Diversity Pathogen Communities Present in the Gut of Humans during Prolonged Critical Illness

Alexander Zaborin,^a Daniel Smith,^{b*} Kevin Garfield,^c John Quensen,^c Baddr Shaksheer,^a Matthew Kade,^a Matthew Tirrell,^a James Tiedje,^c Jack A. Gilbert,^{a,b} Olga Zaborina,^a John C. Alverdy^a

ORIGINAL

Critically ill patients demonstrate large interpersonal variation in intestinal microbiota dysregulation: a pilot study

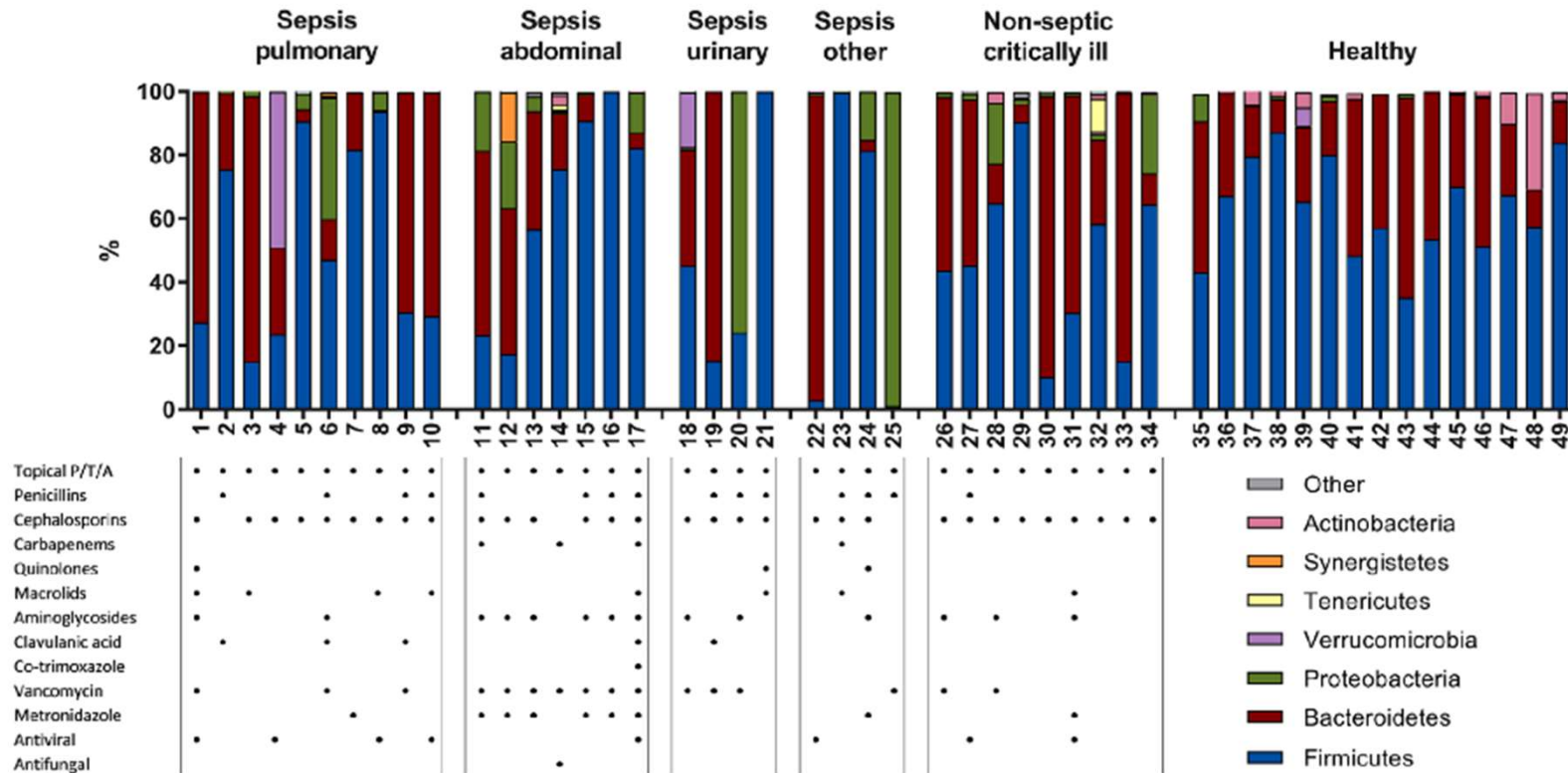
Jacqueline M. Lankelma^{1*} , Lonneke A. van Vught¹, Clara Belzer², Marcus J. Schultz³, Tom van der Poll^{1,4}, Willem M. de Vos^{2,5} and W. Joost Wiersinga^{1,4}

Extreme Dysbiosis of the Microbiome in Critical Illness

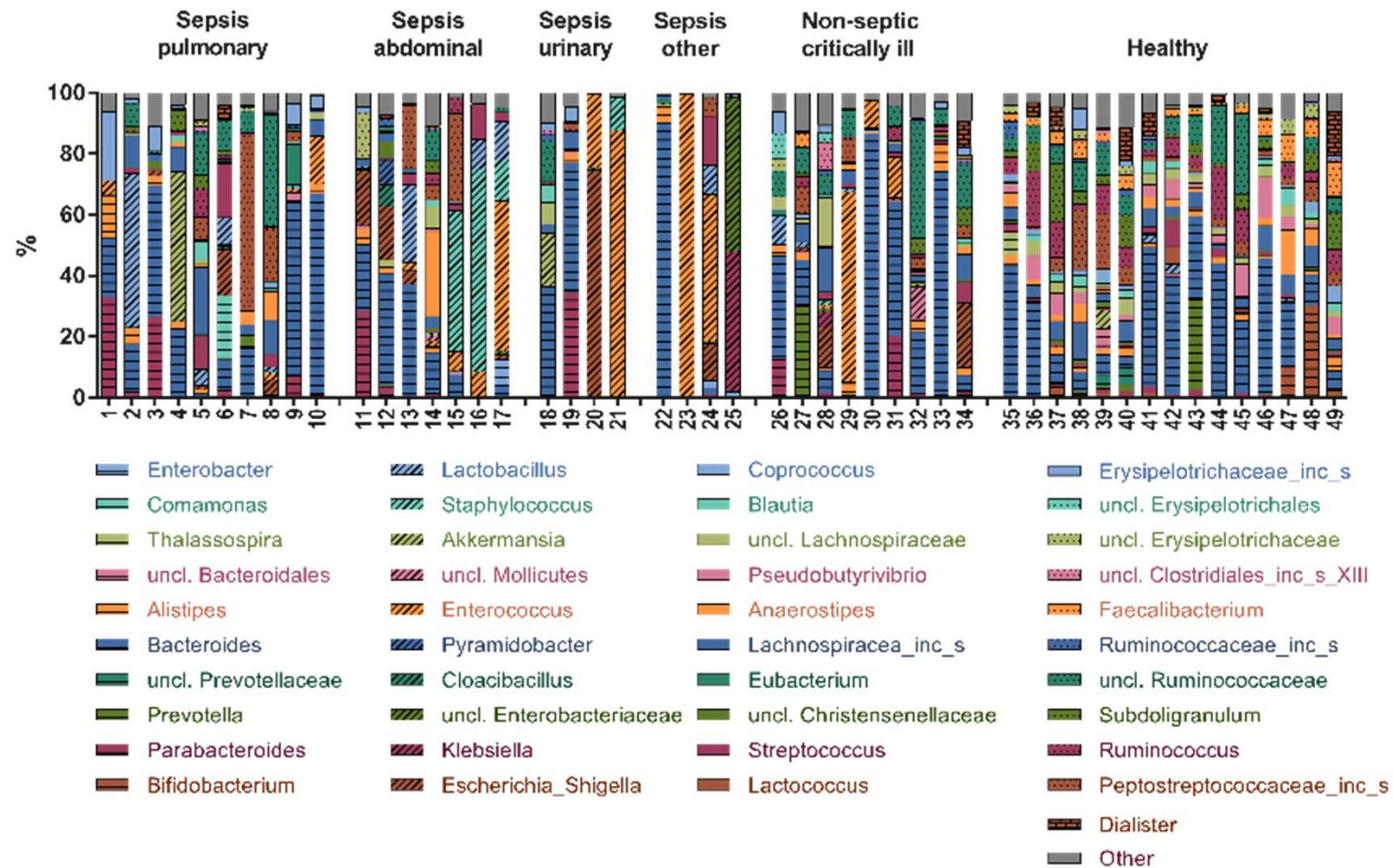
Daniel McDonald,^a Gail Ackermann,^a Ludmila Khailova,^b Christine Baird,^b Daren Heyland,^c Rosemary Kozar,^d Margot Lemieux,^c Karrie Derenski,^e Judy King,^f Christine Vis-Kampen,^f Rob Knight,^a Paul E. Wischmeyer^b

Zaborin, *mBio*, 2014; McDonald, *mSphere*, 2016; Lankelma, *Intensive Care Med*, 2017

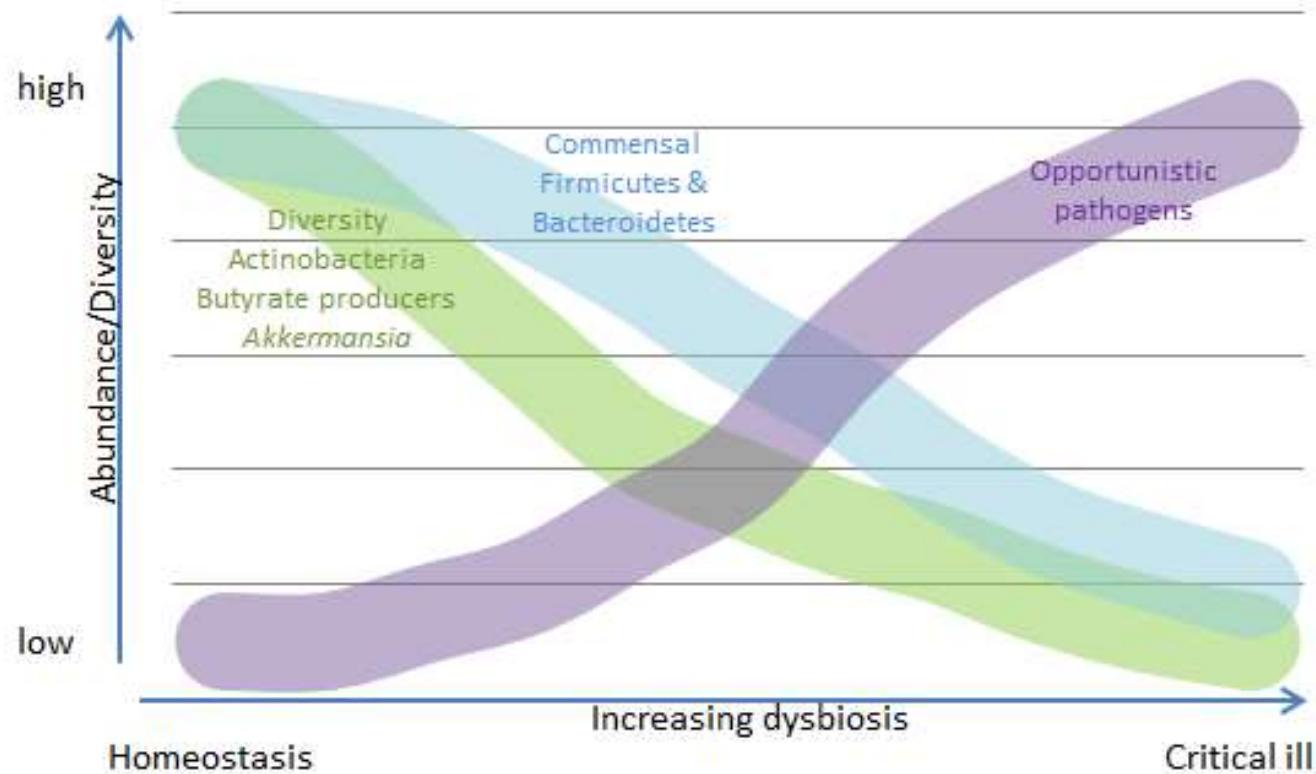
High interindividual diversity in fecal microbiota composition at the phylum level in both septic and non-septic critically ill patients.



High interindividual diversity in fecal microbiota composition at the genus level in both septic and non-septic critically ill patients.



The critically ill microbiome: loss of diversity and overgrowth of opportunistic pathogens



What are the causes of the observed microbiome disruption in sepsis?



Causes and consequences of microbiota disruption in sepsis

Dysbiosis in sepsis linked to AKI, ARDS, encephalopathy and muscle weakness

Endogenous modulators of the gut microbiota during sepsis

Increased production of opioids

Decreased bile-salt concentration

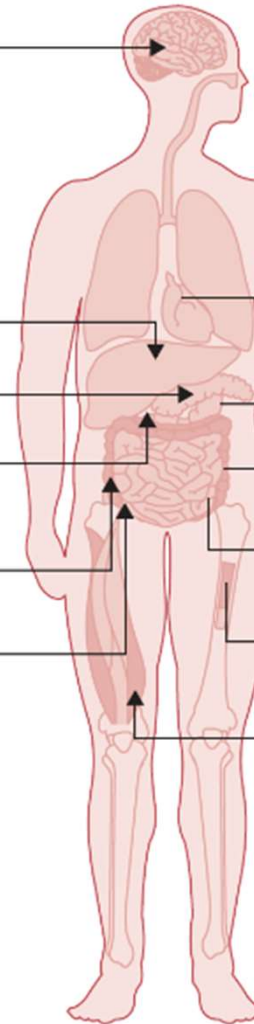
Gastrointestinal dysmotility

Increased production of catecholamines

Loss of epithelial integrity in the intestine

External modulators of the gut microbiota during clinical sepsis care

Antibiotics
SOD/SDD
Gastric-acid inhibition
Enteral/parenteral feeding
Sedatives
Opioids
Catecholamines



Potential consequences of dysbiosis during sepsis

Decreased systemic SCFA levels

Potentially increased risk of acute kidney injury

Increased microbial virulence

Bacterial translocation in systemic and lymphatic circulation

Reduced modulation of systemic immune responses

Potentially increased risk of sepsis-induced muscle wasting

What is the function of the gut microbiome in sepsis?



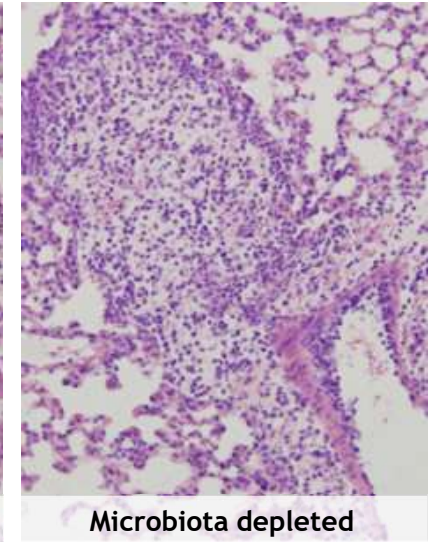
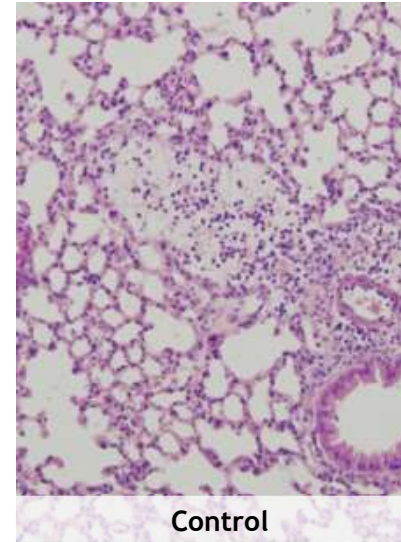
Gut

ORIGINAL ARTICLE

The gut microbiota plays a protective role in the host defence against pneumococcal pneumonia

Tim J Schuijt,^{1,2,3} Jacqueline M Lankelma,¹ Brendon P Scicluna,¹
Felipe de Sousa e Melo,¹ Joris J T H Roelofs,⁴ J Daan de Boer,¹ Arjan J Hoogendijk,¹
Regina de Beer,¹ Alex de Vos,¹ Clara Belzer,⁵ Willem M de Vos,^{5,6}
Tom van der Poll,^{1,2} W Joost Wiersinga^{1,2}

LUNG PATHOLOGY



nature
medicine



The microbiota regulates neutrophil homeostasis and host resistance to *Escherichia coli* K1 sepsis in neonatal mice

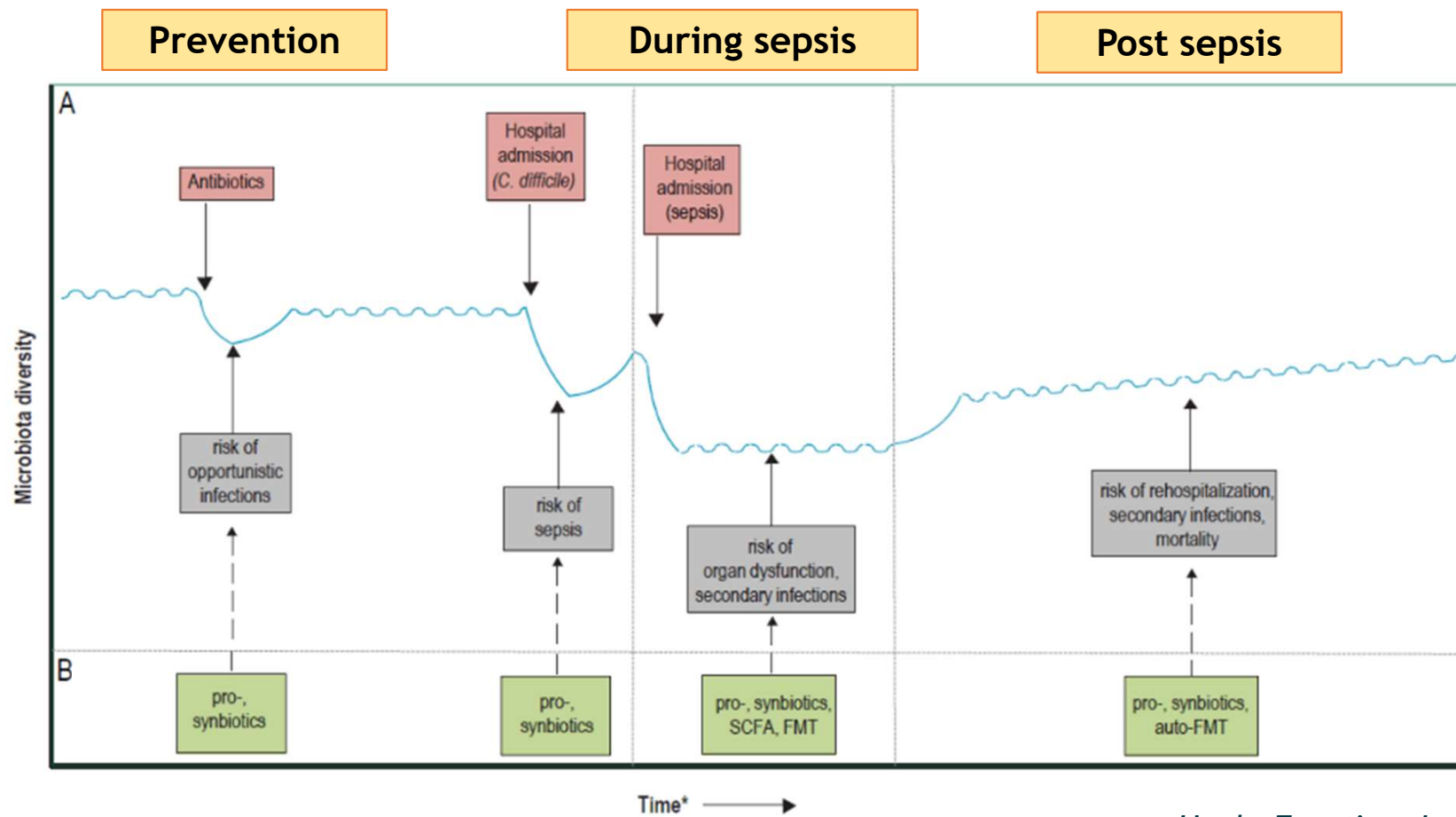
Hitesh S Deshmukh^{1,2}, Yuhong Liu¹, Ogechukwu R Menkiti^{1,2}, Junjie Mei¹, Ning Dai¹, Claire E O'Leary³,
Paula M Oliver³, Jay K Kolls⁴, Jeffrey N Weiser^{2,5} & G Scott Worthen^{1,2}

Deshmukh, *Nat Med*, 2014; Schuijt, *Gut*, 2015

Could one therapeutically manipulate the gut microbiome in sepsis?



Potential microbiota-associated interventions prior to, during and post-sepsis



A randomized synbiotic trial to prevent sepsis among infants in rural India

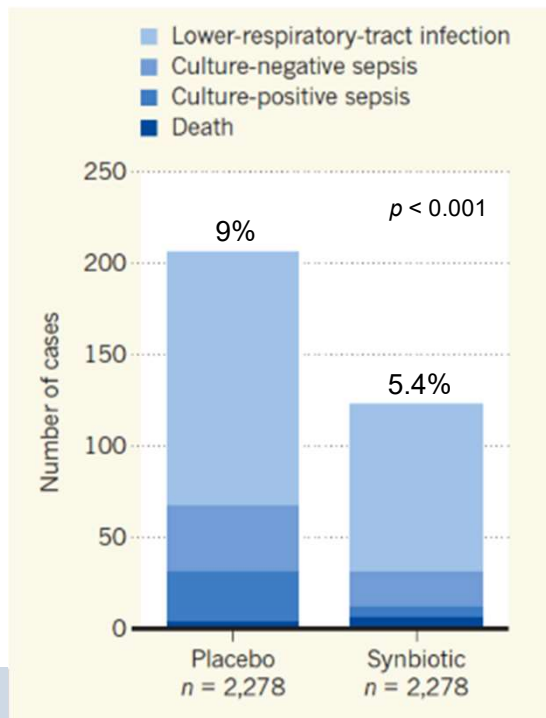
Pinaki Panigrahi^{1,2}, Sailajanandan Parida³, Nimai C. Nanda⁴, Radhanath Satpathy⁵, Lingaraj Pradhan⁶, Dinesh S. Chandel⁷, Lorena Baccaglioni¹, Arjit Mohapatra⁵, Subhranshu S. Mohapatra⁵, Pravas R. Misra⁵, Rama Chaudhry⁸, Hegang H. Chen⁹, Judith A. Johnson¹⁰, J. Glenn Morris Jr¹⁰, Nigel Paneth¹¹ & Ira H. Gewolb¹²



- Double-blind, placebo-controlled RCT trial among 4556 infants: >2,000g at birth, >35 wks of gestation, no sepsis/comorbidity
- Intervention: oral *Lactobacillus plantarum* + fructooligosaccharide or placebo in first week of life
- Primary outcome: combination of sepsis + death in first 60 days of life
- Study terminated halfway to target enrolment size: interim results convincingly in favour of synbiotic preparation

A randomized synbiotic trial to prevent sepsis among infants in rural India

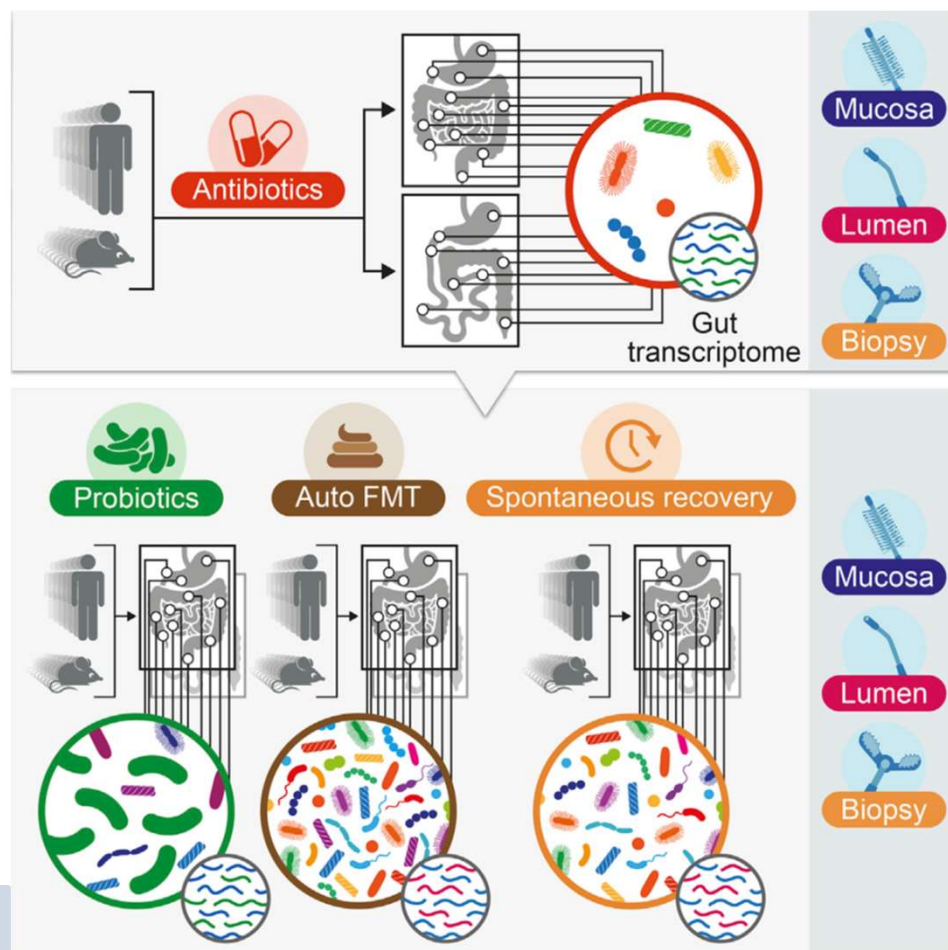
Pinaki Panigrahi^{1,2}, Sailajanandan Parida³, Nimai C. Nanda⁴, Radhanath Satpathy⁵, Lingaraj Pradhan⁶, Dinesh S. Chandel⁷, Lorena Baccaglini¹, Arjit Mohapatra⁵, Subhranshu S. Mohapatra⁵, Pravas R. Misra⁵, Rama Chaudhry⁸, Hegang H. Chen⁹, Judith A. Johnson¹⁰, J. Glenn Morris Jr¹⁰, Nigel Paneth¹¹ & Ira H. Gewolb¹²



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- Primary outcome: combination of sepsis + death in first 60 days of life
- Study terminated halfway to target enrolment size: interim results convincingly in favour of synbiotic preparation
- The week-long treatment costs US\$1 with a NNT of 27: the investment needed to prevent one sepsis case is about \$27

Post-Antibiotic Gut Mucosal Microbiome Reconstitution Is Impaired by Probiotics and Improved by Autologous FMT

Cell




Authors

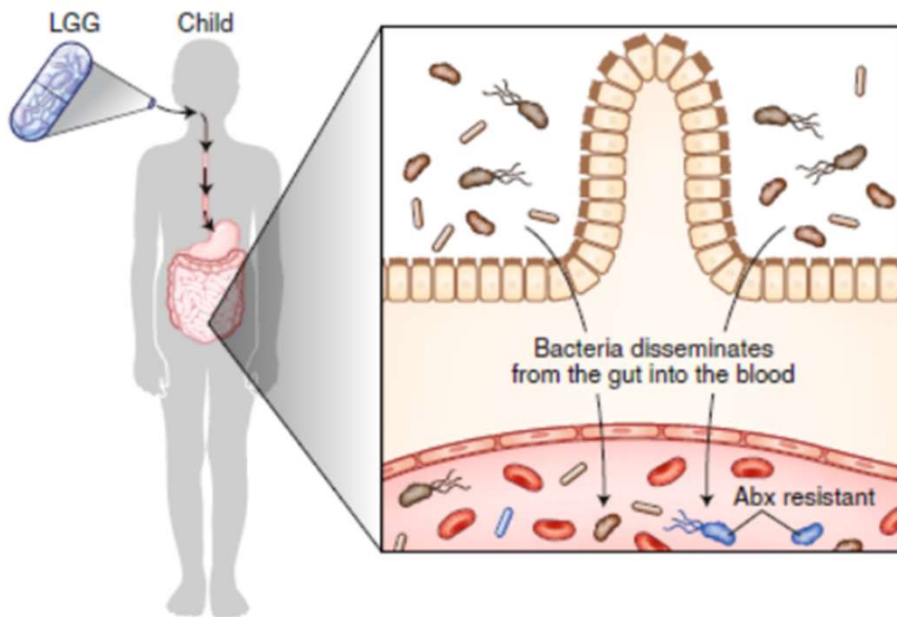
Jotham Suez, Niv Zmora,
Gili Zilberman-Schapira, ...,
Zamir Halpern, Eran Segal, Eran Elinav

Probiotics perturb rather than aid in microbiota recovery back to baseline after antibiotic treatment in humans.

Suez, Cell, 2018

Genomic and epidemiological evidence of bacterial transmission from probiotic capsule to blood in ICU patients

Idan Yelin ^{1,10}, Kelly B. Flett^{2,3,9,10}, Christina Merakou^{3,4,10}, Preeti Mehrotra^{2,5}, Jason Stam⁶, Erik Snestrud⁶, Mary Hinkle⁶, Emil Lesho⁶, Patrick McGann⁶, Alexander J. McAdam^{2,3,7}, Thomas J. Sandora ^{2,3,11*}, Roy Kishony ^{1,8,11*} and Gregory P. Priebe ^{2,3,4,11*}



- Surveillance study among 22,000 ICU patients at Boston Children's Hospital
- *Lactobacillus* bacteremia diagnosed in 6 of 522 ICU patients (1.1%) receiving LGG-containing probiotics compared to only 2 of 21,652 ICU patients (0.009%) not receiving the LGG probiotic
- *L. rhamnosus* GG strains can directly cause bacteremia and adaptively evolve in critically ill patients becoming antibiotic resistant

Medical News & Perspectives

Are Probiotics Money Down the Toilet? Or Worse?

Jennifer Abbasi

With interest growing in natural therapies, the popularity of probiotics is on the rise. In 2012, almost 4 million US adults reported using probiotics or prebiotics—4 times more than in 2007. Probiotics were used in more than 50 000 hospitalizations in 139 US hospitals in 2012. And last year alone, US consumers spent an estimated \$2.4 billion on the supplements.

Two recent studies by researchers in Israel, however, are raising questions about the widespread use of probiotics to impart general wellness and restore intestinal flora after the use of antibiotics, 2 common indications.

In 1 study, the bacteria in a probiotic supplement failed to colonize the guts of a proportion of participants, suggesting that the bugs may pass through some people with no effect. In the other study, the same bacteria took up residence in the intestines



Fecal Microbiota Transplantation for sepsis?

Harnessing the microbiome in sepsis: during sepsis



Therapeutic Modulation and Reestablishment of the Intestinal Microbiota With Fecal Microbiota Transplantation Resolves Sepsis and Diarrhea in a Patient

Qirong Li, MD, PhD¹, Chenyang Wang, MA¹, Chun Tang, BA¹, Qin He, MA¹, Xiaofan Zhao, BA¹, Ning Li, MD¹ and Jieshou Li, MD¹

RESEARCH

Open Access

Successful treatment of severe sepsis and diarrhea after vagotomy utilizing fecal microbiota transplantation: a case report

Qirong Li¹, Chenyang Wang, Chun Tang, Qin He, Xiaofan Zhao, Ning Li and Jieshou Li¹

Critical Care

RESEARCH

Open Access

Successful treatment with fecal microbiota transplantation in patients with multiple organ dysfunction syndrome and diarrhea following severe sepsis

Yanling Wei, Jun Yang, Jun Wang, Yang Yang, Juan Huang, Hao Gong, Hongli Cui^{*} and Dongfeng Chen^{*}



Li, *Am J Gastroenterol*, 2015; Li, *Crit Care*, 2015; Wei, *Crit Care*, 2016

WHAT'S NEW IN INTENSIVE CARE

Fecal microbiota transplantation in the ICU: perspectives on future implementations



Laura Alagna¹, Bastiaan W. Haak² and Andrea Gori^{1,3*}

Infection Control in the Multidrug-Resistant Era: Tending the Human Microbiome

Pritish K. Tosh^{1,2} and L. Clifford McDonald²

¹Epidemic Intelligence Service, and ²Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia

- Restore the microbiome, e.g. use “microbiome auto-banking and transplantation”

Harnessing the microbiome post sepsis

Original article

A 5-day course of oral antibiotics followed by faecal transplantation to eradicate carriage of multidrug-resistant *Enterobacteriaceae*: a randomized clinical trial

B.D. Huttner^{1,2,3,*}, V. de Lastours^{4,5}, M. Wassenberg⁶, N. Maharshak⁷, A. Mauris⁸, T. Galperine¹, V. Zanichelli¹, N. Kapel⁹, A. Bellanger¹⁰, F. Olearo¹, X. Duval^{11,12,13}, L. Armand-Lefevre^{5,14}, Y. Carmeli¹⁵, M. Bonten^{6,16}, B. Fantin^{4,5}, S. Harbarth^{1,2,3} for the R-Gnosis WP3 study group[†]



Commentary

Manipulation of the microbiota to eradicate multidrug-resistant *Enterobacteriaceae* from the human intestinal tract

E.J. Kuijper^{1,*}, K.E.W. Vendrik², M.J.G.T. Vehreschild³

July 2020: FDA Safety Alert for FMT

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.

DeFilipp, *New Engl J Med*, 2019

What lies ahead?

MENU ▾

nature
International journal of science

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COMMENT · 29 MAY 2019

Priorities for the next 10 years of human microbiome research

The dream of microbiome-based medicine requires a fresh approach – an ecological and evolutionary understanding of host-microbe interactions – argues Lita Proctor.

Proctor, Nature, 2019

Future perspective on fecal microbiota transplantation

Preliminary Communication

Oral, Capsulized, Frozen Fecal Microbiota Transplantation for Relapsing *Clostridium difficile* Infection

Ilan Youngster, MD, MMSc; George H. Russell, MD, MSc; Christina Pindar, BA; Tomer Ziv-Baran, PhD;
Jenny Sauk, MD; Elizabeth L. Hohmann, MD

LETTER

doi:10.1038/nature13828

Precision microbiome reconstitution restores bile acid mediated resistance to *Clostridium difficile*

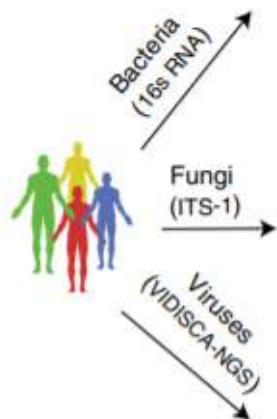
Charlie G. Buffie^{1,2}, Vanni Bucchi^{3,4}, Richard R. Stein³, Peter T. McKenney^{1,2}, Lilan Ling², Asia Gobourne², Daniel No², Hui Liu⁵, Melissa Kinnebrew^{1,2}, Agnes Viale⁶, Eric Littmann², Marcel R. M. van den Brink^{7,8}, Robert R. Jenq⁷, Ying Taur^{1,2}, Chris Sander³, Justin R. Cross⁵, Nora C. Toussaint^{2,3}, Joao B. Xavier^{2,3} & Eric G. Pamer^{1,2,8}

- Rational design of targeted antimicrobials, b.v. *C. scindens* for *C. difficile* infectie
- Next-generation probiotics to reestablish colonization resistance and eliminate potential gut pathogens

Youngster, JAMA, 2014; Buffie, Nature, 2015; Kim, Nature, 2019



What about the other kingdoms? The virome, fungiome, parasitome..



RESEARCH ARTICLE



Integrative Transkingdom Analysis of the Gut Microbiome in Antibiotic Perturbation and Critical Illness

© Bastiaan W. Haak,^a © Ricard Argelaguet,^b Cormac M. Kinsella,^c Robert F. J. Kullberg,^a Jacqueline M. Lankelma,^a Martin Deijs,^c Michelle Klein,^c Maarten F. Jebbink,^c Floor Hugenholtz,^a Sarantos Kostidis,^d Martin Giera,^d Theodorus B. M. Hakvoort,^e Wouter J. de Jonge,^e Marcus J. Schultz,^f Tom van Gool,^g Tom van der Poll,^{h,i} Willem M. de Vos,^{h,i} Lia M. van der Hoek,^c W. Joost Wiersinga^{a,j}

- Sepsis is characterized by a loss of the anaerobic intestinal environment which is directly correlated with an overgrowth of aerobic pathobionts and their corresponding bacteriophages as well as an absolute enrichment of opportunistic yeasts capable of causing invasive disease



Take home: the gut microbiome in sepsis

- Highly heterogeneous patterns of intestinal microbiome in patients with sepsis with a significant decrease in bacterial diversity
- Protective effect of the gut microbiome in mouse models of sepsis
- Limitations: differences in techniques, sampling, time points, a mouse is not a man.., role of the other microbiomes!
- How to use this novel knowledge to the advantage of patients in the setting of the prevention and treatment of sepsis?

Thank you!



Sepsis research group Amsterdam UMC

Further reading:

The role of the gut microbiota in sepsis

Bastiaan W Haak, W Joost Wiersinga

w.j.wiersinga@amsterdamumc.nl

Haak, Lancet Gastroenterol Hepatol, 2017