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Therapeutic potential of the gut microbiota in the prevention and treatment of sepsis

Joost Wiersinga, MD, PhD, MBA
Div. Infectious Diseases, Amsterdam UMC

SFAI-Conference, 13th of September 2019

SFAI VECKAN

INTERNATIONAL SEPSIS FORUM

Microbiota Center Amsterdam

CONFERENCE REPORTS AND EXPERT PANEL

Surviving sepsis campaign: research priorities for sepsis and septic shock

Craig M. Coopersmith[1], Daniel De Backer[2*], Clifford S. Deutschman[3,4], Ricard Ferrer[5,6], Ishaq Lat[7], Flavia R. Machado[8], Greg S. Martin[9], Ignacio Martin-Loeches[10], Mark E. Nunnally[11], Massimo Antonelli[12], Laura E. Evans[13], Judith Hellman[14], Sameer Jog[15], Jozef Kesecioglu[16], Mitchell M. Levy[17] and Andrew Rhodes[18]

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

Coopersmith, Intensive Care Med, 2018

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

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?

Rello, Clin Microbiol Infect, 2018

Composition of the microbiome in criticall 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 Shakhsheer,[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

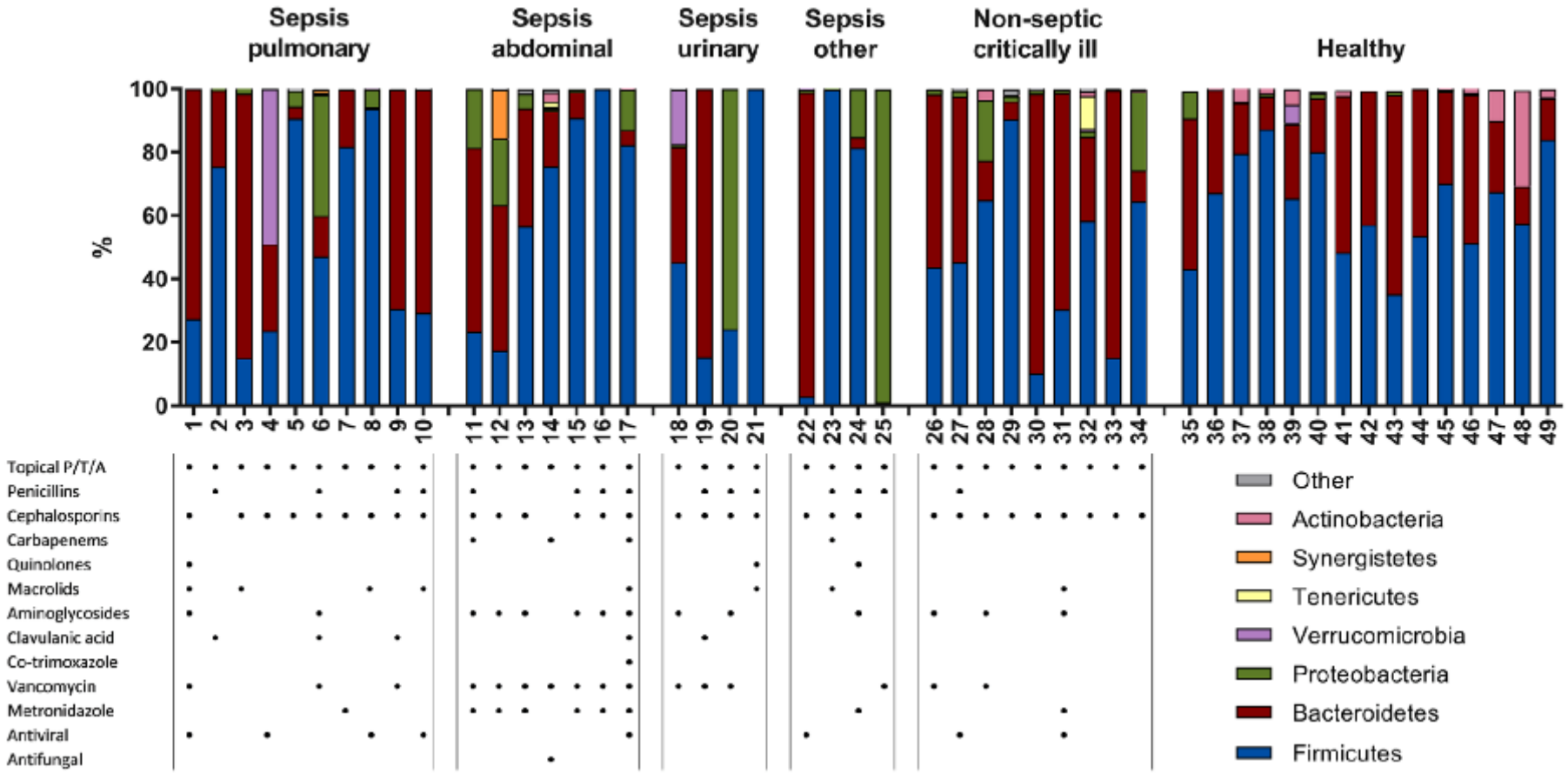
Jacqueline M. Lankelma[1*], Lonneke A. van Vught[1], Clara Belzer[2], Marcus J. Schultz[3], Tom van der Poll[1,4], Willem M. de Vos[2,5] and W. Joost Wiersinga[1,4]

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]

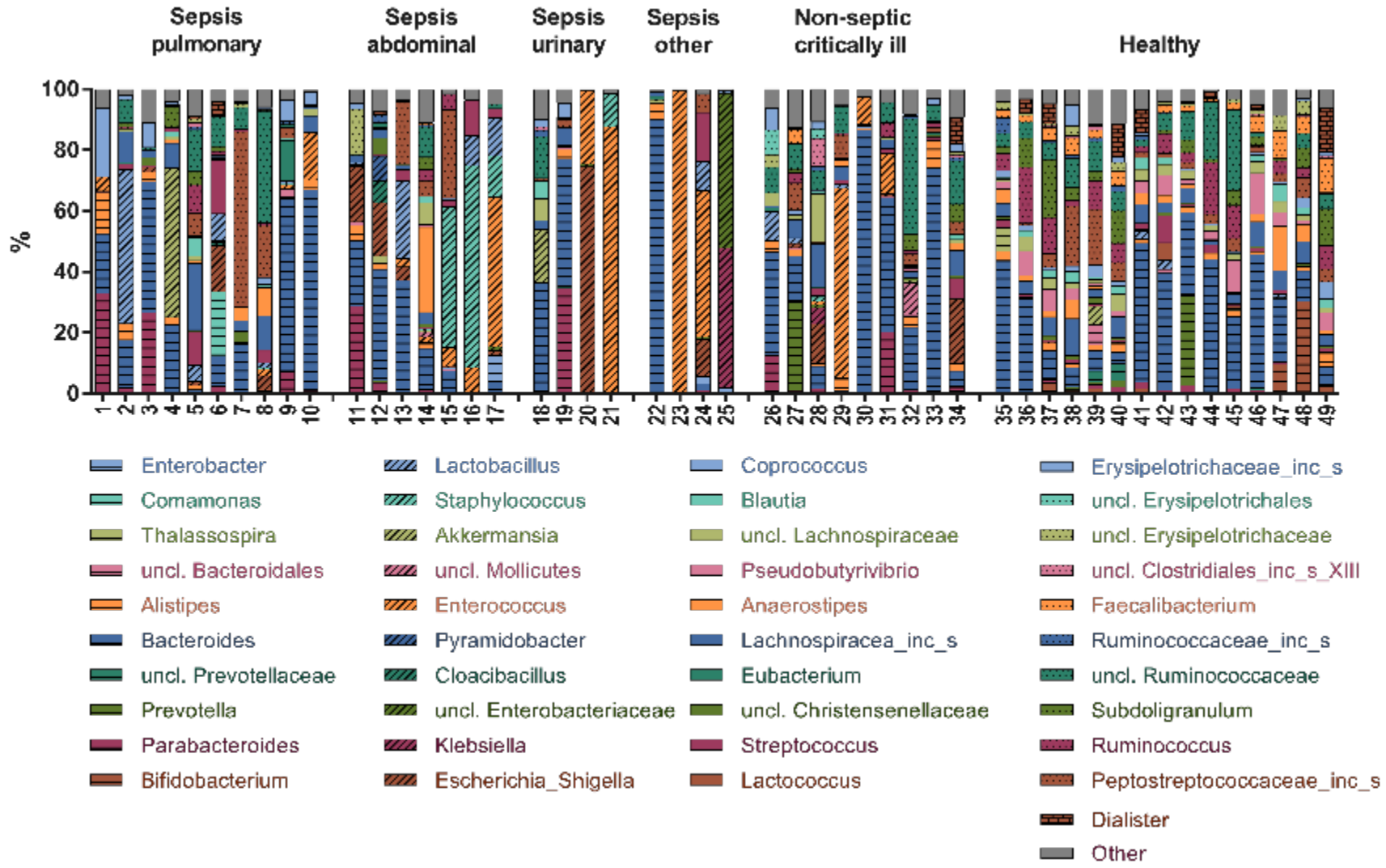
Zaborin, mBio, 2014; McDonald, mSphere, 2016; Lankelma, Intensive Care Med, 2017

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

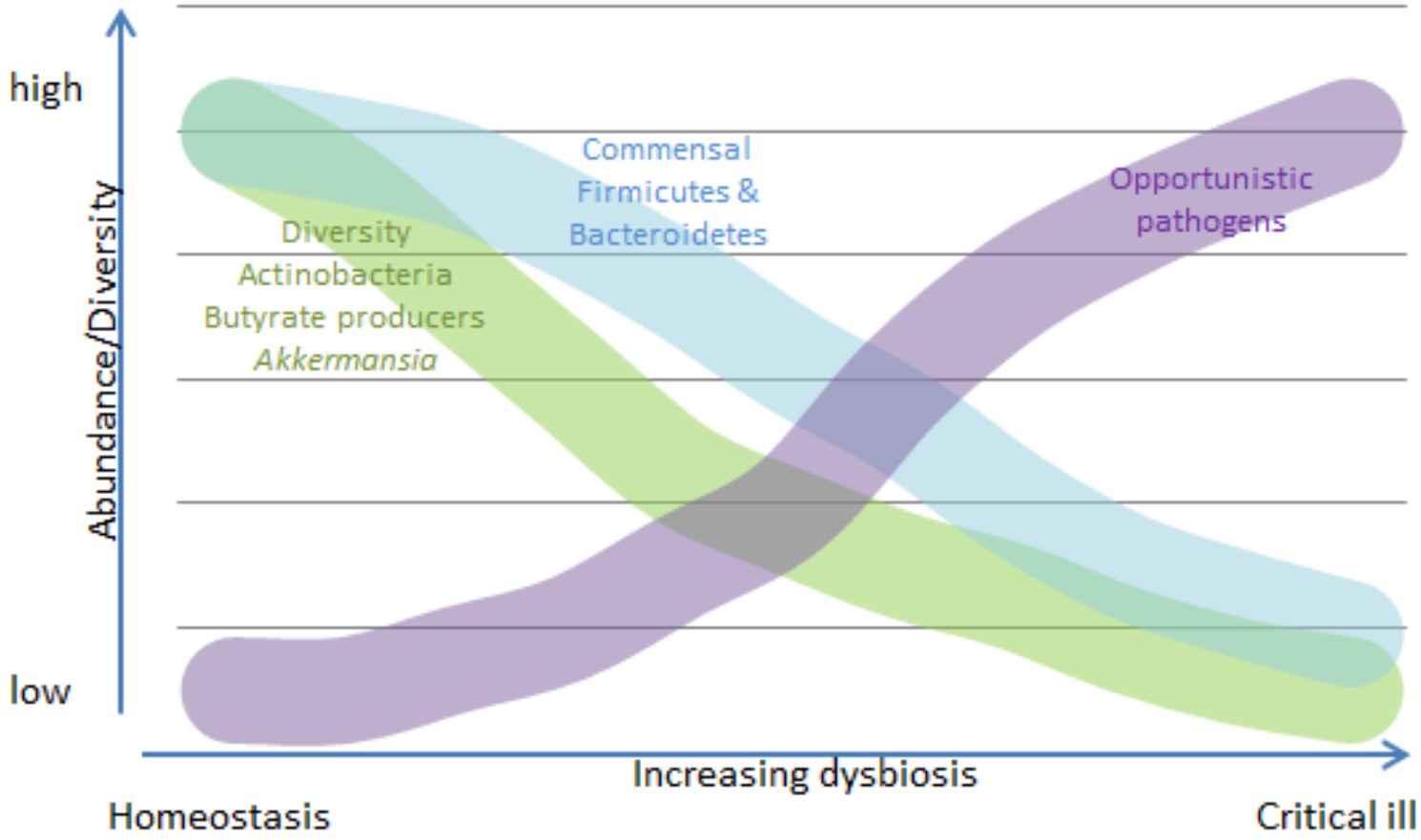


16S rRNA gene sequencing Wageningen - Lankelma, Intensive Care Med, 2017

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



Lankelma, Intensive Care Med, 2017; Jacobs, Curr Opin Crit Care, 2017

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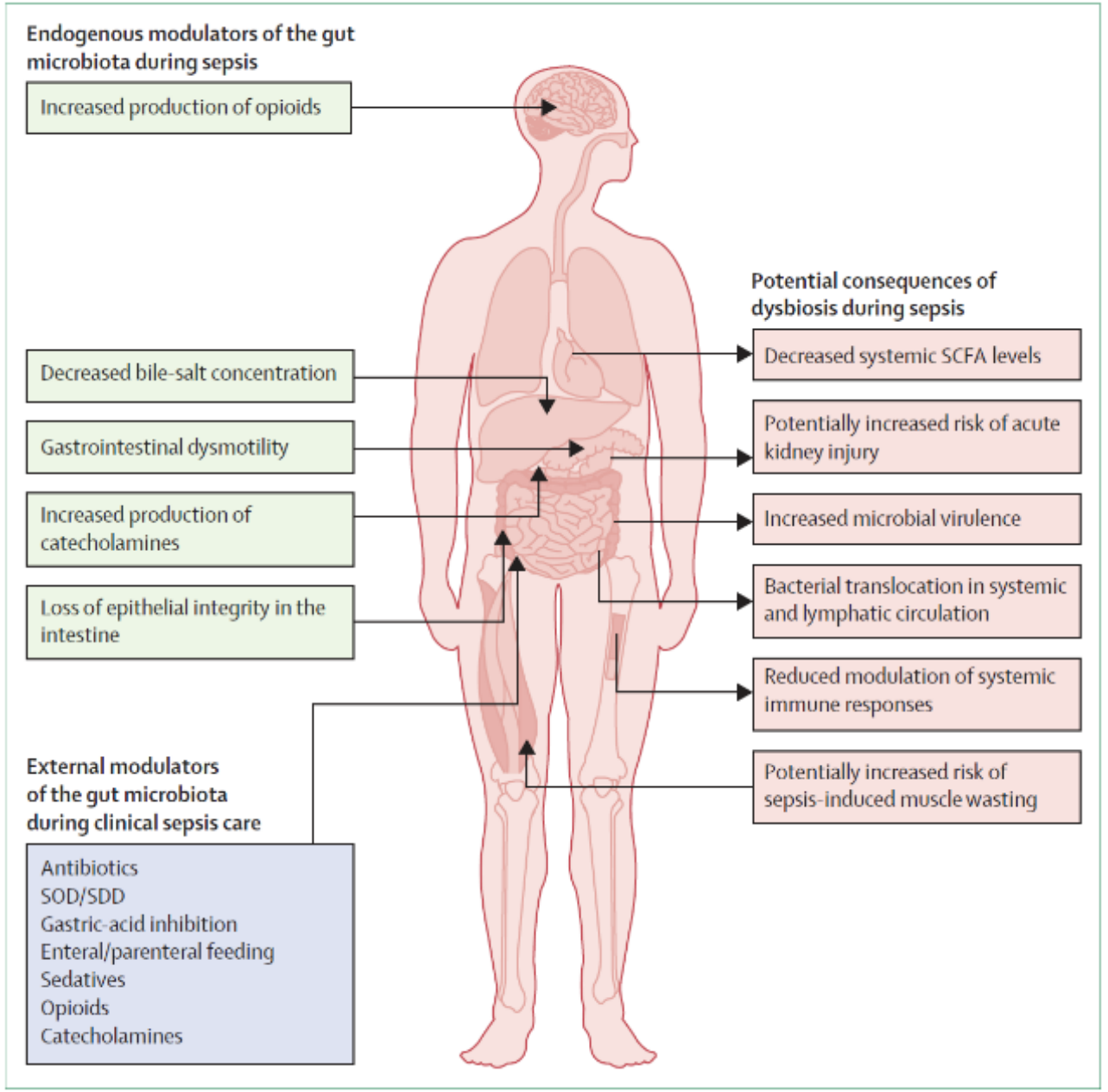
What are the causes of the observed microbiome disruption in sepsis?

Causes and consequences of microbiota disruption in sepsis

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



Haak, Lancet Gastroenterol Hepatol, 2017

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What is the function of the gut microbiome in sepsis?

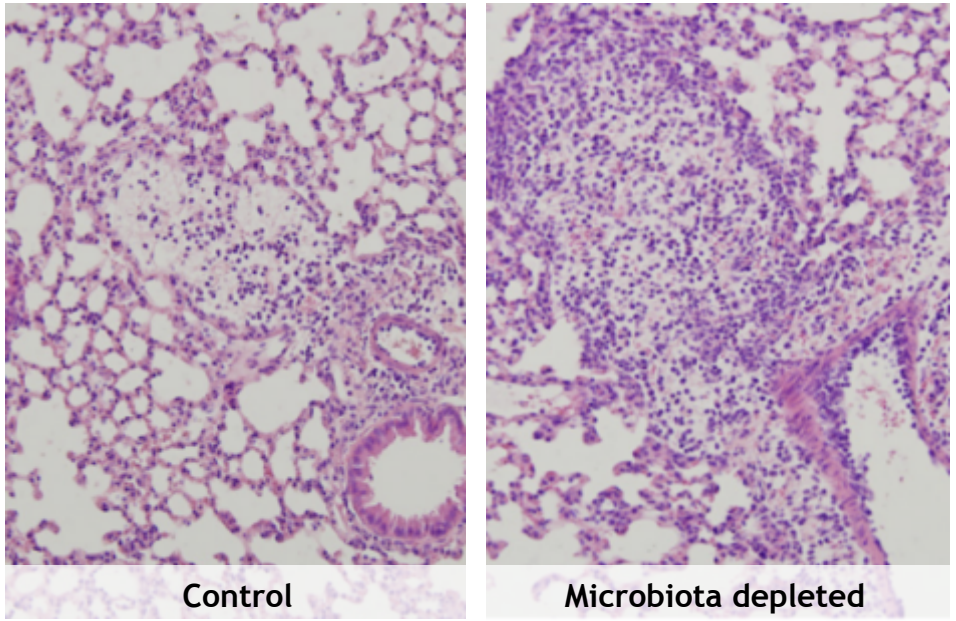
Gut

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



Control | Microbiota depleted

nature medicine

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

Hitesh S Deshmukh[1,2], Yuhong Liu[1], Ogechukwu R Menkiti[1,2], Junjie Mei[1], Ning Dai[1], Claire E O'Leary[3], Paula M Oliver[3], Jay K Kolls[4], Jeffrey N Weiser[2,5] & G Scott Worthen[1,2]

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

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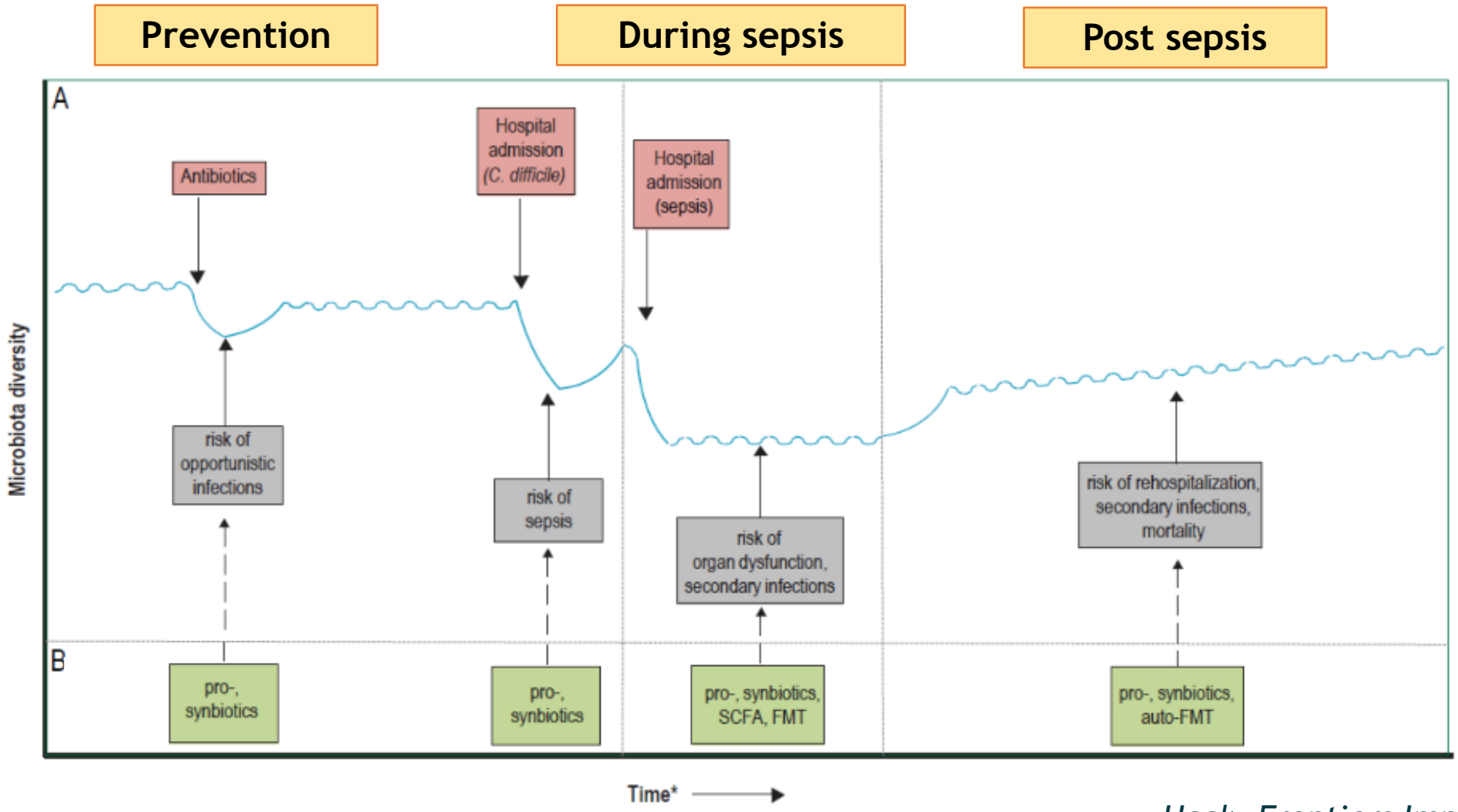
Could one therapeutically manipulate the gut microbiome in sepsis?

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



Haak, Frontiers Immunol, 2018

nature

Harnessing the microbiome in sepsis: prevention

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

Pinaki Panigrahi[1,2], Sailajanandan Parida[3], Nimai C. Nanda[4], Radhanath Satpathy[5], Lingaraj Pradhan[6], Dinesh S. Chandel[7], Lorena Baccaglini[1], Arjit Mohapatra[5], Subhranshu S. Mohapatra[5], Pravas R. Misra[5], Rama Chaudhry[8], Hegang H. Chen[9], Judith A. Johnson[10], J. Glenn Morris Jr[10], Nigel Paneth[11] & Ira H. Gewolb[12]

- 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

Panigrahi, Nature, 2017

nature

Harnessing the microbiome in sepsis: prevention

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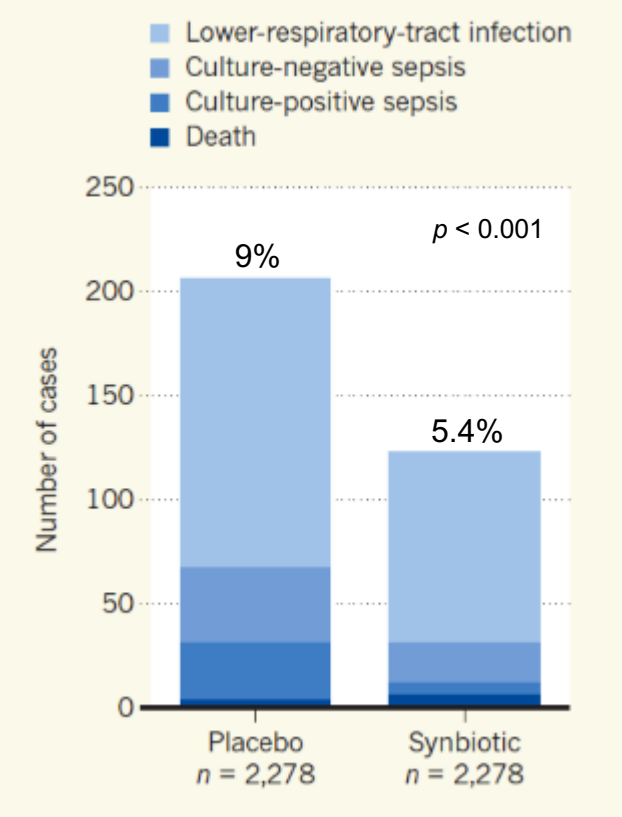

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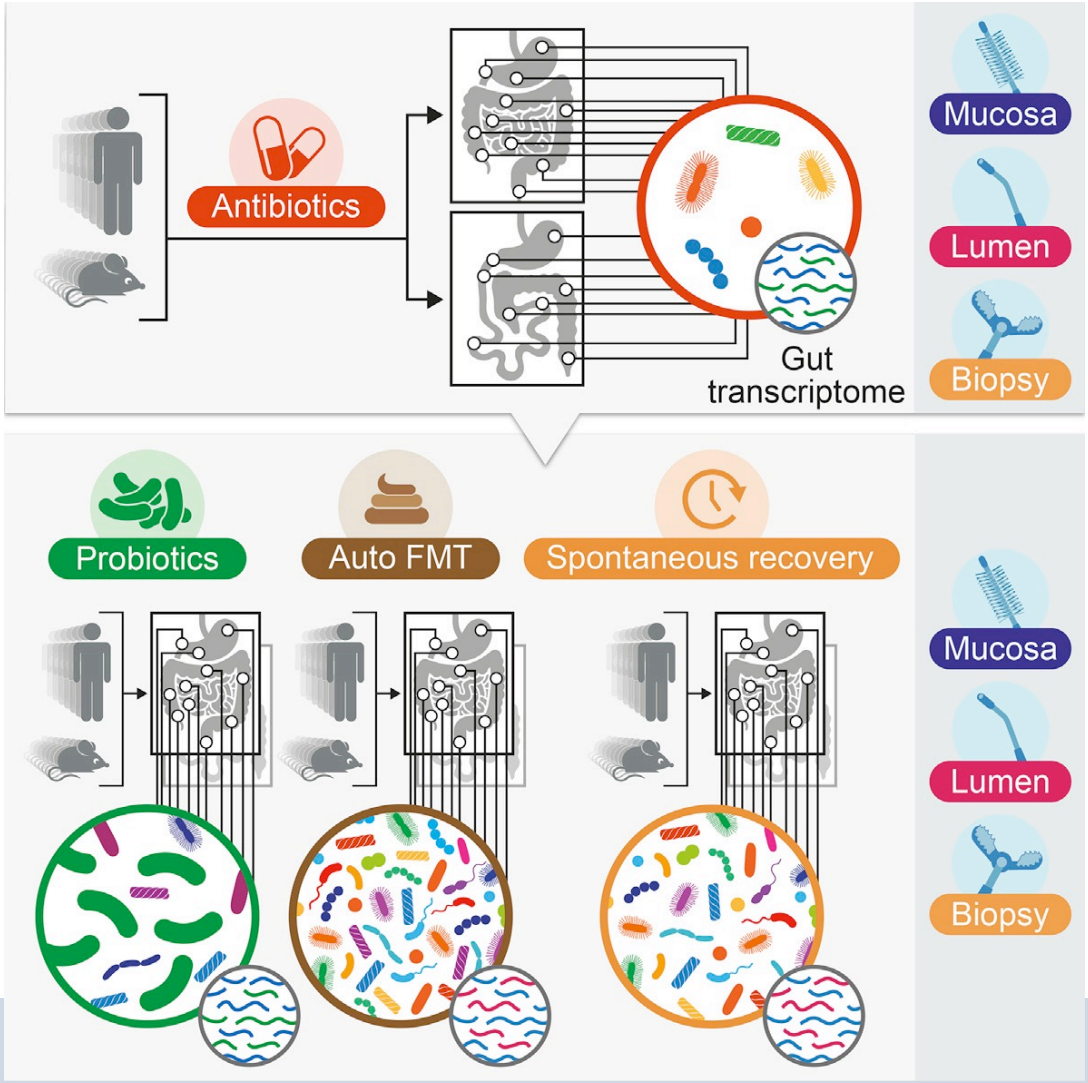
- Primary outcome: combination of sepsis + death in first 60 days of life
- Study terminated halfway to target enrolment size: interim results convincingly in favour of synbiotic preparation
- The week-long treatment costs US$1 with a NNT of 27: the investment needed to prevent one sepsis case is about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

Panigrahi, Nature, 2017

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



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

Medical News & Perspectives

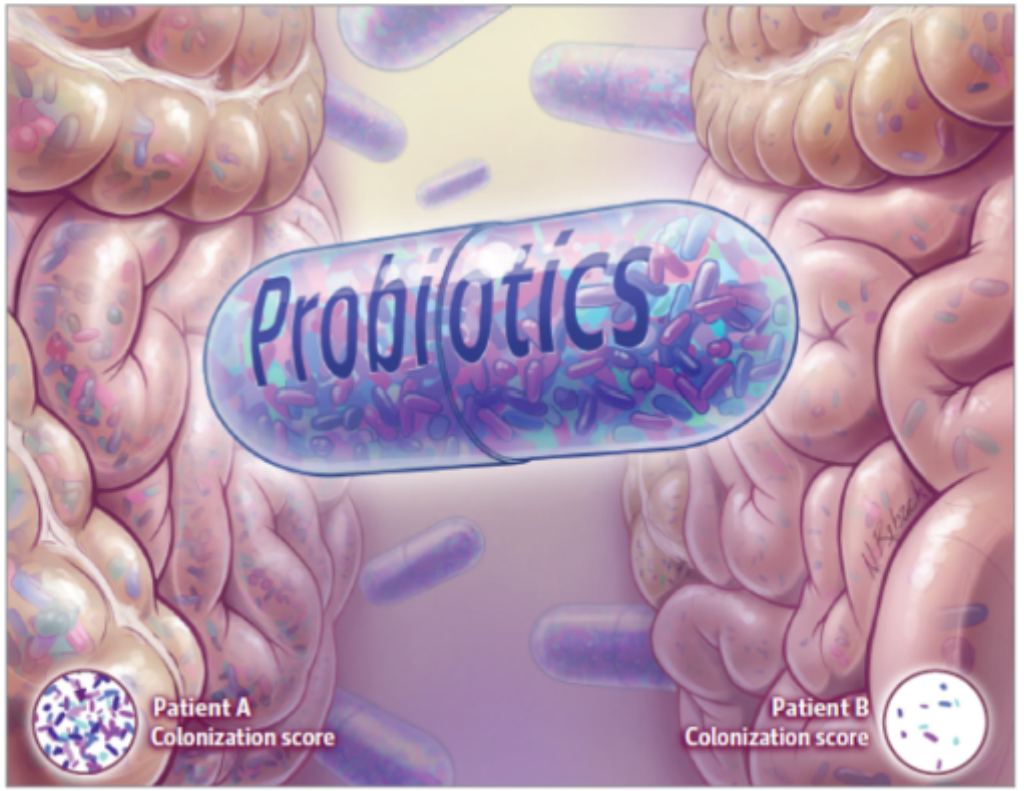
Are Probiotics Money Down the Toilet? Or Worse?

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



Abbasi, JAMA, 2019

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

Qiurong Li, MD, PhD[1], Chenyang Wang, MA[1], Chun Tang, BA[1], Qin He, MA[1], Xiaofan Zhao, BA[1], Ning Li, MD[1] and Jieshou Li, MD[1]

RESEARCH Open Access

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

Qiurong Li*, Chenyang Wang, Chun Tang, Qin He, Xiaofan Zhao, Ning Li and Jieshou Li*

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

Harnessing the microbiome post sepsis

WHAT'S NEW IN INTENSIVE CARE

Fecal microbiota transplantation in the ICU: perspectives on future implementations

Laura Alagna[1], Bastiaan W. Haak[2] and Andrea Gori[1,3*]

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

Pritish K. Tosh[1,2] and L. Clifford McDonald[2]

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

- **Restore the microbiome, e.g. use "microbiome auto-banking and transplantation"**

Tosh, Clin Infect Dis, 2012; Alagna, Intensive Cate Med, 2019

Harnessing the microbiome post sepsis

new

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. Wassenberg [6], N. Maharshak [7], A. Mauris [8], T. Galperine [1], V. Zanichelli [1], N. Kapel [9], A. Bellanger [10], F. Olearo [1], X. Duval [11, 12, 13], L. Armand-Lefevre [5, 14], Y. Carmeli [15], M. Bonten [6, 16], B. Fantin [4, 5], S. Harbarth [1, 2, 3] for the R-Gnosis WP3 study group[†]

CMI CLINICAL MICROBIOLOGY AND INFECTION
ESCMID

Commentary

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

E.J. Kuijper [1, *], K.E.W. Vendrik [2], M.J.G.T. Vehreschild [3]

Huttner, Clin Microbiol Infect, 2019; Kuijper, Clin Microbiol Infect, 2019

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!

Bas Haak
Brendon Scicluna
Vanessa Harris
Alex Schuurman
Harjeet Virk
Tjitske van Engelen
Max Jacobs
Nora Wolff
Alex de Vos
Floor Hugenholz

Further reading:

The role of the gut microbiota in sepsis

Bastiaan W Haak, W Joost Wiersinga

Haak, Lancet Gastroenterol Hepatol, 2017

w.j.wiersinga@amsterdamumc.nl