

Don't forget the microbiome: the example of sepsis

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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,**}

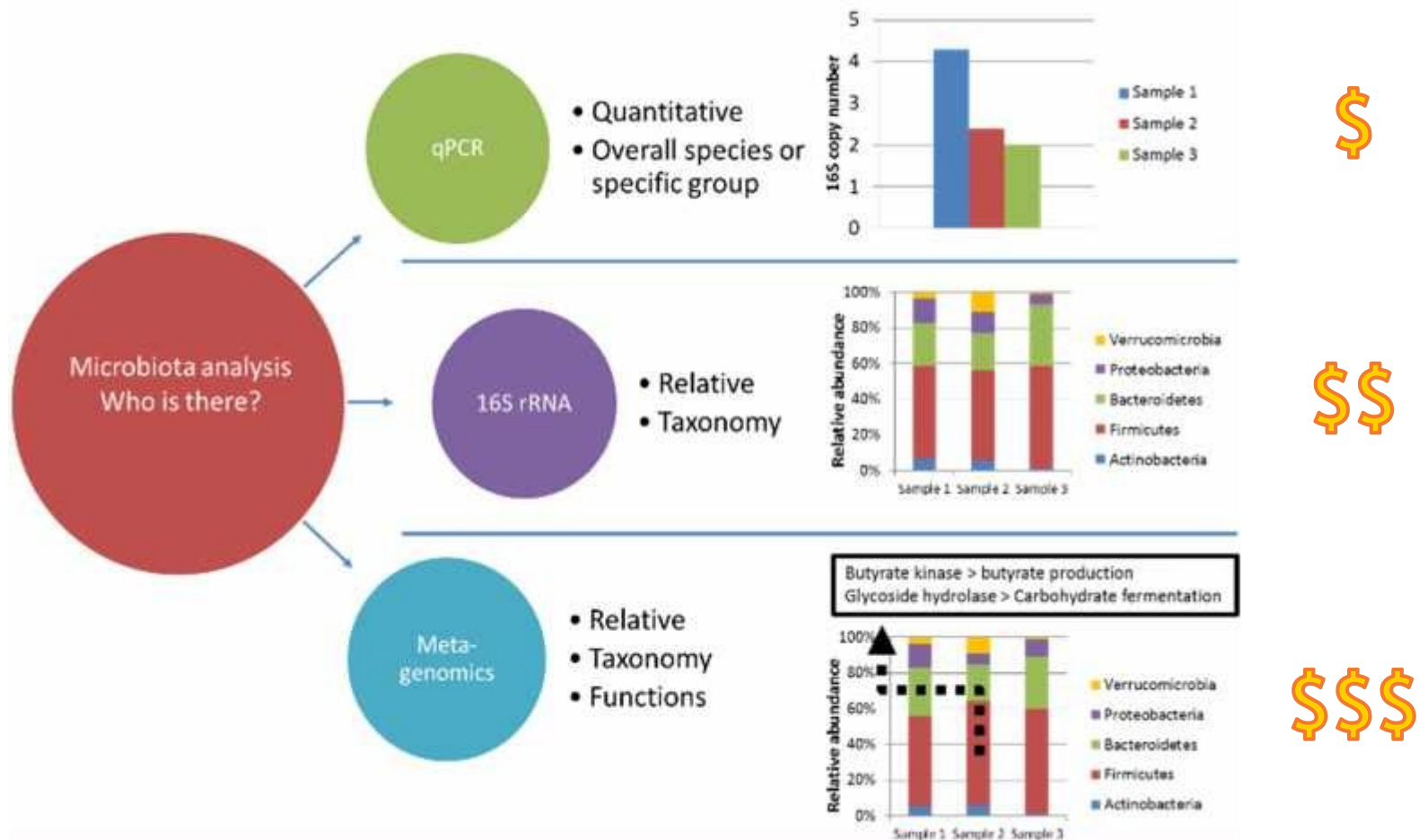
“In order to restore the microbiome after antibiotic treatment or to promote a functional microbiome, novel strategies should be evaluated such as Fecal Microbiota Transplantation (FMT) and the use of probiotics..”

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

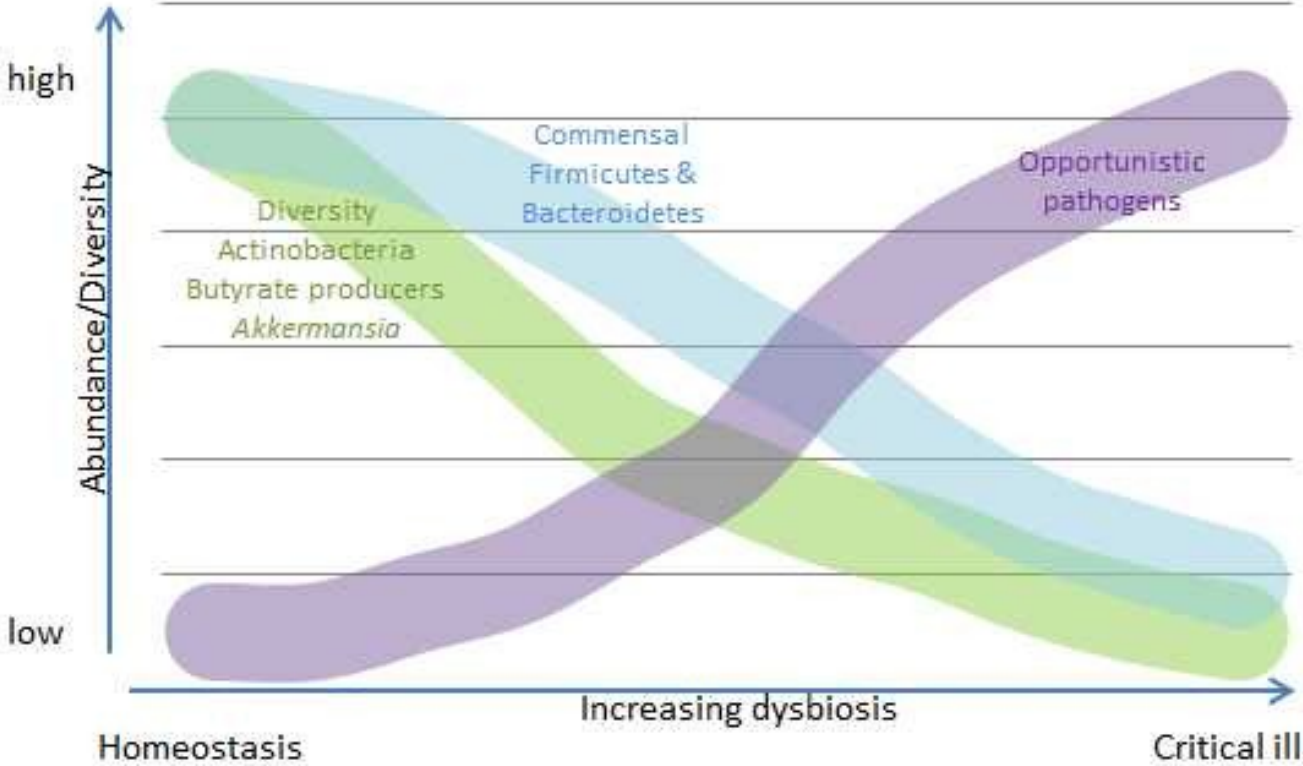
How to measure the bacterial gut microbiome?



Technologies to study the microbiome



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



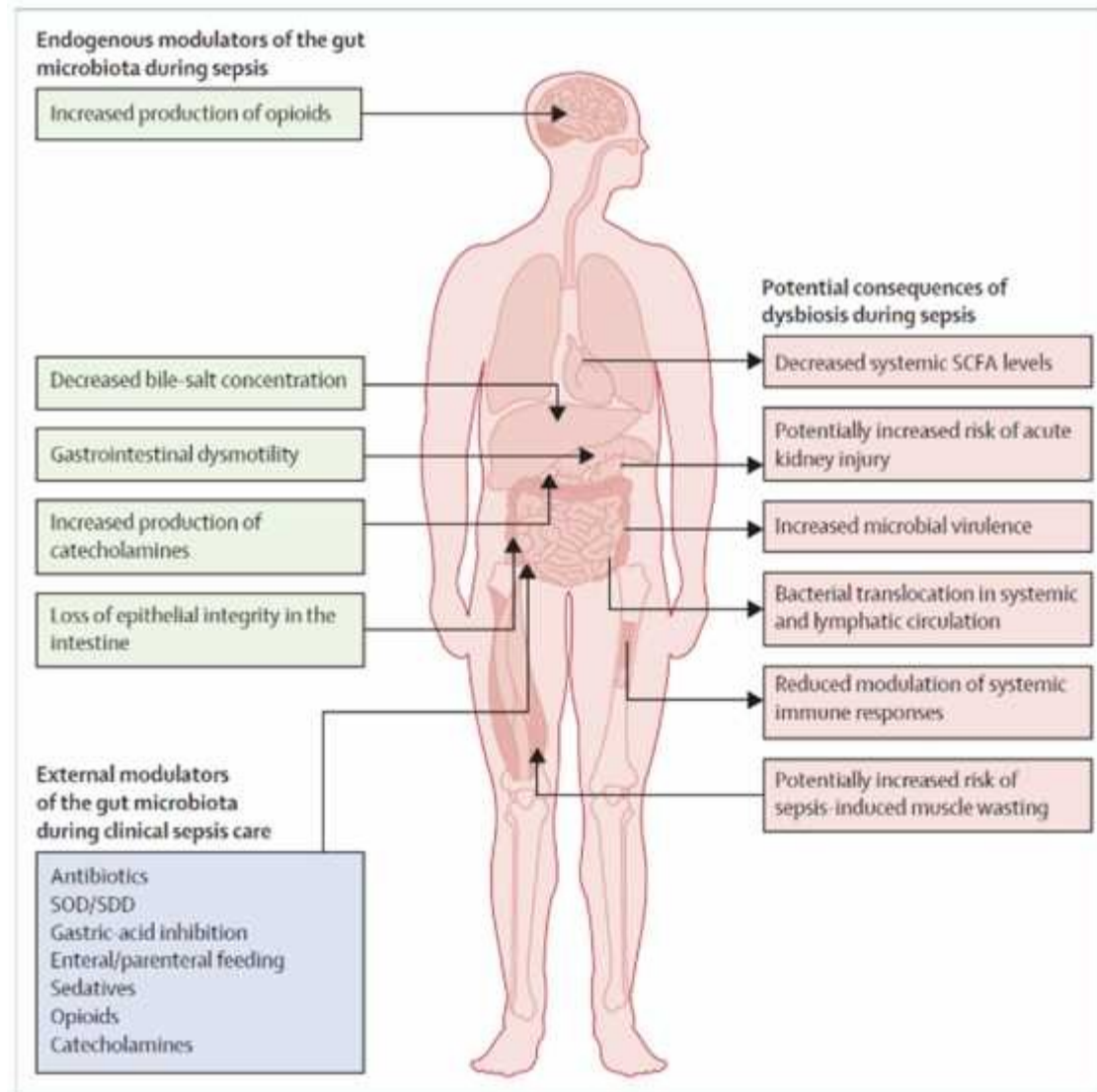
Lankelma, Intensive Care Med, 2017; Jacobs, Curr Opin Crit Care, 2017

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



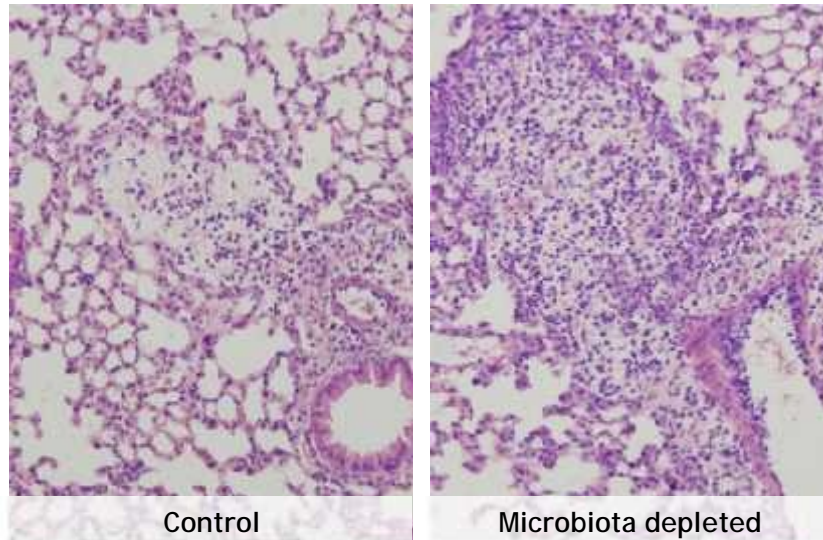
What is the function of the gut microbiome in sepsis? For instance in pneumosepsis?



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



Could one therapeutically manipulate the gut microbiome in sepsis?



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

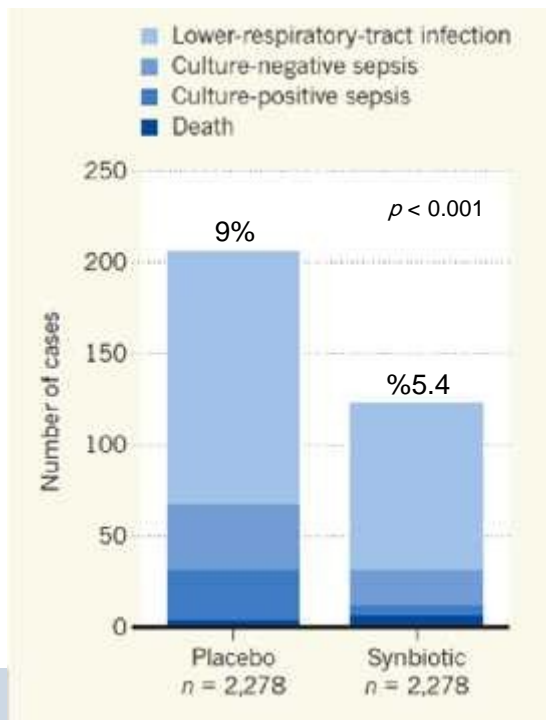
Pinaki Panigrahi^{1,2}, Sailajanandan Parida³, Nimai C. Nanda⁴, Radhanath Satpathy⁵, Lingaraj Pradhan⁶, Dinesh S. Chandel⁷, Lorena Baccaglioni¹, Arjit Mohapatra⁵, Subhranshu S. Mohapatra⁵, Pravas R. Misra⁵, Rama Chaudhry⁸, Hegang H. Chen⁹, Judith A. Johnson¹⁰, J. Glenn Morris Jr¹⁰, Nigel Paneth¹¹ & Ira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



- Double-blind, placebo-controlled RCT trial among 4556 infants: 2,000<g 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

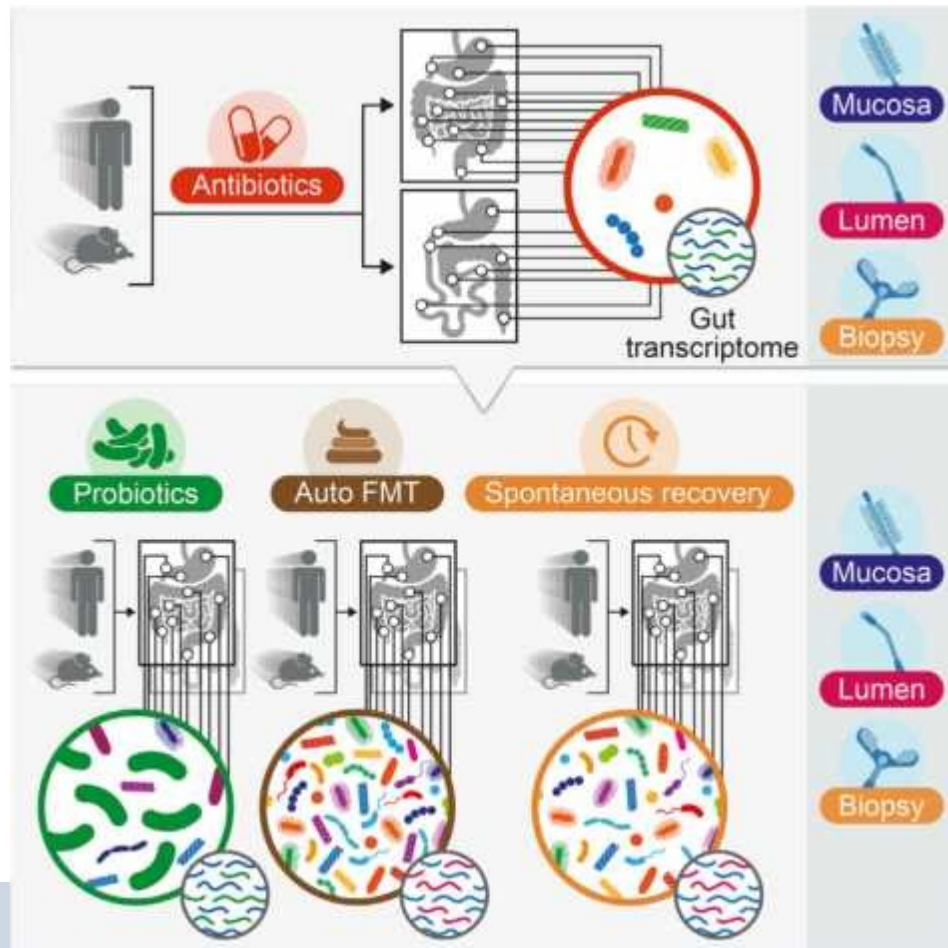
A randomized synbiotic trial to prevent sepsis among infants in rural India

Pinaki Panigrahi^{1,2}, Sailajanandan Parida³, Nimai C. Nanda⁴, Radhanath Satpathy⁵, Lingaraj Pradhan⁶, Dinesh S. Chandel⁷, Lorena 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



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- 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



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.

Medical News & Perspectives

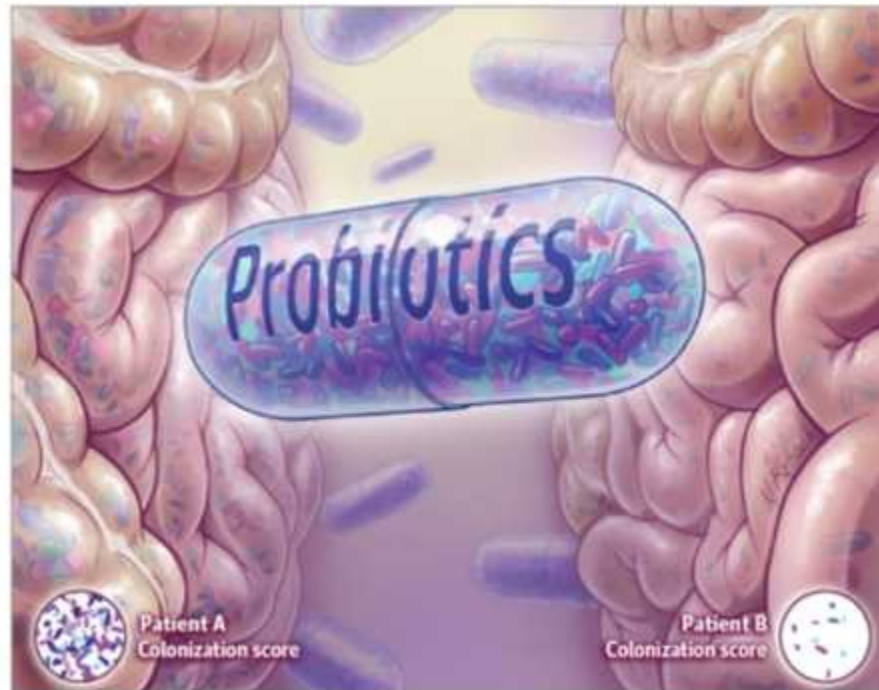
Are Probiotics Money Down the Toilet? Or Worse?

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, MD²

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 Li²

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 Cui¹ and Dongliang Chen²



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



Take home: the gut microbiome in sepsis

- Rapid developments in techniques: 16S very useful to tell “who is there”, metagenomics useful to see “what they are doing”
- 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 prevention, diagnostics and therapeutics?



 Microbiota Center Amsterdam



Thank you!

Bas Haak

Brendon Scicluna

Vanessa Harris

Alex Schuurman

Harjeet Virk

Tjitske van Engelen

Max Jacobs

Nora Wolff

Alex de Vos

Floor Hugenholtz

Further reading:

The role of the gut microbiota in sepsis

Bastiaan W Haak, W Joost Wiersinga



Haak, Lancet Gastroenterol Hepatol, 2017

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