# Microbiome Gut-Brain-Lung-Skin Axis: Clinical Perspectives

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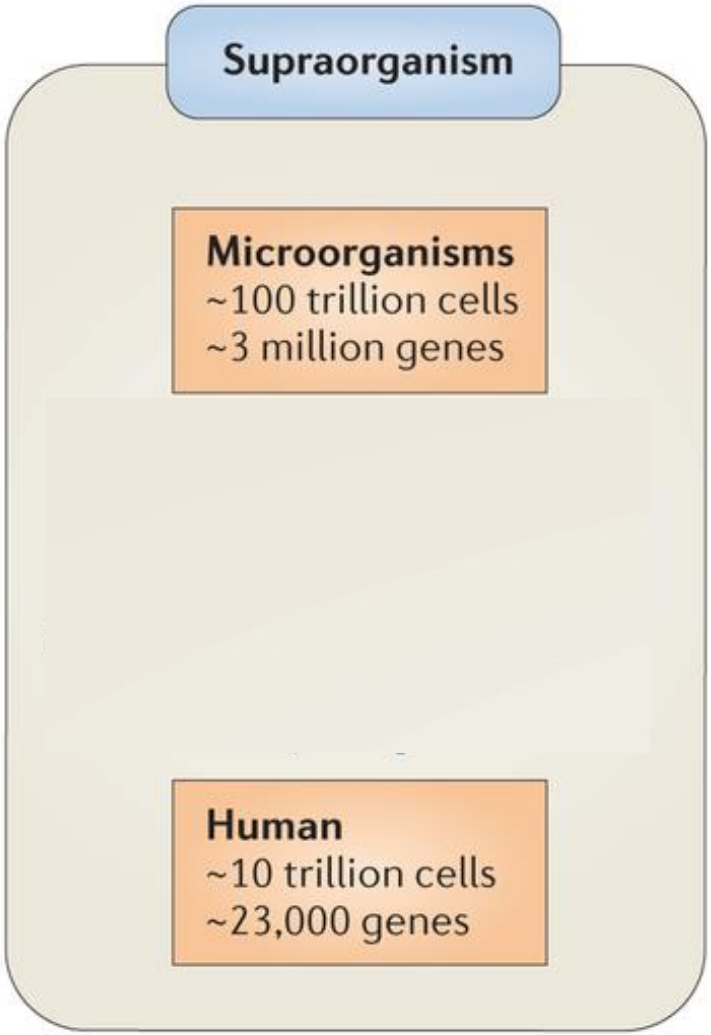
# Outline

- Introduction
- Gut-Lung Axis
- Gut-Brain Axis
- Current limitations
- Potential clinical applications

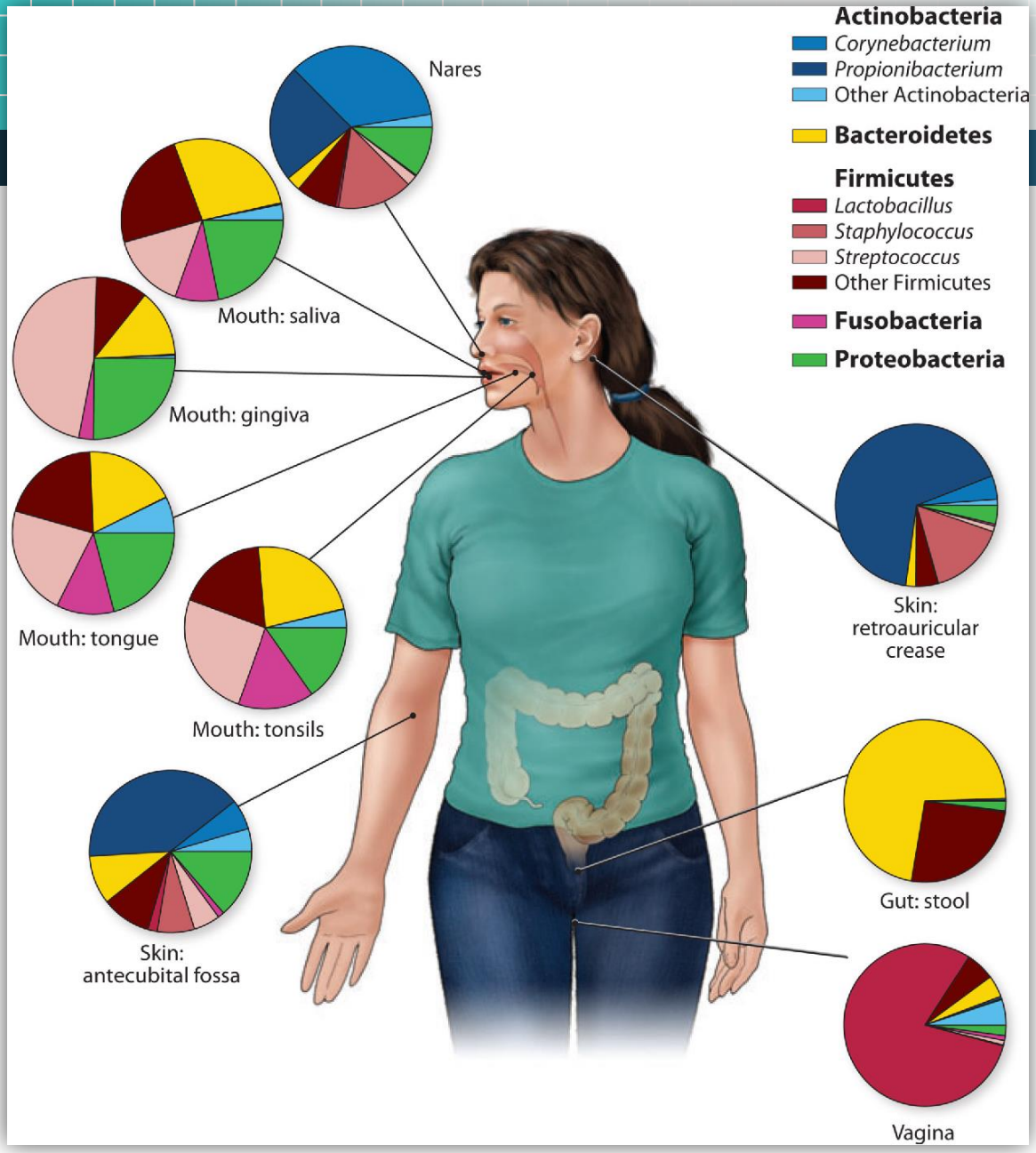
# What is the "microbiome" ?

# The Microbiome - a Rediscovered Organ



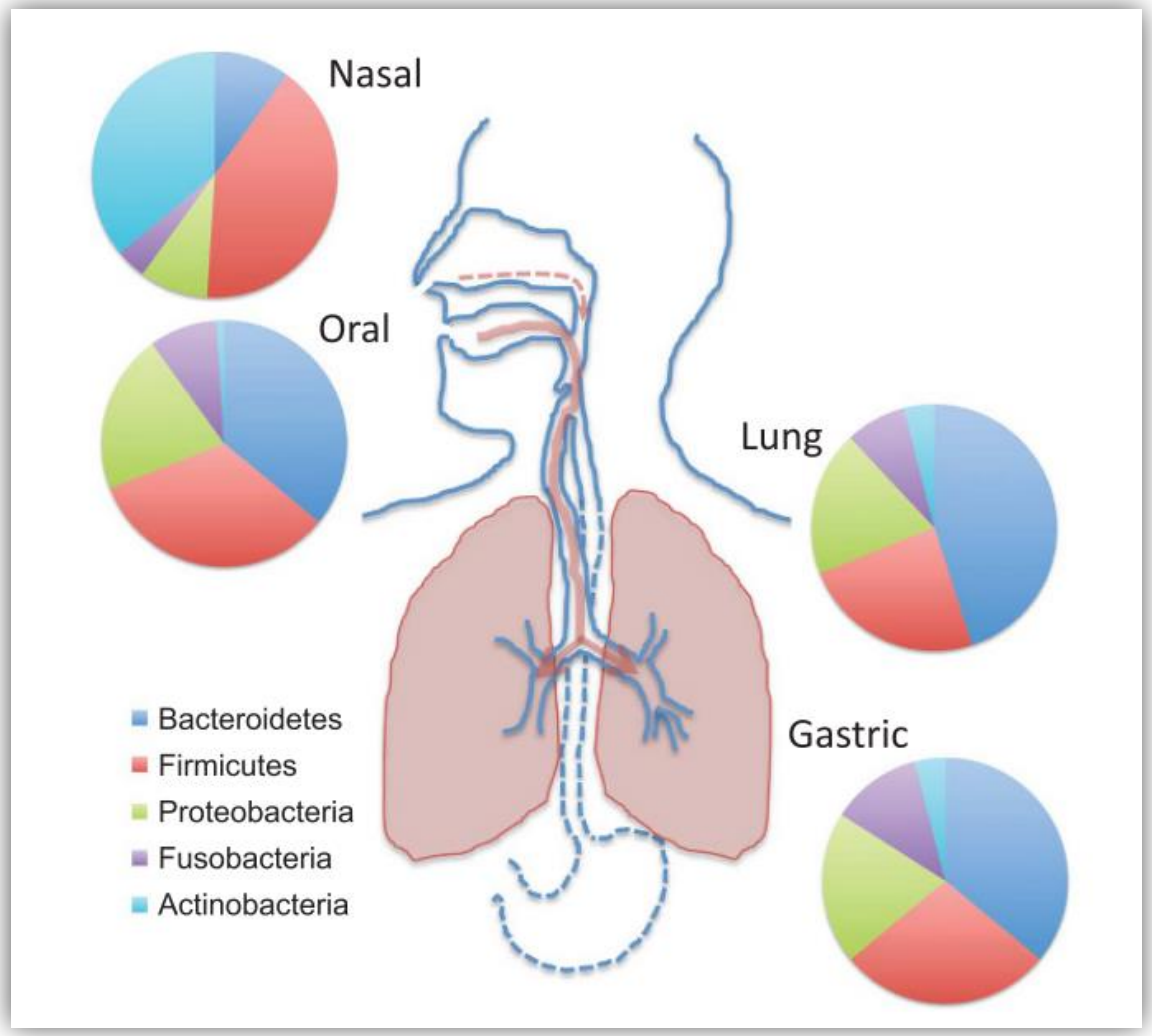

Nature Reviews | Microbiology

**Zhao L. Nature Reviews Microbiology 11, 639–647 (2013)**




# Diversity of the Microbiome across Organ Sites

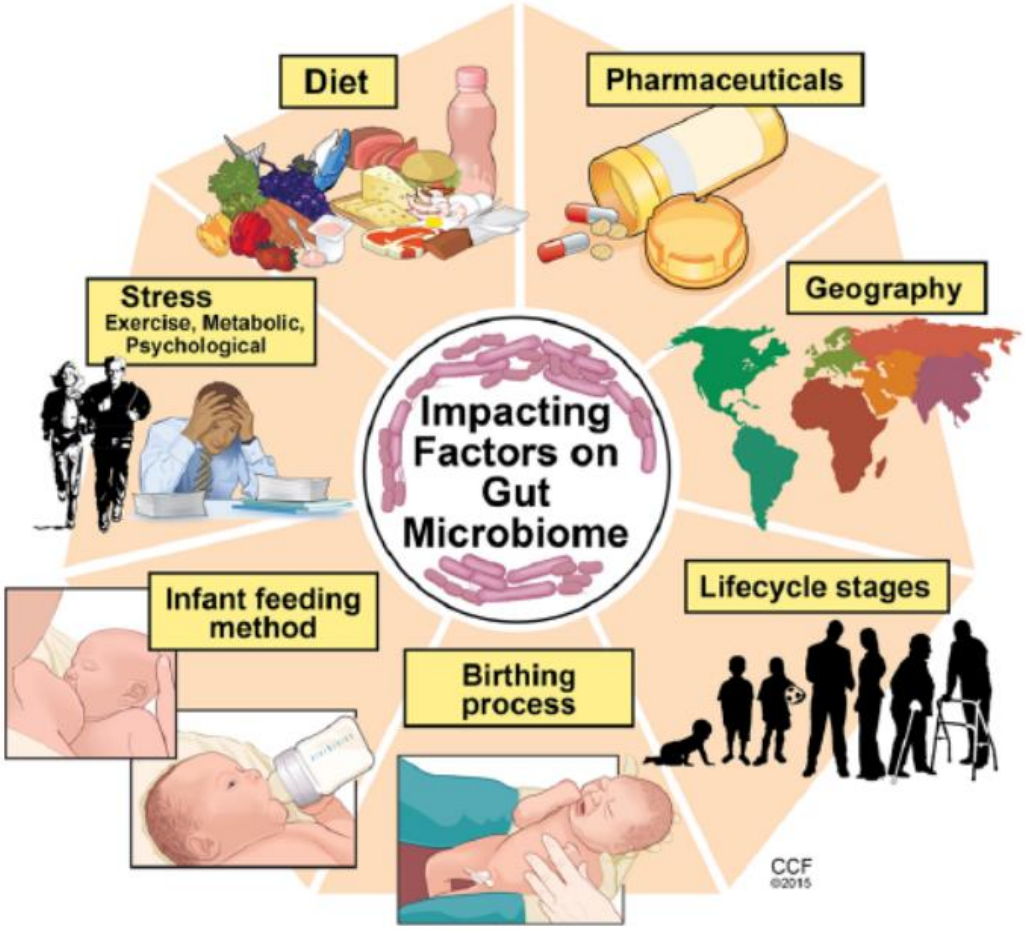
Annu Rev Genomics Hum Genet. 2012;13:151-170.




# Diversity of the Microbiome across Organ Sites

Mucosal Immunol. 2017;10(2):299-306.

# Factors Influencing the Microbiome

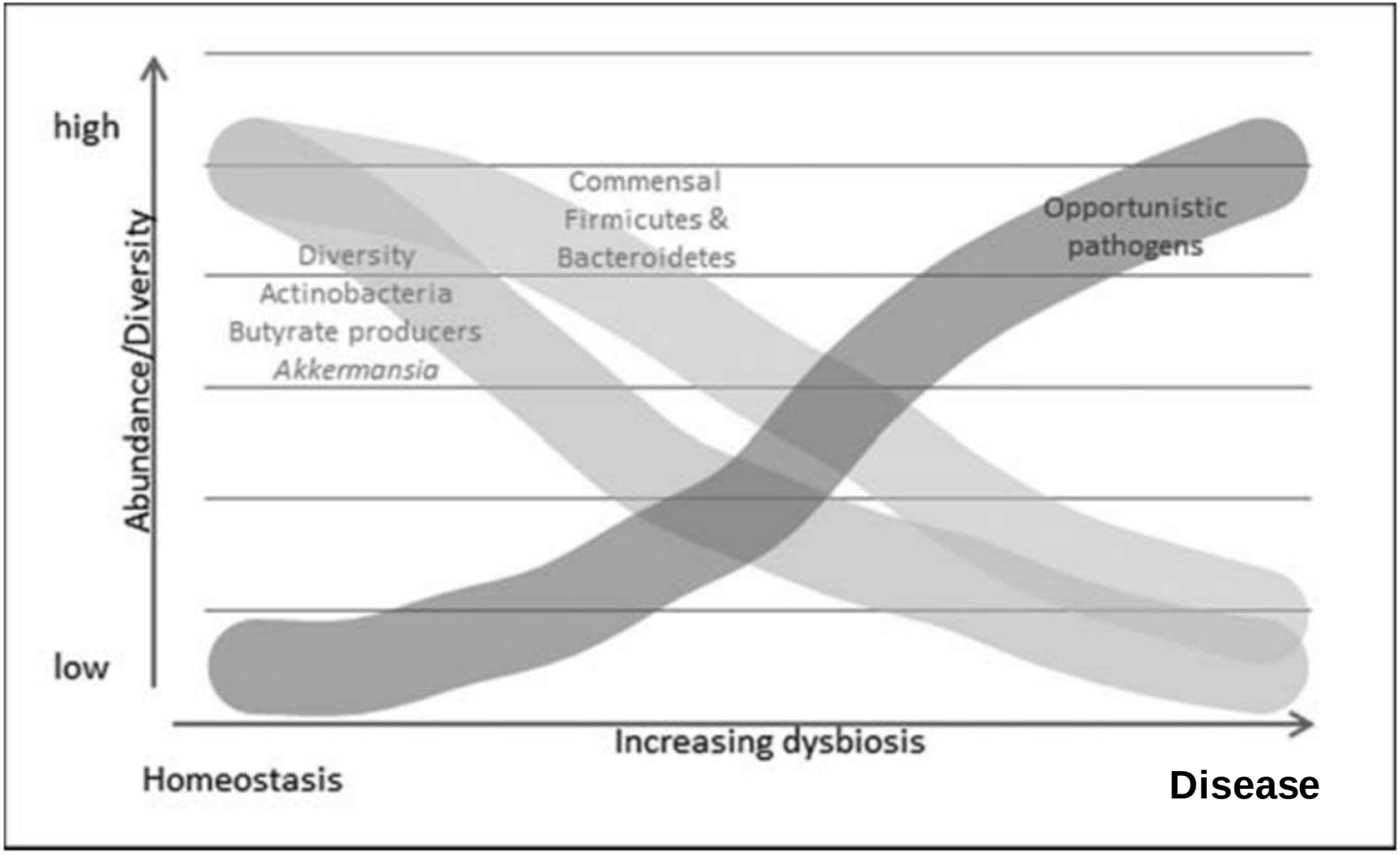



**The Microbiome is Highly Unique to Each Individual**

Cresci G. Nutr Clin Pract. 2015;30:734-746

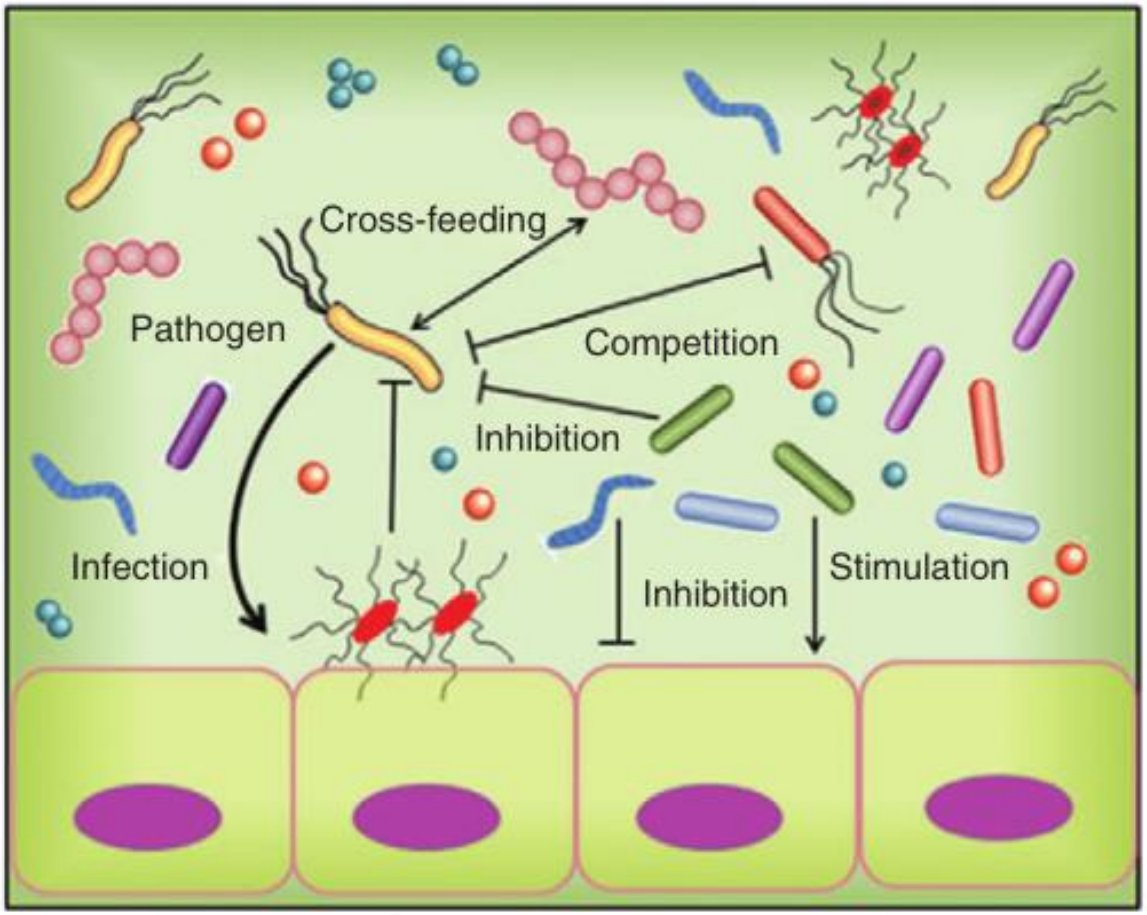
# What happens to the gut microbiota during diseases and illnesses?

Healthy gut microbiota
High diversity
Stable ecosystem
"DYSBIOSIS"
Unhealthy gut microbiota
Low diversity
Unstable ecosystem



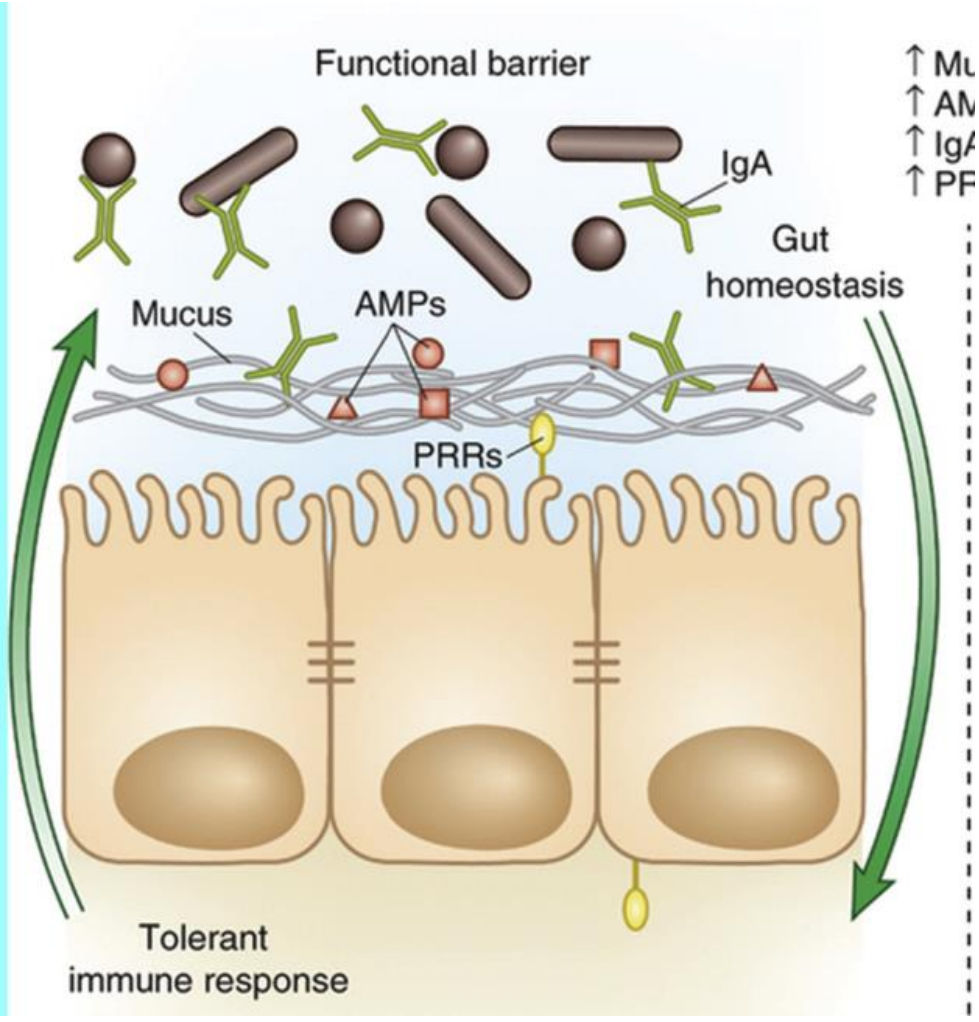

Jacobs MC et al. Curr Opin Crit Care 2017, 23:257–263

# Normal microbiota helps prevent development of the “pathobiome”




**BJS 2017; 104: e14–e23**

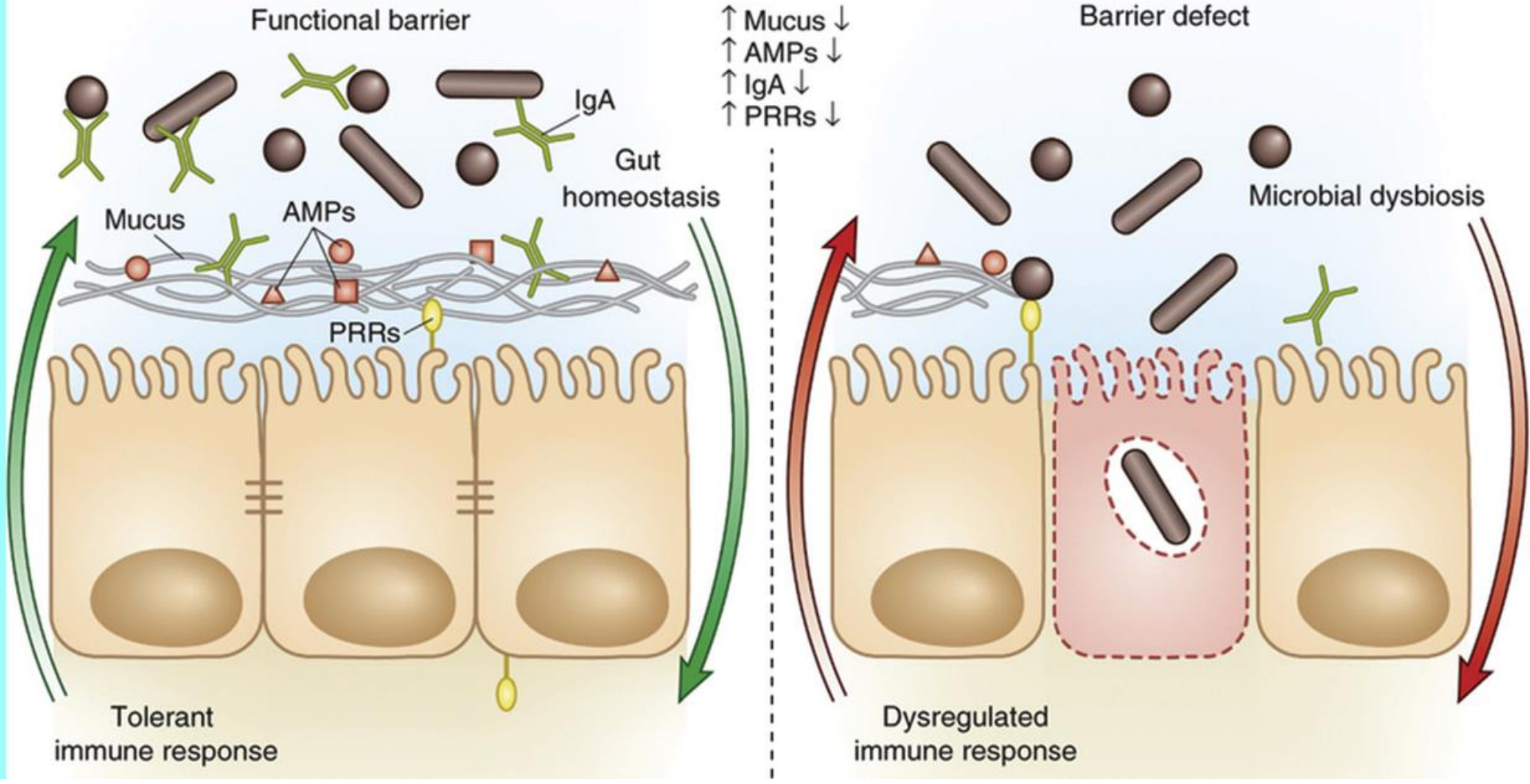
# Healthy Microbiome




Brown EM et al. Nat Immunol 2013 Jul;14(7):660-7.

# Healthy Microbiome

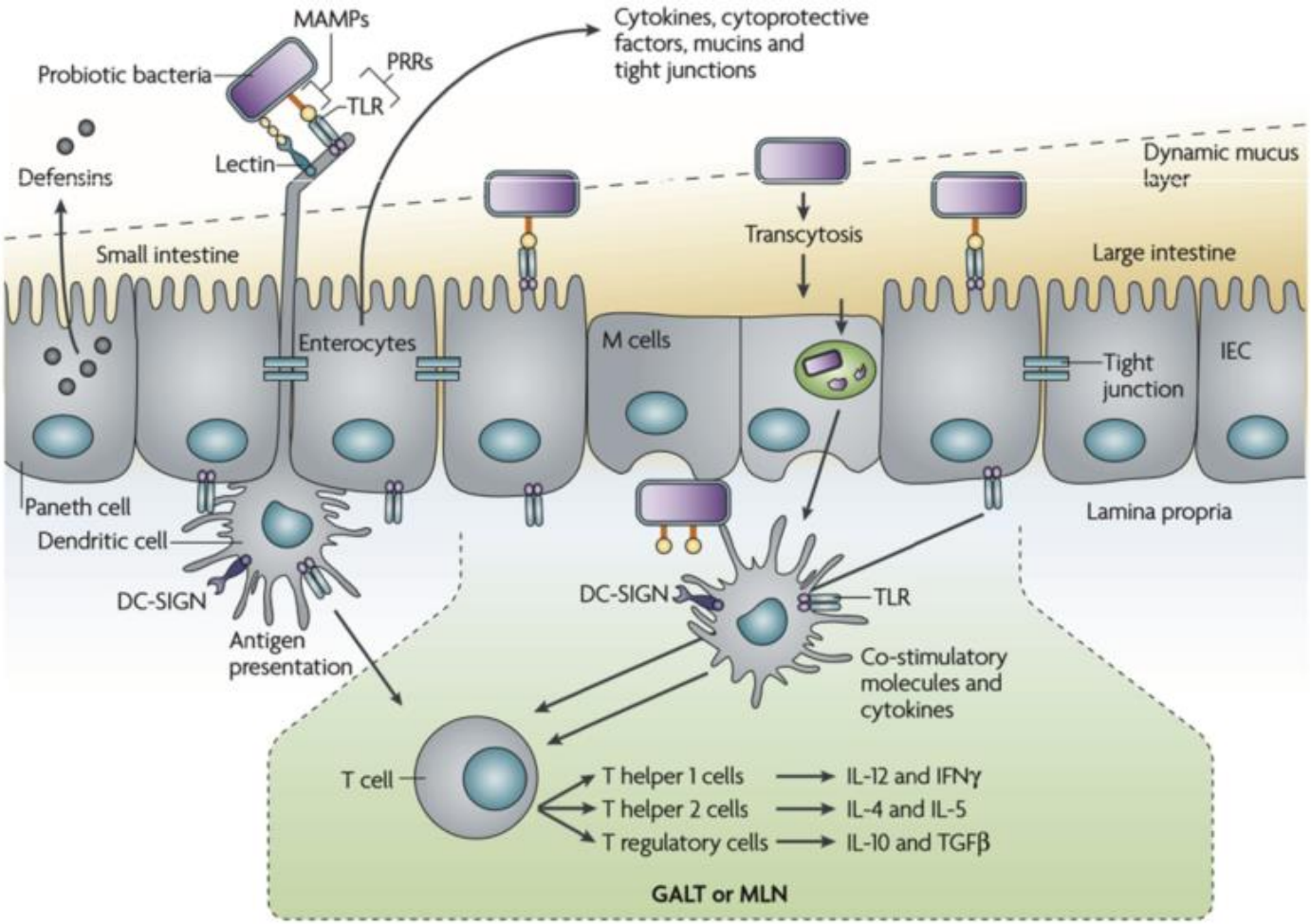
# Dysbiosis




Brown EM et al. Nat Immunol 2013 Jul;14(7):660-7.

# The Microbiome Mediates the Immune System through MAMPs

## MAMPs: Microbial-associated molecular patterns




Lebeer S, et al. Nat Rev Microbiol 2010;8(3):171e84.

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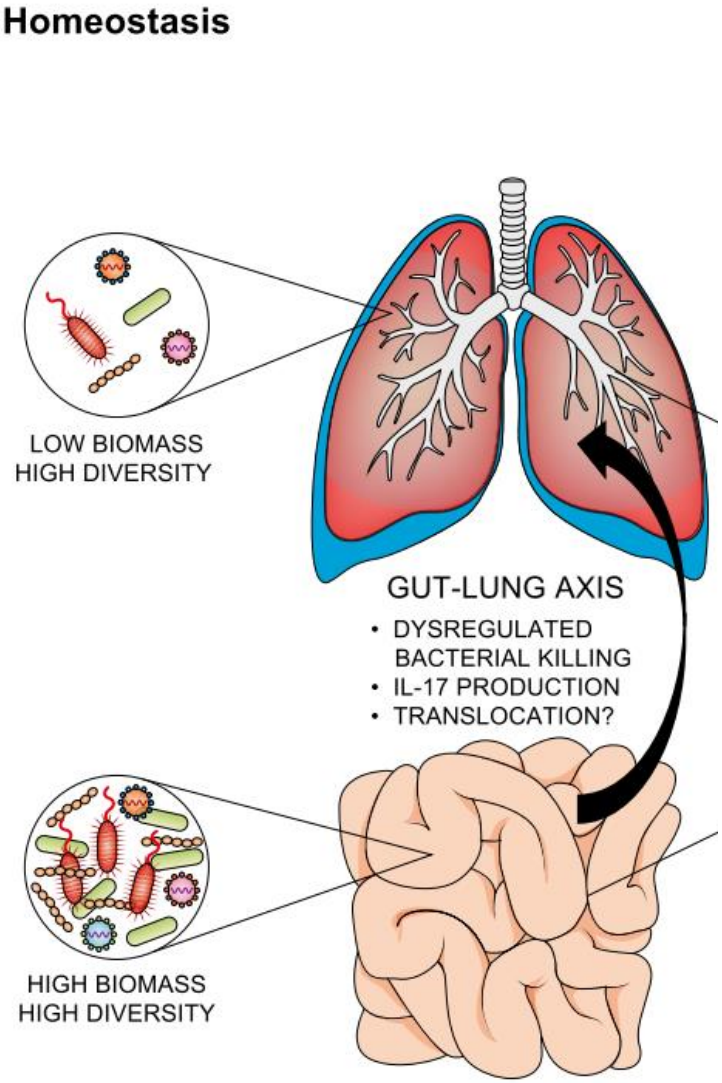
- **Gut-Brain Axis**
- Current limitations
- Potential clinical applications

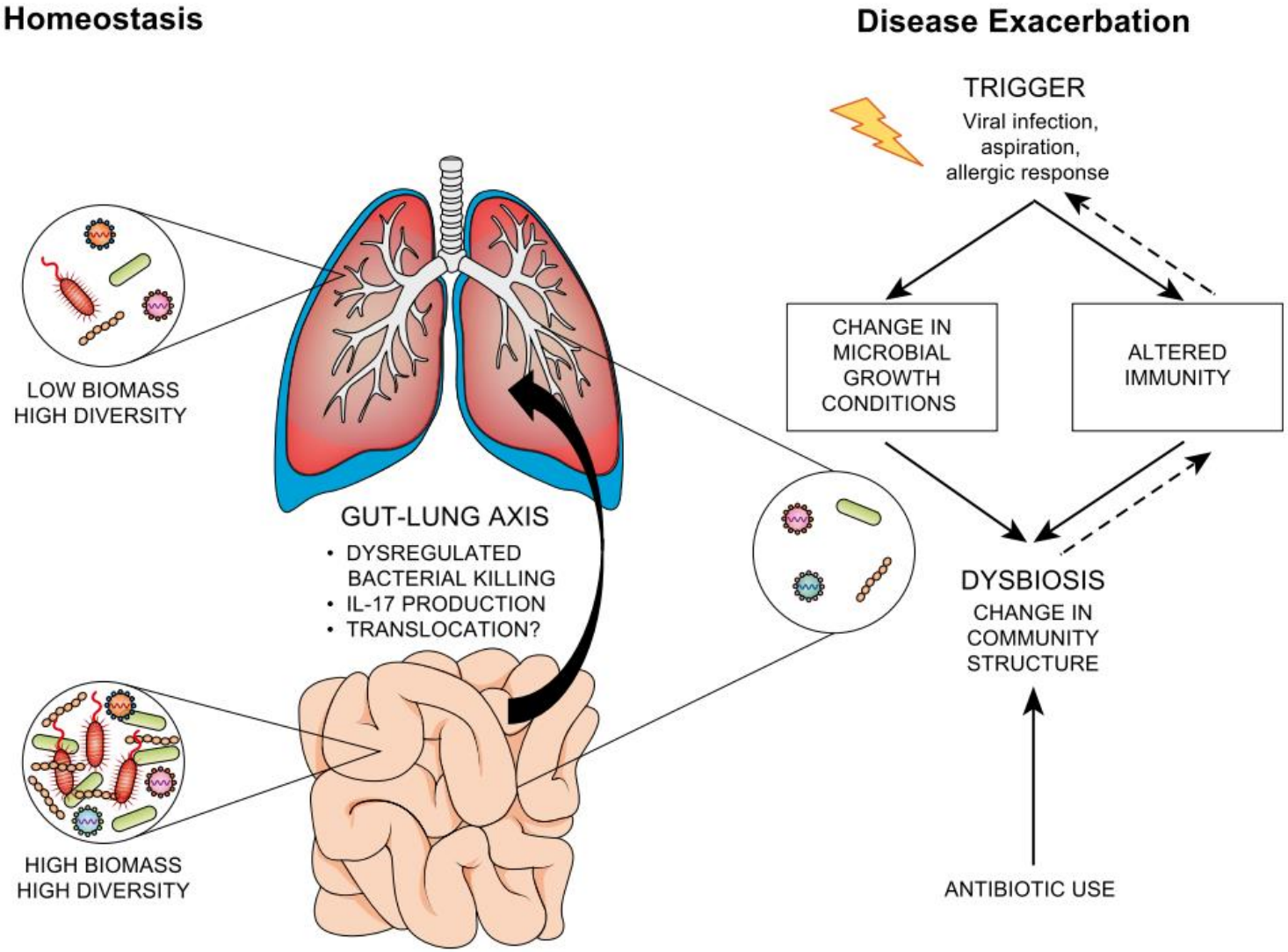
# The Gut-Lung Axis vs. COVID-19

# The Gut-Lung Axis




J Immunol 2016; 196:4839-4847

# The Gut-Lung Axis



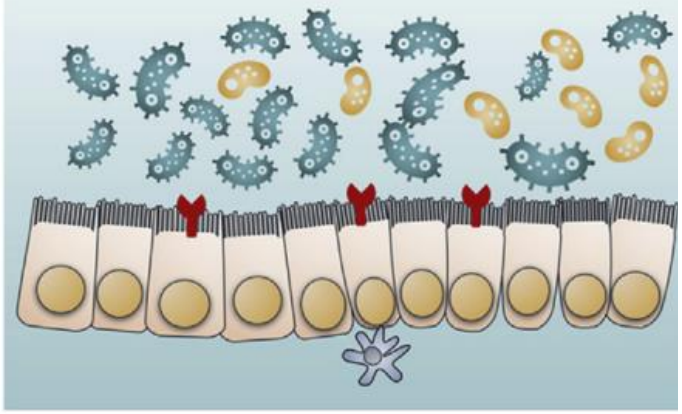

J Immunol 2016; 196:4839-4847

# Potential Role of the Gut Microbiome in SARS-CoV-2 Infection

**Health**

**Prevalent Commensals**:
*Eubacterium*, *Faecalibacterium prausnitzii*,
*Roseburia*, *Lachnospiraceae* taxa

short-chain fatty acids (especially butyrate) producer
immunity maintenance
anti-inflammatory properties



Gastroenterology 2020;159:944–955

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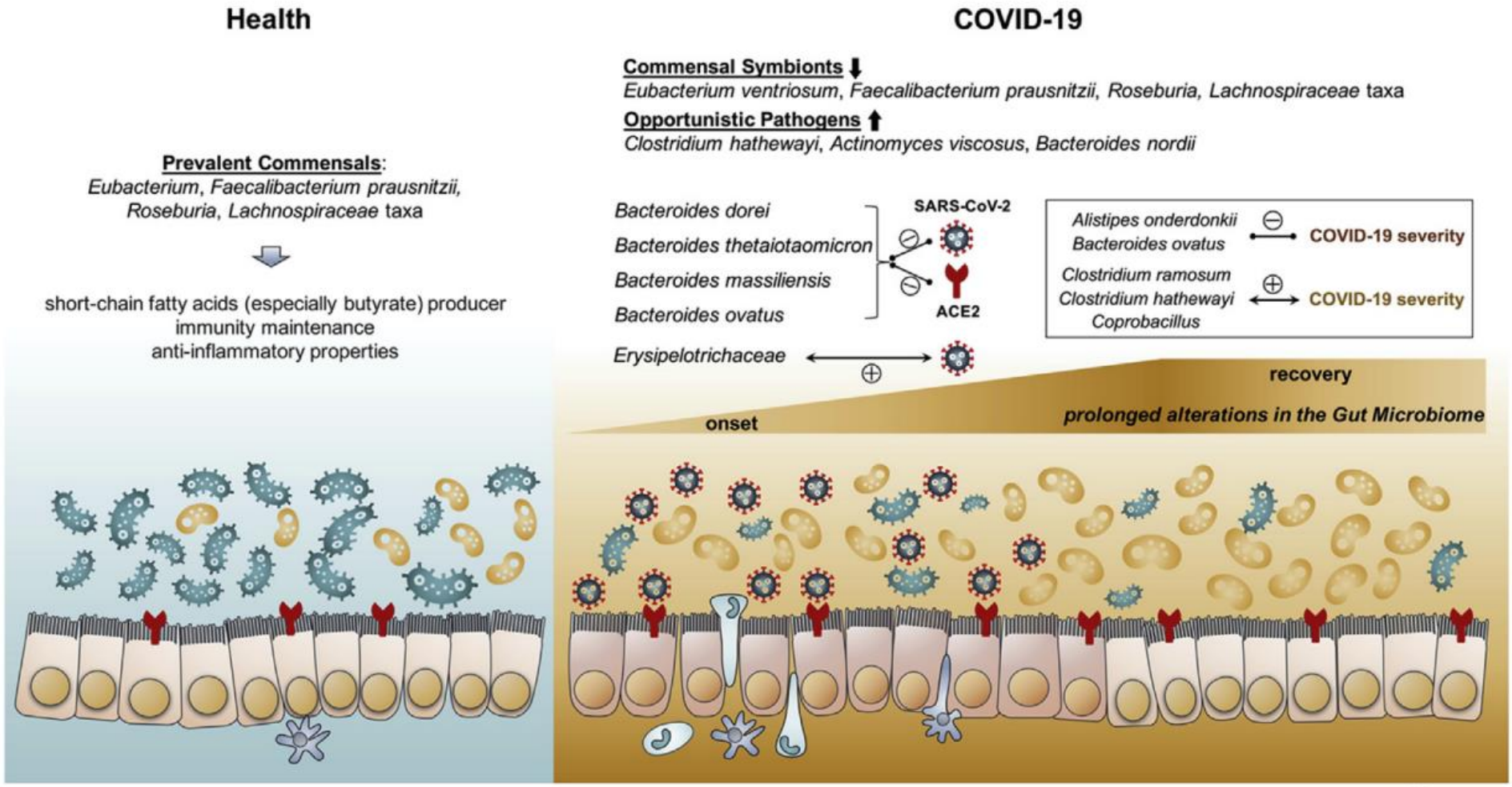


Gastroenterology 2020;159:944–955

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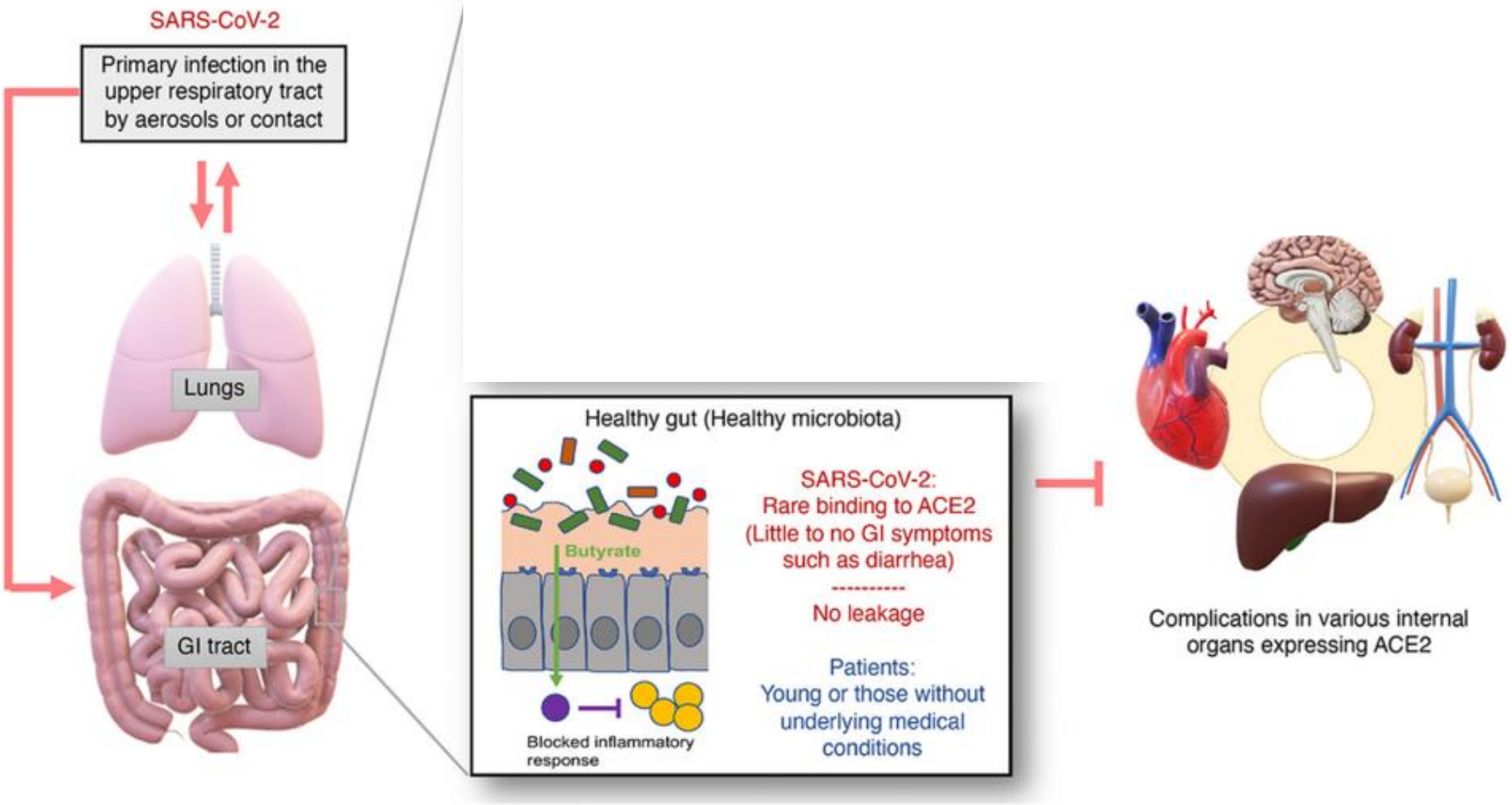
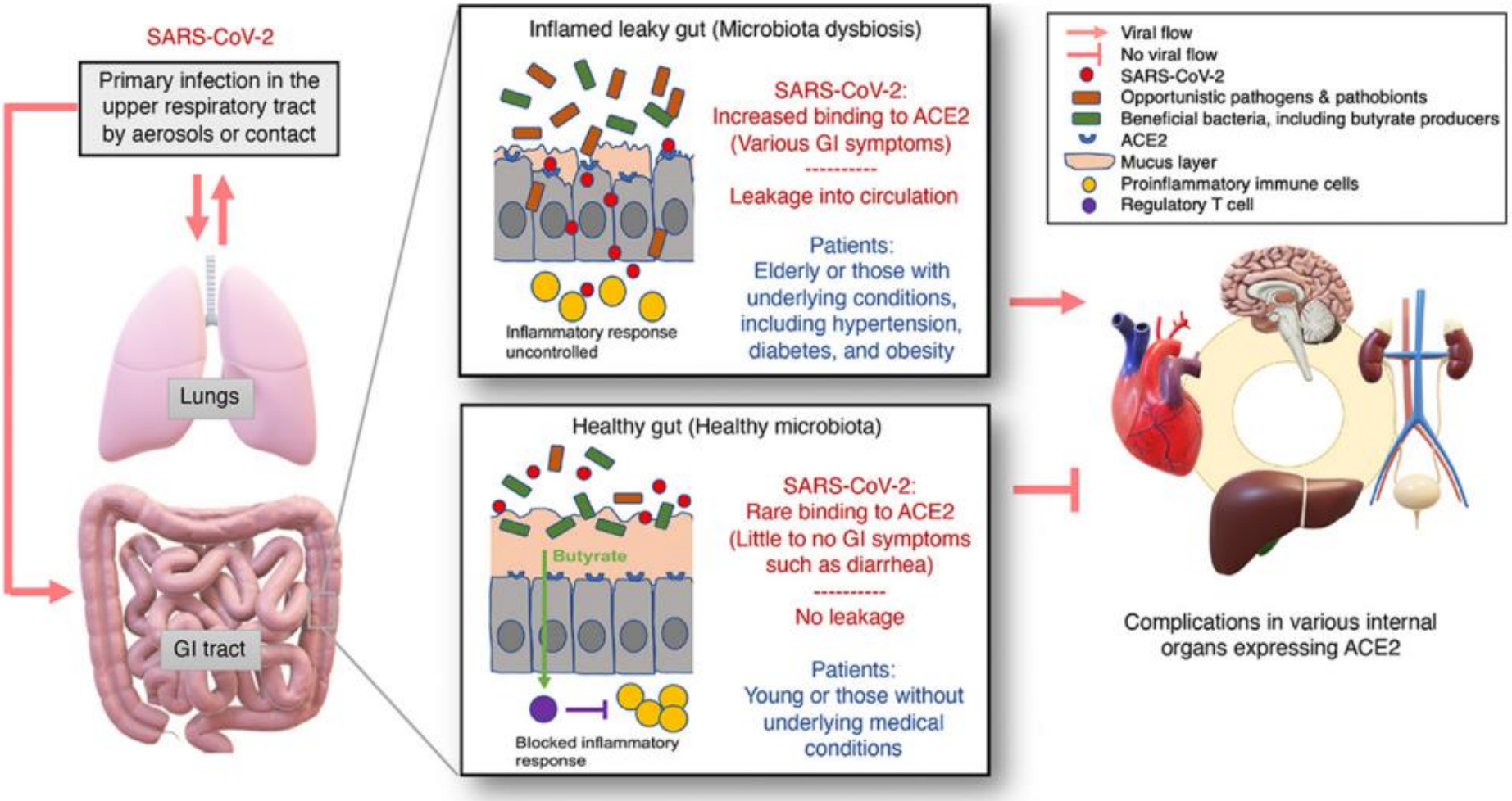



mBio. 2021;12(1):e03022-20.

# Potential Role of the Gut Microbiome in SARS-CoV-2 Infection




mBio. 2021;12(1):e03022-20.

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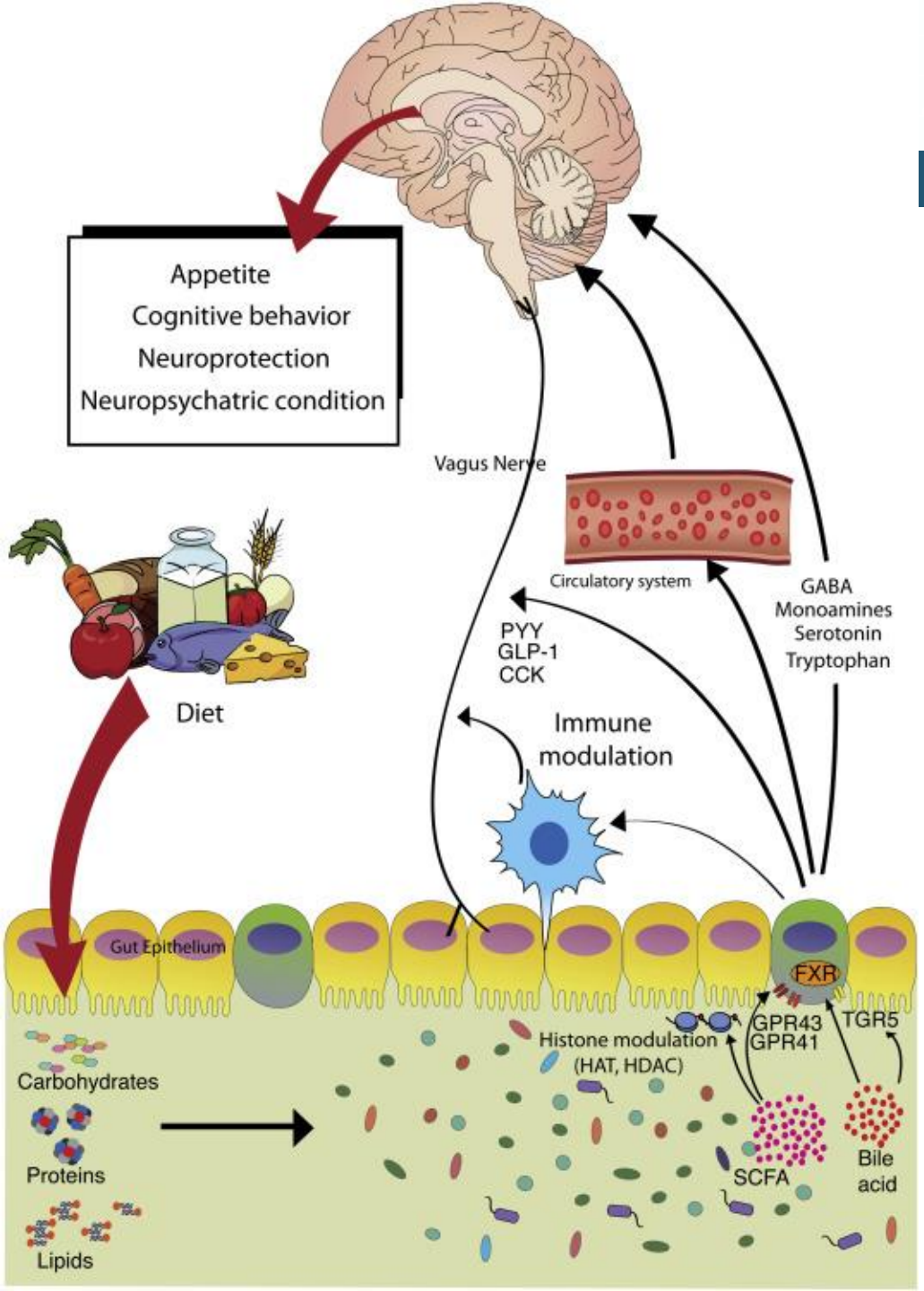



# Microbiota-Gut-Brain Axis

Sandhu KV et al.
Translational Research 2017;
179:223–244

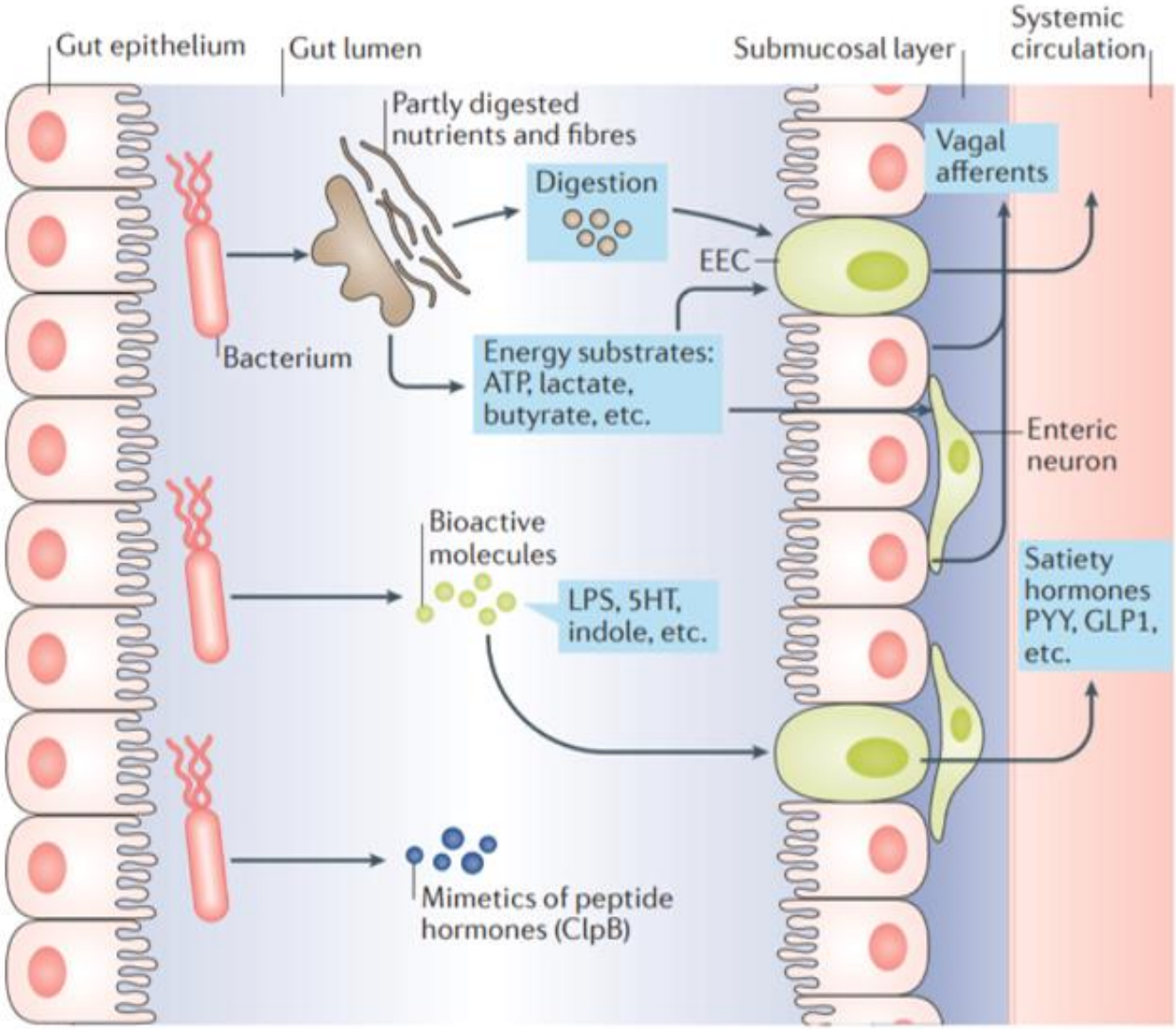
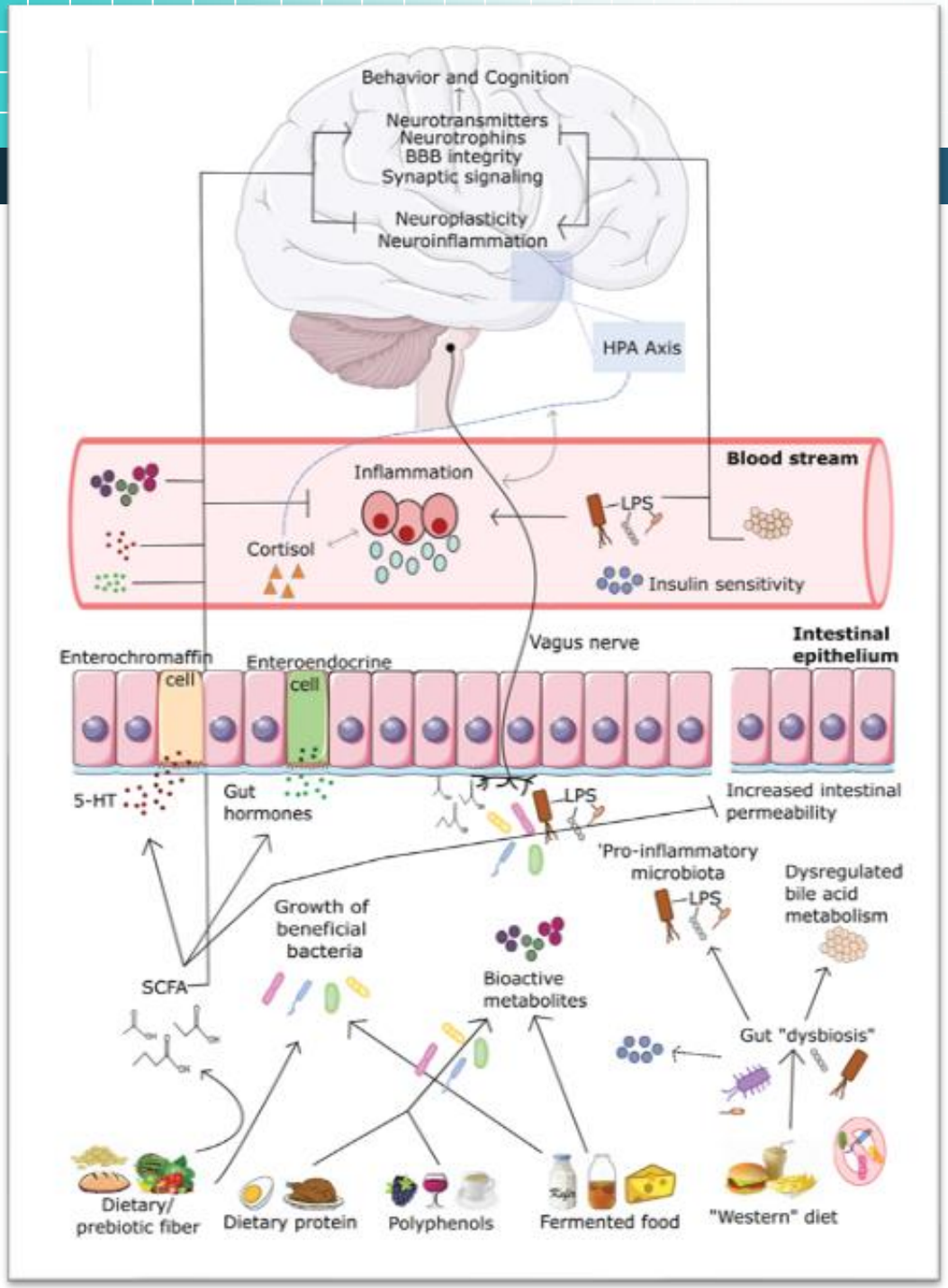



Figure 5 | **Gut bacteria-derived chemical signals that might activate intestinal satiety pathways.** During their life in the gut, bacteria metabolize non-digestible fibre

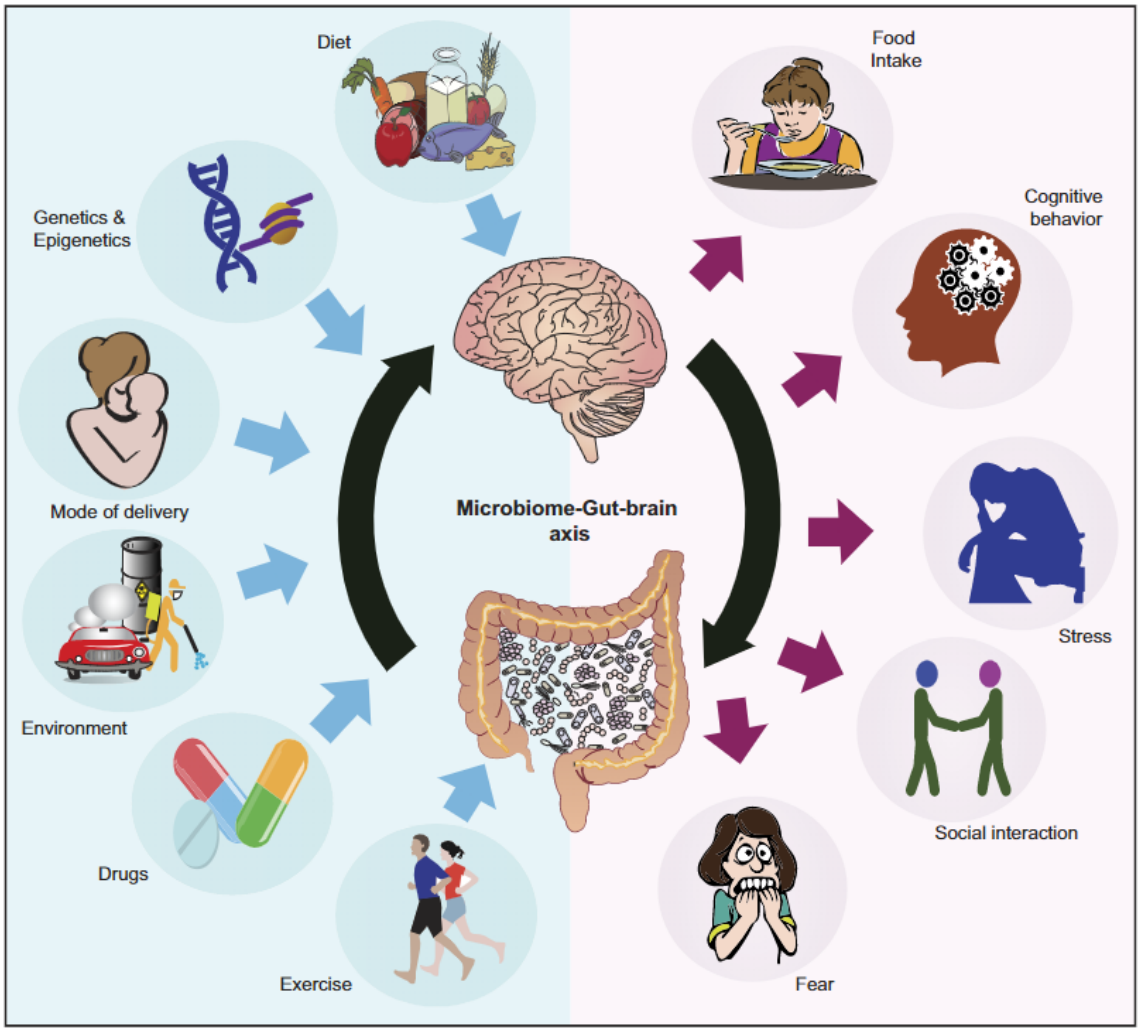
Nat Rev Endocrinol. 2017 Jan;13(1):11-25.



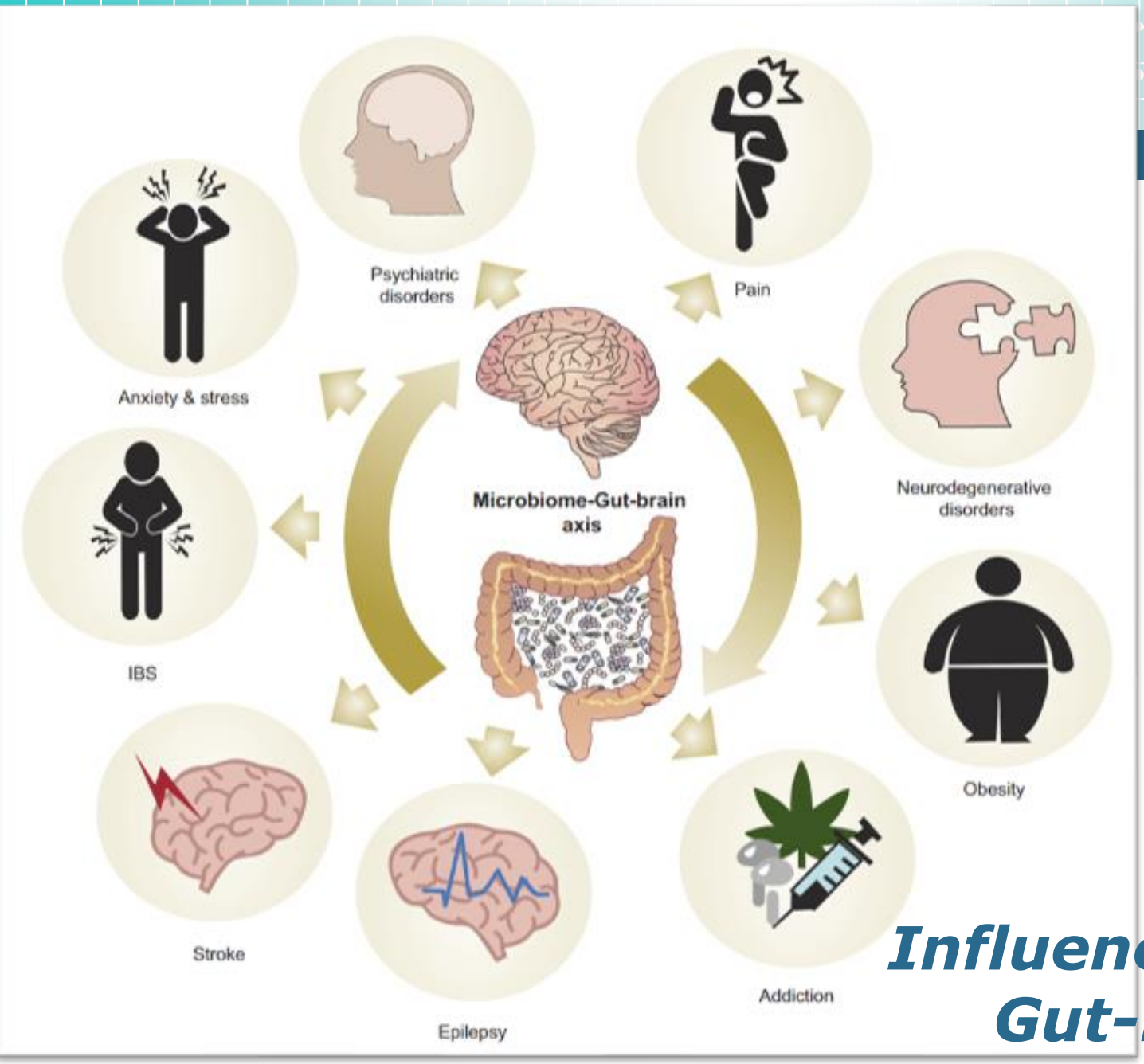

# *Role of Diet in the Gut-Brain Axis*

**Adv Nutr 2021;12:1239–1285.**

# The GUT controls the BRAIN



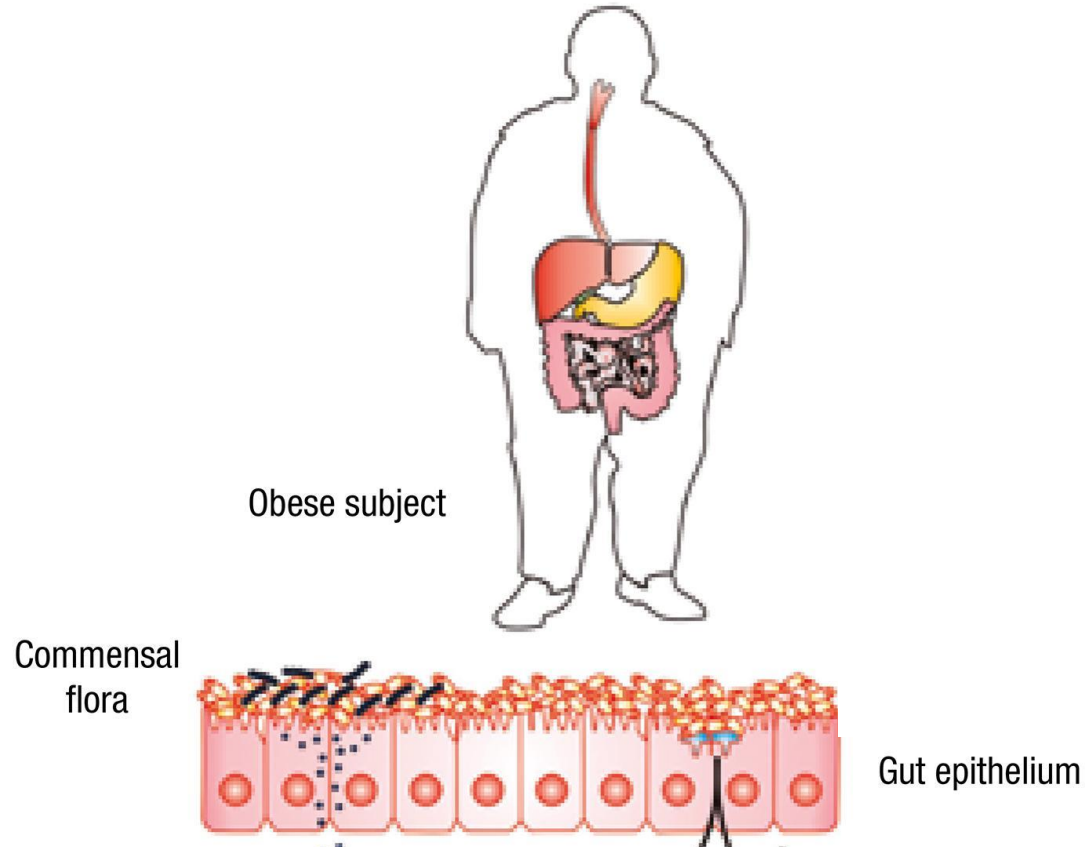

Physiol Rev VOL 99 OCTOBER 2019 pp 1877-2013




# Diseases Influenced by the Gut-Brain Axis

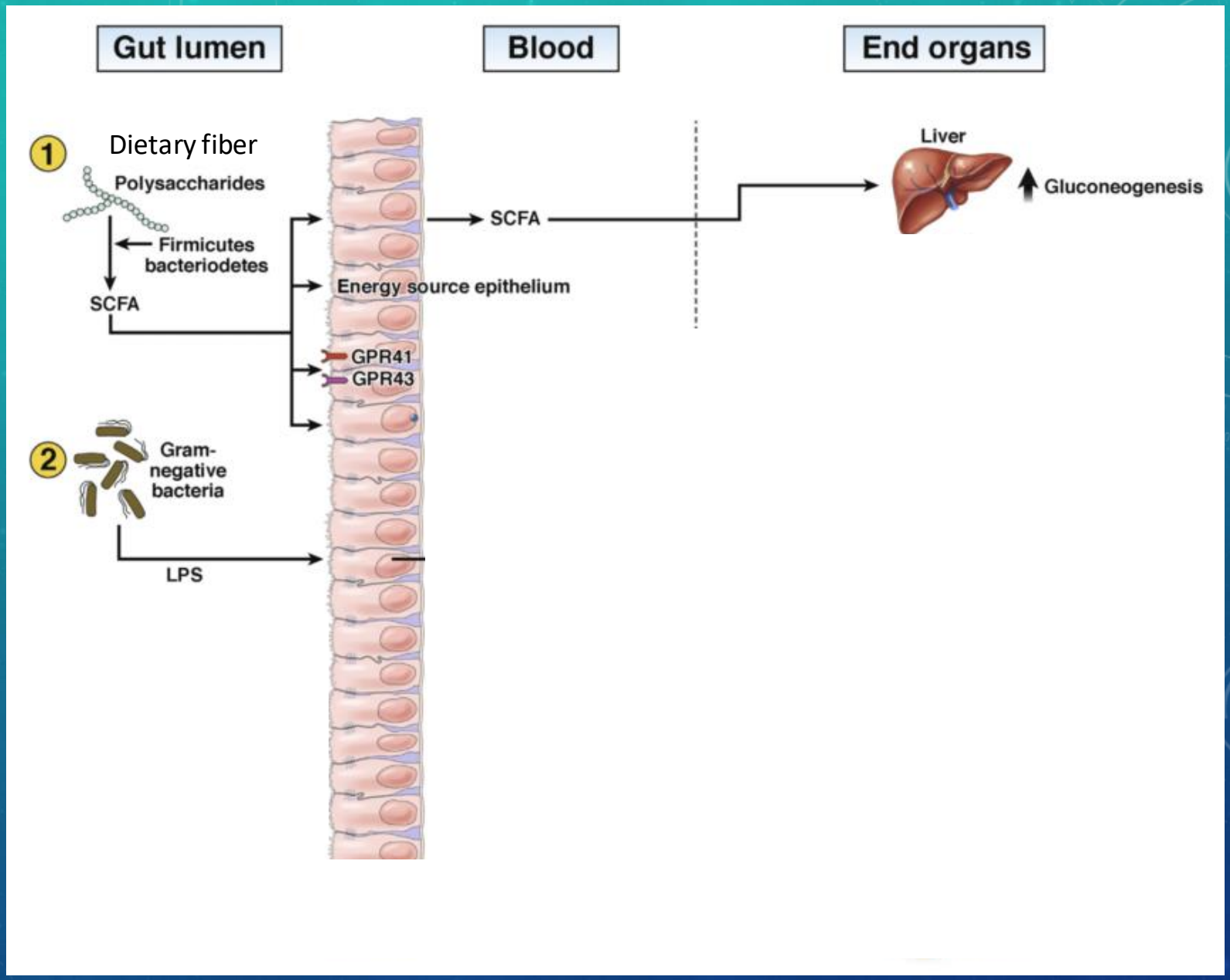
Physiol Rev VOL 99 OCTOBER 2019 pp 1877-2013

# The Gut-Brain Axis and Obesity & Type 2 Diabetes



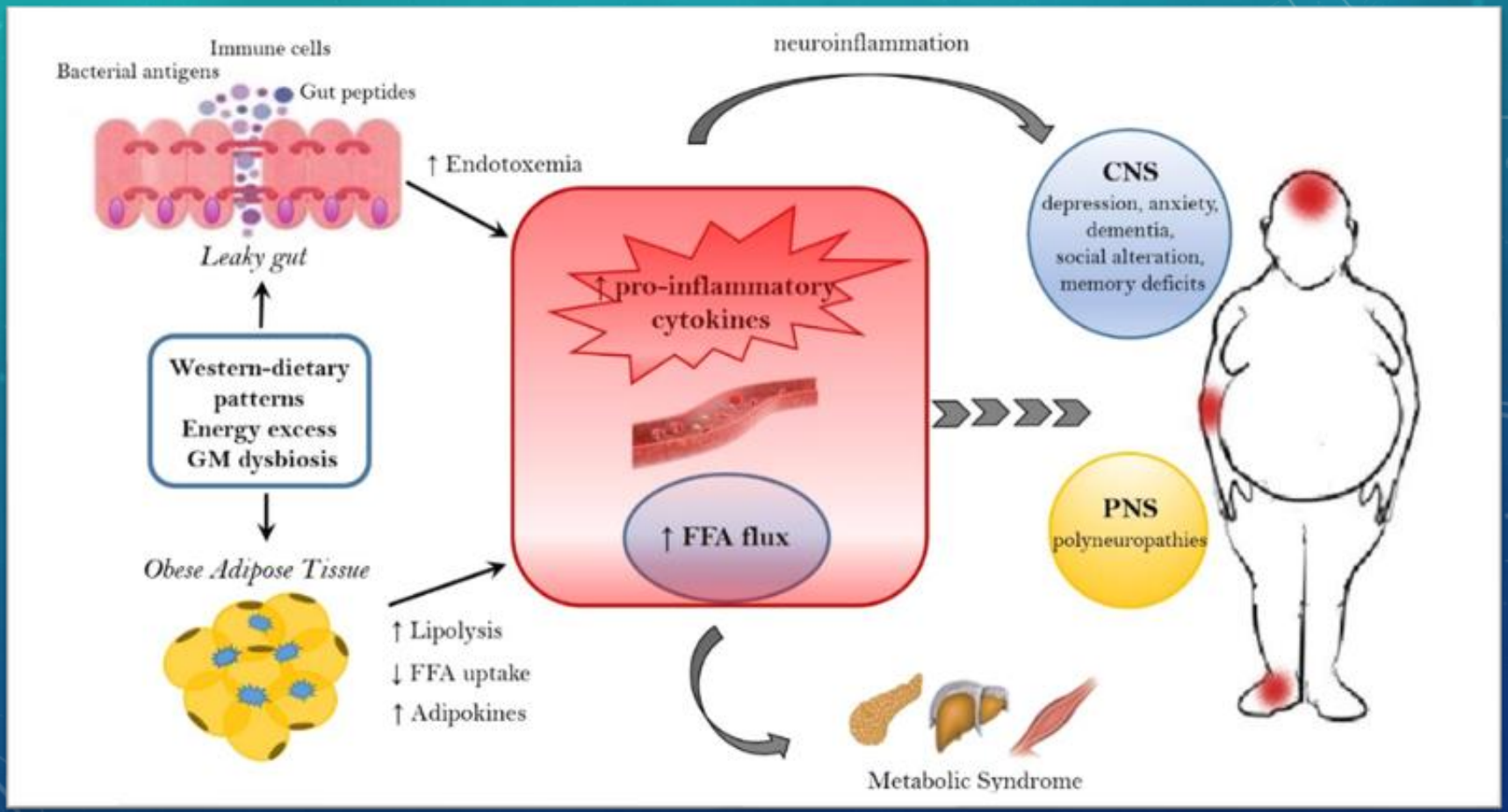

# GUT MICROBIOTA VS. OBESITY AND TYPE 2 DIABETES

Tsukumo DM et al.
Arch. Endocrinol. Metab. vol.59 no.2. 2015



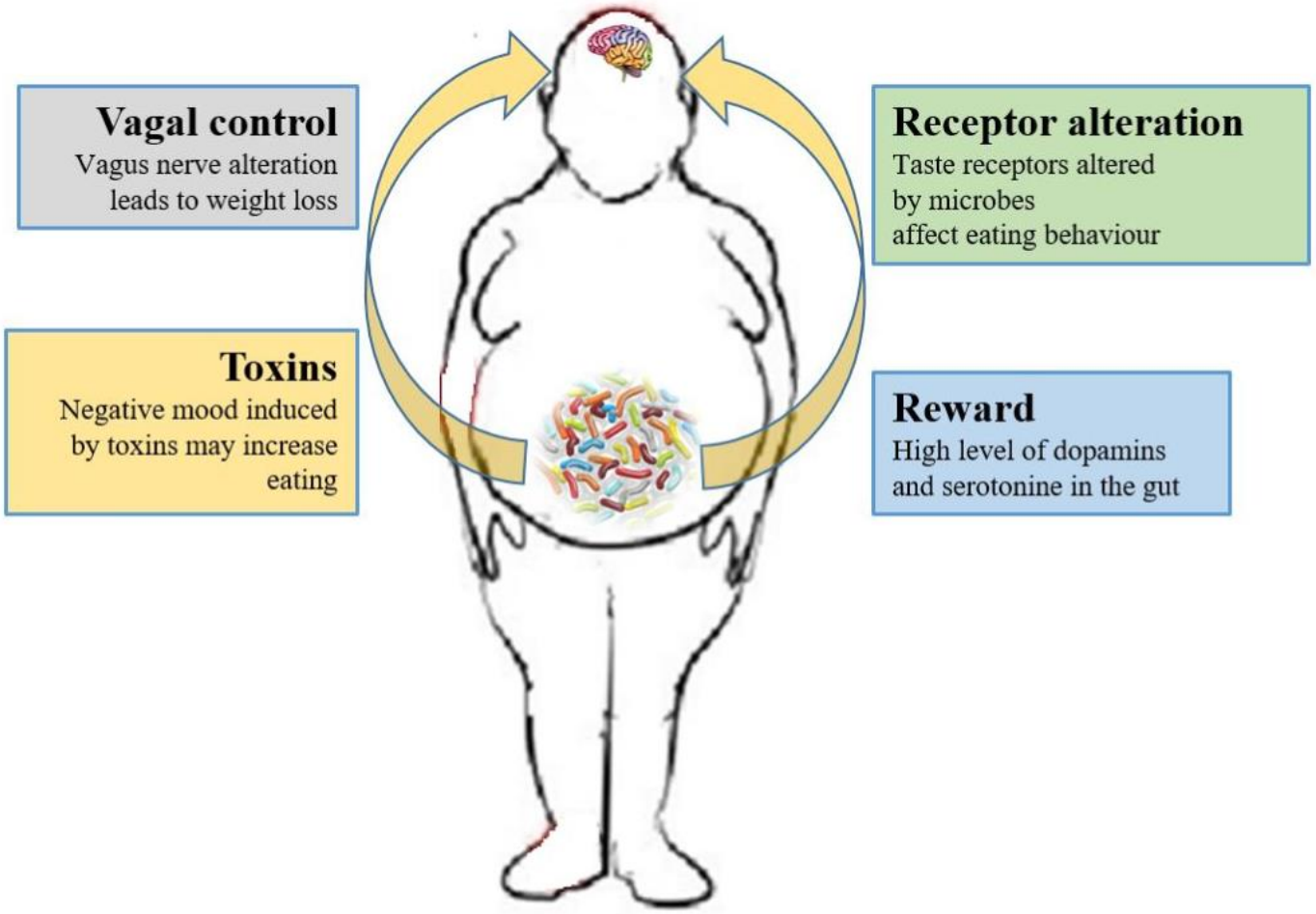

Bouter KE et al. Gastroenterology 2017;152:1671–1678

# OBESITY-RELATED NEUROLOGICAL AND PSYCHOLOGICAL COMPLICATIONS ARE MEDIATED THROUGH THE GUT-BRAIN AXIS




Nutrients 2019, 11, 156

# Eating Behavior is Influenced by the Gut-Brain Axis




Nutrients 2019, 11, 156

# AND
# Epilepsy Treatment

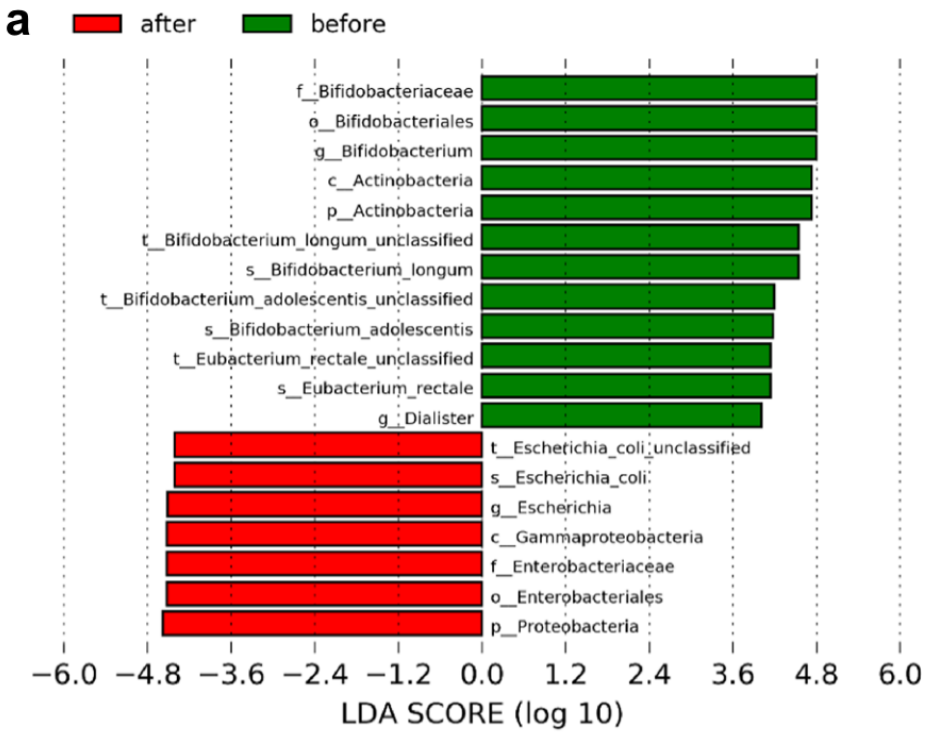
npj | Biofilms and Microbiomes

www.nature.com/npjbiofilms

ARTICLE OPEN

# The ketogenic diet influences taxonomic and functional composition of the gut microbiota in children with severe epilepsy

Marie Lindefeldt[1], Alexander Eng[2], Hamid Darban[3], Annelie Bjerkner[4], Cecilia K Zetterström[5], Tobias Allander[4], Björn Andersson[3], Elhanan Borenstein[2,6,7,8,9], Maria Dahlin[1] and Stefanie Prast-Nielsen[10]

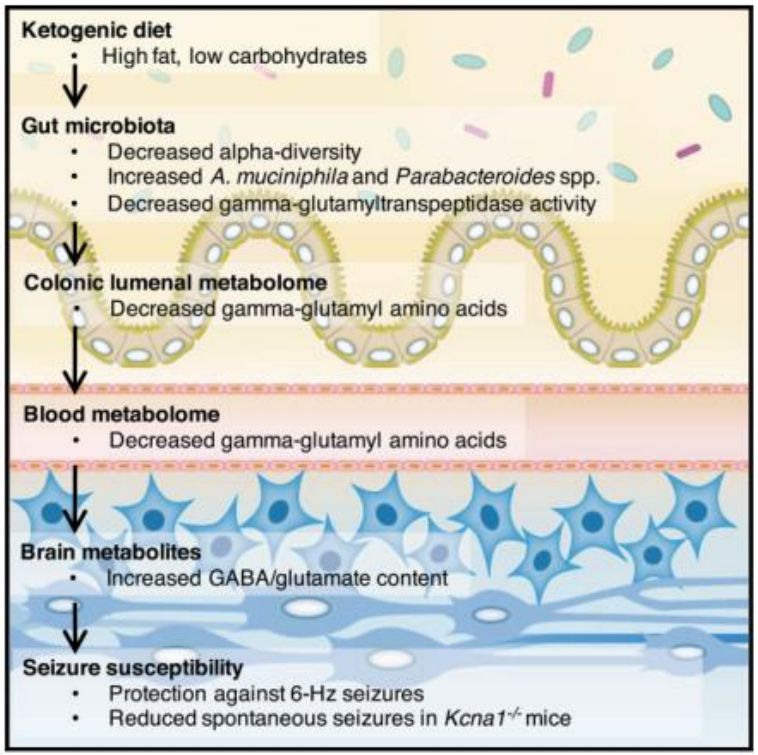



Lindefeldt M et al.
npj Biofilms and Microbiomes (2019); 5:5

Cell

# The Gut Microbiota Mediates the Anti-Seizure Effects of the Ketogenic Diet

## Graphical Abstract




## Highlights

- Changes in the gut microbiota are required for the anti-seizure effects of the KD
- Specific KD-associated bacteria mediate and confer the anti-seizure effects of the KD
- KD microbiota regulate amino acid γ-glutamylation and hippocampal GABA/glutamate

## Authors

Christine A. Olson, Helen E. Vuong, Jessica M. Yano, Qingxing Y. Liang, David J. Nusbaum, Elaine Y. Hsiao

## Correspondence

ehsiao@ucla.edu

## In Brief

The beneficial effects of a ketogenic diet on epileptic seizures are mediated by the gut microbiome through their modulation of hippocampal GABA/glutamate ratios.

Olson et al., 2018,
Cell 173, 1728–1741

# Outline

- Introduction
- Gut-Lung Axis
- Gut-Brain Axis
- **Current limitations**
- Potential clinical applications

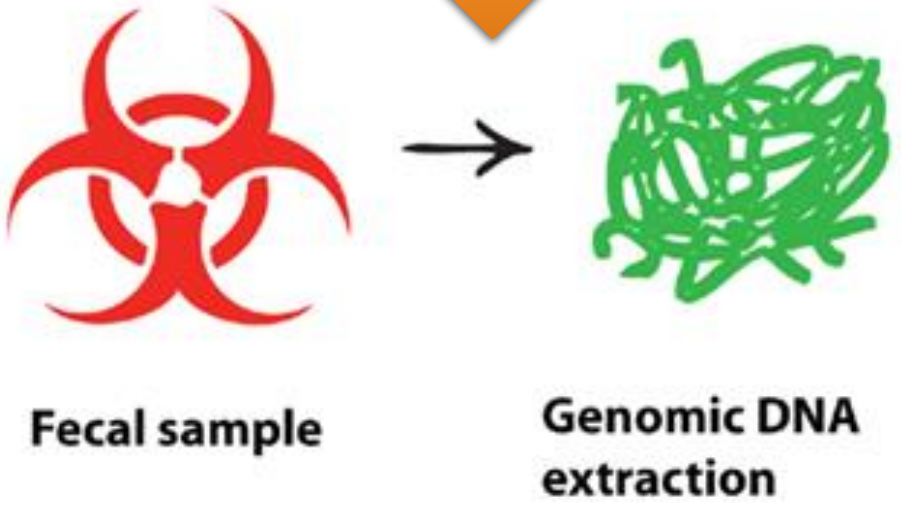
# *What is preventing us from using this approach at the bedside ?*

# Current Limitations of this Approach

- What is an “optimal microbiome” ?
  Is there one ?
- High interindividual variability
  age, sex, diet, genetics, medications
- Limited generalizability
- Data analysis platforms lack consensus
- Lack of clinician access/understanding to current tools

***PAST:***

**STOOL CULTURE**

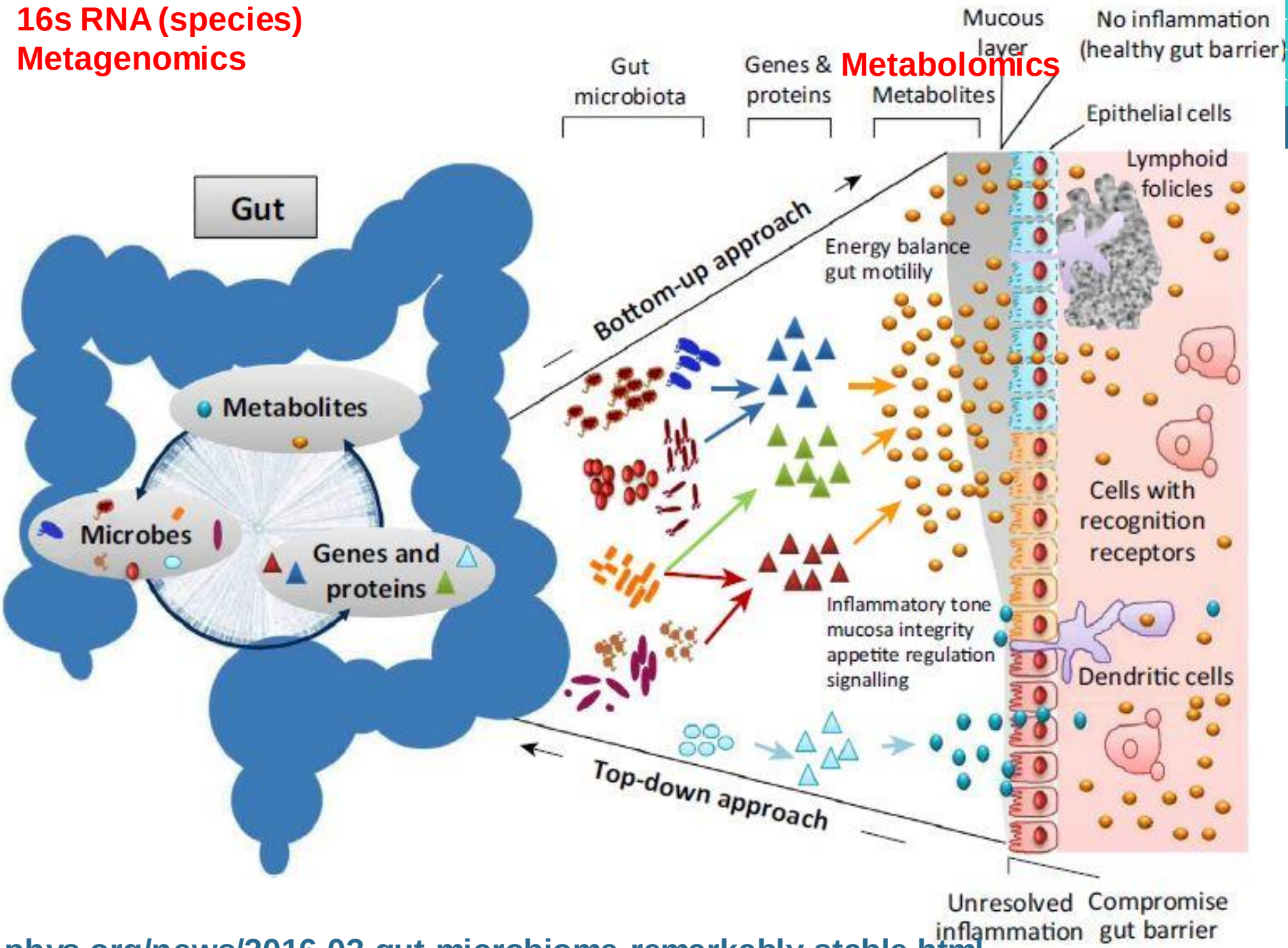



***PRESENT:***

**CULTURE-INDEPENDENT METHODS**

**NEXT-GENERATION SEQUENCING**

16s RNA (species)
Metagenomics




phys.org/news/2016-03-gut-microbiome-remarkably-stable.html

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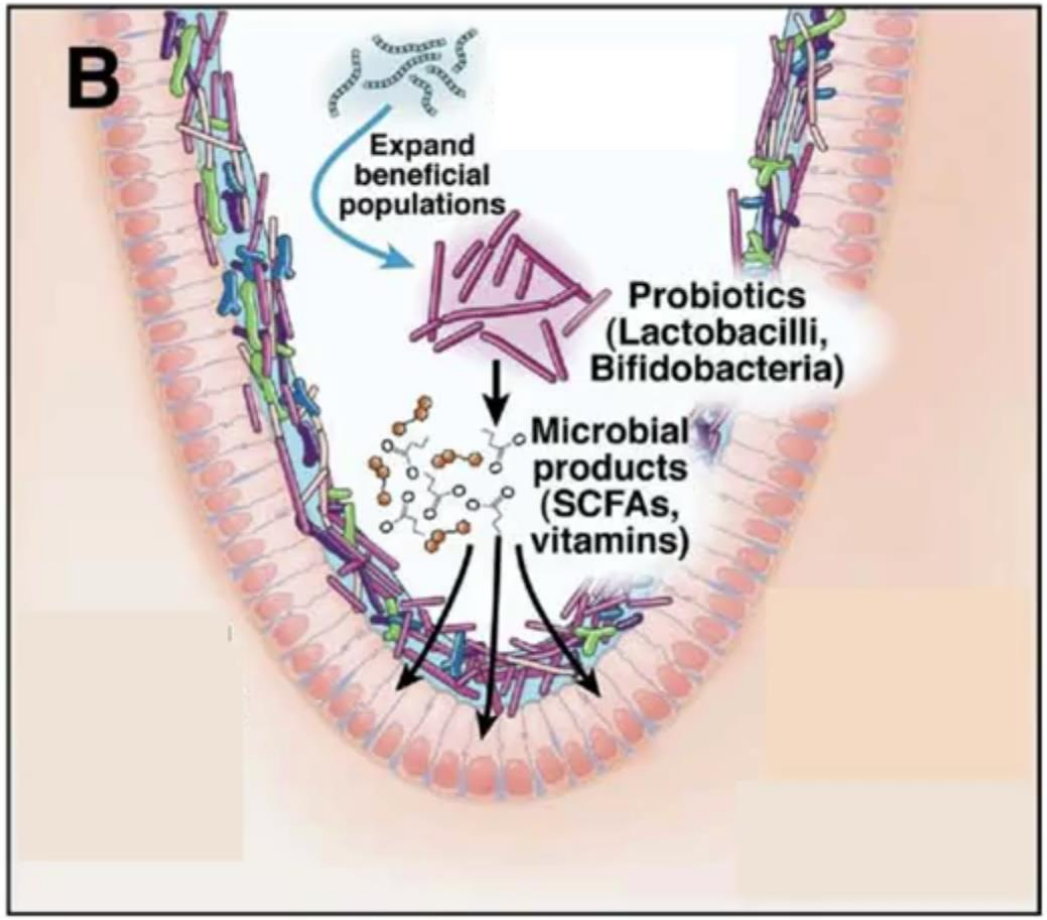
# *What can we currently do to help patients?*

# Potential gut microbiota-based interventions

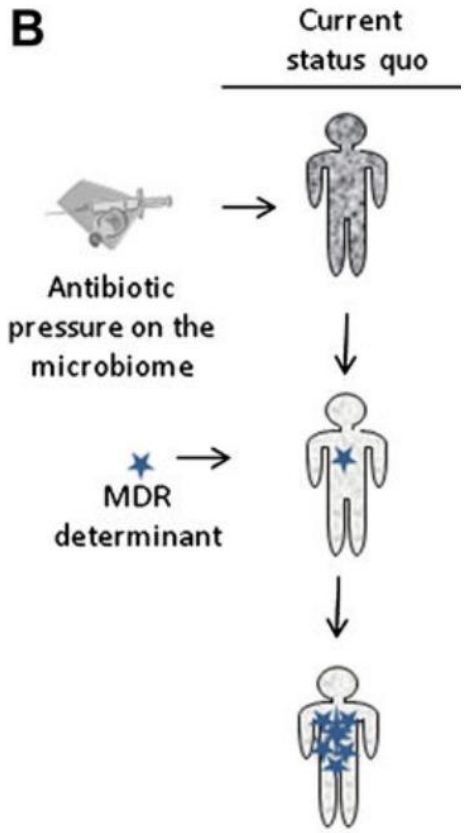
- *Judicious use of antibiotics*
- Nutrition: early EN
- Surgery: ERAS protocol




Preidis and Versalovic 2009, Gastroenterology

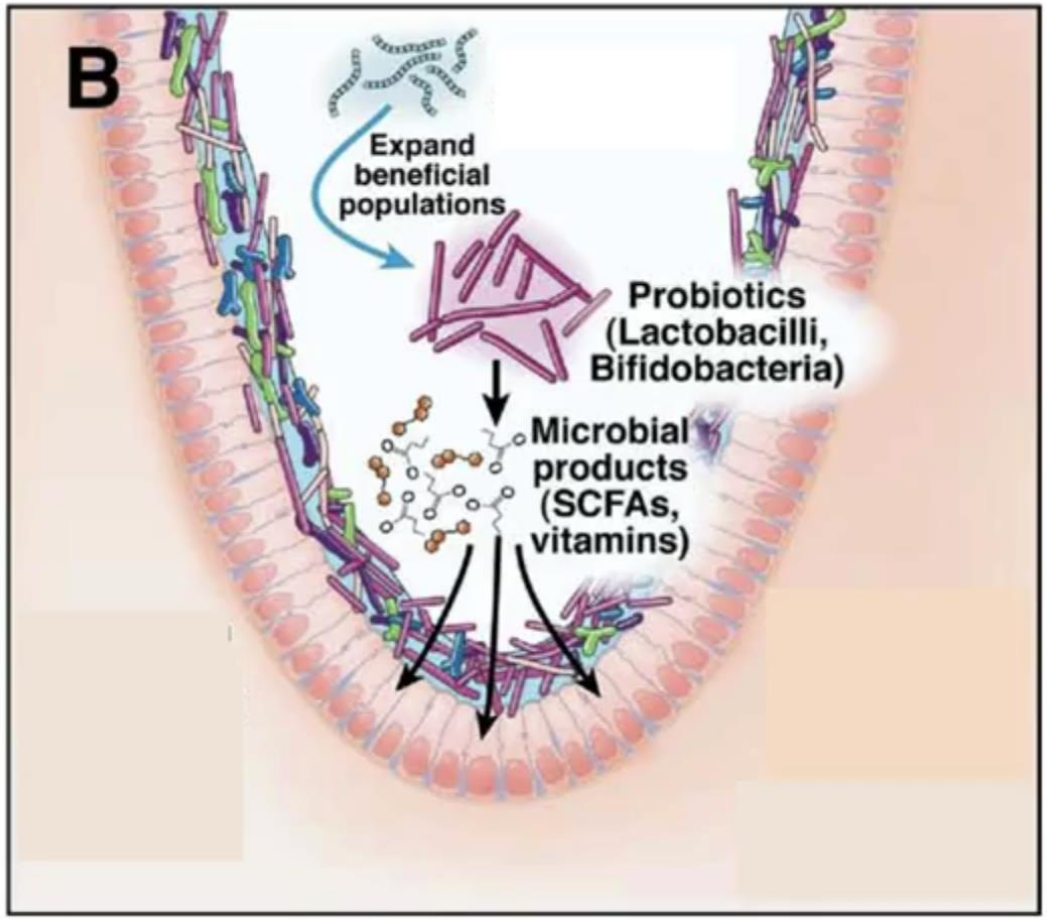
INVITED ARTICLE HEALTHCARE EPIDEMIOLOGY
Robert A. Weinstein, Section Editor

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



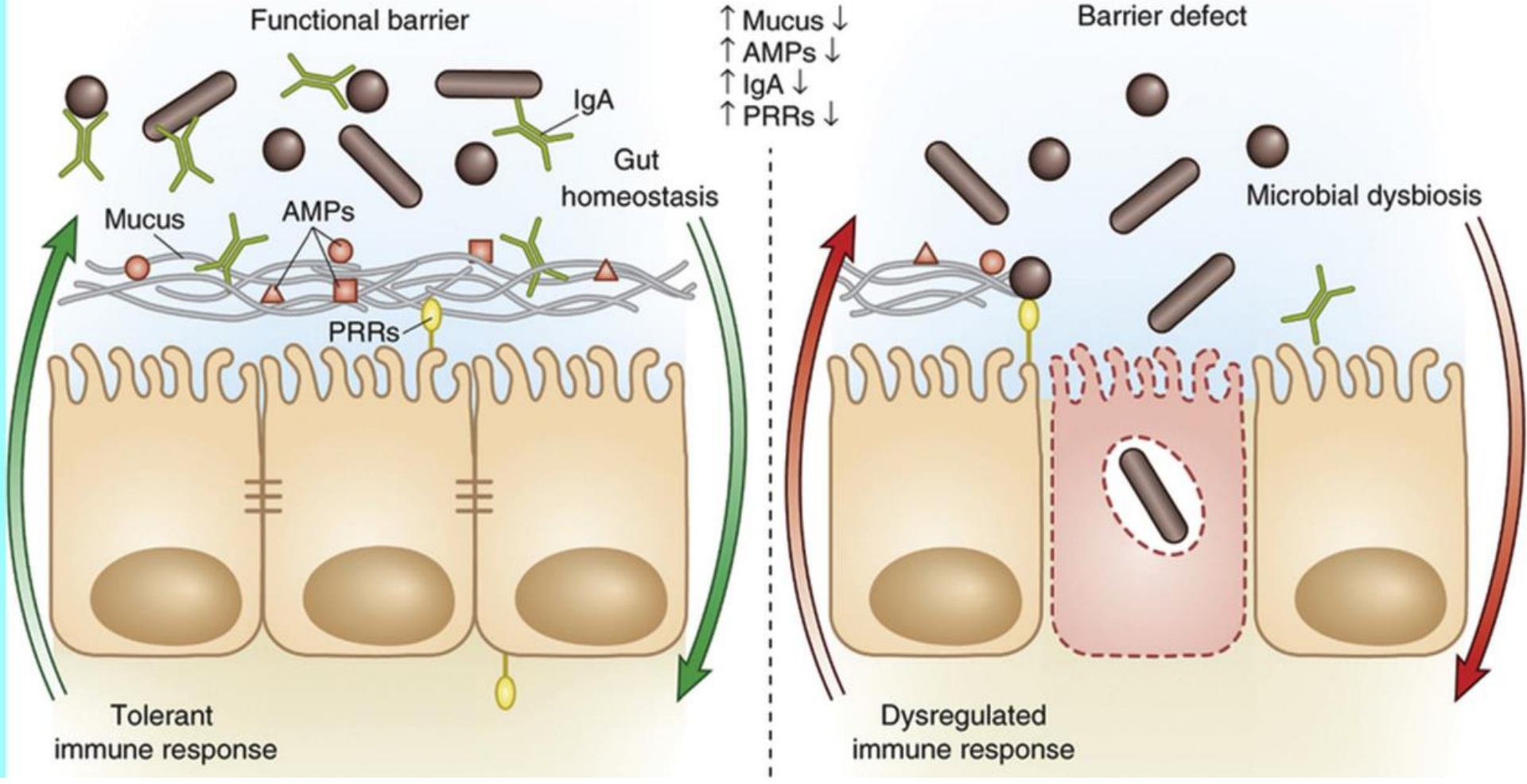
# Potential gut microbiota-based interventions

- Judicious use of antibiotics
- *Nutrition: early EN*
- Surgery: ERAS protocol




Preidis and Versalovic 2009, Gastroenterology

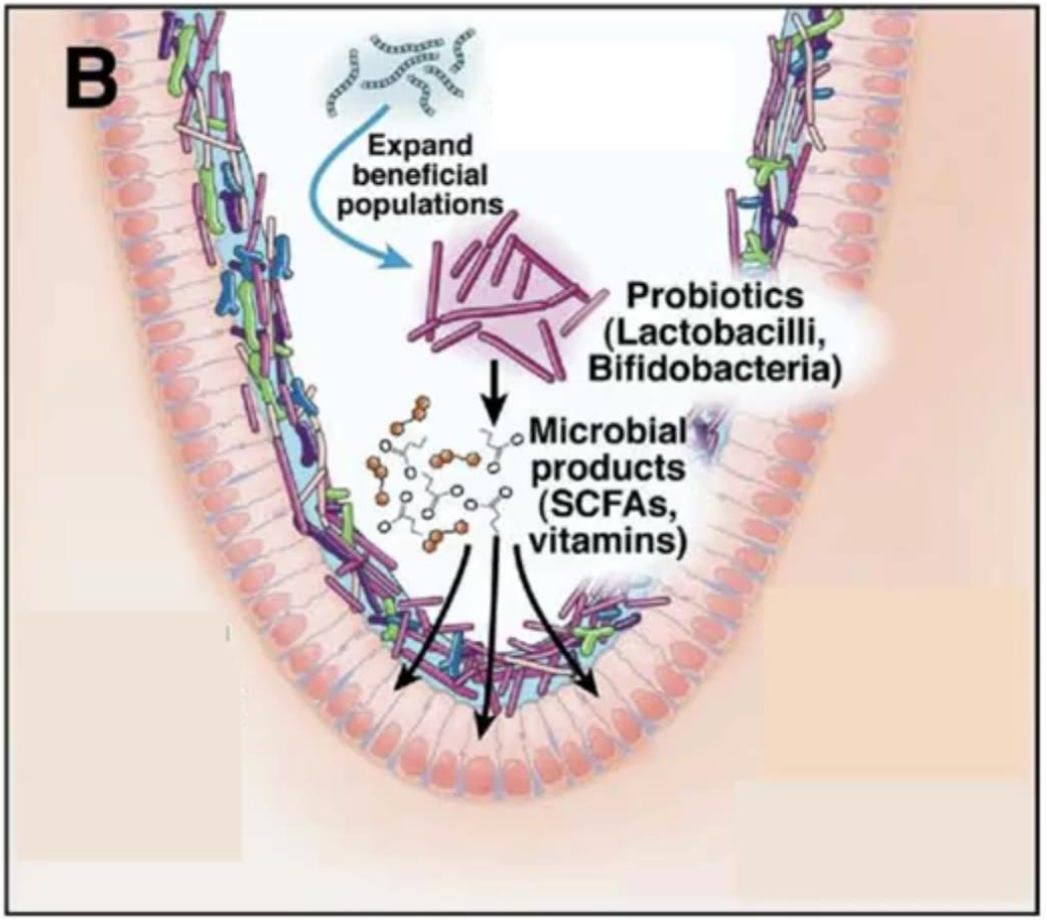
# EN helps maintain gut barrier & reduces bacterial translocation




Brown EM et al. Nat Immunol 2013 Jul;14(7):660-7.

# Potential gut microbiota-based interventions

- Judicious use of antibiotics
- Nutrition: early EN
- *Surgery: ERAS protocol*

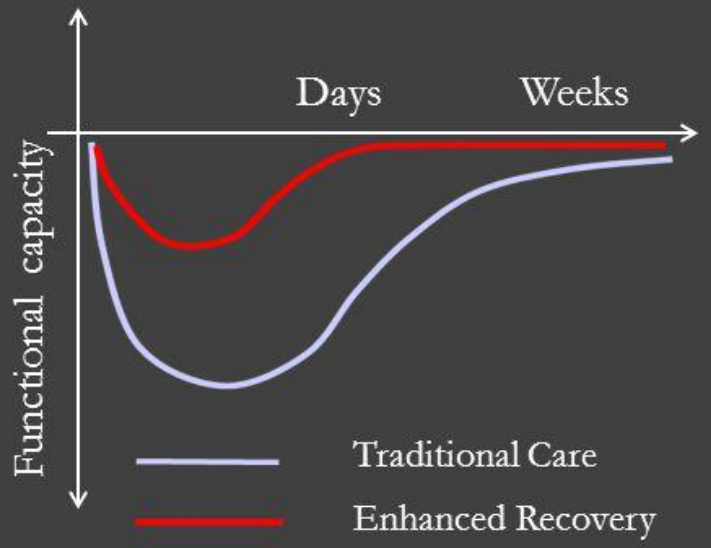



Preidis and Versalovic 2009, Gastroenterology

# What is ERAS ?

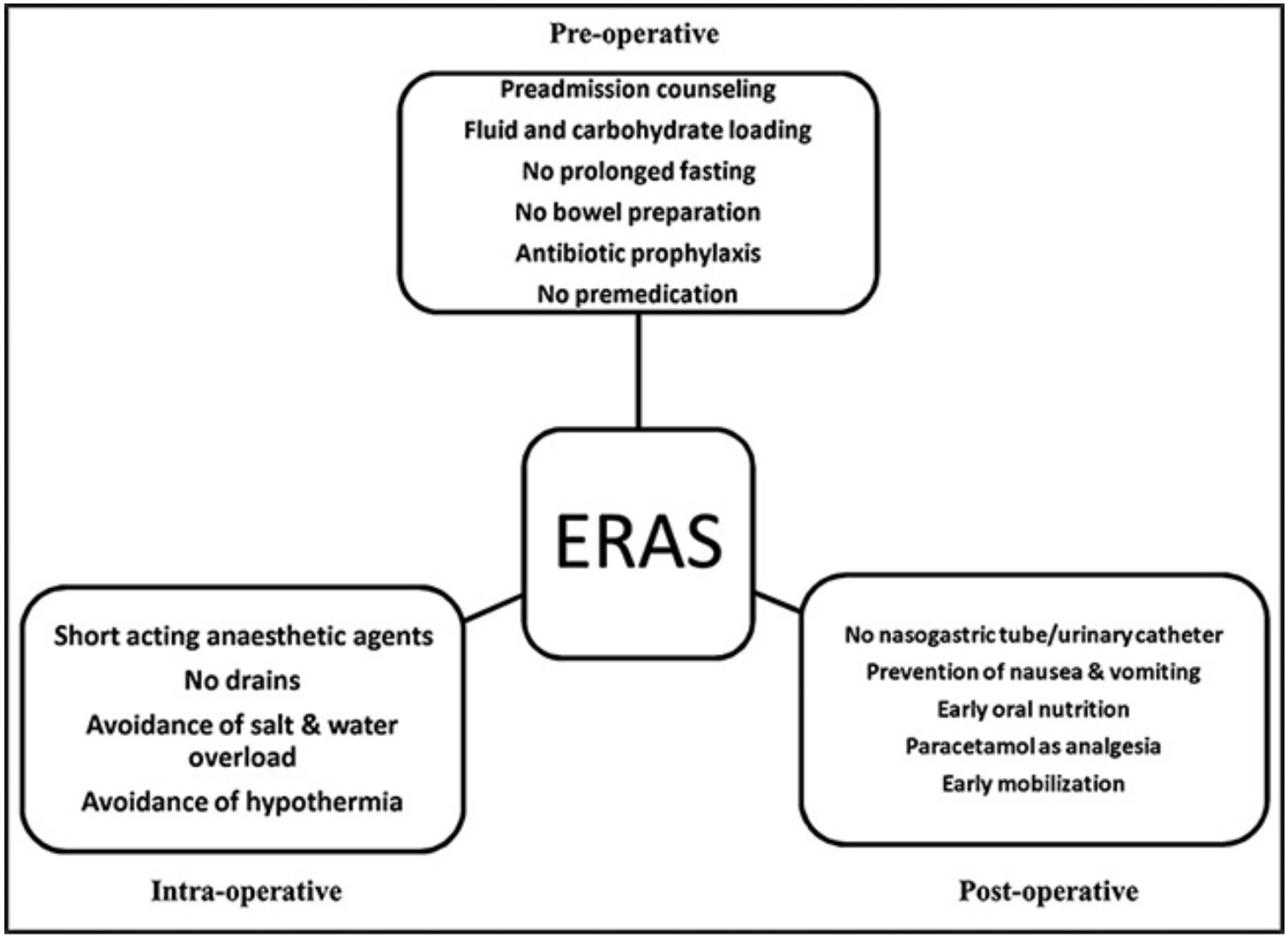
## Standardized protocol for perioperative care

- Multi-modal intervention
- Reduce operative stress
- Support organ function
- Reduced morbidity
- Accelerate convalescence

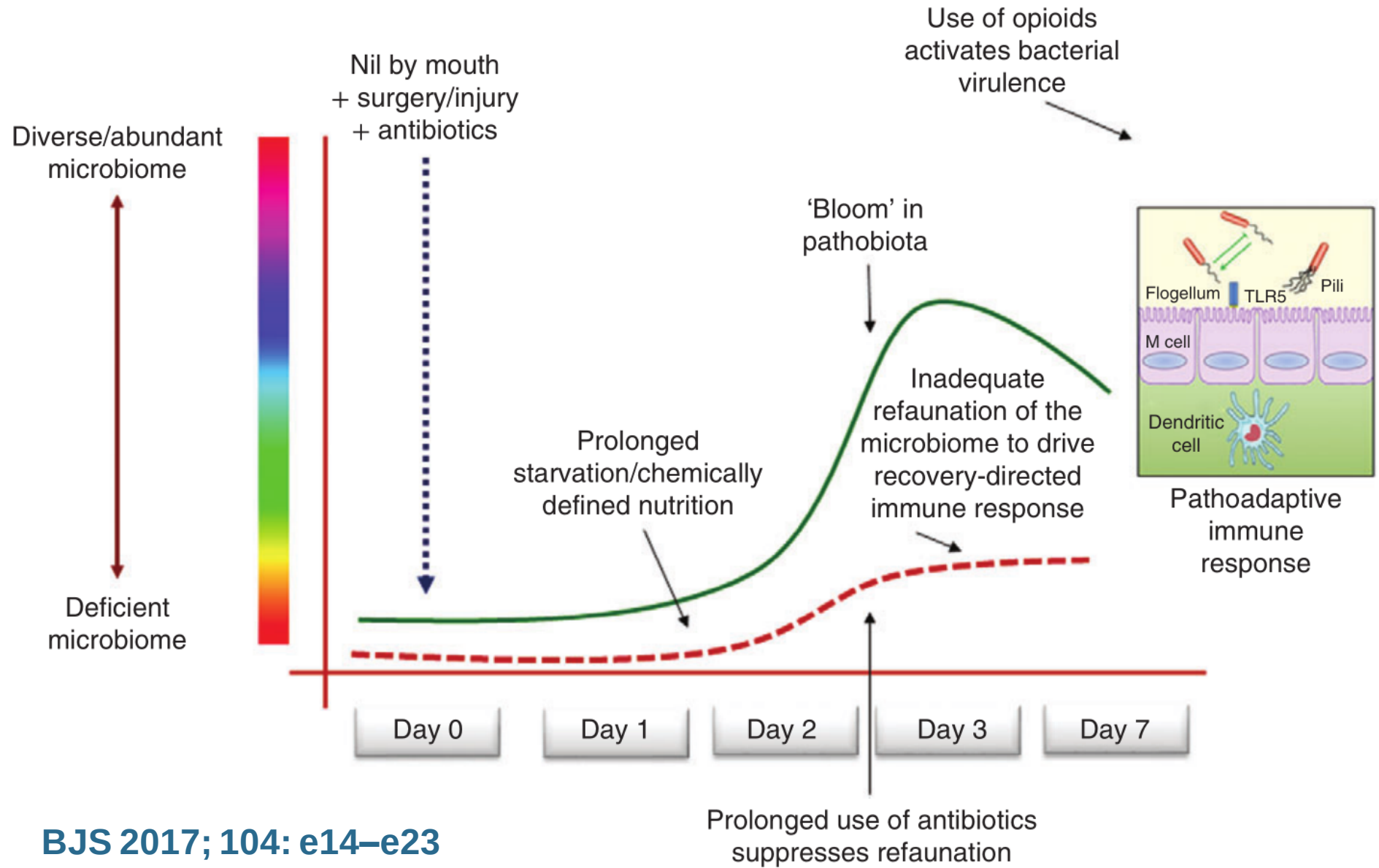



Henrik Kehlet, Br J Anaesth 1997; 78 : 606

# Enhanced Recovery after Surgery (ERAS)

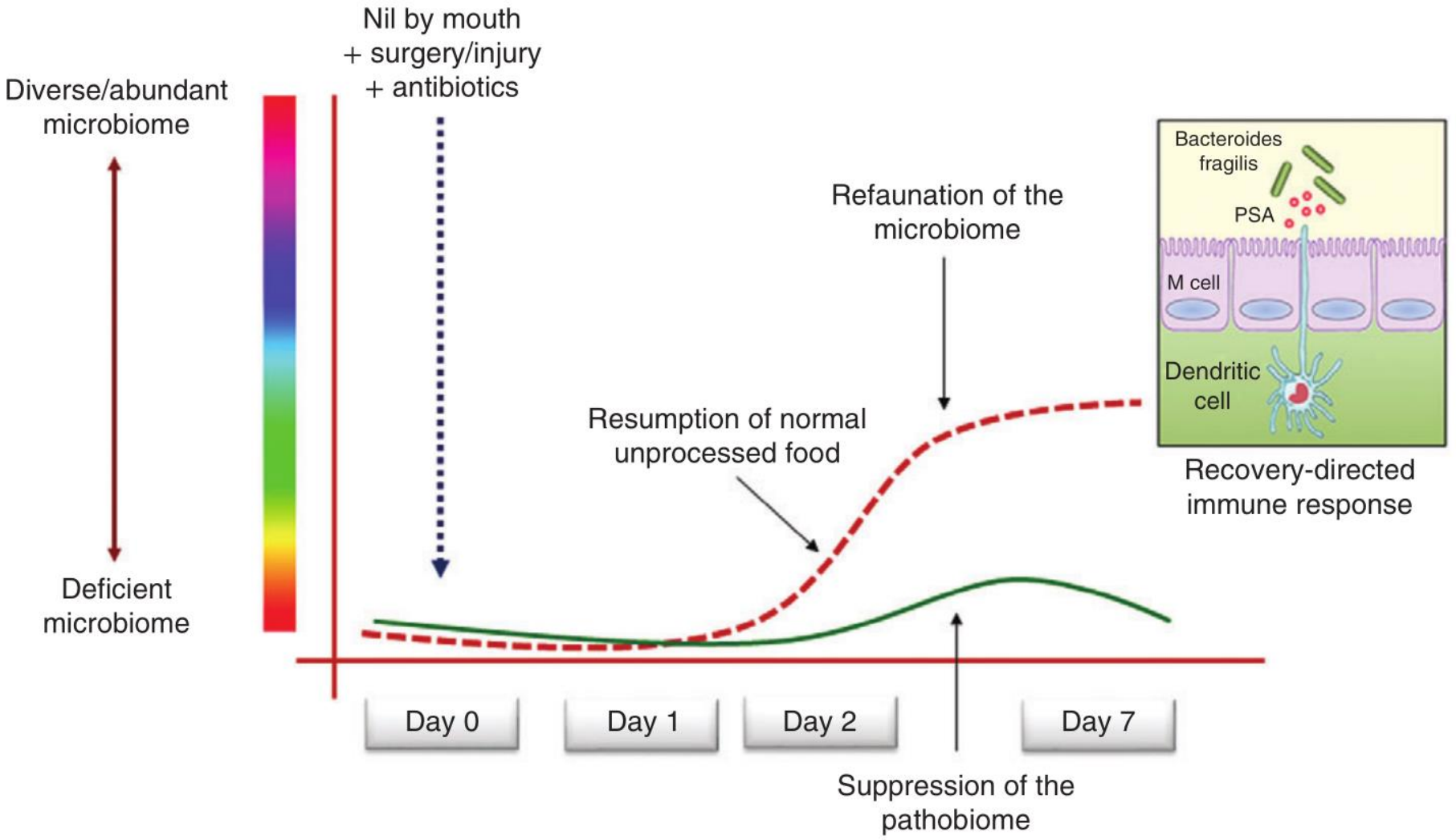


# "Severe" Surgical Injury




BJS 2017; 104: e14–e23

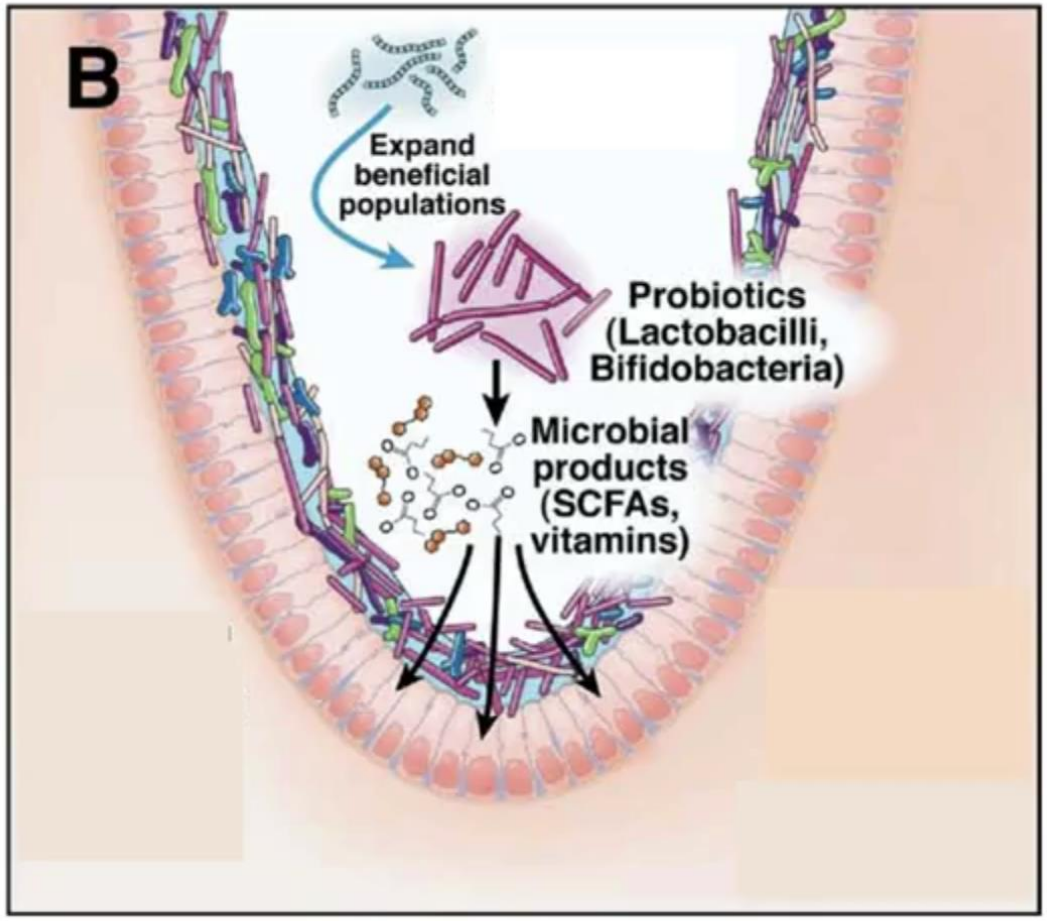
# ERAS: "Limited" Surgical Injury




BJS 2017; 104: e14–e23

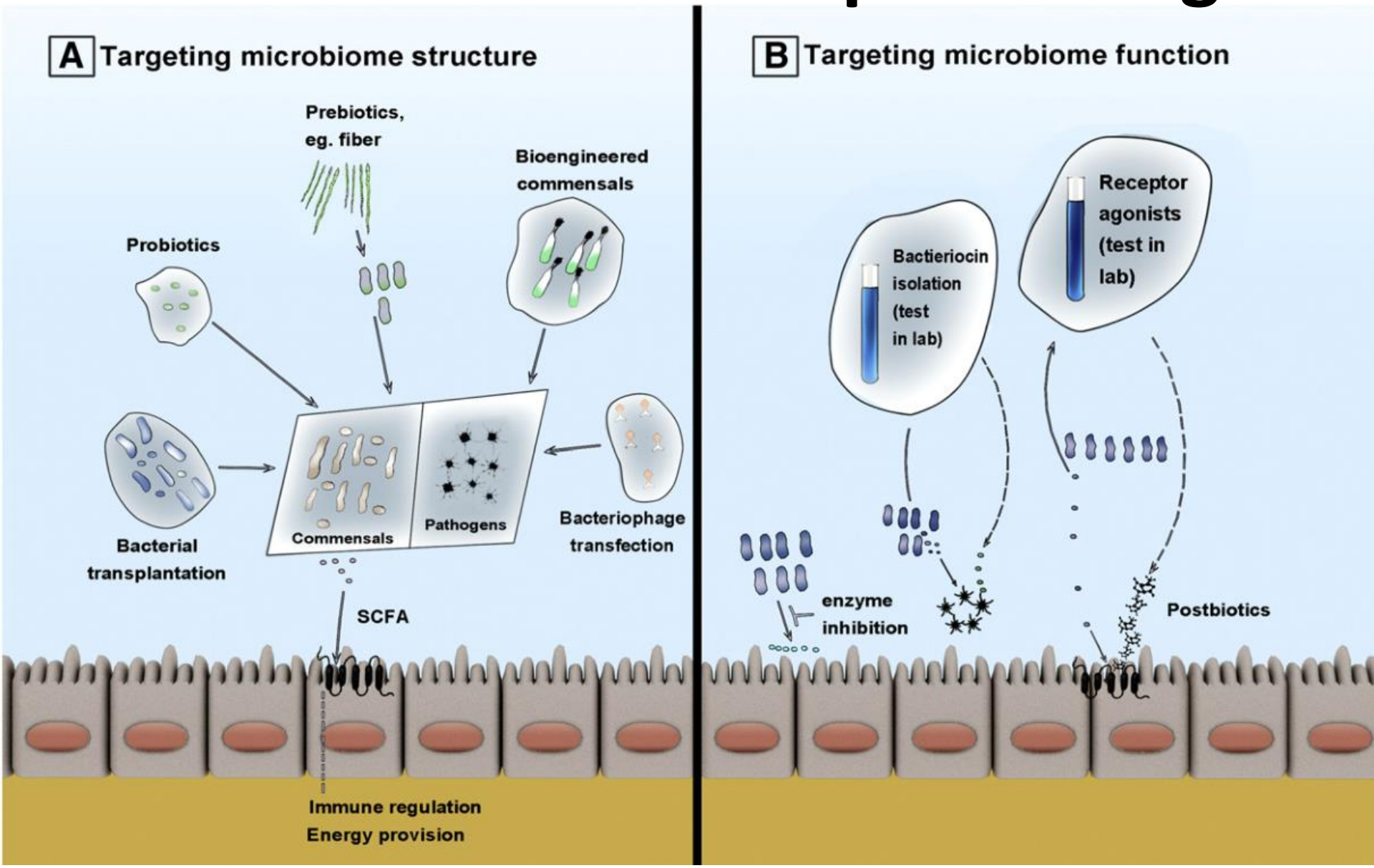
# Potential gut microbiota-based interventions

- Judicious use of antibiotics
- Nutrition: early EN
- Surgery: ERAS protocol
- *Prebiotics*
- *Probiotics*
- *Fecal microbiota transplantation (FMT)*




Preidis and Versalovic 2009, Gastroenterology

# Microbiota as a Therapeutic Target




G.D. Kitsios et al. / Journal of Critical Care 38 (2017) 84–91

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 31, 2013 VOL. 368 NO. 5

# Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

Els van Nood, M.D., Anne Vrieze, M.D., Max Nieuwdorp, M.D., Ph.D., Susana Fuentes, Ph.D., Erwin G. Zoetendal, Ph.D., Willem M. de Vos, Ph.D., Caroline E. Visser, M.D., Ph.D., Ed J. Kuijper, M.D., Ph.D., Joep F.W.M. Bartelsman, M.D., Jan G.P. Tijssen, Ph.D., Peter Speelman, M.D., Ph.D., Marcel G.W. Dijkgraaf, Ph.D., and Josbert J. Keller, M.D., Ph.D.

## ABSTRACT

### BACKGROUND

Recurrent *Clostridium difficile* infection is difficult to treat, and failure rates for antibiotic therapy are high. We studied the effect of duodenal infusion of donor feces in patients with recurrent *C. difficile* infection.

### METHODS

We randomly assigned patients to receive one of three therapies: an initial vancomycin regimen (500 mg orally four times per day for 4 days), followed by bowel lavage and subsequent infusion of a solution of donor feces through a nasoduodenal tube; a standard vancomycin regimen (500 mg orally four times per day for 14 days); or a standard vancomycin regimen with bowel lavage. The primary end point was the resolution of diarrhea associated with *C. difficile* infection without relapse after 10 weeks.

### RESULTS

The study was stopped after an interim analysis. Of 16 patients in the infusion group, 13 (81%) had resolution of *C. difficile*–associated diarrhea after the first infusion. The 3 remaining patients received a second infusion with feces from a different donor, with resolution in 2 patients. Resolution of *C. difficile* infection occurred in 4 of 13 patients (31%) receiving vancomycin alone and in 3 of 13 patients (23%)

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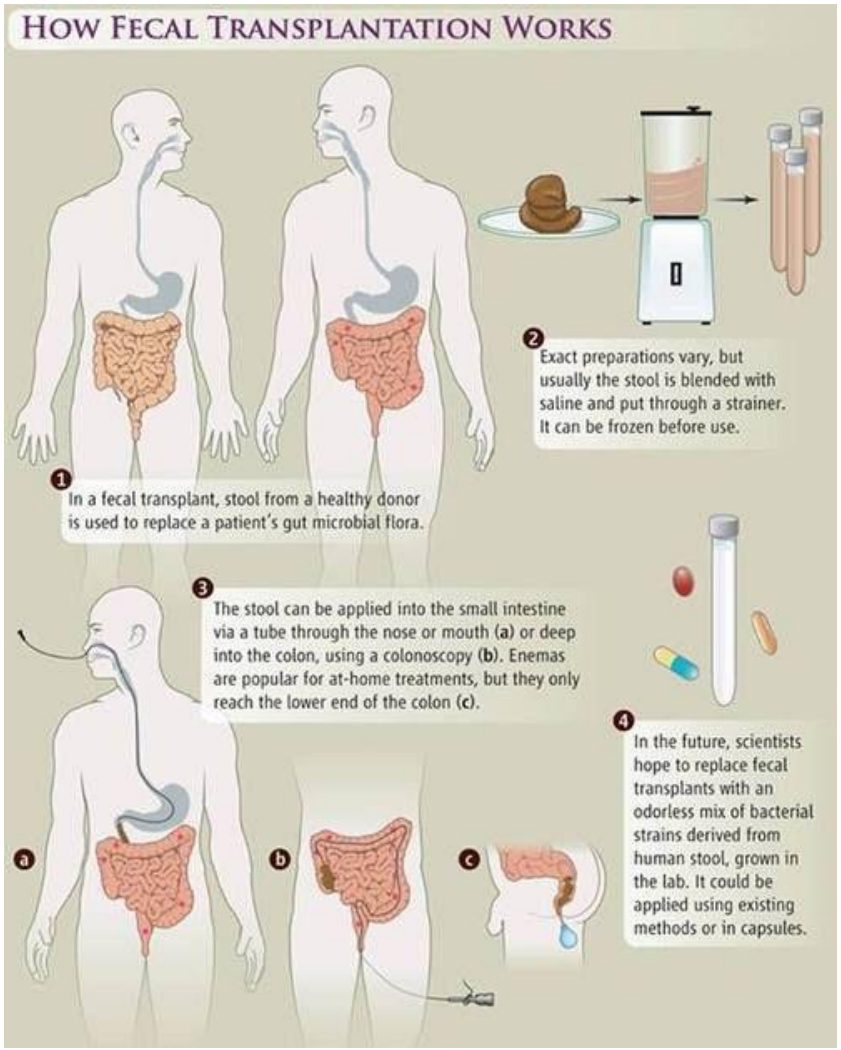

# Take Home Messages (1)

- The microbiome is highly unique to each individual
- “Dysbiosis” occurs during disease states
- The gut-lung axis controls the severity of COVID-19 infection through host immune response and the respiratory microbiome

# Take Home Messages (2)

- The gut-brain axis is responsible for numerous brain functions including mood, cognition, stress, and food intake
- The gut-brain axis is altered in obesity and type 2 diabetes
- Clinical applications are limited by inter-individual microbiome variability, heterogeneity in analyses, lack of access
- Potential applications include prebiotics, probiotics, postbiotics, FMT

# Thank you for your attention