Microbiome Modulation:

A New Frontier or a Passing Fad?

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Division of General and Gastrointestinal Surgery
Medical Director Hospital Nutrition Services
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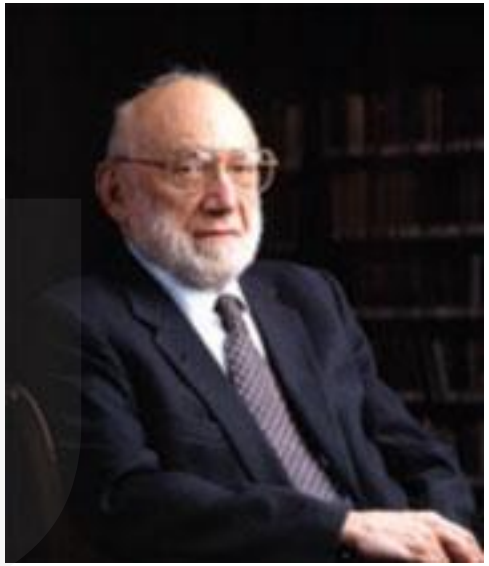
Portland, Oregon

Human Microbiome

- Joshua Lederberg suggested the term microbiome. He won Nobel Prize in 1958 for discovery of genetic transfer in bacteria.
- Described microbiome as the "collective genome of our indigenous microbes (microflora), the idea that a comprehensive genetic view of *homo sapiens* as a life form should include the genes of our microbiome"
- Includes bacteria, fungi, archaea

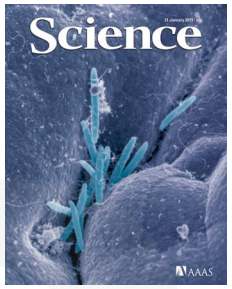


Joshua Lederberg, PhD
1925-2008

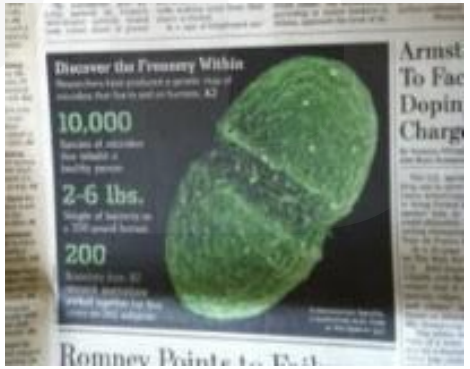
99% of our total genome is absent at birth

Microbiome literature: From quackery to hard science?

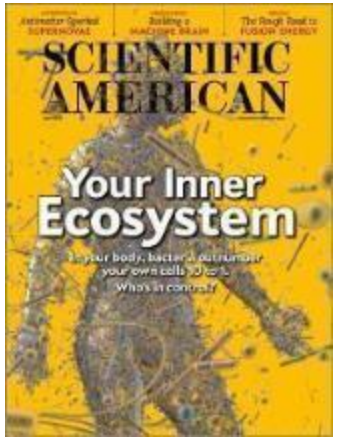
- **Recent lead articles:**
  - **All major medical journals 2018-2025**
  - **JAMA 2017, Nature 2017, Ann Surg 2017**
  - **PNAS 2016**
  - **Nature 2015**
  - **Science 2014**
  - **NY Times 2013**
  - **Wall Street Journal 2012**
  - **Scientific American 2012**
  - **Economist 2012**
  -



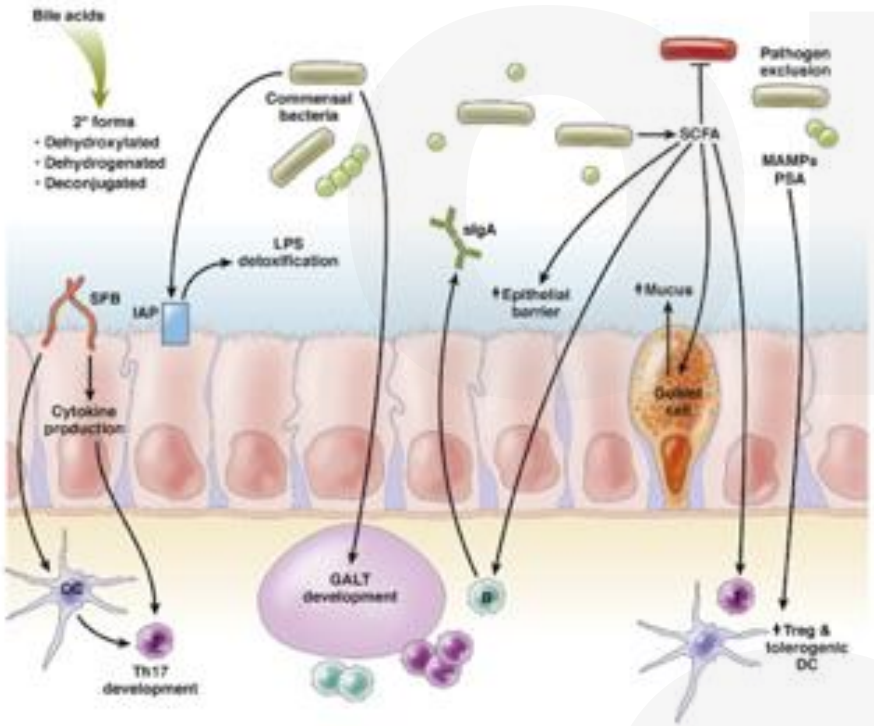
New York Times 2013



Wall Street Journal 2012



The gut and “healthy” microbiome have multiple methods to protect the host



John Alverdy MD

Protective effects of heathy microbiome

Competitive exclusion of pathogens

Enhance epithelial barrier function

Increase IgA production

Promote tolerance (Treg)

Inhibits NFkB translocation from cytosol to nucleus

Stimulate protective mucus

Stabilizes hypoxia-inducible factor

Increases fermentation to produce SCFAs

Normal host protective mechanisms:

Secretory IgA
Acidic gastric environment
Gut peristalsis
Thick mucus barrier
Antibacterial peptides

CL Ohland Cell Molec Gastro Hepat 2015
M Latorre World J Gastro 2015
R Dickson Lancet Respir 2016
Alverdy, Gershuni Nat Rev Gastr Hep 2021
Martindale RG et al Curr Opin Nutr Met Care 2024

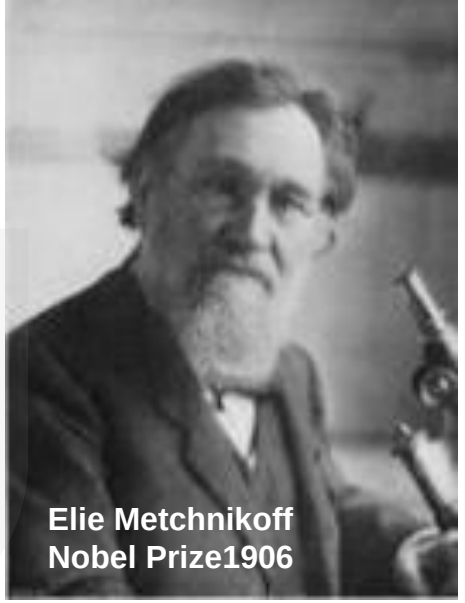
Have we gone too far with specialized formulations for nutrition ?

- Stig passed away in 2023 at 95 years old

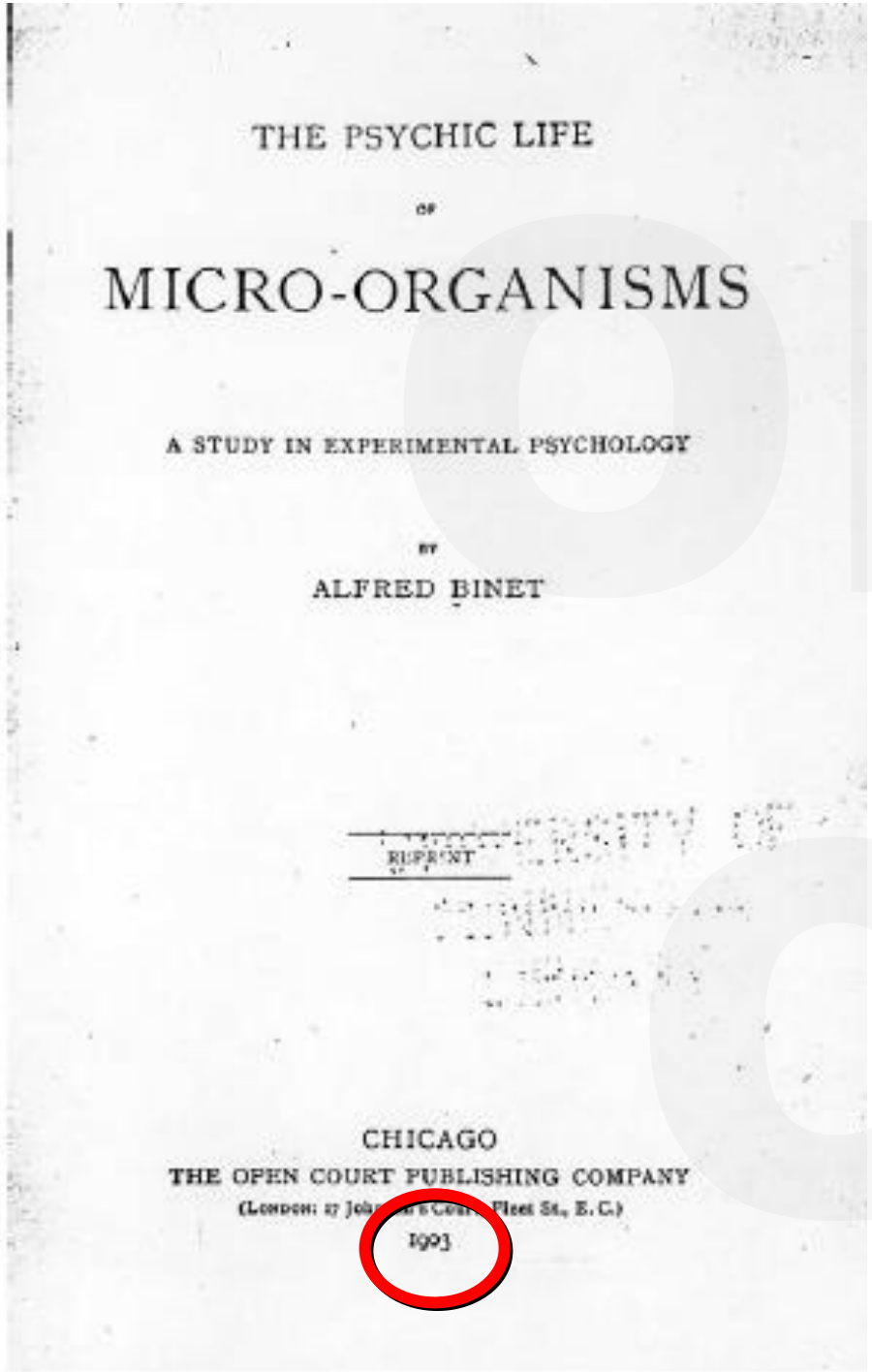
We give our sickest patients the “worst food”

Stig Bengmark 1994

Where “man meets microbe” dynamic mutualism


Elie Metchnikoff
Nobel Prize1906

- Concepts are not new
  - Referenced in Bible, Koran and in ancient Hindu text
  - Metchnikoff “father” of modern probiotic concepts
- Surface area of GI tract 100 to 200 sq meters
  - About ½ the size of a tennis court
- 2 million genes in the bacterial genome vs 20 to 25,000 in the human
  - approximately 1.3 bacterial cells to 1.0 human cells
    - Only about 10 trillion cells in human body
  - Several thousand species of bacterial in human colon, most non-culturable
  - Extensive # of microenvironments (skin, R vs L hand etc)
  - Metagenomics is exploding now that it is cost effective
    - Metagenomics studies the structure and function of nucleotide sequences from all organisms in a sample. The goal is to understand the diversity, abundance, and interaction of microbes in any system. Original studies were to evaluate DNA at bottom of ocean
- We are exposed to “pro and prebiotics” from day one of life
  - 13 to 15% of CHO in breast milk not absorbed by infant
- Probiotics expected to be >100 Billion $ industry by 2030 (87.7 billion in 2023)


THE PSYCHIC LIFE

OF

MICRO-ORGANISMS

A STUDY IN EXPERIMENTAL PSYCHOLOGY

BY

ALFRED BINET

REPRINT

CHICAGO

THE OPEN COURT PUBLISHING COMPANY

(London: 17 John[illegible] Fleet St., E. C.)

1903

- **The Gut Brain connection is not new !**
  - From 1914: *"The control of man's diet is readily accomplished, but mastery over his intestinal bacterial flora is not... They are the cases that present...malaise, total lack of ambition so that every effort in life is a burden, mental depression often bordering upon melancholia...A battle royal must be fought and when this first great struggle ends in victory for the Bacillus bulgaricus it must be kept on the field of battle forever at guard..."*
    - *Stow, Medical Record Journal of Medicine and Surgery, 1914*

on autointoxication and Lactobacillus bulgaricus"

Bond Stow 1914

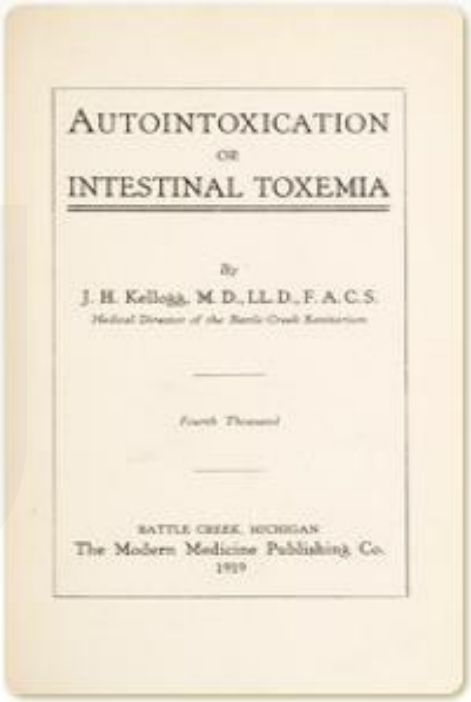
"Just as gut bacteria affect the brain, the brain can also exert profound influences on the gut microbiome—with feedback effects on behavior.

Numerous studies, for example, have shown that psychological stress suppresses beneficial bacteria".

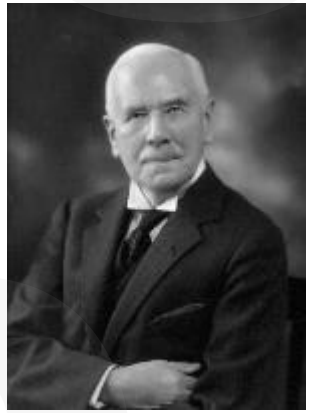
- **Statement from the American Psychological Association**

2012

Evolution of current concepts



- **Ancient Egypt**
  - First description of putrefaction, intestinal autointoxication
- **Hippocrates "all disease begins in the gut" >2000 years ago**
  - another Hippocrates quote "Let food be thy medicine and medicine be thy food"
- **1896 Scientific American publication "Is Insanity Due to a Microbe?"**
- **Autointoxication theories in 1920's**
  - "bacterial therapy" prescribed for psychiatric disorders
    - Several preparations of Lactobacillus marketed to improve mental health
    - Numerous commercial products, stemmed from tx of neuro syphilis
  - Sir W. Arbuthnot- popularized **colectomy** to prevent "autointoxication"



Surgical History

William Arbuthnot Lane (1856–1943): Surgical Innovator and His Theory of Autointoxication

MACKENZIE MORRIS, M.D., THEA PRICE, M.D., SCOTT W. COWAN, M.D., CHARLES J. YEO, M.D., BENJAMIN PHILLIPS, M.D.

  - Concepts fell from favor in late 1920's -1930's
    - Lack of sound mechanistic understanding or data at the time
      - **Blood brain barrier felt to be impermeable**
      - Fleming's discovery of Penicillin 1928 (Florey and Chain at Oxford purified, studied 1939)
        - First patient treated was Albert Alexander 43 yo London policeman, treated Feb 12, 1941
- **Antibiotic Era**
  - Several reports of anxiety, depression, etc associated with antibiotic intake, little objective data

Rogers GB et al Molecular Psychiatry 2016
Bested AC Gut Pathogens 2013
Kellogg JH Autointoxication 1929
Bransfield RC et al Healthcare 2023

Historical Perspective: The roots of the concept

MULTIPLE ORGAN FAILURE

Surg Gyn Obstet 1977

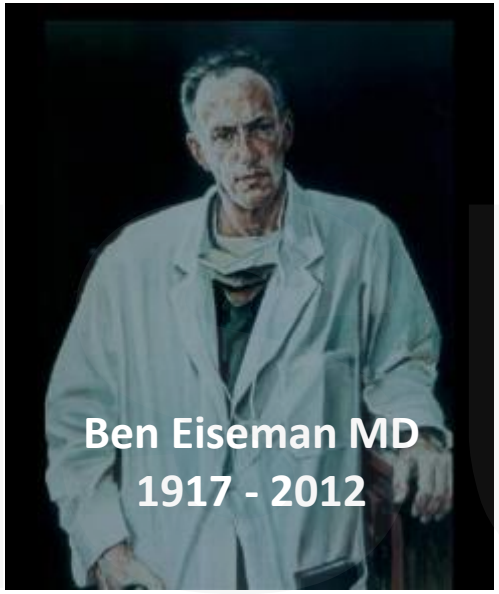
B. Eiseman, M.D., F.A.C.S., R. Beart, M.D., *and* L. Norton, M.D., F.A

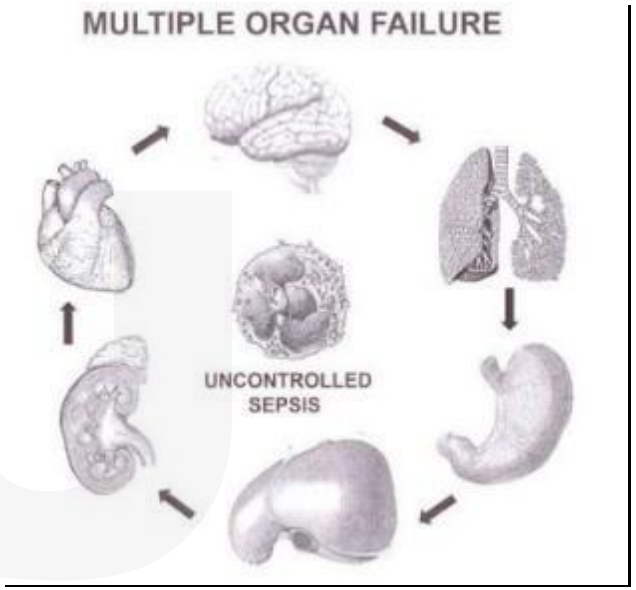
Denver, Colorado

Multiple-Organ-Failure Syndrome

CJ Carrico (Archives Surg 1986;121:196)

C. James Carrico, MD; Jonathan L. Meakins, MD, DSc, FRCSC, FACS; J. C. Marshall, MD, FRCSC; Donald Fry, MD; Ronald V. Maier, MD





- Pasteur in 1868 suggested the GI tract can release systemic factors that cause fever, tachycardia and obtundation
- MOF described 1969-77 primarily attributed to sepsis [1]

  Assumed intra-abdominal abscess, need for exploratory laparotomy
- Awareness of non-bacteremic clinical sepsis [1]

  Clinical course identical to those with bacteremia

  No clinical focus of infection was ever isolated or present in > 40%
- Marshall and Meakins suggested GI tract was "motor" of MOF syndrome in 1985

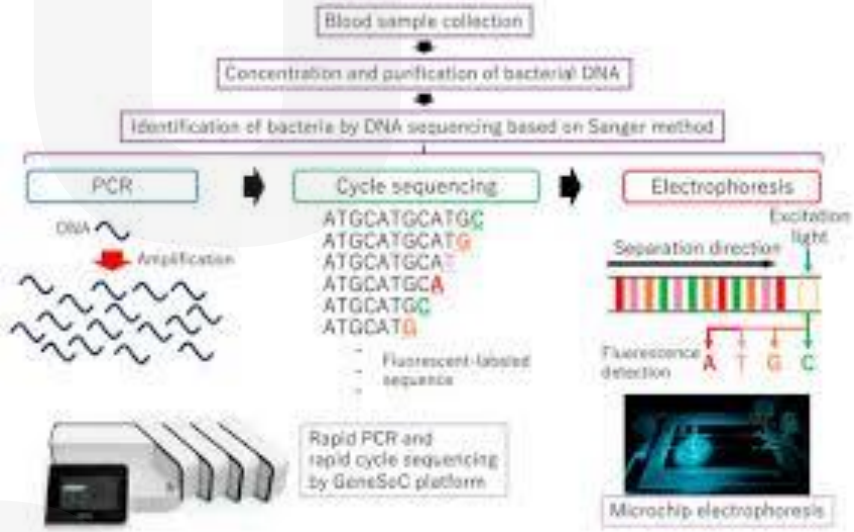
  Described loss of GI barrier function, pathogenic organisms enter the systemic circulation
- Documented bacterial translocation to mesenteric lymph nodes in post-op pts (5-21% all gut origin) [2]

(1)CJ Carrico (Archives Surg 1986;121:196)
(2) EA Deitch (Surgeon 2012;10:350)
(3) Patel J et al Curr Gastro Reports 2025

Searching for the link between microbiome and human maladies

- Diseases commonly accepted to be associated with alterations in microbiome: obesity, inflammatory bowel, arthritis, autism, colon cancer, depression, type 2 DM, autoimmune diseases, etc etc etc

- Why is this happening now. Rapid DNA sequencing has led to the explosion of knowledge



- Challenge now is attempting to understanding the data
  - "…strategies that leverage the existing knowledge from correlation to causation and ultimately to transition into therapies."

We are at a critical inflection point – transitioning from description to developing disease specific treatment strategies

Gilbert JA et al Nature Medicine 2018

Why do current strategies for optimal nutritional therapy neglect the microbiome?

Stephen A. McClave M.D. [a,*], Robert G. Martindale M.D., Ph.D. [b]

- **Current enteral and parenteral nutrition therapy does not specifically address evolutionary interaction and mutualism between host and luminal bacteria**
  - **Current dogma has primary concern for:**
    - **Macronutrients (fat, CHO, protein), micronutrients (vitamins and trace minerals)**
  - **Starting to consider gut derived metabolites which can signal cellular responses both locally and systemically (example - butyrate)**
    - **Amount of interactions and crosstalk between microbiome, metabolic end products, host local and systemic immune system, gut epithelial is currently too complex**
      - **Human gut heterogeneity- approximately 4000 species, 15,000+ metabolites, etc**
      - **It will take "big data" to sort out**

McClave SA, Martindale RG. Nutrition 60:100-105, 2019

Gut microbial metabolites and its impact on human health

Shahrose Rahman, Amber L. O'Connor, Sarah L. Becker, Ranish K. Patel, Robert G. Martindale, Vassiliki Liana Tsikitis

Oregon Health and Science University, Portland, OR, USA

Annals of Gastroenterology 2023

Table 3 Effects of tryptophan metabolites

Tryptophan		
Food sources	Various metabolites	Documented effects
Meats, fish, eggs, nuts	Indole-derivatives, tryptamine, and skatole	Antimicrobial effects Modulating innate and adaptive immune system Maintain intestinal barrier Anti-obesity: affects insulin secretion, suppress appetite, slow gastric emptying Acts as free oxygen radical scavenger

Table 5 Polyamines and their effects

Polyamines	Source of polyamines	Documented effects
Putrescine Spermidine Spermine	Upper gastrointestinal system – Derived from food Lower gastrointestinal system – Synthesized by gut microbiome	Gene and stress regulation Cell proliferation and differentiation Regulation of enzymatic activity Antioxidant effects, inhibits production of inflammatory cytokines Undetermined role in cancer

Table 4 Bile acids and their effects

	Site of production	Documented effects
Primary bile acids – Cholic acid – Chenodeoxycholic acid	Liver, through cholesterol metabolism	Aid with fat digestion and nutrient absorption Metabolic regulation Mucosal barrier protection
Secondary bile acids – Deoxycholic acid – Lithocholic acid	Produced in colon through interaction between primary bile acids and gut microbiota.	Inhibit *Clostridioides difficile* spore germination Low levels seen in inflammatory bowel disease Associated with colorectal and hepatocellular carcinogenesis

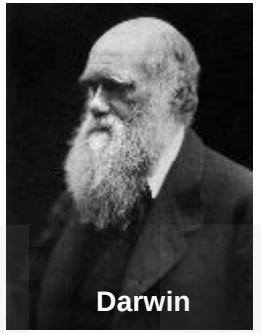
Table 1 Effects of the various short chain fatty acids

Short chain fatty acid	Mechanism of production	Documented effects
Acetate	1.Directly from diet 2.Endogenous through acetyl-CoA 3.Dietary fiber fermentation	Increased satiety, weight loss, suppress appetite, improves insulin sensitivity, reduce proinflammatory cytokines Substrate for lipogenesis May serve to promote cancer cell survival
Propionate	1.Dietary fiber fermentation: Succinate pathway, Acrylate pathway, or Propanediol pathway	Intestinal and hepatic gluconeogenesis Anti-obesity effect: reduces weight gain, intra-abdominal adipose tissue distribution. Decreases proinflammatory cytokines
Butyrate	1. Dietary fiber fermentation: Acetyl-CoA pathway, Lysine pathway, Glutarate pathway, Succinate pathway	Maintains mucosal integrity Modulates both local and systemic immunity Protects against colonic neoplasia, Anti-obesity effects: stimulates the release of anorexigenic hormones and leptin synthesis

Table 2 Effects of TMAO

Trimethylamine-N-oxide (TMAO)		
Food Sources	Main precursors	Documented effects
Eggs, milk, meat (red meat, poultry), and fish	Phosphatidylcholine L-carnitine Ergothioneine	Increased levels are associated with increased risk of major adverse cardiovascular events

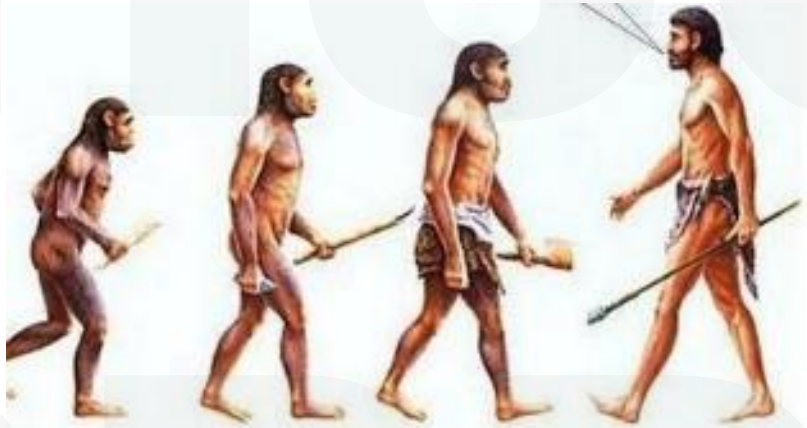
The "Western" Diet:
Is inflammatory disease epidemic being at least partially driven by microbiome changes?



Can we evolve enough fast enough for our dramatic change in diet and lifestyle ?

- Sedentary lifestyles
- Newborns in USA
  - 1/3 C section, majority bottle fed
- Immunizations
- Domestic pets
- Decrease in parasitic infection
- Refrigeration
- Sanitation and hygiene standards
- Urban life in cities and concrete
- Major dietary changes
  - Fats, protein, fiber, additives, emulsifiers, sweeteners, anti-oxidants, preservatives, refining and de-germination of grains, highly "refined" and processed diets, microplastics
- Dramatic changes in the way we feed our sick in patients
  - Increased use of antibiotics
    - Indicated or not !
    - Now beginning to understand "collateral damage" of antibiotics

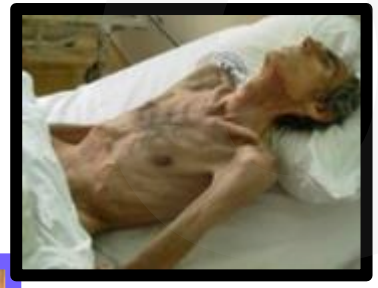
Go back we messed up



Clinical Nutrition Continues to Evolve

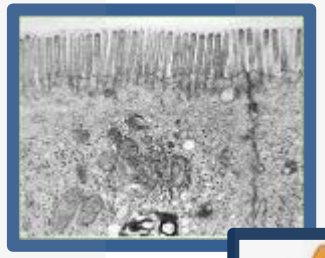
Nutrition Support

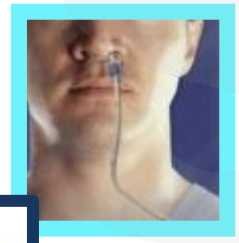
1960-1982



- "Skeletons in the Closet"
- PEM in 50% pts US hospitals
- Support to prevent PEM
- PN-based

1982-2014

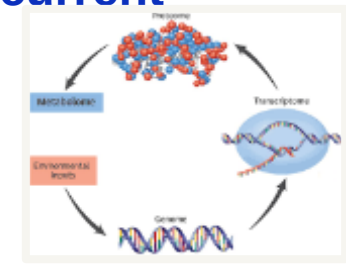


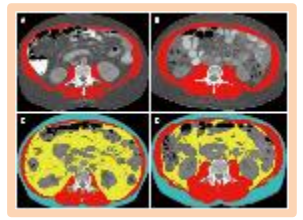


- EN for macronutrients
- EN for non-nutritional benefits
  - Immune/metabolic-modulation
  - Attenuates inflammation
  - Maintains gut integrity
  - Maintaining the microbiome
- Increase protein delivery
- Immunonutrition – surgery, critical care

Nutrition Therapy

2015- to current





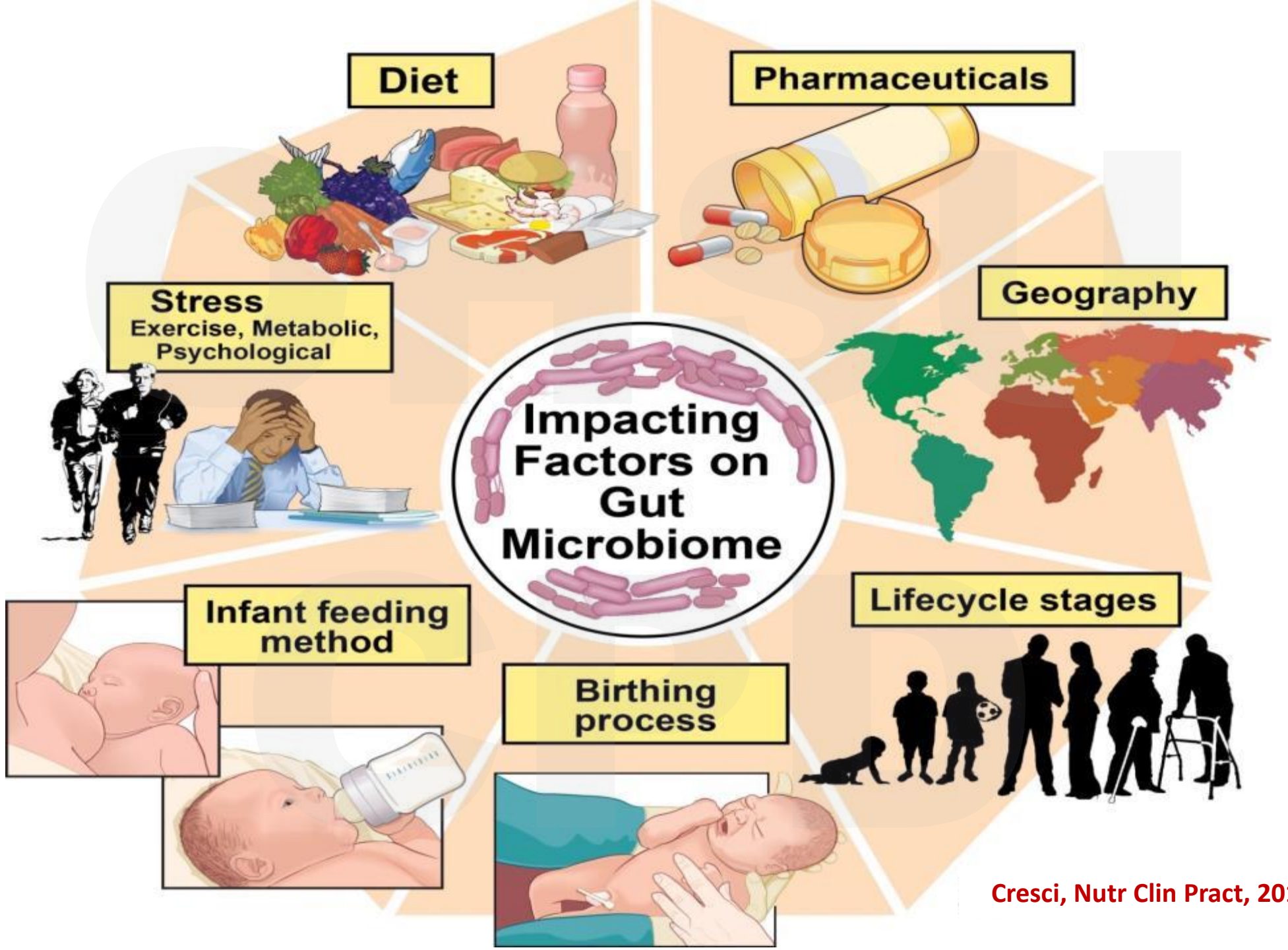
- EN remains 1st choice
- "Gradual" increase in nutrient delivery
- Better understanding of physiology of IMN
  - Arginine, FO, Gln, nucleic acids
  - SPM's
- Altering the Microbiome now a focus
  - Fermentable fibers in ICU
  - Prevent microbiome to pathobiome
- Metabolomics—"omics"
- Resistance exercise
- Nutrition focus on the mitochondria

ICU admission is an assault on our microbiome ?

- **Broad spectrum antibiotics**
  - Changes noted within hours, decrease alpha diversity
- **Oral antiseptics**
- **PPI / H_2RA**
- **Vasopressors**
  - Changes in pH ,decrease pO_2 increase pCO_2
    - This activates virulence gene expression in bacteria
- **Opioids**
  - Decrease motility and bacterial clearance mechanisms
  - Alters bacterial pathogenicity
- **Decrease in luminal nutrient delivery**
  - Delays in feeding
  - Parenteral nutrition
    - Gut luminal scarcity of nutrients
  - Altered bile salt production
  - Decrease IgA production with lack of EN feeding
  - Decrease SCFA substrate
- **Invasive devices**
  - Ventilators
  - Central lines

Gilbert JA et al Nature Medicine 2018

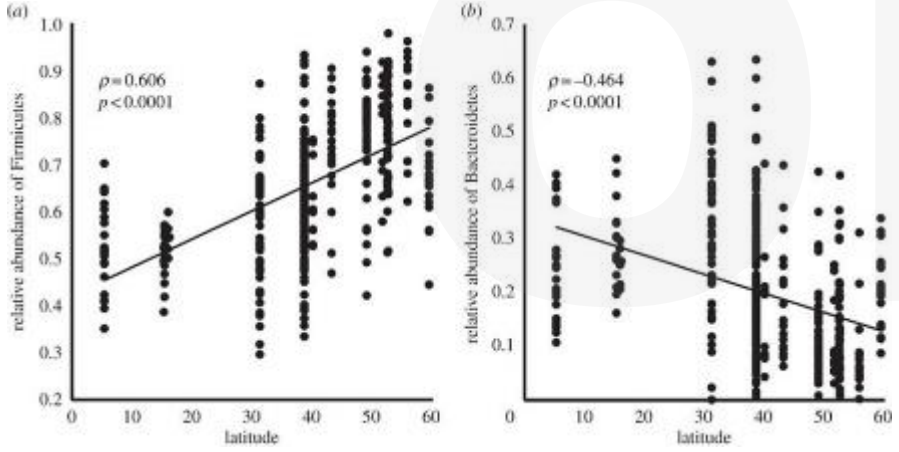
Miller WD Alverdy JC J Inf Dis 2021



Cresci, Nutr Clin Pract, 2015

It takes very little to rapidly change our microbiome

- International travel

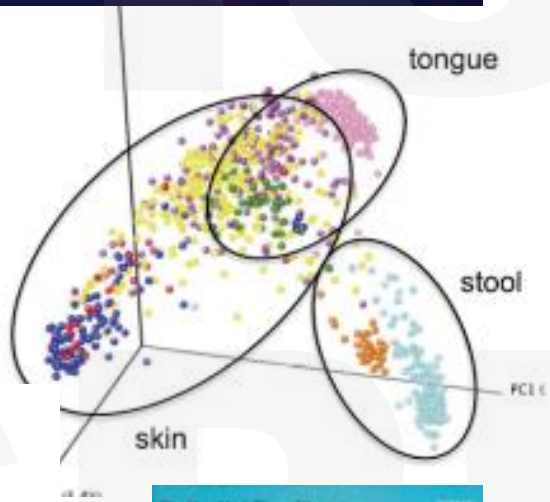


What about space travel?

Microbial Tracking-2 (MT-2) studies by NASA 2024 on the International Space Station

94 fungal strains
96 bacterial strains of 14 species.
Staphlococcus – bacterial
Malassezia –fungi
Multi-Resistance and biofilm formation increasing

- Cohabitating with pets



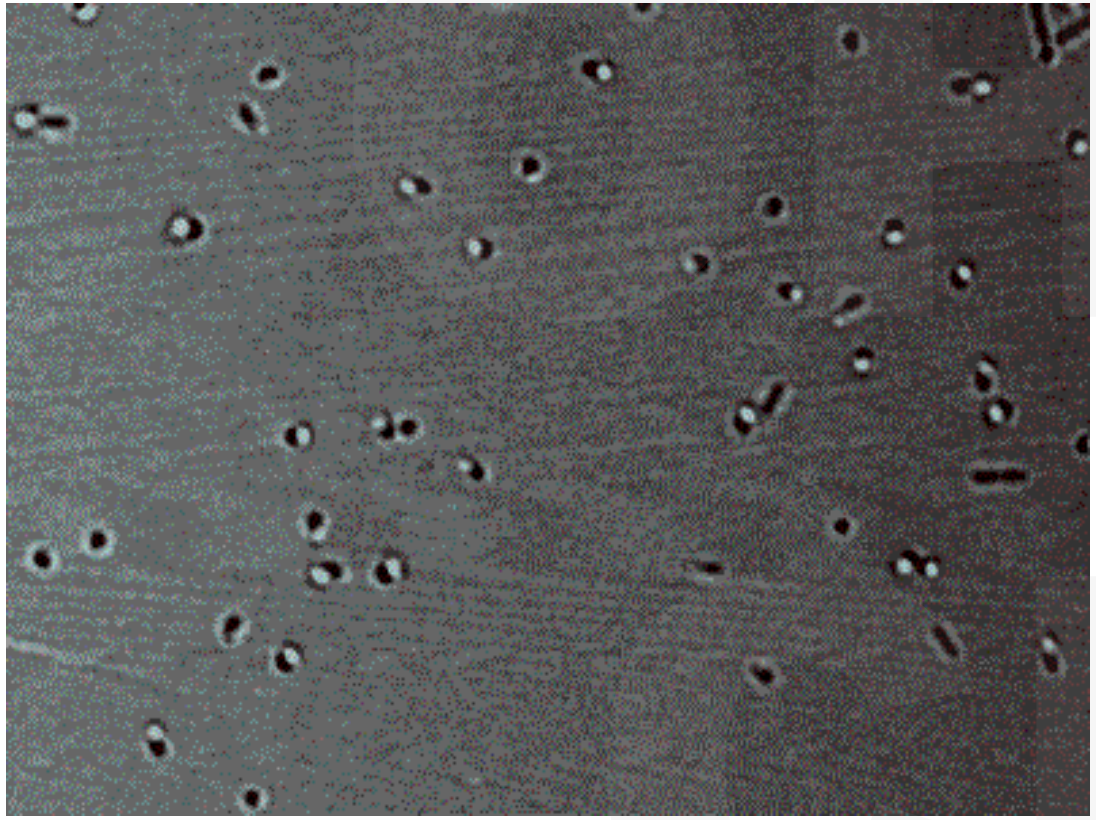
Cohabiting family members share microbiota with one another and with their dogs

Se Jin Song[1], Christian Lauber[2], Elizabeth K Costello[3], Catherine A Lozupone[4†b], Gregory Humphrey[2], Donna Berg-Lyons[2], J Gregory Caporaso[5,6], Dan Knights[7,8], Jose C Clemente[4†a], Sara Nakielny[9], Jeffrey I Gordon[10], Noah Fierer[1,2], Rob Knight[11,12*]

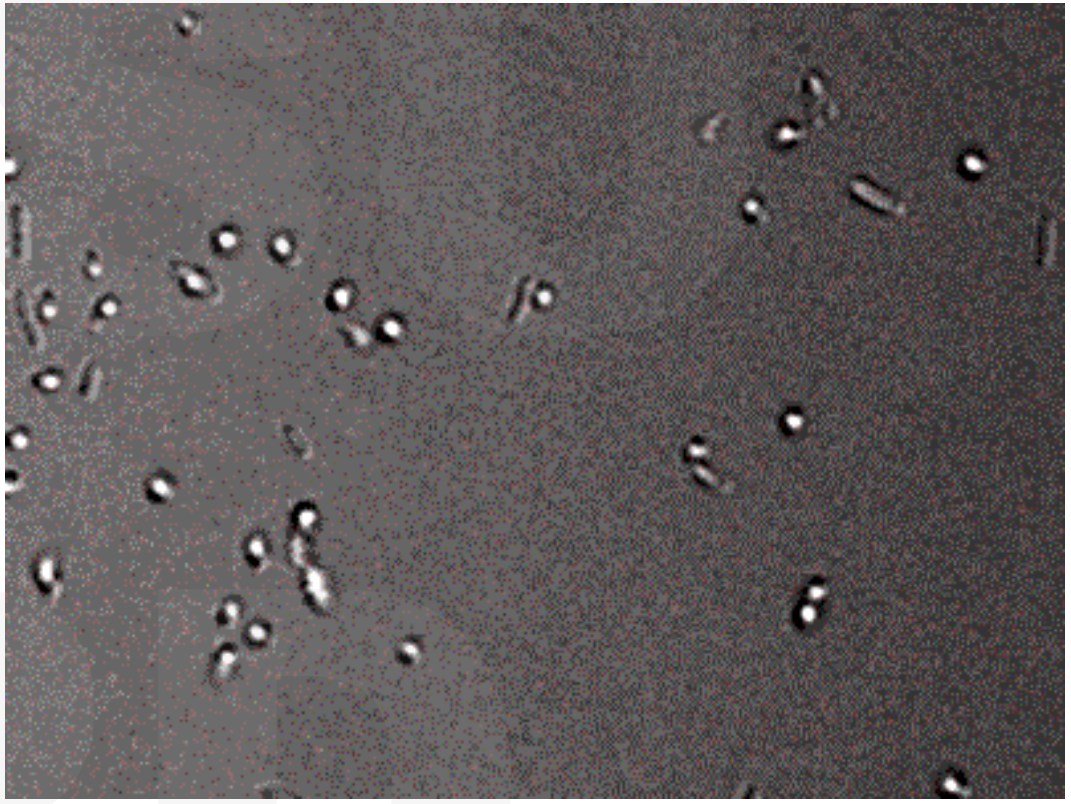
David LA et al Genome Biol 2014

Song SJ et al Elife 2013

It takes very little to cause the normal non-pathogenic bacteria to turn against us: *P. aeruginosa* PA27853/PLL-RedT1 exposure to host tissue factors released during surgical injury induces virulence activation



Host tissue factors: Norepi, hypoxia, host defense peptides LL 37



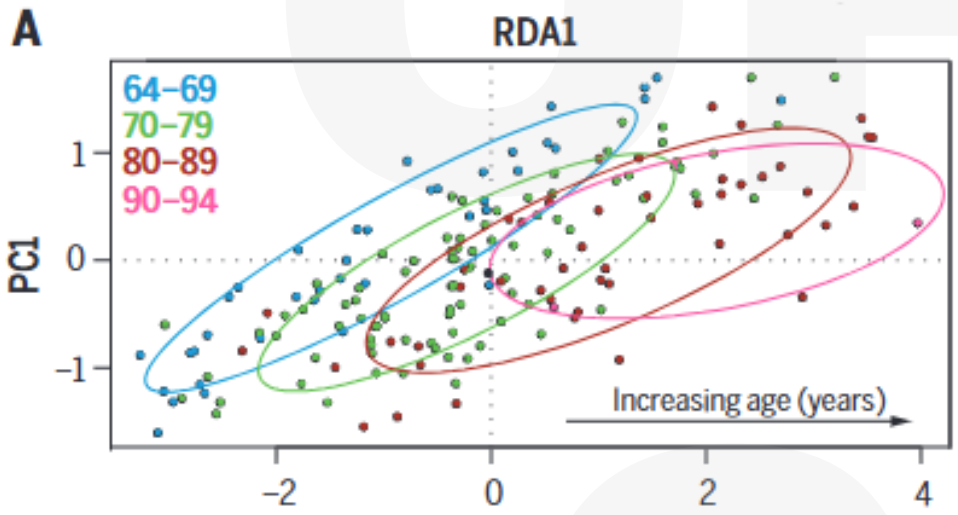
vehicle

Alverdy J et al Ann Surg 2000
Kohler JE et al Am J Physiol.GI Liver Physiology 2005
Strempel N et al PloS One 2013

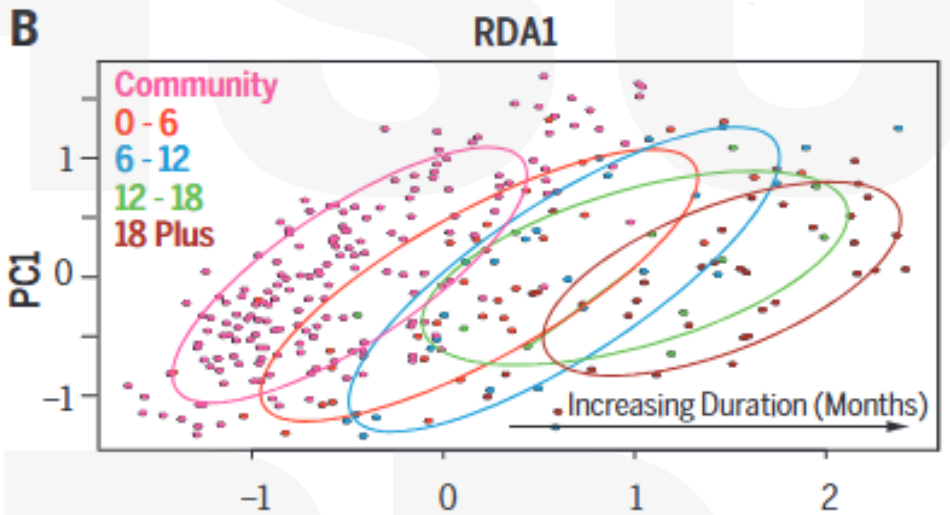
Gut microbiota and aging

Paul W. O'Toole* and Ian B. Jeffery

Science 350(6265) 1214-1215. 2015



Distribution by age

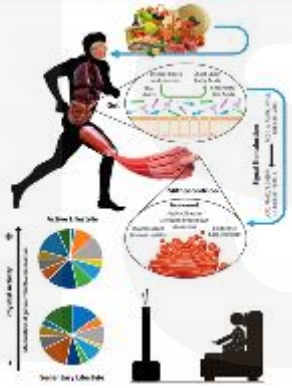


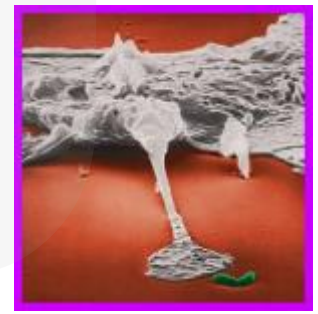
Distribution by months in "elderly" community living

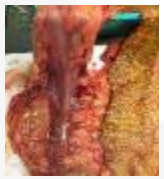
"with chronological aging, loss of diversity in the core microbiota groups is associated with increased frailty"

Does Modulating the Microbiome Really Have Data to Support the Claims ?

- Enhancing immune response to viral challenge[1]
- Short chain fatty production[2,3,4]
  - Anti-inflammatory (local and systemic)
  - Enhance WBC function
  - Decrease insulin resistance
  - Decrease cancer development
  - Enhanced muscle function
  - Enhanced mitochondrial biogenesis
- Decrease sick days from work[5]
- Decrease duration of URI symptoms[6]
- Decrease antibiotics, MD visits, missed preschool[7]
- Decrease gestational DM[8]
- Decrease
  - necrotizing enterocolitis
  - C. difficile
  - VAP +/-
  - Post op surgical infections
  - Increase viral clearance in COVID 19







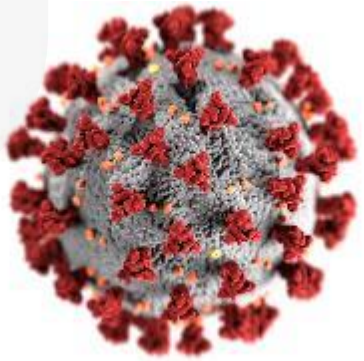
1. Razzardini G et al Br J Nutrition 2012
2. Bhat M et al Nutrition Reviews 2017
3. Scheiman J et al Nature Medicine 2019
4. Tecinesi A et al Nutrients 2017
5. Tubeilus P et al Environ Health 2005
6.Hao Q et al Cochrane 2015
7. Weizman et al Pediatrics 2005
8. Lindsay KL et al J Maternal-Fetal Med 2013
9. Janviar A et al J Pediatrics 2014
10. Rahman S Martindale R Ann Gastro 2023

Probiotic improves symptomatic and viral clearance in Covid19 outpatients: a randomized, quadruple-blinded, placebo-controlled trial

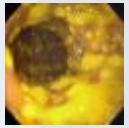
Pedro Gutiérrez-Castrellón[a,b], Tania Gandara-Martí[a], Ana T. Abreu Y Abreu[c], Cesar D. Nieto-Rufino[a], Eduardo López-Orduña[d], Irma Jiménez-Escobar[a], Carlos Jiménez-Gutiérrez[a], Gabriel López-Velazquez[b], and Jordi Espadaler-Mazo[e]

Gut Microbes 2022

- n = 300 probiotics vs placebo
- Endpoints followed
  - Complete viral remission
  - % progressing to moderate of severe disease and/or death
  - Days required in ICU



- Probiotics
  - Increases IgM, IgG against SARS-CoV2
  - Reduced nasopharyngeal and lung viral load
  - Reduced symptoms

Clinical Condition	Probiotic	References
Antibiotic associated diarrhea 	*L casei, LGG,* *L plantarum* *S Boulardii*	Hempel 2012,Morrow 2012 Barraud 2013, Surawicz 2009, Doron 2008, Hickson2007, Alberda 2018
C. difficile 	*LGG, S.Boulardii* *Numerous*	Na 2011, Katz 2006, Johnson 2012, Shen NT 2017, Johnson 2018, Bommioasamay Am J Surg 2018, Johnstone 2021,
Ventilator associated pneumonia 	*L. rhamnosus* GG *L casei, Bifidobacterium bifidum*	Bo 2014 – Cochrane review Morrow 2010, Barraud 2010 Giamaerellos Bourboulis 2009 Knight 2009, Forestier 2008, Shimuzu 2018 Johnson 2021 (no benefit)
Abdominal surgery, Liver transplant 	*L plantarum* 299v *L casei B breve* *L rhamnosus*	Rayes 2002, 2005, Chanmao 2007, Kanazawa 2005, Sugawara 2006, Horvat 2010, Liu 2011, Eguchi 2011, Lytvynl 2016
Sepsis 	*L plantarum* *L casei, L rhamnosus*	Panigranhi 2017, Arumugam 2016, Sun 2017, Argenta 2016, Wang 2022 (no benefit)
Trauma 	*Bifidobacterium breve, L rhamnosus* *L casei*	Kotzampassi 2006, Spindler-Vesel 2007, Tan 2011

Use of Probiotics to Prevent Ventilator Associated Pneumonia

- *Lactobacillus GG* vs placebo (DBPCT)
  - (2871 patients screened 146 met criteria)
  - On vent > 72 hours
  - Oral *and* via feeding tube
  - 1.0 x 10^{10} BID to each site
- Evaluated
  - Oral flora pathogen vs normal flora
  - Gastric flora pathogen vs normal flora
  - Incidence of VAP
- Results
  - Less antibiotics used
  - Less C.difficile 5.8% vs 18.6% (p<.05)
  - Clinical VAP 35% vs 47% (p<.05)
  - Microbiologic VAP 19% vs 40% (p<.05)
  - Mortality 14% vs 24% (NS)

Morrow S, Kollef M et al 2010 AJRCCM

Probiotic and synbiotic therapy in critical illness: a systematic review and meta-analysis

Critical Care (2016) 20:262

William Manzanares[1], Margot Lemieux[2], Pascal L. Langlois[3] and Paul E. Wischmeyer[4*]

- **RCT of probiotic or synbiotic interventions with clinical outcomes**
- **Primary outcome: new infections**
- **Secondary outcomes: mortality, ICU and hospital LOS, diarrhea**
- **Subgroup analysis: probiotic type, patient mortality risk on effect of probiotics on outcomes**
- **Results:**
  - **30 trials (n=2972)**
  - **Probiotics associated with:**
    - **Reduction in infections**
    - **Decreased incidence ventilator-associated pneumonia**
    - **No effect on mortality, LOS or diarrhea**

JAMA | Original Investigation

Effect of Probiotics on Incident Ventilator-Associated Pneumonia in Critically Ill Patients
A Randomized Clinical Trial

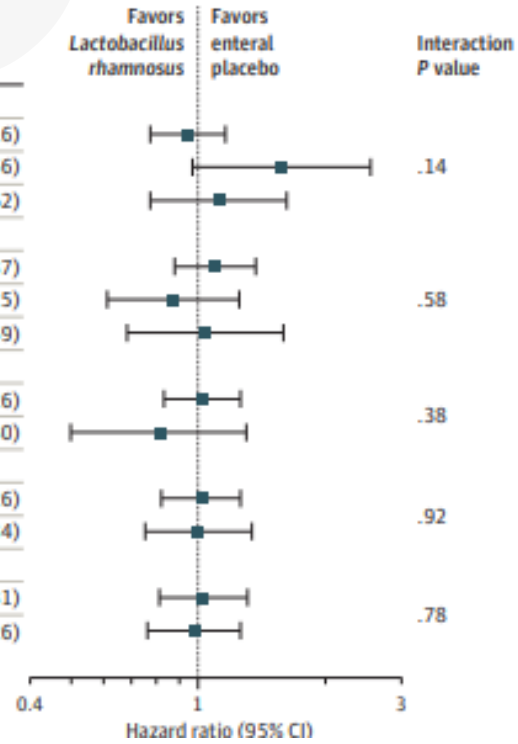
Johnstone J et al 2021

- 44 ICU's Canada, USA, Saudi Arabia
- N = 2653 randomized to L. rhamnosus GG 1.0 x 10^{10} CFU BID vs placebo
  - 1321 L. rhamnosus vs 1332 placebo
- Ventilator > 72 h

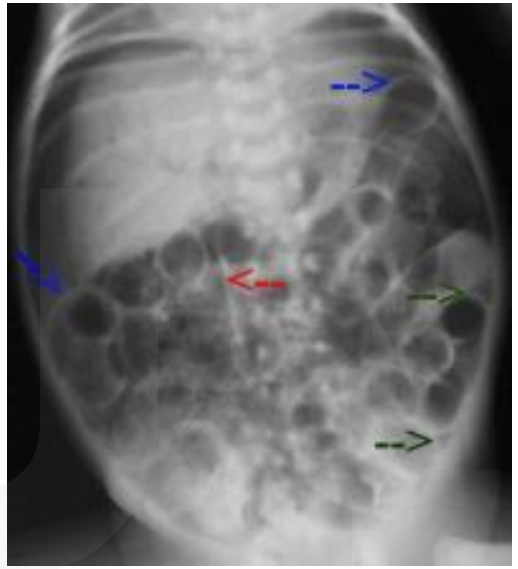
- **Results:**
  - **No differences in any primary or secondary outcomes**
    - **VAP, C.diff, ICU acquired infections, antimicrobial use, mortality**

Figure 2. Subgroup Analyses: Ventilator-Associated Pneumonia

Subgroup	No./total patients *Lactobacillus rhamnosus*	No./total patients Enteral placebo	Hazard ratio (95% CI)	Interaction *P* value
Admission type				
Medical	184/1006	199/1021	0.94 (0.77-1.16)	
Surgical	44/141	29/129	1.58 (0.97-2.56)	.14
Trauma	61/171	56/182	1.12 (0.77-1.62)	
Age, y				
<65	173/752	168/767	1.10 (0.88-1.37)	
65-75	69/335	66/319	0.87 (0.61-1.25)	.58
>75	47/231	50/246	1.04 (0.68-1.59)	
Clinical frailty score				
≤4	188/844	191/866	1.02 (0.83-1.26)	.38
≥5	37/240	40/232	0.81 (0.50-1.30)	
Received antibiotics on day of randomization and 2 preceding days				
No	193/766	181/739	1.02 (0.82-1.26)	.92
Yes	96/552	103/593	1.00 (0.75-1.34)	
Prevalent pneumonia as primary diagnosis or comorbid infection				
No	168/542	151/532	1.03 (0.81-1.31)	.78
Yes	121/776	133/800	0.98 (0.76-1.26)	



Probiotics in the prevention of necrotizing enterocolitis in neonates



- 7% of VLBW < 1500 gm
  - 20 to 30% mortality
  - Etiology is clearly multifactorial
    - Premature birth, Abnormal intestinal microbiota
    - Enteral feeding , alterations in perfusion

- Janvier A et al N=566 infants — Janvier A et al J Pediatrics 2014
  - 5 probiotic genera (4 bifidobacteria and 1 lactobacillus
    - 2 .0x 10^9 CFU /day
- Results
  - Reduction in Nec 9.8% vs 5.45 % (p<.05)
  - Reduction in Mortality 9.8 vs 6.8 % (NS)

Meyer MP et al J Neonatal Perinatal Med 2019

NEC 3% to 1%, NNT 50

Underwood MA et al J Ped Surg 2019

Review: human, animal data – Strong evidence to support

The effect of oral probiotics on response to vaccination in older adults: a systematic

Hediye Arioz Tunc ✉ , Caroline E Childs , Jonathan R Swann , Philip C Calder

Age and Ageing 2024

- 10 RCTs ---1,560 patients
- Primarily influenza seasonal vaccine and one study evaluation of COVID-19 vaccine
- Mostly Lactobacilli some in combination with bifidobacterial
- Results:
  - Probiotics showed increased seroconversion rates in all three strains of seasonal flu vaccine
- Conclusion:
  - Significant enhancement in vaccine response

Can Probiotics be used for prevention of disease in "Healthy People"

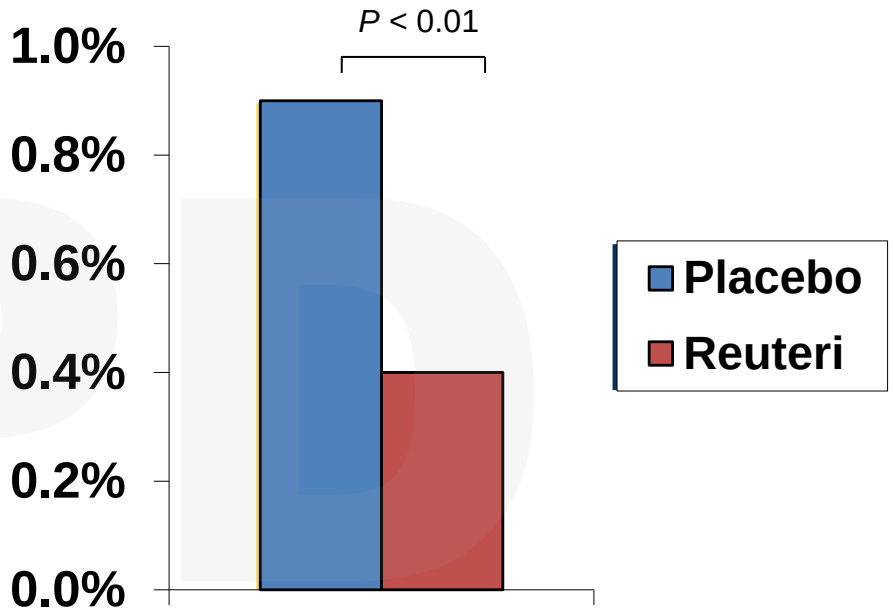
Sick days at home with short term gastro-intestinal or respiratory illness. PRCT N=262 subjects, 80 days to complete study

Placebo: 0.9 % sick days

2 days per individual and year

Reuteri: 0.4 % sick days

<1 day per individual and year **

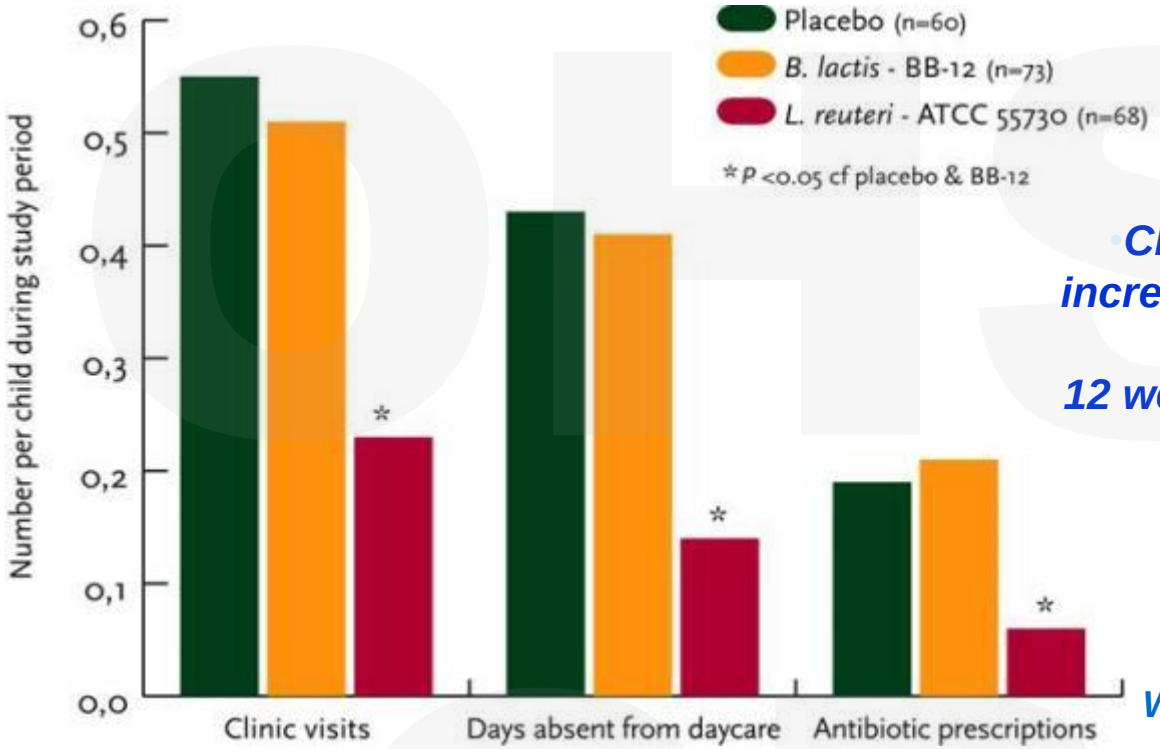


Number of people sick

26% on placebo (23 persons)
11% on Reuteri (10 persons) p<.01**

Tubelius P et al., Environ Health 2005

Pre and Probiotics:
Use probiotics in healthy school children



Children (4-10m) with increased risk for infection

12 weeks supplementation in baby formula

Weizman et al., Pediatrics (2005)

- **Saavedra JM et al 2004**
- PRDBPCT N=118, 3-24 months, 210 day
- +/- Probiotics
- **Results: Probiotic group**
  - **Decrease colic, antibiotic use**

Mugambi MN et al Nutr J 2012

- Meta-analysis: Pre/Pro/Synbiotics, 25 studies total
- **Conclusion:**
- **No consistent high quality data to support;**
  - **Growth development, GI issues**

- **Laursen RP et al**
- **Pediatrics 2017**
- 290 infants
- 8 to 14 months
- B animalis, L rhamnosus
- No benefit

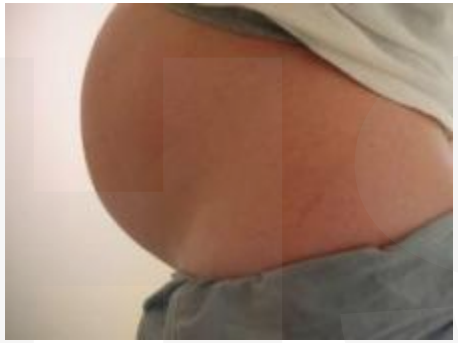
Probiotics, Pregnancy and Maternal Outcomes

- Finland N=256 (3 groups)
- Strict definition of Gestational diabetes (GTT)
- Control, placebo, probiotics
- Results:
  - Control 36%
  - Placebo 34%
  - Probiotics 13%
  - No change in pregnancy outcome
  - No change in children at two years

Luoto R British J Nutrition 2010

New Zealand n=423 pts
Prospective trial
Probiotic supplementation
Significantly decrease GDM
Greatest benefit seen in older women

Wickens KL British J Nutrition 2017



- Systematic review: 189 articles
- Primary outcomes;
  - Gestational DM
- Secondary outcomes;
  - Pre-eclampsia
  - Inflammatory markers
  - Lipid profiles
  - Gestational weight
- Conclusion: Probiotics reduce
  - gestational DM
  - Maternal fasting glucose
  - Pre-eclampsia
  - CRP-inflammation

Lindsay KL et al J Maternal-Fetal Neonatal Med 2013

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

nature
International journal of science
2017

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]

- RDBPCT of L. plantarum + FOS n=4,556 infants >2,000gm, 35wk gestation
- WHO criteria for sepsis, NIH funded 42% reduction in sepsis 1 week of tx $1

Table 2 | Effect of synbiotic treatment on sepsis and other morbidities in the first 60 days of life

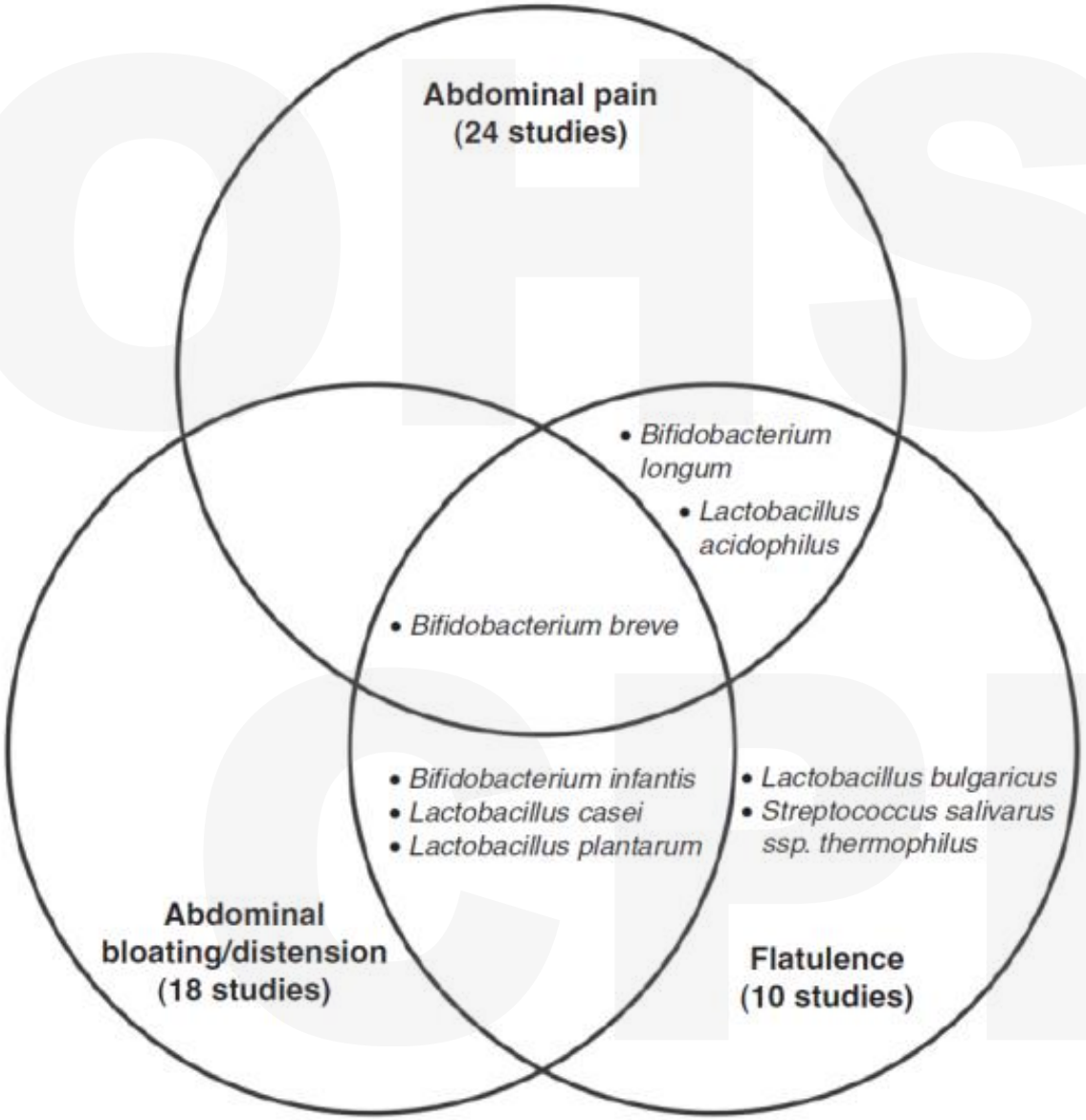
Outcome variables	Control $n=2,278$ (%)	Synbiotic $n=2,278$ (%)	RR (95% CI)	NNT (95% CI)	*P* value
Death and sepsis (primary outcome)	206 (9.0)	123 (5.4)	0.60 (0.48, 0.74)	27 (19, 47)	<0.001
Deaths	4 (0.2)	6 (0.3)	1.50 (0.42, 5.31)	NA*	0.526†
Sepsis (A + B + C)	202 (8.9)	117 (5.1)	0.58 (0.46, 0.72)	27 (19, 44)	<0.001
A. Sepsis/pSBI—culture-positive septicaemia	27 (1.2)	6 (0.3)	0.22 (0.09, 0.53)	108 (71, 232)	<0.001
Gram-negative sepsis	16 (0.7)	4 (0.2)	0.25 (0.08, 0.75)	190 (110, 699)	0.007
Gram-positive sepsis	11 (0.5)	2 (0.1)	0.18 (0.04, 0.82)	253 (142,1,169)	0.012
B. Sepsis/pSBI— culture-negative sepsis (Culture-negative clinical sepsis warranting hospitalization and IV antibiotics)	36 (1.6)	19 (0.8)	0.53 (0.30, 0.92)	134 (72, 890)	0.021
C. Sepsis/pSBI—LRTI (LRTIs requiring antibiotic therapy)	139 (6.1)	92 (4.0)	0.66 (0.51, 0.88)	48 (30, 126)	0.002
Diarrhoea	59 (2.6)	12 (0.5)	0.20 (0.11, 0.38)	48 (36, 74)	<0.001
Local infections (including >10 pustules, oral thrush, conjunctivitis)	33 (1.5)	16 (0.7)	0.48 (0.27, 0.88)	134 (74, 677)	0.015
Abscess/ otitis media	11 (0.5)	5 (0.2)	0.45 (0.16, 1.33)	NA*	0.133*
Omphalitis	13 (0.6)	3 (0.1)	0.23 (0.07, 0.81)	228 (128,1,045)	0.014

Individual Probiotics in Irritable Bowel Syndrome

- Influence appears to be strain specific
  - *L.GG, L. plantarum, L. acidophilus, L. casei*,
  - (VSL#3), *Bifidobacterium animalis, B. infantis* (35624)
- Well done studies showing improvement in symptoms (72 RCT – 49 showing benefit in at least one outcome parameter)
  - Bloating, flatulence, constipation
  - Few alter symptoms and pain / global score
- *B. infantis* best studied (highest quality studies)
  - PRCT > 360 pts, 10^8 bacteria
  - Improved global score by > 20%
- *B.regularis* (Activa®)
  - Constipation predominate – 16 RPCT, 11 +

- A meta-analysis in the AGA Guidelines reviewed 37 trials involving 4,403 subjects and found that combination probiotics demonstrated a significant pooled effect for symptom improvement (RR 0.79, CI 0.68–0.91), but there was significant heterogeneity and publication bias
  - Lacy BE et al Am J Gastro 2021

Summary: Probiotics in Irritable Bowel Syndrome ?



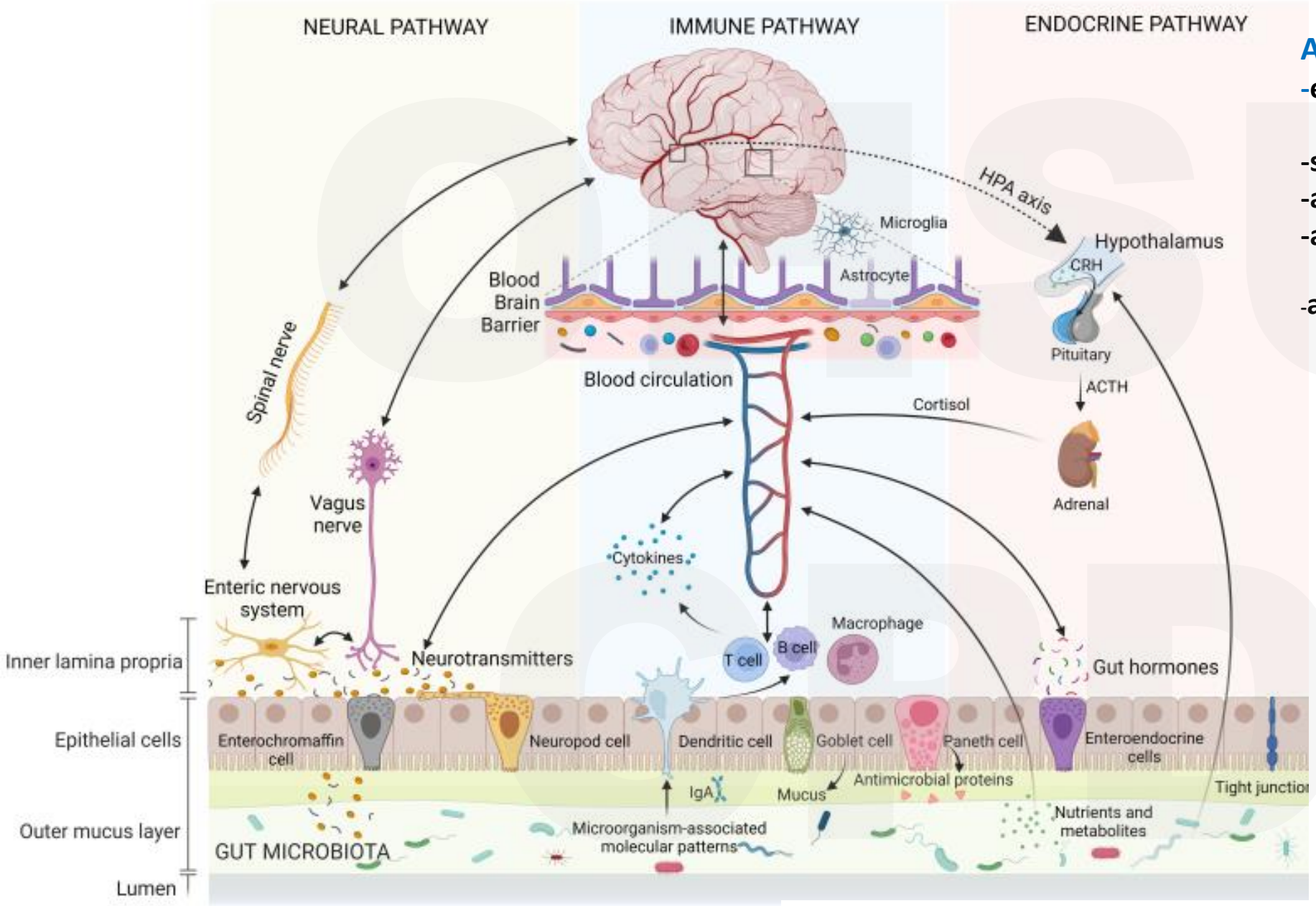
Results mixed:

Limited #'s

Variable species

Variable dosing

The brain gut connections are beginning to be understood



Acute Stress

- -enteric NS activated altering gut contractility
- -suppression of adaptive immune system
- -activation of innate immune system
- -altered serotonin metabolism (90% from EC cells)
- -alters microbiome – induces pathobiome - decreases biome diversity

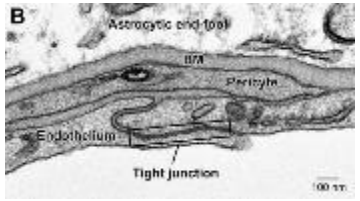
Chronic stress

- -impairs vagal signaling and enteric nerve function
- -impairs gut motility
- -induces visceral hypersensitivity
- -cellular and humoral immunity is suppressed
- -reduced mucous layer
- -increased paracellular permeability
- -increased mast cell degranulation
- -reduced stability of microbiome
- -conversion of microbiome to pathobiome

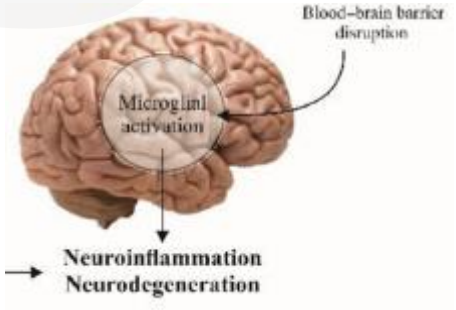
Zheng Y et al Nutrients 2023
Leigh SJ et al J Physiol 2023

How do SCFAs produced from fermentation in the gut microbiome benefit the CNS in the ICU patient ?

- SCFAs – primarily butyrate, acetate, and proprionate



  - Enhances blood brain barrier
    - Decrease paracellular permeability via enhancing tight junction proteins (occludin and ZO-1)
      - Decreases neuroinflammation and neuronal damage

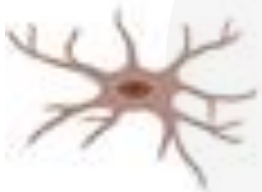


  - Modulate microglia activity
    - Binding free fatty acid receptors inhibiting histone deacetylase
      - Reduces expression of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α)
  - Improve cognitive function in sepsis associated encephalopathy (SAE)
    - Reducing neuroinflammation and neuronal degeneration
      - Binding of GPR-43
  - Increase production of IL-10
    - Decrease CNS inflammation

Fock E et al Cells 2023
Liao H et al Frontiers in Neurology 2022
Zhang Q et al Frontiers in Cellular and Infection Micro 2023
Liu J et al Frontiers in Immunology 2021
Wang F et al Neurobiology of Disease 2024
O'Riordan KJ et al Molecular and Cellular Endocrinology 2022

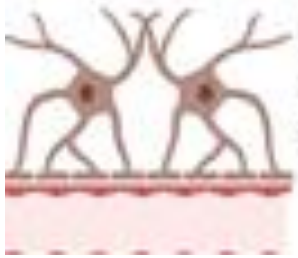
Microbiome produced SCFA effects in CNS

Neurons and function
- Increased neurogenesis
- Improved cognitive development
- Improved memory
- "Antiaging" effect

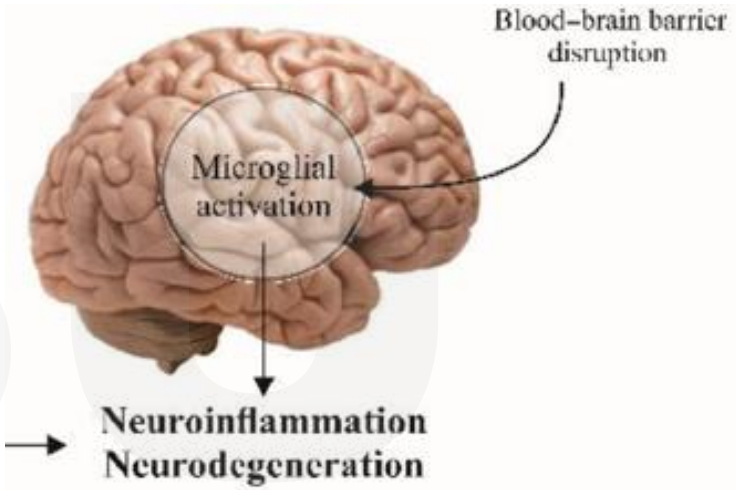


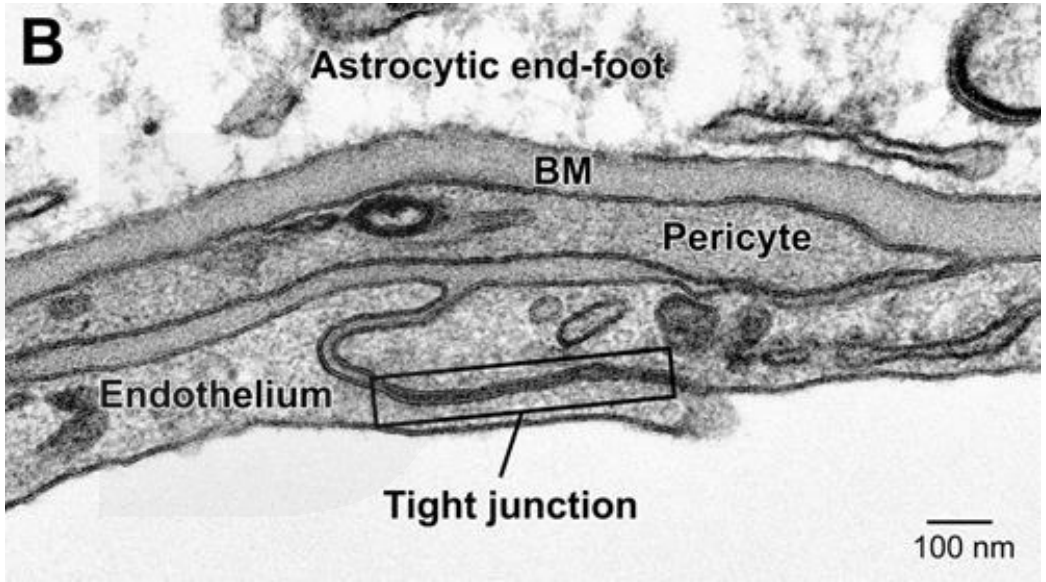
Microglia
- Development and function
- Induced homeostatic profile
- Reduced inflammatory signaling

Astrocytes
- Reduced inflammatory signaling



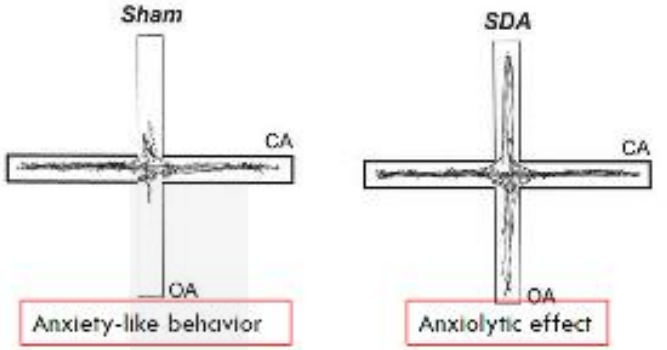
Blood-brain barrier
- Improved integrity
- Reduced permeability





Silva YP et al Front Endo 2020
Fusco W et al Nutrients 2023

- **Preclinical / non-human studies**
  - Evidence to support vagal afferent signals involved
    - *Lactobacillus rhamnosus* directly activates vagal neurons
    - Region specific alterations in GABA receptor expression
    - Reduced stress-induced cortisol
      - Reduce anxiety and depression like symptoms
    - Vagotomized mice do NOT exhibit these changes



- **Human: microbiome manipulation**
  - Messaoudi M et al Br J Nutr 2011 DBPCRCT
    - Decrease psychological stress, urinary cortisol
  - Rao AV et al Gut Pathogens 2009: Chronic fatigue
    - L casei Shirota v placebo x 2 months
    - Improved fatigue feeling, less anxiety
  - MDD

Foster JA Biological Psychiatry 2017
Bravo JA et al PNAS 2011
Medina-Rodriguez EM et al Pharm Biochem Behavior 2023
Zhao S et al Nutr Rev 2025

Probiotics for adults with major depressive disorder compared with antidepressants: a systematic review and network meta-analysis

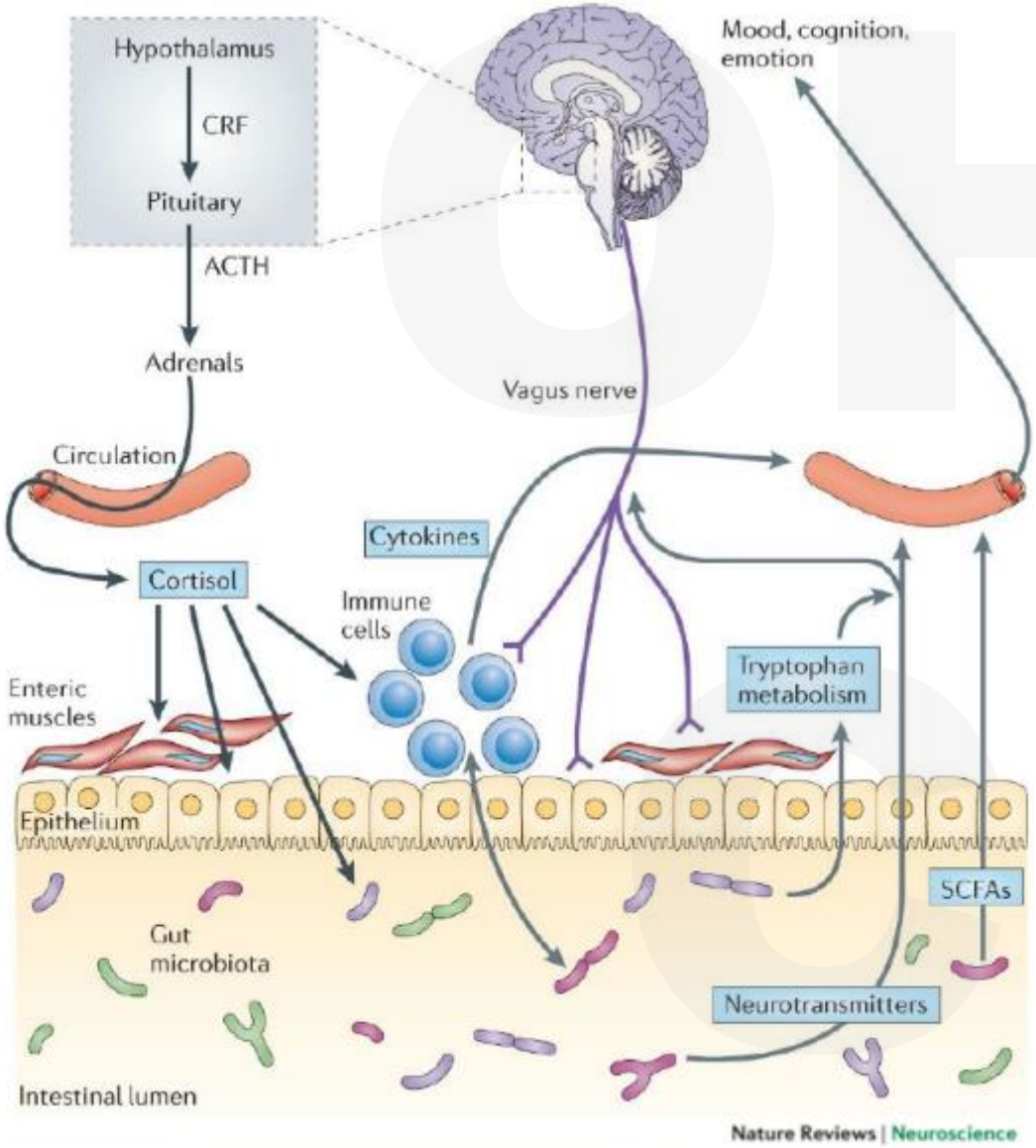
Shilin Zhao , Suisha Liang , Jun Tao , Ye Peng , Siqi Chen , Hogan K F Wai , Feng-Ying Chung , Zhen Y Sin , Matthew K L Wong , Andrea M Haqq ... Show more

Nutrition Reviews, Volume 83, Issue 1, January 2025, Pages 72–82,

16 OF 22 showed improvements
8 weeks shows best response

"Probiotics, compared with antidepressants and placebo, may be efficacious as an adjunct or standalone therapy for treating MDD"

Microbiome and Brain Function
"Gut-Microbiota-Brain Axis"



Recently shown to alter:

- **Behavior**
  - **Anxiety, depression**
  - **Learning, memory**
- **Neurogenesis**
- **Neuroplasticity**
- **Microglial activity**
- **BBB integrity**
- **AD, Parkinson's**

Human data for:

- **Anxiety / stress**
- **Depression**
- **OCD / ADHD**
- **Others**

Cryan FJ et al Nature Rev Neuroscience 2012 Minter MR et al Sci Rep 2016, Ho P 2017 Clerici L Curr Nutr Rep 2025

RCT's continue to be published

Contents lists available at ScienceDirect

Nutrition

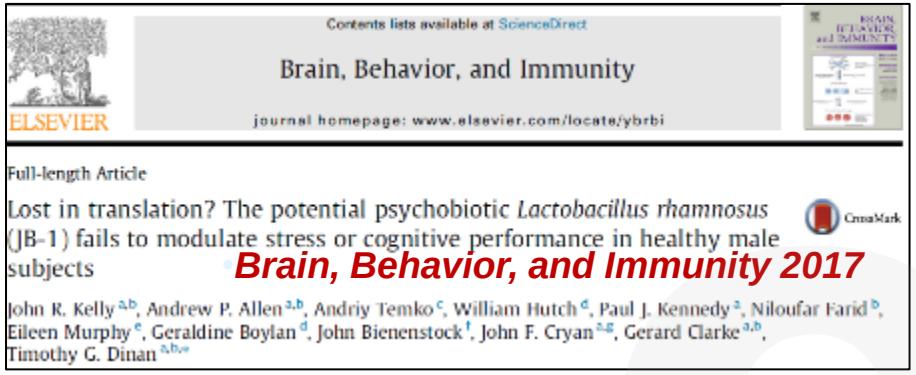
journal homepage: www.nutritionjrnl.com

Applied nutritional investigation

Clinical and metabolic response to probiotic administration in patients with major depressive disorder: A randomized, double-blind, placebo-controlled trial

Ghodarz Akkasheh M.D. [a], Zahra Kashani-Poor M.D. [a], Maryam Tajabadi-Ebrahimi Ph.D. [b], Parvaneh Jafari Ph.D. [c], Hossein Akbari Ph.D. [d], Mohsen Taghizadeh Ph.D. [c], Mohammad Reza Memarzadeh Ph.D. [f], Zatollah Asemi Ph.D. [c,*], Ahmad Esmaillzadeh Ph.D. [g,h,i]

Nutrition 2016



Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Full-length Article

Lost in translation? The potential psychobiotic *Lactobacillus rhamnosus* (JB-1) fails to modulate stress or cognitive performance in healthy male subjects

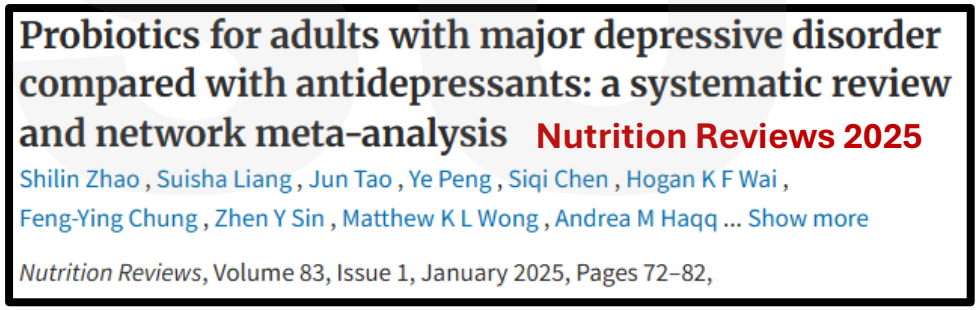
Brain, Behavior, and Immunity 2017

John R. Kelly [a,b], Andrew P. Allen [a,b], Andriy Temko [c], William Hutch [d], Paul J. Kennedy [a], Niloufar Farid [b], Eileen Murphy [e], Geraldine Boylan [d], John Bienenstock [f], John F. Cryan [a,g], Gerard Clarke [a,b], Timothy G. Dinan [a,b,*]

A randomized controlled trial to test the effect of multispecies probiotics on cognitive reactivity to sad mood ☆

Laura Steenbergen [a,b,*], Roberta Sellaro [a,b], Saskia van Hemert [c], Jos A. Bosch [d], Lorenza S. Colzato [a,b]

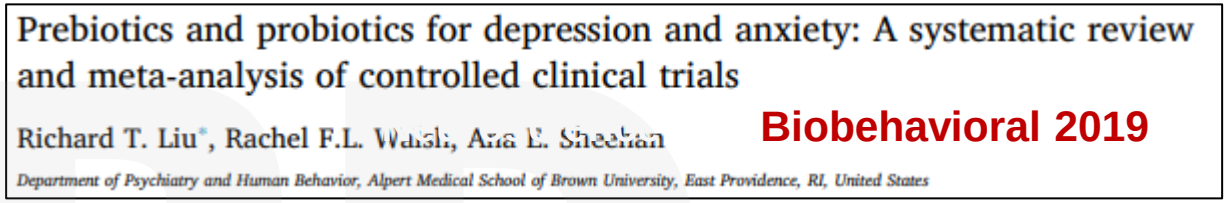
Brain, Behavior, and Immunity 2015



Probiotics for adults with major depressive disorder compared with antidepressants: a systematic review and network meta-analysis **Nutrition Reviews 2025**

Shilin Zhao , Suisha Liang , Jun Tao , Ye Peng , Siqi Chen , Hogan K F Wai , Feng-Ying Chung , Zhen Y Sin , Matthew K L Wong , Andrea M Haqq ... Show more

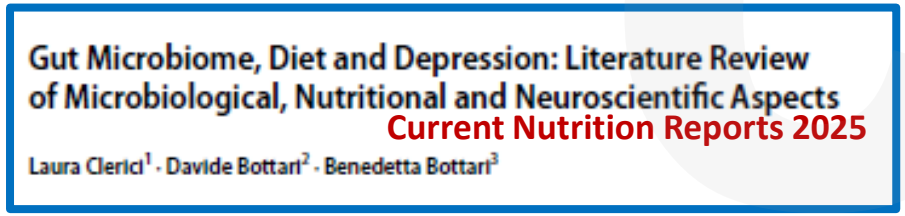
Nutrition Reviews, Volume 83, Issue 1, January 2025, Pages 72–82,



Prebiotics and probiotics for depression and anxiety: A systematic review and meta-analysis of controlled clinical trials

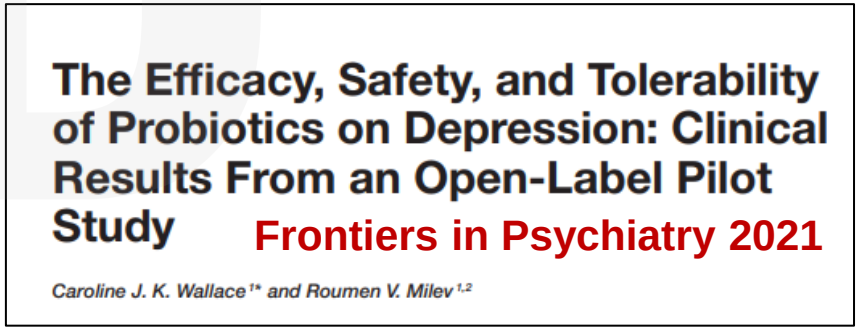
Richard T. Liu*, Rachel F.L. Walsh, Ana E. Sheehan **Biobehavioral 2019**

Department of Psychiatry and Human Behavior, Alpert Medical School of Brown University, East Providence, RI, United States



Gut Microbiome, Diet and Depression: Literature Review of Microbiological, Nutritional and Neuroscientific Aspects **Current Nutrition Reports 2025**

Laura Clerici[1] · Davide Bottari[2] · Benedetta Bottari[3]



The Efficacy, Safety, and Tolerability of Probiotics on Depression: Clinical Results From an Open-Label Pilot Study **Frontiers in Psychiatry 2021**

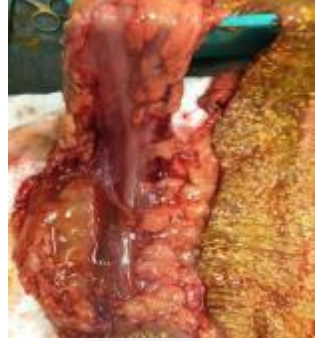
Caroline J. K. Wallace[1] and Roumen V. Milev[1,2]*

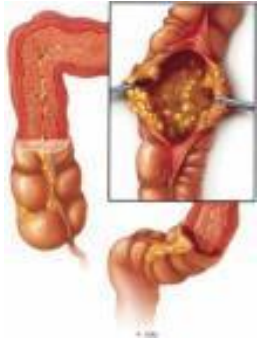
Can Probiotics Alter Treatment of Gastroenteritis Duration and Severity

- **Freedman SB et al NEJM 2018**
  - **PRDB trial N=866 ages 3 to 48 months**
    - **Presentation to 6 ED's across Canada with gastroenteritis**
  - **2 probiotics BID (L.rhamnosus and L. Helvetica, 4 x 10^9)**
  - **NO benefit to addition of probiotics**
    - **No difference in duration or severity of symptoms**
- **Schnadower D et al NEJM 2018**
  - **PRDBPCT children 3 to 48 months**
  - **Presenting with gastroenteritis**
  - **5 day course L.rhamnosus GG (1 x 10^{10} BID vs Placebo)**
  - **No Benefit**

- **Appears to show treatment not beneficial once gastroenteritis is established !**

Use of probiotic preparations to prevent C.difficile associated diarrhea





- RDBPCT N=135
- Age 64 all taking antibiotics
- 100 gm BID L. casei as drink
- Results:
  - AAD: 7/57 (12%) vs 19/56 (34%)
  - 21% relative risk reduction, NNT 5
  - C.diff 0/57 vs 9/53 (17%)

Hickson M, et al . BMJ 2007

- Meta-analysis 28 studies
- N=3818 patients

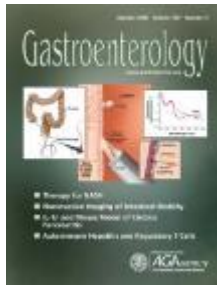
- *"Moderate quality"* of evidence probiotics as prophylaxis
  - decreases incidence of CDAD by 66%
  - No adverse influence by receiving probiotics

Johnston BC Ann Internal Medicine 2012

Probiotics Use In Hospitalized Patients: Meta-Regression Analysis

Shen NT et al Gastroenterology 2017

- 19 published series, N=6261 subjects
- More effective when given near first antibiotic dose
- Incidence of C.diff 1.6% vs 3.9%
- No increased risk of adverse events in probiotic group
- **Quality of evidence *high***



Microbial Preparations (Probiotics) for the Prevention of *Clostridium difficile* Infection in Adults and Children: An Individual Patient Data Meta-analysis of 6,851 Participants

INFECTION CONTROL & HOSPITAL EPIDEMIOLOGY

Pietro Pozzoni, MD;[9] Agostino Colli, MD;[9] Elisabet Lönnermark, MD;[10] Christian P. Selinger, MD;[11] Samford Wong, PhD;[12] Susan Plummer, MD;[13] Mary Hickson, PhD;[14] Rozha Pancheva, MD, PhD;[15] Sandra Hirsch, MD;[16] Bengt Klarin, MD;[17] Joshua Z Goldenberg, ND;[18] Li Wang, MD;[19,20] Lawrence Mbuagbaw, PhD;[2] Gary Foster, PhD;[21] Anna Maw, MD;[22] Behnam Sadeghirad, MPH;[2] Lehana Thabane, PhD;[2] Dominik Mertz, MD[2,23]

Johnston BC et al Infection Control Hospital Epidem 2018

- **Probiotics decrease risk or C. difficile by > 60%**
- Moderate quality of evidence supporting probiotics
  - Multi-species appears better than single species
- If patient receiving > 2 antibiotics benefit of probiotics event greater

Do C.*difficile* bundles work ?

- Evaluation of probiotic bundle targeted for *C.diff*
  - *Clostridium difficile* infection (CDI)
- Review pre and post implementation
  - 2008 through 2014 (trauma ICU)
  - Probiotics protocol 2010
  - 4632 pts (49%) received antibiotics
  - 21% received probiotics

- Conclusion:
  - **CDI decreased from 11.2 to 4.8 per 1000 admissions (p=.03)**
  - **CDI in patients receiving antibiotics went from 2.2% to 0.7% (p=.01)**

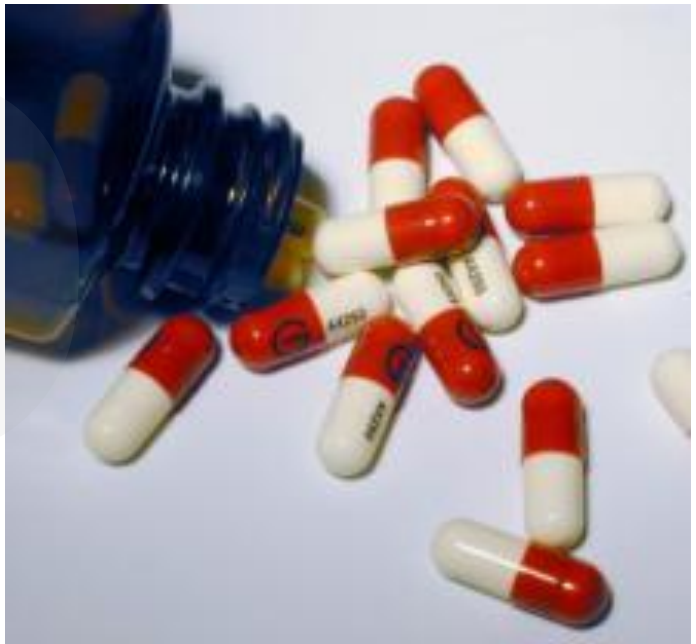
Bommiasamy AK, Martindale RG, Kiraly LN Am J Surgery 2018

Antibiotic Associated Diarrhea: Preventable or Inevitable ?

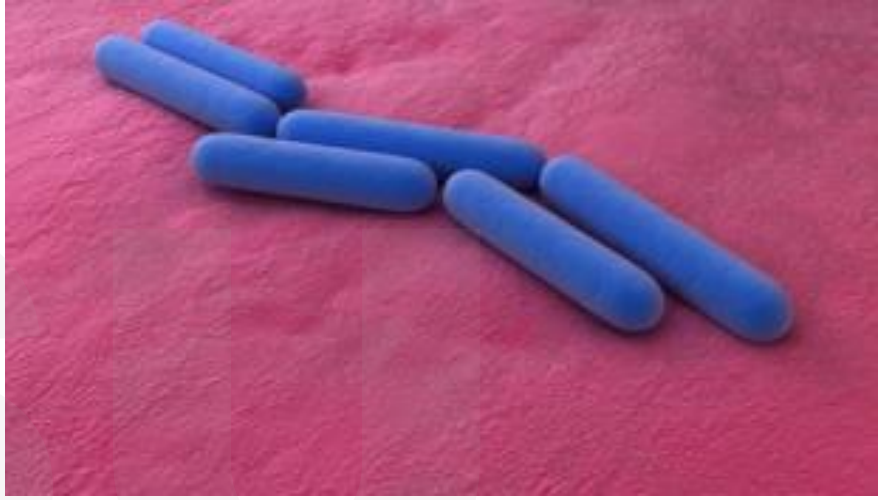
- Hempel S et al JAMA 2012
- Meta-analysis 82 RCT met criteria for inclusion
- Probiotics strains were poorly documented
- N=11,811 participants (pooled data)
- Conclusion:
  - Probiotics confer significant decrease in AAD (p<.001)
  - # needed to treat N=13

Hempel S et al JAMA 2012

Similar benefit in Cochrane Analysis of summary 23 studies Goldenberg JZ 2015 Probiotics started when antibiotics started most benefit



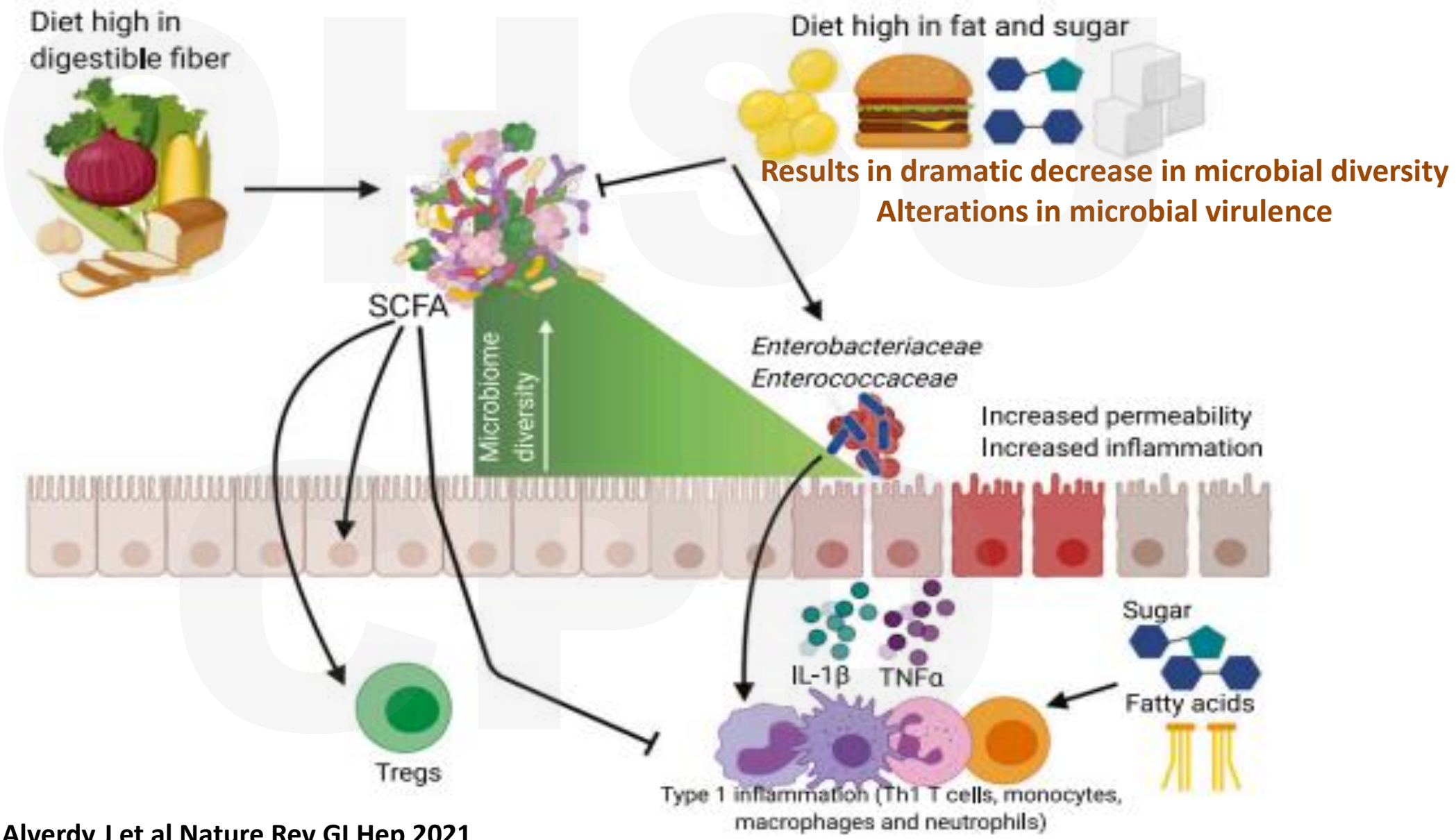
Probiotics: Importance of choosing the correct bacterial species



- **PLACID Trial: MRDBPCT**
- **17,480 screened 2,971 met criteria**
  - **> 65 yo**
  - **All received antibiotics**
  - **70% received either placebo of probiotic for at least 7 days**
    - » **L.acidophilus x 2**
    - » **B.bifidum x 2**
- **Conclusion:**
  - **AAD 10.8 vs 10.4 %**
  - **CD 0.8 vs 1.2 %**
  - **Essentially no differences between groups**

Allen SJ et al Lancet 2013

Can we alter the microbiome to improve Surgical outcomes with prebiotics?



Modified from Toni T, Alverdy J et al Nature Rev GI Hep 2021

Probiotics and Synbiotics Decrease Postoperative Sepsis in Elective Gastrointestinal Surgical Patients: a Meta-Analysis

Sudha Arumugam[1] · Christine S. M. Lau[1,3] · Ronald S. Chamberlain[1,2,3]

J GI Surg 2016

Role of probiotics in the prevention and treatment of meticillin-resistant *Staphylococcus aureus* infections

Inter J Antimicrobial Agents 2013

Hanna Sikorska[a,*], Wanda Smoragiewicz[b]

Probiotics and synbiotics for the prevention of postoperative infections following abdominal surgery: a systematic review and meta-analysis of randomized controlled trials

Lytvyn L et al J Hosp Infections 2016

L. Lytvyn[a,b], K. Quach[a], L. Banfield[c], B.C. Johnston[a,b,d,e], D. Mertz[a,f,g,h,*]

Review

The Effect of Perioperative Administration of Probiotics on Colorectal Cancer Surgery Outcomes

Nutrients 2021

Louise Pitsillides[1], Gianluca Pellino[2,3], Paris Tekkis[1,4,5] and Christos Kontovounisios[1,4,5,*]

Perioperative Probiotics or Synbiotics in Adults Undergoing Elective Abdominal Surgery

A Systematic Review and Meta-analysis of Randomized Controlled Trials

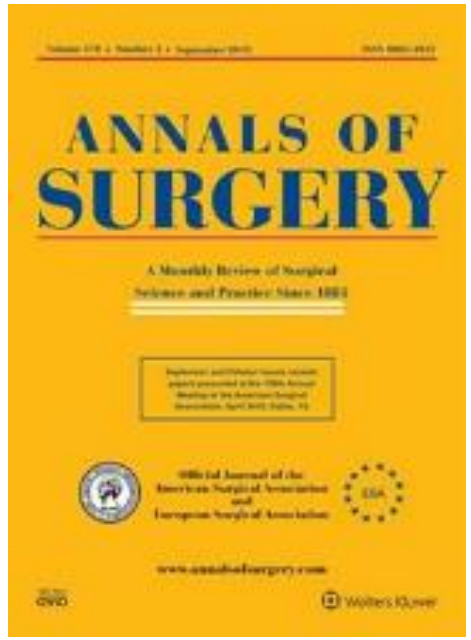
Abeed H. Chowdhury, PhD, FRCS, Alfred Adiamah, MRCS,* Anisa Kushairi, BMedSci, BM BS,* Krishna K. Varadhan, PhD, MRCS,* Zeljko Krznaric, MD, PhD,† Anil D. Kulkarni, MSc, PhD,‡ Keith R. Neal, DM, FRCP,§ and Dileep N. Lobo, DM, FRCS, FACS, FRCPE*¶*✉

2020

34 RCT n=2753

1354 treated with Synbiotics or Probiotics
1369 control

Synbiotics and Probiotics decrease risk of infections 56% p<0.00001
Synbiotics > than probiotics alone p<0.00001



Conclusions:

1) **Synbiotics and Probiotics decrease infections, LOS**
   - **No adverse effects**
2) **No change in mortality**

Low-fat/high-fibre diet prehabilitation improves anastomotic healing via the microbiome: an experimental model

S. K. Hyoju[1], C. Adriaansens[1,2], K. Wienholts[1,2], A. Sharma[1], R. Keskey[1], W. Arnold[1], D. van Dalen[1,2], N. Gottel[1], N. Hyman[1], A. Zaborin[1], J. Gilbert[1], H. van Goor[2], O. Zaborina[1] and J. C. Alverdy[1]

Departments of Surgery, [1]University of Chicago, Chicago, Illinois, USA, and [2]Radboud University Medical Centre, Nijmegen, the Netherlands

Correspondence to: Professor J. C. Alverdy, Department of Surgery, University of Chicago, 5841 S Maryland MC6090, Chicago, Illinois 60025, USA (e-mail: jalverdy@surgery.bsd.uchicago.edu)

Short course (2 days) of high fiber diet prevented anastomotic leaks in colorectal anastomosis

British J Surg 2020

Low-fat/high-fibre diet prehabilitation improves anastomotic healing via the microbiome: an experimental model

S. K. Hyoju[1], C. Adriaansens[1,2], K. Wienholts[1,2], A. Sharma[1], R. Keskey[1], W
N. Gottel[1], N. Hyman[1], A. Zaborin[1], J. Gilbert[1], H. van Goor[2], O. Z

Departments of Surgery, [1]University of Chicago, Chicago, Illinois, USA, and [2]Radb
Correspondence to: Professor J. C. Alverdy, Department of Surgery, Univers
(e-mail: jalverdy@surgery.bsd.uchicago.edu)

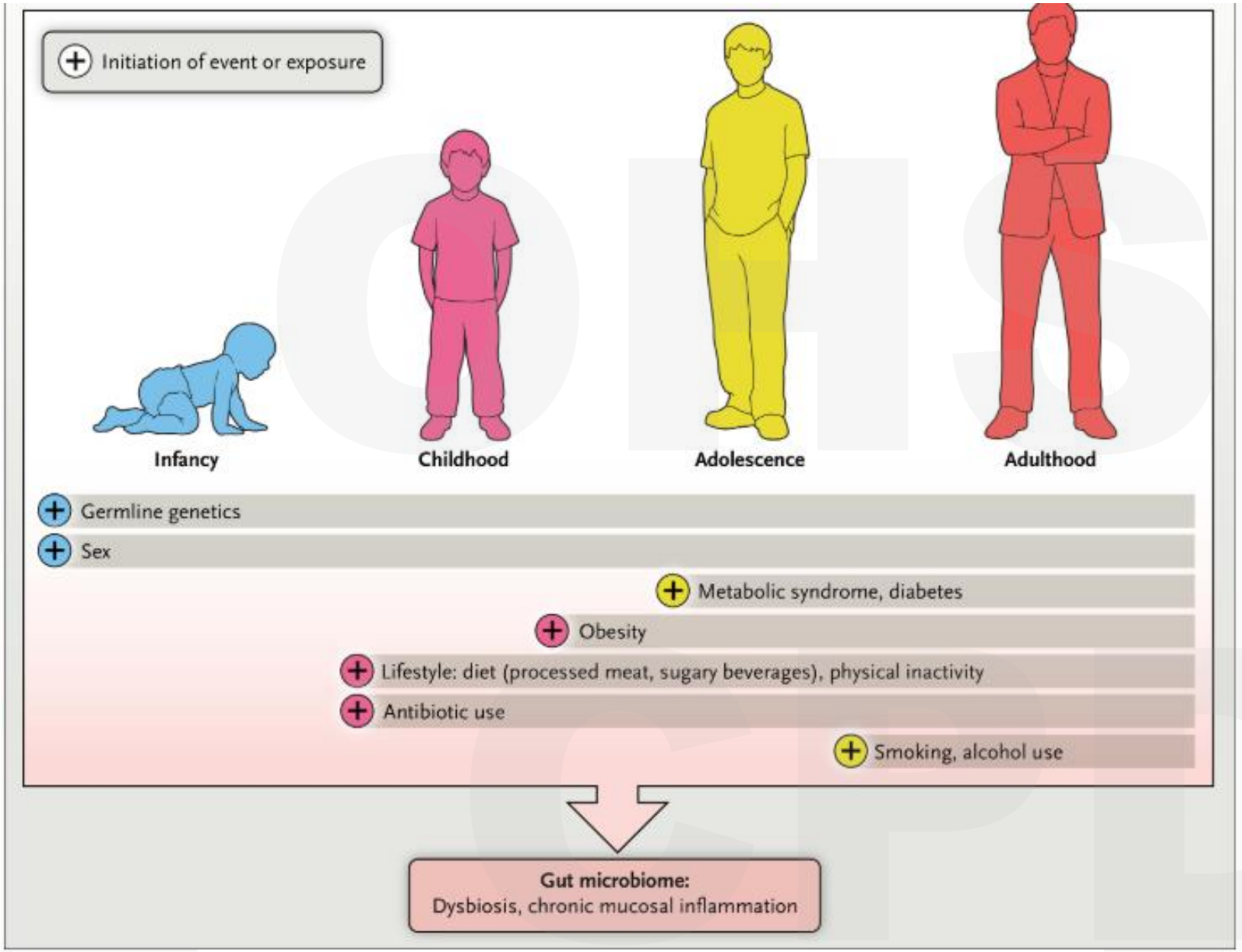
JAMA Surgery | Original Investigation

Association of Habitual Preoperative Dietary Fiber Intake With Complications After Colorectal Cancer Surgery

Dieuwertje E. Kok, PhD; Melissa N. N. Arron, MD; Tess Huibregtse, BSc; Flip M. Kruyt, MD; Dirk Jan Bac, MD, PhD; Henk K. van Halteren, MD, PhD; Ewout A. Kouwenhoven, MD, PhD; Evertine Wesselink, MSc; Renate M. Winkels, PhD; Moniek van Zutphen, MSc; Fränzel J. B. van Duijnhoven, PhD; Johannes H. W. de Wilt, MD, PhD; Ellen Kampman, PhD

JAMA Surgery 2021

British J Surg 2020



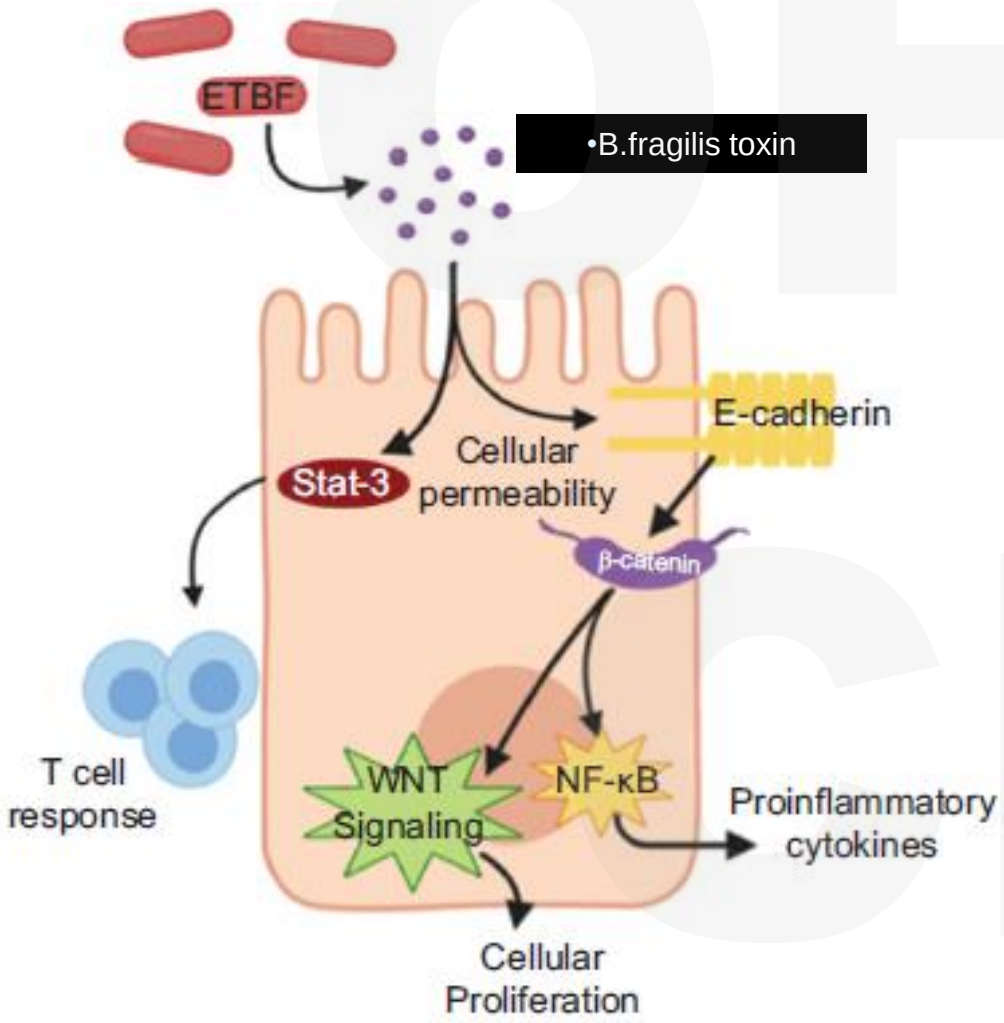
Factors Influencing the Risk of Colorectal Cancer

Primary mechanisms by which gut microbiome are believed to induce CRC

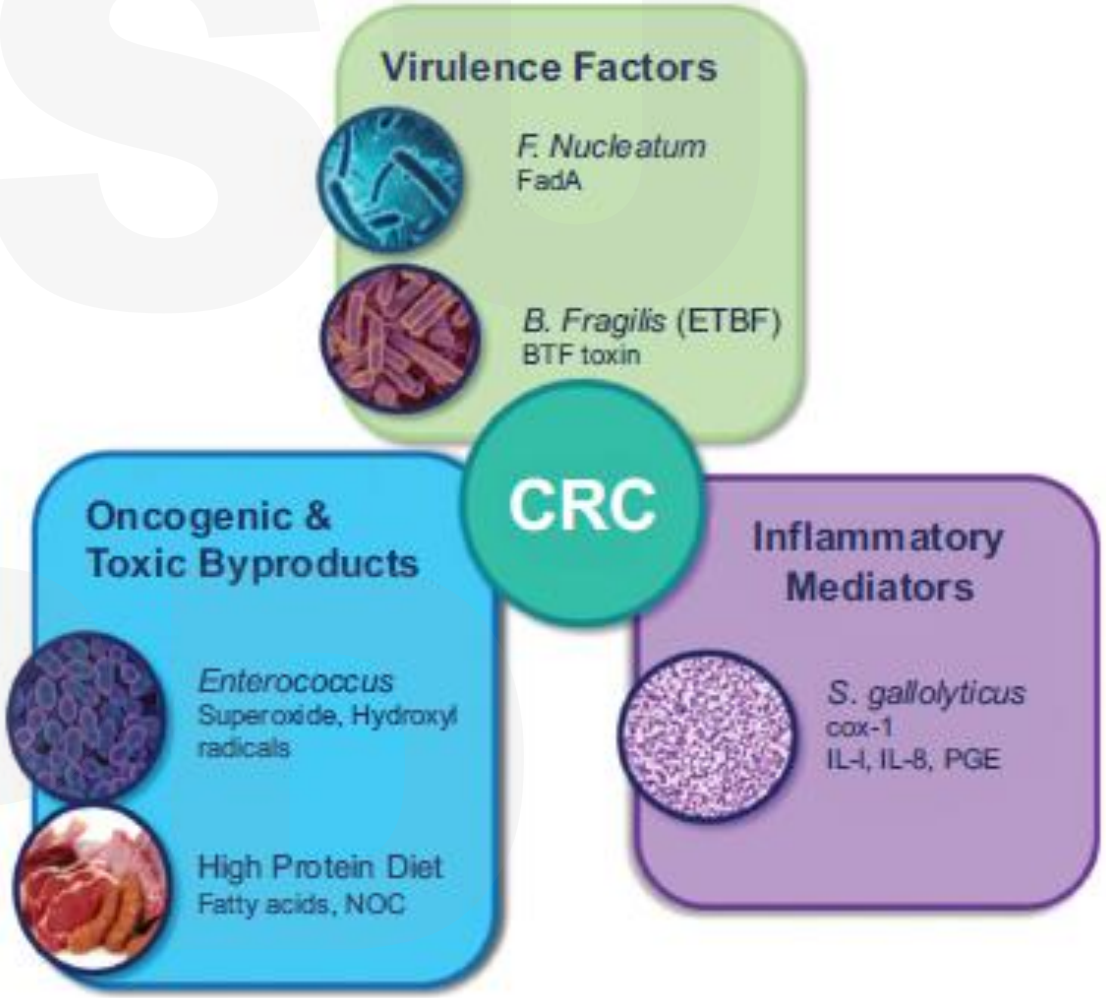
1. **Inflammation**
   - Induces DNA damage
2. **Genotoxicity**
   - Some bacteria produce toxins which induces DNA breaks, chromosomal instability
3. **Metabolic alterations**
   - Bacterial metabolites that promote CRC. Dysbiosis reduces SCFA

Sinicrope FA. NEJM 2022

Understanding the microbiome: a primer on the role of the microbiome in colorectal neoplasia



Annals of Gastroenterology 2020



Watson KM, Garner IH, Martindale RG, Tsikitis VT Ann Surg 2021

Long-term yogurt intake and colorectal cancer incidence subclassified by *Bifidobacterium* abundance in tumor

Satoko Ugai[a,b*], Li Liu[c*], Keisuke Kosumi[c*], Hidetaka Kawamura[a,d*], Tsuyoshi Hamada[c,e], Kosuke Mima[c], Kota Arima[a], Kazuo Okadome[a], Qian Yao[a], Kosuke Matsuda[a], Yuxue Zhong[a], Hiroki Mizuno[b], Andrew T. Chan[f,g], Wendy S. Garrett[h,j,k], Mingyang Song[b,f,g,l], Marios Giannakis[j,m,n], Edward L. Giovannucci[b,l], Xuehong Zhang[l,o], Shuji Ogino[a,b,j,p,q#], and Tomotaka Ugai[a,b#]

- Utilized prospective cohort tumor biobank
  - Included 132,056 participants with 3,079 with documented colon Ca
  - Tissue with microbiome associated tumor data 1,121
  - Bifidobacterium is an excellent SCFA producer

- Results:
  - Association of low Bifidobacterium with increased colon CA
    - Greatest effect in more proximal lesions

- **Conclusion:**
  - **Anti-tumor potential for the probiotic Bifidobacterium**
  - **Maintaining a “balanced” microbiome is key to mucosal physiology**

Gut Microbes 2025

The Many Faces of Metabolic Dysfunction-Associated Fatty Liver Disease Treatment: From the Mediterranean Diet to Fecal Microbiota Transplantation

Ludovico Abenavoli [1,*], Maria Luisa Gambardella [1], Giuseppe Guido Maria Scarlata [1], Ilaria Lenci [2], Leonardo Baiocchi [2] and Francesco Luzza [1]

Table 2. Summary of clinical trials about the use of probiotics in MAFLD patients.

Study Design	Study Groups	Intervention	Outcomes
Randomized controlled trial [34]	MAFLD group (*n* = 59)	Administration of Symbiter or placebo for 8 weeks	FLI significantly decreased in probiotic group. Probiotics significantly reduced the level of serum AST and GGT No significant difference in liver stiffness among groups
Randomized controlled trial [35]	Obese-MAFLD group (*n* = 69)	Administration of probiotics or placebo for 12 weeks	Significant decrease in the intrahepatic fat fraction and in TG levels in the probiotics group
Randomized controlled trial [36]	MAFLD group (*n* = 28)	One tablet per day with 500 million *Lactobacillus bulgaricus* and *Streptococcus thermophilus* or with one placebo tablet (120 mg of starch) for 3 months	ALT, AST, and GGT levels significantly decreased in the group treated with probiotics. No significant changes in anthropometric parameters
Randomized controlled trial [37]	MAFLD group (*n* = 46)	Administration of probiotics or placebo for 6 months	Significant improvement in intestinal permeability with a reduction in fat absorption after probiotics treatment

Abbreviations: MAFLD, metabolic dysfunction-associated fatty liver disease; FLI, fatty liver index; AST, aspartate amino transferase; GGT, gamma-glutamyl transferase, TG, triglycerides; ALT, alanine amino transferase.

Abenavoli L et al Medicina 2024

What is the optimal timing to attempt to manipulate the microbiome ?

CLINICAL PRACTICE GUIDELINES

AGA Clinical Practice Guidelines on the Role of Probiotics in the Management of Gastrointestinal Disorders

Grace L. Su,[1,2] Cynthia W. Ko,[3] Premysl Bercik,[4] Yngve Falck-Ytter,[5,6] Shahnaz Sultan,[7] Adam V. Weizman,[8] and Rebecca L. Morgan[9]

[1]Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor, Michigan; [2]Gastroenterology Section, Veterans Administration Ann Arbor Healthcare System, Ann Arbor, Michigan; [3]Division of Gastroenterology, University of Washington Medical School, Seattle, Washington; [4]Division of Gastroenterology, McMaster University, Hamilton, Ontario, Canada; [5]Division of Gastroenterology, Case Western Reserve University, Cleveland, Ohio; [6]Louis Stokes Veterans Affairs Medical Center, Cleveland, Ohio; [7]Division of Gastroenterology, University of Minnesota, Minneapolis, Minnesota; [8]Division of Gastroenterology, Mount Sinai Hospital, Department of Medicine, University of Toronto, Toronto, Ontario, Canada; and [9]Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada

Gastroenterology 2020;159:697-705

- "Although there has been a substantial number of studies examining probiotics in various gastrointestinal diseases, the **studies have been extremely varied**, including **differences in the strain of microbes used, dose, and route of administration**, as well as the research methodology, including differences in the reporting of end points and outcomes"
- **Almost all recommendations state: No recommendation, or low quality except in neonates which receives high to moderate recommendation**

- **In 2024 several societies now state that selective use in specific disease states with specific bacteria can be recommended. SCCM, ACS, still silent**

It is all about “Risk vs. Benefit”

Primum non nocere

Canadian ICU Pharmacists Survey:
Assess attitudes toward probiotic use in ICU

- 303 surveys sent / 191 returned (63%)
- 69% had probiotics available
- 62% had used in last year

- 80% said they would *NEVER* recommend probiotics to prevent VAP
  - Unsure of safety

Wheeler KE et al J Critical Care 2016

RESEARCH AND REPORTING METHODS Annals of Internal Medicine
2018;169:240-247

Harms Reporting in Randomized Controlled Trials of Interventions Aimed at Modifying Microbiota

A Systematic Review

Aïda Bafeta, PhD; Mitsuki Koh, MPH; Carolina Riveros, MSc; and Philippe Ravaud, MD, PhD

- **Evaluated 384 trials**
  - **Combined ICU, inpatient and outpatient**
- **Conclusion:** Harms reporting in published reports of RCTs assessing probiotics, prebiotics, and synbiotics often is lacking or inadequate. We cannot broadly conclude that these interventions are safe without reporting safety data

Few trials collect or report adverse events well !!

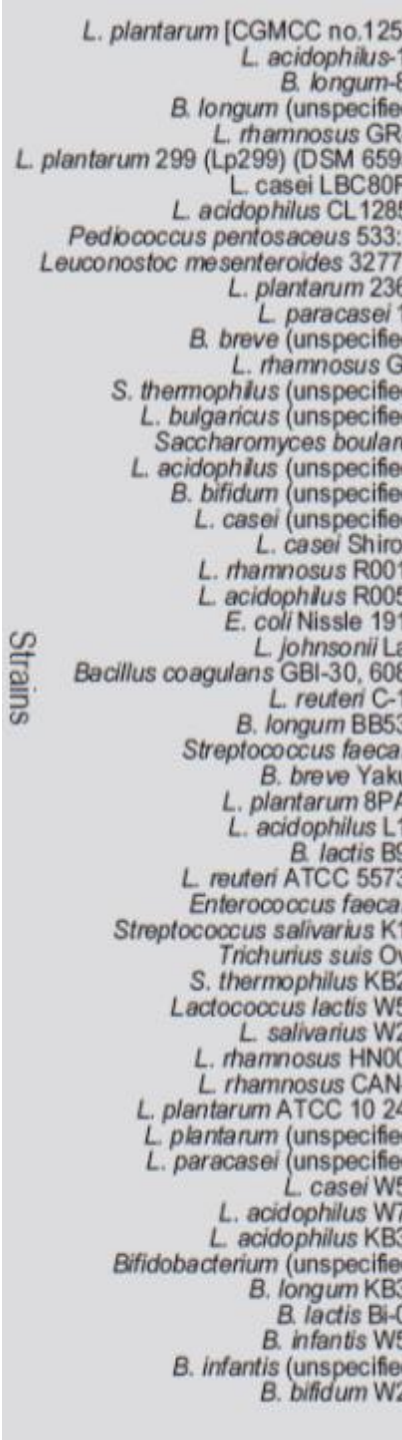
Safety of Probiotics

- > 400 human clinical trials from the last 15 years (2008-2021)
- Quantity and nature of the reported adverse events (AEs)
  - AE= occurrence of a complication or illness, or worsening of the condition throughout the study
- Examined 60> different strains of bacteria
- Virtually no significant attributable morbidity or mortality

- Conclusion [2]
  - The use of probiotics seems to play a role in decreasing the incidence of ICU-acquired infections. Also, a potential reduction in terms of the incidence of diarrhea has been reported, with no examples of adverse incidents, **suggesting probiotics are safe**

1)Van den Nieuwboer M et al, Benef Microbes, 2015

2)Alsuwaylihi AS et al Nutrition Reviews 2022



Tips on keeping a healthy microbiome

High-fiber Diet

- Non-starch polysaccharides
- Resistant oligosaccharides
- Resistant starch

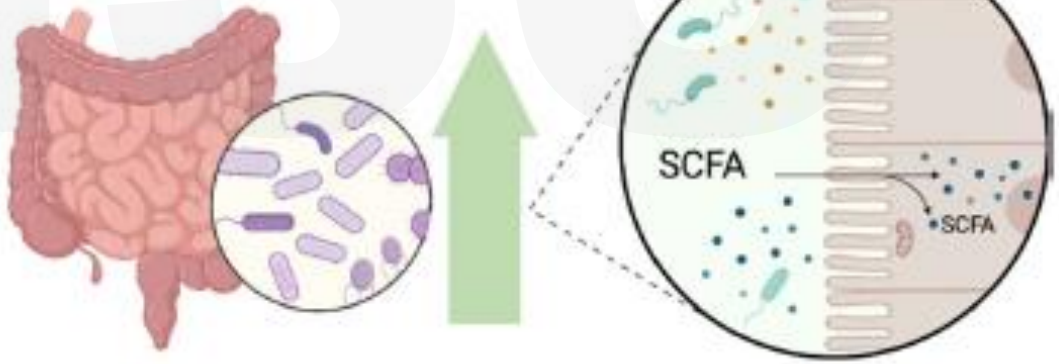
Prebiotics

- AXOS ↑
- GOS ↔
- XOS ↔
- Inulin ↔
- Starch ↔
- Raffinose ↔

Probiotics

- *Lactobacillus Plantarum* ↑
- *Lactobacillus paracasei* ↑
- *Lactobacillus rhamnosus* ↑

Diet can increase alpha diversity, decrease in CRP, fecal calprotectin, HbA1c, increase in GLP-1, increase in total SCFA



Gut Microbiota

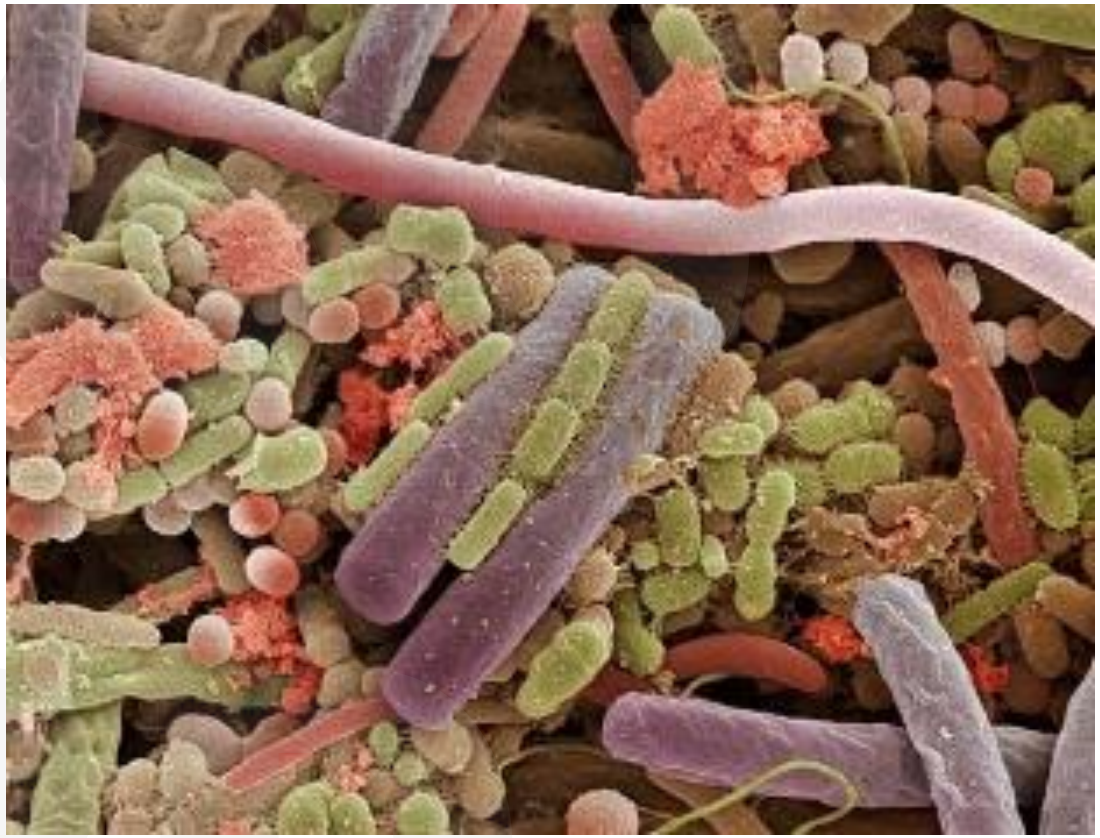
Oats and cereal grains are main source for AXOS (arabinoxylan-oligosaccharides)

Probiotics consistently increase serum levels of SCFA

Fusco W et al Nutrients 2023

Bacterial (probiotic) Strains with Significant #s of Supportive Clinical Published Data in ICU Populations

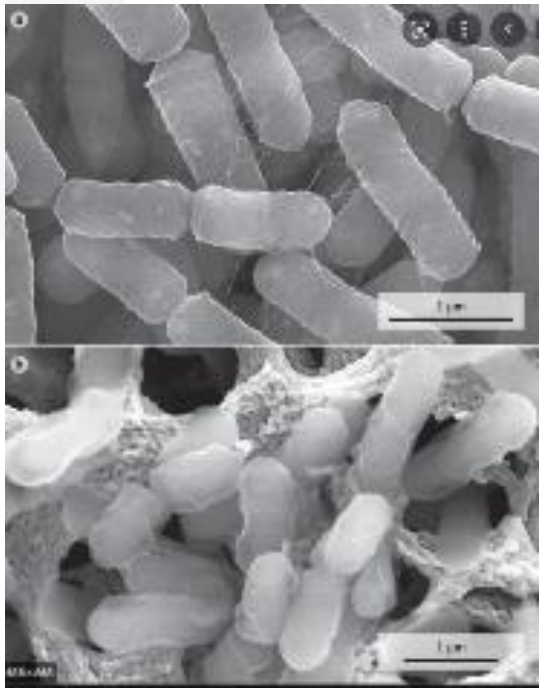
- Lactobacillus rhamnosus
- Bifidobacterium lactis BB-12
- L. casei 431
- L. acidophilus LA-5
- Lactobacillus salivarius UC118
- L. plantarum
- B. animalis lactis
- L. reuteri



- Disclaimer:
  - many other probiotic have published data to support in specific disease and health states
  - Some effects are strain specific effects
  - Strain “drift” is real

Limitations of Viable Probiotics

- **Probiotics must survive the GI tract**
  - Survival to IC valve 1% to 90% depending on species
    - L *acidophilis* vs L *plantarum*
- **Colonization resistance**
  - Host factors and compositional patterns of baseline microbiota
    - Example: L.*GG* of human origin with marginal data that it can permanently colonize
  - Processing for “packaging and distribution” alter viability of bacteria
- **What about safety**



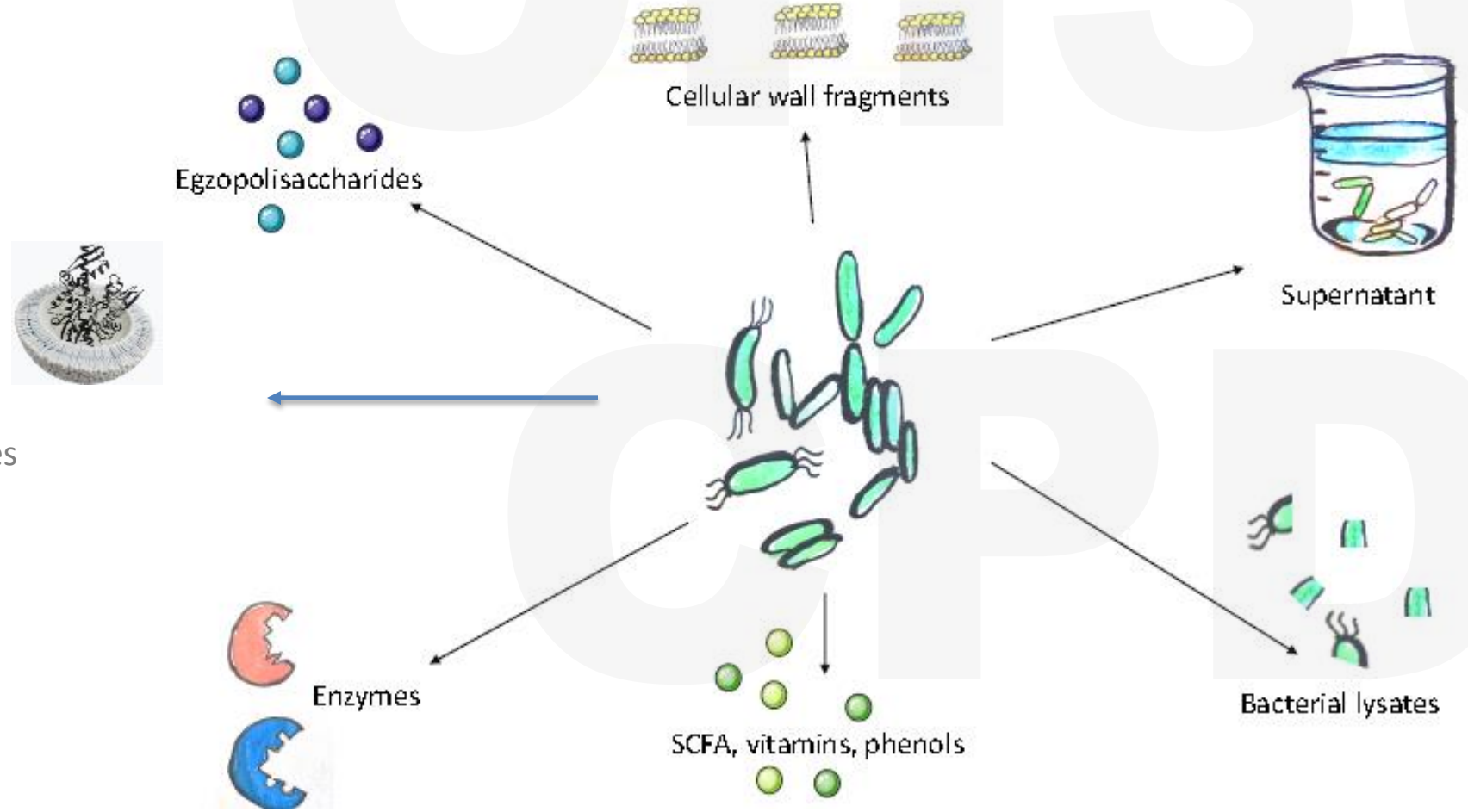
Definitions

- **Prebiotics** -compounds in food that induce the growth or activity of beneficial microorganisms such as bacteria and fungi.
- **Probiotics** -live microorganisms promoted with claims that they provide health benefits when consumed, generally by improving or restoring the gut flora.
- **Synbiotics** - food ingredients or dietary supplements combining probiotics and prebiotics in a form of synergism, hence synbiotics
- **Postbiotics** - are soluble factors (metabolites), secreted or generated by live bacteria during fermentation, or released after bacterial lysis providing physiological benefits to the host.

Marco ML et al Nature Reviews: Gastro and Hepatology 2021

Postbiotics – can this answer some of the questions without the risk ?

- **Postbiotics** - are soluble factors (metabolites), secreted or generated by live bacteria during fermentation, or released after bacterial lysis providing physiological benefits to the host.



osomes

Note: NO live bacterial needed

Stelmach V et al Nutrients 2024

General Guidelines for Use of Pre, Pro, Syn and Postbiotics in ICU

- All probiotics are not the same
  - Critically evaluate and use only when data supports
  - Base choice on molecular typing, metabolic characteristics and interaction in the environment
  - Needs to be evaluated for “functionality” down to strain level
  - Caution with meta-analysis, heterogeneity is key in studies
  - Do not extrapolate from one strain to another
  - Many mechanisms are strain and/or **metabolite** specific

- **In my opinion: Better to use microbiome manipulation as a preventative treatment option in the high risk populations**

Is it time to start sending off stool specimens for microbiome analysis ?

- Results obtained are NOT ready for prime time !
  - Large amount of data with no clear path on how to treat ?
    - Antibiotics
    - Probiotics
    - Prebiotics
    - Dietary changes
    - Exercise

Wall Street Journal June 2019

FBI, Insurers Probe Microbiome Startup

By Anna Wilde Mathews And Amy Dockser Marcus

Lab-testing startup uBiome Inc. is under scrutiny from law enforcement and insurers for billing practices regarding its tests for the microbiome, the class of microorganisms that live in the digestive tract and other parts of the body, ac-

Insurers including Anthem Inc., Aetna Inc. and Cambia Health Solutions's Regence Blue Cross Blue Shield unit are also examining the company's billing practices, according to people with knowledge of the matter.

In an interview last week, uBiome Chief Executive Jessica Richman said that "com-

Altering the microbiome can *prevent, mitigate* and *treat* many of the current health crisis facing the western world

- Cancer
  - Multiple mechanisms
  - Protects mucosa from radiation effects
  - Increases benefit from chemo agents
- Heart disease
  - Metabolic syndrome
  - Atherosclerosis
  - Hypertension
- Hepatic diseases
  - NASH
  - Hepatic encephalopathy
- Infectious disease
- Diarrheal diseases
  - AAD
  - Bacterial
  - *Clostridium difficile*
  - Viral
- Inflammatory diseases
  - IBD ?
  - Allergy
  - Asthma
  - arthritis
- Autoimmune diseases
- Aging
- Obesity
- CNS- Psychiatry
- Renal disease
- Critical Care / Surgery
  - Trauma
  - General surgery
  - Pancreatitis +/-
  - Transplantation
  - Sepsis
  - VAP prevention

In 2025 we need to think of the microbiome as another organ

- Functions of the microbiome
  - Metabolizes drugs
  - Produces and metabolizes nutrients
    - Vitamins (folate, vitamin K)
    - SCFA-multiple metabolic effects
    - Amino acids
    - Provide 10% of daily calories from SCFA
  - Stimulation of hormone secretion
    - Highest concentration of L cells in distal colon and rectum
  - Modulates immune function
  - Maintains mucosal barrier function
  - Modulates systemic inflammation

- We have not yet been able to define the ideal community of microbes
  - We can define a healthy set of metabolic functions
  - We can say that increased microbial diversity is associated with better outcomes
  - Do no extrapolate one probiotic strain to another
    - Many mechanisms are strain or metabolite specific

If microbiome not maintained:

Alterations in microbial virulence

Phenotypic switch in microbiome to "pathobiome"

Sobara MT et al Nature Rev Microbiology 2022
Reynolds T et al Surg Infect 2023
Zheng Z et al Frontiers in Cell and Inf Microbiology 2023
Napolitano LM Surg Infections 2023
Hyoju SK et al Br J Surg 2020
Guyton K, Alverdy JC. Nature Rev GI Hepatology 2017

To summarize the limitations with the probiotic literature

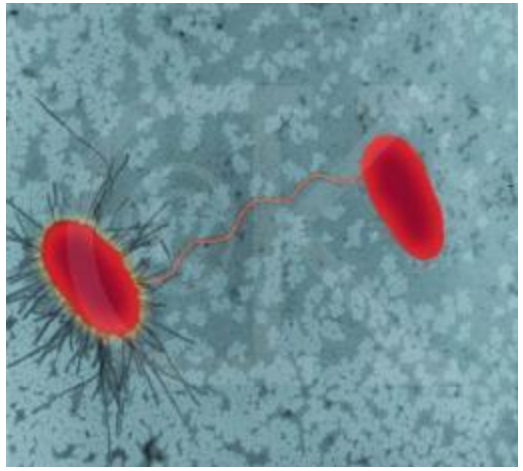
- **Efficacy-** most studies report positive results, VAP widely variable
- **Safety**- lack of consistent reporting in most reports
- **Mechanisms** – animal models excellent with proof of concept, humans difficult to show causal link between intervention and improved outcome
- **Heterogeneity**- of microbes and the patients
  - Wide variability in the composition (strain drift)
  - Viability and function of specific bacteria not universal
  - Probiotic delivery with or without prebiotics
- **Dosing** - probiotic preparations widely variable
- **Small study sizes -** most studies, more recent trials improving
- **Failure to overcome confounding factors –**
  - medications, treatments, during hospital and ICU stay etc

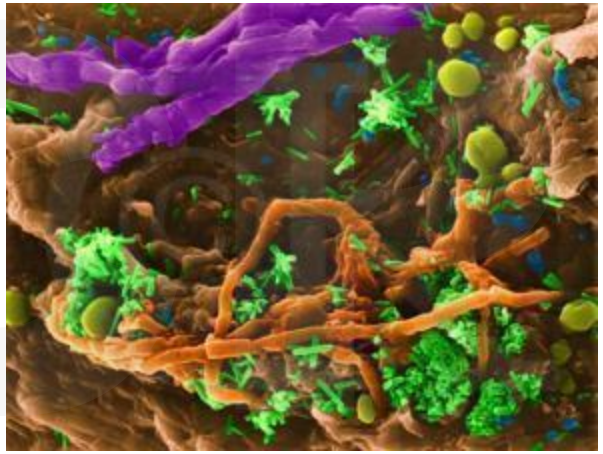
It time for a paradigm shift !

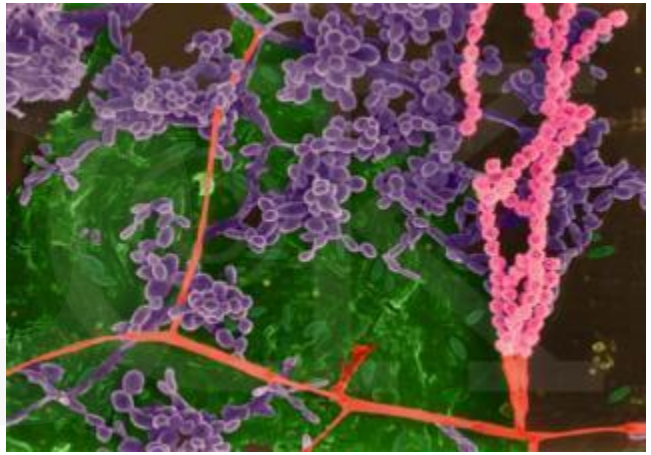
Supply adequate viable beneficial bacteria or a substrate which enhances these specific beneficial bacteria instead of trying to eliminate the pathogen ?

“Bioecological control”

Shift from Germ Theory to Germ Therapy







The most dangerous phrase in the English language is;

"We've always done it this way!"

Grace Murray Hopper