“ Incorporating Probiotics Into Your Clinical Practice: Does the science support the adoption?”

62 Annual NMAFP Family Medicine Seminar

Ruidoso Convention Center, August 2019

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Clinical Nutrition Continues to Evolve

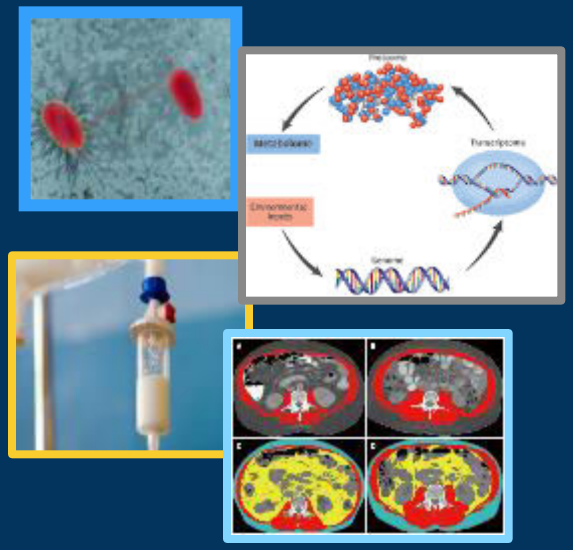
Nutrition Support

Nutrition Therapy

1960-1982 → **1982-2014** → **2015-?**

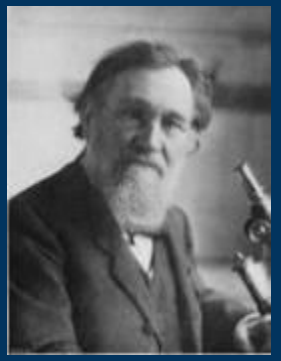
- "Skeletons in the Closet"
- PEM in 50% pts US hospitals
- Support to prevent PEM
- PN-based

- EN for macronutrients
- EN for non-nutritional benefits
  - Immune/metabolic-modulation
  - Attenuates inflammation
  - Maintains gut integrity
  - Maintaining the microbiome
- Increase protein delivery
- Inception of microbiome concept



- EN remains 1st choice
- Supplemental PN
- EN maybe = to PN in ICU
- More physiologic ILE
  - SPM's
  - Resolution vs inhibition
- Microbiome moves to mainstream
- Metabolomics—"omics"
- Resistance exercise
- Nutrition focus mitochondria

Where "man meets microbe" Dynamic Interplay of Mutualism



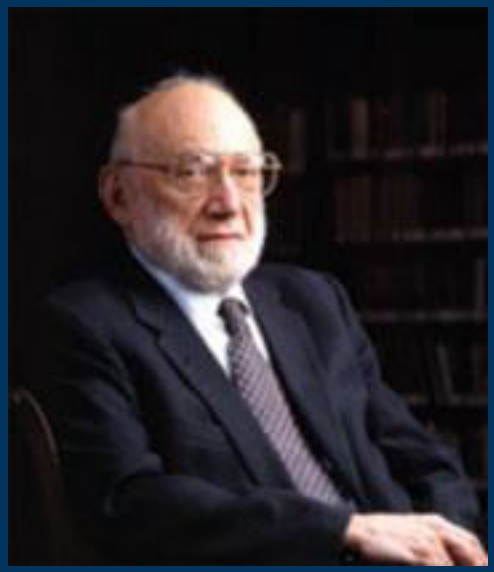
Metchnikoff 1906

- Concepts are not new
  - Referenced in Bible, Koran and in ancient Hindu text
  - Metchnikoff "father" of modern probiotic concepts

- Surface area of GI 300 to 400 sq meters
- > 8 million genes in the bacterial genome vs 20,000 in the human
  - 100 trillion living bacteria in the human intestine
    - » Only about 10 trillion cells in human body
  - Several thousand species in human colon, many non-culturable
  - Extensive # of microenvironments (skin, R v L hand etc)
- 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 2025

Human Microbiome

- Term suggested by Nobel Prize Winner Dr. Joshua Lederberg
- 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

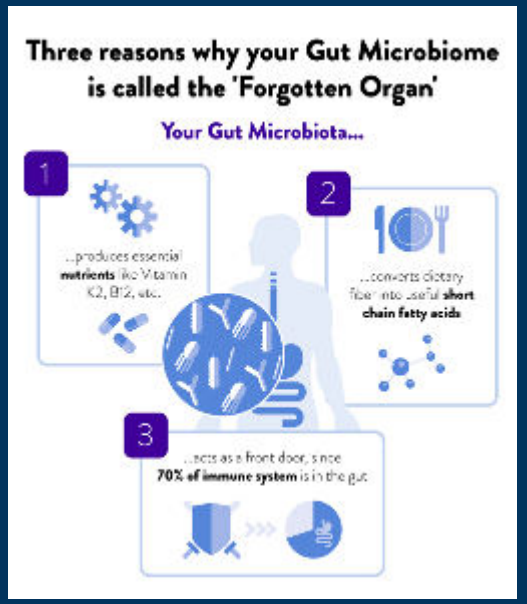


Joshua Lederberg, PhD
1925-2008

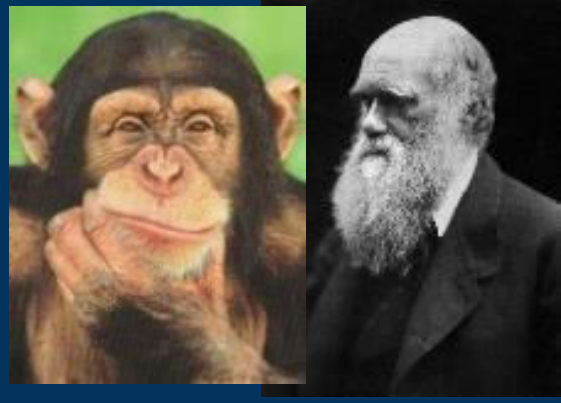
99% of our total genome is absent at birth

We need to think of the microbiome as another organ, and how this organ can fail !

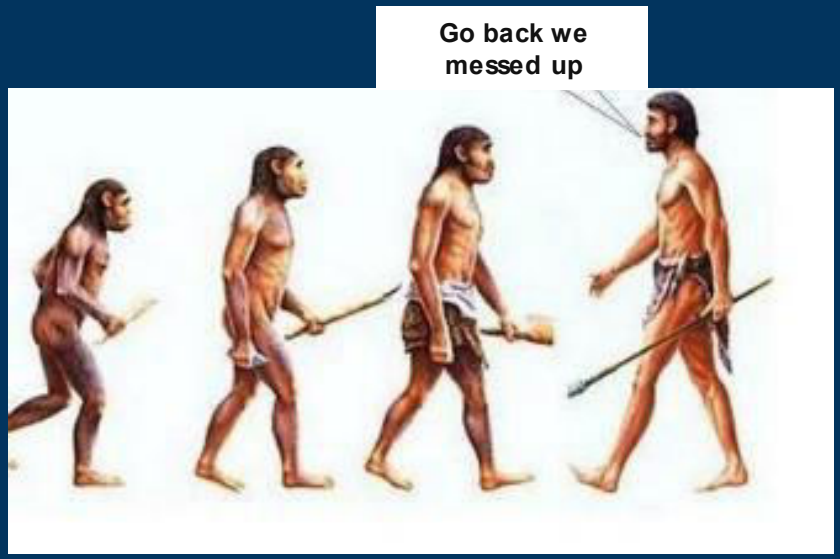
- Functions of microbiome:
  - Metabolizes drugs
  - Produces and metabolizes nutrients
    - Vitamins
    - SCFA
    - Amino acids
  - Stimulation of hormone secretion
  - Modulates immune function
  - Maintains mucosal barrier function
  - Attenuates systemic inflammation



The "Western" Diet: Are the microbiome changes driving inflammatory disease epidemic?

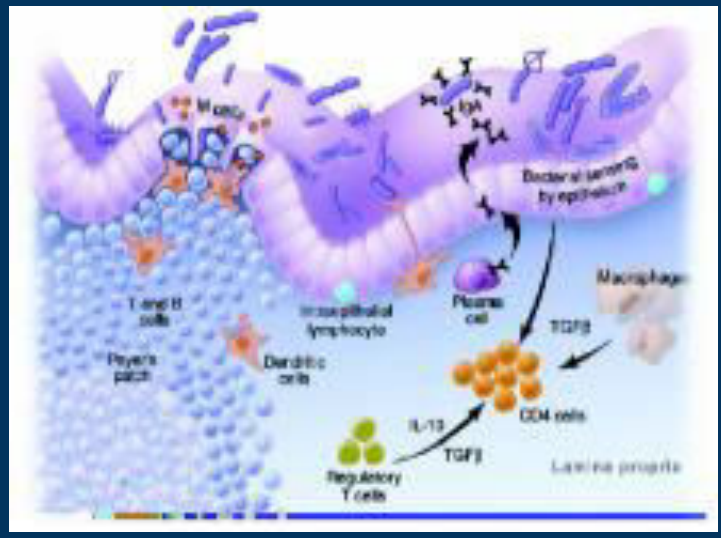


- Sedentary lifestyles
- Newborns in USA
  - 1/3 C section, majority bottle fed
- Immunizations
- Domestic pets
- Decrease in parasitic infection
- Refrigeration
- Sanitation and hygiene standards
- Urban life in cities and concrete
- Major dietary changes
  - Fats, protein, fiber, additives, emulsifiers, sweeteners, anti-oxidants, preservatives, refining grains, de-germination of grains
- 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



Could some of the problem be iatrogenic ?

- Broad spectrum antibiotics
  - Changes noted within hours
- Oral antiseptics
- PPI / H_2RA
- Vasopressors
  - Changes in pH ,dec pO_2 inc pCO_2
- Opioids
  - Decrease motility and bacterial clearance mechanisms
  - Alters bacterial pathogenicity
- Decrease in luminal nutrient delivery
  - Delays in feeding
  - Parenteral nutrition
  - Altered bile salt production
  - Decrease IgA production
- Invasive devices



Keeping Healthy Gut Bacteria:

"The good, the bad and the ugly"

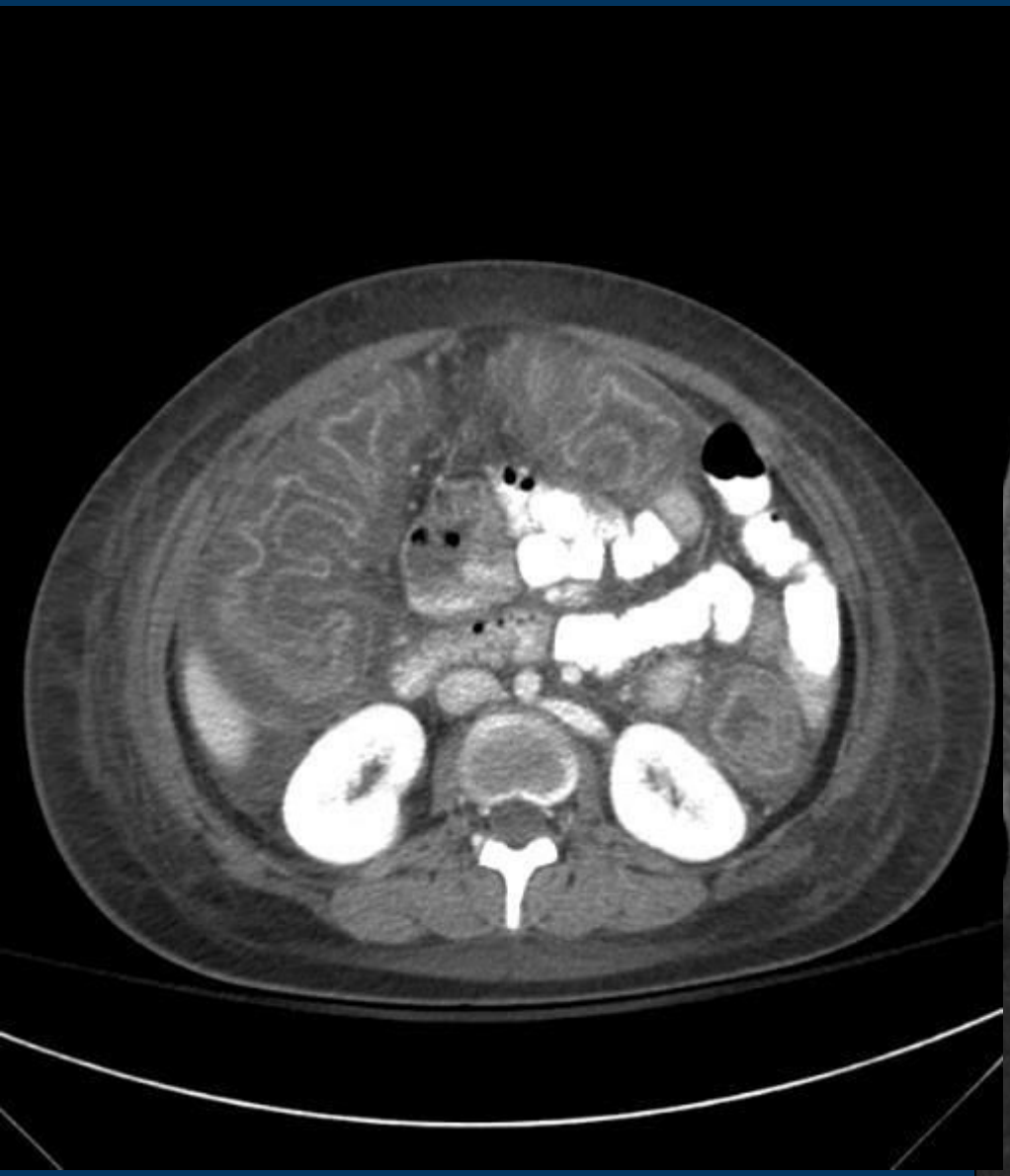
- Case study: 23 yo female – previously healthy
- Presents to Emergency Department 5 days s/p term cesarean
  - C section history: Premature rupture of membranes, induction, prolonged labor (16h) → C-section.
  - Received prophylactic antibiotics
- Cramping abdominal pain, malaise, low urine output, watery diarrhea 5-7x / day – prompting Emergency visit
-

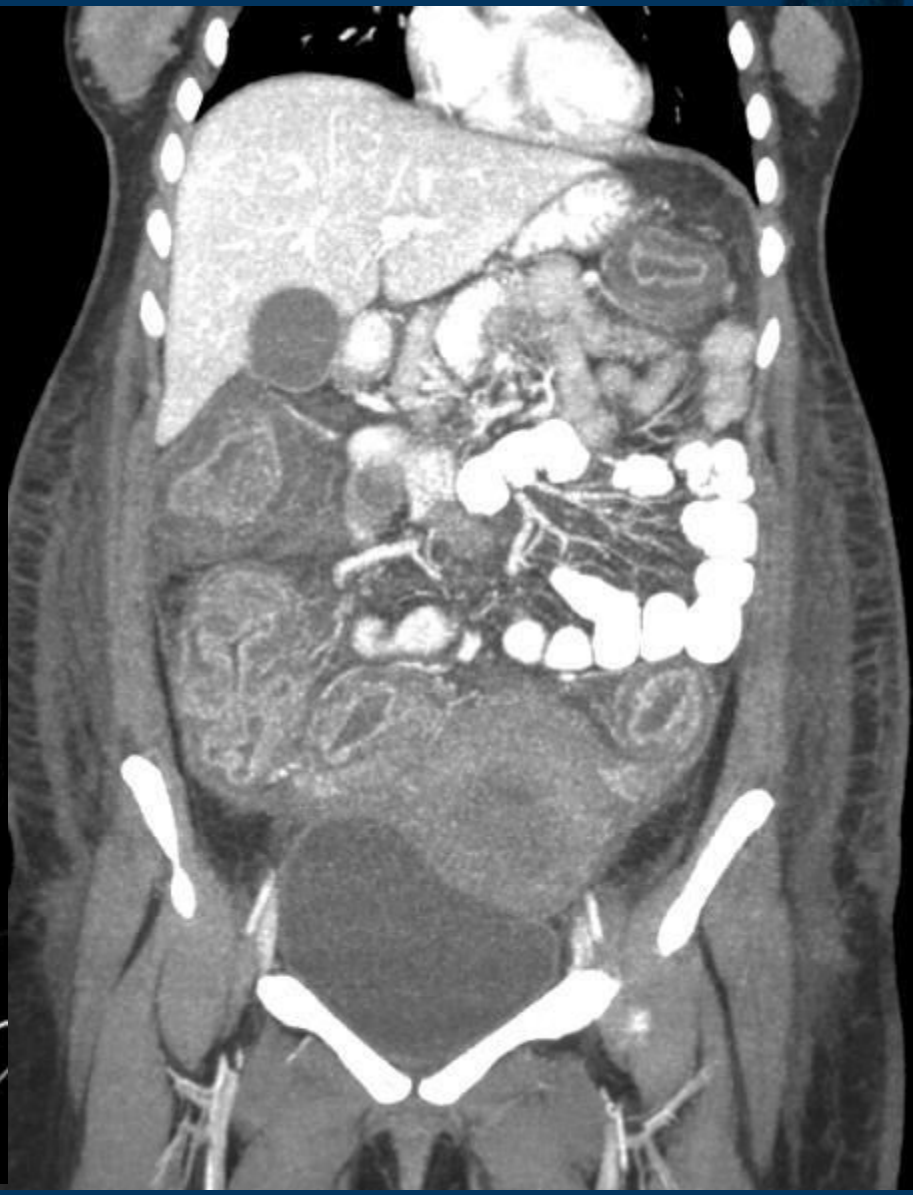
Case

- T – 37.9 HR – 112 BP – 96/50 Sat – 96% room air
- WBC 16K Cr – 1.10
- Stool Studies, including C.*difficile* toxin sent off
- 2Liters IV fluids given
  - T – 37.1 HR – 89 BP – 110/61
  - Feels better, urinates, eats a cracker
  - Adamant about going home to be with new baby

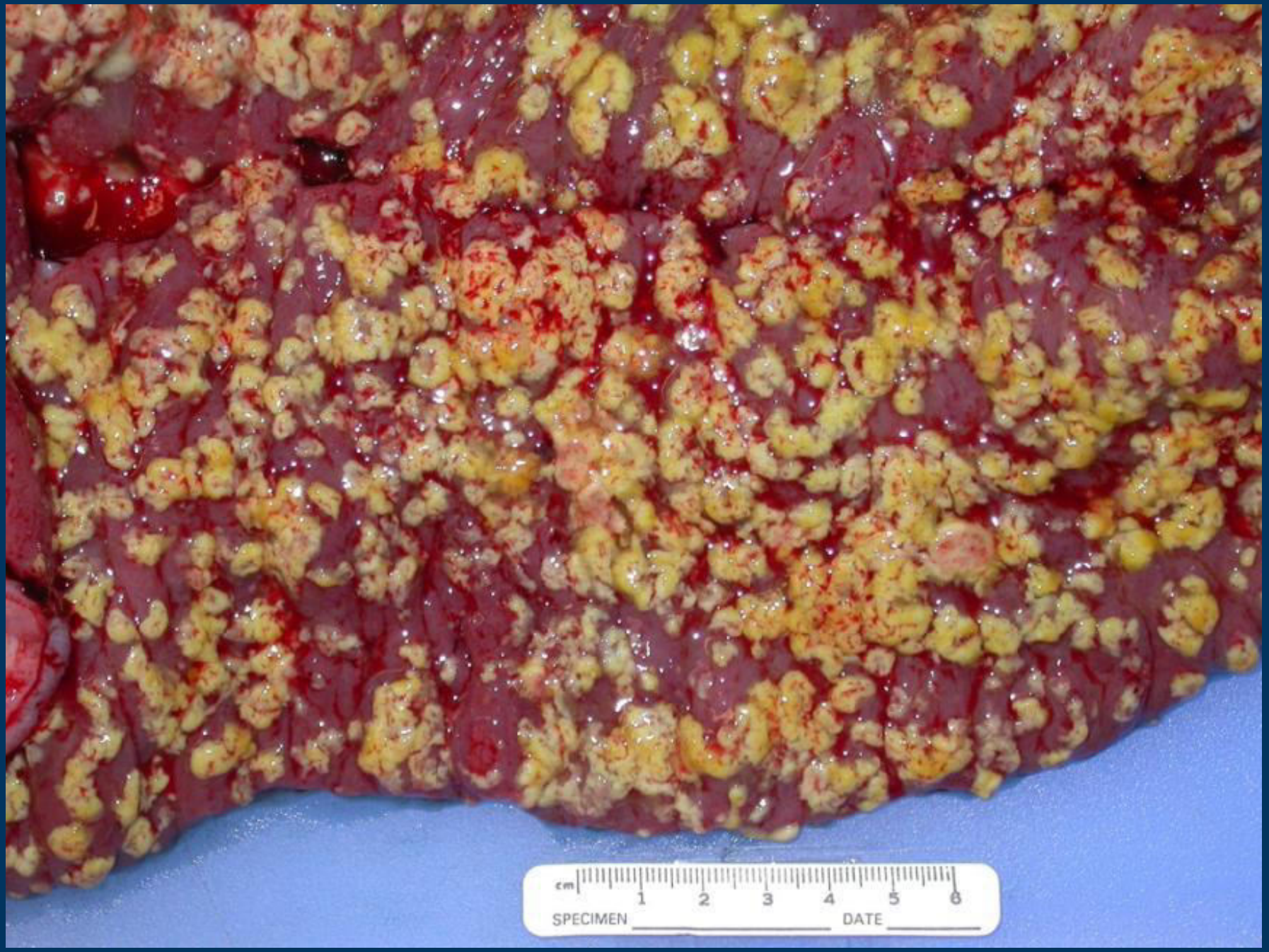
Case

- Next day….. C.diff comes back positive
  - Patient called to inform regarding + C.diff stool
    - Husband states she is worse than previous day
  - On arrival to ED: Looking very ill and septic
  - Admitted from Emergency department with working diagnosis of endometrial infection from prolonged rupture of membranes
  - CT ordered





- Chief Resident in surgery tells me, “she is too sick to operate on”
- My response: “She is too sick not to operate on”
- Taken to the OR in septic shock, on 3 pressors with MAP of 50 !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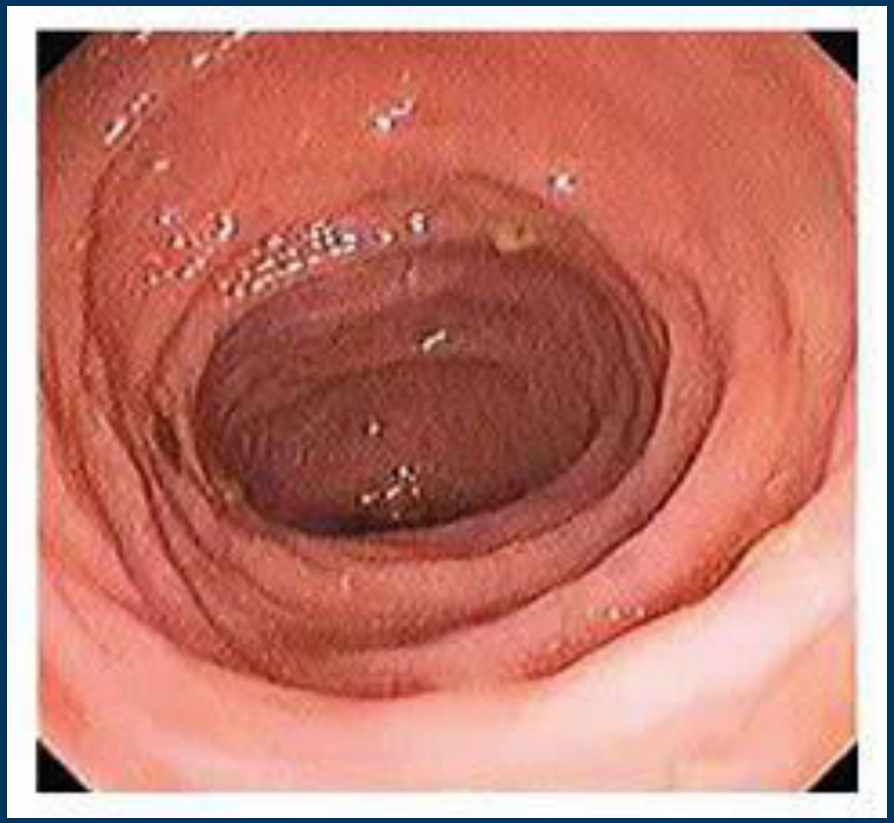
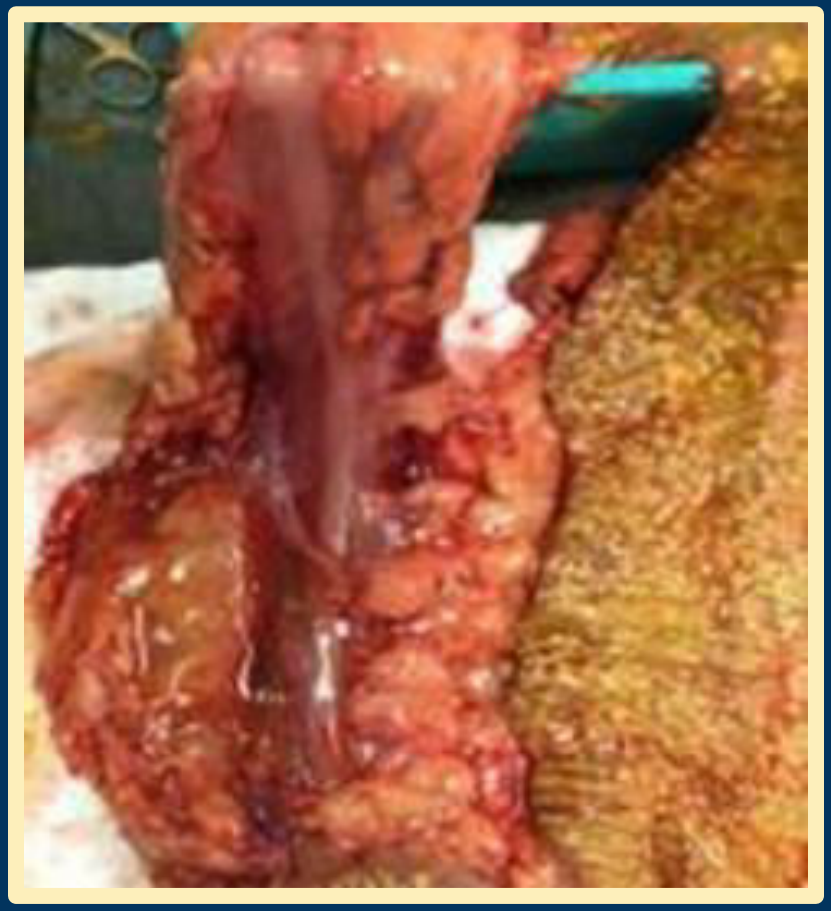
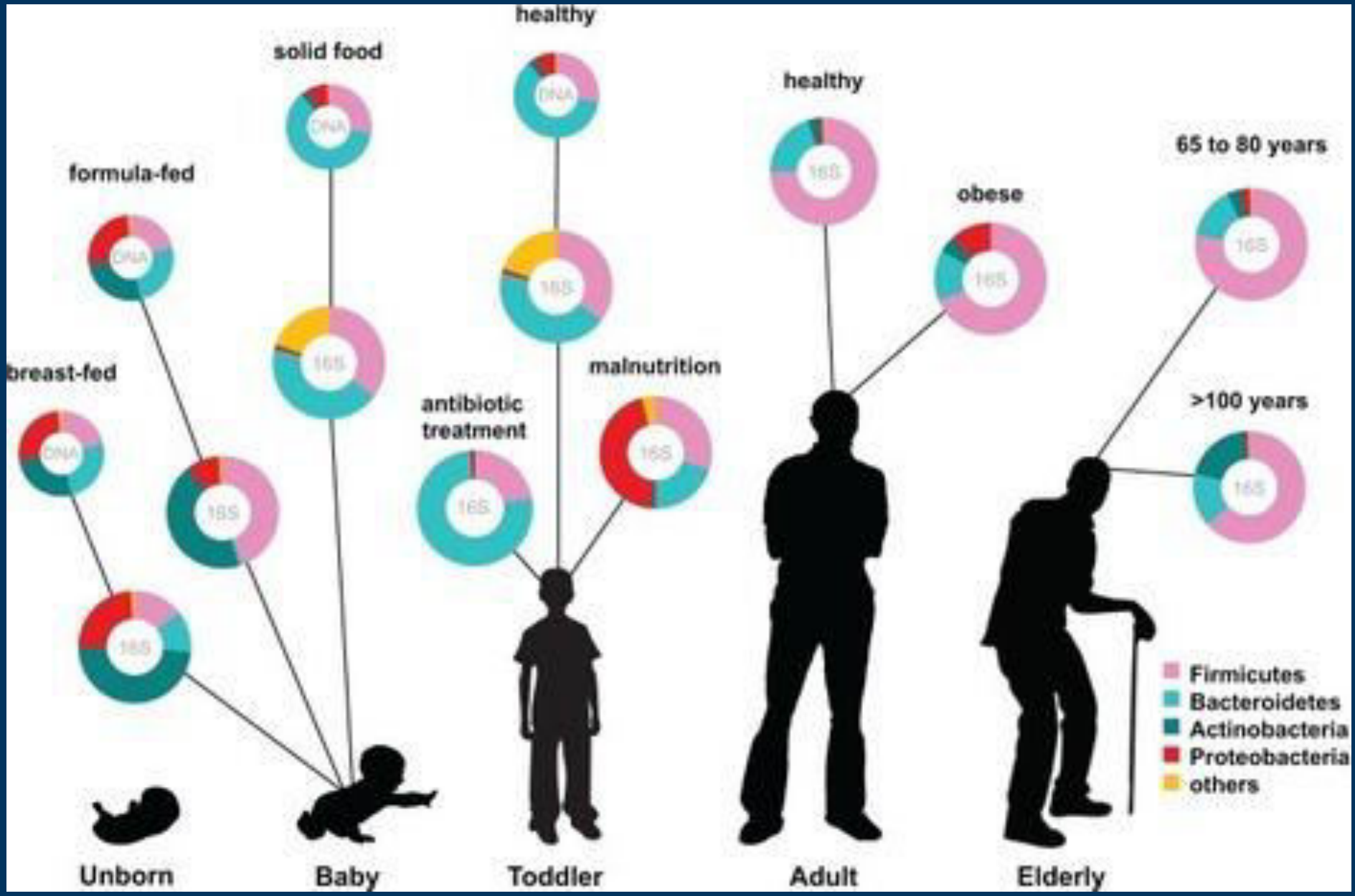
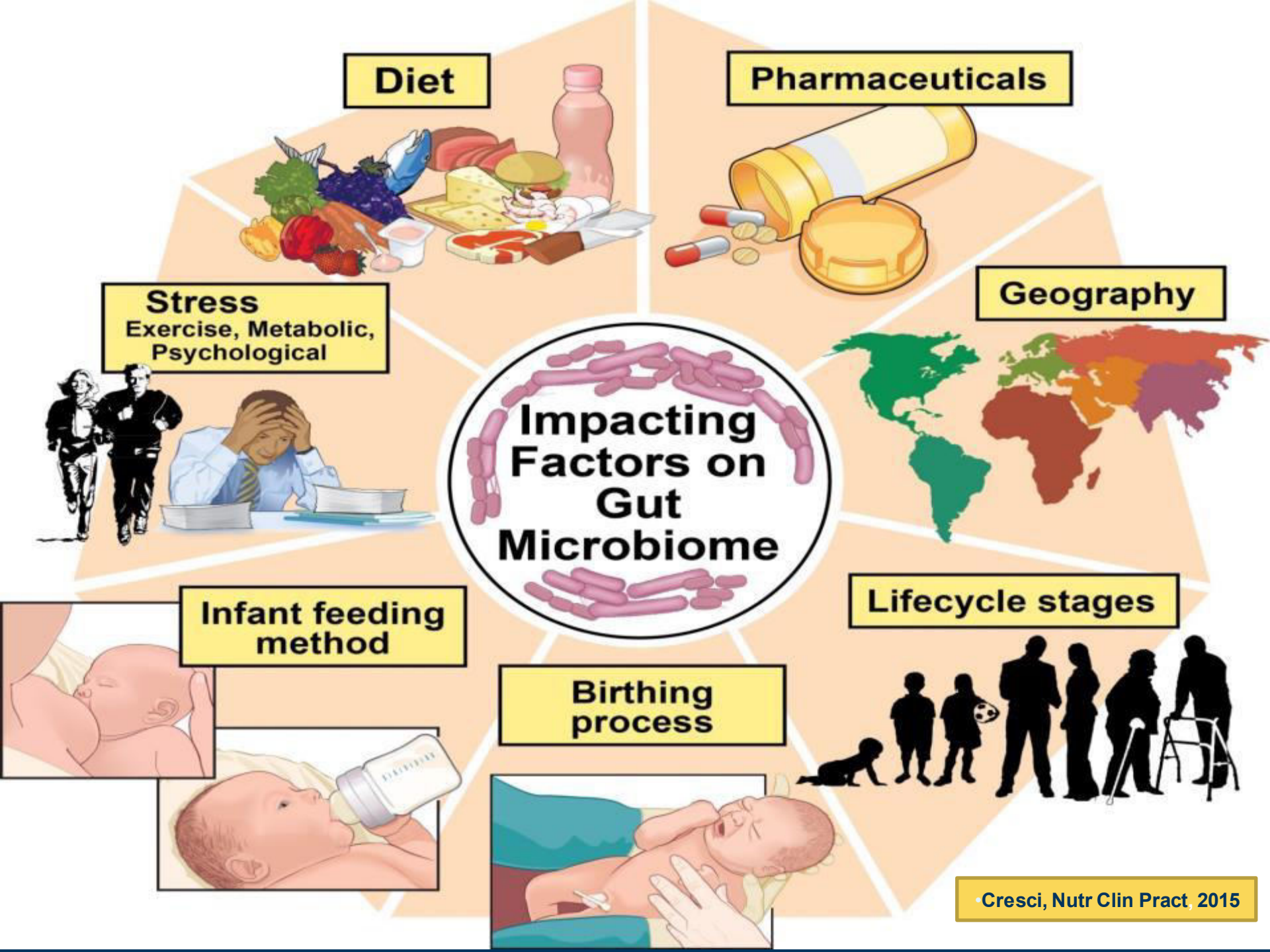




How can keeping healthy microbiome prevent this ?

Your Intestinal Microbiota Evolves as You Age!

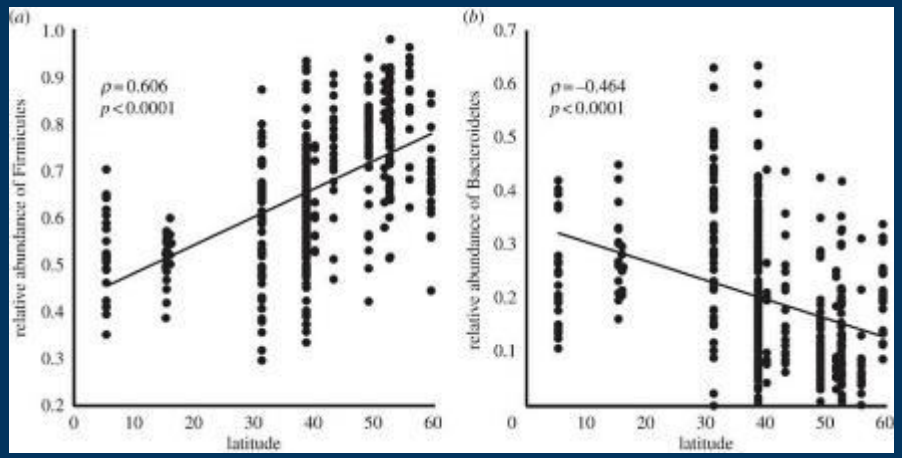


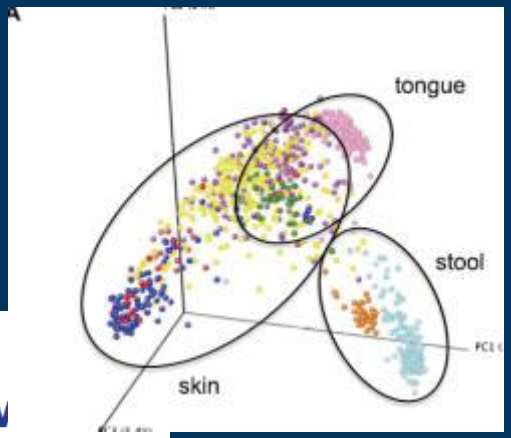


•Cresci, Nutr Clin Pract, 2015

It takes very little to rapidly change our microbiome

- International travel





- Cohabitating with pets

Cohabiting family members share microbiota with one another and w 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

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

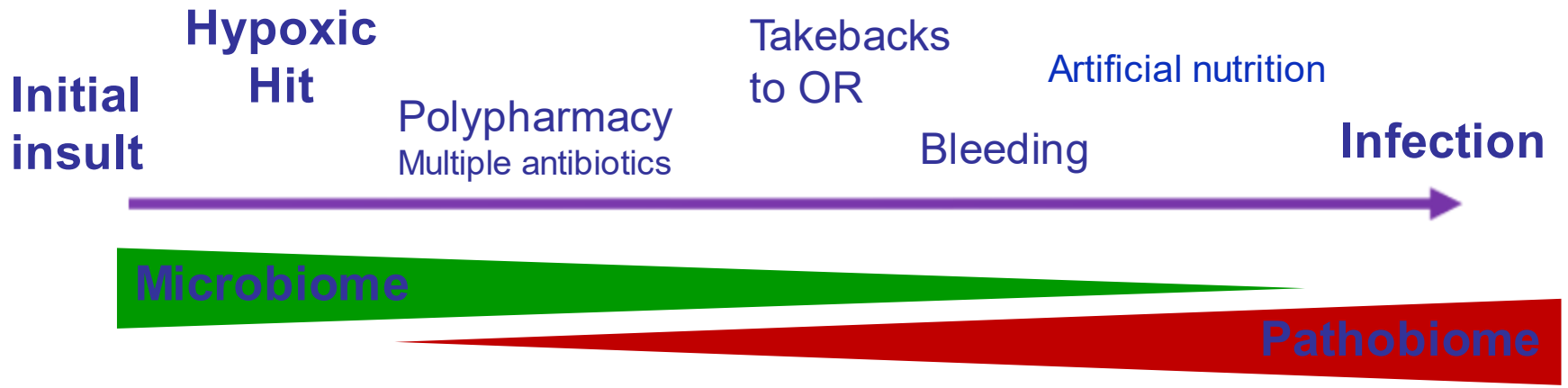
- Cancer
  - Multiple mechanisms
  - Protects mucosa from radiation effects
  - Increases benefit from chemo agents
- Heart disease
  - Metabolic syndrome
  - Atherosclerosis
  - Hypertension
- Hepatic diseases
  - NASH
  - Hepatic encephalopathy
- Infectious disease
- Diarrheal diseases
  - AAD
  - 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

The intestinal environment of surgical injury transforms *Pseudomonas aeruginosa* into a discrete hypervirulent morphotype capable of causing lethal peritonitis

Surgery
Volume 153, Number 1
2013

Trissa Babrowski, MD,[a] Kathleen Romanowski, MD,[a] David Fink, MD,[b] Moses Kim, MD,[a] Vissagan Gopalakrishnan,[c] Olga Zaborina, PhD,[a] *and* John C. Alverdy, MD,[a] *Chicago, IL, Boston, MA, and Baltimore, MD*

During critical illness, time is the enemy



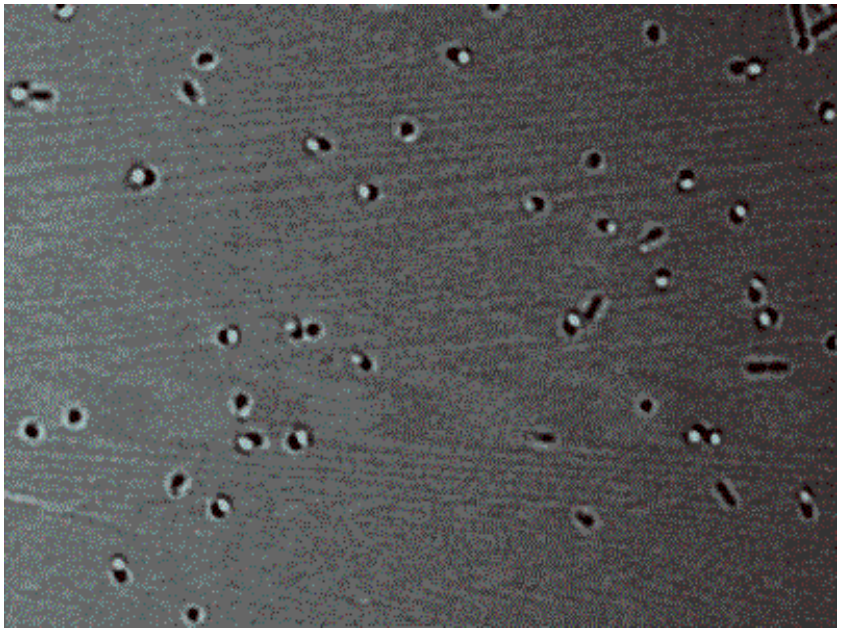
Critical loss of commensalism and the emergence of pathogens expressing enhanced virulence drives the immunopathology of critical illness

"Microbiome becomes Pathobiome"

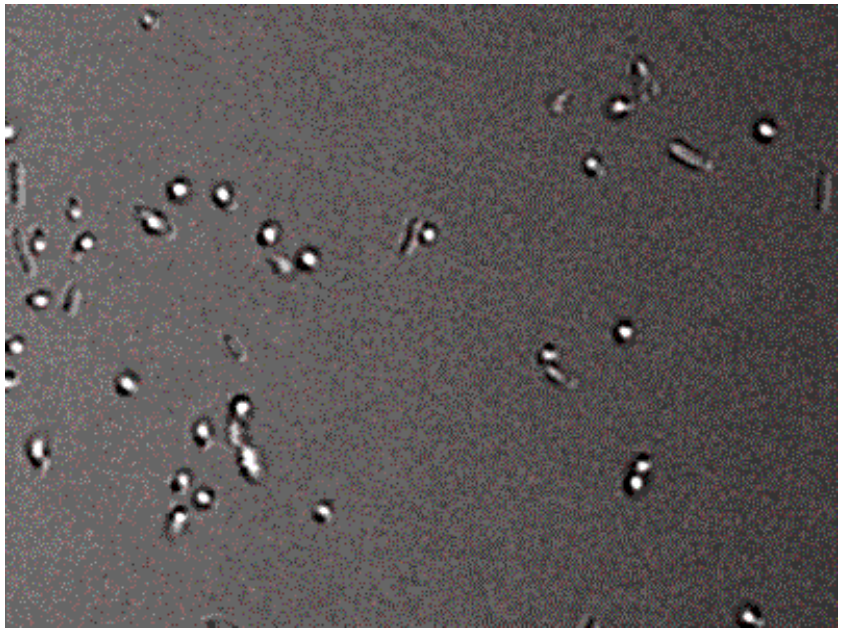
Guyton K, Alverdy JC et al Nature Rev GI 2016

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



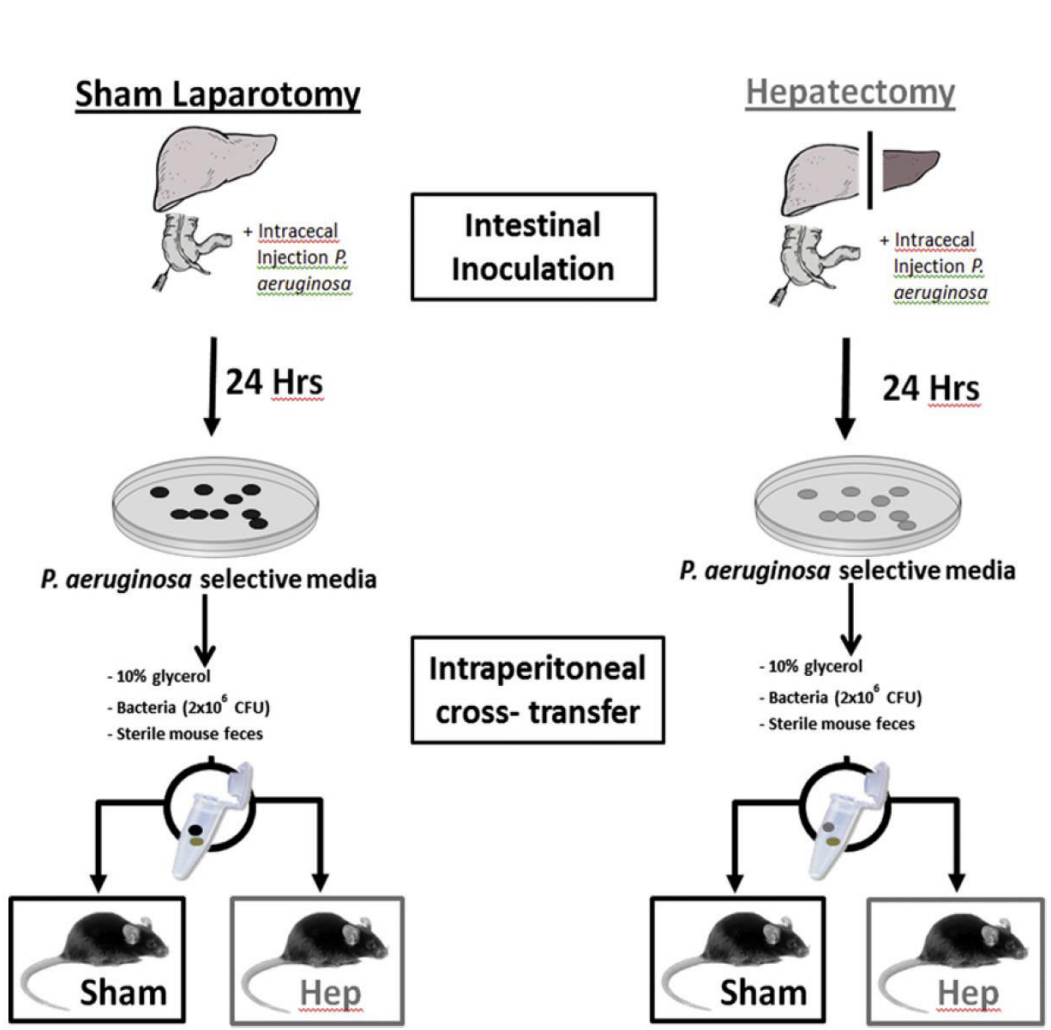
opioid

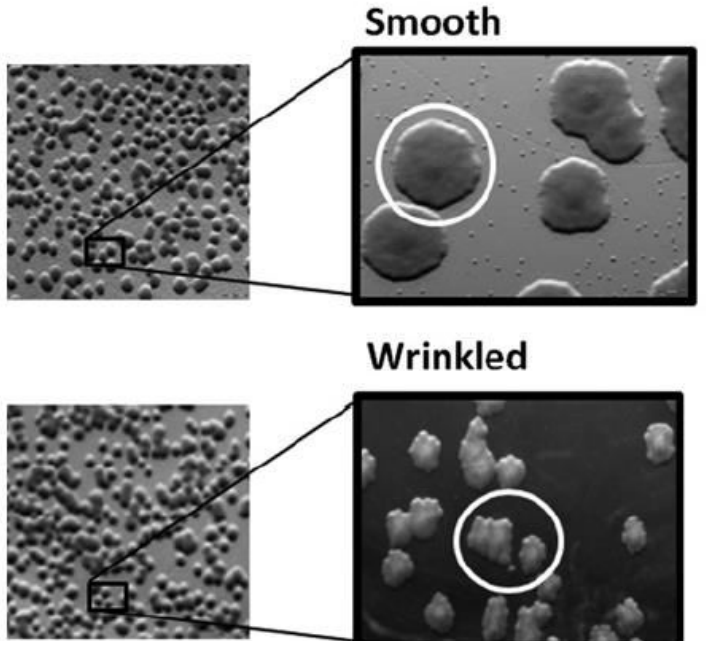


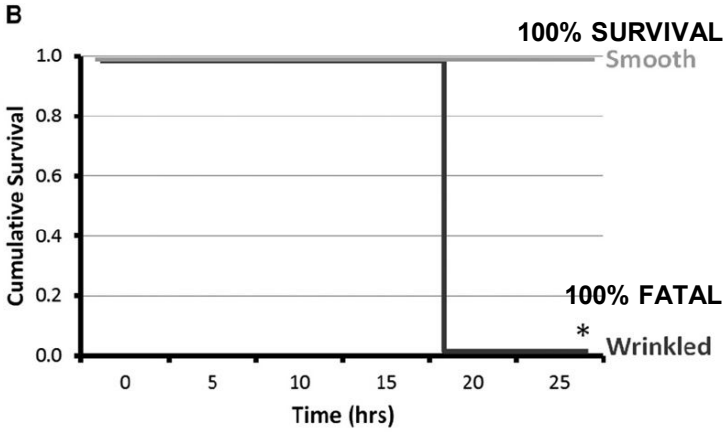
vehicle

Ming J eta al Science 2015

Within 24 hours, a lethal *P. aeruginosa* morphotype develops







Microbial phenotype- NOT species, NOT immune background- caused death- so then what actually drives sepsis outcome?

Delicate balance which surgery disrupts !

Impact of previous antibiotic therapy on outcome of Gram-negative severe sepsis*

Michael T. Johnson, PharmD; Richard Reichley, PharmD; Joan Hoppe-Bauer, BA, BS, MT; W. Michael Dunne, PhD; Scott Micek, PharmD; Marin Kollef, MD

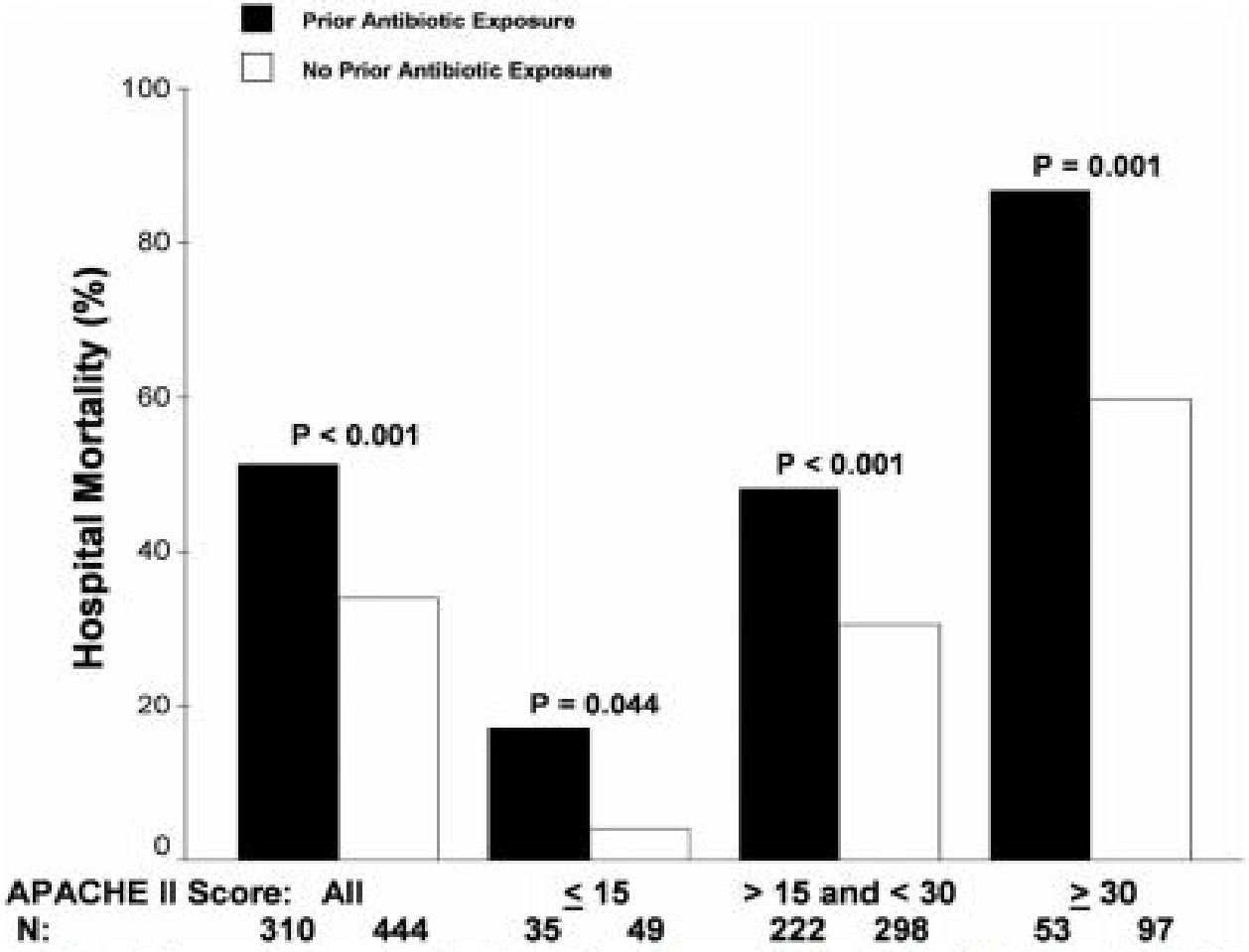


Figure 1. Hospital mortality stratified by Acute Physiology and Chronic Health Evaluation II (*APACHE II*) score.

- **Is this real?**
- **What are the possible mechanisms?**

Crit Care Med 2011

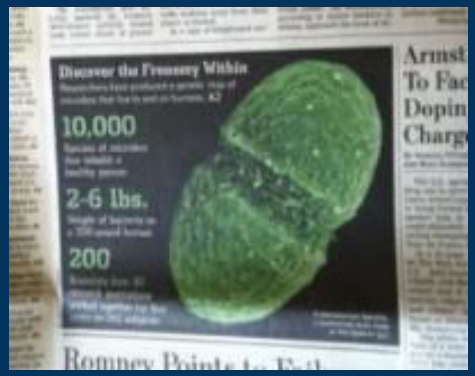
The Million Dollar Question ?

Can addition of probiotics to the daily diet "prevent or mitigate" onset of disease ?

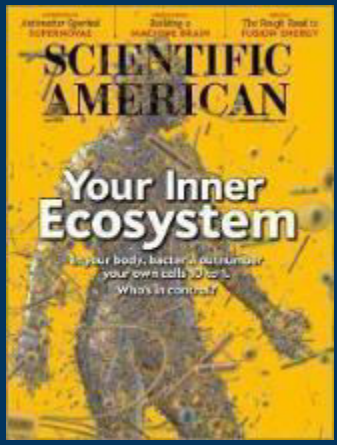
Clinical Application:
Microbiome literature: Science or Quackery?

- Recent lead articles:
  - All major journals 2018-2019
  - 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
  -

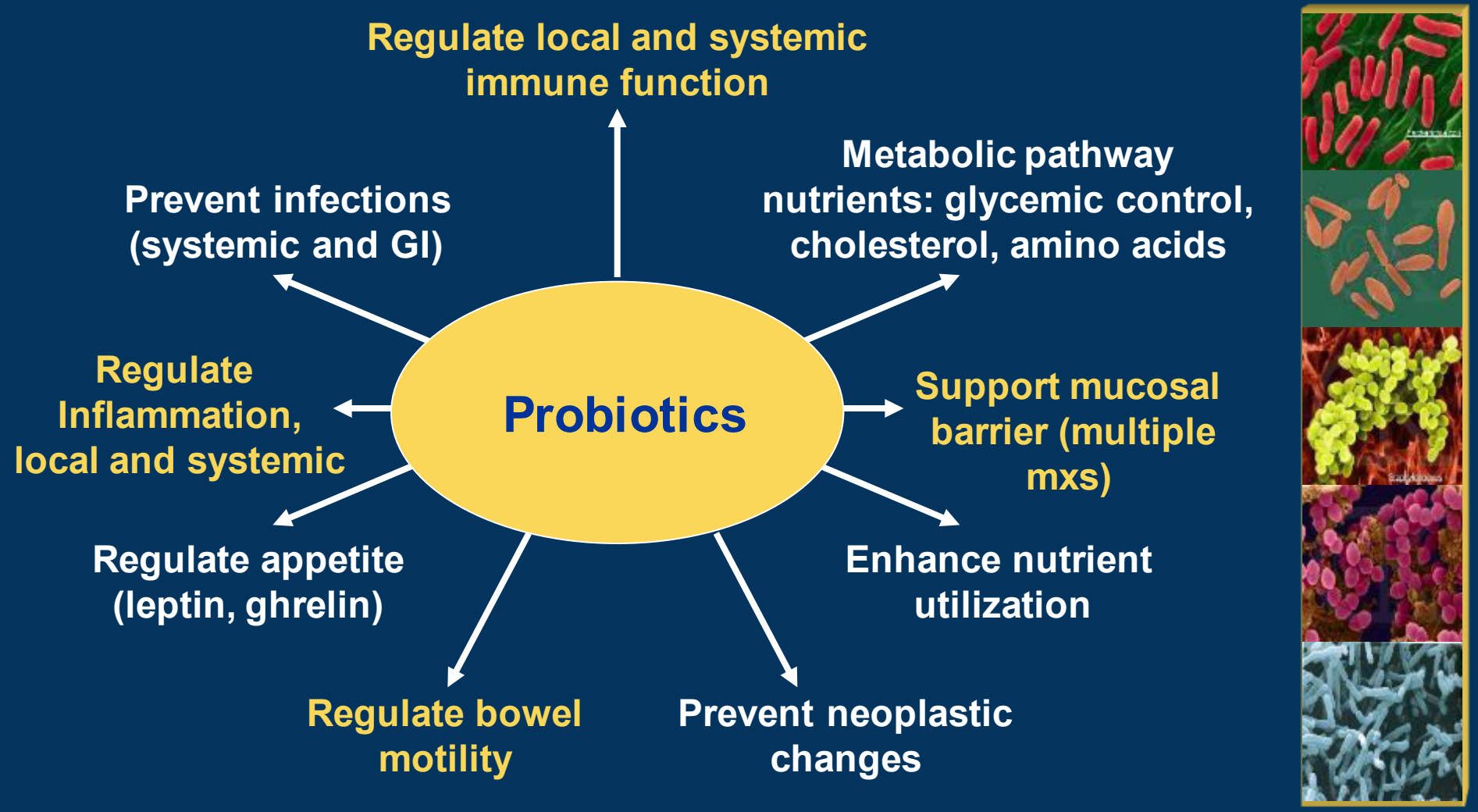
New York Times 2013



Wall Street Journal 2012



Probiotics: Exploring the Mutually Beneficial Effects of Bacteria and Their Substrates in the Human Host



Has Our Fear of "Bacteria" Made Us More Susceptible to Disease

Production of antimicrobials

Destruction of toxin receptors

Competitive exclusion

Organic acid production

Enhanced barrier function

Enhanced IgA secretion

Pathogens

Probiotics

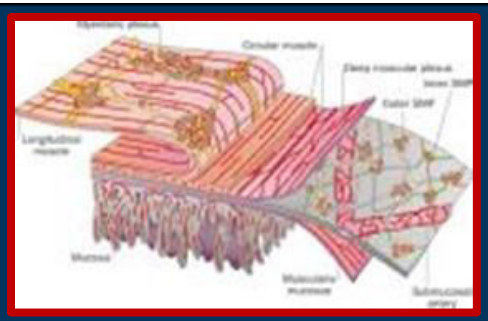
Immunoregulation

Lymphocyte

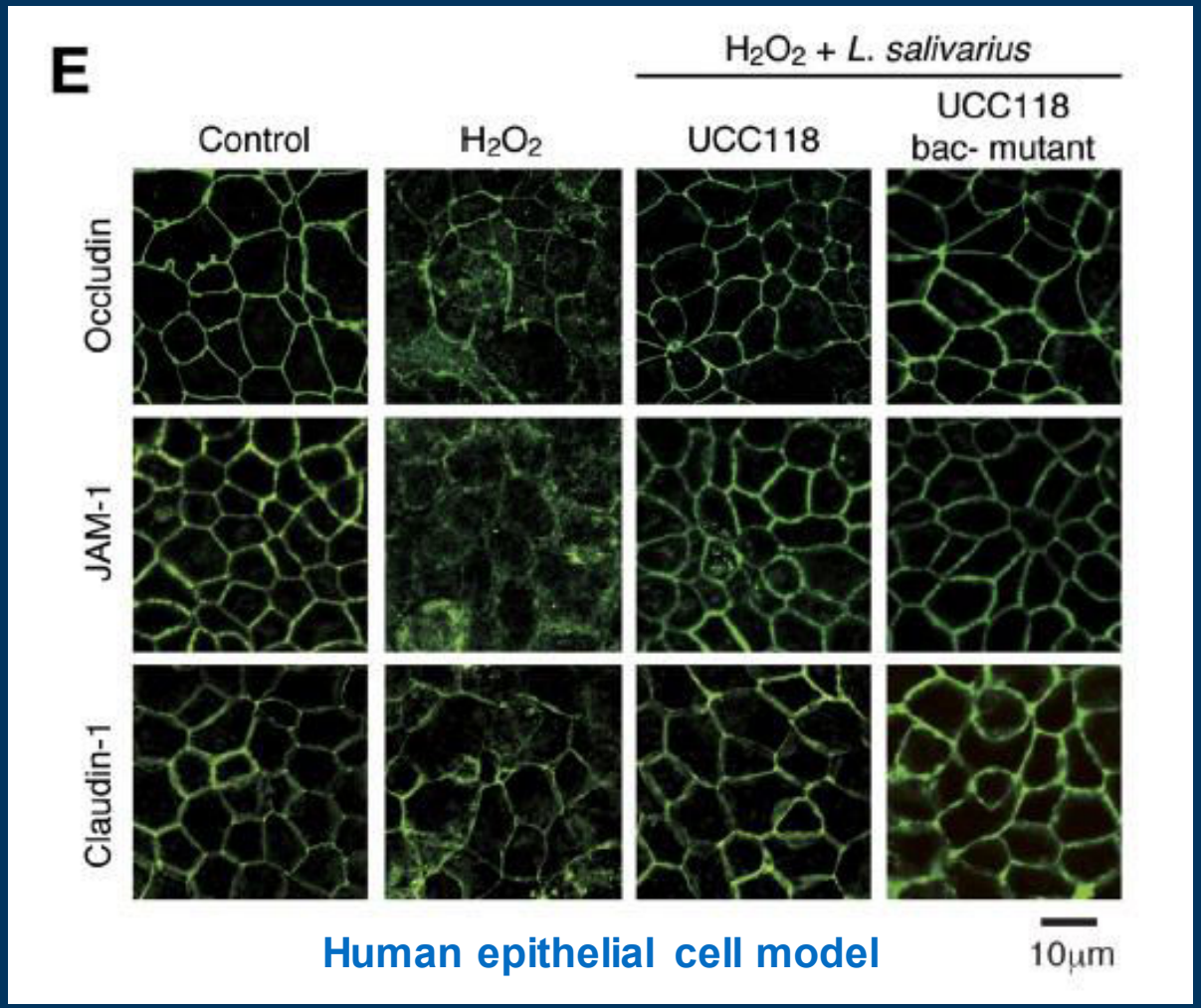
Enhanced visceral blood flow

L. reuteri inhibits *H. pylori*

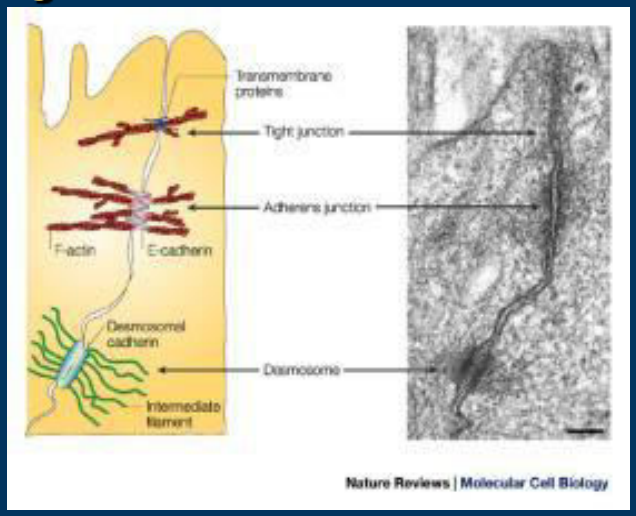
L. reuteri inhibits *Staph aureus*



Lactobacillus *salivarius* (UCC118) prevents disruption of epithelial cell tight junctions

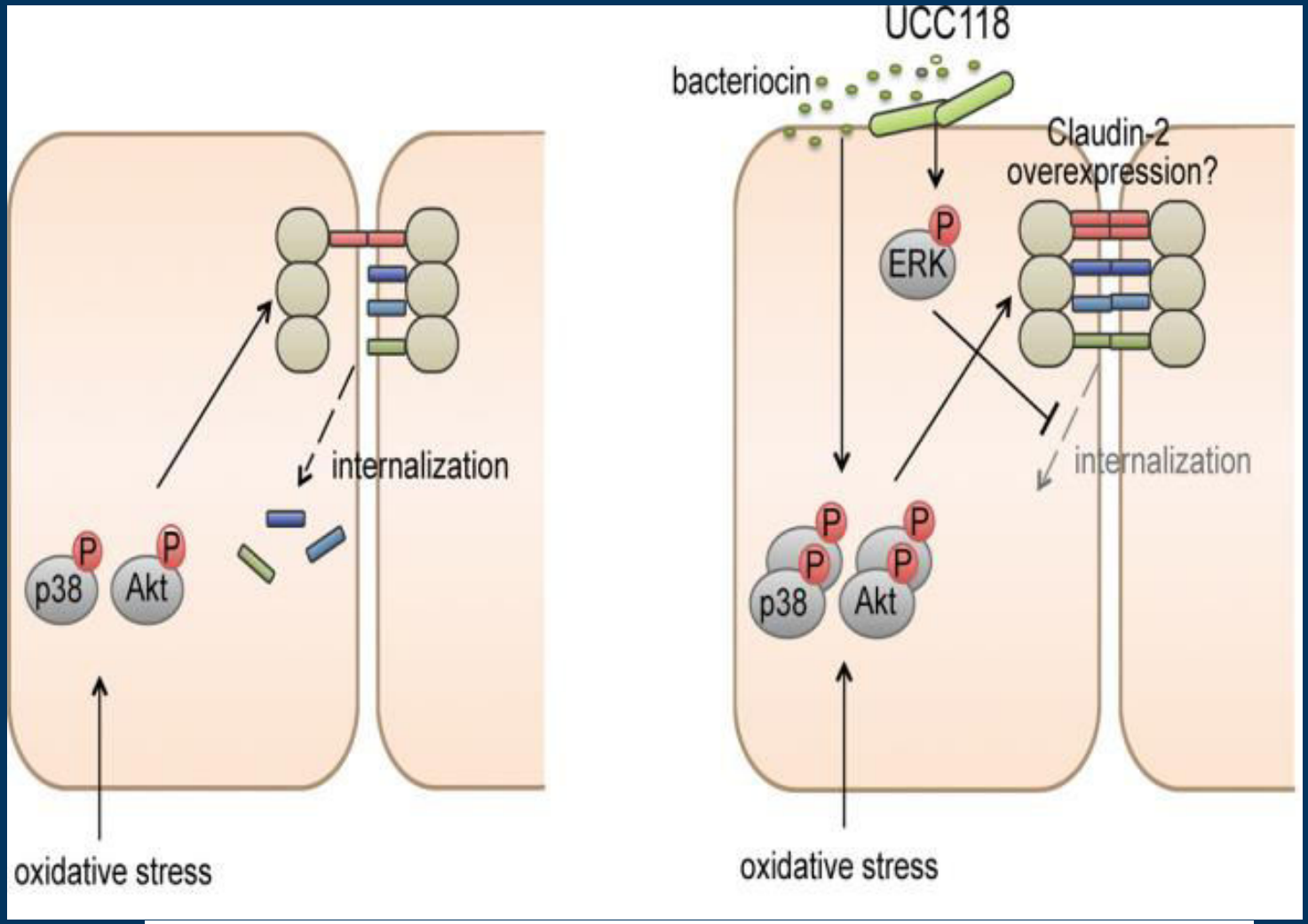


Human epithelial cell model



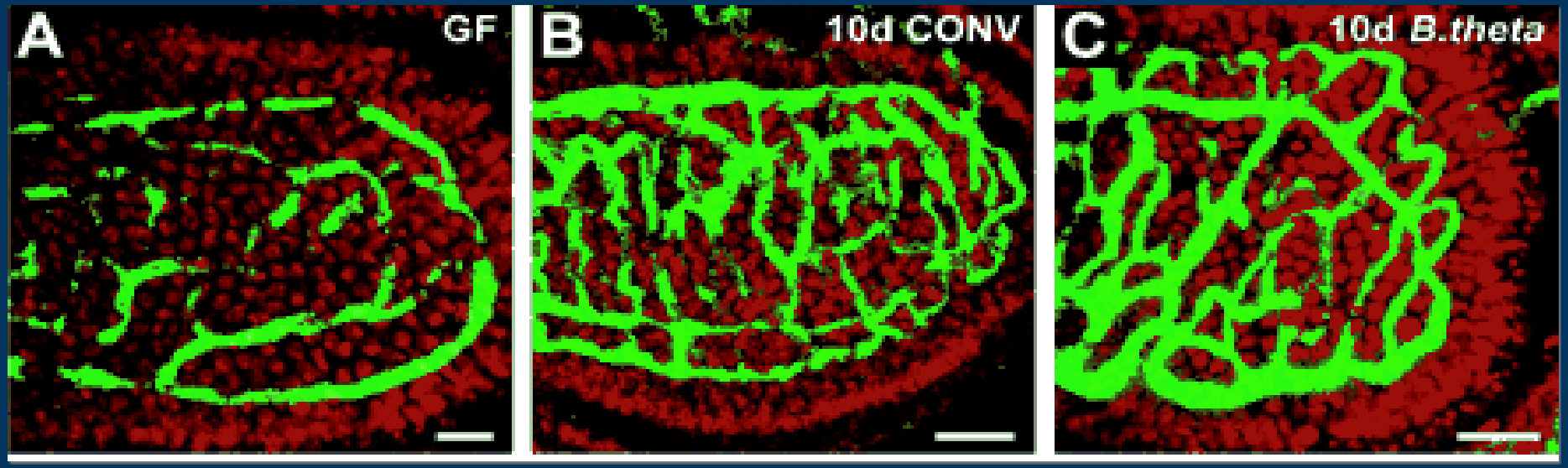
Miyauchi et al Am J Physiol Gastrointest Liver Physiol 2012
Sinead C PNAS 2010

UCC118 alters tight junction protein localization.



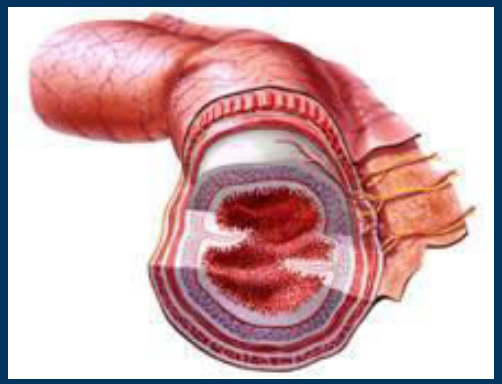
Tight junction proteins

Mechanisms:
Enhancing mucosal blood flow

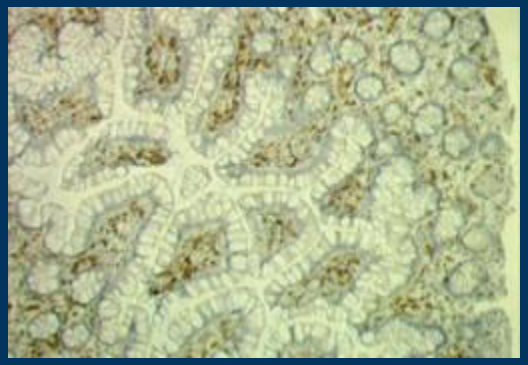


- Stappenbeck TS, Hooper LV et al Proc Natl Acad Sci 2002

Mechanisms: Stimulation the immune system in the small intestine of healthy subjects

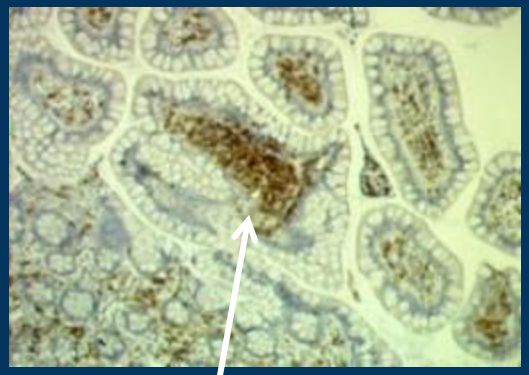


Before L.reuteri intake



Resting CD4+ T-helper cells

After L.reuteri intake



Activated CD4+ T-helper cells

Clinical Equivalent

Probiotics prior to Immunization seasonal flu vaccine:

Enhances anti-body response

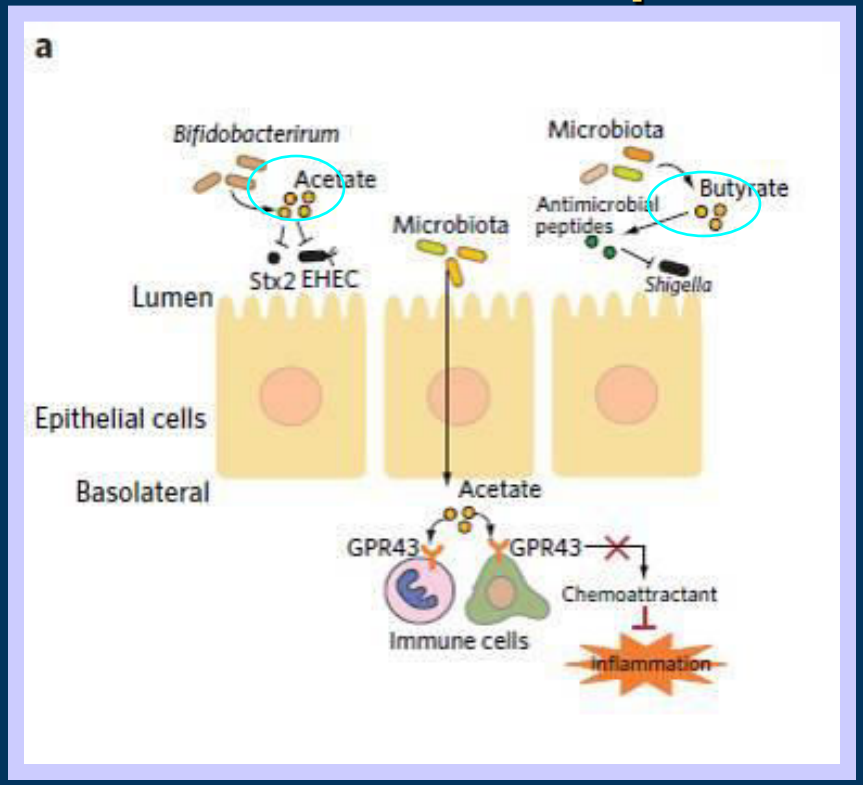
Specific IgG, IgG1, IgG3

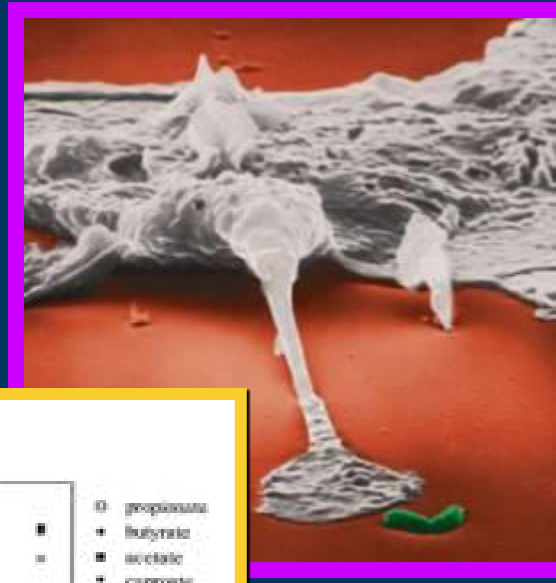
No change in inflammation

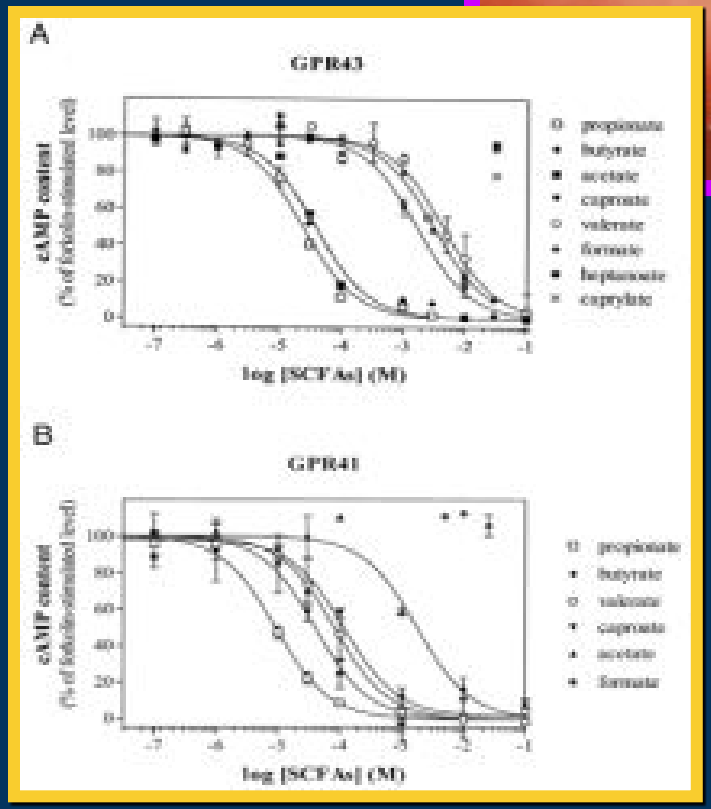
Razzardini G, et al Br J Nutr 2012

Valeur et al., Appl Environ Microbiol 70 1176-1181 (2004)

SCFAs, Fiber Fermentation and Butyrate Receptors

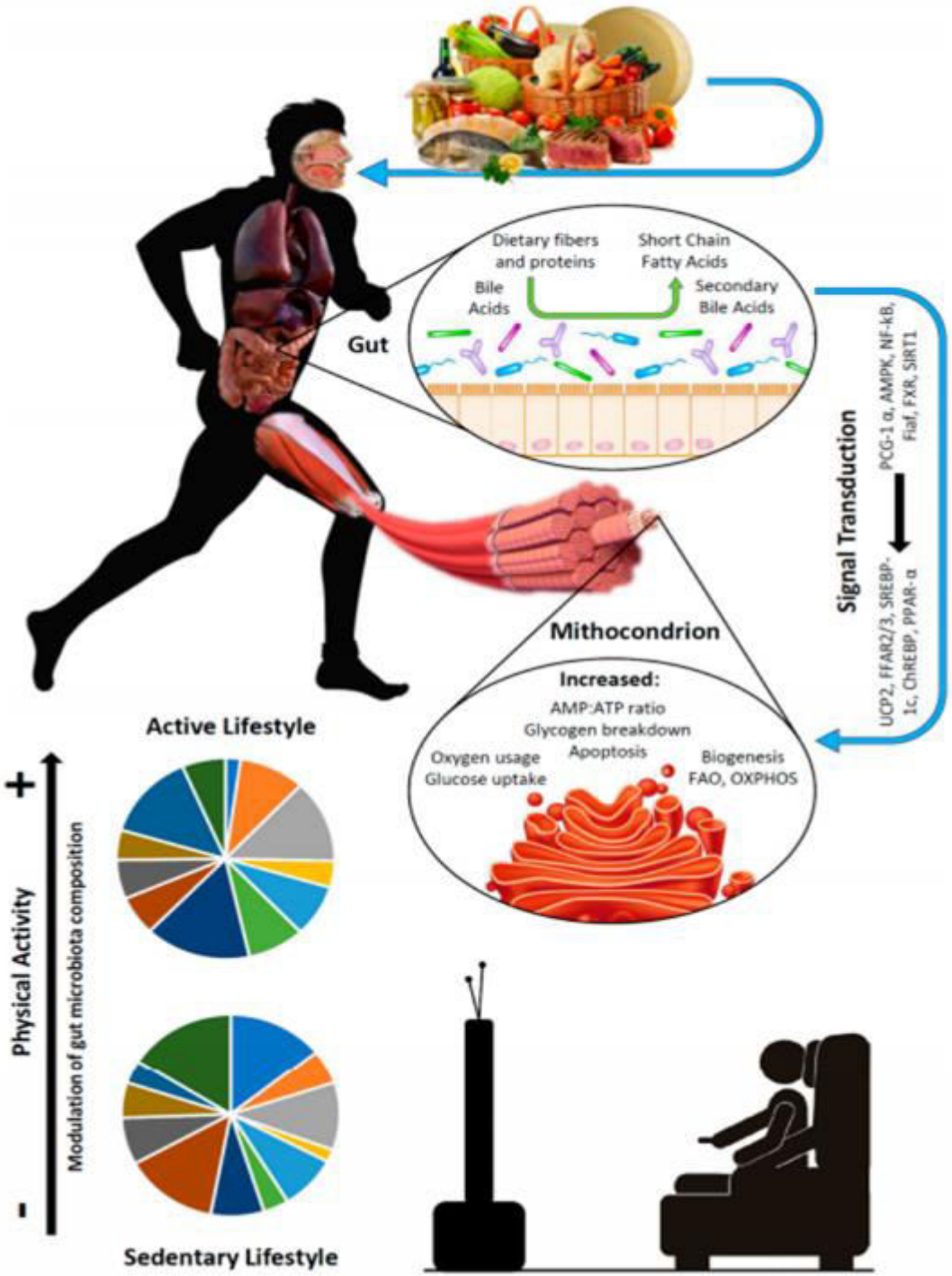






- Trophic effect, colonocyte fuel
- Anti-inflammatory
- Enhance WBCs, macrophage
- ↓Adhesion molecules
- ↓microvascular thrombosis
- Decrease insulin resistance
- Prevents cancer development

Thangaraju M et al J GI Surg 2008
Ganapathy V 2011
Bhat MI et al Nutrition Rev 2017



Evidence supports SCFA enhancing muscle function and mitochondrial biogenesis in the myocyte.

Essentially potentiating the benefit of exercise in muscle maintenance

Scheimen J et al Nature Med 2019
Ticinesi A et al Nutrients 2017

Table 1. Fields of study in which there are meta-analysis concerning the evaluation of efficacy of the consumption of probiotics.

Rondanelli M Gut Microbes 2017

Diseases	Main results
	METABOLIC DISEASES
Type II diabetes	Reduction of glucose and glycated hemoglobin
Dyslipidemia	Reduction of total cholesterol and LDL cholesterol
Hypertension	Improvement in blood pressure, especially if the basal blood pressure is high
Overweight and Obesity	Different effects on body weight changes
	GASTRO INTESTINAL TRACT DISEASES
Helicobacter Pylori	Significant improvement of the eradication rate of bacteria
Cronic Inflammatory Bowel Diseases	Practical option in ulcerative colitis both as induction therapy that maintenance
Irritable bowel syndrome	Reduction of the pain and the severity of related-symptoms
Costipation	Improve in whole gut transit time, stool frequency and stool consistency
Antibiotic-associated diarrhea	Prevention of diarrhea
Diarrhea associated with chemotherapy	Prevention of diarrhea, specially of second degree
Diarrhea associated with Clostridium Difficile	Risk reduction of 64 %
	ALLERGIC DISEASES
Atopic syndrome and hypersensitivity to food	Reduction in eczema infant, improvement of atopic syndrome
Allergic riniti	Improvement of the quality of life and nasal symptom
	RESPIRATORY TRACT INFECTIONS
Respiratory tract infections	Reduction in the incidence of symptoms of respiratory tract infections
ventilator-associated pneumonia	There are insufficiency evidence to recommend probiotics as a routine therapy
	LIVER DISEASES
Non alcholic fatty liver disease (NAFLD)	NAFLD: decrease in liver aminotransferase levels and improving insulin resistance
Encephalopathy	Probiotics decrease overt hepatic encephalopathy in patients with liver cirrhosis
	OTHER DISEASES
Acute pancreatitis	No significant effect
Bacterial vaginosis	No significant evidence
Urinary tract infections	No significant evidence
Periodontitis	Use as an adjunct to non-surgical periodontal treatment of chronic periodontitis
Depression	Decrease in the score on the depression scale
Children born prematurely	Reduction of sepsis, both bacterial and fungal origin, that reduced incidence of severe necrotizing enterocolitis
Post-trauma patients	Reduction in the incidence of hospital infections, Ventilatory-associated pneumonia and length of intensive care

Attempting to prevent or treat acute and chronic disease with probiotics

No all "probiotics" are equal

Association does NOT Equal causation

Mechanisms of action are key

Need the right strain and research to prove it

Kriebs A Nature 2019

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

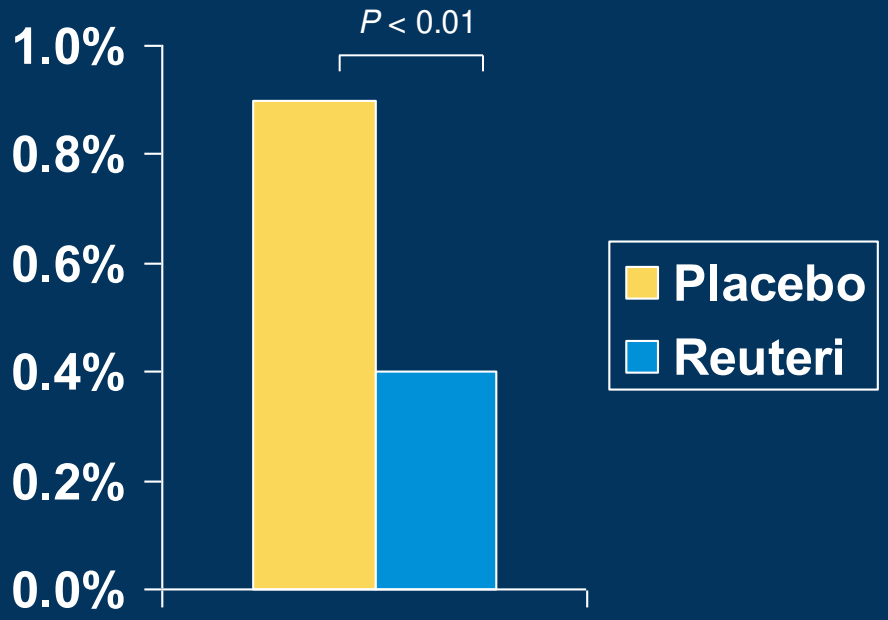
Sick days at home with short term gastro-intestinal or respiratory illness. PRCT N=262 subjects, 80 days to complete study

Placebo: 0.9 % sick days
2 days per individual and year

Reuteri: 0.4 % sick days
<1 day per individual and year **

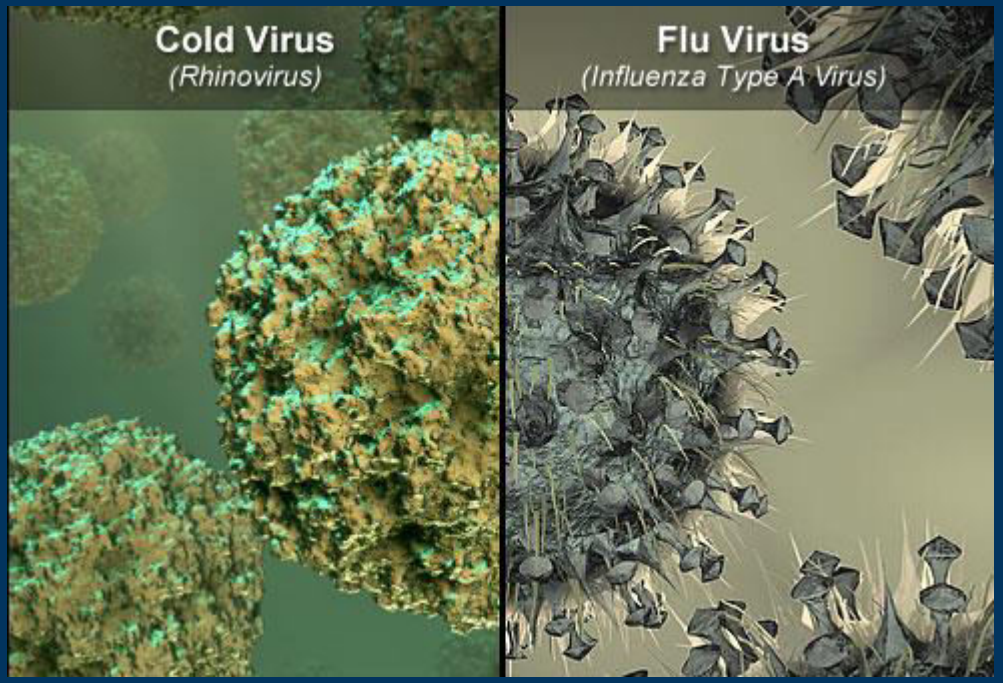
Number of people sick

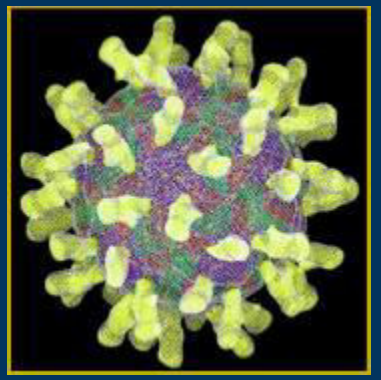
26% on placebo (23 persons)
11% on Reuteri (10 persons) p<.01**



Tubelius P et al., Environ Health 2005

Probiotics and Prevention of Common Cold





Probiotics for preventing acute upper respiratory tract infections (Review)

Hao Q, Dong BR, Wu T

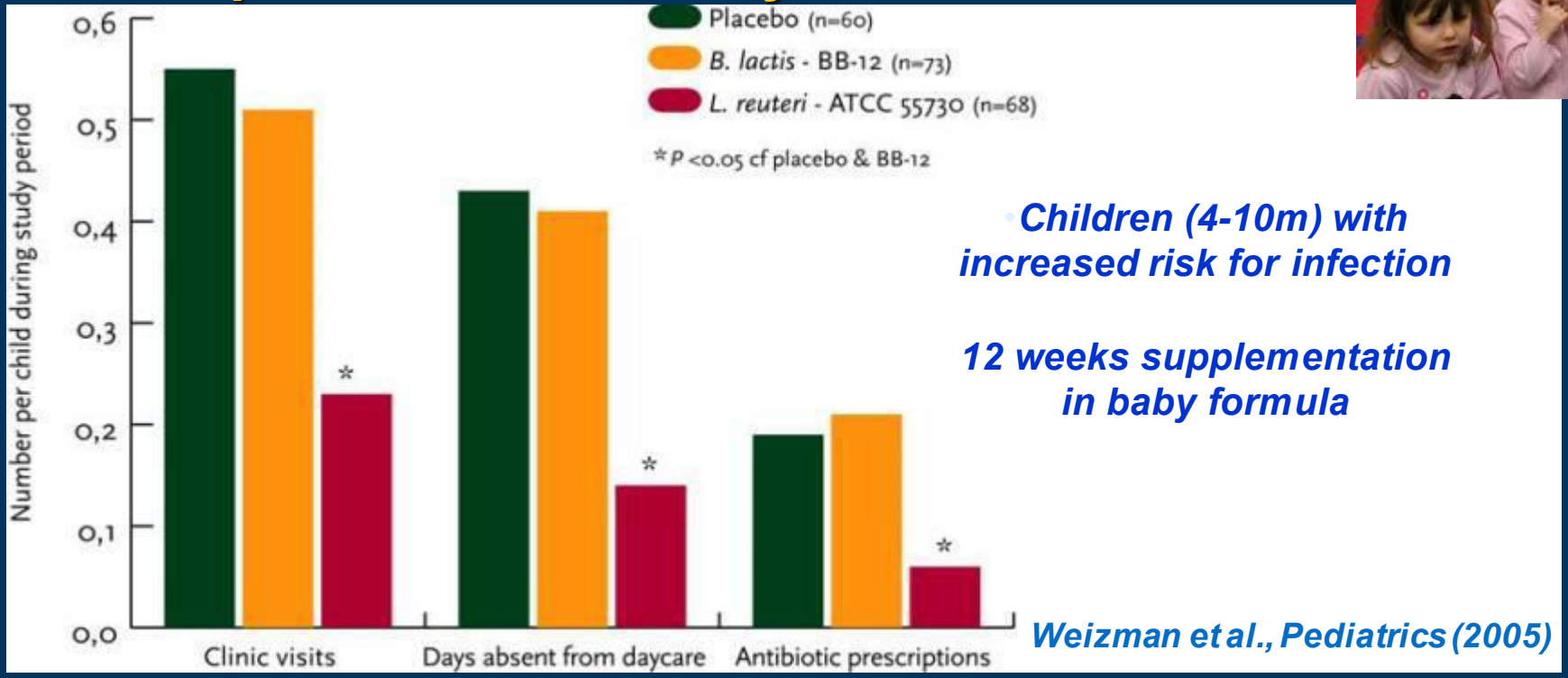
- To assess the effectiveness and safety of probiotics (any specified strain or dose), compared with placebo, in the prevention of acute URTIs in people of all ages
- 12 Studies included in the analysis
  - 3720 Participants (Children+Adults)
  - Placebo versus Probiotics
- Probiotics were better than placebo in number of acute URI
  - OR 0.53 95% CI 0.36-0.76 p<0.001
- Probiotics were better than placebo in reducing the mean duration of URI
  - OR -1.89 days 95% CI -2.03 to -1.75 p<0.001

THE COCHRANE COLLABORATION®

Cochrane Feb 3, 2015

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**

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

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

nature
International journal of science

2017

- RDBPCT of L. plantarum + FOS n=4,556 infants >2,000gm, 35wk gestation
- WHO criteria for sepsis 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

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 dec GDM
  - Most 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

Probiotics to Prevent Pediatric Asthma:
It's a crap shoot

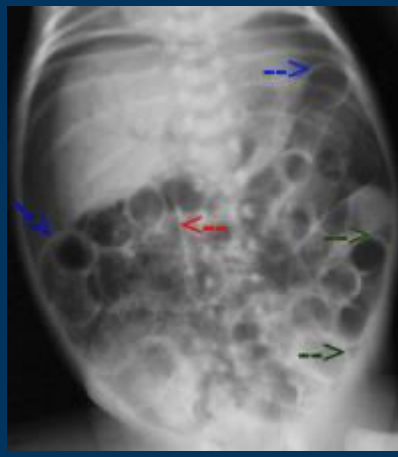
nature medicine

Farm-like indoor microbiota in non-farm homes protects children from asthma development

July 2019

Pirkka V. Kirjavainen[1,2*], Anne M. Karvonen[1], Rachel I. Adams[3], Martin Täubel[1], Marjut Roponen[4], Pauli Tuoresmäki[1,5], Georg Loss[6], Balamuralikrishna Jayaprakash[1], Martin Depner[7], Markus Johannes Ege[8,9], Harald Renz[10], Petra Ina Pfefferle[11], Bianca Schaub[8,9], Roger Lauener[12,13,14,15], Anne Hyvärinen[1], Rob Knight[16], Dick J. J. Heederik[17], Erika von Mutius[7,8,9,18] and Juha Pekkanen[1,5,18]

Probiotics in the prevention of necrotizing enterocolitis in neonates

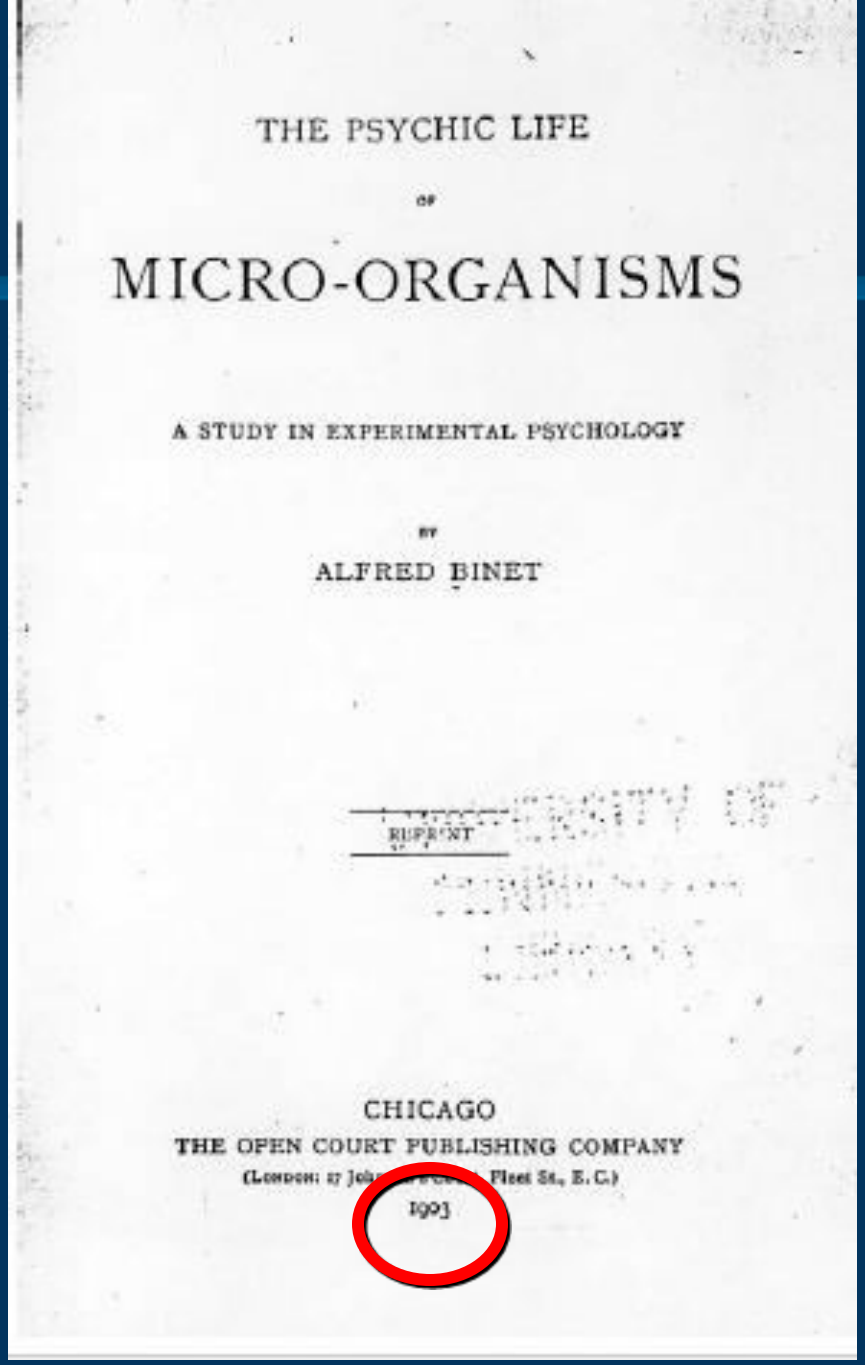


- 7% of VLBW < 1500 gm
  - 20 to 30% mortality
  - Etiology is clearly multifactorial
    - Premature birth, Abnormal intestinal microbiota
    - Enteral feeding , alterations in perfusion

- 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

What about gut metabolites altering CNS function ?


THE PSYCHIC LIFE

OF

MICRO-ORGANISMS

A STUDY IN EXPERIMENTAL PSYCHOLOGY

BY

ALFRED BINET

REPRINT

CHICAGO

THE OPEN COURT PUBLISHING COMPANY

(London: 17 John... 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**

Pathways linking the gut and CNS

Intestinal lumen

Intestinal barrier

CNS

Vagus nerve

Vagal stimulation

Circulatory system

Neurotransmitters
Hormones
Metabolites
Immune signaling

Immune system

MAMPs (Microbe associated molecular pattern)
Metabolites

Sampson, TR & SK Mazmanian, Cell Host & Microbe, 2015

Review Article

Probiotic supplementation can positively affect anxiety and depressive symptoms: a systematic review of randomized controlled trials

Meysam Pirbaglou[a], *Joel Katz*[a,b], *Russell J. de Souza*[c], *Jennifer C. Stearns*[d], *Mehras Motamed*[a], *Paul Ritvo*[a,b,e,*]

10 well designed RCT

Collected between 1990-2016

Conclusion:

Support for microbiome manipulation via probiotics

- **Anxiety**
- **Depressive disorders**

Nutrition Research 2016

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

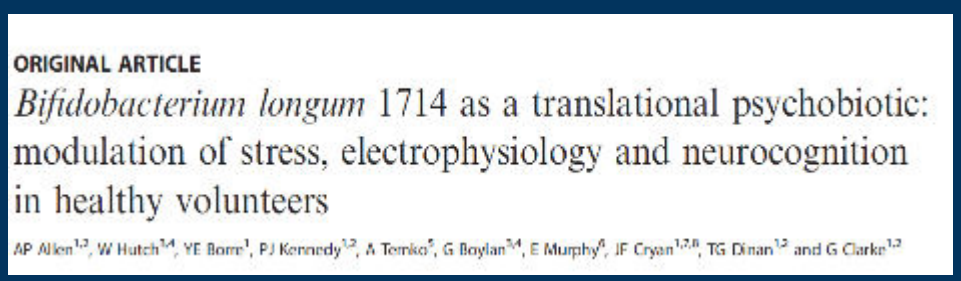
Ghodarz Akkasheh M.D. [a], Zahra Kashani-Poor M.D. [a], Maryam Tajabadi-Ebrahimi Ph.D. [b], Parvaneh Jafari Ph.D. [c], Hossein Akbari Ph.D. [d], Mohsen Taghizadeh Ph.D. [e], Mohammad Reza Memarzadeh Ph.D. [f], Zatollah Asemi Ph.D. [e,*], Ahmad Esmaillzadeh Ph.D. [g,h,i]

Nutrition 2016

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

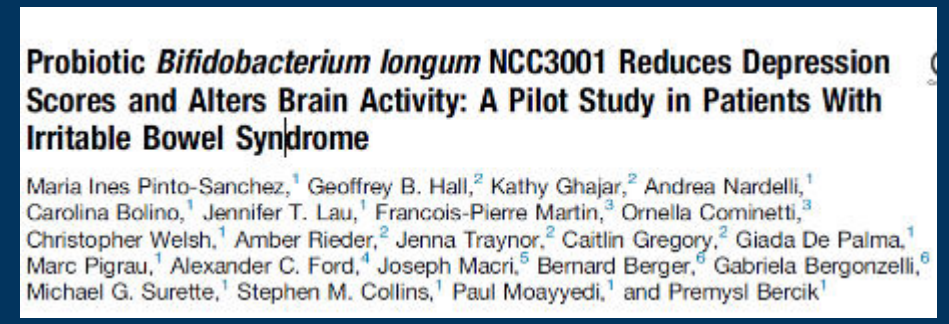


ORIGINAL ARTICLE

Bifidobacterium longum 1714 as a translational psychobiotic: modulation of stress, electrophysiology and neurocognition in healthy volunteers

AP Allen[1,2], W Hutch[3,4], YE Borre[1], PJ Kennedy[1,2], A Temko[5], G Boylan[3,4], E Murphy[6], JF Cryan[1,2,6], TG Dinan[1,2] and G Clarke[1,2]

•Translational Psychiatry 2016



Probiotic *Bifidobacterium longum* NCC3001 Reduces Depression Scores and Alters Brain Activity: A Pilot Study in Patients With Irritable Bowel Syndrome

Maria Ines Pinto-Sanchez,[1] Geoffrey B. Hall,[2] Kathy Ghajar,[2] Andrea Nardelli,[1] Carolina Bolino,[1] Jennifer T. Lau,[1] Francois-Pierre Martin,[3] Ornella Cominetti,[3] Christopher Welsh,[1] Amber Rieder,[2] Jenna Traynor,[2] Caitlin Gregory,[2] Giada De Palma,[1] Marc Pigrau,[1] Alexander C. Ford,[4] Joseph Macri,[5] Bernard Berger,[6] Gabriela Bergonzelli,[6] Michael G. Surette,[1] Stephen M. Collins,[1] Paul Moayyedi,[1] and Premysl Bercik[1]

Gastroenterology 2017

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

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,*]

•Brain, Behavior, and Immunity 2017

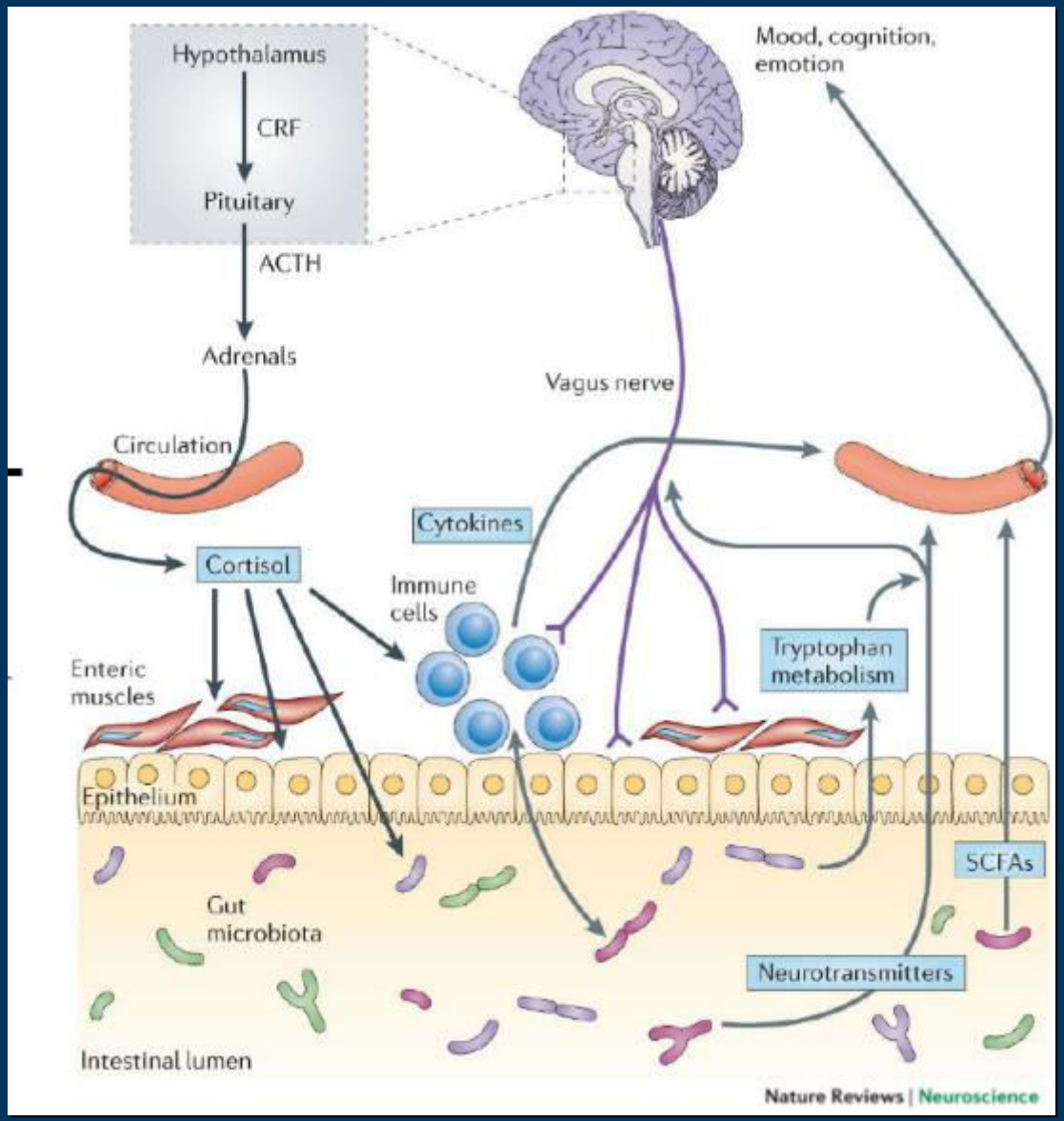
2019

Potential roles of gut microbiome and metabolites in modulating ALS in mice

Eran Blacher[1,11], Stavros Bashiardes[1,11], Hagit Shapiro[1,11], Daphna Rothschild[2,3,11], Uria Mor[1], Mally Dori-Bachash[1], Christian Kleimeyer[1], Claudia Moresi[1], Yotam Harnik[1], Maya Zur[1], Michal Zabari[4], Rotem Ben-Zeev Brik[1], Denise Kviatcovsky[1], Niv Zmora[1], Yotam Cohen[1], Noam Bar[2,3], Izhak Levi[2,3], Nira Amar[1], Tevie Mehlman[5], Alexander Brandis[5], Inbal Biton[6], Yael Kuperman[6], Michael Tsoory[6], Leenor Alfahel[7], Alon Harmelin[6], Michal Schwartz[8], Adrian Israelson[7], Liisa Arike[9], Malin E. V. Johansson[9], Gunnar C. Hansson[9], Marc Gotkine[4,12*], Eran Segal[2,3,12*] & Eran Elinav[1,10,12*]

nature Accelerated Article Preview

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
-

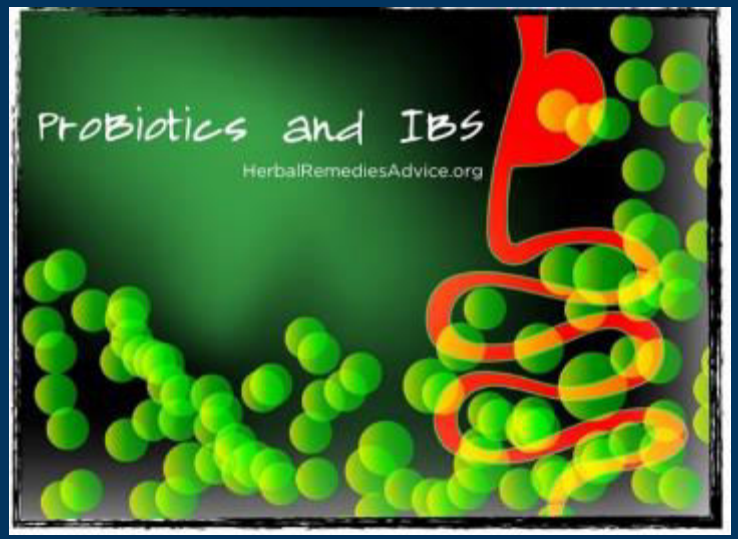
Cryan FJ et al Nature Rev Neuroscience 2012 Minter MR et al Sci Rep 2016, Ho P 2017

Inflammatory Bowel Disease

- Crohn's disease
  - 34 PRCT – 15 slight improvement in symptoms little if any objective data showing benefit
  - 19 PRCT – no benefit
- Ulcerative Colitis
  - Data slightly better than Crohn's
  - Widely variable depending on strain, age, severity of disease
  - Increase remission rates UC
  - Greater # remain in remission
  - Associated Inflammatory Bowel Disease issues with best data
    - IA Pouchitis – VSL#3 better than placebo
- Good News:NO HARM NOTED in UC or Crohn's
- New work focusing on mucous
  - Penetration of mucous
  - Formation of dense deeper mucous

- Derwa Y Aliment Pharm Ther 2017
- Shen Z et al J Gastroenter Hep 2017
- Wasilewski A et al IBD 2015
- Whelan K Curr Opinion Gastro 2013
- Shen J et al IBD 2014
- Haag LM Best Pract Clin Gastro 2014
- Thomas L et al British J Nutr 2014

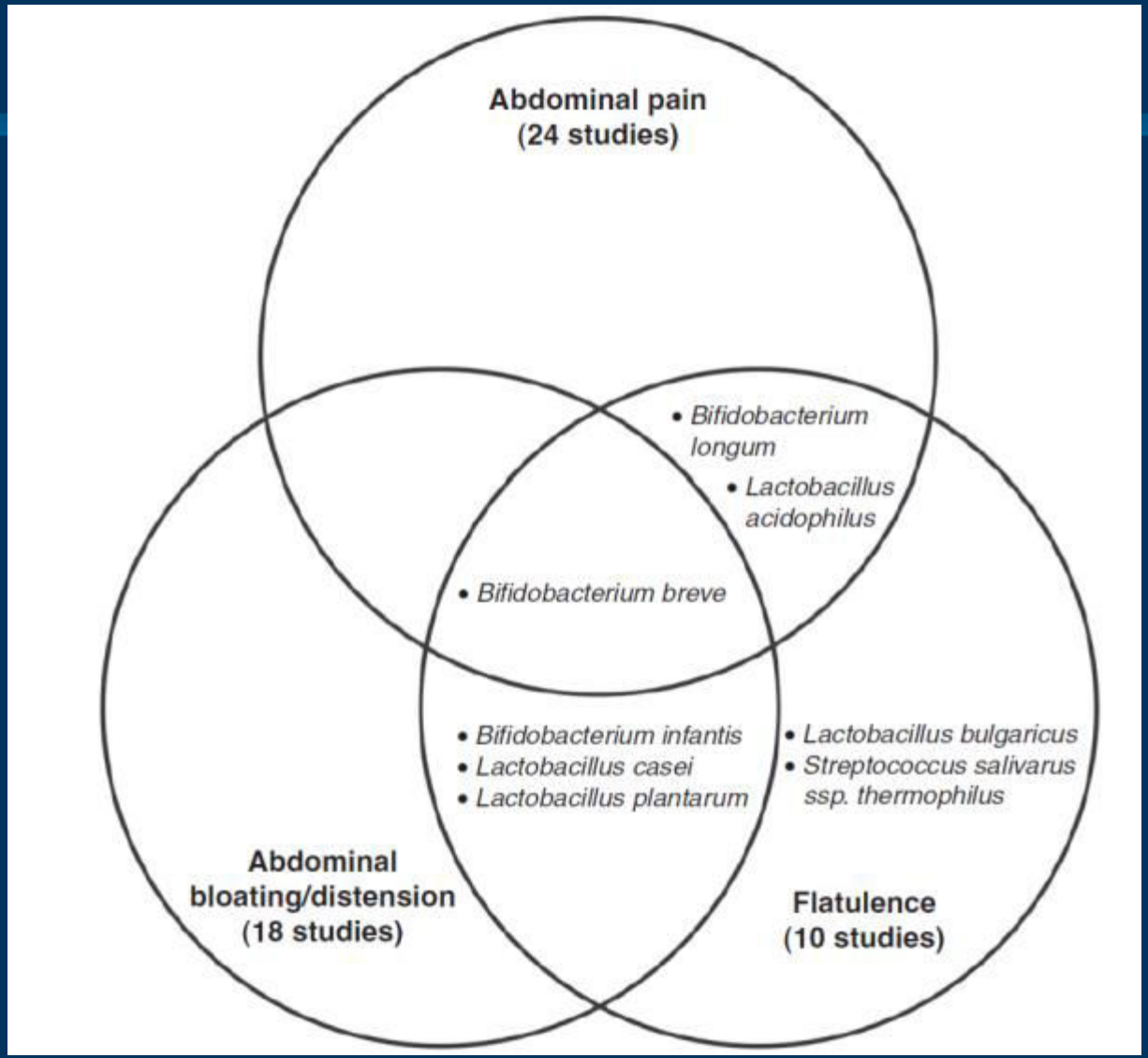
Probiotics and Irritable Bowel Syndrome (IBS)



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
  (62 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 +

Summary: Probiotics in Irritable Bowel Syndrome ?



Results mixed:

Limited #'s

Variable species

Variable dosing

Cash DB et al Curr Med Res Opin 2014

Can Probiotics to Alter Gastroenteritis Duration and Severity

The NEW ENGLAND JOURNAL of MEDICINE

- 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 !**

What about Ca prevention ?

Gut Microbiome and Colon Cancer: A Plausible Explanation for Dietary Contributions to Cancer.

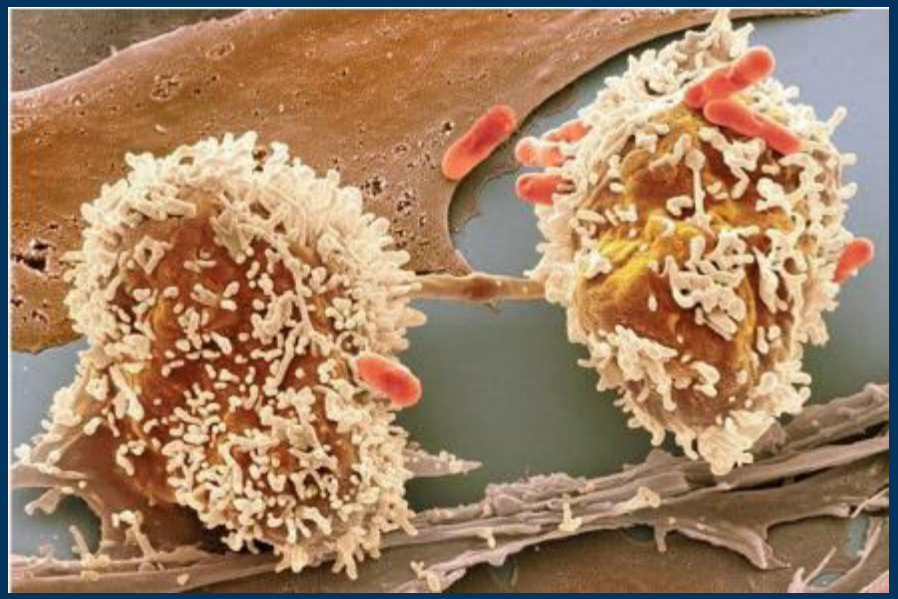
Nelson H[1], Chia N[2].

J Am Coll Surg 2019

the gut microbiota in patients with early hepatocellular carcinoma

Therapeutic Advances in Medical Oncology 2019

Francesca Romana Ponziani, Alberto Nicoletti, Antonio Gasbarrini* and Maurizio Pompili*



- **Multiple proposed mechanisms**
  - **SCFA**
  - **Epigenic changes**
  - **miRNA**
  - **Modification peri-tumor environment**
  - **HDAC**
  - **Anti-inflammatory**

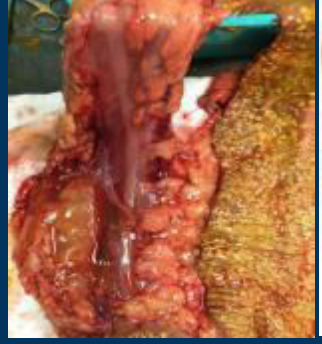
Antibiotic Associated Diarrhea: Preventable or Inevitable ?

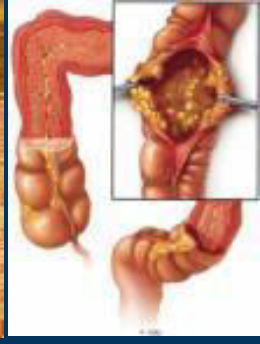
- Hempel S et al JAMA 2012
- Meta-analysis 82 RCT met criteria for inclusion
- Probiotics strains were poorly documented
- N=11,811 participants (pooled data)
- Conclusion:
  - Probiotics confer significant decrease in AAD (p<.001)
  - # needed to treat N=13

Hempel S et al JAMA 2012

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

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

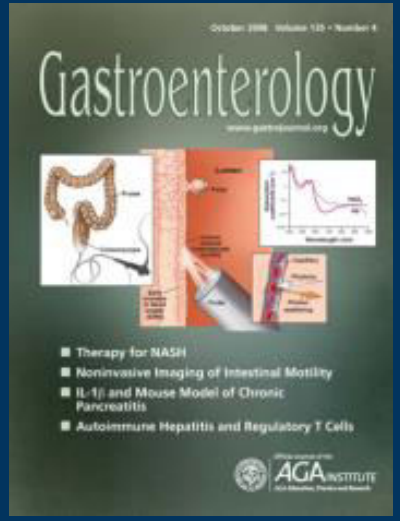
- Meta-analysis 28 studies
- N=3818 patients

- "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***

INFECTION CONTROL & HOSPITAL EPIDEMIOLOGY

Bradley C. Johnston, PhD;[1] Lyubov Lytvyn, MSc;[2] Calvin Ka-Fung Lo, BHSc;[3] Stephen J. Allen, MD;[4] Duolao Wang, PhD;[4] Hania Szajewska, MD;[5] Mark Miller, MD;[6] Stephan Ehrhardt, MD;[7] John Sampalis, MD;[6] Deniz G. Duman, MD;[8] 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] Ruzha Pancheva, MD, PhD;[15] Sandra Hirsch, MD;[16] Bengt Klarin, MD;[17] Joshua Z Goldenberg, ND;[18] Li Wang, MD;[19,20] Lawrence Mbuagbauw, PhD;[2] Gary Foster, PhD;[21] Anna Maw, MD;[22] Behnam Sadeghirad, MPH;[2] Lehana Thabane, PhD;[2] Dominik Mertz, MD[2,23]

- **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**

Johnston BC et al Infection Control Hospital Epidem 2018

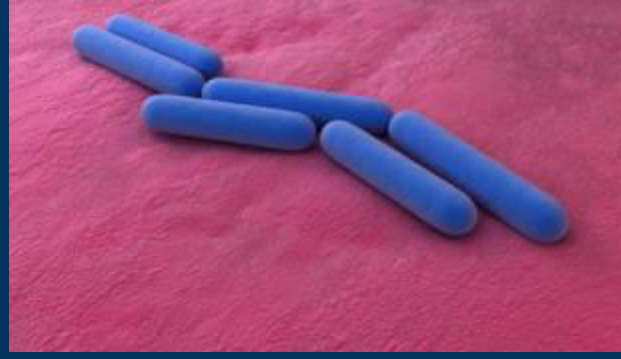
Do *C.difficile* bundles work ?

- 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

Probiotics: Importance of choosing the correct bacterial species

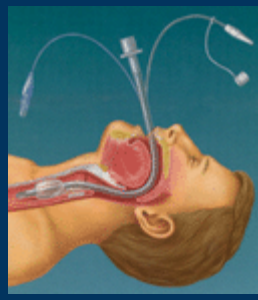


- PLACID Trial: MRDBPCT
- 17,480 screened 2,971 met criteria
  - > 65 yo
  - All received antibiotics
  - 70% received either placebo of probiotic for at least 7 days
    - » L.acidophilus x 2
    - » B.bifidum x 2
- Conclusion:
  - AAD 10.8 vs 10.4 %
  - CD 0.8 vs 1.2 %
  - Essentially no differences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

Allen SJ et al Lancet 2013

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

Impact of administration of probiotics on VAP: Meta-analysis

- RCT with mechanical ventilation +/- probio
- 5 RCT included
- Results:
  - Probiotics decrease VAP
  - Decrease in Pseudomonas colonization
  - No change in mortality
  - No change in ventilator days

I Siempos et al Crit Care Med 2010

- Review of the literature
  - Issues to resolve
    - Which bacteria
    - How long
    - What population to deliver to
    - Heterogeneity of literature at this point makes firm conclusion difficult
    - L. rhamnosus seems to be most actively being studies

Bailey JL. Ann Pharmacotherapy 2011

- Bo L, et al Cochane Collaboration 2014
- Evidence suggests that probiotic use is associated with reduction in incidence of VAP.

Surgical Infections: What does the clinical data show?

A Four-Probiotics Regimen Reduces Postoperative Complications After Colorectal Surgery: A Randomized, Double-Blind, Placebo-Controlled Study

June 2015 World J Surg

Katerina Kotzampassi[1] · George Stavrou[1] · Georgia Damoraki[2] · Marianna Georgitsi[2] · George Basdanis[1] · Georgia Tsaousi[1] · Evangelos J. Giamarellos-Bourboulis[2]

Efficacy of prophylactic probiotics in combination with antibiotics versus antibiotics alone for colorectal surgery: A meta-analysis of randomized controlled trials

Wu XD et al J Surg Oncology 2018

- 14 trials, 1524 Patients
  - Combination of probiotics and prophylactic antibiotics v prophylactic antibiotics
  - 28% decrease in SSI, NNT 18

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

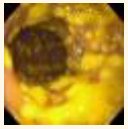
Hanna Sikorska[a,*], Wanda Smoragiewicz[b]

Inter J Antimicrobial Agents 2013

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,*]

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
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
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
Trauma 	*Bifidobacterium breve, L rhamnosus L casei*	Kotzampassi 2006, Spindler-Vesel 2007, Tan 2011

Rationale for FMT

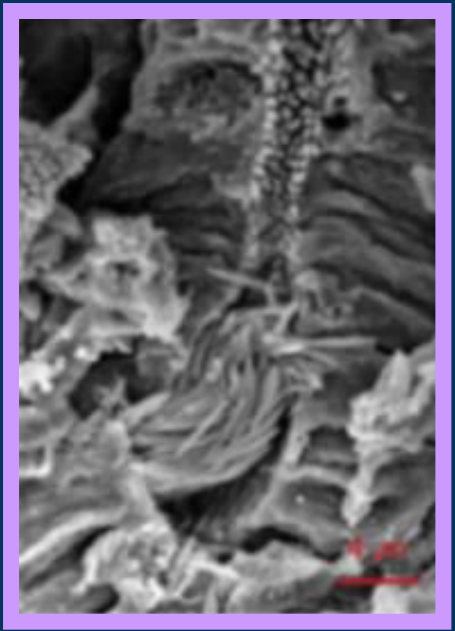
- **Critical illness/injury:**
  - **Lose 90% of commensals with in 6-12 hrs**

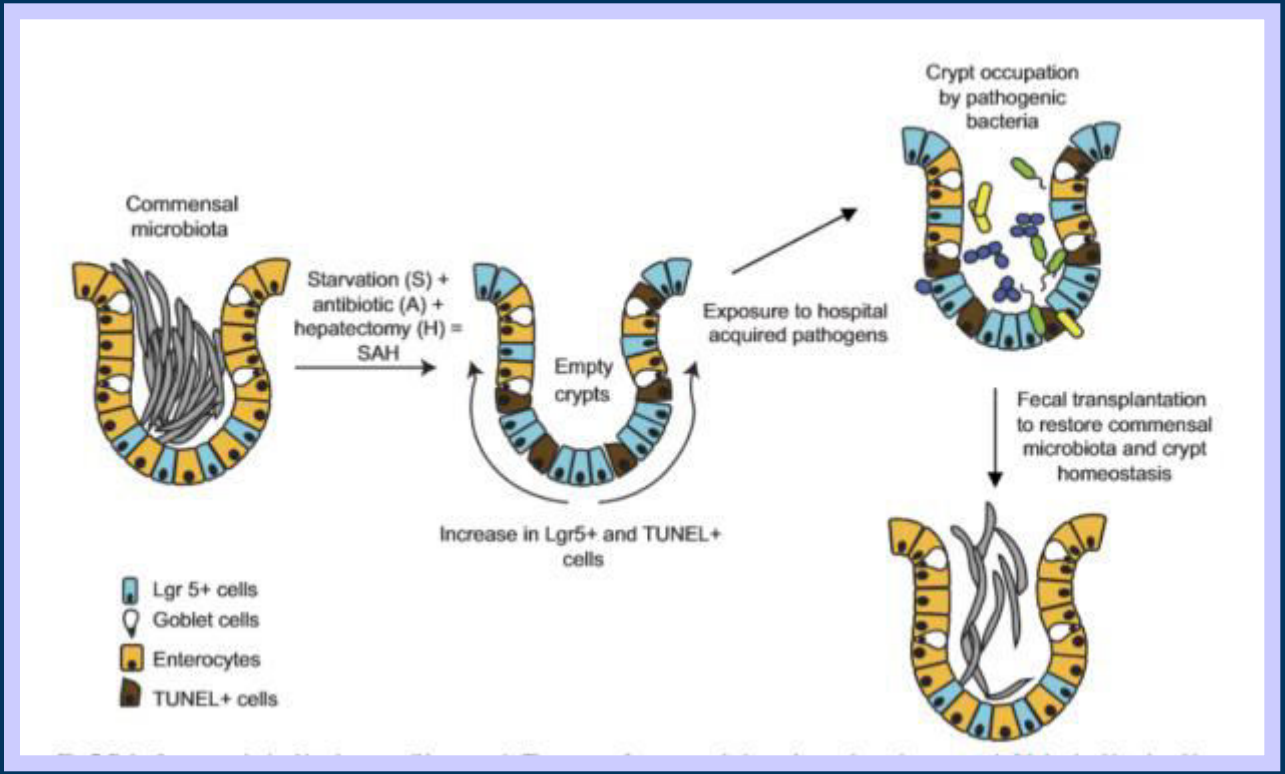
Loss of biodiversity, emergence of virulent pathobiome

Krezalek, Alverdy (Shock 2016;45:475) Morowitz, Alverdy (Ann Surg 2011; 253:1094)
- Zaborin, Alverdy (Am J Phys Gastroint Liver Physiol 2017;312:G112)

Re-establishing microbiome signaling:

- Rationale for FMT in the ICU
  re-establishing crypt niches and metabolic communication with refaunation





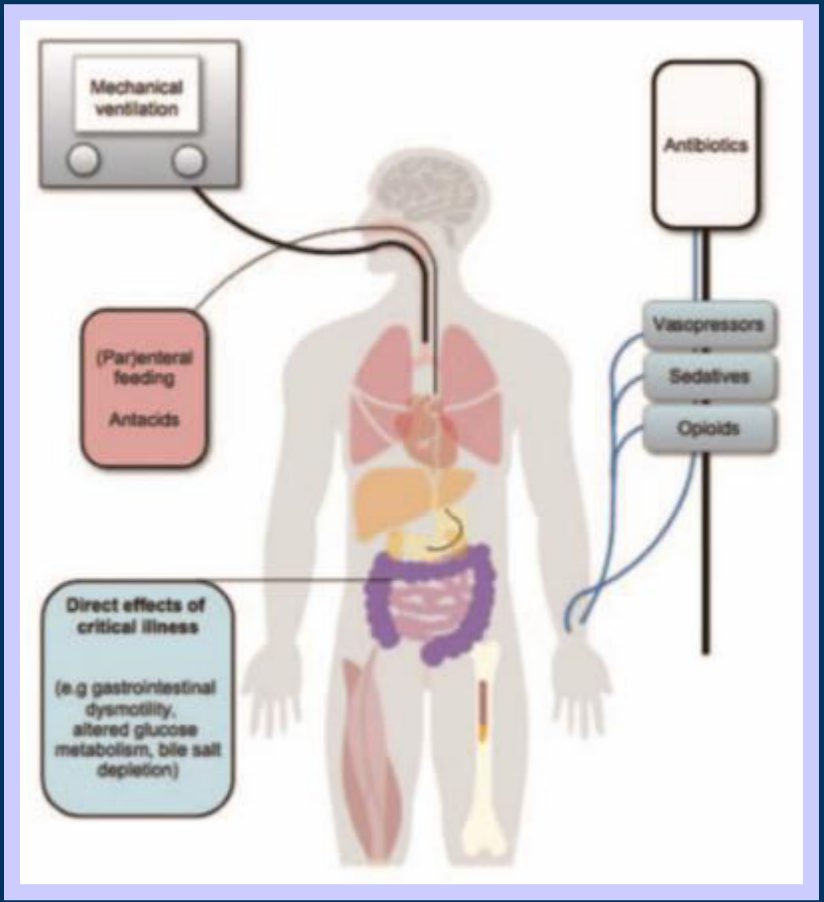
- A Zaborin, J Alverdy(Am J Phys Gastroint Liver Physiol 2017;312:G112)

FMT in ICU

- Naïve to just replenish garden? Key is to re-establish communication of the gut microbiome
- Issues: Choice, number, butyrate generation, growth rate
- What's most important? Lower pH, alter signaling

FMT Safety

- Transient GI complaints
  - Gas bloat
  - Cramping
  - Borborygmi
  - Constipation
- Infection
  - Peritonitis (E.Coli, Proteus, Klebsiella, Listeria)
  - Norovirus, CMV
  - MDRO transfer
- Procedure related
  - Perforation
  - Sedation-related events
  - Regurgitation of feces
  - Fatal aspiration
- Long term (case reports)
  - Weight gain
  - Sjogren's, Rheum Arthritis, Lymphoma



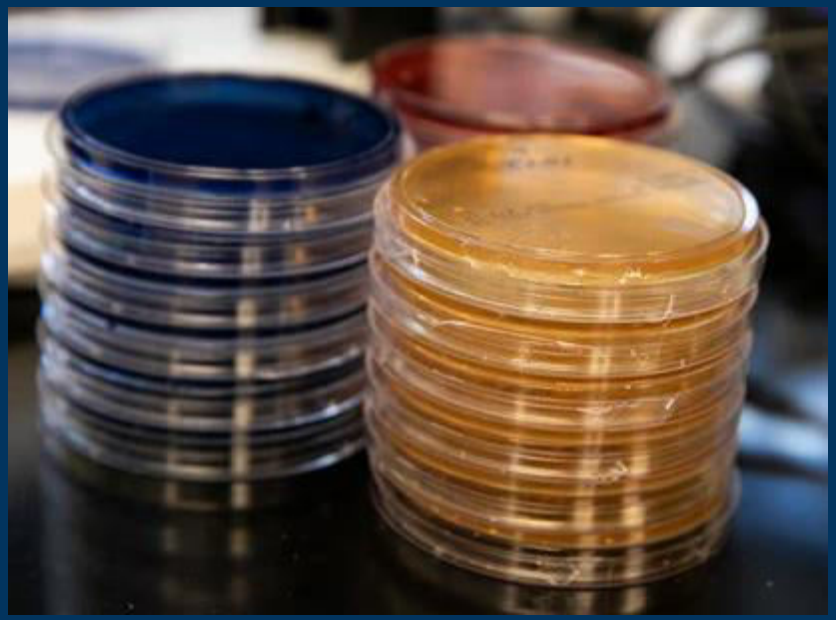
M Schwartz (AJG 2013) CR Kelly (AJG 2014) N Alang (Open Forum Infect Dz 2015)

June 19, 2019

ecal Transplant Is Linked to a atient's Death, the F.D.A. Warns

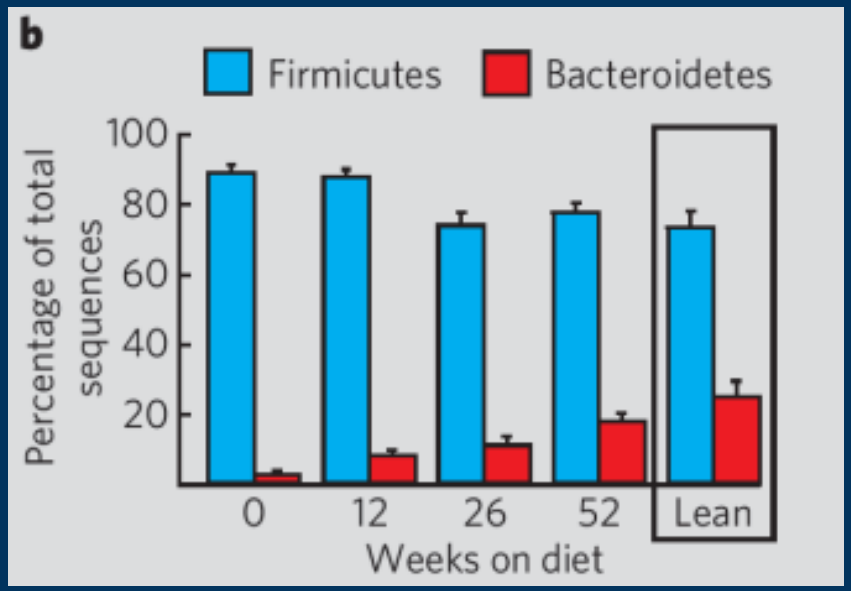
e agency said two patients received donated stool that had not been screened for ug-resistant germs, leading it to halt clinical trials until researchers prove proper ting procedures are in place.

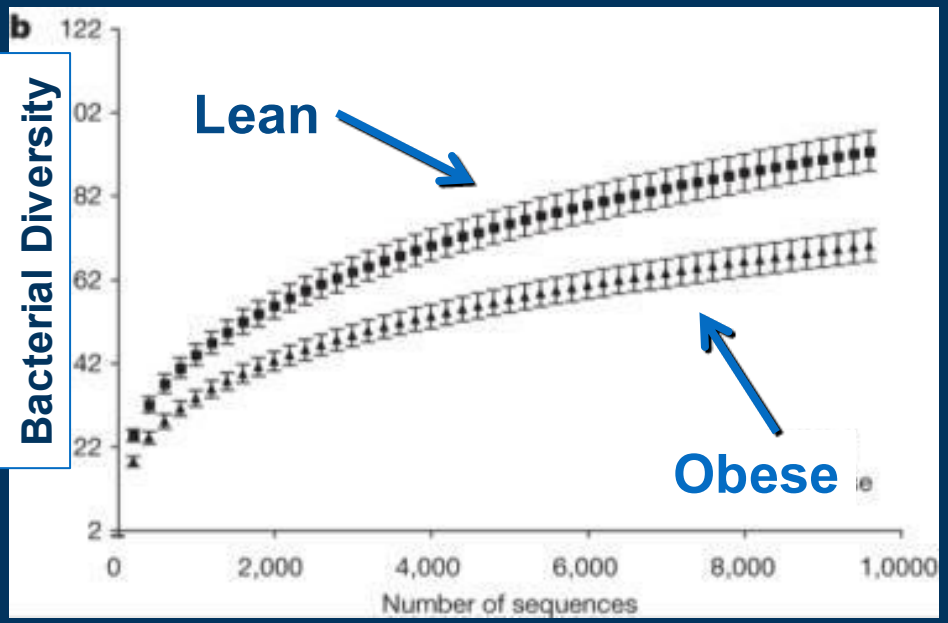
- **Mortality from E. coli bacteria that produced an enzyme called ESBL's**



Could manipulation of the "Microbiome" help with weight control *or* be responsible for obesity ?

Reduced diversity of the gut microbiota in obese individuals





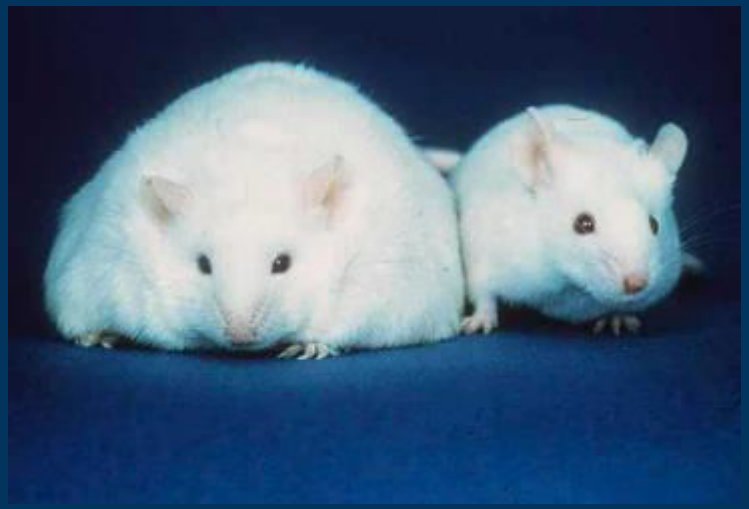
Large inter individual variation in flora composition but trends are consistent between multiple trials

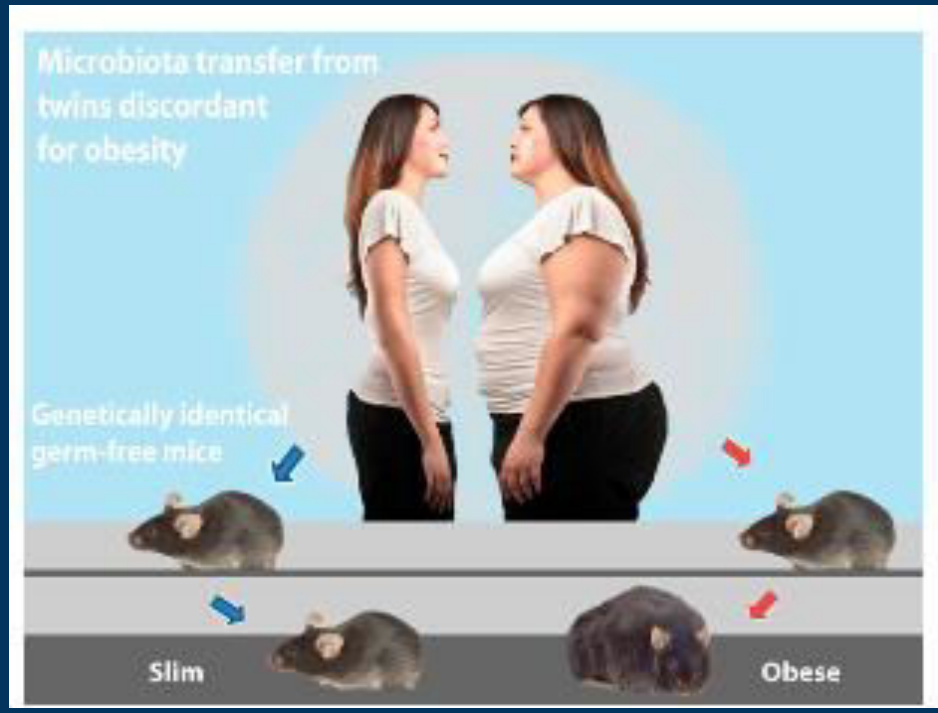
Ley et al. Nature 2006
Turnabugh et al. Nature 2009
Sonnenberg JL et al Nature 2016

The Battle of the Microbiota

Jeffrey Gordon, PhD
Washington University

- Human Twins
- Microbiota transplanted to germ free mice
- Obese human twins microbiota conferred obesity to mice

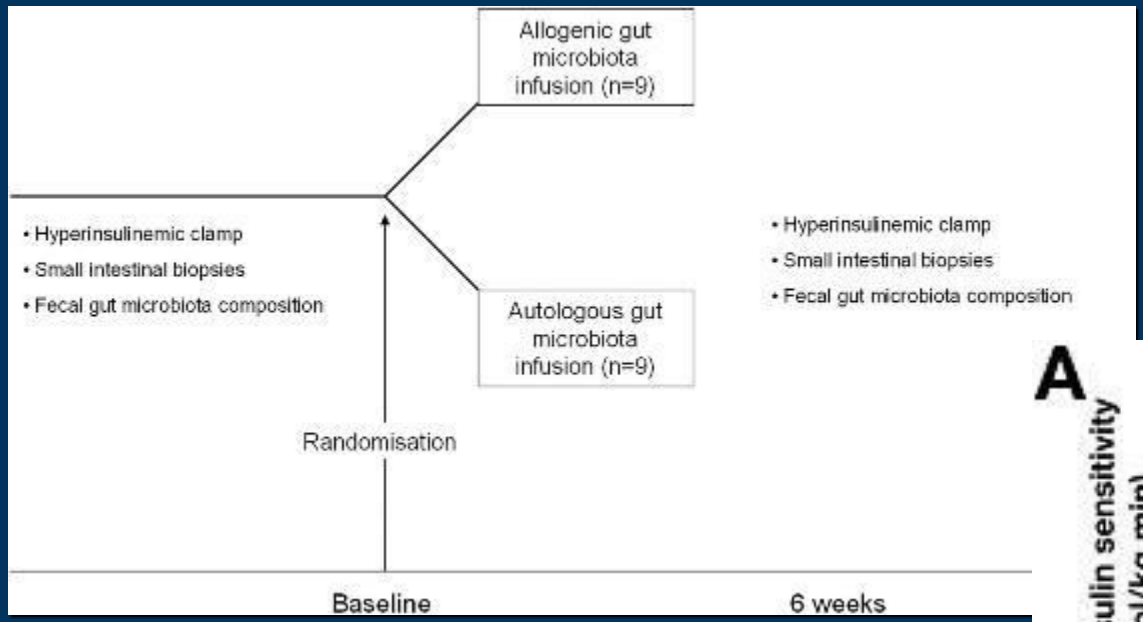


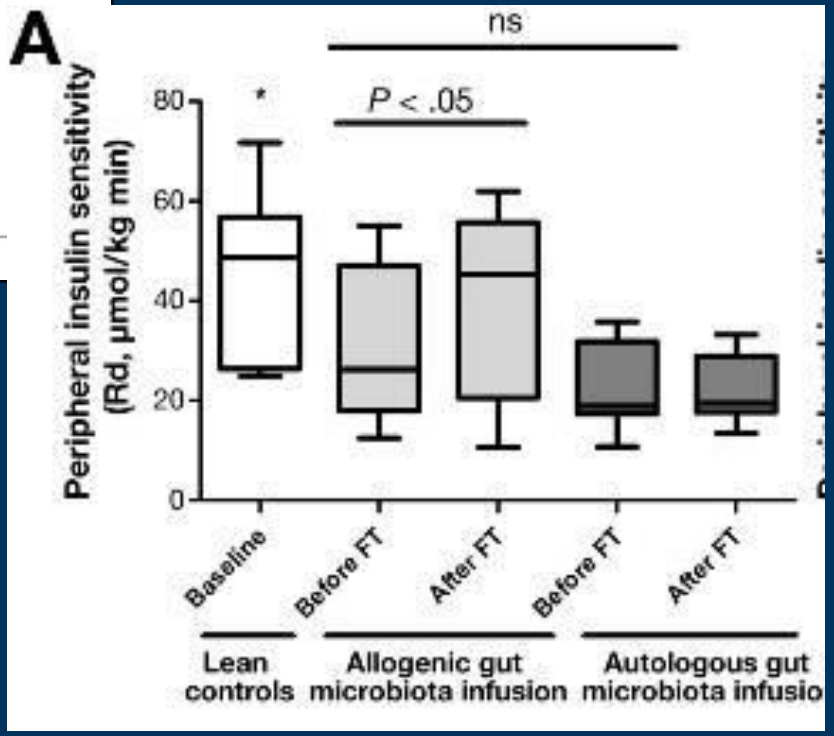


Turnbaugh PJ et al Nature 2009

Insulin Sensitivity is Transplantable

Gut microbiota in T2DM

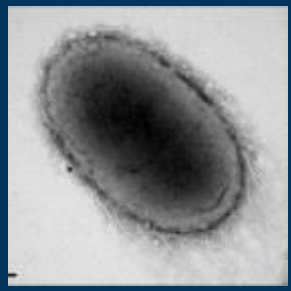




Gut microbiota affects insulin sensitivity in humans

Vrieze A et al. Gastroenterology 2012

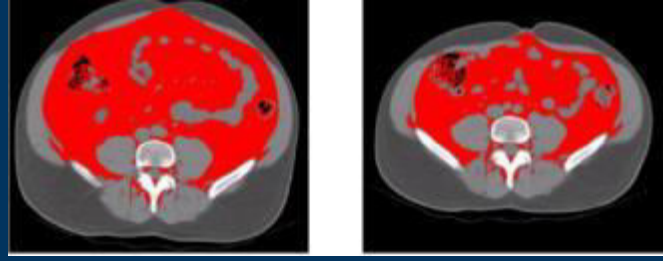
Could *Akkermansia muciniphila* be a candidate ?



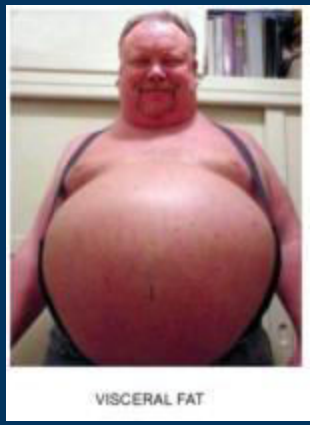
- Gram negative anaerobe functions to degrade mucin
- Represents 1-3% of entire gut microbiota
  - Quantity is inversely correlated with body weight in both mice and humans
  - Prebiotics can "enrich" species 100x
- Show to:
  - Increase SCFA production
  - Improve gut barrier – via increase goblet cell mucous production
  - Alters Tregs in adipose to decrease inflammation
    - » TGR5 via a BS mechanism
  - Decrease hepatic inflammation
    - » Multiple mxs: Increase BSH, SCFA, and decrease FGF15
  - Improve glucose homeostasis – improves insulin resistance
  - Increased intestinal 2-oleoglycerol (lipid endocannabinold system)
  - Decrease fat mass - ? Mx (SCFA - GPR43 controls FA metabolism)

Everrard D et al PNAS 2013
Cani PD et al Curr Opin Biotech 2015

Visceral vs peripheral adipose

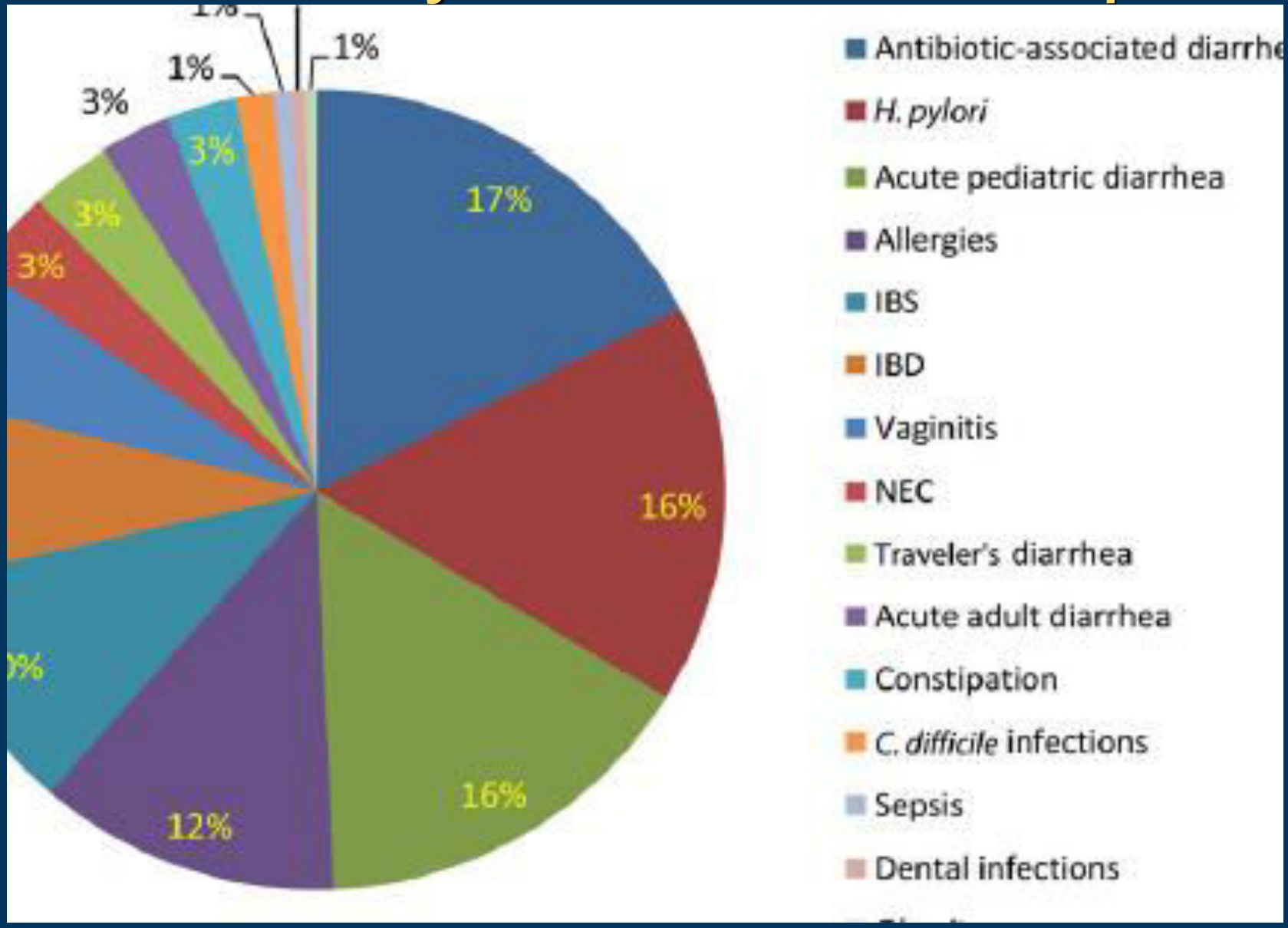


- Human MCRPC interventional trial
- 12 weeks, N=87, CT to evaluate at L3
- 200 ml/d L. gasseri
- Findings:
  - Decrease abdominal visceral and subQ fat ($p<.01$)
  - Decrease in weight 1.4%
  - Increase in high MW Adiponectin
- Mechanisms
  - Fat absorption ?
    - Rat lymphatic data
  - No change in energy intake



Kadooka Y et al Eur J Clin Nutr 2010

15 most commonly studied indications for probiotic



MacFarland LV CID 2015

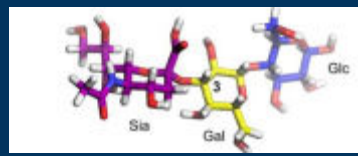
Where do *prebiotics* fit in to the attempt to beneficially alter the microbiome ?

Prebiotics

- Three necessary criteria of ingredient
  - Non-digestible by host enzymes
  - Fermented in GI tract
  - Selective stimulation of gut microbiota and metabolic activity

- Naturally occurring or synthetic sugars, starches
  - Used as a carbon source by certain colonic bacteria for growth and metabolism
  - Examples: Inulin, fructooligosaccharides (FOS), galactooligosaccharides (GOS), lactulose

- Breast milk the ultimate prebiotic solution
    - 15% of CHO in breast milk is prebiotic
  - Selectively enhancing desired colonic bacteria
  - Anti-adhesive for pathogens
  - Blocking pathogen colonization and invasion
  - Changing glycosylation of epithelial cells altering expression to limit infections



Prebiotics:
Fermentable Fibers;
Benefits for the General Population

- Immune regulation – SCFA, multiple others
- Gastrointestinal motility
- Large reproducible observation studies to show:
  - Decrease risk of type 2 Diabetes and obesity
    - » 57% of type 2 Diabetes resulting from obesity
  - Decrease risk of coronary artery disease
  - Decrease Cancer (primarily visceral Ca)
  - Recent data on benefit in OCD, ADHD (altering microbiome)
    - » Animal models of Alzheimer's show improvement
- **Decrease in all cause mortality**

Aune D et al Br Med J 2016
Zong G et al Circulation 2016
Makarem N et al Nutr Rev 2016
Obata Y et al Gastroenterology 2016
Wang J et al Nature Med 2015
Winer DA et al Cell Metab 2016
Reynolds A et al Lancet 2019

Dietary supplementation with non-fermentable fiber alters the gut microbiota and confers protection in a murine model of sepsis

Michael Morowitz, MD[1,2], Valentina Di Caro, PhD[3], Diana Pang, MD[3,4], Jessica Cummings[3], Brian Firek, MS[1], Matthew B. Rogers, PhD[1], Sarangarajan Ranganathan, MD[5], Robert S. B. Clark, MD[3,4], and Rajesh K. Aneja, M.D[3,4]

Critical Care Medicine 2017

The non-fermentable fibers are also beneficial !

- Murine model: 3 groups, 2 sepsis models (CLP, Endotoxin)
  - High fiber vs normal fiber vs no fiber , +/- antibiotics
- Conclusions:
  - High fiber increased survival, decrease inflammation etc
  - High fiber increased Akkermansia and Lachnospiraceae
  - Antibiotics negated benefits of fiber

It is all about “Risk vs. Benefit”

Safety of Probiotics

- 57 human clinical trials from the last 5 years (2008-2013)
- 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 54 different strains of bacteria
- Virtually no significant attributable morbidity or mortality

•Van den Nieuwboer M et al, Benef Microbes, 2015

Strains

L. plantarum [CGMCC no.1258]
L. acidophilus-11
B. longum-88
B. longum (unspecified)
L. rhamnosus GR-1
L. plantarum 299 (Lp299) (DSM 6595)
L. casei LBC80Rfi
L. acidophilus CL1285fi
Pediococcus pentosaceus 533:3
Leuconostoc mesenteroides 3277:1
L. plantarum 2362
L. paracasei 19
B. breve (unspecified)
L. rhamnosus GG
S. thermophilus (unspecified)
L. bulgaricus (unspecified)
Saccharomyces boulardii
L. acidophilus (unspecified)
B. bifidum (unspecified)
L. casei (unspecified)
L. casei Shirota
L. rhamnosus R0011
L. acidophilus R0052
E. coli Nissle 1917
L. johnsonii La1
Bacillus coagulans GBI-30, 6086
L. reuteri C-14
B. longum BB536
Streptococcus faecalis
B. breve Yakult
L. plantarum 8PA3
L. acidophilus L10
B. lactis B94
L. reuteri ATCC 55730
Enterococcus faecalis
Streptococcus salivarius K12
Trichurius suis Ova
S. thermophilus KB27
Lactococcus lactis W58
L. salivarius W24
L. rhamnosus HN001
L. rhamnosus CAN-1
L. plantarum ATCC 10 241
L. plantarum (unspecified)
L. paracasei (unspecified)
L. casei W56
L. acidophilus W70
L. acidophilus KB31
Bifidobacterium (unspecified)
B. longum KB35
B. lactis Bi-07
B. infantis W52
B. infantis (unspecified)
B. bifidum W23

Probiotic Beverages- examples
100's now available

Chilled dairy

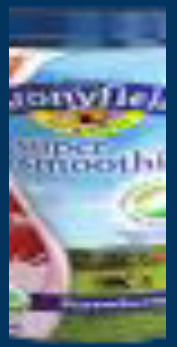
Yakult

Danactive / Actimel

Stonyfield

BioQ

etc, etc, etc



Chilled non-dairy

ProViva

Good belly

Kombucha

Bravo Friscus

Shelf stable

Cocobiotic, Dong Quai, Innergy Biotic

Vehicle for Delivery:

(Tablets, capsules, sachets, wafers, fermented milks or drinks, in yogurts, cheese, even chocolates)

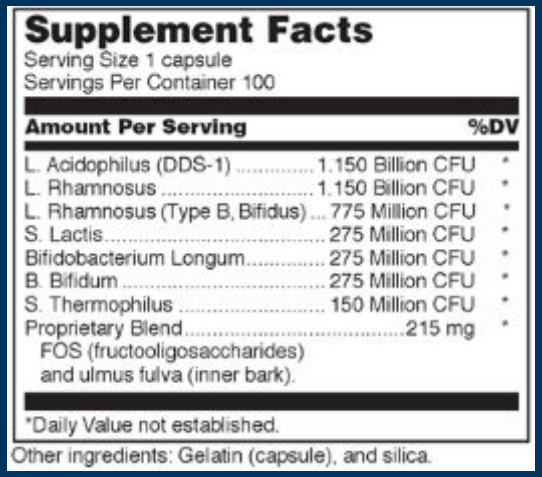
Yogurt	Pills or Capsules
• Contains nutrients that may protect the viability of the probiotic (protein, prebiotic) • Contains additional nutrients that are beneficial to the patient (protein, prebiotic, calcium, vitamin D etc.) • Perceived benefit by family and/or patient for receiving "real food" • No AEs associated with food source probiotic	• Reliable CFU count (reputable brand) • Targeted and selective therapy • Can still be given if patient is NPO • May be an alternative for patients with food allergies or intolerances

Recent OHSU data showing more viable probiotic when taken with yogurt

Gutgsell J, Warren M , Gillingham M, Lasarev M, Martindale R 2017 in preparation

What's in a label?

- Marcobal et al tested 14 US commercial probiotic products:
  - 93% incorrectly labeled
  - 57% had contaminants
  - 36% did not list strains on the label
- Masco et al tested 58 different products from EU, UK, Asia, Japan, Canada:
  - Only 38% had the dose stated on the label
  - 29% did not contain strains on the label
- Product claims:
    - curative vs "supportive"
    - Drug vs supplement



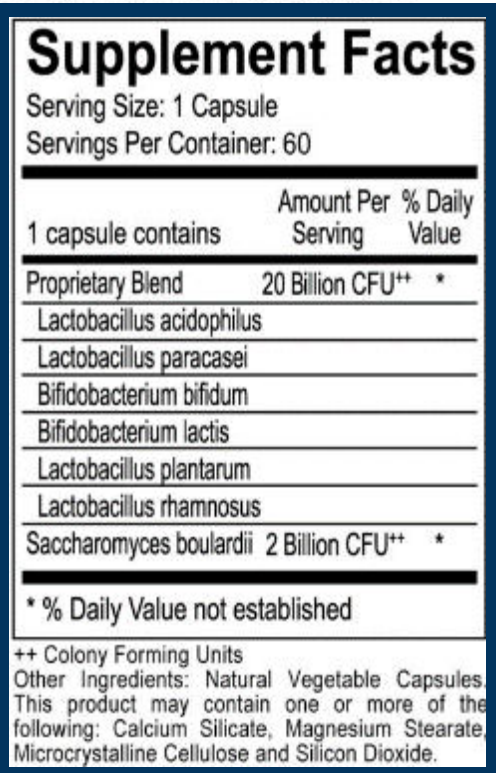
Supplement Facts

Serving Size 1 capsule
Servings Per Container 100

Amount Per Serving		%DV
L. Acidophilus (DDS-1)	1.150 Billion CFU	*
L. Rhamnosus	1.150 Billion CFU	*
L. Rhamnosus (Type B, Bifidus)	775 Million CFU	*
S. Lactis	275 Million CFU	*
Bifidobacterium Longum	275 Million CFU	*
B. Bifidum	275 Million CFU	*
S. Thermophilus	150 Million CFU	*
Proprietary Blend	215 mg	*
FOS (fructooligosaccharides) and ulmus fulva (inner bark).		

*Daily Value not established.

Other ingredients: Gelatin (capsule), and silica.



Supplement Facts

Serving Size: 1 Capsule
Servings Per Container: 60

1 capsule contains	Amount Per Serving	% Daily Value
Proprietary Blend	20 Billion CFU++	*
Lactobacillus acidophilus		
Lactobacillus paracasei		
Bifidobacterium bifidum		
Bifidobacterium lactis		
Lactobacillus plantarum		
Lactobacillus rhamnosus		
Saccharomyces boulardii	2 Billion CFU++	*

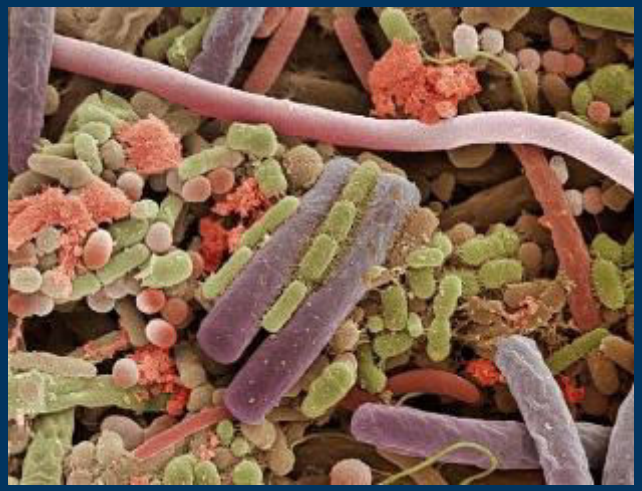
* % Daily Value not established

++ Colony Forming Units
Other Ingredients: Natural Vegetable Capsules. This product may contain one or more of the following: Calcium Silicate, Magnesium Stearate, Microcrystalline Cellulose and Silicon Dioxide.

Masco et al Int J Food Microbiol 2005
Hoffman DE Science 2013

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

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



- Disclaimer:
  - Some effects are strain specific effects
  - many other probiotic have published data to support in specific disease and health states

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-

General Guidelines for Use of Pre and Probiotics

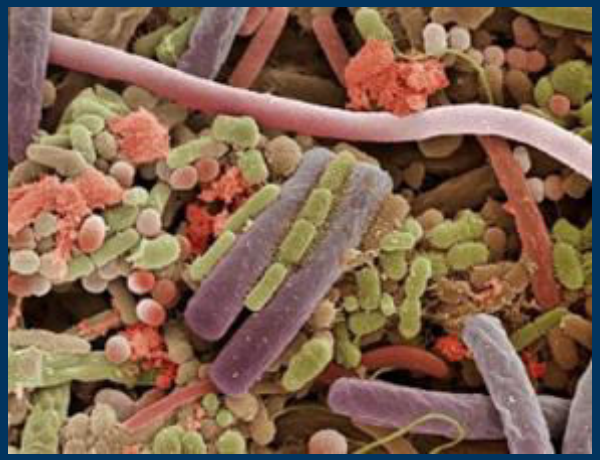
- All probiotics are not the same
  - Critically evaluate and use only when data supports
    - Base choice on molecular typing, metabolic characteristics and interaction in the environment
    - Needs to be evaluated for "functionality" down to strain level
    - Caution with meta-analysis, heterogeneity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

- How much do one need to take to obtain the benefit ?
  - Depends on probiotic species, viability, form taken, etc etc
  - ~Probiotic: 10^{9-11} viable cells per day ?
  - ~Prebiotic: 20-30 gm/day ?
- In ***my opinion*** better to get probiotics from fermented consumer sources rather than capsules

General guidelines (continued)

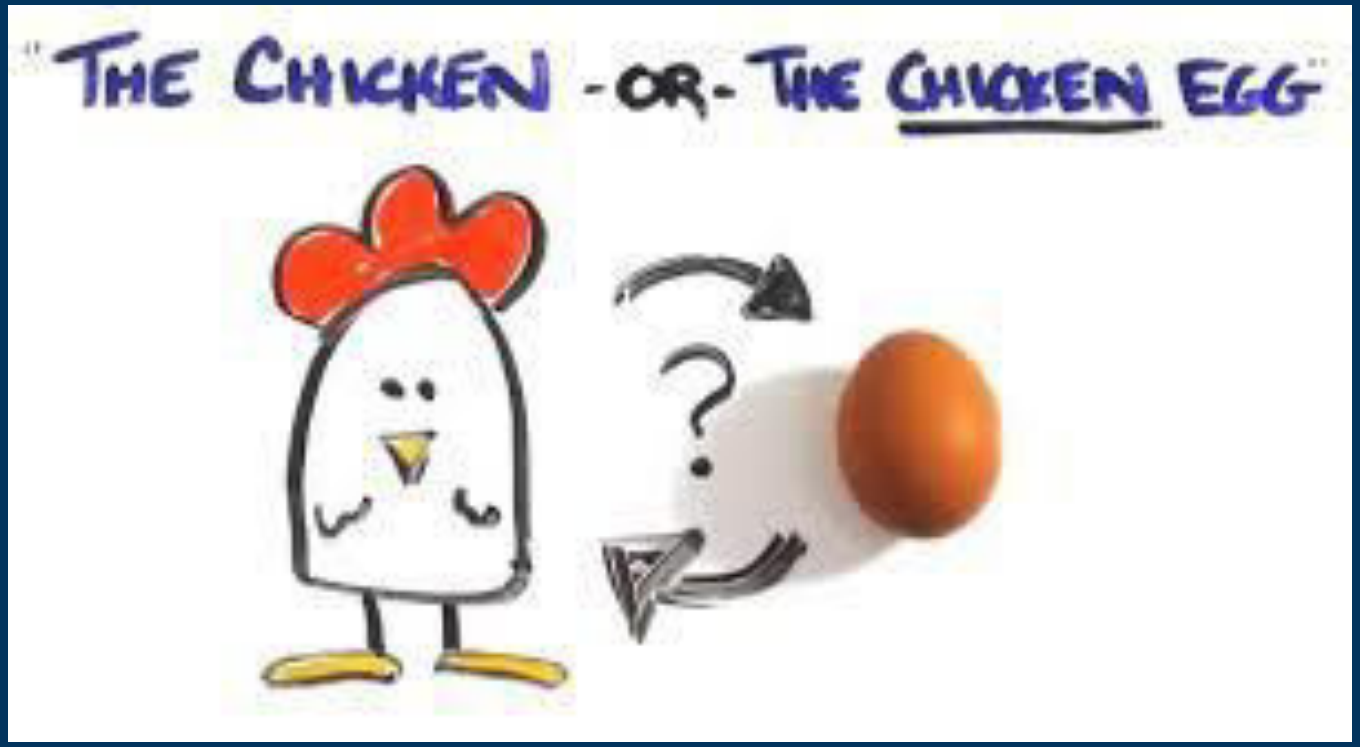
- Continued intake of probiotic is required to maintain colonization and benefits

- Prebiotic are an excellent option to modify flora on long term basis
  - Persistent levels require continuous intake !
  - Whole grain prebiotics now shown to decrease all cause mortality

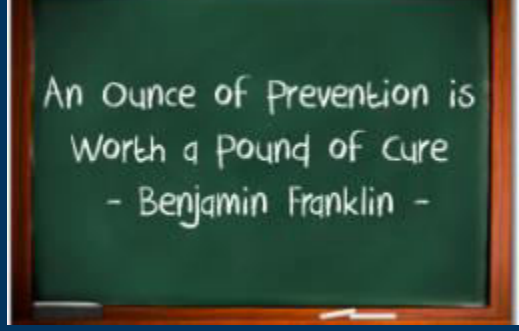


Knowledge Gaps:

- **Does intestinal dysbiosis cause the disease of does the disease cause the dysbiosis ?**

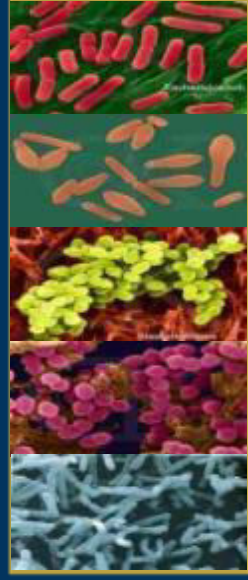


Gut Health: Practical Applications for Everyday Life !



- Eat a wide variety of foods
  - Try to add fermented foods and prebiotics when possible
  - Minimize food additives (sweetners, emulsifiers, etc)
  - Consider blenderized diets for pts needing formulas
- Locate a good local source of probiotic that has strains of bacteria that have <u>data</u> to support benefit
- Do not spend a lot of money
- Daily intake with a good prebiotic is beneficial
- Be cautious of overstatement of claims stating benefits
  - Association does NOT equal causation
- More bacteria #'s does not automatically mean better

Ongoing Trials : Targeted Probiotics



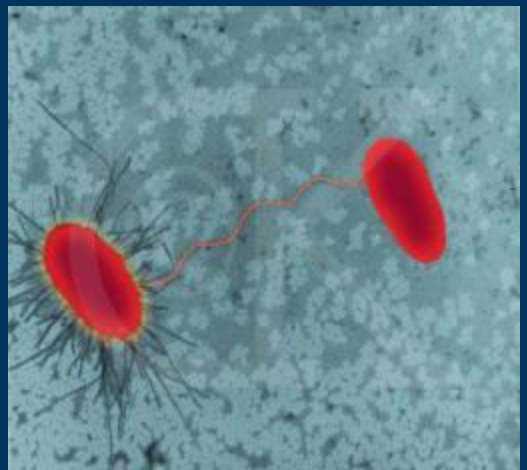
- Neurologic disorders
  - Pain control, ADHD, Tourette syndrome, depression, ALS
- Inflammatory diseases
  - Aging, IBD, arthritis, diabetes,
  - asthma in children now in question
- AIDS prevention
  - Changing the pH of the vagina alters HIV receptors
    - » Already done for L. jensenii (Yamamoto HS BMC Micro 2013)
- Cancer prevention
  - Multiple mechanisms – primarily epithelial based
    - » Dietary procarcinogens by commensal bacteria
    - » Histone deacetylase inhibitor
- Nephrology
  - Decrease frequency of dialysis required
- Use on non-GI surfaces
  - Burns, tracheostomy sites, skin in ICU, chronic wounds, STSG, Vagina, Pulmonary epithelium
  - Breaking up biofilms
- Allows efficient use of colonic fermentation for energy production

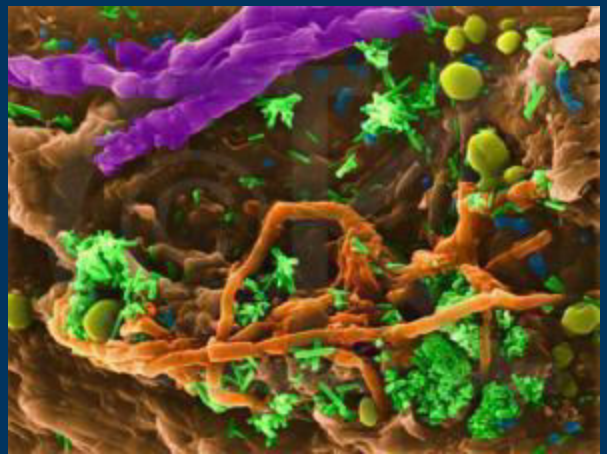
It time for a paradigm shift !

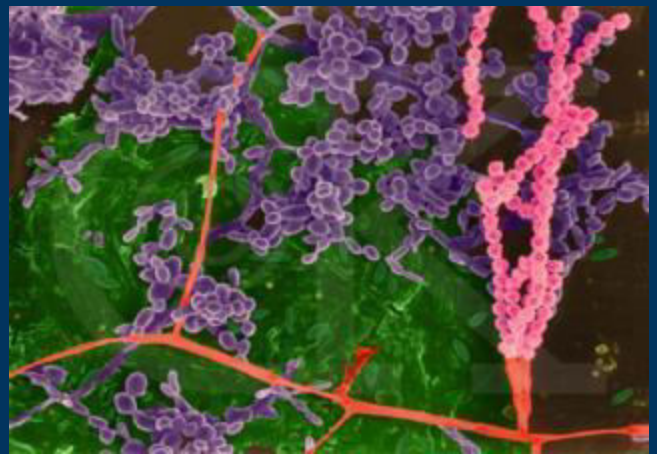
Supply adequate viable beneficial bacteria or a substrate which enhances these specific beneficial bacteria instead of trying to eliminate the pathogen ?

“Bioecological control”

Shift from Germ Theory to Germ Therapy







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  - Sarah Larimer RD
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  - Sherry Garrelts
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