Can Addition of Probiotics to the Diet Really Change People’s Health?

Oregon Dairy Association
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Why care about gut bacteria?

All life has evolved in presence of bacteria

As humans, they surround us and we surround them!

Our immune system reacts to bacterial presence.

Bacteria produce numerous beneficial metabolites and peptides

4.5 pounds of bacteria is on or "in" us

**Trophic**
- Control of epithelial cell growth and differentiation
- Promote intestinal angiogenesis
- Development and homeostasis of the immune system

**Protective**
- Protection against pathogens

**Metabolic**
- Fermentation for SCFA
- Stimulates mucus
- Production of vitamin K
- Some AA, Neurotransmitters
- Xenobiotic metabolism
- Distant organ signaling
Human Microbiome

• Term suggested by Nobel Prize Winner Dr. Joshua Lederberg
• Describe 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
• Microbiome = Microbiota
• Includes bacteria, fungi, archaea

99% of our total genome is absent at birth
Gut Microbiota Communication with Other Organs

<table>
<thead>
<tr>
<th>Organ</th>
<th>Process influences by gut microbiota</th>
<th>Disease associated with dysbiosis/microbial metabolites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adipose tissue</td>
<td>Adipocyte volume, Thermogenesis, Browning, Inflammation</td>
<td>Obesity/insulin resistance, Insulin resistance</td>
</tr>
<tr>
<td>Liver</td>
<td>Bile acid metabolism, Lipogenesis, Energy expenditure</td>
<td>NAFLD/NASH</td>
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<tr>
<td>Pancreas</td>
<td>Insulin secretion</td>
<td>Type 2 diabetes</td>
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<tr>
<td>Whole body</td>
<td>Body growth</td>
<td>Undernourishment</td>
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<td>Cardiovascular system</td>
<td></td>
<td>Stroke</td>
</tr>
<tr>
<td>Lung</td>
<td>Gene expression</td>
<td>Allergic asthma</td>
</tr>
</tbody>
</table>

Schroeder BO, Backhed F. Nature Medicine 2016
Cohabiting family members share microbiota with one another and with their dogs

Se Jin Song, Christian Lauber, Elizabeth K Costello, Catherine A Lozupone, Gregory Humphrey, Donna Berg-Lyons, J Gregory Caporaso, Dan Knights, Jose C Clemente, Sara Nakielny, Jeffrey I Gordon, Noah Fierer, Rob Knight

Dog saliva may join yogurt as source for probiotics

Song SJ et al Elife 2013
Overseas travel dramatically alters your microbiome

Intestinal Microbiota by Latitude (n=438)

David LA et al Genome Biol 2014
Application to Humans: Microbiome literature: Science or Quackery?

- Professional Literature improving yet;
  - Advanced techniques
  - Meta-analysis not consistent
- Recent lead articles:
  - PNAS 2016
  - Nature 2015
  - Science 2014
  - Wall Street Journal 2012
  - Scientific American 2012
  - Economist 2012
  - NY Times 2013

Skeptics view:
“….probiotics can’t cure everything….”

New York Times 2013
Wall Street Journal 2012
Clinical Nutrition is a Changing Paradigm: Nutrition Support → Nutrition Therapy

Old School 1960-1982
- EN for macronutrients
- EN for non-nutritional benefits
- Immune/metabolic modulation
- Attenuates inflammation
- Maintains gut integrity
- Maintaining the microbiome
- Increase protein delivery

New School 1982-2017
- "Skeletons in the Closet"
- PEM in 50% pts US hospitals
- Support to prevent PEM
- PN-based
- Support to prevent PEM

- Supporting healthy growth
- Enhancing immune function
Pro and Prebiotics 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

- **Hepatic diseases**
  - NASH
  - Hepatic encephalopathy

- **Infectious disease**

- **Diarrheal diseases**
  - AAD
  - Bacterial
  - *Clostridium difficile*
  - Viral

- **Inflammatory diseases**
  - IBD
  - Allergy
  - Asthma

- **Autoimmune diseases**
- **Aging**
- **Obesity**
- **CNS - Psychiatry**
- **Renal disease**
- **Critical Care / Surgery**
  - Trauma
  - General surgery
  - Pancreatitis +/-
  - Transplantation
  - Sepsis
  - VAP prevention
  - AAD / C. difficile
Hospital Induced Changes in Microbiome

- **Broad spectrum antibiotics**
  - Changes noted within hours
- **PPI / H₂RA (acid reducing agents)**
- **Cardiovascular pressor agents**
  - Changes in pH,
  - Decrease $pO_2$
  - Increase $pCO_2$
- **Opioids**
  - Decrease motility and bacterial clearance mechanisms
- **Decrease in nutrient delivery to gastrointestinal tract**
  - Delays in feeding
  - Parenteral feeding
The Gut: A highly evolved and balanced ecosystem

Nutrients “IN”

Antibiotic exposure - an unavoidable side effect of human progress

>20 M length
200M² in surface area

Effect of Nutrients/Abx on microbiota?
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”

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!**
The Million Dollar Question?

Can addition of probiotics to the daily diet will we “prevent or mitigate” onset of disease?
Gastroenterologist Survey: Probiotics

- Evaluate MD opinions regarding probiotics
- Large metropolitan area in midwest

**Results:**

- Safe for most patients 100%
- 98% felt probiotics had a role in treating GI disease
- 93% had patients currently taking probiotics
- Most common bacteria used
  - Yogurt based, B.infantis (Align®), VSL#3,
- Most common clinical diagnosis used
  - IBS, AAD, C.difficile
- Most believed their practice was *not supported by scientific data*

Williams MD J Clin Gastro 2010
Where “man meets microbe”
Dynamic Interplay of Mutualism

- Concepts are not new
  - Reference in Bible, Koran and in Hindu text
  - Metchnikoff “father” of modern probiotic concepts

- 300 to 400 sq meter surface area of GI

- > 8 million genes in the bacterial genome vs 23,000 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

- Expected to be 56 Billion industry by 2018
**Probiotics: Exploring the Mutually Beneficial Effects of Bacteria and Their Substrates in the Human Host**

- Prevent infections (systemic and GI)
- Regulate local and systemic immune function
- Regulate bowel motility
- Regulate appetite (leptin, ghrelin)
- Regulate Inflammation, local and systemic
- Metabolic pathway nutrients: glycemic control, cholesterol, amino acids
- Support mucosal barrier (multiple mxs)
- Enhance nutrient utilization
- Prevent neoplastic changes
Interpreting Scientific Evidence: Different Perspectives May Result!

US Perspective
Interpreting Scientific Evidence: Many Different Perspectives!

US Perspective

Canadian Perspective
Has Our Fear of “Bacteria” Made Us More Susceptible to Disease

Germ Farm

Scrub'em!
Actions at the mucosal border: The Critical Balance!

Barrier function

Selective absorption

Life or death is only one cell layer away

Fishman JE et al
Ann Surg 2014
Mechanisms:
Colonization Resistance
Antimicrobial Factors

- Competitive inhibition
- Physical barrier (mucous)
- ↓ Adherence, attachment
- Produce bacteriocins
  Defensins, Trefoil
  Bind pathogens
- ↓ pH reduces growth
- Interferes quorum sensing
  ↓ Virulence expression
- Breaks up biofilms

Bacteria
- *Escherichia coli* (pathogenic)
- *Salmonella typhimurium*
- *Shigella spp.*
- *Campylobacter jejuni*
- *Streptococcus mutans*
- *Bacillus subtilis*
- *Clostridium perfringens*
- *Helicobacter pylori*
- *Staphylococcus aureus*
- *Listeria monocytogenes*
- *Pseudomonas fluorescens*

Fungi
- Candida albicans
- Aspergillus flavus

*L. reuteri* inhibits
*H. pylori*

*L. reuteri* inhibits
*Staph aureus*
Multiple clinical mechanisms of probiotics well described

- Competitive inhibition of pathogens
  - Alverdy data – GI anastomosis
- Enhance HSP in gut mucosa
- Tight junction protein synthesis
- Enhance mucosal blood flow
- Stimulate gut immunity
- Butyrate (fermentive end product) enhances neutrophil killing, chemotaxis, resolution of inflammation
- Butyrate: anti-neoplastic activity
- Increases return of GI motility
- Helps maintains microbiome diversity in colon
Additional mechanisms

- Alterations in metabolism/energy utilization
  - Vitamin production in infant greatest effect (folate, B12)
  - Production and absorption of AA
- Bile salt hydroxylase – decrease fatty liver
  - Microbiome activates Ca++ binding protein expression
- Interacts with ENS bidirectional communication
  - Nerve Growth Factor stimulated by Lactobacillus sp
  - Increases IL-10 which attenuates inflammation
  - Alters GABA in brain and shown to be anxiolytic
    - Blocked by vagotomy
  - Microbiome required for normal gut brain signaling

Bienenstock J et al Gut Microbes 2013
McVey-Neufeld KA et al Neurogastro and Motility 2015
Attempting to prevent or treat acute and chronic disease with probiotics

No all “probiotics” are equal
Mechanisms of action are key
Need the right strain and research to prove it
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

Can Probiotics be used for prevention of disease in “Healthy People”

Sick days at home with short term gastro-intestinal or respiratory illness
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**
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
Results:

- *Lactobacillus rhamnosus* GG influences the composition of intestinal microbiome
- Use prevents some of the changes associated with cephalosporin antibiotic use
- Decrease in GI complaints
- Treatment prevents subsequent infections up to 3 yrs

Korpela K et al PLOS One 2016
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

- 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

- New Zealand n=423 pts
- Prospective trial
- Probiotic supplementation
  - Significantly dec GDM
  - Most benefit seen in older women

Wickens KL British J Nutrition 2017
Mechanisms: Enhancing mucosal blood flow

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

- N=566 infants
  - 5 probiotic genera (4 bifidobacteria and 1 lactobacillus
    - $2.0 \times 10^9$ CFU/day

- Results
  - Reduction in Nec 9.8% vs 5.45 % (p<.05)
  - Reduction in Mortality 9.8 vs 6.8 % (NS)

Janvier A et al J Pediatrics 2014
L. *salivarius* (UCC118) prevents *Listeria* infection, in mice

Control  UCC118  UCC118, bacteriocin KO

• Sinéad C. Corr, PNAS 2010
Lactobacillus salivarius (UCC118) prevents disruption of epithelial cell tight junctions

Miyauchi et al Am J Physiol Gastrointest Liver Physiol 2012
UCC118 alters tight junction protein localization.
Protecting the mucosal lining:
“Soluble factors for Lactobacillus rhamnosus GG activate MAPKs and induce cytoprotective heat shock proteins in intestinal epithelial cells”

- 70% of energy for colonocyte derived from luminal butyrate
- Cell culture model
- DNA microarray methods, real-time PCR and electrophoretic mobility shifts studied
- Studies confirm:
  - L. GG modulates signaling pathways
  - Activates via MAP kinase
  - L.GG protects mucosa from oxidant stress via expressing HSP

Tao K, Drabik K, Waypa T
Am J Physiol Cell Physiol 290;1018-1030,2006
Microbiome and the Brain

• Germ free mouse model:
  • Substantially ↑↑ cortisol response to stress
  • Decreased brain derived neurotrophic factors
    – Neurogenesis, synaptic growth, synaptic plasticity altered
  • Partially reversed by re-colonization with a normal mouse gut microbiota

• Significant bidirectional (Gut-Brain-Gut) communication
  • D-serine, GABA, Nerve growth factor

• Recent work with dramatic benefit it outcome;
  • Depression, anxiety, Alzheimer’s, OCD, ADHD
  • Very early work in Multiple Sclerosis, Parkinson’s disease

O’Mahoney SM Neuroscience 2015
Bienenstock J et al Gut Microbes 2013
McVey-Neufeld KA et al Neurogastro and Motility 2015
Huang R et al Nutrients 2016
Ho P et al More Than a Gut Feeling 2017
Probiotic based control of *H. pylori* infection

*H. pylori* infects at least half of the world’s population. The prevalence among middle-aged adults is over 80% in many developing countries, as compared with 20% to 50% in industrialized countries.

**WHO classifies *H. pylori* as class one carcinogen**

Suerbaum & Michetti *NEJM* 2002; 347:1175

Morowitz MJ *Ann Surg* 2011; 253:1094-1101
Specific probiotics have surface proteins that inhibit the binding of *H. pylori* in the stomach.

- *H. pylori* attached to gastric cells
- *L. reuteri* inhibits *H. pylori* binding

**Mukai et al. FEMS 32:105 (2002)**
HP Eradication Therapy with and without Probiotics - Meta-analysis

<table>
<thead>
<tr>
<th>Outcomes</th>
<th># Trials / (n)</th>
<th>with</th>
<th>w/o</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eradication Rates</td>
<td>11(1074)</td>
<td>85%</td>
<td>75%</td>
<td>11</td>
</tr>
<tr>
<td>Total Side Effects</td>
<td>7(625)</td>
<td>22%</td>
<td>38%</td>
<td>6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8(997)</td>
<td>6.1%</td>
<td>16%</td>
<td>11</td>
</tr>
<tr>
<td>Epigastric Pain</td>
<td>7(608)</td>
<td>16%</td>
<td>23%</td>
<td>14</td>
</tr>
<tr>
<td>Nausea</td>
<td>7(608)</td>
<td>16%</td>
<td>25%</td>
<td>12</td>
</tr>
<tr>
<td>Taste Disturbance</td>
<td>5(418)</td>
<td>14%</td>
<td>25%</td>
<td>5</td>
</tr>
</tbody>
</table>

Optimal dosing and probiotic strains will vary results

Tong, A Pharm Therap 2007
Probiotics in the prevention, treatment and management of Colorectal Cancer

• **Globally, 3rd most common cancer**
  – Risk factors; diet, obesity, smoking, inflammatory bowel
  – Inherited genetic disorders
  – Probiotics alters enzyme systems
    – Histone deacetylase inhibition

• **Microbiome**
  • Key to sporadic colon Ca

• **New data** – microbiome changes during tx CRC
  • Microbiome alters chemotherapeutic agents to enhance immune host immune function
  – “drugs need bugs”
  • Probiotics partially protective from effects of chemo and radiation

  Azcarate-Peril MA et al. Am J Physiol (GI Liver Physiol) 2011
A Four-Probiotics Regimen Reduces Postoperative Complications After Colorectal Surgery: A Randomized, Double-Blind, Placebo-Controlled Study

Katerina Kotzampassi\textsuperscript{1} · George Stavrou\textsuperscript{1} · Georgia Damoraki\textsuperscript{2} · Marianna Georgitsi\textsuperscript{2} · George Basdanis\textsuperscript{1} · Georgia Tsaousi\textsuperscript{1} · Evangelos J. Giamarellos-Bourboulis\textsuperscript{2}

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

L. Lytvyn\textsuperscript{a, b}, K. Quach\textsuperscript{a}, L. Banfield\textsuperscript{c}, B.C. Johnston\textsuperscript{a, b, d, e}, D. Mertz\textsuperscript{a, f, g, h, *}

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

Sudha Arumugam\textsuperscript{1} · Christine S. M. Lau\textsuperscript{1, 3} · Ronald S. Chamberlain\textsuperscript{1, 2, 3}
Prevention of GI Anastomosis failure

- Animal and human models (John Alverdy’s group)
  - Pseudomonas, enterococcus after anastomosis
    - Expression of barrier disrupting MMP9, PA-IL, etc
- Bacteria at sight of anastomosis change phenotype and become more aggressive and produce toxic metabolites and enzymes (MMP9) which increase risk of anastomotic disruption
  - Altered by MBP, antibiotic bowel prep, ischemia etc

Early data showing a “healthy” microbiome will limit anastomotic leaks

Fink D, et al J Trauma 2011
Stern JR et al J Surg Res 2013
Shogan, BD et al J GI Surg 2013
Shogan BD et al Microbiome 2014
Shogan BD et al Science 2016
Meta-analysis: Probiotics in Trauma

• Gu, WJ  JPEN 2013
• 5 RCT  N=281 patients:
  • Use of probiotics reduction;
    – Nosocomial infections
    – Ventilator associated pneumonia
    – Length of stay in ICU
    – No mortality advantage

• Caution: large heterogeneity between groups
• Use of meta-analysis for hypothesis generation not hypothesis confirmation !!!
SCFAs, Fiber Fermentation and Butyrate Receptors

- Trophic effect, colonocyte fuel
- Anti-inflammatory
- Enhance WBCs, macrophage
- ↓ Adhesion molecules
- (↓ microvascular thrombosis)

Thangaraju M et al J GI Surg 2008
Ganapathy V 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
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

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 studied

I Siempos et al Crit Care Med 2010
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.
Antibiotic-associated disease

Altering the Microbial Biodiversity
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
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%)


- **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**
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 or 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
<table>
<thead>
<tr>
<th>Clinical Condition</th>
<th>Probiotic</th>
<th>References</th>
</tr>
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</table>
The ultimate microbiome delivery: Is stool from a “good friend” or family member the answer for refractory *C. difficile* diarrhea

- RTC 39 patients with proven refractory *C. difficile*
- 16 got Donor feces / 13 received QID vancomycin
- Results:
  - Feces group
    - 13/16 resolved with single infusion
    - 2/3 resolved with second infusion
  - Vancomycin group
    - 4/13 resolved

*Nood EV NEJM 2013*
Could manipulation of the “Microbiome” help with weight control or be responsible for obesity?
Is altering the microbiome the origin of the obesity problem?

Early antibiotics: “associations” with other diseases include inflammatory bowel, asthma, food allergies, colon Ca
Feb 2016: CDC announces Obesity in USA from 29.9 to 30.6 BMI
Complications of Obesity

**Metabolic**
- Diabetes, NAFL, gallstones

**Structural**
- GERD, pseudotumor cerebri

**Inflammatory**
- Arthritis, autoimmune disease
- Degenerative joint disease

**Degenerative**
- Prostate, breast, ovarian, endometrial, cervical, lymphoma, renal cell

**Neoplastic**
- Prostate, breast, ovarian, endometrial, cervical, lymphoma, renal cell

**Psychological**
- Depression, anxiety, panic attacks, eating disorders
Economic Cost of Obesity on Chest Pain Presentation

Difference in Emergency Room Costs for Patients Presenting With Chest Pains Compared with a Normal-weight Patient

- Overweight: 22% Higher
- Obese: 28% Higher
- Severely Obese: 41% Higher
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
Human obesity is transplantable

Transplantation of stool flora from twins discordant for obesity into germ-free mice show causal effect of microbiota.

Ridaula et al. Science 2013
Insulin Sensitivity is Transplantable
Gut microbiota in T2DM

Vrieze A et al. Gastroenterology 2012

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 endocannabinoid 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
It is all about “Risk vs. Benefit”
Probiotic Safety:
Generally Recognized as Safe (GRAS) USA
Qualified Perception of Safety (QPS) EU

Can probiotic species transfer resistance genes?

• Lactobacillus bacteremia
  • 180 cases in 30 years
  • 69 cases of endocarditis in 30 years
    – (majority of L. rhamnosus)
  • Hepatic Lactobacillus abscess in transplanted liver and immune compromised host reported

• Saccharomyces *boulardii*
  • Recent data showing several outbreaks of S. Cervesiae fungemia when giving S.boulardii
  • *S. boulardii* not true probiotic?

• Host risk factors
  • Immunocompromised
    » This is theoretical, clinical data would support use
  • Recent major dental work (theoretical anecdotal reports)

• Caution in severe pancreatitis (Lancet Feb 2008)

Reid G Best Practice Res Clinical Gastro 2016
Sanders ME Ann NY Acad Science 2011
Salminen MK et al Clinical Infectious disease 2004
A word of caution:

Preventing an over zealous response

- Many probiotics advocates have made extravagant claims without data to support

- Effects will depend on
  - Not just species but strain specific
  - Host
    - Medications, inflammatory state, exercise level etc etc
    - Recent weight changes
    - Diet changes, even on a meal to meal basis
    - Metabolic state
    - Meds: motility, narcotics

- Current “guidelines” on use are very confusing
  - SCCM, AGA, ESPEN
15 most commonly studied indications for probiotic

Antibiotic-associated diarrhea: 17%
H. pylori: 16%
Acute pediatric diarrhea: 16%
Allergies: 12%
IBS: 12%
IBD: 12%
Vaginitis: 12%
NEC: 9%
Traveler’s diarrhea: 9%
Acute adult diarrhea: 8%
Constipation: 8%
C. difficile infections: 8%
Sepsis: 3%
Dental infections: 3%
Probiotics: So many questions, so few answers!!!

- Monostrain vs multistrain?
- Pre, pro, synbiotic or just cell free extracts?
- Quantity and quality of probiotic needed for desired effect?
- How best to assess the activity / viability / safety?
- When are probiotics contraindicated?
- Resistant patterns if any?

Saxelin MJ CID 2009

McFarland L CID 2015
General Guidelines for Use of Pre and Probiotics

• 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

• Identify optimal strain, insoluble fiber and commercially available product
  • ~Probiotic: $10^9$-$11$ viable cells per day ?
  • ~Prebiotic: 20-30 gm/day ?

• Continued intake of probiotic is required to maintain benefits

• Prebiotic are an excellent option to modify flora on long term basis
  • Persistent levels require continuous intake !
  • Now shown to decrease all cause mortality
Ongoing Trials : Targeted Probiotics

- **Neurologic disorders**
  - Pain control, ADHD, Tourette syndrome

- **Inflammatory diseases**
  - Aging, IBD, arthritis, asthma, diabetes

- **AIDS prevention**
  - Changing the pH of the vagina alters HIV receptors
  - Gene transfer HIV receptor into probiotics-BT take up virus not epi cell
    » Already done for L. jensenii (Yamamoto HS BMC Micro 2013)

- **Cancer prevention**
  - Multiple mechanisms
    » 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
Who needs Viagra or mosquito repellent?

Alterating mating behavior changes with changes in bacteria (PNAS 2013)

Mosquitos attraction altered by changes in bacteria (Verhulst NO FEMS Microecology 2012)
Individualized focus

Backhed F et al Cell Metab 2016
Currently limited by our technology
Future Trends:

- More data on specific strains in microbiome
- Management of “big data”
- Better acceptance by “public and scientific community”
- New attention to gut / microbe symbiosis
  - “we need to listen to our microbiome”
  - Individualized “fiber” to promote specific microbiota
    - Short bowel, IBD, obesity, depression, etc
- Specific bacteria as drug delivery tools genetically engineered
- “Designer probiotics”
It time for a paradigm shift in dietary prevention and management of disease states in the USA!

“We are starving our microbial self”

JL Sonnenburg 2016

Supply in the diet adequate viable beneficial bacteria (probiotic) or a prebiotic which enhances a “healthy” microbiome!
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“..., one of the greatest opportunities to improve patient outcomes will probably come not from discovering new treatments but from more effective delivery of existing therapies.”

Pronovost PJ et al., Lancet 2004; 363:1061-7