Leaky Gut Syndrome

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Medical Director Nutrition Services
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“Leaky Gut”

- Is “Leaky Gut Syndrome” real?
  - Data supporting
  - Data refuting

- Gut permeability

- What are the proposed mechanisms?

- It is time to start treatment?
  - Who needs treatment?
  - What is the treatment?

Odenwald MA et al Clinical GI and Hepatology 2013
**Definition:** Wikipedia access May 18, 2015

- **Leaky gut syndrome** is a proposed condition some health practitioners claim is the cause of a wide range of serious long-term conditions, including diabetes, lupus, and multiple sclerosis. Proponents of leaky gut syndrome state that an altered or damaged bowel lining or gut wall results from poor diet, parasites, infection, or medications, and that this allows substances such as toxins, microbes, undigested food, or waste to leak through. They say this prompts the body to initiate an immune reaction leading to potentially severe health conditions. This theory is vague and largely unproven, and there is no evidence that the remedies marketed for treating leaky gut bring the benefits they claim. The scientific community continues to debate whether there is a connection between a leaky gut and autism, and whether "leaky gut syndrome" exists at all.

**MD’s answers to question “what is Leaky Gut Syndrome”**
- Don Kirby MD: “From the MD standpoint it’s a very gray area. Physicians don’t know enough about the gut …. “
- Linda Lee MD: “We don’t know a lot but we do know that it exists. In the absence of evidence, we don’t know what it means or what therapies can directly address it”
- Leaky gut not a recognized diagnosis in ICD-9 or NHS in UK
Leaky Gut Progression

- Stress
- Toxins
- Food Particles
- Drugs
- Pathogens
- Organ Malfunction

GI Inflammation

- Food Intolerences
- Immune System Issues
- Autoimmunity

Dr. Axe
FOOD IS MEDICINE
What We Do know:
The Critical Balance!

Barrier function

Selective absorption

Life or death is only one cell layer away

Fishman JE et al
Ann Surg 2014
Protective mechanisms

**Mechanical**
- Epithelial barrier
- Mucous layer
- Tight Junctions

**Non-Mechanical**
- Normal gut flora
- Secretory IgG
- GALT
- Dendritic cells
- Macrophages
- Antigen receptors

Modified from Clark J Shock 2007
Leaphart CL Surgery 2007
Protecting the intestinal barrier is a tough job; Microbial diversity seems to play a major role

Host response (immune system, intestine, brain-gut axis, ENS)

Shanahan *Gastroenterology* 2010;139:1808-12
The organization of the ENS of human

Innervation of the GALT and gut endocrine cells not illustrated here

Furness, J. B. (2012) The enteric nervous system and neurogastroenterology
Enteric Nervous System

- Estimated 400-600 million enteric neurons
  - > total of all sympathetic and parasympathetic ganglia combined. ENS is almost equal to the number of neurons in the spinal cord
- Internal system which can function autonomously
  - Chemoreceptors
  - Baroreceptors
    - Subject to outside regulation under normal conditions (integration)
Classification of Enteric Neuropathies

- Congenital and developmental neuropathies
  - Ex: Hirschsprungs

- Sporadic and acquired neuropathies
  - Ex: IBS

- Neuropathies secondary to or associated with other diseases
  - Ex: Parkinson’s

- Iatrogenic or drug-induced neuropathies
  - Ex: ICU dysmotility
Diseases “associated” with leaky gut

- **Strong data to support:**
  - IBD
  - IBS
  - Celiac
  - MOF

- **Organ system diseases with some supportive data**
  - DM1
  - GVHD
  - AIDS
  - Multiple sclerosis
  - Rheumatoid arthritis
  - Autism
  - Migraines
  - Food sensitivities
  - NASH (fatty liver)

- **Little objective data currently supports:**
  - Fibromyalgia
  - Depression
  - Allergies
  - Skin disorders

- **No objective data**
  - Weight gain
  - Chronic fatigue
Models evaluating barrier function
mostly rodent models

- Dextran sulfate
  - Epithelial injury
- IL-10 KO
- Immunodeficiency mouse models
- MLCK mouse model
  - Very promising – allows loss of barrier w/o damage
- Cytokine changes
  - TNF, IL-13
- Various infectious models
- Various inflammatory models
- Tight junction protein synthesis and redistribution
- Expression of zona occuldens
- Electrical resistance (MAPK)
- Mucosal apoptosis
- Claudin protein evaluations

MLCK – Myosin light chain kinase
The beginnings of human data to show disease associated with loss of barrier dysfunction

MULTIPLE ORGAN FAILURE

B. Eiseman, m.d., f.a.c.s., R. Beart, m.d., and L. Norton, m.d., f.a.c.s., Denver, Colorado

Surg Gyn Obstet 1977

A New Syndrome

ICU Technology Allows Patients To Survive Single Organ Failure

Ben Eiseman
Infections felt to be the cause

Infectious etiology concept supported by key papers in 1970’s Polk, Fry etc.

Research in the 70’s focused on infectious etiology
Pathophysiology of Splanchnic Hypo-perfusion

Trauma- Sepsis- Shock- MOF

- Increased catecholamines
- Increased vasoconstriction
- Hypovolemia
- Proinflammatory cytokine release
- Cardiac output

Splanchnic hypoperfusion

- Reduced mucosal blood flow
- Barrier disruption
- Altered GI motility
- Changes in bacterial flora and virulence

Barrier Dysfunction, MOF, worsening sepsis

1970’s > 50% of cases of MOF from intraabdominal infections

- By 1980’s IAI showing better outcomes but MOF still occurring at the same rate as in the 70’s?
  - Better initial management of trauma and post op patients
  - More potent and appropriately dosed antibiotics
  - Earlier recognition of IAI with the use of CT
  - Interventional radiologic techniques allowing drainage of abscess without open surgery

- Series of papers from EU reporting MOF without infectious source
  - Faist- 1983 MOF in polytrauma
  - Nuytinck – 1987 “whole body inflammation in trauma…”
  - Waydhas – 1992 Inflammatory mediators infection, trauma, MOF
  - All supporting a convincing story that MOF in trauma often occurs without infectious etiology
Question 1980’s: if not infection what was driving MOF?

- Shock (septic, hemorrhagic, cardiogenic etc) seemed to be consistent with patients getting MOF

- Concept that low flow states and tissue ischemia / reperfusion is etiology becomes popular;
  - Giving rise to gut origin of sepsis (multiple authors)
    » Gut as “Motor for Multiple Organ Failure”
  - “unrecognized flow-dependent oxygen consumption”
    » Supranormal oxygen delivery (Shoemaker)

- Supporting evidence at the time
  - Animal models of bacterial translocation following trauma
  - Selective gut decontamination in humans (+/-)
  - Most patients dying with MOF with negative cultures
  - Early enteral feeding showing benefit
    » Primarily pneumonia outcome was decreased
Major research discoveries supporting hypothesis of gut as the “motor” for MOD

- **Moore et al**: shock and hypoperfusion allows gut release of proinflammatory cytokines increasing ARDS/Sepsis (1)
- **Fink et al**: epithelial tight junctions are compromised leading to increased permeability....inflammation (2)
- **Teixeira et al**: Germ free animal showing increased survival following I/R (4)
- **Clark et al**: epithelial apoptosis elevated in sepsis, prevented by over expression of anti-apoptotic protein Bcl-2 (6)
- **Deitch et al**: Toxin from gut damages lung via lymphatics (5)
- **Alverdy et al**: interaction between bacteria and host. Most patients dying of “MOF” have no + cultures (3)

Data collection from 20 institutions 2003 to 2010
  • 1643 patients with MOF

Strict criteria for sepsis / injury / MOF

Results
  • MOF incidence decreased over time 17% 2003 to 9.8% in 2010
  • MOF death 33% 2003 to 36% 2010
    » No change in ventilator days or length of stay in ICU
  • Most MOF death occurred within 2 days of MOF diagnosis
  • Lung dysfunction decrease 58 to 51%
  • Cardiac dysfunction decrease from 21 to 13 %
  • Renal and hepatic failure rates did not change
    » Now shown to be most likely from gut failure leading to hepatic and renal failure

Sauaia A et al J Trauma and ACS 2014
Most of discussion on “leaky gut” is not in the ICU. What are symptoms for the “routine” leaky gut syndrome?

- **Commonly reported:**
  - Bloating
  - Gas
  - Cramping
  - Food sensitivities
  - Fatigue

- **Less commonly reported:**
  - Asthma
  - Chronic joint and muscle pain
  - Recurrent vaginal infections
  - Constipation
  - Behavior changes
  - Anxiety

All seem vague and difficult to collect objective data.
Treatment: Protecting mucosal barrier function

- Maintaining visceral blood flow
- Glucose control
- Enteral feeding
- Minimize pharmaceutical agents which alter flora and motility
- Pro and prebiotic supplements
- Lower inflammatory stimuli
  - Dietary changes
  - Anti-inflammatory or agents to enhance resolution of inflammation
What are the mechanisms?
Splanchnic Hemodynamics

GI tract receives 25% of cardiac output (varies widely)
- 1.25 L/min at rest, 3.0 L/min with meal, 0.5 L/min with exercise
- Dilates to nutrient bolus in segmental fashion

Uses 20 to 30% of total body O₂ consumption at rest
Small intestine receives nearly 50% of arterial blood flow to splanchnic bed (uneven distribution)
Villous tips are at highest risk

**Blood flow (ml/min*100g)**
- Splanchnic: 50
- Kidneys: 400
- Brain: 55
- Skeletal Muscle: 3
- Heart: 80
Cells at the villus tip are exposed to greater hypoxic stress during hemodynamic instability.
Compromised Bowel

- Relative ischemia can result in loss of villous tips
- SB at high risk due to countercurrent mechanism
- Villous tips affected first – Absorption
  - Peptide transporter is first to return after injury
Cholinergic anti-inflammatory pathway

- Activation of vagal efferents results in regulation of cytokine production of macrophages in the gut wall.
- Shown to improve survival in septic animal models (rat model).
- Enteral dietary fat can activate the cholinergic anti-inflammatory pathway.
  - Gut permeability, ileal lipid binding protein, intestinal myeloperoxidase, mast cell protease.
  - CCK antagonists blocks benefit.

Conclusion:

- Luminal delivery of nutrient required to show benefit.
- Lumen macronutrient content critical in supporting barrier function.

Gut Associated Lymphoid Tissue
G.A.L.T.

- BM, spleen, LN
  $2.5 \times 10^{10}$ Ig producing cells

- Gut
  $8.5 \times 10^{10}$ Ig producing cells
Feeding Maintains GALT / MALT
Etiology of Induced Changes in Commensal Microflora

- Broad spectrum antibiotics
- PPI / H₂RI
- Vasoactive pressor agents
  - Changes in pH,
  - Decrease pO₂
  - Increase pCO₂
- Opioids
  - Decrease motility and bacterial clearance mechanisms
- Anticholinergic agents
- Decrease in luminal nutrient delivery
- “stress”
Dysbiosis

Eubiosis Defined

<table>
<thead>
<tr>
<th><strong>Eubiosis</strong></th>
<th><strong>Dysbiosis</strong></th>
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<tbody>
<tr>
<td>Protection of intestinal epithelium integrity</td>
<td>Damage to intestinal epithelium</td>
</tr>
<tr>
<td>Anatgonistic effect on undesired microorganisms</td>
<td>Toxic metabolic substances (NH2, biogenic amines, toxins)</td>
</tr>
<tr>
<td>Contribution to host immune defense (maturation and stimulation of immune system)</td>
<td>Decomposition and increased gas production</td>
</tr>
<tr>
<td>Nutrient digestion</td>
<td>Immune system weakening</td>
</tr>
<tr>
<td>Vitamin syntheses</td>
<td>Immune reactivity/inflammation</td>
</tr>
<tr>
<td>Protein syntheses</td>
<td>Accelerated cell turnover and increased need for energy</td>
</tr>
</tbody>
</table>

Modified from: http://en.engormix.com/MA-
What contributes to dysbiosis

- Host genetics: Mutations in NOD2, IL23R, ATG16L and IGRM
- Lifestyle: Diet, Stress
- Early colonization: Birth in hospitals, Altered exposure to microbes
- Medical practices: Vaccination use, Antibiotic Hygiene

Modified from:
Why care about gut bacteria?

• All eucaryotes have evolved in presence of bacteria.
• They surround us and we surround them!
  – Our immune system reacts to bacterial presence.
  – Bacteria produce metabolites and peptides.

**Trophic**
• Control of epithelial cell proliferation and differentiation
• Promote intestinal angiogenesis
• Development and homoeostasis of the immune system

**Protective**
• Protection against pathogens

**Metabolic**
• Fermentation for SCFA
• Endogenous mucus
• Production of vitamin K
• Some AA, Neurotransmitters
• Xenobiotic metabolism
Where “man meets microbe” a Dynamic Interplay of Mutualism

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

- 300 to 400 sq meter surface area of GI

- > 2 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
Man and Our Microbiome Continue to Evolve

- Newborns in USA
  - 1/3 c section, majority bottle fed
- Major dietary changes
  - Fats, protein, fiber, additives, sweeteners
- Changes in activity
  - Obesity, sedentary lifestyles
- Immunizations
- Decrease in parasitic infection
- Refrigeration
- Sanitation and hygiene standards
- Urban life in cities and concrete
- Increased use of antibiotics
  - Indicated or not
Does the microbiome change?

• Diet, inflammation, pH, drugs
• Bacterial changes with host stress situations
  • Bacterial use environmental clues
    – pH, temperature, redox potential, osmolality
  • When energy supply is limited genes “switch on” virulence factors
    – Ex: E.coli and Pseudomonas can rapidly become virulent with host stress (epinephrine, cortisol, morphine etc)
• New data showing microbiome even changes between meals

Alverdy J et al Molecular Biol 2008
Cani PD et al Curr Opin Biotech 2015
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
- Metabolic pathway nutrients: glycemic control, cholesterol, amino acids
- Support mucosal barrier
- Regulate bowel motility
- Prevent neoplastic changes
- Regulate appetite (leptin, ghrelin)
- Enhance nutrient utilization
- Regulate Inflammation, local and systemic
Starting From Day 1 We Are Exposed To Pro and Prebiotics

What are they?
- **Probiotics**: live microorganisms that confer a health benefit on the host when administered in adequate amounts
- **Prebiotics**: substrate for probiotics

Where found?
- **Probiotics**: found in fermented foods
- **Prebiotics**: found in many unprocessed foods

![Probiotics](image1)

![Prebiotics](image2)

![Synbiotics](image3)
Human Milk Oligo-saccaride (HMO)

- HMOs have prebiotic effects:
  - Selectively enhancing desired colonic bacteria
  - Anti-adhesive for pathogens
  - Blocking pathogen colonization and invasion
  - Changing glycosylation of epithelial cells altering expression to limit infections

Human breast milk: 15% of the carbohydrates are not able to be absorbed in the proximal gut and are clearly there as substrate for optimizing colonic bacteria
Mechanisms:

1. Enhancement of the epithelial barrier
   - Mucins and defensins
   - Probiotics
   - Pathogens
   - Mucus

2. Increased adhesion to intestinal mucosa

3. Inhibition of pathogen adhesion

4. Competitive exclusion of pathogenic microorganisms

5. Production of anti-microbial substances
   - Example: bacteriocins

6. Modulation of the immune system
   - IL-10
   - TGFβ
   - Immature DC
   - Macrophage
   - Th1, Th2, Th17
   - Treg
Multiple clinical mechanisms well described

- Competitive inhibition of pathogens
- Enhance HSP in gut mucosa
- Tight junction protein synthesis
- Enhance mucosal blood flow
- Stimulate gut immunity
- Butyrate (fermentive end product) enhances neutrophil killing
- Increases return of motility
- Helps maintains diversity in colon
Mechanisms:
Colonization Resistance
Antimicrobial Factors

L. reuteri inhibits Staph aureus

Mechanisms
• 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

PM Sherman (NCP2009)
Morowitz M J (SCNA 2011)
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
Mechanisms: Enhancing mucosal blood flow

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

Human epithelial cell model

Miyauchi et al Am J Physiol Gastrointest Liver Physiol 2012
UCC118 alters tight junction protein localization.

- Tight junction proteins

Miyauchi et al. Am J Physiol Gastrointest Liver Physiol 2012
L. salivarius UCC118 and L. salivarius AH43324 have very different effects upon barrier function

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
SCFA = Fermentation end product of some probiotics (from prebiotics):
Multiple Mechanisms Described

• Energy source;
  – Colonic mucosa;
    • Stimulates cell proliferation, Promotes sodium and water absorption
  – Cardiac, skeletal muscle, brain
    • Acetate, butyrate, propionate

• Regulation of gene expression for ICAM-1 and E-Selectin on endothelial cells
• Decrease COX-2 expression
  • (butyrate and propionate)
• Prevention of neoplastic transformation
  • Inhibits histone deactylase by DNA hypermethylation to promote differentiation in cancer cell lines
• Enhances Leptin secretion
• pH control; Inhibition of pathogen overgrowth in gut lumen,
• ROS scavenger
  • Pyruvate is anti-inflammatory and decrease NFKB expression
• Activation of polymorphonuclear cells
  • Both local and systemic immune benefit
  • G-protein receptors on circulating PMN’s

Thangaraju M et al J GI Surg 2008
Additional mechanisms

- Alterations in metabolism/energy utilization
  - vitamin production in infant greatest effect (folate, B12)
  - Production and absorption of AA
- Stimulation of intestinal motility
- Butyrate anti-neoplastic activity

- 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 with 28 day continuous feeding (blocked by vagotomy)
  - Microbiome required for normal gut brain signaling
  - Microbiome required for gut Ca++ binding protein expression

Bienenstock J et al Gut Microbes 2013
McVey-Neufeld KA et al Neurogastro and Motility 2015
Probiotics 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 diseases**
- **Diarrheal diseases**
  - AAD
  - Bacterial
  - *Clostridium difficile*
  - Viral
- **Inflammatory diseases**
  - IBD
  - Allergy
  - Asthma
- **Autoimmune diseases**
- **Aging**
- **Obesity**
- **Depression**
- **Renal disease**
- **Critical Care / Surgery**
  - Trauma
  - General surgery
  - Pancreatitis +/−
  - Transplantation
  - Sepsis
  - VAP prevention
  - AAD / C. *difficile*
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.
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

**INFLAMMATION**

*L. reuteri*

* • 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>

Tong, A Pharm Therap 2007
Probiotics in Irritable Bowel Syndrome

• IBS
  – 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
Inflammatory Bowel Disease

- Crohn’s disease
  - 29 PRCT – 13 slight improvement in symptoms little if any objective data showing benefit
  - 16 PRCT – no benefit

- Ulcerative Colitis
  - Data slightly better than Crohn’s
  - Widely variable depending on strain, age, severity of disease
  - Increase remission rates UC

- Associated Inflammatory Bowel Disease issues with best data
  - Pouchitis – VSL#3 better than placebo

- Good News: NO HARM NOTED

References:
- Whelan K Curr Opinion Gastro 2013
- Holubar SD et al Cochrane 2010
- Shen J et al IBD 2014
Metabolic Syndrome: Can Pre and/or Probiotics Be a Solution?

• 93 of 123 obese subjects completed the trial of 9 weeks of dietary changes 14 week maintenance period
  – changes included;
    • Whole grains, Chinese medicine, prebiotics

  – Results:
    • Mean wt loss 5.7 +/- 4.6 kg
    • Improved insulin sensitivity, lipid profiles, and blood pressure
    • Improved “beneficial” bacteria species
    • Improved gut permeability (lactulose / mannitol ratio)
    • Decrease TNF, IL-6

Xiao I et al 2013 FEMS Microbiology
Could probiotics or changing the “Microbiome” help with weight control?
Is altering the flora the origin of the problem?
Reduced diversity of the gut microbiota in obese individuals

Large inter individual variation in flora composition and variation in study design has made studies difficult to compare

- Turnabugh et al. Nature 2009
Human obesity is transplantable

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

Ridaula et al. Science 2013
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
Pathogenesis of CDAD

Antibiotic therapy

Alteration in colonic microflora

*C. difficile* exposure and colonization

Release of toxin A and Toxin B

Colonic mucosal injury and inflammation

Spores can survive up to 5 months on surfaces

Badger, VO et al JPEN 2012
Emergence of B1/NAP1 Strain

- Produces 16-23 times C. diff. toxins A and B in vitro,
- represented 50% of isolated strains between 2001-2003
  - Produces a 3rd binary toxin
- Increased risk of relapse
- Less responsive to standard therapies

McDonald NEJM 2005
Johnson BC Ann Int Med 2012
Pattani R et al Medicine 2013
Use of probiotic preparations to prevent C. difficile Associated Diarrhea

<table>
<thead>
<tr>
<th>RDBPCT  N=135</th>
<th>Meta-analysis 28 studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 64  all taking antibiotics</td>
<td>N=3818 patients</td>
</tr>
<tr>
<td>100 gm BID L. casei as drink</td>
<td></td>
</tr>
<tr>
<td>Results:</td>
<td>“Moderate quality” of evidence probiotics as prophylaxis</td>
</tr>
<tr>
<td>• AAD: 7/57 (12%) vs 19/56 (34%)</td>
<td>• decreases incidence of CDAD by 66%</td>
</tr>
<tr>
<td>• 21% relative risk reduction,</td>
<td>• No adverse influence by receiving probiotics</td>
</tr>
<tr>
<td>NNT 5</td>
<td></td>
</tr>
<tr>
<td>• C. diff 0/57 vs 9/53 (17%)</td>
<td></td>
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</tbody>
</table>

Johnston BC Ann Internal Medicine 2012
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
Ongoing Trials: 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
Fecal Microbiota Transplantation for MOF and Sepsis?

- Dysbiosis postulated at etiology on ongoing sepsis following vagotomty
  - 44 yo with 30 days of low grade sepsis tx with antibiotics, probiotics and supportive therapy
- 16S RNA and DNA based molecular techniques
  - Pre and post treatment analysis
  - Nasoduodenal delivery for FT
- Results:
  - Septic symptoms resolving rapidly
  - Stool microbiome changes over 7 days
    - Rapid rise in Firmicutes and decrease in Proteobacteria
  - Inflammatory markers improved

Li Q, Wang C et al Critical Care 2015
Where do we stand with Leaky Gut Syndrome?

- Growing data to support integrity of GI tract is vital to a growing number of disease:
  - MOF
  - IBS
  - IBD
  - CKD
  - Hepatic Steatosis
  - Celiac
  - Sepsis
  - Obesity
  - Diabetes

- Current management:
  - Dietary changes
  - Microbiome considerations
  - Limit meds which alter barrier
  - Control barrier function

- Need better information and models to test suspected etiologies of Leaky Gut before the diagnosis is widely given and treated!!
Thank You