The Human Microbiome: Friends or Foes

Part 2
SIBO from Amy Nett, M.D.

- SIBO = Small Intestinal Bacterial Overgrowth
- Can lead to leaky gut and several other symptoms
- Small intestine--<10,000 bact./ml fluid
- Large intestine-->1 billion bact./ml fluid
- SIBO is usually overgrowth of various bact. normally found in colon (I.I.)
- SIBO causes small bowel mucosal damage which can lead to “leaky gut”—allows large protein molecules to enter bloodstream
SIBO: Leaky Gut

- Complications include immune reactions causing food allergies/sensitivities, generalized inflammation, and autoimmune diseases
- Body prevents SIBO in several ways: gastric acid secretion, bowel wall muscular activity, immunoglobulins in intestinal fluid, and the ileocecal valve
- Risk factors for SIBO: low stomach acid, Irritable Bowel Syndrome (IBS), Crohn’s disease, prior bowel surgery, types I and II diabetes, multiple courses of antibiotics, organ system dysfunction, moderate alcohol consumption, and oral contraceptive pills
- 80% of people with IBS have SIBO
- SIBO not contagious, but is very complex as to origin
SIBO Symptoms

- Abdominal pain/discomfort
- Bloating and abdominal distention
- Diarrhea
- Constipation
- Gas and belching
- Severe cases: weight loss and vitamin deficiency symptoms
Treatment of SIBO

- Antibiotics: rifaximin most common
- Botanical antimicrobials: aromatic herbs (phenols), bitter herbs (alkaloids), garlic, ginger, sour plum
- Prokinetic agents: octreotide and naltrexone (low dose)
- Personal (brother) info.: Anxiety before, Xifaxan for SIBO—3 X 550 mg daily for 2 weeks—resolved nicely—normally given for traveler’s diarrhea, less anxious afterward
Dr. Hazen: Nothing is always black and white in cardiovascular disease

TMAO levels in fish
• Some forms of fish have very high TMAO levels, e.g., Arctic deep sea fish, which use TMAO as “antifreeze”
• Surface fish, e.g., trout, have very low TMAO levels

L-carnitine may be good for you
• Paper by James DiNicolantonio et.al. in Mayo Clinic Proc.: Metaanalysis (13 studies) of L-carnitine given immediately after heart attack resulted in sig. reduced mortality, arrhythmias, and angina
• Hazen: interpret metaanalyses with caution and acute/brief L-carnitine admin. not same as chronic consumption in diet
Microbiome and Obesity / T2DM

- Fecal microbiota transplant (FMT) = Transplantation of stool bacteria from healthy donor into a recipient
- Restoration of colonic microflora via infusion of stool by enema, orogastric tube, or by mouth in form of capsule of freeze-dried material
- Effective treatment of *Clostridium difficile* infection and obesity in rodent experiments
- Lean male donor FMT in males with metabolic syndrome resulted in increased insulin sensitivity with increased intestinal microbial diversity
Microbiome and Butyrate

• Hartstra, Bouter, Backhed, Nieuwdorp (2015) review article in *Diabetes Care*
• Significant improvement in insulin sensitivity also included distinct increase in butyrate-producing bacterial strains
• Microbial products (butyrate, propionate, acetate) may induce beneficial metabolic effects through enhancement of mitochondrial activity, prevention of endotoxemia, and activation of gluconeogenesis via different routes of gene expression and hormones
Abbreviation Glossary

• SCFA = short-chain fatty acid, e.g., butyrate, propionate, and acetate
• GPCR = G-protein-coupled receptors—signaling pathways activation
• HDAC = Histone deacetylase—butyrate is signaling inhibitor
• IGN = intestinal gluconeogenesis (glucose produced from noncarbohydrate sources, e.g., fats and proteins
• LPS = lipopolysaccharide—origin of endotoxemia
Obesity and T2DM

**COLON**

- **Dietary Fibers**
  - Microbial degradation
  - SCFAs
    - Propionate
    - Acetate
    - Butyrate
  - GPCR signaling
  - HDAC inhibition

**Lean**

- Intestinal epithelium
- Lipogenesis
- Liver
- Muscle
- Adipose tissue
- Satiety
- IGN
- LPS inflammation

**SYSTEMIC**

- Intestinal epithelium
- Lipogenesis
- Liver
- Muscle
- Adipose tissue
- Satiety
- IGN
- LPS inflammation

**Obese/T2DM**

- Intestinal epithelium
- Lipogenesis
- Liver
- Muscle
- Adipose tissue
- Satiety
- IGN
- LPS inflammation
Future Considerations

• Such differences in gut microbiota composition might function as early diagnostic markers for development of type 2 diabetes mellitus (T2DM) in high-risk patients

• Research should focus on whether butyrate and other bact. products have same effects as bacteria that produce them to pave way for superior interventions for obesity and T2DM
Microbiome and Asthma

• Associated with differences in microbiome, but not clear whether this reflects differences in early life when immune system most malleable—inflammation-free airways key

• Brett Finlay (microbiologist) and Stuart Turvey (pediatrician), UBC, 9/30/15—Four bacteria that help prevent asthma identified: Faecalibacterium, Lachnospira, Veillonella, and Rothia

• These FLVR low in stool of asthmatic Canadian children, followed by young mice experiments

• FLVR chemical byproducts train immune system in early days of life??
Rob Knight TED talk

http://www.ted.com/talks/rob_knight_how_our_microbes_make_us_who_we_are
Probiotics

• The opposite of antibiotics which kill or inhibit bacteria.
• Probiotics are live health promoting microorganisms, especially bacteria, that are swallowed or applied to the skin, nose, mouth, and vagina to repopulate an area.
• Example: Tablets containing the bacterium, *Lactobacillus reuteri* have effectively reduced the inflammation of periodontal disease.
Probiotics Have Been Part of the Human Diet for Many Centuries

• Fermented Foods contain many probiotic bacteria of the *Lactobacillus, Streptococcus, Leuconostoc*, and many other genera. Some examples are:

• Pickled vegetables: Dill Pickles, Sauerkraut, Kim Chi, Kombucha, Miso, Tempeh, Chicha (a Central and South American beer made from corn, cassava, potatoes, quinoa, rice)

• Fermented dairy products: Yogurt, Cheese, Cottage cheese, Kefir, sour cream, Amasi (African countries)

• Fermented meat and fish: sausage, pickled herring

• Fermented grains: beer, Kvass, sourdough bread
What is a microbiome supportive diet like?

• Fermented foods are a natural way to introduce beneficial bacteria (probiotics) and the metabolic chemicals they produce.

• Prebiotics are foods designed to promote the growth of beneficial microbial partners.

• Prebiotics include fiber and sugars that are not digested by humans, but feed the microbes.
Prebiotic Foods

• Resistant starches such as those in raw bananas
• Inulin, a group of polysaccharide molecules found in onion, chicory, garlic, asparagus
• Fructo-oligosaccharides (many are derived from breakdown of inulin)
• Galacto-oligosaccharides (derived from breakdown of lactose, a cow milk sugar)
Taking Care of our Friends

• Feeding the microbiome of the gut maintains their presence - prebiotics.
• MAC - Microbiota-accessible-carbohydrates are fiber rich foods.
• Examples of MAC include:
  – Brown rice
  – Cooked whole barley
  – Beans and lentils
  – Roasted vegetables such as beets
  – Fruits, dark chocolate (85% cacao)
More About Prebiotics

• Prebiotics are soluble dietary fiber molecules not digested by human enzymes.
• Beneficial gut microbes can digest soluble dietary fiber molecules.
• Prebiotics are naturally found in some plants including onions, garlic, bananas, chicory root and Jerusalem artichokes at low levels.
• Some foods have added prebiotics but the food label does not say prebiotics.
Food Labels for Prebiotics Molecules

- Ingredients lists on foods with prebiotics use the chemical terms:
  - Galacto-oligosaccharides (GOS)
  - Fructo-oligosaccharides (FOS)
  - Oligofructose (OF)
  - Chicory fiber or Inulin

Dietary Recommendation by Karen Scott, PhD, Senior Research Fellow, Rowett Institute of Nutrition and Health, University of Aberdeen, Scotland:
Try to get 5 grams of prebiotics in your diet every day.
Breast Milk as Prebiotics Source

• Human breast milk contains prebiotic oligosaccharides.
• It is likely that these prebiotics enhance the population of *Bifidobacteria* in the infant gut.
• The prebiotics may discourage pathogens and the infections they produce.
• Many brands of infant formula are supplemented with oligosaccharide prebiotics.
Prebiotics in Pet Foods

• Some pet foods also contain prebiotics in kibble and as pill-type supplements.
• The function of the prebiotics is the same as in humans, to enhance the growth of beneficial gut bacteria.
Do Prebiotics Benefit Humans Directly?

• Some health benefits that have been studied:
  – Improved calcium absorption
  – Modifying the glycemic index
  – Enhancing colonic bacterial fermentation thus reducing the time it takes for food/feces to pass through the gut
  – Physiological benefits such as these have positive effects on osteoporosis, diabetes, and colorectal cancer, respectively.
Human Microbiome Development in Infants

• Prior to birth, humans are free of microorganisms.

• During vaginal birth, the newborn is colonized by the mother’s microbiota of the vagina and anus.
  – The newborn “inherits” mother’s microbiota as well as half of her genes.
  – *Bifidobacteria* are commonly transferred to newborns in this delivery.

• This post partum period allows the microbiota to grow and colonize the newborn’s body surfaces.
What do babies born prematurely teach us?

- Early, premature, birth adds the risk of neurological problems, immature lungs, and greater risk of infections.
- One risk of an immature gut in premature infants is an immune response that damages or destroys part of the intestine – necrotizing enterocolitis – and may result in death.
- One idea for this risk is the low diversity of microbiota in the gut of “preemies”, less beneficial microbiota, and more “blooms” of less beneficial microbes leading to disease.
- Some evidence shows that “preemies” given beneficial bacteria, such as in the *Lactobacillus* family, are less likely to develop necrotizing enterocolitis.
- Why? Unknown, but ideas abound. Perhaps the development of the gut and the beginning education of the immune system in the infant require the help of beneficial microbiota.
In Pregnancy, does the Microbiota Change?

- Ruth Ley, PhD, Professor at Cornell University studied the microbiota of 91 pregnant women and also, the microbiota of their infants up to 4 years of age.
- Information was collected on the mother’s food intake, and health during pregnancy.
- The mother’s microbiota changed to a simpler, less diverse population, that is, one resembling the microbiota of an obese individual.
Does The Microbiota of Obesity Nurture A Newborn Infant?

- Ruth Ley’s studies of pregnant women showed that the microbiota in the third trimester were the species that are more efficient at extracting calories from food.
- One conclusion may be that these microbiota species were highly beneficial to a mother.
- Having more food calories from less food would enable to mother to feed the growing infant more efficiently.
Which Microbiota Types Develop in the Newborn Infant’s Gut?

- Ruth Ley’s studies showed that the newborn’s microbial species resembled those found in the first trimester of the mother’s gut.
- One conclusion is that the microbiota associated with obesity do not appear to persist in the developing infant’s gut environment.
- The newborn “inherited” members of the microbiota normally found in the mother’s gut during the first trimester.
- Some evidence shows that environmental factors and the child’s genetic factors may determine which species “bloom” in the newborn’s early development.
Breast Milk – It May Feed the Superorganism?

• Ingredients in breast milk:
  – lots of fats, protein, and carbohydrates, and other compounds to promote health
  – Antibodies and other immune system molecules to give the developing infant the immunity protection that the mother has
  – Human milk oligosaccharides (HMOs)
    • HMOs are complex carbohydrates that humans do not digest.
    • Microbiota species are being nourished by HMOs, especially the beneficial species, such as *Bifidobacteria*.
    • *Bifidobacteria* are most likely species found in a healthy infant’s gut.
    • Another beneficial species, *Bacteroides*, is aided by HMOs. *Bacteroides* thrive on plant material and may be important in preparing the infant’s gut for solid food.
Gut Microbiota of Colicky Babies

- Willem de Vos, Netherlands scientist, studied the gut microbiota of 24 infants for their first 100 days of life.
- Half of the infants had colic and the other half did not.
- Infants with colic had more *Proteobacteria* bacteria and less *Bifidobacteria* and *Lactobacillus* populations.
  - *Proteobacteria* are more common in the guts of babies delivered by C-section, and babies that are fed infant formula.
- One conclusion may be that gut microbiota may play a role in the development and severity of infant colic.
Caesarean section birth and the Microbiota

• During Caesarean section birth, the newborn is colonized by the microbiota of the mother’s skin and of the hospital staff, other people, and environmental surfaces.
  – The newborn “inherits” less of the mother’s microbiota.
  – More *Proteobacteria* and less *Bifidobacteria* are found in the newborn delivered by C-section.
  – Recent studies indicate C-section babies have more experiences with allergy, asthma, celiac disease, obesity, and even cavities.
Human Skin Microbiome: Some Facts and Figures

• Number of microorganisms per square inch of skin: up to 6000 billion

• Number of square inches on average human body: 3000

• The total is up to 18 quadrillion, that is 18 with 15 zeroes after it.

• Number of different species on the skin: 850 species of bacteria, plus uncounted viruses, fungi, and parasites.
Skin Microbiome

• Bacteria, yeast, and molds are common on the skin.
• The dry skin of the feet have more yeast and molds and bacteria.
• The warm, moist areas of the armpit and groin have different species than the areas that are drier and cooler.
• One of the common bacterial species of the skin is *Staphylococcus aureus*, a spherical cell that is usually seen growing in grapelike clusters.
Premature Birth and the Microbiome

• Premature = Babies born >3 weeks early
• 450,000 premature infants born each year in U.S.
• Is leading cause of newborn deaths
• ~half premature births occur after spontaneous preterm labor—triggers not well understood
• Recent study at March of Dimes Prematurity Research Center, Stanford Univ., involving the microbiome:
• Studied 49 pregnant women, 15 delivered prematurely
• Characterized bacteria in vagina, lower gut, saliva, and tooth/gum area
• In these sites bacterial communities didn’t change much during pregnancy, despite changes in maternal hormone levels, metabolism and body weight
• Four patterns of bacteria—little bact. diversity, dominance of variety lactobacilli
• Fifth pattern—greater bact. diversity, high levels Gardnerella and Ureaplasma bact.—linked with increased risk for preterm birth, especially when persisting for several weeks
Stanford: Relman & Dan DiGiulio, MD

• In all women vaginal bacteria changed significantly after birth—for both vaginal and cesarean deliveries
• For up to a year after birth, women tended toward a more diverse bacterial pattern—possibly explains increased risk for prematurity in closely spaced pregnancies??
• Probiotics may be useful in warding off prematurity??
• Microbiome’s role in premature birth may be something that is relatively long in the making, e.g., an event in first trimester or even prior to pregnancy that starts clock ticking toward prematurity??
Early Study Linking Autism To Gut Microbes

• Prof. Rob Knight, Univ. of Colorado, co-authored commentary piece about research published in Cell, Dec. 2013:

• Elaine Hsiao, Cal Tech, used a technique called maternal immune activation in pregnant mice to induce autism-like behavior and neurology in their offspring

• Hsiao’s team found gut microbial community of offspring differed markedly from control mice

• Feeding autism-like mice *Bacteroides fragilis* reduced aberrant behaviors
Microbiome-Autism Connection

• Integrated research program at Arkansas Children’s Hospital Research Institute
• Dr. Richard E Frye, Director
• Gut may have influences on cognition and behavior
• Gathering on 7 May 2015 discussed relative topics and design of clinical trial to elucidate role of microbiome in autism
Microbiome-Autism (cont.)

- Increasing number of studies show different bacterial composition in gut of children with autism spectrum disorder (ASD)
- John Slattery, CCRP—Highly controlled clinical trial aimed at systematically modulating or manipulating gut microbiome in developing children
- Very difficult to acquire funding for autism research beyond view that autism is an inherited disorder of the brain; Genome Web Daily News, 12/12/16—Variants in Essential Genes Linked to ASD
Maternal Immune Environment During Pregnancy and ASD—12/12/16

• Normally uniquely regulated to maintain pathogen-free, noninflammatory environment for developing fetus
• Sometimes, factors such as cytokines and chemokines produced during gestation can have consequences
• Webinar will discuss findings from largest prospective study to date examining relationship between mid-gestational maternal cytokines and chemokines and risk for autism
• Targets multiplex protein detection assays
Fungus Among Us

- Sarah Everts, 7/25/16, on the mycobiome:
- Thomas Auchtung (Baylor)—When considering role of mycobiome, fungi (including yeasts and molds) are often ignored
- Thousand times more bacteria than fungi living with us—still millions of fungi in close association
- Mahmoud Ghannoum (Case Western Reserve)—All members of human microbiome must be studied for true understanding
Mycobiome Friends and Foes

Foes

• *Candida albicans*: causes thrush in mouth, yeast infections in vaginal tract, life-threatening invasions of bloodstream

• *Candida parapsilosis*: forms life-threatening biofilms on stents and catheters

Friends

• *Pichia sp.*: counters thrush, proteins block germ tube formation in *Candida*

• *Saccharomyces boulardii*: protective effect against pathogens and helps gut microbiome and immune system stay in health balance—probiotics?!
Fungi By Anatomical Region

- **Oral cavity**
  - Genera identified: Potentially pathogenic lineages
  - Alternaria, Aspergillus, Aureobasidium, Candida, Cladosporium, Cryptococcus, Fusarium, Gibberella, Glomus, Pichia, Saccharomyces, Teratosphaeria

- **Lungs**
  - Aspergillus, Candida, Cladosporium, Penicillium, Cryptococcus

- **Gastrointestinal tract**
  - Aspergillus, Candida, Cladosporium, Cryptococcus, Fusarium, Penicillium, Pneumocystis, Mucor, Saccharomyces

- **Skin**
  - Aspergillus, Candida, Chrysosporium, Cryptococcus, Debaryomyces, Epicoccum, Epidermophyton, Leptosphaerulina, Malassezia, Microsporum, Penicillium, Phoma, Rhodotorula, Saccharomyces, Trichophyton, Ustilago
Fungi difficult to study

• Cannot easily be grown in lab (some bacteria also)—must sequence DNA and turn to genome databases
• Have very rigid cell wall (compared to bact.), accessing fungal DNA difficult
• Different barcode than bacteria and don’t have genome sequence for many fungi
• Many discrepancies in fungal databases—fungi lead complex lives
Future Fungi Studies

• Bacteria just part of the picture
• Many more answers forthcoming by sequencing mycobiome
• Must consider other microbiome minorities like archaea and viruses
• To be continued…