HEALTH BEGINS ON THE INSIDE: PROBIOTICS AND THE GUT

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INTRODUCTION

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BOARD CERTIFIED
- Internal Medicine
- Gastroenterology

BACKGROUND
- Private Practice
  - Gastroenterology 1975-2000
  - Prevention/Early Detection 2000-present...
  - Health By Design...Associate Director of Executive Health
- Special Interest:
  - Preventive Medicine
  - Intestinal Microflora (Gut Bacteria)

Hippocrates
418 BC

“All disease begins in the gut”
Presentation Outline

- Facts about our gut flora
- What are probiotics
- How probiotics work
- Clinical Benefits of probiotics
- Recent scientific studies about the intestinal microbiome
- Fecal Microbial Transplants (FMT)

Facts about our Gut Flora

- There are over 100 trillion bacteria in our gastrointestinal tract
- Most bacteria reside in the colon
- Most bacteria are beneficial but some are pathogens or harmful
- Maintaining the balance of the bacteria (microflora) promotes our health
### Facts about our Gut Flora

- There are 500-1000 identifiable bacterial species in the intestines. (old)
  - 10-20% of microbiome detected by culture techniques
  - Ribosomal RNA gene studies indicate there are > 15,000 bacterial species known to inhabit human GI tract
  - Each individual hosts roughly 500-1500 species, but 40-50 species make up 80-90%
- While breastfed, Bifidobacteria is major the bacteria genus in our intestines
- After two years of age, we generally maintain the same type of bacteria flora for most of our adult life

### Dysbiosis
- Imbalance of intestinal microflora with overgrowth of harmful organisms
  - Chronic intestinal inflammation
  - Increased intestinal permeability
  - Disruption of normal intestinal digestion

### The Human Microbiome Project (HMP)
- Launched in 2008 by the NIH
- Goal of identifying and characterizing the microorganisms which are found in association with both healthy and diseased humans.
- The 16S rRNA gene is used for phylogenetic studies as it is highly conserved between different species of bacteria.

### Facts about Our Gut Flora
- By mapping the normal microbial make-up of healthy humans using genome sequencing techniques, the researchers of the HMP have created a reference database of the normal microbial variation in humans.
Facts About Our Gut Flora

- HMP Findings:
  - There is a vast array of composition and diversity in the human intestinal microbiome.
  - Many intestinal and extra-intestinal disorders are related to the composition of the intestinal microbiome.
  - Diet and environment impact the composition of the microbiome.
  - Specific disorders associated with bacterial composition.

Presentation Outline

- Facts about our Gut Flora
- What are probiotics

What are probiotics

- Definition
  - Probiotic – Greek “For Life”
  - Coined by Lilly and Stillwell in 1965: substances secreted by one organism that stimulate growth of another.
  - 2001 FAO/WHO definition:
    - Live microorganisms which when administered in adequate amounts confer health benefits on the host.

*Food and Agriculture Organization of the United Nations/World Health Organization.*
What are Probiotics

- **Probiotics**...Live micro-organisms
  - Bacteria and yeast
  - Able to survive
    - Gastric acid
    - Pancreatic digestive enzymes and bile acids
  - Reach large bowel alive
  - Adhere to the intestinal lining cells
  - Nonpathogenic, nontoxic and free significant adverse side effects

What are Probiotics

- Isolated from human and animal intestines
- **Common probiotics**
  - *Lactobacillus* acidophilus
evis
  - *johnsonii*
  - *rhamnosus*
  - *salivarius*
  - *Bifidobacterium* animalis
  - *bifidum*
  - *brev*
  - *Streptococcus* thermophilus
  - *Saccharomyces* boulardii

  More than 25 different probiotic species plus all the different strains

Presentation Outline

- Facts about our intestinal bugs
- What are probiotics
  - **How probiotics work**
HOW PROBIOTICS WORK

- An Intestinal Barrier
- Modulate Intestinal Immune Response
- Support Intestinal Function And Motility

Act As An Intestinal Barrier
- Adhere to the intestinal lining cells
- Compete for colonization of intestinal lining
- Produce Bacteriocins/Defensins (Antibacterial Compounds)
- Decrease luminal pH (acetic, butyric, propionic acid)
- Stimulate intestinal epithelium to produce proteins to maintain tight junction between cells
- Stimulate mucus production

Act As An Intestinal Barrier

- Modulate The Intestinal Immune Response
  - 70% Of The Human Immune Cells Are In The Intestines
  - Probiotics Stimulate Growth And Function Of The Immune System
  - Intestinal Immune Cells Monitor (Do Surveillance) Of Our Gut Contents
  - Probiotics “Cross Talk” With The Intestinal Immune System And Signal The Development Of Tolerance Or Production Of An Immune Reaction To Intestinal Microbes
HOW PROBIOTICS WORK

- Act As An Intestinal Barrier
- Modulate The Intestinal Immune Response
- Support Intestinal Function and Motility
  - Ease Symptoms of Lactose Intolerance
  - Ferment Resistant Starches Called Prebiotics* Producing Short Chain Fatty Acids
    - Butyrate
    - Propionate
    - Acetate
  - *wheat bran, banana, onion, leeks, artichokes, FOS
- Ease Symptoms of Lactose Intolerance
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HOW PROBIOTICS WORK

- Reduce Methane Producing Archea
  - Methane has been associated with slowed intestinal motility
- Deconjugation of Bile Acids Preventing Intestinal Reabsorption
  - Lowering total and LDL cholesterol
- Inhibiting Carcinogen Producing Bacteria
  - Nitrosamines, Heterocyclic aromatic amines [HCA],

METABOLIC ACTIVITY OF THE INTESTINAL BACTERIA

Metabolic activity of intestinal microflora. CH₄, methane; CO₂, carbon dioxide; H₂, hydrogen.
Presentation Outline

- Facts about our intestinal bugs
- How probiotics work
- Clinical Benefits

Clinical Benefits of Probiotics

- Are Probiotics Beneficial?
- Evidence Based Medicine
  "The use of scientific data to confirm that proposed diagnostic or therapeutic procedures are appropriate in light of their high probability of producing the best and most favorable outcome"
- Meta-Analysis
  "Any systematic method that uses statistical analysis to integrate the data from a number of independent studies"
Clinical Benefits of Probiotics

**Are They Beneficial?**
- Criteria for review of clinical trials
  - Human Studies
  - Randomized double-blinded placebo-controlled
  - Meta-analysis reviews

**Limitation of the Studies**
- Not apples to apples
- No standardization for
  - Genus, species, strains
  - Exact strain not identified
  - Dosage, cfu in serving size
  - Single species vs. multiple species/strains
  - Duration of Rx...weeks/months

**Meta-Analysis Reviews**
- Adults...Treatment/Prevention...Improvement
  - Irritable Bowel Syndrome (IBS) 40-60%
  - Antibiotic Associated Diarrhea (ADD) 42-47%
  - Clostridia Difficle Disease (CDD) 71%
  - Ulcerative Colitis ? ........
  - Pouchitis 85%
  - Infectious Diarrhea 34%
    - Acute Bacterial
    - Viral ?
  - Traveler’s Diarrhea 15%
Clinical Benefits of Probiotics

Meta-Analysis Reviews
- Children...Treatment/Prevention Improvement
  - Antibiotic-Associated Diarrhea 54%
  - Atopic Dermatitis...Eczema 45-60%
  - Necrotizing Enterocolitis 65%
  - Infectious Diarrhea 48%
  - Rotavirus

Clinical Benefits of Probiotics

Clinical Trials
- Adults
  - Plasma Lipid Profile
  - Prevention of Female UTI's
  - Prevention of Vaginal Yeast Infections
  - Hepatic Encephalopathy
  - Nonalcoholic Fatty Liver Disease (NAFLD)

Clinical Benefits of Probiotics

Clinical Trials
- Children
  - Infantile Colic
  - URI's...cold and Flu Symptoms
Presentation Outline

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- Recent scientific studies about the intestinal microbiome

Intestinal Microbiome and Our Health

- Human Microbiome
  - The human microbiome is defined as the collection of microbes - bacteria, viruses, and parasites - that inhabit the human body.
  - Disruption of the normal diversity may be associated with:
    - Gastrointestinal disorders
      - IBS, IBD
    - Systemic disorders
      - Autoimmune Type I Diabetes and Type 2 DM
      - Obesity
      - Autism

Gut bacteria may be key to fighting obesity

CBS News
Intestinal Microbiome and Our Health

- **Hypothesis of Metabolic Disorder**
  - Increase in high fat, high carbohydrate diet changes the gut microbacteria from the phyla Bacteroidetes to Firmicutes
  - Innate and adaptive intestinal immune system respond with immune mediated inflammation
  - There is a breakdown in the tight junction resulting in increased intestinal permeability.
  - LPS “leaks” into the tissues and blood leading to endotoxemia

Intestinal Microbiome and Our Health

- **Metabolic Endotoxemia**
  - **Definition:**
    - Subclinical elevation of circulating endotoxin levels
    - Endotoxin is synonymous with LPS which is a major constituent of the outer cell membrane of gram negative bacteria, e.g. E. coli
    - Endotoxin causes a low grade inflammation resulting in obesity, insulin resistance, CV disease, and hepatic steatosis and steatohepatitis

Intestinal Microbiome and Our Health

- Our finding that microbial suppression of intestinal Fiaf promotes adiposity, through the mechanism summarized in Fig. 5, suggests that increasing Fiaf expression and/or activity may promote leanness. We also speculate that changes in microbial ecology prompted by Western diets, and/or differences in microbial ecology between individuals living in these societies, may function as an “environmental” factor that affects predisposition toward energy storage and obesity.
Intestinal Microbiome and Our Health

- **Metabolic Endotoxemia**
  - Hypothesis of Metabolic Disorder
    - LPS interacts with toll-like receptors to release cytokines like TNF-alpha leading to:
      - Insulin resistance
      - Reduced lipoprotein lipase
      - Leptin resistance
    - Resulting in:
      - Obesity
      - Type 2 DM
      - NAFLD and NASH
      - Hyperlipidemia

Intestinal Microbiome and Our Health

- Studies have found:
  - Change in intestinal microbiota related to diet
    - Obesity associated with Firmicutes
    - Lean associated with Bactroidetes
  - Inflammatory Bowel Disease: Crohn's and UC
    - Change in microbial diversity and composition in humans with inflammatory bowel disease
    - Genetic predisposition by TLR's to stimulate inflammatory cascade response to Lipopolysaccharides (LPS)

Microbiome and Obesity Hypothesis: Increased energy harvest from diet

![Diagram showing microbial colonization of the gut, increased hepatic lipogenesis, and triglyceride storage in adipocytes.]

- Fat: Fasting induced adiponectin
- LPL activity
- Suppression of Puri in the gut epithelium
- Processing of dietary polysaccharides
- Increased hepatic lipogenesis (CHS/BP/SREBP-1c)
The GI microbiota and their genetic products exist in a complex, but balanced, homeostasis and have important roles in nutrition, energy metabolism, host defense, and immune system development [8–10, 11••]. Dysbiosis, or abnormal compositional disturbance of this homeostasis, can be associated with various disease states. Such conditions are potentially amenable to therapy with FMT to correct these changes.

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- Fecal Microbial Transplants...Ultimate Probiotic
Fecal Microbial Transplants

History of FMT
- First fecal enemas for pseudomembranous colitis 1958
- First fecal enema for recurrent C difficile colitis 1989
- First nasogastric infusion for CD colitis 1991
- First colonoscopic FMT infusion 2000
- Review 2011: FMT reported for 325 cases for recurrent CDI
  - 75% via colonoscope or retention enema
  - 25% via nasogastric tube or endoscope
  - 91% cure rate

Fecal Microbial Transplant trials
- Relapsing Clostridia Difficle infectious colitis
- Ulcerative colitis
- Crohn's Disease
- Obesity
- Diabetes

FMT... Gastrointestinal Disorders associated with an altered intestinal microbiome
- Cholelithiasis
- Colorectal cancer
- Hepatic encephalopathy
- Idiopathic constipation *
- IBS *
- IBD *
- Familial Mediterranean Fever
- Gastric carcinoma and lymphoma
- Recurrent Clostridium difficile *
  * Indicates some reports on transient or long-term improvement or cure with fecal microbiota transplant.
FMT…Non-Gastrointestinal

- Arthritis
- Asthma
- Atopy
- Autism *
- Autoimmune disorders
- Chronic fatigue syndrome *
- Diabetes mellitus and insulin resistance *
- Eczema
- Fatty liver
- Fibromyalgia *
- Hay fever
- Hypercholesterolemia
- Idiopathic thrombocytopenic purpura *

*reports on transient or long-term improvement or cure with fecal microbiota transplant.

FMT…Non-Gastrointestinal

- Ischemic heart disease
- Metabolic syndrome
- Mood disorders
- Multiple sclerosis *
- Myoclonus dystonia *
- Obesity
- Oxalic acid kidney stones
- Parkinson’s disease *

*reports on transient or long-term improvement or cure with fecal microbiota transplant.

New Paradigm

“Our health is determined by the microbiota in our gut”.

“We are witnessing a paradigm shift in the way we understand health and treat disease and in its center is our microbiota”

Lawrence Brandt MD

Chief Emeritus of Gastroenterology and Professor of Medicine and Surgery at the Albert Einstein College of Medicine.

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Probiotics and the Gut

- Thank you for your attention
- Any Questions?