Balancing the Gut Ecosystem: An Integrative Approach

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The Enterocyte:
Regenerate every 3-5 days!

- Transcellular
- Paracellular
- Apical membrane
- Tight Junction
- Lateral Membrane
- Basolateral membrane

The Gut Associated Lymphoid Tissue (GALT)

- >60% of total immune activity
- Utilizes the majority of the body’s IgA production
- Has $10^{10}$ Lymphocytes per meter of bowel
- Integrity of this barrier is vital to health

You are more prokaryotic (foreign cells) than eukaryotic (self-DNA)

- 10% Human Cells, 90% Bacteria
- 100 Trillion bacteria = 3 lbs of body weight.
- You are a symbiotic “super organism!”
3 Main Modes of Defense

- **Mucous Barrier** (Prostaglandins, IgA)
  - NSAIDS, Chemotherapy, Lack of fiber, Infection, Stress
- **Microflora** (Probiotics, Prebiotics)
  - Antibiotics, Poor nutrition, Infection, Stress
- **Local Immune system** (GALT)
  - Food allergy, food intolerance, Infection, Stress

Positive Balance

- Proper Acidity (pH 1-3)
- Healthy Mucous Layer
- Low bacterial growth
- Intact gut-immune barrier
- Balanced bacterial growth & balanced flora
- Regular evacuation

Negative Balance

- Low acidity
- Poor Mucous Layer
- High bacterial growth
- Intestinal permeability
- Imbalanced bacterial growth (dysbiosis)
- Irregular evacuation

Maternal Acid Suppression

- **Swedish Medical Birth Registry**
- 860,215 Children
- Acid suppression (PPI or H2 blocker) = 51% Asthma Incidence

Acid Activates Pepsin

Pepsinogen

PH=1.8-3.2

Active Pepsin Protease

PH=>4.5

Inactive Pepsin Protease

Amino Acids

Immune Response

Intact Protein

5 days of PPI=PH>4.0

Rebound Dyspepsia W/ D/C of PPI

How to Stop a PPI

- Slow taper off PPI
- Get energy moving down and out with:
  - Aerobic Exercise
  - Improve diet (consider elimination diet)
  - DGL (De-Glycyrrhizanated Licorice)
  - Sucralfate (Carafate) 1 gm w/ meals, qhs
  - Melatonin if symptoms ↑ at night
- Consider: Iberogast....

Promise? Iberogast®...

- Proprietary blend of the following herbal extracts:
  - German chamomile (Matricaria recutita)
  - Clowns mustard (Iberis amara)
  - Angelica (Angelica archangelica)
  - Cardamom (Carnum carvi)
  - Milk thistle (Silybum marianum)
  - Lemon balm (Melissa officinalis)
  - Calendula (Chelidonium majus)
  - Licorice (Glycyrrhiza glabra)
  - Peppermint (Mentha x piperita)

- 1 mL orally three times daily over a period of 4 weeks significantly reduces severity of acid reflux, epigastric pain, cramping, nausea, and vomiting compared to placebo.


Developmental Programming

Process whereby an environmental factor acting during a sensitive developmental period has an effect that may persist throughout life

Gut Bacteria influence....

- GI Barrier Function/Immunity
- Cortisol/ACTH
- Vagal Nerve Signaling
- Serotonin levels ↑ by 2.8x
- Brain Development/Behavior

Method of Birth……

Vagina
- Inoculates GI tract with healthy flora
- Less Atopy (asthma, eczema)

Abdomen
- Not exposed to vaginal flora
- More atopy (asthma, eczema)
- Less Bifidogenic flora
- More IgE mediated cow’s milk allergy


Method of feeding…

Breast
- Prebiotics (FOS) = ↑ Bifidobacteria & Lactobacilli = ↑ IgA (Mucosal defense)
- Balance of Th1=Th2

Bottle
- Enterococci, Enterobacteria & Clostridia = Imbalance of humoral response = ↑ Th2 = Atopy


3 Strikes and your Atopic!

① GBS + (Peripartum Abx)
② Cesarean Section
③ Bottle Fed

Prebiotics in Infant Formula
1,130 Healthy newborns at low risk for atopy

<table>
<thead>
<tr>
<th>Formula vs Prebiotic Formula vs Breast Milk</th>
<th>Atopy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9.7%</td>
</tr>
<tr>
<td></td>
<td>5.7%</td>
</tr>
<tr>
<td></td>
<td>5.7%</td>
</tr>
</tbody>
</table>

Followed for one year
NNT = 24

Gruber, et al. J Allergy Clin Immunol 2010; 126(4)

Gut Bacteria & Obesity

- Birth-7 yrs: Stools sampled at 6, 12 mths.
- Obese Children = ↓ Bifidobacteria

General Rule:
Obese: ↓ Bifidobacteria, Bacteroidetes
↑ Firmicutes
Backhed F et al. The Gut Microbiota as an Environmental factor that Regulates Fat Storage. Proc Natl Acad Sci. 101(44), 2004

Germ Free Mice

• Fat Mass by 60%
• Developed Insulin Resistance within 2 weeks.

Conventional Germinated Mice

Firmicutes Bacteroidetes

Energy Absorption

Energy Storage (TG)

Insulin Resistance & Inflammation

One treatment option:

- Exercise
- Change diet: Saturated Fat, Sugar
- Prebiotics:
  - Soluble fiber: Inulin, guar gum
  - Conjugated Linoleic Acid (CLA) 4 gms daily
- Probiotics:
  - Bifidobacteria
  - Lactobacillus rhamnosus PL60
- Stool transplant form your thin cousin?

Good Review Paper:


An evolving GI environment...

- Eat on the run
- New proteins (Wheat, Dairy, pasteurization)
- Sugar, ETOH
- Nutrient dense foods
- Different bacteria
- Less fiber
- More Rx (PPI, steroids, Abx)

Key Questions to Ask….

- Was there a disruption to the normal GI environment?
  - Infection
  - Trauma
  - Antibiotics/Chemo
  - Chronic Stress
  - Surgery

Treatment

“4 R” Approach

- Remove (Foods, Pathogens, Rx)
- Replace (Acid, Enzymes)
- Re-Inoculate (flora)
- Repair (Gut Mucosa)

Remove…..

- Stress (Change interpretation)
- High risk foods
  - Gluten (wheat), dairy
- What food do you crave the most?
- Chronic acid suppression (PPI, H2 blocker) if able.
- If able: Antibiotics, steroids

Mind Body

- Neuropeptides from the gut influence our emotions.
- Metaphor
  - “Gut Instinct”
  - “Something’s eating me up inside”
  - “Listen to your gut”
Soderholm JD. Stress and gastrointestinal tract. II. Stress and intestinal barrier. Am J Physiol Gastrointest Liver Physiol, 280(1), G7-G13. 2001

Mind-Body Influences (Stress)

Monkeys:
- Separation of infant and mother → fecal flora (Lactobacillus)

Rats:
- Chronic stress → Permeability
- Cortisol results in:
  - Mucin production
  - IgA secretion

Stress induced changes reversed with nutrition

- Rat pups separated from mothers = ↑ Permeability
- Reversed with:
  - Omega-3 fatty acids (DHA)
  - Arachidonic Acid
  - Probiotics (Lactobacillus)
  - Prebiotics (FOS)
  - Probiotics (Lactobacillus)
  - Omega-3 fatty acids (DHA)


Elimination Diets

Ogle KA, Bullock JD. Children with allergic rhinitis and or bronchial asthma treated with elimination diet: A five-year follow-up. Annals of Allergy. 44(5)273. 1980, May.

- Asthma
  - 1980 study of 322 <1 year olds w/ negative skin tests
  - ate only Meat Base Formula, beef, carrots, broccoli, apricots
  - 91% with improvement of respiratory symptom scores
  - 51% reproduced symptoms with food challenges
  - Milk, eggs, chocolate, soy, legumes (peanuts), cereals, in that order

Food Intolerance: The Usual Suspects

**Most prevalent in infants and children
- Dairy (Cow’s Milk Protein)**
- Wheat (Gluten)**
- Peanut**
- Corn (including corn syrup)
- Eggs**
- Citrus
- Soy**
- Beef
- Refined sugar
- Food additives
  - Tartrazine (Yellow dye #5)
  - Aspartame

• Validity of IgG testing still under question
• Allergen-specific IgG may block IgE mediated anaphylaxis in vivo and protect against severe allergic reaction
• Questions remain!
Figure 2: Mean change in symptom severity score at 12 weeks according to degree of adherence. Difference between the groups with high adherence: 101 (95% confidence interval 54, 147); ***p<0.001.

Replace…
- Acid (Betaine HCL)
- Elderly
- Significant indigestion
- Digestive Enzymes
  - Short term use only
- Consider Stool Pancreatic Elastase
- Consider Lactulose/Mannitol permeability test

Re-inoculate…
- Probiotics
- Prebiotics
- Consider Comprehensive Diagnostic Stool Analysis
- Rifaximen Clearance

Lactulose (Big Sugar)
- Mannitol (Small Sugar)

Results:
- Mannitol > Lactulose = Normal
- Lactulose and Mannitol = Malabsorption
- Mannitol < Lactulose = ↑ Permeability

Stool Transplant!? Human Probiotic Infusion (HPI)
HPI via retention enema for UC

Before

After

Helminthic Therapy (Worms)

Hookworm (A. ceylanicum)

- Worms trigger “Tolerization” in the host.
- TH1 response by worm glycans
- Tx Autoimmune Dz
- MS, IBD, RA, DM1

Whipworm (T. trichiura)

- Eradication = ↑ Autoimmune Dz

Rifaximin Clearance (fish kill)

- 87 pts IBS-D
- 400 mg TID x 10 Days
- 550 mg TID x 14 Days may work better.
- $$$ 10 day course ~ $600


Rifaximin for IBS

- 1,200 with non-C IBS
- Followed for 10 weeks
- 41% ↓ IBS symptoms with Rifaximin
- 30% ↓ IBS symptoms with placebo

Pinmental, et al. NEJM, 2011

Repair…

Emotional Balance
Exercise
Nutrition
Supplements

Change in American Diet

- Rich in refined sugars and vegetable oils = 36.2% of total energy in the American Diet.
- These foods are essentially void of nutrients (empty foods...just energy)
Fiber!
- Viscous fiber absorbs water, slows glucose absorption (lowers glycemic index), cholesterol absorption.
- Is needed for healthy mucous layer
- Increases thermogenesis during digestion.
- Prolongs digestion = satiety
- Reduces insulin secretion by glycemic index.

Sources of Viscous Fiber
Consider 1/2-1 tsp TID qAC with 8 oz of Water
- Guar Gum (Prebiotic, gluten substitute) 5-10 gms/d
- Wheat Dextrin (Benefiber)
- Psyllium (Metamucil)
- Ground Flax seed

Amazon.com $2.30 per 8 oz.
Caution: these agents expand like sponges and if taken with little water can cause obstruction.

Zinc
- HCL Acid depends on Zinc for its secretion
- Needed for IgA and immune function
- Beneficial for shortening infectious diarrhea and pneumonia in kids.
- Inhibits copper absorption

Percentage of all Individuals >2 yo NOT meeting 100% US Recommended Dietary Allowances
1. Zinc 73.3%
2. Calcium 65.1%
3. Magnesium 61.6%
4. Vitamin A 56.2%
5. Vitamin B6 53.6%
6. Iron 39.1%
7. Vitamin C 37.5%
8. Folate 33.2%
9. Thiamine 30.2%
10. Riboflavin 30.0%


Zinc and Endothelial Repair
- 10 Patients given Indomethacin to cause permeability
- Randomized Cross-over trial
- Zinc 37.5 mg resulted in 75% in gastric and small bowel injury & 50% less villous shortening.
- Indomethacin = 34x permeability vs none in those tx with Zinc

Mahmood A, Zinc carnosine, a health food supplement that stabilizes small bowel integrity and stimulates gut repair processesGut. 2006

L-Glutamine
- Non-essential Amino Acid
- Used as energy source for rapidly growing cells
- Good evidence to support use for the very sick (intensive care, chemo & Rx therapy)
- 5-10 gms BID (Powder)
Glutamine MOA
- Reduces inflammation by reducing gut-associated cytokine release
- Reduces risk of gut-derived septicemia in critically ill
- Antioxidant, increases glutathione
- Enhances heat shock protein (HSP) that protects enterocytes from injury
- Does not reduce permeability in those without inflammation who are nutritionally deprived

IBS Summary
- Ever since that illness, Abx or sentinel event = IBS:
  - Q4 R approach
  - Chronic IBS:
    - #1 Mind-body tools (hypnosis, CBT)
    - Exercise
    - Trial of elimination diet
    - Fiber (Guar Gum, Psyllium)
    - Peppermint Oil 0.2-0.4 mg enteric-coated capsules TID
    - Cromolyn (Gastrecorm) 400 mg TID
      - Best if > response to elimination diet

Inflammatory Bowel Disease

<table>
<thead>
<tr>
<th>Crohn's Disease</th>
<th>Ulcerative Colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunity</td>
<td>DMI Dominant</td>
</tr>
<tr>
<td>Labs</td>
<td>CRP Elevated</td>
</tr>
<tr>
<td>Nutrition</td>
<td>More FODS</td>
</tr>
<tr>
<td>Omega-3 Fats</td>
<td>Inflammation may be protective and diet</td>
</tr>
<tr>
<td>Probiotics</td>
<td>Saccharomyces</td>
</tr>
<tr>
<td>Botanicals</td>
<td>Tobacco increases risk and severity</td>
</tr>
</tbody>
</table>

What Worked?
- Food elimination?
- Supplements?
- Having a plan?
- Increased sense of control?
- Relationship?
- All or One?

Practitioner Effects on IBS
IBS Pts Randomized to Improvement in Symptoms:
- Wait List Control..................................28%
- Limited Clinical Visit..............................44%
- Augmented Clinical Visit...........................62%

Kapschuk TJ et al. Components of the Placebo Effect: RCT in patients with IBS. BMJ 336 (7651), 2008

IBS and Known Placebo

Alosteron (Lotronex) vs Open Placebo

- Alosetron: Benefit: 51%
- Placebo: Benefit: 38%

Known Placebo: Benefit: 59%
No Treatment: Benefit: 35%


Handouts
Modules & Resources
UW Integrative Medicine
www.fammed.wisc.edu/integrative
www.fammed.wisc.edu/mindfulness