Treating GUT Imbalance

Improving Diagnostic and Therapeutic Decisions in GUT–Related Illness

Patrick Hanaway, MD
Asheville, NC
Naturopathic maxim …
“Death begins in the colon.”

The practical application …
“When in doubt, treat the gut.”
Digestion/ Absorption
Inflammation/ Immune/ Infection
Gut Bacterial Flora/ Dysbiosis
The 5-R Program

- Remove
- Replace
- Repopulate
- Repair
- Re-Balance!
The 5-R Program

- Remove
  - pathogenic organisms
  - allergic foods

Removing the source of the imbalance is the critical first step, but the functional medicine approach does not stop here…
The 5-R Program

- Replace
  - hydrochloric acid
  - digestive enzymes
The 5-R Program

➢ Repopulate
  • Lactobacilli
  • Bifidobacteria
  • Saccharomyces if using antibiotics
The 5-R Program

- **Repair**
  - SI: glutamine, N-acetyl glucosamine
  - LI: fiber → butyrate
  - Boswellia, licorice, quercetin, aloe
  - Cabbage, rice protein
  - Essential Fatty Acids (GLA, EPA)
  - Fasting
The 5\textsuperscript{th} R

- Rebalance

Modify attitude, diet and lifestyle of the patient to promote a healthier way of living
Regenerative/ Metabolic Medicine
Key Components

- A Continuum of Health & Wellness
- Balance
- Biochemical Individuality
- Patient-centered Treatment
Optimizing Gut Function

- Digestion - Interaction
- Absorption - Assimilation
- Metabolism - Gut Milieu
- Excretion – Elimination

“You are what you eat!”
Optimizing Gut Function

- Digestion - Interaction
- Absorption - Assimilation
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- Excretion – Elimination

- Immune System Modulation
  - 1st Line of Recognition
  - 1st Line of Defense
Optimizing Gut Function

Immune System Modulation
- 1st Line of Recognition
- 1st Line of Defense
1st Line of Recognition

aka ‘Oral Tolerance’

The first critical step is **differentiation** between self and non-self.

Mucosal immune development requires environmental contact with commensal microflora
1st Line of Defense

aka Inflammation

Cell-mediated Immunity – TH1 Activation
  – Delayed HyperSensitivity
  – Macrophage/Phagocytosis

Humoral Immunity – TH2 Activation
  – Allergic Response
  – Antibody Formation
There is a constant state of balanced chronic inflammation present in the gastrointestinal tract.

This **physiologic inflammation** is essential for the maturing of the immune system and development of the normal morphology of the intestinal mucosa.

Pathways of Microbial-Host Interactions in the Intestine. NEJM 2002;348:615
With Permission
Pathways of Microbial-Host Interactions in the Intestine. NEJM 2002;348:615
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Genes
- Cytokines
- Immune Response

Environment
- Infections
  - Dysbiosis
  - Probiotics
  - Prebiotics
- Normal Flora
- Food Antigens

BALANCE!
Optimizing Gut Function

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Bacterial count

100,000/ml

Bacteroides, Lactobacillus, Clostridium, Fusobacterium, Bifidobacterium, Eubacterium, Peptococcus, Peptostreptococcus, Escherichia, and Veillonella.
Bacterial count

>400 different microbial species

Bacteroides, *Lactobacillus*, *Clostridium*, *Fusobacterium*, *Bifidobacterium*, *Eubacterium*, *Peptococcus*, *Peptostreptococcus*, *Escherichia*, and *Veillonella*.

---

Mucosal barrier present

Bacterial count

\[ 10^{12}/\text{ml} \]

\[ 100,000/\text{ml} \]

Motility ↓

↑ Absorption of macromolecules
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Immune System Modulation
– 1st Line of Recognition
– 1st Line of Defense
1st Line of Recognition
aka ‘Oral Tolerance’

The first critical step is differentiation between self and non-self.

Mucosal immune development requires environmental contact with commensal microflora and infections

i.e. Immuno-Exercise = FITNESS!
Colonization begins with birth and breast-feeding and continuing through life, leading to:

- 100 trillion bacteria
- 70% of human immune system localized in digestive tract
- accounts for half of the volume of contents in the colon
• At birth - digestive tract of humans is sterile.
• Colonised by microbes within the first few days of life
• At first, predominantly bifidobacteria (breast fed infants).
• With the introduction of other foods, a diverse microbial population develops in the gastrointestinal tract.
• By now, of all the cells in a human body, the overwhelming majority are non-human.
Post-Natal Development of Mucosal Immunity

Healthy gut flora:

- plays a crucial role
- maturation of the immune system
- constant stimuli are required
- ‘timing is everything’

✓ prolonged re-introduction of flora does NOT promote oral tolerance
✓ delayed re-introduction of flora leads to a decrease in circulating IgA and IgM-secreting cells

Hygiene Hypothesis

Altered microbial education:
- Improved sanitation
- Increased refrigeration
- Increased sterile food consumption
- Decreased fermented food consumption
- Decreased infection
- Increased antibiotics
- Vaccination
- Delayed exposure to childhood infections
Let them eat . . . dirt?

- Children who are “too clean” are more likely to develop asthma & atopy
- Mycobacteria in dirt stimulate cell-mediated (TH-1) immunity whereas vaccinations stimulate humoral immunity (TH-2)
- A modern, sanitized, vaccinated child is likely to over-develop TH-2 immunity and under-develop TH-1 immunity, rendering him or her susceptible to asthma & atopy

Post-Natal Development of Mucosal Immunity

Antigen Exposure and Nutrition – sub-optimal stimulation of the sIgA-dependent mucosal barrier function leads to the increased frequency of:
- allergies,
- asthma,
- inflammatory mucosal disorders (e.g. Crohn’s).

Infants with a family history of atopic allergy had a 100% higher prevalence @ 2yo than infants who received a *Lactobacillus* probiotic.

Post-Natal Development of Mucosal Immunity

Mucosal Homeostasis vs. Allergy

Intestinal TH1 cell activity is minimal
- due to decreased microbial stimulation
- requires the presence of commensal bacteria to drive TH1 dominance.

Breast milk contains immunoregulatory factors that stimulate lactic-acid producing bacteria. This also promotes a TH1 cytokine balance and oral tolerance.

Gut on FIRE!
GUT on FIRE!

There is a constant state of balanced chronic inflammation present in the gastrointestinal tract. This *physiologic inflammation* is essential for the maturing of the immune system and development of the normal morphology of the intestinal mucosa.

GUT in Balance!

There is a constant state of balanced chronic inflammation present in the gastrointestinal tract.

This *physiologic inflammation* is essential for the maturing of the immune system and development of the normal morphology of the intestinal mucosa.

T-helper 1 & 2 (TH-1 and TH-2)

TH-1 subset of cytokines are more involved with cell-mediated immunity and delayed hypersensitivity response.

TH-2 subset of cytokines are more involved with humoral immunity and allergic response: stimulate cell growth and differentiation, and recruitment of mast cells, basophils, eosinophils, and B-cells.
Cytokine Classification

Pro-inflammatory
IL-1β

TH-1
Cell-mediated Immunity
(viruses & CA)

TH-2
Humoral Immunity
(allergy)

Anti-inflammatory
IL-1RN

IL-2
TNF-α

IL-4
IL-6
IL-13

IFN-γ

IL-10
Important immune system effects of intestinal flora:

- activation of mucosal-associated lymphoid tissue (MALT)
- immunologic sampling via M cells
- dendritic cells and antigen-presenting cells (APCs) initiate immune response
- balancing TH1/TH2 cytokine profiles
Oesophagus
Trachea
Left subclavian vein
Mediastinal lymph nodes
Lungs
Heart
Spleen
Thoracic duct
Large intestine
Small intestine
Right subclavian vein
Superior vena cava
Liver
Stomach
Mesenteric nodes
Peyer's patches
Appendix

With Permission.
Important immune system effects of intestinal flora:

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GUT in BALANCE!

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Host-Microbe CrossTalk

There is a delicate BALANCE:

Innocuous Food Antigens
VS.
Normal Flora
VS.
Invasive Pathogens

Responsiveness

NonResponsiveness
Contact with “old friends” is greatly diminished in rich countries but increased on farms, in cowsheds, and through contact with pets.
Self Or Non-Self?

• Differentiation between normal flora and pathogenic organisms

• Pattern Recognition Receptors (PRCs):
  – toll-like receptors (TLRs)
  – C-type lectins

• Different PRCs respond to different stimuli
• Toll-like Receptors (TLRs) act as gates [tolls!] for controlling the immune system.
• TLRs react to gut flora and bacterial DNA, recognizing them as normal or *foreign*
Gut on FIRE!

• Toll-like Receptors (TLRs) act as gates [tolls!] for controlling the immune system.
• TLRs react to gut flora and bacterial DNA, recognizing them as normal or foreign.
• Crohn's Disease more commonly has the NOD2 portion of TLR altered, leading to an increase in the NF-κB induced inflammation.

Bacteria and/or bacterial products (peptidoglycan)

NOD2 defect

Normal path

Activated APC

Strong effector response or weak regulatory response and inflammation

Nature Reviews Immunology 2003;3:528
With Permission
IBD/ Crohns Disease

- Exaggerated immune response to normal intestinal microflora
- Different genetic changes lead to similar clinical pictures of inflammation
- Host genetic background determines susceptibility to intestinal inflammation

Critical gene-environment interaction:

- Bacterial species (commensal & pathogenic) have different abilities to cause inflammation
- Host genetic backgrounds have
  - Different dominant antigenic stimuli [food & flora]
  - Selectively respond to different antibiotic, probiotic, and prebiotic therapies!
Pathways of Microbial-Host Interactions in the Intestine. NEJM 2002;348:615
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Genes + Immune Dysregulation + Environmental Triggers
Inflammation

Genes + Immune Dysregulation + Environmental Triggers

This statement is TRUE for all chronic immune-mediated diseases

But is it . . .
Inflammation

Genes + Immune Dysregulation + Environmental Triggers

Abnormal immune response to normal flora in a genetically susceptible host?
Inflammation

Genes + Immune Dysregulation + Environmental Triggers

Normal immune response to abnormal flora in a genetically susceptible host?
Inflammation

Genes + Immune Dysregulation + Environmental Triggers

Abnormal immune response to normal flora in a genetically susceptible host?
Genomic Risk?

- IL-6 activates T-cells → inflammation, SNP further activates.
- IL-1β stimulates inflammatory response, SNP increases.
- IL-10 decreases inflammation, those with SNP cannot decrease inflammation.
- We can offer treatments to modify phenotypic expression (ECGC, turmeric, etc)
Genomic Risk?

Increasing IBD in Industrial Countries
- Steady increase since WWII
- Lifetime risk = 0.5 – 1.0%
- Rapid rise in Juvenile IBD since 1990

Increasing incidence of IBS

THERE HAS BEEN NO CHANGE IN OUR GENES!!
Inflammation

Genes + Immune Dysregulation + Environmental Triggers

Normal immune response to abnormal flora in a genetically susceptible host?
Recent evidence demonstrates the anti-inflammatory and anti-allergic effects of probiotics on healthy infant gut.

One mechanism of action includes reversal of increased intestinal permeability (aka ‘Leaky Gut’).

Normal Flora & Probiotics
Decrease Inflammation

• PROGID; www.vtt.fi/virtual/proeuhealth - large, multicenter trial in Europe
1. Has there been an alteration of normal flora?

2. Has there been a loss of tolerance to normal flora?

3. We can measure gut flora in stool. How do we measure gut inflammation?
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Maladigestion

- Inadequate mastication
- Hypochlorhydria
- Pancreatic insufficiency
- Bile insufficiency
- Villous atrophy – brush border enzyme destruction
MalDigestion Assessment

Stool fat

- 72 hour stool collection
- Single stool analysis
  - Fecal fat concentration
  - Sudan III stool staining
  - Stool steatocrit
    - Centrifugation
    - Fecal acidification

Breath testing
MalDigestion Assessment

Tests for protein loss

Vegetable and meat fibers

Non-invasive pancreatic function testing

• Serum testing
• Fecal lipase
• Fecal chymotrypsin
• Fecal Pancreatic Elastase (PE)
Maldigestion Assessment

Hypochlorhydria
– Empiric testing
– Gastro string test
– Heidelberg test
Hypochlorhydria

- Bloating, belching, burning and flatulence *within 1 hour* after eating
- Skin rashes, acne, anal itching
- Peeling, cracking finger nails
- Food sensitivities or allergies
Hypochlorhydria - Causes

- **Aging**
  - 50% of people over 60
  - 80% of people over 80
- **Fasting**
- **Viral or bacterial infection (fever)**
- **Any debilitated chronic condition**
  - (~600-800 Cal/day to concentrate enough H⁺ ions)
- **H₂ blockers and antacid abuse**
Hypochlorhydria – Consequences

• Small Intestinal Bacterial Overgrowth
  (SSx: carbohydrate intolerance + immediate bloating)
• Dysbiosis
• Chronic Candida Infections
• Mineral Deficiencies
  (Ca, Mg, Zn, Fe, Cr, Mo, Mn, Cu)
• $B_{12}$ deficiency
Maldigestion

- Triglycerides
  - Ref Range %: 0.3
  - Range: 0.3 to 1.0

- Chymotrypsin
  - Ref Range U/g: 6.2 to 41.0
  - Range: 10.0 to 25.0

- Putrefactive SCFA (Total)
  - Ref Range umol/g: 24.8

- Meat Fibers
  - Inside Range: 0
  - Outside Range: 0

- Vegetable Fibers
  - Inside Range: 1
  - Outside Range: 0-4

**Occ = Occasional**
Putrefactive
Short Chain Fatty Acids
Valerate, Iso-Valerate, & Iso-butyrate:

– inadequate protein digestion
  low HCl, protease insufficiency
– bacterial overgrowth of the small intestine
  (ssx: bloating and distention immediately after meals)
Maldigestion

- Villous atrophy – brush border enzyme destruction
  - Endoscopy
  - Amino Acid Evaluation
  - Pancreatic Elastase 1
# Maldigestion Markers

## Dietary Peptide Related Markers

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<tr>
<th></th>
<th>Marker</th>
<th>Value</th>
<th>Reference Range</th>
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<tbody>
<tr>
<td>12</td>
<td>Anserine (dipeptide)</td>
<td>484</td>
<td>10-145</td>
</tr>
<tr>
<td>13</td>
<td>Carnosine (dipeptide)</td>
<td>122</td>
<td>10-135</td>
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<tr>
<td>14</td>
<td>1-Methylhistidine</td>
<td>2,511</td>
<td>120-1,250</td>
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<tr>
<td>15</td>
<td>Beta-alanine</td>
<td>108</td>
<td>&lt;= 22</td>
</tr>
</tbody>
</table>
Maldigestion Assessment

- Villous atrophy – brush border enzyme destruction
  - Endoscopy
  - Amino Acid Evaluation
  - Pancreatic Elastase 1
Pancreatic Insufficiency

• Common dysfunction of GI system
• Pancreatic enzymes commonly prescribed empirically
• A number of conditions are associated with pancreatic insufficiency without overt symptoms of maldigestion
Pancreatic Insufficiency

Common signs & symptoms
– Post-prandial bloating, pain, or nausea
– Loose or watery stools
– Undigested food in stool
– Hypochlorhydria
– Food intolerances
– Gastroesophageal reflux symptoms
Pancreatic Insufficiency

Pancreatic Elastase provides the most accurate non-invasive measure of the exocrine pancreas
Pancreatic Elastase

- PE is a proteolytic enzyme secreted exclusively by the human pancreas
- Reflects overall enzyme production (amylase, lipase and protease)
- PE is a simple, non-invasive marker for evaluating exocrine pancreatic function
  - Sensitivity = 90 - 100%
  - Specificity = 93 - 98%

Pancreatic Insufficiency

• Diabetics \(^1,^2\) – PE is reduced in:
  – 50% of Type 1 diabetics
  – 35% of Type 2 diabetics
  – Poor glycemic control in diabetics associated with a higher risk of low PE (OR = 5.6)

Osteoporosis – Nearly one third of patients with osteoporosis have reduced concentrations of PE$^{1,2}$


Pancreatic Insufficiency

Villous atrophy - Celiac disease
– Extrinsic impairment of exocrine pancreas
– Pancreatic hypostimulation
– Gold standard (secretin-cerulin test) ineffective in hypostimulation

Pancreatic Insufficiency

Celiac disease

– 30 Celiac patients eating gluten
– 33% had low PE
– 8 of 10 returned to normal after 2 months on gluten free diet
– All returned to normal after 6 months
– Pancreatic insufficiency correlated with diarrhea (7/10 vs. 8/20)

### Pancreatic Elastase - Treatment

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Description</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 400 μg/g</td>
<td>Normal pancreatic function</td>
<td></td>
</tr>
<tr>
<td>200-400 μg/g</td>
<td>Declining pancreatic function</td>
<td>Consider supplement with pancreatic enzymes</td>
</tr>
<tr>
<td>100-200 μg/g</td>
<td>Moderate pancreatic insufficiency</td>
<td>Supplement with broad array of pancreatic enzymes</td>
</tr>
<tr>
<td>&lt;100 μg/g</td>
<td>Severe pancreatic insufficiency</td>
<td>Supplement with broad array of pancreatic enzymes</td>
</tr>
</tbody>
</table>
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• Digestion - Interaction
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• Metabolism - Gut Milieu
• Excretion – Elimination

• Immune System Modulation
Optimizing Gut Function

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- Immune System Modulation
Absorption

Intestinal mucosa’s paradoxical role
– Absorbing nutrients
– Excluding toxins and larger molecules

Any breach of the mucosa can lead to
– Malabsorption
– Increased exposure to toxins & antigens
Malabsorption - Causes

- Maldigestion
- Hypochlorhydria
- Bacterial overgrowth of the small intestine
- Deficient bile production
- Chronic inflammation of the small intestine
  - Food sensitivities
  - Gluten enteropathy
  - Inflammatory bowel disease
- Rapid transit time (irritable bowel)
Malabsorption - Assessment

- Endoscopy and histological assessment
- Pancreatic imaging
- Non-invasive tests for small bowel enteropathy
  - Fecal Fats
  - Testing for Celiac Disease
  - Intestinal Permeability testing
Healthy Gut

Healthy Villi/Good Absorption

Healthy Cell Junctions
Leaky Gut & Malabsorption

- Damaged Villi/ Poor Absorption
- Damaged Cell junctions
Increased Intestinal Permeability

CAUSES:
- IBD (Crohn’s disease)
- NSAID therapy
- Small bowel bacterial overgrowth
- Celiac sprue
- Protozoal infections
- Food allergy
Increased Intestinal Permeability

**CAUSES:**
- Chronic alcoholism
- Diarrhea
- Strenuous exercise
- Increasing age
- Nutritional depletion
Leaky Gut - Pathophysiology

- Poor Dietary Choices
- Stress & Emotions
- Infection
- Lectins
- Systemic Disease
- Low Stomach Acid
- Toxic Exposure
- Food Allergy
- Malnutrition
- Dysbiosis
- Toxic Overload
- Elevated Total Toxic & Antigenic Burden

Systemic Disease
Measuring Intestinal Permeability

A fasting subject ingests a solution of two biologically non-metabolized sugars:

- Lactulose (a disaccharide)
- Mannitol (a monosaccharide)

Urine is collected for the next 6 hours.

Lactulose (<1%) and Mannitol (~ 15%) recovery is measured.
Lactulose and Mannitol

Mannitol corresponds to the enterocyte pores and **intracellular** passage
→ A measure of the ability to absorb nutrients

Lactulose corresponds to the rupture of the desmosomes and **intercellular** clearance
→ Macromolecules, toxins and antigens crossing the intestinal barrier and entering the lymph and circulatory system

Annals of Allergy. 1987;59:127-130
Intestinal Permeability

- **Lactulose Percent Recovery**
  - Ref Range: <= 0.8
  - Normal: 1.0
  - Abnormal: > 1.0

- **Mannitol Percent Recovery**
  - Ref Range: 5 - 30
  - Normal: 0.20
  - Abnormal: > 0.20

- **Lactulose/Mannitol Ratio**
  - Ref Range: <= 0.07
  - Normal: 0.20
  - Abnormal: > 0.20

*Intestinal permeability refers to the extent of osmotic water movement across the gut barrier from blood to gut lumen.*
Increased Intestinal Permeability – Treatment Options

**Endogenous Protection:**
- sIgA (blocks potentially antigenic proteins)
- Mucin

**Exogenous Protection:**
- N-acetyl-D-glucosamine (mucous enhancement)
- Quercetin (anti-inflammatory)
- Probiotics (normalize gut flora and increase sIgA)
- L-Glutamine (supports enterocytes and microvilli)
L-Glutamine

Supplemental L-Glutamine

- Preferred fuel for enterocytes of small intestine
- Increases intestinal villous height
- Stimulates gut mucosal cellular proliferation
- Maintains mucosal integrity
- Prevents intestinal hyperpermeability and bacterial translocation

Other Therapeutic Considerations

L-arginine
Larch arabinogalactans
Bovine colostrum
Fish oils
Zinc, Vitamin A
Increasing n-butyrate production
  – Insoluble fiber
<table>
<thead>
<tr>
<th><strong>IgE</strong></th>
<th><strong>IgG</strong></th>
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<tbody>
<tr>
<td>• immediate sensitivity</td>
<td>• delayed sensitivity</td>
</tr>
<tr>
<td>• fixed to mast cells</td>
<td>• stimulate phagocytosis</td>
</tr>
<tr>
<td>• histamine release</td>
<td>• antigen-antibody complexes</td>
</tr>
<tr>
<td>• reintroduction of foods very difficult</td>
<td>• reintroduction possible after 3-6 mo. avoidance</td>
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# Food Antibody Evaluation

## Food Antibody Assessment IgE & IgG

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<thead>
<tr>
<th>Patient:</th>
<th>Order Number:</th>
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<tbody>
<tr>
<td>Age: 37</td>
<td>Completed: January 26, 2001</td>
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<tr>
<td>Sex: M</td>
<td>Received: January 25, 2001</td>
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<td>MRN:</td>
<td>Collected: January 25, 2001</td>
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### Dairy

<table>
<thead>
<tr>
<th>Food</th>
<th>IgE</th>
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<tbody>
<tr>
<td>Casein</td>
<td>0</td>
<td>1+</td>
</tr>
<tr>
<td>Cheddar cheese</td>
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<td>2+</td>
</tr>
<tr>
<td>Cottage cheese</td>
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<td>1+</td>
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<tr>
<td>Cow's milk</td>
<td>0</td>
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<tr>
<td>Goat's milk</td>
<td>VL</td>
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<tr>
<td>Lactalbumin</td>
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<tr>
<td>Yogurt</td>
<td>0</td>
<td>1+</td>
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</table>

### Fish/Shrimp

<table>
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<tr>
<th>Food</th>
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<th>IgG</th>
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<tr>
<td>Clam</td>
<td>0</td>
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<tr>
<td>Cod</td>
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<tr>
<td>Crab</td>
<td>0</td>
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</tr>
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<td>Lobster</td>
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<td>VL</td>
</tr>
<tr>
<td>Oyster</td>
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<td>VL</td>
</tr>
<tr>
<td>Red Snapper</td>
<td>0</td>
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<td>Salmon</td>
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</tr>
<tr>
<td>Sardine</td>
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<tr>
<td>Shrimp</td>
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<td>Sole</td>
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<td>3+</td>
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<td>Trout</td>
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<td>3+</td>
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### Fruits

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<th>Food</th>
<th>IgE</th>
<th>IgG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apple</td>
<td>0</td>
<td>VL</td>
</tr>
<tr>
<td>Apricot</td>
<td>0</td>
<td>2+</td>
</tr>
<tr>
<td>Banana</td>
<td>0</td>
<td>1+</td>
</tr>
<tr>
<td>Blueberry</td>
<td>0</td>
<td>VL</td>
</tr>
<tr>
<td>Cranberry</td>
<td>0</td>
<td>VL</td>
</tr>
<tr>
<td>Grape</td>
<td>0</td>
<td>VL</td>
</tr>
<tr>
<td>Grapefruit</td>
<td>0</td>
<td>VL</td>
</tr>
<tr>
<td>Lemon</td>
<td>0</td>
<td>VL</td>
</tr>
<tr>
<td>Orange</td>
<td>0</td>
<td>VL</td>
</tr>
<tr>
<td>Papaya</td>
<td>0</td>
<td>VL</td>
</tr>
<tr>
<td>Peach</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pear</td>
<td>0</td>
<td>VL</td>
</tr>
<tr>
<td>Pineapple</td>
<td>0</td>
<td>VL</td>
</tr>
<tr>
<td>Plum</td>
<td>0</td>
<td>VL</td>
</tr>
<tr>
<td>Raspberry</td>
<td>0</td>
<td>1+</td>
</tr>
<tr>
<td>Strawberry</td>
<td>0</td>
<td>VL</td>
</tr>
</tbody>
</table>

### Poultry/Meats

<table>
<thead>
<tr>
<th>Food</th>
<th>IgE</th>
<th>IgG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beef</td>
<td>1+</td>
<td>VL</td>
</tr>
<tr>
<td>Chicken</td>
<td>0</td>
<td>VL</td>
</tr>
<tr>
<td>Egg white</td>
<td>0</td>
<td>VL</td>
</tr>
<tr>
<td>Egg yolk</td>
<td>0</td>
<td>VL</td>
</tr>
<tr>
<td>Lamb</td>
<td>3+</td>
<td>VL</td>
</tr>
<tr>
<td>Pork</td>
<td>0</td>
<td>VL</td>
</tr>
<tr>
<td>Turkey</td>
<td>0</td>
<td>VL</td>
</tr>
</tbody>
</table>

The reported levels are an indication of the distribution of antibodies relative to levels from healthy individuals selected on the basis of well-defined criteria.
Food Allergy & IBS

• IgG Food Allergy testing with ELISA performed on 150 patients.
• TRUE Elimination diet given to 75 patients
• SHAM Elimination diet given to 75 patients

– 26% decline in IBS symptoms and improved QOL, which reversed when ‘allergens’ added back
IgG Sensitivity Treatment Protocol

Eliminate reactive foods

- 3+ foods should be avoided for ~6 months
- 2+ foods should be avoided for ~3 months
- avoid all IgE reactive foods permanently

Rotate non-reactive foods

- 4 day rotation for individual foods
- 2 day rotation for food families

Re-introduce reactive foods in 3-6 months

- 1 new food every four days
- watch for immediate and delayed reactions
"Relax, it's just a yeast infection"
Yeast overgrowth

• Microscopy and culture
• Organic acids
  – Arabinose
  – Citramalic Acid
  – Tartaric Acid
  – BetaKetoGlutaric Acid
Dietary Treatment of *Candida albicans*

- Eliminate all sugar:
  - fruit juice
  - white flour
  - refined grains
- Eat a higher protein, lower carbohydrate, high fiber diet
- Avoid fermented foods including alcohol
Botanical Medicines with Anti-Fungal Activity

- **Allium** (garlic)
- **Astragalus**
- Barberry, Oregon Grape
- Citrus Seed Extract
- **GrapeFruit Seed Extract**
- **Hydrastis** (Golden Seal)
- Olive Leaf
- **Tebebuia** (Pau d’Arco)
- Plant Tannins

Volatile Oils (enteric-coated)

- Anise
- Oregano
- Rosemary
- Sage
- Thyme
Secondary Investigations

Microbiology and Parasitology

- Culture
- Microscopy
- EIA testing
Bacterial Overgrowth of the Small Intestine (BOSI)

A frequently-overlooked contributor:

**Irritable Bowel Syndrome**

- 78% of patients tested positive; 48% of successfully-treated patients no longer met Rome Criteria for IBS

**Fibromyalgia and CFS**

- 78% and 77% of subjects, respectively, have BOSI
- Both disorders overlap with IBS
Bacterial Overgrowth of the Small Intestine (BOSI)

Dysmotility syndromes
- Systemic disease, e.g., DM, scleroderma
- Prior intestinal surgery
- Strictures of the small intestine

Jejunal Diverticulosis

Crohn’s disease

Symptoms in celiac disease, despite no gluten

Aging
- 64% of individuals > 75 yrs with chronic diarrhea
- BOSI is common cause of malabsorption in elderly
Pathophysiology of BOSI

- Bacteria don’t normally inhabit the small intestine in large numbers
- Growth controlled by:
  - Intestinal peristalsis
  - Gastric acid secretion
  - Pancreatic enzymes
  - Ileoceleval valve
  - Bile acids
  - Luminal pH
  - Immunoglobulins
  - Mucous barrier
Flora in BOSI

Composition varies:
- Coliforms and strict anaerobes
Concentrations always higher than normal

Bacteria that are normal in the colon may produce deleterious effects within the delicate environment of the small intestine…
Clinical Consequences of Bacterial Overgrowth

Gas & bloating, abdominal discomfort

- Bacterial fermentation of intraluminal sugars

Classic BOSI syndrome:

- Megaloblastic anemia (B12 deficiency)
- Weight loss and diarrhea secondary to fat malabsorption
Mechanisms of Fat Malabsorption in BOSI

1) Bacteria deconjugate bile salts to free bile acids
   - Mucosal damage $\rightarrow$ malabsorption (also disaccharidase and peptidase deficiencies)
   - Low bile salts leads to impaired micelle formation $\rightarrow$ fat malabsorption and steatorrhea

2) Pseudomembrane $\rightarrow$ mechanical interference with absorption
Malnutrition in BOSI

Unabsorbed fatty acids may form insoluble soaps with minerals such as Ca and Mg →
  – Osteomalacia, night blindness, hypocalcemic tetany, metabolic bone disease possible

Vitamin B12 deficiency
  – Bacteria utilize B12 and detach B12 from intrinsic factor
  – Serum folate usually normal or elevated

Hypoproteinemia
  – Protein-losing enteropathy or protein malabsorption
  – Bacterial metabolism of proteins to ammonia and fatty acids

Iron deficiency anemia (rare)
Flora in BOSI is typically comprised of both coliforms and strict anaerobes

Conventional approach is broad-spectrum antibiotics X 7-10 days:

- Tetracycline: 250 mg QID (ineffective in 60% of patients)
- Quinolones (e.g., Cipro)
- Augmentin
- Clindamycin
- Metronidazole
Other antibiotics:

- Ampicillin, erythromycin, lincomycin, cephalosporins, chloramphenicol
- Poorly-absorbed ABs may minimize side effects: Rifaximin
  - 10-14 day course of Rifaximin (550 mg TID) normalized breath $H_2$ in 70% of pts;
  - TCN normalized breath $H_2$ in 27% of pts.

Probiotics to minimize side effects
Treatment for BOSI (cont)

Probiotics to minimize side effects

Natural approach:
- Broad-spectrum botanicals
- Enteric-coated peppermint oil to reduce symptoms?
- Lactobacillus acidophilus and L. casei

Address underlying causes!
- Stasis, slow transit time, low stomach acid (betaine HCl, stop PPIs), maldigestion, lactose intolerance

Temporarily restrict CHOs, especially disaccharides such as lactose
Optimizing Gut Function

- Digestion - Interaction
- Absorption - Assimilation
- Metabolism - Gut Milieu
- Excretion – Elimination

- Immune System Modulation
  - 1st Line of Defense
  - 1st Line of Recognition
# Digestive Stool Analyses

## Comprehensive Digestive Stool Analysis

### Digestion/Absorption

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Result</th>
<th>Ref Rg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic Elastase</td>
<td>100-200 µg/gid</td>
<td>210-0 µg/gid</td>
</tr>
<tr>
<td>Amylase</td>
<td>50-200 µg/gid</td>
<td>100-0 µg/gid</td>
</tr>
<tr>
<td>Lipase</td>
<td>10-50 µg/gid</td>
<td>20-0 µg/gid</td>
</tr>
<tr>
<td>Bile Acids</td>
<td>10-50 µg/gid</td>
<td>20-0 µg/gid</td>
</tr>
</tbody>
</table>

### Gut Immunology

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Result</th>
<th>Ref Rg</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-reactive Protein</td>
<td>&lt; 150 mg/l</td>
<td>150-0 mg/l</td>
</tr>
<tr>
<td>Calprotectin</td>
<td>&gt; 200 µg/gid</td>
<td>200-0 µg/gid</td>
</tr>
</tbody>
</table>

### Metabolic

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Result</th>
<th>Ref Rg</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>6.0-7.2</td>
<td>6.0-7.2</td>
</tr>
<tr>
<td>Pyruvate</td>
<td>0-100 µmol/L</td>
<td>100-0 µmol/L</td>
</tr>
<tr>
<td>Lactic acid (LOA)</td>
<td>2-1 mg</td>
<td>2-0 mg</td>
</tr>
<tr>
<td>Deoxyribonuclease (DNA)</td>
<td>10-0 U/L</td>
<td>10-0 U/L</td>
</tr>
<tr>
<td>Carbohydrate (CHO)</td>
<td>10-0 U/L</td>
<td>10-0 U/L</td>
</tr>
<tr>
<td>Lactate Dehydrogenase (LDH)</td>
<td>2-0 U/L</td>
<td>2-0 U/L</td>
</tr>
</tbody>
</table>

### Microbiology

#### Bacteriology

- **Beneficial Bacteria**
  - *Lactobacillus acidophilus*
  - *Bifidobacterium*

- **Additional Bacteria**
  - *Escherichia coli*
  - *Staphylococcus aureus*
  - *Enterobacter aerogenes*
  - *Klebsiella pneumoniae*

#### Mycology

- *Candida albicans*

### SCFA distribution

<table>
<thead>
<tr>
<th>SCFA</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetate</td>
<td>40-75%</td>
</tr>
<tr>
<td>Propionate</td>
<td>10-30%</td>
</tr>
<tr>
<td>Butyrate</td>
<td>10-30%</td>
</tr>
</tbody>
</table>

### Metabolic Markers

<table>
<thead>
<tr>
<th>Marker</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>n-Butyrate</td>
<td>24-454 µmol/L</td>
</tr>
<tr>
<td>n-Valerate</td>
<td>71-4,900 µmol/L</td>
</tr>
<tr>
<td>n-Propionate</td>
<td>65.7-2 µmol/L</td>
</tr>
</tbody>
</table>

### Dysbiosis Risk Index

- **Normal**: 0-12
- **Mild**: 13-24
- **Moderate**: 25-36
- **Severe**: 37-48

---

Critical gene-environment interaction:
• Bacterial species (commensal & pathogenic) have different abilities to cause inflammation
• Host genetic backgrounds have
  – Different dominant antigenic stimuli [food & flora]
  – Selectively respond to different antibiotic, probiotic, and prebiotic therapies!
“Personalized Medicine”

“Smart” Immune Interventions

- **IL-1β**: Fish Oils, Milk Thistle, Boswellia, Curcumin
- **TNF-α**: Onions, Green Tea, NAC, Lactobacillus
- **IL-4**: Allergen Elimination, Fish Oils, Quercetin
- **IL-6**: Stress Reduction, C, B5, Ginseng, Ashwaganda
- **IL-10**: Licorice, Ginger, Hesperedin
- **IL-13**: Allergen Elimination, Fish Oils, Quercetin
Inflammation

Genes + Immune Dysregulation + Environmental Triggers

Abnormal immune response to normal flora in a genetically susceptible host?
Pathways of Microbial-Host Interactions in the Intestine.
NEJM 2002;348:615
With Permission
Optimizing Gut Function Management and Therapeutics

- Digestion - Interaction
- Absorption - Assimilation
- Metabolism - Gut Milieu
- Excretion – Elimination
- NeuroEndocrine Regulation
- Immune System Modulation
Integrative Therapies

Find the SOURCE!

- Infection
- Inflammation
- Immune Dysfunction
- Dysbiosis
- NeuroEndocrine
- Maldigestion
- Malabsorption
- Food Intolerance/ Allergies
Integrative Therapies

Infection & Inflammation

• Prebiotics
• Probiotics
• Antibiotics
• Antimicrobial Herbs
• Fish Oils & EPO/GLA
• COX-2 inhibitors
• Immunoglobulins/ Colostrum
Integrative Therapies

NeuroEndocrine
- Serotonin Excess/ Deficiency?
- Natural Therapies?
  - Mast cell inhibitors(?)
    - Vitamin C, Bioflavonoids
    - Cromolyn
  - Anti-histamines(?)
Integrative Therapies

Digestion/Absorption

- Digestive Enzymes
- Betaine HCL
- Nutritional Supplements
- Enteric-coated Peppermint (& Caraway) Oil
Integrative Therapies

Metabolism

• Medical Foods
• Dietary Fiber (e.g. psyllium)
• Diet Improvement – Eat your vegetables!
Integrative Therapies

Mind-Body Therapies

- Biofeedback
- Stress Reduction
- Hypnosis
- Acupuncture
The 4-R Program

- Remove
- Replace
- Repopulate
- Repair
The 4-R Program

Remove

- pathogenic organisms
- allergic foods

Removing the source of the imbalance is the critical *first* step, but the functional medicine approach does not stop here…
The 4-R Program

Replace

• hydrochloric acid
• digestive enzymes
• herbal support
• lipotropic factors
The 4-R Program

➢ Repopulate

• Lactobacilli
• Bifidobacteria
• Saccharomyces if using antibiotics
The 4-R Program

Repair

- SI: glutamine, gamma oryzanol, duodenum glandular, N-acetyl glucosamine
- LI: fiber, butyrate
- Boswellia, geranium, licorice, quercetin, hydrastis, cheledonium, artemisia, aloe
- okra, cabbage, rice protein, GLA, EPA
- fasting
The 5th R

- Rebalance

Modify attitude, diet and lifestyle of the patient to promote a healthier way of living
Genes
- Cytokines
- Immune Response

Environment
- Infections
  - Dysbiosis
  - Probiotics
  - Prebiotics
- Normal Flora
- Food Antigens

HEALTH!

Pathways of Microbial-Host Interactions in the Intestine. NEJM 2002;348:615
With Permission