FUNCTIONAL MEDICINE
Continuing Education

The Immune System & The Gut Immune Patient Cases

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Partners

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Disclosures

- Dr. Hartzler is the owner of PharmtoTable, LLC and is on the speaker's bureau for Salix Pharmaceuticals.

Objectives

- Discuss the 5 R Approach for addressing gastrointestinal imbalances
- Apply knowledge of immune interventions to patient cases.

Understanding the Root Cause

- GI system is complex
- Significant Interrelationships between
  - **D**igestion/Absorption
  - **I**ntestinal Permeability
  - **G**astrointestinal Flora
  - **I**mmune Regulation & Inflammation
  - **N**ervous System

Basic Functions of the GI System

- Digestion
  - Enzymes (pancreas & Small intestine microvilli), HCL, bile salts, transport proteins
- Phase I and Phase II start in intestinal mucosa
- Communication to endocrine and immune systems

Jones DS, et al. Textbook of Functional Medicine 2010.

Basic Functions of the GI System

- Immune Function
  - Gut Associated Lymphoid Tissue (GALT)
    - B cells, T Cells, and phagocytes
    - As much as 70% of the total body reserves of lymphoid tissue
  - Developing oral tolerance is an important mechanism of immune regulation

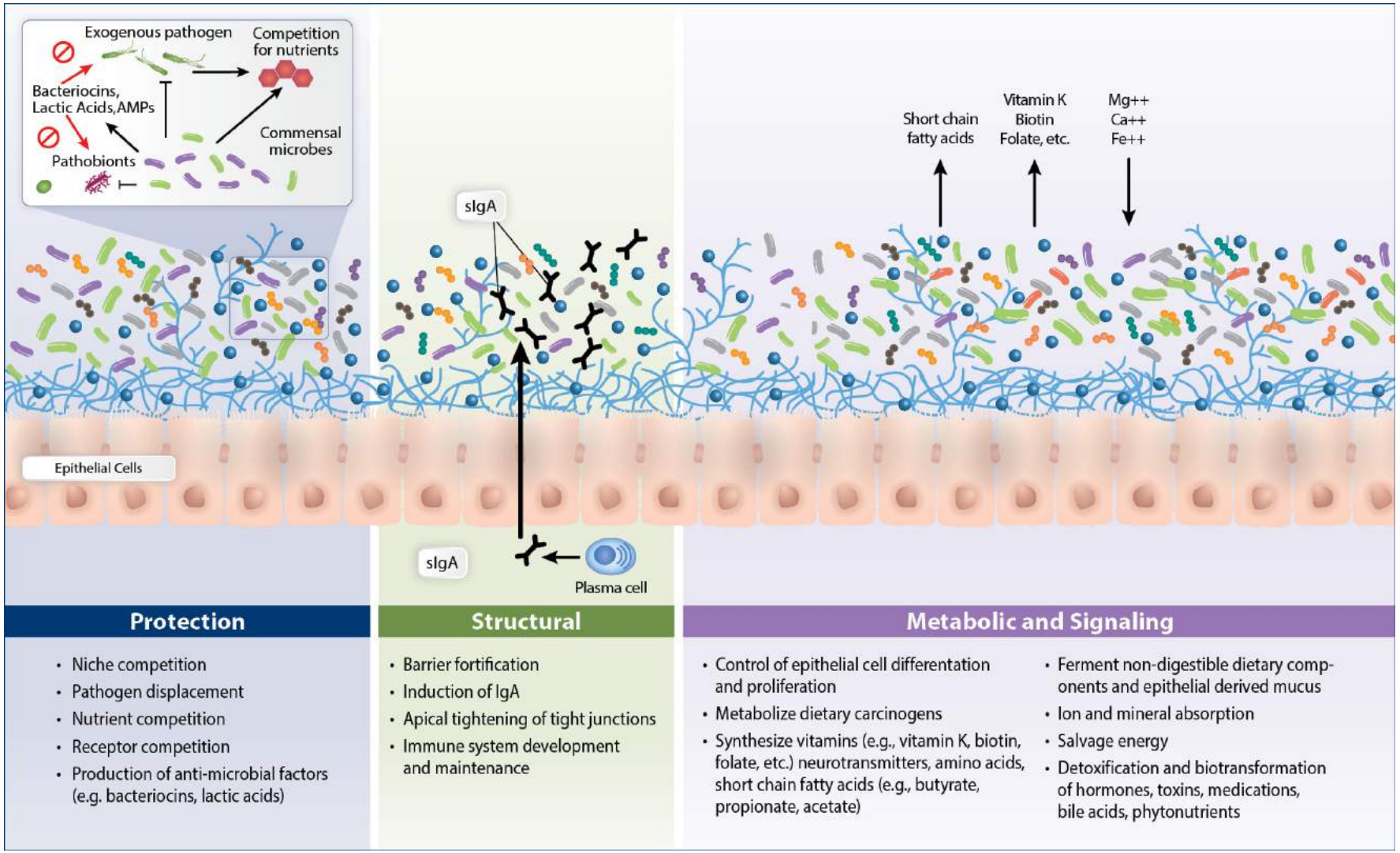
Jones DS, et al. Textbook of Functional Medicine 2010.

Basic Functions of the GI System

- Antigens that survive the digestive process are examined by the GALT tissue
  - Generally non-beneficial will be processed and inhibit the development of allergy by increasing IgA and cytokines at the mucosal and luminal level
  - Secretory IgA binds to and neutralizes microbes and other antigens before they cross the mucosal barrier
  - Chronic intestinal infection or inflammation can leaded to more immunogenic responses to common antigens

Jones DS, et al. Textbook of Functional Medicine 2010.

Commensal Gut Microbiome



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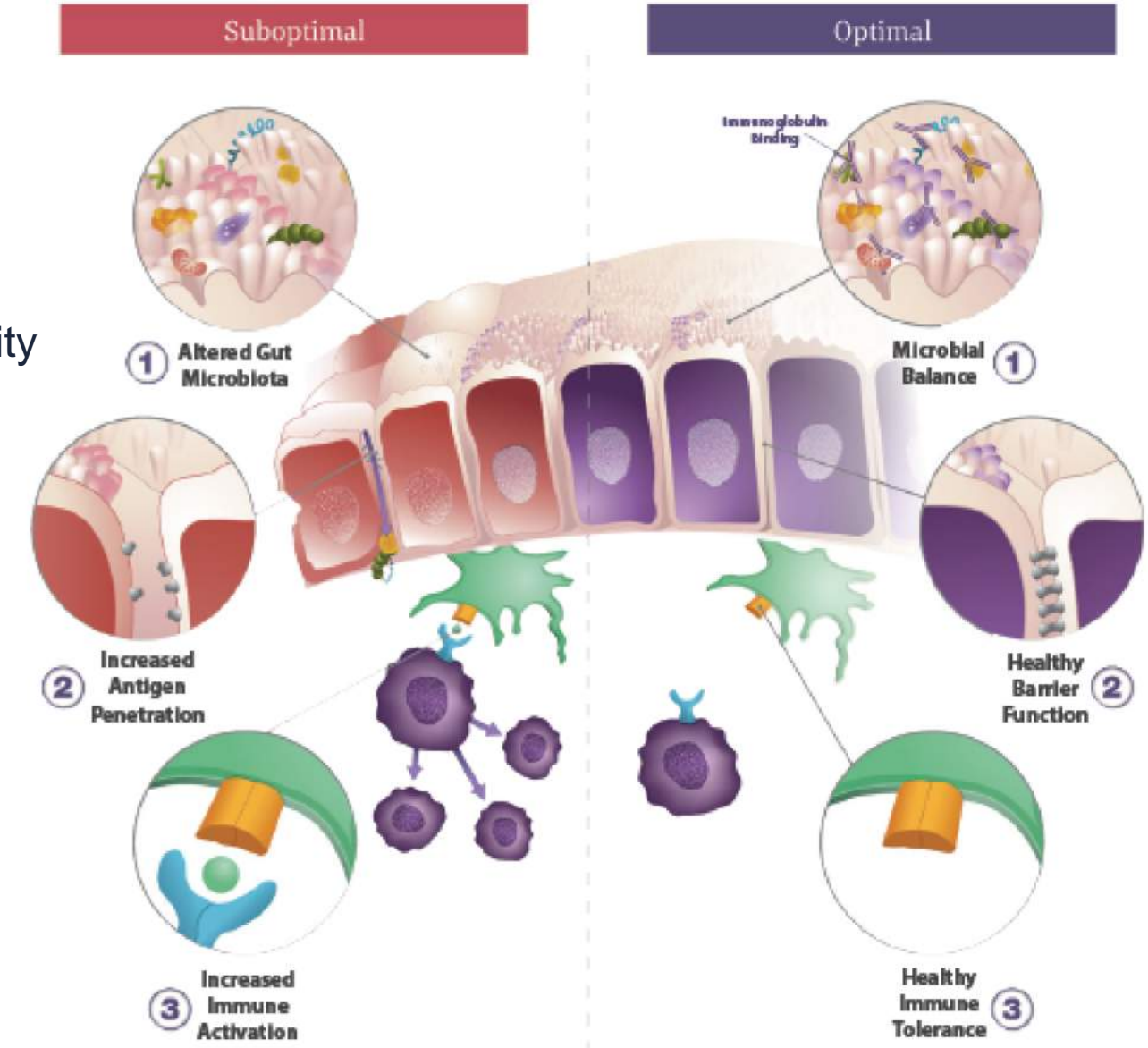
“Leaky Gut”

- Translocation
  - The process of a large molecule moving through a biologic barrier
  - May result in allergy, autoimmunity, or high levels of inflammation.
  - Can overwhelm the liver “detox” mechanisms

Increased Permeability



Healthy Tight Junctions

Image reprinted with permission Lifestyle Matrix Resource Center-
Oral IgG/Immune Dysfunction Handout.

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Dysbiosis & & Immune Activation

- Lipopolysaccharide (LPS)
  - Highly studied component of gram-negative bacteria
  - Stimulates immunological responses
  - Stimulates production of numerous inflammatory mediators
  - Leads to intestinal permeability & chronic inflammation
  - Linked to depression
- Dysbiosis
  - Increases intestinal permeability (IP)

Creely SJ, et al. Am J Physiol Endrocrinol Metab.2007 Mar; 292(3):E740-7.
Dagci, H et al. Acta Tropica. doi:10.1016/S0001-706X(01)00191-7.
Maes M, et al. *Journal of Affective Disorders*. doi:10.1016/j.jad.2006.08.021.

Management of Dysbiosis

Step 1: Identify & correct underlying causes

- Test

Step 2: Manage & treat

- 4 R/5R Approach

Step 3: Reduce likelihood of relapse

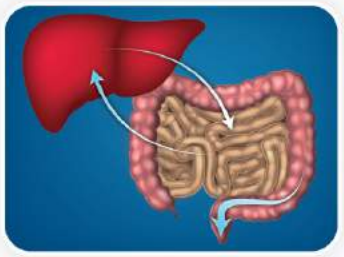
- Address Motility

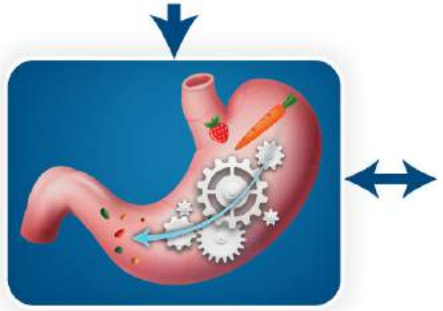
REMOVE *(Important First Step in 4R Model)*

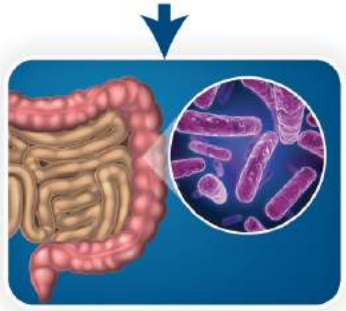
Promote Elimination and Detoxification

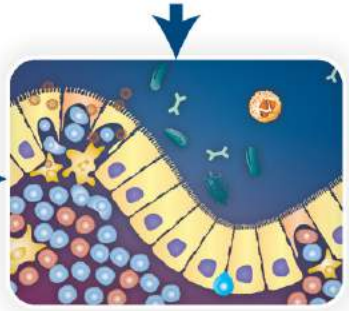
Remove Allergens and Toxins
- Elimination diet
- Detoxification protocol

Remove Harmful Organisms
- Stool testing for pathogens
- Eliminate pathogens









REPLACE

Promote Digestion and Absorption

- Supplement or stimulate
  - Stomach acid
  - Digestive enzymes
  - Bile for fat absorption
  - Easy to absorb nutrients

RE-ESTABLISH

(Re-inoculate)

Ecosystem for Microbiome

- Microbiome-friendly diet
- Avoiding certain drugs/antibiotics
- Probiotics
- Prebiotics

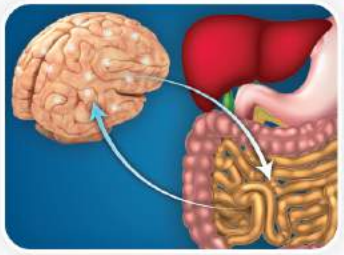
REPAIR

Barrier Function/ Immune Interface

- Reduce gut inflammation
- Provide nutrients for GI cells
- Improve tight junctions
- Increase signals for immune modulation

SUPPORTING NEUROENDOCRINE (GUT/BRAIN) FUNCTION

- Modulate the effects of HPA axis/stress
- Control neurotransmitter synthesis and function
- Manage satiety signals from gut
- Coordinate signals from microbiome, immune system, bowel transit to and from the CNS



Reprinted with permission: Page 22. Guilliams, T. Functional Strategies for the Management of Gastrointestinal Disease. The Standard Road Map Series. Pointe Institute 2016.

4R/5R Framework

Remove

Food Allergies

Pathogens

Stress

Guilliams, T. Functional Strategies for the Management of Gastrointestinal Disease. The Standard Road Map Series. Pointe Institute 2016.

SIBO treatment

- Good Eradication Rates (50%)/Non-absorbable Antibiotic
  - Rifaximin 1200–1600 mg daily.
  - Neomycin 500 mg BID X 10 days (added for methanogens)

- Systemic Antibiotics (Eradication 44-100%)
  - Ciprofloxacin
  - Metronidazole 750 mg daily (in divided doses, usually 250 mg TID)
    - Sometimes given in combination with Rifaxamin to address methanogens

Herbal Treatment

- Limited Evidence
  - Multi-center study (n=140) did find herbal therapy to be equivalent to Rifaximin
    - Preparations used in next slide.
  - 2 herbal combination formulas together, at a dose of 2 caps 2 x day x 4 weeks, for each formula.
    - Biotics FC Cidal with Biotics Dysbiocide, or
    - Metagenics Candibactin-AR with Metagenics Candibactin-BR

Chedid V. Glob Adv Health Med. 2014 May;3(3):16-24
http://www.siboinfo.com/herbal-antibiotics.html

Herbal Preparations for the Treatment of Small Intestine Bacterial Overgrowth

FC Cidal	Dysbiocide	Candibactin-AR	Candibactin-BR
Proprietary blend - 500 mg: 1 capsule	Proprietary Blend 950 mg per 2 capsules	One Capsule contains:	Two Capsules contain:
Tinospora cordifolia (stem)	Dill seed	Red Thyme oil (thymus vulgaris, providing 30%-50% thymol) 0.2 mL	Coptis root and rhizome extract (coptis chinensis, containin berberine) 30 mg
Equisetum arvense (stem)	Stemona Sessilifolia powder and extract	Oregano Oil (origanum vulgare, providing 55% to 75% carvacrol) 0.1 mL	Indian Barberry root extract (berberis aristata, containing berberine) 70 mg
Pau D'Arco (inner bark)	Artemisia Absinthium shoots and leaves extract,	Sage leaf 5.5:1 extract (salvia officinalis) 75 mg	Berberine Sulfate 400 mg • Proprietary 4:1 Extract 300 mg: Coptis root and rhizome (coptis chinensis)
Thymus vulgaris (aerial part)	Pulsatilla Chinensis rhizome powder and extract	Lemon Balm leaf 5:1 extract (melissa officinalis) 50 mg	Chinese Skullcap root (scutellaria baicalensis)
Artemisia dracunculus (leaf)	Brucea Javanica powder and extract		Philodendron bark (phellodendron chinense)
Sida cordifolia (aerial part)	Picrasma Excelsa bark extract		Ginger rhizome (zingiber officinale)
Olea europaea (leaf)	Acacia Catechu stem extract		Chinese Licorice root (glycyrrhiza uralensis)
	Hedyotis Diffusa powder and extract		Chinese Rhubarb root and rhizome (rheum officinale)
	Yarrow leaf and flower extract (achillea millefolium).		Chinese Rhubarb root and rhizome (rheum officinale).

Other Herbal Treatment

- Allicin from Garlic (the highest potency formula I know of is Allimed)
- Oregano
- Berberine- found in Goldenseal, Oregon Grape, Barberry, Coptis, Phellodendron
- Neem
- Cinnamon
- Blends like Biocidin®

Chedid V. Glob Adv Health Med. 2014 May;3(3):16-24
http://www.siboinfo.com/herbal-antibiotics.html

Low- FODMAP

- FODMAP stands for fermentable oligosaccharides, disaccharides, monosaccharides, and polyols, all of which are particular types of carbohydrate.
- **Excess fructose**: honey, apple, mango, pear, watermelon, high-fructose corn syrup, agave syrup, dried fruit, fruit juice
- **Fructans**: artichokes (globe), artichokes (Jerusalem), asparagus, beetroot, broccoli, Brussels sprouts, cabbage, eggplant, fennel, okra, chicory, dandelion leaves, garlic (in large amounts), leek, onion (brown, white, Spanish, onion powder), radicchio, lettuce, spring onion (white part), wheat, rye, pistachio, inulin, fructo-oligosaccharides.
- **Lactose**: milk, ice cream, custard, dairy desserts, condensed and evaporated milk, milk powder, yogurt, soft unripened cheeses (such as ricotta, cottage, cream, and mascarpone cheese).
- **Galactans**: legumes (such as baked beans, kidney beans, soybeans, lentils, chickpeas).
- **Polyols:** apple, apricot, avocado, blackberry, cherry, longan, lychee, nectarine, pear, plum, prune, mushroom, sorbitol, mannitol, xylitol, maltitol, and isomalt.

Gibson PR, Shepherd SJ. Journal of gastroenterology and hepatology. 2010;25(2):252-258.
http://med.monash.edu.au/cecs/gastro/fodmap/

Elemental Diet

- This approach seeks to starve the bacteria, but feeds the person, by replacing meals for 2 weeks with an Elemental Formula.
- Elemental formula: powdered nutrients in a pre-digested, easily absorbed form.
- The formula studied for SIBO is Vivonex Plus.
- Contains protein as amino acids, carbohydrate as maltodextrin, fat as various oils, and vitamins & minerals.
- **80-84% success in eradicating of SIBO.**

http://www.siboinfo.com/heral-antibiotics.html

4R/5R Framework

Replace

Digestive Enzymes

Betaine HCl Pepsin

Bile

Jones DS, et al. Textbook of Functional Medicine 2010.

4R/5R Framework

Re-establish

Diet

Probiotic

Prebiotics

Probiotics

- Consume probiotic rich foods
  - Kefir
  - Raw Sauerkraut
  - Kimchi
- Probiotic Supplement Success
  - It must contain strains that are normally found in the human gut.
  - It must be able to survive the acidic environment of the stomach and capable of colonizing (i.e., establishing permanent residence in) the G.I. tract.
  - It must be supplemented in concentrations higher than what is found in the gut.
- In clinical trials, probiotics appear to be useful for the treatment of various clinical conditions such as food allergy, atopic dermatitis, and allergic rhinitis.
- Some studies even show improvement in depression symptoms with probiotics

Bischoff SC, et al. (2014). *BMC Gastroenterology, 14*, 189.
Messaoudi, M. (2011). Beneficial psychological effects of a probiotic formulation (Lactobacillus helveticus R0052 and Bifidobacterium longum R0175) in healthy human volunteers. Gut Microbes, 2, 256-261.

Probiotic Supplements

- Soil-Based Organisms
  - Firmicutes, Bacteroidetes, Actinobacteria and Proteobacteria. (Product example Prescript Assist)
  - May be helpful/better tolerated for patients with SIBO since overgrowth can sometimes be from common bacteria such as lactobacillus species
- Saccharomyces boulardii
  - Good for preventing and treating diarrhea
  - Recurrent C-Diff (with other antibiotics)
  - IBD
- VSL #3 (3.6 trillion bacteria per day)
  - Good evidence in treatment of Ulcerative Colitis (Am J Gastroenterol. 2005 Jul;100(7):1539-46)
    - Remission achieved in 53% of patients.
    - Response in 24%

Prebiotics

- Prebiotics are food ingredients that cannot by digested by humans but can be digested by the bacteria in our gut
- Most prebiotics are FODMAPs
  - Start low and go slow!
- Examples
  - Arabinogalactan, beta-glucan, inulin, and oligofructose
  - Partially-hydrolyzed guar gum
    - Suppresses methane production
    - Not a FODMAP
  - SupraFiber
    - Blends of fruits, whole food fiber

4R/5R Framework

Repair

Reduce GI Inflammation

Nutrients for GI Tract cells

Improve tight junctions

Improve Immune Signaling

Guilliams, T. Functional Strategies for the Management of Gastrointestinal Disease. The Standard Road Map Series. Pointe Institute 2016.

Supplements

- **To restore the gut barrier**
  - **L-glutamine**: glutamine is an important nutritional substance for healthy intestinal cells, particularly in the gut, and it's essential in maintaining proper intestinal barrier function.
    - 2-4 grams per day intestinal healing
    - 10-40 grams per day critically ill
  - **MSM and quercetin**: these anti-inflammatory substances can reduce chronic inflammation, which is a major cause of leaky gut.
  - **N-acetyl glucosamine**: N-acetyl glucosamine helps support proper health of the gut mucosa and reduces intestinal permeability.
  - **Mucin**: mucin is a particular kind of protein (glycoprotein) that is normally produced by the intestinal cells. It protects the intestinal lining and reduces inflammation.

Supplements

- **DGL, aloe vera leaf gel, slippery elm, marshmallow, chamomile, and cat's claw**: these botanicals produce a soothing, gel-like substance that coats the digestive tract, which can help heal ulcers and inflamed tissue.
- **Zinc Carnosine:** essential mineral widely recognized for it's role in gut and immune health. Shown to strength GI barrier supporting tight junctions.
- **Serum-Derived Bovine Immunoglobulin** (Medical Food)
  - Improves inflammatory balance, gut barrier function and immune cell counts in duodenal GALT Immune response.
  - Can significantly improve diarrhea

1. Wilson D et al. Evaluation of Clinical Medicine Insights:Gastroenterology. 2013;6:49-60.
2. Asmuth DM, et al. Aids. 2013;27:2207-17.

Extra R..in 5 R Framework

Rebalance

Acupuncture

Biofeedback

Hypnotherapy

Mindfulness

Yoga

Examples of Diagnostic Testing Options

- Genova
  - NutraEval
  - GI Effects
- Diagnostics Solutions Laboratory
  - GI Map
- Doctor's Data
  - GI 360
- ZRT labs
- SpectraCell

Patient Case 1

Case 1

- KT is a 27 y/o female
- Treated for SIBO over the last 9 months with 2 rounds of rifaximin and 1 round of ciprofloxacin
- Symptoms are GERD, bloating, abdominal pain, diarrhea, anxiety, painful periods (3 days with debilitating cramps), frequent colds, rosacea
- Medications:
  - Omeprazole 20 mg twice daily
  - Multivitamin

What potential Medication related nutrient depletions are present for KT?

- Type your answer in the chat box.

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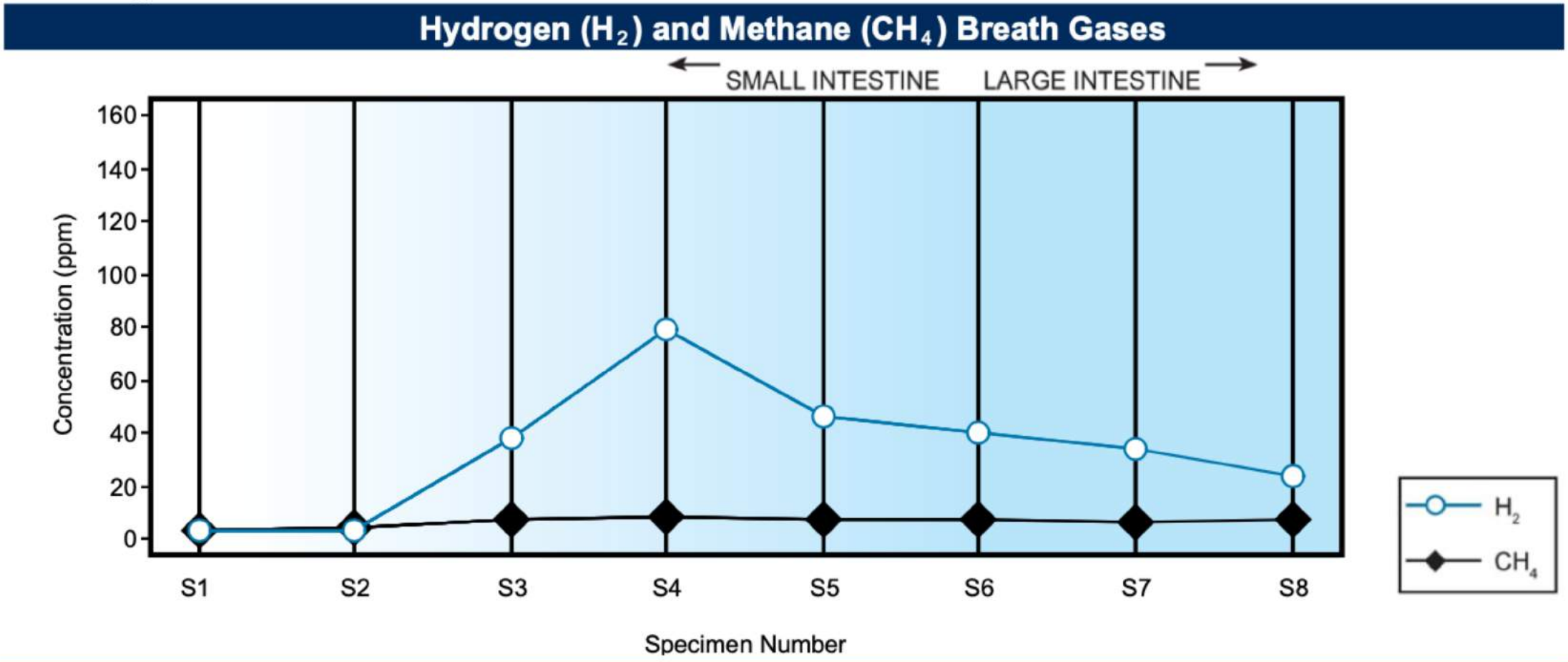
Case 1

- Labs:
  - Ferritin 6 ng/ml (15-150)
  - TSAT 10% (15-55)
  - Vitamin B12 459 (232-1245)
  - B6 7.4 ug/L (2-32.8)
  - Hgb/Hct 10.4/32.6
  - MCV 74 (79-97)
  - CMP, Folate WNL
- Zinc 80 ug/dl (56-134)
- Copper 125 ug/dl (72-166)
- TSH 2.2
- Negative TPO and Thyroglobulin antibodies
- Vitamin D 23.8 ng/ml
- EGD shows esophagitis.

2337 Small Intestinal Bacterial Overgrowth (SIBO) 3 Hour - Breath

Methodology: GC-TDC/SSS



Hydrogen (H_2), Methane (CH_4) and Carbon Dioxide (CO_2) (ppm)								
	Baseline 0 min (S1)	20 min (S2)	40 min (S3)	60 min (S4)	90 min (S5)	120 min (S6)	150 min (S7)	180 min (S8)
H_2	3	3	37	78	46	40	33	23
CH_4	3	4	7	8	7	7	6	7
$H_2 + CH_4$	6	7	44	86	53	47	39	30
CO_2 **	✓	✓	✓	✓	✓	✓	✓	✓
Actual Collection Times								
Actual Time	7:41	8:02	8:21	8:41	9:11	9:42	10:11	10:42
Actual Interval	0 min	21 min	40 min	60 min	90 min	121 min	150 min	181 min

**CO_2 is measured for quality assurance. ✓ indicates the CO_2 level is acceptable. X indicates room air contamination exceeding acceptable limits.

Evaluation for Hydrogen (H_2)

Hydrogen increase over baseline by 90 minutes

	Result		Expected Value
Change in H_2	75	H	<20 ppm

A rise of ≥ 20 ppm from baseline in hydrogen by 90 min should be considered a positive test to suggest the presence of SIBO.

Evaluation for Methane (CH_4)

Peak methane level at any point

	Result	Expected Value
CH_4 Peak	8	<10 ppm

A peak methane level ≥ 10 ppm at any point is indicative of a methane-positive result.

Pathogens		
Bacterial Pathogens	Result	Normal
Campylobacter	**<dl**	<1.00e3
C. difficile, Toxin A	**<dl**	<1.00e3
C. difficile, Toxin B	**<dl**	<1.00e3
Enterohemorrhagic E. coli	**<dl**	<1.00e3
E. coli O157	**<dl**	<1.00e3
Enteroinvasive E. coli/Shigella	**<dl**	<1.00e2
Enterotoxigenic E. coli LT/ST	**<dl**	<1.00e3
Shiga-like Toxin *E. coli* stx1	**<dl**	<1.00e3
Shiga-like Toxin *E. coli* stx2	**<dl**	<1.00e3
Salmonella	**<dl**	<1.00e4
Vibrio cholerae	**<dl**	<1.00e5
Yersinia enterocolitica	**<dl**	<1.00e5
Parasitic Pathogens	Result	Normal
Cryptosporidium	**<dl**	<1.00e6
Entamoeba histolytica	**<dl**	<1.00e4
Giardia	**<dl**	<5.00e3
Viral Pathogens	Result	Normal
Adenovirus 40/41	**<dl**	<1.00e10
Norovirus GI/II	**<dl**	<1.00e7

Patient: Mary Lamme Accession: 20191212-0153

H. pylori

	Result	Normal
Helicobacter pylori	**<dl**	<1.0e3
Virulence Factor, babA	**N/A**	Negative
Virulence Factor, cagA	**N/A**	Negative
Virulence Factor, dupA	**N/A**	Negative
Virulence Factor, iceA	**N/A**	Negative
Virulence Factor, oipA	**N/A**	Negative
Virulence Factor, vacA	**N/A**	Negative
Virulence Factor, virB	**N/A**	Negative
Virulence Factor, virD	**N/A**	Negative

Normal Bacterial Flora

	Result	Normal
Bacteroides fragilis	**8.26e10**	1.60e9 - 2.50e11
Bifidobacterium spp.	**1.56e10**	>6.70e7
Enterococcus spp.	**4.81e5**	1.9e5 - 2.00e8
Escherichia spp.	**1.51e8**	3.70e6 - 3.80e9
Lactobacillus spp.	**4.42e6**	8.6e5 - 6.20e8
Clostridia (class)	**8.02e6**	5.00e6 - 5.00e7
Enterobacter spp.	**2.83e7**	1.00e6 - 5.00e7
Akkermansia muciniphila	**<dl**	1.00e1 - 5.00e4
Faecalibacterium prausnitzii	**1.12e3**	1.00e3 - 5.00e8

Phyla Microbiota	Result	Normal
Bacteroidetes	**1.46e12**	8.61e11 - 3.31e12
Firmicutes	**2.09e11**	5.70e10 - 3.04e11
Firmicutes:Bacteroidetes Ratio	**0.14**	<1.00

Opportunistic Bacteria			
Additional Dysbiotic/Overgrowth Bacteria	Result		Normal
Bacillus spp.	**1.52e6**	**High**	<1.50e5
Enterococcus faecalis	**3.60e2**		<1.00e4
Enterococcus faecium	**5.68e2**		<1.00e4
Morganella spp.	**9.88e3**	**High**	<1.00e3
Pseudomonas spp.	**<dl**		<1.00e4
Pseudomonas aeruginosa	**<dl**		<5.00e2
Staphylococcus spp.	**<dl**		<1.00e4
Staphylococcus aureus	**1.10e3**	**High**	<5.00e2
Streptococcus spp.	**4.79e3**	**High**	<1.00e3
Methanobacteriaceae (family)	**3.41e8**		<5.00e9
Potential Autoimmune Triggers	Result		Normal
Citrobacter spp.	**<dl**		<5.00e6
Citrobacter freundii	**<dl**		<5.00e5
Klebsiella spp.	**<dl**		<5.00e3
Klebsiella pneumoniae	**<dl**		<5.00e4
M. avium subsp. paratuberculosis	**<dl**		<5.00e3
Prevotella spp.	**8.57e6**		<1.00e8
Proteus spp.	**<dl**		<5.00e4
Proteus mirabilis	**<dl**		<1.00e3
Fusobacterium spp.	**9.78e5**		<1.00e8

Fungi/Yeast

	Result	Normal
Candida spp.	**<dl**	<5.00e3
Candida albicans	**<dl**	<5.00e2
Geotrichum spp.	**<dl**	<3.00e2
Microsporidium spp.	**<dl**	<5.00e3
Rodotorula spp.	**<dl**	<1.00e3

Viruses

	Result	Normal
Cytomegalovirus	**<dl**	<1.00e5
Epstein Barr Virus	**<dl**	<1.00e7

Parasites

Protozoa	Result	Normal
Blastocystis hominis	**<dl**	<2.00e3
Chilomastix mesnili	**<dl**	<1.00e5
Cyclospora spp.	**<dl**	<5.00e4
Dientamoeba fragilis	**<dl**	<1.00e5
Endolimax nana	**<dl**	<1.00e4
Entamoeba coli	**<dl**	<5.00e6
Pentatrichomonas hominis	**<dl**	<1.00e2

Worms	Result	Normal
Ancylostoma duodenale	**Not Detected**	Not Detected
Ascaris lumbricoides	**Not Detected**	Not Detected
Necator americanus	**Not Detected**	Not Detected
Trichuris trichiura	**Not Detected**	Not Detected
Taenia spp.	**Not Detected**	Not Detected

Intestinal Health			
Digestion	Result		Normal
Steatocrit	**<dl**		<15 %
Elastase-1	**444**		>200 ug/g
GI Markers	Result		Normal
b-Glucuronidase	**658**		<2486 U/mL
Occult Blood - FIT	**1**		<10 ug/g
Immune Response	Result		Normal
Secretory IgA	**2180**	**High**	510 - 2010 ug/g
Anti-gliadin IgA	**130**		0 - 157 U/L
Inflammation	Result		Normal
Calprotectin	**11**		<173 ug/g

What do we suggest for KT?

Gut healing plan?

What do we suggest for KT?

Nutrient Repletion & Immune Support?

What do we suggest for KT?

Other Testing?

Case #2

- JD is a 35 y/o female presenting to the functional medicine consult with joint pain, fatigue, muscle aches, brain fog, bloating, abdominal pain, and anxiety.
- Hx of Hashimotos, EBV (past infection)
- Strenuous exercise, menstrual cycles, and stress make her symptoms worse.
- Sensitive to artificial fragrances,
- Hx of breast implants- had them removed 6 months ago
- Current medications: Armour Thyroid 120mg once daily

Case #2 Labs

- TSH 1.86 uIU/ml (0.45-4.500)
- Thyroxine (T4) 7.2 ug/dl (4.5-12)
- T3 update 26% (24-39)
- Triiodothyronine (T3) 87 ng/dl (71-180)
- Vitamin D 25-OH 60.2 ng/ml)30-100
- ANA negative
- TPO Positive, 145 IU/ml (0-34)
- CRP 6 mg/L (0-10)
- Sed Rate 14 mm/hr (0-32)

What should be in our work-up?

Hormones?

Nutrients?

Detoxification?

Salivary Hormone Results

Estradiol ♦ pmol/L	6.8

	Reference Range
Follicular	2.8-8.8 pmol/L
Peak *	4.5-19.1 pmol/L
Luteal	2.8-8.2 pmol/L
Menopausal	3.7-9.4 pmol/L
Male	3.1-7.4 pmol/L
* Peak = Days 11 and 12	

Testosterone ♦ pmol/L	<30

	Reference Range
Premenopausal	34-148 pmol/L
Menopausal	34-148 pmol/L
Male	110-513 pmol/L

Estrone pmol/L	64.4

	Reference Range
Menopausal	31.9-183.4 pmol/L

Progesterone ♦ pmol/L	606

	Reference Range
Follicular	17-321 pmol/L
Peak *	151-829 pmol/L
Luteal	33-452 pmol/L
Menopausal	45-370 pmol/L
Male	31-280 pmol/L
* Peak = Days 18 and 20	

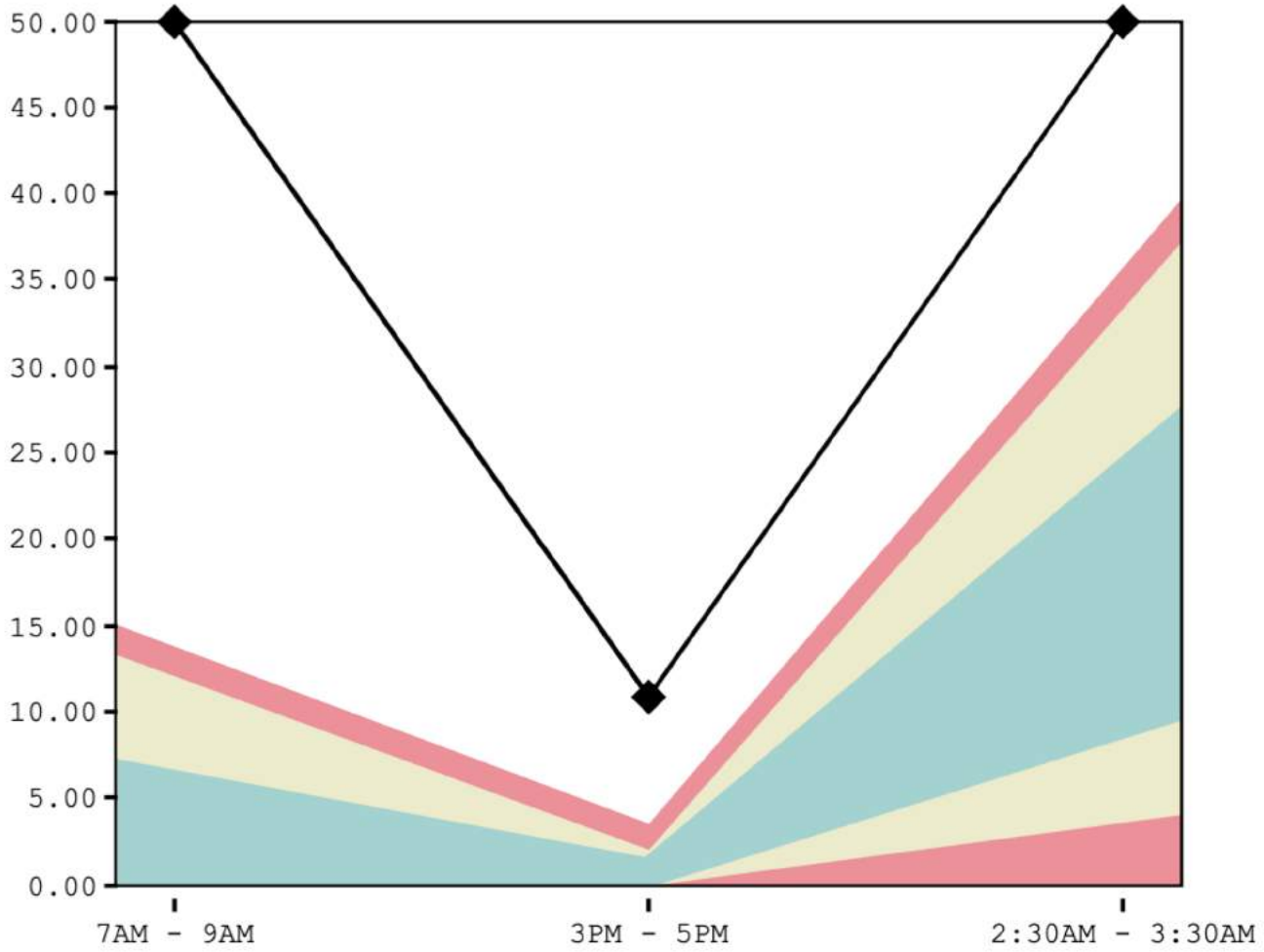
Estriol pmol/L	<70

	Reference Range
Menopausal	<= 133 pmol/L

P/E2 Ratio	89

	Reference Range
Follicular	10-85
Luteal	8-80
Menopausal	12-62

Salivary Melatonin

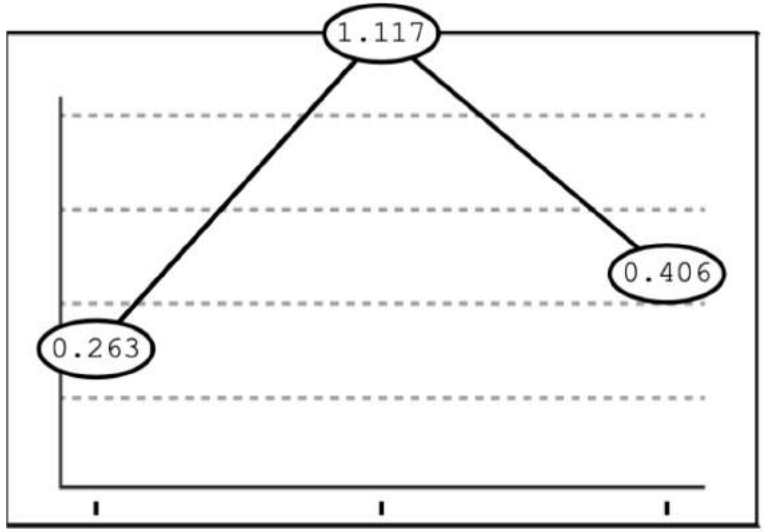


Results

	7AM-9AM*	3PM-5PM*	2:30AM - 3:30AM*
Patient Results (pg/mL) >>	**>50.00**	**10.76**	**>50.00**
Reference Range (pg/mL) *Based on Collection Times	<=12.12	<=1.97	3.71-33.38

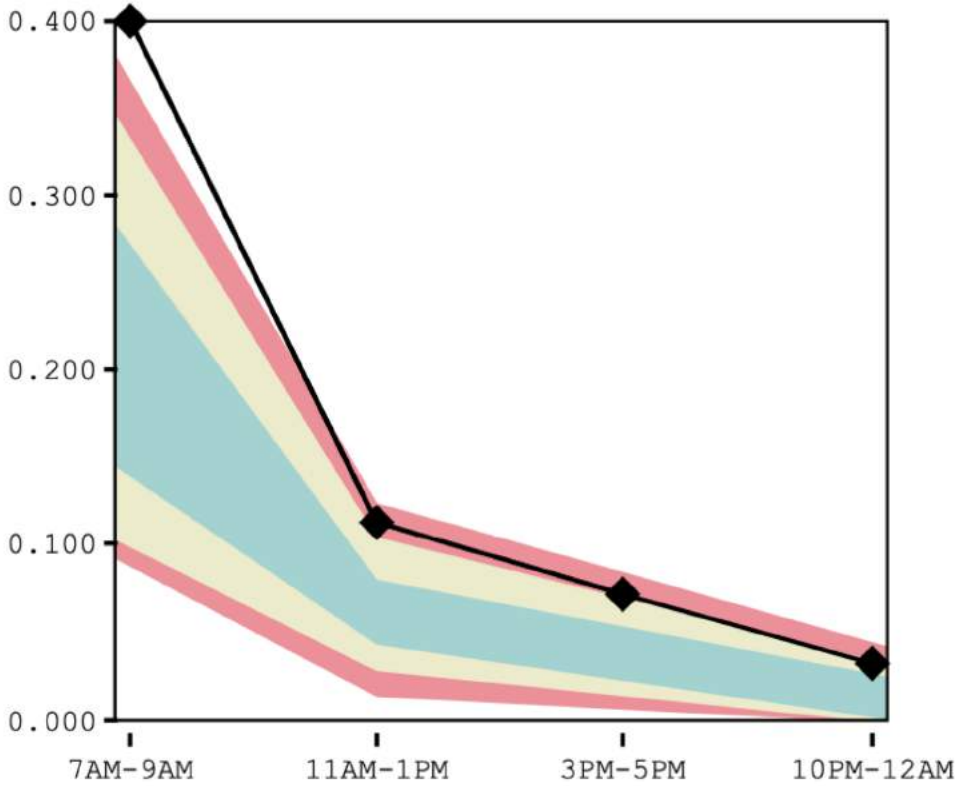
Salivary Cortisol, Cortisol Awakening Response, and DHEA

Cortisol Awakening Response



Percent Increase	325	Expected: >= 50 %

Salivary Cortisol



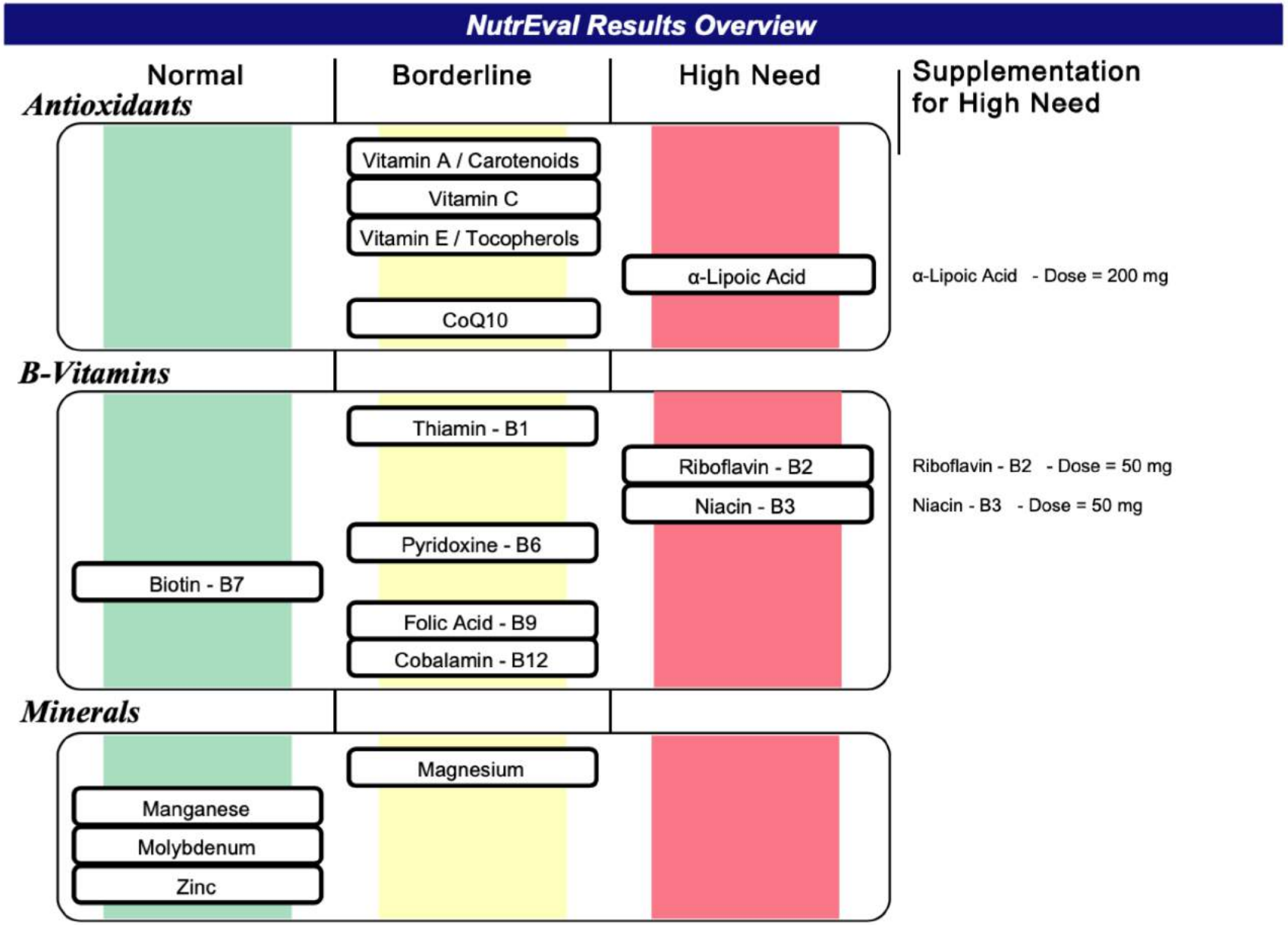
DHEA

		Reference Range
DHEA 7AM - 9AM◆	446	71-640 pg/mL

		Reference Range
DHEA: Cortisol Ratio/10,000◆	1,099	358-2,538

Results

	Waking	30 Minutes	7AM-9AM*	11AM-1PM*	3PM-5PM*	10PM-12AM*
Patient Result (mcg/dL) >>	**0.263**	**1.117**	**0.406**	**0.113**	**0.071**	**0.031**
Reference Range (mcg/dL) *Based on Collection Times	N/A	N/A	0.097-0.337	0.027-0.106	0.013-0.068	<=0.034
Actual Collection Time	6:32AM	7:02AM	8:05AM	12:05PM	4:10PM	10:16PM


NutrEval Results Overview
Normal
Borderline
High Need
Supplementation for High Need
Antioxidants
Vitamin A / Carotenoids
Vitamin C
Vitamin E / Tocopherols
α-Lipoic Acid
CoQ10
α-Lipoic Acid - Dose = 200 mg
B-Vitamins
Thiamin - B1
Riboflavin - B2
Niacin - B3
Pyridoxine - B6
Biotin - B7
Folic Acid - B9
Cobalamin - B12
Riboflavin - B2 - Dose = 50 mg
Niacin - B3 - Dose = 50 mg
Minerals
Magnesium
Manganese
Molybdenum
Zinc

Malabsorption and Dysbiosis Markers

Malabsorption Markers		Reference Range
Indoleacetic Acid (IAA)	5.9	<= 4.2
Phenylacetic Acid (PAA)	0.22	<= 0.12
Bacterial Dysbiosis Markers		
Dihydroxyphenylpropionic Acid (DHPPA)	2.9	<= 5.3
3-Hydroxyphenylacetic Acid	<dl	<= 8.1
4-Hydroxyphenylacetic Acid	28	<= 29
Benzoic Acid	0.14	<= 0.05
Hippuric Acid	165	<= 603
Yeast / Fungal Dysbiosis Markers		
Arabinose	115	<= 96
Citramalic Acid	7.2	<= 5.8
Tartaric Acid	<dl	<= 15

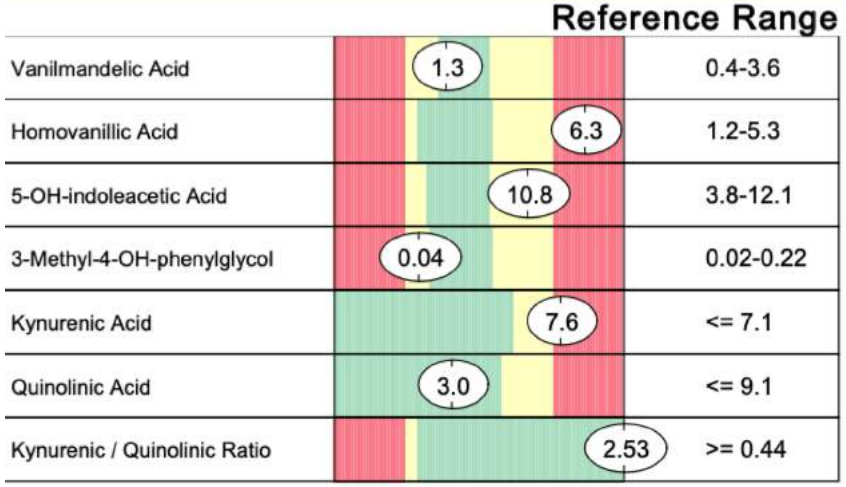
Creatinine Concentration

		Reference Range
Creatinine ◆	4.5	3.1-19.5 mmol/L

Cellular Energy & Mitochondrial Metabolites

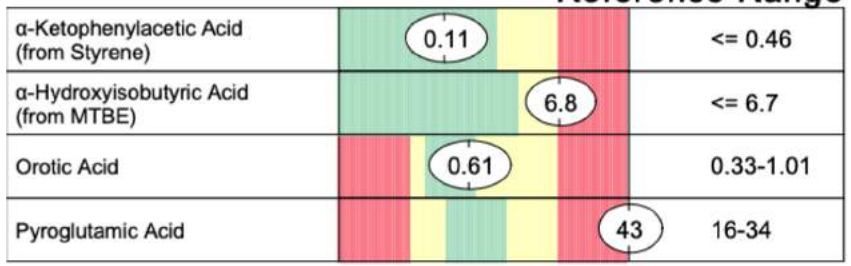
Carbohydrate Metabolism		Reference Range
Lactic Acid	3.7	1.9-19.8
Pyruvic Acid	6	7-32
β-OH-Butyric Acid (BHBA)	2.3	<= 2.8
Energy Metabolism		
Citric Acid	398	40-520
Cis-Aconitic Acid	12	10-36
Isocitric Acid	55	22-65
α-Ketoglutaric Acid (AKG)	<dl	4-52
Succinic Acid	9.1	0.4-4.6
Malic Acid	5.1	<= 3.0
β-OH-β-Methylglutaric Acid (HMG)	4	<= 15
Fatty Acid Metabolism		
Adipic Acid	4.4	<= 2.8
Suberic Acid	2.3	<= 2.1

Neurotransmitter Metabolites



		Reference Range
Vanilmandelic Acid	1.3	0.4-3.6
Homovanillic Acid	6.3	1.2-5.3
5-OH-indoleacetic Acid	10.8	3.8-12.1
3-Methyl-4-OH-phenylglycol	0.04	0.02-0.22
Kynurenic Acid	7.6	<= 7.1
Quinolinic Acid	3.0	<= 9.1
Kynurenic / Quinolinic Ratio	2.53	>= 0.44

Toxin & Detoxification Markers

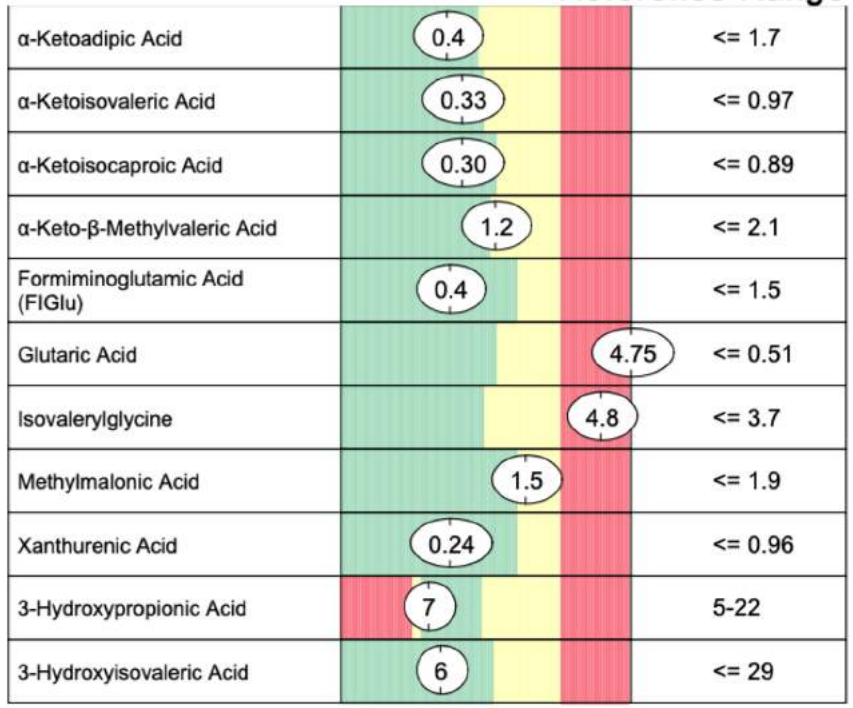


		Reference Range
α-Ketophenylacetic Acid (from Styrene)	0.11	<= 0.46
α-Hydroxyisobutyric Acid (from MTBE)	6.8	<= 6.7
Orotic Acid	0.61	0.33-1.01
Pyroglutamic Acid	43	16-34

Tyrosine Metabolism

		Reference Range
Homogentisic Acid	45	<= 19
2-Hydroxyphenylacetic Acid	0.72	<= 0.76

Vitamin Markers



		Reference Range
α-Ketoadipic Acid	0.4	<= 1.7
α-Ketoisovaleric Acid	0.33	<= 0.97
α-Ketoisocaproic Acid	0.30	<= 0.89
α-Keto-β-Methylvaleric Acid	1.2	<= 2.1
Formiminoglutamic Acid (FIGlu)	0.4	<= 1.5
Glutaric Acid	4.75	<= 0.51
Isovalerylglycine	4.8	<= 3.7
Methylmalonic Acid	1.5	<= 1.9
Xanthurenic Acid	0.24	<= 0.96
3-Hydroxypropionic Acid	7	5-22
3-Hydroxyisovaleric Acid	6	<= 29

Omega 3 Fatty Acids

Analyte	(cold water fish, flax, walnut)	Reference Range
α-Linolenic (ALA) 18:3 n3	<dl	>= 0.09 wt %
Eicosapentaenoic (EPA) 20:5 n3	0.35	>= 0.16 wt %
Docosapentaenoic (DPA) 22:5 n3	1.35	>= 1.14 wt %
Docosahexaenoic (DHA) 22:6 n3	2.9	>= 2.1 wt %
% Omega 3s	4.6	>= 3.8

Omega 9 Fatty Acids

Analyte	(olive oil)	Reference Range
Oleic 18:1 n9	13	10-13 wt %
Nervonic 24:1 n9	4.3	2.1-3.5 wt %
% Omega 9s	17.4	13.3-16.6

Saturated Fatty Acids

Analyte	(meat, dairy, coconuts, palm oils)	Reference Range
Palmitic C16:0	20	18-23 wt %
Stearic C18:0	18	14-17 wt %
Arachidic C20:0	0.23	0.22-0.35 wt %
Behenic C22:0	0.84	0.92-1.68 wt %
Tricosanoic C23:0	0.15	0.12-0.18 wt %
Lignoceric C24:0	2.5	2.1-3.8 wt %
Pentadecanoic C15:0	0.05	0.07-0.15 wt %
Margaric C17:0	0.27	0.22-0.37 wt %
% Saturated Fats	41.5	39.8-43.6

Delta - 6 Desaturase Activity

	Upregulated Functional Impaired	
Linoleic / DGLA 18:2 n6 / 20:3 n6	8.9	6.0-12.3

Cardiovascular Risk

Analyte		Reference Range
Omega 6s / Omega 3s	7.6	3.4-10.7
AA / EPA 20:4 n6 / 20:5 n3	47	12-125
Omega 3 Index	3.3	>= 4.0

Omega 6 Fatty Acids

Analyte	(vegetable oil, grains, most meats, dairy)	Reference Range
Linoleic (LA) 18:2 n6	14.4	10.5-16.9 wt %
γ-Linolenic (GLA) 18:3 n6	0.07	0.03-0.13 wt %
Dihomo-γ-linolenic (DGLA) 20:3 n6	1.61	>= 1.19 wt %
Arachidonic (AA) 20:4 n6	16	15-21 wt %
Docosatetraenoic (DTA) 22:4 n6	2.24	1.50-4.20 wt %
Eicosadienoic 20:2 n6	0.39	<= 0.26 wt %
% Omega 6s	35.1	30.5-39.7

Monounsaturated Fats

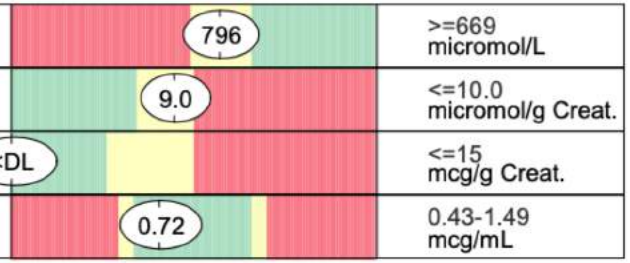
Omega 7 Fats		Reference Range
Palmitoleic 16:1 n7	0.17	<= 0.64 wt %
Vaccenic 18:1 n7	1.02	<= 1.13 wt %
Trans Fat		
Elaidic 18:1 n9t	0.23	<= 0.59 wt %

FUNCTIONAL MEDICINE
Continuing Education

Oxidative Stress Markers

Methodology: Colorimetric, thiobarbituric acid reactive substances (TBARS), Alkaline Picrate, Hexokinase/G-6-PDH, LC/MS/MS, HPLC

	Reference Range
Glutathione (whole blood)	>=669 micromol/L
Lipid Peroxides (urine)	<=10.0 micromol/g Creat.
8-OHdG (urine)	<=15 mcg/g Creat.
Coenzyme Q10, Ubiquinone (serum)	0.43-1.49 mcg/mL



Nutrient Elements

Element	Reference Range	Reference Range
Copper *(plasma)*	134.1	75.3-192.0 mcg/dL
Magnesium *(RBC)*	42.4	30.1-56.5 mcg/g
Manganese *(whole blood)*	10.2	3.0-16.5 mcg/L
Potassium *(RBC)*	2,366	2,220-3,626 mcg/g
Selenium *(whole blood)*	225	109-330 mcg/L
Zinc *(plasma)*	95.4	64.3-159.4 mcg/dL

Toxic Elements*

Element	Reference Range	Reference Range
Lead	1.02	<= 2.81 mcg/dL
Mercury	3.65	<= 4.35 mcg/L
Arsenic	<DL	<= 13.7 mcg/L
Cadmium	0.23	<= 1.22 mcg/L
Tin	0.38	<= 0.39 mcg/L

* All toxic Elements are measured in whole blood.
Methodology: ICP-MS

What do we suggest for ?

Nutrient Repletion & Immune Support?

What do we suggest for KT?

Gut healing plan?

Other Testing?

Take-Aways

1. Dysbiosis and Chronic infections in the gut can lead to impairment of the immune system.
2. A systems-based approach to care, can work to restore immune function.