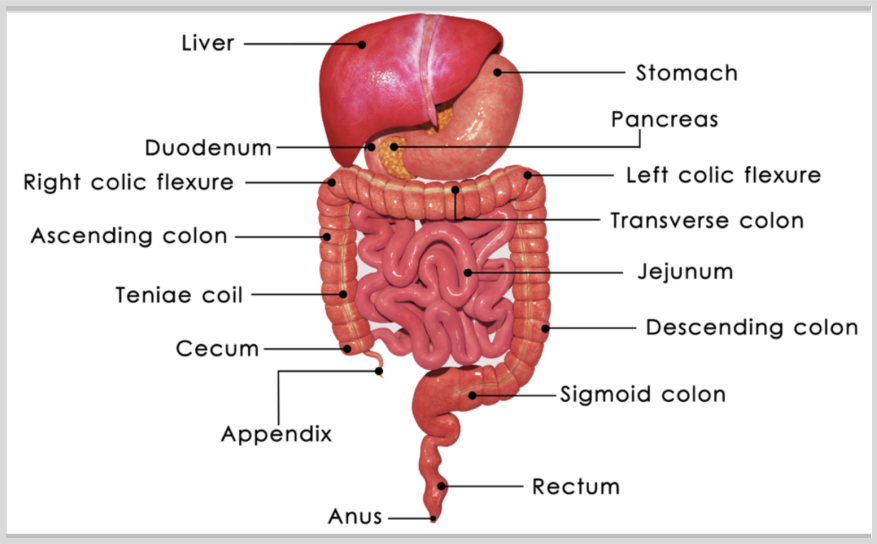
KRESSER INSTITUTE FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

A-CFMP Certification Exam Review Guide

Lesson 1: No Review

Lesson 2: Gut Basic Physiology Review

The gastrointestinal (GI) tract is a hollow tube starting with the mouth and ending with the anus, consisting of the mouth, pharynx, esophagus, stomach and intestines, rectum, and anus, as well as the accessory organs that assist the GI tract like the salivary glands, liver, gallbladder, and pancreas.



The GI tract has two primary purposes:

1. It breaks food into nutrients, which are then absorbed to provide us with energy.
2. It serves as a barrier system that protects against antigens and keeps foreign substances from getting inside the bloodstream and the body.

COMPONENTS OF THE GI TRACT

1. Oral cavity
    - Amylase begins to break down complex carbohydrates.
    - Salivary glands produce immune substances that can assist us in fighting microorganisms that we might be exposed to.
2. Pharynx
    - From the mouth, food passes through the pharynx.
3. Esophagus
    - The esophagus transports substances to the stomach.
4. Stomach
    - The stomach is a J-shaped organ that is divided into four regions: the cardia, the fundus, the body, and the pylorus.
    - The primary functions of the stomach are:
        - Short-term food storage
        - Mechanical breakdown of food
        - Chemical digestion of food via stomach acid and enzymes
        - Killing of ingested microorganisms via stomach acid
        - Absorption of some substances, like alcohol
5. Small intestine
    - Chyme, consisting of food mixed with stomach acid and enzymes, passes into the small intestine from the stomach.
    - The small intestine is composed of three sections. In descending order:
        - The duodenum, which combines enzymes produced in the pancreas and bile salts from the liver
        - The jejunum, where the majority of digestion takes place
        - The ileum, which is the longest segment and empties into the cecum, the first section of the colon

ACCESSORY ORGANS

The Liver

The liver is situated in the upper-right quadrant of the abdomen. Its main role in digestion is to produce bile and metabolize nutrients. All nutrients that are absorbed by the gut pass through the liver, where bile salts break down lipids into smaller particles so that pancreatic enzymes can act upon them.

The Gallbladder

The gallbladder's main function is to store and concentrate bile produced by the liver.

The Pancreas

The primary function of the pancreas is to produce enzymes that break down food. These enzymes include carbohydrases that break down carbohydrates, lipases that break down fat, nucleases that break down nucleic acids, and proteolytic enzymes that break down protein.

We have 10 times more microbes in the human body than human cells!

Gut microbes are crucial to health; they promote normal GI function, protect against infection, regulate metabolism, and are home to a majority of the immune cells in our body.

An altered gut microbiome is implicated in just about every chronic inflammatory disease.

For example, there is a link between the gut and the brain. Problems in the gut, like inflammation, can lead to a higher risk of problems associated with the brain, such as dementia, autism spectrum disorders, neurological conditions, depression, and anxiety.

INFANTS AND THE GUT MICROBIOME

Research has shown that the location of an infant's initial microbiome exposure strongly affects the composition of the infant's gut for several years after and perhaps permanently. This explains why children who are born via C-section are at greater risk for asthma, obesity, type 1 diabetes, and several other conditions.

Babies who are exclusively formula-fed are known to have significant differences in gut microbiota compared to fully or partially breastfed babies. This is important because pioneer bacteria, which are the first bacteria to colonize the infant's gut, have been shown to alter gene expression to create a more favorable environment for themselves and a less favorable

environment for later bacteria.

FACTORS AFFECTING THE GUT MICROBIOME

Several factors are known to influence the gut microbiota, including:

- Diet, proteins, fats, and especially carbohydrates and fiber, or fermentable carbohydrates
- Medications, particularly antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs)
- Chronic stress
- Chronic infections
- Physical inactivity

THREE PRIMARY FUNCTIONS OF GUT MICROBIOTA

1. **Metabolic**
    - Bacteria in the gut break down dietary compounds that might otherwise cause cancer; synthesize vitamins like biotin, folate, and vitamin K; convert non-digestible carbohydrates to short-chain fatty acids like butyrate, which play an important role; provide energy and benefit cells lining the gut; and help with the absorption of minerals like calcium, iron, and magnesium. Microbes also determine how we process and store the food we eat. We know that certain patterns of gut microbes increase energy storage and lead to obesity, whereas other patterns have the opposite effect and tend to lead to a lean phenotype.
2. **Structural**
    - Bacteria ferment carbohydrates to produce short-chain fatty acids like butyrate or propionate. Short-chain fatty acids then stimulate the growth and differentiation of epithelial cells. They also inhibit cell proliferation in the colon.
    - Dysbiosis can lead to the production of endotoxins like lipopolysaccharide (LPS), which activates zonulin, a protein that regulates intestinal permeability via its effect on tight junctions. This LPS production can make the gut barrier more permeable.

3. **Protective**

    - The mucosal lining is the primary interface between the gut and the external environment. The gut contains the gut-associated lymphoid tissue (GALT), which comprises 70 to 80 percent of the immune cells in our body. The microbial composition of the gut has been shown to affect the composition and function of the GALT.

GUT PERMEABILITY

The protein zonulin, discovered by Alessio Fasano, plays a major role in increasing intestinal permeability. Zonulin levels have been shown to be high in celiac disease (CD), type 1 diabetes, multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease (IBD), and other autoimmune conditions. Researchers have found that exposing mice to zonulin induces type 1 diabetes almost immediately. These mice developed leaky gut and then began producing antibodies to cells that are responsible for making insulin.

Several known factors can increase gut permeability, including:

- Diet. For example, increased gut permeability is seen in CD and even non-celiac gluten sensitivity (NCGS).
- Flour, sugar, and seed oils have been shown to alter the gut microbiota, resulting in increased production of LPS, which causes the release of zonulin, thereby triggering leaky gut.
- Things like small intestinal bacterial overgrowth (SIBO); chronic stress; infections like *Helicobacter pylori*, parasites, or bacteria like *Clostridium difficile*; excess alcohol consumption; and medications, particularly aspirin, antibiotics, and acid-blocking drugs like proton pump inhibitors (PPIs) or NSAIDs, can all contribute to leaky gut via their effect on the microbiome.
- Environmental toxins like bisphenol A (BPA) and heavy metals have been shown to contribute to leaky gut.

Lesson 3: Gut Pathology Review

MAIN RISK FACTORS FOR DEVELOPING DIGESTIVE PATHOLOGY

- Having a family history
- Being birthed via cesarean section
- Being formula-fed
- Eating a Standard American Diet
- Having had food poisoning
- Having taken antibiotics or other medications
- Having chronic stress
- Sleep deprivation
- Physical inactivity
- Hypothyroidism
- Hypothalamic–pituitary–adrenal axis dysfunction
- Consuming excessive amounts of alcohol
- Smoking cigarettes
- Exposure to environmental toxins

THE SEVEN PRIMARY GUT PATHOLOGIES

1. Hypochlorhydria and bile/enzyme insufficiency
2. SIBO
3. Parasitic and bacterial infections
4. Dysbiosis and fungal overgrowth
5. Food intolerances
6. Intestinal permeability

7. Autoimmunity

Hypochlorhydria and Bile/Enzyme Insufficiency

The stomach produces hydrochloric acid, which aids the chemical breakdown of food and the absorption of nutrients and protects against pathogens. Research shows four primary consequences of low stomach acid:

1. Increased bacterial overgrowth in the small intestine, or SIBO
2. Impaired nutrient absorption
3. Decreased resistance to infection
4. Increased risk of cancer and other diseases

Low stomach acid leads to bacterial overgrowth, which in turn causes the production of gasses that put pressure on the lower esophageal sphincter. This pressure causes the lower esophageal sphincter to open inappropriately, allowing acid from the stomach to reflux into the esophagus. This condition is called gastroesophageal reflux disease (GERD).

Risk factors for hypochlorhydria include:

- PPIs or any acid-suppressing drugs, chronic stress, bacterial overgrowth, vegetarian diets (which are low in protein and reduce acid production)
- *H. pylori* infection, genetic factors such as polymorphisms and interleukin 1 that promote inflammation associated with hypochlorhydria
- Food poisoning and food intolerances
- Pernicious anemia

Testing for hypochlorhydria

The Heidelberg radiotelemetry test is the most accurate, but it is not commonly used. The hydrochloric acid challenge is another test for hypochlorhydria.

Impaired production of pancreatic enzymes can be caused by low stomach acid, CD, chronic pancreatitis, and excess alcohol intake. Causes of bile production or metabolism issues include impaired liver function, which is where bile is produced; gallbladder problems, where gluten can be a major factor; intestinal dysbiosis; and GI pathology.

Diagnosis of bile and pancreatic enzyme production issues is mostly based on symptoms.

Symptoms of bile insufficiency include poor fat digestion; bitter, metallic taste in the mouth; itchy skin; clay-colored stools; stools that float; and a history of gallstones, malabsorption of protein, fat, and carbohydrates.

Fecal elastase is a useful marker for poor enzyme production.

Small Intestinal Bacterial Overgrowth

Risk factors of SIBO

- Poor diet
- Low stomach acid
- Antibiotic use
- Acid-suppressing drugs
- Impaired function of the migrating motor complex (MMC)
- Constipation
- Gut infections
- Structural abnormalities of the GI tract
- Immune dysfunction

SIBO is more likely in people with irritable bowel syndrome (IBS), metabolic disorders, CD, chronic constipation and diarrhea, long-term antibiotic use, and other organ dysfunction, particularly liver disease and pancreatitis, both of which can alter the function of the MMC, and in the elderly.

Consequences of SIBO

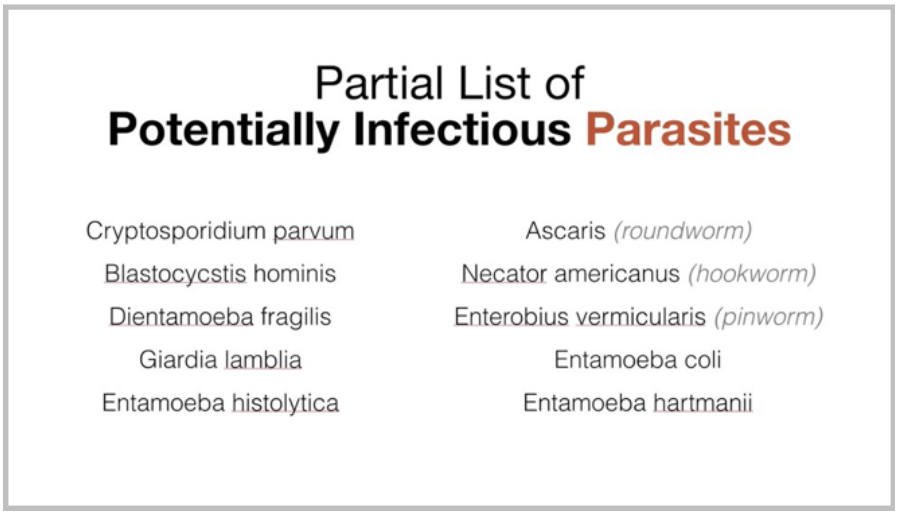
- Decreased vitamin/mineral absorption and related conditions (anemia, neuropathy, etc.)
- Carbohydrate malabsorption leading to a vicious cycle
- Gas production leading to bloating, pain, constipation, and/or diarrhea
- Autoimmunity from increased permeability and efflux of bacteria/LPS
- Decreased fat absorption from bacterial deconjugation of bile salts
- Protein malabsorption due to the prevalence of bacteria that digest protein

- Intestinal permeability and damage to the lining of the small intestine mucosa
- Neurological symptoms from toxins produced by bacteria

Diseases and health problems associated with SIBO

- Acne vulgaris/rosacea
- Anemia
- Atrophic gastritis
- CD
- Cystic fibrosis
- Diabetes
- Diverticulitis
- Fibromyalgia
- Gastroparesis
- GERD
- Hepatic encephalopathy
- IBD
- IBS
- Intestinal permeability
- Liver cirrhosis
- Muscular dystrophy
- Non-alcoholic fatty liver disease
- Parkinson’s disease
- Restless leg syndrome

Parasitic and Bacterial Infections



Parasitic Infections

Some of these parasites are considered by most researchers and physicians to be non-pathogenic commensals, meaning they can be normal residents of the digestive tract—"old friends" that may provide some benefit to the host like *Necator americanus*, or hookworm. Others are considered unequivocally pathogenic, like *Giardia* and *Cryptosporidium*.

Risk factors for parasites

Risk factors include consuming contaminated food and water, increased use of daycare centers, travel to developing countries, household pets, consumption of uncooked foods, antibiotic use, insect vectors, and sexual contact.

Symptoms associated with parasitosis are often general and nonspecific. They vary from fatigue and malaise to GI distress, diarrhea, and constipation to brain fog, sleep disturbance, or skin issues.

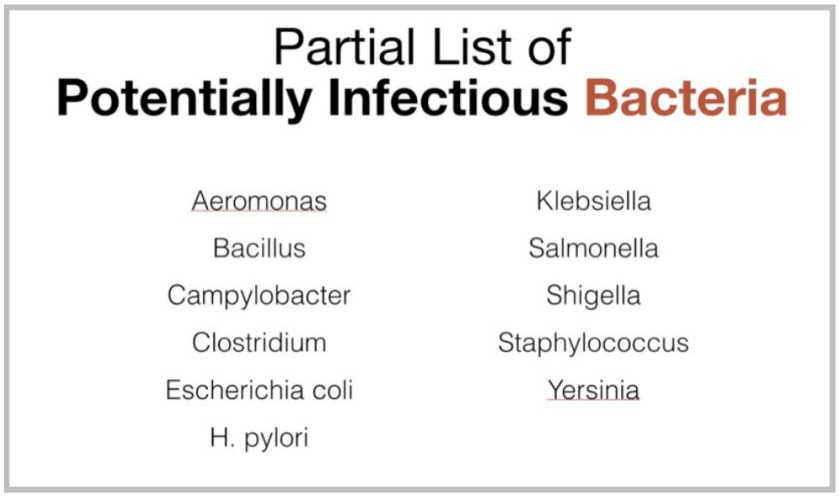
Patients may present with cyclical symptoms because parasites have lifecycles that can influence their pathogenicity in the host. So one red flag for parasitic infection is if someone feels relatively normal, and then they feel really rotten, and then they feel normal again, and that alternates in a consistent way. Patients may have **no GI symptoms**.

Diagnosis

Parasites are notoriously difficult to detect. One reason is that they can assume different forms, like the cystic form that is dormant in tissue and not shed in the stool.

Use labs that specialize in parasite detection, and use different methods like stool microscopy, proteomic analysis, and immunological essays like fecal antigen together because you increase the likelihood of catching something that would be missed using only one methodology.

Bacterial Infections



Bacterial infections can be self-limiting and require no treatment, whereas others can become chronic, requiring treatment.

Symptoms can range from mild GI discomfort to severe pain.

Studies have found that transient, self-limiting infections can have chronic consequences. For example, *Campylobacter*, which causes food poisoning, has been associated with subsequent reactive arthritis, IBS, delayed gastric emptying, dyspepsia, chronic constipation, and diarrhea.

Another is post-infectious IBS caused by *Giardia* infection. It's also possible that some infections that are currently considered to be self-limiting have chronic expressions.

Dysbiosis and Fungal Overgrowth

Dysbiosis is a situation where there's an underrepresentation of beneficial microbes and an overrepresentation of harmful microbes.

For example, *Candida* is a normal resident of the human GI tract. However, *Candida* can become overrepresented when levels of beneficial microbes that protect against that colonization are low. *Candida* colonization has been shown to promote low-level inflammation, delay healing of inflammatory lesions, and potentially elevate levels of pro-inflammatory cytokines like interleukin 17.

Overall, host immune status and the body's own ability to protect against unfavorable overgrowth also influence gut dysbiosis and fungal overgrowth.

Symptoms range from obvious things like GI discomfort to less obvious symptoms like depression, anxiety, brain fog, attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder, skin disease, and neurological problems.

Disrupted gut microbiota can lead to the production of compounds that have a neurotoxic effect and to inflammatory cytokine production, which can suppress the activity of the frontal cortex and cause all kinds of other problems.

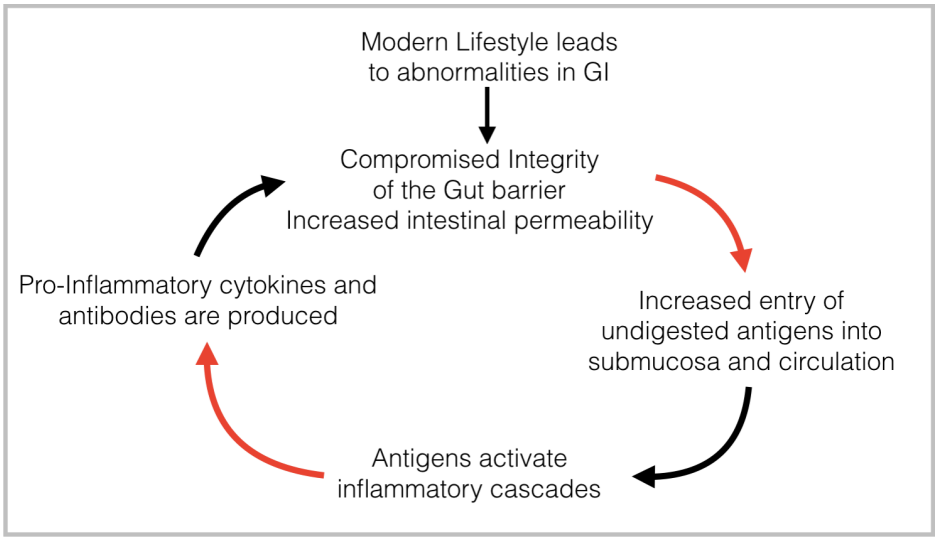
Diagnosis:

- Stool tests
- Some markers on urine organic acids tests, like D-arabinitol for fungal overgrowth

Food Intolerances

In many cases, food intolerances are a consequence of other pathologies, such as disrupted gut microbiome, SIBO, or intestinal permeability. However, food intolerances can also cause problems like intestinal permeability. Thus, food intolerances need to be addressed independently.

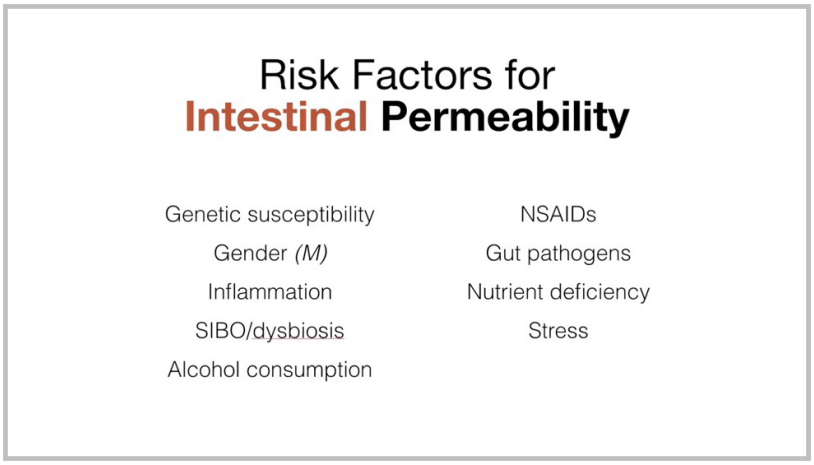
Intestinal Permeability



Intestinal permeability was formerly known as leaky gut. Respected researcher Dr. Alessio Fasano, who is well-known for his discovery of zonulin, a protein that regulates tight junction permeability, believes that leaky gut is actually a precondition to developing autoimmunity, along with genetic vulnerability and environmental triggers.

Testing for intestinal permeability

The two primary methods used are the lactulose-mannitol test and the antigenic intestinal permeability screen.



Autoimmunity

IBD, primarily Crohn's disease and ulcerative colitis.

Ulcerative colitis is restricted to the colon or rectum and affects only the superficial layer of the mucosa.

Crohn's disease can occur anywhere in the GI tract and can affect all layers of the GI tract.

Risk factors for IBD

- Genetics
- Cigarette smoking
- Diet
- Physical inactivity
- Obesity
- Infections
- Antibiotics
- NSAIDs
- Oral contraceptives
- Chronic stress
- Sleep deprivation

Symptoms of IBD

- Bleeding, abscess, fistulas, and vitamin B12 deficiency
- Extra-intestinal symptoms like skin conditions, arthritis, kidney stones, osteoporosis, macrocytic anemia, pulmonary involvement, and eye disease (many of which are related to nutrient deficiencies that can be caused by IBD)

Testing

- IBD is often diagnosed by colonoscopy, endoscopy, or capsule endoscopy.
- Basic blood markers include erythrocyte sedimentation rate and C-reactive protein.

- Newer antibodies include ASCA, ANCA, anti-OMPC, and anti-CBIR.
- Stool markers for IBD include calprotectin, lactoferrin, and lysozyme.

Lesson 4: Gut Diagnosis Cyrex Array 3X Review

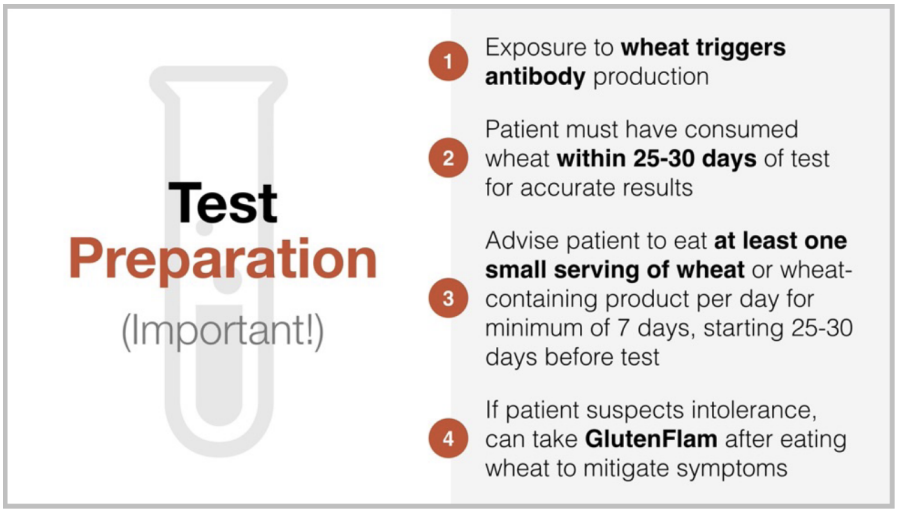
TESTING FOR WHEAT AND GLUTEN SENSITIVITY

Typically, gastroenterologists screen for CD with antibodies to alpha-gliadin, transglutaminase-2 (tTG2), and sometimes deamidated gliadin and endomysium. If the tests are positive, a biopsy might be performed to determine if tissue damage or enteropathy is present.

However, patients are often missed if these are the only markers tested. Research shows that people can and do react to several other components of wheat. These include other epitopes of gliadin like beta-gliadin, gamma-gliadin, and omega-gliadin; glutenin; wheat germ agglutinin; gluteomorphin; other types of tissue transglutaminase aside from tTG2, including type 3, which is primarily found in the skin, and type 6, which is primarily found in the brain and nervous system tissue. Patients may not have GI symptoms!

Who should be tested?

1. Anybody who is currently eating wheat and gluten
2. Anyone who wants to eat wheat and gluten, even if only occasionally



Cyrex Array 3X Markers

Wheat Immunoglobulin G/Immunoblobulin A (IgG/IgA)

- This is a very general marker for wheat intolerance and is associated with a wide range of conditions.
- It cross-reacts with rye, barley, and soy.

Non-gluten Proteins A and B

- Non-gluten proteins make up the remainder of the wheat proteome.
- Several non-gluten proteins, including α-amylase/protease inhibitor, thiol reductase, serine protease inhibitor (serpin), and β-amylase, have been identified as potent allergens in immunoglobulin E (IgE)-mediated wheat allergy and baker's asthma.

Gliadin Toxic Peptide

- It is a strong indicator of possible CD, Crohn's disease, and other chronic inflammatory processes.
- This peptide lies within the larger gluten protein and has proven to be exceptionally resistant to digestion. The ability to identify a reaction to gliadin toxic peptide allows patients to remove the trigger before the intestinal barrier becomes damaged and causes serious long-term health issues.

Alpha-Gliadin

- Gliadins are a class of protein present in wheat and several other grains, with gluten itself being made up of a fairly even mix of gliadins and glutenins.
- Alpha-gliadin antibodies are elevated in CD and may also be elevated in NCGS.
    - Also associated with autism spectrum disorders and wheat allergy
    - May cross-react with cerebellar proteins
- If antibodies to tTG-2 are also present, this is most consistent with CD.
    - Confirmation with biopsy may be considered.

Omega-Gliadin

- This is another type of gliadin that may be associated with CD, exercise-induced anaphylaxis, and wheat allergy.
- Omega- and gamma-gliadin antibodies are not routinely tested in conventional medicine.

Gamma-Gliadin

- Suspected to play a significant role in the pathogenesis of CD.

Glutenin

- Glutenin is the other major fraction of gluten protein.
- Antibodies IgG and IgA to glutenin are found in patients with CD.
- IgA antibodies to glutenin are found in dermatitis herpetiformis.

Wheat-Germ Agglutinin (WGA)

- Antibodies to WGA associated with CD, diabetes, GI disorders, and IgA nephropathy.

Diamidated Gliadin

- Associated with CD and autism spectrum disorder.
- Cross-reacts with numerous tissues and proteins, including myelin basic protein, synapsin, myocardial peptide, dairy products, corn, and oats.
- May be a cause of hidden food sensitivities since it's used in many different roles for a variety of prepared/baked foods.
- Randomized controlled trials have shown that even people who don't react to wheat flour can react to deamidated gliadin peptides.

Gluteomorphin and Prodynorphin

- Gluteomorphin and prodynorphin are opioids produced from wheat, and antibodies to these opioids may indicate that gluten is affecting a patient's brain.
- In patients with antibodies to these opioids, beginning a gluten-free diet may cause symptoms of withdrawal.
- Such antibodies are associated with autism spectrum disorder, attention deficit disorder/ADHD, CD, NCGS, and behavioral problems in children.
- Gluteomorphins also bind to lymphocytes and alter messages they send to the brain, potentially disrupting mood and causing cognitive symptoms.

Gliadin-Transglutaminase Complex

- Associated with CD.
- These complexes can adhere to intestinal walls. They are recognized by antigen-presenting cells and trigger an immune response.

Transglutaminases are a family of enzymes that form protein polymers, essential in the formation of barriers and structures such as gut tissue. Antibodies may appear in serum before the clinical onset of symptoms.

Tissue Transglutaminase-2

- Commonly recognized as a diagnostic test for CD.
- Transglutaminase-2 is an enzyme in the digestive tract targeted in an autoimmune attack triggered by gluten.

Tissue Transglutaminase-3

- Transglutaminase-3 is expressed mainly in the skin and to a lesser extent in the placenta and the brain.

Tissue Transglutaminase-6

- Transglutaminase-6 is expressed in neural tissue.

- Antibodies to tTG-6 may be associated with gluten reactivity-related neurological dysfunction such as gluten ataxia.

Microbial Transglutaminase

- Microbial transglutaminase is an enzyme produced by bacteria, which can send signals impacting brain and nervous system function.
- Patients who consume gluten substitutes may have a reaction to the non-tissue transglutaminase contained within these foods.

In Functional Medicine, most equivocal results should be considered positive.

Silent CD

Several studies show that the **majority of patients with CD** don't test positive for antibodies to alpha-gliadin or transglutaminase-2. This is especially true when **GI enteropathy** is mild.

- For every one case of diagnosed CD, there are **6.4 cases undiagnosed**.
- Silent CD is every bit as harmful as obvious CD (possibly more, since unrecognized).
- The reason CD is so often missed is that tests rely only on alpha-gliadin and tTG2 antibodies, and one in two new patients diagnosed with CD **doesn't have gut symptoms**.

See the Clinician Handout "Interpretation of Antibodies Against Wheat, Gluten and Enzyme Antigens" for a review of Cyrex 3X pattern recognition.

Lesson 5: Gut Diagnosis Cyrex Array 4 Review

TESTING FOR CROSS-REACTIVE PROTEIN INTOLERANCE AND OTHER FOOD SENSITIVITIES

Cyrex Array 4 tests for gluten-associated cross-reactive foods and food sensitivities. Since there is antigenic similarity across proteins in dairy, grains, eggs, and other foods, some patients who are going gluten-free still have symptoms. The Cyrex Array 4 tests for sensitivities for a wide range of non-gluten-containing foods.

Who should get tested?

- Anyone still experiencing symptoms on a gluten-free diet
- Anyone who wants to consume the foods on Cyrex Array 4 and wants to know their reactions to them

Test preparation

- Patient must have consumed a food on the Cyrex Array 4 within 25 to 30 days of the test for accurate results.
- Patients can either try to consume each food on the test within 25 to 30 days or only those they wish to test.

Most common cross-reacting foods

- Not everyone with gluten intolerance will react; these are just the biggest concerns.
- Other foods may cause issues via other mechanisms.

Foods known to **cross-react with gliadin**

Foods known to cross-react with **purified alpha-gliadin-33-mer**

Cow's milk	Gluten grains *
α + ß Casein	Yeast
Casomorphin	Oats
Milk butyrophilin	Millet
Whey protein	Rice
Chocolate (milk)	Corn

* Polish wheat is also known as Camel's wheat, Egyptian wheat and Kamut®

Adapted from: Cyrex Array 4 Clinical Applications Guide (http://cyrexlabs.com)

Specific Markers

Rye, barley, spelt, and Kamut®

- Gluten-containing grains
- Cross-react with sesame seed, omega-gliadin, and wheat, barley, and soy flours

Yeast

- *Saccharomyces cerevisiae*: yeast used as a leavening agent in baking and as a fermenting agent in brewing
- Cross-reacts with *Candida albicans*, multiple bacteria, human colon tissue, and gliadin
- Patients with antibodies to yeast should be screened for intestinal permeability

Buckwheat

- Gluten-free, but some studies show antigenicity with patients with CD and NCGS
- Cross-reacts with latex; patients with buckwheat reactivity should avoid latex products

Milk butyrophilin

- Protein of the milk fat globule membrane
- Cross-reacts with myelin oligodendrocyte glycoprotein and gliadin

Oats

- Oats do not contain gluten unless cross-contaminated.
- Cross-reacts with gliadin.

Coffee

- According to Cyrex, it has the highest cross-reactivity with gliadin!
- Important notes:
    - Cyrex tests for instant coffee antigen, which has shown to be wheat contaminated.
    - Whole coffee beans not contaminated with wheat do not show gliadin cross-reactivity.
- Cross-reacts with gum arabic.

Teff

- Used to make injera, an Ethiopian flatbread, and sometimes found in gluten-free baked goods
- Very little published research
- Probably one of the safest gluten-free alternatives

Potato

- Sensitivity to potato is rare and more often occurs in children (who usually outgrow it)
- Cross-reacts with corn/maize

Casein

- Protein in milk and other dairy products
- Most common food intolerance in kids
- Cross-reacts with gliadin, cerebellar, and soy
- Up to 50 percent of patients with CD are intolerant of casein/dairy

Sorghum

- Traditionally used as a sweetener
- Common ingredient in gluten-free baked and processed goods and gluten-free beer
- Cross-reacts with corn and millet

Millet

- Consumed as whole grain; also commonly found in gluten-free cereals, baked products, crackers, etc.
- Cross-reacts with sorghum, rice, gliadin
- Goitrogenic; patients with thyroid disease should be cautious

Egg

- Egg sensitivity is more common in kids than adults; kids will often outgrow it.
    - Cooked egg introduced at four to six months may protect against allergy.
- Some patients may react only to the white or only to the yolk (run Cyrex Array 10 to find out; Array 4 tests combined white/yolk antigen)

Rice

- Consumed as whole grain and is a common ingredient in gluten-free foods
- Cross-reacts with wheat, gliadin, corn/maize, soy, and millet

Casomorphin

- Opioid peptide formed from undigested casein
- Cross-reacts with cerebellar and gliadin

Whey protein

- Cross-reacts with gliadin
- Dried whey contains lactose and should be avoided by patients with lactose intolerance

Hemp protein

- Used in gluten-free products and as a source of protein and polyunsaturated fatty acid (hemp oil)
- Very little published research

Amaranth

- Consumed as whole grain; also commonly used in gluten-free cereals and baked goods
- Cross-reacts with quinoa, rice, and sunflower

Quinoa

- Consumed as whole grain; common ingredient in gluten-free cereals and baked goods
- Cross-reacts with amaranth, rice, and sunflower

Tapioca

- Also known as yuca, cassava, or manioc
- Tuber that is cooked and eaten peeled, as pudding or flatbread, and in gluten-free products
- Cross-reacts with banana, avocado, chestnut, and kiwi

Sesame

- Common ingredient in baked foods, processed foods, and tahini
- Cross-reacts with almonds, kiwi, poppy seeds, hazelnuts, and rye

Chocolate milk

- This antigen is a combination of milk and chocolate, known to cross-react with gliadin
- Cross-reacts with tobacco, ragweed leaves, and instant coffee

Soy

- Used to make milk, tofu, soy sauce, fermented bean paste, natto, tempeh, and oil

- Extremely common ingredient in processed foods
- Cross-reacts with birch pollen, cow's milk, and casein
- Studies suggest that soy allergy is becoming more common

Corn

- Eaten whole, also in vegetable mixes, breads, stews, soups, chili, salsa, supplement/pharmaceutical fillers, and much more
- Processed into syrup and used as a sweetener for beverages, treats, and pre-packaged foods
- Cross-reacts with potato, rice, soy, and gliadin

Not all the antigens listed on Cyrex Array 4 cross-react with gliadin.

Also, cross-reactivity does not happen in all cases.

CUSTOMIZING PALEO: MACRONUTRIENT RATIOS

The primary focus is mostly on carbohydrate intake as the most variable macronutrient and the easiest one to work with. Protein is important, as well, but it doesn't typically require as much adjustment, and fat will adjust in an inverse way, typically, with carbohydrates. So as carbohydrate consumption goes up, fat will naturally go down; as carbohydrate consumption goes down, fat will naturally go up.

	% Carbs	Carbs (Grams) for Men (2600 kcal diet)	Carbs (Grams) for Women (2000 kcal diet)	Goal/Population
Very Low Carb	<10%	<65g	<50g	• Neurological issues (Epilepsy, Alzheimer's, etc.) • Severe blood sugar problems
Low Carb	10-15%	65-100g	50-75g	• Weight loss • Blood sugar regulation • Mood disturbances • Digestive problems
Moderate Carb	15-30%	100-200g	75-150g	• Generally healthy • Maintain weight • Adrenal fatigue • Hypothyroidism • Familial Hypercholesterolemia
High Carb	>30%	>200g	>150g	• Athletes and highly active people • Trying to gain weight/ muscle • Fast metabolism • Pregnant/breastfeeding

GUT DIAGNOSIS CYREX ARRAY 10

Cyrex Array 10 is the newest reactivity test. It tests reactivity for 180 antigens, basically, everything Array 3 and Array 4 do not test for. Unlike most tests, it tests for cooked foods in addition to raw foods. Additionally, it tests for combined proteins. Combined proteins occur when food proteins combine in a day-to-day diet.

Who should get tested?

- Anyone still experiencing symptoms after going on a gluten-free diet
- Anyone with ongoing symptoms that have not resolved after addressing gut pathologies (and other pathologies)

Test Preparation

- Exposure to particular foods is what triggers antibody production, so the patient must have consumed foods on Cyrex Array 10 within 25 to 30 days of the test for accurate results.
- Since the purpose of Cyrex Array 10 is to identify foods still causing symptoms in their day-to-day diet, it's best to have them continue their normal diet leading up to testing.

Results

- Equivocal: represents the range between normal and low-positive results.
- Advise patients to remove both equivocal and positive foods.
- Equivocal foods can be reintroduced one at a time, after at least 30 (preferably 60) days, with three to five days between reintroduced foods.

Specific tests

Cross-reactive, pan-antigen isolates

- Some food antigens cross-react with human tissue and cause autoimmunity, inflammation, etc.
- Cross-reactive antigens include gliadin, casein, food aquaporin, shrimp tropomyosin, and fish parvalbumin.
- Pan-antigens are proteins found in multiple foods.

- They include shrimp tropomyosin, fish parvalbumin, and hevein, found in latex and some fruits, nuts, and vegetables.

Large gum molecules

- Gums are present in many processed foods, especially gluten- and dairy-free products, and can cross-react with other food proteins.
- They are found in soups, juices, jams, salad dressings, soy products, dairy products such as milk and yogurt, and dairy alternatives (nut/soy milk).

Binding isolates

- Lectin and agglutinin are binding isolates found in about 30 percent of foods.

Tissue-bound food coloring

- Artificial food colors used extensively in processed foods that may create sensitivity for otherwise tolerated foods

Amplified antigenic proteins

- Specific proteins and peptides that are smaller compounds within larger food proteins.
- These include shrimp tropomyosin, shrimp protein, cashew vicilin, cashew proteins, pineapple bromelain, pineapple proteins, rice endochitinase, and rice proteins.
- A patient may test negative for the whole protein antigen but positive for the specific peptides.

Oleosins

- Oil proteins found in seeds and nuts.
- Some patients may not react to proteins in nuts and seeds but may react to oleosins.

Meat glue

- Meat glue (aka transglutaminase or thrombin) is a powder used in food processing to “glue” smaller pieces of meat together into one larger piece.
- Patients may react to the meat glue, while not reacting to the meat itself.

Dual antibody detection

- IgA is an indication of the mucosal immune response, and IgG is an indication of the circulatory immune response.

Lesson 6: Gut Diagnosis Stool Testing Review

The two primary categories of techniques for stool testing are:

1. Culture-based techniques:
    - Includes high-complexity culture and proteomic-based spectrometry (matrix-assisted laser desorption/ionization time-of-flight [MALDI-TOF]) stool testing.
    - One limitation of culture-based methods like MALDI-TOF is that they rely on successfully culturing the microbe first. Because less than 5 percent of microbes in the human gut are typically picked up using commercial laboratory cultures, the MALDI-TOF method does not tell us about abundance.
2. Molecular or sequence-based techniques:
    - **DNA-polymerase chain reaction (PCR)** - very accurate for identifying microorganisms but requires a specific primer for each microorganism, which increases the cost for the lab. DNA-PCR may be able to provide susceptibility information, but the use of this is still clinically limited.
    - **16s rRNA gene sequencing** - identifies bacteria at a genus level, without species or strain information. There's no eukaryote, fungi, or parasite testing, so it's not comprehensive.
    - **Whole-genome sequencing** - likely to provide more information on microbial richness and diversity, but the clinical utility at this stage is still lacking and it needs to be combined with other stool testing techniques to provide well-rounded results and data.

Overall, when the goal is to use the stool test diagnostically on an individual subject and apply that information to make clinical decisions, we feel that combining multiple methodologies is best because it allows you to capture a wide array of data.. If having to decide on one, the most appropriate methodology is PCR, and a quantitative method such as qPCR is preferred. In our opinion, a false negative is a bigger risk to the patient/client than a false positive, especially because the first round botanical treatments are generally safe and well tolerated.

LAB COMPANIES AND TESTS

Doctor's Data: GI360 Profile

- Uses multiplex PCR technology, coupled with the MALDI-TOF proteomics

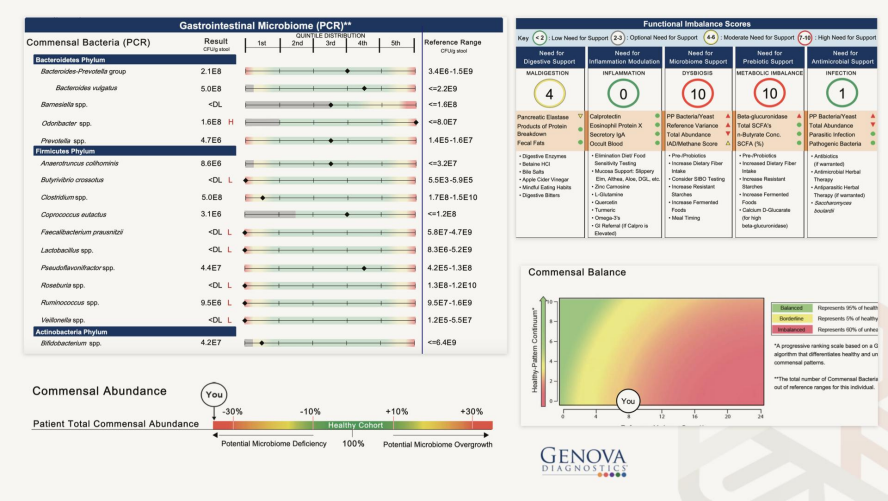
Genova Diagnostics: GI Effects Comprehensive Stool Profile

- Uses a combination of PCR, culture, and microscopic methods.

Diagnostics Solutions Lab (DSL): GI-MAP | GI Microbial Assay Plus

- Relies exclusively on qPCR, so it requires a bit more clinical correlation with symptoms and toxin testing to determine appropriate treatment since the presence of DNA material or pathogenic strain does not always indicate illness.

BENEFICIAL BACTERIA



In this Genova Diagnostics report, commensal balance and abundance are reported in several ways. We can see it's a case of dysbiosis that is in part insufficiency or lack of beneficial bacteria and also pretty significant overgrowth of a couple of pathogenic species. When insufficiency dysbiosis is the primary imbalance, rebuilding the beneficial bacteria with pre and probiotics is often warranted.

POTENTIAL PATHOGENS

Klebsiella

- It can be a normal resident of the digestive tract but can become overgrown in dysbiosis and has been reported in IBS and other gut issues.
- It is associated with joint pain and autoimmune conditions like ankylosing spondylitis, reactive arthritis, and rheumatoid arthritis.
- When you see a positive result for *Klebsiella*, especially in someone with joint pain, you should run the HLA-B27 test.
- Patients with ankylosing spondylitis have elevated levels of antibodies to *Klebsiella*. The theory is this is due to molecular mimicry. Only a small percentage of people with the HLA-B27 gene develop ankylosing spondylitis, which suggests there may be an environmental trigger.

Citrobacter freundii

- A facultative aerobic gram-negative bacilli of the *Enterobacter* family and close relative of the better-known food poisoner, *Salmonella*.
- Often found in soil, water, sewage, food, and intestinal tracts of animals and humans

Heliobacter pylori

- Associated with stomach and duodenal ulcers
- Possibly increases the risk of gastric cancer

H. pylori: pathogen or not?

1. Dr. Martin Blaser gathered evidence suggesting that *H. pylori* is not always harmful. It may even be helpful in some circumstances. Dr. Blaser's research shows that *H. pylori* has beneficial functions that actually begin in infancy if a baby acquires it. For example, it appears to protect against the development of allergies and asthma and decreases ghrelin and increases leptin, which can help regulate appetite.
2. Other factors determining the pathogenicity of *H. pylori* include the strain and host environment.
3. Considerations should be taken when deciding when and how to treat different patient populations.

Treatment decision

Children	Young adults (<30)	Older adults (>30)
No evidence that eliminating H. Pylori results in benefits	Evidence is unclear	Benefits may outweigh potential harm, but full eradication may not be necessary
Some evidence that eradication may cause harm	May be beneficial, but may also be harmful (increased risk of obesity, allergies, asthma)	Eradication of H. Pylori may increase esophageal cancer, Gerd, obesity

YEAST AND PATHOGENS

- These are normal residents of the digestive tract, but they can be a problem if they are overrepresented.
- Common causes of yeast overgrowth include antibiotic use, hypochlorhydria, impaired immune function, dysbiosis, and high intake of sugars and starches consistent with a Standard American Diet.
- There is a strong correlation between an **acidic environment** and **fungal overgrowth**.

PARASITES

- Detection is difficult in stool; therefore, you may need to use more than one sample.
- Parasite infections are often overlooked in many patients because there are instances where parasites cause extra-intestinal problems without any gut symptoms and many people believe that one must travel to a third-world country to acquire parasites.
- Long-term health consequences like cancer, gastrointestinal disorders and arthritis can persist even after eradication of the parasite.

Blastocystis

- Most common parasite in North America.
    - May be a normal resident of the gut. DNA/PCR studies have found *Blastocystis* in 80 percent of healthy individuals.
- Likely nonpathogenic in healthy hosts

- Pathogenic in people with underlying health conditions.
- Multiple types of *Blastocystis*, some being more pathogenic.
    - At the time of this recording, the only commercial lab offering subtyping as a part of their stool testing is Genova Diagnostics, in their GI Effects Comprehensive stool panel, and some other panels that include parasite testing.
- Treatment is not risk-free, so the decision to treat requires clinical judgment.

Blastocystis symptoms:

- A wide variety of GI issues, including pain, gas, bloating, diarrhea, constipation, greasy stools that tend to float, and nausea.
- Extra-intestinal symptoms, including fatigue, skin rash, brain fog, and joint pain.

Dientamoeba fragilis

- *It is* very often a co-infection with pinworm.
- It is unclear if it is commensal or pathogenic.
- Symptoms are similar to *Blastocystis*.
- If you find *D. fragilis*, consider further testing/treating for pinworm because that's how it's often transmitted.
- **BadBugs.org** is a website that's a great source of information for *Blasto* and *D. fragilis*.

Endolimax nana

- Nonpathogenic in immunocompetent people.
- Pathogenic in immunocompromised people.
- Common co-infection with *Blastocystis*.
- If you see it on a test alone, there is concern of missing others; consider retesting. (Do a follow-up test with a specialized lab such as **Parasitology Center**.)

Entamoeba coli

- *It is* generally considered to be a nonpathogenic commensal parasite.
- There are two concerns:
    - Often occurs with other pathogenic parasites.

    - Sometimes confused with *Entamoeba histolytica* (highly pathogenic).
- If you see it on a test alone, consider retesting, as there is concern of missing others.

Giardia

- Immunoassays or antigen detection are preferred due to difficulty detecting in stool.
- Universally considered pathogenic, so treat if detected.
- Many associated complications like arthritis, allergies, ocular pathologies, nutritional deficiencies, chronic fatigue syndrome and more.

Cryptosporidium

- Similar symptoms to other parasites, with watery diarrhea most common in the acute phase.
- Can be serious to life-threatening in immunocompromised patients.
- Often self-limiting, but reinfection and chronic infection are possible.
- Treat if detected.

OTHER MARKERS

Other stool test markers like red blood cells, white blood cells, short chain fatty acids (SCFAs), fecal elastase, fat stain, muscle fibers and vegetable fibers are supporting markers of digestive function, microbial metabolic activity and infection. They can be critical to the development of a comprehensive gut treatment plan.

INFLAMMATORY AND IMMUNE MARKERS:

Lactoferrin

- Significantly elevated lactoferrin is a marker for IBD.
- Marker for gut inflammation/infection at lower levels.

Calprotectin

- Marker of GI inflammation in the mucosa and presence of neutrophils.

- May be more accurate for IBD diagnosis than lactoferrin.

>200 µg/g	50-200 µg/g	<50 µg/g
Active IBD, colitis, cancer	Chronic inflammation, NSAIDs, inactive IBD	Normal

- If calprotectin is >200 or lactoferrin is >50, run an IBD expanded antibody panel with Labcorp (test #162045).

Lysozyme

- General marker for gut inflammation.
- Moderately elevated level associated with overgrowth or food antigens.
- High levels (>2,000 ng/ml) associated with IBD and non-IBD GI disease with diarrhea; often require further testing.

Secretory IgA

- High levels may indicate activation of the gut immune system, possibly due to a viral or bacterial pathogen, or a more chronic, pathological issue.
- Can take several months to normalize.
- Low levels may indicate chronic problems and increase the risk of dysbiosis, pathogen invasion, and leaky gut. Fungal overgrowth is one possible cause.
- With extremely low or undetectable levels, consider ordering a quantitative immunoglobulin panel through Labcorp or Quest to rule out genetic deficiencies.

Lesson 7: Gut Diagnosis Small Intestine Bacterial Overgrowth Review

Small intestinal bacterial overgrowth (SIBO) is defined as the presence of excessive numbers of bacteria in the small bowel, causing gastrointestinal (GI) symptoms. It develops when the

normal homeostatic mechanisms that control small intestinal bacterial populations are disrupted.

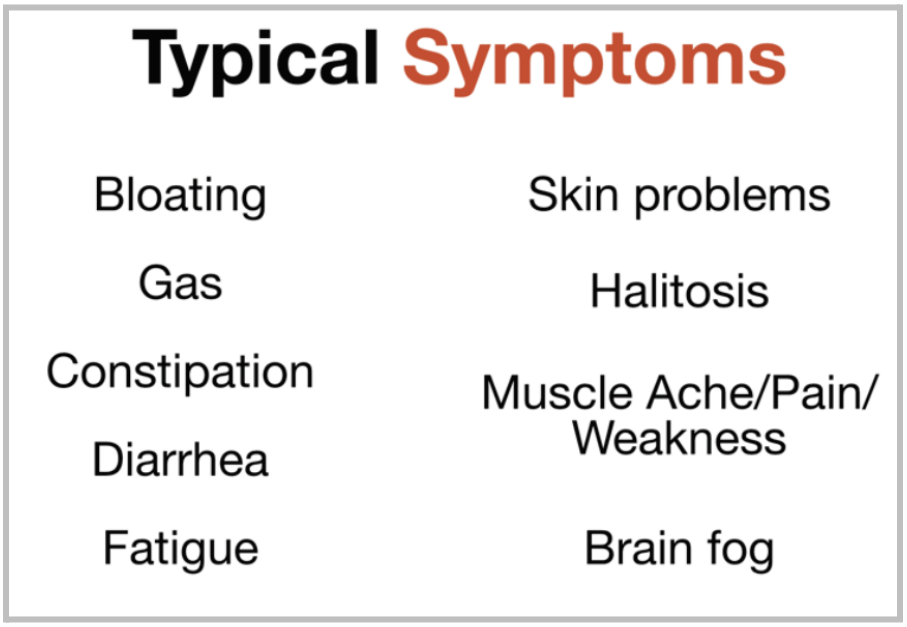
- Normal small bowels should have lower levels of microbial colonization when compared with the colon.

PRIMARY CONTRIBUTING PROCESSES:

In Functional Medicine practice, 3 primary processes that contribute to SIBO are:

1. Gastric acid secretion
2. Small intestine dysmotility (impairments in the MMC or delayed stomach emptying seen in diabetes)
3. Disrupted gut microbiome

GENERAL SIBO SYMPTOMS AND COMPLICATIONS:



Symptoms are diverse, nonspecific, and not limited to the gut. Patients may present only with non-GI symptoms such as fatigue, skin issues, or muscle aches/pain

The type of flora plays a role in the signs and symptoms of SIBO. Microorganisms that preferentially metabolize carbohydrates vs. those that preferentially metabolize fats can cause different symptoms.

Complications include:

- Malabsorption
- Nutrient deficiency
- Metabolic bone disorders
- Small intestine inflammation

TYPES OF SIBO:

1. Hydrogen-dominant SIBO is characterized by:
    - Gas
    - Bloating
    - Fatigue
    - Some propensity for diarrhea over constipation
    - A positive lactulose test with a first peak before 90 minutes
    - A positive glucose test with an early increase between 15 and 30 minutes

2. Methane SIBO, or intestinal methanogen overgrowth (IMO), is characterized by:
    - Gas
    - Bloating
    - Fatigue
    - Some propensity for constipation over diarrhea
    - A breath test measuring above 10 parts per million (ppm)

3. Hydrogen sulfide excess is characterized by:

- Cellular damage
- Inflammation
- Upregulation of immune activity
- Toxic burdens and genetic variance in Cystathionine Beta Synthase (CBS) enzymes that impact sulfur metabolism
- Diarrhea
- Sulfur-smelling gas
- A positive breath test with a rise greater than or equal to 3 ppm at any time (updated from 5 ppm in August 2021)

SIBO TESTING:

There are 2 main tests for SIBO:

1. An endoscopy with bacterial culture, where the levels of bacteria in the sample are quantified.
    a. This is the gold standard and most direct method.
    b. It's a very invasive and costly procedure
    c. The endoscope and catheter can be contaminated.
2. Breath test
    a. This test is more commonly used as it is noninvasive and easy to perform at home.
    b. It's more affordable.
    c. It's based on the premise that bacteria in the intestines metabolize carbohydrates like lactulose, glucose, sucrose, and xylose and produce gases like hydrogen and methane, which can be measured in the breath.

GLUCOSE VS. LACTULOSE AS SUBSTRATES

Substrate	Advantage	Disadvantage	Risk
Glucose	More specific	Greater risk of *false negative*	Under-treatment
Lactulose	More sensitive	Greater risk of *false positive*	Over-treatment

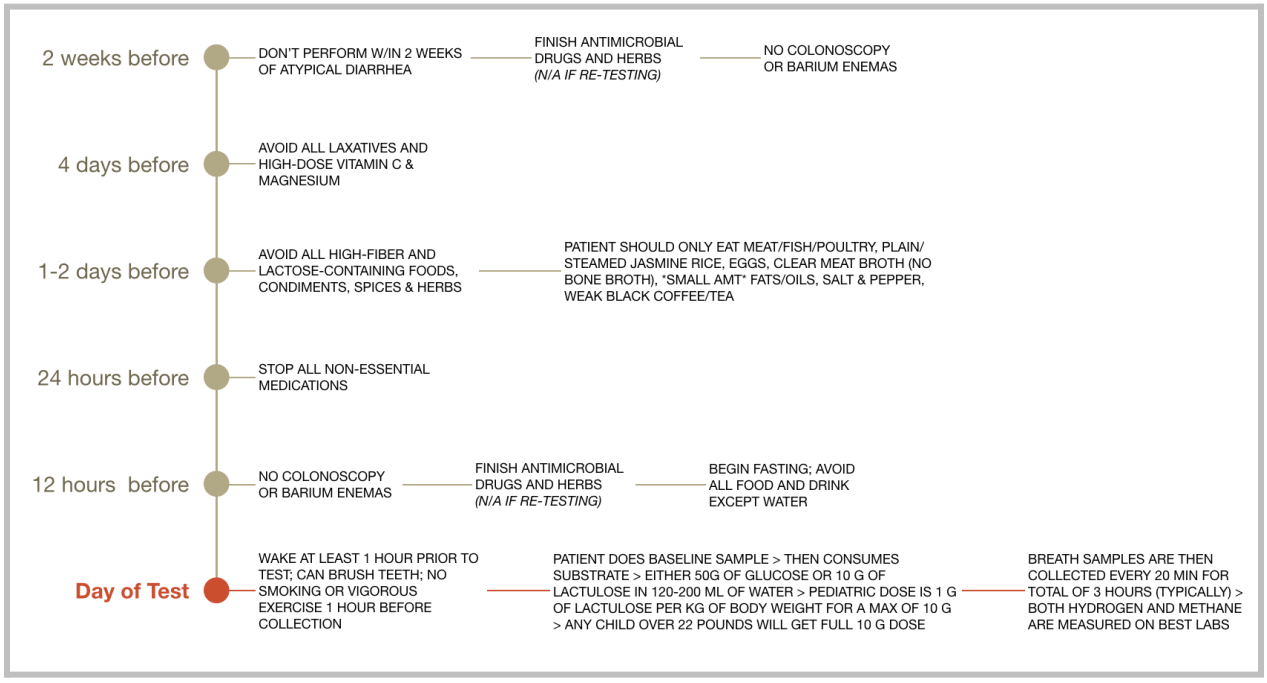
Glucose is absorbed in the proximal small intestine and the duodenum, so if overgrowth of bacteria is occurring in the jejunum or ileum, you may get a false negative.

Lactulose is not absorbed at all in the small intestine. It is fermented by bacteria in the colon. The issue with lactulose as a substrate is that the lactulose breath test is based on the idea that orocecal transit time, or the amount of time it takes for a substance to go from the mouth to the cecum, which is the first part of the colon, in healthy people is always 90 minutes.

The lactulose breath test has been criticized for high false-positive results because of accelerated transit and colonic fermentation in some individuals, and alternatively, the glucose breath test for being absorbed in the proximal duodenum and therefore having low sensitivity for detecting distal SIBO, in other words, missing overgrowth in the distal small bowel.

Despite its drawbacks, we prefer lactulose because the potential benefits of treatment outweigh the potential consequences of false positives because of the safety of the treatment interventions.

SIBO TEST PREPARATION:



Improper Test Preparation:

- High levels of baseline hydrogen can be a result of SIBO, but it can also be a result of improper test preparation. Typically, when you see improper test prep, you'll see a high baseline level of hydrogen and maybe high at 20 minutes, and then it drops down into the normal range.
- High levels of baseline methane can be normal, and it's usually not caused by improper test preparation. Most often, it indicates a positive result.

2017 North American Consensus

- An increase in hydrogen greater than or equal to 20 ppm before 90 minutes is positive.
    - The "double peak" has no validity and should not be used.
    - A rise in hydrogen that occurs after 90 minutes is not a positive result.
- A methane level greater than or equal to 10 ppm at any point during the test is considered positive for methane.

CONSIDERATIONS FOR WHICH LABS TO USE FOR BREATH TESTING:

1. Labs should use a QuinTron machine or Novel 4-Gas machine
2. At least tests for both hydrogen and methane
3. Follows 2017 North American Consensus

Trio-smart breath test from Gemelli Biotech

- This test measures hydrogen, methane, and hydrogen sulfide levels using the Novel 4-Gas device over 135 minutes.
- It reports the observed peak within 100 minutes instead of the 90-minute mark.
- Use the North American Consensus guidelines for interpretation.
- Lactulose substrate requires a prescription by a practitioner.

Genova SIBO Breath Test

- They have adopted the 2017 North American Consensus criteria but lack a 90-minute value.
- They offer a 2- or 3-hour breath test option via QuinTron.
- The test measures hydrogen and methane gasses.
- Both glucose and lactulose are included in the kit.
- Test timing is every 20 minutes for either 120 or 180 minutes.
- To estimate a 90-minute value, look at the 80-minute and 100-minute values and halve the increase between them.

NUNM (NCNM)

- Three-hour breath test via QuinTron.
- They have not updated their criteria to match the 2017 North American Consensus; they use QuinTron guidelines.

- It measures hydrogen and methane gasses.
- Both glucose and lactulose are included in the kit.

OVER-TREATING VS. UNDER-TREATING SIBO:

In practice, we tend to use lactulose, with a higher risk of false-positive results, but take note of any special considerations when interpreting the results using the 2017 North American Consensus guidelines.

Some say that the risk of false positives for SIBO is that you may miss other underlying issues. However, SIBO can be a symptom of a deeper problem, like dysbiosis, heavy metal toxicity, mold toxicity, or a gut–brain axis issue.

If you just keep treating the overgrowth itself without addressing the underlying cause that's leading to overgrowth, you won't experience success in eliminating SIBO, and you could harm the patient with repeated botanical, antimicrobial, or antibiotic use. If the patient is treated and does not improve, especially with both botanicals and drugs, you should consider whether something else might be going on that's driving the bacterial overgrowth and decide to look deeper.

IBS-SMART TESTS AND SIBO:

The IBS-Smart test is a blood test that was designed to detect 2 biomarkers: anti-cytolethal distending toxin B (CdtB) and anti-vinculin. Studies have shown these markers to be elevated in the majority of patients with irritable bowel syndrome (IBS) with diarrhea (IBS-D) and IBS mixed type (IBS-M), and the presence of these markers indicates the cause was infectious gastroenteritis. Clinically, we have also used this test for people with constipation who have very persistent SIBO and other IBS symptoms, like abdominal pain, bloating, and gas, and some have come back positive. This test is used as a test of inclusion for the diagnosis of IBS, and it may be considered in some of those patients who fit the profile in every other way.

Scenarios

Anti-CdtB	Anti-Vinculin	Clinical Association
Low	Low	No recent infection and no autoimmune basis for functional symptoms
High	Low	Recent infection and may be developing IBS
Low	High	Infection long past, now autoimmunity driving condition with IBS
High	High	Recent with or without remote infection, now autoimmune with IBS
Either	Very High	Pseudo-obstruction (neuropathy)

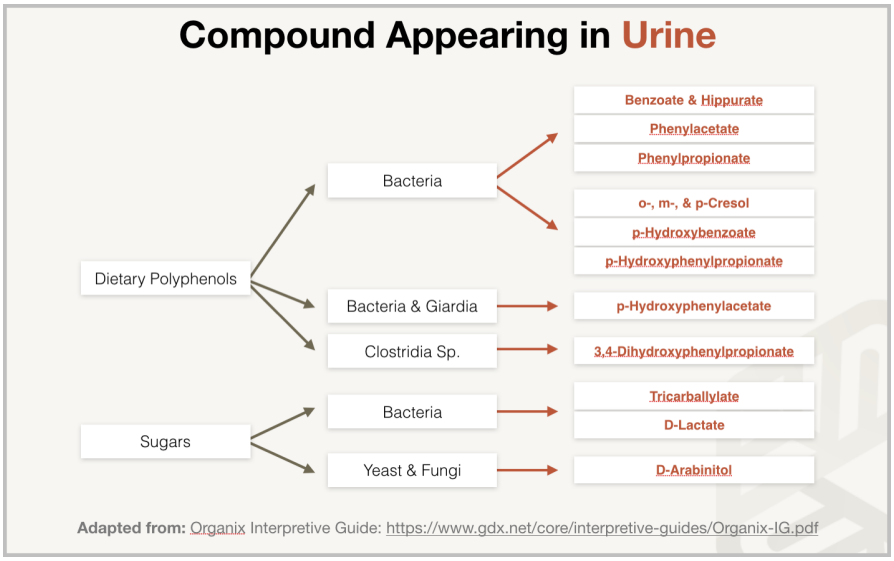
Adapted from: Dr. Pimentel's presentation with Gemelli Labs

CUSTOMIZING PALEO

There is no one size fits all when it comes to personalizing the frequency and timing of meals for particular conditions. We find that generally healthy patients who do not have blood sugar or immune problems do best with three meals a day. Those who are trying to lose weight or have metabolic dysfunction should start by not having any snacks between meals.

Intermittent fasting is alternating periods of fasting and non-fasting and there are a lot of different ways to do it. Intermittent fasting is a hormetic stressor, so it's a positive stressor, which is something that causes … hormesis is something that contributes to positive adaptation by promoting cellular repair process called autophagy IF is not idea for a variety of people and conditions, including pregnancy, kids and teenagers, adrenal fatigue, eating disorders and possibly hypothyroidism.

Lesson 8: Gut Diagnosis Organic Acids Review



MARKERS FOR MICROBIAL OVERGROWTH

- Bacteria and yeast produce metabolites of small molecular weight that can appear in urine.
- These compounds reveal metabolic activities of the microbes that inhabit the mucosal layer and the lumen of the gut.

Specific compounds that are generated by each person depend on available substrates and the species of organisms that are present. Substrates include dietary polyphenols: flavones like parsley, celery, and peppermint; flavonols like cranberries, onions, and peppers; flavanones like citrus; catechins like grapes and plums; anthocyanins like cherries, raspberries, and blueberries; and epicatechins like green and black tea and chocolate. Amino acids and carbohydrates can also serve as substrates for some organic acids.

CONCERNS REGARDING USING ORGANIC ACIDS TESTING IN PRACTICE

1. Research supporting these markers is not as strong as stool markers or breath testing.
2. We see a lot of variation in test results depending on what the patient is eating. We've seen some strange variation in results across relatively short time periods, without a lot of explanation for why the results vary that much.
3. Uncertainty regarding optimal ranges.
4. It cannot differentiate if microbial overgrowth is in the small or large intestine.

Benzoate

- Produced by bacterial metabolism of dietary polyphenols.
    - If elevated with no other markers, may just indicate high dietary intake of polyphenols.
- Elevation can be a marker of bacterial overgrowth or impaired phase 2 detox capacity due to glycine and/or pantothenic acid insufficiency.
- High benzoate can also be caused by ingestion of a benzoic acid, which is found in processed and packaged foods like pickles, soda, or lunch meats, or naturally in foods like cranberries.
- Often elevated in conjunction with hippurate, which is a normal byproduct of benzoate metabolism.

Phenylacetate (PAA)

- Byproduct of intestinal action on polyphenols, tyrosine, or phenylalanine.
    - Normally present in low concentrations
- Phenylketonuria (PKU), an inherited disorder that leads to accumulated PAA levels.
    - Can lead to neurotoxicity and brain damage
- In most patients there is slight elevation, which is indicative of microbial overgrowth.
    - High levels should be referred to an inherited disease specialist.

Phenylpropionate (PPA)

- Byproduct of intestinal action on polyphenols and phenylalanine.
- Metabolized by medium-chain acyl-CoA dehydrogenase (MCAD) and normally not in urine.
- Very high levels indicate MCAD deficiency.
- Signs and symptoms (vomiting, lethargy, hypoglycemia) occur early in childhood.
- Mild elevation is a sign of microbial overgrowth.
- Refer out for very high levels.

P-hydroxybenzoate

- From bacterial metabolism of polyphenols and tyrosine.
- Elevations indicate microbial overgrowth, especially E. coli.

P-hydroxyphenylacetate

- From bacterial metabolism of tyrosine.
- Useful in detecting small bowel disease caused by overgrowth of anaerobes.
- Very high in patients with cystic fibrosis or other conditions that impair amino acid absorption.

Indican

- From bacterial metabolism of tryptophan.
- Elevations can be indicative of bacterial overgrowth in upper small bowel.
- Can help differentiate pancreatic insufficiency from biliary stasis as a cause of steatorrhea (fatty stools).
    - High indican → pancreatic insufficiency
    - Normal indican → biliary stasis
- Can also signify low stomach acid since incomplete protein digestion can cause elevations.

Tricarballylate

- Produced by aerobic bacteria.
- Extremely high affinity for magnesium, preventing magnesium absorption.

- When elevated, supplementation with magnesium in addition to gut treatment is necessary.

D-Lactate

- Major metabolic byproduct of beneficial bacteria species in the gut like Lactobacillus acidophilus.
    - A different isomer of lactic acid than the ones produced during exercise.
- Elevated in cases of carbohydrate malabsorption, which allows L. acidophilus to flourish.
- Lactobacillus species are common in probiotics; best to avoid these when D-lactate is elevated.
    - Red flag for SIBO if patient gets worse with these probiotics.
- Symptoms include GI distress and neurological and cognitive symptoms.

3,4-Dihydroxyphenylpropionate (3,4-Dhpp)

- Produced by Clostridia species and elevated in overgrowth.
- Can lead to increased dopamine due to inhibited dopamine metabolism/breakdown.
    - Potential neurologic symptoms, as well as mood and behavioral problems.

D-arabinitol

- Metabolite of most pathogenic Candida species.
    - One of the most sensitive markers for invasive candidiasis.
- A better indicator for fungal overgrowth than blood cultures.

Lesson 9: Gut Diagnosis Intestinal Permeability Review

Gut barrier consists of multiple layers:

1. External physical barrier.

2. Inner, functional physiological barrier.

Successful interaction of these two barriers allows appropriate permeability to be maintained, and when either system malfunctions, permeability becomes inappropriate, and this is what we refer to as leaky gut.

The intestine should be leaky to some degree because that is how we absorb nutrients. If the intestine wasn't at all leaky, we couldn't get any of the nutrition that we need, so leaky gut is actually referring to intestinal permeability to the wrong molecules at the wrong times.

Possible causes of impairment of intestinal barrier

Nutrition	e.g. Western diet, lack of fermentable carbohydrates and fermented foods
Infections and toxins	e.g. bacterial, viral, parasitic infections; fungal overgrowth; heavy metals; mycotoxins
Medications	e.g. PPIs, antibiotics, NSAIDs
Lifestyle	e.g. chronic stress, sleep deprivation, inappropriate physical activity
"Hygiene hypothesis"	Inadequate immune stimulation during crucial developmental period
Endogenous factors	Chronic inflammation, SIBO, gut-brain dysfunction, low MSH
Genetic susceptibility	e.g. 70% of asymptomatic relatives of CD patients positive for ↑ intestinal permeability

A combination of genetic susceptibility and environmental triggers cause the mucosal barrier to become permeable, and this leads to enlarged spaces between the cells of the gut wall and disassociation of tight junction proteins.

Key transport and immune provoking mechanisms of antigens through the gut barrier:

- **Transcellular** means through the cell, and that's where the antigen passes through the cell itself.
- **Paracellular** means between cells, where the antigen passes between the cells.
- Endotoxins pass through the gut barrier into the blood and **elicit an autoimmune response**.

- Bacterial toxins act as superantigens to T-lymphocytes or provoke a response through **molecular mimicry**. Many bacteria have antigenic sites that are similar to human tissue antigens, so the body will attack both the endotoxins and the self tissue during the defensive response (autoimmunity).

Taking a functional medicine approach to intestinal permeability:

- We find that leaky gut is almost always caused by something else: poor diet, gut infections, chronic stress, etc.
- We want to remove all these triggers before addressing intestinal permeability specifically.
- In many cases, we found that once you remove the triggers, the barrier integrity is restored without additional intervention because the intestinal epithelium regenerates itself every five days.

ASSESSING LEAKY GUT

In clinical practice, there are two primary methods of assessing leaky gut

1. Lactulose/mannitol permeability assay (Genova)
    a. Measures levels of both sugars in a patient's urine after oral ingestion. Lactulose and mannitol are both oligosaccharides
    b. Their differing molecular weights help determine if permeability is transcellular (mannitol) or paracellular (lactulose).
    c. In a healthy person, the **smaller mannitol molecules are expected to be measured in larger amounts**, normally from 10 to 30 percent of the orally ingested dose. Lactulose would be expected to be recovered at **only about 1 percent of the oral dose due to its larger size.**
    d. A higher lactulose-to-mannitol ratio is indicative of intestinal permeability.
    e. See the lactulose mannitol test interpretation matric for more information.
2. Antigenic permeability screen (Cyrex Array 2)
    a. Measures immune reactivity and permeability to three molecules:

i. **Lipopolysaccharides (LPS-IgG, IgM and IgA)**, an endotoxin present in the cell membrane of Gram-negative bacteria. Abnormal level of antibodies indicates infiltration of large endotoxins through the intestinal barrier into systemic circulation

ii. **Occludin**, the main component of proteins that hold tight junctions together and antibodies (IgG, IgM and/or IgA) can indicate breakdown of these tight junctions and **Zonulin**, regulates the opening and closing of tight junctions. Antibodies (IgG, IgM and/or IgA) suggest that regulation of these tight junctions may be compromised.

iii. **Actomyosin**, a protein that regulates plasticity of tight junctions. Antibodies (IgA) can indicate transcellular permeability and movement of molecules through cells.

Interpretation of antibodies against LPS, occludin / zonulin and actomyosin network

LPS IgA, IgG, IgM	+	+	-	+	-
Occludin/Zon. IgA, IgG, IgM	-	+	+	-	-
Actomyosin IgA	-	-	-	+	+
Clinical indication	Gut dysbiosis	Bacterial paracellular permeability	Non-bacterial paracellular permeability	Bacterial transcellular permeability	Autoimmunity against epithelium/ cell cytoskeleton

Adapted from: Cyrex Array 2 Clinical Applications Guide. http://cyrexlabs.com

Antigenic permeability screen vs. L/M assessment

Lactulose mannitol assessment	Antigenic permeability screen
Upper small intestine	Entire length of small intestine and large intestine
Small sugar molecules <350 Da in size; not antigenic	Large molecules >10,000 Da; strongly antigenic
Small sugar molecules don't always correlate with uptake of larger dietary and microbial antigens	Positive correlation between large molecules and dietary and microbial antigens
Permeability to small molecules not always pathological; high risk of false positives	Permeability to large molecules indicates damage to tight junctions and pathological permeability; low risk false positive
Small openings in tight junctions can be repaired in hours; high risk of false negative	Large openings in tight junctions take longer for repair; low risk of false negative
L/M affected by GI motility, renal clearance, variations in gastric emptying, smoking, alcohol, etc.	Permeability to large molecules is not affected by these factors

Adapted from: Vojdani Altern Ther Health Med. 2013 Jan-Feb;19(1):12-24

Overall, the lactulose-mannitol screen has a higher risk of false positive. It's not reliable on its own but may be worthwhile in conjunction with the antigenic permeability screen.

CUSTOMIZING PALEO: PALEO FOR ATHLETES

Individual needs will vary depending on a person's sport or athletic activity, as well as their overall health status and goals. When determining caloric need, you can use a standard formula that includes activity factor to determine the optimal calorie intake for each person that you're working with. Clinical examples of these kinds of formulas include the Harris-Benedict Formula or the Mifflin-St. Jeor Formula.

- For a quick and dirty approximation, you can multiply weight in pounds by 12 to 14 to get a baseline range of calorie needs, and then you would add 100 calories to this number for every 10 minutes of moderate- to high-intensity activity.

Key Takeaways

- Recommend a range of 25 to 35 percent of calories from protein for athletes
- The ideal carbohydrate range for most athletes is 20 to 50 percent of calories in their diet, but if they are doing more intense, explosive activity, you'd want to up that range to maybe 40 to 50 percent of calories from carbohydrate.

- Fasted training at high intensity may cause increased muscle breakdown and impair recovery, so consuming carbohydrates 30 to 45 minutes pre-workout can help to increase muscle building; it has an anabolic effect, where training in a fasted state can help them lean out.
- General rule of thumb for hydration is to drink about two liters of water daily. You would add an extra 500 milliliters of water per hour of vigorous exercise
- Electrolytes like sodium, potassium, and magnesium all help to maintain proper fluid balance in the body and are all crucial for people who are performing intense athletic activity.
- Special considerations for female athletes include:
    - Females are at risk for what's known as the female athlete triad when they're training hard, and that is energy deficiency, not eating enough calories; menstrual changes; and bone loss, osteopenia or osteoporosis

Lesson 10: Gut Treatment SIBO Review

GUT TREATMENT APPROACH

Treating the gut is often a two stage process. Stage 1 involves addressing present pathologies in the gut and stage 2, involves rebuilding a healthy gut ecosystem

The Herxheimer Reaction

A reminder that patients may feel worse on certain treatment plans before they begin to feel better. This phenomenon, known as a Herxheimer reaction or Herx response, happens when treatment disrupts the biofilms that protect the gut pathogens, allowing them to release toxins into the gut and bloodstream (in cases of leaky gut).

To avoid a Herx reaction, start patients on lower doses and gradually ramp up to a full dose over time. If a patient still reacts, you may stop supplementation and add them back in one at a time to see which is causing the biggest issue.

SIBO TREATMENT PROTOCOLS

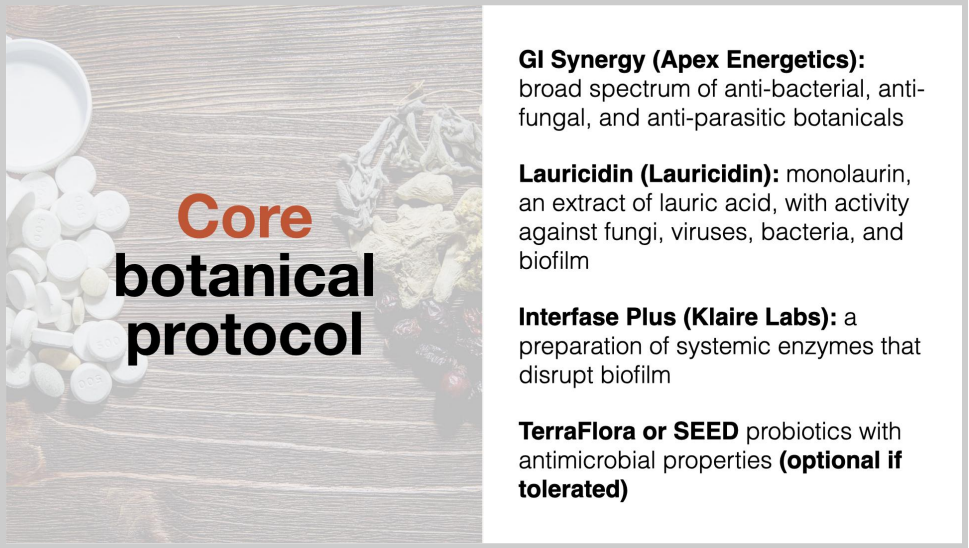
There are three general considerations to begin with when treating SIBO:

1. Duration of the treatment, which should correlate with breath test results, clinical experience, and recent studies.
2. Treatment depends on whether hydrogen, methane, hydrogen-sulfide, or some combination of these gasses are elevated.
3. Retesting is crucial.

Core Botanical Protocol for SIBO

Studies have shown that botanical protocols are equivalent to or better than the prescription rifaximin treatment for SIBO.

This core botanical protocol can be used with minor tweaks for elevated hydrogen, methane, and even suspected or confirmed hydrogen sulfide excess.

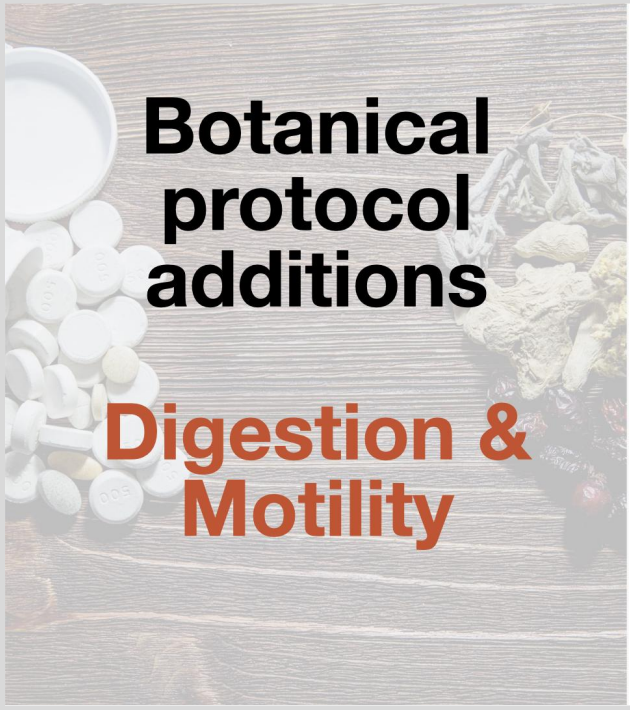


PHGG has been included in this botanical protocol in the past, but clinical practice did not indicate that it was beneficial for our patients. However, PHGG has been shown to improve gut motility and may encourage cell division by providing bacteria with a food source, thus making treatment more effective. There are differing opinions as to whether PHGG or prebiotic fiber should be included in SIBO treatment protocols.

Core botanical protocol dosages

Nutraceutical	Dosage
GI Synergy	1 packet BID *(with breakfast and dinner)*
Lauricidin	1 scoop TID *(with each meal)*
Interfase Plus	3-4 capsules BID *(on empty stomach)*
TerraFlora or SEED	TerraFlora is 1 capsule *(with lunch); SEED is 2 capsules daily*

Core Botanical Protocol Add-ons for Digestion and Motility



Iberogast (Tribute Pharmaceuticals in the U.S./ Can.): prokinetic; contains 9 botanical "bitters" that stimulate bile production and motility. Can be helpful for gas, diarrhea, nausea, and dyspepsia.

MotilPro (Pure Encapsulations): prokinetic containing 5-HTP, acetyl-L-carnitine, vitamin B6, and ginger to help support motility

Betaine HCL with pepsin (many brands): hydrochloric acid (HCL) supplement with pepsin; HCL and pepsin help with protein digestion, which is often impaired in SIBO patients

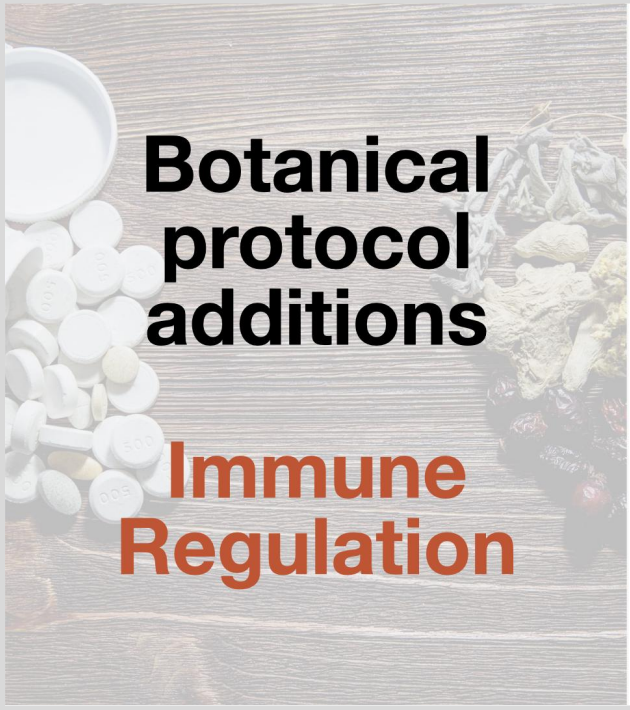
Digestive enzymes (many brands): helps with the breakdown of protein, carbs, and fat; can be used with patients with severe gas, bloating, etc.

PC (Seeking Health/Body Bio): phosphatidylcholine for patients with fat malabsorption and impaired bile metabolism.

Botanical protocol dosages: Digestion & Motility

Nutraceutical	Dosage
Iberogast	20–30 drops TID just before meals
MotilPro	1–2 capsules TID on an empty stomach
Betaine HCL with pepsin	1–5 650 mg capsules before meals; sensitive patients can use 200 mg capsules
Digestive enzymes	Depends on the manufacturer; take just before meals
Phosphatidylcholine	3,000–6,000 mg per day with or without food

Core Botanical Protocol Add-ons for Immune Regulation



Serum-derived bovine immunoglobulins (SBI Protect or MegaIgG2000): dairy-free immunoglobulin concentrate that supports healthy digestion and healthy gut barrier function; it is anti-inflammatory and protective.

ProButyrate (Tesseract): essential gut nutrient; helpful for most GI disorders and symptoms like bloating and gas. Tesseract is a butyric acid supplement with a delivery system to offer higher bioavailability to the gut mucosa; it is anti-inflammatory and immune regulatory.

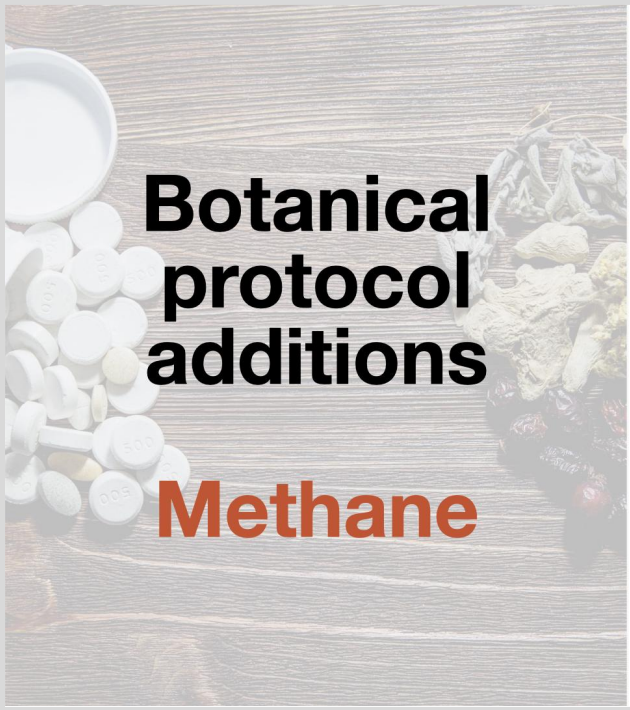
Serum-derived bovine immunoglobulins bind to irritants like bacteria and toxins, halting the cycle of inflammation and allowing the interstitial cycles of the Cajal cells and other gut tissues to heal. This is especially helpful for patients who do not respond to the first round or two of treatment. May also be added to the core protocol if a patient is experiencing immune dysregulation.

ProButyrate supplies the important short-chain fatty acid butyrate, which has been connected to anti-inflammatory and intestinal immune regulatory effects of the gut mucosa.

Botanical protocol dosages: Immune Regulation

Nutraceutical	Dosage
SBI Protect	4 capsules BID with or without food
MegaIgG2000	5 capsules BID with or without food
ProButyrate	3 capsules BID with or without food

Core Botanical Protocol Add-ons for Methane



Atrantil: a blend of polyphenols that addresses gut bacteria; effective for bloating and abdominal discomfort and supports overall digestive health.

Allimax Pro (Allimax Nutraceuticals): stabilized form of allicin; potent antimicrobial.

Ideal Bowel Support LP299V (Jarrow Formulas): probiotic that contains *L. plantarum* 299v; it resists stomach acid and bile salts, adheres to gut lining, promotes intestinal health and function, and may help with constipation.

***L. reuteri* (BioGaia Gastrus):** probiotic that suppresses methanogen activity; it improves symptoms of constipation.

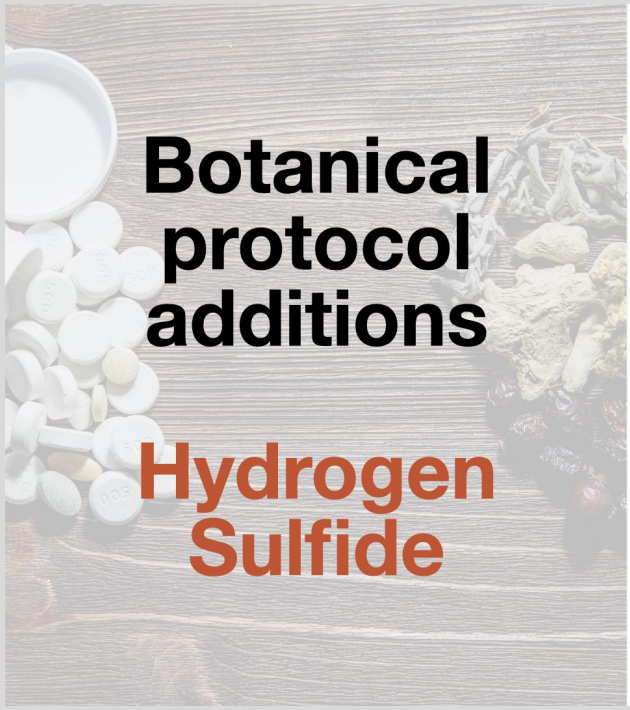
Atrantil may be used in practice alongside rifaximin if a patient does not want to take neomycin.

L. reuteri may also exhibit antifungal properties and reduce proinflammatory cytokines.

Botanical protocol dosages: Methane

Nutraceutical	Dosage
Atrantil	2 capsules TID at the beginning of meals Maintenance dose: 1–3 capsules per day
Allimax Pro	1 capsule TID with food
Ideal Bowel Support	1 capsule BID; can be taken with food but away from antimicrobials or antibiotics
BioGaia Gastrus (*L. reuteri*)	1 tablet per day but away from antimicrobials or antibiotics

Core Botanical Protocol Add-ons for Hydrogen-Sulfide



Molybdenum (Mo-Zyme Forte by Biotics Research): cofactor for sulfite oxidase enzyme and essential for the breakdown of sulfite to sulfate.

Hydroxocobalamin (Hydroxo B12 lozenge by Seeking Health): binds to H2S and reduces the biologic activity of H2S.

Bismuth (Pepto Bismol, Bio-HPF): reduces H2S-producing/sulfate-reducing bacteria.

Zinc acetate (many brands): binds to H2S and replaces potential loss as a result of environmental toxin burden (like glyphosate).

Activated charcoal (many brands): binder for endotoxins and H2S.

Korean Red Ginseng (Pure Encapsulations): suppresses activity of CBS and CSE enzymes, reducing H2S production internally.

Botanical protocol dosages: Hydrogen Sulfide Excess

Nutraceutical	Dosage
Molybdenum	150 mcg BID with food
Hydroxocobalamin	2000 mcg qAM before meals or on an empty stomach
Bismuth	400–525 mg TID for 4 weeks Bio-HPF: 2 capsules TID before meals
Zinc acetate	60–75 mg daily on an empty stomach or with food if nausea occurs
Activated charcoal	1200–1500 mg daily (can be taken as a single dose or split up) away from food, supplements and medications
Korean red ginseng (aka Panax or Asian ginseng)	400 mg BID with or without food

Hydrogen sulfide excess in the body

We still do not understand the driving force behind an overproduction of H2S in the body, but there are a handful of different theories.

In the body, sulfur is responsible for

1. Helping detox in the liver and excrete molecules in the urine
2. Assisting in the production of collagen, which forms connective tissues, cell structures, and artery walls
3. Helping synthesize proteins

In the gut, hydrogen sulfide can be produced by a variety of bacteria. It can also be produced in the gut from the enzymatic conversion of amino acid cysteine. Research suggests that the majority of hydrogen sulfide production occurs in the upper digestive tract—the stomach and small intestine—rather than in the colon.

Hydrogen-sulfide SIBO additional therapies

For hydrogen sulfide excess SIBO, we often use portions of the core SIBO protocol, plus some detox support and support for sulfur metabolism. We also generally test for urine glyphosate

and talk about ways to reduce glyphosate exposure. In some cases, we also test for the CBS variants using 23andMe or Genova's methylation plus genomic add-on panel.

Additional therapies for hydrogen sulfide excess SIBO that may be beneficial include:

1. Infrared sauna therapy
2. Epsom salt baths
3. Low-sulfur diet

Combining Core and Specific Botanical Treatment Protocols

Botanical protocol for IMO + motility

Nutraceutical	Dosage
GI-Synergy	1 packet BID (with breakfast and dinner)
Atrantil	2 capsules TID at the beginning of meals Maintenance dose: 1–3 capsules per day
Interfase Plus	3–4 capsules BID (on an empty stomach)
Ideal Bowel Support®	1 capsule BID; can be taken with food but away from antimicrobials or antibiotics
MotilPro	1–2 capsules TID on an empty stomach
Allimax Pro	1 capsule TID with food

Botanical protocol for H2 SIBO + immune + digestive support

Nutraceutical	Dosage
GI-Synergy	1 packet BID (with breakfast and dinner)
SBI Protect	4 capsules BID with or without food
InterFase Plus	3–4 capsules BID (on an empty stomach)
Betaine HCL with pepsin	1–5 650 mg capsules before meals; sensitive patients can use 200 mg capsules
Digestive enzymes	Depends on the manufacturer; take just before meals
Terraflora or Seed (optional)	Terraflora 1 capsule (with lunch); Seed 2 capsules daily

Below is an example of a hydrogen sulfide excess SIBO botanical protocol:

Botanical protocol for H2S SIBO

Nutraceutical	Dosage
GI-Synergy	1 packet BID (with breakfast and dinner)
InterFase Plus	3–4 capsules BID (on an empty stomach)
Molybdenum	150 mcg BID with food
Hydroxocobalamin	2000 mcg qAM before meals or on an empty stomach
Bismuth	400–525 mg TID for 4 weeks Bio-HPF: 2 capsules TID before meals
Zinc acetate	60-75 mg daily on an empty stomach or with food if nausea occurs
Activated charcoal	1200–1500 mg daily (can be taken as a single dose or divided) away from food, supplements, and medications

Botanical Treatment Duration Based on LBT Results

When deciding the duration of the botanical protocol for a particular patient, consider the results of the lactulose breath test. General duration guidelines are:

Length of botanical treatment
based on LBT **hydrogen (H2)**
results

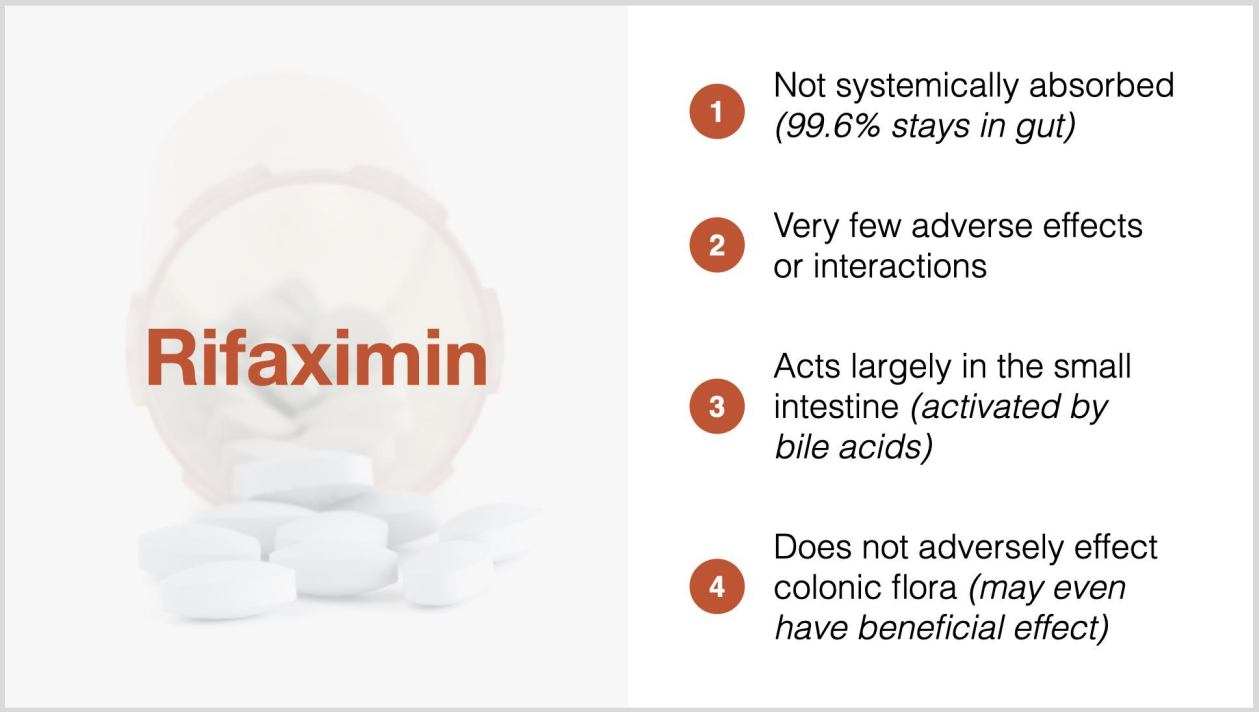
H2 @80/90 min	**Duration**
<45 ppm	**4 weeks**
45-70 ppm	**8 weeks**
>70 ppm	**12 weeks**

Recommendations for the duration of the botanical treatment based on lactulose breath test methane levels:

Length of botanical treatment based on LBT **methane (CH4)** results

Presentation	Duration
The highest value on the test is between 10 ppm and 25 ppm	30 days
The highest value on the test is between 25 ppm and 50 ppm	60 days
The highest value on the test is greater than 50 ppm	90 days

RIFAXIMIN FOR TREATING SIBO



.Rifaximin is generally safe

When to consider rifaximin

1. If a patient has failed botanical protocol.
2. If a patient cannot tolerate botanical protocol.

Common Rifaximin Dosing Regimens

Population	Dosage
Adults	400 mg TID for 10-14 days
Adults	550 mg TID for 10-14 days
Children	200 mg TID for 10 days
Children	10-30 mg/kg/d for 10 days

Rifaximin Treatment Duration Based on LBT Results

These guidelines apply if rifaximin is used alone at dosages of 1200 milligrams per day or 1650 milligrams per day but should always be considered in the context of the patient presentation:

H2 @80/90 min	**Duration**
<45 ppm	**4 weeks**
45-70 ppm	**8 weeks**
>70 ppm	**12 weeks**

Rifaximin + Nutraceutical Treatment Duration Based on LBT Results

H2 @80/90 min	Duration
<45 ppm	2 weeks
45-70 ppm	3 weeks
>70 ppm	4 weeks

Combination Treatment Considerations

- Rifaximin dose is lowered to 1200 mg/day.
- Less time may be required than indicated due to increased efficacy of combinations.
- Combination treatment can be more practical since it reduces the high cost of rifaximin.
- Rifaximin is activated by the bile acids in the small intestine, so patients with bile issues might benefit from a two-week lead-in with phosphatidylcholine and bitters to stimulate that bile production.

DRUG ADDITIONS FOR METHANE

Standard is **Neomycin** 500 mg BID for 10 days

Pimentel/Cedars Sinai trial with metronidazole (Flagyl) with some success > 250 mg TID for 10 days

Metronidazole doesn't appear to adversely affect gut microbiota > but not as well tolerated as rifaximin/ neomycin

If you use **neomycin** or **metronidazole** with longer course of rifaximin then limit their use to 10 days

Alternative additions for methane

1. Lactobacillus plantarum at a dose of 10 billion CFU per day;
2. Atrantil at a dose of two capsules three times a day; and/or
3. A longer course, like 30 days or more, of rifaximin.

Pharmaceutical/combo protocol for SIBO

Therapeutic Agent	Dosage
Rifaximin	Depends on breath test results
Lauricidin	1 scoop TID with each meal
InterFase Plus	3–4 capsules BID on an empty stomach
Terraflora	1 capsule BID upon rising and before bed
Atrantil (optional)	(Only if methane elevated) 2 capsules TID
L.plantarum* and/or *L.reuteri (optional)	(Only if methane elevated) 10 billion CFU/d
Iberogast (optional)	(Only with bile issues) 20 drops TID with meals
Ox bile (optional)	(Only with bile issues) 100–500 mg with meals

Rifaximin for 2–4 weeks	Dosage
Rifaximin	1200 mg to 1650 mg daily for the first 2–4 weeks
Botanical protocol for 4–8 weeks	**See previous slides for dosage**
GI-Synergy or Biocidin	Core protocol
Terraflora or Seed	Core protocol
InterFase Plus	Core protocol
Allimax Pro and/or Atrantil (optional)	IMO add-on
L.plantarum* and/or *L.reuteri (optional)	IMO add-on
Iberogast or Ox bile (optional)	Bile issues add-on
Bismuth (optional)	H2S add-on

TREATING IMPAIRED MOTILITY CONNECTED TO POST-INFECTIOUS IBS

When a patient has positive anti-vinculin and/or anti-CdtB antibody levels on an ibs-smart test, it indicates some sort of post-infectious gastritis as a likely cause of persistent IBS and/or SIBO. Consider ordering an ibs-smart test for patients with persistent SIBO or IBS that have not responded to initial treatments, have high gas levels, or have a known history of food poisoning. If the ibs-smart test comes back positive, then treatment should focus on supporting and restoring proper small intestine motility and supporting the function of the MMC.

Prokinetics stimulate and coordinate GI motility by increasing transit in the GI tract and improving the coordination of GI movement downward.

Examples of prokinetics include metoclopramide, cisapride, domperidone or Motilium, erythromycin in low doses, prucalopride, ginger, ginger root, and Iberogast.

The goal of prokinetic therapy is to move food, acid, gas, or stool through and out of GI organs and to encourage the GI muscles to properly contract.

Herbal prokinetics

Prokinetic	Dose
Iberogast	**IBS/dyspepsia:** 20 gtts with meals **SIBO relapse prevention**: 30–60 gtts nightly **Symptom management** 20–30 gtts TID to QID or PRN **Pediatrics**: 10–20 gtts TID-QID
Ginger/Ginger root	**General:** 1000 to 2000 mg daily (up to 6 g QD) **SIBO relapse prevention:** 1000 to 2000 mg QHS **Pediatrics**: 250 mg QHS
Products:	**MotilPro** *(Pure Encapsulations)*, **Motility Activator** (*Integrative Therapeutics*), **SIBO-MMC** (*Priority One*)

Pharmaceutical prokinetics may be used as well, including **low-dose erythromycin**, **prucalopride** or **Montegrity**, and **low-dose naltrexone**.

Pharmaceutical prokinetics

Prokinetic	Dose
Low-dose erythromycin	**Gastroparesis:** 250 mg TID, 30 min before meals (ac) **SIBO relapse prevention**: 50 or 62.5 mg nightly **Symptom management:** 50 or 62.5–100 mg 30 min ac **Pediatrics**: 25 mg (liquid Rx) or cut 150 mg into 1/4 (37.5 mg in an older child)
Prucalopride	**Constipation:** 2 mg QHS (at night) range 0.5–4 mg **SIBO relapse prevention (low dose):** 0.5 mg QHS (range 0.25–1 mg) **Pediatrics**: 0.01 mg/kg
Low-dose naltrexone (LDN)	**IBS:** 0.5 mg once daily **IBD:** 4.5 mg daily **SIBO relapse prevention**: 2.5 mg QHS (diarrhea)/2.5 mg BID or 4.5 mg QHS (constipation) **Symptom management:** 0.5–5 mg daily **Pediatrics**: 0.01 mg/kg

THE ELEMENTAL DIET FOR SIBO TREATMENT

The Elemental Diet is a liquid diet of powdered nutrients in a pre-digested and easily absorbed form, replacing solid food for two weeks (up to three weeks). Studies show an 80 to 84 percent success rate in eradicating SIBO, so it's arguably the most effective SIBO treatment. It is also shown to be safe without risks and complications.

The main ingredients are amino acids, carbohydrates (such as dextrose), fat (may be vegetable oil in prepared formulas, but healthy oils can be used in homemade versions), vitamins, and minerals.

The Elemental Diet should be used alone and as a last resort after rifaximin and botanicals have failed and test results remain unequivocally positive. These patients will often relapse and require retreatment, so continue looking for their underlying cause.

Nutrient	Ingredient	Notes
Protein	Amino acid powder	Should contain full range of amino acids; dose at 15-20% of total calories per day
Carbohydrate	Honey, dextrose, glucose-flavored liquid, or grape syrup	Should comprise 20-50% of total calories per day
Fat	MCT, coconut oil, Udo's oil, flax oil, avocado oil, macadamia oil	Should comprise 30-65% of calories per day
Vitamins & minerals	Must not contain fiber, food, or anything other than synthetic nutrients	Options: Freeda SCD Multi, Klaire VitaSpectrum Powder, Pure Encapsulations Nutrient 950
Sodium	Sea salt; 1,500 mg/d is adequate daily intake	Can mix with formulas or take separately in water

THE IMPORTANCE OF RETESTING

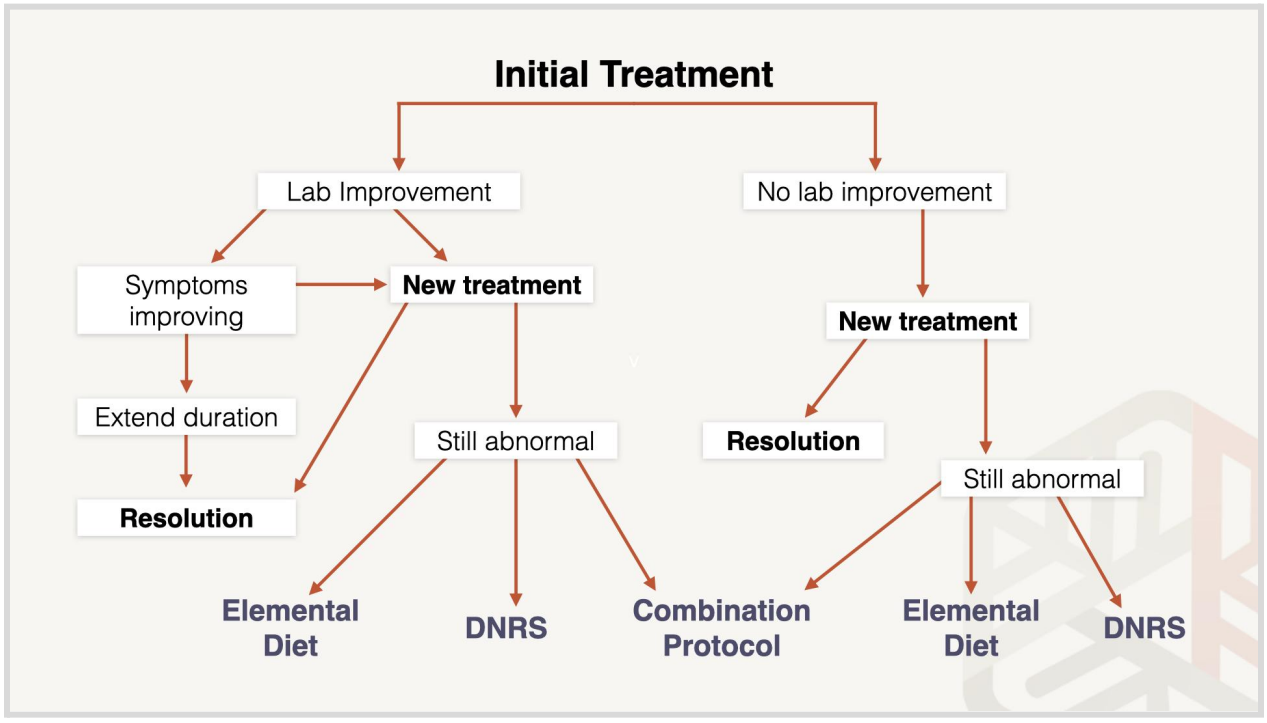
Re-testing is **crucial to success** of treatment

Symptom **improvement** occurs before normalization of breath test

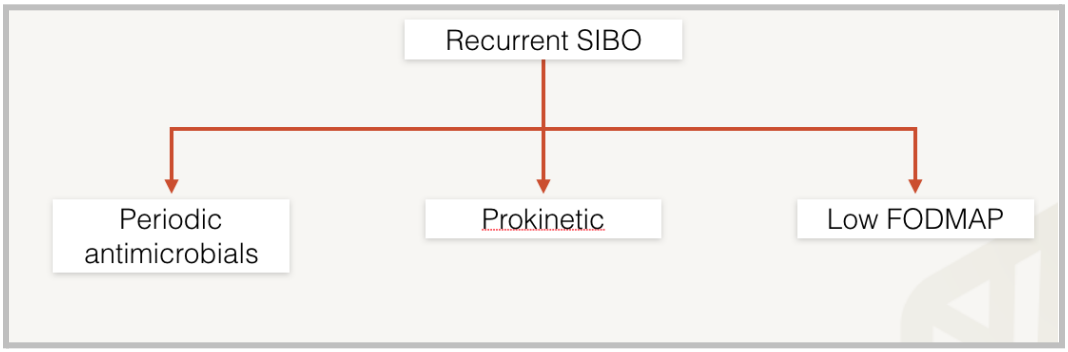
If patient doesn't improve from treatment, doesn't mean treatment didn't work

Ask patient to **stop** antimicrobials for at least **2 to 4 weeks before re-test**

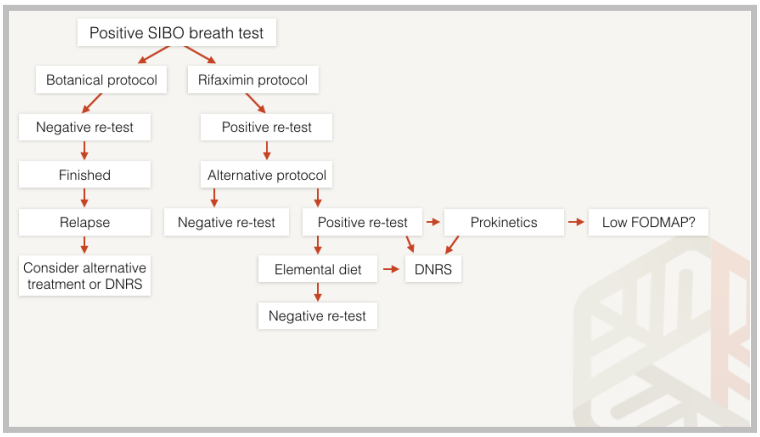
TREATMENT ALGORITHM



Patients may need periodic retreatment with botanical or rifaximin protocols or a maintenance dose of Atrantil if they have methane-predominant SIBO and constipation. Additional steps can be taken to reduce the likelihood of recurrence.



Overall Treatment Algorithm



Note: Remember, the gut is essentially an extension of the nervous system/brain, and, in fact, some researchers refer to it as the "second brain." This is why stress management and lifestyle/behavior modification should always be part of a gut protocol.

Lesson 11: Gut Treatment Dysbiosis and Parasites Review

Two-stage treatment approach:

- First stage is to eradicate or reduce pathological organisms.
- Second stage is to restore a healthy gut microbiome.

Botanicals often have activity against multiple classes of pathogens, and the cause of insufficiency dysbiosis is not necessarily the overgrowth of pathogens or the presence of pathogens. It is more often the lack of beneficial microorganisms that can protect against the overgrowth of commensal bacteria or the invasion of pathogenic organisms.

CORE BOTANICAL PROTOCOL FOR DYSBIOSIS, MILD FUNGAL OVERGROWTH, AND PARASITES

Botanical protocol for dysbiosis & mild fungal overgrowth

Nutreceutical	Dosage
GI Synergy	1 packet BID with breakfast and dinner
Lauricidin	1 scoop TID with each meal
Interfase Plus	3-4 capsules BID on empty stomach
SEED Daily Synbiotic	2 capsules at bedtime
TerraFlora	One capsule with lunch

The typical treatment course is 30 to 60 days, followed by a gut restoration protocol.

Additions for Moderate to Severe Fungal Overgrowth

Additions for moderate to severe fungal overgrowth

Nutreceutical	Dosage
A-FNG (Byron White Formulas)	Slowly build to 10 drops daily w/meals, as tolerated
Biotin	5 mg (5,000 mcg) per day with meals
Molybdenum	200 mcg TID with meals
Activated charcoal (or PectaSol if patient is constipated)	2-6 capsules taken away from other medications and food (or 2-4 capsules PectaSol)

DIET FOR FUNGAL OVERGROWTH

PARASITES

- Treatment depends on several factors such as which parasite it is, how certain you are it's contributing to pathology, your scope of practice, the patient's history, whether the patient has tried other treatments, and the composition of the patient's gut flora.
- Other markers on the Doctor's Data stool test can be useful to determine whether treatment is necessary.
- The most common parasites include *Blastocystis*, *Dientamoeba fragilis*, *Giardia*, and *Cryptosporidium*. Other common parasites include commensals or non-pathogenic organisms like *Endolimax nana* and *Entamoeba coli*, which often do not require treatment.

In most cases, and especially if other gut pathologies like small intestinal bacterial overgrowth (SIBO) and dysbiosis are present, we'll start patients with the core botanical antimicrobial protocol, shown on the preceding pages.

- We typically suggest a minimum of 60 days for antimicrobial protocols if parasites are present and contributing to pathology.

Blastocystis and *D. Fragilis*

Blasto & D. Fragilis	
Nutreceutical	**Dosage**
GI Synergy	1 packet BID (with breakfast and dinner)
Lauricidin	1 scoop TID with each meal
Interfase Plus	3-4 capsules BID on empty stomach
SEED Daily Synbiotic	3 capsules at bedtime
TerraFlora	One capsule with lunch
Saccharomyces boulardii	One BID upon rising and before bed

Use the core botanical protocol with the addition of *Saccharomyces boulardii* at 250 milligrams twice a day. Look for a **dairy-free** brand such as Florastor or Saccharomycin DF.

Caution in patients with risk factors for adverse events such as those who have intravenous catheters or increased bacterial translocation, structural gastrointestinal (GI) problems, or severe immune dysregulation.

First-line pharmaceutical treatment for *Blasto/D. fragilis* (if botanical treatment has failed)

Intervention	Dosage
Nitazoxanide (Alinia)	500 mg BID for 10–30 days

Follow-up pharmaceutical treatment for *Blasto/D. fragilis*

Nutreceutical	Dosage
Iodoquinol (Yodoxin)	325 mg TID with meals for 10 days
Nitazoxanide (Alinia)	500 mg BID with meals for 10 days
Paramomycin	500 mg TID with meals for 10 days

The Centre for Digestive Diseases in Australia has developed a triple-drug therapy, shown above, that their internal research shows is almost 90 percent effective.

Giardia

Botanical Protocol for *Giardia*

The first line is the core botanical protocol with *S. boulardii*.

Pharmaceutical Protocol Options for *Giardia*

Intervention	Dosage
Albendazole	400 mg QD for 5 days
Tinadazole	2 g single dose
Nitazoxanide	250 mg BID for 3 days
Saccharomyces boulardii	3-4 billion CFU BID

If the botanical treatment fails, consider one of the following three options:

1. **Albendazole** 400 mg once a day for five days
2. **Tinidazole** single dose of 2 grams
3. **Nitazoxanide** 250 mg three times a day for three days

In each of these, add ***S. boulardii* at 250 mg twice a day or 3 to 4 billion CFU**.

Cryptosporidium

Cryptosporidium Botanical Treatment

Again, start with the core botanical treatment plus *S. boulardii*.

Pharmaceutical Treatment for *Crypto*

Intervention	Dosage
Nitazoxanide (Alinia)	500 mg BID for 3 days

If the botanical treatment fails, studies show that Alinia clears it in about 70 to 90 percent of cases.

In recalcitrant cases, consider combining botanical therapy with Alinia.

In some cases in which *Blasto*, *Giardia*, or *Crypto* keeps recurring, treatment of family members may be necessary.

CORE BOTANICAL PROTOCOL FOR *HELICOBACTER PYLORI*

Core protocol

Nutreceutical	Dosage
GI Synergy	1 packet BID (with breakfast and dinner)
Lauricidin	1 scoop TID with each meal
Interfase Plus	3-4 capsules BID on empty stomach
SEED Daily Sybiotic	3 capsules at bedtime
TerraFlora	One capsule with lunch

Botanicals in plants that have shown activity against *H. pylori* include garlic, oregano, magnolia, *Cammelia*, *Alchornea*, *Bacopa*, propolis, hydrocatis, *Salvia*, curcumin, *Nigella sativa*, resveratrol, licorice, and *Artemesia*, to name a few.

H. pylori

Additions to Core Protocol for Treatment of *H. pylori*

H. Pylori: additions to core protocol

Nutreceutical/Dietary intervention	Dosage
Sulforaphane	150 mg BID with breakfast and dinner
DGL	750 mg BID empty stomach
Mastic gum	500 mg BID empty stomach
Saccharomyces boulardii	3-4 billion CFU BID at lunch and before bed
100% cranberry juice	500 mL per day
Eat cruciferous vegetables	As much as tolerated; preferably at least 2 cups/d

Saccharomyces boulardii has activity against *H. pylori*.

Sulforaphane

- Broccoli sprouts are one of the best studied compounds with activity against *H. pylori*.
    - They also reduce inflammation caused by *H. pylori*.

Licorice

- Several studies show that licorice is as effective as bismuth in the eradication of *H. pylori* in patients with ulcers.

Mastic gum

- This has also been shown to be beneficial in some studies.

100 percent cranberry juice

- It has been shown to be helpful, since it reduces adhesion of bacteria against mucosal surfaces.

I suggest a **treatment duration of 30 days with this protocol, followed by a retest**.

If the results are still positive:

- Treat for another 30 days, and add **apolactoferrin** at a dose of 300 milligrams twice a day. Apolactoferrin is a natural antibiotic found in cow's milk that binds iron, which *H. pylori* needs to thrive.

Three conditions for pharmaceutical treatment of *H. pylori* are:

1. Peptic ulcer disease
2. Gastric mucosa-associated lymphoid tissue (MALT) lymphomas
3. Strong family history or other risk factors for gastric cancer

First-Line Drug Treatment for *H. Pylori*

Medication	Dosage
PPI (lansoprazole, omeprazole, pantoprazole, etc.)	Dose depends on medication used
Amoxicillin	1 g BID
Clarithromycin	500 mg BID

The first-line treatment consists of a triple therapy using a proton pump inhibitor (PPI), or ranitidine bismuth citrate, combined with clarithromycin and amoxicillin, or metronidazole for those with penicillin allergy, all given twice daily for one to two weeks. The failure rate from this treatment is anywhere between 10 and 24 percent.

Augmented Drug Treatment for *H. pylori*

You could consider improving the efficacy by adding InterFase Plus (biofilm disruption), Lauricidin (has biofilm activity and medium-chain triglycerides), sulforaphane, *S. boulardii*, and apolactoferrin as seen below:

Augmented drug treatment for H. pylori	
Medication	**Dosage**
PPI	Dose depends on medication used
Amoxicillin	1 g BID
Clarithromycin	500 mg BID
Interfase Plus	3 capsules BID on empty stomach
Lauricidin	1 scoop TID with each meal
Sulforaphane	150 mg BID with breakfast and dinner
Saccharomyces boulardii	3-4 billion CFU BID at lunch and before bed
Apolactoferrin	300 mg BID on empty stomach

Second-line Drug Treatment for *H. pylori*

Medication	Dosage
PPI	Dose depends on medication used
Bismuth subsalicylate	524 mg QDS
Metronidazole	250 mg QDS
Tetracycline	500 mg QDS

NUTRITION: WOMEN'S HEALTH

Common premenstrual syndrome (PMS) symptoms include mood swings, changes in appetite, insomnia, brain fog, bloating and water retention, headache, fatigue, depression, anxiety, breast tenderness, acne flare-ups, constipation or diarrhea, and back pain.

Frequent causes of PMS are:

- Estrogen to progesterone imbalance
- Autoimmune disease

Premenstrual dysphoric disorder (PMDD) is a more severe form of PMS. Three to 8 percent of women have PMDD. It's diagnosed when at least five major symptoms of PMS are experienced within seven days before menstruation and are alleviated soon after the start of menstruation.

Polycystic ovary syndrome (PCOS) is diagnosed in women with at least two of the following symptoms: irregular or absent menstrual cycles, elevated testosterone or other androgenic hormones, and polycystic ovaries diagnosed via ultrasound.

Amenorrhea is associated with increased risk of osteoporosis and poor bone density, so it's important to recover menstrual function if possible in order to protect bone health. Loss of estrogen is a common cause of poor density in young women, and if women cannot recover their menstrual cycle for any reason, exogenous hormone replacement may be required in order to preserve bone density.

Pregnancy, fertility, and breastfeeding

- Eliminating any nutrient deficiencies is crucial.
- Avoid white sugar, white flour, highly processed soy products, and industrial seed oils like soy, corn, canola, etc.
- Optimize circadian rhythm.
- Optimize thyroid function and monitor for autoimmune thyroiditis.
- Overweight women may actually need very few extra calories.
- Energy needs are different in each trimester, so that's important to be aware of, and there's typically no increase needed during the first trimester. During the second trimester, women may need about 200 to 300 additional calories daily, and then during the third trimester, when the fetal skeleton is rapidly developing, women may need an extra 400 to 500 calories above their baseline needs.
- For breastfeeding, women need about 300 to 500 extra calories a day to promote a good milk supply.

Menopause

- Many women gain belly fat during menopause. Weight gain is most likely related to slowed metabolic rate rather than menopause itself, and fat gain around the midsection can be due to a drop in estrogen.
- Recommendations for the symptoms of menopause might include strength training; reducing the intake of caffeine, alcohol, and sugar; managing cortisol levels; stress management; blood sugar control; and good social support, which can help keep cortisol from spiking.
- Hormone replacement therapy can significantly reduce perimenopausal symptoms.
- A very-low-carb diet is more effective for women who are sedentary or significantly overweight with significant blood sugar issues, so that might be 7 to 20 percent of calories from carbohydrate. But other women do better on a moderate- or even high-carbohydrate intake, especially if they're exercising regularly.

Lesson 12: Gut Treatment for GERD and IBS Review

The primary focus is to address the underlying pathologies that contribute to these gut syndromes, diseases, and symptoms.

GASTROESOPHAGEAL REFLUX DISEASE (GERD)

- Caused by malfunction of the lower esophageal sphincter, which allows acid to reflux into the esophagus.
- Carbohydrate malabsorption theory that leads to bacterial overgrowth, which in turn causes an increase in gas production, intra-abdominal pressure, and leads to a malfunction of the lower esophageal sphincter.

What might be causing the carbohydrate malabsorption in the first place?

- I believe the cause, in many cases, is low stomach acid (hypochlorhydria).
- Stomach acid inhibits bacterial overgrowth.

- It is well-documented that acid-suppressing drugs promote bacterial overgrowth.
- Stomach acid supports the digestion and absorption of carbohydrates by stimulating the release of pancreatic enzymes into the small intestine.
    - The fermentation of carbohydrates that haven't been digested properly is what produces gas. The resulting gas increases intra-abdominal pressure, which is the driving force behind reflux and GERD.

HOW WE APPROACH TREATING GERD

1. Reduce factors that promote bacterial overgrowth and low stock acid.

How and When to Stop Proton Pump Inhibitors (PPIs)

- In some cases, the patient can stop cold turkey if they switch to a Paleo very-low-carb diet and start taking hydrochloric acid (HCl) and enzymes.
- In other cases, you have to address the underlying pathologies like small intestinal bacterial overgrowth (SIBO), *Helicobacter pylori*, nutrient deficiency first, and then transition the patient off of the PPIs afterward.
- If a patient has been on the drugs for a long time, you may need to titrate off the acid blockers gradually because their endogenous production of stomach acid has been suppressed for such a long time.

Reduce consumption of carbohydrates and/or poorly absorbed carbohydrates if SIBO or hypochlorhydria is present.

Reducing Consumption of Carbohydrates that Feed Bacteria in the Small Intestine

We typically start with a lower-carb Paleo diet as a foundation, and then we might add low-FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) recommendations if they are not getting the success that we would like.

High-FODMAP Foods

Excess fructose	Lactose	Fructans	Galactans	Polyols
Fruit: apple, mango, nashi, pear, tinned fruit in natural juice, watermelon	**Milk:** milk from cows, goats or sheep, custard, ice cream, yogurt	**Vegetables:** asparagus, beetroot, broccoli, brussels sprouts, cabbage, eggplant, fennel, garlic, leek, okra, onion (all), shallots, spring onion	**Legumes:** baked beans, chickpeas, kidney beans, lentils	**Fruit:** apple, apricot, avocado, blackberry, cherry, lychee, nashi, nectarine, peach, pear, plum, prune, watermelon
Sweeteners: fructose, high fructose corn syrup	**Cheeses:** soft unripened cheeses eg. cottage, cream, mascarpone, ricotta	**Cereals:** wheat and rye in large amounts eg. bread, crackers, cookies, couscous, pasta		**Vegetables:** cauliflower, green capsicum (bell pepper), mushroom, sweet corn
Large total fructose dose: concentrated fruit sources, large serves of fruit, dried fruit, fruit juice		**Fruit:** custard apple, persimmon, watermelon		**Sweeteners:** sorbitol (420), mannitol (421), isomalt (953), maltitol (965), xylitol (967)
Honey: corn syrup, fruisana		**Miscellaneous:** chicory, dandelion, inulin		

Another option is a low-fermentation potential diet.

Fermentation potential is a measure of how likely carbohydrates are to be fermented by intestinal microflora. Carbohydrates that are rapidly absorbed high up in the small intestine are given a low fermentation potential.

Foods are categorized as low, medium, or high in terms of their propensity to feed gastrointestinal microbes.

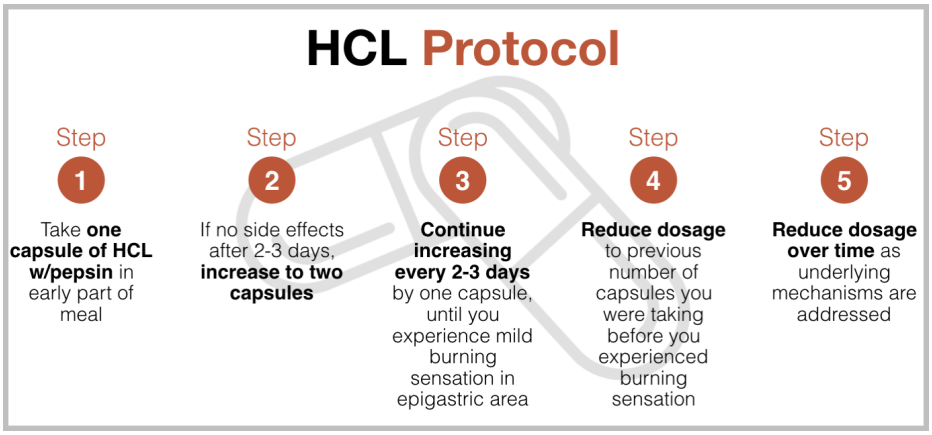
Avoid Foods with Moderate or High Fermentation Potential

Vegetables	Fruits	Starches	Other
Green peas	Banana	Green plantain	Milk
Jerusalem artichoke	Blueberry	Taro root	Fruit juice
	Apple	Basmati rice	Beer
	Cherries	Sweet potato	
	Payaya	Yam	
	Passionfruit	Yuca *(cassava)*	
	Persimmon		

Start with a low-FODMAP diet. It is less restrictive and healthier for beneficial bacteria in the colon. If symptoms don't improve sufficiently, consider adding low-fermentation potential on top of low-FODMAP. This should only be used therapeutically short-term and is not intended for use while the patient is on an antimicrobial protocol.

2. Replace stomach acid, digestive enzymes, and key nutrients for digestion and health.

Acid replacement: Betaine HCl (not recommended if ulcers or gastritis are present or highly suspected), bitter herbs, or apple cider vinegar.



HCl should never be taken, and this HCl challenge should never be performed, by anyone who is using any anti-inflammatory medication such as corticosteroid, prednisone, aspirin, ibuprofen, or other non-steroidal anti-inflammatory drugs (NSAIDs).

3. Restore beneficial bacteria and a healthy mucosal lining in the gut.

Use probiotics, prebiotics, fermented foods, etc. Consider supplements to aid in gastrointestinal (GI) mucosal healing like GI Revive or GastroMend from Designs for Health.

GERD TREATMENT SUMMARY

STEP ONE	Identify & address SIBO & other pathologies	Transition patient off acid-suppressing drugs	Consider low-carb, low-FODMAP, or low-FP diet
STEP TWO	Replace/stimulate stomach acid	Replace/stimulate bile & enzymes	Replace nutrients required for acid, enzymes, bile
STEP THREE	Restore gut ecosystem	Repair gut mucosal lining	

IRRITABLE BOWEL SYNDROME (IBS)

- A diagnosis of exclusion; when diseases such as inflammatory bowel disease (IBD), GERD, or diverticulitis that have a structural effect on the gut are ruled out.
- Symptoms must be present for at least three months, with onset at least six months previously.
- Symptoms of recurrent abdominal pain or discomfort associated with two or more of the following: improvement with defecation and/or onset associated with a change in frequency or consistency of the form of stool.

Potential Causes of IBS:

Gluten/food intolerance	Toxins (biotoxins, heavy metals)
SIBO	Temporomandibular disorder
Disrupted gut microbiome	Immune dysregulation
Infections	Intestinal permeability
Hypochlorhydria	Genetic polymorphisms
Gut-brain axis dysfunction	

How We Approach Treating IBS:

Intervention	Comments
Modified Paleo diet	Avoid gluten & grains; regulate insoluble fiber and FODMAPs
Peppermint oil	Over-the-counter formulations, or IBgard
Stress management	Gut-directed hypnotherapy, mindfulness-based stress reduction (MBSR), etc.
Probiotics	Should be customized according to patient symptoms
Soluble fiber	Soothes digestive system and improves stool frequency and consistency

Rifaximin:

Try all other interventions first, but it can be very effective, and it's safe.

Constipation Remedies

Intervention	Notes
Magnesium glycinate	200–600 mg/d (caution with higher doses over long term)
Magnesium citrate (e.g. Natural Calm)	1–2 tsp before bed; can also help with sleep
Soluble fiber	Glucomannan, PHGG, citrus pectin, acacia (as directed by manufacturer; start slowly & build up)
Probiotics	L. plantarum, B. infantis, SBOs, kefir, fermented foods (start slowly and build up)
Vitamin/electrolyte blend (e.g. Ageless Hydro-C)	Vitamin C, Mg, K, Ca (as directed on website/bottle)
Prokinetics	Iberogast, MotilPro, LDN, low-dose erythromycin
Ozonated magnesium	i.e. Mag 07 (as directed; avoid long-term use)
Atrantil	2 capsules three times a day

Interventions for Loose Stool/Diarrhea

Interventions	Notes
Soluble fiber	Glucomannan, PHGG, citrus pectin, acacia (higher doses may be required)
Probiotics	SBOs, transient commensals, S. Boulardii, VSL#3, Elixa (as directed by manufacturer)
GAPS diet	See IBD section for more info
Rifaximin	May be taken repeatedly if necessary (for IBS-D, start with 10-14 day course)

INFLAMMATORY BOWEL DISEASE (IBD):

- Includes Crohn's disease and ulcerative colitis (UC).
- Thought to be autoimmune diseases.
- Current theory is that the body inappropriately attacks commensal bacteria, which leads to altered gut bacteria, inflammation, and intestinal permeability.
- Risk factors for IBD include genetic predisposition, antibiotic use, and infection.

Three Main IBD Considerations:

1. Address gut pathologies.
2. Address immune triggers and focus on balancing and regulating the immune system.
    a. Identify food intolerances.
    b. Consider 60 days of an autoimmune protocol (AIP), which removes eggs, nightshades, and dairy strictly.
3. Other triggers to consider are heavy metals, mold, or biotoxins, and chronic stress hypothalamic–pituitary–adrenal (HPA) axis activation.

Specific Protocols for Managing IBD:

- If diarrhea is severe and/or the AIP doesn't work, try the GAPS diet.
- Increase butyrate levels.
- Glutathione
- Vitamin D levels are normal
- Vitamin D is a T-regulatory cell promoter as well, and it probably explains part of why low vitamin D is associated with IBD.
- Curcumin
- Colostrum

Probiotics and Treatments for Managing IBD:

- VSL#3
    - Combination of *Bifidobacteria*, *Lactobacillus*, and *Streptococcus* strains.
- Elixa DS: contains 900 billion beneficial bacteria and requires a prescription
- MegaSporeBiotic and SBOs like Prescript-Assist work well for IBD.
- *Saccharomyces boulardii* can help in patients with diarrhea.
- Escherichia *coli* Nissle
    - More effective for constipation.
    - Must be ordered from Germany.
- Fecal microbiota transplant (FMT), is being investigated for IBD.
    - Approved by the FDA for antibiotic-resistant *Clostridioides difficile*.
    - Offered at Taymount Clinic. Our results have been generally good overall, although mixed, some people are not improving and a couple are even getting worse.
- Low-dose naltrexone has been shown to be effective for Crohn's disease in small studies.
- Rifaximin has shown promising results in inducing remission of Crohn's disease and UC.

- Elemental diet can be an effective treatment for Crohn's disease, especially during flare-ups.

Inducing Remission/Treating Active Flare of IBD

Intervention	Notes
GAPS Intro or Elemental Diet	Either can be effective; elemental for 2-3 weeks only
Rifaximin	1,650 mg/d (550 TID) for 12 weeks
Butyrate	Sodium-potassium form (3-4 g/d) & prebiotics
Probiotics (& FMT*)	VSL#3, Elixa, MegaSporeBiotic, Prescript Assist, Mutaflor (E. Coli Nissle 1917)

Maintaining Remission/Ongoing Treatment for IBD

Intervention	Notes
Low-dose naltrexone	4.5 mg used in studies; 1.5–3 mg most used in practice
Probiotics (& FMT*)	VSL#3, Elixa, MegaSporeBiotic, Prescript Assist, Mutaflor (E. Coli Nissle 1917)
Curcumin	NovaSOL, BCM-95, liposomal, Theracurmin
Glutathione	Liposomal form best; 2 tsp per day
Colostrum*	Tegricel form best; 1.5 g/d
Vitamin D	Aim for serum level of 40-60 ng/mL

Lesson 13: No Review (Break Week)

Lesson 14: Gut Treatment Leaky Gut Review

STEPS TO RESTORING GUT BARRIER INTEGRITY:

1. Address underlying pathologies, such as small intestinal bacterial overgrowth (SIBO), parasites, dysbiosis, food intolerances, etc.

2. Rebuild a healthy gut ecosystem.

If you have addressed the underlying pathologies and the patient is already on a

Paleo template diet, but they're still having symptoms, consider running Cyrex Array 3, Array 4, and/or Array 10. Then have the patient remove the foods that have been identified as either equivocal or out of range on these arrays for 60 days.

Permanent removal of all these foods is not necessary in all cases.

For patients who have tested positive for cross-reactive antigens such as dairy products or corn, we've healed their gut and taken steps to restore their gut barrier integrity. Then we've retested them a few months down the line after doing a challenge with corn and dairy, and they are no longer producing antibodies.

Specific Nutrients Play an Important Role in Regulating Gut Barrier Integrity, Including:

- Vitamin A
    - Regulates the growth and differentiation of intestinal cells.
- Vitamin D
    - Deficiency has been correlated with the severity of inflammatory bowel disease and is characterized by intestinal permeability.
- Zinc
    - Supplementation improved mucosal repair in patients with diarrhea.
    - High dose is needed (110 mg TID).
    - There's an 8-week maximum duration as long-term supplementation can cause copper deficiency with serious consequences.

- Short-chain fatty acids:
    - Low butyrate can cause tight junction lesions and impaired intestinal permeability.
    - Best way to increase butyrate over the long term is to increase consumption of fermentable fiber and possibly use prebiotics.
- Prebiotics
    - Galacto-oligosaccharides (GOSs) and fructo-oligosaccharides (FOSs) have been shown to aid intestinal barrier function.
- Probiotics:
    - *Escherichia coli* Nissle 1917 (Mutaflor) was shown to prevent barrier disruption caused by infection of intestinal cells.
    - *Lactobacillus plantarum* in products such as VSL#3 and Ideal Bowel Support was shown to increase tight junction function and improve barrier integrity.
    - *Saccharomyces boulardii* has been shown to restore barrier integrity, according to lactulose/mannitol tests.
- Glutamine
    - Plays a key role in maintaining mucosal cell integrity and gut barrier function.
- Colostrum
    - Protects against non-steroidal anti-inflammatory drug (NSAID)-induced permeability in rats. There's, unfortunately, little research on its effect in humans.

** To get the benefits of both colostrum and glutamine, you can use a high-quality bioactive whey protein powder. ProSerum is one brand that I recommend.

- Lubiprostone:
    - A prokinetic, chloride channel activator used for constipation-predominant IBS.
    - It also improves barrier function in some studies.
- Elemental diet:
    - Can be very effective if severe intestinal permeability doesn't respond to anything else (for example, in patients with severe inflammation and inflammatory bowel disease [IBD]).

- The reason it works is that it contains only foods that are absorbed extremely high up in the small intestine, so it gives the gut a rest. That reduces the inflammation and permeability because the enterocytes of the cells in the small intestine regenerate on their own every three days. If the enterocytes are not being triggered by food, then they can heal.
- Can be problematic because it will starve the beneficial bacteria in the colon, as well.

Summary of Interventions to Restore Intestinal Barrier Integrity

Intervention	Notes
Elimination diet	Run Cyrex Arrays 3, 4 & 10 and remove positive/equivocal foods
Vitamins A & D	Best obtained from high-vitamin cod liver oil
Zinc	Very high dose (110 mg TID) required; **8 week maximum duration, don't do long term!**
Butyrate/SFCAs	3-4 g/d of sodium-potassium butyrate, and/or prebiotics and fermentable fiber
Probiotics	E. coli Nissle 1917, L. plantarum, S. boulardii, SBOs, transient commensals
Glutamine or whey	20-40 g/d of glutamine, and/or bioactive whey if tolerated (whey has colostrum too)
Lubiprostone	May be particularly useful in IP w/ constipation
Elemental diet	For severe IP that doesn't respond to anything else

Lesson 15: Gut Treatment Probiotics and Prebiotics Review

Prebiotics, probiotics, fermentable carbohydrates, and fermented foods all play an integral role in the maintenance of gut health. One of the biggest differences between ancestral and current diets is how much fermentable fiber people consume.

Probiotics:

- Primarily help to balance and regulate the immune system and reduce inflammation in the gut.
- However, most probiotics do not quantitatively change the composition of the gut microbiome over time (soil-based organisms may be an exception to this).

Prebiotics:

- Prebiotics increase the beneficial bacteria over time because they provide food for those beneficial species of bacteria.

All long-term gut healing protocols should include both probiotics and prebiotics for optimal results. However, it is sometimes necessary to avoid prebiotics early in the treatment process because in certain cases, they can make conditions such as small intestinal bacterial overgrowth (SIBO), parasite infections, and fungal overgrowth worse.

Fermentable fibers:

- Prebiotics that selectively stimulate a limited number of favorable species, in particular, *Lactobacillus* and *Bifidobacterium*.
- Increase the production of short-chain fatty acids (SFCAs), increase the acidity of the colon, and make the gut less hospitable to pathogens and more hospitable to beneficial species of bacteria.
- Intake can be low even on a Paleo diet because of limited fruit and starches. An informal study showed lower fiber intake when compared to vegetarian or vegan diets.

SOURCES OF DIFFERENT TYPES OF FERMENTABLE FIBER IN THE DIET

Fiber type	Where it's found in diet
Inulin	Garlic, onions, leeks, chicory root, jerusalem artichoke, dandelion root, burdock root, yacon
Beta-glucans	Mushrooms, dates, oat fiber
Pectins	Fruit *(esp. peaches, apples, oranges, grapefruit and apricots)*, vegetables (*esp. carrots, tomatoes, potatoes)*, legumes *(esp. peas)*
Resistant starch	Cooked & cooled potatoes, cooked and cooled rice, legumes *(esp. lentils)*, green plantains

There are three classes of fermentable fiber: soluble fiber, nonstarch polysaccharides, and resistant starch.

Soluble fiber:

- Best tolerated by patients with gut issues in general because they're not FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides and polyols), and they tend to have a soothing effect on the digestive tract.
- Helpful for patients with both diarrhea and constipation.
- Modified citrus pectin:
    - Advise patients to start slowly because of potential detox reactions if they have toxins.

Summary of Soluble Fiber Options:

Fiber	Comments
Partially hydrolyzed guar gum (PHGG)	Very well tolerated; not viscous; easy to mix with water and food
Glucomannan (konjac root)	Well tolerated; shown to reduce blood sugar
Psyllium husk	Tendency to cause bloating; can be purchased as pure, organic powder
Acacia	Well tolerated; can be purchased as pure, organic powder
Modified citrus pectin (MCP)	Well tolerated; chelates heavy metals especially when combined with alginate comples

We generally start with PHGG or glucomannan if the patient has blood sugar or weight regulation issues. Advise patients to rotate back and forth between different forms of fermentable fiber.

NONSTARCH POLYSACCHARIDES (NOTE THAT MANY OF THESE ARE FODMAPs):

Fiber	Comments
Larch arabinogalactan	Immune stimulator and regulator
Beta-glucan	Immune stimulator and regulator
Inulin and oligosaccharide (FOS)	Often used in functional foods; most likely to cause GI distress
Galacooligosaccharide (GOS)	Potent promoter of bifidobacteria and lactobacilli

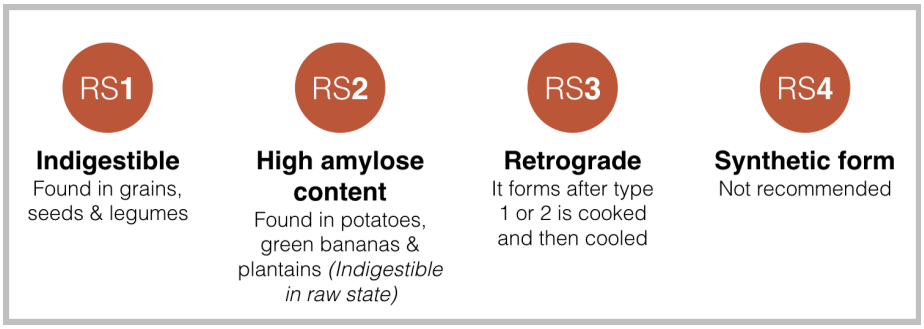
I recommend two products, BiotaGen and Galactomune, from Klaire Labs, and if you take both of these products, it covers the entire spectrum of nonstarch polysaccharides, so you can use them together or you can rotate them back and forth.

Resistant starch (RS):

- Is not digested in the stomach or small intestine and reaches the colon intact.

- Although it is a starch, it is not broken down into glucose, and it doesn't hit the bloodstream, so it doesn't have any effect on blood sugar.
- Is an insoluble fiber, but unlike other insoluble fibers, resistant starch is fermented by colonic bacteria.
- Resistant starch selectively stimulates the growth of beneficial species like bifidobacteria and lactobacilli.
- It increases the concentration of SCFAs like butyrate and propionate and has been shown to protect against colon cancer, improve metabolic health, reduce fasting blood sugar and body weight, and improve insulin sensitivity.

Four Types of Resistant Starch



Food sources of prebiotics:

- Cooked and cooled potatoes, sweet potatoes, and yams
- Cooked and cooled parboiled rice or other properly prepared rice
- Cooked and cooled properly prepared (soaked or sprouted) legumes
- Dehydrated plantain chips

Note that these cooked and cooled foods can be reheated at low temperatures less than 130 degrees Fahrenheit and maintain the benefits of RS.

Empirically, resistant starch can also help with sleep and mood, so patients who have insomnia, depression, anxiety, and other issues like that can actually improve with resistant starch, and that effect is possibly mediated via the gut–brain axis.

BRIEF SUMMARY OF BENEFICIAL EFFECTS OF PROBIOTICS

Probiotics help patients by temporarily (only when the patient is taking them) tuning and regulating the immune system, promoting anti-inflammatory pathways, and creating a favorable environment for beneficial bacteria.

Direct protection of the intestinal barrier	Modulation of neurotrophic chemicals, including brain-derived neurotrophic factor
Influence on local and systemic antioxidant status, reduction in lipid peroxidation;	Limitation of carbohydrate malabsorption
Direct, microbial-produced neurochemical production, for example, gamma-aminobutyric acid (GABA)	Improvement of nutritional status, for example, omega-3 fatty acids, minerals, dietary phytochemicals
Indirect influence on neurotransmitter or neuropeptide production	Limitation of small intestinal bacterial overgrowth
Prevention of stress-induced alterations to overall intestinal microbiota	Reduction of amine or uremic toxin burden
Direct activation of neural pathways between gut and brain	Limitation of gastric or intestinal pathogens (for example, Helicobacter pylori)
Limitation of inflammatory cytokine production	Analgesic properties

Fermented Foods:

Fermented foods have several advantages over commercial probiotic products.

1. Hominids have been eating fermented foods for more than two million years, and we're adapted to getting microbes from these foods for this reason.
2. Some evidence suggests that probiotic bacteria in foods may be better able to survive the stomach acid.
3. They increase the bioavailability of mood-regulating B vitamins, magnesium, and zinc, and they may improve vitamin D status.
4. The concentration of probiotic organisms is significantly higher in some fermented foods. For example, one cup of kefir contains approximately 2.35 trillion colony-forming units (CFUs). Most probiotic supplements only have a few billion.
5. Fermented foods are much cheaper than commercial probiotics.

Commercial Probiotics:

Commercial probiotics can be used as part of an antimicrobial protocol to address a particular symptom such as constipation or diarrhea or to provide strains that may not be available in

fermented foods. Also, commercial probiotics are useful for patients who do not tolerate fermented foods very well, especially patients with amine or histamine intolerance.

ANTIBIOTIC RECOVERY PROTOCOL

Intervention	Comments
Fermented foods	Dairy kefir particularly beneficial if tolerated
Fermentable fiber	Onions, garlic, jerusalem artichoke, chicory, etc.
Probiotics	SBOs + lactic acid bacteria, including *Saccharomyces boulardii*
Prebiotics	Soluble fiber, non-starch polysaccharides, and/or RS

POST-ANTIBIOTIC TREATMENT:

- Suggest plenty of fermented foods, fermentable fiber, and bone broth.
- Consider SBOs like Terraflora or MegaSporeBiotic.
- Add something with *Saccharomyces boulardii* in it, alone or in a product like ABX Support from Klaire Labs, which has *Saccharomyces boulardii, Lactobacillus rhamnosus*, *Bifidobacterium bifidum*, and *Bifidobacterium breve* to help with side effects while on antibiotics.
- Recent studies have made us question the benefit of post-antibiotic probiotic therapy, with some results indicating that taking probiotics after antibiotic therapy may slow recovery of the normal microbiome by up to five months. More research will need to be done, but in the meantime, we are more reluctant to recommend probiotics after antibiotic therapy unless there are circumstances that warrant probiotic support.

Lesson 16: Gut Treatment Lifestyle and Behavior Review

LIFESTYLE AND BEHAVIORAL MODIFICATIONS FOR ADDRESSING GASTROINTESTINAL ISSUES

It is helpful to keep in mind that the gut is just one big bundle of nervous system tissue. In fact, the gut has been referred to as the second brain. There is 400 times more serotonin produced in the gut than in the brain and 500 times more melatonin produced in the gut than in the pineal gland.

THREE MODALITIES PARTICULARLY HELPFUL FOR GUT-RELATED PATHOLOGIES

1. Mindfulness-based stress reduction, in particular the body scan
2. Acupuncture
3. Hypnotherapy for irritable bowel syndrome (IBS)

MINDFUL EATING

1	2	3	4	5
Take **smaller bites** of food to begin with *(easier to chew smaller pieces)*	Chew **slowly** and steadily	Chew until your mouthful of food is **liquefied** or lost all of its texture	**Finish chewing** and swallowing completely before taking another bite of food	Wait to **drink fluids** until you've swallowed

SUMMARY OF BEHAVIOR AND LIFESTYLE MODIFICATION RECOMMENDATIONS

Intervention	Comments
Manage stress	MBSR, acupuncture, hypnotherapy
Eat mindfully	Chew food well, eat in relaxed environment until only 3/4 full
Get adequate sleep	7-8+ hours recommended
Exercise appropriately	Depends on overall health status of patient

Gut Treatment: Advanced Treatments

These are only recommended when the patient is still not better after everything we have previously discussed in this ADAPT course.

PROBIOTIC AND PREBIOTIC IMPLANTS:

These can be appropriate for patients who can't tolerate oral prebiotics or probiotics.

FECAL MICROBIOTA TRANSPLANT (FMT):

- This is a transfer of stool or its microbial isolates from one human donor to another.
- The U.S. Food and Drug Administration (FDA) approved to treat antibiotic-resistant *Clostridioides difficile*.
- Studies have suggested it may be effective for other gastrointestinal (GI) conditions such as IBS, possibly inflammatory bowel disease (IBD), metabolic disease, chronic fatigue, and even depression.
- Clinically, we have seen some miraculous turnarounds but have also seen patients get significantly worse, and it's difficult to tell how each patient will respond.

Clinical Options for FMT:

1. Send the patient to a clinic outside the United States that offers FMT.
    a. Taymount Clinic in the UK and Bahamas
        i. Pros: Experienced with FMT, professional staff, prescreened donors, comfortable accommodations nearby, rotate donors for a particular patient to get microbiota from five different donors or more.
        ii. Cons: Can be cost prohibitive.
2. The Centre for Digestive Diseases in Australia is an option for people who live in Australia.
3. Supervise the patient through a DIY home procedure.
    a. Legal gray area.
    b. Suitable donors can be difficult to find.
    c. Procedure is not likely to be as effective as it would be in a clinical environment like the Taymount Clinic.
4. Mark Davis of the Bright Medicine Clinic in Portland has a center that does FMT that you may consider contacting.

Helminthic Therapy:

- Based on the “old friends” hypothesis, which suggests that part of what is causing the dramatic rise in autoimmune disease and other immune-related dysfunction is the disappearance of organisms that we co-evolved with for the vast majority of human history, and they include organisms such as *Necator americanus*, or hookworm.
- From a clinical perspective, I can’t recommend helminthic therapy due to a lack of regulation or standardization or even any resource that I can point you to to legally use as a clinician.

NUTRITION: WEIGHT LOSS

Spontaneous and intentional reduction in calories engages survival mechanisms that aid in weight loss.

Particular strategies that can be used to improve weight loss include the following:

- Keeping the food simple leads to eating less, thanks to homeostatic and hedonic mechanisms that regulate food intake.
- Eat enough food. Paradoxically, under-eating can stall weight loss as a result of metabolic adaptations that promote weight storage.
- Carbohydrate intake must support activity levels.
- Move throughout the day and increase non-exercise physical activity.
- Include whole life modifications like sleep, stress, and social support.
    - Stress impacts the physiological function of the gut, but it may also impact the composition of the gut that may be due to changes in inflammatory cytokine levels and neurotransmitters.
- Track calorie intake to deepen awareness around overeating and under-eating.

NUTRITION: HIGH CHOLESTEROL

Studies show that about 75 percent of the population's cholesterol levels are not affected at all by their dietary intake. The remaining 25 percent do experience an increase in low-density lipoprotein (LDL), but they also experience an increase in high-density lipoprotein (HDL), so there's no net change in their LDL-to-HDL ratio. It's thought that because of that, there's no clinical significance to any increase that that 25 percent sees when they eat cholesterol-rich foods like eggs.

Primary influences on high cholesterol, in terms of pathology, are:

- Genetics
- Metabolic dysfunction or insulin resistance
- Inflammation
- Infections
- Poor thyroid function

Key lipid markers to use for monitoring cardiovascular disease (CVD) risk are LDL particle (LDL-P) and/or apolipoprotein B (ApoB).

The best dietary approach to start with for insulin resistance is a low-carb diet. The best dietary approach for familial hypercholesterolemia or for someone with a high ApoB that has not been

reduced by addressing all other potential imbalances is the Mediterranean Paleo diet with lower fat and higher starch.

Focusing on monounsaturated fats like olive oils, avocados, nuts, omega-3 fats, and shellfish may help reduce atherogenic markers like LDL-P or ApoB if there are genetic causes that drive CVD risk.

Everyone with higher risk of heart disease should focus on eating cold-water fish, which is a great source of long-chain omega-3 fats, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), as well as other nutrients like highly bioavailable protein and selenium. These have been shown to decrease the risk of CVD by decreasing inflammation, increasing membrane fluidity, and positively changing gene expression.

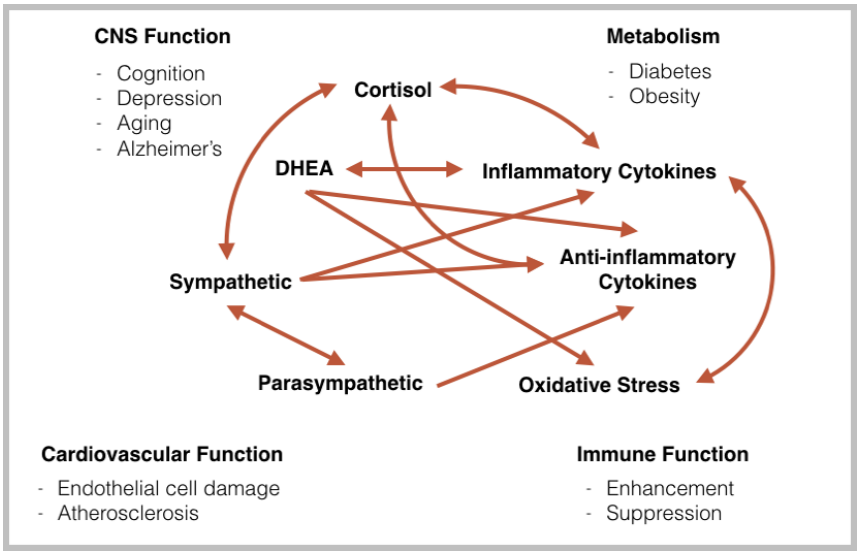
Lesson 17: No Review (Case Studies)

Lesson 18: HPA-D Basic Physiology Review

Allostasis refers to the process of adaptation to acute stress.

The factors that mediate allostasis are interconnected, as you can see below, which means that too much or too little of any mediator can disturb the entire network, leading to dysfunction and disease.

ALLOSTASIS: MAINTAINING STABILITY THROUGH CHANGE



When cytokine production exceeds the anti-inflammatory capacity of cortisol, we end up with chronic inflammation.

On the other hand, when cortisol suppresses inflammatory cytokines too much, then we have a weakened immune response, and we can see this in increased capacity to get colds and flus and possibly even things like cancer.

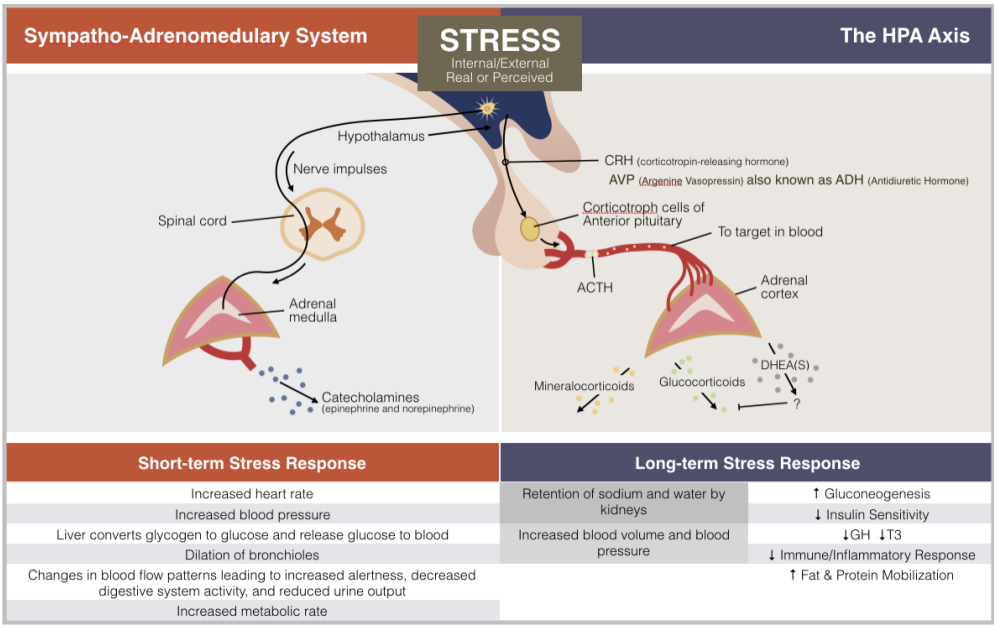
Allostatic Load

Allostatic load refers to the wear and tear produced by imbalances in the mediators of allostasis. Examples include hypertension, atherosclerosis, and diabetes, as well as stress-induced remodeling in the parts of the brain that support memory, executive function, and mood.

Some of the presentations that can manifest with allostatic load include:

1. Normal stress response, where there is a stressor and the activity of the system goes up, and then a recovery period when the activity drops.
2. Prolonged response to stress, where the patient is under continual stress, and the system gets activated and stays activated over time.
3. In some people, this prolonged activity can progress into an inadequate response where they are unable to mount a sufficient response to future stressors.

WHAT HAPPENS WHEN WE EXPERIENCE STRESS?

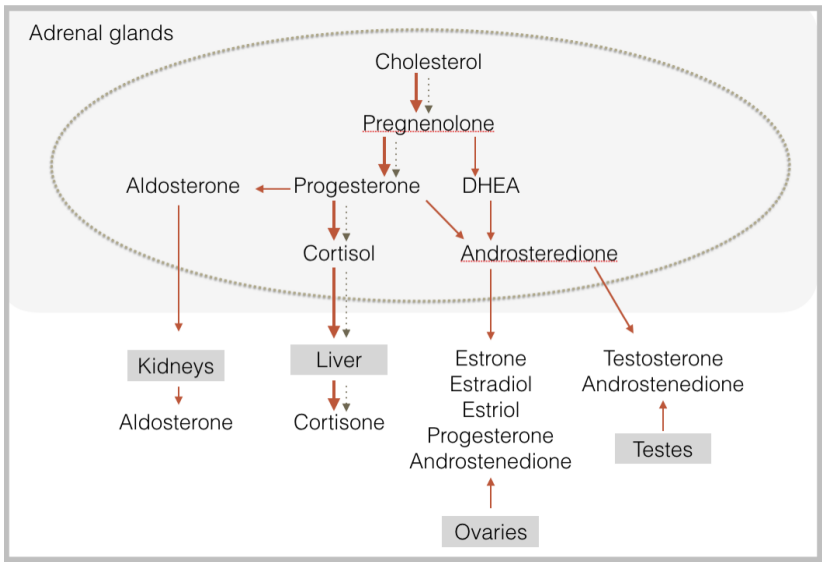


Short-term Stress Response	Long-term Stress Response	
Increased heart rate	Retention of sodium and water by kidneys	↑ Gluconeogenesis
Increased blood pressure		↓ Insulin Sensitivity
Liver converts glycogen to glucose and release glucose to blood	Increased blood volume and blood pressure	↓GH ↓T3
Dilation of bronchioles		↓ Immune/Inflammatory Response
Changes in blood flow patterns leading to increased alertness, decreased digestive system activity, and reduced urine output		↑ Fat & Protein Mobilization
Increased metabolic rate		

When the hypothalamus is triggered by a stressor:

- Corticotropin-releasing hormone (CRH), aka corticotropin-releasing factor (CRF), and another hormone called arginine vasopressin (AVP), aka antidiuretic hormone (ADH), are released.
- They travel down the pituitary and provoke the production of ACTH. They also activate noradrenergic neurons from the locus coeruleus norepinephrine (LC-NE) system.

The hypothalamus is the major control tower of all hormone production in the body and the governor of the stress response. Two hypothalamic nuclei with the biggest influence on the stress response system are the paraventricular nucleus (PVN), which releases CRH and AVP, and the suprachiasmatic nucleus (SCN), the main controller of the circadian clock.



The adrenal glands produce steroid hormones as part of the stress response. Cortisol, DHEA, testosterone, progesterone, and estrogen are all steroid hormones with molecular structures similar to each other. The adrenals also produce DHEA and pregnenolone, which are known as pro-hormones. They function as hormones themselves, but they also act as precursors to downstream hormones such as cortisol and testosterone, seen in the diagram above.

The adrenal glands have two compartments, the adrenal medulla, which secretes epinephrine and is responsible for the fight-or-flight response, and the adrenal cortex, which comprises 80 percent and produces glucocorticoids such as cortisol, mineralocorticoids such as aldosterone, and androgens such as DHEA. The adrenal cortex also produces some sex hormones in limited amounts.

PREGNENOLONE

Pregnenolone is a pro-hormone made from cholesterol that is produced in the adrenals and the central nervous system (CNS). It is a precursor of progesterone, mineralocorticoids, glucocorticoids, androgens, and estrogens, as well as the neuroactive steroids.

Pregnenolone naturally declines with age and has been proposed as a marker for age-related cognitive decline. In young, healthy populations, it protects the brain, supports cognition, memory, and mood, improves stress tolerance and well-being, and boosts energy.

DEHYDROEPIANDROSTERONE (DHEA)

DHEA is considered the daughter of pregnenolone. It is a precursor to testosterone, estrogen, and other corticosteroids. It is also classified as a neurosteroid and has many of the same effects as pregnenolone, but it's more potent.

It plays a fundamental role in the maintenance of hormonal balance and vitality, which is why some have referred to it as an anti-aging hormone.

DHEA is converted into DHEA sulfate in the blood and then back to DHEA when it's taken up by the tissues. The levels of DHEA sulfate are typically much higher than DHEA, so that is often the form that is tested. It promotes blood flow, protects the brain, supports cognitive function and mood, opposes effects of cortisol, promotes bone health, and regulates blood sugar and insulin sensitivity.

CORTISOL

- Glucocorticoid produced in the adrenal cortex.
- Primary stress hormone released in response to stressors but also to low blood sugar.
- When blood sugar drops, cortisol works in tandem with insulin to provide adequate glucose to cells for energy.
- Cortisol is involved with resolution of the inflammatory response.
    - Patients with low cortisol will not be able to turn off that inflammatory cascade, and that can lead to chronic inflammation.
- High cortisol weakens immune function.
- Cortisol reduces bone formation and calcium absorption in the intestine.
- It increases sodium retention and potassium excretion.
- Cortisol damages the hippocampus, which impairs learning and inhibits retrieval of stored memories.

Cortisol Rhythm

- The highest levels of cortisol would be produced around 8:00 a.m.
- It gradually declines throughout the day.

- It is lowest between midnight and 4:00 a.m.
- The production of cortisol is regulated by information about the light–dark cycle that's transmitted from the retina to the paired suprachiasmatic nuclei in the hypothalamus.

Cortisol Production Is Regulated by a Negative Feedback Cycle

Under stress:

Hypothalamus produces CRH –> pituitary produces ACTH –> adrenals produce cholesterol –> cholesterol is manufactured into pregnenolone → converted into cortisol and released into the blood stream → hypothalamus detects higher levels of cortisol and downregulates CRH and ACTH production.

Epinephrine Is Regulated by a Positive Feedback Loop

Epinephrine in the blood acts on CRH to secrete more epinephrine. This ensures that the body's primed and ready to deal with acute stress. This loop is interrupted by cortisol.

More cortisol	More cortisone
Genetic polymorphisms	Genetic polymorphisms
Hypothyroidism	Hyperthyroidism
Inflammation	Human growth hormone
Visceral obesity	Estradiol
Insulin resistance	Testosterone
Excess sodium	Quality sleep
Licorice	Magnolia, Scutellaria, Zizyphus, Citrus peel
Obesity and insulin resistance	Ketoconazole

Seven Primary Mechanisms that Determine the Tissue-specific Regulation of Cortisol:

1. Metabolic clearance of cortisol
2. Binding proteins that carry cortisol through the body
3. Activation / inactivation of cortisol to cortisone and back
4. Genomic signaling
5. Heat shock proteins and co-chaperones
6. Nongenomic signaling

7. Adrenal brain DHEA production

Important Takeaways:

1. Physiology governing cortisol bioavailability is extremely complicated, far more complicated than the adrenal fatigue model has led on.
2. Sometimes we may need to treat empirically for hypothalamic-pituitary-adrenal (HPA) axis dysfunction rather than relying solely on test results because there are effects that govern cortisol's function and bioavailability in the body that won't necessarily show up on the test results.
    a. Consider therapeutic trials.

ALDOSTERONE

- Mineralocorticoid that is produced in the adrenal cortex under the direction of ACTH.
- Secreted in a diurnal rhythm similar to cortisol, so it peaks at 8:00 a.m. and has a low point of midnight to 4:00 a.m.
- Plays a central role in regulating blood pressure by increasing reabsorption of ions in water in the kidneys and causing the conversion of sodium and secretion of potassium, increasing water retention and blood volume.
    - Where sodium goes, water will follow.
    - Sodium opposes potassium.
- Low aldosterone can lead to low blood pressure, high pulse rate, postural hypotension, getting dizzy when standing up quickly, salt cravings, palpitations, and, in severe cases, may lead to hyperkalemia and hyponatremia.

CATECHOLAMINES: EPINEPHRINE AND NOREPINEPHRINE

Together, they comprise the sympathoadrenal medullary system (SAS). The SAS has two components: the adrenomedullary hormone system, which is mediated by epinephrine and adrenaline, and the sympathetic nervous system, mediated by norepinephrine.

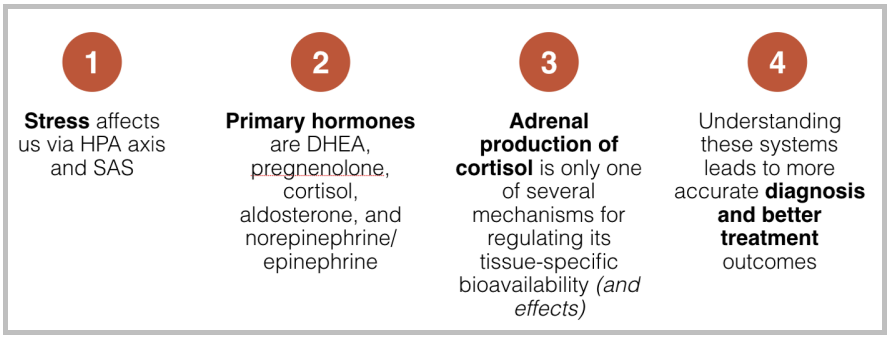
NOREPINEPHRINE

- Synthesized and released in the CNS, as well as the sympathetic nervous system, and a smaller amount of norepinephrine, about 7 percent, is made in the adrenal glands.
- Stress enters the body via our senses. It activates the LC, which is an area of the brainstem, and then norepinephrine is released.
- Norepinephrine activates the HPA axis and triggers the cascade that ultimately results in the production of cortisol and DHEA immediately.
- Norepinephrine stimulates arousal, so low levels of this neurotransmitter and hormone are associated with brain fog, poor memory, and depression.
- Elevations of norepinephrine can lead to panic, including anxiety, restless sleep, increased startle reflex, palpitations, muscle tension, and teeth grinding.

EPINEPHRINE/ADRENALINE

- A hormone and the primary mediator of the adrenomedullary hormone system.
- Ninety percent of it is produced by the adrenal glands in the adrenal medulla, and the remaining 10 percent is produced in certain neurons in the body.
- Plays an important role in the fight-or-flight response.
- Increases heart rate and the strength of heart contractions.
- It constricts blood vessels in veins, it’s a bronchodilator, and it inhibits histamine release.
- It stimulates the breakdown of glycogen into glucose in the liver, which results in an increase in blood sugar.

KEY TAKEAWAYS



Steroid hormone production begins with the conversion of cholesterol into pregnenolone.

This primarily happens in the organs themselves, such as the adrenal glands and the gonads. This is really important to understand because when you know that the conversion of cholesterol into pregnenolone primarily happens in the organs and glands, not in the bloodstream, that explains why taking supplemental DHEA and pregnenolone does not significantly increase estrogen and testosterone levels.

Cortisol

Adrenal gland: Cholesterol –> pregnenolone –> 17-OH-pregnenolone –> 17-OH-progesterone –> cortisol

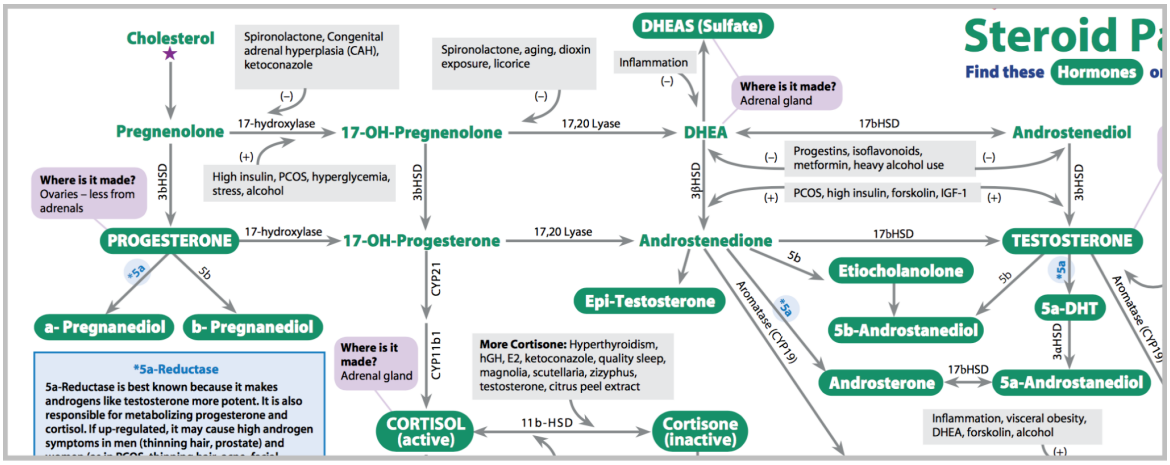
Active cortisol can be converted into cortisone, which is relatively inactive. The factors that favor more cortisone include hyperthyroidism, human growth hormone, estradiol, good sleep, drugs such as ketoconazole, and adaptogenic herbs such as magnolia, *Scutellaria*, and *Ziziphus*, and, finally, testosterone. The factors that favor more cortisol include hypothyroidism, inflammation, visceral obesity, high insulin, excess sodium, and licorice, which increases the half-life of circulating cortisol.

Adrenal Gland: DHEA

Cholesterol –> pregnenolone –> 17-OH-pregnenolone –> DHEA.

DHEA has several metabolites. One is DHEA sulfate, also produced in the adrenal gland.

DHEA itself is not present in the urine, but DHEA sulfate is. The conversion of DHEA to DHEA sulfate is inhibited by inflammation, so it's possible to have normal DHEA but low DHEA sulfate when inflammation is present.



5-Alpha Reductase

- Metabolizes progesterone, cortisol, and some of the androgens.
- Responsible for turning testosterone into dihydrotestosterone, which is 10 times more potent than testosterone.
- Upregulated 5-alpha reductase metabolism is associated with prostatitis and prostate cancer in men, hirsutism and polycystic ovary syndrome (PCOS) in women, and other conditions caused by elevated androgens.
- The factors that increase 5-alpha reductase metabolism include high insulin, PCOS, and obesity.
- Agents that are known to decrease 5-alpha reductase activity include saw palmetto, nettle, immunoglobulin M (IgM), epigallocatechin gallate (EGCG), progesterone, zinc, and finasteride.

5-Beta Reductase

- Less is known about this pathway, but it's seen as a more favorable conversion pathway for androgen metabolism than the 5-alpha pathway.

- When 5-beta reductase is favored, you see higher tetrahydrocortisol relative to alpha-tetrahydrocortisol and tetrahydrocortisone, which is the less active form of cortisol, as well as higher levels of etiocholanolone and 5-beta androstenediol.

NUTRITION: HYPERTENSION

- Normal blood pressure is 120 over 80.
- Prehypertension is between 120 over 80 to 139 over 89.
- Stage one hypertension is 140 over 90 to 159 over 99.
- Stage two hypertension is anything over 160 systolic or 100 diastolic.
- Major diet and lifestyle changes include the following:
    - Reduce intake of refined carbohydrates and sugar.
    - Paleo template is a great starting place; be sure to match carb intake with activity levels.
    - Pay attention to intake of minerals (potassium, magnesium, calcium). For example, eating a high-potassium diet is actually probably more effective and a better choice for most people than a very-low-sodium diet. It's the ratio between potassium and sodium that makes the biggest difference.
    - Consuming grass-fed dairy (if tolerated), specifically consuming enough vitamin K2 (ghee, butter, hard cheeses, poultry liver, fermented vegetables) may be protective against hypertension via effects on vascular stiffness and arterial calcification.
    - Consume a pound of cold water fatty fish per week.
    - Consider teas like hibiscus, hawthorn, or green tea.
    - Eat beets.
    - Get more sunshine.
    - Reduce stress.
    - Focus on sleep.
    - Exercise regularly.

NUTRITION: GERD, IBS, AND OTHER DIGESTIVE DISORDERS

- The microbiota has three core functions:
    - Metabolic: breaks down nutrients and creates nutrients
    - Structural: short-chain fatty acids that are produced after the metabolism of carbohydrates stimulate the growth of epithelial cells
    - Protective function: the gut lining acts as a barrier between the outside world and the interior of the body
- Preventing and treating intestinal permeability
    - Reduce or eliminate the intake of substances that can provoke intestinal permeability, like gluten.
    - Follow a Paleo diet because it is nutrient-dense and anti-inflammatory.
    - Be aware of different types of fiber, preparation, and digestive symptoms that can occur because of them (for some patients).
    - Limit alcohol intake.
    - Limit/avoid medications like non-steroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs), and antibiotics.
    - Be aware of environmental toxins like bisphenol A (BPA) and their impact on gut permeability.
    - Address chronic stress.
    - Consume bone broth (rich source of glycine and gelatin for digestive health).
- Low stomach acid
    - Signs and symptoms for screening
        - Feelings of fullness after meals with gas bloating one to three hours after meals
        - Skin, nails, and hair with acne, eczema, dry skin, brittle hair, and hair loss in women
        - Chronic fatigue, anemia, hypoglycemia, neuropathy, poor concentration

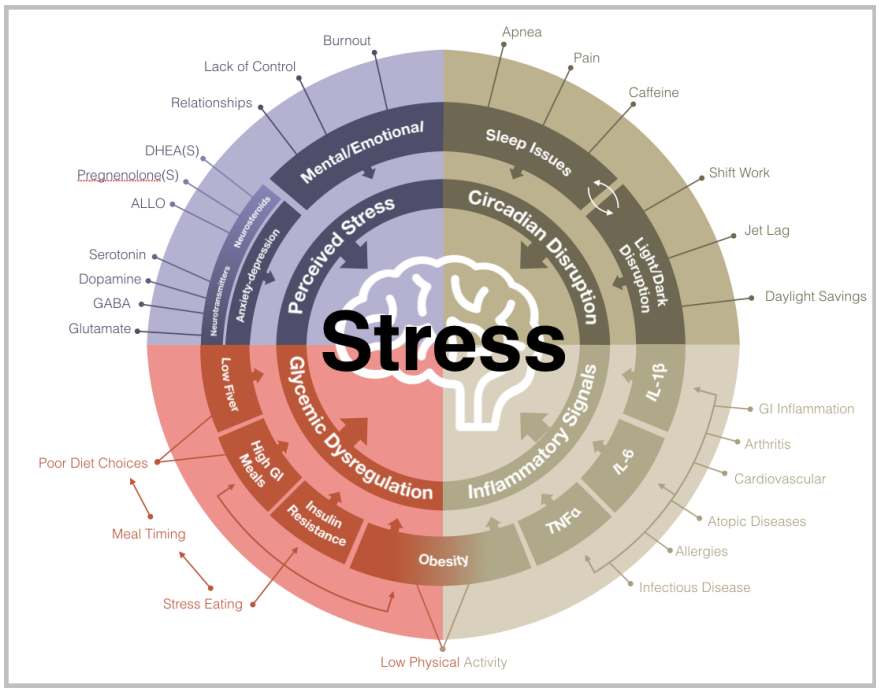
- If symptoms present, the patient should slowly titrate hydrochloric acid and take up to one capsule at a time until they experience a slight burning sensation or sense of warmth in their epigastric area, then back down to the lowest dosage that they were taking before they experienced the sensation.
- Address underlying issues while helping support symptoms.
- Consider supplementing with digestive enzymes if warranted.

NUTRITION: ANXIETY, DEPRESSION, AND MENTAL HEALTH DISORDERS

- Focus on reducing inflammation, particularly gut inflammation and improving gut health.
  - Reduce sugar and improve blood sugar stability.
  - Consider the impact that caffeine may be having on each patient, individually.
  - High intake of Omega-6 from seed oils may contribute to depression.
  - Complete gluten elimination.
  - Avoid chemicals and preservatives in high processed and refined foods.

Lesson 19: HPA-D Basic Physiology Review

Hypothalamic-pituitary-adrenal axis (HPA) axis dysfunction can be caused by several aspects of the modern lifestyle. Below is a chart by Dr. Guilliams, which refers to four categories of stressors that lead to chronic HPA axis dysregulation.



The first category is perceived stress (relationship difficulties, financial troubles, public speaking, work stress, chronic illness of a family member, an event perceived as harmful and uncontrollable, internal stress caused by neurotransmitter imbalances). Four key factors determine the magnitude of the HPA axis response to perceived stress, and thus the relevance of a stressor. The mnemonic for them is NUTS:

1. Novelty of the event
2. Unpredictable nature of an event
3. Perceived threat to the body or ego
4. Sense of loss of control

Control is a key factor in protecting an animal or a human being from stress-induced disease. This is one reason that psychological stressors can actually be more harmful to us than physical stressors. We generally have more control over, or at least the ability to respond to, physical stressors. In most cases, psychological and emotional stressors tend to last much longer than physical stressors, and, therefore, they are more likely to cause illness and disease.

In the face of psychological stressors that are more common in our modern life, however, we don't often discharge the buildup of stress hormones and neurotransmitters that are flowing through our body to get us ready for fight or flight. The chemicals that produce the stress response continue to flow through our body, and we end up in a chronic state of hyperarousal. This overstimulation of our sympathetic nervous system is a major causative factor of stress-related disease, including high blood pressure, arrhythmias, digestive problems, chronic headaches, backaches, sleep disorders, and chronic anxiety.

CIRCADIAN DISRUPTION

- The HPA axis is intertwined with mechanisms that control the circadian rhythm.
- It is affected by the 24-hour light–dark cycle.
- Sleep deprivation is probably the most significant type of circadian disruption for most people.
- Sleep loss negatively affects mood and emotional processing and leads to significantly higher subjective experiences of stress.
- It has also been shown to increase cortisol levels.

Exposure to light has a profound influence on the HPA axis

- Environmental light is the strongest influence on the circadian system.
- Light exposure has been shown to shift the natural human biological clock.
- Short-wavelength or blue light is the most melatonin-suppressive and is typically emitted by devices such as televisions, computer screens, cell phones, and tablets. This means that products like tablets, smartphones, and other devices are major sources for suppressing melatonin at night, which reduces sleep duration and disrupts sleep.
- Along with blue light emitted from electronic devices, research has shown that even being exposed to normal levels of room lighting can have a similar negative impact on melatonin and the HPA axis.
- Bright light exposure during the day helps regulate cortisol levels and balance the HPA axis, and this anchor light, as it's referred to, anchors your circadian rhythm, causing it to be less fragile so that light at night has less of an ability to shift your rhythm.

- The first 30 to 60 minutes of outdoor light exposure creates about 80 percent of that anchoring effect, so just going outside for about half an hour at lunchtime or in the morning can provide you with the majority of anchoring light you need to maintain a healthy circadian rhythm.

Jet Lag

- Jet lag alters the natural circadian clock.
- Chronic jet lag has been shown to decrease sleep quality, reduce cognitive function, raise cortisol levels, and even increase the risk of cancer due to disturbances of melatonin levels.

Shift Work

- Shift work also alters the circadian clock.
- Alternating shift work causes the most disruption.

Caffeine

- Caffeine can disrupt the HPA axis and sleep.
- This is particularly true for the 50 percent of the population that has a variant in the CYP1A2 gene that leads to slow metabolism or processing of caffeine.
- Timing of intake, when coffee is consumed, also matters.

GLYCEMIC DYSREGULATION

- Cortisol is known as a glucocorticoid.
- HPA axis dysregulation causes glycemic dysregulation.
- For example, elevated cortisol levels increase visceral and abdominal fat, and visceral or abdominal fat produces **inflammatory mediators** like interleukin-1 beta, interleukin-6, and tumor necrosis factor (TNF) alpha, all of which activate the HPA axis and trigger further cortisol production.
- Hypoglycemia, or low blood sugar, is a powerful HPA axis activator.
- An insulin tolerance test, which causes hypoglycemia, is considered one of the most reliable measures of HPA axis responsiveness or function.

The HPA axis is also involved in mechanisms that manage overall energy balance, insulin sensitivity, metabolic function, food selection, and satiety. Factors that cause glycemic dysregulation, like poor diet, lack of sleep, and exercise will dysregulate the HPA axis, which in turn causes glycemic dysregulation.

These bidirectional relationships should be considered when you're treating patients because they can affect treatment plans.

SPECIFIC EXAMPLES OF THINGS THAT AFFECT THE HPA AXIS:

1. Physical activity, both too much and too little.
    a. Exercise causes inflammation, and that stimulates the HPA axis, which has a lot of benefits when adequate time is allowed for recovery.
    b. Overtraining, which is characterized by not enough time for recovery, can dysregulate the HPA axis.
    c. Physical inactivity is also associated with sleep apnea and other sleep disorders that can disrupt the HPA axis
2. Social isolation
    a. A landmark study found that social support was a stronger predictor of survival than physical activity, body mass index, hypertension, air pollution, alcohol consumption, and even smoking 15 cigarettes a day.
    b. Try giving your patients some ideas and support for how they can reach out and create more social connections in their lives.
3. Gut issues can also dysregulate the HPA axis.
    a. Gut pathogens such as *Escherichia coli* can provoke intestinal permeability and activate the HPA axis, causing repeated stress response.
    b. Beneficial microbiota might play a role in regulating the HPA axis.
4. Food intolerances can also activate the HPA axis.

a. They induce intestinal permeability. Antigens cross the gut barrier and provoke immune response and inflammation, leading to an altered composition of the gut microbiota, which activates the HPA axis.

b. Chronic infections also affect the HPA axis, primarily via inflammation.

5. Environmental toxins can play a significant role in disrupting the HPA axis.

    a. In animals, fetal exposure to environmental endocrine-disrupting chemicals (EDCs) such as bisphenol A (BPA), and phthalates lead to altered HPA axis signaling and cortisol dysregulation.

    b. EDCs have also been shown to alter DNA methylation.

    c. Inflammation is probably a key mechanism governing the effect of toxins on the HPA axis. For example, higher mercury levels increase proinflammatory cytokine activity.

6. Thyroid function

    a. Higher thyroid-stimulating hormone (TSH) levels are correlated with higher cortisol.

    b. Hypothyroidism has been shown to cause increases in cortisol by reducing the metabolism or disposal of free cortisol.

7. Certain drugs and substances affect the HPA axis.

    a. Selective serotonin reuptake inhibitors (SSRIs)

        i. Reduce morning cortisol levels and responsiveness of the HPA axis.

        ii. Cortisol levels are often high in major depressive disorder.

        iii. In people who are depressed or who have normal or low cortisol, these effects of SSRIs could be undesirable.

    b. Corticosteroids have the biggest impact on HPA axis (for example, prednisone and hydrocortisone).

        i. They are more powerful than endogenous cortisol, and both target tissue signaling and HPA axis feedback inhibition.

        ii. The most common cause of true adrenal insufficiency is ongoing corticosteroid therapy.

The takeaway from this is you cannot supplement your way out of HPA axis dysfunction. You have to address behavior, lifestyle, and underlying pathologies such as gut issues, chronic infection, toxic exposure, hypothyroidism, and things that lead to glycemic dysregulation, inflammation, and you have to address circadian disruption along with perceived stress.

Lesson 20: HPA-D or Adrenal Fatigue Review

An argument should be made that the concept of adrenal fatigue is not supported by the current scientific evidence. It should be replaced by more specific terms that are in line with decades of research on how stress impacts physiology.

SELYE'S GENERAL ADAPTATION SYNDROME

Hans Selye proposed the general adaptation syndrome. Acute or chronic stressors eventually cause the hypothalamic-pituitary-adrenal (HPA) axis to move from being hyperresponsive in the early stages to hyporesponsive in the later stages.

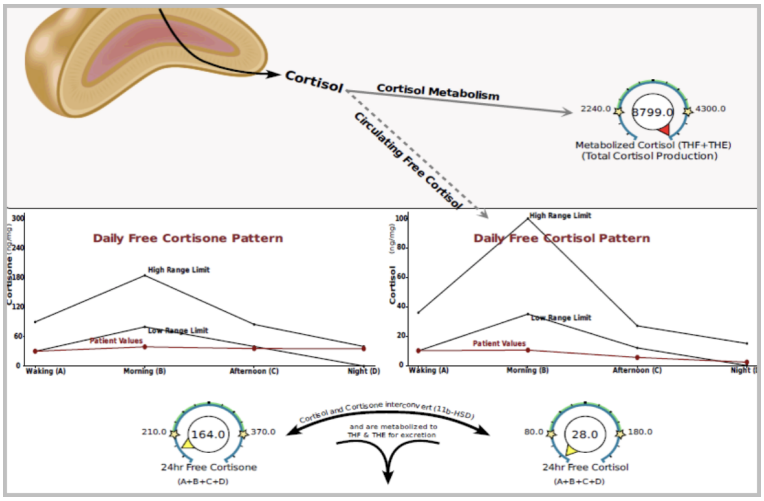
- **Stage one:** Increase in cortisol and a decline in pregnenolone and dehydroepiandrosterone (DHEA). This stage could last many months or even years.
- **Stage two:** An adaptation occurs that results in reduced cortisol production such that cortisol may actually even be in the normal range. What distinguishes stage two from normal HPA axis function would be the lower levels of DHEA and pregnenolone.
- **Stage three:** All three hormones continue to fall until they reach failure or exhaustion.

ADRENAL FATIGUE CONCEPT

- Many people who are diagnosed with or self-diagnose adrenal fatigue don't actually have low cortisol.
- Salivary cortisol testing, particularly the adrenal stress index, is commonly used to identify adrenal fatigue.

- Cortisol measured in saliva is free, and this is the most potent form because only free cortisol has cell signaling effects and is available to activate the cellular transcription response.
- Free cortisol is only about 3 to 5 percent of the total cortisol in the body at any given time. The rest of the cortisol in the body is cleared by several metabolic pathways before it's conjugated and excreted into the urine.
- In the serum, cortisol is bound to cortisol-binding globulin, and cortisol binding globulin varies a lot, even among healthy individuals, and is affected by many disease states and drugs.
- Therefore, free cortisol is not the best marker for overall cortisol production.
- Measuring the urinary metabolites of cortisol (as measured in the Dried Urine Test for Comprehensive Hormones [DUTCH]), since most cortisol is excreted in the urine, is the best way of estimating overall production.

Studies have found that many people who have low free cortisol actually have high total cortisol. This is observed in subjects who have insulin or leptin resistance and are overweight, which, of course, accounts for about two-thirds of the U.S. population right now. It can also be caused by things such as chronic stress, glucocorticoid use, including steroid inhalers for things such as asthma, hyperthyroidism, and chronic fatigue syndrome.



Above is an example of a patient who has low free cortisol, low free cortisone, a flattened diurnal cortisol rhythm, and would be diagnosed with so-called adrenal fatigue.

However, their metabolized cortisol level on the upper right is two times the upper end of the lab range, and this person does not have low total cortisol. In fact, they have very high total cortisol production.

Another factor that contributes to the adrenal fatigue concept is different ranges used by labs that do saliva testing can indicate different results. It's very difficult to compare results from saliva labs, making reliable evaluation difficult. This is why our preference for testing is with the DUTCH hormone test as they use a tighter range, which is appropriate, as often the functional lab ranges are a little bit tighter because we're looking for optimal function rather than just disease.

Saliva cortisol testing often returns falsely low values, especially in the morning.

- About 30 to 45 minutes after we wake up, light activation of the suprachiasmatic nucleus leads to an increase of up to 50 percent in cortisol secretion. This is called the cortisol awakening response (CAR).
- The cortisol that is produced during the CAR within the first 30 to 45 minutes of awakening accounts for more than half of the total cortisol reported on a full day's saliva test.
- This means that the timing of the first sample collected is absolutely crucial to getting accurate results because the adrenal stress index estimates the total cortisol production for the day based on those four readings.
- This is a huge problem because most labs only suggest doing the waking sample during a window of time, for example, between 6:00 and 8:00 a.m., with no regard for waking time.

The term "adrenal fatigue" is virtually absent from the scientific literature, whereas there are thousands of studies detailing the effects of stress on human physiology via dysregulation of the HPA axis. Things such as high cortisol, cortisol resistance, or disruption of the diurnal rhythm are far more common than low cortisol as a mechanism.

Even if cortisol is low in some patients, it's rarely because the adrenals are fatigued or exhausted and unable to produce it. Instead, the control mechanisms for cortisol are mostly found in the brain and the central nervous system, as well as in local tissues.

SEVERAL MECHANISMS LEADING TO LOW CORTISOL:

Developmental Factors

The theory is that early life stress can permanently program the HPA axis to a maladaptive response.

Corticotropin-Releasing Hormone (CRH) Receptor Downregulation

Animal studies have shown a decrease in CRH receptor sensitivity in the pituitary gland after prolonged exposure to stress.

Impaired Cortisol Signaling

Refers to a group of related dysfunctions; chronically high cortisol levels will lead to cortisol resistance.

Decreased Cortisol Bioavailability

This is one cause of increased levels of cortisol-binding globulin. Another cause is the increase of the conversion of cortisol, which is the more active form, into cortisone.

Maladaptive Response

In people suffering from recurrent or chronic infections or chronic inflammation, the body may reduce cortisol production or signal an attempt to deal with the infection.

Enhanced Sensitivity to Negative Feedback

This is associated with conditions such as rheumatoid arthritis, post-traumatic stress disorder (PTSD), sexual abuse, burnout syndrome, and chronic pelvic pain.

None of these mechanisms leading to low cortisol has anything to do with the adrenals being fatigued or unable to produce it.

There is some evidence that low cortisol may occasionally be caused by a reduced ability of the adrenal glands to produce it. A few studies in chronic fatigue syndrome have suggested low cortisol is caused by adrenal insufficiency, and these studies measured free cortisol but not total cortisol. It may just be that in these studies, they're not measuring total cortisol, so it only appears that cortisol is low.

PREGNENOLONE STEAL

- Pregnenolone is the precursor of all steroid hormones, and in times of stress, pregnenolone is diverted into the production of cortisol at the expense of DHEA, testosterone, and estrogen.
- It is true that chronic stress can lead to a drop in DHEA, but this effect is not caused by a reduced availability of pregnenolone because it's being "stolen" for cortisol production. That theory assumes that there's a single pool of pregnenolone in the adrenal glands from which both DHEA and cortisol are produced.
- DHEA and cortisol are produced in the mitochondria of individual cells, not from a central pool of pregnenolone.
- Cortisol and DHEA are produced in different parts of the adrenal cortex.
    - DHEA is produced in the zona reticularis.
    - Cortisol is produced in the zona fasciculata.
- There is no known mechanism by which pregnenolone can be stolen from inside of the mitochondria of cells in the zona reticularis, which are producing DHEA, and be transferred to the mitochondria of cells in the zona fasciculata to produce cortisol.
- Cortisol production is regulated primarily by cell-specific enzyme concentration and signaling coming from outside of the adrenal glands themselves.
- The amount of cortisol produced is significantly higher than the amount of DHEA produced.
- If there were an adrenal pregnenolone pool that had enough pregnenolone to handle the higher levels of cortisol, then that pool would also be available for the much smaller amount of DHEA we need when cortisol synthesis decreases even a little.
- Finally, there's no convincing research suggesting that oral pregnenolone supplements increase DHEA levels.

So what does lower DHEA when cortisol is high? It is governed by regulatory processes such as negative feedback inhibition, receptor signaling, and genomic regulation of enzymes.

ADRENAL FATIGUE THREE-STAGE MODEL

1. This is a complicated process with multiple contributing factors, and thus, it is not as neat and tidy as in this three-stage model.
2. Not everybody progresses through it in the proposed adrenal fatigue order.
3. Even when people do progress from a hypercortisol state to a hypocortisol state, they may do that at very different rates.

Why does this matter?

1. A clear understanding of what's actually happening leads to more appropriate and better treatment outcomes.
2. If we want to maintain credibility among patients and other medical providers and continue to advance Functional Medicine, we need to align our diagnostic and therapeutic methods as much as possible with research related to the HPA axis.

A more appropriate term for the syndrome that we're referring to would be HPA axis dysfunction or HPA axis maladaptation.

NUTRITION: DIABETES AND OTHER BLOOD SUGAR DISORDERS

- The most common contributor to metabolic disease is diet (the Standard American Diet or Standard British or Standard Industrialized European diet, etc.) because it can lead to high glucose levels.
- For those with metabolic issues, a Paleo-type diet is recommended, and most will do better on a lower-carb version of this diet, though that's not always the case.
- Glucometer tracking can be a useful tool for assessing blood sugar disorders and carbohydrate tolerance. The goal should be attaining the following targets: 140 milligrams per deciliter or lower one hour after a meal and 120 milligrams per deciliter or lower two hours after a meal.
- High-protein diets have been shown to have a stabilizing effect on blood sugar levels. Now, the caveat or contraindication here would be if the patient already has kidney disease.

- High blood sugar meal timing strategy includes not snacking between meals and intermittent fasting.
- Low blood sugar meal timing strategy includes eating more frequently throughout the day, sometimes as often as every two to three hours, having a little bit of protein just to keep the blood sugar from dropping too much and keep it balanced, eat within 30 minutes of waking up and make sure that their breakfast contains at least 30 grams of protein, as that can really help stabilize their blood sugar throughout the day.

NUTRITION: THYROID DISORDERS

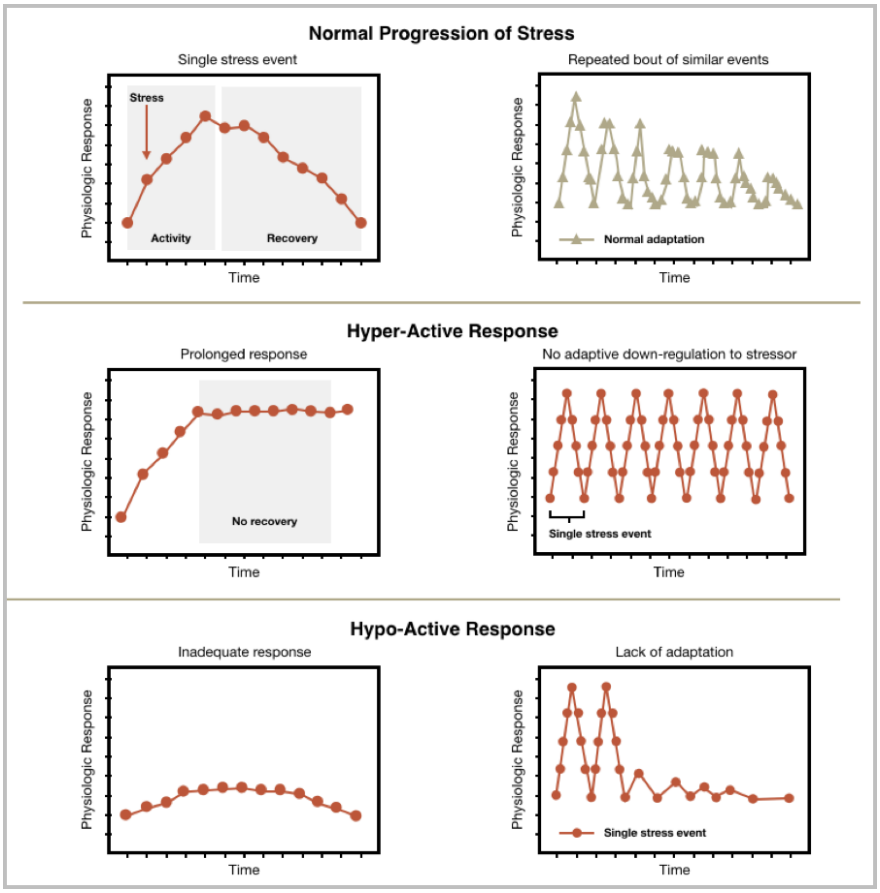
- Autoimmune hypothyroidism is called Hashimoto's disease or Hashimoto's thyroiditis, and hyperthyroidism with an autoimmune component is known as Graves' disease
- Hashimoto's disease is the most common autoimmune disorder.
- Measuring only thyroid-stimulating hormone (TSH) may cause you to miss other causes of thyroid dysfunction like pituitary dysfunction or poor conversion of thyroxine (T4) to triiodothyronine (T3).
- Dietary recommendations for hypothyroidism, Hashimoto's disease, and Graves' disease, hyperthyroidism, depend on the etiology of the condition. Different patterns of thyroid dysfunction require different focuses for treatment, including diet and lifestyle recommendations.
- Two major causes of non-autoimmune thyroid disorders are iodine and selenium deficiency.
- Adequate selenium protects against the effects of iodine toxicity; selenium deficiency is more common in people with impaired digestion or serious inflammation.
- Improving gut health is critical for all forms of thyroid disease. Thyroid hormones strongly affect tight junctions and immune functions of the small intestine and stomach; T3 and T4 have been shown to protect the gut lining against stress-induced ulcers, and TSH influences the development of gut-associated lymphoid tissue.
- The 60-day Autoimmune Protocol (AIP) Paleo diet is the preferred diet for autoimmune thyroid disease.
- A six-month gluten elimination is also recommended for autoimmune thyroid disease.

NUTRITION: AUTOIMMUNE DISORDERS

- Three dietary approaches to addressing autoimmunity are:
    - Removing foods that may trigger or exacerbate an immune response, like the AIP Paleo diet
    - Increasing intake of nutrients that promote optimal immune function like glutathione, eicosapentaenoic acid and docosahexaenoic acid, vitamin D, niacin, riboflavin, vitamin B2, vitamin B6, vitamin C, magnesium, iron, copper, zinc, and manganese
    - Increasing intake of foods that promote a healthy gut microbiota

Lesson 21: HPA-D Pathology Review

General categories of dysfunction caused by allostatic load.



1. **Normal progression of stress**
    a. The stress response increases during the event, and then it declines over time after the stressful event has passed.
    b. Repeated bouts of similar events.
        i. At first, the stress response is higher, but repeated bouts of the same event result in the stress caused by that event to be lower.
2. **Hyperactive stress response**
    a. Prolonged response to a single stressor. An example would be posttraumatic stress disorder (PTSD).
    b. No adaptive downregulation to the stressor.

i. Single stress event and then a repeated bout of similar events, but instead of seeing the healthy normal adaptation, we see repeated activation that's similar to the first time we experienced the event.

3. **Hypoactive response**
    a. Inadequate response to a single stressor
        i. This often happens when the hypothalamic–pituitary–adrenal (HPA) axis has become downregulated, and then the patient is unable to mount an effective response to future stressors.
    b. Lack of adaptation to a repeated bout of similar events,
        i. The whole HPA axis gets downregulated, and the patient is not able to mount a successful stress response to these repeated events.

There are two additional key concepts related to allostatic load:

RESILIENCE

- The immediate capacity of cells, tissues, and organ systems to respond to changes in physiological need, which would be induced by stress.

METABOLIC RESERVE

- Long-term capacity of tissues and organ systems to withstand repeated changes to physiological needs.
- Put in simpler terms, metabolic reserve is the stored-up reserve that's available for each metabolic and organ system to maintain and rebuild its physiological resilience.
- Metabolic reserve can be depleted, and it can also be replenished and strengthened.

The goal of the stress response is to keep us alive through physiological challenges and threats.

FIGHT-OR-FLIGHT RESPONSE

- Sympathetic nervous system is activated.

- Heart rate and blood pressure increase.
- Pupils dilate to take in as much light as possible.
- Veins in the skin constrict.
- Blood glucose level increases.
- Muscles tense up.
- Smooth muscle relaxes.
- Nonessential systems shut down.
- Patients have trouble focusing on small tasks.

Once the threat has passed, the parasympathetic nervous system is activated, and the body starts using resources for activities that promote long-term survival again.

REST-AND-DIGEST RESPONSE

- Heart rate and blood pressure decrease.
- Saliva and digestive enzymes increase.
- Bronchial tubes in the lungs constrict.
- Muscles relax.
- Pupils in the eyes constrict.
- Blood flow to the gastrointestinal (GI) tract and endocrine organs increases.
- Immune function is restored.

Most of our patients are in a nearly continual fight-or-flight response. The body was never designed for the constant nature of modern stressors. This directly contributes to chronic inflammatory disease and all the symptoms that our patients experience.

Only one of these systems can be activated at a time: the parasympathetic or sympathetic system. It's not just constant stressors such as traffic, circadian disruption, poor diet, sleep deprivation, shift work, jet lag, financial stress, or relationship stress that's are issues. It is mental or emotional stressors that have increased in the modern world.

The three other categories that we've discussed, glycemic dysregulation, circadian disruption, and inflammation, are also far bigger players today than they were for our ancestors.

Constant activation of the HPA axis increases allostatic load and then stretches physiological resilience and depletes the metabolic reserve in nearly every tissue in the body. Inflammation and continued activation of the sympathetic nervous system contribute to HPA axis dysfunction (HPA-D) and thus a vast majority of chronic disease.

The repeated activation of the HPA axis eventually leads to a downregulated response to new stressors. This is the body's attempt to protect itself from chronically elevated cortisol levels.

This leads to an ongoing semipermanent catabolic state where breakdown and wear and tear are happening faster than the body can rebuild itself.

Most of the stress-induced changes in physiological function are mediated by alterations in gene regulation triggered by glucocorticoids.

CONDITIONS RELATED TO HPA AXIS HYPERFUNCTION

Depression	Alcoholism
Anorexia nervosa	Diabetes
Obsessive-compulsive disorder	Central obesity
Panic disorder	PTSD in children
Excessive exercise	Hyperthyroidism

CONDITIONS RELATED TO HPA AXIS HYPOFUNCTION

Atypical/seasonal depression	Nicotine withdrawal
Postpartum depression	Rheumatoid arthritis
Chronic fatigue syndrome	Asthma
Fibromyalgia	Eczema
Premenstrual tension syndrome	Hypothyroidism

Lesson 22: HPA-D Diagnosis Review

The three basic categories of assessment are:

1. Signs, symptoms, and history
2. Laboratory tests
3. Perceived stress questionnaires

Although it's not desirable to make a diagnosis based on symptoms alone, it's important to know that not all patterns of hypothalamic–pituitary–adrenal (HPA) axis dysfunction (HPA-D) will show up in lab test results. Remember, cortisol signaling issues can be tissue-specific, not just systemic, which means that you can't necessarily detect them in saliva, blood, and urine.

Increased salivary, serum, or urine cortisol levels may be compensated for by glucocorticoid receptor resistance in specific tissues, and low cortisol may be compensated for by upregulated receptor function in particular tissues, which would not be detected by commercial lab tests either.

This means that HPA-D is a clinical diagnosis, and history, signs, and symptoms play a very important role.

RISK FACTORS FOR HPA AXIS DYSFUNCTION

Trauma *(including early life)*	Circadian disruption
Poor diet	Mental/emotional stress
Food intolerances	Environmental toxins
Chronic illness	Chronic infections
Inappropriate physical activity	Injury
Poor sleep	Lack of social support

"RED FLAG" SYMPTOMS OF HPA AXIS DYSFUNCTION

Difficulty falling or staying asleep	Impaired exercise tolerance or recovery
Waking up feeling tired even after 7-8 hours of sleep	Weakened immune system
Afternoon energy crashes	"Brain fog" and memory issues
"Second wind" late at night	Extreme hunger, irritation, or agitation before meals
Waking up with heart pounding in middle of the night	Postural hypotension
Inability to handle stress	

OTHER SIGNS AND SYMPTOMS OF HPA-D

Muscle fatigue/weakness/pain	Increased or decreased appetite
Headaches	Difficulty with word recall
Teeth grinding	Dizziness
Cold/clammy hands and feet	Dry skin
Dry mouth/problems swallowing	Loss of muscle tone
Digestive distress	Dark circles under the eyes
Shortness of breath	Weight gain
Depression and/or anxiety	Frequent urination

PERCEIVED STRESS IS ONE OF THE FOUR MAJOR HPA AXIS TRIGGERS

It may seem unnecessary to assess perceived stress. It's pretty obvious when we're stressed out, right? But patients often have differing levels of awareness around this. This is why I suggest using questionnaires to assess perceived stress and stress inventories. When patients see a very high score on these assessment tools, they're more likely to treat it as a real problem.

PERCEIVED STRESS SCALE

The 10-question version is the most commonly used in clinical settings and is included as a handout for this ADAPT course. It measures the degree to which situations in one's life are appraised as stressful, and it is designed to assess how unpredictable, uncontrollable, and overloaded respondents find their lives to be.

Markers that research suggests are most effective for evaluating HPA-D are free cortisol, metabolized cortisol, the diurnal free cortisol and free cortisone rhythm, the cortisol awakening response (CAR), dehydroepiandrosterone (DHEA), and the DHEA-to-cortisol ratio.

CORTISOL

There are four primary methods of assessing cortisol levels:

1. **Serum**
    a. Total cortisol levels represent both bound cortisol, which is 95 percent of the cortisol in the body, and unbound or free cortisol, which is 3 to 5 percent of the cortisol in the body.
    b. Most of that cortisol is bound to cortisol-binding albumin or globulin and is not bioavailable. We know that several conditions and medications affect cortisol-binding globulin levels, so using total serum cortisol is not a great idea.
    c. Free cortisol can be calculated from measurements of total cortisol plus cortisol-binding globulin.
2. **Hair**
    a. Cortisol accumulates in the hair via passive diffusion from the blood.
    b. It's being investigated as a historical measure of HPA-D.
    c. It is possible for about 6 centimeters worth of hair, equivalent to six months of cortisol production.
3. **Saliva**
    a. Saliva only contains free cortisol.
    b. It's a noninvasive, time-specific marker that allows you to capture the diurnal rhythm of cortisol production in a convenient setting, and you can, through those four different readings, estimate total cortisol production.
4. **Urine cortisol**
    a. This is a 24-hour collection.
    b. Urine contains free cortisol, but it also contains many cortisol metabolites, such as cortisone.
    c. Assuming normal cortisol clearance rates, most cortisol synthesized by adrenal glands will be metabolized in the liver and cleared in the urine within 90 minutes. Urine cortisol is a reflection of cortisol production over 90 minutes.

d. Precision Analytical's test called DUTCH—dried urine test for comprehensive hormones—involves collection of a small amount of urine on filtered paper four times a day. This allows estimate diurnal production, like saliva, but it also provides information on both total free cortisol and overall cortisol using metabolites as well as free cortisone and metabolized cortisone.

One of the most commonly used markers for HPA axis function in the scientific literature is called the cortisol awakening response, or CAR.

- CAR is the increase of cortisol that occurs in the morning just after awakening.
- The proper procedure for capturing the CAR would be testing at waking, and then again at 30, 45, and 60 minutes.
- Rising cortisol begins several hours before awakening due to normal HPA axis activity, and then there is a transient 30- to 45-minute additional increase of up to 50 percent in cortisol secretion when light comes into the retina and activates the suprachiasmatic nucleus.
- CAR is a marker of how the HPA axis responds to stress.
    - For example, lower CAR is observed in people with posttraumatic stress disorder (PTSD), chronic fatigue, and burnout, and it's higher in people with ongoing job stress and higher levels of perceived stress.

DHEA:

For DHEA and DHEA sulfate, assessment options include serum, saliva, and urine.

Note that the concentration of DHEA sulfate is 300 times higher than DHEA in serum.

1. **Serum:**
    a. DHEA and DHEA sulfate are often combined into a measurement called DHEA-S.
2. **Saliva:**
    a. Testing of DHEA in saliva is somewhat controversial, in part because we understand so little about DHEA.
    b. Salivary DHEA sulfate levels are only 2.5 times higher, versus 300 times in serum, than salivary DHEA.
    c. Also, levels of DHEA-S drop quickly in the first hour after awakening, and this can make timing difficult.

3. **Urine:**
    a. DHEA sulfate can be measured but not DHEA.
    b. Some studies suggest that a combination of DHEA sulfate, androsterone, and etiocholanolone may be a more accurate indication of total DHEA production.

The **cortisol-to-DHEA ratio** is another important marker to consider.

- It can be an indicator of catabolism versus anabolism.
- Anabolism means building things up, tissue repair, growth, and recovery.
- Catabolism means breaking things down and is defined as breaking down molecules into smaller units that are oxidized to release energy.
- Clinically, I use the ratio as a rough relative guide. If DHEA is low or low-normal and cortisol is high or high-normal, the ratio is out of whack.

SALIVA VERSUS DUTCH TESTING:

- Differentiates between free/total cortisol
- Measures not only DHEA-S but also etiocholanolone and androsterone
- Measures sex hormones and sex hormone metabolites
- Captures CAR with DUTCH Plus test

Internal research at Precision Analytical that's ongoing suggests that the morning cortisol value correlates pretty well with the CAR.

NUTRITION: SKIN CONDITIONS

- Certain vitamins, minerals, and other dietary nutrients impact skin growth and immunity.
- Vitamin A and synthetic retinoids promote epidermal differentiation and cell turnover, prevent the formation of comedones that cause acne, modulate dermal growth factors, inhibit sebaceous gland activity, and suppress androgen formation.
- Zinc plays a role in the skin's immune function, protein synthesis, wound healing, DNA synthesis, and cell division.

- Vitamin C is an antioxidant that's crucial for the production and regulation of collagen, and collagen maintains extracellular stability of the skin.
- Omega-3 fats play an important role in skin health. They are anti-inflammatory and reduce systemic inflammation.
- Biotin is an essential cofactor for enzymes that regulate fatty acid metabolism. Fatty acids in the skin help protect cells against damage and water loss, and inadequate biotin intake causes hair loss and scaly red dermatitis, seborrheic dermatitis in adults, and it can also contribute to dandruff.
- Selenium in the diet may be protective against skin cancer; patients with acne have been shown to have low levels of selenium compared to controls.
- Silica is an important nutrient for the skin. A silica-deficient diet has been shown to cause poorly formed connective tissue, including collagen.
- Deficiency of vitamin B3 or niacin is called pellagra, and symptoms are dermatitis and a dark, scaly rash on the skin.
- Vitamin K2 prevents calcification of the skin's elastin.
- Probiotics are really important for skin conditions. The skin–gut axis has been studied since the 1930s. Gut microbiota and oral probiotics influence systemic inflammation, oxidative stress, glycemic control, and tissue lipid content.
- Sulfur is necessary for collagen synthesis, and inadequate sulfur intake has been shown to reduce collagen formation and increase wrinkles in the skin.
- Vitamin E is secreted on the skin's surface through the sebum. It has potent anti-inflammatory effects and defends the skin against free radicals that cause skin damage.
- Pantothenic acid, or vitamin B5, supports wound healing and growth and differentiation of keratinocytes.

NUTRITION: FERTILITY, PREGNANCY, AND BREASTFEEDING

- You should definitely be testing both your female and male patients for these conditions: methylation defects, thyroid conditions, gastrointestinal dysfunction,

nutrient imbalance, autoimmune disease, polycystic ovary syndrome (PCOS), etc., because these are the underlying conditions that cause infertility.

- Hypo- and hyperthyroidism can affect fertility. Thyroid dysfunction reduces the likelihood of conception and increases the risk of miscarriage.
- Methylation defects: we know that MTHFR polymorphisms and other polymorphisms of methylation-related genes are prevalent in the population.
- A great starting place, of course, is a nutrient-dense Paleo type of diet, but make sure calorie intake is adequate to promote fertility. Low-calorie dieting is common among women and may contribute to infertility.
- Suggest a moderate carbohydrate intake of 20 to 40 percent of calories from carbohydrate, rather than a very low or very high carbohydrate intake. Make sure the patient is getting enough fat; between 40 and 50 percent of calories is often ideal, 40 to 60 percent, and patients should not be avoiding saturated fat or cholesterol, as these can be important nutrients for supporting healthy fertility.
- Folate is necessary for the production of new DNA in fetal cell division. The absorption of folate is dependent on zinc status, and I would say a minimum supplementation is maybe 400 micrograms per day, both before and during pregnancy.
- Choline is required for optimal brain development in the fetus. Choline deficiency can cause neural tube defects, as well. Higher choline intake is associated with improved cognition in the child.
- Vitamins A, D, and K2, the fat-soluble vitamins, are all very important for fertility.
- Iron is, of course, a very important nutrient for conception and healthy pregnancy. It's important to avoid iron deficiency, and that's much more common globally, but iron overload can also be an issue, and iron supplementation without any regard for pre-existing iron levels during pregnancy has been shown to be harmful.
- Vitamin B12 deficiency can also contribute to anemia and low hemoglobin levels, and that's important to understand, as well. It works together with folate and protects against developmental problems in babies. B12 deficiency has been associated with both male and female infertility.
- Omega-3 fats, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA, are particularly important for nutrition for conception and pregnancy.

- Iodine is the next nutrient. Studies have shown an increased risk of mental retardation and even cretinism in babies of mothers with iodine deficiency. This can be a potential issue in women who are on a Paleo type of diet who are avoiding iodized salt and not eating sea vegetables or dairy products, which are the primary sources of iodine in the diet.
- Biotin deficiency is relatively rare in women eating an omnivorous diet, but ensure that your patients are eating enough egg yolks and not just egg whites, and definitely not raw egg whites, which can induce biotin deficiency.
- Glycine helps balance methionine intake in a diet that's rich in muscle meats.

Lesson 23: HPA-D DUTCH Test, Part 1 Review

DUTCH COMPREHENSIVE HORMONE PROFILE

- Covers free cortisol, free cortisone, cortisol metabolites, dehydroepiandrosterone (DHEA), androgens such as etiocholanolone and androsterone, melatonin, and sex hormones such as progesterone, estrogen, estrogen metabolites, testosterone, and 5α-DHT.

ADVANCED ADRENAL PANEL:

- Provides the information on the adrenal hormones only: free cortisol, cortisone, cortisol metabolites, and DHEA sulfate.
- Doesn't contain melatonin or androsterone/etiocholanolone.

DUTCH COLLECTION INSTRUCTIONS

Timing of DUTCH Testing

	Timing (Adrenal only)	**Timing** (Comprehensive)
Male	Doesn't matter	Doesn't matter
Female (normal cycle)	Doesn't matter	Between days 19-22
Female (longer cycle)	Doesn't matter	Add # of days beyond 28 day cycle
Female (shorter cycle)	Doesn't matter	Subtract # of days less than 28 day cycle
Female (no cycle)	Doesn't matter	Watch irregular cycle collection video*

- Irregular cycles or amenorrhea: Direct patients to watch the irregular cycle collection video in the video library at dutchtest.com for suggestions on collection, but the basic idea is to aim for midway through the luteal phase in cycling women. They can take their basal body temperature to determine when they're ovulating and then sample six to seven days after that.
- A more foolproof way is to measure luteinizing hormone (LH) levels with an ovulation predictor kit.
- Testing should be done on a day that is average in terms of stress levels. If they work during the week, they should do the testing on a weekday, not the weekend.
- Avoid caffeine on the day of the test.
- No vigorous exercise right before or during the test.

If they're taking hormones, they need to follow the instructions (see the links above) in the test kit carefully.

- Skip all oral hormones except progesterone on the day of the test, and skip pregnenolone if they're taking it for two days.
- No need to skip any hormone creams or gels while taking that test.

- Hormones taken at night and oral progesterone, as usual, should be taken after sample number 2.
- On collection day two, they would take their morning hormones and medications after sample number 4. They wouldn't take any morning hormones before sample number 3 or sample number 4.
- Glucocorticoids will affect the results, so you have a couple of options:

1. See what the results look like when they are on the glucocorticoids.
2. If they can manage without taking them for a couple of days, have them stop a couple of days ahead of time, and then do the test.

Note on melatonin:

1. If the patient is dependent on melatonin for sleep and skipping it leads to poor sleep, that will mess up cortisol results, and I think accurate cortisol results are more important. In this case, they can keep taking it. Just know that the melatonin levels you see on the test results won't be accurate.
2. Alternatively, if they can stop taking melatonin for one to two nights, instruct them to do so in order to get an accurate test reading.

MARKERS IN THE DUTCH TEST

1. 24-hour free cortisol
2. 24-hour free cortisone
3. Daily free cortisol pattern, so it is cortisol produced in the proper diurnal fashion
4. Daily free cortisone pattern
5. Balance between cortisol and cortisone
6. Metabolized cortisol, which is a combination of tetrahydrocortisol and tetrahydrocortisone, and this is the best indicator of total or overall cortisol production
7. Total DHEA production, which is DHEA sulfate plus etiocholanolone plus androsterone
8. Melatonin

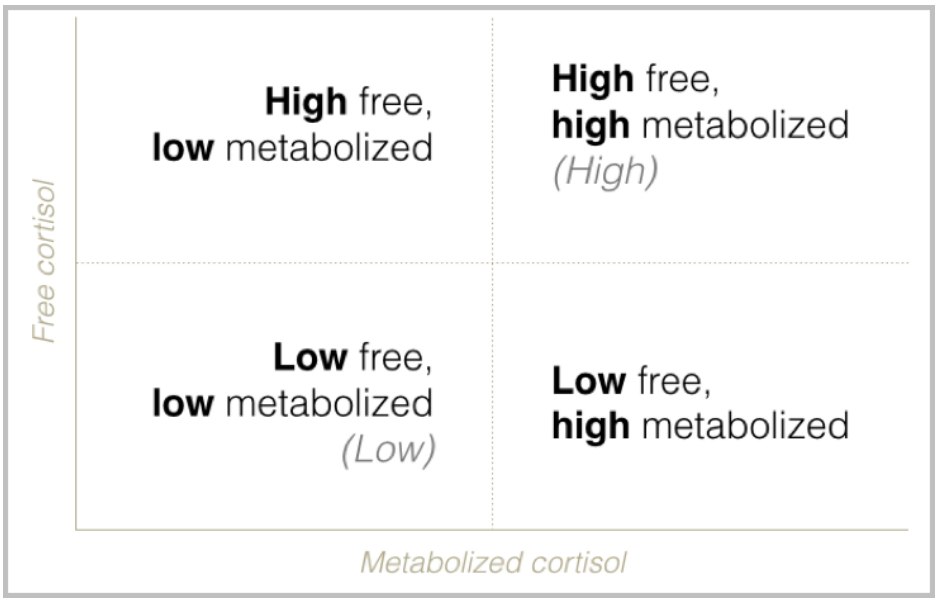
THERE ARE SIX FREE CORTISOL PATTERNS:

1. **Normal**
2. **High free cortisol**
    a. Perceived stress
    b. Inflammation
    c. Circadian disruption
    d. Cushing's syndrome/disease. There is virtually no diurnal drop in cortisol, which means the midnight reading will be almost the same as the waking reading. In pseudo-Cushing's syndrome, patients still have circadian rhythm, but the late morning, afternoon, evening, and midnight readings are higher. You would see a nighttime value that is three to four times above the lab range, and then you would look for high cortisol metabolites.
3. **High free cortisol with disrupted diurnal rhythm**
    a. High evening/nighttime cortisol
        i. Depression
        ii. Sleep deprivation. Patient might be a night owl and get a second wind at night.
        iii. Posttraumatic stress disorder (PTSD)
        iv. Cognitive impairment
        v. Low bone density
        vi. Circadian disruption
        vii. Polycystic ovary syndrome (PCOS)
        viii. Type 2 diabetes
        ix. Cushing's syndrome/disease
        x. Very high waking cortisol often indicates overproduction of cortisol through the night. This would explain why a patient might be waking up throughout the night because their cortisol is high. It can have a suppressive effect on melatonin.
4. **Disrupted diurnal cortisol rhythm**

a. Sleep disturbance
b. Circadian disruption
c. Perceived stress
d. Fatigue
e. Trauma
f. Flipped diurnal rhythm. Patients can have a disrupted rhythm with normal cortisol. Cortisol is low when it should be high in the morning and high when it should be low at night. It's common in patients with chronic fatigue. They will often feel really tired in the morning. They might have that second wind at night, but they're going to have really nonrestorative sleep and significant fatigue.

5. **Low free cortisol (normal rhythm)**
    a. Metabolic syndrome
    b. Fibromyalgia
    c. Chronic fatigue syndrome
    d. Chronic pain
    e. Cardiometabolic disease
    f. Mood disorders
    g. Autoimmune disease
    h. Cancer
6. **Hypocortisolism (no rhythm)**
    a. Addison's disease. Free cortisol below 10. Remember that Addison's disease is rare. Most cases of very low or flat-line cortisol are caused by medication use, so both glucocorticoids and opioids can suppress cortisol production.
    b. Glucocorticoid/opioid use

OVERALL CORTISOL PATTERNS



1. High free cortisol with high metabolized cortisol
    a. Most often seen in Cushing's disease or pseudo-Cushing's syndrome, high perceived stress, and inflammatory conditions such as PCOS, inflammatory bowel disease (IBD), and depression.
    b. Markers such as low vitamin D, functional anemia, and decreased mitochondrial function activate the hypothalamic–pituitary–adrenal (HPA) axis and cause an increase in cortisol.
2. Low free cortisol and low metabolized cortisol
    a. Commonly seen in Addison's disease, medication-induced adrenal insufficiency (such as glucocorticoid use), trauma, PTSD, and possibly chronic fatigue syndrome. For example, remember that cortisol helps resolve the inflammatory response, so when cortisol is low, the patient can't turn off the inflammation, which can contribute to conditions like gut issues and food sensitivities. However, the gut issues likely contribute to low cortisol levels, so you can see a vicious cycle.
3. Low free cortisol and high metabolized cortisol
    a. Main causes are obesity, insulin resistance and metabolic dysfunction, hyperthyroidism, chronic stress, glucocorticoid use, and chronic fatigue syndrome.

b. This has been studied extensively in the literature. In obesity, we typically see normal or low free cortisol, and then we'll see high cortisol metabolites.

c. We also tend to see high DHEA in obesity and impaired cortisol to cortisone conversion.

4. High free cortisol and low metabolized cortisol

   a. Observed in hypothyroidism, licorice supplementation, inflammation, and, in some cases, it may be normal and nonpathological.

CORTISOL AND THYROID FUNCTION

Hyperthyroidism	
Free cortisol	Low or normal
Total metabolites	High
THE/a-THF ratio	Increased

Hypothyroidism	
Free cortisol	High or normal
Total metabolites	Low
THE/a-THF ratio	Decreased

Researchers are considering using urinary cortisol metabolites or cortisol test results as a way of diagnosing subclinical hypothyroidism.

INFLAMMATION AND CORTISOL/DHEA

Free cortisol	High
Total metabolites	Normal or low
Cortisol to cortisone ratio	Increased
DHEA (S)	Normal
DHEA-Sulfate	Low

DHEA sulfate is often low because inflammation inhibits sulfation.

Lesson 24: HPA-D DUTCH Test, Part 2 Review

The DUTCH comprehensive hormone profile provides the total dehydroepiandrosterone (DHEA) value, which is a combination of DHEA sulfate and two DHEA metabolites, etiocholanolone and androsterone. Measuring this combination gives you a better idea of overall DHEA production than looking at DHEA sulfate alone. One reason for this is that sulfation can be upregulated or downregulated in certain disease states. This can give a falsely low or high impression of DHEA if you only measure DHEA sulfate. The DUTCH advanced adrenal panel only reports DHEA sulfate.

OTHER MARKERS

1. High DHEA
    a. The DHEA range is age- and gender-specific, and the DUTCH test results report takes that into account.
    b. Primary causes of high DHEA are polycystic ovary syndrome (PCOS), acute stress, obesity, benzodiazepine use (drugs such as Xanax), and antidepressant use.
2. Low DHEA
    a. DHEA can be low with stress, aging, rapid weight loss, opioids, glucocorticoids, birth control pills, hormone replacement therapy, antipsychotics, and some diabetes medications.
3. Normal total DHEA with low/high DHEA sulfate (DHEA-S)
    a. This is not a common presentation.
    b. You will sometimes see discordance between total DHEA and DHEA-S.
    c. The two primary causes of low DHEA-S are inflammation and glucocorticoid use.
    d. A slightly elevated DHEA-S is probably not pathological if all the other markers are normal.

e. Possible causes of significantly elevated DHEA-S and normal total DHEA are things that upregulate sulfation such as a high-protein diet, some liver detox supplements or botanicals, and methylation supplements.

4. Cortisol/cortisone imbalance

    a. Cortisol is the more active form of the hormone, and cortisone is the less active form. These are interconverted back and forth, primarily by 11β-HSD.

    b. Factors that favor more cortisone include hyperthyroidism; human growth hormone; estradiol; good sleep; drugs such as ketoconazole; adaptogenic herbs such as magnolia, scutellaria, ziziphus; and hormones such as testosterone.

    c. Factors that favor more cortisol include hypothyroidism, inflammation, visceral obesity, high insulin, excess sodium, and licorice, which increases the half-life of circulating cortisol.

    d. If cortisol is normal or low but cortisone is high, mentally, I pull the cortisol level up a bit.

        i. Low/normal cortisol and high cortisone indicates that a large amount of free cortisol is being inactivated into cortisone in the kidney.

        ii. Poor thyroid function can lead to sluggish clearance of cortisol and cortisone into their terminal metabolites.

    e. If cortisol is normal or high but cortisone is very low, I would mentally pull cortisol down a bit. Example: A patient's thyroid dose was too high. This was causing a facetious hyperthyroid condition, which led to inactivation of cortisol to cortisone.

5. Low/high melatonin

    a. 6-OH melatonin sulfate is a good representation of the night's production of melatonin, but it cannot be used to monitor therapy.

    b. Melatonin plays a crucial role in regulating body temperature, the sleep-wake cycle, female reproductive hormones, and cardiovascular function.

    c. Low melatonin has been observed in anxiety, stress, depression, seasonal affective disorder, sleep disorders, delayed sleep phase syndrome, immunological disorders, cardiovascular disease, and cancer.

d. High melatonin without supplementation has been observed in certain neuroinflammatory conditions.

e. Cortisol opposes melatonin, and melatonin opposes cortisol.

f. For example, a patient with a primary concern of sleep issues:

    i. He had high cortisol, which can suppress melatonin production, and this explains why he wakes up at 3:00 to 4:00 a.m. and can't get back to sleep.

g. Patient with Lyme disease had a slightly high melatonin:

    i. This is consistent with Lyme disease because Lyme disease often affects the brain and central nervous system and causes neuroinflammation.

CORTISOL AWAKENING RESPONSE (CAR) INDICATIONS

Elevated	Decreased
Job-related stress	Depression
High perceived stress	Schizophrenia
Depression	PTSD
Anxiety	Psychosocial burnout
Faster M.S. progression	Chronic fatigue syndrome
Acute coronary syndrome	Type 2 diabetes

SUMMARY

Pattern	Indication
High free cortisol (with normal or high total) **& elevated C.A.R.**	Perceived stress, inflammation, circadian disruption, Cushing's
High nighttime/evening free cortisol	Depression, sleep deprivation, PTSD, cognitive impairment, circadian disruption, type 2 diabetes, Cushing's syndrome/disease
Disrupted diurnal rhythm only	Fatigue, sleep disturbance, stress/HPA axis activation, non-pathological
Low free cortisol (with low or normal total) & **low C.A.R.**	Metabolic syndrome, fibromyalgia, CFS, chronic pain, cardiometabolic disease, mood disorders, autoimmune disease, cancer, Addison's disease, corticosteroid/opioid use
High free cortisol with low total	Hypothyroidism, licorice supplementation, inflammation, normal/nonpathological
Low free cortisol with high total	Obesity, insulin resistance, hyperthyroidism, chronic stress, glucocorticoid use, chronic fatigue syndrome
High DHEA	PCOS, acute stress, obesity, benzodiazapenes (e.g. Xanax), antidepressants (e.g. Wellbutrin), A.D.D. meds
Low DHEA	Stress, aging, rapid weight loss, opioids, glucocorticoids, birth control, HRT/estrogens, antipsychotics, diabetes meds
High cortisol:cortisone ratio	Hypothyroidism, inflammation, visceral obesity, high insulin, excess sodium, and licorice
Low cortisol:cortisone ratio	Hyperthyroidism, hGH, estradiol, good sleep, ketoconazole, magnolia, scutellaria, zizyphus, and testosterone
Low melatonin	Anxiety, stress, depression, seasonal affective disorder, sleep disorders, immunological disorders, cardiovascular disease, cancer
High melatonin	Neuroinflammatory conditions

SUPPLEMENTATION:

- Vitamin A
    - It's critical for vision. It is a component of rhodopsin, a protein that absorbs light in the retina. It's required for assimilation of protein, minerals, and water-soluble vitamins. It supports cell growth and differentiation. It acts as an antioxidant, and it plays a crucial role in reproduction and promotes full-term pregnancy along with proper development of the fetus, particularly with regard to the facial structure.
    - Most of the body's vitamin A is stored in the liver in the form of retinyl esters. Serum levels of vitamin A do not decline until liver stores are almost completely depleted.
    - Both beta-carotene and retinol require some fat for absorption, and this is true of all the carotenoids

    - Frank vitamin A deficiency is rare in the United States, and it is more common in third-world countries. A long-term, severe deficiency leads to blindness, xerophthalmia, chronic diarrhea, and increased mortality from infections, but symptoms of suboptimal vitamin A status are more common and include poor vision at night, keratosis pilaris or chicken skin, dry skin, dry eyes, frequent infections, acne, eczema, psoriasis, menstrual dysfunction, hypothyroidism, and autoimmune disease.
    - Taking vitamin A together with adequate amounts of vitamin D and K2 significantly reduces the toxicity threshold for vitamin A.
- Vitamin D
    - Vitamin D is a vitamin-like hormone, actually, that is largely produced in the skin when exposed to ultraviolet radiation.
    - The best-known role of vitamin D is increasing intestinal absorption of calcium. Vitamin D maintains calcium and phosphate levels in the blood. It enables proper mineralization of bone. It protects against osteoporosis, rickets, and fracture, and it plays a number of important roles in the body.
    - Ethnicity plays a major role in determining optimal vitamin D need.
    - Vitamin D can be obtained from three sources: food, sun, and supplements. A mix of all three of these sources tends to work best for most patients.
    - Factors impacting how much vitamin D is converted include the time of day you are exposed, skin color, and amount of skin exposed.
    - There is no best dose of vitamin D, or, put a different way, the best dose of vitamin D supplement is the one that is required to maintain a level between 35 and 50 ng/mL.
- Magnesium
    - Magnesium is vital to the human body. Over 300 enzymes need it, including every enzyme involved with ATP and enzymes involved in DNA and RNA production. It plays an important role in bone health, and most of the body's magnesium is stored in bone. Magnesium helps transport ions across the cell membrane surface.

- Magnesium deficiency can cause several symptoms, such as muscle cramps, heart arrhythmias, tremor, headaches, and acid reflux. It is also associated with increased risk of heart disease, hypertension, metabolic syndrome, type 2 diabetes, migraines, premenstrual tension syndrome, asthma, and hypothyroidism.
- Magnesium has been shown to be better absorbed with a higher protein intake, so make sure that patients aren't skimping on protein.
- Too much magnesium will tend to first manifest as loose stool. That is one of the first side effects that you can see, and, of course, magnesium is used as a laxative for this reason.

Lesson 25: HPA-D Treatment Diet Review

You cannot successfully treat a patient with chronic illness without addressing their hypothalamic–pituitary–adrenal (HPA) axis. Diet and lifestyle changes should come before supplements. Patients cannot supplement themselves out of HPA axis dysfunction (HPA-D).

The four key drivers of HPA-D are perceived stress, circadian disruption, glycemic dysregulation, and inflammation.

- Treating HPA-D from a Functional Medicine perspective means addressing the core pathologies that are causing it, such as dysglycemia or inflammation, and this requires a more holistic approach.
- It's not just about the adrenals or taking steps such as modulating exposure to light, resting, or reducing physical activity, although those all may be part of it.
- Individuals need to change their relationship with themselves and the world around them.

Glycemic dysregulation and inflammation are two of the four key drivers of HPA-D, so a recommended diet should be anti-inflammatory and should also regulate blood sugar.

- Start with a Paleo template diet as it removes most foods that tend to be inflammatory.

- HPA-D specific modifications for the Paleo-type diet include a higher protein intake overall, but especially in the morning and backloading the carbs, later in the day.

For patients who are overweight or insulin and leptin resistant, have high blood sugar, or have high blood pressure:

- Consider starting with a high-protein, lower-carb approach.
- If this approach has not been effective, it can often be helpful to add some Paleo-friendly carbs back into the diet.
- Avoiding snacking between meals can also help with blood sugar stabilization.

For patients who are normal weight, normal glucose, and insulin sensitive or have a tendency more toward low blood sugar and low blood pressure:

- Consider starting with a high-protein, moderate-carbohydrate, moderate-fat approach.
- Also, these patients generally do better eating every two to three hours.
    - Three regular meals but snacks in between or
    - Five to six smaller meals throughout the day

SPECIFIC MICRONUTRIENTS

Vitamin C. The adrenal glands have one of the highest tissue concentrations and greatest active uptake of ascorbic acid of any tissue in the body.

- Fruit sources: papaya, strawberries, pineapple, oranges, kiwi, cantaloupe, raspberries, blueberries, and cranberries
- Vegetable sources: broccoli, Brussels sprouts, cauliflower, kale, cabbage, and bok choy

B vitamins. Many biochemical pathways for producing steroid hormones have B vitamin-dependent enzymes.

- Top sources: liver, clams, seafood, dark leafy greens, lentils, mushrooms, spices, poultry, egg yolks, peppers, squash, nuts, and seeds

Sodium. Low intake can cause increased renin, cholesterol, triglycerides, and all-cause mortality. Symptoms can include lethargy, nausea, and hypotension.

- Patients may need to reduce their potassium intake if they're eating a lot of potassium or supplementing with potassium because it opposes the lack of sodium.
- Take one-half to one teaspoon of sea salt in a glass of water upon rising.
- Add salt and/or kelp flakes to food if needed.

Potassium. High levels are associated with lower blood pressure, and low levels or a deficiency is associated with hypertension, high blood sugar, and being overweight.

- Top sources: potato, halibut, plantains, rockfish, sweet potato, beet greens, bananas, sockeye salmon, acorn squash, avocado, parsnips, pumpkins, kohlrabi, duck, and mushrooms

Calcium, zinc, and magnesium. Deficiencies can lead to a number of alterations in neurotransmitter and HPA axis dysfunction. When included in multivitamin formulations, they show some stress-lowering effects in clinical studies. Magnesium is especially important. It's been shown to improve sleep, metabolic function, fatigue, and energy.

- Calcium: sesame seeds, sardines (with bones), yogurt, collard greens, spinach, cheese, turnip greens, sockeye salmon (with bones), molasses, and mustard greens
- Magnesium: oysters, liver, crab, lobster, beef, lamb, endive, pork, nuts, dark chocolate, and cremini mushrooms
- Zinc: dark leafy greens, nuts and seeds, fish (mackerel), avocados, dairy products (if tolerated), bananas, figs, and dark chocolate

Caffeine. Most patients experiencing symptoms of HPA axis dysregulation should avoid or at least cut down on caffeine until they have fully recovered from their condition. Often, the more someone needs caffeine to function, the more likely it is not good for them.

Alcohol. Limit to two to three drinks per week during treatment, possibly in a social situation. Remember, there's a tendency for people to underreport their alcohol intake.

Lesson 26: No Review (Break Week)

Lesson 27: HPA-D Treatment Lifestyle Review

Several of the primary considerations for behavior and lifestyle modification when addressing hypothalamic–pituitary–adrenal (HPA) axis dysfunction (HPA-D) include:

1. REDUCE PERCEIVED STRESS

a. Take steps to reduce total exposure to psychological and emotional stress.

b. Mitigate the harmful effects of stress we can't avoid.

There are a few behavior and lifestyle strategies you can provide to patients to improve the chances of recovery.

Reducing the amount of stress you experience

- Learn to say "no."
- Avoid people who stress you out.
- Go on a news fast, or at least limit your exposure to the news.
- Give up pointless arguments, and agree to disagree.
- Limit your to-do list.
- Stop internet debating.

Strategies for mitigating the harms of unavoidable stress

- Reframe the situation. Look at it in a more positive light or in a different context.
- Lower your expectations. "Don't let the perfect be the enemy of the good."

- Practice acceptance. Accept the things we can't change.
- Be grateful.
- Cultivate empathy.
- Manage your time.

General tips for stress management

Stress management practices

- Mindfulness practice (mindfulness-based stress reduction)
- Meditation
- Yoga
- Tai chi
- Qi gong
- Biofeedback, a mind-body technique that helps teach patients how to influence their autonomic nervous system
    - HeartMath is an example.

2. CONTROL LIGHT EXPOSURE

a. Two main issues are too little exposure to natural light during the day and too much exposure to screens (i.e., blue light) at night.

b. Minimize computer, tablet, and phone use to two to three hours before bedtime.

c. Increase light exposure during the day, and get 15 to 30 minutes of bright light exposure daily.

Shift work

- In the case of both jet lag and shift work, you are working to mitigate harm because both are associated with significantly higher morbidity and mortality.
- Changing a career is not easy, but we can make some adjustments to try to help.
    - Advise your patient to avoid rotating shifts (working night shift two or three times a week and then the day shift two or three times a week).
    - If your patient works a regular night shift, advise as regular of a routine as possible.
        - Wear the orange glasses when they get home from work.
        - Use blackout shades in the room.
        - Encourage regular mealtimes.
- Consider a career change if necessary.

3. OPTIMIZE SLEEP HYGIENE, DURATION, AND NUTRITION

a. Explain the importance of sleep to your patient

i. Most people should aim for at least eight hours of sleep a night

b. Sleep hygiene. Create an environment that is conducive to sleep.

c. Sleep nutrition

i. People with digestive issues often do better with light dinners.

ii. People with hypoglycemia do best with late snacks.

iii. Low-fat and low-carb diets can cause insomnia; experiment with macronutrients when insomnia is a problem.

iv. Avoid stimulants such as caffeine after noon or earlier.

4. OPTIMIZE PHYSICAL ACTIVITY

a. Aerobic exercise has antidepressant and antianxiety effects and protects against the harmful consequences of stress, in addition to physical benefits.

b. Avoid overtraining

c. Heart rate variability monitor

i. Helps to better manage recovery by providing an estimate of when we're overly stressed versus well recovered.

5. SPEND TIME OUTDOORS TO CONNECT WITH NATURE AND FOR NATURAL LIGHT EXPOSURE

6. ENGAGE IN REGULAR PLAY AND PLEASURE AND SOCIAL SUPPORT

Optimizing the Exposome: Basic Supplementation

VITAMIN K2

- Vitamin K2 is needed to activate proteins such as osteocalcin that regulate calcium metabolism via a process called carboxylation.
- It also prevents calcification of soft tissues such as arterial lining, and this can reduce the risk of atherosclerosis and heart attack.

- It's required for the proper function of vitamin D- and A-dependent proteins and prevents deficiency symptoms for each of those vitamins.
- The research is currently unclear on just how much vitamin K2 is optimal for health. There is no upper limit or toxicity level at this point, so like vitamin B12, K2 is remarkably safe even in high doses.
- Vitamin K2 is best combined with optimal levels of vitamins A and D.
- The major forms of vitamin K2 that we consume in the diet would be MK4, which is found in animal fats, so dairy fats, organ meats, or fat tissue of ruminant animals that we consume, and MK7, which is primarily found in fermented foods.
- The highest sources of MK4 are from grass-fed, full-fat dairy products, and the reason that grass-fed dairy products are so much higher in vitamin K2 is because the grass is what contains the K1 that the animals convert into K2.
- Cheese, of all the dairy products, is the highest in vitamin K2.
    - Poultry liver, particularly goose liver
    - Pastured egg yolks; not conventional egg yolks as much
    - Organ meats from pastured animals such as pancreas and kidney
    - Natto, a fermented soy product from Japan, which is the highest source of K2 per gram of any food

VITAMIN C

- Vitamin C cannot be made by humans, unlike most other mammals. We have to get it from the diet.
- Antioxidant
- Cofactor for enzymatic reactions
- Helps production of collagen and catecholamines
- Helps maintain proper levels of glutathione
- The Recommended Dietary Allowance (RDA) for vitamin C is 90 mg per day for men and 75 mg per day for women, and you would add 35 mg per day for smokers since they're under significant oxidative stress.

- Low intake is even more common in the elderly and those struggling with chronic disease and women on estrogen-containing birth control since birth control pills lower plasma vitamin C.
- Recommend at least 150 mg a day for optimal health and even higher for those who are struggling with a chronic disease.
- Symptoms of insufficient vitamin C intake vary, but the most common symptoms would be poor wound healing and fatigue.
- Food sources of vitamin C are plentiful. Red peppers, one of the highest sources, have 95 mg per half-cup. One orange has 70 mg. A medium kiwi has 64 mg. A half-cup of cooked broccoli has 51 mg. One cup of fresh strawberries has 49 mg. A half grapefruit has 38 mg.
- Combining vitamin C with iron-containing foods will increase the absorption of iron.
- For those with chronic illness who would like to prevent some of the conditions I mentioned earlier that benefit from higher vitamin C intake, I recommend about 500 to 1,000 mg per day.

IODINE

- Iodine is required to make thyroid hormones, both thyroxine (T4) and triiodothyronine (T3).
- Iodine deficiency is recognized as one of the common preventable causes of brain damage, and deficiency can cause mental retardation, goiter, and other growth and developmental issues and possibly increase the risk of cancer.
- The RDA for adults is 150 mcg per day, or 220 mcg per day for pregnant women and 290 mcg per day for breastfeeding women.
- Typically, one of the first signs that you will see of iodine deficiency is goiter, which is an enlargement of the thyroid gland. Iodine deficiency can also cause hypothyroidism.
- If your patient is not consuming sea vegetables, fish heads, cod, or other common sources of iodine, and they are not using iodized salt, they very well may be deficient.
- The top four sources by iodine content are sea vegetables.
- Cod is the highest non-sea vegetable source in terms of iodine.

- For a maintenance dose, recommend somewhere between 800 mcg and 1 mg a day.
- While you want to ensure that all patients are getting enough iodine, there are two groups of patients that getting the right amount of iodine for is crucial: the first is patients with hypothyroidism and the second is pregnant and breastfeeding women.
- As far as drug interactions, you should be wary of high doses of iodine when your patient is on Coumadin, as it may decrease the anticoagulant properties of that drug. Otherwise, iodine has relatively few interactions with medications.

Lesson 28: HPA-D Treatment Therapies and Supplements Review

ADJUNCTIVE THERAPIES

MINDFULNESS-BASED COGNITIVE THERAPY

When we talk about perceived stress, four key factors determine

how stress is perceived (acronym NUTS):

- Novelty
- Unpredictability
- Perceived threat to body or ego
- Sense of loss of control

The first two aren't particularly modifiable, but the second two can be influenced by how we frame the event in our mind.

An example is job loss. You perceive that event as a sign of your worthlessness and an indicator that you'll never be successful, or you can perceive the loss of your job as an opportunity to pursue a long-time dream that you've ignored or a chance for a fresh start.

Reframing can be a powerful ally in stressful situations, but it depends on your capacity to stay present in a difficult situation. A mindfulness practice helps here.

Mindfulness-based cognitive therapy is one methodology for doing this. It combines the ideas of cognitive behavioral therapy with meditative practices and attitudes based on the cultivation of mindfulness.

MASSAGE

Massage is another modality shown to reduce cortisol and regulate the hypothalamic–pituitary–adrenal (HPA) axis.

ACUPUNCTURE

- It has been shown to reduce subjective markers of stress, and most people who receive acupuncture report feeling a deep sense of relaxation.
- Acupuncture also has been shown to regulate the HPA axis in both animal and human studies.

BASIC NUTRIENTS

Nutrients that play an important role in HPA axis function include:

- Vitamin C, B vitamins like B5 (pantethine), potassium, sodium, calcium, zinc, and magnesium.
- These can all be obtained from a high-quality multivitamin.
- However, there is some concern with long-term calcium supplementation increasing risk for cardiovascular disease in both men and women, so using a multivitamin with calcium in it long-term is not best.
- If eating a nutrient-dense diet, you may not need to supplement with all these nutrients and may be able to supplement selectively, with higher but appropriate doses.

Vitamin C	Magnesium	Pantethine
2 grams/d in liposomal form	400-600 mg/d in glycinate form	450-900 mg/d

Remember that glycemic dysregulation, circadian disruption, and inflammatory signaling are three of the four drivers of HPA-D, so below are some supplements to address those issues.

GLYCEMIC CONTROL

1. Diet, exercise, and sleep as first interventions.
2. Metabolic Synergy and GlucoSupreme from Designs for Health (DFH).
3. Soluble fibers such as PGX or glucomannan and resistant starch such as potato starch can also be helpful.
4. Patients with advanced blood sugar issues may require medication such as metformin.

INFLAMMATION

Consider curcumin, boswellia, skullcap, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA).

- Curcumin reduces inflammation, promotes T-regulatory cell production and differentiation, is a COX-2 inhibitor, and reduces oxidative stress.
    - Bioavailability of curcumin varies widely.
    - Boswellia
    - Inhibits tumor necrosis factor alpha, interleukin-1 beta, nitric oxide, and mitogen-activated protein kinases.
    - Standard dose is 400 mg per day.
    - More concentrated or isolated Boswellia AKBA dose is 100 mg per day.

There is some logic to taking curcumin and boswellia together because they work with complementary mechanisms/pathways.

CHINESE SKULLCAP

- Reduces the expression of nitric oxide.
- Is a COX-2 inhibitor, as well as inhibiting other inflammatory cytokines.
- Reduces neuroinflammation, supports memory and learning, reduces anxiety, and can improve blood glucose.

EPA AND DHA

EPA and DHA have been found to reduce inflammatory markers in a wide variety of conditions such as rheumatoid arthritis, diabetes, and pain conditions.

1. Recommend eating a pound of coldwater, low-mercury, fatty fish per week.
2. An alternative is cod liver oil or wild salmon oil supplement.

CIRCADIAN DISRUPTION

- Botanicals such as valerian, passionflower, jujube, and hops.
- Best taken in low to medium doses.
- Bedtime Tea from Yogi Tea is a great blend.
- Tranquility from Natura Health Products is also a good supplement blend.

GABA (GAMMA-AMINOBUTYRIC ACID)

- Major inhibitory neurotransmitter, the off switch for the nervous system.
- PharmaGABA and phenibut are supplemental forms that cross the blood–brain barrier.
- Phenibut may be difficult to find in supplemental forms; if so, recommend 250 to 500 mg/day (maximum) and then usually about 2 to 3 times a week to reduce risk of dependence.

PHOSPHATIDYLSERINE (PS)

- Naturally occurring phospholipid essential for the membranes of all cells, especially in the central nervous system.
- Studies have shown it to reduce cortisol levels.
- Dose used for a therapeutic effect of PS ranges from 400 to 800 mg a day, though some have shown benefits at 200 to 300 mg per day.
- Integrative Therapeutics has a good brand of PS that is soy-free.

TAURINE

- Supports sleep and is the second-most abundant amino acid in the central nervous system.
- If used on its own, I suggest a dose of 2 to 3 g taken before bedtime.

5-HYDROXYTRYPTOPHAN (5-HTP)

- Naturally occurring in seed pods of *Griffonia simplicifolia*, a West African medicinal plant.
- In humans, 5-HTP is the immediate nutrient precursor to serotonin.
- Dose for 5-HTP is 50 to 100 mg taken in the evening at dinnertime or before bed.

MELATONIN

- Hormone secreted by the pineal gland in the brain that helps regulate other hormones and maintains the body's circadian rhythm.
- For sleep-onset insomnia, use the sublingual form of melatonin.
- Oral form is best for sleep-maintenance insomnia, 30 to 60 minutes before bed.
- Some evidence suggests that lower doses from 250 mcg to 1 mg may be more sedating than higher doses, which are used for treating neuroinflammation and cancer.
- Special considerations:

- Contraindicated in young children and pregnant and nursing women.
- May reduce the effectiveness of antidepressant drugs and/or worsen depression.
- Melatonin has quite a few potential drug interactions; use with caution.

L-THEANINE

- Unique amino acid found only in green tea and certain mushrooms.
- At higher doses, it can have a calming and focusing effect.
- It improves natural sleeps at night but does not cause sedation during the day.

Nutrients that support the cholinergic system may help reset the circadian clock and can be useful when the diurnal cortisol rhythm is disrupted.

- Alpha glycerylphosphorylcholine (alpha-GPC) 200 to 300 mg/d
- N-acetyl L-carnitine 50 to 100 mg/d
- Huperzine A 150 to 300 mcg/d
- Pantothenic acid high dose up to 1 g/d

Nutrient	Dosage
Alpha-GPC	200–300 mg/d
N-acetyl L-carnitine	50–100 mg/d
Huperzine A	150–300 mcg/d
Pantothenic acid	High dose, up to 1 gram/d

SUMMARY OF NUTRIENTS FOR HPA-D

Category	Dosage/Comments
Basic HPA axis support	Vitamin C, B vitamins, potassium, sodium, calcium, zinc, magnesium; take in multivitamin (without calcium), or individually
Glycemic control	Chromium, zinc, manganese, vanadium, gymnema, bacopa, etc. Metabolic Synergy & GlucoSupreme from DFH good options (no need for multi if you use Metabolic Synergy)
Inflammatory signaling	Curcumin, boswellia, skullcap, EPA/DHA
Circadian disruption	Botanicals (valerian, passionflower, jujube, hops), GABA, PS, taurine, 5-HTP, melatonin, L-theanine, pantothenic acid, alpha-GPC, huperzine A, N-acetyl L-carnitine

ADAPTOGENS

- Are botanicals that should increase resilience in metabolic reserve and improve stress tolerance and recovery.
- Recognized to have a balancing effect.
- Reduce stress-induced damage, so they are anti-fatigue, anti-infectious, antidepressant, and restorative.

SIBERIAN GINSENG

- Improves mental performance under stress and helps with exercise recovery.
- Studies have shown measurable improvements in chronic fatigue and quality of life.
- Also shown to relieve depression in teens with bipolar disorder.
- Safe in both high- or low-cortisol states.

SCHISANDRA CHINENSIS

- Shown to protect against stress and support energy production, cardiovascular, immune, respiratory, endocrine, and gastrointestinal systems.
- Can be used in both high- and low-cortisol states.

RHODIOLA

- Studies show improvements in fatigue, burnout, and saliva cortisol awakening response.

ASHWAGANDHA

- Has shown some benefit in neurodegenerative conditions such as Alzheimer's disease.
- Sensoril ashwagandha is the most potent form available, eight times the strength of standard ashwagandha.

- A therapeutic dose of Sensoril is 450 mg per day, standardized to 10 percent withanolides, which are other compounds in ashwagandha. A lot of other ashwagandha contains lower levels of withanolides of 2 to 3 percent.

CORDYCEPS

- Long history of use in China and Tibet as a remedy for weakness and fatigue.
- Also believed to enhance athletic performance and improve aerobic capacity.
- Dose for cordyceps is 5 to 10 g per day. Note that there is a really wide variety in the quality of cordyceps preparations, so make sure to get it from a reputable source. The highest quality you can afford is the best quality to get, which can get expensive.

PANAX GINSENG (ALSO KNOWN AS KOREAN OR ASIAN GINSENG)

- More stimulating; thus, I don't recommend it for nonspecific HPA-D or high cortisol.
- May be useful as tonics or for their stimulating effects in hypocortisolism, but use cautiously and over the short term.

LICORICE

- Its metabolites have been shown to block 11-β HSD2, which is the enzyme that converts cortisol to cortisone. This results in increased levels of circulating cortisol. Understand that it doesn't actually raise or increase cortisol production, but it increases the circulating half-life of cortisol.
- Be aware that chronic high intake of licorice can raise blood pressure.
- With low cortisol, licorice can be helpful in maintaining adequate cortisol levels.
- European studies caution against consuming more than 100 mg/d per day.
- Studies have shown that a very safe upper limit for glycyrrhizin is 0.23 mg/kg per day for all people, including those with higher cortisol.
- Licorice is contraindicated with high blood pressure, blood sugar medication, corticosteroid use, insulin, laxatives, oral contraceptives, and digoxin.

MAGNOLIA OFFICINALIS AND *PHELLODENDRON AMURENSE*

- *Magnolia officinalis* is one of the other few natural substances along with phosphatidylserine and GABA that has been shown to decrease cortisol.
- Magnolia and phellodendron are combined in a product called Relora, which has been shown to reduce sleep latency, increase overall well-being, and prevent weight gain by reducing cortisol that contributes to belly fat.
- Dose of Relora is typically 500 mg a day taken in two divided doses, though up to 750 mg per day has been shown to be safe for shorter durations of a few weeks or months.

CANNABIDIOL (CBD)

- One of the 85 active compounds found in the marijuana plant, cannabis.
- Has a number of medicinal properties that could help reverse HPA-D. In fact, it addresses all four primary triggers of HPA-D: perceived stress, inflammation, dysglycemia, and circadian disruption.
- CBD is not psychoactive, so it can be sold over the counter and shipped to all 50 states.
- For the water-soluble form, I suggest a starting dose of 5 to 20 mg per day. You can increase to a maximum of 50 mg.
- If using fat-soluble standard preparations, start at 50 to 100 mg per day, with a maximum dose of 400 to 600 mg per day.
- I typically start with other interventions that we've talked about earlier such as adaptogens and supplemental nutrients first, and then, if not successful, add CBD.
- Consider using CBD initially in cases of a lot of inflammation and anxiety.

ADRENAL GLANDULARS

- Drawback: In most cases, dessicated organ products are not standardized for any peptides or hormones, and none that I know of have been clinically tested for HPA-related function in humans using modern research techniques.
- However, they appear to be safe after many years of clinical use.
- I have found them helpful in patients in both hypercortisol and hypocortisol states.
- When taken in the morning, they have a stabilizing (calming but also energizing) effect.
- I like the Dr. Ron's brand of adrenal glandulars because he uses dessicated adrenal glands from pasture-raised animals in New Zealand.

HORMONES: BIOIDENTICAL FORMS OF DHEA AND PREGNENOLONE

- Shown to improve bone mineral density in elderly women; increase the dehydroepiandrosterone (DHEA)-to-cortisol ratio and blunt cortisol's catabolic effects; and improve cardiovascular, sexual, and cerebral functions, especially in the elderly.
- Newer studies show that DHEA benefits autoimmune disease, specifically in lupus, rheumatoid arthritis, and inflammatory bowel disease, at higher doses around 200 mg per day.
- For HPA axis dysfunction, the dose tends to range from 25 to 100 mg a day and up to 200 mg per day for autoimmune conditions.
- Although DHEA is a precursor to estrogen and testosterone, studies have shown that DHEA supplementation does not increase the levels of downstream hormones.
- Side effects of DHEA include agitation, painful skin breakouts (most common side effect I see), and sleep disturbances.

PREGNENOLONE

Less data than on DHEA; however, some studies suggest that pregnenolone supplementation may provide benefits for the HPA axis.

See the HPA-D protocol matrix handout for a summary of treatment protocols based on DUTCH (Dried Urine Test for Comprehensive Hormones) test results.

Lesson 29: Nutrients to Be Cautious of Supplementing With

IRON

- Iron is a part of several enzymes and proteins in the body, and it's found in foods as both heme and nonheme iron.
- Nonheme iron is found in plants, dairy products, and some meats. Unlike heme iron, nonheme iron absorption is significantly influenced by food components in the same meal.
- The Recommended Dietary Allowance (RDA) for iron is 8 mg, except for in menstruating females, who need to get 18 mg, or pregnant women, who need to get 27 mg.
- While iron is clearly an important nutrient, it is also essential to make sure a patient doesn't get too much of it. Hemochromatosis is a genetic disorder that causes aggressive iron storage and iron overload.
- Iron is a pro-oxidant. It causes oxidative stress, and it literally leads to the organs and tissues in our body rusting.
- Iron overload is significantly associated in particular with impaired insulin sensitivity and glucose tolerance.
- If you see a patient with metabolic disease, diabetes, metabolic syndrome, liver abnormalities, weakness, lethargy, or skin hyperpigmentation, and they have iron levels that are outside the functional ranges, then you should be thinking about hemochromatosis or iron overload.
- Treatment for iron overload is typically either blood donation or prescription phlebotomy, so it's the same. Phlebotomy is the removal of blood, typically a unit of blood at one time.

- There is also a substance called apolactoferrin. It's a natural protein that can help remove iron from tissues in the body, iron that is already stored in the body. The dosage would be 300 mg of lactoferrin one to two times a day on an empty stomach.
- Patients can actually absorb a significant amount of iron from iron skillets.
- We also advise them to avoid substances that enhance the absorption of iron:
    - Alcohol, so we ask them to limit consumption to two drinks a week or avoid entirely if they can.
    - Supplemental vitamin C, which we limit to 200 mg taken between meals.
    - Betaine hydrochloric acid, which, of course, many take to improve digestion.
    - High doses of zinc interfere with copper and iron metabolism.
    - Beta-carotene actually enhances the absorption of iron and may increase cancer risk as a result.

CALCIUM

- Calcium is a main structure element of bones and teeth. It also plays a role in cell signaling. Calcium levels are tightly regulated by parathyroid hormone and vitamin D.
- The RDA for calcium is 1,000 to 1,200 mg a day, though other experts have suggested that lower levels are probably adequate, especially if vitamin D and K2 levels are sufficient, because those nutrients help to regulate calcium metabolism. We recommend a minimum of 600 mg and preferably above 800 mg per day.
- You should be aware that higher-protein diets also increase calcium absorption, and higher intakes of calcium through supplements but not through diet can lead to hypercalcemia, which can be fatal if left untreated.
- Overwhelming research shows that calcium supplementation not only doesn't reduce fracture rates in the elderly, but it may also increase them.
- While calcium is a crucial mineral, supplemental calcium has been shown to increase the risk of cardiovascular disease and cardiovascular events.
- Make sure your patients are getting adequate amounts of vitamin K2 and consuming enough vitamin D and vitamin A because all of those play a role in regulating calcium homeostasis.

VITAMIN E

- Vitamin E is a potent fat-soluble anti-inflammatory vitamin that protects us from free radicals and reactive oxygen species. It's also involved in immune function, cell signaling, regulation of gene expression, and other metabolic processes.
- There are phenols, tocopherols, and tocotrienols.
- Alpha-tocopherol is the form that most supplements contain. While vitamin E is an important nutrient to get in the diet, I definitely don't recommend supplementing with it, with the possible exception of tocotrienols.
- Alpha-tocopherol shows no benefit, but in several studies, it actually shows harm.
- Aim for whole-food sources of vitamin E only. These include nuts and seeds primarily but also tomato sauce, cranberry juice, some fruits such as apricots and avocado, and fish such as trout. The RDA is 15 mg a day.

BETA-CAROTENE

- Beta-carotene gives plants an orange or yellow color, and this is a precursor for active vitamin A, retinol. Beta-carotene can also be converted into potentially harmful substances, and it can increase the risk of oxidative stress. It can interfere with vitamin A metabolism.
- It's better to get a normal amount of beta-carotene from food, and this is easy to do on a Paleo-type diet. Foods that are rich in beta-carotene include carrots, tomatoes, sweet potatoes, broccoli, cantaloupe, winter squash, bell peppers, spinach, lettuce, pumpkin, and kale.

FOLIC ACID

- Folic acid is an oxidized synthetic compound that is only found in dietary supplements and fortified foods. This is not a natural form of folate found in nature.
- It can be converted into natural folate, but unfortunately, that conversion is limited in humans.
- It undergoes initial reduction and methylation in the liver using dihydrofolate reductase as an enzyme, and if the patient has low activity of this enzyme, they can end up with high levels of unmetabolized folic acid in their system and circulation.

- High levels of unmetabolized folic acid in the blood can mask vitamin B12 deficiency and can lead to deterioration of central nervous system function, especially in the elderly. They can cause anemia and cognitive impairment. They can accelerate the progression of certain cancers, including colon and prostate cancer. They can depress immune function, and they are associated with an increased risk of death from all causes.
- Folate, natural folate, on the other hand, which is found in foods in nature and in supplements with natural forms of folate such as 5-methyltetrahydrofolate, folinic acid, or metafolin, is not only very necessary for health but is also safe to supplement with.
- Foods that are naturally rich in folate include beef liver, and chicken liver is actually the highest source of folate and the best source; also, dark, leafy greens such as spinach and collards. Lentils are a good source of folate if your patients tolerate legumes, as are beets, cauliflower, parsley, mustard greens, turnip greens, and even some lettuces.

SUMMARY OF SUPPLEMENT RECOMMENDATIONS

- **Vitamin A**
    - Adequate amounts can be obtained by consuming about four ounces of liver per week. If supplementation is necessary, 10,000 to 15,000 IU per day is appropriate for most people. The best form is cod liver oil because it also contains vitamin D, which works synergistically with vitamin A, and it's an animal source, which means that it will be preformed retinol, the active form of vitamin A, rather than beta-carotene.
- **Vitamin D**
    - Functional lab range is 35 to 60 ng/mL, especially when vitamin A and vitamin K2 levels are adequate. Sun exposure is the preferred source of vitamin D production for a number of reasons. There is lower risk of toxicity than with supplements and it provides a range of other health benefits and nutrients.
    - How much you supplement with depends on the level of deficiency, so the common doses might range from 1,000 to 4,000 IU per day. Sometimes up to 10,000 IU per day for a short period may be necessary, but you have to be very

careful with vitamin D, as with other nutrients such as iron, because while too little is problematic, too much is also problematic.

- **Magnesium**
  - Most patients benefit from magnesium supplementation. Very few people actually get enough of it in their diet, even on a nutrient-dense diet, so somewhere from 300 to 500 mg per day in chelated supplemental form is ideal.
  - Glycinate and malate are well absorbed and have fewer side effects.
- **Vitamin K2**
  - The two major supplemental forms are MK4 and MK7. The supplemental dose ranges from 100 to 1,000 mcg per day for optimal health, although for those suffering from osteoporosis, doses way up in the milligram quantities, as high as 30 to 45 mg, have been used successfully in studies.
- **Vitamin C**
  - 500 to 1,000 mg daily is safe and well tolerated by most people. Several grams a day can be taken without toxicity, but you need to watch out for side effects such as loose stools or diarrhea.
- **Iodine**
  - Many patients don't get enough iodine in their diets, especially after they remove iodized salt and other processed foods where iodine has been added.
  - The recommended dose is 800 mcg a day, and that is safe for most people, but be cautious in supplementing with iodine in patients with Hashimoto's thyroiditis or other autoimmune thyroid conditions.

Lesson 30: Blood Chemistry Basics Review

BASIC PRINCIPLES OF FUNCTIONAL BLOOD CHEMISTRY:

1. Patterns are typically much more important than individual markers.
    a. Evaluate individual blood chemistry markers in the context of other markers to determine the presence of a functional imbalance, pathology, or disease.
2. In some cases, additional markers will need to be ordered to clarify the pattern or diagnosis.
3. Blood chemistry should never be used in isolation. It should always be combined with a thorough medical history, including current symptoms, diet and lifestyle, medications and supplements review, and, if you do this in your practice, a physical examination.
    a. For example, a patient's test results show elevated serum B12 levels.
        i. Are they supplementing with vitamin B12? If they are, the elevation is simply a sign of that, and it's nothing to worry about.
        ii. If they aren't, it can be a sign of impaired vitamin B12 metabolism and methylation, and you'd want to order additional testing to clarify.
4. The reference ranges that we use to interpret results in functional blood chemistry are often, but not always, different than the reference ranges that are used in conventional medicine and printed on the lab results. Conventional ranges are designed to diagnose disease. The functional ranges are designed to diagnose imbalances or pathologies before they progress to full-blown disease.
5. It is important to retest after you've addressed the imbalances or conditions you identified with the comprehensive screening panel. Test, don't guess.

LAB RANGES

- Ancient Chinese proverb, "The wise physician treats disease before it occurs."
- The conventional medicine reference range is typically constructed using a bell curve of results from a reference sample of a population. However, an accurate range is dependent on the sample population used, and this can be an issue.

FUNCTIONAL RANGE

- In some cases, the functional range is determined by organizations that embrace functional or at least preventative medicine.
- In other cases, the functional ranges are established by individual clinicians or groups of researchers based on extensive review of the published scientific literature.
    - For example, most recent studies where they took more measures to eliminate people who had hypothyroidism and autoimmune hypothyroidism found that the range of thyroid-stimulating hormone (TSH) for someone with a completely normally functioning thyroid gland is probably 0 to 2.
- Finally, in some cases, functional ranges have been created simply by shrinking the conventional range by 20 to 30 percent.

The initial functional blood chemistry panel is a screening tool where the goal is to be thorough and cost-effective. I start with markers that I feel are most important and are most likely to reveal underlying patterns that need to be addressed or need to be followed up on with additional testing.

COMPREHENSIVE METABOLIC PANEL (WITH ADD-ONS)

Glucose	Magnesium
Sodium	Total protein
Potassium	Albumin
Chloride	Globulin
Carbon dioxide	Albumin/Globulin ratio
Blood urea nitrogen (BUN)	Total bilirubin
Creatinine	Alkaline phosphatase
BUN/Creatinine ratio	AST
eGFR	ALT
Calcium	

- Gamma-glutamyl transferase
- Parathyroid hormone

- Phosphorus
- High-sensitivity C-reactive protein

ADDITIONAL METABOLIC MARKERS

- Hemoglobin A1c
- Uric acid
- Lactate dehydrogenase
- Insulin

IRON PANEL PLUS FERRITIN

- Over two billion people in the world suffer from iron deficiency, and iron overload is a much more common condition than is typically recognized. Iron is an absolutely crucial nutrient. It's essential for life, and yet it can be deadly when it is elevated. It is a contributing factor in many health conditions.
    - Serum iron
    - Total iron binding capacity
    - Unsaturated iron binding capacity
    - Iron saturation (%)
    - Ferritin

OTHER IMPORTANT NUTRIENTS

- Vitamin B12 deficiency is not uncommon, even in omnivores, due to low stomach acid, digestive issues, and autoimmune conditions such as pernicious anemia. Serum B12 is not always accurate, and it misses a lot of people who are deficient, so I add serum methylmalonic acid (MMA).

- Serum copper and serum zinc: An altered serum copper-zinc ratio is associated with immune and inflammatory issues, more so than it is with dietary or supplemental intake of copper and zinc, as we'll discuss.
- Vitamin D is one of the most common deficiencies that we'll see.
    - Vitamin B12
    - Serum folate
    - Serum MMA
    - Homocysteine
    - Serum copper
    - Serum zinc
    - Calcitriol (1, 25-dihydroxyvitamin D)
    - Vitamin D (25-hydroxyvitamin D)

STANDARD LIPID PANEL

- More advanced testing is often necessary in someone with abnormal lipid values, but you can get a surprisingly useful amount of information just from this standard lipid panel. For example, it turns out that the total cholesterol-to-high-density lipoprotein (HDL) ratio correlates very well with the low-density lipoprotein (LDL) particle number, which is probably one of the more important lipid markers. Don't totally ignore this. It's still an important part of a basic blood panel.
    - Total cholesterol
    - LDL cholesterol
    - Very low-density lipoprotein cholesterol
    - HDL cholesterol
    - Trigylcerides
    - Total cholesterol-to-HDL ratio
    - LDL-to-HDL ratio

THYROID PANEL

- TSH
- Total thyroxine (T4)
- Total triiodothyronine (T3)
- Free T4
- Free T3
- T3 uptake
- Reverse T3
- Thyroid peroxidase antibodies
- Thyroglobulin antibody

COMPLETE BLOOD COUNT (CBC)

- The CBC helps identify conditions such as anemia, infection, inflammation, autoimmunity, bleeding disorders, and cancer. Platelet count and differential are often added. I do this in my panel. This gives you additional information that can be useful. The differential identifies and counts the number of white blood cells that are present.

WBC	Lymphocytes (%)
RBC	Monocytes (%)
Hemoglobin	Eosinophils (%)
Hematocrit	Neutrophils (absolute)
MCV	Lymphocytes (absolute)
MCH	Monocytes (absolute)
MCHC	Eosinophils (absolute)
RDW	Immature granulocytes (%)
Platelets	Immature granulocytes (absolute)
Neutrophils (%)	

Lesson 31: Blood Chemistry Hyperglycemia Etiology and Diagnosis Review

CAUSES OF HYPERGLYCEMIA

- Industrialized diet
- Physical inactivity
- Sleep deprivation
- Chronic stress
- Environmental toxins
- Disrupted gut microbiota

Hyperglycemia is a risk factor for many other serious diseases, including cardiovascular disease, nerve damage, kidney damage, diabetic retinopathy, bone and joint problems, skin problems, and periodontal infections.

Current reference ranges for markers related to blood sugar are too high on the upper end.

Many studies have shown that even high-normal blood sugar, according to the current lab reference ranges, is associated with a significantly higher risk of diabetes, heart disease, and other conditions, so we need to identify and address blood sugar issues early.

PRIMARY HYPERGLYCEMIA MARKERS

Marker	Value
Glucose (fasting)	High
Hemoglobin A1c	High
Fructosamine	High
Post-meal glucose (GlycoMark, OGTT, glucometer)	High (Low for GlycoMark)
Triglycerides	High
HDL	Low
Triglycerides:HDL	High

SECONDARY HYPERGLYCEMIA MARKERS

Marker	Value
Uric acid	High
Fasting insulin	High
ALT	High
AST	High
LDH	Low
GGT	High

FASTING GLUCOSE

- Measures the concentration of glucose in the blood after an eight- to 12-hour fast.
- Fasting glucose varies a lot from day to day and is affected by multiple factors, including recent food intake, sample storage, high intraindividual variability, acute stress, and diurnal variations.
- Drugs that influence glucose metabolism include corticosteroids, fibrates, cyclosporine, beta-blockers, methoxazole, thiazide diuretics, and thyroid hormones, among many others.

Fasting glucose is the least sensitive marker for predicting future diabetes and heart disease.

This is due to the first- and second-phase insulin response.

- First-phase insulin response is the early release of stored insulin by beta cells immediately when you eat a meal. If blood sugar rises above 100 mg/dL, the beta cells release more insulin into the blood.
- In a healthy person, it keeps blood sugar from rising too high.
- After completing the first phase, the beta cells pause. If blood sugar is still not below 100 mg/dL 10 to 20 minutes later, they push out another smaller second-phase insulin response.
- In a healthy person, this should bring blood sugar back down to the starting level that it was at before a meal within one to one and a half hours after they finish the meal.
- As blood sugar control worsens, it may take four to five hours for beta cells to make enough insulin to bring blood sugar back down to a fasted level after a meal.
- During the day, this may never happen because glucose increases after the next meal before glucose from the previous meal has been cleared out.
- Blood sugar may only return to normal at night after sleeping seven to eight hours without eating. This allows enough time for the impaired second-phase response to get blood sugar down, and the patient will wake up with normal fasting blood sugar. This is why fasting glucose can be high-normal or even completely normal in someone who is already well on the way to diabetes.
- You need to look at postmeal glucose and A1c to get a complete picture.

WHAT IS "NORMAL" FASTING GLUCOSE?

- 80 mg/dL = average fasting glucose levels in healthy people.
- Less than 85 mg/dL = cardiovascular disease risk progressively increases with fasting glucose.
- Conventional range is 65 to 99 mg/dL.
- Functional range is 75 to 85 mg/dL.
- Fasting glucose is highly variable; we're looking for patterns, not individual markers.
- Look at multiple markers of metabolic function, including fasting glucose and A1c.
- Many factors affect blood sugar. For example, high iron can cause high blood sugar.

High fasting glucose with normal A1c and postprandial glucose could indicate a defect in basal insulin secretion.

HEMOGLOBIN A1c

- Theory behind the A1c test:
    - Red blood cells live an average of three months, so if we measure the amount of sugar stuck to these cells, which is what the hemoglobin A1c test does, it will give us an average measure of blood sugar over a three-month period with greater focus on the most recent six weeks.
- The number reported in the A1c indicates the percentage of hemoglobin that has become glycated, or stuck, to sugar.
- A1c has a closer association with cardiovascular disease than fasting glucose.
- A1c is considered to be a more stable marker.
- The biological variability is lower than fasting glucose and the oral glucose tolerance test.

Hemoglobin A1c downsides

- Some people's A1c results are always a little higher or lower than their fasting glucose or postmeal glucose numbers would predict.
    - This is likely due to the fact that several factors can influence red blood cells.

- Anything that affects red blood cells and hemoglobin, such as anemia, dehydration, and genetic disorders, will skew A1c results.
- Two-hour postmeal blood sugar and impaired glucose tolerance are stronger predictors of heart disease than A1c.
- There is a wide range of red blood cell survival time, which affects A1c levels and makes them less accurate in individuals.

This is a partial list. Please see the presentation video or transcript PDF for a more comprehensive list.

On a population basis, a truly normal A1c is 4.6 to 5.3 percent, but we treat individuals, not populations.

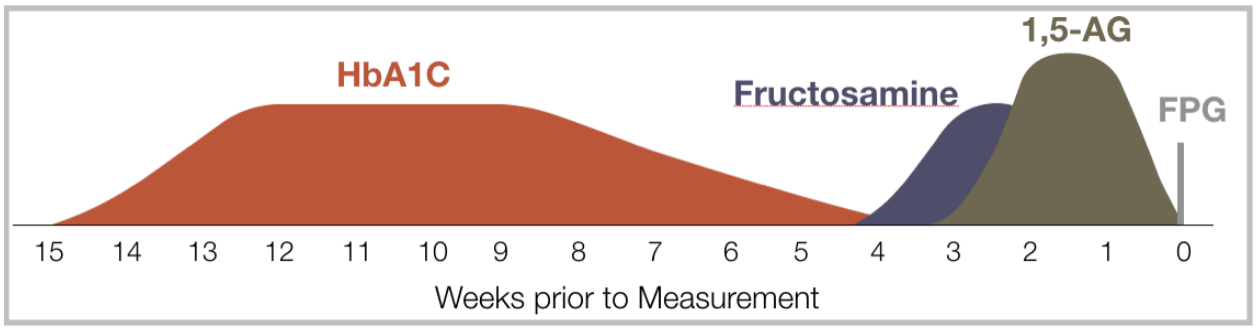
As with fasting glucose, we need to consider other markers to determine the relevance of A1c.

Mean corpuscular volume (MCV) can be useful in interpreting A1c values.

- Red blood cells start out large and decrease in size over their lifespan.
- If A1c is high and MCV is high-normal, this indicates that an elevated A1c is not due to long-lived red blood cells.
- If A1c is high and MCV is normal or low, it suggests that high A1c could be due to long-lived red blood cells.

Fructosamine

- During the glycation of serum proteins such as albumin, the aldimine intermediate can be reconverted to glucose and protein or form into a fructosamine derivative.
- A1c is a measurement of blood sugar control over two to three months, whereas fructosamine is a measurement of blood sugar control over the previous two weeks, and this is illustrated below.



Fructosamine can detect changes in blood glucose before they show up in A1c.

POSTMEAL BLOOD SUGAR OR POSTPRANDIAL BLOOD SUGAR

- Looks at the blood sugar response to meals or a two-hour glucose challenge, in the case of the OGTT.
- These measurements reflect the pathophysiology behind diabetes better than any other glycemic marker.
- Normal blood glucose levels two hours after a glucose load indicate good beta cell capacity.
- High two-hour postprandial glucose (PPG) level indicates an impairment of beta cell function.
- PPG is superior to fasting glucose or A1c in predicting cardiovascular disease outcomes.

THREE WAYS TO MEASURE PPG

1. **Oral glucose tolerance test**
    a. Patient fasts, and then is given 75 g of glucose dissolved in water.
    b. Then they test the patient's blood glucose one and two hours after. If the blood sugar is above 140 mg/dL two hours after the test, this indicates prediabetes. If blood sugar is above 199 mg/dL two hours later, this indicates diabetes.
    c. Advantage: It is highly validated, and there is tons of research correlating it with clinical outcomes.
    d. Disadvantage: It's artificial. I don't know anyone who drinks a pure solution of 75 g of glucose outside of this OGTT setting.
    e. Instruct patients to eat at least 150 g of carbohydrates for three days before an OGTT if they are having that test done in a lab.
2. **Glucometer testing**

a. Tests blood sugar just before and then one, two, and three hours after a meal.

b. Advantages

   i. Convenient

   ii. Better reflection of the response to actual meals that that patient is eating

   iii. Objective way of determining carbohydrate tolerance

   iv. Better compliance and also fewer adverse reactions in patients

c. Cons

   i. It's not validated to the same degree as OGTT.

   ii. Glucometers are notoriously variable in accuracy and consistency.

   iii. Overall, we prefer glucometers to OGTT because we're looking for patterns. A single reading is not super important. We also consider other markers such as fasting glucose, A1c, etc.

d. Glucometer testing targets

Marker	Target
Fasting (before meal)	75-85
1 hour post-meal	<140
2 hour post-meal	<120
3 hour post-meal	75-85

Caveats to this kind of testing

- Even reliable glucometers have about a 10 percent margin of error, so a reading of 100 mg/dL could be anything between 90 and 110 mg/dL, but this is okay because what we're doing here is trying to identify patterns.
- If the patient normally eats a low-carb diet, postmeal glucose readings on the third day following the simple carbohydrate challenge will be abnormally high.

- If the patient has been eating a low-carb diet for at least a couple of months before doing the carbohydrate challenge, on day three of the test, you can subtract 10 mg/dL from your one- and two-hour readings.

3. **GlycoMark**
    a. Measures the 1,5-anhydroglucitol (1,5-AG) molecule in the blood.
    b. One- to two-week measure related to average daily maximum blood glucose.
    c. For people with well-controlled blood sugar, 1,5-AG is stored at a steady state in the tissues and the bloodstream, which keeps blood levels of 1,5-AG high and produces a high GlycoMark score.
    d. For people with blood glucose averaging over 180 mg/dL a day, 1,5-AG is low.
    e. This is an inverse marker. High 1,5-AG indicates normal or well-controlled blood sugar, and low 1,5-AG indicates high blood sugar.
    f. This test has advantages over a test such as A1c because it shows glycemic variability and blood sugar spikes.
    g. Spikes are better predictors of cardiovascular disease and other complications and are more damaging than just a high average A1c level.

OTHER MARKERS OF METABOLIC DYSFUNCTION AND DYSGLYCEMIA

Triglycerides

- Triglycerides are one of the major lipids found in the serum.
- They are elevated in conditions characterized by abnormal blood sugar such as obesity and type 2 diabetes.

High-density lipoprotein (HDL)

- So-called good cholesterol.
- Low levels of HDL are observed in patients with insulin resistance, obesity, and type 2 diabetes.
- The ratio of triglycerides to HDL is one of the best-studied markers of metabolic dysfunction. It should be below 2 optimally.

ALT, AST, and GGT are enzymes that may be out of range in dysglycemic conditions. GGT is an enzyme responsible for the extracellular catabolism of glutathione, and high GGT may be linked to increased oxidative stress and beta cell destruction.

Uric acid

Studies have shown significant associations between increased uric acid and metabolic syndrome such as obesity, type 2 diabetes, hypertension, and gout.

Lesson 32: Blood Chemistry Hyperglycemia and Hypoglycemia Treatment Review

The main considerations in the treatment of hyperglycemia are:

1. Diet
    a. A Paleo diet is effective for glucose control and reversal of type 2 diabetes.
    b. Moderate carb intake, with 25 to 35 percent of calories with Paleo-friendly (cellular) carbs: starchy tubers and whole fruits, as opposed to acellular carbs that impact human physiology differently. If this is not sufficient, consider a low-carb (15 percent) or very low-carb (10 percent or less) ketogenic approach.
    c. Remind the patient not to snack between meals.
    d. Intermittent fasting can reduce blood sugar and improve insulin sensitivity.
        i. Consider compressing food intake into an eight-hour window each day.
        ii. Fasting is not recommended during pregnancy or nursing; for patients with significant hypothalamic–pituitary–adrenal (HPA) axis dysfunction, particularly hypocortisolism; or for patients with eating disorders.
    e. Protein-sparing modified fast (PSMF) approach: high-protein, low-carb, low-fat, and low-calorie diet. Consider adding a multivitamin for adequate nutrient intake.
        i. Unlike voluntary calorie restriction, patients will spontaneously reduce their calorie intake.

ii. It doesn't lead to muscle breakdown like some other low-calorie diets and it's easier to follow than other severe calorie-restricted diets.

iii. You could do a PSMF three to four days a week and eat normally the other days. Weight loss would be slower, but compliance will be higher.

f. Potato hack: All-potato diet

i. This low-calorie, low-fat, and high-carbohydrate diet can be effective for diabetes treatment.

ii. Consider modifying the diet to potatoes that have been cooked and cooled, which creates resistant starch. This will not have a significant impact on blood sugar because resistant starch is not absorbed in the human digestive tract.

1. Consider this for patients who have a blood sugar spike on glucometer testing after eating one or two potato-only meals.

iii. The potato diet spontaneously decreases calorie intake as patients are eating foods that are not highly palatable or rewarding.

iv. It reduces inflammation and improves gut microbiota.

v. A variation patients may prefer is potatoes by day, where patients eat potatoes only for breakfast and lunch. Then, they eat a normal dinner with their family.

Increase nonexercise physical activity; for example, standing at least 50 percent of the day and taking 10,000 steps a day.

Get enough exercise; for example, high-intensity interval training and other steady-state activities as desired.

1. Sleep

a. A single night of poor sleep can impair insulin sensitivity the next day.

b. Get at least seven to eight hours of sleep a night, use proper sleep hygiene, and control exposure to light at night and during the day.

2. HPA axis dysfunction

a. Prescribe stress management for your patients.

3. Nutrients associated with hyperglycemia: low vitamin D, low magnesium, low and high levels of iron, low choline, and low chromium
4. Assess and correct gut pathologies

NUTRIENTS FOR BLOOD SUGAR REGULATION

Nutrient	Dose
Chromium chelate	100-300 mcg/d
Alpha-lipoic acid	200-400 mg/d
Magnesium	300-500 mg/d
Biotin	200-500 mcg/d
Green tea extract	200-300 mcg/d

Metabolic Synergy from Designs for Health contains chromium, alpha-lipoic acid, taurine, green tea extract, manganese, magnesium, potassium, vanadium, and other nutrients that can be helpful in regulating blood sugar. The dosage is two capsules three times a day or three capsules two times a day.

BOTANICALS FOR BLOOD SUGAR REGULATION

Botanical	Dose
Berberine	400-600 mg/d
Gymnema	200-400 mg/d
Banaba	40-60 mg/d
Fenugreek	200-300 mg/d

Berberine targets AMP-activated protein kinase (AMPK), which stimulates uptake of glucose into cells, improves insulin sensitivity, and reduces glucose production in the liver. Some studies have shown it to be just as effective as metformin in treating diabetes.

Gymnema reduces insulin requirements, decreases fasting blood sugar, enhances the action of insulin, and may even promote regeneration of the beta cells of the pancreas, which produce insulin. It is also very helpful for reducing sugar cravings.

Banaba lowers blood sugar, reduces inflammation, and protects against oxidative damage.

Fenugreek slows enzymatic digestion of carbohydrates, reduces gastrointestinal absorption of glucose, and thus reduces postprandial glucose levels. It also stimulates glucose uptake in peripheral tissues and improves insulin production.

GlucoSupreme from Designs for Health combines several of these botanicals. The recommended dose is two capsules twice a day with meals.

FIBER

High-fiber diets reduce the risk of diabetes and aid in the treatment of high blood sugar. Fiber may decrease insulin peaks after meals because it slows absorption of carbs and increases insulin sensitivity. Instruct patients to follow a diet high in microbiota-accessible carbohydrates.

FIBER SUPPLEMENTS

Glucomannan (PGX) soluble fiber

- Reduces hyperglycemia and improves insulin sensitivity.
- Suggested dose is 0.5 g per 100 kcalories consumed per day, which works out to about 8 to 13 g a day for most patients. In powder form, where a half teaspoon is 2 g, the dose would be two to four teaspoons per day depending on the patient's calorie intake.

Resistant starch has also been shown to be helpful in regulating blood sugar.

- Can be obtained in the diet from cooked and cooled potatoes, white rice, and lentils.
- As a supplement, you can use green banana, green plantain flour, or Bob's Red Mill potato starch, which is gluten-free.
- Maximum therapeutic dose is four tablespoons a day.
    - Start at a much lower dose such as half a teaspoon.

HYPERGLYCEMIA TREATMENT

Intervention	Comments
Diet	Basic Paleo, Low-carb/ketogenic Paleo, IF, PSMF
Lifestyle	Physical activity, sleep, stress management
Address pathologies	Primarily gut and HPA axis
Rebalance nutrients	Vitamin D, iron, magnesium
Therapeutic supplementation	Metabolic Synergy, GlucoSupreme
Fiber	Glucomannan, resistant starch

METFORMIN (GLUCOPHAGE)

- Long track record of safety.
- Associated with lower risk of death from cardiovascular disease and cancer in patients with diabetes.
- Inhibits gluconeogenesis, stimulates glucose uptake in muscles, blocks triglyceride synthesis, and promotes fat burning.
- Takes three days to kick in and three weeks to achieve the maximum effect.
- Most common side effect is gastrointestinal (GI) disturbance.
- Taking metformin ER at night results in a stronger effect on fasting blood glucose (FBG).
- Taking metformin in the morning gives the best coverage for lunch/dinner but results in the highest FBG and most GI discomfort.
- Contraindications: kidney/liver damage, congestive heart failure.
- Avoid alcohol.
- Watch vitamin B12 and folate levels.

INSULIN

- If there has already been significant beta cell destruction, and type 2 diabetes is advanced or the patient has autoimmune diabetes, they will often need insulin.
- One important note: If you're treating a patient on insulin, and you implement some of the diet, lifestyle, and supplement botanical interventions we've talked about, you should warn them that their required dose of insulin may decrease. Ask them to coordinate with their endocrinologist.

HYPOGLYCEMIA

- True hypoglycemia is far less common in clinical practice than hyperglycemia.
- In order for a patient without diabetes to be diagnosed with hypoglycemia in the conventional setting, he has to meet criteria known as Whipple's triad. This includes:

    - Symptoms consistent with hypoglycemia
    - Low plasma glucose measured with a precise method, meaning not a glucometer, when symptoms are present
    - Relief of those symptoms if plasma glucose is raised
- The symptoms of hypoglycemia are diverse and nonspecific. They're primarily broken into two categories: neurogenic, or autonomic, and neuroglycopenic.
    - Neurogenic symptoms include tremor, palpitations, anxiety, and arousal, which are catecholamine-mediated and adrenergic; and then sweating, hunger, and paresthesias, which are acetylcholine-mediated and cholinergic.
    - Neuroglycopenic symptoms include cognitive impairment, behavioral changes, psychomotor abnormalities, and, at lower plasma glucose concentrations, seizure and coma.
- Hypoglycemia may also be asymptomatic due to what is known as hypoglycemia unawareness. This is thought to be the result of reduced sympathoadrenal responses to a given degree of hypoglycemia.
- In patients without diabetes, the most common causes of hypoglycemia according to the conventional model are certain medications, alcohol, critical illness, malnourishment, cortisol deficiency, islet cell tumors, and endogenous hyperinsulinism.
- Follow-up testing includes fasting glucose, fasting insulin, C-peptide, beta-hydroxybutyrate, and proinsulin.
- Evaluation of low fasting glucose and hypoglycemia in children is a little different. One of the primary possible causes in kids is mitochondrial dysfunction or mitochondrial disease.
- The next consideration is hypoglycemia in patients with diabetes and impaired glucose tolerance. This typically occurs in the postprandial state rather than the fasted state.
- The goal is to document Whipple's triad and demonstrate low glucose below 50 mg/dL at the time symptoms are occurring, within four hours after a meal. The difference is patients with reactive hypoglycemia should be evaluated in the postprandial state after a mixed meal. OGTT is actually no longer recommended as the test for postprandial.

Lesson 33: Blood Chemistry Iron Review

IRON:

- Iron is an essential micronutrient, needed for many functions in the body, including hemoglobin, myoglobin, enzyme production, and our immune system.
- Iron cannot be absorbed by the body. It must be oxidized to ferric oxide first, then exposed to an acidic environment, hydrochloric acid in the stomach to be turned into ferrous iron, which can be absorbed, primarily in the duodenum.
- Unabsorbed iron, about 90 percent obtained in a typical diet, is excreted in the feces.

IRON DISTRIBUTION

Location	Amount
Hemoglobin	70%
Myoglobin and enzymes	15%
Ferritin	14%
In transit in serum	1%

Transferrin is the main transport protein of iron. Normally, 25 to 35 percent of the transferrin protein is saturated with iron (transferrin saturation 25 to 35 percent).

Ferritin is the long-term storage form of iron. Ferritin is produced in nearly every cell in the body, which stores iron when it is in ample supply or when it has the potential to be harmful.

The average adult requires 8 to 12 mg of iron per day, of which 85 to 90 percent is absorbed, and we excrete about 1 to 1.5 mg of iron per day, and that allows us to maintain iron balance.

TWO PRIMARY CAUSES OF IRON DEFICIENCY

Increased demand	Decreased intake/absorption
Heavy menstruation	Plant-based diets
Pregnancy	Foods that inhibit iron absorption
Fibroids	Medications (e.g. PPIs)
GI bleeding	Low stomach acid
Surgeries and accidents	Low intrinsic factor
Excessive blood donations	Celiac disease
Medications & supplements	Crohn's disease
Alcohol abuse	Autoimmune disease
Lead/metal poisoning	Hormone imbalance

Populations that are most at risk for iron deficiency include women; children; the elderly; people on vegetarian and vegan diets; endurance athletes or those who perform intense exercise; women with heavy menstruation or fibroids; patients with inflammatory bowel disease, celiac disease, and atrophic gastritis; long-term PPI users; and alcoholics.

SYMPTOMS OF IRON DEFICIENCY

Fatigue	Poor cognitive function
Tachycardia	Reduced exercise tolerance
Palpitations	Inability to maintain proper body temperature
Rapid breathing on exertion	Brittle & spoon-shaped nails
Restless leg	Sores at corner of mouth
Infections	Pica

THREE STAGES OF IRON DEFICIENCY

1. Ferritin 10 to 15 ng/mL; may be asymptomatic
2. Iron stores exhausted; ferritin less than 10 ng/mL
3. Iron-deficiency anemia

IRON DEFICIENCY MARKERS

Marker	Value
Serum iron	Low
Serum ferritin	Low
Transferrin saturation	Low
Total iron binding capacity	High
Unsaturated iron binding capacity	High
RDW	High
Soluble transferrin receptor	High

Ferritin, transferrin saturation, and unsaturated iron-binding capacity (UIBC) are the most sensitive for detecting iron deficiency, in that order.

These iron markers go out of range much sooner than you'll see changes in the red blood cell indices on the complete blood count.

SERUM IRON

- Least reliable marker for determining iron status.
- Tests iron contained in plasma that is generally bound to transferrin.
- Alcohol and drugs such as oral contraceptives and methotrexate can increase iron levels in serum.
- Testosterone, large doses of aspirin, metformin, and adrenocorticotropic hormone can decrease them. Stress and sleep deprivation can also temporarily decrease serum iron levels.

FERRITIN

- Considered the most sensitive marker for detecting iron deficiency, and it's often the first to go out of whack along with RDW.
- However, ferritin is also an acute-phase reactant that increases in the inflammatory response, much like C-reactive protein.

RED CELL DISTRIBUTION WIDTH

- Measures variation of red blood cell size or volume.
- One of the first markers to go out of range in iron deficiency.
- However, it can also be high in vitamin B12 and folate deficiency.
- RDW is an inverse marker, which means that when it is high, it indicates low iron.

TRANSFERRIN SATURATION

- Percentage is calculated by dividing serum iron by total iron-binding capacity (TIBC) and then multiplying by 100.
- The optimal range of transferrin saturation, or iron saturation as it's also known, is generally between 25 and 35 percent on standard lab tests.
- Less than about 17 percent indicates iron deficiency.

UNSATURATED IRON-BINDING CAPACITY (UIBC)

- Refers to the portion of transferrin binding sites that are not bound with iron, which is usually about one-third of the binding sites.
- UIBC at or above the high end of the lab range indicates an excess capacity for transferrin molecules to accept iron = iron deficiency (inverse marker).

TIBC = UIBC PLUS SERUM IRON (INVERSE MARKER).

SOLUBLE TRANSFERRIN RECEPTOR, ALSO KNOWN AS SERUM TRANSFERRIN RECEPTOR (STFR)

- Cleaved extracellular portion of the transferrin receptor 1 that is released in the serum.
- Used to clarify iron deficiency or overload in patients who may have inflammation, infection, chronic disease, and other conditions in which ferritin does not correlate with iron status, such as cystic fibrosis or insulin-dependent diabetes.
- Iron deficiency = increased sTfR levels.
- Iron overload = decreased sTfR levels, so it's an inverse marker.
- For example, a patient has transferrin saturation percentage and UIBC levels that indicate iron deficiency but has a high ferritin level.
    - Order a soluble transferrin receptor to determine if it truly is iron deficiency, and perhaps the ferritin is elevated because of an inflammatory condition.

RETICULOCYTE HEMOGLOBIN CONTENT (CHR)

- Measures the amount of hemoglobin in reticulocytes.
- CHr provides an indirect measure of the functional iron available for new red blood cell production over the previous three to four days.
- Can be ordered at some Quest Diagnostics locations and through Spectra Labs.

Functional ranges for iron markers

Marker	Men	Pre-menopausal women	Post-menopausal women
Serum iron	40–135 ug/dL	40–135 ug/dL	40–135 ug/dL
Serum ferritin	30–200 ng/mL	30-100 ng/mL	30-100 ng/mL
Transferrin saturation	17–45%	17-45%	17-45%
TIBC	275–425 ug/dL	275-425 ug/dL	275-425 ug/dL
UIBC	175–350 ug/dL	175-350 ug/dL	175-350 ug/dL
sTfR	14.5-25 nmol/L	13-25 nmol/L	14.5-25 nmol/L
CHr	24.5–31.8 pg	24.5–31.8 pg	24.5–31.8 pg

TREATMENT OF IRON DEFICIENCY

1. Diet
    a. Vegetarians and vegans are at higher risk of deficiency.
    b. Heme iron, found in animal products, is much better absorbed than nonheme iron, which is found in plant sources of iron. Bioavailability of plant sources of iron is lower.
    c. Absorption of plant-based forms of iron is inhibited by other commonly consumed substances such as coffee, tea, dairy products, supplemental fiber, and supplemental calcium.

HIGHEST SOURCES OF HEME IRON

Food	Amount (mg per 100g)
Clam	28
Chicken liver	13
Oyster	12
Octopus	10
Beef liver	7
Venison	5
Mussel	4
Beef chuck	4
Bison, ground	3
Crab	3
Duck breast	3
Lamp shoulder	3
Pork shoulder	2

If possible, shellfish and organ meats should be a part of the diet, especially when iron is deficient.

HIGHEST SOURCES OF NONHEME IRON

Food	Amount (mg per 100g)
Spices (thyme, parsley)	15-128
Pumpkin seeds	15
Sesame seeds	15
Tomatoes, sun-dried	9
Natto	9
Baked potatoes	7
Sunflower seeds	7
Hazelnuts	5
Soybeans, boiled	5
Spinach, cooked	4
Tomatoes, canned	3
Spinach, raw	3
Beet greens, cooked	2
Swiss chard, raw	2

SUBSTANCES THAT DECREASE IRON ABSORPTION

Substance	Comments
Calcium	Inhibits both heme/nonheme
Eggs	Contain phosvitin, which inhibits iron absorption
Oxalates	Spinach, kale, beets, nuts, chocolate, tea, berries, some spices/herbs
Polyphenols	Cocoa, coffee, teas, apples, berries, walnuts, some spices
Phytate	Walnuts, almonds, sesame, dried beans, lentils and peas, and cereals and whole grains
High doses of zinc	Limit to 20 mg per dose, taken between meals
Medications	Proton pump inhibitors (PPIs) and other antacids

SUBSTANCES THAT INCREASE IRON ABSORPTION

Substances that increase iron absorption

Substance	Comments
Vitamin C	100 mg increases iron absorption in a meal by over 4-fold
Beta-carotene	Apricots, beets, carrots, collards, red grapes, red peppers, spinach, tomatoes, etc.
Hydrochloric acid	HCL supplements
Meat (especially red meat)	100g of red meat increases non-heme absorption by fourfold
Sugar	Fruit, honey, black-strap molasses
Alcohol	In moderation with meals; excess alcohol in conjunction with excess iron damages liver

IRON SUPPLEMENTATION

- Until 1999, in the United States, the majority of iron supplements were made with ferrous iron salts.

- Stomach acid is required to dissolve the iron salt, which is an issue for individuals with low stomach acid.
- There are a few specialty manufacturers that make iron tonics or capsules that keep iron soluble so it can be absorbed even by people with low HCl, but this is still not my preferred form of iron.
- Heme iron supplements are a much better option than iron salts.
- Proferrin from Colorado Biolabs contains heme iron.
- Heme iron is much better tolerated and less likely to cause GI distress.
- As an additional benefit, patients can take Proferrin with meals, unlike ferrous salts that have to be taken away from meals.
- Don't take Proferrin at the same time as calcium supplements.

LIPOSOMAL IRON IS THE NEWEST FORM

- Like heme iron, it has a high bioavailability and a low side effect profile.

PARENTERAL IRON IS ADMINISTERED BY INFUSION OR INJECTION.

- Often given to patients who have malabsorption or who have had gastric bypass or portions of their intestine removed.
- Studies have found liposomal iron is equivalent or better than IV iron in many studies.

If a combination of diet, supplements, foods that increase iron absorption, Proferrin, and liposomal iron doesn't work, consider referring that patient out for parenteral iron.

With all forms of supplementation, and even diet, remember that more is not always better.

FUNCTIONAL MEDICINE TREATMENT OF IRON DEFICIENCY

Intervention	Comments
Address underlying causes	e.g. GI bleeding, malabsorption, infection, intense exercise, PPI use, etc.
Diet	Increase intake of foods high in iron
Improve absorption	Consume substances that increase iron absorption; avoid substances that decrease absorption

For both omnivores and vegetarians, I recommend supplementing with hydrochloric acid (HCl), and 100 to 300 mg of vitamin C with meals in order to increase iron absorption. It is also not a bad idea to have a glass of wine with meals if your patient tolerates alcohol.

SUPPLEMENTATION FOR MODERATE TO SEVERE IRON DEFICIENCY

Supplementation for moderate to severe iron deficiency

Severity of iron deficiency	Comments
Mild	**1 capsule** of Proferrin ES/Clear or **6 capsules** of Ancestral Supplements desiccated liver or spleen per day
Moderate	**2 capsules** of Proferrin ES/Clear and/or **3-6 capsules** of Ancestral Supplements desiccated liver or spleen per day
Severe	**3 capsules** of Proferrin ES/Clear and **6 capsules** of Ancestral Supplements desiccated liver or spleen per day

Lesson 34: Blood Chemistry Iron Overload Review

CAUSES OF IRON OVERLOAD

More Common	Less Common
Hereditary hemochromatosis	Sideroblastic anemia
Iron supplementation	Dysmetabolic iron overload syndrome
African siderosis	Glucose-6-phosphate-dehydrogenase (G6PD)
Beta-thalessemia	
Sickle-cell anemia	
Alcohol abuse	
Viral hepatitis	

The most common causes you'll see in clinical practice are genetic mutations that contribute to excess iron storage and excess iron supplementation. Impaired iron metabolism causes excess iron to accumulate in the organs and tissues.

HEMOCHROMATOSIS

- Classic hereditary hemochromatosis is an autosomal recessive disorder. A mutation of both copies of the *HFE* gene on chromosome 6. Two major types are C282Y and H63D.
- At least 20 other mutations of the *HFE* gene have been identified.
- Mutations in other genes that can cause iron overload, including transferrin receptor 2, ferroportin 1, chromosome number 19, hepcidin, and CDA2.
- Unfortunately, the effects of these mutations are still poorly understood.

- One of the most common misconceptions about iron overload is that heterozygous carriers of these mutations are not affected. However, research over the last two decades has shown this to be clearly false.

It's well established in the scientific literature that iron overload is associated with a long list of pathologies and diseases, including metabolic conditions affecting the liver, metabolic syndrome, gout, cardiovascular disease, neurological issues, endocrine problems, immune imbalances, infections of all types, and musculoskeletal disorders.

EVIDENCE FROM PHLEBOTOMY

- Frequent blood donors have lower rates of diabetes.
- Phlebotomy has also been shown to decrease iron levels, blood pressure, resting heart rate, fasting glucose, hemoglobin A1c, and low-density lipoprotein (LDL)-to-high-density lipoprotein (HDL) ratio.

PREVALENCE OF SYMPTOMS OF IRON OVERLOAD

Symptom	Reported
Extreme fatigue	46%
Joint pain	44%
Impotence (or loss of libido)	26%
Skin bronzing	26%
Palpitations	24%
Depression	21%
Abdominal pain	20%

Remember that ferritin is also an acute-phase reactant that is elevated in the inflammatory response, so if you see elevated ferritin with normal iron saturation and unsaturated iron-binding capacity (UIBC), further investigation is often required. Soluble transferrin receptor decreases with reduced cellular need for iron, and unlike ferritin, it's not affected by inflammation.

Other useful markers for distinguishing between iron overload and inflammation:

- C-reactive protein and A1-acid glycoprotein.
- Acute-phase reactants that are elevated in the inflammatory response.
- A1-acid glycoprotein elevated in chronic inflammatory conditions.
- Red blood cell indices such as hemoglobin and mean corpuscular volume (MCV) may be elevated in iron overload. However, this is more true with hemochromatosis than with mild or functional iron overload.
- Increased gamma-glutamyl transferase (GGT) is correlated with increased disease risk and premature mortality.

Please refer to the handouts provided this week as a quick reference to calculating FeGGT LifePro Scores.

HEREDITARY HEMOCHROMATOSIS DNA ANALYSIS

- Mutations in C282Y, H63D, and S65C are present in 90 percent of cases of iron overload.
- The most affordable way to get a patient's *HFE* gene status is 23andMe. See the patient handout for instructions on how to use 23andMe raw data to obtain this information.
- Heterozygous carriers have increased iron levels and are at increased risk of disease.

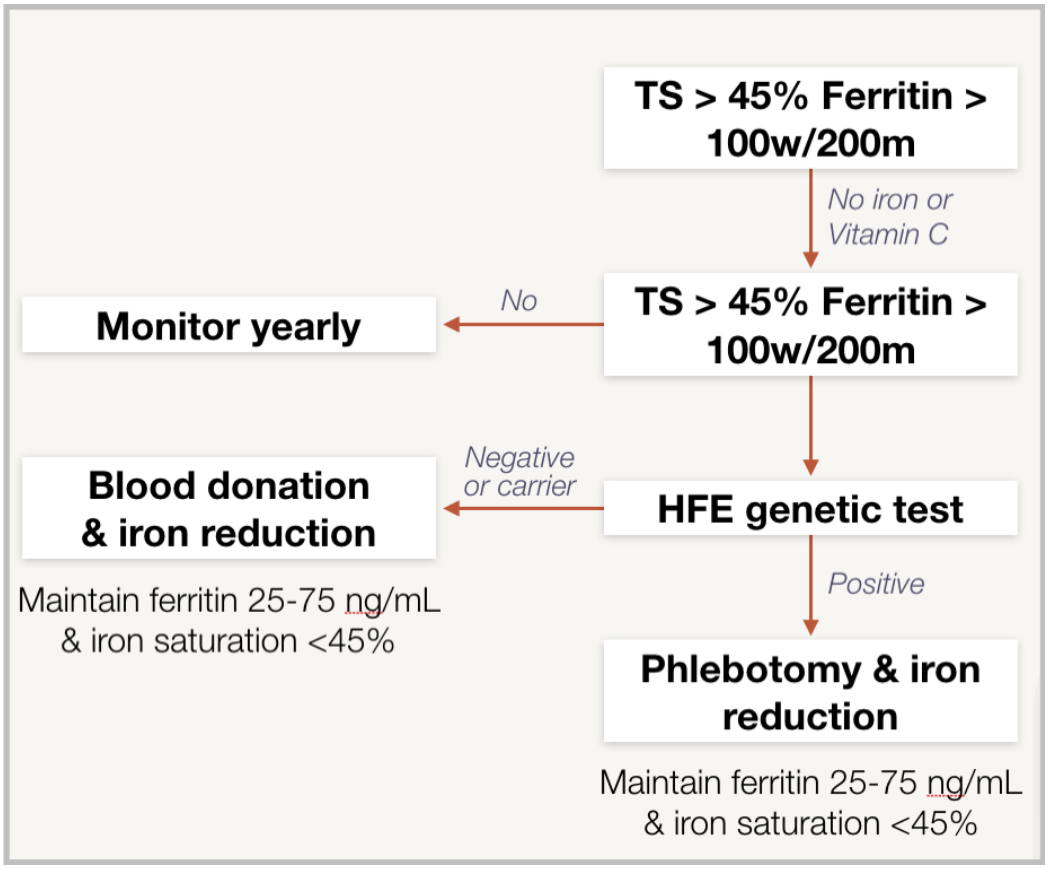
If serum iron markers are elevated with or without *HFE* gene mutations, other tests may be required to confirm the hemochromatosis diagnosis. Consider FerriScan magnetic resonance imaging (MRI) and quantitative phlebotomy.

High iron saturation with normal ferritin can occur in the earliest stage of iron overload.

I recommend that you have patients complete an iron panel in a fasted state. Iron levels are highest after meals, so postprandial transferrin saturation level may be falsely elevated.

Transient iron overload is possible, so always retest to confirm iron overload.

ALGORITHM FOR IRON OVERLOAD WORKUP



PREVENTION AND TREATMENT

- Avoid iron supplements unless a patient is deficient and specifically needs it.
- Regularly screen patients for iron overload.
- Consider advising, particularly male patients and menopausal females, to donate blood one to three times a year as a precaution.

APOLACTOFERRIN

- Produced in breast milk and has antimicrobial properties.
- Suppresses the growth of iron-dependent pathogens.
- Lactoferrin can remove stored iron. The prefered form is apolactoferrin.
- Supplement with Lactoferrin by Life Extensions 300 mg two times a day between meals, not with food.

PHYTIC ACID OR INOSITOL HEXAKISPHOSPHATE, OR IP6

- Inhibits absorption of ferrous iron, plant-based forms of iron.
- Does not inhibit heme iron absorption and doesn't remove stored iron.
- Can be helpful but will not treat iron overload once it has already occurred.

In addition to removing accumulated iron, follow these three steps to reduce iron levels:

1. Reduce iron intake.
    a. No iron supplements.
    b. Reduce intake of the most iron-rich foods, particularly foods rich in heme iron, mostly shellfish and organ meats.
    c. Limit the use of cast iron cookware; use ceramic or stainless steel cookware instead.
2. Avoid substances that increase iron absorption
    a. Vitamin C: 100 mg of vitamin C increases iron absorption in a meal by over fourfold.
    b. Beta-carotene: Found in apricots, beets, carrots, collards, red grapes, red peppers, spinach, tomatoes, etc.
    c. Hydrochloric acid (HCL) supplements.
    d. Sugar: Avoid refined sugar and limit natural forms such as molasses and honey.
    e. Alcohol: Consume in moderation only.
3. Consume substances that decrease iron absorption.

a. Calcium: Inhibits both heme/nonheme iron absorption.
b. Eggs: Contain phosvitin, which inhibits iron absorption.
c. Oxalates: Found in spinach, kale, beets, nuts, chocolate, tea, berries, and some spices/herbs.
d. Polyphenols: Found in cocoa, coffee, teas, apples, berries, walnuts, and some spices.
e. Phytate: Found in walnuts, almonds, sesame, dried beans, lentils and peas, cereals, and whole grains.

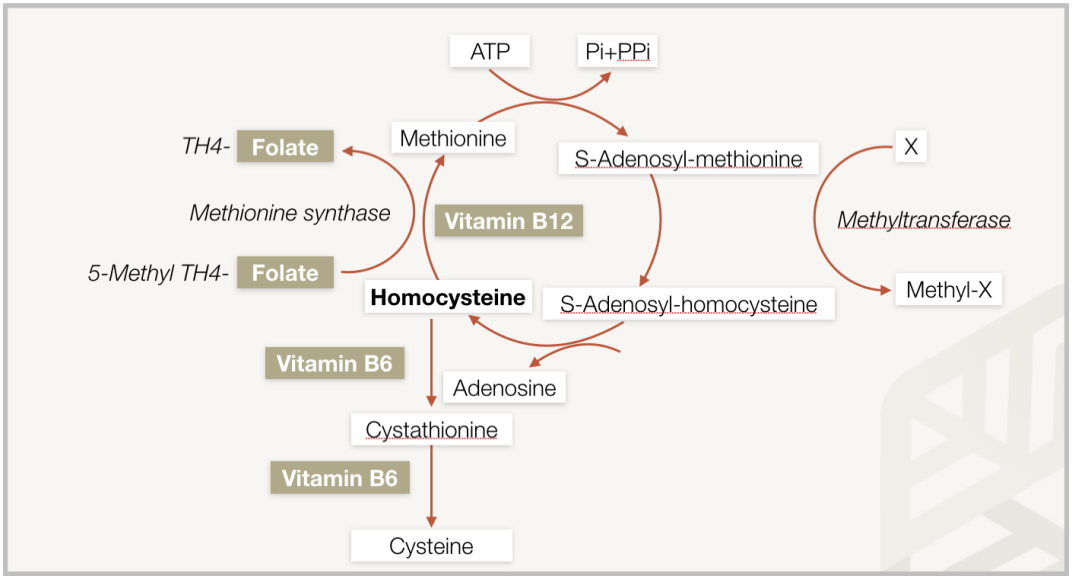
See the summary handout on iron reduction strategies.

Lesson 35: Blood Chemistry Vitamin B12 Deficiency Review

Vitamin B12 works with folate in the synthesis of DNA and red blood cells.

- It's also involved in the production of the myelin sheath around the nerves and the conduction of nerve impulses.
- Methylcobalamin is a cofactor for methionine synthase. This enzyme is required for the synthesis of the amino acid methionine from homocysteine in the methylation cycle. Methionine in turn is required for the synthesis of S-adenosylmethionine, a methyl group donor used in many biological methylation reactions, including the methylation of a number of sites within DNA, RNA, and proteins.

VITAMIN B12 AND HOMOCYSTEINE METABOLISM



- Vitamin B12 also plays a role in energy production.
- New research suggests that vitamin B12 may play a role in nitric oxide production and may explain why B12 supplementation has been shown to reduce the severity of autoimmune conditions.
- Forty percent of Americans have low-normal vitamin B12 levels.
- Forty percent of people over age 60 are vitamin B12 deficient, which can mimic the signs and symptoms of diseases that are commonly associated with aging such as Alzheimer's disease, dementia, cognitive disorders, multiple sclerosis, Parkinson's disease, and other neurological problems; mental illnesses such as depression and anxiety; cardiovascular disease; cancer; and low libido.
- Serum B12. "Normal" isn't always normal, as the scientific literature has shown that people with vitamin B12 levels between 200 and 350, normal levels in the United States, may exhibit clear B12 deficiency symptoms and does not rule out functional B12 deficiency.

MORE SENSITIVE MARKERS OF VITAMIN B12 DEFICIENCY

- Methylmalonic acid (MMA)

- Homocysteine
- Holotranscobalamin-2 (holoTC)

CAUSES OF VITAMIN B12 DEFICIENCY

- Inadequate intake.
- Intestinal malabsorption due to low stomach acid or gastrointestinal (GI) disorder.
- Pernicious anemia, an autoimmune condition resulting in the destruction of parietal cells that produce intrinsic factor or antibodies to intrinsic factor itself. Intrinsic factor is required to absorb vitamin B12.
- Atrophic gastritis, often caused by *Helicobacter pylori* infection in the elderly.
- Pancreatic enzyme insufficiency.
- Alcoholism, which reduces the absorption of vitamin B12 in the terminal ileum.

POPULATIONS AT RISK

- Vegetarians and vegans. Vitamin B12 is only found in animal products.
    - I recommend all vegetarians and vegans, especially children or pregnant women, supplement with B12.
- The elderly, who may have low stomach acid due to *H. pylori* infection and chronic proton pump inhibitor (PPI) use.
- Those with digestive disorders that lead to malabsorption; for example, celiac disease and Crohn's disease since vitamin B12 is absorbed in the terminal ileum.
- Women with frequent or recurrent miscarriage or infertility.
- Those with genetic polymorphisms affecting vitamin B12 assimilation and metabolism. I recommend using functional B12 markers over genetic testing as they are more clinically relevant.
- Metformin depletes vitamin B12 levels.

SYMPTOMS OF VITAMIN B12 DEFICIENCY

- Weakness
- Fatigue
- Strange sensations, numbness, or tingling in the hands, legs, or feet
- Difficulty walking (staggering, balance problems)
- Anemia
- Swollen, inflamed tongue
- Yellowed skin, jaundice
- Difficulty thinking and reasoning (cognitive difficulties) or memory loss
- Paranoia or hallucinations

FOUR STAGES OF VITAMIN B12 DEFICIENCY

- Stages one and two: Plasma and cell stores of vitamin B12 become depleted, and the concentration of holoTC is reduced.
- Stage three: Elevated homocysteine and urinary or serum MMA concentrations. I've found urine MMA to be a more sensitive marker than serum MMA, but consider the clinical picture. In impaired kidney function, serum MMA would probably be more accurate, but if the patient has small intestinal bacterial overgrowth (SIBO) or gut dysbiosis, urine MMA would be more accurate.
- Stage four: The clinical signs and symptoms of vitamin B12 deficiency become evident, such as macrocytic anemia and symptoms such as peripheral neuropathy or brain fog.

METHYLMALONIC ACID

Serum and urine MMA can be run. The Organix Comprehensive Profile from Genova has urine MMA, and serum MMA is available through Labcorp, Quest, and other conventional labs.

- I use the provided lab range for serum MMA. Remember, it's an inverse marker. MMA is high in vitamin B12 deficiency.

    - Serum less than 300 mol/L, urine less than 1.5 mcg/mg
- Genova Diagnostics' lab lists a normal reference range for urinary MMA of less than 2.3 mcg/mL of creatinine with a suggested optimal range below 1.7, yet a study with elderly subjects suggests that a value of 1.5 may be a better threshold for detecting clinical vitamin B12 deficiencies.

SERUM HOMOCYSTEINE

- I have set the lower end of the functional range to be 7 (µmol/L).
- High homocysteine levels are not specific to vitamin B12 deficiency. It may indicate deficiency of folate, B12, or both.

SERUM B12

- Lower end of B12 functional range is 450 pg/mL.
- Be aware that a high serum B12 does not necessarily rule out functional or active B12 deficiency. Some clinicians view high serum B12 in the absence of any supplementation as a sign of impaired B12 metabolism and possibly low active B12 levels, and I have seen this several times in my practice.
- It's really important to be aware that evaluating patients' B12 status using only MMA, homocysteine, and serum B12 may still miss cases of B12 deficiency.

Once vitamin B12 deficiency gets to the final stage, it can cause megaloblastic or macrocytic anemia. At that point, you'll see other markers of B12 deficiency in the comprehensive blood chemistry or complete blood count, such as low red blood cell count, low hemoglobin, low hematocrit, and elevated mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular hemoglobin (MCH), and red cell distribution width (RDW), and we'll cover these in more detail in the macrocytic anemia unit.

Pernicious Anemia

- Consider running intrinsic factor antibodies on patients with low vitamin B12.

- Intrinsic factor antibodies approach 100 percent specificity, so if it's positive, you can be virtually sure they have it. However, they are only 50 to 70 percent sensitive, so that test would miss 30 to 50 percent of patients with pernicious anemia.
- Elevated serum gastrin levels, low pepsinogen I levels, and a low ratio of pepsinogen I to pepsinogen II are highly sensitive for diagnosing pernicious anemia, but those tests lack specificity. If one of those is positive and intrinsic factor antibodies are negative, you can't really confirm the diagnosis of pernicious anemia without further workup.
- Pepsinogen is also not widely available in the United States.
- I usually follow up with serum gastrin and intrinsic factor antibodies.

Testing for pernicious anemia is clinically relevant because patients who have pernicious anemia need to supplement for the rest of their lives, even after addressing other conditions that may impair vitamin B12 absorption. It helps patients take B12 deficiency seriously and stay consistent with supplementation. Patients with pernicious anemia will need sublingual B12 supplements or B12 injections because they don't absorb B12 orally through food or oral supplements.

The treatment of vitamin B12 deficiency falls into two main categories:

1. Inadequate intake, primarily vegetarians and vegans
2. Impaired absorption, which can be GI issues such as hypochlorhydria, celiac disease, inflammatory bowel disease, or dysbiosis; pernicious anemia; alcoholism; or pancreatic insufficiency.

There is no known tolerable upper intake level for vitamin B12, and no toxicity threshold has been found. Therefore, I believe it's safer to advise higher intakes than lower intakes.

HIGHEST DIETARY SOURCES OF VITAMIN B12

Food	Amount (mcg per 100g)
Clam	99
Lamb liver	90
Beef liver	83
Duck liver	54
Oyster	35
Pork liver	26
Caviar	20
Mackerel	19
Herring	19
Mussel	12
Crab	11
Sardine	9
Salmon	6

DO THE FOLLOWING TO INCREASE VITAMIN B12 ABSORPTION

- Address GI issues.
- Supplement with Betaine HCl.
- Drink cranberry juice.
- Increase calcium from food sources.

AVOID THE FOLLOWING, WHICH DECREASE VITAMIN B12 ABSORPTION

- Alcohol
- Metformin

- Acid-suppressing drugs

THERE ARE FOUR TYPES OF SUPPLEMENTAL VITAMIN B12 AVAILABLE

1. Methylcobalamin, which is a natural form.
2. Hydroxocobalamin, which is a natural form.
3. Adenosylcobalamin, which is a natural form.
4. Cyanocobalamin, which is a synthetic form that can be converted into adenosylcobalamin and methylcobalamin, but its bioavailability is poor compared to the other forms.

The best approach is probably to use all three natural forms together.

- Ensure adequate folate when supplementing with vitamin B12.
- Methylcobalamin is formed and regenerated with the methyl group provided by 5-methylfolate or SAM-e.
- Lithium is another nutrient that must be present for adequate B12 metabolism.
- Can supplement with 5 mg of lithium orotate per day, which is a much lower dose of lithium than the one that is used in mental health disorders.

I like Designs for Health's Trifolamin, as it has all three natural forms of vitamin B12 with a combined dose of 3 mg plus 400 mcg of Quatrefolic, a form of active folate. It is a sublingual form, so it can be used by patients with pernicious anemia and other absorption issues.

Appropriate therapeutic doses are 3 to 5 mg per day, with little to no concern of overdose.

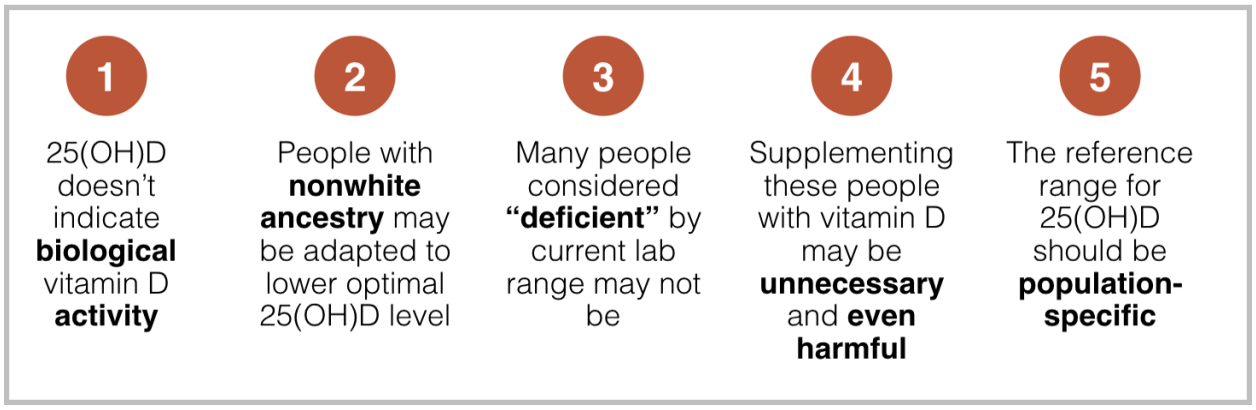
- Consider adding Betaine HCl supplement to increase vitamin B12 absorption. Remember that HCl is contraindicated with gastric or duodenal ulcers and patients who are taking non-steroidal anti-inflammatory drugs.
- Retest after 60 days. Treatment ranges from two months to ongoing.
- Consider vitamin B12 injections for patients not responding to oral or sublingual therapy.
- Take hydroxocobalamin at a dose of 1 mg (1,000 mcg) per day.

Lesson 36: Blood Chemistry Vitamin D Imbalance Review

VITAMIN D:

- Promotes calcium absorption in the gut.
- Maintains calcium and phosphate levels in the blood.
- Regulates cell growth and neuromuscular and immune function.
- Vitamin D in the circulation is converted by hepatic hydroxylase into 25(OH)D, calcidiol, which is what is typically measured on a blood test.
- As needed, 25(OH)D is converted into 1,25(OH)2D, calcitriol.
- Calcitriol increases the level of calcium in the blood by increasing the uptake of calcium from the gut, decreasing renal excretion of calcium, and possibly increasing the release of calcium into the blood from the bone.
- Conversion of 25(OH)D to calcitriol is tightly regulated by parathyroid hormone (PTH).
- PTH increases calcitriol formation and helps increase serum calcium by acting on kidney and bone.
- The two potential ways to increase calcitriol are increasing the supply of calcidiol through sun exposure, supplements, or diet or increasing demand for calcitriol via PTH.
- Different ethnicities may convert calcidiol to calcitriol more effectively, and they require less calcidiol to achieve the necessary amount of calcitriol.
- Another possibility is that people with nonwhite ancestry require less PTH to convert calcidiol to calcitriol.

FIVE KEY TAKEAWAYS



PTH and calcitriol can help clarify when low 25(OH)D is pathological versus normal.

- A low-normal 25(OH)D level and low PTH (below 30) suggests the patient is not vitamin D deficient from a biological perspective and that supplementation, diet, and lifestyle changes aren't required.
- A low or borderline low 25(OH)D with PTH above 30 suggests biological deficiency.
- The higher the PTH is above 30, the more biologically deficient the person is.

Most people obtain vitamin D from cutaneous production, meaning sun exposure and supplementation, not food sources.

- Dietary vitamin D contributes only 10 to 20 percent.
- Only a few foods such as cold-water fatty fish or shellfish are rich in vitamin D.

VITAMIN D TOXICITY

- A hallmark sign is hypercalcemia due to intestinal calcium hyperabsorption and calcium resorption from bone.
- Excess vitamin D also causes hyperphosphatemia.
- Hypercalcemia and hyperphosphatemia cause mineralization of various soft tissues, which can lead to kidney stones and increased risk of cardiovascular disease, among other health problems. Vitamin D-intoxicated patients suffer from headache, nausea,

vomiting, diarrhea, anorexia, weight loss, polyuria, and polydipsia, and excess vitamin D intake has also been shown to contribute to several documented deaths.

STATUS OF SERUM MARKERS IN VITAMIN D DEFICIENCY AND TOXICITY

Vitamin D status	25(OH)D	1,25(OH)2D	PTH	Calcium	Phosphorus
Toxicity	High	Low, normal, or high	Low or normal	Normal or high	Normal or high
Deficiency	Low	Low, normal, or high	>30	Low or normal	Low or normal

IMPORTANT NOTES

- In most cases of vitamin D toxicity due to supplements, 1,25(OH)2D is not elevated.
- Toxicity leads to hypercalcemia and hyperphosphatemia and depresses calcitriol, so vitamin D toxicity cannot be ruled out in cases of high calcidiol and normal calcitriol.
- When calcidiol or 25(OH)D levels are extremely high, calcitriol levels can fall to undetectable levels because PTH and fibroblast growth factor-23 (FGF23) suppress the conversion of calcidiol into calcitriol in an attempt to protect against hypercalcemia and hyperphosphatemia.
- When 25(OH)D is high and 1,25(OH)2D is low, it could actually be vitamin D toxicity, or it could be vitamin D deficiency, so it is important to use other markers such as PTH, serum calcium, and serum phosphorus to clarify the diagnosis.

CONCLUSIONS GIVEN THE RESEARCH AND GIVEN AN EVOLUTIONARY PERSPECTIVE

- Sunlight or ultraviolet (UV) light exposure is the optimal source of vitamin D and accounts for the majority of 25(OH)D serum levels in the absence of supplementation.

- The range of serum 25(OH)D, which the majority of researchers agree, that avoids deficiency or toxicity is between 30 and 60 or 65 ng/mL.
- The 25(OH)D range likely varies depending on ethnicity, genetics, PTH activity, and nutritional status, especially vitamins A and K2, potassium, and magnesium, as well as fluid intake.
- In the absence of specific ranges, clinicians should use other markers such as PTH, calcitriol, serum calcium, and serum phosphorus to clarify biological vitamin D status.

HYPERPARATHYROIDISM

- High vitamin D 25(OH)D, serum calcium, and PTH.
- 25(OH)D is not always out of the lab range in hyperparathyroidism, and, in fact, it can even be normal or low. In those cases, 25(OH)D deficiency or low levels of 25(OH)D can obscure hyperparathyroidism, which doesn't become evident until vitamin D is repleted through sun exposure or supplements.
- Elevated serum calcium is the most important indicator of hyperparathyroidism.

The functional vitamin D reference range is from 35 to 60 ng/mL.

The benefits of sunlight go far beyond vitamin D. When human skin is exposed to sunlight, it produces several peptides and hormones that contribute to systemic wellness. When making recommendations to patients about sun exposure, remember that many variables affect the conversion of ultraviolet light to vitamin D, including skin type, season, time of day, latitude, age, and health status, but here are some general guidelines:

RECOMMENDED SUN EXPOSURE BY SEASON

- Late fall, winter, and early spring: Spend half as much time as it takes the skin to turn pink in the sun three to seven times per week depending on solar angle.
- Late spring, summer, and early fall: Spend half as much time as it takes the skin to turn pink in the sun at least three times per week.

Most people who follow the recommendations above for food, including cod liver oil and UV light exposure, won't need vitamin D supplements. However, following these recommendations is not possible for everyone, and in these cases, supplementation should be considered.

VITAMIN D SUPPLEMENTATION CONSIDERATIONS

- Take with fat for maximum absorption.
- Vitamin D3 is better absorbed than D2.
- Dose should be adjusted by weight and inflammatory/gut status, and an increased dose may be needed in obesity and digestive issues/malabsorption.
- Weekly or daily dosing results in a similar increase in serum vitamin D levels; large monthly or semi-annual doses are not recommended.

The only way to know for sure how much vitamin D you need is to test blood levels, change the vitamin D regimen, and then test again three to four months later to determine if it had the desired effect.

NEXT STEPS BASED ON 25(OH)D LEVELS

25(OH)D level (ng/mL)	Suggested action
<25	Begin treatment
25–35	Use PTH to determine whether treatment is necessary
>35	No treatment necessary; continue diet & lifestyle for maintaining adequate vitamin D

In fall or early winter, it may make sense to take a half-teaspoon per day or even a teaspoon per day of cod liver oil and then retest in 60 days to be sure that deficiency isn't developing, given the time of year.

TREATMENT BASED ON OUTCOME OF STEP ONE

25(OH)D level (ng/mL)	Suggested action
<15	1 tsp/d EVCLO, diet/UV exposure, plus 10,000 IU/d D3
15–25	1 tsp/d EVCLO, diet/UV exposure, plus 5,000 IU/d D3
26–35 with PTH >30	1 tsp/d EVCLO, diet/UV exposure
26–35 with PTH <30 >35	No treatment necessary; continue diet & lifestyle for maintaining adequate vitamin D

In all cases, advise them to eat one pound of coldwater fatty fish such as salmon, herring, mackerel, or sardines; six to eight egg yolks per week, pasture-raised. Ultimately, food is the best source of nutrients because there are various cofactors that are required for the absorption of certain nutrients that are present in food that are not present in synthetic supplements.

TREATMENT BASED ON OUTCOME OF STEP TWO

25(OH)D level (ng/mL)	Suggested action
<15	1 tsp/d EVCLO, diet/UV exposure, consider D3 injections
15–25	1 tsp/d EVCLO, diet/UV exposure, plus 5,000-10,000 IU/d D3
26–35 with PTH >30	1 tsp/d EVCLO, diet/UV exposure
26–35 with PTH <30 >35	No treatment necessary; continue diet & lifestyle for maintaining adequate vitamin D

Step three is to retest 25(OH)D levels and PTH levels after 60 days. Note that you may need to retest at least twice a year, after spring and in the fall, to determine what their natural 25(OH)D levels are at different times of the year.

The 25(OH)D range for autoimmune disease is 45 to 60 ng/mL. Phototherapy, or UV exposure, is superior to supplementation for patients with autoimmune disease.

Serum copper and serum zinc are poor markers for dietary intake of copper and zinc.

NUMEROUS NON-NUTRITIONAL FACTORS INFLUENCE ZINC AND COPPER SERUM LEVEL

- Zinc in serum goes down in oxidative stress and inflammation.
- Copper is elevated in the inflammatory response in a wide range of conditions

HIGH COPPER-TO-ZINC RATIO: CAUSE OR EFFECT?

- Blood copper level correlates strongly with the marker of inflammation C-reactive protein (CRP), yet substantially increasing copper intake doesn't increase CRP.
    - This suggests that elevated blood copper is likely a symptom of inflammation rather than its cause.
    - This could explain why high copper is a risk factor for heart attack.
- Some studies suggest that copper deficiency worsens inflammation.
- Finally, prolonged use of zinc supplements may cause secondary copper deficiency.

SERUM COPPER AND ZINC DO NOT DETECT MILD TO MODERATE DEFICIENCY OR EXCESS

- Serum copper levels are now considered to be rather worthless for determining copper deficiency or copper overload.
- Serum copper and ceruloplasmin concentrations are useful to diagnose Menkes and Wilson's diseases and moderate-to-severe copper deficiency. However, these markers are not sensitive enough to detect changes of a lesser magnitude.
- They also act as acute-phase proteins and increase during inflammation, pregnancy, aging, and a number of diseases.
- Serum zinc is better than serum copper and may be the best of all available zinc biomarkers.

- Vegetarians may require 50 percent more zinc than omnivores.

SIGNS AND SYMPTOMS OF COPPER DEFICIENCY

- Bone malformation during fetal/childhood development
- Osteoporosis
- Impaired melanin synthesis
- Poor immune function
- Cardiovascular disease
- Altered cholesterol metabolism
- Iron deficiency anemia

POPULATIONS THAT ARE AT RISK FOR COPPER DEFICIENCY INCLUDE:

- Babies who have been fed cow's milk formula, which is low in copper
- Premature infants
- People with gastrointestinal malabsorption issues
- People with cystic fibrosis
- People taking a high dose, meaning over 40 mg per day, of zinc

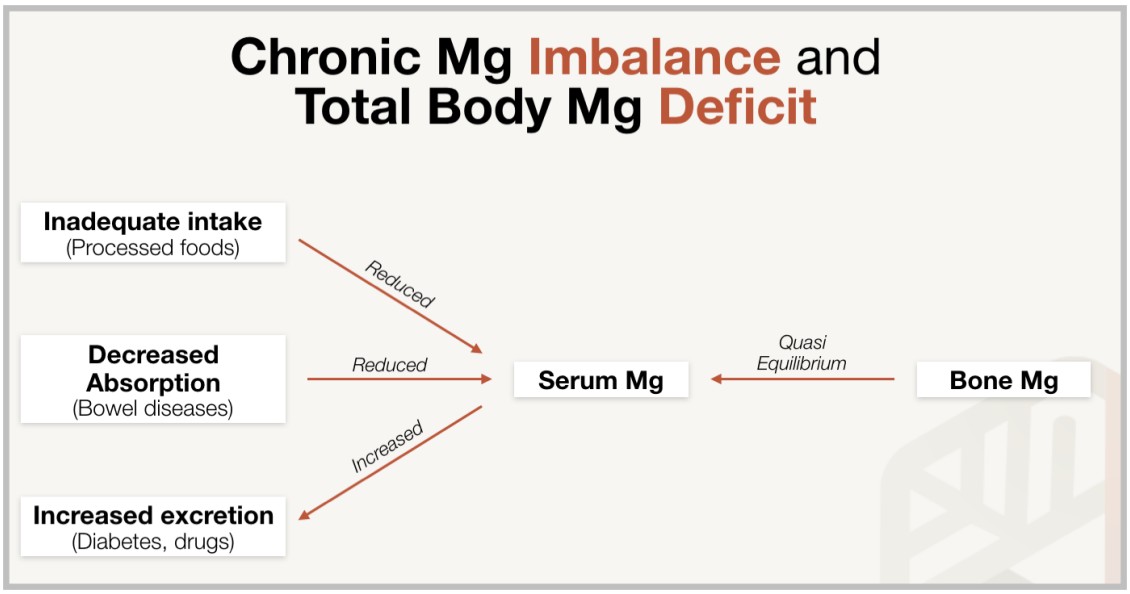
KEY TAKEAWAYS

- A high copper-to-zinc ratio may indicate inflammation, hypothalamic–pituitary–adrenal axis dysregulation, estrogen dominance, or pregnancy, not necessarily excess copper or inadequate zinc intake.
- A high copper-to-zinc ratio is associated with numerous chronic inflammatory diseases.
- The presence of high serum copper or low serum zinc does not always warrant zinc supplementation, and it may even be harmful.
- Serum copper values are just a starting point and should never be used in isolation. If serum copper is elevated or decreased, use markers such as ceruloplasmin, 24-hour urine copper, alanine aminotransferase, aspartate aminotransferase, and possibly liver biopsy to clarify the diagnosis.

Lesson 37: Blood Chemistry Magnesium Deficiency and Thyroid Hypofunction, Part I Review

MAGNESIUM

- Magnesium (Mg) is an essential mineral and cofactor for hundreds of enzymes. It's involved in many physiological pathways, including the examples below.
- It's the fourth most abundant mineral in the body after calcium, potassium, and sodium. It's necessary for phosphorylation.
- Magnesium deficiency is one of the most common nutrient deficiencies in the United States and likely in the industrialized world.
- Primary causes of magnesium deficiency are increased excretion, decreased absorption, or inadequate intake.
    - Increased excretion of magnesium occurs primarily with diabetes and diuretic drugs that cause increased urination.
    - Magnesium absorption may be decreased by gastrointestinal (GI) pathologies such as inflammatory bowel disease (IBD), celiac disease, and small intestinal bacterial overgrowth (SIBO). Very high-dose zinc, very high fiber intake, and low-protein diets below 30 g per day also decrease magnesium absorption. Magnesium absorption is decreased in alcoholics.
    - Inadequate intake is in part due to soil depletion, but also due to a reduction in the consumption of nutrient-dense wild plant foods. The cultivated plants that we eat today don't contain as much magnesium as the wild plants that our ancestors ate.



POPULATIONS AT RISK FOR MAGNESIUM DEFICIENCY

FACTORS THAT DECREASE MAGNESIUM STATUS

GI pathologies
High-dose zinc
High fiber intake
Low-protein diets
Alcoholism
High calcium intake

Magnesium deficiency is associated with a wide variety of pathologies and diseases from type 2 diabetes and metabolic syndrome to elevated C-reactive protein, hypertension, atherosclerotic vascular disease, sudden cardiac death, osteoporosis, migraine headache, asthma, and colon cancer.

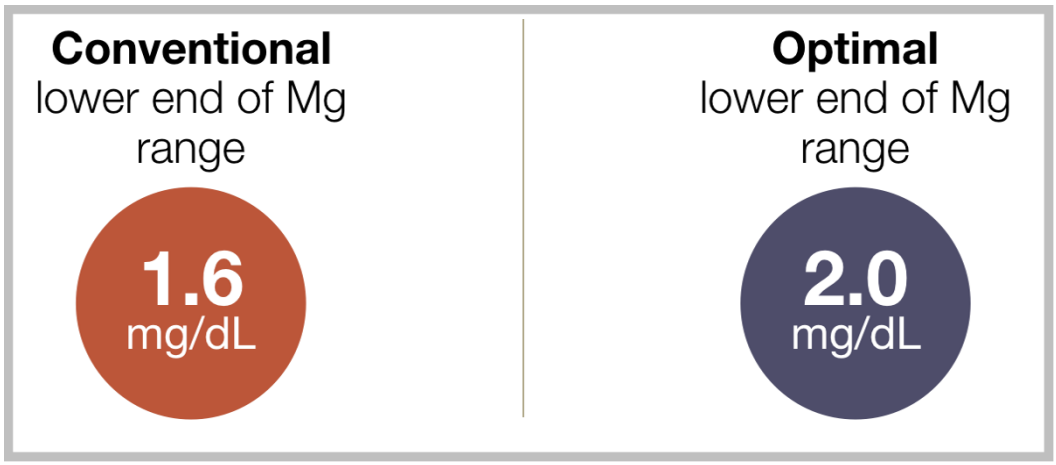
SIGNS AND SYMPTOMS OF MAGNESIUM DEFICIENCY

Early	Late	
Loss of appetite	Hypomagnesia	Hypertension
Headache	Hypocalcemia	CVD
Nausea	Hypokalemia	Pregnancy complications
Fatigue	Sodium retention	Infertility
Weakness	Low serum PTH	Neurological/muscular
	Osteoporosis	Personality changes
	Diabetes	Vomiting

Over 60 percent of the magnesium in the body is found in the skeleton, about 27 percent is found in the muscle, 6 to 7 percent is found in other cells, and less than 1 percent of magnesium is found in serum. Therefore, serum magnesium is not necessarily an accurate representation of what is in the soft tissue and inside the cells where it is used and needed.

The lab reference range of 1.8 to 2.3 was determined by the NHANES I cohort study.

Studies support the lower end of the functional magnesium range should be 2.0.



CLINICAL MAGNESIUM DEFICIENCY AT VARIOUS SERUM MAGNESIUM LEVELS

Serum Mg level (mg/dL)	**% with clinical Mg deficiency**
1.7	90
1.85	50
1.95	10
2.2	1

TESTING FOR MAGNESIUM

- I recommend using the serum magnesium cutoffs discussed above and do therapeutic trials of magnesium supplementation.
- This is because other options for testing for magnesium are either not widely available or cost-prohibitive.

MAGNESIUM REPLETION

- Recommend about 500 mg per day for adult males and 400 mg per day for adult females and increasing the other minimums by a 20 percent safety margin.
- Even people on a nutrient-dense, healthy diet may need to supplement magnesium.
- If serum levels are low, you can give your patients a list of foods that are high in magnesium, but you should probably also give them supplements.
- People with kidney damage are at the greatest risk of toxicity such as lethargy, confusion, disturbances in normal cardiac rhythm, and deterioration of kidney function. This is mostly related to severe hypotension caused by excess magnesium.
- I suggest retesting serum magnesium after 60 to 90 days, and you should see an increase in the serum magnesium concentration. Then you can drop to a maintenance dose of 200 to 250 mg per day.

Highest dietary sources of magnesium

Food	**Amount** (mg per 200cal)
Canned clams	1,100
Swiss chard, cooked	860
Purslane	850
Spinach, cooked & raw	756
Beet greens, cooked & raw	636
Kelp	563
Basil, fresh	556
Kale	407
Arugula	376
Okra, cooked	327
Chives, raw	280
Coconut water	263

MAGNESIUM FORMS AND INDICATIONS

Form	Indication
Orotate	Cardiovascular
Glycinate	Sleep and constipation
Malate	Energy and pain relief
Taurate	Blood sugar imbalances and anxiety
Citrate	Sleep and hard stools
Oxide	Poor bioavailability; causes loose stools
Sulfate	Not generally used in oral supplements; little evidence on topical absorption

For magnesium, different forms are best for different purposes. Refer to the chart above for some specifics. In addition, L-threonate improves brain and memory function, and it is highly absorbable.

THYROID HYPOFUNCTION

- More than one in 10 individuals will develop a thyroid condition in their lifetime, and most will be unaware of their condition.
- Women are five to eight times more likely than men to have thyroid problems.
- Pregnant women with undiagnosed or inadequately treated hypothyroidism have an increased risk of miscarriage, preterm delivery, and severe developmental problems in their children.
- Thyroid dysfunction is often a symptom or result of a deeper underlying problem.
- Free thyroxine (T4) and free triiodothyronine (T3) are better indicators of what is happening at the cellular level than total T4 and total T3.

- Low T4-to-T3 conversion, high reverse T3, or a high reverse T3-to-free T3 or -total T3 ratio, can be a sign of inflammation, hypothalamic–pituitary–adrenal (HPA) axis dysfunction, or nutrient imbalance.
- Antibody production
    - Precedes the development of clinical thyroid disease by many years.
    - Identifying patients with positive antibodies and normal thyroid-stimulating hormone (TSH) and thyroid hormones can prevent future problems.
- Our functional reference range for TSH is 0.5 to 2.0.
    - That does not mean that everyone with a TSH above 2.0 requires treatment, but you should start looking more carefully when you see a TSH above that level to decrease the chance of developing into clinical hypothyroidism in the future.

SUBCLINICAL HYPOTHYROIDISM

- Defined by elevated TSH but normal thyroid hormone levels.
- Prevalence of subclinical hypothyroidism increases with age and is approximately 10 percent in women over 60 years old and somewhat lower in men.
- Many studies have found that subjects with subclinical hypothyroidism have higher total cholesterol, low-density lipoprotein (LDL), and C-reactive protein than euthyroid subjects.
    - May increase the risk of cardiovascular disease by 60 percent.
- Treatment of subclinical hypothyroidism has been shown to improve cardiovascular markers.
    - There is a risk of overtreatment.

SECONDARY HYPOTHYROIDISM

- Low TSH due to low pituitary output and low T4 or T3.
- Caused by a dysfunction of the hypothalamus or pituitary gland, leading to decreased activity of the thyroid gland.

- Also will have low growth hormone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and adrenocorticotropic hormone (ACTH).
- Rare, 46 cases out of 100,000 people, so you're less likely to see it in clinical practice.

CENTRAL HYPOTHYROIDISM

- Due to insufficient stimulation by TSH of an otherwise normal thyroid gland.
- Can be secondary to hypothyroidism caused by pituitary malfunction or tertiary hypothyroidism caused by hypothalamic malfunction.
- Usually due to pituitary macroadenomas, pituitary surgeries, or post-radiation.
- This presentation can also occur in Hashimoto's disease, especially in the early stages when the immune attack is relapsing and remitting.
- Confirmed by a TSH stimulation test.

HASHIMOTO'S THYROIDITIS

- High TSH, low T3 and T4, and high thyroid peroxidase (TPO) antibodies as seen in the example below is textbook Hashimoto's.
- Is the cause of hypothyroidism in up to 90 percent of cases.
- Patients with elevated thyroid antibodies are far more likely to develop hypothyroidism, whether overt, clinical, or subclinical.
- However, the presence of thyroid antibodies alone does not guarantee progression to clinical disease.
- Seventy percent of the risk of developing Hashimoto's is genetic
- Most common time of onset in women is after childbirth.
- Up to 20 percent of patients with autoimmune thyroid disease don't produce antibodies, and 13 percent have only low levels of antibodies.
- If only clinical and serum findings were used to diagnose Hashimoto's, the diagnosis would be missed in at least half of patients.
- Antibodies can vary from high to normal.

    - Low levels of antibody production may not be abnormal as autoantibodies often occur in healthy individuals and play an important role in the homeostasis of the immune system.
- Thyroid ultrasound can be performed to confirm a suspected Hashimoto's diagnosis.
- Prevalence of celiac disease is much higher in patients with autoimmune thyroid disease.
- Antigliadin antibodies are more likely to be present in patients with autoimmune thyroid disease.

NUTRIENTS FOR THYROID HEALTH

- Thyroid needs several nutrients to function properly, including iodine, selenium, iron, zinc, vitamin B12, vitamin B2, vitamin C, vitamin A, vitamin D, and magnesium.
- **Iodine**
    - An essential nutrient required for reproduction and growth; its only known function is the synthesis of thyroid hormone.
    - Iodine supplementation can be helpful to normalize TSH and improve thyroid symptoms.
    - Serum iodine is not considered to be a very accurate indicator of iodine levels.
    - If you have a patient with hypothyroidism, two to three negative antibody tests, and a negative thyroid ultrasound, consider iodine deficiency.
    - Some studies have shown that increased iodine intake, especially in supplement form, can increase the autoimmune attack on the thyroid. Iodine reduces the activity of TPO, and TPO is required for proper thyroid hormone production.
    - Selenium may protect against the harmful effects of iodine. Other studies have shown that selenium prevents the triggering and flaring of autoimmune disease that excess iodine without selenium can cause.
    - You can begin iodine supplementation with or without testing.
- **Selenium**

    - Long-term high-dose selenium supplementation can lead to complications such as GI upset, hair loss, white blotchy nails, garlic breath odor, fatigue, irritability, and mild nerve damage.
    - I usually recommend that patients obtain adequate selenium intake through their diet and possibly to use testing for selenium levels at baseline to determine whether selenium supplementation is warranted.
- **Iron**
    - Deficiency reduces heme-dependent TPO activity in the thyroid, resulting in impaired production of thyroid hormone.
- **Magnesium, vitamin B12, and zinc**
    - Required for synthesis of TSH
- **Riboflavin and vitamin C**
    - Required for iodine symporter
- **Vitamins A and D**
    - Required to activate the nuclear thyroid receptor

Lesson 38: Blood Chemistry Thyroid Hypofunction, Part II and Hyperfunction Review

THYROID HYPOFUNCTION TREATMENT

Overt Hypothyroidism

- High thyroid-stimulating hormone (TSH) and low thyroxine (T4)/triiodothyronine (T3).
- Treat with replacement hormone and address other pathologies.

Subclinical hypothyroidism

- TSH higher than 10

    - Treat with replacement hormone and address other pathologies.
- TSH less than 10
    - Address other pathologies first; retest TSH.Then, if still elevated, use the Thyroid Events Amsterdam (THEA) score to further evaluate.

Euthyroid with high antibodies

- Address immune dysregulation and other pathologies; use the THEA score to further evaluate.

If the patient only has high TSH and/or high thyroid antibodies, you can use the THEA to predict the progression of overt hypothyroidism. THEA is based on TSH, thyroid peroxidase (TPO) antibodies, and family history of autoimmune thyroid disease.

ADDRESS UNDERLYING CAUSE OF HASHIMOTO'S DISEASE

- Treatment should consider mechanisms such as environmental toxins, gastrointestinal (GI) dysfunction, hypothalamic–pituitary–adrenal (HPA) axis dysregulation, blood sugar dysregulation, reduced oxygen deliverability or anemia, nutrient imbalance, immune dysregulation, and chronic infections.
- Also, addressing things like sleep deprivation, chronic stress, inappropriate physical activity, lack of social connection, and not enough pleasure or play is key and leads to improvement in autoimmune conditions. These factors may be the most important things for people with autoimmunity to address along with diet.

DIETARY NUTRIENTS AND THEIR SOURCES FOR THYROID HEALTH

Nutrient	Sources
Iodine	Sea vegetables, dairy products, iodized salt
Selenium	Ocean fish, Brazil nuts, ham
Iron	Oysters, clams, liver, venison, beef
Zinc	Oysters, liver, crab, lobster, beef
B12	Clam, liver, oyster, mackerel, sardine
B2	Liver, mushrooms, seaweed, spinach
Vitamin C	Red pepper, kiwi, broccoli, citrus
Vitamin A	Organ meats, CLO, seafood, grass-fed dairy
Vitamin D	CLO, cold-water fatty fish, UV exposure
Magnesium	Clams, Swiss chard, spinach, beet greens, kelp

HIGHEST FOOD SOURCES OF IODINE

Food	**Iodine** (mcg/serving)	**Iodine** (percent DV)
Kelp, 1 gram	1,542	10,280%
Kombu, 1 gram	1,350	900%
Hijiki, 1 gram	629	419%
Arame, 1 gram	586	391%
Cod, baked, 3 ounces	99	66%
Dulse, 1 gram	72	48%
Iodized salt, 1/4 teaspoon	71	47%
Wakame, 1 gram	42	28%
Shrimp, 3 ounces	35	23%
Egg, 1 large	24	16%
Tuna, canned in oil, 3 ounces	17	11%
Nori, 1 gram	16	11%
Prunes, dried, 5 prunes	13	9%
Banana, 1 medium	3	2%

Using kelp flakes in place of or in addition to sea salt just a few times a week should provide about 100 to 200 mcg a day, which is a sufficient level of iodine intake for most people and probably not enough to trigger or exacerbate autoimmunity in most patients.

Iodine is also present in dairy because iodine is in the cleansers that are used to sterilize the tanks that dairy products are stored in.

HIGHEST FOOD SOURCES OF SELENIUM

Food	**Se** (mcg/serving)	**Se** (percent DV)
Brazil nuts, 1/2 ounce (3–4 nuts)	277	389%
Tuna, yellowfin, cooked, 3 ounces	92	131%
Halibut, cooked, 3 ounces	47	67%
Sardines, canned in oil, 3 ounces	45	64%
Ham, roasted, 3 ounces	42	60%
Beef steak, bottom round, roasted, 3 ounces	33	47%
Turkey, boneless, roasted, 3 ounces	31	44%
Chicken, light meat, roasted, 3 ounces	22	31%
Beef, ground, 25% fat, broiled, 3 ounces	18	26%
Egg, hard-boiled, 1 large	15	21%
Spinach, frozen, boiled, 1 cup	11	16%

SELENIUM SUPPLEMENTATION

- Remember that most Americans are not deficient in selenium, but people with autoimmune thyroid disease may benefit from higher dietary intake.
- Two to three nuts a day would provide 200 mcg, more than enough selenium, especially if the patient is consuming fish.
- If they can't or won't eat fish or Brazil nuts, they can supplement with 200 mcg per day of selenomethionine.
- Retest two to three months later. Tell the patient to stop supplementing if selenium levels are then sufficient.

AVOID SUBSTANCES THAT IMPAIR THYROID FUNCTION, PRIMARILY GOITROGENS

- Goitrogens are substances that cause goiter, which is swelling of the thyroid gland.
- Goitrogenic foods (see table below) or chemicals have been associated with both hypothyroidism and hyperthyroidism, autoimmune thyroid disease, and thyroid cancer.
- Exposure to large amounts of goitrogens impairs the incorporation of iodine into thyroid hormone itself, which means that even the iodine that gets taken up by the thyroid gland can't be properly utilized.
- Examples of goitrogens include bok choy, Brussels sprouts, cauliflower, kale, cabbage, radishes, horseradish, peaches, spinach, and yuca.
- It is highly unlikely that consuming sauerkraut as a condiment, such as a tablespoon or two, with meals or three to six servings of cooked, not raw, cruciferous veggies or other mildly goitrogenic foods will have a negative impact on the thyroid gland if iodine intake is sufficient.

REGULATE AND BALANCE THE IMMUNE SYSTEM

- Paleo-type or autoimmune protocol (AIP) diet.
- Nutrients especially important for optimizing immune function are glutathione, curcumin, and vitamin D.
    - Optimize vitamin D through diet, UV exposure, and supplements.
- Get adequate eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), probiotics, and prebiotics.
- Lifestyle and behavior to balance the immune system: appropriate physical activity, sleep, stress management, play, pleasure, and social connection.
- Low-dose naltrexone (LDN) dose is 1.5 to 4.5 mg.

THYROID HORMONE REPLACEMENT

- Tirosint, liquid T4, works better than levothyroxine, but it doesn't address conversion issues.
- The best option for a T4-T3 combo for most patients is natural desiccated thyroid (NDT).

    - NDT by prescription is real thyroid hormone that is isolated from several different pigs.
    - NDT does meet the stringent guidelines of the U.S. Pharmacopeia.
    - Desiccated thyroid gives you what your own thyroid would be giving you: T4, T3, T2, T1, and calcitonin. Both prescription and nonprescription options for NDT are available.
    - NDT dosage is 1 to 3 grains; start at 1/2 grain (30 to 32.5 mg).
- Another option is combining synthetic T4 such as levothyroxine or Synthroid with synthetic T3 such as Cytomel.

THYROID HYPERFUNCTION

There are two main forms of hyperthyroidism: overt and subclinical.

1. Overt/primary hyperthyroidism
    a. Patient has low TSH and high T4 and T3.
    b. In Graves' disease. Patients have higher levels of T3 than T4, but a subset of patients will have high T4 and normal T3, and this is called T4 toxicosis.
    c. In patients with inflammatory diseases, that reduces the conversion of T4 to T3.
2. Subclinical hyperthyroidism.
    a. Patient has low TSH but normal T4 and T3 levels.

ETIOLOGY

- Graves' disease is an autoimmune disorder that results in the production of TSH receptor antibodies, which stimulate thyroid growth and release thyroid hormone.
    - Primarily women aged 20 to 40 are affected.
    - Signs and symptoms of Graves' disease include anxiety, nervousness, weariness, hair/nail changes, weight loss, increased heart rate, increased systolic blood pressure, heat intolerance, tremors, change in libido, increased temperature, sweating, frequent bowel movements, headaches, hives, nausea, vomiting, muscle weakness, fatigue, swollen lymph nodes, and increased appetite.

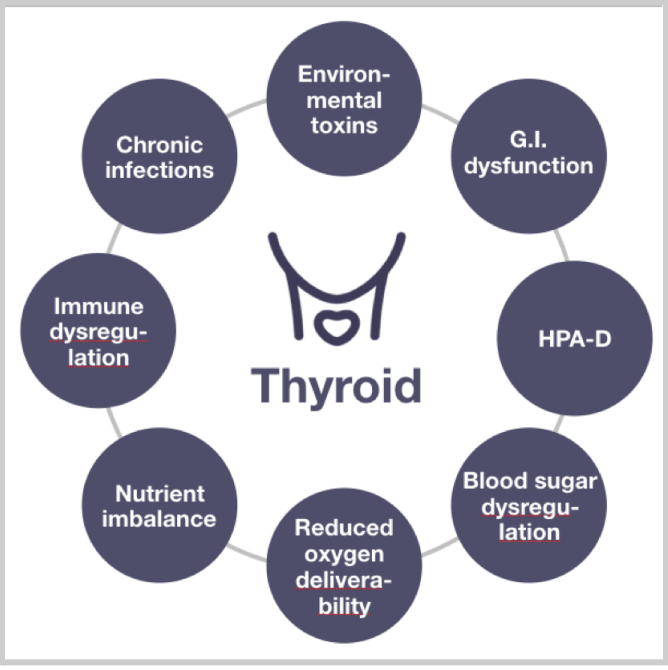
  - There is an association between *Helicobacter pylori* and Graves' disease in scientific literature.
  - Graves' disease is associated with both hyperglycemia and hypoglycemia.
- Hashitoxicosis is present with TSH receptor antibodies, high radioiodine uptake, and low TSH and high T4 or T3.
- Toxic adenoma
- Toxic multinodular goiter
- Other rare causes

TREATMENT FOR GRAVES' DISEASE

Conventional approach: propylthiouracil (PTU) or methimazole, radioactive ablation, or surgical removal.

Note: Do not take patients off these medications without close supervision to prevent a thyroid storm, which includes a high T3, leading to risk of heart attack, stroke, and even death.

FUNCTIONAL APPROACH TO THYROID DYSFUNCTION



CORE MARKERS

TSH	Reverse T3
Total T4	Free Thyroxine Index
Free T4	T3 Uptake
Total T3	TPO and Thyroglobulin antibodies
Free T3	TSI / TSH receptor antibodies

It is crucial to add TSI, also known as TSH receptor antibodies. TSI is used to distinguish Graves' disease from thyroiditis, Hashimoto's disease, and other causes of hyperthyroidism.

ADJUNCT MARKERS

- Alanine aminotransferase (ALT) and aspartate transaminase (AST) may be elevated in Graves' disease.
- Test urine iodine and hair iodine in patients who have been supplementing with it to rule out excess iodine as a potential cause.

FUNCTIONAL RANGES FOR CORE THYROID MARKERS

Marker	Functional range
TSH	0.5–2.0 mU/L
Total T4	6.0–12 ug/dL
Total T3	100–180 ng/dL
Free T4	1.0–1.5 ng/dL
Free T3	2.5–4.0 pg/mL

REFERENCE RANGES FOR THYROID ANTIBODIES (JUST USE THE LAB RANGES)

Marker	Range (IU/mL)
Thyroid peroxidase (TPO) Ab	0–34
Thyroglobulin (TG) Ab	0.0–0.9
TSH receptor Ab (TSI)	0–139

Beware of falsely low TSH with thyroid hormone replacement.

TREATMENT OF THYROID HYPERFUNCTION

If only TSH is low, and free T4 and T3 are normal, address underlying causes and retest every two to three months, or sooner if hyperthyroid symptoms increase. Up to 25 percent of Graves' disease cases spontaneously remit.

- If free T4 is high and/or free T3 is normal or high, that could be hashitoxicosis, especially if the free T3 is very high. You want to refer out for additional workup.

Treatment options if free T4 and/or free T3 are significantly elevated, and the patient has tachycardia and other concerning symptoms:

- Currently, antithyroid drugs such as PTU or methimazole are favored because they can actually reduce TSI production and help the immune system to recover.
- Surgery and radioiodine are not recommended. Refer to the presentation for more details.
- I highly recommend you refer to an endocrinologist. You can continue helping the patient with the underlying conditions.

HIGH-DOSE IODINE

- Can lead to a temporary inhibition of iodine organification in the thyroid gland and reduce the output of thyroid hormone, called the Wolff-Chaikoff effect.
- However, some studies have shown that high doses of iodine can induce hyperthyroidism.
- I think treatment of hyperthyroidism with high doses of iodine is best left to an endocrinologist or someone who does that regularly.

One note with LDN: You need to warn patients they can become hypothyroid as they start to implement the treatment because LDN helps regulate the immune system. Also, ask them to let their endocrinologist know to expect that so that they are ready to adjust the dose unless you are the one who is prescribing the PTU or the methimazole.

NATURAL AGENTS THAT CAN BE HELPFUL IN HYPERTHYROIDISM

- L-carnitine. In high doses of 2 to 4 g per day, it inhibits the entry of both T4 and T3 into the cell nucleus, which reduces the effects of hyperthyroidism.
- High doses of L-carnitine such as 4 g daily are not associated with toxicity.
- Best supplement form is acetyl-L-carnitine.

- Botanicals that have shown efficacy in treating hyperthyroidism:
    - Bugleweed, or gypsywort
    - Lemon balm
    - Herb Pharm has a formula called Thyroid Calming with both bugleweed and lemon balm. It also has motherwort and cactus, both of which are used in traditional medicine for hyperthyroidism, anxiety, and related symptoms. The dose is one full squeeze of the dropper bulb in two ounces of water two to four times a day, and it is best taken between meals.

SUMMARY OF TREATMENT RECOMMENDATIONS

TSH	Free T4/T3	Comments
Low	Normal / high-normal (high in functional range)	Address underlying mechanisms and re-test in 3 months; if TSI high, focus on immune balancing
Low	Slightly above lab reference range	Address underlying mechanisms and use 2-4 g L-acetyl-carnitine + Thyroid Calming daily; if TSI +, focus on immune balancing and consider LDN
Low	Significantly above lab reference range	Refer to endocrinologist for further workup (esp. if TSI –) and ATD if necessary; continue addressing underlying mechanisms and focus on immune balancing (inc. LDN) if TSI +

Lesson 39: No Review (Break Week)

Lesson 40: Blood Chemistry Impaired Kidney Function and Other Metabolic Problems Review

KIDNEYS

- Function. The kidneys regulate fluid levels, filter waste and toxins from the blood, release hormones that regulate blood pressure and red blood cell production, activate vitamin D for healthy bones, and maintain balance of sodium, phosphorus, and potassium.
- Chronic kidney disease (CKD) indicates the presence of kidney damage, urinary albumin excretion of 30 mg/kg per day or more, decreased kidney function, and/or an estimated glomerular filtration rate (eGFR) below 60 for three or more months irrespective of the cause.
    - Symptoms include fatigue; weakness; difficult and painful urination; foamy urine or pink and dark urine, which is indicative of hematuria; increased need to urinate, especially at night; puffy eyes; swelling of the face, hands, abdomen, ankles, and feet; and increased thirst.

CAUSES OF CKD

- Top two causes are diabetes and hypertension.
- Decreased renal perfusion due to hypovolemia can be caused by vomiting, diarrhea, diuretic use, etc.; hypotension; infection; or the use of non-steroidal anti-inflammatory drugs (NSAIDs) and angiotensin-converting enzyme (ACE) inhibitors.
- Nephrotoxic drugs including aminoglycoside antibiotics, NSAIDs, and ACE inhibitors. The use of these drugs should be avoided in people with diabetes.
- Urinary obstruction.

KIDNEY STONES

- Most common stones are made of calcium oxalate.
- Factors that increase risk of kidney stones include:
    - Fat-soluble vitamin imbalance (vitamin A, D, or K2). Excess vitamin D in absence of sufficient vitamin A and K2 is a particular concern.
    - Excess sodium intake.
    - Magnesium deficiency.
    - Very-low-carb diets (increased demand for vitamin C).
    - Excess fructose intake.
    - High-protein diet with adequate carb intake will not necessarily increase risk for kidney stones unless you already have kidney disease.

MARKERS FOR IMPAIRED KIDNEY FUNCTION

Marker	Level
BUN	High
Creatinine	High
eGFR	Low
Phosphorus	High
Sodium	High
Potassium	High
AST	High
ALT	High
GGT	High

FOLLOW-UP TESTING FOR IMPAIRED KIDNEY FUNCTION

Marker
Urinalysis with microscopy
Urine microalbumin / creatinine ratio
Ultrasound (to check for obstruction)
Cystatin-C

If you suspect the patient has kidney dysfunction, you can either refer them to a nephrologist immediately or do further workup. Note that it is better to refer early than late.

Proteinuria is the most common finding in kidney disease due to metabolic disorders and hypertension. High cystatin C levels are indicative of reduced glomerular filtration and kidney disease.

LABORATORY AND FUNCTIONAL RANGES FOR KIDNEY MARKERS

Marker	Lab Range	Functional Range
BUN	5–18 mg/dL	13–18 mg/dL
Creatinine	M: 0.72–1.27; W: 0.57–1.0	M: 0.85–1.1; W: 0.7–1.0
eGFR	Age/gender specific	Use lab range
Phosphorus	2.5–5.3 mg/dL	3.0–4.0 mg/dL
Sodium	134–144 nmol/L	135–140 nmol/L
Potassium	3.5–5.2 nmol/L	4.0–4.5 nmol/L
AST	0–40 IU/L	F: 0–23 IU/L; M: 0–25 IU/L
ALT	0–24 IU/L	F: 0–20 IU/L; M: 0–26 IU/L
GGT	0–60 IU/L	F: 0–21 IU/L; M: 0–29 IU/L

- When only BUN is elevated, and there aren't any other markers of kidney dysfunction, the two most likely causes are dehydration or high protein intake. With dehydration, red blood cell count and/or hemoglobin will often be slightly above the upper limit of the functional range but not out of the lab range.
- Potential causes of a high BUN-to-creatinine ratio include heart failure, liver cirrhosis, very-high-protein diet, and upper gastrointestinal bleeding.
- BUN-to-creatinine ratio over 20 indicates the problem is prerenal, meaning before the kidney. Dehydration or hypoperfusion from hypovolemia, vomiting, diarrhea, diuretic use, hypotension, infection, and the use of NSAIDs and ACE inhibitors are the most common causes in this case.
- One possible cause of slightly elevated creatinine alone is increased muscle mass.

Functional treatment of impaired kidney function almost exclusively involves addressing underlying causes. People with kidney disease have a decreased ability to excrete byproducts and waste products, and some botanicals contain substances that people with kidney disease need to limit.

PROMOTE OVERALL KIDNEY HEALTH AND PROTECT AGAINST KIDNEY STONES

1. Balance fat-soluble vitamin intake (vitamins A, D, and K2).
2. Ensure adequate magnesium intake.
3. If you have a patient with obesity, metabolic syndrome, and hypertension, experiment with salt intake.
    a. Moderate sodium intake.
    b. Be careful not to go too low. Very low sodium intake is associated with higher risk of cardiovascular disease, just like very high sodium intake.

Gout

- Type of inflammatory arthritis caused by elevated levels of uric acid in the blood, forming crystal deposits in the joints, tendons, and surrounding tissue.
    - Typically affects the feet, specifically the big toe joint.

- Purines are higher in many Paleo-friendly foods, such as red meat, turkey, organ meats, and certain types of fish and seafood. Patients with gout are often advised to reduce or eliminate these purine-rich foods with the goal of preventing excess uric acid production and thereby reducing the symptoms of gout.
- Purine intake alone is not enough to trigger these attacks, and systemic inflammation (Western diets) is likely a key factor.
- Studies have shown that purine restriction doesn't improve gout.
- Other risk factors include:
    - Excess fructose intake, mostly in the form of liquid fructose as fructose in whole foods is less likely to contribute to metabolic disease.
    - Insulin resistance
    - Dehydration
    - Vitamin C deficiency
    - Increased alcohol intake
    - Iron overload

Rhabdomyolysis

- Involves a rapid breakdown of skeletal muscle tissue.
- May see elevated LDH, AST, ALT, and potassium as well as low serum calcium.
- Primary diagnostic marker is creatine kinase, which may be five times above the normal upper limit.
    - Also high LDH, AST, ALT, and potassium with low calcium.
- Possible symptoms include muscle pain, tenderness, weakness, swelling of the affected muscles, and tea-colored (brownish) urine, caused by the myoglobin in urine.
- Uncommon but documented side effect of statin drugs.
- Refer to a nephrologist immediately as this can cause irreversible kidney damage.

Lesson 41: Blood Chemistry Impaired Kidney Gallbladder and Liver Disease Review

MARKERS OF IMPAIRED LIVER FUNCTION

Marker	Value
ALT	High
AST	High
GGT	High
LDH	High
Alkaline phosphatase	High

AMINOTRANSFERASES (ALT AND AST)

- ALT is a specific indicator of liver damage that is present in the highest amount in the liver.
- AST is present in tissues with high metabolic activity, including liver, heart, and kidney. It's not specific to the liver, but liver dysfunction is the most common cause of elevated AST.
- Elevated aminotransferases typically reflect abnormalities in liver cells or the bile duct.

GAMMA-GLUTAMYL TRANSFERASE (GGT)

- Primarily found in the hepatocytes and biliary epithelium. However, due to its presence in many tissues, it is not specific for liver and gallbladder disease.

- GGT and alkaline phosphatase levels increase in the blood with hepatobiliary obstruction.
- Unlike alkaline phosphatase, GGT is not found in the bone.
- Primarily to confirm liver or gallbladder as a source of elevated alkaline phosphatase rather than breakdown in the bone.
- GGT is also a sensitive marker for metabolic dysfunction.

LACTATE DEHYDROGENASE (LDH)

- Primarily a marker for tissue or cellular damage.

ALKALINE PHOSPHATASE

- Primarily a marker for liver and bone damage.
- When bone disease is excluded, an elevation of alkaline phosphatase suggests biliary obstruction, injury to the bile duct, injury to the epithelium, or cholestasis.
- Always retest to confirm high alkaline phosphatase.
- It is most likely a marker of liver dysfunction when GGT is also high.
- If GGT is normal or equivocal, consider running alkaline phosphatase isoenzymes to see whether the elevation is coming from the intestine, the liver, or the bone.

LIVER DISEASE/CAUSES OF ELEVATED LIVER ENZYMES

1. Chronic viral hepatitis

Form	Prevalence	Risk factors	Comments
Hepatitis C	1.8% of general population; rate much higher in people with known risk factors and ALT >40 IU/L	Blood transfusions (esp. before 1992), IV drug use, cocaine use, hemodialysis, organ transplantation, birth in endemic region	Many patients will have no symptoms or mild symptoms and only mildly elevated ALT/AST; if risk factors present, early testing warranted
Hepatitis B	0.2–0.9% of general population; as high as 20% after travel to endemic areas	Same as above; more commonly transmitted sexually than Hep C	Many patients will have no symptoms or mild symptoms and only mildly elevated ALT/AST; if risk factors present, early testing warranted

2. Iron overload
3. Alcoholic liver disease
    a. Risk: 10-plus years of more than five drinks, (12 ounce beer, 1.5 ounces of spirits, 5 ounce glass of wine)
    b. Often see AST-to-ALT ratio of 2 to 1
4. Nonalcoholic fatty liver disease
    a. Risk factors include patients with components of metabolic syndrome: abdominal obesity, insulin resistance, hyperlipidemia, hypertension, certain medications (corticosteroids, tetracycline, valproic acid, amiodarone)
5. Autoimmune hepatitis
    a. More common in women and those with other autoimmune diseases
    b. Diagnosis by exclusion of viral hepatitis, pathologic findings, and presence of autoimmune markers such as antinuclear antibodies, smooth muscle antibody, liver kidney microsomal antibodies
6. Wilson's disease

   a. Anyone under age 40 with abnormal liver enzymes should be evaluated, even in the absence of neurologic or ocular findings; routine screening is rarely helpful in patients over age 50.
   b. Genetic testing is of limited value because of the large number of potential mutations of the *ATP7B* gene;
   c. If a patient does have Wilson's disease, screen family members.

7. Alpha-1 antitrypsin deficiency
   a. A protease inhibitor made in the liver that protects both the liver and the lungs.
   b. Patients with emphysema or with a young sibling with liver failure are at higher risk.
   c. Common cause of liver disease in young children, but only a portion develop liver failure as adults.
8. Drug- and toxin-related liver diseases
9. Extrahepatic causes
   a. Thyroid disorders. Screen for thyroid antibodies and run the full thyroid panel.
   b. Celiac disease. Test tissue transglutaminase levels.
   c. Hemolysis. Test the LDH level, haptoglobin level, and reticulocyte count; infection is a possible cause.
   d. Muscular disorders. Test creatine kinase and aldolase levels; screen for systemic lupus erythematosus.

Hepatitis B, hepatitis C, iron overload, and nonalcoholic fatty liver disease are the most common causes of elevated AST and ALT. If you're able to exclude iron overload, hepatitis B, and hepatitis C, it is very likely that the patient has nonalcoholic fatty liver disease, especially if you can rule out Wilson's disease with copper, ceruloplasmin, and urine copper testing.

GALLSTONES

- The majority of people with gallstones will not develop symptoms.
- When symptoms do present, they can be either episodic or steady, and the pain is located in the upper abdomen. It can be severe and last for more than 30 minutes, and

then there can be some accompanying features such as nocturnal onset, nausea, vomiting, and radiation through to the back.

GALLSTONE RISK FACTORS

Not modifiable	Modifiable
Family history	Obesity/metabolic syndrome/diabetes mellitus/dyslipidemia
Genetic predilection	Drugs - ceftriaxone, octreotide, thiazide diuretics, female sex hormones
Ethnic background	Reduced physical activity
Female sex	Rapid weight loss
Age	TPN
	Diet
	Underlying disease: cirrhosis, Crohn's disease

Cholecystitis usually occurs as a complication of gallstone disease. Chronic cholecystitis is chronic inflammatory cell infiltration of the gallbladder seen on histopathology. It is almost always associated with gallstones and is thought to be the result of recurring, acute cholecystitis attacks, which lead to fibrosis and thickening of the gallbladder.

Cholecystitis without gallstones is called acalculous cholecystitis or biliary dyskinesia.

Acalculous cholecystitis has numerous risk factors, and the mechanism primarily involves gallbladder stasis and ischemia, resulting in local inflammatory responses in the gallbladder wall.

MARKERS OF IMPAIRED GALLBLADDER FUNCTION

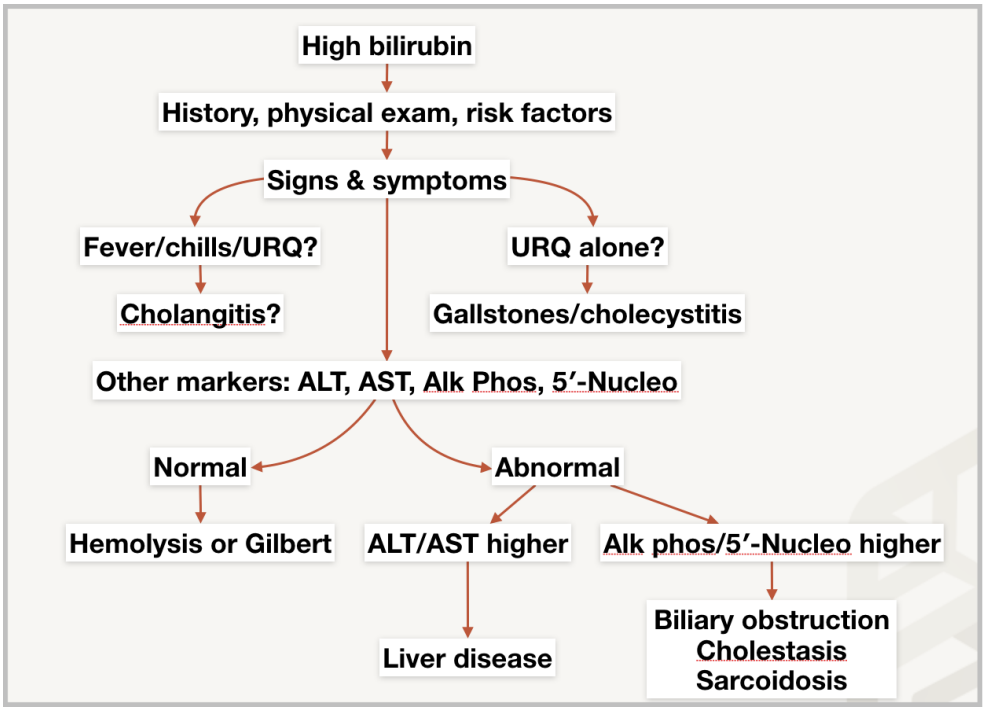
Similar to markers of liver dysfunction but with the addition of bilirubin and 5'-nucleotidase.

Marker	Value
ALT	High
AST	High
Bilirubin	High
Alkaline phosphatase	High
5'-Nucleotidase	High
LDH	High
GGT	High

BILIRUBIN

- Normally, about 96 percent of bilirubin is unconjugated.
- Abnormalities of any of the four stages result in hyperbilirubinemia, with either high unconjugated bilirubin or both high unconjugated and conjugated bilirubin.
- In cases of high bilirubin, do a follow-up test for conjugated (direct) versus unconjugated (indirect).
- Labcorp can test total and direct bilirubin.
- Then you could subtract the direct (conjugated) bilirubin from the total bilirubin to get indirect (unconjugated).

ALGORITHM FOR HIGH BILIRUBIN



- High indirect or unconjugated bilirubin evaluation is based on whether the abnormalities are due to biliary obstruction, intrahepatic cholestasis, hepatocellular injury, or an inherited condition.
- If there is evidence of biliary obstruction such as high unconjugated bilirubin and high alkaline phosphatase and/or 5'-nucleotidase, then you can refer out for hepatic imaging such as ultrasound or magnetic resonance imaging.
- If there is evidence of liver disease, such as higher AST and ALT than alkaline phosphatase or 5'-nucleotidase, do further testing for causes of liver issues such as Wilson's disease, hemochromatosis, hepatitis, etc.

ALKALINE PHOSPHATASE

Note that when the values of alkaline phosphatase are markedly elevated, such as more than four times the upper end of the range, it is more likely to be due to obstructive pathology such as bile duct stones, an infection, or cirrhosis. Intestinal alkaline phosphatase could increase in states of dysbiosis or disrupted gut microbiome as a means of detoxifying lipopolysaccharides.

5'-NUCLEOTIDASE

The primary purpose of 5'-nucleotidase clinically is to confirm that high alkaline phosphatase is a marker of liver or gallbladder dysfunction and not bone or intestinal issues.

LACTATE DEHYDROGENASE (LDH)

- LDH is elevated in gallbladder cancer, cholelithiasis, and chronic cholecystitis.
- If LDH is elevated, look at bilirubin and alkaline phosphatase.
    - If those two are elevated, run LDH isoenzymes.
    - If LDH isoenzymes 3 and 4 are significantly elevated, refer for a gallbladder cancer screen.
- If there is another pattern, address the underlying causes and retest.
- If bilirubin and alkaline phosphatase are not elevated, you should still run LDH isoenzymes to see where the elevation is coming from.

INDICATIONS FOR HIGH GGT

- Confirmed liver/gallbladder origin of high alkaline phosphatase
- Alcohol abuse or alcoholic liver disease
- Metabolic dysfunction
- Cardiovascular disease
- Iron overload

TREATMENT/PREVENTION OF GALLBLADDER DYSFUNCTION

- Weight loss
- Increased physical activity
- Paleo (gluten-free) diet

- Discontinuation of drugs that harm the gallbladder
- Addressing underlying conditions

SUPPLEMENTS AND BOTANICALS FOR GALLBLADDER DYSFUNCTION

Intervention	Comments
Bitters	Help with bile synthesis and metabolism
Other botanicals	Help with bile synthesis and metabolism
Phosphatidylcholine	Prevents and possibly dissolves gallstones
Vitamin C	Prevents gallstones
Rowachol	May dissolve gallstones
Ox bile / bile salts	Acts as “bile replacement”

Lesson 42: Blood Chemistry Iron-Deficiency Anemia Review

DEFINITIONS OF ANEMIA

1. A condition in which the number of red blood cells is below normal.
2. A hemoglobin level below 12 g/dL in women or 13 g/dL in men.
3. A decreased ability of red blood cells to provide adequate oxygen supplies to body tissues.
4. Any condition characterized by an abnormal decrease in the body’s total red blood cell mass.
5. An abnormal reduction in red blood cells.

6. Anemia is a symptom, not a disease.

CAUSES OF ANEMIA

- Nutritional deficiency (iron, zinc, vitamin B12, folate)
- Increased demand for iron (pregnancy, growth spurt)
- Blood loss (menstruation, childbirth, surgery, injury)
- Disease (infections, autoimmune disease, inflammatory bowel disease [IBD], cancer, bleeding)
- Hormone imbalance (hypothyroidism)
- Bone marrow function (leukemia, aplastic anemia)
- Chronic hemolysis
- Poisoning (lead and other heavy metals)
- Medications (aspirin, anticonvulsants)
- Genetics (inherited blood-forming diseases)

The most common causes you'll see in general practice are nutritional deficiency, whether iron, vitamin B12, or folate; increased demand; blood loss; and disease.

Category	Conditions
Iron deficiency	Diet
	Increased demand (growth, pregnancy)
	Blood loss (menstruation, parasites, etc.)
Malabsorption	H. pylori
	Crohn's
	Hypochlorhydria
Vitamin and mineral deficiencies	B6 (alcohol)
	Vitamin A, B, C, E, K, zinc, copper
	B12
Premature hemolysis	Hemolytic anemias
	Enzyme deficiencies
	Autoimmune disease
Dysfunctional erythropoiesis	Kidney failure
	Bone marrow failure
	Thalassemia
	Cancer
	Sideroblastic anemia
Bleeding disorders	Von Willebrand's
	PNH
	Hemophilia

SIGNS AND SYMPTOMS OF ANEMIA

Fatigue - most common	Brittle or spoon nails
Weakness	Pica (desire to eat non-food items)
Twitching/flinching	Headache
Restless legs syndrome (RLS)	Dizziness
Pale skin, tongue, fingernails, palms	Shortness of breath
Loss of tongue papillae	Tachycardia
Hyposalivation	Chest pain
Thrush	Splenomegaly

ANEMIA MARKERS

Marker	Lab range (female)	Fx. range (female)	Lab range (male)	Fx. range (male)
RBC	3.77–5.28	4.4–4.9	4.14–5.8	4.4–4.9
HGB	11.1–15.9	13.5–14.5	12.6–17.7	14–15
HCT	34–44.6	37–44	37.5–51.0	40–48
MCV	79–97	85–92	79–97	85–92
MCH	26.6–33.0	27.7–32.0	26.6–33.0	27.7–32.0
MCHC	31.5–35.7	32–35	31.5–35.7	32–35
RDW	12.3–15.4	11.5–15.0	12.3–15.4	11.5–15.0

All of these markers are included on the complete blood count (CBC). A reminder that RBC, Hgb, and Hct are often the last lab markers to drop in iron-deficiency anemia.

IRON-DEFICIENCY ANEMIA

Marker	Value
RBC	Low
HGB	Low
HCT	Low
MCV	Low
MCH	Low
MCHC	Low
RDW	High

POPULATIONS AT RISK FOR IRON-DEFICIENCY ANEMIA

- Young children
- Adult females; common causes are heavy menstruation and diet
- The elderly; common causes are gastrointestinal (GI) malabsorption such as hypochlorhydria, *H. pylori*, and diet
- People with bleeding disorders
- People with GI malabsorption (IBD, celiac disease, small intestinal bacterial overgrowth [SIBO], hypochlorhydria, etc.)
- Vegans and vegetarians

ADDITIONAL NOTES

1. Remember, in iron-deficiency anemia, you'd expect MCV, MCH, and MCHC to be low, whereas in vitamin B12 or folate-deficiency anemia, you'd expect those markers to be high.
    a. In some cases, where you have concurrent vitamin B12 or folate deficiency and iron-deficiency anemia, MCV, MCH, and MCHC will be normal because you have the B12 and folate deficiency pushing them up and the iron deficiency pushing them down.
2. Copper deficiency can cause iron-deficiency anemia, and high doses of zinc supplements can induce copper deficiency.
3. Low magnesium levels can also contribute in cases of iron-deficiency anemia.
4. Hemoglobin A1c may not be accurate where anemia is present because A1c is a measurement of glycation of red blood cells.

Treatment of iron-deficiency anemia involves addressing the underlying cause.,which could include nutrient deficiency, GI pathology, metal toxicity, hypothyroidism, autoimmunity, inflammation, infection, etc.

Refer to the iron-deficiency presentation for detailed information on how to restore iron levels.

If the patient does have iron-deficiency anemia, I suggest increasing dietary copper intake, especially if background copper intake is low or there are other signs of deficiency.

Remember that some studies have shown that increasing copper intake alone without giving the patient iron can resolve iron-deficiency anemia, in some cases, because copper helps iron get into the cells.

Lesson 43: Blood Chemistry Vitamin B12 and Folate-Deficiency Anemia and Anemia of Chronic Disease Review

FOLATE

- A water-soluble B vitamin and a necessary cofactor in the methylation cycle.
- It is a key to synthesizing new red blood cells.
- Most common cause of folate deficiency is nutritional.
    - Also, MTHFR genetic polymorphisms.
    - MTHFR homozygotes have 70 to 75 percent loss of enzyme activity, but with a nutrient-rich diet and no other significant mutations, there can be enough enzymatic activity to avoid deficiency without supplementing.
    - Compound heterozygotes, heterozygous for C677T and for A1298C, may lose up to 50 percent of enzyme activity.
- Gastrointestinal (GI) malabsorption and inflammation, infections such as *Helicobacter pylori*, hypochlorhydria, alcoholism, and certain drugs such as metformin when used long-term can also cause folate deficiency.
- Populations that are at risk for folate deficiency include children; people who don't eat folate-rich foods, which include organ meats such as liver, dark leafy greens, and some legumes; people with GI disorders and infections; alcoholics; people with diabetes taking metformin; and pregnant and lactating women who have an increased demand for folate.

MARKERS OF FOLATE DEFICIENCY

- Serum folate is the best serum marker for assessing recent nutritional intake of folate. Optimal range is above 8 mcg/L.
- Red blood cell (RBC) folate reflects body stores during the last three to four months, not diet.
- Homocysteine is sensitive, but a high level can indicate vitamin B12 and/or folate deficiency.
- Formiminoglutamate (FIGLU) can be used to differentiate between vitamin B12 and folate deficiency when homocysteine is elevated. High urine FIGLU indicates folate deficiency.

Treatment of vitamin B12- or folate-deficient anemia starts with addressing underlying causes.

You can refer back to the vitamin B12 deficiency presentation/review for more information on the diagnosis and treatment of B12 deficiency.

CONCERN WITH HIGH DOSES OF METHYL DONORS

- Examples include 5-methyltetrahydrofolate (5-MTHF), folinic acid, S-adenosyl-L-methionine (SAM-e), etc., in the treatment of folate deficiency.
- Overmethylation may be detrimental.
- Side effects observed in the scientific literature with high doses, especially of 5-MTHF, include anxiety, agitation, and insomnia.
- Overmethylation is also associated with primarily immune dysregulation.
- We don’t have enough research on the long-term effects of taking high doses of methyl donors for many years, so diet and lifestyle change, in my opinion, are the safest options.

OTHER NUTRIENTS THAT ARE REQUIRED FOR OPTIMAL METHYLATION

Methionine	Niacin
Cysteine	Pyridoxine
Taurine	Folate
DHA	Vitamin B12
Zinc	Betaine (TMG)
Magnesium	Choline
Potassium	Sulfur
Riboflavin	

DIETARY SOURCES OF FOLATE

Food	mcg DFE per serving
Chicken liver, one	254
Beef liver, 3 ounces	215
Spinach, boiled, 1/2 cup	131
Black-eyed peas, boiled, 1/2 cup	105
Asparagus, boiled, 4 spears	89
Lettuce, romaine, shredded, 1 cup	64
Avocado, raw, sliced, 1/2 cup	59
Spinach, raw, 1 cup	58
Green peas, frozen, boiled, 1/2 cup	47
Kidney beans, canned, 1/2 cup	46
Peanuts, dry roasted, 1 ounce	41
Crab, Dungeness, 3 ounces	36
Orange, fresh, 1 small	29

In certain cases, it may be necessary to supplement, at least temporarily, until the underlying mechanisms are addressed. Start with a diet rich in folate as well as other nutrients that support methylation, retest in 60 days, and if the markers are still high, consider a trial of supplementation. If you do supplement, avoid folic acid.

Folic acid is a synthetic compound used in dietary supplements and food fortification. The form of folate that can enter the main folate metabolic cycle is tetrahydrofolate.

Folic acid undergoes initial reduction and methylation in the liver where conversion to the tetrahydrofolate form requires dihydrofolate reductase. Activity of that enzyme is quite low in many humans. This can result in unnatural levels of unmetabolized folic acid entering the systemic circulation.

Several studies have shown that excess unmetabolized folic acid is associated with several health conditions, including cancer, depressed immune function, deterioration of central nervous system function, anemia, and cognitive impairment.

The best forms of folate to supplement with are:

- 5-MTHF, 5-methyltetrahydrofolate, or folinic acid, which is 5-formyl tetrahydrofolate (THF).

- Remember, 5-MTHF is the cofactor for methionine synthase, which converts homocysteine back into methionine.
- I prefer starting with a lower dose of 200 to 400 mcg per day.
- Note that a pretty substantial number of people, in my experience, have side effects with folate, including anxiety, agitation, insomnia, and overstimulation in general.
- In these cases, you can use folinic acid at a dose of 800 mcg. It is better tolerated than 5-MTHF and typically still works well for normalizing folate levels.
- Retest after 60 days. Consider testing serum folate level, which is a better marker of recent intake than RBC folate, as well as the complete blood count (CBC), anemia markers, and FIGLU.
- Once underlying issues are addressed, transition the patient to a dietary approach.
- If the patient can't maintain folate levels ongoing with diet, you have to weigh the risk of high homocysteine versus the risk of supplementing longer-term with high doses of folate, which we don't really understand much about.
- We do know that very high levels of homocysteine are associated with both cardiovascular disease and neurocognitive problems such as Alzheimer's disease and Parkinson's disease. It is not an easy question to answer.
- I would probably lean toward supplementing but using folinic acid perhaps instead of methylfolate and using the lowest effective dose to get homocysteine back into the optimal range.

ANEMIA OF CHRONIC DISEASE (ACD)

- Also referred to as anemia of chronic inflammation.
- It can be caused by something as simple as a viral infection, a urinary tract infection, an *H. pylori* infection, or an autoimmune disease.
- Anemia of chronic inflammation is an adaptive or protective mechanism to limit the amount of iron a person absorbs when pathogens are present.
- All living things, including bacteria and cancer cells, depend on iron to sustain life.
- The body can regulate how much iron it absorbs and absorb only what is needed to make red blood cells but not enough to nourish pathogens or feed cancer cells.

- In this situation, hemoglobin levels often decrease slightly, typically to the range of 9.5 to 10.5 g/dL, and stabilize at that level until the underlying condition is cured.
- Ferritin can be used to distinguish between iron-deficiency anemia and ACD in about two-thirds of patients, but it is not reliable in the other third.
- Hemoglobin is often low in both anemias but typically not below 9.5 g/dL in ACD.

	Serum iron	Serum ferritin	Iron saturation	TIBC/ UIBC	Soluble transferrin receptor	Reticulocyte hemoglobin content	Hemoglobin	MCV	RDW	White blood cell
Anemia of Chronic Disease (ACD)	Low	High	Low	Low	Normal	Normal	Low, but rarely <9.5 g/dL	Normal to slightly low	Normal	High, low, or normal
Iron Deficiency Anemia (IDA)	Low	Low	Low	High	High	Low	Low; may be <9.5 g/dL	Low	High	Normal

POPULATIONS AT RISK FOR ACD

Population	Risk factors
Elderly	H. pylori, other chronic inflammatory conditions common with aging
People with chronic infections	H. pylori, tick-borne illness, reactivated viral infections, GI pathogens
People with autoimmune disease	Rheumatoid arthritis, IBD, Hashimoto's, etc.
People with other chronic, inflammatory conditions	Osteoarthritis, interstitial cystistis, etc.

ACD is the most common cause of anemia in the elderly.

- If you see markers of anemia such as low serum iron or iron saturation, check TIBC and ferritin.

    - If TIBC is low and ferritin is high, it is likely that it is ACD, especially if RDW is normal, MCV is normal or low normal, and white blood cells are high or low.
    - If there is any question, run soluble transferrin receptor and reticulocyte hemoglobin content. If those are normal, it is virtually certain you're looking at ACD.
- Address any underlying causes you've identified that can result in ACD.
- If the patient has ACD and iron deficiency concurrently, do what you can to resolve the ACD first, particularly if a pathogen is present, because if you feed that pathogen iron, it could get worse.
- If you are absolutely certain there is no pathogen and it is just inflammation that is present, try to get the inflammation under control before supplementing with iron, or just focus on more iron-rich foods.
- If ACD doesn't resolve after addressing the underlying causes you identify, or if there are signs of more serious disease present, refer to a hematologist, a gastroenterologist, or a nephrologist.

Lesson 44: Blood Chemistry Dyslipidemia Review

MISCONCEPTION

- Heart disease is caused by too much "bad" cholesterol.
- Low-density lipoprotein cholesterol (LDL-C) is the most important marker for heart disease risk and the only one you need to track during treatment.

TRUE CAUSE OF ATHEROSCLEROSIS

The truth is that atherosclerosis is caused by an inflammatory response to sterols in artery walls, and sterols are delivered by lipoproteins. Thus, the number of low-density lipoproteins in

the blood, rather than the amount of cholesterol they carry, is a far greater predictor of heart disease risk.

LIPOPROTEIN(A)

- Important marker of cardiovascular disease risk.
- Lipoprotein(a), or Lp(a), levels are strongly influenced by genetics.
- Important notes on Lp(a):
    - Although observational studies show a strong association between Lp(a) and coronary heart disease, there has not yet been an interventional study that has shown that lowering Lp(a) leads to better outcomes.
    - With Lp(a), we can test for particle mass and particle number. The best marker is Lp(a) particle number, and this is expressed in nanomoles per liter, not milligrams per deciliter (mass).
    - With Lp(a) particle number in nanomoles per liter, the optimal value is below 75. Intermediate is 75 to 125, and high risk is above 125.
    - In the Copenhagen Heart Study, they found that people with Lp(a) levels above 50 mg/dL had a two- to threefold increased risk for heart attack.
    - Lp(a) is the strongest single predictor of coronary heart disease and aortic stenosis, and the association isn't affected by adjustment for classic risk factors.

The two most important lab markers for assessing cardiovascular disease (CVD) risk are low-density lipoprotein particle (LDL-P) and Lp(a)-P.

MODIFIABLE RISK FACTORS FOR HIGH LDL-P

1. **Insulin resistance**
    a. Note that LDL particles don't just carry cholesterol. They also carry triglycerides, fat-soluble vitamins, and antioxidants, so you can think of LDL as a taxi service that delivers important nutrients to the cells and tissues of the body. An increase in triglycerides, for example, will contribute to increased LDL particles to carry them around.

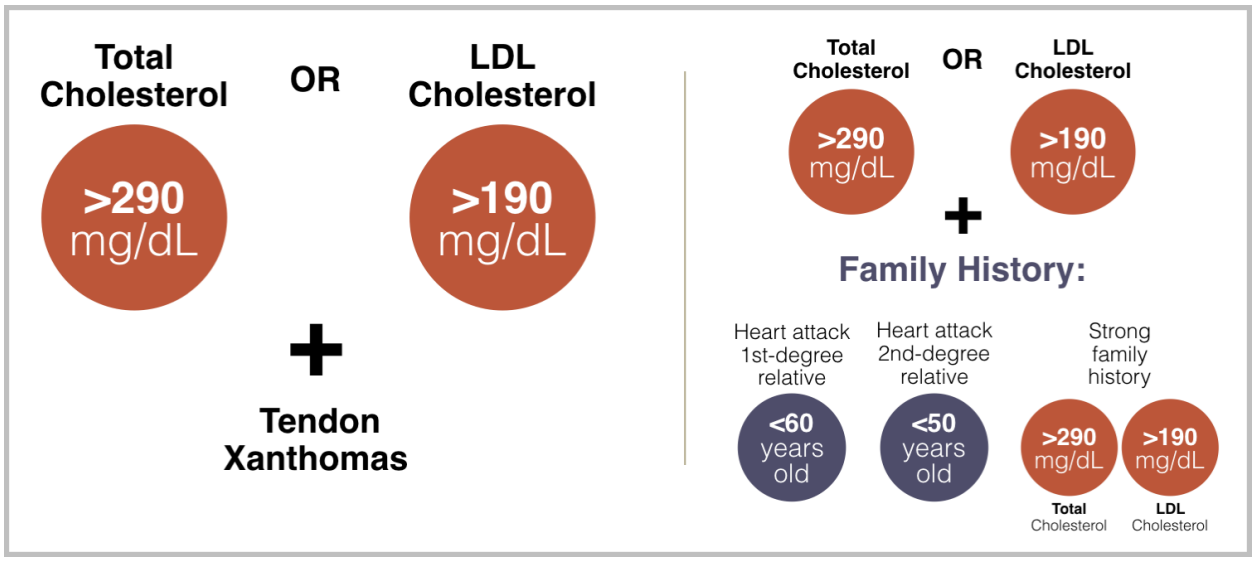
2. **Thyroid hypofunction**
    a. It stimulates the expression of HMG-CoA reductase, which is an enzyme in the liver involved in the production of cholesterol.
    b. It increases the expression of LDL receptors on the surface of cells in the liver and other tissues. In hypothyroidism, the number of receptors for LDL on cells will be decreased. This leads to reduced clearance of LDL from the blood and thus higher LDL levels.
3. **Infection**
4. **Gastrointestinal (GI) pathology**
    a. Studies have shown significant increases in lipopolysaccharide (LPS)-binding protein and thus LDL particles in cases of endotoxins reaching the bloodstream.
    b. Studies have also shown that the gut microbiota disrupts lipid metabolism.
5. **Environmental toxicity**
    a. Mercury toxicity
    b. Bisphenol A (BPA)
6. **Hypothalamic–pituitary–adrenal (HPA) axis dysfunction**
7. **Healthy diet and lifestyle behaviors**

NONMODIFIABLE CAUSES OF HIGH LDL-P

- Familial hypercholesterolemia (FH) involves a mutation of a gene that codes for the LDL receptor or the apolipoprotein B (apoB) protein that decreases LDL-P clearance from the bloodstream.
- Size doesn't matter, at least not as much as number.
    - People with FH have primarily large, buoyant LDL particles and yet are still at a much higher risk for CVD.
    - The idea was that small, dense LDL particles were more atherogenic, and large, buoyant LDL particles were protective and nothing to worry about.
    - Studies now show that particle size loses its significance when controlled for particle number. Particle number always trumps particle size as a risk factor.
- Genetics: ApoE and others

- In my experience, genetic testing does not change the treatment plan or outcome.
- My approach has been to address underlying causes, and then if the numbers are still elevated, assume that the remaining influence is genetic.

In the absence of genetic tests, you can use the Simon Broome criteria to diagnosis FH.



Pure hypercholesterolemia equals high total cholesterol, high LDL, and normal triglycerides and high-density lipoprotein (HDL).

Dyslipidemia usually involves high triglycerides, low HDL, normal or high total cholesterol, and normal or high LDL cholesterol, and that pattern is caused by metabolic dysfunction, whereas FH and pure hypercholesterolemia are often caused by genetics and other risk factors previously mentioned.

It is possible to have normal and even low total cholesterol and a high LDL particle number. This happens most often in patients with metabolic syndrome.

TREATMENT

1. Address underlying mechanisms.
2. Retest and if the numbers are still high, use diet and lifestyle to further lower them.
3. Discuss further treatment options and risks and benefits with the patient.
    a. Family history

b. Other risk factors for heart disease

c. Medication options

d. Supplements

e. Note: We have very little data on the significance of high LDL-P in a population that has no other significant risk factors, is consuming a healthy, nutrient-dense diet, and is living a healthy lifestyle.

DIETARY APPROACHES

- For patients with high LDL-P and normal metabolic function, I suggest a Mediterranean Paleo diet. This is a moderate-carbohydrate and moderate-fat approach.
- In patients with metabolic syndrome, a lower-carb Paleo approach is often better for lowering LDL-P because the pathology in that case is insulin resistance. Try to promote weight loss and improve insulin sensitivity.
- Other dietary considerations include emphasizing tree nut consumption, ensuring adequate intake of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), consuming fermented foods and fermentable fibers, eating a broad spectrum of colors, and maximizing intake of antioxidant-rich foods.

SUPPLEMENTS

1. **Tocopherols**
    a. The recommended dose is 200 mg of delta- and gamma-tocotrienols.
2. **Pantethine**
    a. Dose 450 mg twice daily.
    b. Need four to nine months to see significant results.
3. **Red yeast rice**
    a. Reduce cholesterol production by inhibiting the HMG-CoA reductase enzyme.
    b. Two capsules of Thorne Choleast-900 contain about 5 mg of lovastatin, similar to taking a very low dose of a statin, but it has much lower side effects.

   c. The brand of red yeast rice is very important. The Thorne product has been shown to have a consistent dose of monacolin K and to be free of citrinin.

4. **Coenzyme Q10 (CoQ10)**
   a. Jarrow Formulas QH-absorb. Dose is 200 mg once a day. Take with a meal that contains fat. Patients may find it to be stimulating; recommend taking the CoQ10 with breakfast.

5. **Glutathione**
   a. Consume at least a cup a day of homemade beef, chicken, or fish stock.
   b. Consume fattier cuts of meat (skin, cartilage, and bones, as well) rather than only lean cuts to get extra glycine.
   c. Fresh fruits/vegetables and raw dairy are great sources of glutathione.
   d. High-quality, grass-fed, nondenatured whey protein powder.
   e. I prefer a liposomal supplement form of glutathione.

6. **Curcurmin and turmeric.** These increase the LDL receptor MRNA.
7. **Fish oil.** For patients who are at risk for heart disease, aim for between 12 and 16 ounces of coldwater fatty fish a week.
8. **Fermentable fibers**
   a. Examples include glucomannan, partially hydrolyzed guar gum, acacia, or others from the gut unit, or just increase the intake of these fibers in food.
9. **Probiotics**

TREATMENT MATRIX

Presentation	Diet	Supplements
High LDL-P / Lp(a)-P without **inflammation**	Mediterranean Paleo	Tocotrienols, pantethine, RYR, fiber, probiotics; niacin & L-carnitine (Lp(a)-P)
High LDL-P / Lp(a)-P with **inflammation**	Mediterranean Paleo	Tocotrienols, pantethine, RYR, fiber, probiotics, CoQ10, curcumin, glutathione; niacin & L-carnitine (Lp(a)-P)
High LDL-P/Lp(a)-P with **metabolic syndrome**	Low-carb Paleo	Tocotrienols, pantethine, RYR, fiber, probiotics, CoQ10, curcumin, glutathione; niacin & L-carnitine (Lp(a)-P)
Normal LDL-P/Lp(a)-P with **inflammation**	Paleo	CoQ10, curcumin, glutathione

A note about statins: Most research suggests that the only population for which statins extend lifespan is in middle-aged men with pre-existing heart disease.

Lesson 45: Blood Chemistry Infection and Immune Dysregulation Review

The basic complete blood count (CBC) markers are not sufficient to make any conclusive diagnoses of infection or immune dysregulation. For that, we need to do much more extensive testing to determine the presence and cause of infection. The diagnosis and treatment of infections—from tick-borne illnesses such as Lyme disease and *Bartonella* to intracellular infections such as *Chlamydophila pneumoniae* and mycoplasma to reactivated viral infections such as Epstein-Barr—is one of the most complex and murky topics in medicine.

The CBC can be high or low in cases of infection and may highlight the need for further testing.

LAB AND FUNCTIONAL RANGES FOR INFECTION/IMMUNE MARKERS

Marker	Lab range	Functional range
WBC	3.4–10.8 x 10^3/µL	5.0–8.0 x 10^3/µL
Neutrophils	Relative: 49–74% Absolute: 1.4–7.0 x 10^3/µL	Relative: 40–60% Absolute: N/A
Lymphocytes	Relative: 26–46% Absolute: 0.7–3.1 x 10^3/µL	Relative: 25–40% Absolute: N/A
Monocytes	Relative: 2–12% Absolute: 0.1–0.9 x 10^3/µL	Relative: 4–7% Absolute: N/A
Eosinophils	Relative: 0–5% Absolute: 0.0–0.4 x 10^3/µL	Relative: 0–3% Absolute: N/A
Platelets	150–379 x 10^3/µL	150–379 x10^3/µL

White blood markers for infection lack specificity and sensitivity. You need to follow up with more specific testing to confirm/rule out. Below are a few general patterns:

Marker	Acute bacterial infection	Acute viral infection	Acute parasitic infection	Chronic Infection	Allergies
WBC	High	High	High	Low	Low, Normal, or High
Neutrophils	High	Low		Low, Normal, or High	
Lymphocytes	Low	High		Low, Normal, or High	
Monocytes	High	High	High	High	
Eosinophils			High		High

In an acute parasitic infection, we'd expect high WBC count and high eosinophils. Eosinophils are drawn to areas of inflammation through chemotaxis, at which point they activate and release substances contained within their granules. Eosinophilia has many potential causes, grouped into six broad categories: infection, allergy, neoplasm, lung disorders, skin disorders, and miscellaneous conditions. We can't assume that high eosinophils are necessarily caused by a parasite infection, but that's certainly one possibility.

Marker	Autoimmunity	Inflammation	Cancer
WBC	Low	High	High or Low
Lymphocytes	Low	High or Low	High or Low
Neutrophils	Low	High	Low
Platelets	High or low		High or Low
CRP	High	High	
Ferritin	High	High	
Vitamin D	Low		
HDL	High	High	
Monocytes			High or Low
Eosinophils			High

T-lymphocytes are the prime players in cell-mediated immunity, and they play an important role in fighting viral infections.

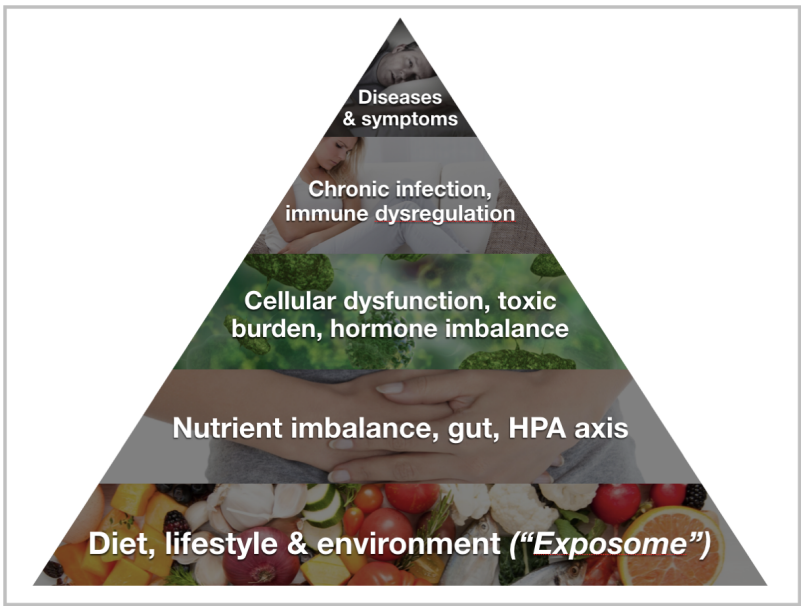
THROMBOCYTOSIS: ELEVATED PLATELET COUNTS

- Typically elevated in hematologic conditions (cancer and noncancer).
- Can be caused by inflammation and autoimmunity.
- If a patient doesn't have iron-deficiency anemia but has high platelets, retest them.
- If persistently elevated, refer to a hematologist.

THROMBOCYTOPENIA: LOW PLATELET COUNT

- Bone marrow is not making enough platelets.
- Platelets are being destroyed in the bloodstream.
- Liver or spleen is removing platelets from circulation.
- Genetic (nonpathological) (typically 5 to 10 percent below the lab reference range).
- If levels are persistently low, refer to a hematologist.

The treatment of infection and immune dysregulation and autoimmunity depends on the cause.



Lesson 46: Blood Chemistry Impaired Methylation Review

Methylation is a biochemical process involving the transfer of an active methyl group between molecules. Methyl groups consist of hydrogen attached to three carbon atoms.

1. Production of methyl groups results in either 5-methyltetrahydrofolate (5-MTHF) or S-adenosylmethionine (SAMe).
2. As it is used, SAMe is converted into S-adenosylhomocysteine, which is in turn converted into homocysteine.
3. Homocysteine is then recycled back into methionine via the dominant methionine synthase pathway, which requires 5-MTHF as the cofactor, or the lesser pathway, homocysteine methyltransferase in the liver and kidneys.

If methylation is impaired, homocysteine will not be converted back into methionine, and you'll see a buildup of homocysteine.

MOST IMPORTANT FUNCTIONS OF METHYLATION

Function	Comments
Cell division, DNA, and RNA synthesis	Folate crucial for DNA and RNA synthesis
Early CNS development	Folate deficiency during pregnancy > neural tube defects
Gene expression	DNA and histone methylation regulate expression of genes
Post-transcription modification	Regulatory function on microRNA translation and protein synthesis
Immune cell differentiation	Maturation of T-cells and other immune cells
Neurotransmitter synthesis and metabolism	Methylation via SAMe required for production of dopamine, norepineprhine, epinephrine & serotonin
Histamine clearance	Histamine N-methyltransferase, which requires SAMe, clears histamine
Detoxification	Methylation required for biotransformation of xenobiotics during phase II liver detoxification
Hormone clearance	Methylation of estrogens via COMT required for effective estrogen clearance
Cellular energy metabolism	Production of CoQ10, carnitine, and ATP > mitochondrial energy
Phospholipid synthesis	Synthesis of phosphatidylcholine, supports integrity of cell membranes
Myelination of peripheral nerves	Deficiency of SAMe in CSF causative in demyelination

If we simplify the above table for discussion with patients, impaired methylation can lead to:

- Depression and anxiety
- Histamine intolerance
- Weak immune function
- Higher risk of cancer
- Poor detox capacity
- Hormone imbalance
- Infertility/birth defects
- Fatigue and low energy

Deficits in methylation are associated with a wide range of conditions.

Risk factors for impaired methylation can be broken down into two categories: environmental and genetic, with environmental being the most significant and common of the two.

The first environmental cause is nutrient deficiency.

NUTRIENTS INVOLVED IN METHYLATION PATHWAYS

Methionine	Niacin
Cysteine	Pyridoxine
Taurine	**Folate**
DHA	**Vitamin B12**
Zinc	Betaine (TMG)
Magnesium	Choline
Potassium	Sulfur
Riboflavin	

DIETARY SOURCES OF FOLATE

Food	mcg DFE per serving
Chicken liver, one	254
Beef liver, 3 ounces	215
Spinach, boiled, 1/2 cup	131
Black-eyed peas, boiled, 1/2 cup	105
Asparagus, boiled, 4 spears	89
Lettuce, romaine, shredded, 1 cup	64
Avocado, raw, sliced, 1/2 cup	59
Spinach, raw, 1 cup	58
Green peas, frozen, boiled, ½ cup	47
Kidney beans, canned, ½ cup	46
Peanuts, dry roasted, 1 ounce	41
Crab, Dungeness, 3 ounces	36
Orange, fresh, 1 small	29

VITAMIN B12 INTAKE RECOMMENDATIONS

- Current Recommended Dietary Allowance (RDA) is 2.4 mcg.
- Studies on minimizing chromosomal damage and improving DNA repair suggest taking 7 mcg.
- The average daily intake of hunter–gatherers is 17.6 mcg.

There is no tolerable upper intake level for vitamin B12, and no toxicity threshold has been found. Therefore, advising higher intakes is safer than advising lower intakes.

HIGHEST DIETARY SOURCES OF VITAMIN B12

Food	**Amount** (mcg per 100g)
Clam	99
Lamb liver	90
Beef liver	83
Duck liver	54
Oyster	35
Pork liver	26
Caviar	20
Mackerel	19
Herring	19
Mussel	12
Crab	11
Sardine	9
Salmon	6

If the patient is not eating organ meats or fish, it's possible they are not getting enough vitamin B12.

Additional risk factors for impaired methylation:

- Competition for methyl donors. One particular function of methylation may be in overdrive and sucking up available methyl donors at the expense of other functions of methylation. This could be due to:
    - Environmental toxins
    - Mast cell activation syndrome (MCAS) or histamine intolerance

    - High estrogens
    - Acute or chronic stress
    - Chronic infection or immune challenge
- Inhibition of methylation
    - Methylation inhibitors can interfere with methylation-dependent functions in the body.
        - Elevated homocysteine levels, which are most often caused by vitamin B12 and folate deficiency, will increase S-adenosylhomocysteine and impair methylation.
        - Valproic acid is a histone deacetylase inhibitor.
        - Cholestyramine interferes with the absorption of folate, fat-soluble vitamins, and other nutrients required for methylation.
        - Oral contraceptive pills deplete magnesium, vitamin B6, vitamin B2, and riboflavin, and increase estrogen levels, which both impairs methylation and increases the need for methylation.
        - Proton pump inhibitors reduce the absorption of folate and other methyl donors.
        - Antibiotics deplete beneficial bacteria.
        - Nitrous oxide oxidizes cobalamin.

GENETICS

- Polymorphisms in methylation-related genes can lead to reduced methylation capacity.
- Methylenetetrahydrofolate reductase (MTHFR) is the best known, but many other genes affect methylation, including COMT, MTR, MTRR, and BHMT.
- Most common MTHFR polymorphisms are C677T and A1298C.
- Homozygous C677T: 70 to 75 percent loss of enzyme activity.
- Heterozygotes, or people with one polymorphism in MTHFR C677T, lose 33 to 35 percent of enzyme activity.

- Homozygous A1298C has a 39 percent reduction in enzyme activity
- Heterozygotes for A1298C have a 17 percent reduction of enzyme activity.
- Compound heterozygotes who have one copy of C677T and one copy of A1298C may lose as much as 52 percent of enzyme activity.

MARKERS OF IMPAIRED METHYLATION

Marker	Value
Serum folate	Low
RBC folate	Low
Serum B12	Low
Serum MMA	High
Serum homocystine	High
Urine MMA	High
Urine FIGLU	High

The bolded markers are included in the case review panel.

- Homocysteine is also an inverse marker. When it's high, it means that more vitamin B12 and folate are required to convert homocysteine back into methionine. Thus, high homocysteine can indicate B12 and/or folate deficiency.
- MMA (urine organic acids) is high in vitamin B12 deficiency.
- High urine FIGLU (urine organic acids) indicates folate deficiency.

Follow-up testing for impaired methylation: functional methylation testing. Consider the Methylation Pathway Panel from Health Diagnostics and Research Institute.

TREATMENT

- There has been a recent trend toward using high-dose methyl donors in supplement form to treat methylation-related problems.

- There is some evidence that suggests that overmethylation may be detrimental.
- Overmethylation has been associated with adverse effects, primarily immune dysregulation.
- We don't really have enough research on the effects of long-term supplementation with high-dose methyl donors.
- Methylation status depends on diet and lifestyle inputs, and I think diet and lifestyle change is the safest option.

Refer to the handout on methylation nutrients and foods. All the nutrients involved in the methylation cycle can be obtained from food in a nutrient-dense diet.

SUPPLEMENT PROTOCOL

- Avoid folic acid.
    - Folic acid undergoes initial reduction and methylation in the liver, where a conversion to the tetrahydrofolate (THF) form requires dihydrofolate reductase. Unfortunately, a lot of human beings have a relatively low activity of dihydrofolate reductase in the liver, and combined with a high intake of folic acid from fortified foods, this may result in unnatural levels of unmetabolized folic acid entering the systemic circulation.
- The best forms to supplement with are 5-MTHF or folinic acid, 5-formyl-THF.
    - Remember, 5-MTHF is a cofactor for methionine synthase, which converts homocysteine back into methionine.
- Start with a lower dose of 200 to 400 mcg per day of 5-MTHF.
- Many individuals experience side effects even with lower doses of 5-MTHF, including anxiety, agitation, insomnia, and overstimulation. These effects may pass after a short period of time.
- However, some patients just cannot tolerate 5-MTHF. In these cases, use folinic acid at a dose of 800 mcg per day, which is much better tolerated than 5-MTHF, and typically works pretty well for normalizing folate.
- Retest after 60 days.

- Once underlying mechanisms are addressed, consider transitioning to a dietary approach.
- If the patient is unable to maintain their folate levels with diet alone, weigh the risk of high homocysteine, which is an inflammatory protein associated with cardiovascular disease and cognitive disorders such as Alzheimer's disease, versus the risk of supplementing long-term with higher doses of methyl donors, which, as you know, has been shown to have some adverse effects in certain studies.
- As far as I can tell, the best option in these cases is probably to supplement, but use the lowest effective dose, and then continue to address the mechanisms that are known to impair methylation.