**Autism Spectrum Disorders**

- ADHD
- Asperger Syndrome
- PDD-NOS
- Autism

**Psychologically defined**

Communication
Stereotypical behaviors
Social interaction

**Understanding the underlying pathophysiologies that result in the biomedical conditions associated with autism**

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**Autism is treatable**

- Recent research shows that autism is treatable
- Early interventions lead to the best outcomes
- Be aware of symptoms, and begin addressing them as soon as possible
- Complementary approaches often provide optimal results

There is still not a cure, but there are many treatments to consider

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**Outline**

- The science of the body
- Dietary changes/modifications
- Metabolic imbalance and the basis of biochemical treatment
- Nutritional supplements

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**Autisms Spectrum of Symptoms**

- Metals
- Pesticides
- Inflammation
- Oxidative Stress
- Low Glutathione

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**Today's Presentation**

Will present discuss the scientific basis of available medical treatment options for autism, and review some of the medical approaches for implementing them.
How do you begin to treat autism biomedically?

- Look for a physician or other healthcare practitioner who considers an integrative approach to treatment – combining mainstream medical therapies and CAM (Complementary and Alternative Medicine) therapies
- No single treatment works for every child
- What works for no child may not work for another, and a successful course of treatment often includes a combination of approaches

Expected key benefits of biomedical treatment for autism

- Improvements in immune function, resulting in healthier children who seem to be very resistant to coughs, colds, runny noses, ear infections, and who seem to get over viral infections quicker than the rest of the family.
- Improvements in digestive function, resulting in more normal stool frequency and consistency; reduction or elimination of lower abdominal pain or discomfort; reduction or elimination of loose stools or diarrhea.

The science of the body

- The body is made up of specific systems, including skeletal, circulatory, digestive, immune, cardiovascular, and nervous
- Digestive system
  - Anatomy and function
  - Food allergies/food intolerances
  - Leaky gut/intestinal dysbiosis
  - Basic biochemistry
- Immune system function
Digestive system
- Mouth
- Tongue and glands
- Esophagus
- Stomach
- Small intestine
- Large intestine/Cecum
- Rectum
- Anus
- Liver
- Pancreas

Digestion-digestive tract function
- The digestive system is a series of hollow organs joined in a long tube from the mouth to the anus.
- The main function of the digestive system is to break down the food we eat into smaller parts so the body can use them for energy and cell nourishment.

Which organs make digestive enzymes?
- The salivary glands, stomach, pancreas, and small intestine all produce digestive enzymes.
- These enzymes break down proteins, carbohydrates, and fats into the units they are made up of—amino acids, sugars, and fatty acids.
- These tiny units are so small they can pass into the villi lining the intestine.

How are nutrients from foods absorbed?
- The lining of the small intestine is covered with microscopic projections called villi which dramatically increase its surface area.
- Molecules of nutrients dissolve in fluids in the intestine and pass into the villi.
- From there, nutrients pass through the thin walls of the blood vessels in the villi, and into the body.

What can go wrong with the digestive system?
1. Maldigestion/Malabsorption
2. Increased intestinal permeability
3. Intestinal dysbiosis
   i. Constipation
   ii. Diarrhea
   iii. Enterocolitis
4. Allergy

1. Maldigestion/Malabsorption
- Maldigestion is a gastrointestinal issue characterized by malfunctions with the digestive system which cause it to work improperly i.e. poor motility, insufficient enzyme function.
- Chronic poor digestion can lead to malabsorption, which results in an inability of the nutrients required from diet to fuel the cells and tissues of the body, and consequently, health problems result.

2. Increased intestinal permeability
- Definition: an abnormal or unfavorable increase in intestinal permeability.
- Epithelia are either "tight" or "leaky" depending on the ability of the tight junctions to prevent water and solute movement.
- The intestinal lining is supposed to be the protective barrier between the gut and the bloodstream.
- If the intestinal lining becomes damaged, it is possible for incompletely digested proteins and/or other by-products to "leak" through the intestinal lining, and they can be recognized as foreign by the immune system, and/or "leak" into bloodstream.

How do you get nutrients from foods?
- The process of breaking down food into molecules the body can absorb is called digestion.
- The digestive system begins with the mouth and involves many organs in the abdomen.
- The digestive organs produce enzymes which break down food chemically.

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3. Intestinal dysbiosis

- Intestinal flora (yeast and bacteria) are a normal part of digestive tract
- Intestinal dysbiosis occurs when there is an overgrowth/imbalance of intestinal flora
- Dysbiosis results from:
  - Increased use of antibiotics, steroids, etc.
  - Poor diet
  - Diets high in sugar
  - Stress
  - Immune system dysregulation

Lauren W. Underwood PhD

Adams et al., 2010
BMC Gastroenterology 11:22

Potential intestinal dysbiosis or “yeast” symptoms

- Diarrhea
- Bloating and gas
- Abdominal pain and cramping
- Fatigue
- Insomnia
- Lethargy
- Sensory disturbances
- Chemical sensitivities

Lauren W. Underwood PhD

If a child suffers from GI distress, like constipation, diarrhea

- Cramping, bloating cause distraction
- Posturing to relieve pain
- Pain may cause distress
- Pain may lead to self-injurious behavior

Lauren W. Underwood PhD

Autistic disorder and gastrointestinal disease

Kanyj Horvath, MD, PhD,* and Jay A. Purman, MD

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Lauren W. Underwood PhD

Horvath et al., 2002
Curr Opin Pediatr 14(5):583-7

Lezon A. Kimora et al., Ph.D.
Behaviors that can be associated with gastrointestinal disease...

- Crying
- Unexplained tantrums
- Night time wakening
- General irritability
- Vocalizing complaints
- Posturing
- Irritability just prior to bowel movement
- Hyperactivity and distractibility
- Self-injurious behavior

Summary of findings:

Physical visual cues for signs of potential gastrointestinal distress

- Posturing
- Bloated belly
- Tearing tissues
- Dry cracked lips

Consequences of increased intestinal permeability or intestinal dysbiosis if left untreated...

- Nutrients and vitamins aren’t absorbed properly—vitamin deficiencies
- Intestinal distress
- Food allergies are created
- Detoxification is compromised
- Bacteria and yeast can be mobilized
- Formation of antibodies you might not want—because of immune dysregulation

3. Allergy: Immune system function

- Normal immune system function, depends upon proper immune system responses
- The immune response is how your body recognizes and defends itself against bacteria, viruses, and substances that appear foreign and harmful to the body
- Protects and defends against foreign cells
- Memory gets smarter
- Responds appropriately
- Do no harm

Overview of the immune system

Acquired Immunity

White blood cells associated with acquired immune system are called lymphocytes—T Cells—B Cells

Normally, there is a balance between infection and immunity
However the balance can be altered . . . .

Lauren W. Underwood PhD

Jyonouchi et al., 2005
J Neuroinflammation 5:52

What can go wrong with the immune system?
1. Hypersensitivity
2. Autoimmunity
3. Inflammation
4. Allergy
5. Immune system dysregulation

Hypersensitivity, Autoimmunity & Inflammation

1. Hypersensitivity - an immune response that damages the body’s own tissues
   - undesirable (damaging, discomfort-producing and, in extreme cases, life-threatening)
   - reactions produced by the normal immune system

2. Autoimmunity - overactive immune responses
   - immune system fails to properly distinguish between self and non-self, and attacks part of the body

3. Inflammation - one of the first responses of the immune system to infection
   - symptoms of inflammation include redness and swelling, which are caused by increased blood flow into a tissue

4. Allergy
   - Allergy is a disorder of the immune system that is often referred to as “hypersensitivity” affecting parts of the body not in direct contact with the allergen
   - It may involve eczema (atopic dermatitis), allergic conjunctivitis, allergic rhinitis and asthma
   - There appears to be a strong hereditary component

5. Immune system dysregulation
   - Immune system dysregulation causes an abnormal immune response
   - There is a “shift or skewing” — lack of balance
   - The immune system loses the ability to respond appropriately . . . and when this happens, it is possible that the body develops abnormal responses to things it might not normally react to . . . like foods

Immune system response in the digestive tract

EVALUATION OF AN ASSOCIATION BETWEEN GASTROINTESTINAL SYMPTOMS AND CYTOKINE PRODUCTION AGAINST COMMON DIETARY PROTEINS IN CHILDREN WITH AUTOIMMUNE SPECTRUM DISORDERS

Prevalence of food allergy in children with autism spectrum disorders (ASD): A systematic review and meta-analysis

Jyonouchi et al., 2005
J Pediatrics 146(5): 605-610

Lauren W. Underwood PhD
What happens if the immune system is compromised

- Immune dysregulation
  - Abnormal balance and communication between immune cells
- Chronic Inflammation
  - An abnormal, persistent activation of immune cells in the tissues
- Autoimmune reactions
  - Antibodies targeting and causing injury to normal body tissues

Disorders in the immune system can cause disease

If there are immune system issues

- Increased infections, inflammation can affect attention and concentration
- Allergic reactions can cause pain, irritation and distraction

Physical signs reflecting issues associated with the immune system

- Signs of immune system distress
  - eczema
  - rashes
  - allergy

The immune system is closely connected to virtually every other system of the body.

Dietary changes/modifications and treatments in autism

- Signs of immune system distress
  - eczema
  - rashes
  - allergy

A Comparison of Eating Behaviors between Children with and without Autism

- Schreck et al., 2004
- J Autism Dev Disord 34(4):433-8

Lauren W. Underwood PhD

Dietary changes/modifications and treatments in autism

- Many autistic children suffer from inflammatory response/immune system dysregulation
- Many autistic children don’t/can’t digest their foods efficiently
- diet options: GF/CF, SCD, BED, LOD
- Pick one that works best for you and your family
- regardless of diet choice, it is important to ensure proper nutrition

Lauren W. Underwood PhD

Are special diets important and which one do I choose?

- Many autistic children suffer from inflammatory response/immune system dysregulation
- Many autistic children don’t/can’t digest their foods efficiently
- diet options: GF/CF, SCD, BED, LOD
- Pick one that works best for you and your family
- regardless of diet choice, it is important to ensure proper nutrition

Lauren W. Underwood PhD

Healthier Diet

- McCann et al., 2007
- Lancet 370(9598):1560-7

Lauren W. Underwood PhD
A gluten-free diet as an intervention for autism and associated spectrum disorders:
preliminary findings

Lauren W. Underwood PhD

Whitney et al., 1999 Autism 3(1):45-55

Autism

Casein/casomorphin and gluten/gliadorphin

Casein is a protein found in milk and products containing milk.
Casomorphin (or casomorphin) is a peptide derived from the milk protein casein.
Gluten and gluten-like proteins are found in wheat and other grains.
Gliadorphin (or gliadorphin) is a peptide derived from the wheat protein gluten.

Diet: Gluten-free Casein-free Diet

A restrictive diet that removes all food items that contain both gluten and casein.
The are two main theories currently present in scientific literature that explain why some people with autism and PDD respond positively to a GFCF diet:
1. Improperly broken down dietary peptides
2. Immune system dysregulation

Immune Response to Dietary Proteins, Glutathione, and Gliadorphin in Children with Autism

Immune activity:
- is dependent on specific cofactors and coenzymes (vitamins and minerals)
- can be inhibited by toxins, fungi, oxidative stress and malnutrition
- can be optimized with proper nutrition and elimination of lectins

Enzyme activity:
- Bacteria break down sugars
- Lipase breaks down fats
- Protease breaks down proteins

Treat with digestive enzymes

Enzyme activity:
- is dependent on specific cofactors and coenzymes (vitamins and minerals)
- can be inhibited by toxins, fungi, oxidative stress and malnutrition
- can be optimized with proper nutrition and elimination of lectins

Enzyme function:
- Saccharidase breaks down sugars
- Lipase breaks down fats
- Protease breaks down proteins

Lauren W. Underwood PhD

Brudnicki et al., 2003, Treatment Letters for Doctors and Patients 104-107

Beneficial Effects of Enzyme-based Therapy for Autism Spectrum Disorders

Lauren W. Underwood PhD

Vojdani et al., 2004 Nutrition 17(3):151-61

Whiteley et al., 2004 Autism 8(1):45-55

Genuis and Bouchard 2010 J Child Neurol 25(1): 114-119

Lauren W. Underwood PhD
2. Immune system dysregulation

- Immune system loses its ability to respond properly
- Body develops abnormal responses to things it might not normally react to
- An abnormal immune response can result in:
  - Allergy
  - Inflammation
  - Hypersensitivity
  - Autoimmunity

Food allergy vs. Food intolerance

- **Food allergies**
  - An immune system response... to foods
  - Body mistakes a protein in foods as harmful, and creates a defense against it (antibody)

- **Food intolerances**
  - Digestive system response to foods
  - Not an immune system response
  - Something in food irritates digestive system or person is unable to breakdown digested food

Symptoms associated with abdominal pain...

- Crying
- Unexplained tantrums
- Night time wakening
- General irritability
- Vocalizing complaints
- Posturing
- Irritability just prior to bowel movement
- Hyperactivity and distractibility
- Self injurious behavior

Nutritional Supplementation
**Why nutritional supplementation?**

- **Nutritional deficiency**
  - Results in a lack of one or more nutrients obtained from food essential for normal cell and body function
  - **cause**
    - Malabsorption/poor absorption in the small intestine
    - Unhealthy eating
    - Self-imposed/imposed dietary restrictions
    - Poor utilization of nutrients because of genetic or environmental factors

- **Oxidative Stress**
  - Imbalance between the production and manifestation of reactive oxygen species and a biological system's ability to readily detoxify the reactive intermediates or to repair the resulting damage.

**There are nutritional deficiencies associated with disease**

- Rickets: vitamin D deficiency
- Scurvy: vitamin C deficiency
- Beriberi: thiamine deficiency
- Pellagra: niacin deficiency
- Goiter: iodine deficiency

**Commonly deficient nutrients**

- Vitamin B12
- Vitamin B6
- Folate or folic acid
- Vitamin A
- Vitamin D
- Zinc
- Magnesium
- Omega 3 fatty acids

**Signs and symptoms associated with nutritional deficiency**

- Neurological symptoms
- Memory loss
- Psychosis
- Bruising
- Confusion
- Impaired learning
- Growth retardation
- Loss of appetite
- Poor immune function

**Oxidative Stress**

- Caused by an imbalance between the production of reactive oxygen species (ROS), like free radicals, and a biological system's ability to readily detoxify the reactive intermediates or easily repair the resulting damage.

- Damaging byproducts can impose stress upon the cells, and affect normal cell function, causing oxidative stress.

- Oxidative stress is involved in many diseases.

- Can give antioxidants to counteract effects of oxidative stress upon the cell.
Oxidative stress can affect all systems of the body

Nutritional supplementation to combat oxidative stress
- Vitamin E
- Vitamin C
- Zinc
- Selenium
- Vitamin B6 or its activated form, pyridoxal-5-phosphate (PLP), with Magnesium

Sleep

A happier, healthier child is going to be more responsive to behavioral, social, and sensory interventions

Detoxification


Lauren W. Underwood PhD

Metabolic biomarkers of increased oxidative stress and impaired detoxification capacity in children with autism

James et al., 2004 Am J Clin Nutr 80(6):1611-1617

Lauren W. Underwood PhD

Schreck et al., 2004 Res Dev Disabil 25(1):57-66

Anderson et al., 2008 J Child Neurol 23: 482-485

Lauren W. Underwood PhD

Original article

Melatonin for Insomnia in Children With Autism Spectrum Disorders

Lauren W. Underwood PhD
What we do know now

- In 2001, the Institute of Medicine (IOM) determined that such a relationship between thimerosal and neurodevelopmental disorders is biologically plausible, but that not enough evidence exists to support or reject this hypothesis.
- Thimerosal neurotoxicity is associated with glutathione depletion — James et al., 2005.
- Recent work by Dr. Mark Geier and David Geier have shown strong epidemiological evidence for a causal relationship between thimerosal and neurodevelopmental disorders in children — Geier and Geier, 2007.

We live in a toxic world

Why detoxification?

- To prevent injury to the cells and ultimately cell death.
- Cell injury and cell death is bad.
- In autism, toxins may be a cause of the neurological and immune dysfunction.
- Detoxification may help the cells to recover which will enable for healing.
- If toxins accumulate too rapidly, without being safely eliminated, they can cause damaging effects upon cells and tissues of the body.

How does your body detoxify?

- Designed to remove/eliminate toxic substances from the body.
- Primary function of liver and kidney.
- Glutathione. Once toxins are bound they are eliminated via bile and urine.
- Can also be achieved via artificial (chelation) or supplementary (sauna) means...

The liver & detoxification

- Designed to remove toxic matter from the bloodstream.
- Produces bile.
- Metabolizes proteins and fats.

The liver & detoxification

Nutrients that support detoxification

- If detoxification systems are overloaded, destruction of nutrients necessary for proper detoxification occurs.
- If detoxification pathways are overloaded, build up of toxins can occur.
- If transsulfuration is disrupted, there is less antioxidant production, and oxidative stress can occur.
If you don’t detoxify, a vicious cycle of toxic overload perpetuates

- Heavy metal exposure, environmental toxins, foreign proteins
- Detoxification problems
- GI distress
- Allergy
- Immune problems
- Infections
- Treat with antibiotics, steroids, antifungals

Detoxification biochemistry

- Methylation and sulfation
  - A healthy body’s way to rid itself of toxic substances
  - Methylation: transferring a methyl group
  - Transulfation: responsible for production of glutathione, the body’s number one antioxidant

- Children with autistic spectrum disorders often need supplements to provide them with the raw materials their bodies need to efficiently carry out methylation and sulfation

Methionine/Thiol Transsulfuration Pathway

- Sulfate
- Methionine
- Cysteine
- Glutathione (GSH)

Methionine/Glutathione Transsulfuration Pathway

- Critical to the body’s ability to remove toxins!

If detoxification problems compile...

- Build up of toxins can build up in the body, which leads to increased oxidative stress.
- Oxidative stress affects systems of the body—symptoms develop—affect attention.
- Additional health problems can develop.

Association of MTHFR Gene Variants with Autism

- If essential nutrients for biochemical pathways and maximum metabolism are not available for proper cell function—can affect all systems of the body.

Reduced GSH production

- Oxidative stress affects systems of the body—symptoms develop—affect attention.
- Additional health problems can develop.
If biochemical pathways compromised

– Neurotransmission can be under or over stimulated

Physical signs associated with detoxification issues

+ Signs of detoxification issues
  - sleep issues
  - hyperactivity
  - Lethargy
  - aggression

How do you implement a detoxification program?

+ Should be done under the direction of an experienced physician or other practitioner
+ Support the body’s own detoxification system—nutrients,
  – Methyl B12
  – Glutathione
  – DMG/TMG
+ Removes accessible toxins—detoxification via chelation
+ Monitor closely

Maximize metabolism: normalize biochemical pathways

HBOT-Hyperbaric Oxygen Therapy

Effective way to get more oxygen into the body at the cellular level by using pressurized air chambers

+ healing the gut and brain inflammation (two that may be separate issues or experienced simultaneously)
+ blood flow to key areas of the brain
+ dealing with gut parasites, yeast or bacteria
+ or if it helps all four areas

Immune globulin therapy

+ Immune globulins are – produced by B-cells and are also known as antibodies
  – naturally occurring in the blood plasma serum of healthy individuals
  – neutralize and mark pathogens for antibody recognition
+ There are 5 classes of immune globulins/antibodies
  – IgG: most prevalent, found in all body fluids
  – IgM: first type of antibody made in response to an infection
  – IgA: produced in mucous membranes and found in secretions
  – IgE: responsible for allergic reactions and antibodies binding to allergens produce inflammatory substances (histamine)
  – IgD: may be involved in cell differentiation; how they work is unclear

Immune globulin therapy

+ Administration routes of immune globulin therapy
  – Intramuscular (IMIG)
  – Subcutaneous (SCIG)
  – Intravenous (IVIG)
+ FDA Approved Indications
  – Primary immune deficiency
  – Malignant Thrombotic Thrombocytopenia Purpura
  – Kawasaki Disease
  – Recurrent Lymphomatoid Granulomatosis
  – HIV-Related Pneumonia
  – Bone Marrow Transplantation

Off label use of IVIG

+ Autism
+ Chronic fatigue syndrome
+ Chronic inflammatory demyelinating polyneuropathy (CIDP)
+ Clostridium difficile colitis
+ Dermatomyositis and polymyositis
+ Graves’ ophthalmopathy
+ Guillain-Barré syndrome
+ Kawasaki disease
+ Lyme disease
+ Muscular dystrophy
+ Multiple sclerosis
+ Myasthenia gravis
+ Neonatal alloimmune thrombocytopenia

Rossignol, D. 2007
BMC Pediatrics
7:36
Rossignol, et al., 2007
Med Hypoth
68
1208-1227

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+ Neonatal alloimmune thrombocytopenia

Rossignol, D. 2007
BMC Pediatrics
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Rossignol, et al., 2007
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1208-1227
What does immune globulin therapy have to do with autism?

- Some people believe that people with autistic spectrum disorders are susceptible to immune deficiencies and that these deficiencies may produce some of the symptoms of autism.
- By injecting or swallowing immune globulin, an antibody used by the immune system to identify and neutralize foreign objects like bacteria and viruses, it is believed those abnormalities can be overcome and the symptoms of autism reduced.

IVIG side effects

- Usually well tolerated. Most adverse effects are mild and are usually related to the rate of infusion.
- It can cause kidney failure, especially in those with a history of kidney disease, diabetes, renal, plasma cell disease, or volume depletion, or in those taking medications that can cause kidney damage.
- IVIG may carry the risk of potentially fatal transmission of blood-borne pathogens (i.e. HIV, hepatitis, etc.). Pharmaceutical grade immune globulin is prepared commercially by separating immunoglobulin fractions from pooled human blood specimens. Several steps in the process are added to ensure that any live viruses or bacteria in the specimens are inactive, but there is still a risk.
- There is potentially an unknown risk of contracting variant Creutzfeldt-Jakob disease (vCJD).

Methyl B12-Methylcobalamin

- B12 (cobalamin) is a vitamin “family” with five unique compounds:
  - a) cyanocobalamin;
  - b) hydroxycobalamin;
  - c) adenosylcobalamin;
  - d) glutathionylcobalamin;
  - e) methylcobalamin.
- Out of the B12 family, only Methyl-B12 has the ability to activate the methionine/homocysteine biochemical pathway directly.
- It is this pathway that is responsible for the formation of homocysteine, the “crossroads” molecule that is responsible either to recycle back to methionine and SAMe or create cysteine, taurine, and glutathione.
- Glutathione is the body’s primary intracellular antioxidant and is responsible for many detoxification reactions.
- Methyl-B12 is closely allied with the folic acid biochemical pathway. A precursor folic acid molecule must interact with the enzyme MTHFR (methylenetetrahydrofolic acid) to become 5-methyltetrahydrofolic acid, the molecule that donates its methyl group to B12 so it can become Methyl-B12.

Paradigm switch

- Autism is not a psychological condition—it is a neuro-gastro-immunological disorder resulting from a genetic susceptibility and an environmental insult.
The abnormal metabolic profile in children with autism is consistent with the abnormal genetic profile and strengthens the hypothesis that may predispose these children genetic susceptibility to oxidative stress and reduced methylation capacity to neurological, immunological, and gastrointestinal dysfunction that occurs with autism—Dr. Jill James


Lauren W. Underwood PhD


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Theoharides et al., 2009. Expert Opin Pharmacother. 10(13):2127-2143

Lauren W. Underwood PhD

Deth et al., 2008. Neurotoxicology. 29:190-201

Lauren W. Underwood PhD

A new paradigm in autism

- Autism is an environmental illness with a genetic component
- It is a complex metabolic disease, not just a developmental disability
- Autism is treatable, but . . .
- We must continue fighting for a cure!

What you can do now . . .

1. Initiate early intervention
2. Improve diet
3. Remove gluten and casein from the diet
4. Introduce supplements, one at a time
5. Stabilize intestinal dysbiosis
6. Consider advanced biomedical intervention,
   - HBOT
   - IVIG
   - methyl B12

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