The Great Plains Laboratory, LLC

Clostridia Detection by Organic Acids Test

Why the GPL Organic Acids Test is Superior to Stool Tests for Detecting Clostridia

Continued research at The Great Plains Laboratory (GPL) has resulted in new information on several Clostridia bacteria markers that are now included in the urine organic acids test. These markers include 3-(3-hydroxyphenyl)-3-hydroxypropionic acid (HPHPA), 4-cresol, 4-hydroxyphenylacetic acid, and 3-indoleacetic acid. With this new information, The Great Plains Laboratory urine organic acids test now provides information not available in common stool tests for Clostridia bacteria that are involved in gastrointestinal diseases and neuropsychiatric disorders.

Benefits of Organic Acids Testing for Clostridia

Organic Acids Test	Stool Test
The Organic Acids Test has a quantitative marker for *C. difficile* on every test.	Many stool tests only test total Clostridia species. *C. difficile* testing is an additional cost.
The Organic Acids Test has markers for 3 other species of Clostridia bacteria that produce toxic compounds, that alter neurotransmitter metabolism.	No stool test for total Clostridia provides differentiation of beneficial and harmful Clostridia species.
The Organic Acids Test assesses the inhibitory effect of Clostridia metabolites on the key enzyme dopamine beta-hydroxylase that converts dopamine to norepinephrine.	No stool test evaluates effect of Clostridia on neurotransmitters.
The Organic Acids Test on urine is much easier to collect than stool.	All stool tests are considered messy, unsanitary, and unpleasant to collect.
The Organic Acids Test includes the marker, HPHPA, for pathogenic Clostridia species.	Stool tests do not detect these specific Clostridia species.

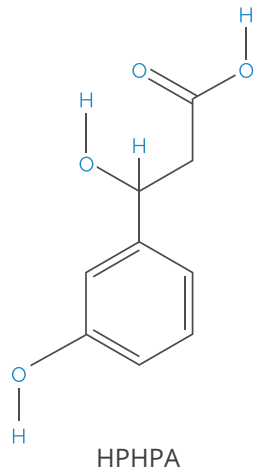
Disorders with Elevated HPHPA and/or 4-Cresol

- Autism and Pervasive Developmental Disorder
- Obsessive Compulsive Disorder
- Bipolar Depression
- Chronic Fatigue Syndrome
- Depression
- Arthritis
- Attention Deficit Disorder
- Seizure Disorder
- Ulcerative Colitis
- Tourette's Syndrome
- Parkinson's Disease
- Alzheimer's Disease
- Schizophrenia
- Anorexia
- Tic Disorders
- Anxiety
- Psychosis
- Irritable Bowel Syndrome

Toxic Metabolites of Clostridia Bacteria

HPHPA (3-(3-hydroxyphenyl)-3-hydroxypropionic acid)

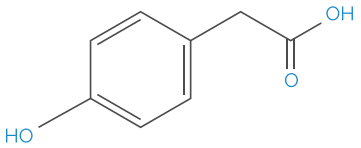
The primary Clostridia species which produce HPHPA include *C. botulinum, C. sporogenes,* and *C. caloritolerans. C. botulinum* is a Gram-positive, rod-shaped, anaerobic, spore-forming, motile bacterium with the ability to produce the neurotoxin botulinum. Symptoms of botulism include weakness, impaired vision, fatigue, and difficulty with speech. These may then be followed by weakness of the arms, chest muscles and legs. In food borne botulism, symptoms generally begin 18 to 36 hours after eating a contaminated food, but they can occur as early as 6 hours or as late as 10 days. *C. sporogenes* is virtually identical to *C. botulinum* except it is lacking the gene for the botulinum neurotoxin. Like *C. botulinum*, it is an anaerobic Gram-positive, rod-shaped bacterium that produces oval, subterminal endospores and is commonly found in soil. *C. caloritolerans* is named after the fact that it is extremely heat (calor) resistant (tolerans). It can survive at the water temperature boiling point for 8 hours; its extreme resistance to heat may allow transmission even in well-cooked food.



HPHPA
3-(3-hydroxyphenyl)-3-hydroxypropionic acid

4-Hydroxyphenylacetic Acid

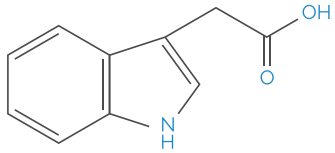
High 4-hydroxyphenylacetic acid may be associated with small intestinal bacteria overgrowth (SIBO) due to its production by *C. difficile, C. stricklandii, C. lituseburense, C. subterminale, C. putrefaciens,* and *C. propionicum. C. difficile* can be distinguished from the other species by its production of 4-cresol. No other Clostridia species produce 4-cresol. Elevated values of 4-hydroxyphenylacetic acid are common in celiac disease and cystic fibrosis and have been reported as elevated in jejuna web, transient lactose intolerance, Giardia infection, ileal resection, ileo-colic intersusseception, septicemia, and projectile vomiting. Elevations of 4-hydroxyphenylacetic acid in celiac disease and cystic fibrosis are common enough to suggest that these Clostridia bacteria may play a role in these illnesses.



4-Hydroxyphenylacectic Acid

3-Indoleacetic Acid

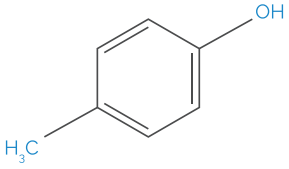
High 3- indoleacetic acid in urine is a tryptophan byproduct of *C. stricklandii, C. lituseburense, C. subterminale,* and *C. putrefaciens*. No information is available on the pathogenicity of these species producing indoleacetic acid. However, very high amounts of this metabolite derived from tryptophan might indicate a depletion of tryptophan needed for other physiological functions.



3-Indoleacetic Acid

4-Cresol

4-Cresol is predominantly produced by *C. difficile*, a pathogenic bacteria, that is one of the most common pathogens spread in hospitals and nursing homes. Toxin-producing strains of *C. difficile* can cause illness ranging from mild or moderate diarrhea to pseudomembranous colitis, which can lead to toxic dilatation of the colon (megacolon), sepsis, and death. 4-cresol (para-cresol) has been used as a specific marker for *C. difficile*. It is classified as a toxic agent and can cause rapid circulatory collapse and death in humans. Intestinal production of 4-cresol may be responsible for growth-suppressing effect in animals. Signs of acute toxicity in animals typically include hypoactivity, salivation, tremors and convulsions. High amounts of 4-cresol have been found in the urine of patients with Autism.



4-Cresol

How Clostridia Metabolites Inhibit Key Neurotransmitters in the Brain and Peripheral Nervous System

The combined metabolic pathway for production of human neurotransmitters in the brain, adrenal gland, and sympathetic nervous system is outlined in Figure 1 on the back page, along with the production of Clostridia bacterial substances that alter the this pathway. The key starting material for both human and Clostridia pathways is the amino acid phenylalanine.

In humans, phenylalanine and/or tyrosine from dietary proteins or amino acid supplements are absorbed into blood from the intestinal tract where these amino acids cross the blood-brain barrier and enter the brain. Phenylalanine in the brain is converted to tyrosine by phenylalanine hydroxylase. The ring of tyrosine is then hydroxylated to dihydroxyphenylalanine (DOPA) by tyrosine hydroxylase. DOPA is then converted to dopamine by DOPA decarboxylase which requires a vitamin B6 cofactor. The fate of further dopamine metabolism depends on the neuron type. In dopamine-secreting neurons, dopamine is the final product. In these neurons, dopamine is metabolized into homovanillic acid which can be measured in the urine organic acid test. In norepinephrine-containing brain neurons, neurons in the peripheral central nervous system, and in the adrenal gland, dopamine is converted to norepinephrine by dopamine-beta-hydroxylase. Dopamine-beta-hydroxylase requires ascorbic acid and copper as cofactors. In the adrenal gland, norepinephrine is further converted to epinephrine. Both epinephrine and norepinephrine may then be metabolized into vanillylmandelic acid (VMA).

In the species of Clostridia bacteria mentioned at the beginning of the article, phenylalanine is converted to HPHPA by a pathway that requires both human and bacterial enzymes. If *Clostridia difficile* is present, tyrosine is largely converted to 4-cresol. These byproducts are then absorbed into the body through the intestinal tract where they have the ability to inhibit dopamine-beta-hydroxylase. These byproducts covalently bind to the enzyme active site, irreversibly inhibiting conversion of dopamine to norepinephrine.

Interaction Between Clostridia Markers and Neurotransmitters

The Great Plains Laboratory Organic Acids Test is very sensitive and can differentiate between harmful and beneficial bacteria, which is is unique among tests for Clostridia. It is also the only organic acids test available that measures HPHPA, one of the primary toxic metabolites of Clostridia. In the sample results below, the patient has a high level of HPHPA, but a low level of 4-Cresol, the main marker for *C. difficile*. Other tests that only measure 4-Cresol, and not HPHPA, would have missed this harmful bacterial overgrowth.

Clostridia Bacteria Markers

15	4-Hydroxyphenylacetic *(C. difficile, C. stricklandii, C. lituseburense & others)*	≤	19	H	20	20
16	HPHPA *(C. sporogenes, C. caloritolerans, C. botulinum & others)*	≤	208	H	275	275
17	4-Cresol *(C. difficile)*	≤	75		15	15
18	3-Indoleacetic *(C. stricklandii, C. lituseburense, C. subterminale & others)*	≤	11		5.7	5.7

Another benefit to The Great Plains Laboratory Organic Acids Test is that it evaluates Clostridia metabolites that can inhibit metabolism of important neurotransmitters. As shown in the sample results below, the test measures Homovanillic Acid (HVA), a metabolite of dopamine, as well as vanillylmandelic acid (VMA), a metabolite of norepinephrine and epinephrine. Clostridia bacteria can produce toxins that may inhibit the conversion of dopamine to norepinephrine. This can lead to a buildup of dopamine and a disruption in the dopamine to norepinephrine ratios. By assessing these metabolites, the Organic Acids Test is able to better determine the possible underlying cause of many different conditions.

Neurotransmitter Markers

33	Homovanillic (HVA) *(dopamine)*	0.80	-	3.6	H	14	14
34	Vanillylmandelic (VMA) *(norepinephrine, epinephrine)*	0.46	-	3.7		1.2	1.2
35	HVA / VMA Ratio	0.16	-	1.8	H	12	12

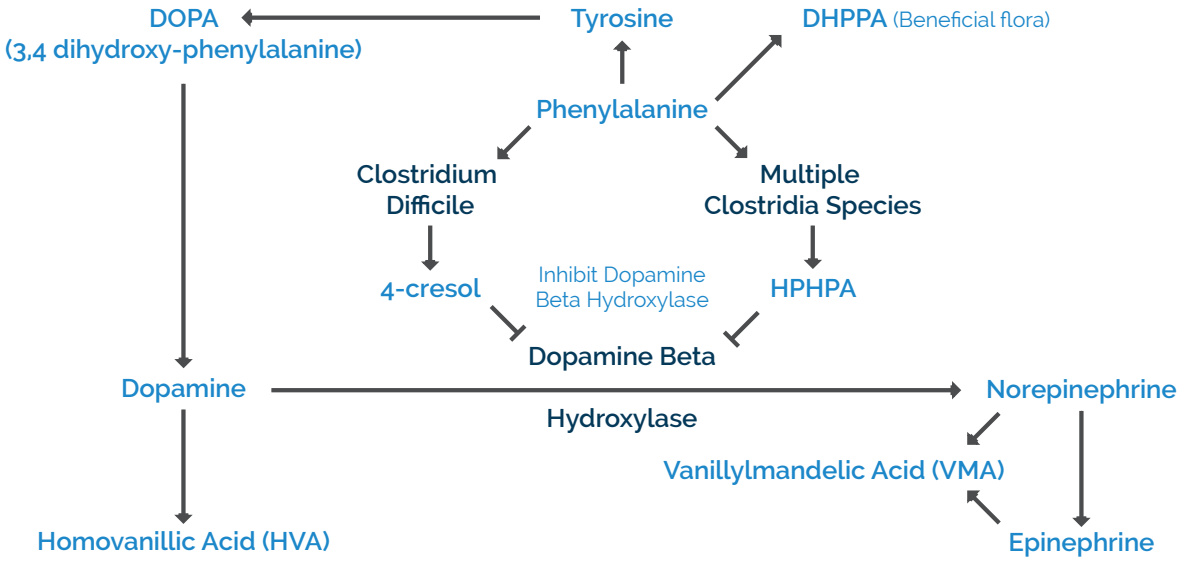


Figure 1. Combined Human and Clostridia Metabolic Effects on Neurotransmitters

More About the Organic Acids Test

The Organic Acids Test (OAT) offers a comprehensive snapshot of many crucial metabolic processes. Besides offering a thorough assessment of intestinal yeast and bacteria, it also provides information about Krebs cycle functionality, neurotransmitter levels, nutritional markers, glutathione status, and oxalate metabolism. The test offers a total of 76 urinary metabolite markers that can reveal underlying causes of chronic health conditions including mental health disorders, autoimmune diseases, ADHD, Autism, and other illnesses. This reliable test detects the overgrowth of yeast and toxigenic Clostridia bacteria, commonly missed by conventional culture methods. These organisms and their metabolites can produce or magnify symptoms of many disorders. Once abnormalities are detected, a variety of options are available for treatment. Treatments include antifungal or antibacterial products, probiotic supplementation, vitamins, antioxidants and dietary modification. Patients and physicians have reported significant improvement after treatment, including decreased fatigue, regular bowel movements, increased energy and alertness, increased concentration, improved verbal skills, less hyperactivity, better sleep patterns, and less abdominal pain.

Possible Treatments for Clostridia

The oral antibiotics metronidazole and vancomycin are very effective in treating the growing vegetative cells of Clostridia, but are ineffective against spores. Pulsing protocols that include a waiting period without antibiotic treatment allow antibiotic resistant spores to revert to their antibiotic-susceptible vegetative forms. Use of these pulsing protocols markedly reduces the recurrence rate for Clostridia. Probiotics have been effective in conjunction with high doses of vancomycin or metronidazole. Several strains of Lactobacilli have proven effective for recurring *Clostridium difficile* infections, including *Lactobacillus rhamnosus GG* (the main probiotic bacteria in Culturelle®), as well as *Saccharomyces boulardii*, a beneficial strain of yeast.

Saccaromyces boulardii is a beneficial and non-colonizing yeast (not related to the Candida species) that can be helpful in supporting the microflora of the gastrointestinal tract. *Saccaromyces boulardii* has over 3 billion CFU's per capsule. Research studies have indicated that *S. boulardii* may work by modulating the body's immune response, helping to improve resistance to harmful bacteria. *S. bouldardii* can be effectively taken with other probiotic strains, but should not be taken within 2 hours of a prescription or natural anti-fungal, such as Nystatin, Diflucan, grapefruit seed extract, and oregano oil.

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