The Great Plains Laboratory, Inc.
William Shaw, Ph.D Director 11813 W. 77th Street, Lenexa, KS 66214 (913) 341-8949 Fax (913) 341-6207

Clinical Significance of the Organic Acids Test

Yeast/Fungal Metabolites

Citramalic (methylmalic) acid – Citramalic acid is a byproduct of *Saccharomyces* yeast species as well as *Propionibacterium acnes*. This metabolite was not found in the culture media of a wide number of other anaerobic bacteria isolated from stool samples. Thus, an increase in citramalic acid may indicate *Propionibacteria* overgrowth rather than a yeast overgrowth of the intestinal tract. Citramalic acid is a chemical relative (analog) of the Krebs cycle compound malic acid. Presumably, this compound may interfere with the production of malic acid in the Krebs cycle.

5-hydroxymethyl-2-furoic acid – A substituted furan that is a byproduct of the fungus *Aspergillus* and probably other species of fungi and yeast as well.

3-oxoglutaric acid – A chemical relative (analog) of the Krebs cycle compound 2-oxoglutaric (alpha-ketoglutaric) acid. Presumably, this compound is a byproduct of the amino acids lysine and tryptophan. The highest value was found in a child with a severely malformed brain. Slightly elevated values are found in autism and other disorders. 2-oxoglutaric, the normal Krebs cycle metabolite may be low when 3-oxoglutaric is elevated, possibly indicating an interference with 3-oxoglutaric acid in the Krebs cycle.

Furan-2,5-dicarboxylic acid – A substituted furan that is a byproduct of the fungus *Aspergillus* and probably other species of fungi and yeast as well.

Furancarbonylglycine – A conjugate of furancarboxylic acid and the amino acid glycine.

Tartaric (hydroxymalic acid) – Tartaric acid is a toxic metabolite of *Saccharomyces* yeast species, the same species of yeast that is used in baking and brewing industries. *Saccharomyces* species may be important organisms in the immunocompromised person. The fungal origin of this compound was confirmed by showing this compound decreased dramatically in the urine after the use of antifungal drugs. Tartaric acid is also found in grapes, grape products, and as a food additive. Cream of tartar, used in baking, is basically tartaric acid.

Arabinose – Arabinose (a five carbon sugar or pentose) is not produced directly by yeast. A closely related sugar derivative called arabitol is produced by *Candida* species, including *Candida albicans*, *Candida tropicalis*, and *Candida parapsilosis*. Arabitol produced in the gastrointestinal tract is absorbed into the portal circulation, converted to arabinose by the liver, and then released into the circulation. Since arabinose is also a major sugar in apples, grapes, and pears, these fruits and their products must be avoided 24 hours prior to urine collection to avoid interfering with the test.

Carboxycitric – A chemical relative (analog) of the Krebs cycle compound citric acid. This compound may interfere with the metabolism of citric acid in the Krebs cycle (also called citric acid cycle).

Bacterial Metabolites

2-hydroxyphenylacetic acid – A metabolite of tyrosine produced by overgrowth of several species of bacteria in the GI tract.

4-hydroxyphenylacetic acid – Also a metabolite of tyrosine, the bacterial origin of this compound was confirmed by finding this compound decreased significantly in urine after the use of the antibiotic neomycin. Very elevated values for these compounds are present in celiac disease (gluten sensitivity), enteritis, and intestinal resection.

HPHPA, 3- (3-hydroxyphenyl)-3-hydroxypropionic acid - This is a compound produced by *Clostridia* species, including *Clostridium difficile*. There are approximately 100 species of *Clostridia* in the gastrointestinal tract so this marker is NOT specific for *Clostridium difficile*. Elevated values are common in autism, depression, schizophrenia, seizures, and chronic fatigue syndrome. This compound is reduced by treatment with vancomycin, Flagyl (metronidazole), an herbal product called Biocidin (www.biobotanicalresearch.com), and probiotics.

VMA analog – Derivatives of the amino acid tyrosine produced by species of the *Clostridia* genus. This byproduct may be important for two reasons: first, dietary tyrosine, which is the raw material for the production of the neurotransmitters dopamine and norepinephrine, may be diverted into the production of these microbial compounds so that there is not enough tyrosine available for neurotransmitters; second, these compounds may act as inhibitors of neurotransmitter production or metabolism. Elevated values are common in autism, depression, schizophrenia, seizures, and chronic fatigue syndrome. This compound is reduced by treatment with vancomycin, Flagyl (metronidazole), an herbal product called Biocidin, and probiotics.

Oxalate Related

Glyceric acid – Values greater than 150 mmol/mol creatinine may be due to microbial sources such as yeast or dietary sources containing glycerol.

Glycolic acid – Elevated glycolic acid may be due to the genetic disease hyperoxaluria type I, if oxalic acid is also elevated. Elevated glycolic without elevated oxalic most likely results from GI yeast overgrowth.

Oxalic acid – Elevated values may be due to primary hyperoxaluria, diabetes mellitus, cirrhosis, vitamin B6 deficiency, sarcoidosis, steatorrhea due to pancreatic insufficiency, celiac disease, bacteria overgrowth, ileal resection, biliary tract disease, small bowel disease, ethylene glycol poisoning, increased intake of foods high in oxalate including rhubarb, spinach, raspberries, and peanuts, and increased vitamin C intake. Hyperoxalurias are genetic diseases; hyperoxaluria type I is associated with elevated glycolic acid while hyperoxaluria type II is associated with elevated glyceric acid.

Glycolysis Intermediates

Lactic and pyruvic acid – Elevated values (100-500 mmol/mol creatinine) may indicate infection, recent vigorous exercise, vitamin B deficiency, poor perfusion, or intestinal bacterial overgrowth.

Lactic and pyruvic acid – Extremely elevated values (500–100,000 mmol/mol creatinine) indicate genetic disease such as pyruvate dehydrogenase deficiency, glycogen storage diseases, and disorders of fructose metabolism, severe trauma, or life-threatening infections.

2-hydroxybutyric acid – Slightly elevated values may indicate infection, recent vigorous exercise, B vitamin deficiency, or poor perfusion.

2-hydroxybutyric acid – Significantly elevated values (> 25 mmol/mol creatinine) may indicate genetic disease such as pyruvate dehydrogenase deficiency, glycogen storage disease, or disorders of fructose metabolism, or may be the result of severe trauma or life-threatening infections.

Krebs Cycle Intermediates

Succinic acid – A Krebs cycle compound that may be elevated due to a deficiency in riboflavin or coenzyme Q10. Values greater than 50 mmol/mol creatinine may indicate genetic disease. High values may also be due to bacterial conversion of glutamine to succinic acid in the gastrointestinal tract.

Fumaric acid – A Krebs cycle compound produced by the dehydrogenation of succinic acid by the enzyme succinic acid dehydrogenase.

2-oxoglutaric acid – A Krebs cycle compound that is also called alpha-ketoglutaric acid (AKG). 2-oxoglutaric acid may be derived from the conversion of glutamic acid to 2-oxoglutaric by deamination or transamination. Very low values may sometimes be encountered in chronic fatigue syndrome. Anecdotal reports indicate that autistic symptoms sometimes improve with AKG supplementation in response to low values of this metabolite.

Aconitic and citric acid – These Krebs cycle compounds may be elevated as a result of a deficiency in glutathione since the enzyme aconitase requires reduced glutathione to metabolize aconitic to citric acid.

Neurotransmitter Metabolites

HVA (homovanillic acid) – A metabolite of the neurotransmitter dopamine. Elevated values are encountered in the tumors neuroblastoma, ganglioblastoma, and pheochromacytoma. Values may also be elevated due to L-DOPA administration or after IV dopamine drips.

VMA (vanillylmandelic acid) – Elevated values are found in the tumors pheochromacytoma, neuroblastoma, ganglioneuroma, and carcinoid tumors. May be elevated after administration of the catecholamine L-DOPA.

5-hydroxyindoleacetic acid – A metabolite of tryptophan that is commonly elevated in carcinoid syndrome, celiac sprue, tropical sprue, Whipple's disease, oat cell carcinoma of the bronchus, and bronchial adenoma of carcinoid type. May be elevated due to intake of foods high in hydroxyindoles such as walnuts, bananas, avocados, eggplants, pineapples, plums, and tomatoes. Low values may be found in depressive illnesses, small intestine resection, mastocytosis, PKU, and Hartnup's disease.

Pyrimidines

Uracil – A pyrimidine (DNA building block) that is elevated in the genetic disease dihydropyrimidine dehydrogenase deficiency. In this genetic disease, the pyrimidine thymine is also elevated. Elevations of uracil and orotic acid are found in the genetic diseases OTC (ornithine transcarbamylase) deficiency and citrullinemia.

Thymine – Thymine is a pyrimidine (DNA building block) that is elevated in the genetic disease dihydropyrimidine dehydrogenase deficiency. In this genetic disease, the pyrimidine uracil is also elevated.

Fatty Acid Metabolites

3-hydroxybutyric and acetoacetic acid– Ketones derived from excessive fatty acid oxidation may be elevated due to fasting or starvation, diabetes mellitus, use of high fat (ketogenic) diets, and several genetic diseases.

Ethylmalonic, methylsuccinic, adipic, suberic, and sebacic acid – These are fatty acid metabolites. Values may be elevated in ketosis, fasting, deficiency of the fat-transporting molecule carnitine, genetic deficiencies of fatty acid metabolism, and the genetic disease multiple acyl dehydrogenase deficiency, excessive intake of adipic acid containing foods such as Jell-O, and by increased intake of foods containing medium chain triglycerides (MCT) such as coconut oil. Isolated high values of adipic acid only may be found in patients with ADD, lethargy, and seizures.

Toxic Indicators

Pyroglutamic acid – Pyroglutamic (oxoproline) is a metabolite of the antioxidant gluthathione and is extremely elevated in the genetic disease pyroglutamic acidurea and following the use of the antibiotics flucloxacillin and netelmicin. Low values may be found due to glutathione depletion following oxidative stress or after exposure to toxic solvents or pesticides such as chloroform, DDT, or polybrominated biphenyls (PBBs) and polychlorinatned biphenyls (PCBs). Supplementation with glutathione and N-acetyl cysteine are useful to replenish glutathione.

Orotic acid – Elevated orotic is most commonly associated with ammonia toxicity. When ammonia is elevated, it is biochemically converted to carbamyl phosphate and then to orotic acid. Elevated ammonia may occur due to liver toxicity, viral liver infection, GI bleeding, portal systemic shunting of blood, drug toxicity, Reye's syndrome, as well as inborn errors of ammonia metabolism. Elevated orotic acid may also be found in leukemias and lymphomas, possibly due to the increased production of pyrimidines.

Hydroxyhippuric acid – A conjugate of the amino acid glycine and hydroxybenzoic acid (salicylic acid). Elevated values may be due to the use of aspirin (salicylates) or due to the growth of GI bacteria producing salicylates. Also increased after the ingestion of the artificial sweetener aspartame (Nutrasweet).

Vitamin Indicators and Metabolites

Methylmalonic acid – Values over 150 mmol/mol creatinine may be due to the genetic disease methylmalonic aciduria. Moderate increases may be due to vitamin B12 deficiency, defective B12 absorption, or bacterial overgrowth of the GI tract that consumes vitamin B12.

Ascorbic acid – Vitamin C, an important antioxidant, with low values may indicate dietary deficiency (scurvy). Vitamin C is also frequently low in chronic fatigue syndrome. High values are usually of no concern except that in individuals with bacteria overgrowth of the GI tract, ascorbic acid may be converted to oxalic acid, which can lead to kidney stones. There is a low probability that elevated vitamin C will cause kidney stones if oxalic acid is in the normal range.

Kynurenic acid – Kynurenic acid is a tryptophan metabolite that may be elevated in vitamin B6 deficiency or due to excessive tryptophan uptake. The reaction by which kynurenine is converted to hydroxyanthranilate is catalyzed by an enzyme requiring vitamin B6. Thus, elevations of kynurenic acid may indicate a vitamin B6 deficiency. High values in individuals with the yeast overgrowth syndrome may be due to yeast interference.

Methylcitric acid – High levels of methylcitric acid indicate biotin deficiency and/or an inborn error of metabolism affecting biotin pathways. Low values of methylcitric acid have no known significance.

Pyridoxic acid – Pyridoxic acid is the main urinary metabolite of pyridoxine (Vitamin B6) and is a measure of recent dietary intake. Low values of pyridoxic acid in the urine indicate low recent intake while high values indicate high recent dietary intake.

Pantothenic acid – Urinary excretion of pantothenic acid (Vitamin B5) reflects dietary intake. High values are not necessarily undesirable. Individuals may have a much higher requirement than usual for this cofactor.

Amino Acid Metabolites

2-hydroxyisovaleric, 2-oxoisovaleric, 3-methyl-2-oxovaleric, hydroxyisocaproic, and 2-oxoisocaproic acid – Elevated values are associated with the genetic diseases maple syrup urine disease (MSUD) or pyruvate dehydrogenase deficiency. Slight elevations may be due to deficiencies of the vitamins thiamine or lipoic acid.

2-oxo-4-methiolbutyric acid – Elevated in the genetic disease methioninemia.

Mandelic, phenyllactic, and phenylpyruvic acid – Elevated in the genetic diseases PKU and tyrosinemia. Slight elevations may result from increased dietary intake of phenylalanine.

Homogentisic acid – Elevated in the genetic disease homogentisic aciduria (alkaptonuria).

4-hydroxyphenyllactic acid – Significantly elevated in the genetic diseases tyrosinemia and in phenylketonuria. Slight increase may be due to increased tyrosine intake.

3-indoleacetic acid – A metabolite of the amino acid tryptophan. Values greater than 200 mmol/mol creatinine may be found in Hartnup's disease, a genetic neurological disease due to defective renal and intestinal transport of certain neutral amino acids. Elevations of lesser magnitude appear to be of bacterial origin.

Miscellaneous

Glutaric acid – Elevated in the genetic diseases glutaric acidemia types I and II. Moderate increases may be to deficiencies in riboflavin and coenzyme Q10, or celiac disease. Moderate increases are common in autism possibly due to defective vitamin absorption or microbial production in the GI tract.

N-acetyl aspartic acid – High values are due to the genetic disease Carnavan's disease, a potentially fatal disease causing spongy degeneration of the brain.

3-hydroxy-3-methylglutaric (HMG) acid – HMG is a precursor in the production of cholesterol in both humans and yeast. Moderate increases as high as 300 mmol/mol creatinine are probably due to yeast overgrowth of the GI tract and might also implicate yeast overgrowth with elevated serum cholesterol. Both yeast and humans produce these same compounds as precursors of steroid hormones. Values from 200 – 11,000 mmol/mol creatinine are found in the genetic disease 3-hydroxy-3-metylglutaric aciduria.

Malonic acid – Elevated values may be associated with the genetic disease malonyl CoA decarboxylase deficiency.

Methylglutaric acid – Elevated values may be associated with the genetic diseases 3-hydroxy-3-methylglutaric aciduria and in 3-methylglutaconic aciduria.

Hippuric acid – Hippuric acid is a conjugate of benzoic acid and glycine formed in the liver. Hippuric acid may be elevated due to bacteria overgrowth of the GI tract. Benzoic acid formed in the gastrointestinal tract by bacteria is absorbed into the portal circulation. In the liver, it is conjugated with the amino acid glycine to form benzoylglycine (hippuric acid). Other sources that increase benzoic acid are the solvent toluene and the food preservative sodium benzoate. Toluene exposure may occur due to industrial exposure or due to outgassing from new carpets. Low values of hippuric acid may result from depletion of glycine due to competing detoxification reactions or due to low amounts of bacteria after antibiotic use.

4-hydroxybutyric acid – Elevated values indicate the rare genetic disease 3-methylglutaconic aciduria or after the intake of the muscle builder 4-hydroxybutyric acid (also called gamma-hydroxybutyric acid) which can cause severe myalgia or death.

Phenylcarboxylic acid – Elevated values indicate overgrowth of GI bacteria.

Indole-like compound acid – Most likely derived from tryptophan. Elevated values indicate overgrowth of GI bacteria and are commonly elevated along with 3-indoleacetic acid.