

URINARY MARKERS OF YEAST OVERGROWTH

Richard S. Lord, PhD, Cheryl K. Burdette, ND, and J. Alexander Bralley, PhD

INTRODUCTION

Because of the serious, life-threatening nature of invasive candidiasis for immunosuppressed individuals, there is strong interest in markers that reveal early stages of this condition.¹ There is still debate about the question of the clinical relevance for less severe yeast growth that manifests as milder forms of *candidiasis*, especially intestinal yeast and fungal overgrowth. A large reason for the uncertainty in this arena is the lack of reliable tests to assess yeast overgrowth and demonstrate the efficacy of antifungal therapeutic interventions. We present here a review of scientific reports of some urinary markers of yeast overgrowth and results from our studies of relevant data from routine laboratory tests ordered for the general outpatient population. Also discussed are possible effects of azole antifungal therapy that are unrelated to yeast growth. Our intent is to improve the utilization of laboratory tools for yeast assessment by clarifying the validity of various markers that have been reported.

D-ARABINITOL—A BENCHMARK FOR YEAST DETECTION

Evidence from multiple studies by independent investigators has led to the recommendation that urinary levels of the sugar alcohol, D-arabinitol, be used as a reliable biomarker for invasive candidiasis.²⁻¹⁰ In newborns, measures of urine D-arabinitol have been reported to be more sensitive than fungal blood cultures for detection of invasive *candidiasis*.⁹ Clinical use of arabinitol has been made possible by extensive studies on accurate, efficient measurement of the compound.¹¹⁻¹⁹ D-arabinitol is a five-carbon sugar alcohol produced from dietary carbohydrates when yeasts are rapidly growing in the anaerobic environment of the small intestine. The enantiomer, L-arabinitol, is not produced by yeast, and some investigators report the ratio of D- to L-arabinitol. Since both isomers are present in small amounts in the diet, the D/L ratio allows detection of increases in the yeast-derived D-isomer, and the assay does not require calibration for absolute concentration measurement. With proper calibration procedures, the measurement of D-arabinitol concentrations without calculation of the D/L ratio has been shown to be at least as sensitive as the ratio method for the detection of yeast overgrowth. (Note: the shortened name, *arabitol*,

is sometimes used in place of the proper name, *arabinitol*.) Urinary D-arabinitol is a sensitive yeast marker, in part because it is eliminated by nearly quantitative urinary excretion (ie, low renal threshold and not excreted via other mechanisms), and it is cleared at the same rate as creatinine. Thus, arabinitol produced anywhere in the body will appear in urine in direct proportion to the concentration of arabinitol in serum.²⁰

The D/L-arabinitol (DA/DL) ratio in urine has been used to detect invasive *candidiasis* in newborns.⁹ One study group exhibited clinical signs of mucocutaneous *candidiasis*, but were not considered to have invasive *candidiasis*. In this group, four infants had positive cultures for *Candida albicans*, and two of these had an elevated DA/LA ratio, indicating that significant amounts of D-arabinitol were being produced. Serum arabinitol is elevated in both disseminated and milder forms of candidiasis. Elevated serum D-arabinitol-to-creatinine ratios were reported in 69%, 36%, and 9% of patients with *Candida* sepsis, *Candida* colonization, and bacterial sepsis, respectively.²¹ In another study, when patients were divided into categories of superficial *candidiasis*; possible deep, invasive *candidiasis*; and definite, deep invasive *candidiasis*, all three groups showed significant serum D-arabinitol elevations.²² Another research group reported highly-elevated, slightly-elevated, and normal serum D-arabinitol levels in 2, 2, and 3 patients, respectively, with superficial *Candida* colonization.² A fourth independent group reported elevated serum D-arabinitol in both disseminated (45%) and simple peripheral (24%) *candidiasis*, as defined by positive culture or biopsy-proven deep *Candida* infection.²³ Taken together, these data provide compelling evidence that elevated levels of D-arabinitol in urine or serum is a positive indication of candida overgrowth, even if invasive *Candidiasis* is not present.

In order to test the relationship of urinary D-arabinitol to signs and symptoms of *Candidiasis* in an outpatient population, a retrospective investigation of 40 patients with elevated urinary D-arabinitol (>73 mcg/mg creatinine) was performed. The respective clinicians were queried regarding the presence of signs or symptoms of fungal overgrowth. Of the 40 patients, 22 had a history suggestive of fungal overgrowth. These 22 cases included 11 with positive stool cultures and/or stool microscopic findings; 8 with cutaneous symptoms

including vaginal yeast, athlete's foot, thrush, ringworm and tinea; and 3 with a history of repeated antibiotic treatment. Of the other 18, three had stool testing for yeast with negative results. The predominant symptoms in these patients were fatigue, brain fog, and environmental and food sensitivities. Whether these symptoms should be considered indicative of fungal overgrowth is a matter of debate.

ARABINOSE—AN UNRELIABLE YEAST MARKER

Arabinose is a five-carbon sugar produced in plants.²⁴ It is an aldopentose with chiral centers similar to arabinitol. Arabinose polymers are found in tomatoes and many other foods.²⁵ A relationship between intestinal yeast and urinary arabinose (stereoisomer unspecified) has been asserted, particularly in reference to the diagnosis of autism. This association is based on a report of compounds found in the urine of two autistic brothers.²⁶ Other than this anecdotal report by a single investigator, there is no evidence of such an association. Several lines of evidence cast doubt upon the association of urinary arabinose and intestinal yeast growth.

Arabinose is a simple sugar of the type typically consumed by yeast. It is the substrate that, under the anaerobic conditions that exist in the human intestinal tract, is reduced to arabinitol as a means of recycling NADH. This is the biochemical rationale that it is arabinitol (the sugar alcohol), and not arabinose (the aldose sugar) that is characteristic of yeast growth. Furthermore, evidence from multiple reports demonstrates that yeast utilize arabinose as a substrate for growth, thus destroying the sugar.^{27,28} The enzymatic reduction of arabinose to arabinitol has been characterized in *Saccharomyces cerevisiae*.^{29,30} Several other species of yeast and bacteria have the capacity to metabolize arabinose as well.^{31,32} Cecal microflora of the rat efficiently degrades over 90% of arabinose in the media.²⁵ Thus, arabinose does not appear to be produced by any strain of yeast, and the extant evidence favors the conclusion that any available arabinose in their environment would be metabolized by intestinal yeast or by a variety of bacterial species.

Analytical difficulties also complicate the use of urinary arabinose as a marker compound. The method that is cited in the report of autistic brothers involves ethyl acetate extraction of acidified urine.²⁶ In general, organic solvent extractions demonstrate very poor recoveries of arabinose from aqueous solutions like urine. This finding is not surprising due to the high water solubility of small molecular weight polyalcohols, and their lack of solubility in non-polar organic solvents. Thus, the reported method would not accurately measure either arabinose or arabinitol.

TARTARIC ACID—NOT FROM YEAST AND NOT A CAUSE OF AUTISM

Pure tartaric acid (tartarate) is sold to the food production industry as an acidity regulator. The US government allows tartaric acid use in food, with no limitation other than current good manufacturing practice. The affirmation of this ingredient as "generally recognized as safe" (GRAS) is based upon the following current good manufacturing practice conditions of use: "The FDA allows its use as a firming agent, flavor enhancer, humectant and as a pH control agent. Currently, there are no sanctions for this ingredient."³³ Cream of tartar is a home and industrial food preparation ingredient commonly used in tartar sauce, meringues, and many other foods.

Dietary intake of tartaric acid can be very high and difficult to control because it is widespread in foods and pharmaceutical products. Tartaric acid comprises about 2% of the dry weight of grapes,³⁴ and up to about 1% of whole fresh grapes (see Table 1). Sun-dried raisins, a common dietary item and food ingredient, are a rich dietary source. A 100 g serving of sun-dried raisins contains as much as 3.5 g of tartaric acid. Tartaric acid plays a role in the acidity of wine, and excess tartaric acid is often removed by winemakers to improve flavor. The tartaric acid in wine is not created by the yeast used for fermentation, but rather derived from the grapes.^{35,36} Tamarind has the highest reported tartaric acid content in foods. The dry pulp of tamarind fruit has been reported to contain 8-18 g/100 g wet weight, which is

TABLE 1
SOURCES OF TARTARIC ACID

Major Sources of Naturally Occurring Tartaric Acid	Amount
Tamarind	8-18 g/100 g ³⁷
Sun-dried raisins	2.0-3.5 g/100 g ³⁸
Raisin juice concentrate	1.8-2.2 g/100 ml ³⁸
Raisin paste	1.5-2.2 g/100 g ³⁸
Grapes (fresh)	0.55-0.9 g/100 g ³⁸
Wine	0.5-0.7 g/100 ml ³⁸
Minor Food/Pharmaceutical Sources of Tartaric Acid	
Nephrolithiasis agent ³⁹⁻⁴¹	Soft drinks ⁴³
Fish fillets as preservative ⁴²	Carrots ⁴⁵
Zinc lozenges ⁴⁴	Lettuce ⁴⁵
HIV-1 protease inhibitor drugs ⁴⁶	Endives ⁴⁵
Potassium tartrate tablets ⁴⁷	Celery ⁴⁵
Chicory ⁴⁵	Cream of tartar ⁴⁹
Toothpaste ⁴⁸	Sweets ⁴⁹
Jams and jelly ⁴⁹	Cocoa powder ⁴⁹
Tinned fruits and vegetables ⁴⁹	Pears ⁵⁰
Frozen dairy produce ⁴⁹	Antacids ⁵¹
Pineapple ⁴⁹	Binder for many pharmaceuticals
Laxatives ⁴⁹	

the apparent reason why it has been used as a laxative drink (see medicinal uses below).

In addition to being found in many other medications, tartaric acid is also found in butorphanol, a drug commonly used to palliate autistic symptoms.⁵² This may be one explanation of why tartaric acid is sometimes elevated in autistic children.

In 1995, Shaw reported that tartaric acid was present in the urine of the two autistic brothers.²⁶ Although the concentrations of tartaric acid in the two individuals' urine were highly variable, Shaw believed that these compounds could be causally related to the autistic symptoms. As the compounds are not human metabolites, Shaw suggested that their origin was an infection with yeast or bacteria. In a subsequent publication, Shaw proposed intestinal yeast overgrowth as the probable origin of the urinary tartarate because its concentration appeared to decrease after therapy with nystatin.⁵³ However, we argue that the appearance of tartarate in urine is not a marker of yeast growth, nor is tartarate likely to cause any metabolic toxicity.

To demonstrate the magnitude of the influence of dietary tartaric acid on urinary levels, we measured urinary tartarate after ingestion of grape juice and wine. Overnight urinary tartaric acid was measured on two successive days for a healthy adult male. A concentration of 3.0 mcg/mg of creatinine was found on the first day with normal dietary intake. On the second day, after consuming 18 ounces of grape juice between 7 and 10 PM on the evening prior to collecting the urine, tartaric acid was above the quantitative limit of detection (>500 mcg/mg of creatinine). No adverse symptoms accompanied the radical increase in tartaric acid. Another healthy subject consumed 12 ounces of grape juice, and two others consumed two glasses of wine during the evening, prior to collection of urine. All three subjects were found to have increases in tartaric acid levels from < 10 to 90.0, 179, and 210 ug/mg creatinine, respectively. None of them experienced any unusual symptoms. In Shaw's study, the two subjects were reported to have tartaric acid levels of 69.2 mmol/mol equivalent to 91.9 ug/mg of creatinine.

In a study of the sleep-waking rhythm effects on organic-acid excretion, samples were collected at approximate 5-hour intervals every day for 14 days. While on a diet in which black currant jam was the only significant source of tartaric acid, two healthy male subjects consistently excreted significant levels of tartarate in urine. When they were shifted to an all-rice diet, urinary tartarate became undetectable. The good health of the two subjects remained unchanged, regardless of tartaric acid levels.⁵⁴

In the intestinal tract, tartarate appears to be metabolized instead of produced by fungi and bacteria. Pasteur first demonstrated this in 1860 when he found that *d*-tar-

taric acid is destroyed by the yeast *Penicillium glaucum*.⁵⁵ Tartaric acid can be used as a medium to grow *Candida tartarivorans*⁵⁶ and a significant number of species of *Basidiomycetous*.⁵⁷ Shaw mentions brewer's yeast as an agent that might produce tartaric acid.²⁶ However, ethanol and glycerol are the predominant metabolic products formed during anaerobic fermentation by *Saccharomyces cerevisiae*.⁵⁸ Concentrations of metabolites produced by *S. cerevisiae* vary depending on the substrate used, but tartaric acid does not appear to be among them.⁵⁹ In addition to its destruction by yeast, at least 23 varieties of bacteria are able to degrade tartaric acid.⁶⁰ Other than the putative association made by Shaw, there is no evidence that any type of yeast or fungus can produce tartaric acid as a metabolic end-product.

Because our laboratory has been reporting urinary D-arabinitol, we were able to retrospectively examine the data for correlation of this well-established yeast test with urinary tartarate. No significant correlation (coefficient = 0.0009) was found as D-arabinitol concentrations varied from < 1.0 to > 500 ug/mg creatinine in 512 patients (see Figure 1). The population included 260 patients < 12 years old, and the remainder was approximately evenly distributed between 15 and 78 years old.

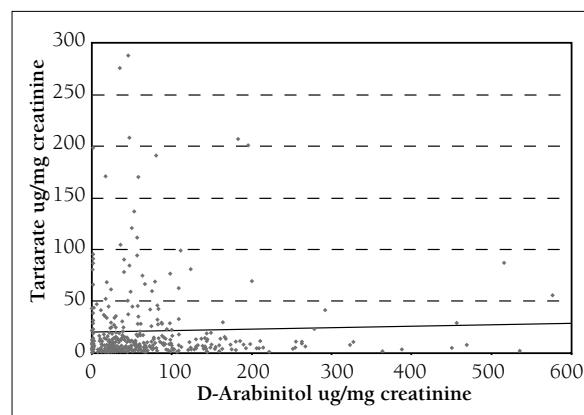


FIGURE 1
RELATIONSHIP BETWEEN URINARY D-ARABINITOL AND TARTARIC ACID IN 512 PATIENTS
(THE TREND LINE IS SHOWN, AND A CORRELATION COEFFICIENT OF 0.0009 WAS CALCULATED)

Since Shaw concluded that both tartarate and citramalate are products of intestinal yeast, we also tested for correlation of these two compounds in our database. Sets of data were extracted for these two analytes from 20,900 specimens submitted for organic acid analysis. The scattergram is shown in Figure 2, where the correlation coefficient is 0.18, showing insignificant correlation. These results further contradict the claim that elevated urinary tartarate and citramalate are results of intestinal yeast overgrowth, since that scenario would theoretically produce concurrent elevations.

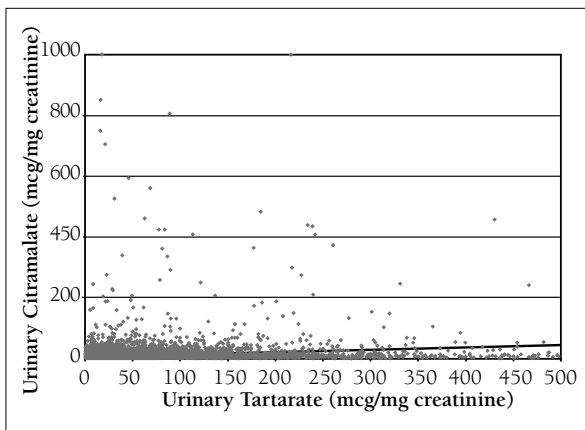


FIGURE 2
RELATIONSHIP BETWEEN URINARY TARTARIC ACID
AND CITRAMALATE IN 20,900 SPECIMENS
 (THE TREND LINE IS SHOWN AND A CORRELATION COEFFICIENT OF 0.18 WAS CALCULATED)

TOXIC EFFECTS OF TARTARATE

As early as 1935, tartaric acid was reported to be inert in the human body.⁶⁰ Oral tartarate may produce a laxative effect, and it is approved medically for this use. Single doses of up to 20 g have been used with only minor side effects noted.⁶¹ Tartaric acid ingestion produced no teratogenic changes in rabbits or rats. Likewise, no effect on maternal or fetal survival was noted.⁶¹ Long-term studies demonstrate that a diet in rats of up to 1.2% tartaric acid for 2 years produces no significant toxic effects. Slight reductions in weight were seen with higher amounts of tartaric acid, possibly due to the sour taste of tartaric acid limiting food consumption.⁶² Only 20% of ingested tartarate is found in urine due to limited absorption. It is destroyed in the intestinal tract by bacterial action.⁶¹

While there are reports of adverse effects following inhalation of large amounts of tartaric acid,⁶³ many careful studies suggest that it has very low toxicity when ingested orally. When metatartaric acid was given to rats at up to 3% in drinking water for 18 weeks, no effects were seen on hematological examination and serum analyses.⁶⁴ At the highest concentration, some reduced growth was seen in males, along with an impairment of urine-concentrating ability during prolonged water deprivation. Histopathologic changes were noted in the stomach, indicative of an inflammatory response in the submucosal layer. Both sexes at the 3% level showed an increase in relative kidney weight without histopathologic concern. No effects were seen at 0.1% metatartaric acid in the drinking water, equivalent to 80 mg/kg body weight in the males and 130 mg/kg in the females.⁶⁴

Not only is the oral toxicity of tartaric acid insignificant to humans, there is evidence of potential benefit. Kniel reported that tartaric acid inhibits growth of

Cryptosporidium parvum, which is associated with water-borne outbreaks of diarrheal illness.⁶⁵ Dietary tartaric acid, either from 120 g of sun-dried raisins or from 5 g of cream of tartar—providing equivalent amounts—was found to improve intestinal transit time, soften the stool, and lower the lithocholic:deoxythocholic acid ratio, which has been associated with increased risk of colon cancer. Test subjects did not report adverse events after ingestion of tartaric acid for 9 weeks. This research concluded that the tartaric acid in sun-dried raisins and cream of tartar modulates the composition of fecal bile acids and short-chain fatty acids in a way that has potential health benefits.⁶⁶ Other studies corroborate this research.⁶⁷ Tartaric acid found in wine was isolated and found to have protective effects against the DNA-damaging and cytotoxic effects of hydrogen peroxide and gamma-radiation *in vitro*. A mixture of phenolic compounds including catechin, caffeic acid, and tartaric acid were found to reduce DNA damage by 30-32%.⁶⁸ Other research also shows that the total antioxidant activity of wine is associated with tartaric acid ester content.⁶⁹

Tartaric acid is also used in medications. When administered to asthmatic patients as a 20% solution of prescription-grade L-tartaric acid dissolved in 0.15 M NaCl, tartaric acid was found to enhance bronchodilation by stimulating the cough response.⁷⁰ Intravenous injections of tartaric acid have been used as a treatment for *Streptococcus pyogenes* and *Staphylococcus aureus* infections.⁷¹ Tartaric acid has been used as an antioxidant to protect against ototoxicity secondary to gentomycin.⁷² In light of these observations, we believe it is unlikely that intestinal production of tartarate has significant metabolic toxic consequences in the etiology of autism.

Initially, Shaw used only two test subjects and an unspecified number of controls,²⁶ while his follow-up report includes 21 boys, including the two boys' data from the first paper.⁵³ Although he found urinary tartaric acid to be higher in autistic males, there was no statistically significant difference between autistic and normal children ($P=0.097$). Likewise, the autistic children who received nystatin therapy for either 10 days or 70 days had tartaric acid levels that did not differ significantly from controls ($P=0.069$ and $P=0.064$, respectively). In light of the evidence reviewed here, even if apparently significant changes had been reported, they would be inconclusive regarding yeast as a tartarate source since there was no control over the multiple sources of dietary tartarate in any period of the study.

We compared data for urinary tartaric acid from 15 patients submitted, with a diagnosis of autism with the same number of non-autistic patients. The data revealed an opposite trend than that seen in Shaw's work. Tartaric acid was found to be higher in non-autistic children than in autistic children ($P=0.0001$). The

difference is very likely to be due to dietary tartarate differences, since many practitioners use dietary restrictions of foods, such as raisins, that are high in tartarate.

CLINICAL EFFECTS OF ANTI-FUNGAL MEDICATIONS

There have been several anecdotal reports of urinary arabinose correlating with the administration and withdrawal of anti-fungal medications. Azole medications such as fluconazole, which have powerful anti-fungal effects, are also known hepatotoxins.⁷³ Low-dose administration of fluconazole has been shown to inhibit hepatic cytochrome P-450 activity, thus lowering hepatic oxidative stress.⁷⁴ Azole anti-fungals modulate estrogen activity,^{75,76} and they lower interleukin-4 and -5 production leading to suppression of T helper-2-mediated allergic reactions.⁷⁷ Anti-fungal medications can alter clinical progress, independent of any effects on yeast populations. Thus, it should not be assumed that improvement with these drugs is necessarily indicative of fungal causation in autism and other conditions. Any study of an apparent correlation of urinary markers with anti-fungal administration must rule out multiple potential confounding factors before a conclusion regarding the etiologic role of intestinal yeast populations can be made.

SUMMARY

An elevated level of serum or urinary D-arabinitol is evidence of yeast infestation. Many analytical investigations have established the validity of laboratory methods for D-arabinitol measurement, and clinical studies have shown the association of elevated levels with abnormal yeast growth. With the exception of invasive candidiasis in immunocompromised patients, the clinical relevance of elevated D-arabinitol, like any other method that reveals abnormal growth of either intestinal or mucocutaneous yeast, is controversial. In contrast to D-arabinitol, arabinose is a common component of carbohydrate-rich foods. It is metabolized by intestinal microbial populations and by human hepatocytes. Arabinose has never been reported to be a metabolic by-product of any strain of yeast or fungus. Similarly, tartaric acid is a common food component that is excreted in highly variable amounts, depending on intake of commonly consumed foods. Tartarate is metabolized by a variety of microbes, and there is no evidence of significant production in the human gut under any conditions. Neither tartarate nor citramalate shows correlation with D-arabinitol, based on data from their simultaneous measurement in a large human patient population. We conclude that yeast growth in humans does not produce significant amounts of arabinose, tartaric, or citramalic acids, and that, when these compounds are found in human urine specimens, they do not constitute evidence of yeast overgrowth. In addition, no toxic effects should be suspected from the

detection of tartaric acid in urine. Conclusions based on clinical changes following treatments with anti-fungal medications must take into account their various effects that are unrelated to die-off of yeast and fungi.

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J. Alexander Bralley, PhD, founder and CEO of Metamatrix, is also a clinical laboratory director licensed by state and federal laboratory agencies. Dr Bralley co-wrote *Laboratory Evaluations in Molecular Medicine* with Richard S. Lord, PhD.

Cheryl K. Burdette, ND, practices in Atlanta in a multi-disciplinary clinic. Dr Burdette also assists clinicians with lab interpretation as a clinical specialist at Metamatrix, and is involved in on-going research initiatives and education efforts.

Richard S. Lord, PhD, director of Science and Education at Metamatrix, develops new testing methodologies and lab report combinations. Dr Lord also lectures, publishes technical articles, and consults with health professionals.