Table 2. Neurological Signs and Symptoms in 29 Patients with D-Lactic Acidosis[80]

Symptom	% of Patients
Altered mental status ranging from drowsiness to coma	100
Slurred speech	65
Disorientation	21
Impaired motor coordination	21
Hostile, aggressive, abusive behavior	17
Inability to concentrate	14
Nystagmus	14
Delirium	10
Hallucinations	10
Irritability	3
Excessive hunger	3
Headache	3
Partial ptosis	3
Asterixis	3
Blurred vision	3

of tryptophan in scleroderma.[65] Increased urinary indican has been shown to correlate with enteric protein loss.[66] Indican elevation has revealed that impaired protein digestion and increased bacterial conversion of tryptophan is a complication of cirrhosis of the liver.[67] Some degree of malabsorption was found in 30 percent of an elderly population by combinations of indican with the Shilling and other tests.[68]

Products of Dietary Carbohydrate

D-Lactate

Although nanomolar concentrations of D-lactic acid may be produced by human tissues,[69] it is a major metabolic product of several strains of bacteria that inhabit the human gut.[70] D-lactate is frequently detected in patients with short-bowel syndrome, due to poor dietary carbohydrate absorption because of impaired absorptive regions in the upper small intestine. Many genres of bacteria can convert simple sugars into D-lactate. However, *Lactobacillus acidophilus* is uniquely adapted to withstand the dramatically lowered intestinal pH resulting from massive accumulation of luminal D-lactate and other organic acids. Under conditions of carbohydrate malabsorption, D-lactate is simultaneously increased in blood and urine.[71] Some D-lactate entering portal circulation can undergo hepatic conversion to carbon dioxide, but this pathway has limited capacity. This limitation is in contrast to the extremely large capacity for metabolism of the L-lactate isomer produced in skeletal muscle and other tissues. With continued increases in intestinal output, rising blood levels are reflected in urinary output of D-lactate.[72] When intestinal production rates exceed the capacity for clearance, D-lactic acidosis is produced.[73] Intestinal symptoms of diarrhea are frequently present due to the disruption of bowel flora.[74,75]

D-lactic acidosis due to overgrowth of *Lactobacillus plantarum* was reported in a child who developed an unusual encephalopathic syndrome due to neurotoxic effects of D-lactate.[76] D-lactic acidosis may be accompanied by any of the various neurological symptoms listed in Table 2.[71,77,78] Attacks are usually episodic, lasting from a few hours to several days. Direct toxic effects of D-lactate in the brain are suspected.[77,79]

Jejuno-ileostomy patients have the highest risk of developing D-lactic acidosis and accompanying encephalopathy because they usually have some degree of carbohydrate malabsorption.[81,82] Procedures as mild as stomach stapling may lead to D-lactic acidosis.[73] Precipitating factors include use of antibiotics[83] and medium-chain triglycerides.[84] Carbohydrate malabsorption associated with pancreatic insufficiency can also induce D-lactic acidosis.[85] Elevated levels of D-lactate were found in blood samples of 13 of 470 randomly selected hospitalized patients.[86] Studies in cattle have confirmed that increases in D-lactate following overloading of grain in the diet corresponded to growth of Lactobacilli rather than coliform bacteria.[87]

The specificity and sensitivity of urinary D-lactate has led to the test being proposed for routine diagnosis of bacterial infections.[88] D-lactate has also been reported to be a marker for diagnosis of acute appendicitis,[89] and for differentiating perforated from simple appendicitis.[90] Whatever the origin, patients are managed with antibiotics and probiotics,[91] including *Saccharomyces boulardii*.[71]

During acidotic episodes in patients with short-bowel syndrome, 24-hour urinary excretion of D-lactate can rise to levels above 600 mcg/mg creatinine, far higher

Table 3. Lactate Isomers Produced by Individual Species of Lactobacillus[94]

Producers of Only D(-)-Lactate
Lactobacillus delbrueckii subsp. delbrueckii
Lactobacillus delbrueckii subsp. lactis
Lactobacillus delbrueckii subsp. bulgaricus
Lactobacillus jensenii
Lactobacillus vitulinus

Producers of Only L(+)-Lactate
Lactobacillus agilis
Lactobacillus amylophilus
Lactobacillus animalis
Lactobacillus bavaricus
Lactobacillus casei
Lactobacillus mali
Lactobacillus maltaromicus
Lactobacillus murinus
Lactobacillus paracasei subsp. paracasei
Lactobacillus paracasei subsp. tolerans
Lactobacillus ruminis
Lactobacillus salivarius
Lactobacillus sharpeae
Lactobacillus rhamnosus

Producers of Racemate DL-Lactate
Lactobacillus acidophilus
Lactobacillus amyiovorus
Lactobacillus aviarius subsp. aviarius
Lactobacillus brevis
Lactobacillus buchnari
Lactobacillus crispatus
Lactobacillus curvanus
Lactobacillus formentum
Lactobacillus gasseri
Lactobacillus graminis
Lactobacillus hamsteri
Lactobacillus helviticus
Lactobacillus homohiochii
Lactobacillus pentosus
Lactobacillus plantarum
Lactobacillus reuteri
Lactobacillus sake

than concurrent L-lactate concentrations of around 24 mcg/mg creatinine.[78] D-lactic acidosis has also been reported in a patient with chronic pancreatitis and renal failure.[85] Compared to controls, significant elevations of D-lactate were reported for ischemic bowel, small bowel obstruction, and acute abdomen, with a negative predictive value of 96 percent and a positive predictive value of 70 percent.[92]

The phenomenon of D-lactic acidosis has been described as turning sugar into acid in the gastrointestinal tract.[93] D-lactate is not the only organic acid produced from simple carbohydrates. Although carbohydrates are also turned into p-hydroxybenzoate and tricarballylate, those compounds are never absorbed at rates that can produce the systemic effects found with D-lactate. When D-lactate is elevated, supplementation with D-lactate-producing species of Lactobacillus is contraindicated, and steps to reduce bacterial populations should be considered. Not all species of Lactobacillus produce significant D-lactate, as shown in Table 3. Once the carbohydrate excess in the small intestine is controlled, a recommended approach to managing recolonization with probiotic species is to supplement with species that do not produce D-lactate.

Urinary D-lactate reference values of 5.9 and 13.7 mcg/mg creatinine for adults and children less than one year old, respectively, have been reported.[77,78,95] Studies that have performed simultaneous plasma and urine specimen collections show that urinary concentrations can frequently be 10-fold higher than plasma.[91] An advance in analytical sensitivity has recently been achieved in which a single chiral chromatographic separation allows resolution and low-level accuracy for simultaneous, quantitative analysis of D- and L-lactate by tandem mass spectroscopy.[96] Since independent enzymatic methods frequently have varying calibration errors and efficiencies of recovery, the simultaneous determination of both isomers allows more accurate detection of patients predominantly excreting the D-isomer. In summary, urinary D-lactate elevation may predict bacterial

overgrowth as a result of: carbohydrate malabsorption, ischemic bowel, certain types of pancreatic insufficiency, acute appendicitis, and surgical procedures that compromise upper gastrointestinal function. Diagnosis and treatment of D-lactic acidosis can significantly improve patient outcomes.

Tricarballylate

Tricarballylate (tricarb) is produced by a strain of aerobic bacteria that quickly repopulates in the gut of germ-free animals.[97] As its name implies, tricarb contains three carboxylic acid groups that are ionized at physiological pH to give a small molecule with three negative charges, akin to the structure of the powerful chelating agent EDTA. Magnesium is bound so tightly by tricarb that magnesium deficiency results from overgrowth of tricarb-producing intestinal bacteria in ruminants.[98] This condition, known as "grass tetany," is also accompanied by lower levels of calcium and zinc, all of which can form divalent ion complexes with tricarb.

Products of Fungi (Yeast)

D-Arabinitol

D-arabinitol (DA) is a metabolite of most pathogenic Candida species, *in vitro* as well as *in vivo*. D-arabinitol is a five-carbon sugar alcohol that can be assayed by enzymatic analysis. It is important to distinguish the sugar alcohol from the sugar D-arabinose that is unrelated to any yeast or fungal condition in humans. A single report of two autistic brothers who were found to have significant concentrations of arabinose in their urine has led to claims about possible associations of yeast infections and autism,[99] although no further evidence in support of this association has been reported. DA, on the other hand, has long been known to be associated with candidiasis in a variety of clinical situations.[100-102] The enzymatic method using D-arabinitol dehydrogenase is precise (mean intra-assay coefficients of variation [CVs], 0.8%, and mean interassay CVs, 1.6%), and it shows excellent recovery of added DA.[103]

Among pathogenic yeasts and fungi, Candida spp. are of widest clinical concern, because of their transmission by direct invasion of the gastrointestinal and genitourinary tracts and their ability to rapidly overwhelm immune responses in many hospitalized patients. Most species of Candida grow best on carbohydrate substrates. Activities of the enzymes aldose reductase and xylitol dehydrogenase are induced in Candida tenuis when the organism is grown on arabinose.[104] The rate of DA appearance in the body equals the urinary excretion rate and is directly proportional to the concentration ratio of DA to creatinine in serum or urine.[105]

Measuring serum DA allows prompt diagnosis of invasive candidiasis.[106] Immunocompromised patients with invasive candidiasis have elevated DA/creatine ratios in urine. Positive DA results have been obtained several days to weeks before positive blood cultures, and the normalization of DA levels correlate with therapeutic response in both humans and animals.[107,108] Elevated DA/creatinine ratios were reported in 69-, 36-, and nine-percent of patients with Candida sepsis, Candida colonization, and bacterial sepsis, respectively.[109] 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 DA elevations.[110] Another group reported highly elevated, slightly elevated, and normal DA levels in two, two, and three patients, respectively, with superficial Candida colonization.[111] Yet a fourth independent group reported the appearance of DA in both disseminated and simple peripheral candidiasis.[112] The somewhat more discriminating elevated urine D-arabinitol/L-arabinitol (DA/LA) ratio has been found to be a sensitive diagnostic marker for invasive candidiasis in infants treated in neonatal intensive care units. Eight infants with mucocutaneous candidiasis were given empiric antifungal treatment, but had negative cultures; five of these had repeatedly elevated DA/LA ratios. Three infants with suspected and four with confirmed invasive candidiasis experienced normalized ratios during antifungal treatment.[113] The ratio of D- to L-arabinitol in serum reveals the presence of disseminated candidiasis in immunosuppressed patients.[108]