



© Williams & Wilkins 1998. All Rights Reserved.

Volume 77(2), March 1998, pp 73-82

D-Lactic Acidosis: A Review of Clinical Presentation, Biochemical Features, and Pathophysiologic Mechanisms

[Article]

Uribarri, Jaime MD; Oh, Man S. MD; Carroll, Hugh J. MD

From the Department of Medicine (JU), Mount Sinai Medical Center, New York, New York; and Department of Medicine (MSO, HJC), State University of New York Health Science Center at Brooklyn, Brooklyn, New York.

Address reprint requests to: Jaime Uribarri, MD, Mount Sinai Medical Center, One Gustave Levy Place, New York, NY 10029. Fax: 212-369-9330.

Introduction

D-lactic acidosis as a disease of humans was first described in 1979 [51], although it had been known as a disease of ruminants for decades [22]. Following this initial report, numerous other cases of this syndrome have been described

[6,8,13,16,24,28,29,31,33,35,36,37,39,40,41,45,46,48,49,54,55,58,59,60,61,63,64,67]. The clinical presentation is characterized by episodes of encephalopathy and metabolic acidosis which are thought to be due to the absorption of d-lactic acid and other unidentified chemicals produced by bacterial fermentation in the colon. Initially d-lactic acidosis was thought to be due solely to overproduction of d-lactic acid because it was thought that d-lactic acid was not metabolized by humans [64]. The subsequent finding that normal subjects have an enormous capacity to metabolize d-lactic acid suggests, however, that the development of d-lactic acidosis requires impaired ability to metabolize d-lactic acid in addition to excessive production [52].

In this report we present a case of d-lactic acidosis previously reported by us [53], followed by a review of other cases of d-lactic acidosis reported in the literature. The purpose of this review is to define the clinical and biochemical features of d-lactic acidosis, and ultimately to shed some light on the pathogenetic mechanism of the disease. Last, we review the literature dealing with the metabolism of d-lactic acid in humans to explore the possible role of impaired utilization of d-lactic acid in the pathogenesis of d-lactic acidosis.

Illustrative Case

A 30-year-old white man was brought to the emergency room by his mother because of mental confusion, disorientation, slurred speech, and delirium [53]. Staggering gait and nystagmus were noted on physical examination. The pertinent laboratory findings on arrival at the emergency room were: arterial blood pH, 7.14; pCO₂, 21 mmHg; pO₂, 112 mmHg; HCO₃, 7 mmol/L; serum creatinine, 2.2 mg/dL; BUN, 18 mg/dL; serum glucose, 85 mg/dL, serum sodium, 143 mmol/L;

serum chloride, 110 mmol/L; serum osmolality, 286 mOsm/L; and the serum anion gap, 26 mmol/L. Urinalysis showed a pH of 5.5, a specific gravity of 1.025, a few calcium oxalate crystals, and was otherwise unremarkable. Serum lactate concentration was 1.6 mmol/L and Acetest was negative in serum and urine. The patient subsequently denied ingestion of any drugs, toxins, or ethanol. Treatment with sodium bicarbonate increased blood pH, but the patient remained confused and disoriented. Over the next 12 hours, the patient gradually recovered from neurologic dysfunction and from acidosis, with normalization of the anion gap.

The medical history obtained subsequently revealed that the patient had been in good health until the development 3 years before of small bowel infarction due to superior mesenteric vein thrombosis, which required resection of most of the small bowel except for 13 inches of the terminal ileum. Following surgery, he developed malabsorption syndrome, manifested by diarrhea and weight loss. His gastroenterologist prescribed *Lactobacillus acidophilus* tablets as a treatment for diarrhea. Soon after he was started on *Lactobacillus acidophilus*, the patient began experiencing episodes of neurologic symptoms similar to those described before. These attacks occurred first once a month, and then at increasingly shorter intervals. The attacks always occurred after a meal, and the symptoms subsided spontaneously after a variable period of time.

Literature Review

A computerized literature search was performed using the headings "d-lactic acidosis" and "d-lactate encephalopathy" from 1979 until 1997. This initial search was supplemented by review of all the references contained in these papers. We have arbitrarily defined d-lactic acidosis as metabolic acidosis accompanied by increase in serum d-lactate in excess of 3 mmol/L. In contrast, l-lactic acidosis is commonly defined by a serum level of lactate greater than 5 mmol/L [44]. The rationale for using a lower serum level for definition of d-lactic acidosis than that for l-lactic acidosis is that the renal threshold for d-lactate is much lower than that for l-lactate, so that clinically significant metabolic acidosis may occur at much lower serum levels of d-lactate. Using this definition, we were able to collect 29 cases of d-lactic acidosis [6,8,13,16,24,31,33,35,36,37,39,40,41,45,46,48,49,51,54,58,59,61,63,64,67] from 29 reports [6,8,13,16,24,28,29,31,33,35,36,37,39,40,41,45,46,48,49,51,54,55,58,59,60,61,63,64,67]. We have not included in this series a case of d-lactic aciduria without acidemia and with a plasma d-lactate level of 0.6 mmol/L reported in 1977 [23] in a mentally retarded infant without apparent intestinal disease and thought to be the result of an inborn error of metabolism, nor we have included a child with the short bowel syndrome with significant lactic aciduria defined by chromatographic analysis of urine but without measurement of the specific stereoisomer of lactic acid [47]. We have also omitted several cases [2,19,25,56,57] of acidosis and/or encephalopathy described in patients with intestinal bypass before the syndrome of d-lactic acidosis was recognized; the clinical presentation in these patients suggests the syndrome of d-lactic acidosis but the diagnosis cannot be confirmed because the levels of d-lactic acid were never measured.

Each report was analyzed for the presence and characteristics of the following variables: sex and age of the patient, cause of short bowel syndrome, neurologic manifestations, serum electrolytes, blood pH, anion gap, renal function, peak serum d-lactate concentration, peak urinary d-lactate concentration, factors precipitating the episodes, and treatment.

A second computerized search was performed using the heading "d-lactic acid metabolism." This search was supplemented by review of all the references contained in these papers.

Results

As shown in [Table 1](#), the disease occurred more often in males than females (18:11). The average age of the patients was 30 +/- 17 years with a range from 18 months to 60 years, and the predominant underlying condition was the short bowel syndrome due to either surgical resection of the intestine (17 cases) or intestinal bypass surgery for treatment of obesity (10 cases). In 1 case the syndrome was acutely precipitated by the accidental placement of a feeding tube into the colon instead of the stomach [\[49\]](#). In another case the underlying abnormality was not clear but the patient was known to have chronic pancreatitis and had been receiving pancreatic enzymes in the past, and it is likely that he suffered from malabsorption secondary to exocrine pancreatic insufficiency [\[45\]](#).

Patient No.	Ref.	Age/Sex (yr)	Underlying Disorder	Peak Blood D-Lactate (mmol/L)	Peak Urine D-Lactate (mmol/L)
1	51	30/M	Intestinal resection	20.2	149.0*
2	8	36/M	Bypass	20.0	73.0 [†]
3	64	44/M	Intestinal resection	7.4	—
4	64	34/F	Bypass	6.6	—
5	59	5.75/M	Intestinal resection	8.5	60.0 [†]
6	67	40/F	Bypass	7.8	—
7	54	5/M	Intestinal resection	10.0	—
8	54	1.5/M	Intestinal resection	7.0	—
9	31	54/F	Bypass	11.5	—
10	16	48/M	Bypass	7.6	38.6
11	16	40/F	Bypass	5.0	52.0
12	58	2.5/M	Intestinal resection	4.0	—
13	45	60/M	Pancreatic insufficiency	6.8	—
14	40	16/M	Intestinal resection	6.7	—
15	49	26/F	Bypass	5.0	—
16	61	29/M	Colonic tube	5.7	200.0
17	46	9/F	Intestinal resection	9.1	—
18	41	9/M	Intestinal resection	8.9	—
19	48	32/F	Intestinal resection	13.2	43.0
20	36	31/F	Intestinal resection	6.5	—
21	36	46/M	Intestinal resection	3.9	—
22	24	24/M	Intestinal resection	4.6	—
23	33	40/F	Intestinal resection	7.4	—
24	63	42/F	Intestinal resection	9.2	—
25	13	50/M	Bypass	6.0	21.9
26	37	35/M	Intestinal resection	6.95	—
27	35	35/M	Bypass	3.1	52.8
28	39	46/F	Bypass	6.8	—
29	4	10/M	Intestinal		

Table 1. Characteristics of 29 patients with d-lactic acidosis, from previous reports

A description of renal function was given for 12 of the patients: in 8 patients the BUN was described as normal [13,24,36,58,64,67], 1 patient had moderate azotemia and a creatinine clearance of 30 mL/min [64], 1 had a serum creatinine of 2.2 mg/dL [45], and 2 patients had end-stage renal disease and were receiving maintenance hemodialysis [33,63].

As seen in Table 2, the neurologic abnormality that was present in every case was altered mental status. Other neurologic abnormalities were slurred speech, confusion, inability to concentrate, somnolence, hallucinations, clumsiness, weakness, ataxia, unsteady gait, nystagmus, excessive irritability, and abusive behavior. The attacks were episodic, lasting from a few hours to several days. Electroencephalograms during encephalopathic episodes showed bilateral, diffuse, high-voltage slow waves without focal abnormality, which normalized after attacks [8,24,51,63]. Partial ptosis has been described during an attack in 1 patient [36] and asterixis in another patient [24]. The presence of d-lactate in the cerebrospinal fluid was reported in 2 patients; the levels were the same as the serum levels [40,61].

Neurologic Manifestation	No. of Patients (%) (n = 29)
Altered mental status*	29(100)
Dysarthria (slurred speech)	19(65)
Ataxia	13(45)
Gait disturbance	10(34)
Disorientation	6(21)
Weakness	6(21)
Impaired motor coordination	6(21)
Hostile, aggressive, abusive behavior	5(17)
Inability to concentrate	4(14)
Nystagmus	4(14)
Hallucinations	3(10)
Delirium, euphoria	3(10)
Paranoid ideation	2(7)
Irritability	1(3)
Excessive hunger	1(3)
Headache	1(3)
Partial ptosis	1(3)
Asterixis	1(3)
Blurred vision	1(3)

*From mild drowsiness to coma.

Table 2. Prevalence of neurologic symptoms and signs

Symptoms were aggravated by excessive oral food intake and alleviated after caloric restriction [6,31,40,46,49,54,58,61]. In fact, craving for and excessive consumption of carbohydrates have been noted in several reports [8,40,61]. In 1 patient, symptoms seem to have been precipitated by the use of medium-chain triglycerides [37] which have been recommended to improve the nutritional status in patients with the short bowel syndrome.

Acidosis was present in all patients, and it was of quite variable degree, as shown in Table 3. The average serum anion gap was increased, but some values were within the normal range. The mean peak serum d-lactate concentration was 8 +/- 4 mmol/L. The amount of d-lactate in the urine was variable, with the highest concentration reported as 200 mmol/L.

Laboratory Value (mmol/L)	Mean \pm SD	Range
Serum sodium	141 \pm 4	136–150
Serum potassium	3.8 \pm 0.7	2.6–5.0
Serum chloride	110 \pm 5	102–119
Serum total CO ₂	10 \pm 4	4–19
Serum anion gap	20 \pm 5	13–29
Lowest blood pH	7.20 \pm 0.06	7.04–7.30

Table 3. Serum electrolytes corresponding to the lowest blood pH

In those cases in which bacteriologic analysis of fecal flora was performed, it showed almost without exception a marked predominance of Gram-positive anaerobic organisms including a variety of lactobacillus, bifidobacterium, and eubacterium, which have been shown to produce d-lactate in vitro [6,33,35,46,54,59,63,65]. Evidence for the production of d-lactate by intestinal bacteria is contained in a number of reports [6,16,35,46,54,59,64].

(Table 4) summarizes the information on metabolism of d-lactate by humans. The data show a substantial rate of metabolism of d-lactate [1,11,17,18,32,42,52,72].

Ref.	Route of Administration	Rate of Metabolism
32	Intravenous	14.9% Urinary excretion after 210 mmol of dl-lactate
1	Intravenous	Complete metabolism in 1 h after 111 mmol of d-lactate
11	Intravenous	Peak plasma level 4 mmol/L after 3 mmol/kg of dl-lactate in 20 min; clearance 9.3 mL/kg per min
52	Intravenous	1.5 mmol/kg per hr metabolized at a serum level of 5.2 mmol/L
18	Oral	Peak plasma level of 0.45 mmol/L after 12.8 mmol/kg of d-lactate; plasma half-life 40 min; renal excretion <2%
17	Oral	Peak plasma level of 0.38 mmol/L after 1.1 mmol/kg of d-lactate; returned to baseline in 120 min
42	Intravenous	Peak plasma level of 0.44 mmol/L after 0.21 mmol/kg of d-lactate
72	Intraperitoneal	Peritoneal dialysis patients metabolized 89 mmol/d with minimal elevation of plasma levels

Table 4. D-lactate metabolism in humans

(Table 5) summarizes the modalities of treatment attempted in each case report of the syndrome.

Patient No.	Ref.	Treatment	Comments
1	51	Oral neomycin 1 g/d for 2 mo	No more attacks in 12 mo of follow-up
2	8	Oral neomycin 2 g/d for 2 d plus ampicillin 2 g/d for 10 d	No more attacks in 10 mo of follow-up
3	64, Case 1	Oral vancomycin 250 mg qid (time?) with fast resolution of symptoms	No follow-up described
4	64, Case 2	Oral vancomycin 500 mg/d qid with a subsequent reduction to 250 mg/d	Asymptomatic thereafter except on 2 occasions when she did not take vancomycin
5	59	Oral kanamycin 750 mg/d for 2 wk	No attacks for 2 mo; then recurred but stopped again after kanamycin was restarted
6	67	Oral neomycin (dose?, time?)	Patient is said to have improved
7	54, Case 1	Oral neomycin 100 mg/kg per day for 14 mo	Asymptomatic even after neomycin was stopped despite biochemical evidence of persistent d-lactic acid production
8	54, Case 2	Oral neomycin 100 mg/kg per day for 14 d and continued as maintenance	Required maintenance neomycin therapy
9	31	Oral vancomycin 250 mg qid for several days	Only 1 mild attack which resolved spontaneously in 6 mo of follow-up
10	16, Case 1	Symptoms improved spontaneously	Patient lost to follow-up
11	16, Case 2	Reanastomosis cured symptoms completely	Symptoms improved when given only liquids orally plus intravenous fluids
12	58	Oral neomycin 100 mg/kg per day improved symptoms rapidly	Symptoms recurred rapidly after carbohydrate overfeeding
13	45	Patient died shortly after admission	No comments
14	40	Prompt resolution of symptoms after discontinuation of oral intake of food	Careful comparisons of parenteral vs enteral feeding were made
15	49	Attack was precipitated by the wrongful placement of gastrostomy tube in the colon	Symptoms disappeared after removal of colonic tube
16	61	Oral neomycin 500 mg qid (time?)	Decrease carbohydrate intake improved his symptoms
17	46	Diet providing starch as source of carbohydrates prevented symptoms	Recurrent attacks during the period of follow-up
18	41	Carbohydrate-modified diet prevented further attacks	No more attacks during follow-up period
19	48	Oral vancomycin 250 mg/d (time?) relieved symptoms	No more attacks in 18 mo of follow-up
20	36, Case 1	Oral metronidazole 400 mg tid for 5 d	No more attacks in 2 yr of follow-up
21	36, Case 2	Oral neomycin (dose?) for 2 wk	Attacks have recurred
22	24	Attack seems to have been precipitated by oral trimethoprim-sulfamethoxazole used for urinary tract infection	No more attacks in 1 mo of follow-up
23	33	Symptoms improved with hemodialysis	Patient also had renal failure
24	63	Oral neomycin 1 g/d for 1 mo	No more attacks in 2 mo of follow-up
25	13	Attack seems to have been precipitated by doxycycline used for bronchitis	A second episode was precipitated by trimethoprim-sulfamethoxazole use for respiratory tract infection
26	37	Attack may have been precipitated by use of medium-chain triglycerides (MCT)	No more attacks after withdrawal of MCT
27	35	Syndrome cured after reanastomosis of intestine	Oral metronidazole (dose?, time?) was used to control attacks
28	39	Oral neomycin 500 mg qid for 14 d cured all symptoms in 7 d	No more attacks in 9 mo of follow-up
29	6	Attacks were corrected by use of bicarbonate, either oral or intravenous	No other comments

Table 5. Modalities of treatment in 29 patients with d-lactic acidosis, from previous reports

Discussion

Clinical manifestations

The characteristic manifestations of d-lactic acidosis are recurrent episodes of encephalopathy and metabolic acidosis occurring in a patient with the short bowel syndrome. Neurologic abnormalities are always present although their nature varies from patient to patient. Common features include slurred speech, confusion, inability to concentrate, somnolence, hallucinations, clumsiness, weakness, ataxia, unsteady gait, nystagmus, excessive irritability, and abusive behavior. These episodes last from a few hours to several days.

Metabolic acidosis is always present but its severity varies from patient to patient and for a

given patient from 1 attack to another. The serum anion gap is usually high at the onset of symptoms but the increase in the anion gap tends to be less than the decrease in the serum bicarbonate concentration; in L-lactic acidosis the increase in the anion gap is usually greater than the reduction in bicarbonate [50]. The discrepancy could be explained by 2 factors: the significantly lower renal threshold for D-lactate (<1 mmol/L) than for L-lactate [52], and the loss of the sodium salt of D-lactic acid in the stool (the H⁺, but not the organic anion is reabsorbed or reacts with secreted HCO₃ in the lumen) [30]. Moreover, these patients can have baseline hyperchloremic acidosis because of chronic diarrhea with loss of HCO₃ in the stool. One patient has been described [36] who might have had underlying renal acidification defects. Several patients have been reported [2,19,25,56,57] with the characteristic neurologic findings of D-lactic acidosis but without systemic acidosis.

Chemistry of L- and D-lactic acids

L- and D-lactate are optical isomers which differ only in the position of the alpha-hydroxy radical. Both compounds are produced from, and metabolized to, pyruvate by the enzyme lactic dehydrogenase (LDH). The latter enzyme is isomer-specific; the production of D-lactate requires D-LDH and that of L-lactate, L-LDH. Mammals have only the enzyme L-LDH.

Small quantities of D-lactate may be found normally in the blood [4] and excreted in the urine [38]. This D-lactate is probably formed in the body through the methyl-glyoxal pathway [65] or within the gastrointestinal tract by bacterial fermentation [10]. Other potential sources of D-lactate are dietary intake [53] and administration for medical use. Humans ingest D-lactate frequently [53]; fermented fruits and vegetables such as pickles, yogurt, and sauerkraut contain both L- and D-lactic acid. Lactated Ringer solution and peritoneal dialysate also contain racemic mixtures of both isomers in the same proportion. Recently, it has been suggested that the metabolism of propylene glycol, an agent frequently used in medications and food, can lead to generation of D-lactate [9].

The predominant form of lactate normally present in the blood of humans and other vertebrates is L-lactate, which is derived from pyruvate by the action of L-LDH.

Metabolism of D-lactate in humans and animals

When D-lactic acidosis was first described in humans in 1979 [51] it was thought that mammals metabolize D-lactate very slowly. It is now clear, however, through the evidence summarized in Table 4, that normal humans metabolize D-lactate efficiently. The most complete data are those of Oh and colleagues [52], who showed that normal subjects were able to metabolize D-lactate at a rate of 1.52 mmol/kg per hour with a serum level of 5.2 mmol/L, when D-lactate was infused intravenously at a rate of 1.92 mmol/kg per hour for each isomer. At such a rate a person weighing 70 kg can metabolize about 2,500 mEq of D-lactate per day. These data are in agreement with those in other studies in humans [1,11,17,18,32,42,72] and in other mammals such as rats [26,27], rabbits [21], dogs [14], and baboons [12].

Smith and colleagues [62] have argued, based on their studies in rats and humans, that

mammals lack a significant ability to metabolize d-lactate. However, a review of their data shows strong evidence that rats metabolize d-lactate efficiently; when d-lactate was given intravenously, it disappeared rapidly from the circulation and only 25% was excreted in the urine. Moreover, ligation of renal arteries and veins did not alter the rate of elimination of d-lactate from the blood. Their data in a normal human subject have a number of inconsistencies. For example, while the total administered dose of d-lactate was 2.15 mmol, the plasma level was 1 mmol/L, an outcome that is impossible since the space of distribution of d-lactate should be at least equal to the extracellular space.

In summary, most of the data available in the literature strongly suggest that d-lactate is efficiently metabolized by mammals [1,11,12,14,17,18,21,26,27,32,42,51,72]. Since mammals lack d-LDH, metabolism of d-lactate must use alternative routes. The enzyme likely to be responsible for metabolism of d-lactate in mammals is d-2-hydroxy-acid-dehydrogenase, a mitochondrial enzyme that converts d-lactate to pyruvate and is found in a variety of animal tissues [7,68]. This enzyme is a nonspecific flavoprotein, and its substrates include d-lactic acid as well as other d-2-hydroxy acids [20]. The enzyme may be important for the synthesis of protein and is active over only a limited pH range [20,68].

Renal handling of d-lactate

The renal threshold for d-lactate is much lower than that of l-lactate, and a significant proportion of d-lactate infused intravenously escapes in the urine [52]. Lactate is normally reabsorbed by a sodium-lactate cotransporter, but it is not clear whether there are different transporters for each isomer or if the difference in reabsorption is the result of different rates of metabolism after reabsorption into the tubules [69]. The fact that l- and d-lactate compete with each other for renal tubular reabsorption suggests that they both utilize the same transporter [52].

Pathogenesis of d-lactic acidosis

The syndrome of d-lactic acidosis is thought to be the result of the production and absorption of d-lactic acid from the intestine. D-lactic acid production results when carbohydrate malabsorption in the small bowel leads to increased delivery of carbohydrates to the colon with subsequent fermentation by colonic bacteria to l- and d-lactate. Only d-lactate accumulates because of its slower metabolism. An increased delivery of substrate to the colon is a constant finding in these patients. The latter point is clearly illustrated by the patient [49] who developed the syndrome following the accidental placement of a feeding tube directly into the colon; rapid reversal of the acidosis followed cessation of feeding and removal of the tube.

The course of events described above has been clearly documented in d-lactic acidosis observed in ruminants overfed with grains [22]. In those cases it has been shown that acidosis is the result of the increased production of d-lactic acid by bacterial fermentation and its subsequent absorption into the blood. Large amounts of l- and d-lactic acid are produced by bacteria but only the d-isomer accumulates since absorbed l-lactic acid is more rapidly metabolized. When the rate of absorption of d-lactic acid into the body overwhelms the body's metabolic capacity to metabolize it, acidosis develops.

The presence of abnormal bacterial flora in the colon is also essential for the development of the syndrome. Stool cultures have invariably shown a marked predominance of Gram-positive anaerobes such as species of lactobacillus which are known to produce d-lactic acid in vitro. Lactobacilli produce not only d-LDH but also dl-lactate racemase which could potentially explain interconversion of d- and l-lactate [35]. Alteration of the flora probably occurred following ingestion of lactobacillus in 1 case [51] and following antibiotic administration in 2 other cases [13,24].

Mild overproduction of d-lactic acid may not be unusual in patients with the short bowel syndrome. For example, Thurn et al [66] have shown that in a group of 33 patients with jejunoileal bypass, 9 (27%) patients had plasma d-lactate levels greater than 0.5 mmol/L (range, 0.7-11.5 mmol/L). Moreover, in 470 randomly chosen hospitalized patients, plasma d-lactate levels were greater than 0.5 mmol/L in 13, and 60% of these had a history of gastrointestinal surgery or disease. Hove et al [34] measured the fecal d- and l-lactate concentration in 100 nonselected patients at a referral center for gastrointestinal disorders and found that 21% had high d-lactate concentrations; the levels were high in 73% of the patients with active inflammatory bowel disease, in 33% of those with malabsorption syndrome, and in only 5% of patients with neither of these 2 conditions. Bustos et al [5] measured d-lactic acid in blood, urine, and feces in 11 patients with the short bowel syndrome and showed that the levels in the stool were increased in 9 patients but that levels were undetectable in the urine in all 11 and in the blood of 10 of these patients (the lower limit of detection of d-lactic acid is not given). Bongaerts et al [3] studied a group of 8 patients with the short bowel syndrome and demonstrated that d-lactate is frequently present in serum and urine of these patients even in the absence of acidosis.

It is not known why d-lactic acidosis develops intermittently and not with every meal although the abnormal colonic flora, once developed, must be present constantly. If malabsorption syndrome with increased delivery of nutrients to the colon led immediately to osmotic diarrhea, there might not be a sufficient amount of substrate in the colon to produce clinical d-lactic acidosis. Hence, colonic stagnation might be another important contributing factor. The fact that the syndrome has not been described with greater frequency in patients with malabsorption syndrome not related to a short bowel may also be explained by the limited substrate availability in these other conditions. In general, malabsorption syndrome is more severe in the short bowel syndrome.

In vitro studies with stool homogenates have shown that the formation of d-lactic acid is stimulated by low pH and inhibited at pH 6.5 or higher [6]; the suggestion has been made that increasing the luminal colonic pH by dietary supplements of CaCO_3 and MgCl_2 may potentially be used to diminish intestinal production of d-lactic acid [6].

Another noteworthy point is the delay in the appearance of symptoms; patients with intestinal resection or bypass surgery usually develop d-lactic acidosis after a delay of several months to a few years. It has been suggested that a change in the intestinal flora occurs during this time [55].

It is useful to estimate the likely rate of d-lactate production with usual food in order to determine whether a defect in d-lactate metabolism plays a role in the pathogenesis of d-lactic

acidosis. For this estimation, we make the following assumptions. First, the daily caloric intake is 3,000 calories. Second, one-half of the calories ingested are absorbed in the small intestine and the other half delivered to the colon. Third, one-half of the daily caloric intake comes from 1 big meal such as dinner. Fourth, one-half of the entire caloric intake is in the form of carbohydrates. Fifth, all the carbohydrates delivered to the colon are converted by bacteria to l- and d-lactate in equal proportions. In this case, if 1,500 calories are ingested during dinner, and 750 calories are delivered to the colon, 375 calories will be as carbohydrates and 375 as some other nutrients. These 375 calories would come from 94 g of carbohydrates, which then would produce 522 mmol of d-lactate and 522 mmol of l-lactate. If we further assume that 522 mmol of d-lactate was produced over a 6-hour period, the production rate will be less than 100 mmol/hour. Since normal humans can metabolize d-lactate at a rate greater than 100 mmol/hour with modest increase in serum concentration [52], one might argue that impaired metabolism is a prerequisite for the production of d-lactic acidosis.

On the other hand, it is also possible that d-lactic acidosis occurs only when the food intake is grossly excessive so that the rate of d-lactate production could exceed the rate estimated above. It is also possible that the rate of d-lactate metabolism is reduced in these patients not because of any specific metabolic defect but as the result of generalized diminution in metabolism due to chronic malnutrition. If there is a specific mechanism of this impaired ability to metabolize d-lactate, it is currently unknown. Metabolism of d-lactate in mammals seems to require d-2-hydroxy-acid-dehydrogenase, which converts d-lactate to pyruvate [7,68]. This enzyme has been found in high concentrations in the liver and kidneys of several animal species including humans [72], and it is possible that disease of these organs might diminish the ability to metabolize d-lactate. For example, it has been shown that loading rats with d-lactate over several days significantly increased the activity of d-2-hydroxy-acid-dehydrogenase in the liver, but that this increase was much less in rats with chronic renal failure than in control animals [71]. Although renal function has been described in only a few patients with d-lactic acidosis, some degree of renal insufficiency is common because volume depletion and calcium oxalate kidney stones are frequent complications in patients with the short bowel syndrome. Unfortunately, the rate of metabolism of d-lactate in patients with d-lactic acidosis has not been measured.

Oxalate is a powerful competitive inhibitor of d-2-hydroxy-acid-dehydrogenase [68]. Patients with the short bowel syndrome frequently have intestinal hyperabsorption of oxalate, and it seems possible that high plasma and tissue levels of oxalate could inhibit enzyme activity. Low pH, which also diminishes the dehydrogenase activity [68], could play a role in the diminished metabolism of d-lactate. The effect of pH on in vivo metabolism of d-lactate has not been investigated fully. Normal subjects metabolize d-lactate and d-lactic acid equally well [17,18] despite the fact that the former tends to increase the blood pH and the latter decreases it, but differences in blood pH in these experiments were quite modest compared with those observed in patients with clinical d-lactic acidosis.

Another mechanism by which renal dysfunction might alter d-lactate metabolism is interference with its renal excretion. The renal threshold for d-lactate is low and the renal fractional excretion is very high [52]. Impaired renal function or volume depletion may decrease renal excretion of d-lactate and thereby increase plasma levels.

The suggestion has been made that thiamine deficiency played a contributory role in the pathogenesis of d-lactic acidosis in 1 patient [36] because d-lactic acidosis did not recur after initiation of thiamine supplementation. However, thiamine deficiency has not been shown to increase production of d-lactate when an specific enzymatic method has been used to measure this compound [70].

On the basis of the available evidence we believe that the development of d-lactic acidosis requires the following conditions:

- 1) Carbohydrate malabsorption with increased delivery of nutrients to the colon,
- 2) Colonic bacterial flora of a type that produces d-lactic acid,
- 3) Ingestion of large amounts of carbohydrate,
- 4) Diminished colonic motility, allowing time for nutrients in the colon to undergo bacterial fermentation, and
- 5) Impaired d-lactate metabolism.

Mechanisms of neurologic manifestations

Two main hypotheses have been proposed to explain the neurologic manifestations of the syndrome: 1) d-lactate itself is toxic to the brain, and 2) unknown compounds produced along with d-lactate are toxic to the brain. Indeed, compounds such as formate, histamine, ethanol, tyramine, and endotoxin have been found in the rumen of cattle with d-lactic acidosis [22], and excessive urinary excretion of hydroxyphenyllactic and phenylacetic acids [8] has been observed in patients with this condition. The role that each of these compounds may play in causing the neurologic abnormalities is uncertain but it is clear that ethanol is not responsible for the symptoms. Although the patients appear drunk, serum levels of ethanol have been normal.

D-lactate can penetrate into the central nervous system by simple diffusion and can thus reach high concentrations in the brain [43]. Although it has been hypothesized that d-lactate may accumulate in the brain because of the low local level of catabolizing enzyme [51], levels of d-lactate in the cerebrospinal fluid have been found to be equal to those in the blood [40,61]. Moreover, the correlation between plasma d-lactate levels and severity of symptoms is poor. Thurn et al [66] found that 16 of 33 patients with jejunioileal bypass reported symptoms consistent with d-lactic acid encephalopathy but only 9 of them had high plasma levels of d-lactate, while some individuals with high plasma d-lactate levels did not have symptoms. The fact that some patients present with encephalopathy but without high plasma d-lactate levels strengthens the suggestion that the encephalopathy results from toxins which may be produced simultaneously with d-lactic acid. A further argument against a direct role for d-lactate in the alteration of mental status is that normal subjects who received an infusion of d-lactate did not develop any neurologic symptoms despite the attainment of serum levels up to 6 mmol/L in 1 study [52] and up to 3.5 mmol/L in another study [17].

Acidosis itself is not likely to be responsible for the neurologic manifestations since patients with other types of acidosis of comparable or greater severity do not present such manifestations. It could be argued, however, that the abnormal pH might have some role in the toxic effect of d-lactate or other chemicals in the brain since patients with d-lactic acidosis usually have significant metabolic acidosis. It is also probable that d-lactate is harmful to the central nervous system only in the presence of another metabolic defect, such as deficiency of certain vitamins, which might be present in patients who develop the syndrome but not in others [15]. Interference on pyruvate metabolism by d-lactate has been postulated based on observation of clinical similarities between d-lactic acidosis and inherited or acquired abnormalities of pyruvate metabolism [15].

Diagnosis

Increased anion gap and rapid onset and recovery are characteristic features in d-lactic acidosis as in other organic acidosis. However, the critical elements that raise suspicion of this diagnosis in a patient with acidosis are 1) increased serum anion gap with normal lactate levels measured by conventional techniques and negative Acetest, 2) presence of short bowel syndrome or other forms of malabsorption syndrome, 3) acidosis that is preceded by food ingestion and that improves after discontinuation of oral intake of food, and 4) characteristic neurologic findings.

Any patient presenting with acidosis and 1 or more of any of the above clinical clues should be strongly considered to have d-lactic acidosis, and urine and serum samples should be obtained for measurement of d-lactic acid. The diagnosis of d-lactic acidosis is confirmed by finding high levels of d-lactate in urine and/or in serum [51]. We have defined d-lactic acidosis as a metabolic acidosis accompanied by a serum d-lactic acid greater than 3 mmol/L. Although there may not be universal agreement about this quantitative definition of d-lactic acidosis, we believe it makes sense since a lower level of d-lactic acid may be present in serum of patients with malabsorption syndrome [3,5,66] but it is unlikely to be the cause of an associated acidosis. D-lactate is measured enzymatically using a specific d-lactic dehydrogenase in the assay [51]; kits to measure d-lactic acid in serum and urine can be obtained from Boehringer Mannheim, (Indianapolis, IN) and can be adapted easily to any clinical laboratory. While waiting for the results of these measurements, the patient should receive no food by mouth and should be given intravenous dextrose solutions as a source of calories; the rapid improvement of acidosis on this regimen is highly suggestive of the diagnosis of d-lactic acidosis.

Titration of an increased amount of organic anions in the urine may be an important clue that suggests this diagnosis [51], but unfortunately this measurement is not available in commercial clinical laboratories.

Modalities of treatment

Treatment modalities that have been tried can be grouped into the following categories and are described in detail in Table 5: 1) attempts to alter the abnormal intestinal flora with the administration of oral antibiotics and recolonization of the intestine by the oral administration of a bacterial flora called "Julia flora" [60]; 2) attempts to diminish the quantity of substrate for intestinal fermentation by prolonged oral fasting with simultaneous intravenous alimentation

[40,54,64], use of low-carbohydrate diets, or use of enteral formulas containing fructose or starch instead of glucose as the main source of carbohydrates [46,58]; 3) correction of the underlying abnormality by reanastomosis of the intestine in case of intestinal bypass [16,35]; 4) nonspecific therapy of acidosis with high doses of bicarbonate [6,46]; and 5) correction of acidosis and simultaneous clearance of dlactate with hemodialysis [33].

No large series from a single institution has been reported, and most of the therapeutic modalities are based on the experience of individual practitioners with only 1 or 2 cases with variable success. The most effective immediate treatment consists of elimination of all oral intake of food while providing intravenous nutrition. Long-term management consists of carbohydrate restriction and suppression of the intestinal flora with nonabsorbable antibiotics.

Antibiotics control symptoms and prevent recurrences of the syndrome in most patients, but in some patients acidosis has recurred despite their continuous use [36], and in others the syndrome may have been precipitated by the use of antibiotics [13]. Therapy with antibiotics has been complicated by the development of diarrhea [55] or unspecified side effects [31]. Antibiotics that have been tried include neomycin, vancomycin, ampicillin, kanamycin, and metronidazole. The optimum duration of antibiotic therapy is unclear since symptoms may recur a few days after discontinuation of antibiotics in some patients, while others may remain without symptoms after several years without therapy.

Summary

This report describes a case of d-lactic acidosis observed by the authors and then reviews all case reports of d-lactic acidosis in the literature in order to define its clinical and biochemical features and pathogenetic mechanisms. The report also reviews the literature on metabolism of d-lactic acid in humans.

The clinical presentation of d-lactic acidosis is characterized by episodes of encephalopathy and metabolic acidosis. The diagnosis should be considered in a patient who presents with metabolic acidosis and high serum anion gap, normal lactate level, negative Acetest, short bowel syndrome or other forms of malabsorption, and characteristic neurologic findings.

Development of the syndrome requires the following conditions 1) carbohydrate malabsorption with increased delivery of nutrients to the colon, 2) colonic bacterial flora of a type that produces d-lactic acid, 3) ingestion of large amounts of carbohydrate, 4) diminished colonic motility, allowing time for nutrients in the colon to undergo bacterial fermentation, and 5) impaired d-lactate metabolism.

In contrast to the initial assumption that d-lactic acid is not metabolized by humans, analysis of published data shows a substantial rate of metabolism of d-lactate by normal humans. Estimates based on these data suggest that impaired metabolism of d-lactate is almost a prerequisite for the development of the syndrome.

REFERENCES

1. Altschule MD, Henneman DH, Holliday P, Goncz RM. Carbohydrate metabolism in brain disease. Arch Intern Med 98: 35-38, 1956. [\[Context Link\]](#)
2. Ayub A, Faloon WW, Heinig RE. Encephalopathy following jejunioileostomy. JAMA 246: 970-73, 1981. [Bibliographic Links](#) | [\[Context Link\]](#)
3. Bongaerts G, Tolboom J, Naber T, Bakkeren J, Severijnen R, Willems H. D-lactic acidemia and aciduria in pediatric and adult patients with short bowel syndrome. Clin Chem 41: 107-10, 1995. [Bibliographic Links](#) | [\[Context Link\]](#)
4. Brandt RB, Siegel SA, Waters MG, Bloch MH. Spectrophotometric assay for d-lactate in plasma. Anal Biochem 102: 39-46, 1980. [\[Context Link\]](#)
5. Bustos D, Pons S, Pernas JC, Gonzalez H, Caldarini MI, Ogawa K, De Paula JA. Fecal lactate and short bowel syndrome. Dig Dis Sci 39: 2315-19, 1994. [Bibliographic Links](#) | [\[Context Link\]](#)
6. Caldarini MI, Pons S, D'Agostino D, DePaula JA, Greco G, Negri G, Ascione A, Bustos D. Abnormal fecal flora in a patient with short bowel syndrome. An in vitro study on effect of pH on d-lactic acid production. Dig Dis Sci 41: 1649-52, 1996. [Bibliographic Links](#) | [\[Context Link\]](#)
7. Cammack R. Assay, purification and properties of mammalian d-2-hydroxy acid dehydrogenase. Biochem J 115: 55-63, 1969. [Bibliographic Links](#) | [\[Context Link\]](#)
8. Carr DB, Shih VE, Richter JM, Martin JB. D-lactic acidosis simulating a hypothalamic syndrome after bowel bypass. Ann Neurol 11: 195-97, 1981. [\[Context Link\]](#)
9. Christopher MM, Eckfeldt JH, Eaton JW. Propylene glycol ingestion causes d-lactic acidosis. Lab Invest 62: 114-18, 1990. [Bibliographic Links](#) | [\[Context Link\]](#)
10. Clausen MR, Bonnen H, Tvede M, Mortensen PB. Colonic fermentation to short-chain fatty acids is decreased in antibiotic-associated diarrhea. Gastroenterology 101: 1497-1504, 1991. [Bibliographic Links](#) | [\[Context Link\]](#)
11. Connor H, Woods HF, Ledingham JGG. Comparison of the kinetics and utilization of d- and l-sodium lactate in normal man. Ann Nutr Metab 27: 481-87, 1983. [Bibliographic Links](#) | [\[Context Link\]](#)
12. Coran AG. The effect of lactated Ringer's solution on blood and urine levels of lactate isomers. J Surg Res 11: 450-53, 1971. [Bibliographic Links](#) | [\[Context Link\]](#)
13. Coronado BE, Opal SM, Yoburn DC. Antibiotic-induced d-lactic acidosis. Ann Intern Med 122: 839-42, 1995. [Ovid Full Text](#) | [Bibliographic Links](#) | [\[Context Link\]](#)
14. Craig FN. Renal tubular reabsorption, metabolic utilization and isomeric fractionation of lactic acid in the dog. Am J Physiol 146: 146-59, 1946. [\[Context Link\]](#)
15. Cross SA, Callaway CW. D-lactic acidosis and selected cerebellar ataxias. Mayo Clin Proc 59: 202-5, 1984. [Bibliographic Links](#) | [\[Context Link\]](#)
16. Dahlquist NR, Perrault J, Callaway CW, Jones JD. D-lactic acidosis and encephalopathy after jejunioileostomy: Response to overfeeding and to fasting in humans. Mayo Clin Proc 59: 141-45, 1984. [Bibliographic Links](#) | [\[Context Link\]](#)
17. De Vrese M, Koppenhoefer B, Barth CA. D-lactic acid metabolism after an oral load of dl-lactate. Clin Nutr 9: 23-28, 1990. [Bibliographic Links](#) | [\[Context Link\]](#)
18. De Vrese M, Barth CA. Postprandial plasma d-lactate concentrations after yogurt ingestion. Z

- Ernahrungswiss 30: 131-37, 1991. [Bibliographic Links](#) | [\[Context Link\]](#)
19. De Wind LT, Payne H. Intestinal bypass surgery for morbid obesity. Long term results. JAMA 236: 2298-2301, 1976. [\[Context Link\]](#)
20. Dibner JJ, Knight CD. Conversion of 2-hydroxy-4-(methylthio)butanoic acid to 1-methionine in the chick. A stereospecific pathway. J Nutr 114: 1716-23, 1984. [Bibliographic Links](#) | [\[Context Link\]](#)
21. Drury DR. Chemistry and metabolism of 1- and d-lactic acids. Ann N Y Acad Sci 119: 1061-65, 1965. [Bibliographic Links](#) | [\[Context Link\]](#)
22. Dunlop RH, Hammond PB. D-lactic acidosis of ruminants. Ann N Y Acad Sci 119: 1109-32, 1965. [Bibliographic Links](#) | [\[Context Link\]](#)
23. Duran M, Van Biervliet JPGM, Kamerling JP, Wadman SK. D-lactic aciduria, an inborn error of metabolism. Clin Chim Acta 74: 297-300, 1977. [Bibliographic Links](#) | [\[Context Link\]](#)
24. Flourie B, Messing B, Bismuth E, Etanchaud F, Thuillier F, Rambaud JC. D-lactic acidosis and encephalopathy in short bowel syndrome occurring during antibiotic treatment. Gastroenterol Clin Biol 14: 596-98, 1990. [Bibliographic Links](#) | [\[Context Link\]](#)
25. Fuller TJ, Garg LC, Harty RF, Cerda JJ. Severe hyperchloremic acidosis complicating jejunoileal bypass. Surg Gynecol Obstet 146: 567-71, 1978. [Bibliographic Links](#) | [\[Context Link\]](#)
26. Giesecke D, Fabritius A. Oxidation and excretion of d-lactic acid by rats. Experientia 30: 1124-25, 1974. [Bibliographic Links](#) | [\[Context Link\]](#)
27. Giesecke D, Wallenberg PV. Metabolism of d-lactic acid in rats given high intragastral doses. Comp Biochem Physiol 82B: 255-58, 1985. [Bibliographic Links](#) | [\[Context Link\]](#)
28. Gurevitch J, Sela B, Jonas A, Golan H, Yahav Y, Passwell JH. D-lactic acidosis: A treatable encephalopathy in pediatric patients. Acta Pediatr 82: 119-21, 1993. [\[Context Link\]](#)
29. Haan E, Brown G, Mitchell D, Hunt S, Blakey J, Barnes G. Severe illness caused by the products of bacterial metabolism in a child with a short gut. Eur J Pediatr 144: 63-65, 1985. [Bibliographic Links](#) | [\[Context Link\]](#)
30. Halperin ML, Kamel KS. D-lactic acidosis: Turning sugar into acids in the gastrointestinal tract. Kidney Int 49: 1-8, 1996. [Bibliographic Links](#) | [\[Context Link\]](#)
31. Halverson J, Gale A, Lazarus C. D-lactic acidosis and other complications of intestinal bypass surgery. Arch Intern Med 144: 357-60, 1984. [Bibliographic Links](#) | [\[Context Link\]](#)
32. Hartmann AF, Perley AN, Basman J et al. Further observations on the metabolism and the clinical uses of sodium lactate. J Pediatr 13: 692-714, 1938. [\[Context Link\]](#)
33. Hingorani AD, Macdougall IC, Browne M, Walker RWH, Tomson CRV. Successful treatment of acute d-lactate encephalopathy by hemodialysis. Nephrol Dial Transplant 8: 1283-85, 1993. [Bibliographic Links](#) | [\[Context Link\]](#)
34. Hove H, Nordgaard-Andersen I, Mortensen PB. Faecal dl-lactate concentration in 100 gastrointestinal patients. Scand J Gastroenterol 29: 255-59, 1994. [Bibliographic Links](#) | [\[Context Link\]](#)
35. Hove H, Mortensen PB. Colonic lactate metabolism and d-lactic acidosis. Dig Dis Sci 40: 320-30, 1995. [Bibliographic Links](#) | [\[Context Link\]](#)

36. Hudson M, Pocknee R, Mowat NAG. D-lactic acidosis in short bowel syndrome. An examination of possible mechanisms. *Q J Med* 274: 157-63, 1990. [\[Context Link\]](#)
37. Jover R, Leon J, Palazon JM, Dominguez JR. D-lactic acidosis associated with use of medium-chain triglycerides [letter]. *Lancet* 346: 314, 1995. [Bibliographic Links](#) | [\[Context Link\]](#)
38. Judge MA, Van Eys J. Excretion of d-lactic acid by humans. *J Nutr* 76: 310-13, 1962. [Bibliographic Links](#) | [\[Context Link\]](#)
39. Kadakia SC. D-lactic acidosis in a patient with jejunioileal bypass. *J Clin Gastroenterol* 20: 154-56, 1995. [Bibliographic Links](#) | [\[Context Link\]](#)
40. Karton M, Rettmer RL, Lipkin EW. Effect of parenteral nutrition and enteral feeding on d-lactic acidosis in a patient with short bowel. *J Parenter Enteral Nutr* 11: 586-89, 1987. [Bibliographic Links](#) | [\[Context Link\]](#)
41. Koletzko S, Waag KL, Koletzko B. Recurrent d-lactic acidosis with encephalopathy in a boy with short bowel syndrome. *Dtsch Med Wochenschr* 119: 458-62, 1994. [Bibliographic Links](#) | [\[Context Link\]](#)
42. Kuze S, Naruse T, Yamakasi M, Hirota K, Ito Y, Miyahara T. Effects of sodium l-lactate and sodium racemic lactate on intraoperative acid-base status. *Anesth Analg* 75: 702-7, 1992. [Bibliographic Links](#) | [\[Context Link\]](#)
43. LaManna JC, Harrington JF, Vendel LM, Abi-Saleh K, Lust WD, Harik SI. Regional blood-brain lactate influx. *Brain Res* 614: 164-69, 1993. [Bibliographic Links](#) | [\[Context Link\]](#)
44. Madias NE. Lactic acidosis. *Kidney Int* 29: 752-74, 1986. [\[Context Link\]](#)
45. Mason PD. Metabolic acidosis due to d-lactate. *Br Med J* 292: 1105-6, 1986. [\[Context Link\]](#)
46. Mayne AJ, Handy DJ, Preece MA, George RH, Booth IW. Dietary management of d-lactic acidosis in short bowel syndrome. *Arch Dis Child* 65: 229-31, 1990. [Bibliographic Links](#) | [\[Context Link\]](#)
47. Mc Cabe ERB, Goodman SI, Fennessey PV, Miles BS, Wall M, Silverman A. Glutaric, 3-hydroxypropionic, and lactic aciduria with metabolic acidemia, following extensive small bowel resection. *Biochem Med* 28: 229-36, 1982. [Bibliographic Links](#) | [\[Context Link\]](#)
48. McNeil A, Walmsley RN. A case of combined d-lactate and renal tubular acidosis [letter]. *Clin Chem* 30: 1722, 1984. [Bibliographic Links](#) | [\[Context Link\]](#)
49. Nghiem CH, Bui HD, Chaney RH. An unusual cause of d-lactic acidosis. *West J Med* 148: 332-34, 1988. [Bibliographic Links](#) | [\[Context Link\]](#)
50. Oh MS, Carroll HJ, Goldstein DA, Fein IA. Hyperchloremic metabolic acidosis during the recovery phase of diabetic ketosis. *Ann Intern Med* 89: 925-27, 1978. [Bibliographic Links](#) | [\[Context Link\]](#)
51. Oh MS, Phelps KR, Traube M, Barbosa-Saldivar JL, Boxhill C, Carroll HJ. D-lactic acidosis in a man with the short bowel syndrome. *N Engl J Med* 301: 1109-32, 1979. [\[Context Link\]](#)
52. Oh MS, Uribarri J, Alveranga D, Lazar I, Bazilinski N, Carroll HJ. Metabolic utilization and renal handling of d-lactate in men. *Metabolism* 34: 621-25, 1985. [Full Text](#) | [Bibliographic Links](#) | [\[Context Link\]](#)
53. Oh MS, Uribarri J, Carroll HJ. Electrolyte case vignette: A case of unusual organic acidosis. *Am J Kidney Dis* 11: 80-82, 1988. [Bibliographic Links](#) | [\[Context Link\]](#)
54. Perlmutter DH, Boyle JT, Campos JM, Egler JM, Watkins JB. D-lactic acidosis in children. An unusual

- metabolic complication of small bowel resection. *J Pediatr* 102: 234-38, 1983. [Full Text](#) | [Bibliographic Links](#) | [\[Context Link\]](#)
55. Ramakrishnan T, Stokes P. Beneficial effects of fasting and low carbohydrate diet in d-lactic acidosis associated with short bowel syndrome. *J Parenter Enteral Nutr* 9: 361-63, 1985. [Bibliographic Links](#) | [\[Context Link\]](#)
56. Ravitch M, Brolin RE. The price of weight loss by jejunoileal shunt. *Ann Surg* 190: 382-88, 1979. [Bibliographic Links](#) | [\[Context Link\]](#)
57. Reynolds AF, Villar HV, Kasniak AW. Jejunoileal bypass: A reversible cause of dementia. *Neurosurgery* 9: 153-55, 1981. [Bibliographic Links](#) | [\[Context Link\]](#)
58. Rosenthal P, Pesce M. Long-term monitoring of d-lactic acidosis in a child. *J Pediatr* 4: 674-76, 1985. [\[Context Link\]](#)
59. Satoh T, Narisawa K, Konno T, Katoh T, Fujiyama J, Tomoe A, Metoki K, Hayasaka K, Tada K, Ishibashi M, Yamane N, Mitsuoka T, Benno Y. D-lactic acidosis in two patients with short bowel syndrome. Bacteriological analyses of the fecal flora. *Eur J Pediatr* 138: 324-26, 1982. [Bibliographic Links](#) | [\[Context Link\]](#)
60. Schoorel EP, Giesberts MAH, Blom W, Van Gelderen HH. D-lactic acidosis in a boy with short bowel syndrome. *Arch Dis Child* 55: 810-12, 1980. [Bibliographic Links](#) | [\[Context Link\]](#)
61. Scully TB, Kraft SC, Carr WC, Harig JM. D-lactate-associated encephalopathy after massive small-bowel resection. *J Clin Gastroenterol* 11: 448-51, 1989. [Bibliographic Links](#) | [\[Context Link\]](#)
62. Smith SM, Eng RHK, Buccini F. Use of d-lactic acid measurement in the diagnosis of bacterial infection. *J Infect Dis* 154: 658-64, 1986. [\[Context Link\]](#)
63. Spillane K, Nagendran K, Prior PF, Tabaqchali S, Wilks M. Serial electroencephalograms in a patient with d-lactic acidosis. *Electroencephalogr Clin Neurophysiol* 91: 403-5, 1994. [Bibliographic Links](#) | [\[Context Link\]](#)
64. Stolberg L, Rolfe R, Gitlin N, Merritt J, Mann L, Linder J, Finegold S. D-lactic acidosis due to abnormal gut flora. Diagnosis and treatment of two cases. *N Engl J Med* 306: 1344-48, 1982. [Bibliographic Links](#) | [\[Context Link\]](#)
65. Thornalley PJ. The glyoxalase system: New developments towards functional characterization of a metabolic pathway fundamental to biological life. *Biochem J* 269: 1-11, 1990. [Bibliographic Links](#) | [\[Context Link\]](#)
66. Thurn JR, Pierpont GL, Ludvigsen CW, Eckfeldt JH. D-lactate encephalopathy. *Am J Med* 79: 717-21, 1985. [Bibliographic Links](#) | [\[Context Link\]](#)
67. Traube M, Bock JL, Boyer JL. D-lactic acidosis after jejunoileal bypass: Identification of organic anions by nuclear magnetic resonance spectroscopy. *Ann Intern Med* 98: 171-73, 1983. [Bibliographic Links](#) | [\[Context Link\]](#)
68. Tubbs PK. The metabolism of d-alpha hydroxy acids in animal tissues. *Ann N Y Acad Sci* 119: 920-26, 1965. [Bibliographic Links](#) | [\[Context Link\]](#)
69. Ullrich KJ, Rumrich G, Kloss S. Reabsorption of monocarboxylic acids in the proximal tubule of the rat kidney. Transport kinetics of d-lactate, Na-dependence, pH-dependence and effects of inhibitors. *Pflugers Arch* 395: 212-19, 1982. [Bibliographic Links](#) | [\[Context Link\]](#)
70. Van Eys J, Judge A, Judd J, Hill W, Bozian RC, Abrahams S. A reinvestigation of methylglyoxal

accumulation in thiamine deficiency. J Nutr 76: 375-83, 1962. [Bibliographic Links](#) | [\[Context Link\]](#)

71. Yasuda T. D-lactate metabolism in chronic renal failure. St Marianna Med J 16: 593-605, 1988. [\[Context Link\]](#)

72. Yasuda T, Ozawa S, Shiba C, Maeba T, Kanazawa T, Sugiyama M, Owada S, Ishida M. D-lactate metabolism in patients with chronic renal failure undergoing CAPD. Nephron 63: 416-22, 1993. [Bibliographic Links](#) | [\[Context Link\]](#)

Accession Number: 00005792-199803000-00001

Copyright (c) 2000-2006 [Ovid Technologies, Inc.](#)
Version: rel10.2.2, SourceID 1.11354.1.251