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D-Lactic Acidosis: More Prevalent Than We Think?

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D-lactate acidosis, in which the D-isomer of lactate accumulates, may be more prevalent than once thought. This uncommon disorder has been reported in the setting of short bowel syndrome, and in particular, with high carbohydrate diets in children. Mental status changes and gait instability, the classic symptoms of D-lactate buildup, may not immediately lead the clinician to consider this uncommon disorder. The purpose of this article is to present information about D-lactate that will increase the readers' level of vigilance for this disorder, which affects a broader group of patients than initially thought.

REPRESENTATIVE CASE

A 60 year old male presented to the emergency department after being referred by his primary care physician for evaluation of ataxia and slurred speech.[1] These symptoms had waxed and waned over the course of five months. He had undergone an MRI previously that showed only chronic small vessel disease; a CT of the head performed on the day of admission revealed similar findings.

Eight months prior to admission, the patient had suffered a small bowel volvulus necessitating resection of 420cm of necrotic jejunum and ileum. He also suffered from end-stage renal disease due to longstanding diabetes mellitus (DM) and hypertension, necessitating hemodialysis 3 times /week.

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Within hours after admission the patient became unresponsive and was intubated. He was found to have a severe metabolic acidosis with a pH of 7.02 and an anion gap of 26. Lactate and blood urea nitrogen levels were normal. No osmolar gap was present and a toxicology screen was negative.

Hemodialysis was performed and the patient regained normal neurologic status. He was quickly extubated. D-Lactate, the dextrorotary isomer of lactate, was found to be markedly elevated on a blood specimen sent prior to dialysis. He recovered and was discharged with antibiotic therapy and counseling on dietary modifications. He was noncompliant with his recommended diet and was subsequently admitted multiple times with similar symptoms necessitating multiple intubations. These admissions usually

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occurred after meals heavy in carbohydrates (CHO) and immediately prior to scheduled sessions of dialysis.

Normal Human Metabolism

Lactic acid, like many organic molecules, consists of two mirror-image isomers. L-lactate is produced by the human body and is the isomer tested for in common "lactate" assays.

D-lactate, the mirror image of L-lactate, is produced in minute concentrations in human metabolism via the methylglyoxal pathway that converts acetone derivatives to glutathione.[2] These concentrations are clinically insignificant in normal human metabolism.

Clinical Presentation and Mechanism of Encephalopathy

D-lactate toxicity generally occurs with serum D-lactate levels over 3 mmol/L[3] and is associated with acidosis and a variably presenting encephalopathy. The clinical presentation of the patient with D-lactate toxicity is characterized by acidosis and encephalopathy in the context of the above risk factors. The encephalopathy of D-lactic acidosis is highly variable. Symptoms may include memory loss, fatigue, and personality changes or cerebellar symptoms such as ataxia or dysarthria. Severe cases may involve syncope, coma and respiratory failure, as occurred in the case described.[1,4,5,6] Symptoms are similar in both humans and in ruminants, which suffer an analogous disease due to malabsorption and dehydration.[2] The cerebellum appears to be most sensitive to elevated D-lactate levels; investigation of potential toxicity should include a careful exam of cerebellar function with speech, gait and balance testing.

The mechanism for D-lactate encephalopathy remains unclear. D-lactate freely passes into the cerebral spinal fluid.[7] Serum and urine levels do not always correlate to symptoms[4] and healthy volunteers infused with D-lactate showed no signs of encephalopathy even when concentrations reached up to 6.7 mmol/L.[8] It has been proposed that given these findings, D-lactate may be a proxy for other neurotoxic organic acids that have not yet been identified.[3,5] Some cases of D-lactate encephalopathy appear related to thiamine deficiency.[9,5,3,10]

Several findings suggest that D-lactate may be a direct player in precipitating neurologic symptoms. L-lactate buildup and acidemia do not by themselves cause encephalopathy. D-lactate directly infused into the brain in animal models, however, impairs memory and reduces brain cell survival.[6]

Symptoms of congenital pyruvate deficiency are similar to those seen in D-lactate toxicity.[11] D-lactate (and acidosis itself) impairs the action of pyruvate dehydrogenase (PDH), interfering with pyruvate metabolism and inhibiting utilization of L-lactate as a fuel in the brain. As cerebellar PDH is already reduced relative to the serum, a relatively low concentration of D-lactate may lead to clinical symptoms, even as serum levels of PDH remain adequate.[6,3]

At-Risk Populations

D-lactate toxicity has been historically associated with patients suffering from short bowel syndrome (SBS). Ingestion, parenteral infusion via D-lactate containing fluids (such as Ringer's lactate), peritoneal lavage, and impaired metabolism and excretion have all contributed to D-lactate toxicity in patients without SBS, though these causes are rare. It is likely that pathologic D-lactate buildup is under diagnosed; surveillance of 470 randomly selected hospital patients revealed detectable D-lactate levels in nearly 3 percent; less than two-thirds of these patients had a history of gastrointestinal surgery.[4]

Patients with SBS, particularly those with colon in continuity, but also those with small bowel bacterial overgrowth (SBBO), are at high risk for derangement of the balance of gut flora, as described below. These patients are most at risk when they suffer from the delivery of excess CHO to colonic bacteria and are unable to effectively metabolize and excrete the D-lactate produced.[2,3,4,5] See Table 1 for at risk populations.

Laboratory Testing

The clinician should suspect D-lactate toxicity in the patient presenting with neurologic symptoms, a gap or non-gap acidosis, and risk factors for D-lactate overproduction or retention. Obtaining a D-lactate level may confirm an often difficult clinical diagnosis.

D-lactate is not detected in standard clinical lactic acid assays and requires a specific request from the lab. Despite this, an elevated concentration of D-lactate in the plasma always causes acidosis and usually leads to an increased anion gap. However, the anion gap may be lower than one would expect with similar concentrations

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of L-lactate or may even be normal.[12] A fraction of D-lactate is excreted with sodium or potassium in the urine, which may lead to a relative non-gap (or low strong ion difference) acidosis. A normal anion gap does not therefore definitively exclude D-lactic acidosis.

Testing for D-lactate requires a targeted assay and usually will require the services of a reference laboratory. This author utilizes Mayo Laboratories (Mayo Medical Laboratories, Rochester MN. http://www.mayomedicallaboratories.com). D-lactate can be measured easily in urine and plasma specimens. Given high levels of urinary D-lactate excretion, a urine specimen will be more sensitive for clinically significant D-lactate toxicity. The turnaround time between specimen receipt and result may be up to 8 days. Because of this, laboratory testing should be considered supportive of a clinical diagnosis; treatment should not be delayed if the suspicion for toxicity is high.

Causes

Bacterial Production and the Short Bowel Syndrome

Bacteria are almost always the predominant generator of D-lactate in mammals. Normal human gut flora is governed by a complex and still incompletely understood balance of factors. Normal human flora consists predominantly of *Bacteroides* and *Firmicutes* species; other species make up approximately 10% of the remainder. Concentrations of bacteria progressively increase by orders of magnitude from the stomach and duodenum to the colon.[13]

Both isomers of lactate are produced by usual human colonic flora as they metabolize small amounts of CHO, protein, non-absorbable starches, and fiber. The principal source of D-lactate production in the human gut is due to *Lactobacillus* and *Bifidobacteri* species.[2] *E. coli*, Klebsiella *pneumoniae* and *Candida freundii* also produce significant quantities of D-lactate while producing minimal amounts of L-lactate.[14] Some lactobacillus species are able to catalyze one lactate isomer to the other.[15,16,2] Much of this lactate is converted to short chain fatty acids, which play an important role in the nutrition and maintenance of the mucosal integrity of the colonic epithelium.[15]

The delicate interplay of the healthy gut microbiome ensures that metabolites are appropriately utilized or excreted. Exposure of the colonic flora to excess (CHO), particularly in those with malabsorption, that presents more than the "usual" amount of CHO to the colon such as SBS or roux en y gastric bypass, can lead to an increase in lactate production via fermentation. This may occur either due to increased transit of CHO to the colon, to SBBO, or both.[12]

The luminal pH in the normal proximal small bowel is between 5.5 to 7.0. It becomes progressively more alkalotic through the jejunum and ileum. The cecal luminal pH is somewhat more acidotic (6.2) than the terminal ileum (7.6), but again becomes more alkalotic through the colon.[17]

As more CHO is fermented into lactate, luminal acidity increases and pH decreases. This decreasing pH selects for an increase in acid-tolerant fermenting bacteria, leading to a vicious cycle of fermenter overgrowth and increasing lactate production. Lactobacilli quickly become the predominant organism in patients suffering from SBS with malabsorption.[14] Some of this lactate is translocated into the systemic circulation. While L-lactate is metabolized fairly readily, the human's limited capacity for D-lactate metabolism and excretion,[17] reduction of D-lactate metabolism due to acidosis,[2] or interconversion between lactate isomers by certain lactobacilli,[15,16,2] can all contribute to increasing concentrations of D-lactate.

Defects in CHO absorption via an anatomic or functional short gut are responsible for most cases of pathologic bacterial overproliferation. D-lactate toxicity has also been reported in patients with SBS after the administration of probiotics consisting of D-lactate producing species, overconsumption of D-lactate producing yoghurt, and with the use of antibiotics that allow *Lactobacillus* overproliferation.[4,10,3,5,18]

Other Sources of D-Lactate

While bacterial production accounts for the vast majority of cases of D-lactate toxicity, other causes have been reported. D-lactate appears to be elevated in at least some cases of diabetic ketoacidosis.[19,20] One metabolic fate of D-lactate is conversion to fatty acids, but this can happen only in the context of high insulin levels,[12] which most patients with DM lack.

D-lactate toxicity has also been reported with propylene glycol ingestion.[21] Propylene glycol is a diluent used in the preparation of many liquid medications, such as lorazepam. While lactic acidosis is a well-known complication of propylene glycol toxicity, controlled infusion of propylene glycol causes dose-dependent increases in D-lactate, even as L-lactate

Table 1. Conditions Increasing the Risk of D-Lactate Toxicity

High Risk
Short Bowel Syndrome
Roux-en-y gastric bypass
Antibiotic or probiotic overuse
Comorbid Conditions that may Increase Risk
Thiamine deficiency
Renal failure
Diabetes Mellitus
Propylene glycol ingestion

(the only isomer measured in common lactate assays), decreases.[22]

D-lactate is sometimes directly administered via some formulations of Ringer's lactate containing both isomers of lactate. One review associated administration of fluids containing D-lactate with worsened clinical outcomes.[23] Peritoneal dialysate may also be a source of D-lactate.[3,5]

Sepsis, gut ischemia, and intestinal perforation have been associated with elevated levels of D-lactate. This is likely due both to increased production and translocation across the damaged intestinal mucosa.[24,25,26] D-lactate has in fact been suggested as a sensitive and specific marker of mesenteric ischemia,[26] though the lack of ready availability of a D-lactate assay in most institutions limits its utility in this respect.

Metabolism and Excretion

Not all patients with SBS suffer from D-lactate toxicity, even when their CHO ingestion is unrestricted. Impaired D-lactate metabolism superimposed on excess production likely plays a significant role in most cases of toxicity.[5,27]

Accumulation of D-lactate in the circulation is abnormal. While early studies suggested that humans could not metabolize D-lactate, a certain quantity of D-lactate can in fact be metabolized into pyruvate via D-2 hydroxy acid dehydrogenase (D-2 HDH).[5]

Unlike L-lactate, which is efficiently metabolized, the metabolism of D-lactate is relatively slow and limited to a relatively small amount.[17] D-2 HDH is found principally in the kidney and liver; impairment of these organs may lead to reduced D-lactate metabolism. Acidemia itself also impairs D-lactate metabolism due to a decrease in PDH activity, potentially leading to a loss of homeostasis should lactate levels accumulate enough to cause significant acidosis.[3]

Low levels of insulin may promote the buildup of D-lactate. Insulin inhibits the conversion of triglycerides to fatty acids, increasing the amount of organic acids, including D-lactate, that are metabolized. Thus, physiologic insulin release concurrent with CHO ingestion may have a protective effect in minimizing D-lactate toxicity.[12] Even otherwise healthy patients with DM demonstrate elevated levels of serum and plasma D-lactate.[28]

Pyruvate acts as an intermediate product in D-lactate metabolism. Thiamine, a cofactor in pyruvate metabolism, may be deficient in patients suffering from malnutrition. Thiamine deficiency has been associated with lactic acidosis.[9] Patients suffering from SBS, abnormal gut flora and/or malabsorption syndromes are at increased risk for thiamine deficiency. This deficiency, when paired with the elevated lactate production from abnormal gut flora, may lead to large amounts of excess lactate that cannot be effectively metabolized.

The kidneys excrete a significant amount of D-lactate; the proportion excreted increases with increasing plasma concentrations.[19] Limited metabolic potential makes renal excretion an important vehicle for elimination in cases of pathologic D-lactate production. While moderately decreased renal function does not seem to significantly reduce excretion,[19] severe renal impairment, as in the case of patients dependent on hemodialysis, may lead to catastrophic levels of D-lactate.[1]

Treatment and Prevention

D-lactate is the product of a substrate (usually CHO), produced largely by fermentative bacteria, which is then ultimately metabolized or excreted. D-lactate toxicity generally arises from excess substrate along with some catalyst for production, from impaired metabolism, excretion, or both.[1,12] Effective prevention and treatment entails targeting each of these pathways. The mainstays of treatment are CHO restriction, hydration, cautious use of probiotics, and avoidance of SBBO (see Table 2).

Table 2. Treatment Options

Substrate Reduction

- Low simple CHO diet
- Fructose and sugar alcohol avoidance
- Temporarily remove all enteral substrates (oral/enteral feedings)
  - Parenteral nutrition if needed in severe cases
- Adequate hydration (avoid Ringer's Lactate)
- Caution when using probiotics consisting of D-lactate producing species

Reduced Production/Increased Excretion:

- Antibiotic therapy for small intestinal bacterial overgrowth (see Table 3)
- Thiamine repletion
- Parenteral bicarbonate
- Hemodialysis in severe cases

Diet

Patients with SBS who are at risk for SBBO should be encouraged to limit simple CHO intake (cakes, cookies, pie, candies, etc.) as well as sugar alcohols (sorbitol, mannitol, xylitol, etc.), fructose and other highly osmolar, fermentable compounds and excess fiber.[29,30] CHO should be complex and modest in quantity (16), with small and frequent meals to avoid exposure of the gut flora to large, poorly absorbed boluses of CHO. It has also been suggested that fermented foods, such as yoghurt, sauerkraut and pickles be avoided given high preexisting concentrations of D-lactate.[3]

In the patient with D-lactic encephalopathy, temporary cessation of all enteric feeding is reasonable. Elimination of substrate to the gut should prevent bacterial production. Fasting has been associated with rapid improvement in D-lactate associated encephalopathy.[7,5] Concomitant parenteral nutrition does not increase D-lactate levels, though it may reduce excretion as other organic acids compete with D-lactate for tubular excretion.[7]

Antimicrobial Strategies

SBBO is responsible for most cases of D-lactate toxicity; prevention of this overgrowth is important.[31]

Antibiotic therapy (see Table 3) may increase or reduce D-lactate production, depending on the gut flora selected for. Trimethoprim-sulfamethoxazole (TMP-SMX), doxycycline, and neomycin, for example, have each been associated with episodes of D-lactate encephalopathy.[7,18,32] Each of these antibiotics has also been used in the *treatment* of SBBO.[1,14,31] Likewise, metronidazole has been used successfully.[30,16] but some lactobacilli in cases of D-lactate toxicity have exhibited metronidazole resistance.[32] Rifaximin is increasingly used in the treatment of SBS with SBBO.[31,33] Though lactobacilli can grow even at high intraluminal concentrations of rifaximin,[34] to date no cases of D-lactate encephalopathy definitively associated with rifaximin use have been reported.

A four-year study of fecal bacteria, lactate production, and resistance patterns in patients suffering SBS demonstrated poor results when attempting to treat D-lactate toxicity with antibiotic therapy; neomycin and oral vancomycin were successful in reducing certain lactobacillus isolates, but did not affect symptomatic resolution.[14] A patient suffering from multiple episodes of D-lactic acidosis after TMP-SMX and doxycycline use suffered no episodes when taking ciprofloxacin, and cultured lactobacilli demonstrated ciprofloxacin sensitivity.[32] Amoxicillin has been used due to its effective coverage of lactobacilli and high intraluminal gut concentration, but did not prevent recurrence when taken chronically.[1]

Antimicrobial therapy should be selected with caution in patients at risk for SBBO as certain antibiotics may select for lactate-producing gut flora. While it is reasonable to treat acute episodes of D-lactate toxicity with antibiotic therapy targeting *Lactobacillus* species, chronic preventive antibiotic therapy has not demonstrated consistent effect. In the patient suffering from recurrent episodes of D-lactate encephalopathy, fecal culture and sensitivities should be considered to ensure appropriately targeted therapy. Given the complexity of the healthy gut milieu, no single antibiotic regimen is likely to yield satisfactory results on its own.

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Enhancement of Metabolism and Excretion

Only a minority of patients who neglect dietary interventions will develop D-lactate toxicity, even if they are actively suffering from SBBO. One study of eleven patients with SBS and no neurologic symptoms demonstrated D-lactate overproduction in most fecal samples, but none in the urine.[27] Symptoms should trigger a search for causes of impaired metabolism and excretion.

Thiamine deficiency may both result from malnutrition and poor absorption, and contribute to reduced clearance of D-lactate due to impaired pyruvate metabolism.[9] The cerebellum is particularly sensitive to thiamine deficiency.[11] In some instances of encephalopathy associated with excess D-lactate, thiamine supplementation alone has led to symptomatic resolution.[11,35] It is reasonable to supplement the patient suffering from neurologic symptoms with thiamine,[9,5,3,10] particularly as this same set of patients is also at high risk for Wernicke's Encephalopathy, which may present with similar neurologic findings. We recommend aggressive treatment, supplementing all patients with neurologic symptoms at risk for thiamine deficiency with 500mg parenterally three times daily for 1-2 days and then 100mg orally or parentally indefinitely thereafter.

A significant proportion of D-lactate that accumulates in the serum is excreted in the urine.[19] Impaired excretion can lead to D-lactate buildup. Maintenance of euvolemia is important in the prevention of D-lactate toxicity; aggressive hydration is crucial in its treatment. SBS is associated with dehydration, particularly in the case of malabsorption due to poor dietary adherence;[29] consequently, patients suffering from SBBO may also suffer from renal hypoperfusion and reduced excretion of D-lactate. Of note, fluids such as Ringer's lactate with racemic mixtures of lactate should be avoided.[23]

Hemodialysis effectively clears both isomers of lactate and has been successful in treating episodes of severe D-lactate toxicity.[1,21,36] Anuric or oliguric patients already undergoing dialysis who suffer

Table 3. Antibiotic Therapy

No duration of therapy has been established but treatment should be short (e.g. 7-14 days) and limited to symptomatic resolution.

Medication	Adult Dose	Daily Frequency
Rifaximin	550mg	2-3 x
Amoxicillin	500mg	2 x
Vancomycin (oral)	125-500mg	1-4 x
Metronidazol	500mg	3 x
Ciprofloxacin	500mg	2 x
Neomycin*	500mg	2 x
Trimethoprim-Sulfamethoxazole*	1 double strength tablet	2 x

**Note that these antibiotics have also been reported to provoke D-lactic acidosis*

recurrent episodes of D-lactate toxicity may benefit from longer or more frequent hemodialysis sessions to promote clearance, as they have no other means of excretion. Patients with D-lactate toxicity already undergoing peritoneal dialysis should be considered for hemodialysis given the presence of D-lactate in peritoneal dialysate.[3,5]

Other Proposed Treatments

Bicarbonate has been given parenterally in the treatment of D-lactic acidosis.[2,1,5] This may enhance D-lactate metabolism, as the responsible enzyme is impaired by acidosis. Notably, this is in contrast to recommendations that undifferentiated lactic acidosis (which is usually principally L-lactate) *not* be treated with bicarbonate.[37] One case report reported symptomatic resolution with oral and intravenous bicarbonate administration.[5] Bicarbonate has also been successful in the treatment of drunken lamb syndrome, an analogous process in ruminants, when given in conjunction with parenteral amoxicillin.[38]

Growth of lactate-producing fermentative bacteria both promotes, and is enhanced by, intraluminal acidosis. Antacids have thus been proposed[3] as a potential treatment, but given the association of acid suppressive therapy with SBBO and increased intestinal transit time,[33] they should be used with caution, if at all.

D-lactate levels in otherwise healthy patients with DM can be elevated,[28] possibly due to insulin deficiency or resistance. Insulin has been suggested as a potential therapy for severe D-lactic acidosis on the principle that it may inhibit lipolysis and thus promote increased metabolism of D-lactate.[12] This has yet to be widely evaluated; at present it seems prudent to simply pursue usual treatment for hyperglycemia.

SUMMARY

D-lactate toxicity remains an uncommon, but likely under recognized syndrome. It occurs principally in patients with SBS who suffer acute processes that impair the limited human capacity to metabolize and excrete D-lactate, but may be missed in other disease processes due to the wide variability in symptoms and delay in obtaining confirmatory testing. Wider recognition of the syndrome and careful monitoring of those at risk for it, paired with a multidisciplinary approach to encourage compliance with dietary recommendations, will help to prevent and reduce its incidence even further. ■

References

1. Htyte N, White L, Sandhu G, et al. An extreme and life-threatening case of recurrent D-lactate encephalopathy. Nephrol Dial Transplant. 2011;26(4):1432-5.
2. Ewaschuk JB, Naylor JM, Zello GA. D-lactate in human and ruminant metabolism. J Nutr. 2005;135(7):1619-25.
3. Petersen C. D-lactic acidosis. Nutr Clin Pract. 2005;20(6):634-45.
4. Rehman A, Badger C, Patel, N, et al. Brain fogginess, gas, bloating and distension: a link between SIBO, probiotics and metabolic acidosis. Poster. Presented (DDW 2014, Chicago, IL). Gastroenterology 2014;146(5):S850-1.
5. Uribarri J, Oh MS, Carroll HJ. D-lactic acidosis A review of clinical presentation, biochemical features, and pathophysiologic mechanisms. Medicine (Baltimore). 1998;77(2):73-82.
6. Gibbs ME, Hertz L. Inhibition of astrocytic energy metabolism by D-lactate exposure impairs memory. Neurochem Int. 2008;52(6):1012-8.
7. Karton M, Rettmer RL, Lipkin EW. Effect of parenteral nutrition and enteral feeding on D-lactic acidosis in a patient with short bowel. JPEN J Parenter Enteral Nutr. 1987;11(6):586-9.
8. Oh MS, Uribarri J, Alveranga D, et al. Metabolic utilization and renal handling of D-lactate in men. Metabolism. 1985;34(7):621-5.
9. Adeva-Andany M, López-Ojén M, Funcasta-Calderón R, et al. Comprehensive review on lactate metabolism in human health. Mitochondrion. 2014;17:76-100.
10. Ku WH, Lau DC, Huen KF. Probiotics provoked D-lactic acidosis in short bowel syndrome: Case report and literature review. Hong Kong J. Paediatr. 2006;11:246-254
11. Vella A, Farrugia G. D-lactic acidosis: pathologic consequence of saprophytism. Mayo Clin Proc. 1998;73(5):451-6.
12. Halperin ML, Kamel KS. D-lactic acidosis: turning sugar into acids in the gastrointestinal tract. Kidney Int. 1996;49(1):1-8
13. Schippa S, Conte MP. Dysbiotic events in gut microbiota: impact on human health. Nutrients. 2014;6(12):5786-805.
14. Bongaerts GP, Tolboom JJ, Naber AH, et al. Role of bacteria in the pathogenesis of short bowel syndrome-associated D-lactic acidemia. Microb Pathog. 1997;22(5):285-93.
15. Wong JM, de Souza R, Kendall CW, et al. Colonic health: fermentation and short chain fatty acids. J Clin Gastroenterol. 2006;40(3):235-43
16. Hove H, Mortensen PB. Colonic lactate metabolism and D-lactic acidosis. Dig Dis Sci. 1995;40(2):320-30.
17. Nugent SG, Kumar D, Rampton DS, et al. Intestinal luminal pH in inflammatory bowel disease: possible determinants and implications for therapy with aminosalicylates and other drugs. Gut. 2001;48(4):571-7.
18. Flourie B, Messing B, Bismuth E, et al. [D-lactic acidosis and encephalopathy in short-bowel syndrome occurring during antibiotic treatment]. Gastroenterol Clin Biol. 1990;14(6-7):596-8.
19. Bo J, Li W, Chen Z, et al. D-lactate: a novel contributor to metabolic acidosis and high anion gap in diabetic ketoacidosis. Clin Chem. 2013;59(9):1406-7.
20. Lu J, Zello GA, Randell E, et al. Closing the anion gap: contribution of D-lactate to diabetic ketoacidosis. Clin Chim Acta. 2011;412(3-4):286-91.
21. Jorens PG, Demey HE, Schepens PJ, et al. Unusual D-lactic acid acidosis from propylene glycol metabolism in overdose. J Toxicol Clin Toxicol. 2004;42(2):163-9.

22. Christopher MM, Eckfeldt JH, Eaton JW. Propylene glycol ingestion causes D-lactic acidosis. Lab Invest. 1990;62(1):114-8.
23. Kuwabara K, Hagiwara A, Matsuda S, et al. A community-based comparison of trauma patient outcomes between D- and L-lactate fluids. Am J Emerg Med. 2013;31(1):206-14.
24. Jørgensen VL, Reiter N, Perner A. Luminal concentrations of L- and D-lactate in the rectum may relate to severity of disease and outcome in septic patients. Crit Care. 2006;10(6):R163.
25. Filiz AI, Aladag H, Akin ML, et al. The role of d-lactate in differential diagnosis of acute appendicitis. J Invest Surg. 2010;23(4):218-23.
26. Murray MJ, Gonze MD, Nowak LR, et al. Serum D(-)-lactate levels as an aid to diagnosing acute intestinal ischemia. Am J Surg. 1994;167(6):575-8.
27. Bustos D, Pons S, Pernas JC, et al. Fecal lactate and short bowel syndrome. Dig Dis Sci. 1994;39(11):2315-9.
28. Talasniemi JP, Pennanen S, Savolainen H, et al. Analytical investigation: assay of D-lactate in diabetic plasma and urine. Clin Biochem. 2008;41(13):1099-103.
29. Parrish CR, DiBaise JK .Short bowel syndrome in adults – Part 2. Nutrition therapy for short bowel syndrome in the adult patient. Pract Gastroenterol 2014;XXXVIII(10):40-51
30. Park B, Fichadia U, Shah A. A 3-year-old boy with ataxia. Pediatr Emerg Care. 2015;31(3):220-1.
31. Chan LN, DiBaise JK, Parrish CR. Short bowel syndrome in adults – Part 4A. A guide ot front line drugs used in the treatment of short bowel syndrome. Pract Gastroenterol 2014;XXXIX(3):28-41
32. Coronado BE, Opal SM, Yoburn DC. Antibiotic-induced D-lactic acidosis. Ann Intern Med. 1995;122(11):839-42.
33. Bures J, Cyrany J, Kohoutova D, et al. Small intestinal bacterial overgrowth syndrome. World J Gastroenterol. 2010;16(24):2978-90.
34. Maccaferri S, Vitali B, Klinder A, et al. Rifaximin modulates the colonic microbiota of patients with Crohn's disease: an in vitro approach using a continuous culture colonic model system. J Antimicrob Chemother. 2010;65(12):2556-65.
35. Hudson M, Pocknee R, Mowat NA. D-lactic acidosis in short bowel syndrome--an examination of possible mechanisms. Q J Med. 1990;74(274):157-63.
36. Hingorani AD, Macdougall IC, Browne M, et al. Successful treatment of acute D-lactate encephalopathy by haemodialysis. Nephrol Dial Transplant. 1993;8(11):1283-5.
37. Boyd JH, Walley KR. Is there a role for sodium bicarbonate in treating lactic acidosis from shock?. Curr Opin Crit Care. 2008;14(4):379-83.
38. Angell JW, Jones GL, Voigt K, et al. Successful correction of D-lactic acid neurotoxicity (drunken lamb syndrome) by bolus administration of oral sodium bicarbonate. Vet Rec. 2013;173(8):193.