Lactic Acidosis: Recognition, Kinetics, and Associated Prognosis

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- Lactic acidosis • Mitochondria • Prognosis
- Critical care • Shock • Metabolic diseases

LACTATE HISTORY

Lactic acidosis in the setting of severe illness has a history dating back into the 1800s when Johann Joseph Scherer first measured lactic acid levels in postmortem blood from two women dying of puerperal fever. Subsequently, Folwarczny in 1858 described elevated lactate levels in a living patient with leukemia1 and was later followed by Salomon in 1878, who observed increased lactate levels in patients with chronic obstructive pulmonary disease, pneumonia, solid tumors, and congestive heart failure.1 Several years later, Fletcher described how lactic acid was produced by skeletal muscle under anaerobic conditions, noting that when oxygen was readily available, it “either restrains by some guidance of chemical event the yield of acid in the muscle, or is able to remove it after its production.”2 These observations made more than 100 years ago represent the groundwork laid in understanding of lactic acid in the disease states of critically ill patients.

In the late 1950s, Huckabee3–6 performed a series of important physiologic experiments, summarizing the relationship of blood lactate and pyruvate levels to various oxygen-deficient states, including extreme exercise, breathing of low oxygen tension gases, and impaired cardiac output. He went on to demonstrate elevated levels from patients in various stages of shock.7 Nearly 2 decades later, Woods and Cohen8 created a classification scheme of lactic acidosis based on Huckabee’s original work, designating type A as that arising from decreased perfusion or oxygenation

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and type B stemming from underlying diseases, medication/intoxication, or inborn error of metabolism. This scheme continues to be used to this day as a means of classifying and understanding the origins of elevated lactate. Further study on lactate metabolism expanded views of lactate use in the body. In the 1980s, the idea of lactate shuttles and lactate itself as a source of energy was first postulated.\textsuperscript{9} Lactate was no longer thought of as a dead-end byproduct of metabolism but a normal and at times a preferred source of metabolic fuel.

**LACTATE METABOLISM**

Lactate is formed from the reduction of pyruvate via the enzyme lactate dehydrogenase:

\[
\text{Pyruvate} + \text{NADH} \leftrightarrow \text{lactate} + \text{NAD}^+
\]

This process produces two molecules of ATP, making formation of lactate a source of cellular energy during anaerobic metabolism. The reaction occurs within the cytosol as the final step of glycolysis.\textsuperscript{10} At a basal physiologic state, the reaction favors lactate formation from pyruvate in an approximately 10:1 ratio.\textsuperscript{6} The reduction of pyruvate is the only known pathway for lactate production, making this a unique way of monitoring anaerobic metabolic processes (Fig. 1).

Lactate levels in the blood result from the balance between production and clearance, a source of significant scientific interest over the past few decades. Normally, blood lactate levels are less than 2 mmol/L.\textsuperscript{11} In normal physiologic conditions, approximately 1500 mmol of lactate are produced daily primarily from skeletal muscle, skin, brain, intestine, and red blood cells.\textsuperscript{11} In severe illness, lactate production occurs in many other tissues. The lungs, for example, can be a significant source of lactate during acute lung injury despite the absence of tissue hypoxia.\textsuperscript{12} Leukocytes may also produce large amounts of lactate during phagocytosis\textsuperscript{13} or when activated in sepsis.\textsuperscript{14} The splanchnic organs, such as the liver and intestines, are another potential source of lactate production and may be particularly vulnerable to disproportionate vasoconstriction in low perfusion states. Whether or not this mechanism contributes to elevated gut lactate in sepsis remains a matter of debate.\textsuperscript{15} De Backer and colleagues\textsuperscript{15} showed, using hepatic venous oximetry, that only 6 of 90 patients with severe sepsis had splanchnic lactate production, even in those with severely elevated serum lactate levels.

Lactate clearance occurs principally in the liver (60%) with important contributions from the kidney (30%) and to a lesser extent other organs (heart and skeletal muscle).\textsuperscript{16} Utilization occurs via the Cori cycle where lactate is converted back to pyruvate and eventually to glucose through gluconeogenesis.\textsuperscript{17} It has been shown that in patients with chronic liver disease (usually grade III or IV encephalopathy),\textsuperscript{18} lactate clearance is diminished, thus also contributing to elevated blood levels.\textsuperscript{14} In addition to metabolic clearance mechanisms, lactate can be excreted by the kidney once the renal threshold is exceeded (approximately 5 mmol/L).\textsuperscript{11} Thus, hepatic and renal impairment can alter lactate clearance.

Lactic acidosis is typically present in shock states in which tissue oxygen delivery \((\text{DO}_2)\) is insufficient to meet cellular demand. In this classic type A lactic acidosis, flux through the glycolytic pathway increases, leading to an accumulation of pyruvate. In a low oxygen tension state, pyruvate does not enter the mitochondria for oxidative phosphorylation. Hypoxia has been known to inhibit pyruvate dehydrogenase (PDH) complex\textsuperscript{19} involved in aerobic breakdown of pyruvate to acetyl coenzyme A (CoA) for entry into the Krebs cycle. It also is known to inhibit pyruvate carboxylase, which
converts pyruvate into oxaloacetate early in the process of gluconeogenesis. This causes rapid accumulation of pyruvate, and pyruvate metabolism is subsequently shifted almost in entirety toward lactate formation. Subsequently, intracellular lactate concentration rapidly increases, leading to excretion into the bloodstream. Clinically significant formation of lactate from low perfusion was most notably shown in a group of cardiogenic shock patients by Levy and colleagues where lactate:pyruvate ratios were calculated at 40:1 as compared with controls (10:1). Further evidence for increased lactate production during shock states came from Revelly and colleagues, who compared seven patients with cardiogenic shock and seven patients with septic shock to seven healthy controls. By infusing $^{13}$C-radiolabeled lactate and $^2$H-labeled glucose continuously, they showed that hyperlactatemia resulted from overproduction of lactate and that clearance was similar in all three groups.

Excess lactate production may not be the only contributor to hyperlactatemia in critically ill patients. Levraut and colleagues showed that in patients with hemodynamically stable sepsis, elevated lactate levels are more related to altered clearance than to overproduction. The overall metabolism of lactate in critical illness is, therefore, a highly complex process with many factors influencing blood lactate levels. Lactate itself is probably not harmful and is shuttled to tissues during stress states as a carbon...
backbone energy fuel. When lactate levels are elevated in the blood, it may be more of an indicator of an underlying stress state and not necessarily the direct cause of the pathogenesis.

ROLE AS A PROGNOSTIC MARKER IN CRITICALLY ILL PATIENTS

Whether or not blood lactate levels are elevated due to increased production or decreased clearance, monitoring levels may prove valuable as a biomarker of an underlying critically ill state, such as shock. Lactate is one of many markers used for prognosis in critically ill patients and a value greater than 4 mmol/L is recommended by the surviving sepsis campaign as suggestive of severe sepsis requiring aggressive resuscitation.

Huckabee performed the first analyses of elevated lactate levels in patients of varying degrees of shock. He reported a case series of nine patients with lactic acidosis complaining of hyperpnea and dyspnea. The clinical syndrome progressed to weakness, stupor, and death during various stages of other severe illnesses (ie, postgastrectomy, poliomyelitis, pneumonia, and bacterial endocarditis). He found a wide range of lactate levels (3–26 mmol/L) at various days into their illness. He noted elevated lactate levels indicative of widespread tissue hypoxia but no apparent cause of the hypoxia. In his article, he states, “the chemical syndrome could be reproduced in animals only by gradual peripheral circulatory failure and this syndrome could not be ruled out in the patients.”

By the 1970s, Weil and Afifi and Cady and colleagues expanded on Huckabee’s experiments showing prospectively that lactate was a strong predictor for death in critically ill patients. Death occurred in two-thirds of patients with lactate levels above 3.8 mmol/L and approached 90% as levels neared 8 mmol/L. Later, in 1994, Stacpoole and colleagues reported on the natural history of elevated lactate in critically ill medical and surgical patients, demonstrating that elevated lactate levels (>5 mmol/L) predicted death over time. Survival was 59%, 41%, and 17% at 1, 3, and 30 days, respectively, for patients with persistently abnormal lactate levels. Median survival overall in this group was 2 days.

More recently, in 2007, Trzcianiak and colleagues observed initial serum lactate levels in more than 1100 patients seen in an emergency department (ED), an intensive care unit (ICU), and general hospital wards. Lactate levels were divided into low (0–2 mmol/L), intermediate (2.1–3.9 mmol/L), and high (>4.0 mmol/L). They found a lactate level of greater than 4 mmol/L to be highly specific (89%–99%) for predicting acute phase of death and in-hospital death in all three groups (Fig. 2). They concluded that initial lactate levels (on suspicion of clinical sepsis) could be used to augment but not replace bedside mortality assessment no matter the location of the patient (ED, ward, or ICU).

Shapiro and colleagues took patients with suspected infection in an ED and hypothesized that initial serum lactate levels would predict hospital mortality. Again, lactate levels were stratified into low (<2.5 mmol/L), intermediate (2.5–4 mmol/L), and high (>4 mmol/L). They showed an increasing likelihood of mortality (4%, 9%, and 28.4%, respectively) for each group and calculated 92% specificity for death. Later, in 2007, Shapiro’s group enrolled normotensive and hypotensive patients presenting to an ED with suspected infection. They showed an odds ratio of death of 2.2 for those patients with intermediate lactate levels and an odds ratio of 7.1 for high lactate levels. These values were independent of hypotension (Fig. 3). Mortality in the normotensive patients with lactate levels greater than 4 mmol/L was similar to normolactatemic patients who had systolic blood pressures less than 70 mm Hg.
The question remains: Is initial lactate level a true risk stratification biomarker or just a manifestation of organ dysfunction? Mikkelsen and colleagues performed a recent single-center cohort of 830 patients with severe sepsis admitted through an ED. They looked at shock and nonshock patients with low (<2.5 mmol/L), intermediate (2.5–4 mmol/L), and high (>4 mmol/L) levels of lactate. They found that initial serum lactate level predicted mortality in both groups and found mortality to be 15.4%, 37%, and 46.9% in the low, medium, and high lactate groups with septic shock, respectively. They also found mortality of 8.7%, 16.4%, and 31.8% in the nonshock groups, respectively. These values were calculated after correction for organ dysfunction with Acute Physiology and Chronic Health Evaluation (APACHE) II scores, showing the predictive power of initial lactate level uniquely as a biomarker. Relatively high mortality was seen in nonshock septic patients with relatively intermediate levels of lactate (2.5–4 mmol/L). Shapiro and Mikkelsen demonstrated predicted mortalities in these patients of approximately 15%. Normotensive patients with presumed sepsis and intermediately high lactate levels likely represent an at-risk subgroup of patients in whom early and aggressive resuscitation may improve mortality. The surviving sepsis campaign recommends early goal directed therapy in individuals with severe sepsis or septic shock, particularly if lactate level is greater than 4 mmol/L. Jansen and colleagues showed that blood lactate levels were strongly associated with Sequential Organ Failure Assessment scores, especially early in the ICU stay. They found that initial lactate levels between 2 and 3 mmol/L corresponded to 60% mortality. Perhaps the initiation of early goal directed therapy as recommended by the surviving sepsis campaign should be expanded to include those patients with presumed sepsis and intermediate lactate levels (2–4 mmol/L). Serum lactate levels as a predictive biomarker may prove most useful in this population.

**LACTATE:PYRUVATE RATIOS**

Lactate:pyruvate ratios have been employed in prognostication and to distinguish type A from type B hyperlactatemia. Pyruvate assays are not always available, however, and can be inaccurate if the specimen is hemolyzed, stored incorrectly, or

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*Fig. 2. Kaplan-Meier survival curves. Kaplan-Meier survival curves (truncated at 28 days) for the three a priori defined groups of initial lactate values: low, 0.0–2.0 mmol/L (n = 827); intermediate, 2.1–3.9 mmol/L (n = 238); and high, 4.0 mmol/L or above (n = 112). Time 0 represents the day of lactate measurement. LA, lactic acid. (From Springer Science+Business Media. Trzeciak S, Dellinger RP, Chansky ME, et al. Serum lactate as a predictor of mortality in patients with infection. Intensive Care Med 2007;33(6):970–7; with permission.)*
not processed within the first 3 hours. An example of their utility can be found in a study by Levy and colleagues in which elevated lactate levels were present in association with increased lactate:pyruvate ratios in nonsurvivors (37:1) relative to survivors (20:1) in patients with septic shock. Suistomaa and colleagues also measured lactate levels and lactate:pyruvate ratios for the first 24 hours of critically ill medical surgical patients. Elevated initial lactate level, continued elevation of lactate, and lactate:pyruvate ratio all predicted mortality. In patients with severe sepsis, lactate elevation was associated with normal lactate:pyruvate ratios whereas in circulatory failure, both were elevated. This gives some support to theories that elevated lactate:pyruvate ratios support a hypoxic mechanism of lactate production. Normal ratios of lactate to pyruvate in the setting of elevated lactate levels may signify a nonhypoxic mechanism. Further studies are necessary. With the many difficulties in obtaining accurate pyruvate levels, it is doubtful that measuring lactate:pyruvate ratio adds any additional prognostic value for shock resuscitation.

**LACTATE CLEARANCE**

Single serum lactate measurements may have limitations and perhaps serial measurements improve prognostic ability. Lactate clearance over time was shown to be
superior to oxygen-derived variables (DO₂ and oxygen consumption [VO₂]) in septic shock patients. Initial and final phase lactate levels were lower in survivors whereas DO₂ and VO₂ were not different. Bakker and colleagues showed that lactime, or duration of elevated serum lactate levels, most accurately corresponded to organ failure and death and did so better than initial lactate levels, DO₂, and VO₂. Abramson and colleagues demonstrated that all trauma patients who normalized their serum lactate levels by 24 hours survived and that those who cleared by 48 hours had a 75% chance of survival. The ability to normalize lactate to a value of less than 2 mmol/L predicted survival (P < .0001) whereas DO₂ and VO₂ did not.

These findings were corroborated by McNelis and colleagues, who demonstrated 100% mortality in surgical ICU patients who had persistently elevated lactate levels. Those who cleared their lactate (lactate level <2 mmol/L) in the first 24 hours had a mortality of 3.9%. Patients who had delayed lactate clearance (>48 hours to lactate level <2 mmol/L) had a mortality of 42.5%. Husain and colleagues furthered the importance of lactate clearance in critically ill surgical ICU patients when he risk-stratified 95 trauma and nontrauma patients into four groups based on their ability to clear lactate: (1) clearance in the first 24 hours, (2) clearance in 24 to 48 hours, (3) greater than 48 hours to normalize, or (4) never normalized. Predicted mortality was calculated as 10%, 20%, 23%, and 67%, respectively, in the four groups. Initial and serial lactate measurements predicted survival with statistical significance.

In a different patient population, Nguyen and colleagues quantified lactate clearance in 111 patients with severe sepsis and septic shock. Survivors had a lactate clearance of 38% versus 12% of nonsurvivors. Low lactate clearance (<10%) within the first 6 hours predicted death two-thirds of the time. It is not clear that any intervention helps improve lactate clearance, but perhaps serial lactate measurements could be used as markers of progress in shock resuscitation.

For many years, it was felt that the lactate itself was harmful and contributed to the worsening acidosis. This has since been shown to likely not be true. In an effort to actively lower lactate levels, however, Stacpoole and colleagues performed a series of experiments with dichloroacetate (DCA). DCA stimulates the PDH complex by binding to and inhibiting PDH kinase, which inactivates the PDH enzyme. Increasing flux through the PDH enzymatic pathway seemed an ideal way to reduce lactate levels and has been studied in a variety of patient populations: children with congenital lactic acidosis, patients with myocardial ischemia, and critically ill patients with shock. All studies have shown that DCA safely lowers circulating lactate levels in the blood. The only controlled trial of DCA, however, by Stacpoole and colleagues, for the treatment of lactic acidosis showed a lowering of lactate levels but no change in any significant hemodynamic measurements or survival. Many patients were enrolled with significantly elevated lactate levels and many were enrolled late into their shock states well into developing multiorgan system failure. Nonetheless, DCA has never proved useful in treating critically ill patients with elevated lactate levels.

**ARTERIAL VERSUS VENOUS LACTATE**

To compare arterial and venous lactate, a series of 74 ED adult patients had arterial and venous lactate drawn within 5 minutes of the other. The correlation between arterial and venous lactate was 0.94 (95% CI, 0.91–0.96). There was a mean venous minus arterial lactate difference of 0.22 mmol/L (95% CI, 0.04–0.41), which ranged from −1.3 to 1.7 mmol/L in individual patients. Of the sample patients, 30% had arterial lactate levels less than 1.6.
In a study of trauma patients, arterial and venous lactate measurements were taken, drawn within 2 minutes of each other in 221 patients. The levels correlated with a correlation of 0.94 (95% CI, 0.94–0.96; \( P = .0001 \)). The equation for the difference in the values was expressed as arterial lactate = 0.0706 + 0.889 (venous lactate). The difference between arterial and venous values was not statistically significant.

**LACTATED RINGER SOLUTION**

Some providers have expressed concern about the use of lactated Ringer solution in the setting of lactic acidosis, theorizing that it could make the lactic acidosis worse. One liter of lactated Ringer solution contains 130 mEq sodium, 4 mEq potassium, 3 mEq calcium, 109 mEq chloride, and 28 mEq lactate mixed in sterile water. The electrolyte content is isotonic (273 mOsm/L, calculated) in relation to the extracellular fluid (approximately 280 mOsm/L). The sterile water is acidic (pH 5 to 7) as a result of interactions with air and the plastic bag. The addition of sodium lactate increases pH to approximately 6.6 (range 6.0–7.5). Hence, the lactate acts as a base and as such cannot cause acidosis. Often, due to the diagnosis of lactic acidosis, physicians choose saline for resuscitation fluids. In a study of sixty patients with severe sepsis or septic shock, hyperchloremic metabolic acidosis due to saline infusion was the predominant cause of metabolic acidosis. Furthermore, to determine if lactated Ringer solution increased circulating lactate concentrations, healthy adult volunteers were given 1-L infusions of lactated Ringer solution or 5% dextrose over 1 hour. Lactate concentrations were not significantly different between the two groups. Therefore, elevated blood lactate levels in the setting of lactated Ringer solution infusion are an unexpected finding and should not be attributed to the infusion.

To summarize, the understanding of type A lactate acidosis, initial serum lactate, serial lactate measurements, and lactate clearance may be useful in the management of critically ill patients. Elevated lactate levels are likely related to increased production and decreased clearance depending on the complex metabolic factors of individual patients. Venous lactate levels are easy to obtain, inexpensive, and can provide valuable information in the prognostication of medical and surgical patients with shock.

**TYPE B LACTIC ACIDOSIS**

Often during the course of critical illness, patients have continued elevations in lactate level without ongoing evidence of cellular hypoxia or ischemia. In these cases it is important to consider what Woods and Cohen labeled type B lactic acidosis. Box 1 lists causes of type B lactic acidosis. Type B lactic acidosis is divided into type B1 (related to underlying diseases), type B2 (related to the effect of drugs and toxins), and type B3 (associated with inborn errors of metabolism.)

**TYPE B UNDERLYING DISEASES**

*Malignancy-Associated Lactic Acidosis*

In the 1920s, Warburg measured \( \text{VO}_2 \) and lactate production in tumor cells in aerobic and anaerobic conditions. He found that tumor cells had high glucose consumption and lactate production in the presence of oxygen. He believed that this “aerobic glycolysis” was due to abnormal function of mitochondria and was the root of malignant transformation. One factor contributing to the high rate of glycolysis is the overexpression of glycolytic enzymes, such as hexokinase. In contrast with Warburg’s hypothesis, the literature supports that, except for a few cancers, the mitochondrial impairment in tumors is a result of tumor-related metabolic shifts and not the
Fig. 4. Proposed etiologies of type B lactic acidosis. Selected pathways in glycolysis, citric acid cycle, and oxidative phosphorylation and the proposed effect of various conditions and medications on those pathways leading to lactic acidosis. ADP, adenosine diphosphate; CoQ, coenzyme Q; FADH$_2$, reduced flavin adenine dinucleotide; H$^+$, hydrogen ion; NAHD, reduced nicotinamide adenine dinucleotide; TCA, tricarboxylic acid; I, complex I; II, complex II; III, complex III; IV, complex IV; V, complex V.
Box 1
Causes of type B lactic acidosis

Type B1—underlying diseases
Renal failure
Hepatic failure
Diabetes mellitus
Malignancy
Systemic inflammatory response syndrome
Human immunodeficiency virus

Type B2—drugs and toxins
Acetaminophen
Alcohols—ethanol, methanol, diethylene glycol, isopropanol, and propylene glycol
Antiretroviral nucleoside analogs—zidovudine, didanosine, and lamivudine
β-Adrenergic agonists—epinephrine, ritodrine, and terbutaline
Biguanides—phenformin and metformin
Cocaine, methamphetamine
Cyanogenic compounds—cyanide, aliphatic nitriles, and nitroprusside
Diethyl ether
Fluorouracil
Halothane
Iron
Isoniazid
Linezolid
Nalidixic acid
Niacin
Propopol
Salicylates
Strychnine
Sugars and sugar alcohols—fructose, sorbitol, and xylitol
Sulfasalazine
Total parenteral nutrition
Valproic acid
Vitamin deficiencies—thiamine and biotin

Type B3—inborn errors of metabolism
Glucose-6-phosphatase deficiency (von Gierke disease)
Fructose-1,6-diphosphatase deficiency
Pyruvate carboxylase deficiency
PDH deficiency
Methylmalonic aciduria
Kearns-Sayre syndrome
Pearson syndrome
Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS)
Myclonic epilepsy with ragged red fibers (MERRF)
etiology of malignancy. Furthermore, not all tumors use glycolysis as the preferred form of energy production. Nonetheless, lactic acidosis has been most frequently reported in hematologic malignancies, such as leukemias and lymphomas, and also reported in melanoma, small cell lung cancer, multiple myeloma, sarcoma, breast cancer, oat cell carcinoma, undifferentiated carcinoma, chol-angiocarcinoma, and pheochromocytoma (although this is likely due to the high circulating catecholamines [discussed later]). In one review of lactic acidosis in hematologic malignancy, reported lactate levels ranged from 5 to 38 mmol/L with reported mortality of 93% to 96%. Management of the hyperlactemia relies on treating the underlying malignancy. Approaches to acute management of the lactic acidosis in these cases include using intravenous insulin to increase conversion of pyruvate to acetyl CoA, thereby facilitating oxidation of lactate to pyruvate and bicarbonate therapy to buffer the extreme acidosis. Bicarbonate has been shown to increase lactate production in patients with malignancy associated chronic lactic acidosis, however.

Systemic Inflammatory Response Syndrome

Systemic inflammatory response syndrome is typically associated with type A lactic acidosis due to the presumption that the hemodynamic instability leads to inadequate DO2. Although this is likely at least a partial contributor, there is evidence that increased production of pyruvate, decreased activity of PDH (in part due to increased PDH kinase), lactate production by the lung, and decreased lactate clearance are contributors to lactic acidosis in systemic inflammatory response syndrome.

Hepatic Failure

In critically ill patients with cirrhosis, lactic acidosis portends a grim prognosis with a 7.64 (95% CI, 3.01–19.34) odds ratio for ICU mortality. Individuals with the combination of cirrhosis, acidemia, lactic acidosis, and acute renal failure had 86% ICU mortality and 94% hospital mortality. Liver failure is associated with decreased lactate clearance, which is further exacerbated in sepsis. In cases of severe liver failure, the liver can be a source of lactate production. When lactate measurements were added to King’s College Hospital criteria for determining outcome after paracetamol intoxication, an early lactate of greater than 3.5 mmol/L or a postresuscitation lactate of greater than 3.0 mmol/L increased sensitivity for predicting death to 95% whereas specificity was relatively unchanged at greater than 90%.

TYPE B2—DRUGS AND TOXINS

Acetaminophen

Acetaminophen and its toxic metabolite, N-acetyl-p-benzoquinonimine, interferes with mitochondrial oxidative phosphorylation by inhibiting cellular respiration at NADH-linked substrates (energy coupling site I) and at succinate stimulated sites (energy coupling site II). In an animal model, the inhibition of mitochondrial respiration preceded overt hepatic necrosis and was completely prevented by treatment with N-acetyl-L-cysteine. Inhibition of oxidative phosphorylation eventually results in a shift toward lactate production. This suggests that the earlier treatment with N-acetyl-L-cysteine is initiated, the better the outcome.

Toxic Alcohols

Toxic alcohol ingestions of ethanol, methanol, ethylene glycol, and diethylene glycol can cause hyperosmolality and lactic acidosis. Propylene glycol intoxication is the
most common alcohol intoxication in ICUs. Propylene glycol is the vehicle carrier for several intravenous medications used in ICUs, including lorazepam, diazepam, digoxin, hydralazine, pentobarbital, phenobarbital, nitroglycerin, etomidate, phenytoin, multivitamins, esmolol, and trimethoprim-sulfamethoxazole (Box 2). Propylene glycol is oxidized by alcohol dehydrogenase in the liver to lactate and pyruvate. There are many case reports of propylene glycol toxicity, manifested as unexplained anion gap, unexplained metabolic acidosis, elevated lactate, and hyperosmolality. The majority of case reports have involved the use of lorazepam, likely due to the relatively higher concentration of propylene glycol in the solution. A 2-mg/mL standard solution of lorazepam contains 830 mg/mL of propylene glycol. A daily dose of propylene glycol of 25 mg/kg of body weight is considered safe. In patients who require greater than 1 mg/kg/day of intravenous lorazepam, following the osmolar gap may help identify those individuals at risk for the development of lactic acidosis, with values greater than 12 mg/dL, suggesting increased risk for propylene glycol toxicity. Treatment includes discontinuation of the agent and in severe cases removal via hemodialysis. Theoretically, fomepizole, which inhibits alcohol dehydrogenase and slows the breakdown of alcohols to their toxic metabolites, might have some utility but its efficacy in propylene glycol intoxication is unclear.

Nucleoside/Tide Reverse Transcriptase Inhibitors

Nucleoside/tide reverse transcriptase inhibitors (NRTIs) have revolutionized treatment of HIV and AIDS (Table 1). A typical regimen of highly active antiretroviral therapy consists of two NRTIs and a protease inhibitor or a non-NRTI. Toxicities due to NRTIs are likely due to mitochondrial toxicity. NRTIs may inhibit DNA polymerase-γ, which interferes with mitochondrial DNA synthesis and can lead to abnormal transcription and translation. Although there is no clinical correlation at present, studies demonstrate that zalcitabine has the greatest inhibition of DNA polymerase γ and lamivudine, abacavir, and tenofovir have the least. Long-chain-fatty-acid oxidation is also impaired by NRTIs. One of the most serious outcomes of the mitochondrial toxicity is lactic acidosis. Elevations in lactic acid is common in individuals treated with NRTIs, affecting approximately 9% individuals in one study. In this group,

<table>
<thead>
<tr>
<th>Box 2</th>
<th>Commonly used medications in propylene glycol vehicle</th>
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<tr>
<td>Diazepam</td>
<td>Esmolol</td>
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<tr>
<td>Hydralazine</td>
<td>Multivitamins</td>
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<tr>
<td>Pentobarbital</td>
<td>Phenytoin</td>
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<tr>
<td>Digoxin</td>
<td>Etomidate</td>
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<tr>
<td>Lorazepam</td>
<td>Nitroglycerin</td>
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<tr>
<td>Phenobarbital</td>
<td>Trimethoprim-sulfamethoxazole</td>
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among those with elevated lactate, a little over one-third had symptoms possibly consistent with hyperlactatemia, including myalgias, fatigue, and vomiting. Lactic acidosis may occur in single or combination NRTI regimens. Risk factors include exposure to didanosine, stavudine, or a combination of the two; female gender; age over 40 years; advanced immunosuppression (lower CD4 counts); and shorter duration of therapy (<12 months), suggesting an idiosyncratic reaction. In patients with symptoms of unexplained nausea, vomiting, abdominal pain, hepatic steatosis, or transaminemia, it may be beneficial to check lactate levels. The lactic acidosis typically resolves with cessation of the NRTI and supportive therapy, although some investigators have suggested supplementation with riboflavin, thiamine, carnitine, and coenzyme Q-10. One study using polymerase chain assay to compare mitochondrial to nuclear DNA in non–HIV-infected controls, HIV-infected individuals not on NRTIs, and HIV-infected individuals on NRTIs with elevated lactate demonstrated that HIV alone can affect the mitochondrial–to–nuclear DNA ratio and, therefore, HIV alone could result in lactic acidosis.

**Metformin**

The biguanides, metformin and phenformin, have been used to treat diabetes mellitus since the 1950s. Phenformin was pulled off the US market in 1976 due to more than 300 reports of lactic acidosis. Metformin, available since 1995, has a much lower risk of lactic acidosis than its predecessor, phenformin. Metformin inhibits gluconeogenesis from lactate in the liver in a time- and concentration-dependent manner.

In overdose, metformin binds to mitochondrial membranes, specifically complex I, resulting in inhibition of the electron transport system, resulting in a shift toward anaerobic metabolism. Most cases of metformin-related lactic acidosis have been in cases of intentional overdose or in individuals with underlying conditions, such as renal failure, congestive heart failure, hepatic failure, sepsis, and shock. The risk of death in these patients correlates better with organ dysfunction than lactate level or metformin level. There is low mortality in intentional metformin overdose with early recognition, hemodynamic and respiratory support, and hemodialysis. With hemodialysis, approximately 12% per hour of the drug is eliminated in the first 2 hours. After 15 hours of hemodialysis the elimination is approximately 1.5% per hour.

**Propofol**

Propofol infusion syndrome is a rare, life-threatening complication of propofol infusion. Characterized by metabolic acidosis, rhabdomyolysis of skeletal and cardiac muscle, arrhythmias, myocardial failure, renal failure, hepatomegaly, and death, it has sudden

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**Table 1**

Currently available nucleoside/tide reverse transcriptase inhibitors

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Abbreviation</th>
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<tbody>
<tr>
<td>Abacavir</td>
<td>ABC</td>
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<tr>
<td>Didanosine</td>
<td>ddl EC</td>
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<tr>
<td>Emtricitabine</td>
<td>FTC</td>
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<tr>
<td>Lamivudine</td>
<td>3TC</td>
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<td>Stavudine</td>
<td>d4T</td>
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<td>Tenofovir</td>
<td>TDF</td>
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<td>Zalcitabine</td>
<td>ddC</td>
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<tr>
<td>Zidovudine</td>
<td>AZT, ZDV</td>
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onset usually resulting in death.\textsuperscript{101} The majority of case reports have been in individuals receiving relatively higher doses (>4 mg/kg/h) for a prolonged period of time (>48 hours),\textsuperscript{102} but it also has been described in low-dose infusion (1.4–2.6 mg/kg/h).\textsuperscript{103} Propofol can alter the mitochondrial respiratory chain in multiple ways. Reduction in cytochrome-c oxidase activity and decreased complex IV activity\textsuperscript{104} and impaired fatty-acid oxidation with secondary impairment in complex II activity has been described in propofol infusion syndrome.\textsuperscript{105} New metabolic acidosis in a patient on propofol infusion should raise suspicion for propofol infusion syndrome. Discontinuation of propofol, resuscitation and cardiocirculatory stabilization, and hemodialysis to eliminate propofol is recommended\textsuperscript{106}; however, the syndrome is often rapidly fatal and patients are unresponsive to pressors and inotropes.

\section*{Linezolid}

Linezolid-related lactic acidosis was not reported during phase III clinical trials,\textsuperscript{107} but many case reports and case series have emerged since those.\textsuperscript{108–110} Most cases occur after a prolonged duration of therapy,\textsuperscript{111} but there are reports with duration of therapy as short as 7 days.\textsuperscript{110} In most cases, discontinuation of the linezolid results in resolution of the lactic acidosis.\textsuperscript{111} Linezolid kills bacteria by binding to the 23S ribosomal RNA (rRNA) of the bacteria.\textsuperscript{112} In mammals, the 16S RNA large ribosomal subunit is homologous to the bacterial 23S rRNA. In two patients with linezolid-related lactic acidosis, polymorphisms were identified in the mitochondrial 16S rRNA, specifically in the region structurally similar to the linezolid binding site located at the bacterial 23S rRNA.\textsuperscript{113} Caution should be used when administering linezolid with selective serotonin reuptake inhibitors as they block p-glycoprotein activity and may raise linezolid levels.\textsuperscript{114} Serotonin syndrome has been reported with concomitant use of linezolid and selective serotonin reuptake inhibitors.\textsuperscript{115}

\section*{\(\beta_2\)-Adrenergic Agents—Epinephrine, Ritodrine, Terbutaline, Salbutamol, and Dobutamine}

\(\beta\)-Agonists cause lactic acidosis in several ways. First, \(\beta_2\)-adrenergic–mediated stimulation of muscle and hepatic phosphorylase and inhibition of glycogen synthetase stimulates glycolysis and, thereby, an increase in pyruvate production.\textsuperscript{116} In skeletal muscle, \(\beta\)-agonists stimulate Na\textsuperscript{+}-K\textsuperscript{+}-ATPase via upregulation of cyclic AMP.\textsuperscript{117} This increases generation of ADP and then phosphofructokinase, which accelerates glycolysis.\textsuperscript{118} Then, the \(\beta\)-agonists inhibit PDH, which leads to decreased oxidation of pyruvate to acetyl CoA and, thereby, increased reduction of the pyruvate to lactate.\textsuperscript{119}

\section*{Salicylates}

Salicylate overdose is characterized by an early respiratory alkalosis and a late metabolic acidosis, mostly due to lactic acidosis.\textsuperscript{120} Respiratory acidosis occurs late and is typically a terminal event.\textsuperscript{121} The toxicity of salicylates is due to multiple mechanisms, including inhibition of \(\beta\)-oxidation of fatty acids,\textsuperscript{122} decreasing the availability of CoA,\textsuperscript{123} inhibition of succinate dehydrogenase and \(\alpha\)-ketoglutarate dehydrogenase,\textsuperscript{124} and increasing permeability of the inner mitochondrial membrane.\textsuperscript{125} Furthermore, the early respiratory alkalosis stimulates an increase in 2,3-diphosphoglycerate level, with subsequent increase in phosphofructose kinase activity resulting in accelerated glycolysis.\textsuperscript{126} Management consists of administering glucose to keep ward off central nervous system hypoglycemia and keeping the pH 7.45 to 7.5 to decrease central nervous system salicylate concentration and augment renal salicylate excretion. Hemodialysis is indicated in severe intoxications.\textsuperscript{127}
**Sulfasalazine**

Sulfasalazine is broken down in the colon to sulfapyridine and 5-aminosalicylic acid (ASA). The sulfapyridine is absorbed and is mostly acetylated in the liver with the remainder undergoing glucuronidation or hydroxylation before being excreted in the urine. Approximately one-quarter of the 5-ASA is absorbed, which is then acetylated to N-acetyl-5-ASA. In one case report, lactic acidosis with coingestion of paracetamol resulted in lactate levels of approximately 20 mmol/L with survival of the patient despite late administration of N-acetylcysteine.

**Other Medications Causing Hyperlactatemia**

Case reports of lactic acidosis due to isoniazid (INH), simvastatin, atorvastatin, niacin, and nalidixic acid have been published. It is unclear whether or not the hyperlactatemia is due to hepatic impairment that occurs with these drugs or if there is additional inhibition of cellular respiration. INH inhibits mycobacterial pyridoxal (the oxidized form of pyridoxine) to block bacterial growth and metabolism. Elevated levels of INH could affect human diphosphopyridine nucleotides and decrease metabolism of lactate to pyruvate. Simvastatin and atorvastatin are in a class of drugs known to reduce serum coenzyme Q10, a central cofactor of the mitochondrial respiratory chain. Lactulose has been a mainstay of treatment of hepatic encephalopathy for decades. Colonic bacteria break down lactulose into lactic, acetic, and formic acids. In a case where a cirrhotic patient received treatment with lactulose, severe lactic acidosis occurred, theoretically due to the formation of lactate in the colon, which diffused back across the gut wall, facilitated by intestinal hypomotility.

**Thiamine, Biotin, and Iron**

Thiamine deficiency resulting in lactic acidosis is most often described in patients with alcoholism, patients receiving total parenteral nutrition, foreign workers whose nutritional habits have changed, and infants receiving a defective soy-based formula. Lactate levels up to 20 mmol/L were recorded in one study. Thiamine, a water-soluble, B-complex vitamin that mammals are unable to synthesize, is an essential cofactor for enzymes in the cytosol and the mitochondria, including ketolase, PDH, and α-ketoglutarate dehydrogenase. Losses in the activity of PDH and α-ketoglutarate dehydrogenase are thought to lead to reduced pyruvate entry into the TCA cycle and increased lactate production. Lack of transketolase leads to reduction of the pentose phosphate pathway and subsequent reduction in NADH, stimulating anaerobic glycolysis and further lactate production. Administration of glucose stimulates excess lactate production.

Biotin is a cofactor in multiple carboxylation reactions, including pyruvate carboxylation to form oxaloacetate. Deficiency of biotin was demonstrated in humans by feeding them a diet of raw egg whites. Raw egg whites have a glycoprotein called avidin, which binds biotin. Cooking the whites denatures avidin and destroys its affinity for biotin. In individuals fed an egg white diet, symptoms of dermatitis, pallor, changes in mental status, myalgias, anorexia, anemia, and EKG changes consistent with coronary ischemia were seen. Administration of injectable biotin resolved all symptoms within 3 to 5 days. Biotin deficiency has also been described in individuals receiving total parenteral nutrition without biotin; with prolonged use of some anticonvulsants, such as phenytoin, carbamazepine, phenobarbital, and primidone; and in genetic mutation. Theoretically, prolonged antibiotic use could lower biotin levels as biotin is generated by bacteria living in the intestine.
and there are specialized receptors in the colon for biotin absorption\textsuperscript{154}; however, primary data for this are lacking.

Iron is essential to cellular respiration as it plays a major role in electron transport via iron-sulfur centers\textsuperscript{155} and cytochrome \textit{a}, \textit{b}, and \textit{c}.\textsuperscript{156} States of iron overload\textsuperscript{157} and iron deficiency\textsuperscript{158} have been associated with lactic acidosis. A syndrome known as GRACILE is named for the clinical findings of growth retardation, aminoaciduria, cholestasis, iron overload, lactic acidosis, and early death.

### Sugar Alcohols (Fructose, Sorbitol, and Xylitol)

Fructose enters the glycolytic pathway as lactate, glucose, or glycogen.\textsuperscript{159} Sorbitol is poorly absorbed in the intestine and is primarily converted to fructose with only a small portion metabolized to glucose.\textsuperscript{159} Xylitol is also poorly absorbed when orally administered but increases over time, due to adaptations in oral flora.\textsuperscript{160} Xylitol is metabolized to glucose, glycogen, lactate, and xylulose. Lactic acidosis has been reported when fructose,\textsuperscript{161} sorbitol,\textsuperscript{162} or xylitol\textsuperscript{163} was used in parenteral nutrition. Lethal xylitol toxicity characterized by increased serum osmolality, increased urine output, and hemoconcentration has been demonstrated in animals.\textsuperscript{164}

### Strychnine

Formerly used as a medication to treat a variety of ailments, strychnine is still used today as a pesticide and is rarely mixed with illegal drugs.\textsuperscript{165} Strychnine is excitatory to the central nervous system and antagonizes the inhibitory neurotransmitter, glycine, at the postsynaptic receptor sites of motor neurons in the ventral horn. This results in anti-inhibition and hyperexcitability, leading to extreme extensor muscle spasms. The resulting convulsions are thought to be the cause of the lactic acidosis. Lactate up to 32 mmol/L was recorded in one patient.\textsuperscript{166}

### Malaria

Malaria has been a major cause of death in illness, particularly in sub-Saharan Africa, for centuries.\textsuperscript{167} Lactic acidosis is used as a prognostic indicator in acute malarial infection.\textsuperscript{168} Etiology of lactate elevation is unclear but may be related to decreased liver blood flow\textsuperscript{169} and decreased lactate clearance,\textsuperscript{170} lactate production of parasites in red blood cells via anaerobic glycolysis,\textsuperscript{171} or mismatch between VO\textsubscript{2} and oxygen demand.\textsuperscript{172} \textit{N}-acetylcysteine administered to adults with severe malaria resulted in a rapid lowering of lactate,\textsuperscript{173} but it is unknown whether or not it would improve mortality.

### Valproic Acid

Valproic acid inhibits oxidative phosphorylation\textsuperscript{174} by decreasing activity of cytochrome \textit{aa\textsubscript{3}}\textsuperscript{175} and cytochrome \textit{c},\textsuperscript{176} by inhibiting succinate transport,\textsuperscript{177} and by changing conformation of mitochondrial membrane proteins.\textsuperscript{178} Reports of lactic acidosis have been associated with valproic acid use in individuals with underlying mitochondrial abnormalities\textsuperscript{179} and in valproate overdose.\textsuperscript{180} Withdrawal of the medication,\textsuperscript{181} hemodialysis,\textsuperscript{180} and supportive care resulted in good outcome.

### Cocaine and Methamphetamine

In the mid-1980s, two elite athletes, Len Bias and Don Rogers, died from cocaine use. Death from cocaine is typically due to seizures, lactic acidosis, hyperthermia, myocardial infarctions, and arrhythmias.\textsuperscript{182,183} Cocaine stimulates adrenergic activity, leading to increased glycolysis and lactic acid production.\textsuperscript{184} Reports of methamphetamine-related lactic acidosis have emerged.\textsuperscript{185} Acute methamphetamine intoxication can present with coma, shock, convulsions, hyperthermia, renal failure, and acidosis.\textsuperscript{186}
Methamphetamine decreases complex I activity in the mitochondria.\textsuperscript{187} It also induces a decrease in proliferation, increase in apoptosis, and disruption of mitochondrial networks resulting in mitochondrial fragmentation.\textsuperscript{188}

**Cyanogenic Compounds—Cyanide, Aliphatic Nitriles, and Nitroprusside**

Cyanide or cyanide-releasing chemicals are found in insulation; pesticides; metal-stripping and metal-plating solutions; the pits of apricots, cherries, and peaches; and cassava roots, almonds, and bamboo shoots.\textsuperscript{189} Aliphatic nitriles are used in the manufacture of synthetic fibers, resins, plastics, pharmaceuticals, and vitamins. The two most studied nitriles, methacrylonitrile and acrylonitrile, release cyanide during metabolism of these substances via epoxidation in the liver.\textsuperscript{190} Sodium nitroprusside is a medication used for its vasodilatory effect. It is composed of one iron molecule bound to five cyanide molecules and one molecule of nitric oxide.\textsuperscript{191} Risk of cyanide toxicity from nitroprusside infusion increases with high doses over a prolonged period of time. This risk is also higher when given to individuals with malnutrition or pre-existing renal impairment.\textsuperscript{192} Cyanide binds to cytochrome $aa_3$, inhibiting cytochrome-c oxidase activity.\textsuperscript{193} This inhibition of oxidative metabolism results in decreased tissue extraction of oxygen and a shift of cellular metabolism to anaerobic glycolysis. A decrease in the arteriovenous oxygen difference should increase suspicion for cyanide intoxication. Treatment of suspected cyanide toxicity involves supportive care and treatment with a methemoglobin-forming agent and subsequently a sulfur donor. Amyl nitrite or sodium nitrite form methemoglobin,\textsuperscript{194} which has a high affinity for cyanide, dissociating it from cytochrome oxidase and thereby restoring oxidative phosphorylation. Sodium thiosulfate is then given as a sulfur-donating substrate for conversion of cyanide a less toxic form, thiocyanate, which is then renally excreted.\textsuperscript{195} Dialysis, in particular continuous venovenous hemodiafiltration, may also be helpful as an additional measure in severe poisonings.\textsuperscript{191} In the case of nitroprusside-induced cyanide toxicity, addition of hydroxocobalamin may decrease the toxicity.\textsuperscript{196}

**General Anesthetics: Diethyl Ether and Halothane**

Diethyl ether is commonly used as a laboratory solvent and is used in the production of cellulose plastics. It was used as a general anesthetic until nonflammable, less-toxic inhaled anesthetics, such as halothane, became available. Diethyl ether and halothane are reported as causative agents in lactic acidosis,\textsuperscript{197} but the mechanisms have not been well described. Diethylether, diethylether derivatives, and halothane have been shown to disrupt oxidative phosphorylation.\textsuperscript{198}

**5-Fluorouracil**

Reports of lactic acidosis, hyperammonemia, and encephalopathy with 5-fluorouracil (5-FU) infusions are rare.\textsuperscript{199} Administration of 5-FU in individuals with inborn deficiencies of dihydropyrimidine dehydrogenase and dihydropyrimidinase is lethal.\textsuperscript{200} In electron micrographs, degradation and alteration in mitochondrial structure is noted\textsuperscript{201} and likely related to 5-FU’s inhibition of DNA and RNA synthesis.\textsuperscript{202}

**TYPE B3—INBORN ERRORS OF METABOLISM**

There are many genetic abnormalities known to cause syndromes of lactic acidosis. Conditions resulting in deficiency in oxidative phosphorylation, such as Kearns-Sayre syndrome; Pearson syndrome; MERRF; and mitochondrial encephalomyopathy, lactic acidosis, and stroke syndrome (MELAS), are mitochondrial encephalomyopathies commonly associated with lactic acidosis.\textsuperscript{203} Management of these individuals is
typically supportive. A trial attempting to use DCA to lower lactic acid in patients with MELAS resulted in peripheral nerve toxicity and was discontinued. Fructose-1,6-diphosphatase deficiency results in life-threatening hypoglycemia and lactic acidemia only when fasting occurs as gluconeogenesis is impaired. This is more pronounced in glycogen storage disease type I, also known as von Gierke disease. A deficiency of glucose-6-phosphatase, glucose-6-phosphate translocase, or the endoplasmic reticulum phosphate translocase results in compromised glycogenolysis and gluconeogenesis. PDH deficiency can be due to several mutations with a gradation in phenotype. The impairment may range from fatal infantile lactic acidosis to ataxia as the primary impairment. Pyruvate carboxylase deficiency also has different phenotypic expressions depending on the degree of impairment. It is also characterized by hypoglycemia, lactic acidosis, and ketosis. The type C phenotype lacks the psychomotor retardation seen in type A. Unlike in type B, where infants typically die by age 3 months, these individuals survive into adulthood with episodes of lactic acidemia. Methylmalonic aciduria is caused by a deficiency of methylmalonyl-CoA mutase or by defects in the transport, uptake, or synthesis of 5′-deoxyadenosylcobalamin. Clinical presentation varies but may include lactic acidosis, hypoglycemia, ketosis, and hyperammonemia. Dialysis has been used to clear the acidemia during metabolic crises, but there has been little success in curtailing the end-organ damage, which results from the accumulation of the toxic organic acids.

**D-LACTIC ACIDOSIS**

D-lactate is the optical isomer of L-lactate. Elevated levels of D-lactate are usually due to bacterial production in the intestinal tract, although they can also be due to D-lactate ingestion, from endogenous production via the methylglyoxylase pathway or from infusion of D,L-lactate solutions in peritoneal dialysis. The clinical presentation is unique for unusual neurologic manifestations, ranging from slurred speech to abusive behavior that lasts from a few hours to several days. High-glucose meals have been shown to exacerbate symptoms. Severe metabolic acidosis is also present, but L-lactate levels are normal. D-lactate must be ordered to make the diagnosis. Most patients presenting with D-lactic acidosis have short bowel syndrome. It is theorized that the neurologic symptoms manifest as a result of D-lactate toxicity to the brain, which lacks D-2-hydroxyacid dehydrogenase, the enzyme that converts D-lactic acid to pyruvate. Treatment of this condition includes a low-carbohydrate diet, saline enema when constipated, and poorly absorbed oral antibiotics in an effort to decrease D-lactate producing intestinal bacteria. During episodes of acidosis, insulin administration may decrease fatty acid levels, which may result in increased D-lactate oxidation and clearance. In severe cases, hemodialysis may be used.

**REFERENCES**


