Lactic Acidosis: From Sour Milk to Septic Shock

Pamela J. Fall, MD
Harold M. Szerlip, MD, FCCP

Lactic acidosis is frequently encountered in the intensive care unit. It occurs when there is an imbalance between production and clearance of lactate. Although lactic acidosis is often associated with a high anion gap and is generally defined as a lactate level >5 mmol/L and a serum pH <7.35, the presence of hypoalbuminemia may mask the anion gap and concomitant alkalosis may raise the pH. The causes of lactic acidosis are traditionally divided into impaired tissue oxygenation (Type A) and disorders in which tissue oxygenation is maintained (Type B). Lactate level is often used as a prognostic indicator and may be predictive of a favorable outcome if it normalizes within 48 hours. The routine measurement of serum lactate, however, should not determine therapeutic interventions. Unfortunately, treatment options remain limited and should be aimed at discontinuation of any offending drugs, treatment of the underlying pathology, and maintenance of organ perfusion. The mainstay of therapy of lactic acidosis remains prevention.

Key words: *lactic acidosis, lactate, pyruvate, hypoxia, hypoperfusion, shock, SIRS, bicarbonate, hemofiltration*

Lactic acidosis is a common problem encountered in critically ill patients. The prevalence is estimated to be approximately 1% of all hospitalized nonsurgical patients [1]. It is associated with a high mortality rate, and as such, critical care physicians need to be adept at diagnosing and treating this grave clinical condition. In this review we describe the pathogenesis, etiologies, and treatment of lactic acidosis.

Lactic acid was first isolated from sour milk by Scheele in 1780. In the latter part of the 19th century, several important clinical observations were made in diabetic patients that ultimately laid the foundation for our knowledge of lactic acidosis. First, it was shown that the urine of diabetic patients turned a purple color on the addition of ferric chloride. Acetoacetate was later identified as the substrate, and it was subsequently postulated that these ketones were responsible for the development of diabetic coma. Some patients with presumed diabetic coma and profound acidosis, however, did not have evidence of urinary ketones. Numerous similar cases were reported through the early 1900s. Finally, in 1918, Cannon made the important observation that metabolic acidosis was also associated with decreased blood flow and shock. Shortly thereafter, Clausen introduced an assay for lactate, and subsequently it was demonstrated that the accumulation of lactic acid accounted for the metabolic acidosis described in these diabetic patients without ketoacidosis. The clinical syndrome of lactic acidosis was first expounded in the seminal work of Huckabee [2,3]. Cohen and Wood [4], building on Huckabee's work, described lactic acidosis in terms we still use today. Their monograph is recommended reading for anyone with an interest in this disorder.

From Section of Nephrology, Hypertension and Transplantation, Department of Medicine, Medical College of Georgia.

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Address correspondence to Harold M. Szerlip, MD, FCCP, Medical College of Georgia, 1120 15th Street, Section of Nephrology, BA9413, Augusta, GA 30912, or e-mail: hszerlip@mail.mcg.edu.

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Biochemistry of Lactate

To understand the clinical syndrome of lactic acidosis requires knowledge of normal lactate metabolism. This subject has been extensively covered in several excellent reviews [5-7]. Lactate is a metabolic end product of anaerobic glycolysis and is produced by the reduction of pyruvate. The normal lactate to pyruvate ratio is approximately 20:1. Under basal conditions, lactate production is ~0.8 mmol/kg body weight/h or ~1300 mmol/day for a 70-kg person. Under hypoxic conditions, pyruvate is preferentially reduced to lactate, and the lactate/pyruvate ratio rises. Although lactate is produced in all tissues, skeletal muscle, brain, red blood cells, and renal medulla are responsible for the majority of the production. As shown originally by Huckabee [2,3], normal arterial blood lactate is approximately 0.620 mmol/L and venous lactate is slightly higher at 0.997 mmol/L.

Lactate can undergo one of two fates: conversion back to pyruvate or excretion by the kidney. Although lactate is freely filtered at the glomerulus,

it is almost completely reabsorbed in the proximal convoluted tubule [8]. Normally less than 2% is excreted in the urine. Even in the setting of experimental hyperlactatemia, when blood lactate levels are maintained at 10 mmol/L, only 10% to 12% of lactate removal is through urinary excretion [9].

Pyruvate is the immediate and only precursor of lactate. It is produced in the cytoplasm primarily from metabolism of glucose via glycolysis by the Embden-Meyerhof pathway (Figure 1) [10]. When oxygen is available, pyruvate enters the mitochondria and undergoes oxidative decarboxylation to acetyl-coenzyme A and then ultimately to CO_2 and H_2O. Pyruvate dehydrogenase (PDH) is the rate limiting mitochondrial enzyme in the oxidation of pyruvate. This overall process generates 36 moles of adenosine triphosphate (ATP) and requires oxidized nicotinamide adenine dinucleotide (NAD+). Pyruvate can also enter the Cori cycle and be converted back to glucose. This is an energy-consuming process that occurs only in the liver and renal cortex.

Both the liver and kidney are important lactate-consuming organs, and under normal conditions, the liver takes up approximately 60% of the circulating lactate [4]. Rowell and colleagues [11] showed that approximately 50% of the lactate produced during moderate exercise in humans was removed by the liver. Lactate is converted back to pyruvate via lactate dehydrogenase, which can then undergo one of the pathways described above and shown in Figure 1. The rate of lactate clearance can reach a level of 320 mmol/L/h, a level far exceeding the normal rate of production.

As noted above, under conditions of hypoxia, pyruvate is unable to enter mitochondria and is converted to lactate instead. The increase in the reduced nicotinamide adenine dinucleotide (NADH)/NAD+ ratio and the concentration of pyruvate both favor the continued production of lactate. Two moles of ATP are produced for every mole of glucose metabolized to lactate. Hence, under anaerobic conditions, energy production continues, albeit at a reduced rate, and at the expense of lactate production [5,7,12].

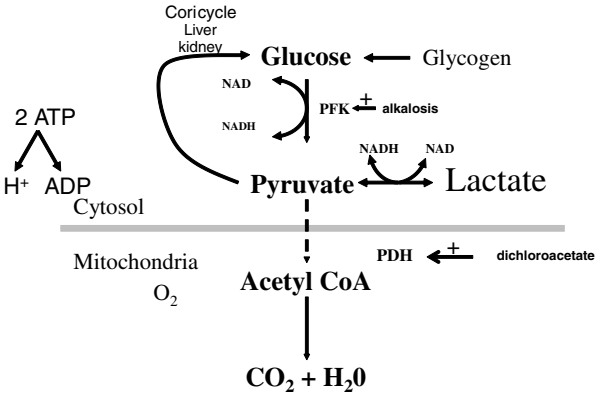

Fig 1. Biochemistry of lactate production. Glycolysis results in the production of pyruvate through anaerobic metabolism. Pyruvate can be (1) converted back to glucose in the liver and kidney via the energy requiring Cori cycle, (2) enter the mitochondria in the presence of oxygen and be metabolized to CO_2 and H_2O, or (3) be reduced to lactate. Under anaerobic conditions and states in which the ratio of reduced nicotinamide adenine dinucleotide (NADH) to oxidized nicotinamide adenine dinucleotide (NAD+) is increased, pyruvate is reduced to lactate, which accumulates. Glycolysis per se does not result in the production of hydrogen ions. Rather it is the hydrolysis of adenosine triphosphate (ATP), which produces the protons. Note that alkalosis can increase the rate of glycolysis and subsequent accumulation of lactate by activating the rate limiting enzyme: phosphofructokinase (PFK). Dicholoroacetate can increase oxidative metabolism of pyruvate by stimulating the pyruvate dehydrogenase complex (PDH). CoA – coenzyme A; ADP – adenosine diphosphate.

Pathogenesis of Lactic Acidosis

The anaerobic metabolism of glucose produces only lactate, ATP, and water [13-15]. No protons are produced. The acidosis occurs when ATP is hydrolyzed to adenosine diphosphate (ADP) and inorganic phosphate (Pi), releasing a hydrogen ion. Both ADP and Pi are reused as anaerobic glycolysis continues. Thus, stoichiometrically, for every mole of glucose metabolized anaerobically, 2 moles of lactate and 2 moles of hydrogen ion are produced (Figure 1). These hydrogen ions are then titrated by bicarbonate and nonbicarbonate buffers. When oxygen is available, hydrogen ions can enter the mitochondria and are used for oxidative phosphorylation [14].

Lactic acidosis occurs whenever production of lactate exceeds its utilization. Both grand-mal seizures and vigorous exercise are examples of transient increase in production of lactate associated with acidosis [14-17]. In these circumstances, lactate is quickly metabolized and the acidosis resolves.

In most cases of clinically significant lactic acidosis, however, lactate is not only overproduced, but there is evidence of defective utilization as well. Hypoxia and hypoperfusion lead to decreased uptake of lactate by the liver, and the liver becomes a lactate-producing organ [5,18,19]. In addition, severe acidosis, by itself, has been shown to impair lactate uptake in experimental animals [20,21].

There are several homeostatic mechanisms in place to limit lactate production and enhance utilization in the setting of acidosis. First, 6-phosphofructokinase, one of the key enzymes in glucose metabolism, is inhibited by intracellular acidosis, limiting the production of lactate [22]. Second, in the setting of acidosis the kidney plays a more important role in lactate disposal. Specifically, gluconeogenesis in the renal cortex is enhanced by increased activity of the rate-limiting enzyme—phospho-enolpyruvate carboxykinase [8,9]. Even in the setting of marked renal hypoperfusion, lactate can still be removed by the kidney through this pathway [23].

The contributions of increased production and decreased utilization of lactate vary with the underlying etiology of lactic acidosis. As detailed below, some of the specific mechanisms have recently been identified.

Clinical Manifestations and Course

Lactic acidosis has been variably defined in the literature. In 1983, Luft [1] applied 11 different definitions of lactic acidosis to 1467 unselected hospitalized patients to estimate the incidence and associated mortality. Depending on the definition used, the incidence varied between 0.5 and 3.8% with a mortality rate ranging from 30% to 88%. Drawing on their analysis, they recommended using a more restricted definition of lactic acidosis. Currently, the most accepted definition of lactic acidosis is a serum lactate level greater than 5 mmol/L and a pH <7.35.

With the exception of exercise and seizures, lactic acidosis usually develops in critically ill patients. Signs and symptoms are highly variable and nonspecific but may include hyperventilation, hypotension, tachycardia, and altered mental status [5-7].

Traditionally, lactic acidosis has been associated with an elevation in the anion gap [24]. If the anion gap is quite large, >35 mEq/L, then lactic acidosis should be a strong consideration in the absence of intoxication with ethylene glycol or methanol [25]. However, the diagnostic utility of the anion gap in lactic acidosis has been questioned [26-28]. In one report, 50% of patients with serum lactate levels between 5.0 and 9.9 mmol/L, levels associated with a mortality of >80%, had an anion gap of <16 mmol/L. Because the anion gap is composed mainly of negatively charged proteins, specifically albumin, a low serum albumin, a common finding in the critically ill patient, can lower the anion gap and mask a high anion gap metabolic acidosis. The calculated anion gap should therefore be increased by 2.5 mEq/L for every 1.0 g/dL decrease in the serum albumin less than 4.0 g/dL [25,29]. Likewise, because lactic acidosis can frequently be associated with a concomitant respiratory or metabolic alkalosis, the arterial pH can be an insensitive indicator of lactic acidosis. The pH may therefore be normal or even elevated [7,30].

The classic Henderson-Hasselbalch approach to acid-base balance has recently been challenged [10,31-33]. In 1981, Stewart [33] proposed a different way to assess acid-base status based on fundamental principles of physical chemistry. One of these principles states that the [H+] of an aqueous solution such as blood is determined by the dissociation of H_2O. The equilibrium equation is $H_2O \leftrightarrow H+ + OH–$. Stewart was able to show that the [H+] (and therefore the pH) is determined by three independent variables: the strong ion difference (SID), the P_{CO_2}, and the total concentration of weak acids (mainly proteins). Both H+ and HCO_3^- are dependent variables and, therefore, do not independently affect acid-base equilibrium. Strong ions are completely dissociated in an aqueous solution, and the SID represents the net charge balance of these ions. Thus, SID = $Na+ + K+ + Ca^{2+} + Mg^{2+} - Cl^- -$ other strong anions [34]. When a strong ion is added to blood, the weak electrolytes (including H_2O) must alter their dissociation to maintain electrical neutrality. Specifically applied to lactic acidosis, the Stewart approach has two main consequences. For one, giving $NaHCO_3$ to treat lactic acidosis will potentially increase the serum HCO_3^-, not because of the addition of HCO_3^- but because Na+ is a strong cation. This shifts the equilibrium equation of H_2O to the left, decreasing the [H+] and increasing the pH. Second, the metabolic acidosis associated with lactic acidosis is secondary to the lactate ion, a strong anion, which will decrease the SID. A decrease in SID results in a metabolic acidosis. Although the Stewart approach to acid-base homeostasis may be more physiologically correct, whether it adds to our clinical understanding of acidosis has yet to be established.

The natural history of lactic acidosis has been described by Stacpoole and colleagues [35]. They used data from 126 patients enrolled in the placebo arm of a clinical trial of dichloroacetate (DCA) for the treatment of lactic acidosis. All patients had an arterial lactate level of >5 mmol/L and a pH <7.35 or a base deficit of >6 mmol/L. This control group received normal saline placebo and conventional therapy. The median survival was less

than 2 days, and only 17% of patients survived 30 days. After adjustment for numerous variables, Acute Physiology and Chronic Health Evaluation (APACHE) II scores, systolic blood pressure, and arterial pH were the strongest predictors of survival at 24 hours.

Etiologies

Huckabee [2,3] was the first to describe the clinical entity of lactic acidosis and recognize the importance of tissue hypoxemia and circulatory failure as a primary cause. In addition to recognizing the role of decreased tissue oxygen delivery in the development of lactic acidosis, Huckabee also described a group of 9 patients who developed lactate acidosis despite normal blood oxygen content and normal blood pressure. Subsequently Cohen and Woods [4] divided lactic acidosis into two types: type A and type B. Type A lactic acidosis refers to conditions in which oxygen delivery is inadequate (Table 1). In contradistinction, Type B lactic acidosis occurs in settings of normal blood pressure and oxygen delivery (Table 2) and is frequently attributable to medications. In critically ill patients, the clinical distinction between Type A and Type B lactic acidosis is often obscure, and patients generally have features of both types [35].

Type A lactic acidosis is most commonly caused by decreased oxygen delivery from hypotension (Table 1). Other causes of impaired oxygen delivery (eg, hypoxia) tend to activate compensatory mechanisms and help preserve tissue oxygenation. However, regardless of the cause, when an oxygen debt develops, pyruvate is reduced to lactate. Both seizures and exercise are examples of increased tissue oxygen demand that transiently exceeds supply [14-17].

Table 1. Causes of Lactic Acidosis

Decreased oxygen delivery
Hypotension
Volume depletion
Blood loss
Cardiogenic shock
Septic shock
Severe anemia
Severe hypoxemia
Carbon monoxide poisoning
Increase oxygen demands
Exercise
Seizures
Shivering

Table 2. Causes of Type B Lactic Acidosis

Inadequate oxygen utilization
Systemic inflammatory response syndrome
Diabetes mellitus
Malignancy
Total parenteral nutrition
Thiamine deficiency
Congenital lactic acidosis
Mitochondrial myopathies
HIV infection
Malaria
Drugs/toxins (see Table 3)
Other
D-lactic acidosis

Systemic Inflammatory Response Syndrome (SIRS)

The most common cause of lactic acidosis in the intensive care setting is the systemic inflammatory response syndrome (SIRS) [35]. Traditionally, this has been classified as a cause of Type A lactic acidosis. Because these patients are frequently hemodynamically unstable, it has been assumed that the increase in lactate production is the result of inadequate oxygen delivery [36,37]. However, findings in experimental animals and septic patients over the past 2 decades have challenged this belief. Increased pyruvate production, decreased PDH activity, regional differences in lactate production, release of lactate from lung parenchyma, and decreased clearance of lactate have all been implicated as possible mechanisms contributing to lactic acidosis in SIRS [38-48].

Gore and colleagues [38] administered DCA to 5 septic patients and 6 controls. DCA stimulates PDH, the rate-limiting mitochondrial enzyme in oxidative metabolism of pyruvate (Figure 1). Septic patients receiving DCA had an increase in oxygen consumption, a decrease in glucose and pyruvate production, and a decrease in lactate concentration. These findings support the notion that lactic acidosis in SIRS is in part attributable to increased production of pyruvate and not solely inadequate tissue oxygenation. If hypoxia were truly the primary reason for the increase in lactate levels, the stimulation of PDH by dichloroacetate should not have been able to decrease the levels of pyruvate and lactate. In an experimental model of SIRS, Vary [39,40] showed a decrease in the proportion of active PDH complex in skeletal muscle of rats. This appears to be mediated by increased activity of PDH kinase, which phosphorylates the PDH complex, inactivating the

enzyme and ultimately leading to increased pyruvate and lactate generation.

A number of experimental studies have also shown regional variations in lactate production in SIRS. In the setting of anaerobic infection with *Bacteroides fragilis*, an increased concentration of lactate in skeletal muscle of animals has been demonstrated [41]. This may in part be attributable to enhanced uptake of glucose by muscle in sepsis leading to increased production of pyruvate and lactate. Vallet and colleagues [42] examined tissue oxygenation and lactate concentration in the ileum and skeletal muscle in endotoxic sepsis in dogs. They found blood flow within the gut wall was redistributed away from the mucosa with a resultant decrease in intracellular pH and increase in lactate production. Muscle tissue oxygenation was unchanged. In a pig model of endotoxic shock, others have shown mucosal injury with increased lactate concentration that is initially confined to the colon [43]. Finally, in septic patients with acute lung injury, it has been shown that there is an increased lactate release from lung parenchyma [44,45].

Decreased clearance of lactate has also been demonstrated in SIRS [46-48]. As previously discussed, the liver and kidney play important roles in lactate utilization. When blood flow to the liver decreases significantly, the liver not only becomes a lactate producer but also becomes ineffective at clearing extrahepatic lactate [41]. Severin and colleagues [47] demonstrated decreased hepatic lactate clearance even in hemodynamically stable septic rats. Chrusch and coworkers [48] found a combination of increased splanchnic production and decreased hepatic clearance of lactate in a model of canine sepsis.

It is clear SIRS represents a combination of Type A and Type B lactic acidosis. Studies have shown that lactic acidosis develops not only in hemodynamically unstable patients but also in the setting of adequate tissue perfusion and oxygenation. The studies described above account for much of our current knowledge on the mechanisms of increased lactate concentration and the development of lactic acidosis seen in SIRS.

Diabetes Mellitus

The initial association of diabetes mellitus and Type B lactic acidosis was made when the oral hypoglycemic phenformin was still available [4]. Sale of this drug was banned by the FDA in 1978, and subsequently the reported cases of lactic acidosis in diabetic patients virtually disappeared [18]. It is unclear whether diabetes mellitus actually predisposes patients to develop lactic acidosis. However, there is some evidence that lactate metabolism is altered in this group. In skeletal muscle of diabetic animals at rest, oxidation of lactate is decreased by 75% compared with control rats [49]. This may be attributable to diminished PDH activity. Also, in patients with Type II diabetes mellitus, basal lactate levels have been shown to be increased compared with normal individuals [50].

Malignancy

Patients with malignant neoplasms may develop lactic acidosis; this observation was first made more than 4 decades ago [51]. Typically, Type A lactic acidosis is seen secondary to hypoperfusion from sepsis, hypovolemia, or cardiogenic shock. Less commonly, patients develop Type B lactic acidosis attributable to liver disease, medications interfering with oxidative metabolism, or a large tumor burden. Most cases of Type B lactic acidosis have occurred in patients with rapidly progressive hematologic malignancies such as leukemia or lymphoma [52-55]. There is evidence for altered carbohydrate metabolism in some cancer cells with increased glycolytic activity [56]. Interestingly, we and others have noted the improvement in lactate levels with disease remission [55]. Finally, Type B lactic acidosis may be caused by decreased clearance of lactate from extensive liver involvement by tumor [57].

Drugs and Toxins

Drugs and toxic substances are a common cause of Type B lactic acidosis. Over the past 30 years, the list of potential drugs and toxic substances associated with lactic acidosis has grown substantially (Table 3).

Metformin is a biguanide oral hypoglycemic agent that was approved for use in the United States in 1995. Both phenformin and metformin enhance the action of insulin on glucose uptake and metabolism [58]. They also have been shown to directly inhibit complex I of the mitochondrial respiratory chain and to inhibit gluconeogenesis [59]. A rare side effect of these actions is the development of lactic acidosis. When phenformin was in use, the overall mortality rate in patients who developed lactic acidosis was between 40% and 50% [28]. Metformin-associated lactic acidosis has

Table 3. Drugs and Toxins

Biguanides	Antiretroviral drugs
Ethanol	Propylene glycol
Propofol	Vasoactive drugs
β-2 Agonists	Theophylline
Salicylate	Isoniazid
Niacin	Nalidix acid
Simvastatin	Acetaminophen
Cyanide	Nitroprusside
Lactulose	Linezolid

been infrequently reported, and most cases have occurred in patients with renal failure [58,60,61]. The use of this drug is contraindicated when renal impairment is present (creatinine >132 μmol/L in males and >123 μmol/L in females) or there is evidence of tissue hypoxia. Suggested guidelines for withdrawing metformin include renal impairment, suspected tissue hypoxia (eg, ischemia, sepsis), before iodine contrast with follow-up creatinine before reinstitution, and before general anesthesia [62]. Whether the incidence of lactic acidosis in patients on metformin is any greater than occurs in patients not taking metformin, however, has come under question [63]. Nevertheless, although the occurrence of lactic acidosis in patients on metformin may be an example of guilt by association, it is recommended to avoid metformin in patients with an estimated glomerular filtration rate using the MDRD formula of <60 mL/min [62-64].

Antiretroviral agents used in the treatment of HIV-infected patients are another class of drugs recently reported to cause lactic acidosis [65]. Nucleoside analogues or nucleoside reverse transcriptase inhibitors (NRTIs) incorporate into viral DNA and inhibit reverse transcriptase and hence viral replication. These drugs also cause injury to mitochondria leading to multiple adverse effects including lactic acidosis, hepatic steatosis, neuropathy, and myopathy [66]. They exert their potential toxic effects through several mechanisms [66,67]. NRTIs decrease cytochrome oxidase and impair β-oxidation of fatty acids. This leads to accumulation of fat droplets within cells and contributes to the clinical manifestations of hepatic steatosis and myopathy. They also selectively inhibit DNA polymerase γ, one of the key enzymes responsible for mitochondrial DNA replication. This results in depletion of components of oxidative phosphorylation with accumulation of pyruvate and lactate.

Cote and colleagues [68], using a polymerase chain assay, compared the ratio of mitochondrial to nuclear DNA in three groups: non-HIV-infected controls, HIV-infected asymptomatic patients naïve to antiretroviral therapy, and HIV-infected patients with symptomatic hyperlactatemia treated with antiretroviral drugs. The mitochondrial to nuclear DNA ratio was significantly higher in the controls compared with both HIV groups. Furthermore, the HIV-infected patients on therapy with hyperlactatemia had the lowest levels of mitochondrial DNA. The observation that HIV-infected patients not on therapy had significantly lower levels of mitochondrial DNA compared with controls lends credence to the theory that HIV infection alone can cause hyperlactatemia and lactic acidosis.

Several recent studies have reviewed the incidence, clinical manifestations, and proposed treatment of hyperlactatemia and lactic acidosis in HIV-infected patients on NRTI. John and colleagues [69] longitudinally followed 349 HIV-infected patients treated with NRTI for 18 months They measured venous lactate levels and found that most of their patient population had mild chronic asymptomatic hyperlactatemia with mean lactate levels between 1.5 and 3.5 mmol/L. Patients taking stavudine had significantly higher mean lactate levels compared with patients on zidovudine. In a similar study, Marceau and colleagues [70] reported on 282 HIV-infected patients receiving NRTI and found that 23% had moderate hyperlactatemia defined as a venous lactate level of 2.25 to 5 mmol/L. Similar to previous reports, stavudine was an independent predictor of hyperlactatemia [71,72]. Recommended treatment options include discontinuing the nucleoside analogue component of therapy and initiating supportive measures, thiamine, riboflavin, and L-carnitine [73].

NRTI-induced severe lactic acidosis is a rare event and is frequently associated with hepatic steatosis [74,75]. What triggers the conversion of asymptomatic mild hyperlactatemia to severe lactic acidosis in these patients has not yet been identified. In a recent report of 4 cases, all patients were on a regimen containing stavudine and had elevated liver function tests, although often only mild elevations [74]. In each case, the stavudine was discontinued, and despite a complicated and prolonged hospital course, each patient recovered. In general, lactate levels should be measured only in patients presenting with symptoms or with evidence of underlying liver disease [76].

Acute ethanol intoxication has been shown to cause increased lactate levels and precipitate lactic acidosis [7,77]. Ethanol is primarily metabolized via alcohol dehydrogenase to acetaldehyde, which is further oxidized to acetate by aldehyde dehydrogenase. Both reactions generate NADH. The increased ratio of NADH/NAD+ favors conversion of pyruvate to lactate. Underlying alcoholic liver disease and

thiamine deficiency may also exacerbate the lactic acidosis. MacDonald [78] measured lactate levels in patients presenting to the emergency room with acute ethanol intoxication. Approximately 12% had a lactate level >2.4 mmol/L and none had levels >5 mmol/L. In addition, all but 1 patient had other potential etiologies for their increased lactate level. Thus, in patients with ethanol intoxication, other causes of lactic acidosis should also be considered.

Several cases of lactic acidosis associated with propylene glycol have been reported in the literature [79-82]. Propylene glycol is a vehicle for numerous medications including intravenous lorazepam and topical sulfadiazine used in the treatment of burn patients. Propylene glycol is metabolized in the liver to pyruvate and lactate, and there is some evidence that renal tubular toxicity may also contribute to the acidosis.

Numerous other medications and toxic substances have been reported to induce lactic acidosis. The propofol syndrome, which has been linked to lactic acidosis, was recently reviewed by Vasile and colleagues [83]. Vasoactive substances, such as epinephrine and norepinephrine, have the potential to increase lactate levels and contribute to lactic acidosis. There have been rare case reports of pheochromocytoma presenting with severe lactic acidosis [84]. The use of epinephrine in the management of status asthmaticus and in critically ill patients has also been described to cause lactic acidosis [85,86]. Salicylate directly inhibits oxidative metabolism and induces a respiratory alkalosis, which stimulates glycolysis through increased activity of phosphofructokinase [87]. Other drugs, such as isoniazid, niacin, nalidixic acid and simvastatin, are potentially hepatotoxic and can cause lactic acidosis through altered clearance of lactate [88-91]. Both cyanide poisoning and use of nitroprusside, which is metabolized to cyanide, cause lactic acidosis by inhibiting mitochondrial respiratory chain activity [92]. Many of these reports in the literature are isolated cases with evidence of multiple possible etiologies of lactic acidosis [93,94].

Other

Lactic acidosis in association with total parenteral nutrition is primarily of historical interest except in more recent isolated reports of vitamin deficiencies [95-98]. Thiamine is a coenzyme in the PDH complex and is therefore important in oxidative metabolism of glucose. Total parenteral nutrition solutions without thiamine supplementation have resulted in several reported cases of Type B lactic acidosis [99,100]. Likewise, biotin is an essential cofactor for pyruvate carboxylate, a mitochondrial enzyme that metabolizes pyruvate to oxaloacetate, the first step in gluconeogenesis. Biotin deficiency has also resulted in cases of Type B lactic acidosis [101].

The vast majority of the cases of lactic acidosis are acquired, but there are rare inborn errors of metabolism that can cause congenital lactic acidosis (CLA). Some of the more common defects include substitution or deletion mutations in a subunit of the PDH complex or in the mitochondrial respiratory chain genes [102]. Defects in gluconeogenesis, such as glucose-6-phosphatase deficiency (or Type I glycogen storage disease), hereditary fructose intolerance (fructose-1,6-diphosphatase deficiency), and pyruvate carboxylate deficiency are all causes of CLA. In addition, defects in pyruvate oxidation leading to CLA include mutations in the PDH complex or in one of the enzymes of the tricarboxylic acid cycle or the mitochondrial respiratory chain. In one recent series of 35 patients with CLA, a deficiency in the PDH complex was the single most common abnormality identified (26%) [103].

The central nervous system is particularly susceptible to defects in oxidative phosphorylation because of the dependence of brain cells on glucose to meet energy requirements. Thus, one of the clinical hallmarks of CLA is progressive neurodegeneration. Patients may go undiagnosed for years and can present subtly with failure to thrive and multiple organ system dysfunction. A comprehensive discussion of this rare but important cause of lactic acidosis is beyond the scope of this review.

Congenital or acquired mitochondrial myopathies are an uncommon but increasingly recognized cause of lactic acidosis [104]. They cause lactic acidosis by impairment of oxidative phosphorylation and increased reliance on anaerobic glycolysis for ATP generation. Acquired myopathies can result from accumulation of mutations in mitochondrial DNA caused by aging, drugs, and other triggers. Acquired myopathies should be suspected in patients with lactic acidosis in the absence of hypoperfusion and sepsis and in patients with other unexplained neurologic abnormalities such as proximal muscle weakness, seizures, or ophthalmoplegia.

D-Lactic Acidosis

The previous disorders discussed are all associated with elevations in L-lactate. D-lactic acidosis is a

unique form of lactic acidosis first described by Oh in 1979 [105]. It occurs in patients with short bowel syndrome or a history of jejuno-ileal bypass surgery for morbid obesity. Since its original description, multiple cases have been reported in the literature [106-111]. The syndrome is characterized by episodes of neurologic symptoms associated with a high anion gap metabolic acidosis and normal lactate level. Because the assay for lactate uses a stereospecific L-lactate dehydrogenase enzyme, only L-lactate is measured. Therefore, a D-lactate level must be specifically requested when considering this diagnosis.

Organic acids are normally produced in the gastrointestinal tract from bacterial metabolism of undigested fiber, sugar, and starch [112,113]. Both D- and L-lactate are end-products of anaerobic metabolism of these organic acids and are usually of no clinical consequence. However, in the setting of carbohydrate malabsorption, the higher concentration of organic acids in the colon leads to a decrease in intraluminal pH favoring overpopulation of certain bacteria such as *Lactobacillus*. *Lactobacillus* is one of the main D-lactate-producing bacteria. Thus, increased D-lactate production can occur because of the large carbohydrate load delivered to the colon with subsequent fermentation. Both isomers of lactate can be absorbed, and D-lactate has the potential to accumulate because of its slower metabolism. Humans lack D-lactate dehydrogenase and rely on clearance of D-lactate by D-2-hydroxyacid dehydrogenase and by renal excretion. The syndrome of D-lactic acidosis usually develops after ingestion of a large carbohydrate meal.

Uribarri and colleagues [114] recently reviewed the clinical manifestations of D-lactic acidosis. They identified 29 cases from the literature, and all patients had evidence of altered mental status ranging from drowsiness to coma. Other common neurologic symptoms were dysarthria, ataxia, and impaired motor coordination. All patients also demonstrated metabolic acidosis with a pH ranging from 7.04 to 7.30, a mean anion gap of 20 ± 5, and a mean peak D-lactate level of 8 ± 4 mmol/L.

The treatment of this syndrome primarily involves limiting carbohydrate exposure to the colon [114-116]. Therapy usually includes bowel rest with use of hyperalimentation acutely and low carbohydrate diets chronically. Nonabsorbable antibiotics (such as neomycin and vancomycin) have also been advocated to suppress the intestinal flora, and some have recommended bicarbonate therapy as well.

Lactate Measurement and Prognostic Significance

Over the past 4 decades, numerous studies in critically ill patients have demonstrated the value of lactate levels in predicting survival. A variety of different patient populations have been studied including critically ill children, patients with septic shock, surgical and trauma patients, and hemodynamically stable postoperative patients [117-130].

An early study by Cady and colleagues [120] measured venous lactate levels on admission in 233 critically ill patients with various forms of shock. The authors found a mortality rate of 67% associated with a level >3.83 mmol/L and only 25% when levels were <3.83 mmol/L. A more recent study by Bernardin et al [121] evaluated 32 patients with septic shock and found that MAP <85 mm Hg and lactate level >3.5 mmol/L were independent predictors of decreased survival.

In another study, arterial lactate levels were measured in a diverse population of critically ill patients along with a simultaneous assessment of acid-base status [122]. The lowest survival rate (30%) was in patients with a primary metabolic acidosis, and their mean lactate level was 10.5 mmol/L. Patients with an uncompensated respiratory alkalosis had the greatest survival rate (65%). The mean lactate concentration in this group was 2.57 mmol/L; however, the range was 0.8 to 7.6 mmol/L. The authors concluded that in clinical conditions associated with a primary alkalosis, elevated lactate levels do not predict survival. Therefore, the acid-base status of the patient must be known to use the lactate level as a prognostic indicator.

The prognostic value of elevated lactate levels has also been examined in the surgical literature. A recent prospective study enrolled 98 severely injured patients and measured serial arterial lactate levels [123]. Blood lactate level on admission did not predict actual survival or survival according to level of injury. However, lactate levels at 12 hours did appear to predict survival. Similar results were found by Meregalli and colleagues [124]. They prospectively studied 44 hemodynamically stable, high-risk postoperative patients. Survivors and nonsurvivors had similar initial blood lactate levels. However, at 12, 24, and 48 hours, nonsurvivors had significantly higher lactate concentrations. In a more recent study by Kaplan and Kellum [125], an initial lactate level of <5 mmol/L in trauma patients requiring vascular surgery was highly predictive of survival.

Several studies have also looked at the clearance of lactate as a predictor of mortality [126-128]. Husain and colleagues [126] did a retrospective review of 137 surgical intensive care patients. Unlike the previous studies, in their patient population, both initial and 24-hour arterial lactate levels did predict survival. In addition, the time to normalize lactate levels was predictive of mortality. If patients cleared lactate by 24 hours, their mortality rate was 10%; if their lactate level remained elevated for 24 to 48 hours, their mortality rate was 20% to 23%, and if it failed to normalize, the mortality rate was 67%. A study by Nguyen and colleagues [127] found similar results. They looked at 111 patients presenting to the emergency department with severe sepsis or septic shock and a lactate level of >4 mmol/L. Higher lactate clearance at 6 hours was associated with a decreased mortality rate.

The level of elevation of lactate was not shown to be predictive of mortality in the DCA-lactic acidosis trial [129]. Stacpoole and colleagues [35] followed 126 patients with lactic acidosis defined as lactate level >5 mmol/L and either a pH <7.35 or base deficit of >6 mmol/L. After adjustment for numerous variables, APACHE II score, systolic blood pressure, and arterial pH were the strongest predictors of survival at 24 hours. Lactate concentration did not predict survival. Of note, many of the previously cited studies enrolled patients with mean lactate concentrations <5 mmol/L.

Finally, lactate levels have also been examined in specific causes of lactic acidosis. Elevated lactate levels have been used to suggest the diagnosis of mesenteric ischemia. An elevated lactate concentration at diagnosis was found to be the only significant predictor of mortality in a retrospective review of 121 patients with intestinal infarction [129]. Baud and colleagues [130] used lactate concentrations to predict acute cyanide poisoning and found a high sensitivity and moderate specificity for toxic cyanide concentration when blood lactate was >8 mmol/L. Similar to Stacpoole's findings, Brinkman [76] noted that lactate levels in HIV patients on antiretroviral therapy did not provide predictive information.

In general, several conclusions can be drawn from the available evidence. Patients presenting with hypotension and an elevated lactate level >5 mmol/L have a grave prognosis with a high mortality rate, >80%. Likewise, patients who are critically ill and do not clear lactate by 48 hours have a high mortality rate. There are no data currently available, however, to suggest that following lactate levels beyond this time frame is prognostically useful. Similarly, there are no data showing that therapeutic maneuvers specifically targeted at decreasing lactate levels are beneficial. The treatment of the patient with lactic acidosis should therefore be aimed at the underlying disease and the maintenance of organ perfusion and not the lactate level per se. Therefore, the routine daily measurement of serum lactate levels in critically ill patients should be discouraged.

Treatment

The decision to treat lactic acidosis is predicated on the belief that it produces harmful effects. In general, metabolic acidosis has been shown to have numerous effects on cardiovascular, neurologic, respiratory and metabolic functions [10]. Some of these effects are listed in Table 4. In the critically ill patient, however, it is often difficult to determine the independent contribution of lactic acidosis per se to the overall illness. In addition, several studies have demonstrated isolated effects of L-lactate anion on myocardial function in the absence of acidosis [131,132]. In one study using an isolated heart muscle, the addition of the L-lactate anion inhibited glycolysis through inhibition of glyceraldehyde-3-P dehydrogenase. This occurred in the setting of a normal pH.

The cardiovascular effects of acidemia, in particular, have continued to fuel the controversy over treatment of lactic acidosis. Cardiac output is determined by multiple components, and it is the sum of the effects on these individual components that determines the net effect of acidemia on cardiac function. Myocardial contractile strength and changes in vascular tone determine cardiovascular performance, and the relative contributions of each in the context of acidemia remain to be clarified. Because of differing effects of acidemia on contractile force, vascular tone and sympathetic discharge, it is difficult to predict what happens to cardiac output from studies using isolated myocytes or perfused hearts.

At mild degrees of acidemia with a pH >7.2, the predominant effect is increase in heart rate and contractility mediated by increased release of catecholamines. However, at more severe degrees of acidosis, there are specific negative effects on the myocardium. Wildenthal and colleagues [133] used an in vivo dog model and provided a continuous infusion of lactic acid. In this study, severe acido-

Table 4. Systemic Effects of Acidosis

Cardiovascular
Increased heart rate and contractility at pH >7.2
Decreased contractility at pH <7.1
Decreased cardiac responsiveness to catecholamines
Decreased renal and hepatic blood flow
Decreased fibrillation threshold
Neurologic
Increased sympathetic discharge of catecholamines
Altered mental status
Decreased neurologic responsiveness to catecholamines
Increased cerebral blood flow
Decreased cerebral metabolism
Respiratory
Increased minute ventilation
Dyspnea
Decreased diaphragmatic contractility
Other
Inhibition of anaerobic metabolism
Increased metabolic rate
Increased protein catabolism

sis with a pH <7.1 had a direct negative inotropic effect on the left ventricle. In addition, there was a decreased responsiveness to the compensatory release of catecholamines from the nerve endings and adrenal medulla. These effects were ameliorated with correction of the acidosis with the buffer tris-hydroxymethyl aminomethane (THAM) although not to control levels. The fact that the correction of the acidosis did not reverse these adverse effects suggests that either the lactate anion itself or possibly THAM may have a negative impact on myocardial function as well.

The effects of acidosis on cardiovascular function are mediated by the intracellular pH and its effects on calcium [134]. A decrease in extracellular pH from respiratory acidosis produces a more rapid negative inotropic effect on contractile function compared with a decrease in extracellular pH from a metabolic acidosis. This is attributable to the rapid diffusion of CO_2 into the cell and lowering of intracellular pH. There is also evidence to suggest that mitochondrial pH may be even more important than intracellular pH [135]. Acidosis has been shown to effect contraction of myocardium through changes in calcium balance and binding to specific proteins in heart muscle.

Despite these findings, certain states of respiratory and metabolic acidosis do not seem to have a negative effect on myocardial function. Permissive hypercapnia in which the pH is decreased to 7.2 or less had no adverse effect on cardiac output in several studies of acute respiratory distress syndrome [136,137]. In addition, diabetic ketoacidosis associated with a pH <7.0 has been shown to be well tolerated by patients, as has lactic acidosis associated with grand-mal seizures and extreme exercise [14-17,138,139].

One of the primary goals in treating critically ill patients is maximizing oxygen delivery to the peripheral tissues. Acidosis influences oxygen delivery through the Bohr effect. Specifically, a decrease in the blood pH shifts the hemoglobin dissociation curve to the right, displacing oxygen from hemoglobin and delivering it to the tissues [140]. This represents a potential beneficial, although transient, effect of acidosis on oxygen delivery.

Given these clinical observations, one has to wonder whether acidosis and a low pH per se are harmful [141]. These data would suggest otherwise. Clearly there is evidence of a negative impact of acidosis on myocardial function in some experimental situations. However, the outcome of acidosis, be it lactic or otherwise, is well tolerated in certain clinical situations as compared with the high mortality of lactic acidosis associated with SIRS. This would suggest that a low pH is not the proximate cause of the dismal outcome in these critically ill patients.

These seemingly contradictory findings also help explain the disappointing results with current treatment options. It seems intuitive that acidosis should be corrected and overall acid-base balance maintained for physiologic functions to occur normally. However, this must be accomplished without impairing oxygen content of the blood or delivery to vital organs (such as myocardium) and without worsening metabolic or respiratory acidosis. Sodium bicarbonate, DCA, carbicarb, THAM, and renal replacement therapy have all been tried in the management of lactic acidosis with little success [142,143].

Despite the continued debate about the proper treatment with buffering agents, proponents on both sides of the argument agree on the need to identify and treat the underlying cause of lactic acidosis. Interventions aimed at reestablishing a minimum perfusion pressure and level of oxygenation using fluids, vasoactive drugs, and mechanical ventilation should be instituted early in the critically ill patient. Discontinuation of offending agents, such as metformin or antiretroviral drugs, treating an underlying malignancy, or use of thiamine or L-carnitine might all be additional appropriate therapies under certain circumstances.

Sodium Bicarbonate

Several studies have examined the effects of $NaHCO_3$ in experimentally induced lactic acidosis

in animals [144]. Arieff and colleagues [145] used a model of phenformin-induced lactic acidosis in dogs. Animals were treated with equimolar amounts of NaCl or $NaHCO_3$, and various parameters were measured. In animals receiving $NaHCO_3$, the authors found a decrease in intracellular pH in liver and red blood cells, a decrease in hepatic portal vein blood flow, an increase in gut lactate, no change in arterial pH, and a decrease in cardiac output. Similar results were found by Graf and coworkers [146] using a model of hypoxic induced lactic acidosis. Finally, Cooper and colleagues [147] studied lactic acidosis in pigs and randomized them to either $NaHCO_3$ or NaCl treatment. Animals receiving $NaHCO_3$ had an elevation of their pH to 7.45. However, there was no increase in cardiac output or left ventricular contractility.

Only 2 human trials have examined the effects of bicarbonate therapy on critically ill patients with lactic acidosis. Cooper et al [148] randomized 14 patients to receive either $NaHCO_3$ or NaCl and measured various hemodynamic parameters. In the group receiving $NaHCO_3$, the authors found that arterial pH, P_{CO_2}, and serum bicarbonate all increased, whereas ionized calcium decreased. In addition, both agents transiently increased pulmonary capillary wedge pressure and cardiac output without a change in mean arterial pressure. Thus, $NaHCO_3$ therapy did not improve hemodynamics in these critically ill patients despite an improvement in acid-base balance as determined by arterial pH. In a similar study, Mathieu and colleagues [149] compared $NaHCO_3$ to NaCl in 10 patients with lactic acidosis in a crossover design and reported no hemodynamic improvement. They also examined tissue oxygenation and found no significant variation with $NaHCO_3$ therapy. Both studies suggest that any change observed in hemodynamics in these patients is likely attributable to an alteration in preload from the NaCl or $NaHCO_3$ administered.

The use of bicarbonate therapy in lactic acidosis would not be an issue if there were no potential adverse effects. Unfortunately, this is not the case, and numerous problems have been reported [10,141]. To begin with, $NaHCO_3$ is often given as a hypertonic solution and can cause volume overload, hypernatremia, and hyperosmolality. $NaHCO_3$ therapy has also been shown to increase lactate production in animal studies [145,146]. In a group of patients with Class III and IV congestive heart failure and normal pH, infusion of $NaHCO_3$ as compared with equimolar infusion of NaCl caused a decrease in arterial oxygen tension and myocardial oxygen consumption and an increase in both arterial and mixed venous P_{CO_2} as well as serum lactate levels [150]. Bicarbonate-induced alkalinization also decreases ionized calcium, and this has the potential to adversely effect excitation-contraction coupling of the myocardium [134]. Finally, one of the strongest arguments against the use of $NaHCO_3$ is the possibility of paradoxically worsening intracellular acidosis [151,152]. Bicarbonate combines with hydrogen to form H_2CO_3, which dissociates into CO_2 and H_2O. As stated above, CO_2 rapidly diffuses into cells and can worsen intracellular acidosis. Forsythe and Schmidt [141] summarized studies looking at the effect of bicarbonate therapy on intracellular pH and found no consistent results. It is unclear whether bicarbonate decreases the intracellular pH of myocardium in humans.

Given the current data available, it is difficult to recommend the routine use of $NaHCO_3$ in the treatment of lactic acidosis in critically ill patients. Admittedly, the 2 clinical trials enrolled small numbers of patients, making any conclusion suspect. However, the animal studies showing deleterious effects, the paucity of human studies showing benefit, and the numerous theoretical disadvantages all argue strongly against the routine use of bicarbonate therapy in this setting.

Carbicarb

Other buffers may be more efficacious in treating lactic acidosis. Carbicarb is a buffer solution containing an equimolar mixture of $NaHCO_3$ and Na_2CO_3 [153]. This agent is unique in that it does not generate CO_2 and therefore does not have the potential to worsen intracellular acidosis [154]. Several animal studies have shown improvements in acid-base balance, including intracellular pH, lactate production, and cardiac hemodynamic parameters when compared with $NaHCO_3$ [153,155]. Only one study in humans has been published. Leung and colleagues [156] examined the effects of carbicarb in mild metabolic acidosis in the perioperative setting. These authors showed improvement in metabolic acidosis with an increase in arterial pH in patients treated with either carbicarb or sodium bicarbonate. Unfortunately, no other clinical trials have been done, and it is therefore unclear whether carbicarb would be beneficial in the setting of lactic acidosis. Carbicarb is currently unavailable for use in the United States.

THAM

Tris-hydroxymethyl aminomethane (THAM) is another interesting buffer. It is a biologically inert amino alcohol that buffers carbon dioxide and acids [157]. Because it has the capacity to buffer and not generate CO_2, THAM is effective in a closed system. It is approved in the United States as THAM acetate for use in prevention and treatment of metabolic acidosis. THAM is renally excreted and should be used cautiously in renal failure. It has the potential to induce respiratory depression, hypoglycemia, and hyperkalemia. Several studies have looked at the use of THAM in the setting of permissive hypercapnia and shown improvement in arterial pH [158,159]. In one study, myocardial contractility decreased significantly less in the group treated with THAM to a pH >7.3 compared with controls [158]. Unfortunately, THAM has not been examined in a randomized controlled trial of critically ill patients with lactic acidosis.

Tribonat

Tribonat is another buffering agent that has been used in Europe to treat the acidosis associated with cardiac arrest [160]. It is a mixture of THAM, $NaHCO_3$, acetate, and phosphate and reportedly has fewer side effects. Tribonat appears to have a more favorable effect on intracellular pH because there is less CO_2 generation, and it also has been shown to increase intracellular calcium, which may benefit myocardial contractility. Unfortunately, there are no studies demonstrating improved outcome with Tribonat in critically ill patients, and it is not approved for use in the United States.

Dichloroacetate

DCA has been used in the treatment of lactic acidosis. It stimulates the activity of the mitochondrial PDH enzyme complex indirectly through inhibition of the PDH kinase [161,162]. It increases the rate of oxidation of pyruvate and decreases lactate as long as oxygen is available. DCA has been used in various forms of acquired and congenital lactic acidosis. A large, randomized, placebo-controlled trial of DCA in the treatment of lactic acidosis in critically ill patients did show improvement in arterial blood lactate concentration and pH in the group receiving DCA [163]. Unfortunately, there was no improvement in hemodynamics or survival. Proponents of the use of DCA have shown that it effectively lowers lactate levels and argue that treatment with the drug may be warranted at an earlier stage of lactic acidosis (ie, lactate level <2 mmol/L) [162]. This has yet to be proven.

Renal Replacement Therapy

Renal replacement therapy is a treatment modality that appears to hold promise in improving outcomes in critically ill patients with lactic acidosis. There are several potential advantages of renal replacement therapy. Bicarbonate-based hemodialysis can provide treatment of acidosis by diffusion of bicarbonate from the dialysate into the serum without the risk of volume overload, hypernatremia, or hyperosmolality. Several studies have shown improvement in acid-base balance with bicarbonate-based continuous renal replacement therapy [164,165]. In addition, peritoneal dialysis has been effective in removing lactate and treating patients with SIRS and lactic acidosis [166]. Hemofiltration also removes lactate [167], and with the use of bicarbonate-buffered replacement fluid, hemofiltration can help correct the acidosis. Finally, renal replacement therapy allows for the maintenance of normal ionized calcium in the setting of bicarbonate buffering. This may eliminate any adverse effects of hypocalcemia on myocardial contractility [168].

Two studies have directly compared bicarbonate to lactate based replacement fluid in continuous venovenous hemofiltration [169,170]. Barenbrock and colleagues [169] found bicarbonate-based replacement fluid to be superior in correcting acidosis and decreasing cardiovascular events in critically ill patients with acute renal failure. However, there was no difference in mortality rate between the 2 groups. In contrast, Thomas et al [170] found no difference between bicarbonate and lactate-buffered replacement fluid in their critically ill patients. Based on these studies, it is difficult to conclude that 1 buffer solution is superior.

Cytokines can also be removed by renal replacement therapy [171]. In the setting of SIRS, there is an increase in proinflammatory cytokines that mediate the inflammatory response. These include tumor necrosis factor-α, interleukin-1β, and interleukin-6. The molecular weight of these mediators is compatible with removal by convective clearance through hemofiltration. DeVriese et al [172] addressed this issue in 15 septic patients and found that continuous hemofiltration removed inflammatory cytokines. However, it also removed inhibitors of inflamma-

tion to the same extent. In addition, the mechanism of cytokine removal was primarily by adsorption to the dialysis membrane and not convective clearance. It is still unclear whether these changes in cytokine levels have a beneficial role in the treatment of lactic acidosis in the setting of SIRS.

Several studies have used high-volume hemofiltration in patients with septic shock and lactic acidosis [165,173]. Honore and colleagues [165] performed high-volume hemofiltration for 4 hours followed by conventional continuous venovenous hemofiltration using bicarbonate based replacement fluid. Thirty-five liters of ultrafiltrate was removed during the 4-hour treatment. Patients who responded to this therapy had an improvement in cardiac index, oxygen delivery, oxygen consumption, and, more important, 28-day survival compared with nonresponders. Nine of 11 patients in the responder group survived compared with none in the nonresponder group. The authors concluded that initiating short-term high-volume ultrafiltration early in the setting of septic shock may improve survival. A similar study compared effects of 3 different rates of ultrafiltration in critically ill patients with acute renal failure [174]. This was a large randomized trial that enrolled 425 patients. Most were postsurgical, but 11% to 14% were septic in each group. Lactate levels were not measured, and lactate-based replacement solution was used in the treatments. The authors of this study found a significant improvement in 15-day survival in the patients receiving continuous hemofiltration at an ultrafiltration rate >35 mL/h/kg of body weight compared with patients receiving lower ultrafiltration rates. These studies are provocative and suggest there may be a role for high volume ultrafiltration in the treatment of critically ill patients with lactic acidosis.

Renal replacement therapy has also been used in the management of drug-induced lactic acidosis. One of the original reports described the successful outcome of a patient with Phenformin-induced lactic acidosis treated with acetate buffered peritoneal dialysis [175]. Hemodialysis and continuous venovenous hemodialysis have also been described in patients with metformin-induced lactic acidosis with some success [58,60,61,176,177].

Other

L-carnitine has been used in the treatment of NRTI-induced lactic acidosis. L-carnitine is important for mitochondrial function, and its metabolism is impaired in HIV-infected patients. Claessens and colleagues [73] treated 6 HIV-infected patients with NRTI-induced lactic acidosis with L-carnitine. All had initial lactate levels >10 mmol/L, which the authors also showed was highly predictive of nonsurvival. Three of the 6 patients survived, suggesting that L-carnitine may have a therapeutic role in this setting.

Conclusion

We have come a long way in understanding the metabolism of lactate and the pathogenesis of lactic acidosis since Huckabee's original description more than 40 years ago. Progress has been made in identifying the numerous etiologies of lactic acidosis, and the list of causative medications has grown substantially. Some of the mechanisms of lactic acidosis in the setting of SIRS have been more clearly elucidated. Lactate levels have been shown to predict mortality at a level >5 mmol/L, as has the lack of clearance of lactate within 48 hours. Despite efforts to the contrary, however, treatment options remain limited. High-volume hemofiltration holds promise as a potential therapeutic modality. Perhaps the use of buffering agents earlier in the course of lactic acidosis when lactate levels are lower (<5 mmol/L) may be beneficial. Still, the old dictum to "treat the underlying cause" remains the mainstay of therapy for lactic acidosis in critically ill patients.

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