REVIEW ARTICLE

DISORDERS OF FLUIDS AND ELECTROLYTES

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Lactic Acidosis

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LACTIC ACIDOSIS RESULTS FROM THE ACCUMULATION OF LACTATE AND protons in the body fluids and is often associated with poor clinical outcomes. The effect of lactic acidosis is governed by its severity and the clinical context. Mortality is increased by a factor of nearly three when lactic acidosis accompanies low-flow states or sepsis,[1] and the higher the lactate level, the worse the outcome.[2] Although hyperlactatemia is often attributed to tissue hypoxia, it can result from other mechanisms. Control of the triggering conditions is the only effective means of treatment. However, advances in understanding its pathophysiological features and the factors causing cellular dysfunction in the condition could lead to new therapies. This overview of lactic acidosis emphasizes its pathophysiological aspects, as well as diagnosis and management. We confine our discussion to disorders associated with accumulation of the L optical isomer of lactate, which represent the vast majority of cases of lactic acidosis encountered clinically.

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PATHOPHYSIOLOGICAL FEATURES

NORMAL LACTATE METABOLISM

The reaction integral to the generation or consumption of lactate is shown below:

$$\text{pyruvate} + \text{NADH} + \text{H}^+ \leftrightarrow \text{lactate} + \text{NAD}^+.$$

Pyruvate is generated largely by anaerobic glycolysis (Embden–Meyerhof pathway). The redox-coupled interconversion of pyruvate and lactate occurs in the cytosol and is catalyzed by lactate dehydrogenase (LDH), a tetramer with five isoforms, each made up of different combinations of two subunits, LDHA and LDHB.[3] The LDHA subunit has a higher affinity for pyruvate and its reduction than does LDHB; thus, the nature of the LDH isoforms in tissues affects lactate metabolism. The blood lactate:pyruvate ratio is normally 10:1, but it rises with an increased ratio of NADH concentration ([NADH]) to NAD^+ concentration ([NAD^+]) (redox state).[4]

Approximately 20 mmol of lactate per kilogram of body weight is produced in the human body daily, primarily by highly glycolytic tissues containing LDHA-rich LDH, such as skeletal muscle.[3,5] Lactate is reconverted to pyruvate and consumed in the mitochondria of the liver, kidney, and other tissues, which have LDHB-rich LDH. The pathways include the Cori cycle, which generates glucose but consumes ATP in the liver and kidney (gluconeogenesis), as well as the tricarboxylic acid cycle and oxidative phosphorylation in the liver, kidney, muscle, heart, brain, and other tissues, which generate ATP when pyruvate is oxidized to carbon dioxide and water. Lactate consumption is subserved by intraorgan and interorgan lactate shuttles facilitated by monocarboxylic acid transporters (MCTs), which mediate the influx and efflux of lactate and accompanying protons. Normally, the generation and consump-

tion of lactate are equivalent, which results in a stable concentration of lactate in the blood.[4,6] Lactate production can rise markedly, as exemplified by its increase by a factor of several hundred during maximal exercise,[5] but it can also be rapidly consumed, as seen after cessation of exercise, seizures, or exogenous lactate loads.[5,7]

The bioenergetics of lactate generation can be summarized as follows:

$$\text{glucose} + 2(\text{ADP} + \text{inorganic phosphate}) \rightarrow 2 \text{ lactate} + 2\ H^+ + 2 \text{ ATP}.$$

Production of lactate ions by means of glycolysis is accompanied by the release of an equivalent number of protons from the hydrolysis of the generated ATP. Conversely, lactate consumption removes an equivalent number of protons, thereby maintaining the internal acid–base balance.[4]

HYPERLACTATEMIA

Hyperlactatemia occurs when lactate production exceeds lactate consumption. It also signifies the addition of a number of protons equivalent to the number of excess lactate ions, regardless of the prevailing acid–base status. Establishing the pathogenesis of hyperlactatemia can be a valuable guide to therapy.

In tissue hypoxia, whether global or localized, lactate is overproduced and underutilized as a result of impaired mitochondrial oxidation (see Fig. S1A and S1B in the Supplementary Appendix, available with the full text of this article at NEJM.org).[4] Even if systemic oxygen delivery is not low enough to cause generalized hypoxia, microcirculatory dysfunction can cause regional tissue hypoxia and hyperlactatemia.[8] Coexisting acidemia contributes to decreased lactate removal by the liver; severe hypoxia and acidemia can convert the liver into a net lactate-producing organ.[4]

Hyperlactatemia can also result from aerobic glycolysis, a term denoting stimulated glycolysis that depends on factors other than tissue hypoxia. Activated in response to stress, aerobic glycolysis is an effective, albeit inefficient, mechanism for rapid generation of ATP. In the hyperdynamic stage of sepsis, epinephrine-dependent stimulation of the β_2-adrenoceptor augments the glycolytic flux both directly and through enhancement of the sarcolemmal Na^+,K^+-ATPase (which consumes large quantities of ATP)[9] (Fig. S1C in the Supplementary Appendix). Other disorders associated with elevated epinephrine levels, such as severe asthma (especially with overuse of β_2-adrenergic agonists), extensive trauma, cardiogenic or hemorrhagic shock, and pheochromocytoma, can cause hyperlactatemia through this mechanism.[9] In inflammatory states, aerobic glycolysis can also be driven by cytokine-dependent stimulation of cellular glucose uptake[10]; in alkalemic disorders, it can be driven by stimulation of 6-phosphofructokinase.[4] Aerobic glycolysis and tissue hypoxia are not mutually exclusive; under certain circumstances, both can contribute to hyperlactatemia.[4,9]

Drugs that impair oxidative phosphorylation, such as antiretroviral agents and propofol, can augment lactic acid production and on rare occasions cause severe lactic acidosis. Patients receiving these drugs should be monitored carefully.

The liver accounts for up to 70% of whole-body lactate clearance.[11] In patients with sepsis, even when they are hemodynamically stable and have normal liver function, lactate clearance can be reduced, possibly through inhibition of pyruvate dehydrogenase.[12] Chronic liver disease exacerbates hyperlactatemia due to sepsis or other disorders,[7,11] but in the absence of such disorders, even severe cirrhosis rarely generates blood lactate levels that are more than minimally elevated. However, hyperlactatemia is common in acute fulminant liver disease, reflecting both reduced clearance and increased production of lactate by the liver,[13] and is an important prognostic factor.

EFFECTS ON CELLULAR FUNCTION

The cellular dysfunction in hyperlactatemia is complex. Tissue hypoxia, if present, is a major factor. If the cellular milieu is also severely acidic, cellular dysfunction is likely to be exacerbated. The latter factor alone can decrease cardiac contractility, cardiac output, blood pressure, and tissue perfusion; can sensitize the myocardium to cardiac arrhythmias; and can attenuate the cardiovascular responsiveness to catecholamines.[14]

In some studies, the severity of the acidemia was a better predictor of cellular dysfunction and clinical outcomes than the hyperlactatemia.[15] However, acidemia is often absent as a result of coexisting acid–base disorders.[7,14] The interaction of systemic acidity and blood lactate and their effect on clinical outcomes require further study.

Whether hyperlactatemia itself has an effect on cellular function remains unclear. In vitro studies suggest that lactate can depress cardiac contractility,[4,16] yet sodium lactate infusions that raised blood lactate to levels as high as 15 mmol per liter did not depress hemodynamic measures in patients after cardiac surgery.[16]

CAUSES

The major causes of lactic acidosis and their presumed mechanisms are listed in Table 1. Typically, they have been divided into disorders associated with tissue hypoxia (type A) and disorders in which tissue hypoxia is absent (type B). However, the evidence of tissue hypoxia can be subtle, and hyperlactatemia can be of both hypoxic and nonhypoxic origin.[4,9,10] Cardiogenic or hypovolemic shock, severe heart failure, severe trauma, and sepsis are the most common causes of lactic acidosis, accounting for the vast majority of cases.[17]

DIAGNOSIS

Evidence of severe cardiopulmonary disease, the systemic inflammatory response syndrome, sepsis, severe trauma, or volume depletion offers important clues for diagnosing lactic acidosis. An elevated serum anion gap, particularly a value higher than 30 mmol per liter, can provide supportive evidence. However, other causes of a raised anion gap, such as ketoacidosis and toxic alcohol ingestion, should always be considered.[18,19] The increase in the anion gap (ΔAG) can mirror the blood lactate level, but a close relationship might not always be found, since anions other than lactate often contribute to the ΔAG.

A normal anion gap does not rule out lactic acidosis. In one study, 50% of patients with a serum lactate level of 5 to 10 mmol per liter did not have an elevated anion gap.[18] Correction of the anion gap for the effect of serum albumin can improve its sensitivity, but many cases will still escape detection. Therefore, the serum anion gap lacks sufficient sensitivity or specificity to serve as a screening tool for lactic acidosis.

Because a 1:1 relationship between the ΔAG and the decrease in serum bicarbonate concentration ($[HCO_3^-]$), ΔHCO_3^-, is often found in ketoacidosis, deviations from this ratio suggest coexisting acid–base disturbances.[19] In lactic acidosis, the $\Delta AG:\Delta HCO_3^-$ ratio is often greater than 1, in part because the apparent space of distribution of protons exceeds that of lactate[19,20]; therefore, an increased ratio might not always suggest a coexisting acid–base disorder.

An elevated blood lactate level is essential for confirmation of the diagnosis. The lower limit of the normal range for the blood lactate level, 0.5 mmol per liter, is consistent among clinical laboratories, but the upper limit can vary substantially, from as low as 1.0 mmol per liter to as high as 2.2 mmol per liter.[6,21,22] Therefore, the cutoff for abnormal values often differs among laboratories. Levels at the upper tier of normal values have been associated with increased mortality among seriously ill patients.[21,23] Thus, blood lactate concentrations at the upper tier of normal values or slightly increased from a previous baseline value, although remaining within the normal range, can augur a poor outcome and call for monitoring of the patient.

Previously, the definition of lactic acidosis included a blood pH of 7.35 or lower and a serum $[HCO_3^-]$ of 20 mmol per liter or lower.[24] However, the absence of one or both of these features because of coexisting acid–base disorders does not rule out lactic acidosis. For example, coexisting respiratory alkalosis can increase the blood pH into the alkalemic range, whereas coexisting metabolic alkalosis can result in both hyperbicarbonatemia and alkalemia (Fig. 1 and 2). In contrast, coexisting respiratory acidosis can cause severe acidemia (Fig. 2).

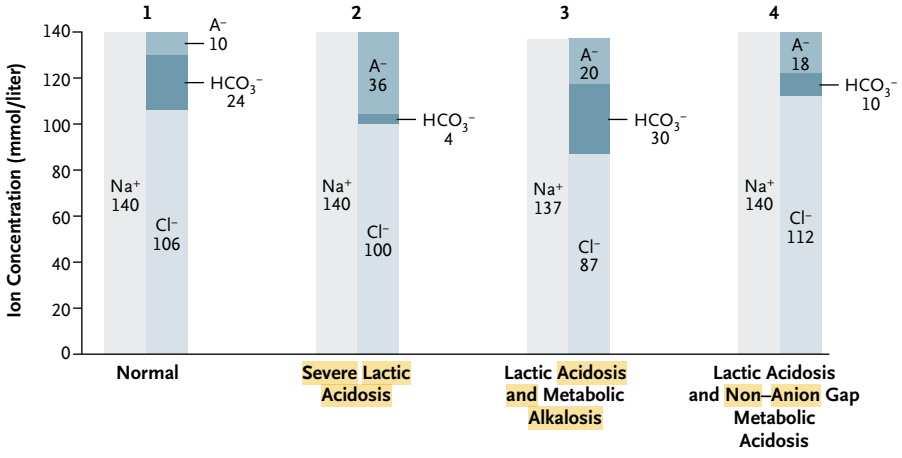
Lactic acidosis due to grand mal seizures is associated with normokalemia, because the concurrent entry of lactate and protons into cells negates the need for potassium exit from cells to maintain electroneutrality. However, hyperkalemia is commonly observed in critically ill patients, because they often have renal failure. In addition, potassium is released from damaged tissues. However, hypokalemia can occur when β_2-adrenoceptor stimulation drives potassium into cells.

A serum osmolal gap of more than 20 mOsm per kilogram of water has been reported in some cases,[25] probably reflecting the release of osmotically active solute from ischemic tissues. However, other disorders characterized by an increased osmolal gap and hyperlactatemia (e.g., exposure to toxic alcohols) should be ruled out.

Table 1. Causes of Lactic Acidosis.*

Cause	Presumed Mechanism or Mechanisms	Comments
Cardiogenic or hypovolemic shock, advanced heart failure, or severe trauma	Decreased O_2 delivery to tissues; epinephrine-induced β_2-adrenoceptor stimulation can be a contributory factor	With sepsis, these causes account for the majority of cases of lactic acidosis
Sepsis	Epinephrine-induced β_2-adrenoceptor stimulation with or without decreased O_2 delivery to tissues; reduced clearance of lactate even in hemodynamically stable patients	Evidence of decreased O_2 delivery can be subtle; even in the absence of macrocirculatory impairment, dysfunction of microcirculation can be present
Severe hypoxemia	Decreased O_2 delivery to tissues	Requires Pa_{O_2} <30 mm Hg
Carbon monoxide poisoning	Decreased O_2 delivery to tissues, interference with oxidative phosphorylation	Hyperbaric O_2 therapy is recommended if pH <7.1
Severe anemia	Decreased O_2 delivery to tissues	Requires hemoglobin level <5 g/dl
Vigorous exercise, seizures, or shivering	Increased O_2 requirements	The decrease in pH and hyperlactatemia is transient; lactic acidosis can impair exercise performance
Diabetes mellitus	Mechanism unclear	The risk of death in patients with ketoacidosis can be increased by coexisting lactic acidosis
Cancer	Increased glycolytic activity of tumor (Warburg effect), tumor tissue hypoxia, decreased clearance of lactate with severe liver metastases	Lactic acidosis can be seen in association with lymphomas, leukemias, and solid tumors; HCO_3^- administration may increase lactic acid production; acidic microenvironment is critical for tumorigenesis, angiogenesis, and metastasis
Liver disease	Lactate clearance decreased	Fulminant liver disease can cause substantial hyperlactatemia; hyperlactatemia is usually mild with chronic liver disease alone; lactate clearance can also be decreased when liver function is normal, in association with sepsis
Pheochromocytoma	Decreased O_2 delivery to tissues and epinephrine-induced β_2-adrenoceptor stimulation	In rare cases, lactic acidosis is a presenting feature of pheochromocytoma
Metformin	Interference with oxidative phosphorylation, suppression of hepatic gluconeogenesis	This is usually seen in association with high plasma metformin levels; treatment with dialysis is beneficial
Nucleoside reverse-transcriptase inhibitors	Interference with oxidative phosphorylation	Marked hyperlactatemia is uncommon in the absence of other predisposing factors
Cocaine	Decreased O_2 delivery to tissues and epinephrine-induced β_2-adrenoceptor stimulation	Marked hyperlactatemia is seen in some patients having seizures or being restrained
Toxic alcohols, methanol, ethylene glycol, diethylene glycol	Interference with oxidative phosphorylation	The increase in lactate is small; a small increase in the osmolal gap (usually <20 mOsm/kg H_2O) can be seen in some cases of lactic acidosis without toxic alcohols
Propylene glycol	D-Lactate and L-lactate are normal products of metabolism	Lactic acidosis can occur in the absence of impaired oxidative phosphorylation
Salicylates	Interference with oxidative phosphorylation	Hyperlactatemia is usually minimal
Cyanide	Interference with oxidative phosphorylation	Lactic acidosis is an important manifestation of poisoning
β_2 agonists	Stimulation of aerobic glycolysis	This is most common with treatment of acute asthma; hypokalemia can result from enhanced cellular uptake of potassium
Propofol	Interference with oxidative phosphorylation	Lactic acidosis can be seen with prolonged high-dose infusion
Thiamine deficiency	Impairment of pyruvate dehydrogenase activity	This is most common in children or adults receiving parenteral nutrition or those with fulminant beriberi

* Pa_{O_2} denotes partial pressure of arterial oxygen.



$Paco_2$ (mm Hg)	40	15	43	26
pH	7.40	7.05	7.47	7.21
Lactate (mmol/liter)	1	18	8	6

Figure 1. Changes in Acid–Base and Electrolyte Composition in Patients with Lactic Acidosis with or without Coexisting Metabolic Acid–Base Disturbances.

From left to right, the bar pairs depict normal acid–base status, severe lactic acidosis induced by hemorrhagic shock, lactic acidosis and metabolic alkalosis in a patient with advanced heart failure who is receiving diuretic agents, and lactic acidosis and non–anion gap metabolic acidosis in a patient with septic shock who has been resuscitated with large quantities of normal saline. In bar pair 2, the increment in the anion gap (the anion gap is calculated by subtracting the serum concentrations of chloride and bicarbonate anions from the concentration of sodium cations) exceeds the decrement in the serum bicarbonate level ($\Delta AG:\Delta HCO_3^-$ ratio, 1.3), a common occurrence in lactic acidosis. In bar pairs 2, 3, and 4, the increment in the anion gap cannot be completely accounted for by the increase in the lactate concentration. Several studies have indicated that unmeasured anions other than lactate account for a substantial portion of the increased anion gap in lactic acidosis. A^- denotes unmeasured serum anions, and $Paco_2$ partial pressure of arterial carbon dioxide. The numbers associated with ions are ion concentrations in millimoles per liter.

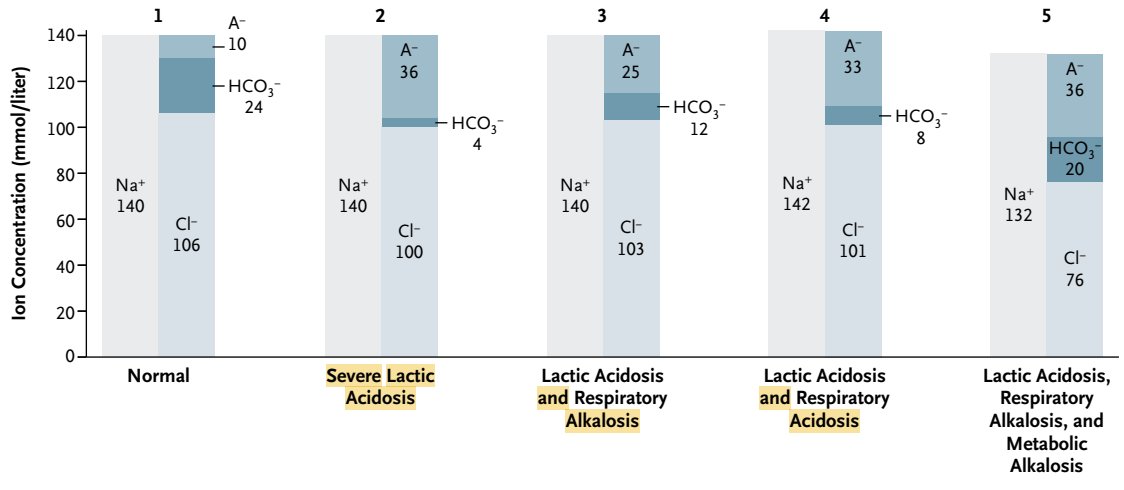
TREATMENT

SUPPORTING THE CIRCULATION AND VENTILATION

Restoring tissue perfusion after hemodynamic compromise is essential in the treatment of patients with lactic acidosis. Vasopressors and inotropic agents should be administered as needed.[26,27] Acidemia blunts the response to catecholamines, thereby increasing the required dose.[14] High doses of catecholamines can aggravate hyperlactatemia by reducing tissue perfusion or overstimulating the β_2-adrenoceptor; therefore, the dose should be adjusted carefully.

Crystalloid and colloid solutions are both effective in restoring tissue perfusion in patients with sepsis or hypovolemia.[28] However, reports of acute kidney injury, bleeding, and increased mortality in association with hydroxyethyl starch synthetic-colloid solutions provide evidence against their use. If a colloid solution is indicated, albumin should be used. Saline administration can generate or exacerbate a non–anion gap metabolic acidosis[29] and reduce ionized calcium levels, factors that could depress cardiac function.[30,31] Also, chloride-rich solutions have been linked to acute kidney injury.[32] Crystalloids containing bicarbonate or its precursors (balanced salt solutions), such as Ringer's solution with lactate and Plasma-Lyte (Baxter International) with acetate and gluconate, will not cause non–anion gap metabolic acidosis and may reduce the risk of acute kidney injury, but they can occasionally cause metabolic alkalosis.[31,33]

A reduced need for renal replacement therapy



	1	2	3	4	5
$Paco_2$ (mm Hg)	40	15	16	42	30
pH	7.40	7.05	7.50	6.90	7.45
Lactate (mmol/liter)	1	18	10	16	17

Figure 2. Changes in Acid–Base and Electrolyte Composition in Patients with Lactic Acidosis with or without Coexisting Respiratory and Metabolic Acid–Base Disturbances.

From left to right, the bar pairs depict normal acid–base status, severe lactic acidosis induced by hemorrhagic shock, lactic acidosis and respiratory alkalosis in a patient with sepsis, lactic acidosis and respiratory acidosis in a patient with trauma-associated lactic acidosis complicated by pulmonary insufficiency and progressive carbon dioxide retention, and lactic acidosis, respiratory alkalosis, and metabolic alkalosis in a patient with sepsis undergoing gastric drainage. The numbers associated with ions are ion concentrations in millimoles per liter.

has been reported in seriously ill patients receiving balanced salt solutions rather than saline,[32,34] but opinions differ regarding which solution should be favored.[28,31] Solutions containing a racemic mixture of D-lactate and L-lactate generate as much base as do solutions with an equimolar concentration of only L-lactate.[35] Infusion of large quantities of Ringer's lactate can increase blood lactate levels, but the increment is often small in the absence of abnormalities in lactate clearance.[36] Citrate-containing solutions can lead to the generation of microthrombi.[33] Randomized, controlled studies are needed to determine the most effective and safe crystalloid.[31,33]

Oxygen delivery to tissues depends on the cardiac output, regional blood flow, hemoglobin concentration, and partial pressure of oxygen (Po_2). Red-cell transfusions should be administered to maintain the hemoglobin concentration at a level above 7 g per deciliter. An adequate Po_2 should be maintained by ensuring an appropriate inspired oxygen concentration, with endotracheal intubation and mechanical ventilation as needed. Invasive ventilation may also be required to prevent hypercapnia, particularly if acidemia persists or worsens.[26]

IMPROVING THE MICROCIRCULATION

Abnormalities of the microcirculation, if persistent, can augur clinical deterioration and death.[8,37] Several agents, including dobutamine, acetylcholine, and nitroglycerin, have been shown to improve microvascular perfusion independently of systemic hemodynamics, to reduce hyperlactatemia, and even to improve the outcome.[38,39] Measures to rescue the microcirculation are likely to become a high priority in the future.

INITIATING CAUSE-SPECIFIC MEASURES

Resuscitative efforts should be complemented by measures targeting the cause or causes of lactic acidosis. Such measures can include treatment of sepsis with the appropriate antibiotic agents; management of arrhythmias, resynchronization therapy, and left-ventricular assist devices for advanced heart failure; coronary intervention for acute myo-

cardial infarction; surgery for trauma, tissue ischemia, or toxic megacolon; dialysis for removal of toxins or drugs; discontinuation of certain drugs; and reduction of tumor mass for cancer.

BASE ADMINISTRATION

Given the potentially deleterious effects of an acidic environment, some clinicians recommend therapy with intravenous sodium bicarbonate for severe acidemia (blood pH, <7.2).[14,40,41] However, the value of bicarbonate therapy in reducing mortality or improving hemodynamics remains unproven.[14,17,30,42] This absence of evidence that bicarbonate therapy is beneficial has been attributed primarily to two adverse events that occur with its administration: intracellular acidification due to the accumulation of carbon dioxide after bicarbonate infusion and a pH-dependent decrease in levels of ionized calcium, a modulator of cardiac contractility.[14,30] Intracellular acidification is presumed to be more frequent and severe when large quantities of bicarbonate are administered rapidly in patients with severe circulatory failure, which impedes the removal of carbon dioxide from tissues and its excretion by the lungs. Circumvention of these complications might allow the putative benefits of bicarbonate to be manifested.

Using dialysis to provide bicarbonate can prevent a decrease in ionized calcium, prevent volume overload and hyperosmolality (potential complications of bicarbonate infusion), and remove substances associated with lactic acidosis, such as metformin. Through an alkalinizing effect, base administration, whether by means of infusion or dialysis, increases net lactic acid production.[43] Substantial clearance of lactate can be achieved with dialysis, although the quantity cleared is much lower than the quantity of lactate produced in severe lactic acidosis. Continuous dialysis is often favored over intermittent dialysis because it delivers bicarbonate at a lower rate and is associated with fewer adverse events in patients with hemodynamic instability. Controlled studies of the effect of dialysis on lactic acidosis are warranted.

Other buffers have been developed to minimize carbon dioxide generation, including THAM (tris-hydroxymethyl aminomethane)[14] and Carbicarb (a 1:1 mixture of sodium carbonate and sodium bicarbonate).[14] Only THAM is currently available for clinical use, but further study of these and other, novel compounds that buffer acid without increasing carbon dioxide — or, even better, that are capable of consuming carbon dioxide — is warranted to determine their potential role in the treatment of metabolic acidosis.

POTENTIAL FUTURE THERAPIES

The sodium–hydrogen (Na^+–H^+) exchanger NHE1 is activated during lactic acidosis, leading to deleterious sodium and calcium overload in the heart; its inhibition reduces cellular injury. In experimental models of lactic acidosis due to sepsis, hypoxia, hemorrhagic shock, or cardiac arrest, NHE1 inhibitors attenuated the lactic acidosis and hypotension, improved myocardial performance and tissue oxygen delivery, enabled resuscitation, and reduced mortality.[44,45] These promising results in animals call for controlled studies in humans.

Cancer cells are programmed to use aerobic glycolysis and lactate production as their main energy source (the Warburg effect).[46,47] The export of lactate and protons in the tumor microenvironment has emerged as a critical regulator of cancer development, maintenance, and metastasis. Inhibitors of LDH and MCT lactate transporters are being investigated as promising cancer therapies.[3] These compounds might also prove effective in the management of tumor-induced and other types of systemic lactic acidosis.

MONITORING OF PATIENTS, GOALS OF THERAPY, AND PROGNOSIS

Measures to monitor and recommended goals of therapy are shown in Table 2. Close assessment of hemodynamic, oxygenation, and acid–base status is paramount.

The detection of tissue hypoxia is important for assessing the effectiveness of resuscitation and the need for other procedures to match oxygen delivery and demand. Although measurement of the blood lactate level is often used for this purpose, hyperlactatemia does not always signify tissue hypoxia.[47,51,52] Central venous oxygen saturation has been suggested as a replacement or complementary measure, with the goal being a value greater than 70%.[27,51,52] A recent study of septic shock indicated that the use of this measure provided no additional benefit as compared with the usual therapy without central hemodynamic targets.[48] Further study of this issue is needed. New methods of detecting tissue hypoxia,

Table 2. Measures for Monitoring and Goals of Therapy in Patients with Lactic Acidosis.*

Measure	Goal of Therapy	Comments
Hemodynamic measures		
Mean arterial blood pressure	65–70 mm Hg	Measures reflect the adequacy of the macrocirculation. Criteria are derived from randomized, controlled studies and expert opinion. A recent study[48] showed no additional benefit of protocol-based therapy or use of central venous catheterization in treatment of septic shock. Ongoing studies might provide new insights into the goals of therapy. Urine volume alone is not an adequate indicator of renal function, and the clinician should also consider changes in serum creatinine.
Heart rate	<100 beats/min	
Central venous pressure	8–12 mm Hg	
Pulmonary wedge pressure	12–15 mm Hg in patients receiving mechanical ventilation	
Urine output	>0.5 ml/kg/hr	
Blood measures affecting O_2 delivery		
Hemoglobin level	>7 g/dl, but can vary on the basis of cardiovascular status of patient; some recommendations are for approximately 10 g/dl	The goal is to provide maximal O_2 carrying capacity by optimizing hemoglobin concentration and O_2 saturation. Monitoring of central venous O_2 saturation requires insertion of catheters and use of special probes. A recent study[48] indicated that there is no additional value of this measure over the usual hemodynamic measures.
Arterial O_2 saturation	≥92%	
Central venous O_2 saturation	≥70%	
Acid–base measures (arterial and central venous blood pH, P_{CO_2}, and $[HCO_3^-]$)	Arterial blood pH, >7.2; P_{aCO_2} appropriate for $[HCO_3^-]$; in lung-protective ventilation, P_{aCO_2} is maintained at hypercapnic levels	Measures should be evaluated every few hours. Acidemia accompanying hyperlactatemia can be a sign of a poor prognosis. The use of central venous blood gases to assess tissue acid–base status has not been established, but measurement should be considered for patients with severe hypoperfusion. Adverse hemodynamic effects of acidemia occur at pH <7.2. The use of base for improvement of acid–base measures remains controversial because of a lack of evidence of clinical benefit and complications of therapy.
Blood lactate	Decrease to the normal range (<1 to 2 mmol/liter)	Blood lactate is a useful tool for screening, risk stratification, and prognosis. Peripheral venous and arterial values are interchangeable. The initial value has prognostic significance, but serial measurements have more value for prognosis and for guiding therapy. Lactate-guided therapy has been beneficial in some studies.[49,50] In one study,[49] reduction of blood lactate by 20% every 2 hr for the first 8 hr was associated with a decrease in morbidity and mortality. The use of lactate clearance to monitor and guide therapy remains under investigation.
Assessment of integrity of microcirculation, near infrared spectroscopy, and orthogonal polarization spectral imaging of microvasculature	Substantial improvement of microvascular indexes, including proportion of perfused small vessels, microvascular flow index, and heterogeneity of perfused small vessels	Microcirculation abnormalities can persist despite improvement in systemic variables, often termed microcirculatory distress syndrome. Documentation of improvement in microcirculatory flow as an important goal remains under study.

* P_{aCO_2} denotes partial pressure of arterial carbon dioxide, and P_{CO_2} partial pressure of carbon dioxide.

such as monitoring the concentration of hypoxia-inducing factor in body fluids, could prove useful.[53]

Measurement of the blood lactate level remains the cornerstone of monitoring for lactic acidosis. Lactate can be measured in arterial or venous blood, since the values are virtually interchangeable.[6] Devices for point-of-care measurement are available. Although a single elevated blood lactate level often predicts an adverse outcome, sustained hyperlactatemia is associated with even worse prognoses. Transient hyperlactatemia does not necessarily predict a poor clinical outcome.[6,49] An interval of 2 to 6 hours has been suggested for repeat lactate measurements,[6] but this issue has not been examined rigorously.

Sustained hyperlactatemia in hospitalized patients with diverse disorders is associated with a large increase in mortality, regardless of status with respect to shock or hypotension.[6,47,49,54-57] Also, there is a dose–response relationship between lactate levels and mortality: the higher the level, the greater the risk of death.[2,6,7,56,57] Some studies have indicated that acidemia accompanying hyperlactatemia increases mortality,[15] but the role of systemic acidity in affecting clinical outcomes remains to be elucidated.

Changes in levels of blood lactate have been used to guide therapy.[47,49-51,58,59] In a randomized, controlled study, a reduction of at least 20% in serum lactate levels every 2 hours was targeted for the first 8 hours of resuscitation; achievement of this target of lactate clearance was associated with decreased morbidity and mortality.[49] Evidence that in seriously ill patients even lactate levels at the upper end of the normal range are associated with poor clinical outcomes argues for the normalization of blood lactate as a primary goal of therapy.[2,47,54] The usefulness of lactate-guided therapy and the level of lactate to target remain under investigation.

Given the central role of the microcirculation in lactic acidosis,[37] its evaluation both before and after various interventions can be useful. Handheld devices allowing direct visualization of the microcirculation have been developed, and their clinical role is undergoing study.[26,60]

In patients with severe circulatory compromise, central venous blood more accurately reflects the acid–base status of tissues than does arterial or peripheral venous blood.[14,61] However, it remains unproven whether monitoring central venous blood gases in patients with severe hypoperfusion improves clinical outcomes. Monitoring of arterial blood gases is, of course, required for assessing pulmonary gas exchange.

Dr. Kraut reports holding pending patents related to the use of selective NHE1 inhibitors in the treatment of metabolic acidosis (lapsed without the filing of a nonprovisional application) and systems, methods, and compositions for improved treatment of acidosis. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Lactic Acidosis

TO THE EDITOR: The review by Kraut and Madias (Dec. 11 issue)[1] presents several explanations for the pathogenesis and pathophysiology of lactic acidosis, but not all these explanations are supported. For example, the concept of tissue hypoxia in sepsis has no empirical basis and can be neither verified nor refuted. Indeed, whether tissue hypoxia exists in patients with sepsis may be challenged.[2] Similarly, during maximal exercise, lactate release occurs during fully preserved intracellular oxygenation.[3] Finally, during extreme hypoxemia (e.g., summiting Mount Everest), lactate levels are either normal or only minimally elevated. Lactate is a major biofuel used for intracellular, intercellular, and interorgan shuttles,[3] processes that appear to increase bioenergetic efficiency. It is doubtful that lactic acidosis is due to the release of "protons from ATP hydrolysis," since no ATP depletion can be shown on magnetic resonance spectroscopy, even in severe septic shock.[4] A simpler and more elegant explanation (although similarly unproven) lies with the Stewart, or "strong ion," approach to acid–base physiology.[5] Lactate is an anion that decreases the strong-ion difference and increases the dissociation of water in plasma to release free hydrogen ions.

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TO THE EDITOR: Kraut and Madias provide an excellent overview of lactic acidosis. But the assertion that it remains unproven that the therapeutic administration of sodium bicarbonate may improve hemodynamics is inaccurate. Two prospective, randomized, blinded, crossover studies specifically examined the effects of sodium bicarbonate or isovolemic aliquots of normal saline on hemodynamics in critically ill patients with lactic acidemia who required vasoactive support.[1,2] Neither study showed any improvement. Mathieu et al. concluded that "sodium bicarbonate did not improve hemodynamic variables in patients with lactic acidosis, but did not worsen tissue oxygenation,"[2] findings that hardly suggest an endorsement.

As noted by Kraut and Madias, sodium bicarbonate therapy decreases levels of ionized calcium and increases intracellular carbon dioxide levels, which worsens intracellular acidosis. Furthermore, increasing the arterial pH shifts the oxyhemoglobin curve leftward, which decreases the unloading of oxygen to hypoxic tissues,[3] shifts potassium ions intracellularly,[4] and is a sodium, volume, and osmolar load.

With both potential and documented detrimental effects, and the absence of any beneficial effect, is it not time to abandon the use of sodium bicarbonate in the critically ill and follow the dictum *primum non nocere*?

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Kraut and Madias suggest that lactate-containing infusions increase serum lactate by only a modest amount and only when there is impaired lactate clearance. Their view does not appear to be consistent with the available evidence. Orbegozo Cortés et al. performed a meta-analysis of studies comparing normal saline with Ringer's lactate.[1] The five studies in the meta-analysis showed that the use of Ringer's lactate led to an increase in serum lactate of 2.0 mmol per liter (95% confidence interval, 4.0 to 3.6; P<0.01), an increase that is substantial and pertinent. The effect may not be clinically harmful yet may affect patient assessment. The 2012 consensus guidelines of the international Surviving Sepsis Campaign (SSC) recommend that serum lactate levels be both measured and normalized in patients with sepsis.[2] Similarly, in trauma, lactate is becoming increasingly important in risk stratification, timing of surgery, and patient treatment.[3] However, the guidelines of both the SSC and Advanced Trauma Life Support recommend the use of Hartmann's solution and Ringer's lactate for patient resuscitation.[4] The use of lactate-containing infusions in our clinical practice is not addressed in the review.

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TO THE EDITOR: We are surprised that Kraut and Madias do not include disorders resulting from primary dysfunction of the mitochondrial respiratory chain among the causes of lactic acidosis. A common variant, MELAS (mitochondrial myopathy, encephalopathy with lactic acidosis and strokelike episodes), is defined by a triad that includes the eponymous acidosis.[1] Although neuromuscular features predominated in the initial description, a much broader clinical spectrum has been appreciated during the past decades.[2] The 3243A→G mutation in the mitochondrial DNA accounts for the majority of MELAS manifestations. In a cohort of 123 matrilineal relatives harboring this mutation (mean age, 29 years; 45 fully symptomatic patients, and 78 carrier relatives), mean venous lactate levels were higher than in the 30 controls (3.0 mmol per liter and 1.8 mmol per liter, respectively, vs. 1.2 mmol per liter).[3] Increased lactate levels in plasma or cerebrospinal fluid are a common, albeit nonspecific, biochemical hallmark of mitochondriopathies and may support the diagnosis.[1] In patients with seemingly obscure lactic acidosis, the possibility of an underlying mitochondrial disorder should be entertained.

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TO THE EDITOR: Kraut and Madias correctly emphasize the importance of using repeated lactate levels to guide therapy. My colleagues and I first proposed, more than 30 years ago, that changes in blood lactate levels should be monitored during treatment for shock: rapid resolution of shock was associated with a decrease of more than 5% in lactate levels during the first hour of treatment.[1] However, as do other authors,[2,3] Kraut and Madias incorrectly refer to a target of "lactate clearance." As for any substance, blood lac-

tate levels represent a balance between production and elimination. In shock, increased production and decreased elimination coexist, and the resolution of hyperlactatemia is dependent on changes in both factors, in contrast to resolution of hyperlactatemia after grand mal seizures, in which overproduction ceases abruptly and clearance accounts for the decrease in blood levels.[4] To study lactate clearance would otherwise require a lactate infusion.[5] Clinicians should indeed be encouraged to monitor the decrease in lactate levels over time, but one should refer to lactate kinetics or time course rather than clearance, since the latter is scientifically and conceptually inaccurate.

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THE AUTHORS REPLY: We agree with Bellomo et al. in their emphasis on the important role of aerobic glycolysis in sepsis,[1] but we also recognize that in low-flow stages of sepsis, there can be a supply-dependent decrease in oxygen delivery and consumption that contributes to tissue hypoxia.[2] Also, we would not challenge the accepted view of the origin of protons in lactic acidosis on the basis of the Stewart approach to the analysis of acid–base disorders. We have previously provided a detailed critique of that approach.[3]

We are not sure how Salon's conclusion concerning the value of bicarbonate in the treatment of lactic acidosis differs from ours. As he did, we state that such value remains "unproven." We do advocate that the use of bicarbonate be examined further to determine whether its deleterious effects can be circumvented and the positive effects expressed. Also, the development of other bases that avoid the negative effects of bicarbonate seems warranted.

Igah et al. point out useful information about an increase in blood lactate with infusion of lactate-containing solutions. The increment in serum lactate of 2.0 mmol per liter that is described is modest. More important, there is no evidence that it has any deleterious effect on cellular function. However, this effect should be considered when interpreting changes in blood lactate during the course of disease and might be a factor when choosing the resuscitation fluid.

We are well aware of the occurrence of lactic acidosis in disorders of the respiratory chain referred to by Windpessl and Wallner. However, we elected to describe only the most common disorders associated with lactic acidosis that are encountered by the clinician. We agree that if the cause of lactic acidosis is not obvious, genetic disorders should be considered.

In our review, we address the factors that are involved in the production and consumption of lactate under various conditions. We emphasize the importance of serial measurements of blood lactate to monitor patients and guide therapy based in part on studies by Vincent's group.[4] Our use of the term "lactate clearance" as a goal of therapy was imported from goal-directed trials, in which the term referred to the fractional decrease in blood lactate in a subsequent measurement as compared with baseline.[5] Most important, the value of serial measurements of blood lactate in patient monitoring was one of the critical messages of our review, and we do not wish to dilute its importance by engaging in a debate about terminology.

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Since publication of their article, the authors report no further potential conflict of interest.

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Two Cases of Heart Failure after Implantation of a CoreValve Prosthesis

TO THE EDITOR: Two patients were hospitalized for recurrent heart failure after the implantation of a CoreValve self-expanding transcatheter aortic-valve prosthesis. In Patient 1, a 73-year-old woman with severe aortic stenosis who declined open surgery, a 29-mm CoreValve was implanted in August 2009. During the 5 years after valve implantation, severe aortic stenosis and progressive coronary artery disease developed, causing repeated cardiac decompensation. In Patient 2, an 80-year-old woman with severe aortic stenosis, chronic renal insufficiency, and a diminished ejection fraction, a 31-mm CoreValve was implanted in July 2013. During the first year after valve implantation, severe aortic regurgitation developed, with a decreasing ejection fraction leading to congestive heart failure.

In Patient 1, reoperation included aortic-valve replacement and coronary-artery bypass grafting in May 2014. In Patient 2, aortic-valve replacement was performed in June 2014, together with ascending aortoplasty for ectasia of the ascending aorta and transaortic mitral-valve repair and tricuspid-valve repair for moderate valvular regurgitation with the use of Alfieri stitches.

Both patients had uneventful postoperative courses. The CoreValve in each patient was firmly bonded to the aortic wall, and explantation was facilitated by means of vertical transsection and rolling up the prosthesis. The intraoperative findings in the two patients revealed thrombotic material on the frame (Fig. 1A), early structural degeneration of the aortic-valve prosthesis, and interference with motion of the anterior mitral leaflet. This interference was more prominent in Patient 2, in whom moderately severe mitral regurgitation had developed since CoreValve implantation.

The CoreValve prosthesis in Patient 1 showed severe calcification resulting in high-grade aortic stenosis (Fig. 1B). In Patient 2, structural leaflet degeneration with dehiscence at two commissures was found, leading to central aortic regurgitation (Fig. 1C). The reason for thrombus formation on the stents remains obscure; both patients were receiving dual antiplatelet therapy from the time of CoreValve implantation until reoperation. Whether early degeneration could be a problem of crimping (the procedure that is used to compress the prosthesis to enable transcatheter delivery), the implan-

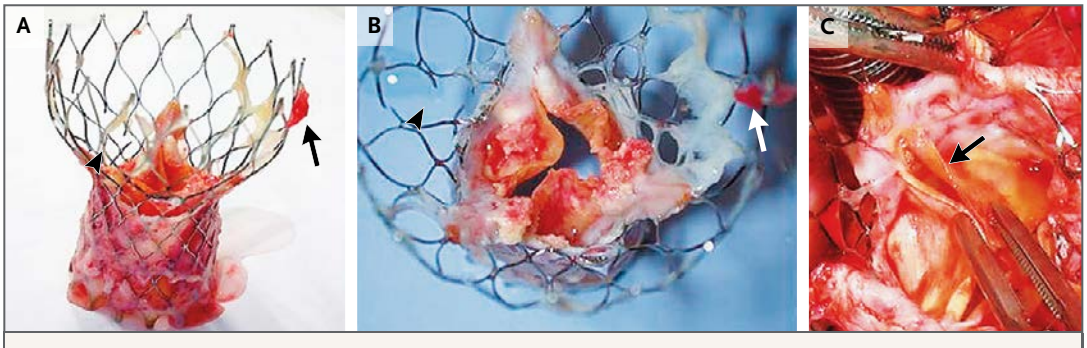

Figure 1. Removal of CoreValve Prosthesis in Two Patients.
Panels A and B show a CoreValve prosthesis that was explanted from Patient 1, with fresh thrombus (arrows), calcification, and rupture of leaflets. The artificial transection of the frame (arrowheads) facilitated extraction. Panel C shows the dehiscence of leaflets at commissures (arrow), which caused regurgitation in Patient 2.