CHAPTER 67

Hyperlactatemia and Lactic Acidosis

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OBJECTIVES

This chapter will:

1. Review the major factors that modulate physiologic lactate production and utilization.
2. Discuss the mechanisms that modulate lactate during critical illness.
3. Review acid-base aspects of lactic acidosis.
4. Review causes of lactic acidosis that have particular relevance to critical care practitioners.
5. Provide a framework for the approach to patients with lactic acidosis of unknown cause.

Hyperlactatemia, clinically defined as an increase in plasma lactate concentration above 2 mmol/L,[1,2] is one of the most frequently encountered metabolic alterations in the critically ill patient. Two important paradigms have framed current understanding of hyperlactatemia in this setting. The first is that lactate is a marker of tissue hypoperfusion and thus of oxygen debt. The trail of evidence supporting this notion can be traced to the work of Hill, Long, and Lupton, who in the early 1920s published a series of papers suggesting the association between "lactic acid and the supply and utilization of oxygen."[3] Huckabee further supported this notion with his studies in the 1950s and 1960s by demonstrating an association between oxygen deficit and excess lactate (Excess lactate = ([Lt − Lo]–[Pt − Po] × Lo/Po) in humans during exercise.[4] Weil and Afifi demonstrated a significant correlation between lactate and oxygen debt in hemorrhaged rats ($r = 0.5$, $p < .0005$), and between lactate and survival in 142 patients with clinical manifestations of circulatory shock.[5]

The second concept is that hyperlactatemia is an ominous sign. This is a conception that has been ingrained rightfully in the psyche of clinicians based on data that originated in Weil's seminal work but that has stood the test of time in demonstrating a clear association between elevated lactate levels and worse outcome.[5–8] The wide embrace of these two concepts has reduced the understanding of lactate to that of being an "evil" molecule, and a marker of tissue hypoxia and anaerobic metabolism. This chapter provides the reader with a different perspective, providing evidence that lactate is not just a waste product of anaerobiosis, but rather a key player in intermediary metabolism and energy homeostasis. Lactate is crucial for intercellular and interorgan cooperation, substrate distribution, and perhaps adaptation to injury, and thus hyperlactatemia cannot be an exclusive reflection of tissue hypoxia.

NORMAL METABOLISM OF LACTATE AND PHYSIOLOGIC HYPERLACTATEMIA DURING EXERCISE

Given the reasons stated above, and as a framework to understanding hyperlactatemia during critical illness, it is important to provide the reader with evidence that supports what it is known about physiologic lactate production and utilization.

Lactate Production

The resting basal rate of lactate production in humans has been quantified by using either isotropic dilution of 14C L-lactate or infusion of unlabeled L-lactate; it has been estimated to be 0.84 mmol/kg/hr with a range of 0.77 to 1.0 mmol/kg/hr, for a total daily production of 1290 to 1500 mmol.[9] Although many cells in the body contribute to this basal lactate production,[10] the largest contributors during normal conditions are skeletal muscle (17%), skin (27%), brain (18%), and red blood cells (23%).[11,12]

Lactate is produced from the reduction of pyruvate by action of the enzyme lactate dehydrogenase (LDH). LDH is expressed in the cytosol and exists in several isoforms with diverse tissue specific distributions.[12] Lactate concentrations are maintained in equilibrium with pyruvate by LDH at a ratio of about 10:1.[13] The equilibrium is represented by the following equation:

$$Pyruvate + NADH + H^+ \leftrightarrow Lactate + NAD^+$$

where NADH is reduced nicotinamide adenine dinucleotide and NAD is oxidized nicotinamide adenine dinucleotide. From this, three important conclusions about lactate production can be drawn. First, any condition increasing glycolytic flux will increase pyruvate and lactate production by the law of mass action, that is, without altering the kinetic rates between substrates.[1,14] Second, lactate accumulation can occur in fully oxygenated tissue (i.e., aerobic glycolysis) as the consequence of stimuli (i.e., cytokines, epinephrine) that increase glycolytic flux. Third, transferring electrons from NADH to pyruvate to form lactate is an efficient and necessary cytosolic mechanism to recycle NAD^+, because without the presence of sufficient NAD^+ as an electron acceptor, glycolysis cannot occur. It is therefore evident that lactate production is much more complex than commonly regarded, and interpreting hyperlactatemia as indicative of the presence of tissue dysoxia is a major oversimplification.

Lactate Utilization (Removal): Gluconeogenesis and Oxidation

Clearance of lactate after maximal exercise depends on recovery intensity, with faster clearance occurring with active than with passive recovery.[15] In critically ill patients, lactate clearance (i.e., volume of plasma that is cleared off of lactate per unit of time) has been estimated by quantifying the disposal of infused sodium L-lactate and was found to be approximately 800 to 1800 mL/minute. Although many organs consume lactate, the liver and the kidney represent the major sites of lactate uptake and clearance as they metabolize approximately 53%[15] and 30%[16–18] of daily lactate production, respectively. Lactate is metabolized by two

main mechanisms: First, lactate can be used as a substrate to regenerate glucose by gluconeogenesis, a process that is exclusive to liver and the kidney. Second, at least 50% of circulating lactate is removed and metabolized by means of oxidation during resting conditions.[19] Unlike gluconeogenesis, which is restricted to liver and kidney, oxidation can take place in many organs, including the heart, brain, and skeletal muscle.

Gluconeogenesis and the Cori Cycle

During normal conditions, at least half[20] of the lactate released into the circulation by the muscle is taken up by the liver and the renal cortex and converted into glucose in the Cori cycle.[21] Glucose generated by gluconeogenesis then is released to the circulation to maintain sufficient availability of energy substrates to organs that are dependent on glucose utilization such as brain, erythrocytes, and leukocytes (Fig. 67.1).

Gluconeogenesis is thus an evolutionarily conserved, fundamental cellular process by which glucose is generated from noncarbohydrate gluconeogenic substrates such as lactate, glutamate, alanine, and glycerol to maintain blood glucose levels during fasting.[19,22,23] More importantly to lactate kinetics, gluconeogenesis is a fundamental mechanism of lactate removal and metabolism because in terms of substrate utilization, lactate is the most important contributor to gluconeogenesis, accounting for approximately 53% of total renal glucose release.[24] Gluconeogenesis is exclusive to the liver and kidney (renal cortex),[25] because they alone contain glucose-6-phosphatase, the enzyme that catalyzes the formation of free glucose that is released into the circulation via glucose transporter membrane proteins.[19,22–24] A human study performed during the anhepatic phase of liver transplantation demonstrated the importance of the kidney in maintenance of lactate homeostasis by showing that the steady-state concentration of lactate in blood increased by only 1 mmol/L after the liver was removed.[16] Indeed, the kidney contributes with approximately 40% of all gluconeogenesis,[22] with 50% of the total conversion of lactate to glucose, and with about 30% of total lactate metabolism.[17,18]

The differential utilization of substrates in the renal cortex and medulla is the result of a particular enzymatic distribution. Although the cortex relies on fatty acid oxidation for its high levels of oxidative enzymes, the medulla depends on glycolysis because of its very low oxidative capacity. This particular enzymatic distribution and differential utilization of substrates in the renal cortex and

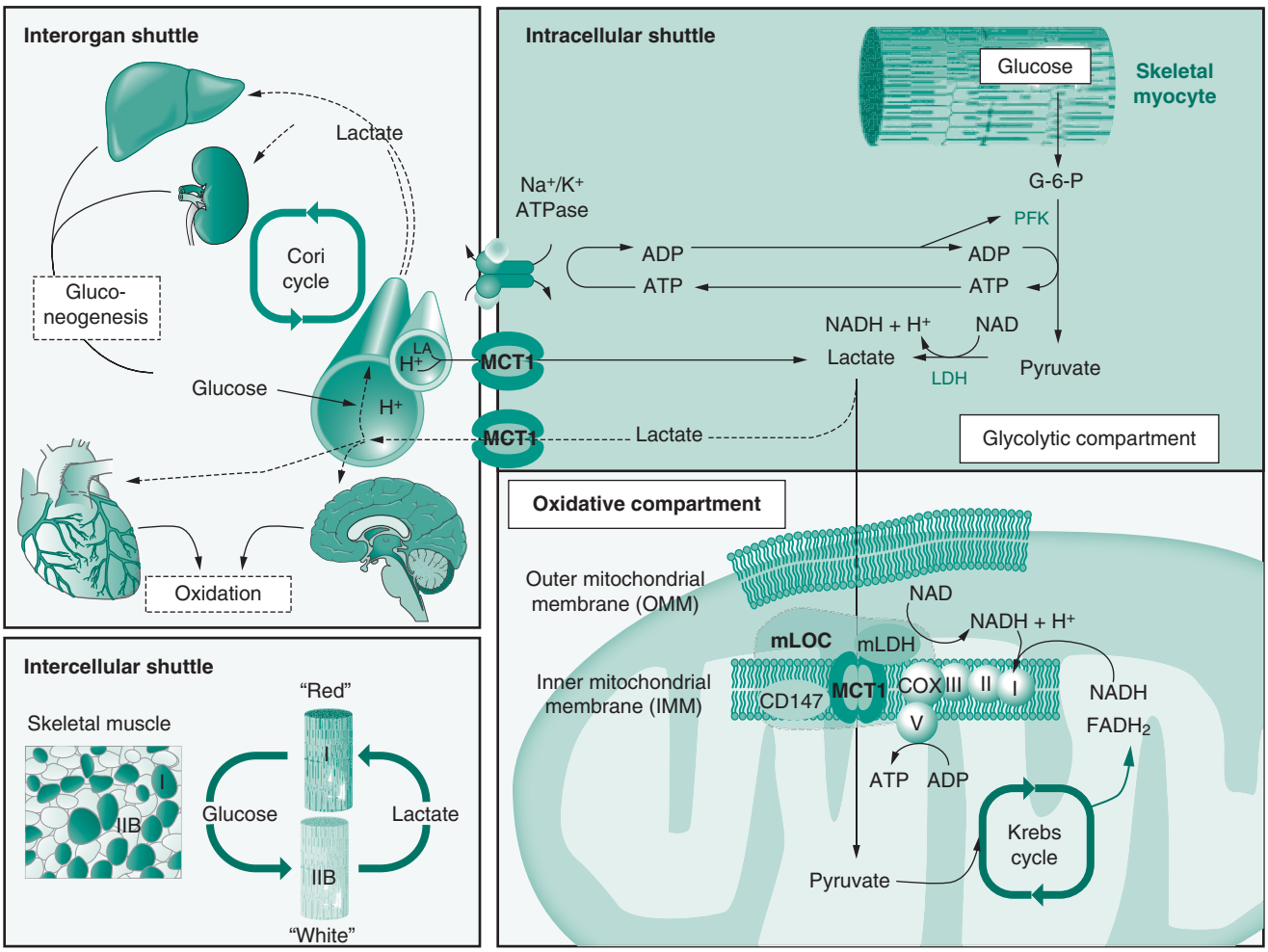

FIGURE 67.1 Schematic representation of the interorgan (Cori cycle), intercellular, and intracellular lactate shuttling systems. The *right panel* also represents the theory of cellular compartmentalization of carbohydrate metabolism into cytosolic glycolytic and mitochondrial oxidative compartments. *COX,* Cytochrome oxidase; *MCT1,* monocarboxylate transporter 1; *mLDH,* mitochondrial lactate dehydrogenase; *mLOC,* mitochondrial lactate oxidation complex.

medulla insinuate the presence of a corticomedullary recycling system[26] and suggest this cooperative substrate utilization, reminiscent of the Cori cycle, as a general (within organ and between organs) metabolic adaptive strategy.

Oxidation of Lactate

Hochachka has described lactate as an efficient energetic currency that can be distributed rapidly to other cells to be used as a carbon source and bioenergetic substrate.[27] Indeed, at least 50% of circulating lactate is taken up by many cells and metabolized by oxidation[20] via the Krebs cycle to generate adenosine triphosphate (ATP). This process has been studied extensively in human skeletal muscle; myocytes have been shown to be simultaneously capable of producing, releasing, and oxidizing lactate.[28] Importantly, exercise increases skeletal muscle uptake of lactate in humans, changing myocyte lactate metabolism from net production and release, to uptake and oxidation.[29] This provides evidence that lactate is indeed a valuable energy substrate, and that depending on the physiologic condition organs and tissues can resort to lactate to supplement their energetic requirements. This capacity for a dual, adaptive function (lactate release vs. uptake) in skeletal muscle is best explained by the presence of compartmentalization of cytosolic carbohydrate metabolism,[12,30] and by the cell-cell and intracellular lactate shuttle theories, which are discussed later[31,32] (Fig. 67.1).

Transport of Lactate Through Lipid Membranes and the Monocarboxylate Transporters

Contrary to prior understanding, transport of lactate through the cell membrane is facilitated by a family of proton-linked monocarboxylate transporters (MCTs).[33] Fourteen MCTs have been described, but MCT1 through MCT4 have been found to account for most of the lactate-pyruvate transport. MCT1 and MCT4 are the two isoforms expressed in skeletal muscle.[34] Highly glycolytic muscle (i.e., white, fast-twitch) expresses more MCT4, whereas highly oxidative muscle (i.e., red, slow-twitch) express more MCT1. The mechanism of transport of lactate through MCTs has been better studied in muscle and in MCT1, and it is known to be a saturable process that involves cotransport of H^+.[34] In this context, the first step is binding of a proton (H^+) to MCT1, followed by binding of L-. Subsequently, the proton and lactate anion are translocated to the opposite side of the sarcolemma and finally released from the MCT. The free carrier returns to start-up position across the membrane, which completes the translocation cycle.[33] Importantly, transport of lactate is stimulated by an increase in H^+ concentration (i.e., lowering pH) at either side of the membrane, suggesting lactate transport has a prominent role in mediating H^+ removal from exercising muscle.[35]

Mitochondrial L-Lactate Dehydrogenase and the Mitochondrial Lactate Oxidation Complex

The existence of a mitochondrial L-lactate dehydrogenase (mL-LDH) was suggested as early as 1951. Subsequently, Brooks et al. used agarose gel electrophoresis to measure LDH isoenzyme fractions in cardiac and skeletal myocytes and in hepatocytes,[34] suggesting the existence of mitochondrial LDH in the matrix and the inner mitochondrial membrane (IMM) and confirming prior findings by other groups.[32] Hashimoto et al. further provided compelling data suggesting that IMM LDH is part of a mitochondrial lactate oxidation complex (mLOC). Using confocal laser-scanning microscopy, Western blotting, and immunoprecipitation, these authors demonstrated co-localization of mLDH with MCT1, CD147 (a single-span transmembrane protein thought to anchor MCT1), and cytochrome oxidase (COX, the oxygen acceptor motif of the electron transport chain) in rat L6 myocytes, and proposed the association of these components as evidence of the existence of a mitochondrial lactate oxidation complex.[36] Hashimoto et al. have shown that the lactate anion induces the release of reactive oxygen species (ROS) from myocytes, and upregulation of genes (mRNA and protein expression) encoding for MCT1 at 1 hour and COX at 6 hours.[37] Furthermore, these authors demonstrated that COX expression correlated with an increase in expression of the peroxisome proliferator activated-receptor γ coactivator-1α (PGC1α) and DNA binding of the nuclear respiratory factor 2 (NFR-2), both of which are involved in mitochondrial biogenesis, a coordinated process between the nucleus and mitochondria to regenerate functional mitochondria,[38] suggesting an additional important role for lactate as a signaling molecule.

Compartmentalization of Cellular Intermediary Metabolism and the Lactate Intracellular and Cell-Cell Shuttle Theories

The observation that lactate can be transported from the cytosol into the mitochondrial matrix through MCT located in the outer mitochondrial membrane, and the discovery of mitochondrial LDH and the mLOC are the basis for the intracellular lactate shuttle (see later),[31,32] the compartmentalization, and the cell-cell lactate shuttle theories as proposed by Brooks. These theories postulate that cells are capable of compartmentalizing generation and use of ATP and that this is achieved by controlled shuttling of lactate from the cytosol to the mitochondria matrix or to the extracellular space via monocarboxylate transporters.[12,32] In this way, the energy needs of working muscle are met by: (1) an increment in glycolytic flux in the "glycolytic compartment" close to the myofibers, which results in glycolysis-derived ATP (and lactate) generation to support sarcolemmal Na+ -K+ ATP pump activity; (2) the transport of cytosolic lactate (generated by increased glycolytic flux or taken up from circulation) into the mitochondria by MCT1, which is transformed into pyruvate by the mLOC or mitochondrial LDH, and used to generate ATP through oxidation via the Krebs cycle and ETC; and (3) "shuttling" cytosolic lactate to the extracellular space to support the energy requirements of neighboring myocytes that are dependent on oxidation (Fig. 67.1). An example of this cell-cell shuttle in muscle occurs between skeletal muscle myocytes, where white, fast-contraction, glycolytic, lactate-producing fibers release lactate, and neighboring red, slow-contraction, oxidative fibers consume this lactate for further oxidation. Cell-cell lactate shuttles are found in other systems and organs, the most commonly known being the Cori cycle in liver and kidney. Other examples include the astrocyte-neuron system, in which astrocytes export lactate produced from glycolysis and neurons take it up for oxidation and the corticomedullary interaction in the kidney, where the renal cortex consumes lactate produced by the renal medulla.

Overall these data suggest that lactate metabolism is far more dynamic than an exclusive reflection of anaerobic

metabolism, and that skeletal muscle plays an important role not only in producing lactate during stress but also in lactate removal from the circulation. Furthermore, these data support the notion that during exercise, lactate is released efficiently to the circulation and distributed to other tissues and organs as a source of carbon and energy, particularly to those tissues with high ATP turnover such as the heart.[27] Finally, these data underscore that hyperlactatemia may not only be important in intracellular and cell-cell intermediary metabolic cooperative adaptations in response to stress but also have key roles as a "pseudohormone" capable of triggering signaling pathways that increase oxidative capacity by inducing the expression of lactate transporters and triggering biogenesis. With this framework in mind, a discussion of the main mechanisms involved in the development of hyperlactatemia in critical illness follows.

PATHOPHYSIOLOGY OF HYPERLACTATEMIA IN CRITICAL ILLNESS

Source of Lactate During Critical Illness

An increase in blood lactate ultimately reflects an imbalance between lactate production and utilization. Lactate production is increased in a variety of critical illnesses, although organ sources may vary, depending on the nature of the insult. During sepsis or after trauma, skeletal muscle is the major contributor.[39] In patients with acute lung injury or ARDS, lactate production by recruited leukocytes and alveolar macrophages plays a significant role.[40] Increased splanchnic lactate production and release can be seen in patients with severe multiple organ dysfunction syndrome (MODS) or with acute liver failure.[41]

Severe injury or infection is associated with enhanced whole-body uptake of glucose resulting from an increase in non–insulin-mediated glucose transport.[42,43] It is likely that this process is mediated by cytokines (i.e., tumor necrosis factor [TNF], interleukin-6).[42,44] Increased glucose uptake augments glycolytic flux that in turn increases production of lactate as the consequence of a mass-action effect. Lactate traditionally had been thought of as a metabolic "dead end" that reflected increased anaerobic metabolism of glucose. However, it is now appreciated that lactate is a valuable metabolic intermediate that interacts with the oxidative phosphorylation pathway to maintain a balance between demand and supply. This balance is reflected by the phosphorylation state, which can be represented as the ratio of ADP + ATP/AMP + ADP + ATP.[45] George Brooks et al. provided evidence that contradicted the anaerobic threshold theory of exercise-induced hyperlactatemia by demonstrating that lactate was produced during strenuous exercise by fully oxygenated muscle.[46] They proposed that glycolytically generated lactate in the cytoplasm is shuttled into the mitochondrial matrix via MCT1, where it supports ATP synthesis by (1) supplying reducing equivalents for the respiratory chain and (2) conversion to pyruvate (by mitochondrial LDH) with subsequent oxidation in the Krebs cycle (see Fig. 67.1). Aerobic formation of lactate therefore may be viewed as a mechanism by which the cytosol and mitochondria interact to maintain adequate oxidative synthesis of ATP in skeletal muscle. Evidence supporting the presence of a lactate shuttle in other organs (myocardium, brain, lung) also has been reported.[47,48]

During circulatory shock (particularly cardiogenic or hemorrhagic), in which severe reductions in organ perfusion may occur, compensatory mechanisms for ATP production may be inadequate, and tissue dysoxia (i.e., oxygen-limited cytochrome turnover[45]) may ensue. However, a number of studies have found that even during conditions of significant hemodynamic compromise, aerobic production of ATP is maintained. Ronco et al. identified the critical oxygen delivery for anaerobic metabolism in critically ill septic and nonseptic patients and found it to be substantially lower than previously reported, a value that would be very uncommon in patients who were being actively treated.[49] Nevertheless, proponents of a dysoxic mechanism for lactate production invoke the presence of alterations in microcirculatory blood flow that promote areas of tissue dysoxia in close proximity to well-oxygenated zones.[50] De Backer et al.[51] demonstrated that pharmacologically induced improvement in microvascular perfusion was proportional to the decrease in lactate level. They also noted that changes in capillary perfusion were independent of changes in systemic hemodynamic variables.[51]

Impaired oxidative production of ATP and augmented lactate production also could occur as the consequence of mitochondrial damage by inflammatory mediators. This process has been documented most clearly in patients with MODS and has been termed cytopathic hypoxia by Fink.[52] The existence of this process is supported by electron microscopic examination of tissue from patients dying of sepsis that demonstrated evidence of significant mitochondrial damage despite little evidence of cell death.[53]

James et al. proposed that persistent hyperlactatemia in injured or septic patients who are hemodynamically stable results from epinephrine-stimulated aerobic glycolysis in skeletal muscle.[39,54] Epinephrine concentrations are typically markedly increased in sepsis and after trauma; this in turn stimulates lactate production by virtue of a β_2-adrenergic receptor-mediated increase in activity of Na^+ -K^+ membrane pumps, which derive their energy from glycolysis (Fig. 67.2). Some of the lactate is oxidized locally via the lactate shuttle, while the remainder is released into the circulation. The increase in circulating lactate serves as an important oxidative substrate for other organs such as heart and brain (i.e., the cell-to-cell lactate shuttle), as well as providing a substrate for gluconeogenesis in liver and kidneys (Cori cycle)[46,55] (see Fig. 67.1).

A number of studies have documented that lactate production during systemic inflammation is most prominent in organs rich in inflammatory cells (i.e., lung, liver, gut).[56] Increased production of cytokines (i.e., TNF, granulocyte-macrophage stimulating factor) activates leukocytes and macrophages; this in turn triggers the respiratory burst that generates reactive oxygen species (ROS) such as peroxides and superoxides.[56] Formation of ROS requires nicotinamide adenine dinucleotide phosphate (NADPH), which is generated by flux of glucose through the pentose phosphate pathway (PPP). Ribose-5 phosphate is a PPP intermediate that can be converted to glycolytic intermediates that ultimately generate lactate.[57] It has been suggested that on a weight-for-weight basis, leukocytes are the most potent source of lactate in the body, outpacing other cell types by orders of magnitude.[56] The immune response to proinflammatory stimuli is most active in the lung in large part because of its constant exposure to environmental stimuli. In this regard, production of lactate by activated leukocytes and alveolar macrophages has been demonstrated in patients with acute lung injury and ARDS.[58,59] Inflammatory cells in gut and liver also may be activated by proinflammatory factors that stimulate lactate production. However, this process does not generally result in hyperlactatemia because of efficient hepatic lactate metabolism. Nevertheless,

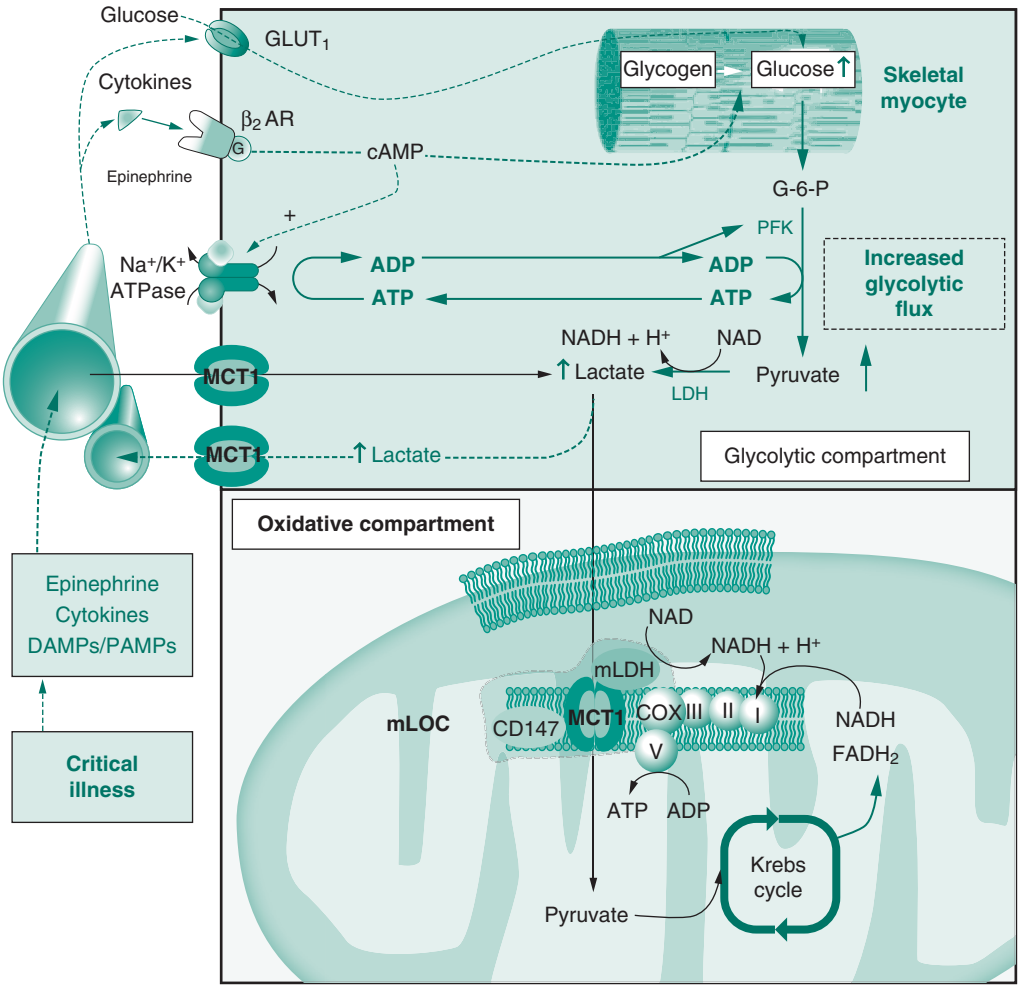

FIGURE 67.2 Inflammatory mediators, including DAMPs and PAMPs, and adrenergic stimulation induced by sepsis or sterile inflammation (such as hemorrhagic shock or exposure to cardiopulmonary bypass) result in changes in skeletal muscle use of lactate. In these circumstances, catecholamines and DAMPs stimulate the activity of Na-K ATPase pumps, which results in increased glycolytic flux to derive ATP. This increased glycolytic phenomenon is enhanced further by stimulation of glycolytic enzymes such as hemokinase, and by increased entrance of glucose into the cell secondary to an increased expression of membrane glucose transporters such as GLUT1. This increase in aerobic glycolysis flux is independent of oxygenation and is thus aerobic. Increased aerobic glycolysis thus results in the increased production of lactate, which is independent of oxygenation. Increased aerobic glycolysis is an important mechanism of lactate production during inflammatory states, particularly sepsis, and an important source of hyperlactatemia. *COX,* Cytochrome oxidase; *DAMP,* damage associated molecular patterns; *MCT1,* monocarboxylate transporter 1; *PAMP,* pathogen associated molecular patterns.

enhanced splanchnic lactate production can promote systemic hyperlactatemia in conditions in which hepatic metabolism of lactate is impaired (i.e., severe MODS or acute liver failure) or in patients with mesenteric infarction in whom marked increase in lactate production overwhelms hepatic clearance.[41]

Lactate Utilization During Critical Illness

Hepatic and renal gluconeogenesis is increased markedly during sepsis and is directed toward providing substrate for organs or tissues involved in the immune response to severe injury or infection (i.e., lung, liver, spleen, wound). Activity of this pathway is stimulated by counterregulatory hormones (glucagon, epinephrine, cortisol), as well as by cytokines (i.e., TNF).[60] Hepatocytes also may metabolize lactate by oxidation; however, the extent to which this process occurs during critical illness has not been quantified (most hepatic energy production results from fatty acid oxidation). The heart also takes up lactate for oxidation, especially during hyperlactatemia.[61] Oxidation of lactate may satisfy up to 60% of myocardial energy needs and is the most efficient energy source because it may be used directly for ATP production via the mitochondrial shuttle. Lactate has a positive inotropic effect, and myocardial lactate deprivation is associated with decreased cardiovascular performance and early death in endotoxic shock.[62] The brain also may oxidize lactate, particularly during increased metabolic demand and hyperlactatemia.[63]

Revelly et al. provided data that suggested that hyperlactatemia in critical illness is mainly the consequence of increased lactate production rather than decreased utilization.[64] In a small study of patients with severe sepsis and cardiogenic shock they found that lactate clearance (using continuous infusion of stable isotopes) was similar to healthy subjects. In addition, increased lactate production was linked to hyperglycemia and increased glucose turnover. This suggested that hyperglycemia and associated increase in glucose turnover was a major determinant of lactate metabolism during critical illness. In contrast, Levraut et al. used bolus infusion of sodium lactate to measure lactate clearance

in stable septic patients with mild hyperlactatemia. They found that hyperlactatemia was due to impaired clearance rather than overproduction.[65] It has been suggested that the discordant findings may be due to the fact that lactate level was higher in the Revelly study and that patients in the Levraut study were weaned from catecholamines.[66] It can be seen therefore that, contrary to previously held opinion, lactate should not be viewed as a metabolic waste product; rather it should be viewed as a valuable metabolic intermediate that functions as a useful energy substrate during stress. In addition, hyperlactatemia should not be interpreted as a specific indicator of tissue dysoxia, because lactate may be generated during fully aerobic conditions. Leverve stated, "Hyperlactatemia in patients with circulatory compromise may be best viewed as a sentinel that signals the upper limit for metabolic adaptation that is not necessarily linked to inadequate oxygen delivery."[67]

DIAGNOSTIC CONSIDERATIONS

The clinical utility of the classic Cohen and Woods categorization of lactic acidosis as type A (clinical signs of hypoperfusion) or type B (absent clinical signs of hypoperfusion) is impractical because overlapping mechanisms are commonly present. In addition, bedside confirmation of the presence of tissue dysoxia is difficult and imprecise. As stated above, hyperlactatemia or lactic acidosis cannot be considered a specific indicator of tissue dysoxia. Conversely, hypoperfusion can be present in the setting of normal plasma lactate levels. Although hypoperfusion may be present during any given moment in the course of disease, persistence of elevated lactate levels after adequate resuscitation may not be secondary to ongoing tissue hypoperfusion but may occur consequent to other mechanisms (i.e., an ongoing cytokine or β_2-adrenergic receptor-mediated increase in glycolytic flux). Thus in this scenario, lactic acidosis cannot be categorized as type A or type B, but rather a combination of both.

These observations have important implications for practice. First, the interpretation of hyperlactatemia in isolation from the patient's clinical context (clinical condition, relevant medical history, physical examination, and additional laboratory workup) will lead to inappropriate conclusions. Second, hyperlactatemia or lactic acidosis is not equivalent to the presence of tissue hypoxia. Third, the diagnosis of hypoperfusion, and thus the decision to treat by improving oxygen delivery, must not be based solely on the plasma level of lactate. Finally, failure to decrease plasma lactate levels does not necessarily imply the persistence of hypoperfusion.

Within this framework, the definition of lactic acidosis includes an increment in lactate levels beyond the normal values. The first important consideration here is that many laboratories will have varying reference values, particularly regarding the higher limit of normality. Most commonly it is accepted that the lower limit of normal lactate concentration is set around 0.5 mmol/L with relative consistency across laboratories, with an upper limit centered around 2 mmol/L (again with more variability).[68] The second consideration, as will be expanded upon in the section on prognosis below, is that even mild elevations of lactate (i.e., 0.75 mmol/L) in the context of critical illness may prognosticate poor outcome, suggesting that even "normal" values (i.e., <2 mmol/L) could still carry key clinically relevant information in this patient population. Indeed, critically ill patients commonly manifest mild elevations of blood lactate (i.e., lactate level >2 mmol/L but <5 mmol/L) that may not be accompanied by a low pH. Although this phenomenon usually occurs as the consequence of the underlying stress response, it also may be an early indicator of a potentially correctable disturbance (i.e., tissue dysoxia, drug toxicity) and should prompt further evaluation.[69]

The mechanism by which acidosis accompanies increased glycolytic production of lactate is controversial. In 1978 Zilva[70] proposed that anaerobic glycolysis was not acidifying[70]; that is, that glycolytic flux generates lactate, ATP, and water but does not directly produce lactic acid. This researcher postulated that the acidosis accompanying hyperlactatemia occurred as the consequence of increased H^+ production resulting from unreversed cytoplasmic ATP hydrolysis, as follows:

$$ATP \rightarrow ADP + P + H^+$$

In this view, a decrease in oxidative regeneration of ATP consequent to tissue hypoperfusion results in an accumulation of H^+ and a fall in pH. Conversely, in the setting of maintained oxidative metabolism, H^+ is buffered when ATP is reconstituted (providing a potential explanation for the occurrence of hyperlactatemia in the absence of acidosis).[71] However, Bellomo et al.[72] questioned the concept of unreversed ATP hydrolysis. In reality, ATP is converted to ADP and orthophosphate (a very weak acid; pK_a = 6.8). If unreversed ATP hydrolysis were occurring, one also would expect to see increased plasma phosphate, which is not the case. In addition, severe septic shock would result in profound ATP depletion, which has not been documented.[73] Finally, the rise in acidity would be small, because the total amount of ATP in the body is less than 0.1 mol. A more likely explanation is provided by Stewart's physicochemical theory of acid-base.[74] In this view, an increase in concentration of a strong anion such as lactate results in a relative excess in anionic charge in the blood. Electroneutrality is maintained by an increase in $[H^+]$ consequent to enhanced dissociation of water, which in turn promotes a fall in pH (see Chapter 71).

Although severe hyperlactatemia (i.e., serum lactate > 10 mmol/L) generally is accompanied by acidemia, the correlation between lactate and pH may not be tight with less severe hyperlactatemia. Critically ill patients with hypermetabolic stress (i.e., sepsis, burn, trauma) commonly display modest elevations in blood lactate (i.e., serum lactate 2–5 mmol/L), which can occur in the absence of acidemia. The term *stress hyperlactatemia* has been proposed to describe this state.[18] As described previously, it was postulated that greater lactate production is not necessarily acidifying provided that oxidative metabolism is maintained, because H^+ ions are consumed when ATP is regenerated. However, it is more plausible that a normal pH is preserved because of intracellular buffering of H^+ or, more likely, as the consequence of an intracellular shift of chloride, thereby maintaining the strong ion difference.[75] In addition, increased production of unmeasured cations has been described during critical illness and also could counterbalance excess anionic charge.[76] It is therefore unlikely that the lack of acidosis during hyperlactatemic stress reflects a distinct pathogenesis.[77]

Anion Gap and Lactic Acidosis

The anion gap cannot be used as a surrogate in the diagnosis of lactic acidosis because the association between hyperlactatemia and the anion gap is poor.[78] Furthermore, correcting the anion gap for hypoalbuminemia does not appear

to improve detection of hyperlactatemia.[78] The lack of tight correlation between lactate concentration and the anion gap may be due to the fact that metabolic acidosis in critically ill patients is commonly multifactorial; hyperchloremia and/or an increase in unidentified anions often accompanies hyperlactatemia.[79] Gunnerson et al.,[80] comparing lactate acidosis with nonlactate metabolic acidosis in 548 critically ill patients, noted that patients with lactic acidosis had the highest mortality rate (56%), whereas mortality was lower in those with strong ion gap (unmeasured anion) acidosis (39%) and hyperchloremic acidosis (29%). The identity of these unmeasured anions (i.e., anions other than lactate, ketoanions, anions from renal failure or toxins) is not completely understood. Forni et al.[81] proposed that these anions were negatively charged intermediates of the Krebs cycle. However, other investigators have provided data suggesting that strong ion gap acidosis is probably multifactorial in nature.[82]

BLOOD LACTATE LEVEL AND PROGNOSIS

Measurement of blood lactate level also may be used as a means to assess prognosis. Early research in patients with circulatory shock suggested that a single—time point measurement of lactate at presentation was useful in predicting mortality. Weil and Afifi[5] found that in patients with circulatory shock, an increase in blood lactate level from 2 to 8 mmol/L was associated with a decrease in the estimated probability of survival from 90% to 10%. This association has been demonstrated in different populations of critically ill patients.[6,83,84] In addition, serial lactate measurements also have been shown to provide important prognostic information.[6,85] Blood lactate levels also have been found to have better prognostic value than arterial blood pressure.[86,87] Importantly, several investigators have shown that even mild elevations of lactate upon admission (i.e., >1.35 or >2)[6,69] have been associated with decreased survival, confirming that regardless of the cause, hyperlactatemia is a sensitive prognostic marker. One study in critically ill patients showed that even mild hyperlactatemia (i.e., >0.75 mmol/L) is associated with increased hospital mortality (OR 2.1, 95% confidence interval 1.3–3.5, $p = 0.01$); the strength of this association was observed to increase with higher lactate concentrations (OR 4.8, 95% CI 1.8–12.4, $p < 0.001$).[6] A retrospective analysis of the VASST trial showed that in septic patients, blood lactate concentrations higher than 1.4 mmol/L were associated with increased mortality.[7] Among the various causes of metabolic acidosis, lactic acidosis carries the worst prognosis.[80] In patients with lactic acidosis secondary to circulatory shock, hemorrhagic shock has a better prognosis than that resulting from either cardiogenic or septic shock,[86] because of a greater chance of reversing hypoperfusion consequent to hemorrhage. In addition, the extent of elevation in blood lactate concentration also is influenced by the patient's ability to clear lactate. Compared with patients with normal liver function, patients with chronic liver disease would be expected to have a higher level of hyperlactatemia after a similar insult.

For those reasons, sequential measurements of blood lactate during resuscitation from circulatory shock have been shown to provide more useful prognostic information than single-point measurements. Failure to decrease plasma lactate levels over time (within 2 to 6 hours after admission) is associated with greater likelihood of multiple-organ failure and higher mortality.[83,84,88] Conversely, decline in blood lactate during hemodynamic resuscitation is a marker of improved prognosis. Sequential measurement of lactate also has been advocated as a tool to guide adequacy of hemodynamic resuscitation.[89–91] Jones et al. showed that attaining lactate clearance of at least 10% as a therapeutic goal during the first hours of resuscitation was noninferior to resuscitation driven by achieving an $ScvO_2$ of 70%.[91] Janssen et al. studied ICU patients admitted with lactate of 3.0 meq/L or greater. The treatment group had resuscitation targeted to attaining a reduction in blood lactate concentration of 20% or more in the first 2 hours of treatment, whereas the control group was treated without ongoing knowledge of lactate levels. The treatment group was found to have a hospital mortality of 33.9%, compared with 43.5% in the control group. In addition, the treatment group had lower Sequential Organ Failure Assessment Score (SOFA) scores between 9 and 72 hours, inotropes could be stopped earlier, and weaning from mechanical ventilation and ICU discharge also occurred earlier.[92] On the basis of this evidence, the latest version of the Surviving Sepsis guidelines has recommended the normalization of lactate as a goal of initial resuscitation with a level of evidence grade 2C.[93] However, others have criticized this approach based on the fact that a reduction of lactate alone cannot discern whether this occurred as the direct consequence of augmented perfusion, or whether it was due to other factors (i.e., reduced lactate production secondary to decreased epinephrine secretion, increased lactate use, or dilutional effects).[94]

In summary, lactate levels at admission and "lactate clearance" within the first few hours of resuscitation carry important information to the clinician as to the probability of complications, development of organ dysfunction, and survival of critically ill patients in the context of a wide range of disease processes. However, lactate clearance during resuscitation cannot be clearly linked to improved tissue perfusion.

Approach to Lactic Acidosis of Uncertain Cause

Clinicians occasionally encounter patients with lactic acidosis in whom the cause is not obvious. Transient lactic acidosis may result from a period of occult hypoglycemia or an unrecognized seizure. Tables 67.1 and 67.2 provide an outline of the mechanisms, associated clinical manifestations, and diagnostic considerations of other less common, yet important mechanisms of lactic acidosis in the critically ill patient. Within that framework, and in patients with persistent lactic acidosis, the following approach is suggested:

- Consider the possibility of thiamine deficiency. Empiric administration of thiamine carries little risk, and a prompt response strongly supports the diagnosis.
- Discontinue potentially causative drugs (i.e., antiretroviral agents, β_2 agonists, nitroprusside, propofol, parenteral lorazepam, metformin).
- Consider the possibility of poisoning (i.e., toxic alcohol, cyanide) and evaluate the need for empiric therapy.
- Congenital mitochondrial dysfunction occasionally may manifest in adults and should be considered in patients with unexplained weakness or difficulty weaning from mechanical ventilation.

CONCLUSION

Lactic acidosis is a cardinal manifestation of circulatory shock. However, lactic acidosis also may occur as the

TABLE 67.1

Other Pathologies Associated With Lactic Acidosis

CONDITION	SOURCE AND/OR MECHANISM	ASSOCIATED CLINICAL MANIFESTATIONS/ IMPORTANT CLINICAL INFORMATION	COMMENTS
Asthma	Increased lactate production from respiratory muscles. However, the peak of hyperlactatemia occurs while the patient is recovering[65], and thus it is more likely that the mechanism relates to stimulatory effect of β_2 agonists on glycolytic flux[64,95]	Initial or delayed hyperlactatemia during status asthmaticus has little prognostic value[96]	Lactic acidosis develops only in some patients after β_2 agonist treatment. The reason for this selectivity is unknown but may be related to polymorphisms in the β_2 receptor gene[97]
Acute liver failure	Increase in lactate production from Kupffer cells and the lung[92,98] Impaired lactate clearance by hepatocytes[99] Increased hepatic lactate production from accelerated glycolytic rate[100]	Common in acute liver failure, consequent to an associated systemic inflammatory response resulting from hepatocellular necrosis[101]	Hyperlactatemia is unusual if there is no increased lactate production during chronic liver dysfunction. Hyperlactatemia has prognostic importance in this patient population
Malignancy	Cytokine-mediated stimulation of glycolytic flux in neoplastic cells	Hypoglycemia[98] resulting from increased glucose utilization by neoplastic cells or may represent a paraneoplastic syndrome[102]	More frequent in leukemia or lymphomas but also in solid tumors with liver or bone marrow metastases. Lactic acidosis persists even after correction of hypoglycemia
Thiamine deficiency	Impairment of PDH because thiamine pyrophosphate is an essential co-factor of PDH. Impairs OXPHOS of pyruvate in the Krebs cycle, which stimulates the glycolytic flux		Can develop rapidly (days) in critically ill patients because of decreased intake or increased urinary or GI losses
Cardiopulmonary bypass	Hyperglycemia, and the administration of epinephrine, norepinephrine, and dobutamine are associated with hyperlactatemia in this setting.[103] The contribution of tissue hypoperfusion to hyperlactatemia has been challenged: Microdialysis measurements during CPB have shown no association between tissue and plasma lactate.[104] Hyperlactatemia has been shown to occur in patients with no evidence of tissue hypoperfusion.[105] Local lung production after CPB has been found to be a significant contributor to hyperlactatemia.[106,107] Cytokine-mediated and systemic inflammation resulting from exposure of blood to the extracorporeal circuit[108,109]	Patients with polymorphisms in the TNF-β or IL-10 genes experienced postoperative lactic acidosis in one study[110]	Hyperlactatemia during cardiac surgery is associated strongly with mortality
Severe hypophosphatemia	Depletion of intracellular ATP and decreased 2,3-diphosphoglyceric acid. Non-anion gap acidosis secondary to impaired tubular reabsorption of bicarbonate[111]	Severe hypophosphatemia (i.e., phosphate < 1.5 mg/dL) can be a cause of hyperlactatemia	
Congenital	Mutations or deletions in respiratory chain genes or in the pyruvate dehydrogenase complex[112]	Manifests as episodes of lactic acidosis with neurologic and developmental abnormalities. Suspect a mitochondrial cause if in the absence of hypoxia or sepsis, the patient has muscle weakness, or it is difficult to wean from mechanical ventilation.[113] Other neurologic manifestations include stoke, seizures, dementia, migraines, and ophthalmoplegia	Usually appears during infancy or early childhood, but some may manifest until adulthood.

CPB, Cardiopulmonary bypass; *OXPHOS,* oxidative phosphorylation; *PDH,* pyruvate dehydrogenase.

Continued

TABLE 67.1

Other Pathologies Associated With Lactic Acidosis—cont'd

CONDITION	SOURCE AND/OR MECHANISM	ASSOCIATED CLINICAL MANIFESTATIONS/ IMPORTANT CLINICAL INFORMATION	COMMENTS
D-lactic acidosis	In patients with short bowel syndrome, ingested carbohydrates are malabsorbed and reach the colon undigested, where they are fermented by bacteria into organic acids. This acidifies the colonic milieu promoting overgrowth of gut flora with acid-tolerant mechanisms that produce D-lactate	Occurs in patients with short bowel syndrome secondary to resection or bypass surgery or with chronic pancreatic insufficiency. Associated with neurologic manifestations—slurred speech, confusion, ataxia, triggered by ingestion of large amounts of carbohydrates lasting hours to days	Suggestive laboratory findings include anion gap acidosis, increased strong ion gap, normal serum lactate level (analyzers only detect L-lactate). Confirmation is done by the finding of serum D-lactate level > 3 mmol/L[114]
Hypoglycemia	Hypoglycemia is a potent stimulant of the sympathetic nervous system, releasing epinephrine, which increases glycolytic flux in muscle and thus the release of lactate. In addition, in hepatic dysfunction, a minimal amount of glucose is required as an energy source for effective conversion of lactate into glucose through gluconeogenesis[115]	Patients with chronic renal or hepatic disease	Hypoglycemia-associated lactic acidosis responds promptly to administration of glucose, in contrast with hypoglycemia resulting from malignancy that does not respond to glucose administration

ATP, Adenosine triphosphate; *CPB,* cardiopulmonary bypass; *GI,* gastrointestinal; *IL-10,* interleukin-10; *OXPHOS,* oxidative phosphorylation; *PDH,* pyruvate dehydrogenase; *TNF-β,* tumor necrosis factor-beta.

TABLE 67.2

Medication or Drug-Induced Lactic Acidosis

CONDITION	SOURCE AND/OR MECHANISM	ASSOCIATED CLINICAL MANIFESTATIONS/ IMPORTANT CLINICAL INFORMATION	COMMENTS
Metformin	Metformin can bind to complex 1 of the mitochondrial electron transport chain.[116] Alternatively, it has been postulated that it blocks gluconeogenesis, decreasing conversion of lactate to glucose[117]	A mortality of 30% of patients with lactate concentrations > 5 mmol/L in the presence of metformin was reported in one study, in comparison with 11% in patients with <5 mmol/L[118]	Occurs in about 4.3 patients per 100,000 patient-years.[119] Metformin plasma concentrations correlates with plasma lactate levels, pH, and creatinine
Alcohols			
Ethanol	Metabolized in the liver to acetaldehyde, which can potentially inhibit the ETC. However, usually it is not associated with hyperlactatemia unless other causes are present, such as thiamine deficiency or presence of salicylates[120]	Treatment includes administration of folic acid and thiamine to avoid Wernicke-Korsakoff syndrome	

TABLE 67.2

Medication or Drug-Induced Lactic Acidosis—cont'd

CONDITION	SOURCE AND/OR MECHANISM	ASSOCIATED CLINICAL MANIFESTATIONS/ IMPORTANT CLINICAL INFORMATION	COMMENTS
Methanol	Methanol is metabolized by hepatic alcohol dehydrogenase to formaldehyde, and then it is rapidly oxidized to formic acid by the cytochrome P450 system. Formic acid is a potent inhibitor of OXPHOS	Treatment options include: 1. Extracorporeal treatment (modality of choice – intermittent hemodialysis or HD) 2. The administration of an antidote—a competitive inhibitor of alcohol dehydrogenase in the form of ethanol or fomepizole. Methanol is eliminated by renal and nonrenal (presumed respiratory clearance) routes. In the absence of antidote therapy, methanol elimination half-life is 2.3–13.7 hours.[121] HD can be terminated when the methanol concentration is <200 mg/L of 6.2 mmol/L and clinical improvement is observed[121]	The use of antidotes significantly increases the elimination half-life of methanol to a mean of 54 hours[122] and thus extracorporeal removal may be beneficial to shorten ICU stay. Extracorporeal therapy has been recommended in the following circumstances with grade 1D evidence (level 1 = strong recommendation by experts, D = very low level of evidence): 1. Severe poisoning characterized by coma, seizures, new vision deficits, persistent metabolic acidosis despite adequate supportive measures, serum AG > 24 mmol/L; 2. High methanol concentration (>700 mg/L with fomepizole treatment; >600 mg/L with ethanol treatment; >500 mg/L in the absence of antidote); in the setting of altered osmolar gap when methanol level is absent. 3. In the context of impaired renal function[121]
Ethylene glycol	Similar mechanism as methanol. However, ethylene glycol is metabolized to glycolate. In addition, can cause spurious hyperlactatemia because glycolate can cross-react with lactate in certain blood chemistry analyzers[123]	Fomepizole can be used in the treatment of ethylene glycol intoxication. The elimination (renal) half life of ethylene glycol is approximately 16 hours during fomepizole treatment. A ≥50 mg/dL of ethylene glycol concentration has been used to determine the use of HD[124,125]	
Propylene glycol	Hyperlactatemia has been reported in patients receiving medications that use propylene glycol as a vehicle (lorazepam, diazepam, diphenylhydantoin, trimethoprim-sulfamethoxazole)	Hyperlactatemia is more frequent in patients with renal or hepatic dysfunction because propylene glycol is metabolized in the liver and kidney Monitoring serum osmolarity has been recommended to detect potentially toxic levels of propylene glycol[126]	Commercial preparations of propylene glycol comes in a 50:50 mixture of D and L isomers. The D isomer is metabolized to D^- lactate, which is cleared more slowly than L^+ lactate. Accumulation of D^- lactate in the brain has been implicated as the cause of the central nervous system manifestations of propylene glycol toxicity
β_2-adrenergic receptor agonists	Stimulation of Na^+/K^+-ATPase in skeletal muscle[64,96]	Described initially in pregnant women undergoing tocolytic treatment with terbutaline, and in patients with asthma undergoing treatment with β_2-adrenergic receptor agonists[96]	
Salicylates	Salicylates induce hyperlactatemia by uncoupling OXPHOS and inhibiting the enzymes of the Krebs cycle	Acidosis decreases renal elimination of salicylates and increases the nonionized fraction, which augments passage through the blood-brain barrier, thus increasing the potential for toxicity	
Cyanide and nitroprusside	Cyanide combines with cytochrome c and inhibits OXPHOS, thus inducing hyperlactatemia Nitroprusside infusion can cause cyanide toxicity	Cyanide poisoning usually occurs as a result of smoke inhalation or in the context of a suicide attempt. Cyanide levels offer little help because of prolonged sample processing time. Cyanide poisoning should be suspected in patients with hyperlactatemia with neurologic and/or cardiovascular manifestations (i.e., confusion, seizures, coma, hypotension) Cyanide toxicity derived from nitroprusside treatment occurs particularly with prolonged infusions (i.e., >72 hours) and with high doses (>2 mg/kg/min). This also can occur with short infusions of very high doses that deplete thiosulfate stores. The best evaluation for possible toxicity in this setting is clinical (i.e., tachycardia, agitation, seizures) and measurement of blood lactate concentrations. Lactic acidosis can be eliminated by routine addition of sodium thiosulfate in the infusion bag	

Continued

TABLE 67.2

Medication or Drug-Induced Lactic Acidosis—cont'd

CONDITION	SOURCE AND/OR MECHANISM	ASSOCIATED CLINICAL MANIFESTATIONS/ IMPORTANT CLINICAL INFORMATION	COMMENTS
Carbon monoxide	Multiple mechanisms: Carboxyhemoglobinemia alters oxygen transport to the tissues and induces a leftward shift of the oxyhemoglobin curve, thus causing tissue dysoxia. More importantly, however, carbon monoxide binds to cytochromes in the electron transport chain, impairing OXPHOS and contributing to ROS production	Leading cause of unintentional poisoning worldwide[127] Occur most commonly in males, during winter, and often involve heating or cooking appliances Burn victims are at risk of CO poisoning CO levels usually do not correlate with symptoms	Signs of CO poisoning[127] Neuro: headache, dizziness, confusion, blurry vision, syncope, seizures, incontinence, coma. (Neuronal excitability $K_{v2.1}$ and Trek-1 channels, activation of soluble guanylyl cyclase and vasodilatation) Cardiovascular: hypotension, palpitations, chest pain, myocardial ischemia. Lung: noncardiogenic pulmonary edema (epithelial sodium channel compromise [ENaC] and ROS generation). Abdominal: nausea, vomiting, abdominal pain (ENaC, ROS generation, increased NO production). LFT elevation. Muscle: rhabdomyolysis (myoglobin binding), rigors (peripheral neuronal hyperexcitability from $Na_{v1.5}$ and $K_{v2.1}$ channels)
Antiretroviral agents	Thought to be caused by mitochondrial toxicity secondary to inhibition of DNA polymerase-γ, which uncouples OXPHOS[128]	Mild-moderate hyperlactatemia (i.e., 2.5–5 mmol/L) occurs in 25% of patients with human immunodeficiency virus under treatment with nucleoside reverse transcriptase inhibitors (particularly stavudine)[128]	
Propofol	Lactic acidosis occurs secondary to uncoupling of OXPHOS and impaired oxidation of fatty acids	Hyperlactatemia occurs in the setting of the "propofol infusion syndrome," or PIS, which consists of lactic acidosis, heart failure, rhabdomyolysis, and acute kidney injury[129]	Usually occurs in patients receiving infusions of propofol exceeding 5 mg/kg/hr for more than 48 hours

AG, Anion gap; *CO,* carbon monoxide; *DNA,* deoxyribonucleic acid; *ETC,* electron transport chain; *HD,* hemodyalisis; *ICU,* intensive care unit; *LFT,* liver function test; *NO,* nitric oxide; *OXPHOS,* oxidative phosphorylation; *ROS,* reactive oxygen species.

consequence of an underlying chronic disease or may be the presenting manifestation of significant drug toxicity or poisoning. The presence of hyperlactatemia is therefore an important indicator of a potentially serious disorder and should prompt further clinical evaluation.

Key Points

1. Hyperlactatemia and lactic acidosis during circulatory shock results from increased lactate production secondary to enhanced aerobic glycolysis in skeletal muscle. This in turn is the consequence of a β_2-adrenergic receptor—mediated stimulation of membrane Na^+-K^+ pumps.
2. A cytokine-mediated increase in lactate production by tissue macrophages plays a significant role in the pathogenesis of hyperlactatemia in patients with a systemic inflammatory response (i.e., sepsis, burn).
3. Sequential determinations of lactate concentration may be useful in guiding resuscitation from circulatory shock as well as in assessing prognosis. However, it is important to recognize that lactate is not a good marker of tissue perfusion and that lactate in this context must be interpreted as a marker of metabolic stress.
4. Occult thiamine deficiency or poisoning should be considered in patients with lactic acidosis of unclear cause.

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