CME CREDIT ***EDUCATIONAL OBJECTIVE:*** Readers will note the risks associated with lactic acidosis and apply the recommended strategy for its treatment

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Lactic acidosis: Clinical implications and management strategies

ABSTRACT

In hospitalized patients, elevated serum lactate levels are both a marker of risk and a target of therapy. The authors describe the mechanisms underlying lactate elevations, note the risks associated with lactic acidosis, and outline a strategy for its treatment.

KEY POINTS

Serum lactate levels can become elevated by a variety of underlying processes, categorized as increased production in conditions of hypoperfusion and hypoxia (type A lactic acidosis), or as increased production or decreased clearance not due to hypoperfusion and hypoxia (type B).

The higher the lactate level and the slower the rate of normalization (lactate clearance), the higher the risk of death.

Treatments differ depending on the underlying mechanism of the lactate elevation. Thus, identifying the reason for hyperlactatemia and differentiating between type A and B lactic acidosis are of the utmost importance.

Treatment of type A lactic acidosis aims to improve perfusion and match oxygen consumption with oxygen delivery by giving fluids, packed red blood cells, and vasopressors or inotropic agents, or both.

Treatment of type B involves more specific management, such as discontinuing offending medications or supplementing key cofactors for anaerobic metabolism.

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Physicians are paying more attention to serum lactate levels in hospitalized patients than in the past, especially with the advent of point-of-care testing. Elevated lactate levels are associated with tissue hypoxia and hypoperfusion but can also be found in a number of other conditions. Therefore, confusion can arise as to how to interpret elevated levels and subsequently manage these patients in a variety of settings.

In this review, we discuss the mechanisms underlying lactic acidosis, its prognostic implications, and its use as a therapeutic target in treating patients in septic shock and other serious disorders.

LACTATE IS A PRODUCT OF ANAEROBIC RESPIRATION

Lactate, or lactic acid, is produced from pyruvate as an end product of glycolysis under anaerobic conditions (**Figure 1**). It is produced in most tissues in the body, but primarily in skeletal muscle, brain, intestine, and red blood cells. During times of stress, lactate is also produced in the lungs, white blood cells, and splanchnic organs.

Most lactate in the blood is cleared by the liver, where it is the substrate for gluconeogenesis, and a small amount is cleared by the kidneys.[1,2] The entire pathway by which lactate is produced and converted back to glucose is called the Cori cycle.

NORMAL LEVELS ARE LESS THAN ABOUT 2.0 MMOL/L

In this review, we will present lactate levels in the SI units of *mmol/L* (1 mmol/L = 9 mg/dL).

Aerobic and anaerobic metabolism

Lactate or lactic acid accumulates under conditions of hypoxia or reduced clearance. Identifying and treating the cause is key.

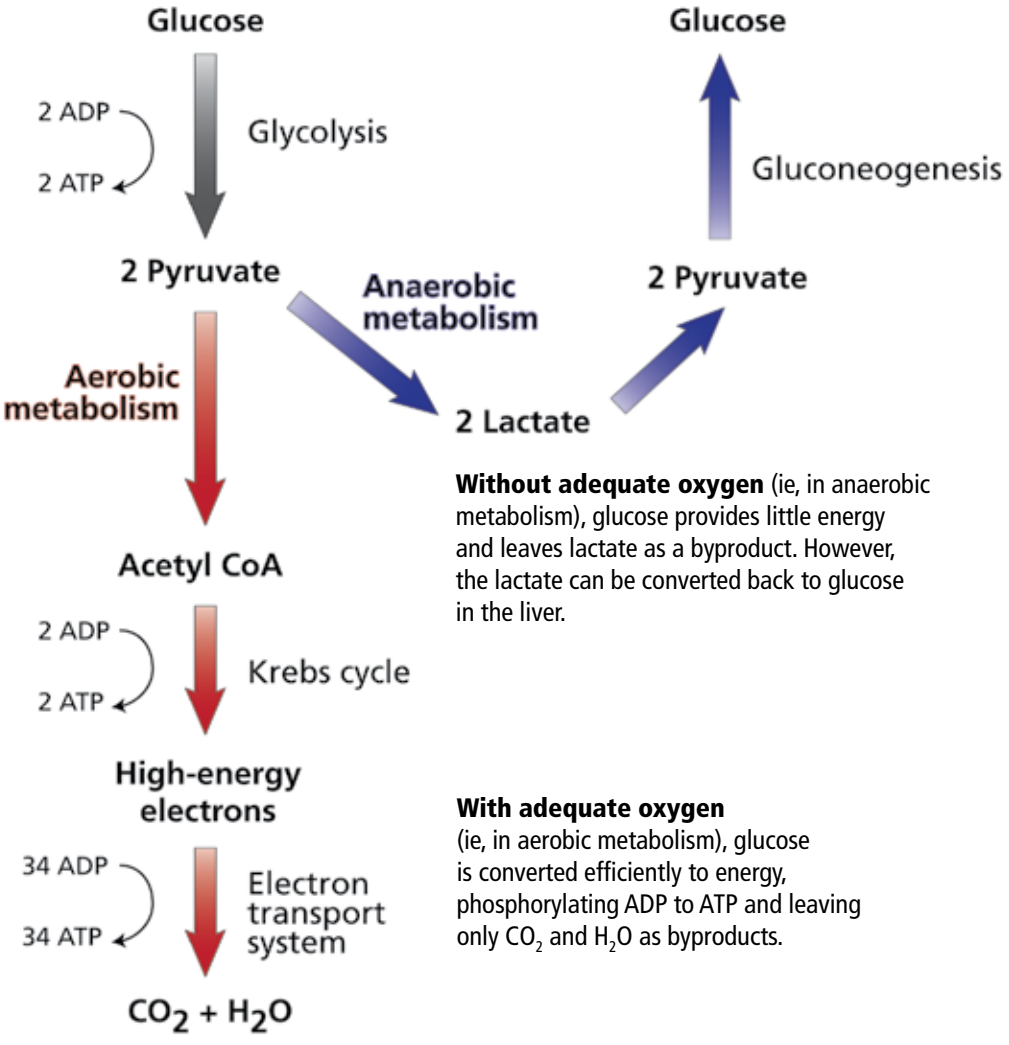

FIGURE 1

Basal lactate production is approximately 0.8 mmol/kg body weight/hour. The average normal arterial blood lactate level is approximately 0.620 mmol/L and the venous level is slightly higher at 0.997 mmol/L,[3] but overall, arterial and venous lactate levels correlate well.

Normal lactate levels are less than 2 mmol/L,[4] intermediate levels range from 2 to less than 4 mmol/L, and high levels are 4 mmol/L or higher.[5]

To minimize variations in measurement, blood samples should be drawn without a tourniquet into tubes containing fluoride, placed on ice, and processed quickly (ideally within 15 minutes).

INCREASED PRODUCTION, DECREASED CLEARANCE, OR BOTH

An elevated lactate level can be the result of increased production, decreased clearance, or both (as in liver dysfunction).

Type A lactic acidosis—due to hypoperfusion and hypoxia—occurs when there is a mismatch between oxygen delivery and consumption, with resultant anaerobic glycolysis.

The guidelines from the Surviving Sepsis Campaign[6] emphasize using lactate levels to diagnose patients with sepsis-induced hypoperfusion. However, hyperlactatemia can indicate inadequate oxygen delivery due to any type of shock (**Table 1**).

Type B lactic acidosis—not due to hypoperfusion—occurs in a variety of conditions (**Table 1**), including liver disease, malignancy, use of certain medications (eg, metformin, epinephrine), total parenteral nutrition, human immunodeficiency virus infection, thiamine deficiency, mitochondrial myopathies, and congenital lactic acidosis.[1–3,7] Yet other causes include trauma, excessive exercise, diabetic ketoacidosis, ethanol intoxication, dysfunction of the enzyme pyruvate dehydrogenase, and increased muscle degradation leading to increased production of pyruvate. In these latter scenarios, glucose metabolism exceeds the oxidation capacity of the mitochondria, and the rise in pyruvate concentration drives lactate production.[8,9] Mitochondrial dysfunction and subsequent deficits in cellular oxygen use can also result in persistently high lactate levels.[10]

In some situations, patients with mildly elevated lactic acid levels in type B lactic acidosis can be monitored to ensure stability, rather than be treated aggressively.

TABLE 1

Causes of lactic acidosis

Type A lactic acidosis (due to tissue hypoxia and hypoperfusion)
Septic shock
Cardiogenic shock
Hypovolemic shock
Obstructive shock
Regional ischemia (limb, mesenteric)
Seizure
Shivering
Type B lactic acidosis (not due to hypoxia and hypoperfusion)
Liver disease
Malignancy
Medications (eg, metformin, epinephrine)
Total parenteral nutrition
Human immunodeficiency virus infection and treatment
Thiamine deficiency
Mitochondrial myopathy
Congenital lactic acidosis
Trauma
Excessive exercise
Diabetic ketoacidosis
Ethanol intoxication

If lactate is elevated, look for causes of decreased oxygen delivery

HIGHER LEVELS AND LOWER CLEARANCE PREDICT DEATH

The higher the lactate level and the slower the rate of normalization (lactate clearance), the higher the risk of death.

Lactate levels and mortality rate

Shapiro et al[11] showed that increases in lactate level are associated with proportional increases in the mortality rate. Mikkelsen et al[12] showed that intermediate levels (2.0–3.9 mmol/L) and high levels (≥ 4 mmol/L) of serum lactate are associated with increased risk of death independent of organ failure and shock. Patients with mildly elevated and intermediate lactate levels and sepsis have higher rates of in-hospital and 30-day mortality, which correlate with the baseline lactate level.[13]

In a post hoc analysis of a randomized controlled trial, patients with septic shock who presented to the emergency department with hypotension and a lactate level higher than 2 mmol/L had a significantly higher in-hospital mortality rate than those who presented with hypotension and a lactate level of 2 mmol/L or less (26% vs 9%, $P < .0001$).[14] These data suggest that elevated lactate levels may have a significant prognostic role, independent of blood pressure.

Slower clearance

The prognostic implications of lactate clearance (reductions in lactate levels over time, as opposed to a single value in time), have also been evaluated.

Lactate clearance of at least 10% at 6 hours after presentation has been associated with a lower mortality rate than nonclearance (19% vs 60%) in patients with sepsis or septic shock

with elevated levels.[15–17] Similar findings have been reported in a general intensive care unit population,[18] as well as a surgical intensive care population.[19]

Puskarich et al[20] have also shown that lactate normalization to less than 2 mmol/L during early sepsis resuscitation is the strongest predictor of survival (odds ratio [OR] 5.2), followed by lactate clearance of 50% (OR 4.0) within the first 6 hours of presentation. Not only is lactate clearance associated with improved outcomes, but a faster rate of clearance after initial presentation is also beneficial.[15,16,18]

Lactate clearance over a longer period (> 6 hours) has not been studied in patients with septic shock. However, in the general intensive care unit population, therapy guided by lactate clearance for the first 8 hours after presentation has shown a reduction in mortality rate.[18] There are no data available on outcomes of lactate-directed therapy beyond 8 hours, but lactate concentration and lactate clearance at 24 hours correlate with the 28-day mortality rate.[21]

Cryptic shock

Cryptic shock describes a state in a subgroup of patients who have elevated lactate levels and global tissue hypoxia despite being normotensive or even hypertensive. These patients have a higher mortality rate independent of blood pressure. Jansen et al[18] found that patients with a lactate level higher than 4 mmol/L and preserved blood pressure had a mortality rate of 15%, while those without shock or hyperlactatemia had a mortality rate of 2.5%. In addition, patients with an elevated lactate level in the absence of hypotension have mortality rates similar to those in patients with high lactate levels and hypotension refractory to fluid boluses, suggesting the presence of tissue hypoxia even in these normotensive patients.[6]

Give fluids until the patient is no longer preload-dependent, but excessive fluids may be deleterious

HOW TO APPROACH AN ELEVATED LACTATE LEVEL

An elevated lactate level should prompt an evaluation for causes of decreased oxygen delivery, due either to a systemic low-flow state (as a result of decreased cardiac output) or severe anemia, or to regionally decreased perfusion, (eg, limb or mesenteric ischemia). If tissue hypoxia is ruled out after an exhaustive workup, consideration should be given to causes of hyperlactatemia without concomitant tissue hypoxia (type B acidosis).

Treatment differs depending on the underlying mechanism of the lactate elevation; nevertheless, treatment is mostly related to optimizing oxygen delivery by giving fluids, packed red blood cells, and vasopressors or inotropic agents, or both (**Figure 2**). The specific treatment differs based on the shock state, but there are similarities that can guide the clinician.

FLUID SUPPORT

Giving fluids, with a goal of improving cardiac output, remains a cornerstone of initial therapy for most shock states.[22,23]

How much fluid?

Fluids should be given until the patient is no longer preload-dependent, although there is much debate about which assessment strategy should be used to determine if cardiac output will improve with more fluid (ie, fluid-responsiveness).[24] In many cases, fluid resuscitation alone may be enough to restore hemodynamic stability, improve tissue perfusion, and reduce elevated lactate concentrations.[25]

The decision to give more fluids should not be made lightly, though, as a more positive fluid balance early in the course of septic shock and over 4 days has been associated with a higher mortality rate.[26] Additionally, pushing fluids in patients with cardiogenic shock due to impaired left ventricular systolic function may lead to or worsen pulmonary edema. Therefore, the indiscriminate use of fluids should be avoided.

Which fluids?

Despite years of research, controversy persists about whether crystalloids or colloids are better for resuscitation. Randomized trials in heterogeneous intensive care unit patients have not detected differences in 28-day mortality rates between those allocated to crystalloids or 4% albumin[27] and those allocated to crystalloids or hydroxyethyl starch.[28]

Hydroxyethyl starch may not be best. In a study of patients with severe sepsis, those randomized to receive hydroxyethyl starch had a higher 90-day mortality rate than patients randomized to crystalloids (51% vs 43%, $P = .03$).[29] A sequential prospective be-

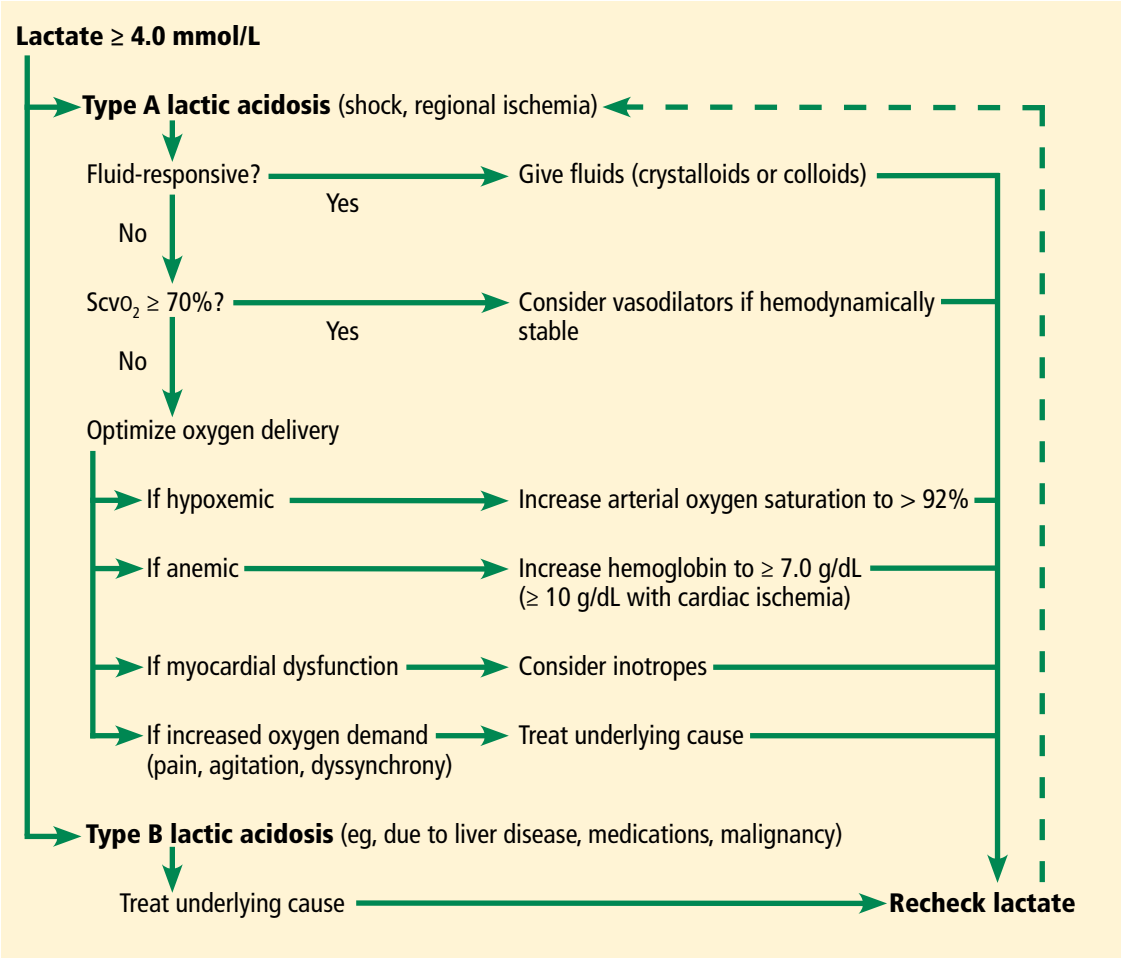

FIGURE 2. Management of hyperlactatemia. $Scvo_2$ = central venous oxygen saturation.

fore-and-after study did not detect a difference in the time to normalization (< 2.2 mmol/L) of lactate (P = .68) or cessation of vasopressors (P = .11) in patients with severe sepsis who received fluid resuscitation with crystalloids, gelatin, or hydroxyethyl starch. More patients who received hydroxyethyl starch in these studies developed acute kidney injury than those receiving crystalloids.[28–30]

Taken together, these data strongly suggest hydroxyethyl starch should not be used for fluid resuscitation in the intensive care unit.

Normal saline or albumin? Although some data suggest that albumin may be preferable to 0.9% sodium chloride in patients with severe sepsis,[31,32] these analyses should be viewed as hypothesis-generating. There do not seem to be differences between fluid types in terms of subsequent serum lactate concentrations or achievement of lactate clearance goals.[28–30] Until further studies are completed, both albumin and crystalloids are reasonable for resuscitation.

Caironi et al[33] performed an open-label study comparing albumin replacement (with a goal serum albumin concentration of 3 g/dL) plus a crystalloid solution vs a crystalloid solution alone in patients with severe sepsis or septic shock. They detected no difference between the albumin and crystalloid groups in mortality rates at 28 days (31.8% vs 32.0%, P = .94) or 90 days (41.1% vs 43.6%, P = .29). However, patients in the albumin group had a shorter time to cessation of vasoactive agents (median 3 vs 4 days, P = .007) and lower cardiovascular Sequential Organ Failure Assessment subscores (median 1.20 vs 1.42, P = .03), and more frequently achieved a mean arterial pressure of at least 65 mm Hg within 6 hours of randomization (86.0% vs 82.5%, P = .04).

Hydroxyethyl starch should not be used for fluid resuscitation in the intensive care unit

Although serum lactate levels were lower in the albumin group at baseline (1.7 mmol/L vs 1.8 mmol/L, $P = .05$), inspection of the data appears to show a similar daily lactate clearance rate between groups over the first 7 study days (although these data were not analyzed by the authors). Achievement of a lactate level lower than 2 mmol/L on the first day of therapy was not significantly different between groups (73.4% vs 72.5%, $P = .11$).[33]

In a post hoc subgroup analysis, patients with septic shock at baseline randomized to albumin had a lower 90-day mortality rate than patients randomized to crystalloid solutions (RR 0.87, 95% CI 0.77–0.99). There was no difference in the 90-day mortality rate in patients without septic shock (RR 1.13, 95% CI 0.92–1.39, $P = .03$ for heterogeneity).[33]

These data suggest that albumin replacement may not improve outcomes in patients with severe sepsis, but may have advantages in terms of hemodynamic variables (and potentially mortality) in patients with septic shock. The role of albumin replacement in patients with septic shock warrants further study.

Norepinephrine, not dopamine, should be the initial vasopressor in most types of shock

VASOPRESSORS

Vasopressors, inotropes, or both should be given to patients who have signs of hypoperfusion (including elevated lactate levels) despite preload optimization or ongoing fluid administration. The most appropriate drug depends on the goal: vasopressors are used to increase systemic vascular resistance, while inotropes are used to improve cardiac output and oxygen delivery.

Blood pressure target

The Surviving Sepsis Campaign guidelines recommend a mean arterial blood pressure target of at least 65 mm Hg during initial resuscitation and when vasopressors are applied for patients with septic shock.[22] This recommendation is based on small studies that did not show differences in serum lactate levels or regional blood flow when the mean arterial pressure was elevated above 65 mm Hg with norepinephrine.[34,35] However, the campaign guidelines note that the mean arterial pressure goal must be individualized in order to achieve optimal perfusion.

A large, open-label trial[36] detected no difference in 28-day mortality rates in patients with septic shock between those allocated to a mean arterial pressure goal of 80 to 85 mm Hg or 65 to 70 mm Hg (36.6% vs 34.0%, $P = .57$). Although lactate levels did not differ between groups, the incidence of new-onset atrial fibrillation was higher in the higher-target group (6.7% vs 2.8%, $P = .02$). Fewer patients with chronic hypertension needed renal replacement therapy in the higher pressure group, further emphasizing the need to individualize the mean arterial pressure goal for patients in shock.[36]

Which vasopressor agent?

Dopamine and norepinephrine have traditionally been the preferred initial vasopressors for patients with shock. Until recently there were few data to guide selection between the two, but this is changing.

In a 2010 study of 1,679 patients with shock requiring vasopressors, there was no difference in the 28-day mortality rate between patients randomized to dopamine or norepinephrine (53% vs 49%, $P = .10$).[37] Patients allocated to dopamine, though, had a higher incidence of arrhythmias (24% vs 12%, $P < .001$) and more frequently required open-label norepinephrine (26% vs 20%, $P < .001$). Although lactate levels and the time to achievement of a mean arterial pressure of 65 mm Hg were similar between groups, patients allocated to norepinephrine had more vasopressor-free days through day 28.

An a priori-planned subgroup analysis evaluated the influence of the type of shock on patient outcome. Patients with cardiogenic shock randomized to dopamine had a higher mortality rate than those randomized to norepinephrine ($P = .03$). However, the overall effect of treatment did not differ among the shock subgroups (interaction $P = .87$), suggesting that the reported differences in mortality according to subgroup may be spurious.

In a 2012 meta-analysis of patients with septic shock, dopamine use was associated with a higher mortality rate than norepinephrine use.[38]

In light of these data, norepinephrine should be preferred over dopamine as the initial vasopressor in most types of shock.

Epinephrine does not offer an outcome

advantage over norepinephrine and may be associated with a higher incidence of adverse events.[39–42] Indeed, in a study of patients with septic shock, lactate concentrations on the first day after randomization were significantly higher in patients allocated to epinephrine than in patients allocated to norepinephrine plus dobutamine.[39] Similar effects on lactate concentrations with epinephrine were seen in patients with various types of shock[40] and in those with cardiogenic shock.[42]

These differences in lactate concentrations may be directly attributable to epinephrine. Epinephrine can increase lactate concentrations through glycolysis and pyruvate dehydrogenase activation by stimulation of sodium-potassium ATPase activity via beta-2 adrenergic receptors in skeletal muscles,[43] as well as decrease splanchnic perfusion.[42,44,45] These effects may preclude using lactate clearance as a resuscitation goal in patients receiving epinephrine. Epinephrine is likely best reserved for patients with refractory shock,[22] particularly those in whom cardiac output is known to be low.

Phenylephrine, essentially a pure vasoconstrictor, should be avoided in low cardiac output states and is best reserved for patients who develop a tachyarrhythmia on norepinephrine.[22]

Vasopressin, also a pure vasoconstrictor that should be avoided in low cardiac output states, has been best studied in patients with vasodilatory shock. Although controversy exists on the mortality benefits of vasopressin in vasodilatory shock, it is a relatively safe drug with consistent norepinephrine-sparing effects when added to existing norepinephrine therapy.[46,47] In patients with less severe septic shock, including those with low lactate concentrations, adding vasopressin to norepinephrine instead of continuing norepinephrine alone may confer a mortality advantage.[48]

OTHER MEASURES TO OPTIMIZE OXYGEN DELIVERY

In circulatory shock from any cause, tissue oxygen demand exceeds oxygen delivery. Once arterial oxygenation and hemoglobin levels (by packed red blood cell transfusion) have been optimized, cardiac output is the critical determinant of oxygen delivery. Cardiac output may be augmented by ensuring adequate preload (by fluid resuscitation) or by giving inotropes or vasodilators.

The optimal cardiac output is difficult to define, and the exact marker for determining when cardiac output should be augmented is unclear. A strategy of increasing cardiac output to predefined "supranormal" levels was not associated with a lower mortality rate.[49] Therefore, the decision to augment cardiac output must be individualized and will likely vary in the same patient over time.[23]

A reasonable approach to determining when augmentation of cardiac output is necessary was proposed in a study by Rivers et al.[50] In that study, in patients randomized to early goal-directed therapy, inotropes were recommended when the central venous oxygenation saturation ($Scvo_2$) was below 70% despite adequate fluid resuscitation (central venous pressure ≥ 8 mm Hg) and hematocrits were higher than 30%.

When an inotrope is indicated to improve cardiac output, dobutamine is usually the preferred agent. Dobutamine has a shorter half-life (allowing for easier titration) and causes less hypotension (assuming preload has been optimized) than phosphodiesterase type III inhibitors such as milrinone.

Mechanical support devices, such as intra-aortic balloon counterpulsation, and vasodilators can also be used to improve tissue perfusion in selected patients with low cardiac output syndromes.

USING LACTATE LEVELS TO GUIDE THERAPY

Lactate levels above 4.0 mmol/L

Lactate may be a useful marker for determining whether organ dysfunction is present and, hence, what course of therapy should be given, especially in sepsis. A serum lactate level higher than 4.0 mmol/L has been used as the trigger to start aggressive resuscitation in patients with sepsis.[50,51]

Traditionally, as delineated by Rivers et al[50] in their landmark study of early goal-directed therapy, this entailed placing an arterial line and a central line for hemodynamic monitoring, with specific interventions directed at increasing the central venous pressure, mean

Serum lactate > 4.0 mmol/L has been used as the trigger to initiate aggressive resuscitation in patients with sepsis

arterial pressure, and central venous oxygen saturation.[50] However, a recent study in a similar population of patients with sepsis with elevated lactate found no significant advantage of protocol-based resuscitation over care provided according to physician judgment, and no significant benefit in central venous catheterization and hemodynamic monitoring in all patients.[51]

Lactate clearance: 10% or above at 8 hours?

Regardless of the approach chosen, decreasing lactate levels can be interpreted as an adequate response to the interventions provided. As a matter of fact, several groups of investigators have also demonstrated the merits of lactate clearance alone as a prognostic indicator in patients requiring hemodynamic support.

McNelis et al[52] retrospectively evaluated 95 postsurgical patients who required hemodynamic monitoring.[52,53] The authors found that the slower the lactate clearance, the higher the mortality rate.

Given the prognostic implications of lactate clearance, investigators have evaluated whether lactate clearance could be used as a surrogate resuscitation goal for optimizing oxygen delivery. Using lactate clearance may have significant practical advantages over using central venous oxygen saturation, since it does not require a central venous catheter or continuous oximetric monitoring.

It seems reasonable to measure lactate every 2 hours for the first 8 hours of resuscitation in patients with type A lactic acidosis

In a study comparing these two resuscitation end points, patients were randomized to a goal of either central venous oxygen saturation of 70% or more or lactate clearance of 10% or more within the first 6 hours after presentation as a marker of oxygen delivery.[53] Mortality rates were similar with either strategy. Of note, only 10% of the patients actually required therapies to improve their oxygen delivery. Furthermore, there were no differences in the treatments given (including fluids, vasopressors, inotropes, packed red blood cells) throughout the treatment period.

These findings provide several insights. First, few patients admitted to the emergency department with severe sepsis and treated with an initial quantitative resuscitation protocol require additional therapy for augmenting oxygen delivery. Second, lactate clearance, in a setting where initial resuscitation with fluids and vasopressors restores adequate oxygen delivery for the majority of patients, is likely as good a target for resuscitation as central venous oxygen saturation.

This study, however, does not address the question of whether lactate clearance is useful as an additional marker of oxygen delivery (in conjunction with central venous oxygen saturation). Indeed, caution should be taken to target central venous oxygen saturation goals alone, as patients with septic shock presenting with venous hyperoxia (central venous oxygen saturation > 89%) have been shown to have a higher mortality rate than patients with normoxia (central venous oxygen saturation 71%–89%).[54]

This was further demonstrated by Arnold et al in a study of patients presenting to the emergency department with severe sepsis.[15] In this study, significant discordance between central venous oxygen saturation and lactate clearance was seen, where 79% of patients with less than 10% lactate clearance had concomitant central venous oxygen saturation of 70% or greater.

Jansen et al[18] evaluated the role of targeting lactate clearance in conjunction with central venous oxygen saturation monitoring. In this study, critically ill patients with elevated lactate and inadequate lactate clearance were randomized to usual care or to resuscitation to adequate lactate clearance (20% or more). The therapies to optimize oxygen delivery were given according to the central venous oxygen saturation. Overall, after adjustment for predefined risk factors, the in-hospital mortality rate was lower in the lactate clearance group. This may signify that patients with sepsis and central venous oxygen saturation of 70% or more may continue to have poor lactate clearance, warranting further treatment.

Taken together, serum lactate may be helpful for prognostication, determination of course of therapy, and quantification for tissue hypoperfusion for targeted therapies. **Figure 2** presents our approach to an elevated lactate level. As performed in the study by Jansen et al,[18] it seems reasonable to measure lactate levels every 2 hours for the first 8 hours of resuscitation in patients with type A lactic acidosis. These levels should be interpreted in the context of lactate clearance (at least 10%,

but preferably 20%) and normalization, and should be treated with an approach similar to the one outlined in **Figure 2**.

TREATING TYPE B LACTIC ACIDOSIS (NORMAL PERFUSION AND OXYGENATION)

Treating type B lactic acidosis is quite different because the goal is not to correct mismatches in oxygen consumption and delivery. Since most cases are due to underlying conditions such as malignancy or medications, treatment should be centered around eliminating the cause (eg, treat the malignancy, discontinue the offending medication). The main reason for treatment is to alleviate the harmful effects of acidosis. For example, acidosis can result in a negative inotropic effect.

Sodium bicarbonate, dichloroacetate, carbicarb, and tromethamine have all been studied in the management of type B lactic acidosis, with little success.[55,56]

Renal replacement therapy has had some success in drug-induced lactic acidosis.[57,58]

L-carnitine has had promising results in treating patients with human immunodeficiency virus infection, since these patients are carnitine-deficient and carnitine plays an important role in mitochondrial function.[59]

Thiamine and biotin deficiencies can occur in patients receiving total parenteral nutrition without vitamins and in patients who drink alcohol heavily and can cause lactic acidosis. These nutrients should be supplemented accordingly.

Treatment of mitochondrial disorders includes **antioxidants** (coenzyme Q10, vitamin C, vitamin E) and **amino acids** (L-arginine).[60]

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