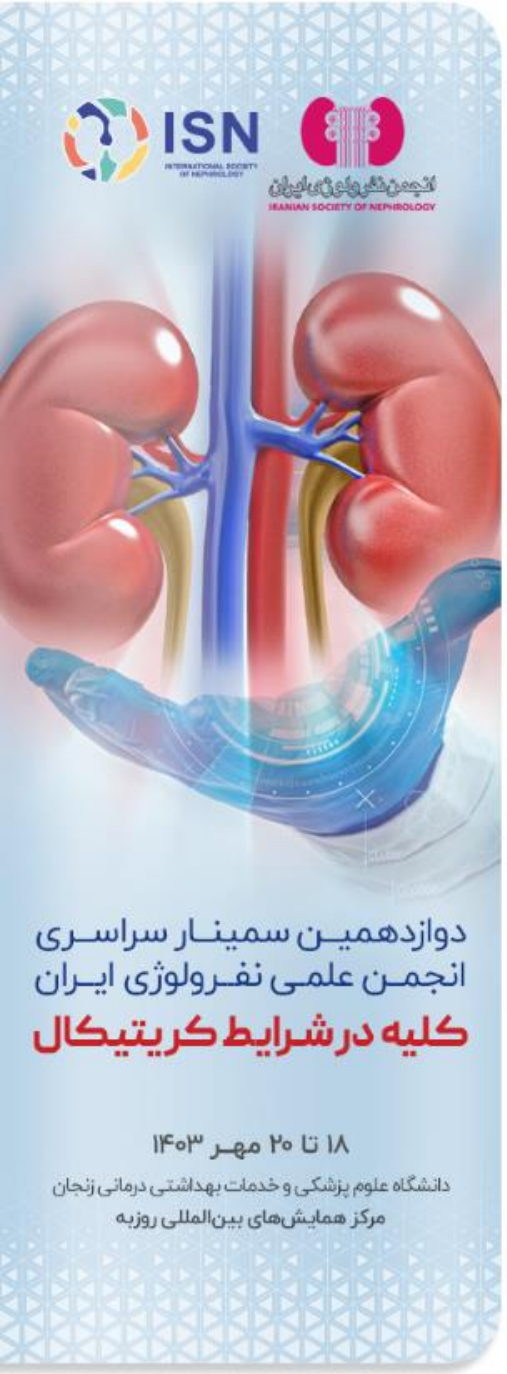


Lactic Acidosis and importance of lactate level in critically ill patients

Dr.R Jafari.Nephrologist

Assistant Professor of Nephrology, Department of Internal Medicine, School of Medicine, Vali-e-Asr Hospital, Zanjan University of Medical Sciences

Indtroduction and Definition

- Hyperlactatemia was common and associated with a high mortality in critically ill patients
- The most common causes of hyperlactatemia were sepsis/septic shock and post-cardiac surgery
- It is important to note that while severe lactic acidosis is linked to higher mortality, it is often more of a contributing factor that exacerbates existing conditions rather than a direct cause of death

Mireia Ferreruela MD. et al, Hyperlactatemia in ICU patients: Incidence, causes and associated mortality./doi.org/10.1016/j.jcrc.2017.07.039

Indtroduction and Definition

Elevated lactate levels are strongly associated with increased mortality, independent of other factors such as organ failure or shock

Even mildly elevated or intermediate lactate levels in patients with sepsis are correlated with higher in-hospital and 30-day mortality rates

Mireia Ferreruela MD. et al, Hyperlactatemia in ICU patients: Incidence, causes and associated mortality./doi.org/10.1016/j.jcrc.2017.07.039

Indtroduction and Definition

- Lactic acidosis is a serious metabolic condition characterized by the accumulation of lactate in the body

- Leads to a decreased pH in the bloodstream, with a pH threshold of < 7.35 indicating acidosis

Karunarathna, Indunil & Gunasena, P & Gunawardana, K & Aluthge, P & Hapuarachchi, T & Bandara, Sau & Jayawardana, Asoka & Alvis, Kapila & Rajapaksha, S & Gunathilake, S. (2024). Comprehensive Overview of Lactic Acidosis Etiology, Pathophysiology, and Management in Clinical Practice.

The condition typically stems from:

- Increased production of lactate
- Reduced metabolism of lactate
- The liver is central to lactate metabolism.Liver dysfunction can exacerbate lactate accumulation in the blood

- Hyperlactatemia: Lactate levels > 2 mmol/L
- Lactic acidosis: Serum lactate levels > 5mmol/L. high-grade hyperlactatemia a lactate level ≥ 10 mmol/L
- Lactic acidosis is identified as the most common cause of metabolic acidosis in hospitalized patients
- Acidosis is typically associated with an elevated anion gap

Principal Sources of Lactic Acid:

- Erythrocytes: Lack enzymes for aerobic oxidation
- Skeletal Muscle
- Skin
- Brain

Pathophysiology

Pathophysiology

- Under typical physiological conditions, blood lactate concentrations are maintained at levels below 2 mmol/L.

- Hyperlactatemia is defined as lactate elevation ranging from 2 mmol/L to 4 mmol/L

- Lactate levels at or above 5 mmol/L are classified as severe

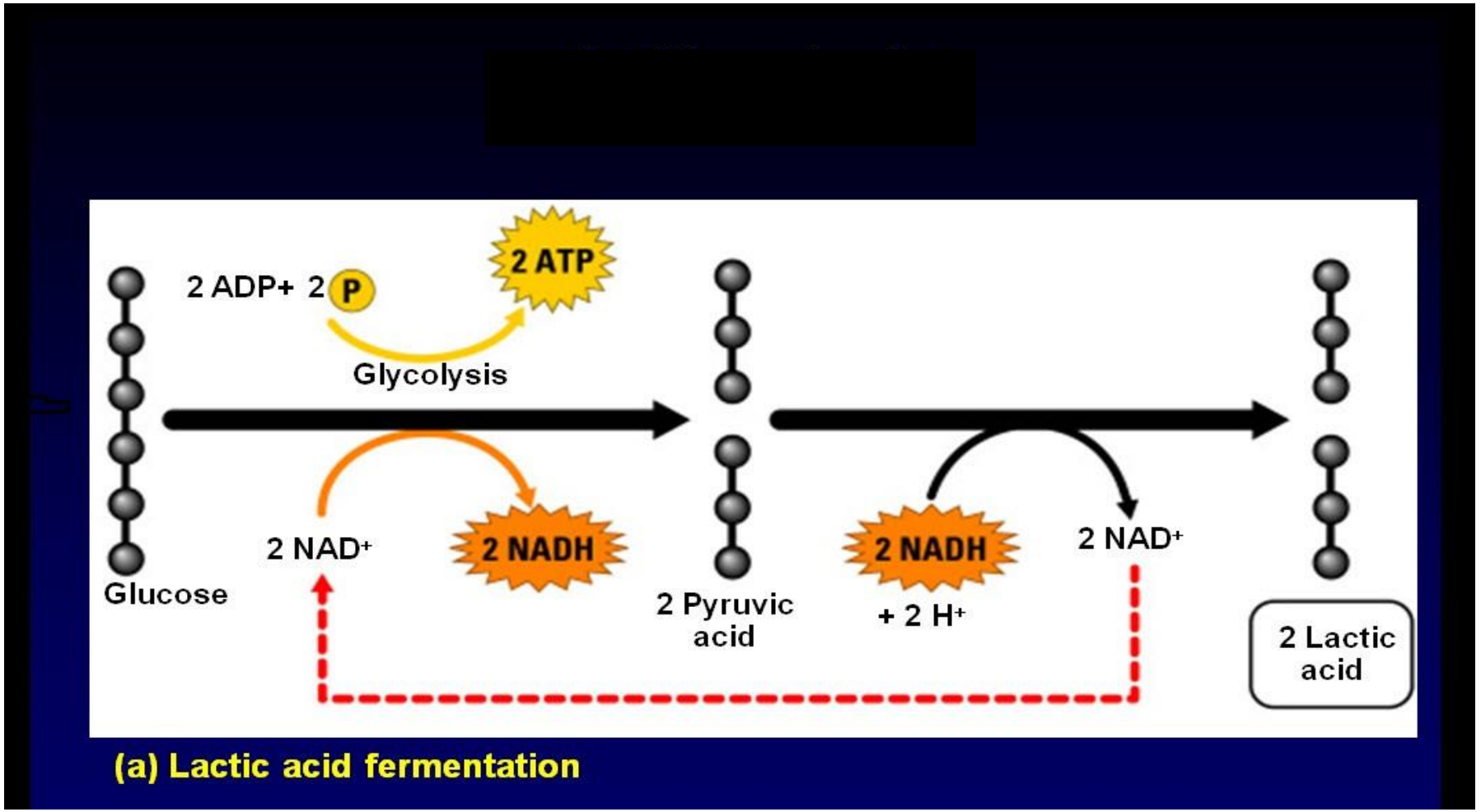
This condition arises from a combination of:

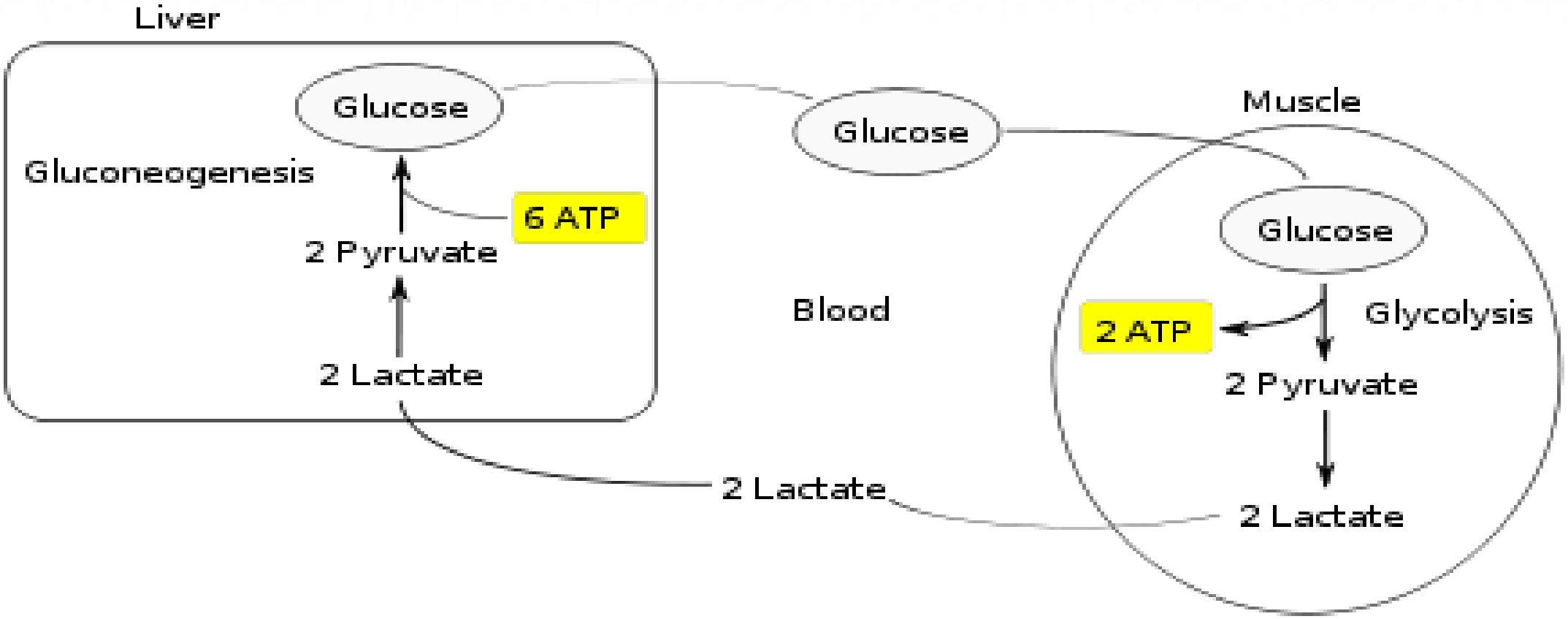
- Excessive lactate production
- Impaired hepatic clearance

- Cellular lactate generation is influenced by the “redox state” of the cell
- The redox state in the cellular cytoplasm is reflected by the ratio of oxidized and reduced nicotine adenine dinucleotide:

NAD+ (oxidized form)

NADH (reduced form)


2 ATP
2 ADP+ 2 P
Glycolysis
2 NAD+
2 NADH
Glucose
2 Pyruvic acid
2 NADH
+ 2 H+
2 NAD+
2 Lactic acid
(a) Lactic acid fermentation


Liver
Glucose
Gluconeogenesis
6 ATP
2 Pyruvate
2 Lactate
Glucose
Blood
2 Lactate
Muscle
Glucose
2 ATP
Glycolysis
2 Pyruvate
2 Lactate

- One of these cellular redox reactions is the equilibrium between pyruvic acid and lactic acid, a reaction catalyzed by the enzyme lactate dehydrogenase, Reduced redox state (low NAD+/NADH ratio) is associated with a shift in the ratio from pyruvate to lactate

- Normal individuals produce 15 to 20 mmol/kg of lactic acid per day. Most is derived from glucose metabolism via the glycolytic pathway, although deamination of alanine also generates lactate

- A marked increase in lactate production, in part due to catecholamine stimulation of glycolysis, also plays an important role in the lactic acidosis associated with shock, especially septic shock

Clinical causes

Causes of lactic acidosis can be categorized into two main types:

- Type A Lactic Acidosis: Characterized by impaired tissue oxygenation

- Type B Lactic Acidosis: Occurs in the absence of systemic oxygenation disturbances

- However, it is important to note that in many cases, a combination of both factors may be present

- For instance, in sepsis, elevated lactate levels can arise from both increased lactate production and mitochondrial dysfunction, as well as reduced lactate clearance

Type A Lactic Acidosis

Type A Lactic Acidosis occurs due to hypoperfusion and hypoxia, where an oxygen supply-demand mismatch leads to anaerobic glycolysis. This type is commonly seen in conditions such as:

- Shock states (septic, cardiogenic, hypovolemic, Distributive)
- Regional ischemia (e.g., limb or mesenteric ischemia)
- Seizures or convulsions
- Severe shivering

- In these situations, the lack of adequate oxygen causes pyruvate, a product of glycolysis, to be converted into lactate at a rate that overwhelms the body's ability to clear it, leading to a buildup of lactic acid

Type B Lactic Acidosis

- Type B Lactic Acidosis, in contrast, is not associated with tissue hypoxia or reduced blood flow

- It is less prevalent than Type A, Type B lactic acidosis occurs due to an imbalance in which the mitochondria cannot adequately process the available pyruvate

This situation compels the body to utilize alternative metabolic pathways that lead to the overproduction of lactate. Factors and conditions linked to Type B lactic acidosis include:

- Liver disease
- Malignancies
- Medications (e.g., metformin, epinephrine ,propofol,linezolid)
- Total parenteral nutrition (TPN)
- HIV infection
- Thiamine deficiency
- Mitochondrial myopathies
- Congenital lactic acidosis
- Trauma
- Excessive exercise
- Diabetic ketoacidosis
- Ethanol intoxication

Shock

- In the context of shock, lactic acidosis is a primary but not exclusive cause of metabolic acidosis

- Shock is defined as a state of acute circulatory failure where there is inadequate oxygen delivery and/or utilization at the cellular level, resulting in cellular hypoxia or dysoxia

Diabetes mellitus

- Metformin, although effective for managing diabetes, can inhibit mitochondrial function and increase lactate production, especially in patients with renal impairment

- Hypovolemia plays an important role in ketoacidosis

- D-lactic acid may accumulate and contribute to the anion gap acidosis of diabetic ketoacidosis

Gonzalez-Lopez, Carolina, and Brian S Wojeck. “Role of metformin in the management of type 2 diabetes: recent advances.” Polish archives of internal medicine vol. 133,6 (2023): 16511. doi:10.20452/pamw.16511

Malignancy

- Lactic acidosis in patients with malignancy is a severe metabolic disturbance caused by increased lactate production, often driven by the Warburg effect
- Malignancies such as leukemias, lymphomas, and some solid tumors are commonly associated with lactic acidosis
- Anaerobic metabolism due to dense, underperfused clusters of tumor cells
- Metastatic replacement of the hepatic parenchyma has been proposed.
- Thiamine and/or riboflavin deficiency

Sillos EM, Shenep JL, Burghen GA, Pui CH, Behm FG, Sandlund JT. Lactic acidosis: a metabolic complication of hematologic malignancies: case report and review of the literature. Cancer. 2001 Nov 1;92(9):2237-46. doi: 10.1002/1097-0142(20011101)92:9<2237::aid-cncr1569>3.0.co;2-9. PMID: 11745277

Alcoholism

- Alcohol can increase the production of lactate through impaired gluconeogenesis, leading to the accumulation of lactate in the blood
- Hepatic dysfunction

- Methanol and ethylene glycol poisoning. The toxic metabolites of these poisons can disrupt normal mitochondrial metabolism.

Pernet P, Bénéteau-Burnat B, Vaubourdolle M, Maury E, Offenstadt G. False elevation of blood lactate reveals ethylene glycol poisoning. Am J Emerg Med. 2009 Jan;27(1):132.e1-132.e2. doi: 10.1016/j.ajem.2008.04.029. PMID: 19041561

HIV

- Increased propensity to serious infection, sepsis-induced lactic acidosis, and Antiretroviral medication-induced mitochondrial dysfunction. (type B lactic acidosis)

Claessens, Yann-Erick et al. “Bench-to-bedside review: severe lactic acidosis in HIV patients treated with nucleoside analogue reverse transcriptase inhibitors.” Critical care (London, England) vol. 7,3 (2003): 226-32. doi:10.1186/cc2162

Beta-adrenergic agonists

- An increase in glycolysis in skeletal muscles and a disturbance in the perfusion of the gastrointestinal tract, which increases lactate production and decreases hepatic reabsorption of lactate, can cause lactic acidosis

- Pheochromocytomas

- Inhalded beta agonists

Dodda VR, Spiro P. Can albuterol be blamed for lactic acidosis? Respir Care. 2012 Dec;57(12):2115-8. doi: 10.4187/respcare.01810. PMID: 22613097

Mitochondrial dysfunction

- Mitochondria play a key role in oxidative metabolism and energy production
- When mitochondrial respiration is impaired, pyruvate cannot be efficiently converted into acetyl-CoA, leading to its accumulation and subsequent conversion into lactate via anaerobic pathways
- Mitochondrial dysfunction can arise from various causes, including genetic mitochondrial disorders, sepsis, drug toxicity (such as antiretrovirals), and ischemia

Stacpoole PW. Lactic acidosis and other mitochondrial disorders. Metabolism. 1997 Mar;46(3):306-21. doi: 10.1016/s0026-0495(97)90259-6. PMID: 9054475

D-lactic acidosis

- D-lactic acidosis is a rare form of lactic acidosis that can occur in patients with short bowel syndrome or other forms of gastrointestinal malabsorption

- High dose iv infusion of propylene glycol

Stacpoole PW. Lactic acidosis and other mitochondrial disorders. Metabolism. 1997 Mar;46(3):306-21. doi: 10.1016/s0026-0495(97)90259-6. PMID: 9054475

Diagnosis

Essentials of Diagnosis:

- Severe metabolic acidosis with compensatory hyperventilation
- Blood pH < 7.30
- Serum bicarbonate < 15 mEq/L
- Anion gap > 15 mEq/L
- Absent serum ketones
- Serum lactate > 5 mmol/L

Mizock, B A. “Lactic acidosis.” Disease-a-month : DM vol. 35,4 (1989): 233-300. doi:10.1016/0011-5029(89)90021-7

Diagnosis requires consideration of the clinical context, including:

- Presence of sepsis
- Hypoxia
- Organ failure
- Medications that impair oxidative phosphorylation

Diagnostic Tools

- Arterial blood gas (ABG) analysis is essential for assessing blood pH and lactate levels

- Serum bicarbonate levels aid in evaluating the severity of acidosis

Clinical findings

- Clinical findings in lactic acidosis vary depending on the underlying cause but generally reflect systemic hypoperfusion and metabolic dysfunction

Common clinical findings

- Malaise and fatigue
- Nausea and vomiting
- Dyspnea
- Confusion or altered mental status
- Hypotension and tachycardia
- Kussmaul respiration
- Signs of multi-organ dysfunction (e.g., renal failure, liver dysfunction)

Differential Diagnosis

- Diabetic ketoacidosis
- Starvation ketoacidosis
- Alcoholic ketoacidosis
- Kidney failure (acute or chronic)
- Ethylene glycol toxicity
- Methanol toxicity
- Salicylate toxicity

Treatment

Treatment options for lactic acidosis:

- Addressing the underlying cause (e.g., sepsis, heart failure, toxins)
- Intravenous fluids to improve perfusion
- Oxygen therapy or mechanical ventilation
- Sodium bicarbonate (in severe acidosis, with caution)
- Renal replacement therapy (e.g., dialysis)
- Medications to improve tissue perfusion (e.g., vasopressors)

Therapeutic Goals

- Reduce lactate production
- Enhance lactate clearance from the body to correct metabolic acidosis
- Optimizing Oxygen Delivery
- Improve perfusion to tissues
- Treat underlying conditions, such as: Sepsis,Cardiac failure,Drug toxicity

Bicarbonate Therapy

- Considered for severe acidosis but used cautiously due to risks, such as paradoxical intracellular acidosis

- Bicarbonate therapy can potentially prevent the need for dialysis and may improve survival

Goals of therapy

- The primary aim of therapy is reversal of the underlying disease (eg, shock).
- When using bicarbonate therapy in patients with lactic acidosis and severe acidemia, the aim is to maintain the arterial pH above 7.1 until the primary process causing the metabolic acidosis can be reversed.
- However, if the patient has severe acute kidney injury, then the goal is to raise the pH above 7.3.

Who should be treated

- Severe acidemia pH <7.1

- PH 7.1 to 7.2+ severe acute kidney injury (twofold or greater increase in serum creatinine or oliguria)

Approach

- In critically ill patients with severe lactic acidosis: [pH <7.1 and Hco3<6 mEq/L]
- Ventilation as a Prerequisite
- Ensure adequate ventilation before using exogenous bicarbonate, as proper CO_2 clearance is necessary for its effectiveness
- For non-intubated patients, aim to reduce PCO_2 to at least 15 mmHg, often as low as 10-12 mmHg, through proper ventilation

Bicarbonate Dosing:

- In patients with severe lactic acidosis (pH <7.1), administer an IV bolus of sodium bicarbonate (1-2 mEq/kg body weight)

- Reassess blood pH and serum electrolytes 30-60 minutes post-administration and repeat the dose if acidosis persists

- Prescribing bicarbonate based on "bicarbonate distribution space" may cause a mistake in the calculated dose according to the patient's condition, so it is better to use this method with caution

Potential harms of bicarbonate

Rapid infusions of sodium bicarbonate have a number of potentially adverse effects:

- Increased arterial and tissue capillary partial pressure of carbon dioxide (PCO2)
- Acceleration of lactate generation
- Reduced ionized calcium
- Hypernatremia
- Extracellular fluid (ECF) volume expansion

Kraut, Jeffrey A, and Nicolaos E Madias. “Lactic acidosis.” The New England journal of medicine vol. 371,24 (2014): 2309-19. doi:10.1056/NEJMra1309483

Potential harms of bicarbonate

50 mL ampule containing 50 mEq of sodium bicarbonate (1000 mmol/L) will raise the serum sodium concentration of a 70 kg person by approximately 1 mEq/L and expand the ECF volume by approximately 250 mL.

Kraut, Jeffrey A, and Nicolaos E Madias. “Lactic acidosis.” The New England journal of medicine vol. 371,24 (2014): 2309-19. doi:10.1056/NEJMra1309483

Alternatives to bicarbonate therapy

- **Tromethamine or tris-hydroxymethyl aminomethane (THAM):**

- An amino alcohol that buffers protons by virtue of its amine (NH2)

- The potential advantage of THAM that is unlike bicarbonate (HCO3), which generates CO2, this chemical reduces CO2

Alternatives to bicarbonate therapy

Carbicarb:

- An equimolar mixture of sodium carbonate (Na_2CO_3) and sodium bicarbonate ($NaHCO_3$) that generates less CO_2 than HCO_3

Alternatives to bicarbonate therapy

Dichloroacetate (DCA):

- An investigational drug that increases the activity of the enzyme pyruvate dehydrogenase and therefore accelerates mitochondrial oxidation of pyruvate and lactate metabolism

None of these alternatives have been proven to be more effective or safer

Nahas, G G et al. “Guidelines for the treatment of acidaemia with THAM.” Drugs vol. 55,2 (1998): 191-224. doi:10.2165/00003495-199855020-00003

Monitoring

- Continuous monitoring of lactate levels, acid-base status, and organ function is crucial to guide therapy and evaluate treatment efficacy

- Monitor for a decrease in ionized calcium, which can have adverse hemodynamic effects when pH rises due to bicarbonate therapy. Treat low calcium if detected

Kraut, Jeffrey A, and Nicolaos E Madias. “Lactic acidosis.” The New England journal of medicine vol. 371,24 (2014): 2309-19. doi:10.1056/NEJMra1309483


Thanks
DELGARM.COM