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Hyperlactatemia in critically ill– A Review

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Abstract

Context- Hyperlactatemia is a common finding in critically ill patients and lactate is being used as a prognostic marker of outcome in a variety of underlying conditions. Lactic acid is produced as a product of anaerobic glycolysis and is reversibly converted to pyruvate under normal physiologic state. High initial blood lactate levels and persistently high lactate levels have been correlated with poor outcome. **Need and purpose-** Though many studies and clinical trials have been instituted in past, it still remains a real challenge to analyze and manage hyperlactatemia in critical care setting. This article aims to review the lactate metabolism, aetio-pathological basis of lactic acidosis and role of lactate as a prognostic marker in critically ill patients. **Evidence acquisition-** Articles were retrieved from the Medline, Cochrane database, Google Scholar, CINAHL, Uptodate and Medscape using the following terms which were searched and combined - 'Hyperlactatemia', 'metabolic acidosis', 'lactic acidosis', 'shock', 'sepsis', 'hypoperfusion' and 'elevated lactate '. In addition, references from each identified article were carefully reviewed for additional suitable references. Studies involving humans or animals were examined and the search was restricted to articles published in the English language. **Conclusion-** Hyperlactatemia is an independent predictor of mortality in different groups of critically ill patients. Serial lactate levels are more significant for predicting the patient outcome and effectiveness of the therapy. Treating the underlying disease is the best measure to control lactic acidosis. Cessation of acid production via the improvement of tissue oxygenation is the ultimate goal.

Introduction

Elevated lactate levels in blood (Hyperlactatemia) has been shown to be an independent predictor of mortality in different groups of critically ill patients such as those with sepsis with or without organ failure. [1-13]In critically ill patients ,therefore, blood lactate level assessment is an established investigation. [14] Although shock is the commonest indication of lactate measurement in the intensive care settings, the physiologic basis of lactate generation during shock has been recently a matter of debate and research. Aperfusion related mechanism seems to be involved at least in early stages of shock.[15-17]Recent clinical studies have confirmed the strong prognostic value of hyperlactatemia and its association to other hemodynamic and perfusion abnormalities in septic shock.[4,18,19]Though mostly found in shock states, hyperlactatemia can also occur in many other clinical conditions as well as administration of drugs.

Historical Aspects

In eighteenth century, Johann Joseph Scherer found lactic acidosis in postmortem blood of two puerperal sepsis patients and in 1858, Folwarczny described elevated lactate levels ina patient with leukemia.[20]Fletcher first described the mechanism of lactic acid production in skeletal muscles under anaerobic conditions, highlighting the role of oxygen on its removal and production.[21]Clausen in 1925 identified lactic acidosis as a cause of acid-base disorder. In 1976, Woods and Cohen classified lactic acidosis broadly into type A and B based on Huckabee's seminal work, establishing the relationship of lactic acidosis with tissue hypoperfusion. [22,23] By 20th century, many physicians found that critically ill patients can have metabolic acidosis without elevated ketones or other measurable anions. The work of Khosravani and colleagues corroborates with prior clinical studies showing that even mild hyperlactatemia portends a poor outcome in

critically ill patients.[2]These include the early observations of increased blood lactate during hemorrhagic shock, the classic work of Weil and Afifi in cardiopulmonary resuscitation, and more recent studies showing mortality rates of nearly 70% being independently associated with lactate levels of at least 3.5 mmol/L.[2,24-26]

Hyperlactatemia versus lactic acidosis[22,23]

The normal blood lactate level is 0.5-2mmol/L. Hyperlactatemia is defined as persistent increase (>2 mmol/L) in blood lactate concentration without associated metabolic acidosis. So, it can occur in the setting of normal tissue perfusion and oxygenation. In contrast, lactic acidosis is defined as persistent increase in blood lactate levels (mostly>5 mmol/L) with presence of metabolic acidosis. It is associated with tissue hypoperfusion, carbohydrate metabolism defects, inborn errors of metabolism, drugs or toxin ingestion, post-seizure status and overall metabolic dysregulation. Lactic acidosis may not always produce acidemia. The development of lactic acidosis depends on the magnitude of hyperlactatemia, body's buffering capacity and other coexisting factors. The blood pH in hyperlactatemia or lactic acidosis can be acidemic, alkalemic or even normal.

Lactate Metabolism

Lactate is formed from pyruvate in the cytosol as a part of glycolysis. The enzyme involved in reduction of pyruvate islactate dehydrogenase enzyme (LDH). The reduction of pyruvate is the only known pathway for lactate production, making this a unique way of monitoring anaerobic metabolic processes. The equation is represented as follows-

$$\text{Pyruvate} + \text{NADH} + H^{+} = \text{lactate} + NAD^{+}.$$

Two molecules of ATPs are only produced by this method. At a basal physiologic state, there action favors lactate formation from pyruvate in an approximately 10:1 ratio.[23]In normal physiological conditions, approximately 1500 mmol of lactate are produced daily(20 mmol/kg/day) primarily from skeletal muscle, skin, brain, intestine, and red blood cells.[27-29]Majority of lactate produced is metabolized in the liver (60%), kidney (30%) and to a lesser extent in other organs (heart and skeletal muscle).[30]Utilization occurs via the Coricycle where lactate is converted back to pyruvate and eventually to glucose through gluconeogenesis.[31]

Lactate Clearance

Clearance represents the removal of a substance from a unit of volume over time, typically expressed in milliliters per minute. The concept of lactate clearance has recently generated a lot of debate and research. In addition to single measurements, changes in lactate concentrations over time may have additional predictive value for organ failure and mortality.[8]Serial measurements have shown to improve prognostic ability in septic shock patients and are even superior to oxygen-derived variables(delivered oxygen, DO_2 and oxygen consumption, VO_2). [32] Nguyen and colleagues reported that "lactateclearance", defined as the percentage decrease in lactate from emergency department presentation to 6 hours later, is an independent predictor of mortality.[33] They concluded that "lactate clearance" in the early hospital course may indicate a resolution of global tissue hypoxia with improved survival rates. Jones and colleagues extended the concept of targeting resuscitation in sepsis to achieve a "lactateclearance" of at least 10% as a marker of restoration of oxygen delivery to the tissues.[34] The most recent Surviving Sepsis Campaign guidelines recommend "targeting resuscitation to normal izelactate in patients with elevated lactate levels as a marker of tissue hypoperfusion" (Grade 2C).[35]

Mc Nelis and colleaguesdemonstrated100% mortality in surgical intensive care (ICU) patients who had persistently elevated lactate levels.[36] Those who cleared their blood lactate (lactate level<2 mmol/L) inthe first 24 hours had a mortality of 3.9% while patients with delayed blood lactate clearance (>48 hours to lactate level <2 mmol/L) had a mortality of 42.5%. Husain et al emphasized the importance of lactate clearance in critically ill surgical ICU patients when they risk-stratified95 trauma and non-trauma patients into four groups based on their ability to clear lactate: (a) clearance in the first 24 hours, (b) clearance in 24 to 48 hours, (c) greater than 48 hours to normalize, or (d) never normalized. [37] Predicted mortality was calculated as 10%, 20%, 23%, and 67%, respectively, in the four groups. Initial and serial lactate measurements predicted survival with statistical significance. For many years, it was felt that the lactate itself was harmful and contributed to the worsening acidosis. This has since been shown not to be true. In an effort to actively lower lactate levels, however, Stacpoole et al performed a series of experiments with dichloroacetate (DCA).[38] DCA stimulates the PDH complex by binding to and inhibiting PDH kinase which inactivates the PDH enzyme. Increasing flux through the PDH enzymatic pathway seemed an ideal way to reduce lactate levels and has been studied in a variety of patient population like children with congenital lactic acidosis, patients with myocardial ischemia and critically ill patients with shock.[39-42]All the studies have shown that DCAsafely lowers circulating lactate levels in the blood. Theonly controlled trial of DCA, however, by Stacpoole et al for the treatment of lactic acidosis showed alowering of lactate levels but no change in any significant hemodynamic measurements or survival.[42] Nonetheless, DCA has never proved useful in treating critically ill patients with elevated lactate levels. Logically, it is impossible to know if the rate and/or amount of decline in lactate is due to increased removal, decreased production, dilution because of fluid administration during resuscitation or all the above in variable combinations. Moreover, increased lactate production can remain concealed by increased utilization in septic patients, suggesting that a normal blood level of lactate does not prove that its metabolism is also normal.[43]

Arterial versus (vs) Venous Lactate levels

A comparison of arterial vs venous lactate levels was done in a series of 74 emergency department adult patients who had

arterial and venous lactate drawn within 5 minutes of the other.[44]The correlation between arterial and venous lactate was0.94 (95% CI, 0.91–0.96). There was a mean venous minus arterial lactate difference of 0.22 mmol/L (95% CI, 0.04–0.41), which ranged from 1.3 to 1.7 mmol/L in individual patients. Of the sample patients, 30% had arterial lactate levels less than 1.6.[44]

Lactate use during stress

The heart takes up and oxidizes lactate at rest.[45] The uptake in heart increases during exercise, β-adrenergic stimulation, elevated after load, fast pacing and during shock.[46-48] During hyperlactatemia, lactate can account for up to 60% of cardiac oxidative substrate and exceeds glucose as a source of pyruvate.[47] During shock, the heart oxidizes lactate for the majority of its energy needs.[46] Lactate infusion increases cardiac output in anesthetized pigs and cardiac performance in patients with acute heart failure and both in cardiogenic as well as septic shock.[43,49]Systemic lactate deprivation is shown to be associated with cardiovascular collapse and early death of these animals.[43,50] Interestingly, the human brain changes to a lactate consumer during increased metabolic demand.[51] Lactate accounts for about 7% of cerebral energy requirement under basal conditions and up to 25% during exercise.[28] Blood lactate is oxidized by neurons in the conscious healthy human brain or gets converted to glycogen in astrocytes. The contribution of lactate as a brain energy source increases during hyperlactatemia.[51,52] Lactate is used as a primary energy source during experimental insulin-induced hypoglycemia and is readily oxidized by the brain in an activity-dependent manner.[53]

Source of lactate in Systemic inflammatory response syndrome (SIRS) and sepsis

SIRS is typically associated with type A lactic acidosis due to the presumption that the hemodynamic instability leads to inadequate DO_2. [54]There is also evidence that increased production of pyruvate and decreased activity of PDH (in part due to increased PDH kinase, lactate production by the lung and decreased lactate clearance) are contributors to lactic acidosis in SIRS.[55-58] Limited information exists about the source of lactate in sepsis. Using experimental models, it is found that lung is the major source of lactate.[59]Also, it is seen that muscle and liver lactate fluxes are neutral and lactate uptake predominantly occurred in the gut and kidneys before and after endotoxemia. Levy and colleagues found that lactate and pyruvate concentrations measured by micro dialysis are higher in muscle than in arteries (muscles are 40% of total cell mass) during septic shock.[17]Muscles could, therefore, have an important role in lactate production. De Backer and colleagues demonstrated that the splanchnic region is an uncommon source of net lactate generation in septic patients, even when arterial lactate concentrations are very high.[60]In sepsis, the splanchnic area consumes lactate rather than producing it. In general, although not specifically studied in sepsis, the brain seems to be a major consumer rather than a lactate producer. As shown in critically ill patients before and after liver transplantation with or without hyperlactatemia, there is a net lactate uptake by the brain.[61]During sepsis the heart changes its metabolic substrate. It shifts from using free fatty acids to increased lactate utilization. Thus, the heart also helps in removal of lactate.

Classification

Cohen and Woods divided lactic acidosis into 2 categories, type A and type B.[62-64]
Type A: Hyperlactatemia with clinical evidence of impaired tissue perfusion or oxygenation(Table-1).
Type B: No clinical evidence of impaired tissue perfusion or oxygenation (Table-2).

Table 1: Causes of type A hyperlactatemia [62-64]
(Tissue hypoperfusion and decreased oxygen delivery)

Intense exercise
Seizures
Shock
Cardiac arrest
Regional ischemia (mesenteric ischemia)
Pulmonary hypoxia
Carbon monoxide
Severe anemia

Table 2: Causes of type B hyperlactatemia [62-66]

Type B1- Associated with systemic diseases
Renal failure, Hepatic failure, Diabetes mellitus, Malignancy
Human immunodeficiency virus
Type B2- Drugs and toxins
Paracetamol
Alcohol - Ethanol, Methanol, Diethylene glycol, Isopropanol,Propylene glycol
Antiretroviral Nucleoside Analogs - Zidovudine, Didanosine,Lamivudine
β Adrenergic agonists - Epinephrine, Ritodrine, Terbutaline
Biguanides - Phenformin, Metformin

Sugars - Fructose, Sorbitol, Xylitol Miscellaneous - Diethyl ether, Fluorouracil, Halothane, Iron, Niacin, Propofol Salicylates, Strychnine,Cocaine, Methamphetamine
Type B3 - Inborn errors of metabolism Glucose-6-phosphatase deficiency (von Gierke's disease) Fructose-1,6-diphosphatase deficiency Pyruvate carboxylase deficiency PDH deficiency Methylmalonic aciduria Kearns-Sayre syndrome Pearson syndrome Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) Myclonic epilepsy with ragged red fibers (MERRF)

Type A Lactic Acidosis

It encompasses hyperlactatemia associated with clinical evidence of impaired tissue perfusion or oxygenation. The only treatment is, therefore, cessation of acid production via the improvement of tissue oxygenation. The effective modalities include shock management with restoration of the circulating fluid volume, augmentation of cardiac function, resection of ischemic areas and treatment of sepsis. Sodium bicarbonate ($NaHCO_3$) therapy is of little value for type A lactic acidosis. Carbicarb is a mixture of Na_2CO_3 and $NaHCO_3$ that buffers similarly to $NaHCO_3$ but without production of CO_2. The results from clinical trials are sparse. Animal experiments done by Bersin and Arieff showed that muscle O_2consumption increased with carbicarb and decreased with $NaHCO_3$. [67] There is less fall of Arterial pressures with carbicarb (-12 *vs* -46 mmHg, $P < 0.006$).Cardiac output was more stable with carbicarb but decreased with $NaHCO_3$ (from 143 to 98 ml/kg per min, $P < 0.004$). Stroke volume also improved without a change in pulmonary capillary wedge pressure, suggesting that carbicarb has beneficial effects on myocardial contractility. Rhee *et al.* administered carbicarb, $NaHCO_3$, and NaCl, in random order, to dogs with hypoxic lactic acidosis.[68] $NaHCO_3$ increased PCO_2 and lactate production. Carbicarb increased pH and cardiac index without increasing lactate levels. But, in another dog study, Blecic *et al.* found that carbicarb was not superior to other regimens in a model of cardiac arrest.[69] DCA exerts multiple effects on pathways of intermediate metabolism and stimulates peripheral glucose utilization and inhibits gluconeogenesis, thus reducing hyperglycemia in diabetes mellitus. It also inhibits lipogenesis and cholesterol genesis. By stimulating the activity of PDH, DCA facilitates oxidation of lactate and decreases morbidity. However, in a randomized controlled trial in patients with lactic acidosis, DCA was disappointing. Stacpoole *et al.* studied this compound in patients with severe type A lactic acidosis.[41,42]They observed that it decreased the lactate concentrations in the treated patients but had no beneficial effects on outcomes. In conclusion, DCA treatment in severe lactic acidosis results in statistically significant but clinically unimportant changes in arterial blood lactate concentrations and pH and fails to alter either hemodynamics or survival rates. Lastly, hemofiltration and "continuous renal replacement therapies" have been advocated as effective modalities for treatments of lactic acidosis.[70]Controlled studies are, however, lacking. Hilton *et al.* claimed that ,in their trial, they were able to correct lactic acidosis without inducing either extracellular volume expansion or hypernatremia.[71] Significant differences at presentation for the group of patients who survived, compared with those who died, were observed in age, mean arterial pressure, and Acute Physiology and Chronic Health Evaluation II scores. Neither the severity of the presenting acidosis nor the arterial blood lactate concentrations appeared to predict outcomes in that series.[71] Mariano *et al.* reported success in using continuous renal replacement therapy for the management of phenformin-induced lactic acidosis.[72] Levraut *et al.* investigated the effects of continual renal replacement therapy on lactate clearance.[73] They found that, at the end of the lactate infusion, the median blood lactate concentration increased despite renal replacement therapy. These investigators concluded that continuous venovenous hemofiltration with dialysis cannot meet lactate overproduction.[71-73]

Type B1 Lactic Acidosis

Systemic disease

In critically ill patients with cirrhosis, lacticacidosis indicates a grim prognosis with a 7.64 (95% CI, 3.01–19.34) odds ratio for ICU mortality.[74]Individuals with the combination of cirrhosis, acidemia, lacticacidosis, and acute renal failure had 86% ICU mortality and 94% hospital mortality. Liver failure is associated with decreased lactate clearance, which is further exacerbated in sepsis. In cases of severe liver failure, the liver can be a source of lactate production. When lactate measurements were added to King's College Hospital criteria for determining outcome after paracetamol intoxication, an early lactate of greater than 3.5mmol/L or a post-resuscitation lactate of greater than3.0 mmol/L increased sensitivity for predicting death to 95% whereas specificity was relatively unchanged at greater than 90%. [75]Research using more sophisticated methods to assess tissue perfusion have now shown that occult tissue hypoperfusion is present in many cases of type B acidosis.[75]

Type B2—Lactic Acidosis

Drugs and Toxins

Acetaminophen. In an animal model, the inhibition of mitochondrial respiration preceded overt hepaticnecrosis and was completely prevented by treatment with N-acetyl-L-cysteine. Inhibition of mitochondrial oxidative phosphorylation by acetaminophen and its toxic metabolite eventually results in a shift toward actate production. This suggests that the earlier treatment with N-acetyl-L-cysteine is initiated, the better the outcome.[76-78]

Anti-retroviral drugs. Nucleoside/tide reverse transcriptase inhibitors (NRTIs) have revolutionized treatment of HIV and AIDS. Toxicities due to NRTIs are likely due to mitochondrial toxicity. Although there is no clinical correlation at present, studies have shown that zalcitabine causes the greatest inhibition of DNA polymerase-g and lamivudine, abacavir and tenofovir have very less inhibitory effect. [79]

β-adrenergic agent. β-agonists stimulate muscle and hepatic phosphorylase and inhibit glycogen synthetase. Thus glycolysis is stimulated with an increase in pyruvate production. [80]In skeletal muscle, β -agonists stimulate Na^+-K^+ATPase via up-regulation of cyclic AMP leading to generation of ADP and accelerated glycolysis by phosphofructokinase. The β -agonists also inhibit PDH, leading to decreased oxidation of pyruvate to acetyl CoA and resulting in increased reduction of the pyruvate to lactate.[81]

Thiamine, Biotin, and Iron. Thiamine deficiency resulting in lactic acidosis is most often described in patients with alcoholism, patients receiving total parenteral nutrition and infants receiving a defective soy-based formula.[82-84]In a study, lactate level up to 20 mmol/L has been reported.[85]

TYPE B3— Lactic Acidosis

Inborn Errors of Metabolism

Disorders resulting in oxidative phosphorylation deficiency, such as Kearns-Sayre syndrome, Pearson syndrome, myoclonic epilepsy with ragged red fiber (MERRF), and mitochondrial encephalomyopathy, lactic acidosis, and stroke syndrome(MELAS) are commonly associated with lactic acidosis. A trial was discontinued, after DCA use to lower lactic acid in patients with MELAS, resulted in peripheral nerve toxicity.[86]Fructose-1,6-diphosphatase deficiency results in life-threatening hypoglycemia and lactic academia during fasting as gluconeogenesis is impaired.[87] This is more pronounced in glycogen storage disease type I (von Gierke disease). A deficiency of glucose-6-phosphatase,glucose-6-phosphate translocase, or the endoplasmic reticulum phosphate translocase results in compromised glycogenolysis and gluconeogenesis.[88]PDH deficiency can be due to several mutations with a gradation in phenotype. The impairment may range from fatal infantile lactic acidosis to ataxia as the primary impairment. Pyruvate carboxylase deficiency also has different phenotypic expressions depending on the degree of impairment. It is also characterized by hypoglycemia, lactic acidosis, and ketosis.[89,90] Methylmalonic aciduria is caused by a deficiency of methyl malonyl-CoA mutate or by defects in the transport, uptake, or synthesis of 5°–deoxyadenosylcobalamin. Clinical presentation varies but may include lacticacidosis, hypoglycemia, ketosis, and hyperammonemia. Dialysis has been used to clear the academia during metabolic crises, but there has been little success in curtailing the end-organ damage, which results from the accumulation of the toxic organic acids.[88]

Role as a prognostic marker in critically illpatients

Shock and Sepsis

In low flow states, increased lactate is related to tissue hypoxia by hypoperfusion.[54-58]In sepsis, increased glycolysis, increased production by the gut, lung or white blood cells are involved in non hypoxic hyperlactatemia.[15]Regardless of metabolism and catecholamine effects on lactate metabolism, lactate clearance seems a useful endpoint.[15,17,29]De Backer et al. studying local sublingual capillary perfusion in patients with septic shock showed that lactate clearance was independently correlated to capillary reperfusion.[15]Simultaneous superior vena-caval oxygen saturation($SCVO_2$) and lactate clearance were also measured in a study of 203 patients with septic shock in which reaching only the $SCVO_2$ goal was inferior to reaching only the lactate clearance goal.[35]Rivers participated in a non comparative study in which both $SCVO_2$ and lactate clearance were used as subsequent endpoints.[91]In a large RCT in septic shock, Jones et al. showed that $SCVO_2$ or lactate clearance performed similarly and concluded that lactate clearance could be used instead of $SCVO_2$. [4]However the real question is not whether lactate clearance should replace $SCVO_2$, but if it should be an additional endpoint. Strikingly, while Jones et al. did not find any difference when replacing $SCVO_2$ by lactate clearance, Nguyen et al., in a study of sepsis bundles, showed that by adding lactate clearance to $SCVO_2$, mortality decreased even further from 24.5% to 17.9%.[3]Lactate is one of many markers used for prognosis in critically ill patients and a value greater than 4 mmol/Lis associated with poor outcome.[88]Huckabee performed the first analyses of elevated lactate levels inpatients of varying degrees of shock and later Weil and Afifi and Cady et al expanded on Huckabee's experiments.[23,25,92,93]He noted elevated lactatelevels indicative of widespread tissue hypoxia but no apparent cause of the hypoxia. More recently, in 2007, Trzeciak et al observed initial serum lactate levels in more than 1100 patients.[94]They found blood lactate level of greater than 4 mmol/L to be highly specific (89%–99%)for predicting death in acute phase and in-hospital death. The values were calculated after correction for organ dysfunction with Acute Physiology and Chronic Health Evaluation (APACHE) II scores, showing

the predictive power of initial lactate level uniquely as a biomarker. The surviving sepsis campaign recommends early goal directed therapy in individuals with severe sepsis or septic shock, particularly if blood lactate level is greater than 4 mmol/L. Jansen and colleagues showed that serum lactate levels were strongly associated with sequential organ failure assessment scores (SOFA score), especially early in the ICU stay.[6] Lactate has again been found to be an early predictor of sepsis and necrotizing enterocolitis in preterm neonates.[95]

Bronchial Asthma- Use of beta agonist may lead to increase in blood lactate level with hypokalemia and respiratory alkalosis. Hyperlactatemia has been shown to decrease the bronchodilator response, produce dyselectrolytemia and affect the cardiovascular system.[96]

Traumatic brain injury- As a prognostic marker, arterial to venous blood lactate difference can be used in judging the severity of the traumatic brain injury with good correlation.[97]

Acute Liver Failure- Hyperlactatemia is common in acute liver failure and after liver transplantation, the levels get normalized because the transplanted liver efficiently utilizes lactate. [61,74,75]

Acute Lung Injury-Lactate levels are found to be high with exaggerated arterial to venous difference across the lungs, in the setting of lung injury. Normal lactate levels have been found in other types of respiratory failures.[4,6,9,23]

Acute Cyanide poisoning-Hyperlactatemia (> 8 mmol/L) is a sensitive (94%) and specific (>70%) indicator in cyanide poisoning in the absence of catecholamine use.[98]

Conclusion

Lactate is a carefully regulated substance under normal physiologic state. Hyperlactatemia and elevated lactate to pyruvate ratio with concomitant lactic acidosis points to a serious underlying pathological process. The lactate level on admission can help in judging the severity of initial insult. Serial rather than single lactate measurements are more significant in predicting response to therapy and eventual outcome. Routine blood lactate measurement in critically ill patients is therefore, highly recommended in conjunction with other tests.

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