ISSN: 2320-9267

Indian Journal of Pharmaceutical and Biological Research (IJPBR)

Journal homepage: www.ijpbr.in

REVIEW ARTICLE

To what extent is hyperlactatemia fundamentally integrated into the definition of septic shock?

Vishnu Datt[1],Diksha Datt[2], Rachna Wadhwa[3], Priyanka Dahiya[1]

ABSTRACT

Under the international consensus definitions (Sepsis-3), diagnosing septic shock requires comprising two specific clinical criteria after adequate fluid resuscitation. Persistent hypotension requiring titrated doses of vasopressors (norepinephrine) to maintain a mean arterial pressure (MAP) of 65 mm Hg or greater and elevated serum lactate levels greater than 2 mmol/L (>18 mg/dL) independent of hypovolemia. However, the rise in the blood lactate levels in the septic shock are due to increased production and reduced clearance, largely independent of simple oxygen deprivation. Hyperlactatemia is deeply integrated into the current definition of septic shock, but it is not biologically synonymous with septic shock. Nevertheless, lactate is not specific for septic shock, tissue hypoxia, or oxygen debt. In addition, it not only occurs secondary to the impaired perfusion and oxygen delivery, but it may also result from adrenergically mediated exaggerated aerobic glycolysis, altered metabolic flux, impaired hepatic or renal clearance, mitochondrial and microcirculatory abnormalities, medications and other causes of type B hyperlactatemia. Even High doses of propofol infusion more than 5mg/kg/hour for over 48 hours can lead to PARIS syndrome, that causes mitochondrial dysfunction and halts effective adenosine triphosphate (ATP) production, and use of sodium bicarbonate to counter the metabolic acidosis, and medications like metformin, paracetamol, albuterol, sodium valproate, salicylates involved in the hyperlactatemia. Therefore, lactate levels may be spuriously high in severe septic shock under all these conditions. Contemporary, guidelines themselves recognize that lactate does not directly measure tissue perfusion and recommend its use within broader clinical assessment. Hyperlactatemia has been witnessed in almost all type of shocks (cardiogenic, vasoplegic, hypovolemic hemorrhagic, obstructive and cryptic), and not an integrated part of septic shock. Therefore, lactate should be regarded as an important prognostic and physiological signal encased within the current operational definition, bearing in mind that its biological specificity for shock remains limited. Serum lactate is a surrogate marker rather than an inherent, defining element of the pathophysiology of septic shock.

Keywords: Aerobic hyper glycolysis, Epinephrine, Hyperlactatemia, Mitochondrial dysfunction, Septic shock, Vasopressors

Indian J. Pharm. Biol. Res. (2026): https://doi.org/10.30750/ijpbr.14.4.66

INTRODUCTION

According to the Surviving Sepsis Campaign (SSC) 2026 Guidelines—septic shock is clinically diagnosed when a patient with an infection meets both of the following criteria; persistent hypotension requiring vasopressors (norepinephrine or vasopressin) to maintain a Mean Arterial Pressure (MAP) of ≥ 65 mmHg along with increased serum lactate level of > 2 mmol/L **(**> 18 mg/dL) despite the adequate intravenous fluid resuscitation with crystalloid at least 30 ml /kg. The septic shock causes widespread profuse vascular dilation, capillaries leak, severe cellular oxygen mismatch, and multi-organ failure including lungs, kidneys, and liver and intestine. However, the Increased lactate levels in septic shock are multifactorial driven by a combination of accelerated production, altered cellular metabolism, and impaired clearance, rather than simple tissue hypoxia alone. The endogenous or exogenous epinephrine drastically accelerates aerobic glycolysis and pyruvate production, outpacing the capacity of downstream metabolic pathways and leaking excess lactate into the bloodstream. Even use of many drugs such as propofol (>5mg/kg/hr for 72 hr), sodium bicarbonate, metformin, linezolid, acetaminophen, even Nucleoside Reverse Transcriptase Inhibitors (NRTIs) are involved in the hyperlactatemia. Persistent or rising lactate in septic shock despite normalized blood pressure and adequate fluid resuscitation should prompt clinicians to evaluate for medication-induced contributions for type -B hyperlactatemia, or as result of occult hypoperfusion, microvascular shunting, or thiamine deficiency. Serum lactate levels exceeding 4 mmol/L are the prognostic markers and correlate with significantly higher mortality rates in septic shock. However, the increased blood lactate levels are not specific to the septic shock only, usually it is witnessed in all type of shocks. Therefore, hyperlactatemia should not be the inherited component of definition of septic shock. This systematic review has described the various causes of hyperlactatemia in septic shock beyond to the anaerobic metabolism and generalized inflammation. Therefore, hyperlactatemia should not be an inherent component of the definition of septic shock. This systematic review describes the various causes of hyperlactatemia in septic shock beyond anaerobic metabolism and generalized inflammation, presenting lactate as an important prognostic and physiological signal rather than an inherent, defining element of the pathophysiology of septic shock.

Material and Methods

"PubMed," "Google," and "Medline" were searched, and over 150 recent relevant articles including RCTs, clinical studies, meta-analysis, reviews, case reports, case series and Cochrane data were analyzed for this systematic review. The filter was applied specifically using key words like septic shock, all types of shock, hyperlactatemia in shocks other causes of

© The Author(s). 2026 Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and non-commercial reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.

[1]Department of Anaesthesiology and Critical Care, SGT Medical College & University, Gurugram, Haryana, India.
[2]Department of PSM, SGT Medical College & University, Gurugram, Haryana, India.
[3]Department of Cardiac Anaesthesia, GIPMER, New Delhi, India.

Corresponding Author: Vishnu Datt, Department of Anaesthesiology and Critical Care, SGT Medical College & University, Gurugram, Haryana, India. Email id: dattvishnu@yahoo.com

How to cite this article: Vishnu D,Diksha D, Rachna W, Priyanka D. To what extent is hyperlactatemia fundamentally integrated into the definition of septic shock? 2026;14(4):451-455.

Source of support: Nil.

Conflict of interest: None.

Received: 11.10.2026 Revised: 18.10.2026 Accepted: 31.10.2026

increased lactate in septic shock, lactate and mortality, hyperlactatemia in cardiogenic shock, hyperlactatemia during and after cardiac surgery, definition of septic shock, increased lactate with propofol, sodium bicarbonate, metformin, epinephrine. This review did not require any ethical approval or consent from the patients.

Discussion

Septic shock is the most advanced stage of sepsis, when an infection triggers a harmful chain reaction in the body. Nonetheless, the body's immune system overreacts to an infection and starts harming its own tissues and organs by releasing massive amounts of inflammatory cytokines [tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin-6 (IL-6, IL-10, IL-12)] into the blood. These are involved in extensive tissue injury, and multi-organ dysfunction and the profound vasodilatation, and capillary leaks resulting in severe hypotension (MAP <65 mmHg) and low perfusion to a level that vital organs are deprived of oxygen rich blood. Septic shock can lead to a dangerously inadequate tissue perfusion, multiorgan failure, and even death.[1] Under the international consensus definitions (Sepsis-3), diagnosing septic shock requires meeting two specific criteria after adequate fluid resuscitation: Persistent hypotension requiring norepinephrine to maintain a mean arterial pressure (MAP) of 65 mm Hg, SBP <90mmHg, and elevated serum lactate levels greater than 2 mmol/L independent of hypovolemia.[1,2] Although serum lactate greater than or equal to 4 mmol/L has historically been the threshold for fluid resuscitation, intermediate lactate elevation (> 2 to < 4 mmol/L) is common in patients with sepsis, and associated with increased mortality, consistent with lactate threshold for the Sepsis-3 definitions of septic shock (> 2 mmol/L).[3,4] However, while, considering the lactate for increasing the mortality risk, the guidelines overlooked the non- anerobic and drugs(epinephrine, propofol, and metformin, paracetamol, albuterol, sodium valproate, salicylates) and stress induced hyperlactatemia. Even use of sodium bicarbonate infusion can increase the lactate production by increasing the activity of the rate limiting enzyme phosphofructokinase and removal of acidotic inhibition of glycolysis resulting in increased pyruvate production and finally lactate. In addition, sodium bicarbonate induced alkalosis shifts the HB-O2 dissociation curve to left side, increasing the oxygen affinity of hemoglobin and thereby decreasing the oxygen delivery to the tissues and so shifting to the same anaerobic pathway of hyperlactatemia. [5,6] Most of the time lactate levels suppress after decreasing or discontinuation of epinephrine or propofol and have no effects on the mortality. This specific combination of vasopressor dependence and elevated lactate levels >4mol/L carries an in-hospital mortality rate ranging from 40% to over 50%.[7,8] The analysis per region with the highest number of studies was the 30-day septic shock mortality analysis, with $n = 46$ studies from Europe, $n = 12$ studies from North America and $n = 2$ studies from Australia, resulting in mortality rates for studies conducted in North America of 33.69%, in Europe of 32.49% and in Australia of 26.38%.[9] However, the rise in the blood lactate levels in the septic shock are as a result of increased production and reduced clearance, largely independent of simple oxygen deprivation. The Major Mechanisms involve the adrenergic Stimulation (Aerobic Glycolysis) in response of release of high amounts of stress hormones like epinephrine during septic shock that speeds up glycolysis faster than the mitochondria can process it. The excess pyruvate turns into lactate through an aerobic process. [10] In addition, severe sepsis can cause Microcirculatory Dysfunction. Where, the delivery of blood to different body tissues becomes unbalanced and faulty, and skips past vital tissue beds, creating localized areas of oxygen deprived, and forces the cells to switch to anaerobic metabolism. [11]

Normally, the liver clears a large portion of the body's lactate. However, during severe septic shock, the decreased blood flow to the liver and direct cellular injury reduces its ability to clear the excess lactate causing hyperlactatemia. [11] Lastly, Severe inflammation causes mitochondria dysfunction, and even if oxygen is present, cells cannot use it properly to produce energy efficiently, and increases lactate production. Therefore, lactate levels may be spuriously high in severe septic shock under all these conditions and rather mislead the physicians.

In fact, all types of the shocks (Vasoplegic, septic, cardiogenic, hypovolemic/hemorrhagic, obstructive, cryptic or hemo-metabolic shocks) are associated with hyperlactatemia. So, it should not be a specific biological marker for septic shock and poor outcome. Hyperlactatemia caused strictly by exogenous epinephrine via stimulating β_2-adrenergic receptors, and accelerating cellular metabolism and glycogenolysis, and the rapid surge of glycolysis generates pyruvate faster than the mitochondria can process it through the tricarboxylic acid (TCA) cycle, and excess pyruvate is converted into lactate by the enzyme lactate dehydrogenase.[12] Epinephrine also increases

metabolic demand and further accelerates glycolytic flux and lactate production by stimulating the Na+/K+-ATPase pumps in skeletal muscle cells and a combined results in type B hyperlactatemia (occurring without poor tissue perfusion or cellular hypoxia). Patients usually present with normal or high oxygen delivery and a benign condition, where lactate levels rapidly normalize after stopping the epinephrine infusion. [12] It does not inherently signal tissue hypoxia or worsen mortality, but when it occurs during critical illness like shock, distinguishing it from hypoperfusion-driven lactic acidosis is vital. Even High doses of propofol infusion more than 5mg/kg/hour for over 48 hours can lead to PARIS syndrome, that causes mitochondrial dysfunction and halts effective adenosine triphosphate (ATP) production. Also inhibits carnitine palmitoyltransferase-1 (CPT-1) a transport enzyme and prevents free fatty acids from entering the mitochondria for β-oxidation, further cells cannot efficiently utilize oxygen or fatty acids to generate ATP via aerobic pathways, and so, tissues switch to anaerobic glycolysis to meet energy demands. This again results in the excessive accumulation of pyruvate and its rapid conversion into lactic acid. [13] However, severe lactic acidosis associated with propofol infusion appears to be reversible when propofol is discontinued. [14]

Even In cardiogenic shock (CS), blood lactate concentration is routinely used to determine shock severity and guide clinical decisions. In CS, lactate elevation primarily reflects the degree and duration of systemic hypoperfusion due to low cardiac output (cardiac index <2.2 L/Min/M2), and often compounded by regional ischemia, particularly in the splanchnic territory. Moreover, anaerobic mechanisms of hyperlactatemia are influenced by adrenergic stimulation, post-cardiac arrest syndrome, ischemia-reperfusion injury, systemic inflammation, and mitochondrial dysfunction. Impaired hepatic and renal clearance further contribute to persistent hyperlactatemia, explaining why lactate may remain elevated despite apparent restoration of macrocirculatory variables. In CS, the mechanisms of high lactate levels are also multifactorial and almost similar to the septic shock. Therefore, the hyperlactatemia should not be confined only in the definition of septic shock. [15] Even biochemical parameters for cardiogenic shock includes increased blood lactate levels along with low mixed venous oxygen saturation (SvO_2) due to decreased CO and blood flow and high Natriuretic Peptides (BNP or NT-proBNP) elevated due to acute ventricular stretch and increased wall stress. [16] The Vasoplegic shock(VPS) or vasodilatory shock or vasoplegic syndrome is a severe form of distributive shock characterized by profound, life-threatening hypotension caused by extreme, uncontrolled vasodilatation of the blood vessels, despite a normal or supra-normal cardiac output. In addition to the persistently low MAP under 65 mmHg despite adequate fluid resuscitation, and low systemic vascular resistance (SVR) below 800 dyn·s/cm^5 and preserved or high cardiac output (e.g., cardiac index >2.2–2.5 L/min/m^2) because the primary failure involves the dilated blood vessels rather than the heart muscle. [17] Therefore, high doses of vasopressors like norepinephrine and or vasopressin are required to maintain the MAP and counter the low SVR. In VPS, the Increased serum lactate is also common and inherent useful marker of tissue oxidative stress. However, here elevated lactate can also indicate accelerated aerobic metabolism and is therefore not specific for tissue hypoxia. [18]

It is worth to describe here that in adult and congenital complex cardiac surgical patients the hyperlactatemia above 2 mmol/L during or after cardiac surgery occurs due to both hypoxic and non-hypoxic mechanisms. Preoperative cardio-respiratory instability can occur in patients with transposition of the great arteries (D-TGA) with intact septum, total anomalous pulmonary venous communications (TAPVC) with restricted ASD, hypoplastic left heart syndrome and aortic dissections, and acute coronary syndrome as a result of hypoxemia, hypotension. Hyperlactatemia during CPB precipitated by inflammatory cytokines, surge of catecholamines, hyperglycemia, capillary and mitochondrial dysfunctions, cardioplegic solution, hypothermia, blood transfusion, use of high doses of drugs like metformin, paracetamol, SGLT2 inhibitors, high doses of epinephrine, microcirculatory failure. In postoperative periods continuation of elevated lactate levels or delayed onset after cardiac surgery or as a result of complications of palliative or corrective surgery such as overflowing BT shunt, residual RVOT or LVOT gradients, low cardiac output syndrome, or various hemodynamic shocks like cardiogenic, septic or vasoplegic shocks or even obstructive and cryptic shocks and cardio-respiratory arrest and PRIS due to high doses and prolonged use of propofol in cardiac ICU. [18,19,20,21].But variably, the etiology is multifactorial and the intensity of hyperlactatemia is aggravated by these additional mechanisms involved in lactate formation. For adults with sepsis and elevated lactate or septic shock, the guidelines have suggested serial lactate measurements to guide resuscitation but with conditional recommendation and low certainty evidence. However, it is applicable for all types of shocks. [1] So lactate cannot be considered as a specific marker of septic shock, rather its value may be disproportionately high due to other mechanisms of increased lactate levels. in addition, high lactate levels due to all these additive factors is not associated with high mortality. So, hyperlactatemia cannot be considered as marker of severe septic shock and increased mortality. Even sepsis guidelines have advised to use selective, rapid diagnostic testing to guide antibiotic therapy, recognizing that sepsis remains a clinical diagnosis that cannot be ruled in or out by a single biomarker or lactate level. [1] Even sepsis guidelines 2026 for adults with possible, probable, or definite sepsis or septic shock, “suggest” measuring blood lactate levels (conditional

recommendation, low certainty evidence) in septic shock. [1]

Conclusion

Hyperlactatemia is incorporated into the current operational definition of septic shock, but it is not biologically synonymous with septic shock. Under Sepsis-3, lactate >2 mmol/L in the presence of persistent vasopressors requirement to maintain the adequate blood pressure despite adequate fluid resuscitation identifies the septic shock phenotype associated with increased mortality. However, lactate is neither specific for septic shock nor a direct measure of tissue hypoxia, or oxygen debt. Hyperlactatemia may result not only from impaired tissue perfusion and oxygen delivery, but also from adrenergically mediated exaggerated aerobic glycolysis, altered metabolic flux, impaired hepatic or renal clearance, mitochondrial and microcirculatory abnormalities, medications, and other causes of type B hyperlactatemia. Consequently, an elevated blood lactate should not automatically be interpreted as evidence of an anaerobic metabolism and or tissue hypoperfusion. Even guidelines themselves recognize that lactate does not directly measure tissue perfusion and recommend its use within broader clinical assessment. The most defensible position, therefore, is not that lactate should be discarded from the definition of septic shock, nor that every elevation represents anaerobic metabolism. Rather, lactate should be regarded as an important prognostic and physiological signal encased within the current operational definition**,** bearing in mind that its biological specificity for shock remains limited. Thus, serum lactate is a surrogate marker rather than an inherent, defining element of the pathophysiology of septic shock.

References

1. Prescott, H.C., Antonelli, M., Alhazzani, W. et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock 2026. Intensive Care Med 52, 863–936 (2026).
2. Singer M, Deutschman CS, Seymour CW et al (2016) The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 315:801–10.
3. Liu V, Morehouse JW, Soule J et al (2013) Fluid volume, lactate values, and mortality in sepsis patients with intermediate lactate values. Ann Am Thorac Soc 10:466–73.
4. Shankar-Hari M, Phillips GS, Levy ML et al (2016) Sepsis Definitions Task Force: Developing a new definition and assessing new clinical criteria for septic shock: for the third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 315:775–87 doi: 10.1001/jama.2016.0289
5. Tang A, Tang A, Li W, Hu J. Efficacy Analysis of Sodium Bicarbonate in the Treatment of Shock Patients: A Systematic Review and Meta-Analysis. Journal of Intensive Care Medicine. 2025;0(0). doi: 10.1177/08850666251377036
6. Velissaris D, Karamouzos V, Ktenopoulos N, Pierrakos C, Karanikolas M. The Use of Sodium Bicarbonate in the Treatment of Acidosis in Sepsis: A Literature Update on a Long Term Debate. Crit Care Res Pract. 2015;2015:605830. doi: 10.1155/2015/605830
7. Bassi E, Park M, Azevedo LC. Therapeutic strategies for high-dose vasopressor-dependent shock. Crit Care Res Pract. 2013;2013:654708. doi: 10.1155/2013/654708
8. *Cluntun AA, Badolia R, Lettlova S, Parnell KM, Shankar TS, Diakos NA, Olson KA, Taleb I, Tatum SM, Berg JA et al (2021b) The pyruvate-lactate axis modulates cardiac hypertrophy and heart failure. Cell Metab 33:629–648.e10.* doi: 10.1016/j.cmet.2020.12.003.
9. Bauer, M., Gerlach, H., Vogelmann, T. et al. Mortality in sepsis and septic shock in Europe, North America and Australia between 2009 and 2019— results from a systematic review and meta-analysis. Crit Care 24, 239 (2020).
10. Nuyttens L, Vandewalle J, Libert C. Sepsis-induced changes in pyruvate metabolism: insights and potential therapeutic approaches. EMBO Mol Med. 2024 Nov;16(11):2678-2698.
11. Serova, V.; Klibus, M.; Marcinkevics, Z.; Rubins, U.; Grabovskis, A.; Sabelnikovs, O. Microcirculation Monitoring in Septic Shock: Focused Review. Medicina 2026, 62, 346.
12. Zhang ZR, Shen YY, Yi RQ,etal. When anaphylactic shock meets epinephrine and blood lactate increases: A case report. Medicine (Baltimore). 2024 Sep 6;103(36):e39263
13. Singh A, Anjankar AP. Propofol-Related Infusion Syndrome: A Clinical Review. Cureus. 2022 Oct 17;14(10):e30383. **DOI:** 10.7759/cureus.30383
14. Choi YJ, Kim MC, Lim YJ,et al. Propofol infusion associated metabolic acidosis in patients undergoing neurosurgical anesthesia: a retrospective study. J Korean Neurosurg Soc. 2014 Aug;56(2):135-40. doi: 10.3340/jkns.2014.56.2.135
15. Levy B, Hernandez G, Merdji H. Lactate in cardiogenic shock: pathophysiology, prognostic value, and clinical interpretation. Ann Intensive Care. 2026 Apr 20;16:100061. doi: 10.1016/j.aicoj.2026.100061
16. Galusko, V., Wenzl, F.A., Vandenbriele, C. et al. (2025), Current and novel biomarkers in cardiogenic shock. Eur J Heart Fail, 27: 1106-1125. doi: 10.1002/ejhf.3531.

17. Mistry R, Winearls J. Management of vasoplegic shock.BJA Education, 2024; 25, 65-73.
18. Lambden S, Creagh-Brown BC, Hunt J, Summers C, Forni LG. Definitions and pathophysiology of vasoplegic shock. Crit Care. 2018 Jul 6;22(1):174. doi: 10.1186/s13054-018-2102-1
19. Teixeira FC, Fernandes TEL, Leal KCDS, et al. Factors associated with increased lactate levels in cardiac surgeries: scoping review. Rev Bras Enferm. 2024 Mar 15;77(1):e20230117.
20. Kikuchi, K.; Kazuma, S.; Masuda, Y. A Rapid Increase in Serum Lactate Levels after Cardiovascular Surgery Is Associated with Postoperative Serious Adverse Events: A Single Center Retrospective Study. Diagnostics 2024, 14, 2082. doi: 10.3390/diagnostics14182082
21. Ludhmila A. Hajjar, Juliano P. Almeida, Julia T. Fukushima, Andrew Rhodes, Jean-Louis Vincent, Eduardo A. Osawa, Filomena R.B.G. Galas,High lactate levels are predictors of major complications after cardiac surgery,The Journal of Thoracic and Cardiovascular Surgery, Volume 146, Issue 2,2013:455-460.