Understanding Acid-Base Homeostasis in Pediatric Sepsis: A Literature Review

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Abstract

Sepsis kills 5 million people worldwide. Sepsis is prone to acid-base imbalances. This study aimed to determine the effect of sepsis towards acid and base homeostasis. A literature review was used to conduct this investigation. We performed a literature search using the databases PubMed and Google Scholar. 1382 publications were identified in the search results, and 5 studies were relevant and matched the requirements for this investigation. Sepsis patients typically develop acidosis due to type II respiratory failure, renal failure, lactic acidosis, and ketoacidosis. pH is impacted by respiratory and metabolic factors. Hence, it may misrepresent acid-base.

Keywords: acid, base, pH imbalance, sepsis

1. Introduction

Sepsis is a globally prevalent, life-threatening condition that causes approximately 5 million fatalities annually. Sepsis frequently leads to metabolic acidosis, which serves as an indicator of the severity of the condition. In addition, around 40% of patients with sepsis experience secondary respiratory failure, putting them at risk of developing respiratory acidosis [1]. Sepsis is a major contributor to death among hospitalized patients globally, and its occurrence has been consistently rising in recent times. Based on epidemiological statistics, the worldwide count of individuals with sepsis remains above 30 million annually, with a fatality rate of 17%. According to a recent study that analyzed hospitalization data from seven wealthy nations, the yearly occurrence of sepsis was 19.4 million cases, resulting in about 5.3 million patient fatalities [2].

Septic shock significantly impacts patient admissions to pediatric intensive care units (PICUs) and is associated with elevated rates of morbidity and mortality in children. Severe sepsis and septic shock continue to be the main causes of infection-related fatalities in children despite significant interventions. An estimated 4 million children under the age of five died globally in 2013 from infectious illnesses; a large number of these deaths were related to the serious outcomes of sepsis and septic shock [14].

The prevalence of sepsis worldwide, as assessed by the Sepsis-3 criteria, was 22.4%, with rates ranging from 20.9% in low-income and lower-middle-income countries (LICs/LMICs) to 24.5% in upper-middle-income nations. The primary etiologies of sepsis were pulmonary, intraabdominal, and urinary infections, whereby gram-negative bacteria constituted almost half of the causative agents. More than 70% of patients received mechanical ventilation [3]. Sepsis is a leading cause of sickness and mortality in children and a substantial driver of healthcare utilization. Globally, the incidence rate of pediatric sepsis is around 22 cases per 100,000 person-years, whereas neonatal sepsis occurs in roughly 2,202 cases per 100,000 live births. This adds up to a total of 1.2 million cases of sepsis in children each year [4]. It can manifest in 1% of patients treated, and 30% of these cases can progress to MODS (Multiple Organ Dysfunction Syndrome), resulting in death in 20% of sepsis patients and 60–80%% of patients with septic shock. The clinical symptoms observed in people with sepsis encompass fever, a declining level of awareness, low blood pressure, decreased urine output, and thrombocytopenia [5].

2. Methods

The study was conducted utilizing the literature review methodology. The articles included in this inquiry are derived from investigations conducted throughout the past decade. We performed a comprehensive literature search using the PubMed and Google Scholar databases. The keywords employed for locating pertinent publications are "acid-base balance," "sepsis," and "complication." Screening is conducted by evaluating individuals using certain criteria to see if they meet the requirements for inclusion or exclusion. This study employed certain criteria for participant selection, including the requirement for original articles that examined the acid-base balance on patient with sepsis. Additionally, the articles were to be available in full-text format, published between 2003 and 2023, and written in English. In addition, review papers were not included in this analysis.

3. Result

Five papers were gathered following a thorough evaluation using both intrinsic and extrinsic criteria. We collected data from these studies for our analysis in this study, including information such as the first author and year of publication, title, country, study design, parameter and instrument used, and the resulting data (Table 1).

Table 1. Summary of included literature

First author (Year)	Country	Study design	Aimed	Participant	Result
Ganesh et al., 2016 [6]	India	A prospective study	To analyze the metabolic acidosis composition in patients with sepsis after their admission to the Intensive Care Unit (ICU) and during the first 5 days.	75 ICU patients with sepsis	In patients with sepsis and septic shock, metabolic acidosis with a high anion gap is the predominant blood gas anomaly.
Diaztagle-Fernández et al., 2018 [7]	Colombia	A prospective study	To evaluate and contrast two diagnostic methodologies for Acute Bacterial Bloodstream Infection (ABB) in patients diagnosed with severe sepsis.	38 patients with severe sepsis	The most commonly suggested cause of acidosis was an increased strong ion difference (SID).
Kreu et al., 2017 [8]	Sweden	A retrospective study	Examine the correlation between metabolic alkalosis and the duration	627 patients with sepsis	After adjusting for age, sex, SAPS III-score, pH and BE before

			of stay in the intensive care unit (ICU).		admission, and AKI in a multivariate analysis, it was shown that metabolic alkalosis did not have any significant effect on 30-day and 12-month mortalities.
Lekhwani et al., 2010 [12]	India	A prospective study	Investigate acid-base imbalance in prevalent pediatric conditions affecting newborns, including bronchopneumonia, diarrhea, sepsis, and birth asphyxia.	50 pediatric patients in pediatric emergency	The most frequent acid-base condition was metabolic acidosis, with hyperlactatemia observed in over half of the instances analyzed.
O'Dell et al., 2007 [13]	UK	A retrospective study	Precisely identificate the type of acidosis to prevent prolonged and perhaps damaging resuscitation as many resuscitation approaches can also result in metabolic acidosis.	81 PICU patients with meningococcal sepsis	Hyperchloremic acidosis is a usual and significant result of meningococcal septic shock resuscitation.

4. Discussion

The pH is influenced by both respiratory and metabolic factors, leading to potential inaccuracies in representing the true acid-base status [2]. The anion gap, blood lactate, and base excess are the three most commonly used bedside instruments for examining acid–base abnormalities. All has its own limitations. The anion gap needs to be adjusted when hypoalbuminemia is present, which is a frequent case in critically ill patients. More crucially, it is unable to distinguish between hyperchloremic and excess unmeasured anions in a mixed metabolic acidosis. Numerous conditions, such as tissue hypoperfusion, cellular dysoxia, and rapid aerobic glycolysis, might result in a raise in blood lactate level during a severe illness. The base excess provided no pathophysiological information as it is solely quantitative [13].

Acidosis is a frequently seen disruption in the acid-base equilibrium of patients with sepsis and is linked to several underlying causes (such as type II respiratory failure, renal failure, lactic acidosis, and ketoacidosis). Chloride (Cl^-) is the main negatively charged ion in the body, making up 66% of all negative charges in plasma and contributing to 33% of plasma tonicity. The significance of chloride in preserving acid-base equilibrium, controlling osmosis, enabling muscle function, and regulating the immune system has been underestimated in comparison to other electrolytes present in the bloodstream. Nevertheless, deviations in chloride levels have been observed in 25% of patients in critical care. The use of excessive doses of chloride-rich crystalloids to forcefully replenish fluids in the treatment of sepsis-induced hypoperfusion may lead to iatrogenic hyperchloraemic acidosis [9]. Metabolic acidosis is commonly observed in people suffering from severe sepsis. Multiple studies have demonstrated that the magnitude of metabolic acidosis and its progression over the duration of hospitalization significantly impact the prognosis. Nevertheless, the exact makeup of metabolic acidosis in these individuals remains poorly understood [6].

Metabolic acidosis in severe sepsis can result from lactic acidosis. In addition, hyperlactatemia is a crucial finding in sepsis and septic shock. It is presumed that each of these disorders has distinct hyperlactatemia mechanisms. Increased lactate levels indicate a rise in glycolytic flux due to hypermetabolism in sepsis, whereas hypoxia causes an increase in glycolytic flux in septic shock. Neonatals have been observed to have more severe manifestations of hyperlactatemia. The finding also stated that there was a negative connection between lactate and pH as well as between lactate and BE in neonates. It indicates that neonates were not able to compensate for metabolic acidosis by hyperventilating in comparison to infants [12].

However research indicates that there is an unknown anion that contributes to large anion gap metabolic acidosis, in addition to lactate [6]. The processes responsible for metabolic acidosis in sepsis remain unclear due to the involvement of several parts of the underlying pathophysiological process and the therapy implemented. The mechanisms encompass lactic acidosis, renal failure, ketoacidosis, hyperchloremia, and several other factors. Metabolic acidosis may be attributed to a disparity in inorganic ions, mostly caused by severe hyperchloremia and increased strong anion gap (SIG). It was not feasible to establish a correlation between this observation with the quantity of crystalloids administered before, as this variable was not noted. Studies of this nature elucidate the specific processes of acid-base change by a physicochemical approach. Water dissociation as a mechanistic explanation for changes in hydrogen ion concentration (H^+) at the nanomolar level. Mathematical models have been developed to understand how pH is regulated within cells and outside of cells. There have also been advancements in the understanding of pH sensors within cells and outside of cells. Additionally, research has been done on how ions are managed in the kidneys [7].

Base excess is commonly used as an indicator in the management of patients in the intensive care unit (ICU). Its function is to diagnose, guide, and intervene in issues pertaining to the equilibrium of acid and base levels in the body. Therefore, elucidating the relationship between bacterial endotoxins (BE) and the mortality rate occurring within 28 days following the beginning of sepsis would provide additional clinical information for studying therapy approaches for sepsis. Metabolic alkalosis is the most common acid-base imbalance seen in critical care patients. It is typically regarded as a reasonably benign condition that only poses a threat to life in severe situations [6]. Sepsis patients who have either hypotension alone or excessive lactate levels of ⩾ 4 mmol/L alone experience a greatly increased death risk. The death rates for the two diseases are 30% and 36.7%, correspondingly. However, in cases when hypotension is present and lactate levels are 4 mmol/L or greater, the mortality rate jumps to 46.1%. Determining the etiology of acidosis is crucial for promptly initiating the appropriate medication, as metabolic acidosis is a sign of a dangerous underlying illness. Metabolic acidosis can be caused by a number of medical conditions, including infections, heart attacks, liver failure, acute hypoxia, and drunkenness [9]. Reduced cellular oxygen supply and impaired mitochondrial oxygen consumption define the bulk of these diseases' pathogenic mechanisms. Nonetheless, more complex anomalies give rise to a number of diseases [10].

The occurrence of lactic acidosis in sepsis is a multifaceted process that leads to severe acidemia. This has significant clinical implications, such as unstable blood flow in the heart due to decreased ability of the left ventricle to contract, dysfunction in the relaxation of the heart during its filling phase, and failure of the right ventricle. It also increases the likelihood of abnormal heart rhythms, widening of the arteries, reduced ability to respond to catecholamines (hormones like adrenaline), decreased blood flow to the liver, and impaired delivery of oxygen to the body's tissues. The metabolic consequences of acidosis encompass diminished cellular ATP generation, elevated levels of ionized calcium, and insulin resistance. The management of metabolic acidosis, particularly organic acidosis like lactic acidosis, is a subject of debate. However, the consensus is that the most efficacious treatment involves reducing acid formation by enhancing the transport of oxygen to the tissues. The aggressive treatment of sepsis involves the use of suitable antibiotics and the management of acidosis by means of fluid resuscitation and restoration of heart function. Sodium bicarbonate temporarily raises the pH of the blood, but this does not lead to improved heart function or better results in patients with sepsis. Therefore, the most effective treatment for metabolic acidosis in sepsis is to address the underlying cause. While acidemia plays a role in causing cardiovascular problems during sepsis, there is no controlled study that has proven that bicarbonate therapy improves the functioning of the heart, independent of its impact on pH levels [10] [11].

5. Conclusion

Sepsis patients often have acidosis, which is caused by several mechanisms, including type II respiratory failure, renal failure, lactic acidosis, and ketoacidosis. pH is affected by respiratory and metabolic variables, so it may not accurately reflect the actual acid-base condition. Most common findings of acid-base disturbance is metabolic acidosis. Sepsis is aggressively treated with antibiotics and fluid resuscitation for acidosis. Sodium bicarbonate momentarily elevates blood pH, but it does not enhance heart function or sepsis outcomes.

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References

[1] Langer, T., Brusatori, S., Carlesso, E., Zadek, F., Brambilla, P., Ferraris Fusarini, C., ... & Grasselli, G., 2021. Low noncarbonic buffer power amplifies acute respiratory acid-base disorders in patients with sepsis: an in vitro study. Journal of Applied Physiology, 131, p. 464-473.

[2] Yuan, J., Liu, X., Liu, Y., Li, W., Chen, X., Chen, Q., ... & Shen, F., 2023. Association between base excess and 28-day mortality in sepsis patients: A secondary analysis based on the MIMIC-IV database. Heliyon, 9.

[3] Tirupakuzhi Vijayaraghavan, B. K., & Adhikari, N. K., 2022. Sepsis Epidemiology and Outcomes in Asia: Advancing the Needle. American Journal of Respiratory and Critical Care Medicine, 206, p.1059-1060.

[4] Yuniar, I., Karyanti, M. R., Kurniati, N., & Handayani, D., 2023. The clinical and biomarker approach to predict sepsis mortality in pediatric patients. Paediatrica Indonesiana, 63(1), 37-44.

[5] Dharmawan, A., Istia, M. J., Tan, H. T., Suparto, S., Anastasia, M. C., & Layanto, N., 2021. The outcome of patients with sepsis at Tarakan Hospital Central Jakarta in 2018. Muhammadiyah Medical Journal, 2., p. 49-56

[6] Ganesh, K., Sharma, R. N., Varghese, J., & Pillai, M. G. K., 2016. A profile of metabolic acidosis in patients with sepsis in an Intensive Care Unit setting. International journal of critical illness and injury science, 6., p.178

[7] Diaztagle-Fernández, J. J., Moreno-Ladino, I. J., Morcillo-Muñoz, J. A., Morcillo-Muñoz, A. F., Marcelo-Pinilla, L. A., & Cruz-Martínez, L. E., 2019. Comparative analysis of acid-base balance in patients with severe sepsis and septic shock: traditional approach vs. physicochemical approach. Revista de la Facultad de Medicina, 67, p. 441-446.

[8] Kreü, S., Jazrawi, A., Miller, J., Baigi, A., & Chew, M., 2017. Alkalosis in critically ill patients with severe sepsis and septic shock. PloS one, 12.

[9] Filis, C., Vasileiadis, I., & Koutsoukou, A. (2018). Hyperchloraemia in sepsis. Annals of intensive care, 8, p. 1-8.

[10] Velissaris, D., Karamouzos, V., Ktenopoulos, N., Pierrakos, C., & Karanikolas, M., 2015. The use of sodium bicarbonate in the treatment of acidosis in sepsis: a literature update on a long term debate. Critical care research and practice, 2015.

[11] Madkour, A. M., ELMaraghy, A. A., & Elsayed, M. M., 2022. Prevalence and outcome of sepsis in respiratory intensive care unit. The Egyptian Journal of Bronchology, 16, pp.29

[12] Lekhwani, S., Shanker, V., Gathwala, G. and Vaswani, N.D., 2010. Acid-base disorders in critically ill neonates. Indian journal of critical care medicine: peer-reviewed, official publication of Indian Society of Critical Care Medicine, 14(2), p.65.
[13] O'Dell, E., Tibby, S.M., Durward, A. and Murdoch, I.A., 2007. Hyperchloremia is the dominant cause of metabolic acidosis in the postresuscitation phase of pediatric meningococcal sepsis. Critical care medicine, 35(10), pp.2390-2394.
[14] Wibowo, A.F., Kusumastuti, N.P., Fitriati, M. and Setyaningtyas, A., 2023. The Epidemiology and Outcomes of Children Septic Shock in Developing Countries: A Literature Review. The Epidemiology and Outcomes of Children Septic Shock in Developing Countries: A Literature Review, 127(1), pp.5-5.