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NEPHROLOGY - REVIEW

Alactic base excess (ABE): a novel internal milieu parameter—its concept and clinical importance

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Abstract
Inspired by the Stewart-Figge acid–base approach, Gattinoni et al. recently introduced a new internal milieu parameter known as alactic base excess (ABE). The authors defined ABE as the sum of lactate and standard base excess. In the context of sepsis, ABE has been proposed as a valuable marker to discern between metabolic acidosis resulting from the accumulation of lactate and the retention of fixed acids, which can occur in cases of renal failure. Multiple studies have demonstrated that a negative ABE value (<−3 mmol/L) represents an early marker of renal dysfunction, and significantly correlates with higher mortality rates in septic patients. In conclusion, ABE is a simple and useful parameter that can be used to better interpret a patient's acid–base status, assess renal function, and general prognosis in sepsis. By incorporating ABE into clinical practice, healthcare professionals can enhance their understanding of the complex acid–base imbalances in their patients and tailor more individualized, effective treatment plans.

Keywords Alactic base excess · Strong ion difference · Sepsis · Biomarker · Acute kidney injury

Introduction

The Stewart-Figge acid–base approach is founded on the idea that there are three primary factors that determine the acid–base status: carbon dioxide partial pressure (pCO_2), strong ion difference (SID), and the total concentration of weak acids and plasma proteins, such as albumin and phosphates. The SID represents the net charge balance of fully or nearly fully dissociated ions, also known as the apparent SID (SIDa). It can be calculated using the following equation (all concentrations in mmol/L) [1, 2]:

$$\text{SIDa} = (\text{Na} + \text{K} + \text{Ca} + \text{Mg}) - [\text{Cl} + \text{strong acids(e.g. : lactate)}]$$

However, to account for the influence of weak acids in maintaining electrical charge balance in plasma water, the effective SID (SIDe) should be determined using the following formula [3–5]:

$$\begin{aligned}\text{SIDe} = {} & 2.46 \times 10^{-8} \times \text{pCO}_2(\text{mmHg})/10 - \text{pH} \\ & + (\text{albumin(g/l)}) \times (0.123 \times \text{pH} - 0.631) \\ & + (\text{phosphate (mg/dl)}) \times (0.309 \times \text{pH} - 0.469)\end{aligned}$$

The difference between SIDa and SIDe, designated as strong ion gap (SIG), can be quantified using the equation:

$$\text{SIG} = \text{SIDa} - \text{SIDe}$$

Normally, the value of SIG should fall within the range of 0–2 mmol/L, adhering to the principle of plasma electroneutrality. Deviations from this range may indicate the presence of unexplained charges, which can be identified as a SIG.

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Traditional acid–base (Henderson–Hasselbach) approach

Traditional acid–base diagnostic method is based on the conception that the protons in the medium come from the acids dissociation. This method is based on the assessment of the two components of the Henderson–Hasselbach equation [pH = p*K*a + log(*A*−)/(HA)]: the metabolic component, represented by the plasma level of bicarbonate and base excess, and the respiratory component, represented by the plasma level of carbon dioxide. The analysis of the metabolic component is complemented by the calculation of the anion gap [natremia − (chloremia + bicarbonatemia)], which allows differentiation of metabolic acidosis due to bicarbonate loss (normal anion gap) from bicarbonate reconversion (high anion gap) [6].

It is worth pointing out that even though both acid–base approaches have similar diagnostic utility, the Stewart–Figge acid–base approach offers the advantage of detecting the impact of weak acids, most importantly albumin in patients with hypoalbuminemia. On a patient's acid–base status, which is frequently observed in critical care units (CCUs) [5].

Hyperlactatemia and acidosis

An increase in lactate concentration can result in metabolic acidosis, characterized by an excess of negative strong ions. However, it does not necessarily lead to acidemia, which is defined as low serum pH. This is because other simultaneous processes may induce a compensatory reduction in negative strong ions, causing a widening of the SID and restoring normal pH. The kidneys play a central role in correcting lactate excess, which is a common type of compensatory mechanism [2]. However, Musso et al. [3] have shown that patients with compromised kidneys, who were unable to regulate their hyperlactatemia, were able to use hemoperfusion as an adequate treatment. Lactate levels were able to be restored to physiologically normal conditions using machine interventions for a temporary period of time, demonstrating that hemoperfusion is a valid treatment option when the kidneys are unable to compensate for this type of ion imbalance.

Gunnerson et al. have classified acid–base disorders based on the primary anion contributing to acidosis. They define lactic acidosis as metabolic acidosis in which lactate accounts for more than 50% of the standard base excess (SBE). On the other hand, SIG (unmeasured ions) acidosis is characterized by the SIG accounting for more than 50% of SBE [7].

Table 1 Causes of lactic acidosis

Tissue oxygenation reduction	Hypoxemia
	Shock status
	Organ ischemia
Oxidative metabolism reduction	Ketosis diabetic
	Malignancy
	Toxicities
Lactate clearance reduction	Liver failure
Excessive energy waste	Seizures
	Hyperthermia
	Extreme exercise
Other causes	D-lactic acidosis

Hyperlactatemia can arise from various causes (Table 1) [8]. While it was previously suggested that increased lactate levels are primarily due to tissue hypoxia resulting from impaired oxygen delivery, this theory fails to account for other factors such as fluid imbalance, anion gap, SID, oxygen extraction, venous oxygen saturation, and metabolic acidosis. Gattinoni et al. [7] proposed a new perspective, suggesting that increased lactate serum levels, known as hyperlactatemia, are often the result of impaired tissue oxygen utilization or extraction rather than impaired oxygen delivery. Moreover, lactate levels have been proposed as a predictive factor for mortality, particularly in cases of sepsis, making it a highly valuable biomarker in CCU patients. For example, lactic acidosis has shown the highest mortality rate in CCU settings, with 56% compared to unidentified anions (39%), or hyperchloremic acidosis (29%). The control group without acidosis has shown a mortality rate of 26% [7].

Alactic base excess concept

Traditionally, it has been recognized that an increase in serum lactate (hyperlactatemia) does not necessarily result in a decrease in serum pH (acidemia). The key determinant of how plasma lactate concentration affects serum pH lies in the functionality of the kidneys. Lactate-induced acidemia is only observed in patients with impaired renal function, defined by a serum creatinine level of ≥2 mg/dL. To better understand the relationship between hyperlactatemia and acidemia, the concept of alactic base excess (ABE) was introduced by Gattinoni et al. [7].

ABE is a novel parameter that aims to differentiate between metabolic acidosis caused by lactate accumulation and metabolic acidosis induced by the retention of fixed acids (e.g.: phosphates, sulfates) due to renal failure. It is defined as the sum of lactate and SBE. ABE has been

proposed as a measurement of renal function in cases of sepsis. The calculation for ABE is as follows:

$$\mathrm{ABE(mmol/L)} = \mathrm{Standard\ Base\ Excess(mmol/L)} + \mathrm{Lactate(mmol/L)}$$

Standard base excess (SBE) represents the amount of acid or base required to restore the serum pH to 7.4, assuming a normal $PaCO_2$ level. It is quantified using the following equation:

$$\mathrm{SBE(mmol/L)} = [\mathrm{HCO_3} - (\mathrm{mmol/L}) - 24.8\ \mathrm{mmol/L}] + 16.2\ \mathrm{mmol/L} \times (\mathrm{pH} - 7.4)$$

SBE is utilized instead of actual base excess as it provides a better indication of the extracellular fluid buffer base status. While it may seem counterintuitive that the ABE equation includes lactate, it is named as such to emphasize the separation of lactate from the standard bases, allowing for individual assessment. It is important not to confuse the term "alactic" with "non-lactic," which is used in other internal milieu equations to indicate the exclusion of lactate from the equation components. The concept of ABE is based on the idea that the renal tubules compensate for increased acid levels in the body (primarily lactic acid, which will be discussed further in this review) by releasing fixed acids to maintain serum pH and other functions.

ABE categories

The results obtained from the ABE equation can be further classified into three categories to provide a proposed diagnosis [1, 7, 9]:

1. Negative ABE value (<−3 mmol/L): This category represents the most concerning result, as it is a strong indicator of mortality in patients with sepsis. Given the complexity of these relationships, the use of ABE as a potential new biomarker to predict sepsis-related mortality becomes extremely useful. Lactate, as a powerful marker of illness severity established by the Sequential Organ Failure Assessment (SOFA), adds further significance to the inclusion of ABE in this context.

   A negative ABE value indicates that the standard bases are not being adequately eliminated in the urine and are instead accumulating in the blood, along with lactic acid. The strain on the renal tubules to excrete fixed acids can eventually overwhelm their capacity, leading to a failure of compensation mechanisms involving organic anion transporters or the proton pump. This can quickly result in acidemia and a worsening glomerular filtration rate (GFR). Notably, research findings have demonstrated that a significant number of patients with a negative ABE value, even without meeting the criteria for acute kidney injury (AKI), later develop worsening kidney function and acidemia to the point of being diagnosed with AKI [1].

   It has been reported an increase in Urinary Strong Ion Difference (SIDu), plasmatic unmeasured anions, and phosphate before the occurrence of AKI. This finding suggests that "subclinical AKI" can be diagnosed by detecting alterations in acid–base regulation. In this sense, it has been documented that a negative ABE value in patients without AKI criteria reflects a "subclinical AKI" secondary to fixed acid retention. It is also associated with poor outcomes independent of AKI criteria. The fixed acid retention without AKI criteria is attributed to the kidney's inability to acidify urine as a compensatory mechanism during metabolic acidosis. This fixed acid retention can be attributed to "acute tubular dysfunction," which reduces acid tubular secretion due to overload or dysfunction of organic anion transporters (OAT1) or reduced proton tubular secretion capability. Therefore, dynamic ABE monitoring appears to be a complementary tool for detecting "subclinical AKI," as its components are widely measured and easy to calculate [1, 9].
2. Neutral ABE value (≥3 to <4 mmol/L): This category indicates that the kidneys are compensating for a buildup of lactic acid. In these cases, patients may have elevated levels of lactic acid in the blood, but the blood pH remains normal as the kidneys effectively concentrate the fixed acids in the urine and maintain pH balance. Prognostically, patients with a neutral ABE value generally have lower mortality rates compared to those with a negative ABE value. However, there are exceptions, particularly in patients with negative ABE values and high renal function (GFR > 60 mL/min/1.73 m^2), which may suggest the possibility of a negative ABE being an indicator of future renal dysfunction rather than a present one [1, 7].
3. Positive ABE value (≥4 mmol/L): This category suggests that there is no significant concentration of standard bases or lactic acid in the blood, as the kidneys have compensated for metabolic acidosis, or the body has employed other compensatory mechanisms to contribute to alkalosis in response to falling blood pH. A positive ABE value can also provide guidance in the decision-making process for fluid resuscitation in CCUs, as metabolic alkalosis can be caused by diuretics or volume contraction.

Lower significant link has been found between positive ABE values and patient mortality in comparison to negative ABE values [1, 7].

Conclusion

In conclusion, capturing the physiological capabilities of the kidneys in restoring acid–base balance through ABE is crucial. ABE provides valuable insights into the underlying causation factors and supports individualized therapeutic approaches. By considering ABE, clinicians can more confidently assess the renal function's impact on acid–base status and make informed decisions tailored to each patient's needs.

Declarations

Conflict of interest All the authors declare that they have no conflict of interest.

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