The association between initial anion gap and outcomes in medical intensive care unit patients☆

Hiren J. Mehta, MD^a, Gautam Bhanusheli, MD^b, Paul J. Nietert, PhD^c, and Nicholas J. Pastis, MD, FCCP^{a,*}

^aMedical University of South Carolina, Division of Pulmonary and Critical Care Medicine, Charleston, SC 29425, USA

^bJohn H. Stroger Jr. Hospital of Cook County, Department of Internal Medicine, Chicago, Ill, USA

^cMedical University of South Carolina, Department of Biostatistics and Epidemiology, Charleston, SC 29425, USA

Abstract

Purpose—Anion gap (AG) metabolic acidosis is common in critically ill patients. The relationship between initial AG at the time of admission to the medical intensive care unit (MICU) and mortality or length of stay (LOS) is unclear. This study was undertaken to evaluate this relationship.

Materials and Method—We prospectively examined the acid-base status of 100 consecutive patients at the time of MICU admission and recorded their mortality and LOS. The etiology of each AG was also recorded. Anion gap was corrected for albumin levels. The patients were divided into 4 stages based on severity of AG. Outcomes based on severity of AG were measured, and comparisons that adjusted for baseline characteristics were performed.

Results—This study showed that increased AG was associated with the higher mortality and that an AG more than 30 had the highest mortality. Mortality was significantly ($P = .013$) increased, even after accounting for AG etiology. Patients with highest AG also had the longest LOS in the MICU, and patients with normal acid-base status had the shortest MICU LOS ($P < .01$).

Conclusion—A high AG at the time of admission to the MICU was associated with higher mortality and LOS. Initial risk stratification based on AG and metabolic acidosis may help guide appropriate patient disposition (especially in patients without other definitive criteria for MICU admission) and assist with prognosis. Mixed AG metabolic acidosis with concomitant acid-base disorder was associated with increased MICU LOS.

Keywords

Anion gap; Mortality; Lactic acidosis; Risk stratification; Length of stay; Prognostication

1. Introduction

An elevated anion gap (AG) metabolic acidosis is common in critically ill patients. An elevation of AG signifies the presence of metabolic acidosis caused by overproduction of organic acids via lactate accumulation, ketoacid production, toxin/drugs, and uremia [1]. It

☆The authors have nothing to disclose.

© 2012 Elsevier Inc. All rights reserved

*Corresponding author. pastisn@musc.edu (N.J. Pastis).

has been shown that patients with high AG have increased admission rates to the hospital, increased rates of admission to intensive care unit, and increased mortality within 1 week of hospital admission compared with patients having a normal AG. An elevated AG is associated with an increased severity of illness that is independent of concomitant severe electrolyte abnormalities [2].

Studies have looked into the correlation between initial AG at admission and outcomes in patients admitted with acute myocardial infarction [3,4]. An emergency department (ED) study on acid-base status used initial acid-base status to discriminate survivors from nonsurvivors in patients with major vascular injuries [5]. Several studies on metabolic acidosis in critically ill patients focus only on lactic acidosis because lactate is considered an indirect marker for conditions that induce metabolic acidosis at the cellular level [6]. Its measurement in the critically ill has traditionally been used to identify patients likely to have poor outcomes [7], guide therapy, and discriminate patients with or without hemodynamic failure [8].

To the authors' knowledge, this is the first study to evaluate the relationship between initial AG (irrespective of cause) at the time of admission to the medical intensive care unit (MICU) and mortality and length of stay (LOS). In today's health care climate, balancing cost containment (ie, avoidance of costly MICU charges when unnecessary) with sound medical decision making is of paramount importance. The authors hypothesize that an evaluation of AG when patients arrive in the MICU may be useful for severity of illness stratification for the purpose of quality assurance and or in clinical studies.

2. Methods

This was a prospective, observational study where data were collected on 100 consecutive patients admitted to the MICU at Cook County Hospital, a tertiary care center in Chicago, Ill, between January 2009 and March 2009. The study was approved by this hospital's institutional review board. The data were collected in the ED on patients being admitted directly to the MICU. Patients on mechanical ventilation before this initial evaluation were excluded because mechanical ventilation can change the acid-base status. We also excluded patients transferred to the MICU from outside hospitals, patients from medical surgical wards who were transferred to the MICU, and those transferred to the MICU from operating room because it was not feasible to determine a consistent point in time to calculate the initial AG.

Data obtained included initial arterial blood gas, serum electrolytes, creatinine, and albumin. We did not use any follow-up data or any measurements after treatment initiation. Anion gap was calculated as $AG = \text{sodium} - (\text{chloride} + \text{bicarbonate})$ and corrected for albumin (2.5 mEq/L per gram albumin difference from 4 g), and acid-base status was analyzed. Patients with an AG less than 12 and HCO_3^- less than 22 mEq/L were considered to have a nongap metabolic acidosis. The etiology of each patient's AG was recorded. Patients were further divided into 4 stages based on the initial AG (milliequivalent per liter): stages 1 (normal AG 6–11), 2 (AG 12–20), 3 (AG 21–30), and 4 (AG >30). Baseline characteristics on the entire patient population were collected. The etiology of elevated AG was based on attending physicians' interpretations of the available information and was classified into 1 of 5 categories (lactic acidosis, uremia, ketoacidosis, intoxications, and rhabdomyolysis). Subjects' Acute Physiology and Chronic Health Evaluation II (APACHE II) scores, length of MICU stay, and inhospital mortality were also recorded.

2.1. Statistical analysis

Baseline characteristics for patients with and without an elevated AG were compared using t tests, Wilcoxon rank sum tests, or χ^2 tests, as appropriate. The relationship between initial acid-base status and clinical outcomes was assessed with the Wilcoxon rank sum test and the Cochran-Armitage test for trend. Multivariable regression models were used to assess the relationships between AG and study outcomes; multivariable logistic regression and negative binomial regression models were used, with inhospital mortality and length of MICU stay serving as the dependent variables, respectively. One set of models compared subjects with an elevated AG with those without an elevated AG (ie, stages 2, 3, and 4 vs stage 1), and a different set of models, restricted to subjects with an elevated AG, was used to examine whether a higher AG stage was associated with worse outcomes. All multivariable models included subjects' age, smoking status, diabetes mellitus, cirrhosis, and APACHE II score as covariates. Models restricted to subjects with an elevated AG also included AG etiology as a covariate. All statistical analyses were conducted using SAS v9.2 (SAS Institute, Inc, Cary, NC), and $P < .05$ was considered statistically significant.

3. Results

Between January 2009 and March 2009, 118 consecutive admissions to the MICU were evaluated for participation in study. Of the patients admitted to the MICU, 100 were chosen for participation in this study. The other 18 patients who were excluded were transferred to the MICU from an outside hospital, operating room, medical-surgical ward or were on mechanical ventilation before arrival to the emergency department. Of the 100 patients evaluated, 72 had an elevated initial AG. As shown in Table 1, the baseline characteristics including age, smoking status, comorbidities, and glomerular filtration rate (GFR) were similar in patients with and without elevated AG. Subjects with an elevated AG had significantly higher APACHE II scores compared with subjects without an elevated AG (23.2 ± 22.3 vs 20.1 ± 18.7 , $P < .001$).

Table 2 highlights the results of the multivariable regression analyses assessing the impact of AG on inhospital mortality and MICU LOS. Study outcomes were significantly worse among subjects with an elevated AG when compared with subjects without an elevated AG, even after adjusting for subject-level covariates (age, smoking status, diabetes mellitus, cirrhosis, GFR, and APACHE II score). The odds of death was almost 11 times higher among subjects with an elevated AG (adjusted odds ratio, 10.8; 95% confidence interval [CI], 2.6–44.1; $P = .001$), and LOS was approximately 3 times longer (adjusted mean ratio, 2.8; 95% CI, 1.8–4.3; $P < .0001$). Table 3 shows the results of the multivariable regression analyses restricted to subjects with an elevated AG. Increasing AG (as defined by AG stages 2 or 4) is strongly associated ($P = .013$) with an increasing likelihood of in-hospital mortality and with LOS ($P = .008$), even after adjusting for relevant subject-level covariates, including AG etiology.

The mean MICU LOS also varied according to acid-base status and was 4.2 days (SD, 3.8 days) in patients with pure AG metabolic acidosis, 13.8 days (SD, 20.9 days) in patients with AG metabolic acidosis with concomitant acid-base disorder, and 3.2 days (SD, 1.3 days) in patients with normal acid-base status. Patients with normal acid-base status had the shortest MICU stay ($P < .01$).

4. Discussion

The major findings of this study include the following. The presence of an AG metabolic acidosis at the time of admission to the MICU had a strong association with in-hospital mortality, and greater degrees of AG were associated with increasing mortality. The AG

retained substantial prognostic significance even when controlling for the other predictors of mortality available at the time of admission. Although it has been shown that lactic acidosis is an independent marker of increased mortality in MICU patients, this study showed that an elevated AG on admission is a marker of increased mortality and MICU LOS, even after adjusting for any differences in AG etiology. Finally, patients with mixed acid-base disorder on admission had the highest LOS.

In the MICU, an elevated AG usually reflects an imbalance between acid generation in hypoperfused tissues and the ability of the kidneys to excrete these acids. Thus, the presence of an elevated AG may indicate subtle hemodynamic abnormalities leading to tissue hypoperfusion but not overt shock. The source of the unmeasured anions remains unclear. One study evaluating several different organ systems for ion fluxes during endotoxin challenge marked the liver as a source of unidentified anions [9]. If hepatic hypoperfusion initiates a cascade similar to that of endotoxin, then the ions may be traceable to the liver. The unmeasured ionic species may represent the release of previously intracellular species into the circulation or a consequence of reprioritization of hepatic protein synthesis. Increased production of negatively charged short-term phase proteins might help explain the increase in AG. Regardless of the genesis of these species, their utility in assessing mortality critically ill patients is readily apparent. A study by Brenner [2] in 1985 showed that an elevated AG was associated with increased severity of illness including increased likelihood of hospital and MICU admission.

Multiple methods to evaluate acid-base status in critically ill patients are available. Options include the Henderson-Hasselbach method, the semiquantitative base excess method, calculating strong ion gap, and the quantitative physical-chemical approaches described by Stewart-Fencel [10–12]. The literature to date, however, has been conflicting on whether any one of these methods has superior diagnostic and/or prognostic performance [13–18]. Serum lactic acid levels are commonly used to risk-stratify critically ill patients to predict morbidity and mortality. Some studies have decried the value of the magnitude of metabolic acidosis in predicting outcome and, instead, correlate only hyperlactatemia with outcome [19]. However, multiple studies have now shown that lactate clearance is more important than serum lactate level. Low lactate clearance in severely ill septic patients with normal or mildly elevated blood lactate is predictive of poor outcome independently of spot serum lactate level and other known risk factors such as age and number of organ failures [20]. However, measuring lactate clearance is cumbersome and not easily available. The use of lactate as an index of tissue perfusion has several other limitations. The presence of liver disease causes a decreased ability to clear lactate during periods of increased production. Various causes of type B lactic acidosis may produce hyperlactatemia in the absence of tissue perfusion abnormalities. Lactic acid levels can also lag several hours after the oxygen delivery critical threshold has been crossed. It has been demonstrated that mixed venous oxygen saturation can fall below 50% before serum hyperlactatemia is evident [21].

We analyzed the AG rather than base deficit, lactic acid level, strong ion gap, or arterial pH because in comparison with these other techniques, the AG is simple to calculate, is readily available in all institutions, and does not require an arterial puncture. Furthermore, although the pH can be impacted by a compensatory respiratory alkalosis, the AG is a sensitive indicator of metabolic derangement relatively independent of short-term respiratory changes. Our study has several limitations. It was a single-center study with relatively few numbers of patients, and the results cannot be generalized to all the centers across the nation. In addition, unmeasured and confounding patient characteristics not included in our multivariate model might remain. Furthermore, we assessed only the initial AG, and serial assessments of the AG might provide additional prognostic information. The study cannot

be applied to alternate patient populations such as pediatric patients treated in a pediatric intensive care unit or to the adult surgical intensive care unit population.

In conclusion, a high AG at the time of admission to the MICU was associated with higher mortality and LOS, even after adjusting for AG etiology. Initial risk stratification based on AG and metabolic acidosis may help guide appropriate patient disposition (especially in patients without other definitive criteria for MICU admission) and assist with prognosis. Future directions might include a larger multicenter trial to validate the predictive value of initial AG.

Acknowledgments

This publication was supported by the South Carolina Clinical and Translational Research Institute, Medical University of South Carolina's Clinical Translational Research Award (CTSA), National Institute of Health (NIH)/ National Center for Research Resources (NCRR) grant number UL1RR029882. The contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH or NCRR.

References

- [1]. Ishihara K, Szerlip HM. Anion gap acidosis. *Semin Nephrol.* 1998; 18:83–97. [PubMed: 9459291]
- [2]. Brenner BE. Clinical significance of the elevated anion gap. *Am J Med.* 1985; 79:289–96. [PubMed: 4036980]
- [3]. Sahu A, Cooper HA, Panza JA. The initial anion gap is a predictor of mortality in acute myocardial infarction. *Coron Artery Dis.* 2006; 17:409–12. [PubMed: 16845247]
- [4]. Lazzeri C, Valente S, Chiostrì M, et al. Evaluation of acid-base balance in ST-elevation myocardial infarction in the early phase: a prognostic tool? *Coron Artery Dis.* 2010; 21:266–72. [PubMed: 20617567]
- [5]. Kaplan LJ, Kellum JA. Initial pH, base deficit, lactate, anion gap, strong ion difference, and strong ion gap predict outcome from major vascular injury. *Crit Care Med.* 2004; 32:1120–4. [PubMed: 15190960]
- [6]. Tuhay G, Pein MC, Masevicius FD, et al. Severe hyperlactatemia with normal base excess: a quantitative analysis using conventional and Stewart approaches. *Crit Care.* 2008; 12:R66. [PubMed: 18466618]
- [7]. Valenza F, Aletti G, Fossali T, et al. Lactate as a marker of energy failure in critically ill patients: hypothesis. *Crit Care.* 2005; 9:588–93. [PubMed: 16356243]
- [8]. De Backer D. Lactic acidosis. *Intensive Care Med.* 2003; 29:699–702. [PubMed: 12682722]
- [9]. Kellum JA, Bellomo R, Kramer DJ, Pinsky MR. Hepatic anion flux during acute endotoxemia. *J Appl Physiol.* 1995; 78:2212–7. [PubMed: 7665420]
- [10]. Constable PD. A simplified strong ion model for acid-base equilibria: application to horse plasma. *J Appl Physiol.* 1997; 83:297–311. [PubMed: 9216976]
- [11]. Fencel V, Jabor A, Kazda A, Figge J. Diagnosis of metabolic acid-base disturbances in critically ill patients. *Am J Respir Crit Care Med.* 2000; 162:2246–51. [PubMed: 11112147]
- [12]. Stewart PA. Modern quantitative acid-base chemistry. *Can J Physiol Pharmacol.* 1983; 61:1444–61. [PubMed: 6423247]
- [13]. Dubin A, Meneses MM, Masevicius FD, et al. Comparison of three different methods of evaluation of metabolic acid-base disorders. *Crit Care Med.* 2007; 35:1264–70. [PubMed: 17334252]
- [14]. Balasubramanian N, Havens PL, Hoffman GM. Unmeasured anions identified by the Fencel-Stewart method predict mortality better than base excess, anion gap, and lactate in patients in the pediatric intensive care unit. *Crit Care Med.* 1999; 27:1577–81. [PubMed: 10470767]
- [15]. Cusack RJ, Rhodes A, Lochhead P, et al. The strong ion gap does not have prognostic value in critically ill patients in a mixed medical/surgical adult ICU. *Intensive Care Med.* 2002; 28:864–9. [PubMed: 12122523]

- [16]. Boniatti MM, Cardoso PR, Castilho RK, Vieira SR. Acid-base disorders evaluation in critically ill patients: we can improve our diagnostic ability. *Intensive Care Med.* 2009; 35:1377–82. [PubMed: 19367388]
- [17]. Rocktaeschel J, Morimatsu H, Uchino S, Bellomo R. Unmeasured anions in critically ill patients: can they predict mortality? *Crit Care Med.* 2003; 31:2131–6. [PubMed: 12973170]
- [18]. Morris CG, Low J. Metabolic acidosis in the critically ill: part 1. Classification and pathophysiology. *Anaesthesia.* 2008; 63:294–301. [PubMed: 18289237]
- [19]. Hatherill M, Waggie Z, Purves L, et al. Mortality and the nature of metabolic acidosis in children with shock. *Intensive Care Med.* 2003; 29:286–91. [PubMed: 12594588]
- [20]. Levraut J, Ichai C, Petit I, et al. Low exogenous lactate clearance as an early predictor of mortality in normolactatemic critically ill septic patients. *Crit Care Med.* 2003; 31:705–10. [PubMed: 12626973]
- [21]. Bloos F, Reinhart K. Venous oximetry. *Intensive Care Med.* 2005; 31:911–3. [PubMed: 15937678]

Table 1

Baseline characteristics of study subjects

Characteristic	Subjects without elevated AG present (n = 28)	Subjects with elevated AG present (n = 72)
Age, mean (SD)	62.4 (12.9)	61.9(15.0)
Smoking status (percentage of current smokers)	51.1	41.7
Diabetes mellitus (percentage with condition)	53.6	54.2
Cirrhosis (percentage with condition)	0.0	9.7
GFR, mean (SD)	62.9 (28.7)	54.6 (32.4)
APACHE II, mean (SD)	20.1 (3.5)	23.2(3.8) *

* $P < .001$.

Table 2

Results of multivariable analyses assessing impact of AG on study outcomes

Study outcome	Subjects without elevated AG present(n = 28)	Subjects with elevated AG present (n = 72)	P
In-hospital mortality			
Percentage who died	10.7	55.6	.001 [*]
MICU LOS			
Mean (95% CI), days	2.3 (1.7–2.8)	6.9 (5.1–8.6)	<.0001 [*]

^{*} Adjusted for age, smoking status, diabetes mellitus, cirrhosis, GFR, and APACHE II score.

Table 3

Results of multivariable analyses assessing impact of stage of elevated AG on study outcomes

Study outcome	Stage 2 (n = 27)	Stage 3 (n = 31)	Stage 4 (n = 14)	P value for trend
In-hospital mortality				
Percentage who died	33.3	61.3	84.7	.013 *
MICU LOS				
Mean (95% CI), days	3.8 (2.9–4.7)	7.8 (5.5–10.1)	10.6 (3.4–17.8)	.008 *

* Adjusted for age, smoking status, diabetes mellitus, cirrhosis, GFR, APACHE II score, and etiology in the context of multivariable regression models.