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Anion Gap, Anion Gap Corrected for Albumin, and Base Deficit Fail to Accurately Diagnose Clinically Significant Hyperlactatemia in Critically Ill Patients

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Anion gap, anion gap corrected for serum albumin, and base deficit are often used as surrogates for measuring serum lactate. None of these surrogates is postulated to predict hyperlactatemia in the critically ill. We prospectively collected data from September 2004 through August 2005 for 1381 consecutive admissions. Patients with renal disease, ketoacidosis, or toxic ingestion were excluded. Anion gap, anion gap corrected for albumin, and base deficit were calculated for all patients. We identified 286 patients who met our inclusion or exclusion criteria. The receiver-operating characteristic area under the curve for the prediction of hyperlactatemia for anion gap, anion gap corrected for albumin, and base deficit were 0.55, 0.57, and 0.64, respectively. Anion gap, anion gap corrected for albumin, and base deficit do not predict the presence or absence of clinically significant hyperlactatemia. Serum lactate should be measured in all critically ill adults in whom hypoperfusion is suspected.

Keywords: lactate; anion gap; albumin-corrected anion gap; base deficit; shock

Serum lactate levels have emerged as an important tool to screen patients in shock. In critically ill patients, elevated lactate levels are strong evidence of severity of illness, and subsequent serum lactate clearance predicts an improved outcome.[1,2] Serum lactate levels can be elevated by inadequate perfusion and as a result of inflammation, cytopathic hypoxia, and increased rates of glycolysis.[3-5] Besides serum lactate, metabolic targets, such as serum bicarbonate, anion gap (AG), base excess, mixed venous oxygen saturation, and central venous oxygen saturation, have all been used as diagnostic and prognostic tools to monitor the resuscitation of critically ill patients.[6-8] Early goal-directed therapy, as described in the seminal paper by Rivers et al,[7] used hypotension and elevated serum lactate levels to identify patients in shock. In this study, it was demonstrated that emergency department patients with presumed sepsis and a serum lactate level of >4.0 mmol/L or frank hypotension are at a significant risk of death (38%-59% mortality).[7] This study used multiple resuscitation targets, including urine output, mean arterial pressure, central venous pressure, and a central venous oxygen saturation of 70% or greater, to produce a significant reduction in

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mortality.[7] Despite this and many other studies that document the value of measuring serum lactate concentrations, the measurement of serum lactate is still not implemented in routine practice. The measurement of serum lactate is not part of a standard admission battery of laboratory tests because the clinicians assume that other commonly measured and calculated laboratory values (AG, anion gap corrected for serum albumin [ACAG], and base deficit [BD]) act as surrogates to predict hyperlactatemia.

The persistent use of an elevated AG as a surrogate for hyperlactatemia is based on the fact that lactate is an organic acid. However, the fact that lactate is a "gap" acid does not necessarily assure the clinician that the presence or absence of an AG signifies that hyperlactatemia is absent or present, especially in critically ill patients. [9] Base deficit, the amount of base needed to restore pH of blood to 7.40 corrected for a normal pCO_2 in the presence of metabolic acidosis, is commonly thought to predict the presence of a lactic acidosis. Because BD and AG are derived from studies commonly acquired on admission to the emergency department and the intensive care unit (ICU), they are usually more readily available than serum lactate levels. However, previous studies have shown that neither BD nor AG is effective at discriminating the presence or absence of hyperlactatemia.[9-13] Hypoalbuminemia, a common finding in critically ill patients, may lead to a decrease in the normal measured AG thereby masking the presence of an elevated AG. Therefore, some researchers have suggested that ACAG is a more appropriate screening tool for the diagnosis of metabolic acidosis in the ICU.[14] Our study attempts to demonstrate whether BD, AG, or ACAG can serve as screening tools for elevated lactate levels in critically ill patients.

Methods

This study was conducted from September 2004 to August 2005, in the hospital ICU. The George Washington University Hospital ICU is a closed, 48-bed-combined medical-surgical unit that admits all critically ill adults, except those with major thermal injuries. A waiver of informed consent was obtained from the Institutional Review Board because the study involved prospective chart review only. In addition, because the study spanned the initiation of the Health Insurance Portability and Accountability Act (HIPAA) law, we obtained a HIPAA waiver from the George Washington University Committee on Human Research and the privacy officer of the hospital.

Patients

We reviewed the records of all medical-surgical ICU admissions over an 11-month period. Demographic, admission diagnoses, clinical, and biochemical data were collected from the chart for all patients entered in the cohort. We reviewed the records of all medical-surgical ICU admissions over an 11-month time span. Patients with an elevated serum creatinine (>1.5 mg/dL), a diagnosis of ketoacidosis, or with a history of toxic ingestion (eg, ethanol, ethylene glycol, methanol, salicylates, toluene, citrate, iron, or isoniazid) were excluded.

Definitions and Analysis

For each patient, standard BD, AG, and ACAG were calculated. Standard base deficit (SBD) was determined using the modified Van Slyke equation.[15] Anion gap was calculated using the formula $[Na] - ([Cl] + [HCO_3])$. Albumin-corrected anion gap was calculated using the Figge equation: $(\{4.4 - [\text{observed serum albumin (g/dL)}] \times 0.25\} + AG)$.[16]

Hyperlactatemia was defined as a serum lactate concentration of greater than or equal to the upper limit of our laboratory normal (2.0 mmol/L).

Statistics

Proportions of patients with certain characteristics were compared using the chi-square test. We assessed the distribution of variables. Variables with normal distribution were compared using two-tailed unpaired *t* tests, whereas data that did not conform to a normal distribution were compared using the Mann-Whitney rank sum test. Anion gap, SBD, and ACAG were compared using Pearson correlations. Receiver operating characteristic (ROC) curves were determined for AG, SBD, and ACAG to detect the presence of hyperlactatemia. Unless otherwise specified, all means are reported as + standard deviation. All statistics were performed with SPSS 11.0 (SPSS, Chicago, Illinois).

Results

We reviewed 1381 consecutive admissions to the ICU from September 2004 to August 2005. In all, 285 patients met our inclusion or exclusion criteria. The mean age was 55.9 + 17.5 years, and 46.1% of the patients were men. Within the cohort, 52.4% of the patients were African American, 36.8% of the patients were European American, 5.2% of the patients were Hispanic, and 4.5% of the patients were Asian American. Among the 286 patients who comprised our study population, hyperlactatemia was present in 34.4% of the patients. The serum lactate range was 0.5 to 15.5 mmol/L. The mean serum albumin was 2.82 + 0.89 g/dL, mean blood urea nitrogen 19.0 + 14.7 mg/dL, mean serum creatinine 0.9 + 0.3 mg/dL, mean serum lactate 1.96 + 1.7 mmol/L, mean AG 6.8 + 4.1, mean ACAG was 10.2 + 4.5, mean BD 2.0 + 5.9, and mean APACHE II score 11.4 + 6.8 (Table 1). Correlation (R value) of AG, CAG, and BD with serum lactate level were .14 (P = .02), 0.22 (P value < .01), and 0.30 (P < .001; Table 2). Receiver operative curves for the prediction of hyperlactatemia for AG, CAG, and BD were 0.55, 0.57, and 0.64, respectively (Figures 1 and 2).

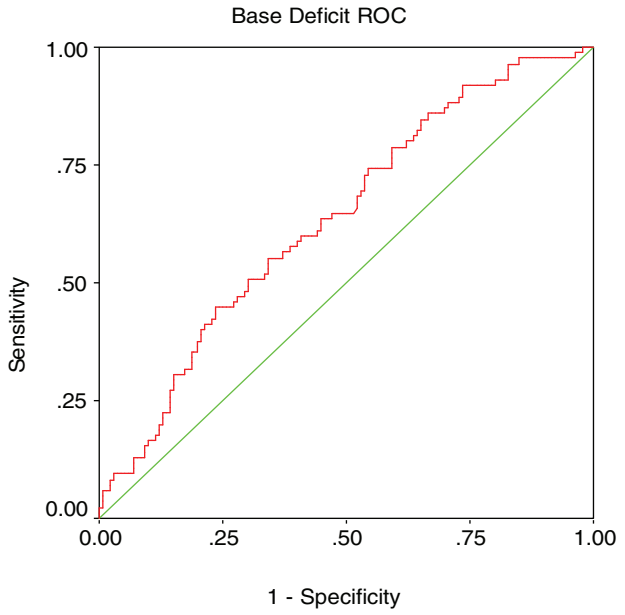

Figure 1. Receiver operating characteristic (ROC) for base deficit.

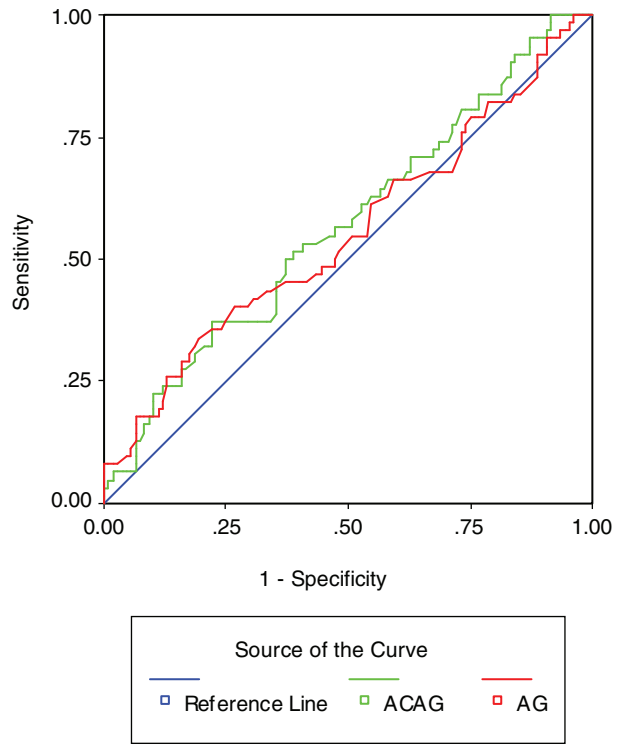

Figure 2. Receiver operating characteristic (ROC) for anion gap and albumin-corrected anion gap (ACAG).

Discussion

In this study, we showed that BD, AG, and ACAG are all well intercorrelated (Table 2). We also show that BD, AG, and ACAG are poor tests to diagnose the presence of hyperlactatemia. Area under the ROC curves ranged from 0.553 to 0.635 for BD, AG, and ACAG (Figures 1 and 2) confirming that all these tests are not helpful in detecting the presence of hyperlactatemia. Moreover, these results were obtained in targeted patients where other causes of gap acidosis were excluded (chronic kidney disease, ketoacidosis, and ingestions). To best assess the diagnostic value and best diagnostic cut-off of any test, ROC curves are helpful. However, in the case of AG and ACAG, normal values and clinical cutoffs are already in place. The upper limit of normal for the AG and ACAG is 12. Unlike AG and ACAG, cut-off values for normal and abnormal BDs for the detection of metabolic acidosis are not as well-defined. In Table 3, the sensitivity and specificity for AG, ACAG, and BD are shown for typical diagnostic cutoffs. Within this cutoff range, the sensitivity of these tests ranged from 19.4% to 64.7%. The specificity for these tests is improved compared with the sensitivity, but because we are concerned with the early detection of hyperlactatemia, sensitivity for a screening test is more important. Table 4 displays

Table 1. Demographics and Clinical Characteristics

Age, y	55.9, 17.5
Sex (% men)	46.1%
Ethnicity	
European American	36.8%
African American	52.4%
Hispanic	5.2%
Asian American	4.5%
BUN, mg/dL	19.0 (14.7)
Serum creatinine, mg/dL	0.9 (0.3)
Serum lactate	1.96 (1.7)
Base deficit	2.0 (5.9)
Anion gap	6.8 (4.1)
Albumin-corrected anion gap	10.2 (4.5)
Serum albumin, g/dL	2.82 (0.9)
APACHE II score	11.4 (6.8)

NOTE: BUN = blood urea nitrogen.

Table 2. Correlations of Base Deficit, Anion Gap, and Albumin-Corrected Anion Gap (ACAG) and Serum Lactate (r value)

	Lactate	Base Deficit	Anion Gap	ACAG
Lactate	xx	0.30[a]	0.14[b]	0.22[c]
Base deficit	0.30[a]	x	0.13[d]	0.23[c]
Anion gap	0.14[b]	0.13[d]	x	0.87[a]
ACAG	0.22[c]	0.23[c]	0.87[a]	x

a. $P < .001$.
b. $P = .02$.
c. $P < .01$.
d. $P = .06$.

Table 3. Selected Sensitivity and Specificity for Base Deficit, Anion Gap, and Albumin-Corrected Anion Gap (ACAG) With Hyperlactatemia Defined as ≥ 2.0 mmol/L

Variable	Cutoff Value	Sensitivity	Specificity
Base deficit	2.0	64.7%	52.9%
	3.0	56.5%	61.4%
	4.0	47.1%	71.4%
	6.0	28.2%	85.0%
Anion Gap	10.0	19.4%	88.9%
	12.0	14.5%	93.5%
	14.0	8.1%	99.1%
ACAG	10.0	56.5%	50.9%
	12.0	32.3%	79.7%
	14.0	22.6%	88.9%

Table 4. Selected Sensitivity and Specificity for Base Deficit, Anion Gap, and Albumin-Corrected Anion Gap (ACAG) With Hyperlactatemia Defined as ≥ 4.0 mmol/L

Variable	Cutoff Value	Sensitivity, %	Specificity, %
Base deficit	2.0	57.9	46.1
	3.0	52.9	55.3
	4.0	42.1	65.0
Anion gap	10.0	27.3	86.2
	12.0	18.2	92.3
	14.0	9.1	96.9
ACAG	10.0	54.5	49.1
	12.0	36.4	75.5
	14.0	27.3	86.8

the performance of these same cutoff values if the threshold for hyperlactatemia was increased from 2.0 mmol/L to 4.0 mmol/L. Despite the increased threshold for hyperlactatemia, sensitivity of AG, ACAG, and BD are still unacceptably low (27.3%-57.9%). In general, our results show that an elevated AG, ACAG, and BD fail to reliably rule in or rule out the presence of hyperlactatemia.

Previous researchers have also shown that AG does not diagnose the presence of hyperlactatemia. Iberti et al[10] showed in his cohort of critically ill patients that only 21% of patients with a serum lactate level between 2.5 mmol/L and 4.9 mmol/L had an elevated AG, consistent with other studies.[9,12,13] As the level of serum lactate rises from 4.0 to 5.0 mmol/L, an elevated AG becomes more specific for detecting severe hyperlactatemia, consistent with our data.[9,17] Similarly, BD is insensitive for detecting hyperlactatemia.[1] In a study of trauma patients by Mikulaschek et al,[12] resuscitation decisions would have been wrong 33% to 58% of the time if BD or AG had been used as the sole criterion rather than serum lactate concentration. Waters et al[18] showed that in a study of surgical patients, elevations in BD without concomitant rise in lactate were attributed to hyperchloremia and were a manifestation of successful resuscitation rather than a fluid deficit.

Why is this issue clinically important? Elevated serum lactate levels identify patients who are at high risk of death.[7] In addition, elevated serum lactate levels may help identify patients in shock before they become overtly hypotensive (a condition called cryptic shock); therefore, early recognition of hyperlactatemia is critical. Given the apparent efficacy of early goal-directed resuscitation using lactate levels of 4.0 mmol/L as a trigger, surrogate measures for

lactate must diagnose lactate levels at 4.0 mmol/L or less. To institute appropriate therapy as early as warranted, screening tests for shock should offer as early a warning as possible. Accurate and rapid serum lactate concentration measurement can now be made widely available in all major hospitals. Serum lactate concentrations should be routinely measured on admission to the ICU and for many patients in the emergency department, and in our opinion, it should be considered an index laboratory measure. The commonplace habit of using BD or any form of AG to detect the presence of hyperlactatemia should be abandoned.

Limitations

Our study has several limitations. First, our samples for determining AG, ACAG, BD, and serum lactate are drawn on admission to the ICU but are not necessarily simultaneous. Although it is our standard practice to obtain all of these laboratory test results at the same time on admission, we cannot rule out that some of the disparity between lactate levels and AG, ACAG, BD could be attributed to intervening changes in patient's physiology, treatment interventions, or both. The exclusion of the 1096 of the 1381 patients evaluated for study enrollment is largely attributable to patients who did not have serum lactate levels available for analysis. However, our results are largely in agreement with previous work. Furthermore, this reflects clinical practice where initial laboratory studies are performed before sepsis or shock are apparent. Second, we used a low cutoff point for a clinically important lactate elevation (>2.0 mmol/L) in our primary analysis. This choice was based on the upper limit of normal in our laboratory, published definitions of hyperlactatemia, and the supposition that a lower level is needed to successfully screen for patients at risk. Indeed, early detection may be the most significant contribution lactate levels have to offer in the setting of critical illness. In our practice, a patient with a serum lactate level of 2.0 mmol/L or greater requires, at a minimum, serial observation. We also analyzed the performance of these diagnostic tests at a serum lactate level of 4.0 mmol/L and found that the performance was poor. Proponents of AG, ACAG, and BD might argue that these values, carefully used or in tandem, with appropriate correction for specific conditions, are just as good as serum lactate. We wonder why anybody would opt for a more complex strategy of screening when serum lactate is so easily and accurately measured.

In conclusion, AG, ACAG, and BD failed to detect the presence of clinically significant hyperlactatemia. We believe that serum lactate levels should be obtained routinely in all patients admitted to the ICU in whom the possibility of shock or hypoperfusion is being considered.

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