ORIGINAL ARTICLE

The anion gap does not accurately screen for lactic acidosis in emergency department patients

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Introduction: Lactic acidosis portends a poor prognosis in trauma, sepsis, and other shock states and is useful for triaging and resuscitating emergency department (ED) patients. The authors sought to determine whether the AG is a reliable screen for lactic acidosis when applied specifically in the ED setting.
Methods: The authors performed a retrospective cohort study over a seven month period. Subjects were all ED patients that had a serum lactate obtained. Sensitivity analyses of the AG for detecting presence of lactic acidosis were calculated for the traditional AG normal value (AG <12) and for the lower AG normal value when using newer ion selective electrode assays (AG <6).
Results: Serum lactate levels were ordered in the ED on 440 occasions. 137 samples were excluded by protocol. Using an AG cutoff of 12, the sensitivity for detecting lactic acidosis was 58.2%, specificity was 81.0%, and the negative predictive value was 89.7%. Using the AG cutoff of 6, the sensitivity was 93.2%, the specificity was 17.3%, and the negative predictive value was 91.8%.
Conclusions: The traditional definition of AG >12 was insensitive for the presence of lactic acidosis. Using the revised AG of >6 is more sensitive but non-specific for lactic acidosis. The authors conclude that employing the AG as a screen for LA may be inappropriate in ED patients. Instead, they recommend ordering a serum lactate immediately upon suspicion of a shock state. A prospective study to confirm these findings is needed.

Lactic acidosis (LA) is an important resuscitation marker for the clinical management of shock.[1] It occurs clinically in two major forms.[2–4] Type B LA is associated with inborn errors of metabolism, toxic substances, and other chronic systemic diseases.[4] Type A LA is the more clinically relevant for emergency physicians, and arises acutely when anaerobic glucose metabolism during tissue hypoxia outstrips the body's metabolic clearance of lactate.[3 4] Serum lactate is valuable in detecting early or occult shock states where the degree of shock may not be clinically evident at the bedside.[1 5 6] LA reliably predicts mortality for a variety of shock states,[1 7] including sepsis,[6 8] trauma,[9 10] burns,[11] cardiogenic shock,[5] and toxidromes.[2 4 12] Of note, these studies were performed in medical, surgical, or trauma intensive care units. Though little research has focused on LA in the emergency department (ED), prompt recognition of LA is critically important in that setting. If ED physicians rapidly recognise the presence of LA and aggressively resuscitate the patient, they may improve mortality outcomes.[6]

There are two possible strategies for the diagnostic detection of LA. The first strategy is to directly order a lactate level upon any clinical suspicion of LA. The second strategy is to calculate a serum anion gap (AG) as a screening test and, if it is elevated, proceed stepwise to work that up with a subsequent lactate level. The presence or absence of an AG has classically been used as a screening tool for lactic acidosis,[4 13 14] but there are some potential problems with the stepwise strategy.[15 16] Firstly, the upper limit of a ''normal'' AG has recently been lowered to as low as 6 because of a technological change in the process that measures electrolyte concentrations.[15 17 18] Using this lower AG threshold would increase the number of secondarily ordered lactates. Secondly, LA is a marker of life threatening illness, and any delay between recognising an increased AG level and then ordering and confirming a lactate level may be risky.

Several studies from ICU settings have demonstrated this problem.[10 15 16 19] To our knowledge, a sensitivity analysis of the AG for LA has not been published specifically for an ED patient population. The distinction is important because intensive care unit and ED patients may manifest different metabolic milieus. For instance, hospitalised patients typically have a lower serum albumin (the single largest component of unmeasured serum anions) than ED patients.[20 21] One could then speculate that the AG might actually be more accurate for ED patients.

We sought to analyse the test performance of the AG as a screening tool for the detection of LA in the ED setting. For a secondary outcome, we also sought to determine whether the initial LA value in the ED was a reliable prognostic indicator.

METHODS

This was a retrospective cohort design of all patients that received the index test (venous or arterial lactate level) in the ED for any clinical reason. The null hypothesis is that there is no relation between the AG and lactic acidosis. The alternative hypothesis is that there is a relation between the AG and lactic acidosis. The study was approved by the institutional review board. The setting was a level-1 trauma center, military academic ED with a 50 000 annual patient census. Participants were all patients that had a serum lactate level obtained in the ED from August 2003 to February 2004. Exclusion criteria included a presence of diabetic ketoacidosis, alcoholic ketoacidosis, or presence of a specific AG inducing toxic ingestion (for example, ethylene glycol). Subjects were also excluded if the basic metabolic profile (from which the AG was calculated) and the serum lactate were drawn more than 60 minutes apart. Subsequent lactate levels during the ED course were included in the sensitivity analysis, but only if they had a separate AG obtained within 60 minutes.

Abbreviations: AG, anion gap; LA, lactic acidosis; NPV, negative predictive value; PPV, positive predictive value; ROC, received operated curve.

All specimens were collected by ED nursing or phlebotomy staff and were processed at the hospital's central laboratory by certified laboratory technicians. Venous or arterial blood samples were drawn from patients into a gray top test tube containing fluoride oxalate and stored on ice until processed by the laboratory. The lactate specimens were analysed on a Vitros 950 (Ortho-Clinical Diagnostics, Raritan, NJ, USA) using colorimetric methodology, with the upper limit of normal set at 2.5 mmol/l. Serum sodium, chloride, and bicarbonate values were measured on a Vitros 950 using potentiometric (ion selective electrode) methodology. The AG was calculated by the traditional equation of AG = [Na–Cl–HCO3]. An adjusted AG using the Figge equation where AGAdjusted = (2.5 × [normal albumin − measured albumin] + AGmeasured) was also performed on those patients with a concurrent albumin measurement.[21] Albumin was measured as part of a serum metabolic profile set on the Vitros 950 using colorimetric methodology with hypoalbuminaemia defined at <3.5 g/dl.[21]

In addition to baseline demographic data, we explicitly recorded from the medical record the patient's ED diagnosis, disposition, and survival to hospital discharge. Sensitivity analyses were calculated for the following test performance characteristics with 95% confidence intervals (CIs): sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy.

Traditionally, the upper limit of normal for the AG has been taught to be approximately 12–16.[10 13 16 22] However with the new ion selective electrode technology, the upper limit of a normal AG at most modern medical centres now is actually much lower because of an upward shift in measured chloride values.[15] Values of the AG for detecting the presence of lactic acidosis were calculated for both the traditional AG normal value of <12 and for the lower AG normal value of <6 when using newer ion selective electrode assays.[18] A sensitivity analysis was also calculated using the Figge AG adjustment for an AG threshold of 12. The mortality predictive value of the ED lactate was compared post hoc to the AG, base deficit, and serum bicarbonate by means of a receiver operated curve (ROC) analysis.

RESULTS

Serum lactate levels were ordered in the ED on 440 occasions. 137 samples were excluded by protocol (131 because the lactate was drawn more than 60 minutes apart from the AG and 6 because of coexistent diabetic ketoacidosis). Three hundred and three lactate and AG pairs were evaluated representing 272 unique ED patients (there were 31 subsequent ED lactates included in the analysis). The average age of the cohort was 68.1 years (standard deviation 0.96 years) and 45.2% of the patients were female. The diagnostic distribution is shown in table 1.

The prevalence of LA was 15.5% for all samples, and 16.2% for all unique patients. The overall admission rate of the entire cohort was 69.9% and the overall mortality rate was 7.7%. Hospital mortality was 36.2% in patients with LA and 2.3% in patients without LA.

Table 1 Distribution of study patients with total mortality rates for each diagnosis and mortality rate for subset with lactic acidosis

ED diagnosis	Patients, n	Gross mortality (%)	LA prevalence (%)	LA mortality (%)
Abdominal pain	112	1.8	11.6	7.7
Sepsis	43	18.6	23.3	70.0
CHF	24	4.2	4.2	100.0
Pneumonia	20	5.0	15.0	33.3
ARF	20	20.0	40.0	50.0
AMS	14	0.0	0.0	0.0
GI bleed	9	0.0	0.0	0.0
Liver failure	7	28.6	28.6	50.0
Trauma	4	0.0	25.0	0.0
Other	19	15.8	10.5	50.0
Total	272	7.7	14.7	40.0

LA, lactic acidosis; CHF, congestive heart failure; ARF, acute renal failure; AMS, altered mental status.

Sensitivity analyses

We performed sensitivity analyses for both of the a priori established AG thresholds as to their overall performance in predicting lactic acidosis (table 2).

The AG threshold of 6 was most sensitive in predicting LA, with a sensitivity of 96.4% but a specificity of only 17.3%. The AG threshold of 12 was more specific at 81.0% but it yielded a sensitivity of only 58.2% (cases from our cohort of severe LA with a ''normal'' AG <12 are detailed in table 3).

The accuracy of the AG threshold of 6 and 12 were 31.7% and 76.9% respectively (see table 2). By post hoc ROC analysis we determined that the optimal AG threshold to screen for the presence or absence of LA was 12.1.

A concurrent serum albumin value was available for 86.1% of our samples, and the prevalence of hypoalbuminaemia was 27.4%. Adjusting the AG >12 threshold with the Figge equation produced a sensitivity of 77.8% (95% CI 51.9 to 92.6%), a specificity of 86.2% (95% CI 74.8 to 93.1%), a PPV of 60.9% (95% CI 38.8 to 79.5%), and a negative predictive value of 93.3% (95% CI 83.0 to 97.8%). Finally, the ROC analysis demonstrated that LA was superior to the AG as a mortality predictor (table 4).

The area under the curve is an index of the goodness of the predictor. Tests with ROC curve areas from 0.600 to <0.700 are considered poor discriminators, from 0.700 to <0.800 are fair, from 0.800 to <0.900 are good, and from 0.900 to 1.000 are excellent.

DISCUSSION

The present study suggests that the AG should not be relied upon to screen for the presence of LA in ED patients for any defined AG threshold value. When using the newly revised AG of greater than 6 on ion selective electrode assays, the AG is sensitive but very non-specific for detection of lactic acidosis (indeed, 84% of our highly selected ED patients had an elevated AG >6). The traditional definition of AG greater than 12 was significantly more specific for presence of lactic

Table 2 Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy (%, with 95% confidence intervals) of the anion gap for predicting the presence of lactic acidosis at different anion gap thresholds

Threshold	Sensitivity	Specificity	PPV	NPV	Accuracy
AG >6	93.2 (86.8–99.6)	17.3 (12.6–22.1)	20.5 (15.6–25.5)	91.8 (84.2–99.5)	31.7 (26.4–36.9)
AG >12	58.2 (45.1–71.2)	81.0 (76.2–85.9)	40.5 (29.7–51.3)	89.7 (85.8–93.7)	76.9 (72.2–81.6)

Table 3 Selected patients admitted to hospital from emergency department with ''normal'' (false negative AG of <12) with severe LA and their clinical course

Age/ sex	ED diagnosis	LA	Calculated AG	Adjusted AG	Albumin	pH	pCo2	Base excess	Hospital outcome
35/M	Severe rhabdomylosis	10.7	9	14.5	1.3	6.918	56	−19.1	Death
70/F	Sepsis	10.4	10	16.25	1.0	7.028	36	−20.3	Death
61/M	Abdominal pain	5.2	11	12.5	2.9	7.463	40	3.8	Discharged alive

LA, lactic acidosis; AG, anion gap.

acidosis than the newly posited AG of 6. Indeed, an ROC analysis determined that the overall best cutoff was actually 12.1 (which for the sake of expediency can be rounded to 12). Unfortunately its sensitivity of 58%, when considering the life threatening implications of LA, is still too low to act as a reliable screening instrument.

Theoretically an increase in lactic acid should directly raise the AG. However, critically ill patients have impaired acid base regulation and may generate an array of unmeasured cations and anions to skew the accuracy of the AG.[10 15 23] The high prevalence of hypoalbuminaemia in our ED patients is also an important source of inaccuracy of the AG for LA. Importantly, a recent study found that hypoalbuminaemia was the single strongest biochemical predictor of mortality in ED patients.[24] Changes in albumin can occur quickly in critical illness and are not confined to those with chronic disease states.[21] Notably, the Figge correction for hypoalbuminaemia improved the sensitivity and specificity in this setting.

There were several limitations to our findings, most notably the retrospective design and our highly selected ED population which would tend to bias towards sicker patients. However, this cohort seems representative of those patients that physicians perceive to be most prone to clinical deterioration. Lactate values can change rapidly during aggressive resuscitation, so the allowance of 60 minutes between lactate samples and serum AG values may have been too liberal.[2 25] We also could not distinguish from our available data whether the lactate values were venous or arterial specimens. A prospective study to verify our findings would overcome these limitations.

Shock should be treated in its earliest state to maximise a patient's survival probability, but it often presents insidiously. The use of ancillary studies, especially serum lactate, can be exceedingly important for recognising and treating these critically ill patients. Our data argue against the notion of using the AG as a screen for LA in an ED population. We recommend directly obtaining a serum lactate immediately upon presentation of potentially critically ill patients. The emerging use of point of care testing products with lactate assays shows special promise, and deserves further study in the ED setting.

Table 4 Receiver operator curve analysis of select laboratory values as a predictor of in-hospital mortality

Laboratory parameter	Area under the curve	95% CI
Lactate	0.895	0.829–0.960
Albumin	0.818	0.698–0.937
HCO_3	0.751	0.625–0.876
Base deficit	0.708	0.564–0.853

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