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# Low sensitivity of anion gap to detect clinically significant lactic acidosis in the emergency department

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ABSTRACT

*Introduction:* Lactic acidosis represents the pathologic accumulation of lactate and hydrogen ions. It is important to efficiently diagnose lactic acidosis as delayed treatment will lead to poor patient outcomes. As plasma lactate levels may not be rapidly available, some physicians may use elevated anion gaps to test for the need to measure lactate. All Edmonton metropolitan hospitals have Radiometer blood gas/electrolyte instruments in the ED or close by. As lactate is measured for each set of electrolytes, we were able to determine the effectiveness of a screening anion gap for lactic acidosis.

*Methods:* Two years of emergency department lactates and electrolytes from Edmonton's 5 metropolitan hospitals were analyzed. We determined the sensitivity, specificity and positive predictive value of detecting an elevated lactate, defined as ≥ 2.5 mmol/L or ≥ 4 mmol/L.

*Results:* Depending on the elevated anion gap cut-off and the definition of elevated lactate, between 40–80% of elevated lactates are missed. In general, the positive predictive value approaches 40% for AGs ≥ 12 mmol/L and 60% for AGs ≥ 16 mmol/L.

*Conclusions:* Anion gap is an inadequate marker of lactic acidosis. We recommend that lactate be done with each set of electrolytes and/or blood gases. In this way lactic acidosis will not be missed.

## 1. Introduction

Lactate is the end product of anaerobic glycolysis from pyruvate. Generally, the blood concentration of lactate does not exceed 2 mmol/L unless its rate of formation exceeds its catabolic rate. Two important diagnostic thresholds are used for classifying lactate elevations, 4.0 mmol/L, and 2.5 mmol/L. Lactic acidosis (LA) is generally defined as a serum lactate concentration above 4 mmol/L. It is well known that persistence of lactate levels exceeding 4 mmol/L is associated with worsening of patient outcomes [1,2]. Newer evidence suggests that ill patients with initial lactate exceeding 2.5 mmol/L should be closely monitored as there is risk of death [3]. Regardless of the threshold, elevated lactates are associated with increased morbidity and mortality, independent of underlying conditions such as infection, organ failure, and shock [4–8]. Hence, prompt recognition is vital to improve patient outcomes.

The causes of lactic acidosis (LA) have been reviewed and Table 1 presents common etiologies [9]. LA can be categorized as either type A or type B. Type A LA is more clinically relevant in the emergency department (ED) as it arises from tissue hypoxia and generally requires rapid, definitive care. Type B LA is associated with non-hypoxemic pathophysiology, such as underlying disease, ingestion of certain drugs and toxins, and inborn errors of metabolism.

LA is best identified with lactic acid quantitation. Some clinicians have suggested using anion gap (AG) as a screen for LA [10,11]. Thus, an AG above a certain cut-off would indicate the need for LA testing. Recent evaluations have shown that AG exceeding 12 mmol/L [12–14] or ≥ 16 mmol/L [15–17] is a poor screen for LA. As these evaluations comprised small numbers of patients, we sought to definitely evaluate the ability of AG to detect LA with electrolyte/lactate data obtained from five Edmonton metropolitan hospital EDs.

## 2. Methods and materials

The five hospitals were University of Alberta Hospital (UAH, 885 beds) offering tertiary-quaternary care, Royal Alexandra Hospital (RAH, 678 beds) offering tertiary care, and three general hospitals including Grey Nuns Community Hospital (GNH, 351 beds), Misericordia Community Hospital (MCH, 259 beds) and Sturgeon Community Hospital (SCH, 167 beds). UAH, RAH and SCH are managed by Alberta Health Services, while GNH and MCH are managed by a non-government religious organization. All Edmonton EDs were equipped with

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**Table 1**
Causes of lactic acidosis.

| Type A: evidence of tissue hypoxia | Type B: no evidence of tissue hypoxia |
|---|---|
| Severe hypoxemia | Subtype B1 - underlying disease |
| Severe anemia | Liver disease |
| Severe muscle activity | Sepsis |
| Carbon monoxide, cyanide, iron poisoning | Diabetes mellitus |
| | Malignancy |
| Hypoperfusion | Pheochromocytoma |
| Shock (hypovolemic, obstructive, septic, cardiogenic) | Thiamine deficiency |
| | Conditions associated with hypoglycemia |
| | Subtype B2 - drugs and toxins |
| | Ingestion of: biguanides, acetaminophen, ethanol, methanol, epinephrine (and other adrenergic agonists), nitroprusside, propofol, salicylates, isoniazid and linezolid |
| | Subtype B3 - inborn errors of metabolism |
| | Glucose-6-phosphatase deficiency |
| | Fructose-1,6-diphosphatase deficiency |
| | Pyruvate carboxylase deficiency |
| | Oxidative phosphorylate defects |

**Table 2**
Summary of lactate/electrolyte testing over two years.

| Hospital | Unique patients with electrolyte and lactate testing | Patients with lactate ≥ 2.5 mmol/L (percentage of patients with testing) | Patients with lactate ≥ 4 mmol/L (percentage of patients with testing) |
|---|---|---|---|
| UAH | 25,347 | 5583 (22.0%) | 1933 (7.6%) |
| RAH | 15,062 | 4013 (26.6%) | 1571 (10.4%) |
| Tertiary care hospitals | 40,409 | 9596 (23.7%) | 3504 (8.7%) |
| SCH | 2682 | 596 (22.2%) | 306 (11.4%) |
| MCH | 1091 | 351 (32.2%) | 197 (18.0%) |
| GNH | 837 | 338 (40.4%) | 199 (23.8%) |
| General hospitals | 4610 | 1285 (27.8%) | 702 (15.2%) |

Radiometer ABL800 FLEX analyzers (Radiometer, Copenhagen, Denmark) which are programmed to measure both lactate and electrolytes. A central data repository was used to download 2 years of lactate and electrolyte results. To preserve patient confidentiality, patient identifiers were anonymized. We were unable to access any other patient information such as age, gender, history, or additional laboratory data including albumin.

We used the initial ED lactate value of each patient to classify whether the patient had elevated lactates. To ascertain the clinical utility of AG for different patient subgroups, we used two definitions of LA (≥ 2.5 mmol/L or ≥ 4 mmol/L).

AG was calculated from the formula:

$$AG = [Na+]-[Cl-]-[HCO_3-].$$

We calculated the diagnostic sensitivity and specificity of the initial patient AG to detect elevated lactates (≥ 2.5 mmol/L or ≥ 4 mmol/L). We also generated corresponding receiver operating characteristic (ROC) curves. The positive predictive values (PPV) were calculated for AGs exceeding 5, 6, 7… up to 35 mmol/L. The laboratory reference interval for AG is 4–16 mmol/L for both the Radiometer blood gas system and our Beckman central laboratory analyzers.

## 3. Results

Table 2 summarizes the numbers and proportions of patients with elevated lactate testing. The yearly incidence of LA is around 550/100,000 (≥ 2.5 mmol) and 200/100,000 (≥ 4.0 mmol) for the Edmonton population.

Table 3 shows the average number of electrolytes ordered on each patient per ED stay depending on the patient's initial lactate value. Not surprisingly, initial lactates of ≥ 2.5 mmol/L or ≥ 4.0 mmol/L led to more follow up testing compared to patients presenting with normal lactates.

Figs. 1–3 show the LA frequency histograms and PPV for UAH, RAH, and the general hospitals respectively. PPV increases as the AG increases. Using an AG cutoff of 12 mmol/L, UAH, RAH, and general hospitals would miss 37.5%, 39.5%, and 48.1% of elevated lactates ≥ 4 mmol/L, and 61.6%, 63.3% and 62.4% of elevated lactates ≥ 2.5 mmol/L respectively. Using an AG cutoff of 16 mmol/L, UAH, RAH, and general hospitals would miss 72.2%, 75.0%, and 70.8% of elevated lactates ≥ 4 mmol/L and 86.9%, 87.8%, and 82.5% of elevated lactates ≥ 2.5 mmol/L respectively. In general, the PPV approaches 40% for AGs ≥ 12 mmol/L and approaches 60% for AGs ≥ 16 mmol/L.

Fig. 4 shows the ROC curves for the three hospital categories. To achieve a diagnostic sensitivity of > 90% (specificity 30%), then all patients with AGs exceeding 7 mmol/L would need a lactate. However, an AG of 7 is within normal range and would be unsuitable as a screen. At an AG of 11 mmol/L, the sum of sensitivity and specificity is maximized at 61% sensitivity and 86% specificity. It is only when an AG is > 16 mmol/L that specificity reaches approaches 95%, but with a low sensitivity of 30%.

## 4. Discussion

All ED patients with LA need expedited management. For a test to be an adequate screen for elevated lactate, it must be highly sensitive. When ED physicians use an elevated AG of 12 mmol/L or 16 mmol/L, 40–70% of the patients with a lactate ≥ 4.0 mmol/L will remain undiagnosed. Lactates between 2.5 and 4.0 mmol/L are even less likely to be associated with an elevated AG. Kraut postulates that the inability for AG to identify most patients with elevated lactates is partly due to AG having a wide range of normal values [18]. Complicating the use of AG is the wide variation in electrolyte analysis. A 7 year study of 8 common analyzers showed that the mean AG values of presumably healthy subjects ranged from 5.9 to 12.4 mmol/L [19]. Therefore, a recommendation on the optimal anion gap based on one analyzer may not apply to another.

Our data demonstrates that the PPV of AGs ≥ 12 mmol/L for elevated lactate ≥ 4.0 mmol/L was low at 50%. This is not surprising as there are many other causes of increased AGs including ketoacidosis, severe volume depletion, severe alkalosis, laboratory error, severe

**Table 3**
Summary of average number of electrolytes done per patient visit to the ED depending on the patient's initial lactate value.

| | Average number of electrolytes (standard deviation) done | | | |
|---|---|---|---|---|
| | Lactate < 2.5 mmol/L | Lactate < 4 mmol/L | Lactate ≥ 2.5 mmol/L | Lactate ≥ 4 mmol/L |
| UAH | 1.52 (1.57) | 1.60 (1.73) | 2.02 (2.25) | 2.43 (2.62) |
| RAH | 1.60 (1.68) | 1.73 (1.92) | 2.19 (2.29) | 2.55 (2.65) |
| General hospitals | 1.39 (1.74) | 1.44 (1.78) | 1.71 (2.21) | 1.76 (2.12) |