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Educational Discussion: Anion Gap

2018-B Chemistry (C)

PSR Supplemental Questions – C-A 2018

1. Do you report anion gap with results?

6243 Total Responses: All Responses Breakdown

1. Do you report anion gap with results?

YES	**Total** (3342)	**K use** (1227)	**ALB cf**	**ALB & K**	**QC**	**K & QC**	**ALB & QC**	**ALB, QC, & K**
With reference interval	3070	1023	26	26	112	40	0	0
"Outliers" *	29	10	2	0	0	0	0	0
Without reference interval	243	85	3	2	8	2	1	0

Anion gap reported with results, with some respondents possibly not using a reference interval (no low or high values given in Survey).

NO	**Total** (1766)	**K use**	**ALB cf**	**ALB & K**	**QC**	**K & QC**	**ALB & QC**	**ALB, QC, & K**
With reference interval	103	39	1	-	6	-	-	-
Without reference interval	1663	20	-	-	6	-	-	-

Respondents reported "NO" but did report low and/or high ranges.

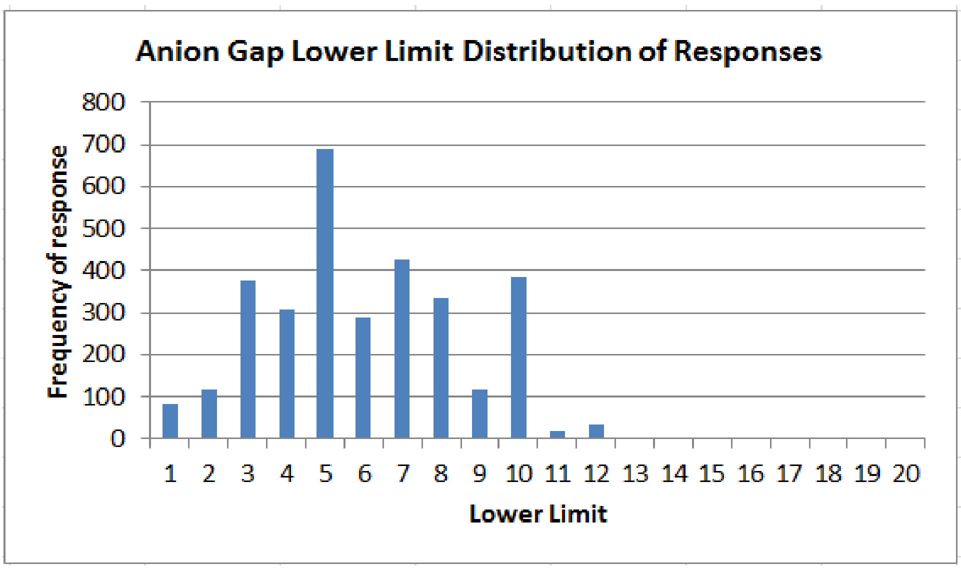
NULL	**Total** (1135)	**K use**	**ALB cf**	**ALB & K**	**QC**	**K & QC**	**ALB & QC**	**ALB, QC, & K**
With reference interval	111	48	0	0	9	-	0	0
Without reference interval	1024	2	0	0	0	-	0	0

Respondents did not report "yes" or "no" but some did report low and/or high ranges.

K = Potassium; ALB = Albumin; CF = Correction Factor

*Outliers were defined as those respondents that listed a reference interval consisting of either ‘bizarre’ results for upper and lower ranges (eg, 8.3–10.1, -20–75, 15–200 etal) or < 2 as the total gap (n=21.)

2. What is your laboratory’s lower limit of the reference interval for anion gap?			
Lower Limit	**No. Responses**	**Lower Limit**	**No. Responses**
1	84	11	17
2	117	12	35
3	376	13	0
4	310	14	5
5	691	15	2
6	291	16	1
7	425	17	0
8	335	18	0
9	118	19	1
10	383	20	2
		Other	325



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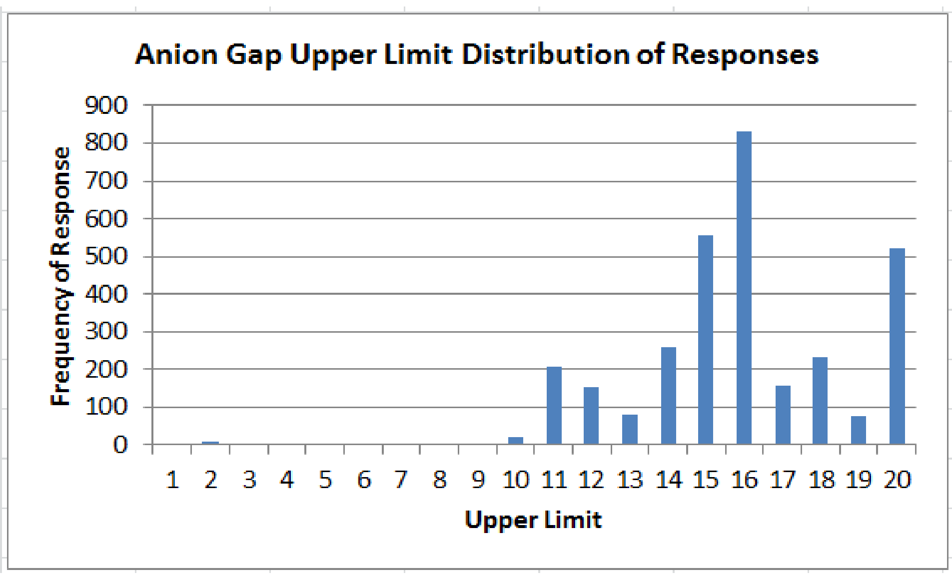
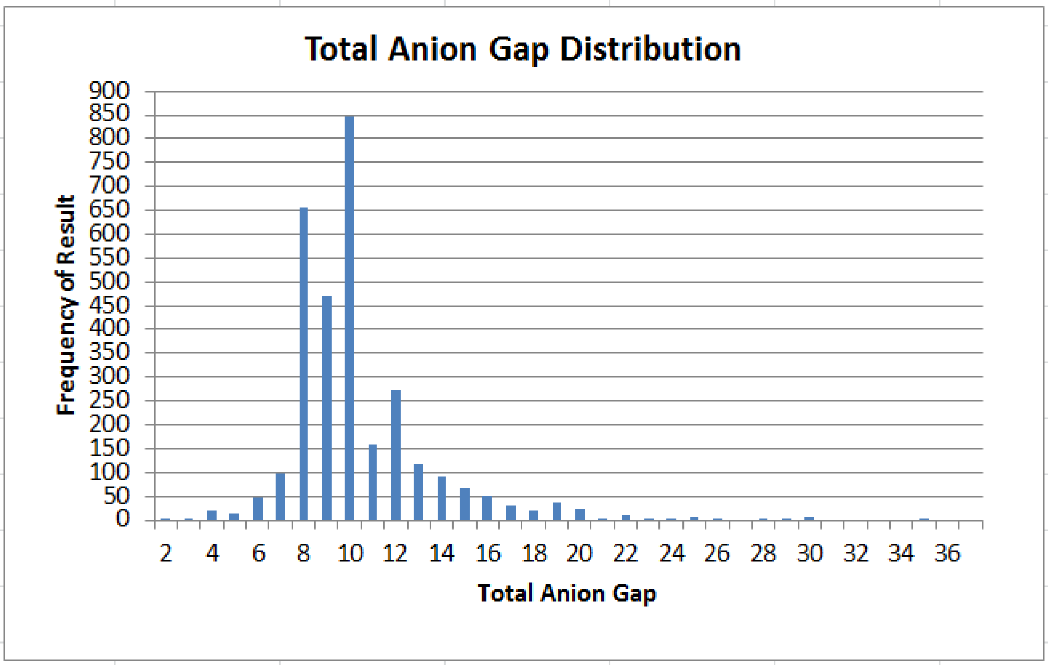
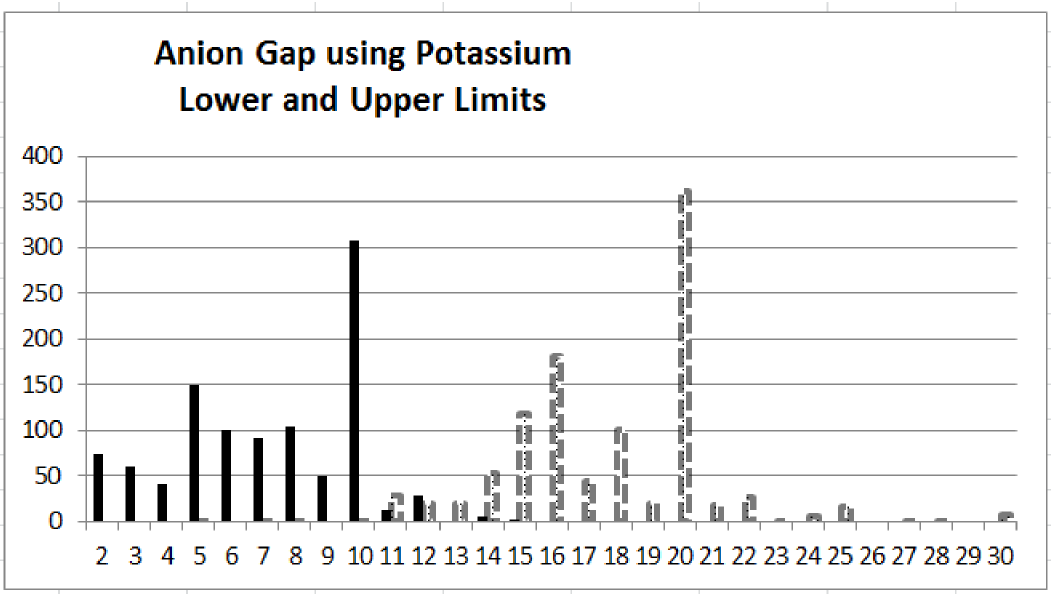
3. What is your laboratory's upper limit of the reference interval for anion gap?			
Lower Limit	**No. Responses**	**Lower Limit**	**No. Responses**
1	0	11	209
2	6	12	154
3	1	13	79
4	0	14	260
5	3	15	555
6	0	16	831
7	1	17	155
8	3	18	234
9	5	19	76
10	19	20	521
		Other	396



Total anion gap was determined by subtracting upper from lower reported limits. In addition, if only one value was reported as "<", that value was used. Total anion gap results less than 2 were excluded from this distribution.





4. Do you use potassium in the calculation of anion gap? (all responses)	No. Responses
Yes	1227
No	2796
Null	2220

5. Do you report an albumin corrected anion gap? (all responses)			No. Responses
Yes			32
No			4044
Null			2167

6. Does your laboratory utilize the anion gap as part of your quality control (QC) procedure? (all responses)			No. Responses
Yes			141
No			4019
Null			2083

The anion gap (AG) is considered to be a measure of unmeasured anions such that when elevated there is an increased probability of an underlying primary metabolic acidosis due to those self-same "unmeasured anions" (UMA). Typical UMA include, but are not limited to, phosphate, sulfate, albumin and organic acids (eg, ketones and lactic acid.) When the AG is elevated, it suggests to the ordering clinician that the patient has an underlying metabolic acidosis to be investigated for a possible etiology. The AG is not an actual physiologic/pathophysiologic parameter as all living things are electrically neutral with the total anionic concentration always equal to the total cationic concentration. As UMA increase, measured anions will decrease as a buffering function and maintain electroneutrality. Importantly, AG elevations are more likely due to increases in UMA than depressions in cationic substances.

The AG arose from a measurement artifact associated with the fact that certain electrolyte assays were developed far later then other electrolyte assays; hence, its alternative term “unmeasured anions”. Two anion assays that arrived late on the scene included ketones and lactic acid. In fact, the term “anion gap” appeared in the initial descriptions of lactic acidosis when it was apparent that certain patients were acidotic due to an unknown etiology illustrated by an “…increase in the unmeasured anions…” with the unknown anion identified as lactic acid. Since then, use of the “anion gap” has become embedded in clinical medicine as an easy tool to determine if an individual has a metabolic acidosis due to an increased UMA (High Anion Gap Metabolic Acidosis, HAGMA) distinguished from other causes of metabolic acidosis (Normal Anion Gap Metabolic Acidosis, NAGMA.)

The anion gap is calculated by subtracting sodium from the sum of chloride and bicarbonate (or total carbon dioxide): **[Na – (Cl + (HCO3 or TCO2)].** For unclear reasons, potassium was not traditionally included in the calculation but some sources support its use: **[(Na + K) – (Cl + (HCO3 or TCO2)]**. Albumin, by itself, represents a large fraction of unmeasured anions such that extremes of albumin can either elevate (hyper) or decrease (hypo) the calculated value. Consequently, hypoalbuminemia can lower the anion gap and mask a true increase of a toxic unmeasured anion. To address this issue, an albumin correction has been proposed consisting of a 2.5 mEq/L increase in anion gap for every 1.0 g/dL drop in albumin from 4.5 g/dL.

As the AG is a calculated value based on an artificial measurement subject to variations in methodology, calibration and use, or not of, potassium and/or albumin; there is no set standard as to what constitutes a normal AG reference interval. Technically, there can be no such thing as a normal AG reference interval because the gap, itself, is an artificial construct. The purpose of these supplemental questions was to determine if there is consistency in AG reference intervals and thus explore the possibility of adding the AG calculation to future proficiency testing Surveys.

Approximately two thirds (62%) who reported “yes” or “no” to the initial question, “Do you report anion gap with results?”, nonetheless included reference interval values. This can be interpreted in many ways that were not covered in the supplemental questions and might warrant additional follow-up. Possible reasons include incorrect answering of the question or use of reference interval values for internal use.

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The AG is a widely used simple calculation that can add value to laboratory reporting and this author expected, with the ubiquity of EMR/middleware software, AG reporting to have approached 100%. Hypothetically, those laboratories that do not report the AG, might be doing so for the following reasons:

- Historically have never reported AG.
- So common that it was unnecessary to report.
- Reporting the AG would have required determination of an associated reference interval, which itself is highly variable.
  - Most of the laboratories that did report an AG also did report a reference interval; however, that might have been a regulatory bias (ie, required in CLIA/CAP for all results to have associated reference intervals.)

The traditional anion gap reference interval had been set at 8–16 mEq/L with discussion over time stating the lower limit as low as 3 and the higher limit as high as 18/20 depending on instrumentation, calibration and potassium inclusion, or not. As you can see from questions 2 and 3, many of the respondents fell very close to the reported anion gap ranges with majority of reporting laboratories using approximately 5 mEq/L as the lower limit and 15/16 mEq/L as the upper limit.

Recent discussions do not utilize an interval but rather an expected total gap of 12 ±4 mEq/L instead. Using the reported ranges from the Survey, a distribution of total gap results was generated with the majority (89%) fitting into the 8–16 mEq/L range. Of note, the majority of respondents that used potassium in their anion gap calculations, unsurprisingly, reported a range slightly higher, 10–20 mEq/L. Approximately 30% of reporting laboratories indicated that they used potassium as part of the calculation and an even smaller percentage (3%) noted using an albumin correction factor. Lastly, very few laboratories used anion gap as part of their QC program.

References

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5. Kraut JA, Xing SX. Approach to the evaluation of a patient with an increased serum osmolal gap and high-anion-gap metabolic acidosis. *Am J Kidney Dis*. 2011;58(3):480-4.

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