additional indices in analysis of metabolic acidosis [created by Paul Young 13/12/07]

Osmolar Gap

general
- An osmole is the amount of a substance that yields, in ideal solution, that number of particles (Avogadro's number) that would depress the freezing point of the solvent by 1.86K
- Osmolality is measured in the laboratory by machines called osmometers. The units of osmolality are mOsm/kg of solute
- Osmolarity is calculated from a formula which represents the solutes which under ordinary circumstances contribute nearly all of the osmolality of the sample. There are many such formulae which have been used. One is:
Calculated osmolarity = (2 x [Na+]) + [glucose] + [urea]
- The osmolar gap is the difference between the 2 values: the (measured) osmolality and the (calculated) osmolarity (which is calculated):-
Osmolar gap = Osmolality - Osmolarity
- An osmolar gap > 10 mOsm/l is often stated to be abnormal.

Importance of the type of osmometer
- Only osmometers using freezing point depression method should be used for determining this calculation because they are the only type of osmometer that can detect all the volatile alcohols which can abnormally increase the osmolar gap. Vapour pressure osmometers can't do this

Significance of an elevated osmolar gap
- An elevated osmolar gap provides indirect evidence for the presence of an abnormal solute which is present in significant amounts. To have much effect on the osmolar gap, the substance needs to have a low molecular weight and be uncharged so it can be present in a form and in a concentration (measured in mmol/l) sufficient to elevate the osmolar gap.
- Ethanol, methanol & ethylene glycol are three such solutes that, when present in appreciable amounts, will cause an elevated osmolar gap. If you suspect that your patient may have ingested one of these substances than you should determine the osmolar gap.
- if the ethanol levels are measured they can be added to the calculated osmolarity to exclude the presence of an additional contributer to the osmolar gap. [NB: To convert ethanol levels in mg/dl to mmol/l divide by 4.6. For example, an ethanol level of 0.05% is 50mg/dl. Divide by 4.6 gives 10.9mmols/l]

anion gap

General:
- The term anion gap (AG) represents the concentration of all the unmeasured anions in the plasma. The negatively charged proteins account for about 10% of plasma anions and make up the majority of the unmeasured anion represented by the anion gap under normal circumstances.
- the AG = [Na+] + [K+] - [Cl-] - [HCO3-] and a the upper range of normal is about 15

Major Clinical Uses of the Anion Gap
(i) To signal the presence of a metabolic acidosis and confirm other findings
- If the AG is greater than 30 mmol/l, than it invariably means that a metabolic acidosis is present. If the AG is in the range 20 to 29 mmol/l, than about one third of these patients will not have a metabolic acidosis.
(ii) Help differentiate between causes of a metabolic acidosis:
-high anion gap versus normal anion gap metabolic acidosis.

The effect of albumin & phosphate
- Albumin is the major unmeasured anion and contributes almost the whole of the value of the anion gap.
- Every one gram decrease in albumin will decrease anion gap by 2.5 to 3 mmoles. A normally high anion gap acidosis in a patient with hypoalbuminaemia may appear as a normal anion gap acidosis.
- This is particularly relevant in Intensive Care patients where lower albumin levels are common.
- the 'normal anion gap depends on the serum phosphate and the serum albumin.
anion gap = 0.2 x [albumin] (g/L) + 1.5 x [phosphate] (mmol/L)

metabolic acidosis with normal anion gap:	metabolic acidosis with increased anion gap:
Ureteroenterostomy (K+ decreased)	Methanol, metformin
Small bowel fistula (K+ decreased)	Uraemia
Extra chloride (K+ increased)	DKA
Diarrhoea (K+ decreased)	Phenformin, paraldehyde, propylene glycol, pyroglutamic acidosis
Carbonic anhydrase (K+ decreased)	Iron, isoniazid
Renal tubular acidosis (K+ decreased - type 1)	Lactic acidosis
Addison's disease (K+ increased)	Ethanol ketoacidosis, ethylene glycol
Pancreatic fistula (K+ decreased)	Salicylates, starvation ketoacidosis, solvent

delta ratio

Definition
- The Delta Ratio is sometimes useful in the assessment of metabolic acidosis.
- The Delta Ratio is defined as:
Delta ratio = (Increase in Anion Gap / Decrease in bicarbonate)

Use
- In order to understand this, consider the following:
- If one molecule of metabolic acid (HA) is added to the ECF and dissociates, the one H+ released will react with one molecule of HCO3- to produce CO2 and H2O. This is the process of buffering. The net effect will be an increase in unmeasured anions by the one acid anion A- (ie anion gap increases by one) and a decrease in the bicarbonate by one.
- if all the acid dissociated in the ECF and all the buffering was by bicarbonate, then the increase in the AG should be equal to the decrease in bicarbonate so the ratio between these two changes (which we call the delta ratio) should be equal to one. The delta ratio quantifies the relationship between the changes in these two quantities.
- the above assumptions about all buffering occurring in the ECF and being totally by bicarbonate are not correct. Fifty to sixty percent of the buffering for a metabolic acidosis occurs intracellularly. This amount of H+ from the metabolic acid (HA) does not react with extracellular HCO3- so the extracellular [HCO3-] will not fall as far as originally predicted. The acid anion (ie A-) however is charged and tends to stay extracellularly so the increase in the anion gap in the plasma will tend to be as much as predicted.
- Overall, this significant intracellular buffering with extracellular retention of the unmeasured acid anion will cause the value of the delta ratio to be greater than one in a high AG metabolic acidosis.

Sources of error:
- Inaccuracies can occur for several reasons, for example:
(i) Calculation requires measurement of 4 electrolytes, each with a measurement error
(ii) Changes are assessed against 'standard' normal values for both anion gap and bicarbonate concentration.

Assessment
< 0.4
- Hyperchloraemic normal anion gap acidosis
- A low ratio occurs with hyperchloraemic normal anion gap acidosis. The reason here is that the acid involved is effectively hydrochloric acid (HCl) and the rise in plasma [chloride] is accounted for in the calculation of anion gap (ie chloride is a 'measured anion').
- The result is that the 'rise in anion gap' (the numerator in the delta ration calculation) does not occur but the 'decrease in bicarbonate' (the denominator) does rise in numerical value.
- The net of of both these changes then is to cause a marked drop in delta ratio, commonly to < 0.4
0.4 - 0.8
- Consider combined high AG & normal AG acidosis BUT note that the ratio is often <1 in acidosis associated with renal failure
1 to 2
- Usual for uncomplicated high-AG acidosis.
- Lactic acidosis: average value 1.6
- DKA more likely to have a ratio closer to 1 due to urine ketone loss (esp if patient not dehydrated)
> 2
- A high delta ratio can occur in the situation where the patient had quite an elevated bicarbonate value at the onset of the metabolic acidosis. Such an elevated level could be due to a pre-existing metabolic alkalosis, or to compensation for a pre-existing respiratory acidosis (ie compensated chronic respiratory acidosis).

urinary anion gap

General
- The cations normally present in urine are Na+, K+, NH4+, Ca++ and Mg++.
- The anions normally present are Cl-, HCO3-, sulphate, phosphate and some organic anions.
- Only Na+, K+ and Cl- are commonly measured in urine so the other charged species are the unmeasured anions (UA) and cations (UC).
Urinary Anion Gap = [Na+]+ [K+] - [Cl-]

Clinical Use
- The urinary anion gap can help to differentiate between GIT and renal causes of a hyperchloraemic metabolic acidosis.
- It has been found experimentally that the Urinary Anion Gap (UAG) provides a rough index of urinary ammonium excretion. Ammonium is positively charged so a rise in its urinary concentration (ie increased unmeasured cations) will cause a fall in UAG

Pathophysiology
- Hyperchloraemic acidosis can be caused by:
(i) Loss of base via the kidney (eg renal tubular acidosis)
(ii) Loss of base via the bowel (eg diarrhoea).
(iii) Gain of mineral acid (eg HCl infusion).
- If the acidosis is due to loss of base via the bowel then the kidneys can respond appropriately by increasing ammonium excretion to cause a net loss of H+ from the body. The UAG would tend to be decreased, That is: increased NH4+ (with presumably increased Cl-) => increased UC =>decreased UAG.
- If the acidosis is due to loss of base via the kidney, then as the problem is with the kidney it is not able to increase ammonium excretion and the UAG will not be increased.
- Experimentally, it has been found that patients with diarrhoea severe enough to cause hyperchloraemic acidosis have a negative UAG (average value -27 +/- 10 mmol/l) and patients with acidosis due to altered urinary acidification had a positive UAG.