Acid Base Disorders in Critical Care - Part 2

Dr Alex Grice

Consultant Anaesthetist, Royal Devon and Exeter, UK

alex.grice@doctors.org.uk

WORLD FEDERATION OF SOCIETIES OF ANAESTHESIOLOGISTS
ANAESTHESIA
TUTORIAL OF THE WEEK
www.wfsahq.org

Clinical Scenarios

Case 4]

A man was brought in to the emergency room heavily intoxicated. He was known to be alcohol dependant and attended regularly. Blood analysis confirmed normal biochemistry apart from a borderline low glucose (3.8 mmol/l) and arterial gas analysis showed pH 7.43, pCO_2 4.8 pO_2 15.7 HCO_3^- 20. He was placed into an observation bed overnight with a diagnosis of alcohol intoxication but later became tachypnoeic and hypotensive. Repeat gas analysis showed pH 7.0, pCO_2 4.2, pO_2 24, and HCO_3^- 9.

What is the cause of his deterioration?

What other information would be useful?

Case 5]

The same man represents a month later heavily intoxicated. Blood analysis confirmed normal biochemistry and arterial gas analysis showed pH 7.43, pCO_2 4.8, pO_2 15.7, and HCO_3^- 20. Toxicology was requested and minimal ethanol was measured and no methanol found. Urinalysis revealed ketones but no blood or protein. He became more deeply unconscious and on intubation his arterial gases showed pH 7.1, pCO_2 9.5, pO2 21, HCO_3^- 27. Serum osmolarity was measured at 336 (calculated 284).

What is the cause of his deterioration?

Case 6]

A drowsy diabetic patient presented to the medical team with a blood glucose of 52 mmol and ketones in the urine. He was known to have hypertension, treated with an ACE inhibitor and bendroflumethazide. The medical SHO was surprised and reassured by the arterial gas analysis which showed pH 7.34, pCO_2 4.7, pO_2 22.4, HCO_3^-20, Na^+ 140, K 4.2 and Cl^- 86

Why are these results not reassuring?

How do you interpret the gas analysis?

Causes of Metabolic Acidosis

Lactic Acidosis

Lactic acid is a weak acid with a pKa of 4.4. The pKa of a compound is the pH at which it is 50% dissociated and so at physiological pH it is almost fully dissociated. It is generated from pyruvate as follows:

$$\text{Pyruvate} + \text{NADH} + H^+ \Longleftrightarrow \text{Lactate} + NAD^+$$

Lactate is normally present in the blood in low levels (1-2 mmol/l) because some tissues (such as skin) produce more pyruvate than their mitochondria can handle. Excess pyruvate is converted to lactate, released into the blood and metabolised by the liver (60%, Cori cycle) or kidney (40%).

A rise in the lactate level in the blood suggests increased lactate production or decreased lactate metabolism. As the liver's capacity to metabolise lactate is large, a rise in blood lactate levels does suggest that a degree of impaired liver lactate handling is present; however, increased lactate production is still the primary feature of lactic acidosis amenable to treatment. Lactic acidosis is categorised according to the perceived state of oxygen delivery.

If oxygen delivery is inadequate (type A) then aerobic metabolism is impaired, pyruvate accumulates and lactate is produced. We know oxygen delivery is a product of cardiac output and blood oxygen content, but in lactic acidosis low cardiac output is invariably the most important consideration. Oxygen content is rarely low enough to create a lactic acidosis in isolation – the haemoglobin would need to be less than 5 g/dl or the pO2 less than 4 kPa.

Treatment aims concentrate on restoring and ensuring correct distribution of cardiac output and, to a lesser extent, ensuring adequate blood oxygen content (this is one situation where the low transfusion threshold of 7g/dl for the critically ill should not apply). You may find it useful to refer back to the ATOTWs on sepsis at this point for further details on resuscitation in the setting of inadequate oxygen delivery.

Type B lactic acidosis occurs when oxygen delivery is normal and a problem in carbohydrate metabolism is present. Multiple causes of type B acidosis exist and it is beyond the scope of this tutorial to cover all causes, however they can be subdivided. B1 lactic acidosis can be a feature of underlying disease (ketoacidosis, haematological malignancy) and has also been called 'stress lactate'. Lactic acidosis associated with a drug or toxin effect is categorised as B2 (phenformin, β agonists such a salbutamol) and lactic acidosis due to an inborn error of metabolism is categorised as B3.

Treatment in this situation depends on determining the cause from the history and clinical signs and addressing the root cause, rather than attempting to correct the acidosis directly.

Ketoacidosis

Ketone bodies include β-hydroxybutyrate, acetoacetate and acetone. When lipids are metabolised by β oxidation, acetyl coenzymeA is produced. This normally binds to oxaloacetate (OAA) to enter the citric acid cycle. However if inadequate levels of OAA are present, then acetyl coA is converted into acetoacetate. If adequate levels of NAD^+ are present then acetoacetate is subsequently converted into β hydoxybutyrate.

The main causes of ketoacidosis include

- Starvation ketoacidosis
- Alcoholic ketoacidosis
- Diabetic ketoacidosis

1. Starvation ketoacidosis

This occurs when glycogen levels in the liver have become exhausted and the liver attempts to make more glucose via the gluconeogenesis pathway. Gluconeogenesis requires OAA and the subsequent drop in OAA levels limit the ability of the citric acid cycle to utilise acetyl coA provided by lipid metabolism. The excess acetyl coA is converted into ketone bodies and ketoacidosis develops. The acidosis tends to be mild, within buffering capacity and the anion gap rise is small. The situation is resolved by supplying glucose in a controlled fashion and allowing the liver to revert back to the usual metabolic pathways.

2. Alcoholic Ketoacidosis

This condition develops when ethanol is taken with an inadequate amount of calories. The starvation response is now complicated by the liver's effort to metabolise ethanol. The conversion of ethanol into acetaldehyde requires NAD^+ and the excess NADH generated inhibits gluconeogenesis. This exacerbates the glucose deficiency and the corresponding drop in insulin levels stimulates lipid metabolism and ketoacidosis.

The anion gap in this instance will be raised and the acidosis more severe (pH approaches 7.0). Analysis of the acid-base balance can be complicated by an appropriate compensatory respiratory alkalosis and a metabolic alkalosis if the patient has been vomiting. If significant dehydration is present these patients can also get a lactic acidosis amplified by the relative excess of NADH.

Treatment involves restoration of adequate circulating volume and the administration of both insulin and glucose. With prompt treatment the acidosis should resolve rapidly.

3. Diabetic Ketoacidosis

Diabetic ketoacidosis develops when inadequate amounts of insulin are available. The insulin deficit reduces available intracellular glucose and increases fat breakdown and free fatty acid levels. The liver responds by increasing lipid metabolism (further encouraged by increased levels of stress hormone) and, as gluconeogenesis depletes available oxaloacetate, the acetyl CoA generated is converted into ketone bodies. Acetoacetic acid and β-hydroxybutyric acid dissociate and the H^+ ion released is buffered by bicarbonate. An increased anion gap acidosis develops and the calculated delta ratio should approach one.

This acid/base picture may be complicated by various factors. Patients are often severely dehydrated and this can cause a lactic acidosis due to inadequate tissue perfusion. Ketoacidosis causes vomiting and the resulting loss of acid can cause the calculated anion gap to under-represent the severity of the acidosis. As well as this, initial resuscitation with chloride rich solutions (0.9% saline) will increase chloride levels and further decrease the anion gap (the delta ratio here, however, would be lower than expected; around 0.4 to 0.8)

Renal Acidosis

The kidney's ability to regulate acid/base balance can be adversely influenced in numerous ways. It is useful to categorise these conditions according to their effect on glomerular filtration.

- **Acidosis associated with decreased glomerular filtration**

The most common forms of renal acidosis seen in intensive care are associated with a profound drop in glomerular filtration. Acute renal failure (commonly due to acute tubular necrosis) and an acute exacerbation of chronic renal impairment both cause a metabolic acidosis because the kidney is unable to excrete fixed acids. (Fixed acids include hydrochloric acid from arginine, lysine and histidine metabolism, sulphuric

acid from methionine and cystine metabolism, phosphoric acid, ketoacids and lactic acid.)

The acidosis is exacerbated by the associated tubule damage. This damage prevents bicarbonate production from CO_2 and ammonia excretion and buffering capacity is reduced as a result. Bicarbonate levels drop and chloride tends to remain stable and as a result the anion gap rises. Treatment involves correction of the precipitating factors and supporting renal function (with dialysis if required).

- **Acidosis associated with preserved glomerular filtration**

Renal tubular acidosis is less common in intensive care and tends to be associated with either inherited disorders or known pre-existing renal disease. Whilst GFR may be depressed the acidosis is disproportionate to this minor reduction and tends to exhibit a normal anion gap.

Renal tubular acidosis (RTA) is subdivided according the site of the tubular defect

- Type 1 : distal tubular defect
- Type 2 : proximal tubular defect
- Type 4 : distal tubular resistance to aldosterone (or aldosterone deficiency)

Type 1 RTA is the most common form and is caused by the distal convoluted tubule failing to excrete hydrogen ions when attempting to reabsorb sodium. A metabolic acidosis develops as a consequence and the urine fails to acidify. Potassium excretion is unaffected and potassium loss in the urine may be increased as a result. This type of RTA has numerous causes including drug induced damage (amphoteracin) autoimmune disorders (SLE) and nephrocalcinosis. It is diagnosed by confirming a high urine pH (greater than 5.5) in the presence of a severe metabolic acidosis. The underlying disorder should be addressed and the episodes of acidosis prevented by giving adequate dietary bicarbonate.

Type 2 RTA is much less common and is caused by a defect in the proximal convoluted tubule that prevents bicarbonate reabsorption. It can be inherited or

associate with Fanconi syndrome (generalised defect of tubular amino acid reabsorption.) Urinary bicarbonate loss is increased and the urine pH is raised. However, as the proportion of bicarbonate filtered by the kidney is proportional to the plasma bicarbonate concentration, the acidosis is less severe than with type 1 RTA. The condition tends to self-limit and the bicarbonate tends not to drop below 15 mmol/l. Potassium loss is less marked than with distal RTA but can be a problem if bicarbonate supplements are given to correct the acidosis. Any supplements need to include both bicarbonate and potassium.

Type 4 RTA is also rare and tends to occur while aldosterone is deficient or the distal tubule becomes resistant (papillary necrosis). Both acid and potassium secretion are reduced and the urine remains relatively alkali whilst a metabolic acidosis develops in the presence of raised potassium. If severe this condition can be treated with oral fludrocortisone (0.1 mg/day).

Other causes of normal anion gap acidosis

Normal anion gap acidosis occurs due to primary bicarbonate loss and this can occur through the kidney or the gut.

Renal loss occurs with renal tubular acidosis as discussed above but can also occur as a drug effect (acetalozamide) or when the ureters are diverted to the bowel (ureterosigmoidostomy). The latter causes a problematic acidosis that responds poorly to dietary supplements and can be difficult to treat.

Gut losses occur with severe diarrhoea or via NG aspirates in patients with small bowel obstruction. Pancreatic fistula, biliary drains and some bowel tumours also lose bicarbonate and cause a hyperchloraemic normal anion gap acidosis.

Metabolic Acidosis due to Exogenous Acids

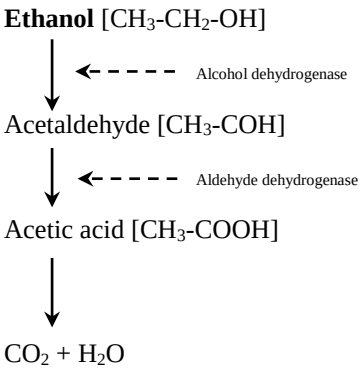
Alcohol Poisoning

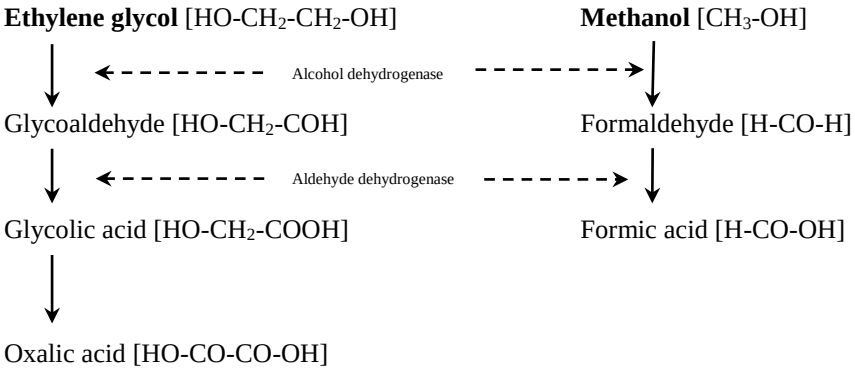
Ethanol, methanol, ethylene glycol and isopropanol represent the main alcohols encountered in poisoning. Ethanol is by far the most common cause of alcohol poisoning and was discussed in relation to alcoholic ketoacidosis earlier in the

tutorial. Specialist laboratories are able to measure plasma alcohols but this is often not immediately available, therefore the diagnosis of alcohol poisoning can be helped by estimation of the osmolar gap as covered earlier. In order to understand the patterns seen in alcohol poisoning it is necessary to discuss how the various alcohols are metabolised.

Metabolism of alcohol (methanol, ethanol & ethylene glycol)

Ethanol, methanol and ethylene glycol are metabolised by the same enzyme systems but produce different metabolites.





With **methanol** and **ethylene glycol** poisoning only the parent compounds and the first metabolites (formaldehyde and glycoaldehyde respectively) are osmotically active. The subsequent metabolites are weak acids that dissociate into electrically charged ions that become balanced by sodium. When balanced they cease to exert an osmotic influence and this accounts for the progression seen in alcohol poisoning. In the initial stages, metabolism generates an osmolar gap with minimal acidosis. Metabolism continues with the production of formic and glycolic acid respectively.

These metabolites account for the metabolic acidosis seen in alcohol poisoning and as they are produced the osmolar gap decreases. The enzyme responsible, alcohol dehydrogenase, metabolises both poisons at a lower rate than **ethanol** and this may result in toxicity being delayed for up to 30 hours for methanol and twelve hours for ethylene glycol. Several authors have criticised the use of the osmolar gap for precisely this reason. When blood is taken for these tests it is impossible to determine which alcohol has been taken and how far the metabolism of the alcohol has progressed. If the osmolar gap is normal then either the alcohol metabolism is advanced or the patient has not ingested a large quantity. However, patients present to hospital with the onset of symptoms and this normally coincides with intermediate alcohol metabolism and a raised osmolar gap.

Methanol poisoning

Methanol is a potent poison and serious toxicity is seen after an intake of 10 ml. Methylated spirits contains 5% methanol and ingestion of over 200 ml is required before serious toxicity is encountered. This toxicity presents after a latent period of twelve hours or more. Patients report headache, breathlessness and visual symptoms ranging from blurring to complete blindness. Severe abdominal pain and nausea are common and patients may present with a rigid abdomen. The cardiovascular system is initially stable until a severe acidosis develops then marked myocardial depression and bradycardia is encountered. [9] Treatment is directed at reducing the rate of organic acid production with intravenous ethanol and haemodialysis. Ethanol treatment consists of a 50g oral loading dose (125ml of spirits will suffice) followed by an intravenous infusion of 10-12 g/hr. Treatment should aim to achieve a plasma concentration of 1-2 g/l. The indications for dialysis are not well defined but should be considered in the presence of a severe metabolic acidosis, marked visual or mental symptoms or in the presence of a high methanol plasma concentration (over 500 mg/l). Folinic acid can also be given intravenously to help prevent ocular toxicity (30mg IV qds). [10]

Ethylene glycol poisoning

Ethylene glycol is less potent than methanol with 100ml ingestion representing a severe overdose. Toxicity initially presents with intoxication - slurring of speech, drowsiness and nausea. This can progress to marked cerebral depression and convulsions. Twelve hours post ingestion significant metabolism to glycoaldehyde will have occurred causing cardiorespiratory depression and acidosis. Aldehydes inhibit oxidative phosphorylation, mechanisms for cellular respiration, glucose metabolism, protein synthesis, nucleic acid replication and synthesis. Myocardial depression can be significant and pulmonary oedema is commonly encountered. Renal tenderness and oliguria may become evident as acute tubular necrosis becomes established. Metabolism of ethylene glycol to oxalic acid causes a demonstrable degree of oxalate crystalluria and accounts for the low plasma calcium seen (chelation to form calcium oxalate). Ethylene glycol poisoning is lethal with levels of 21mg/dl but it must be remembered that this will only generate a late osmolality increase of 4 mOsm/l (delayed presentation). The treatment approach is similar to methanol toxicity with emphasis on the **early** use of ethanol infusions and haemodiafiltration. These treatments should continue until ethylene glycol can no longer be detected in blood.

Isopropanol poisoning

Isopropanol should also be considered when patients present with alcohol toxicity. This alcohol forms a major component of rubbing alcohol and is used in windscreen preparations and de-icer. Unlike methanol or ethylene glycol, isopropanol is metabolised to acetone and excreted in the urine. Acetone is not metabolised further and organic acid production is minimal. Both the parent compounds and metabolites are osmotically active and significant osmolar gaps may be seen with ingestion. Isopropanol toxicity tends to present with intoxication, meiotic pupils and brain stem depression with significant overdose. Isopropanol is irritant and causes marked gastritis, pancreatitis and if aspirated causes tracheitis and pulmonary oedema. It is rapidly absorbed from the stomach and gastric lavage is of little benefit. **Ketosis** is more marked with isopropanol ingestion and this can provide a useful clue to diagnosis. Treatment is supportive and no effort should be made to limit metabolism

of isopropanol with ethanol infusions. Isopropanol is readily cleared by haemodiafiltration but this treatment is rarely required.

Salicylate poisoning

Aspirin (acetylsalicylic acid) poisoning causes over 200 deaths a year in the UK. Therapeutic doses of aspirin are absorbed rapidly and completely from the stomach and larger doses may be absorbed for up to 18 hours after ingestion as the tablets coalescence in the stomach.

Metabolism

Acetylsalicylic acid is hydrolysed to salicylic acid and further metabolised in one of three ways.

1. Conjugation with glycine to salicyluric acid
2. Hydroxylated to gentisic acid
3. Conjugation with glucuronic acid to either salicylacyl glucuronide or salicyl phenolic glucuronide

Conjugation with glucuronic acid is saturable so that levels of non-protein bound salicylate rise disproportionately with increasing dose. The excretion of unchanged salicylate by the kidneys then becomes increasingly important and alkalisation of the urine will therefore maximise its excretion by ion trapping.

Drug effects

Central to the metabolic disturbances initiated by acetylsalicylic acid is the uncoupling of oxidative phosphorylation. The resulting increase in oxygen consumption and carbon dioxide production leads to a respiratory alkalosis that is augmented by direct stimulation of the respiratory centre. Bicarbonate excretion is enhanced and sodium, potassium and water loss also occurs. When this is combined with hyperpyrexia and sweating, then marked dehydration and electrolyte imbalance follow. Stimulation of the chemoreceptor trigger zone may induce vomiting and this will further exacerbate this imbalance.

Uncoupled oxidative phosphorylation enhances glycolysis and increases the peripheral demand for glucose. This occurs mainly in muscle and may provoke hypoglycaemia. The brain is particularly sensitive to this and neuroglycopenia leads to depression of the respiratory centre.

Metabolic acidosis seen in acetylsalicylic acid poisoning is caused by the stimulation of lipid metabolism (increasing the formation of ketoacids) and the inhibition of enzymes within the Kreb's cycle (increasing levels of pyruvic and lactic acid). The acidosis is poorly tolerated due to the reduced buffering capacity, following the initial respiratory alkalosis and bicarbonate excretion.

Clinical Presentation

The clinical picture depends on the age of the patient and on the total dose ingested. Acute overdose in the setting of chronic use will augment toxicity. As a rule of thumb plasma salicylate levels 6 hours after ingestion can be banded to represent three degrees of toxicity; mild (300-500mg/l), moderate (500-750mg/l) and severe (>750mg/l). Below ten years of age respiratory alkalosis tends to be a transient feature with metabolic acidosis predominating. However, respiratory alkalosis is more marked in the adult, where it helps to keep salicylate in the ionised form, preventing it from crossing cell membranes. The following features are usually present regardless of the severity: sweating, vomiting, pyrexia, tinnitus and epigastric pain. As the metabolic acidosis starts to dominate the clinical picture more salicylate enters the central nervous system and tremor, delirium, convulsions and eventually coma ensues. Non-cardiogenic pulmonary oedema and acute renal failure are also features of acetylsalicylic acid toxicity.

Treatment should include vigorous gastric lavage to limit continued absorption. Dehydration and electrolyte disturbances (particularly hypokalaemia) should be corrected. Severe toxicity requires more than these basic manoeuvres and alkalisation of the urine should be performed. Urinary salicylate excretion is encouraged with intravenous infusions of bicarbonate, aiming to raise urinary pH > 7.5 while avoiding a plasma pH > 7.55. Haemodialysis has also been used to augment salicylate excretion.

Summary

Metabolic acidosis is a common feature in critically ill patients. In these tutorials we have covered how to determine the type of acidosis present, assess its severity and from that determine its cause. Once a cause is established, treatment can be targeted in a specific manner and the acid base status used to determine whether this treatment is effective.

Case Examples

Case 4]

This patient was initially felt to be intoxicated with alcohol and the low blood glucose raised the possibility of alcoholic ketoacidosis. This initial arterial gas does not support this as you would expect to see a low bicarbonate and an increased anion gap (which was normal at this stage in this patient). The subsequent deterioration however is classical for methanol poisoning.

Methanol metabolism if often delayed for 12 to 18 hours especially if taken with ethanol. The first stage in metabolism generates formaldehyde which is not an acidic species – metabolic acidosis will not feature at this stage. When the formaldehyde is metabolised into formic acid then the increased anion gap acidosis develops.

It would have been useful to determine whether there was an osmolar gap on initial presentation. If this was raised then it would have alerted the clinicians to the possibility of alcohol poisoning and ethanol treatment would have prevented the deterioration.

Interestingly the subsequent arterial gas shows a severe metabolic acidosis but the pCO_2 has only dropped minimally. The calculated pCO_2 for maximal compensation suggests the pCO_2 should have dropped to 3.0. The relative respiratory acidosis arises from methanol induced respiratory depression and should prompt early ventilatory support.

Case 5]

In this example the same patient represents with an intoxicated picture but ethanol and methanol are not detected on this admission. In spite of this, and the normal arterial gases on admission he proceeds to become comatose with arterial gases suggesting a primary respiratory acidosis (low pH, raised pCO_2). The rise in bicarbonate is appropriate for the rise in pCO_2 (expected bicarbonate rise = 0.75 (pCO_2 – 5.3) for an acute respiratory acidosis), so no metabolic effects are demonstrated.
This presentation is classical for isopropanol poisoning. Isopropanol is metabolised to acetone and this is excreted in the urine. Metabolic acidosis is not a feature of isopropanol poisoning; however the alcohol is heavily intoxicating and can easily cause respiratory depression as seen in this example. The key to aid diagnosis is the presence of the increased osmolar gap combined with the urine ketosis. Treatment is supportive (the airway will need to be secured in this example and respiratory support provided) until the alcohol has been metabolised.

Case 6]

The presentation is typical for diabetic ketoacidosis however the arterial gases do not overtly suggest a severe acidosis is present. The pH of 7.34 and borderline low bicarbonate support the presence of a **mild** metabolic acidosis however the anion gap is 38. This would suggest that the metabolic acidosis is **severe** and this would fit better with the clinical suspicion. Interestingly the delta ratio equals 5.75 which strongly suggest the presence of a pre-existing metabolic alkalosis. It is conceivable that prior to his DKA the bendroflumethazide had created a significant metabolic alkalosis that will have been compensated for with a respiratory acidosis. The bicarbonate would have been increased (to the mid thirties perhaps) and the chloride lowered to maintain electrical neutrality.

With the onset of the ketoacidosis the bicarbonate will have fallen significantly to 20 (a change in keeping with a severe metabolic acidosis) and this will have removed the driving force for the respiratory acidosis. The minute ventilation will have risen and the pCO2 dropped to the values seen in the gas sample.

This is a classical presentation for a severe metabolic acidosis on the background of a compensated metabolic alkalosis. The gases do not overtly appear to suggest a severe acidosis but careful analysis should allow the clinician to confirm this suspicion.

References

1. Vale JA, Meredith TJ Proudfoot AT. Poisoning by alcohols and glycols. In : Weatherall DJ, Ledingham JGG, Warrell DA, eds. *Oxford Textbook of Medicine.* Oxford: Oxford University Press, 1987; 6.41-6.44.
2. Vale JA, Meredith TJ Alcohol poisoning. In: Vale J, Meredith T, eds. *Poisoning – Diagnosis and Treatment*. London: Update Books, 1981; 128-130.
3. Williams HE Alcoholic hypoglycaemia and ketoacidosis. *Medical Clinics of North America.* 1984; 68: 33-38.
4. Almaghamsi A, Yeung C. Osmolal gap in alcoholic ketoacidosis. *Clinical Nephrology* 1997; 48(1):52-53.
5. Brandis K. Acid-base physiology. From http://www.anaesthesiamcq.com/AcidBaseBook/ABindex.php
6. Stewart PA. How to understand acid-base. A quantitative acid-base primer for biology and medicine. From http://www.acidbase.org/