Approach to acid-base disorders – a clinical chemistry perspective

Acid-base disorders are frequently encountered in clinical practice and have a significant impact on patient morbidity and mortality.

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Skill in interpreting biochemical data to correctly identify and treat acid-base disorders is an essential competency for clinicians. Studies have, however, shown that proficiency in this area is lacking and that performance declines as disorders become more complex.[1] This review presents a systematic approach and set of rules that should help clinicians to solve even the most challenging cases.

Systematic approach

Good history-taking and thorough clinical examination are both indispensable for providing clues to the nature and duration of the underlying disorder.

The first step in assessment of the arterial blood gas profile is appraisal of the pH: a reduced pH indicates acidaemia and an elevated pH indicates alkalaemia (Table 1). In simple acid-base disorders, compensation returns the pH toward, but seldom completely to, normal levels (except in mild chronic respiratory alkalosis).[2] A normal pH does not always signify normal acid-base status, but may actually be a clue to the existence of a mixed disorder with components in opposing directions (Table 2).

The second step is appraisal of the pCO_2 and $[HCO_3^-]$ to identify the primary derangement and compensatory response. A low pH with *elevated* pCO_2 and $[HCO_3^-]$ is consistent with respiratory acidosis. A low pH with *decreased* pCO_2 and $[HCO_3^-]$ is consistent with metabolic acidosis. A high pH with *decreased* pCO_2 and $[HCO_3^-]$ is consistent with respiratory alkalosis. A high pH with *elevated* pCO_2 and $[HCO_3^-]$ is consistent with metabolic alkalosis. It is important to note that in simple acid-base disorders deviations in pCO_2 and $[HCO_3^-]$ are in the same direction. In mixed acid-base disorders deviations in pCO_2 and $[HCO_3^-]$ are in opposite directions.[2]

The third step entails assessing the adequacy of the compensatory response by applying the rules of compensation (Table 3). If insufficient time has elapsed to allow for complete compensation, a partially compensated simple acid-base disorder may be misclassified as a mixed one.[2]

The fourth step is to examine the serum electrolytes and anion gap (AG) and to decide whether additional testing is required, e.g. measurement of serum creatinine, plasma lactate or glucose and urinary ketones. Calculation of the delta ratio may assist with detection and characterisation of mixed acid-base disorders (see below). Urinary electrolytes and osmolal gap may be useful in assessment of metabolic alkalosis and normal AG metabolic acidosis.

The serum anion gap

In order to maintain electroneutrality, the sum of total circulating cations and anions must be equal. However, the formula for the AG routinely incorporates only the major ions: $[Na^+] - ([Cl^-] + [HCO_3^-])$ or $([Na^+] + [K^+]) - ([Cl^-] + [HCO_3^-])$. $[HCO_3^-]$ is usually derived from total CO_2 content in serum from venous blood, yielding values that are 2 - 3 mmol/l higher than in arterial blood.[2] In reality, the AG reflects

Table 1. Simple acid-base disorders

Disorder	pH	pCO_2	HCO_3^-	Clinical examples
Respiratory acidosis	<7.35	**↑**	**↑**	Laryngeal oedema, bronchospasm, emphysema, hypoventilation
Metabolic acidosis	<7.35	**↓**	**↓**	Lactic acidosis, renal failure, diabetic ketacidosis, renal tubular acidosis
Respiratory alkalosis	>7.45	**↓**	**↓**	Congestive cardiac failure, raised intracranial pressure, sepsis
Metabolic alkalosis	>7.45	**↑**	**↑**	Vomiting, diuretics, Conn's syndrome, Cushing syndrome

Primary disorder indicated by larger, bold arrows

Table 2. Mixed acid-base disorders

Disorder	pH	pCO_2	HCO_3^-	Clinical examples
Respiratory and metabolic acidosis	Very low	↑	Lower than expected	Cardiopulmonary arrest, cerebrovascular accident and renal failure
Respiratory and metabolic alkalosis	Very high	↓	Higher than expected	Congestive cardiac failure and vomiting, diuretic therapy and liver failure
Metabolic acidosis and respiratory alkalosis	≈7.45	Lower than expected	↓	Salicylate overdose, septic shock, sepsis and renal failure
Metabolic alkalosis and respiratory acidosis	≈7.45	Higher than expected	↑	Diuretic therapy or vomiting and emphysema
Metabolic acidosis and metabolic alkalosis	≈7.45	→	→	Lactic acidosis or diabetic ketoacidosis and vomiting
Triple disorder: mixed metabolic acidosis and alkalosis *plus* respiratory alkalosis or acidosis	Variable	Variable	Variable	Renal failure, vomiting and congestive cardiac failure

Table 3. Adaptive responses to simple acid-base disorders

Disorder	Rule of compensation	Time to completion	Limit of compensation
Respiratory acidosis			
Acute	HCO_3^- increases by 1 mmol/l for every 10 mmHg that pCO_2 is above 40 mmHg	5 - 10 min	HCO_3^- 30 mmol/l
Chronic	HCO_3^- increases by 4 mmol/l for every 10 mmHg that pCO_2 is above 40 mmHg	3 - 4 days	HCO_3^- 45 mmol/l
Respiratory alkalosis			
Acute	HCO_3^- decreases by 2 mmol/l for every 10 mmHg that pCO_2 is below 40 mmHg	5 - 10 min	HCO_3^- 17-18 mmol/l
Chronic	HCO_3^- decreases by 5 mmol/l for every 10 mmHg that pCO_2 is below 40 mmHg	2 - 3 days	HCO_3^- 12-14 mmol/l
Metabolic acidosis			
	pCO_2 decreases by 1.3 mmHg for every mmol/l that HCO_3^- is below 24 mmol/l or expected $pCO_2 = 1.5 \times HCO_3^- + 8 \pm 2$	0.5 - 1 day	pCO_2 10 mmHg
Metabolic alkalosis			
	pCO_2 increases by 0.6 mmHg for every mmol/l that HCO_3^- is above 24 mmol/l	1 - 1.5 days	pCO_2 55 mmHg

Increases/decreases from baseline HCO_3^- of 24 mmol and baseline pCO_2 of 40 mmHg.

Table compiled from references 1, 2 and 4.

the difference between cations and anions unaccounted for ('unmeasured') by the formula. Since 'unmeasured' anions usually exceed 'unmeasured' cations, the reference interval for the AG is typically 5 - 12 mmol/l ($[K^+]$ excluded) or 9 - 16 mmo/l ($[K^+]$ included).[3] The latter ranges, based on measurements by modern ion-selective electrodes, are lower than the 8 - 16 mmol/l ($[K^+]$ excluded) quoted for older flame photometry methods.[4] In light of the wide range of normal values, a significant change in the AG of an individual patient may be easier to detect by comparing the value to a baseline obtained while no acid-base disorder was present.[5]

Decreased anion gap

Because circulating proteins are a major component of serum 'unmeasured' anions, hypoalbuminaemia decreases the AG by 2.5 mmol/l for every 10 g/l that albumin is below 40 g/l.[2] Correction of the AG may be required to unmask a high AG metabolic acidosis, e.g. lactic acidosis, presenting with a normal AG

Table 4. Causes of high AG metabolic acidosis

Mnemonic **CAT MUDPILES**
Carbon monoxide, cyanide
Alcohol intoxication, alcoholic ketoacidosis
Toluene (glue-sniffing)
Methanol
Uraemia
Diabetic ketoacidosis
Paraldehyde, propylene glycol
Inborn errors of metabolism, iron, ibuprofen, isopropyl alcohol
Lactic acid
Ethylene glycol
Salicylates

Table compiled from references 1 and 6.

due to hypoalbuminaemia. Other important causes of low or even negative AGs are laboratory error (measurements of $[Na^+]$ too low or $[Cl^-]$ and/or $[HCO_3^-]$ too high) and overproduction of cationic proteins in IgG myeloma or polyclonal gammopathy.[5]

Increased anion gap

Elevated AGs are more common than decreased AGs and are generally caused by overproduction or decreased excretion of acid. Rarer causes of an elevated AG are metabolic alkalosis, severe hyperphosphataemia and overproduction of anionic paraproteins by IgA myeloma.[5] Spurious increases may also be seen due to loss of water and CO_2 from sera left exposed to air (usually ≤6 mmol/l after 2 hours).[2] Metabolic alkalosis, particularly when it is chloride-responsive, may increase the AG by 4 - 6 mmol/l.[2] Contributing factors include: raised albumin concentration (due to dehydration) and increased net anionic charge of proteins and enhanced lactate production by stimulation of glycolysis (the latter both the result of alkalaemia).[5,6] Exogenous administration of phosphate resulting in serum concentrations of 6.0 - 7.5 mmol/l has been associated with AGs of >50 mmol/l.[5]

High anion gap metabolic acidosis

The greatest clinical utility of the AG, however, is in the differential diagnosis of metabolic acidosis. When an acid (AH) accumulates in the blood, the hydrogen ion $[H^+]$ is buffered by HCO_3^- and the retained acid anion $[A^-]$ contributes to unmeasured anions, raising the AG.[6] The most common causes of high AG metabolic acidosis are: diabetic or alcoholic ketoacidosis, lactic acidosis, uraemic acidosis and intoxication with alcohol, methanol, ethylene glycol, salicylate, or carbon monoxide (Table 4). The offending anion can be identified with relative ease in most cases when the AG exceeds 30 mmol/l, declining to <70% of cases when the AG is <24 mmol/l.[5] Of note is that the nitroprusside method used by dipsticks for detection of ketones reacts only with acetoacetate and not β-hydroxybutyrate. Since the latter often predominates in patients with alcoholic and diabetic ketoacidosis, the dipstick may significantly underestimate the degree of ketosis.[2] In addition to screening tests for toxins, calculation of the osmolal gap (OG) as osmolality – (2$[Na^+]$ + [urea] + [glucose]), may be helpful as an indicator of intoxication. An OG >10 suggests the presence of an osmotically active substance (such as ethanol, methanol, or ethylene glycol) that is detected by measured but not calculated osmolality. Lesser elevations may be found in lactic acidosis and chronic renal failure.[2] In cases of intoxication where blood collection is delayed, only mild increases in the OG may be observed due to conversion of alcohols to toxic metabolites.[2]

Normal anion gap metabolic acidosis

Normal AG metabolic acidosis is caused either by renal or gastrointestinal losses of bicarbonate or by addition of hydrochloric acid to the blood.[5] The latter occurs when administered ammonium chloride or chloride salts of amino acids in hyperalimentation are metabolised to HCl by the liver.[5] In the former conditions, loss of bicarbonate in the urine or stool along with sodium produces volume contraction, stimulating proximal renal tubular absorption of NaCl. Sodium bicarbonate losses are therefore replaced by sodium chloride, leading to a hyperchloraemic acidosis with an unchanged anion gap.[5] However, if acidaemia is severe, the AG may actually drop by up to 4 mmol/l as a result of an increment in the net cationic charge of proteins.[5] If hyponatraemia is present,

Table 5. Causes of normal AG metabolic acidosis

With hypokalaemia	With normo- or hyperkalaemia
Diarrhoea	Early uraemic acidosis
Renal tubular acidosis type 1 and 2	Aldosterone deficiency or resistance
Ureteral diversion to intestine	Obstructive uropathy
Recovery phase of ketoacidosis	Hyperalimentation (lysine, histidine, arginine HCl)
Carbonic anhydrase inhibition	Ingestion/infusion of HCl, NH_4Cl

Table compiled from reference 6.

the [Cl^-] may be within the normal range. Normal AG metabolic acidoses can be classified into those in which serum [K^+] is normal or increased and those in which it is low (Table 5).

Urine electrolytes

Urine chloride measurement is used to divide metabolic alkaloses into those that are chloride-responsive (U-[Cl^-] <25 mmol/l) and those that are chloride-resistant (U-[Cl^-] >40 mmol/l).[1] In the former, the alkalosis is corrected by volume expansion using saline, whereas in the latter it is not. In metabolic alkalosis due to vomiting or nasogastric drainage urine chloride is used instead of sodium to assess volume status, because U-[Na^+] may be high despite volume contraction. This is because the early phase of these conditions is associated with a significant bicarbonate diuresis that causes obligate urinary losses of sodium.[4] Causes of metabolic alkalosis are presented in Table 6.

Measurement of urine electrolytes and osmolality with calculation of urine anion and osmolal gaps may be useful in the differential diagnosis of normal AG metabolic acidoses. Urine [Na^+] and [K^+] are expected to be low in diarrhoea, high in renal tubular acidoses and divergent (high [Na^+] and low [K^+]) in aldosterone deficiency or resistance.[2] In acidosis of extrarenal origin the appropriate renal response is secretion by the collecting tubules of H^+ ions, which combine with NH_3 to be excreted as ammonium (NH_4^+).[6] The urine AG, defined as [Na^+] + [K^+] – [Cl^-], is an indirect way of estimating urinary NH_4^+ excretion. Since NH_4^+ is usually accompanied by Cl^-, a negative urine AG (in the range of -20 to -50 mmol/l) indicates appropriate elevation of urinary NH_4^+ excretion in the face of acidosis.[6] A positive urine AG (in the range of 20 - 30 mmol/l) indicates that impaired secretion of H^+ ions, as found in distal renal tubular acidosis, plays a role in the evolution of the acidosis.[2] Estimation of NH_4^+ excretion by the urine AG is unreliable when the urine contains significant amounts of bicarbonate or unusual anions, such as ketoacids or drugs, including penicillin or salicylate.[6] In such cases, the urine osmolal gap, defined as urine osmolality – (2[Na^+ + K^+] + [urea] + [glucose]) should be used, since the gap mainly reflects the excretion of NH_4^+.[2] In an acidotic patient, the urine OG should be between 150 and 200; values of 50 - 100 are indicative of impaired NH_4^+ excretion, consistent with distal renal tubular acidosis.[2]

Table 6. Causes of metabolic alkalosis

Chloride-responsive (U-[Cl^-] <25 mmol/l)	Chloride-resistant (U-[Cl^-] >40 mmol/l)
Gastric fluid losses (vomiting, nasogastric suction)	Hyperaldosteronism
Diuretics (late)	Apparent mineralocorticoid excess syndromes
Posthypercapnia	Cushing's syndrome
Cystic fibrosis	Liddle's syndrome
Congenital chloride diarrhoea	Bartter or Gitelman syndrome
Villous adenoma	Diuretics (early)
	Excess bicarbonate administration

Table compiled from references 1 and 4.

Table 7. Case 1 results

Arterial blood gases		Serum electrolytes	
pH 7.52 (7.35 - 7.45)		Sodium (135 - 145)	140 mmol/l
pCO_2 50 mmHg (35 - 45)		Potassium (3.3 - 5.3)	2.4 mmol/l
pO_2 70 mmHg (80 - 110)		Chloride (98 - 108)	87 mmol/l
HCO_3^- 40 mmol/l (23 - 33)		Total CO_2 (23 - 33)	42 mmol/l
Urine electrolytes		Urea (2.6 - 7.0)	5.1 mmol/l
Sodium 23 mmol/l		Creatinine (49 - 90)	88 µmol/l
Potassium 68 mmol/l		Albumin (35 - 52)	28 g/l
Chloride <5 mmol/l		Anion gap (9 - 16)	13

Reference intervals in brackets.

Delta ratio

The ratio between the increase in AG (ΔAG) and the decrease in bicarbonate (ΔHCO_3) is called the delta ratio. It is calculated as ΔAG/ΔHCO_3^- where:

ΔAG = patient's AG (corrected for hypoalbuminaemia if present) – laboratory mean 'normal' value; and

ΔHCO_3^- = laboratory mean 'normal' value of 24 mmol/l – the patient's total CO_2 content.

Table 8. Case 2 results

Arterial blood gases	Serum electrolytes	
pH 7.38 (7.35 - 7.45)	Sodium (135 - 145)	136 mmol/l
pCO_2 36 mmHg (35 - 45)	Potassium (3.3 - 5.3)	2.9 mmol/l
pO_2 82 mmHg (80 - 110)	Chloride (98 - 108)	86 mmol/l
HCO_3^- 20 mmol/l (23 - 33)	Total CO_2 (23 - 33)	22 mmol/l
	Urea (2.6 - 7.0)	10.5 mmol/l
Urinalysis	Creatinine (49 - 90)	140 µmol/l
Ketones +++	Anion gap (9 - 16)	31 mmol/l
	Glucose (5.6 - 11.1)	44 mmol/l

Reference intervals in brackets.

The ratio is useful for detecting complex acid-base disorders that include a component of high AG metabolic acidosis. In high AG metabolic acidoses the premise is that total CO_2 will decrease by 1 mmol/l for every 1 mmol/l increase in AG, i.e. a delta ratio of 1:1. However, in practice ratios between 1 and 2 may be observed, because hydrogen ions are not only buffered by extracellular bicarbonate.[7] This is particularly true of lactic acidosis in which ratios are typically between 1.6 and 1.8.[1] In diabetic ketoacidosis the ratio is closer to 1, because of loss of ketoacid anions in the urine.[1,7] A delta ratio between 0.3 and 0.7 indicates that the increase in AG is small compared with the decrease in bicarbonate, suggesting co-existence of normal and high AG metabolic acidoses, e.g. diarrhoea and lactic acidosis.[6] A delta ratio of >2 indicates that the increase in AG is large compared with the decrease in bicarbonate, suggesting co-existence of metabolic acidosis and metabolic alkalosis (see Case 2 below).[7]

Illustrative cases

Case 1

An 18-year-old woman with anorexia nervosa has results as depicted in Table 7. The elevated pH and $[HCO_3^-]$ signify the presence of metabolic alkalosis. The pCO_2 is appropriately elevated for the increase in bicarbonate [40 mmHg + (0.6 x (40-24)) = 40 mmHg + 9.6 = 49.6 mmHg], indicating adequate respiratory compensation. The urine electrolytes indicate volume contraction with secondary hyperaldosteronism. The corrected AG of 16 is high normal (13.4 + [(40-28)/10 x 2.5]), consistent with chloride-responsive metabolic alkalosis.

Case 2

A 55-year-old woman with type 1 diabetes mellitus is admitted to the Casualty Department in a semi-coma (Table 8). Her chronic medication includes insulin, digoxin and a thiazide diuretic. Although the arterial blood gas profile is unremarkable except for mildly decreased $[HCO_3^-]$, the AG suggests the presence of a high AG metabolic acidosis, probably due to diabetic ketoacidosis. Calculation of the delta ratio [(31 – 12)/(24 – 22)] yields a value of 9.5, indicating mixed metabolic acidosis and alkalosis, the latter due to chronic diuretic therapy. The pCO_2 is appropriately decreased for the bicarbonate [40 mmHg – (1.3 x (24-20)) = 40 mmHg – 5.2 = 34.8 mmHg], indicating adequate respiratory compensation.

References available at www.cmej.org.za

In a nutshell

- Recognition and appropriate treatment of acid-base disorders requires a systematic approach and application of a set of rules.
- Information obtained from the history and physical examination is essential for correct interpretation of biochemical data.
- The systematic approach comprises the following steps:
  - appraise the pH: pH <7.35 indicates acidaemia; pH >7.45 indicates alkalaemia; normal or near-normal pH may indicate mixed acidosis and alkalosis
  - identify the primary disorder and compensatory response by examining the pCO_2 and HCO_3^-; deviations are in the same direction in simple disorders, but in opposite directions in mixed disorders
  - assess whether compensation is adequate by applying the rules of compensation, keeping in mind the time interval required for compensation to be complete
  - assess the serum electrolytes and anion gap; calculate the delta ratio if ΔAG and ΔHCO_3^- appear discordant
  - define the acid-base disorder and request further testing if required, e.g. toxic screen, osmolal gap, lactate, ketones.
- Measurement of urine electrolytes and calculation of anion and osmolalgaps may be helpful in the differential diagnosis of metabolic alkaloses and normal anion gap metabolic acidoses.