REVIEW ARTICLE

Metabolic acidosis in the critically ill: Part 1. Classification and pathophysiology

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Summary

Metabolic acidaemia (pH < 7.35 not primarily related to hypoventilation) is common amongst the critically ill and it is essential that clinicians caring for such patients have an understanding of the common causes. The exclusive elimination routes of volatile (carbon dioxide), organic (lactic and ketone) and inorganic (phosphate and sulphate) acids mean compensation for a defect in any one is limited and requires separate provision during critical illness. We discuss the models available to diagnose metabolic acidosis including CO_2/HCO_3^- and physical chemistry-derived (Stewart or Fencl-Stewart) approaches, but we propose that the base excess and anion gap, corrected for hypoalbuminaemia and iatrogenic hyperchloraemia, remain most appropriate for clinical usage. Finally we provide some tips for interpreting respiratory responses to metabolic acidosis and how to reach a working diagnosis, the consequences of which are considered in Part 2 of this review.

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The initial presentation for many conditions including sepsis, trauma, renal and endocrine emergencies is often dominated by a metabolic acidosis despite these insults having different aetiologies and prognoses. It is essential that an appropriate diagnosis of the pathophysiology of acidosis is made, for example identification of sepsis syndrome or liver failure, but this need not always be the same as identification of the individual acid responsible. There is an increasing recognition of the complex interaction that exists between the respiratory, renal and hepatic systems in controlling acid concentrations, and their interaction in disease. The use of physical chemistry-derived parameters (strong ion difference, carbon dioxide tension and weak anion concentrations) has gained much popularity and we examine their possible contributions to diagnosis and determining the mechanism underlying metabolic acidosis. Common pitfalls using derived parameters including the base excess and anion gap are discussed, and we suggest ways of improving their performance in routine clinical use. As our understanding of more complex molecular processes develops it seems the simplest of molecular structures, the proton, is still the subject of study.

Using the following MeSH terms, *acidosis*, *critical illness*, *lactic acidosis*, *physical chemistry*, we searched the PubMed, EMBASE and OVID databases. Additional articles were retrieved by hand searches. We also incorporated our clinical experiences of critical illness and acute medicine. Throughout this paper a value in square brackets, e.g. [H$^+$], denotes the molar concentration of the substance within the brackets. Both mmol and mEq (milli-equivalents) are used in this paper. The mEq of a substance is the electrochemical equivalent and is the product of molar concentration and the valence. Thus mmol and mEq are identical for ions with a single valency (e.g. sodium) but mEq would be twice mmol for ions with a divalent ion (e.g. Ca^{++}).

The word 'acid' comes from the Latin 'acidus' meaning sour [1]. Within this article an acid is regarded as a substance able to donate protons (H$^+$) and a base as a proton acceptor (Lowry-Bronsted model), although the limitations and alternatives of this concept are recognised [1,2]. This moves away from concepts of anions being acidic (therefore including chloride$^-$ and albumin$^-$) and cations being bases (including sodium$^+$ and potassium$^+$), where neutralisation was perceived to occur by forming a

Table 1 pH values and equivalent $[H^+]$ for water. $[H^+]$ is the physical chemistry expression of molar concentration H^+.

pH value	$[H^+]$; nmol.l^{-1}
7.6	25
7.5	32
7.4	**40**
7.3	50
7.2	60
7.1	80
7.0	100
6.9	125
6.8	160

Table 2 Ionic components of plasma including electrochemical equivalents.

Principal cations (mEq.l^{-1})
Na (140)
K (4)
Ca (2)
Mg (2)
Total **148** mEq.l^{-1}
Principal anions (mEq.l^{-1})
Cl (100)
HCO$_3$ (25)
Protein (15)
Phosphate species (2)
Sulphate (1)
Organic acids (5)
Total **148** mEq.l^{-1}

salt. Some of these concepts will be reconsidered below within the physicochemical approach to blood gas analysis.

Acidity is expressed using the logarithmic pH scale which is not intuitive and can be clinically misleading ($pH = -\log_{10}[H^+]$). In acidosis (pH < 7.40), larger changes in H^+ concentration (denoted in physical chemistry as $[H^+]$) are required to decrease the pH by similar units than are required to increase the pH in alkalosis. Many workers have moved towards using actual $[H^+]$ and equivalents are given below (Table 1).

Metabolic acidosis is a non–respiratory process which has a *tendency* to produce a metabolic acidaemia, the correct term when plasma pH < 7.35 ($[H^+] = 45$ nmol.l^{-1}). Strictly, during acidosis the pH may be in the normal range. Clinically, a metabolic acidosis may be distinguished from a respiratory acidosis when alveolar hypoventilation is not the primary cause. This article will use the term metabolic acidosis to include both the tendency towards and actual deviation of pH < 7.35, to reflect clinical usage.

Metabolic acidosis is commonly associated with many conditions within anaesthesia and critical care. It is often unclear whether this is a primary abnormality, i.e. the patient is unwell because they have accumulated H^+, or an epiphenomenon reflecting the effects of an underlying process such as sepsis [3]. Similarly, whether the acidosis itself or the condition that caused the acidosis should be the primary therapeutic target is often not clear, and commonly both are treated concurrently.

The major plasma ions are listed below (Table 2). Figures in brackets indicate equivalence of ionic charge, i.e. valency multiplied by molar concentration. We have used ionised calcium in Table 2, which is typically 1 mmol.l^{-1} and thus 2 mEq.l^{-1}.

This demonstrates the body's adherence to the laws of electrochemical neutrality as both anions and cations total 148 mEq.l^{-1}. Metabolism involves changes in molecular structure to create acids with different dissociation constants (K_a), and may thereby affect changes in proton concentration ($[H^+]$) and thus pH. Examples include the

ketoacid pyruvate (pKa 2.49) and lactate (pKa 3.86). Each individual acid is in dynamic equilibrium between its associated and dissociated (aprote) forms. Furthermore, at the normal plasma pH of 7.40, absolute proton concentrations are in the *nano*molar range, whereas most acids in illness appear in the *milli*molar range (e.g. lactate). It therefore follows that most acid-base disturbances reflect changes in the tendency of water to dissociate chemically rather than the accumulation of acid per se (see isohydric principle below).

## Classes of acid and routes of elimination

The total H^+ turnover in the body is approximately 150 mol.day^{-1}, i.e. 150 000 *milli*moles. Approximately 90% of proton release results from ATP hydrolysis, the majority is 're-captured' by metabolic processes and ultimately rejoins ATP and is thus unable to alter systemic pH. The excretion of the acid load by the body may be considered in three categories:

Class 1 Volatile, i.e. CO_2

The body produces approximately 15 000 mmol equivalents of H^+ in carbon dioxide per day and this is excreted by the lungs. During ketoacidosis, volatile acetone may be cleared by the lungs, a useful clinical sign but quantitatively unimportant.

Class 2 Organic acids

These are principally lactate and ketones. Several thousand millimoles of lactate and ketones are metabolised per day (e.g. lactate 1500 mmol.day^{-1}) and this was traditionally attributed to the liver. More recent work has identified the kidney as contributing a large component of the body's metabolic disposal of lactate, perhaps up to 25–30% [4, 5]. Hepatic urea production itself generates $2H^+$ for every molecule of urea produced:
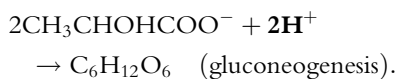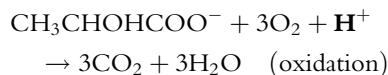
$$2NH_4^+ + CO_2 \rightarrow CO(NH_2)_2 + 2H^+.$$
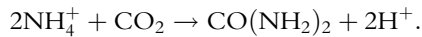
Class 3 Inorganic acids

Sulphate and phosphate are the two most important examples and are generated in the range of 1.5 $mmol.kg^{-1}.day^{-1}$. These acids are bioproducts of dietary protein and amino acid metabolism. Sulphur-containing amino acids methionine and cysteine produce around 70% of the body's total fixed acid per day in the form of sulphuric acid. In chronic renal failure, sulphate may contribute up to 5 $mEq.l^{-1}$ to the anion gap [6].

The three classes of acid and their excretory routes are relatively independent of each other. An excess of one organic acid cannot be compensated for by an increase in excretion of another acid [7, 8]. Therefore, a respiratory acidosis cannot be adequately cleared by the liver; likewise, renal tubular acidosis cannot be cleared by the lungs [9]. Perhaps less intuitively, in providing organ support during critical illness the acid excretory systems which demand most attention are the respiratory, renal and hepatic systems and each requires *separate* provision. Most commonly we support pulmonary carbon dioxide elimination with ventilatory support, and the renal systems with convective and/or diffusive replacement therapy. Hepatic excretory support through extracorporeal albumin-based dialysis and adsorption technology is now available at the bedside, although the indications and efficacy remain to be clarified [10].

The liver is responsible for both the production and elimination of acids. It produces around one fifth of the body's carbon dioxide by complete oxidation of substrates including carbohydrate, lipid and carbon skeletons of amino acids. The liver also consumes H^+ by disposing of lactate by oxidation (to water and carbon dioxide) or gluconeogenesis, and both processes consume protons. In health, 70% of administered lactate undergoes oxidation, and the generation of HCO_3^- has a half-life of 15 min [11, 12]. A 1.0-l bag of Hartmann's solution (29 $mmol.l^{-1}$ racemic lactate) is thus physiologically equivalent to 10 $mmol.l^{-1}$ of glucose (little more than a theoretical risk for diabetics) and consumes 15 mmol of H^+ these figures neglect the slower metabolism of the D-isomer, see below:

$$CH_3CHOHCOO^- + 3O_2 + \mathbf{H^+}$$
$$\rightarrow 3CO_2 + 3H_2O \quad \text{(oxidation)}$$

$$2CH_3CHOHCOO^- + \mathbf{2H^+}$$
$$\rightarrow C_6H_{12}O_6 \quad \text{(gluconeogenesis)}.$$

It is possible to use the liver's ability to clear acid to the patient's advantage in critical illness. For example, the infusion of exogenous buffered lactate (e.g. renal replacement fluid or Ringer's lactate solutions) results in net consumption of protons *providing the liver can metabolise it*, possibly at rates up to 100 $mmol.h^{-1}$ [13–18].

Classification, diagnosis and alternative models of metabolic acidosis

It is perhaps not surprising, considering the various theories of what an acid actually is, that a number of approaches to examining acid-base abnormalities and metabolic acidosis are available. We have summarised these as follows:

Inspection of pH and [H^+] supplemented by calculating the anion gap. Although many alternatives are recognised, this will be the model employed throughout this article as it is the most popular 'bedside' technique and provides at least comparable diagnostic performance to other models;

CO_2/HCO_3^- *based concepts complemented by the Henderson-Hasselbach equation and base excess calculations* [19]:

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

$$pH = pK + \log \frac{[HCO_3^-]}{[H_2CO_3]}.$$
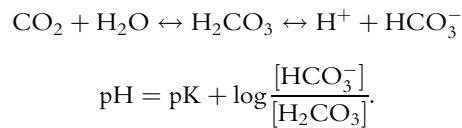
Although the CO_2/HCO_3^- model is familiar, it can fail to explain certain phenomena, e.g. hyperchloraemic acidosis, and many acids, including carbon dioxide itself, are not buffered primarily by this system. However, the *isohydric principle* dictates that for a solution of weak acids (including H_2CO_3, phosphate species and albumin) the aprote anions exist in equilibrium with a pool of common and exchangeable H^+ ions. Therefore, while the mechanism of acidosis may be *described* by the CO_2 : HCO_3^- ratio, changes in these parameters may not be the primary mechanism responsible [20, 21]. Furthermore, this principle dictates that whereas many buffers may be involved in determining the final acid-base status, it may be adequately described by a single buffer system and its relative dynamic changes, e.g. CO_2/HCO_3^- ratios.

3) *Physicochemical approach [1].* This model has been attributed to Stewart [22, 23] and even earlier as the buffer base [24, 25]. It applies the physical chemistry principles of electroneutrality, conservation of mass and dissociation of electrolytes. In doing so, advocates of this approach suggest it allows a quantitative calculation of the source of an acid-base disturbance and thus identifies the causative mechanism [26]. Acids are considered in recognition of the fact that water is the (almost infinite) source of H^+ determined by the three factors below. This model does challenge strict Lowry–Bronsted concepts,

which leaves acids such as Cl^- or carbon dioxide in a 'challenging' position [27]. The three independent variables which determine acid-base status are

- the strong ion difference (SID or buffer base in older texts);
- the P_{CO_2} (note that HCO_3^- and other carbon dioxide species now become *dependent* variables and the Henderson–Hasselbach mechanistic model is rejected);
- the total weak acid concentration including both associated (HA) and disassociated (A^-) anions (A_{tot}), for example albumin (reflecting its weakly acidic histidine moieties) and phosphate species, the latter contributing 9% of the A_{tot} [28–30].

Note that the strong ion difference (SID) is *not* identical to anion gap (AG) and it contains [lactate], although it does share a number of parameters and the trends will often be close. No robust SID has been determined in health, although quoted ranges of 40–42 $mEq.l^{-1}$ may be expected. During critical illness Story et al. [28] determined a median SID of 46.0 $mEq.l^{-1}$ and [weak acid] of 11.1 $mmol.l^{-1}$.

$$SID = ([Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}]) - ([Cl^-] + [lactate]).$$

As the SID approaches zero, anions 'accumulate' and acidity increases; this concept may appear abstract until one considers previous definitions of acids as aprote anions and bases as cations. This provides a physicochemical model for 'hyperchloraemic acidosis' following 0.9% saline administration [21], and the systemic alkalosis of hypoalbuminaemia (regarded as a weak acid). One criticism of the anion gap in the critically ill is it can be non-elevated in the presence of acidosis, although its calculation can be modified in critical illness [31, 32].

An additional concept to attempt to identify 'unmeasured' anions is the strong ion gap (SIG), which identifies a discrepancy between SID discussed above (SID apparent or SID_a) and a calculated SID (SID expected or effective or SID_e) and, as this value becomes positive ($SIG = SID_a - SID_e$), unmeasured anions are suspected [33]. The SID_e has been calculated using a variety of parameters and simplifications thereof, but most commonly relates to the carbon dioxide tension, [albumin], [phosphate] and measured pH with multiplication factors for each term. Other bedside simplification reduces SID_e to $[A_{tot}]$ + $[HCO_3^-]$ but this appears at odds with the physicochemical principle of disregarding $[HCO_3^-]$ as a *dependent* variable.

Although this approach has merits and can explain a number of observed phenomena [34] the equations are cumbersome and have multiple values which can be affected by critical illness and increase errors in calcula-

tion. It can produce counterintuitive scenarios, e.g. hyperalbuminaemia could become a metabolic acidosis due to accumulation of A_{tot} [25, 29]. The distinctions between 'strong' ions and 'weak' ions are also pH dependent and arguably arbitary [25]. On a practical level some workers have simplified the equations for clinical use while retaining their predictive values [35]. Other workers have sought to combine the base excess and accessible components of the Stewart hypothesis (SID and [total weak acid]) [36–38].

It is probably most useful to regard these different approaches as 'perspectives' from which to view changes in $[H^+]$ rather than any one being correct or false. For example, Stewart himself defined the *degree* of acidosis with pH and $[H^+]$ and base excess, but felt alternative models could not explain the *mechanism*. The different models have strengths and weaknesses in research, the laboratory and at the bedside and it is inappropriate to mandate any one approach [25, 39, 40]. A recent comparison of these models demonstrated that, provided the anion gap was corrected for [albumin] (see below), physicochemical approaches add little in terms of diagnosis and/or prognosis when compared to simpler anion gap and base excess/HCO_3^- techniques [41].

Base excess and standard bicarbonate

The base excess is defined as the quantity of strong acid required to titrate blood to pH 7.40 with a P_aCO_2 of 40 mmHg (5.33 kPa) at 37 °C [25]. In practice, acid is not titrated as suggested but calculated using a variety of established formulae or normograms. The base excess thus 'removes' the respiratory element of acid-base disturbance and identifies the metabolic contribution to interpret with pH and $[H^+]$ [42]. The standard bicarbonate is broadly similar and is the calculated $[HCO_3^-]$ at a P_aCO_2 of 5.33 kPa. Although the base excess allows a metabolic acidosis to be diagnosed, it provides few clues as to the pathophysiology or underlying diagnosis.

Some workers suggest a working rule that strong acids may be titrated against the base excess, e.g. lactate of 5.0 $mmol.l^{-1}$ would be expected to have an associated base excess of -5.0 $mmol.l^{-1}$ if lactate were the only strong acid being produced (which is not typical in critical illness) [43]. The base excess is also calculated in vitro, yet in vivo there is a large pool of extracellular and interstitial fluid to equilibrate with, favouring the use of an 'extracellular base excess' using a plasma dilution of whole blood [44]. The genuinely independence of the calculated base excess measurement from concurrent respiratory changes in vivo is not known [45].

The anion gap

The most popular bedside classification of metabolic acidosis is to identify any non-routinely measured dissociated anion (equivalent to acid) utilising the concept of the anion gap. Following the principle of electrochemical neutrality, total [cations] must = total [anions], and so in considering the commonly measured cations and anions and subtracting them, a fixed number should be derived. As, in vitro, the measured cations are in excess, mathematically this 'gap' is filled with unmeasured anions ensuring electrochemical neutrality. There is never a 'real' anion gap, in line with the law of electrochemical neutrality; it is rather an *index* of non-routinely measured anions. The anion gap is calculated using the following formula:

$$\text{Anion gap (AG)} = ([Na^+] + [K^+]) - ([Cl^-] + [HCO_3^-]) \, \text{mmol}^{-1}.$$

The normal quoted range is 15–20 mmol.l^{-1} [46, 47]. By including four terms with inherent measurement errors this range should be interpreted allowing ± 2 mmol.l^{-1}. The normal range has been challenged in the setting of critical illness and some published formulae omit K^+ estimation. Decreasing the upper limit may increase the sensitivity in detecting acidic anions [48]. While the relationship between anion gap and pH changes has become widely accepted, concepts of titration of endogenous buffers, HCO_3^- and non-HCO_3^-, have not been supported by experimental models [49]. In theory the anion gap value increases with the accumulation of (acidic) anions in the body that are not routinely assayed. The anion gap alone has limitations in critical illness [50]. A pragmatic alternative is the $[Cl^-] : [Na^+]$ ratio which, if reduced < 0.79, is suggestive of a 'tissue acid' and thus elevated anion gap source in critically ill [51].

The anion gap in critical illness

Despite its limitations the anion gap represents a clinically useful tool at the bedside and will identify many causes of metabolic acidosis in the critically ill, especially when hypoalbuminaemia and lactate are considered. The metabolic acidosis of critical illness is typically multifactorial, often making a single diagnosis impossible or inappropriate. For example, in sepsis and multiple organ failure, elevated lactate and ketones in conjunction with unmeasured anions are common and overwhelm the alkalinising effects of hypoalbuminaemia.

There are many ways to affect the anion gap through manipulating concentrations of anions and cations [52]. However, two main potential sources of diagnostic error are possible in calculating the anion gap in patients who are critically ill:

1 *Iatrogenic hyperchloraemia* This typically arises due to volume loading in shock. Crystalloid 0.9% saline and most commercially available colloids (which are suspended in the former) are hyperchloraemic. This elevates the plasma chloride above 100 mmol.l^{-1} and thus makes an acidosis appear 'hyperchloraemic' (inferring normal anion gap) rather than a primary elevated anion gap acidosis, e.g. lactate. The possible consequences of hyperchloraemia are considered in the Part 2 of this review, but diagnostic confusion certainly occurs.

2 *Hypoalbuminaemia* and pan-endothelial dysfunction associated with a reduction in capillary reflection coefficient (capillary leak syndrome) is manifest by a rapid fall in the plasma albumin concentration. Albumin is a potent and plentiful contributor towards the normal anion gap, being an anion itself, and in the physicochemical approach is designated within A_{tot}. Therefore, as [albumin] falls it tends to reduce the size of the anion gap, or have an alkalinising effect. Various corrections are available and one (Figge's AG corrected, or AG_{corr}) approach is described below [53]:

$$(\text{normal albumin} = 40 \text{ g.}l^{-1})$$

$$\text{Albumin gap} = 40 - \text{apparent albumin}$$

$$AG_{corr} = AG + (\text{albumin gap}/4).$$

For example a patient with an albumin of 18 would have $(40 - 18)/4 = 5.5$ mmol.l^{-1} added to their original AG. It becomes apparent that with saline loading and hypoalbuminaemia, an apparent 'normal AG hyperchloraemic acidosis' is often more correctly an elevated AG_{corr} acidosis, due to the quirks of the AG formula.

Increased 'unmeasured' cations

The presence of an unmeasured cation will reduce the anion gap, and whilst this is rarely seen in clinical practice, both hypermagnesaemia and lithium toxicity can reduce the apparent anion gap, as can certain drugs, e.g. polymyxin B [54]. Similarly, this may occur with the excess of a paraprotein in conditions such as myeloma or Waldenstrom's macroglobulinaemia (immunoglobulins, unlike most plasma proteins, are strong cations). A reduction in plasma chloride or accumulation of another halide can also 'reduce' the apparent anion gap.

Metabolic and respiratory interactions, compensation, and 'mixed disorders'

Biological compensation mechanisms rarely correct the primary abnormality so the pH usually reflects the

primary or predominating problem. The clinical circumstances will place this in context.

Most metabolic acidosis is accompanied by 'respiratory compensation' and hyperventilation to 'blow off' carbon dioxide and produce a respiratory alkalosis *if the patient is able to manage that*. It is unusual for patients to blow carbon dioxide off much below 1.0 kPa and it is exceptionally rare to be able to sustain this. Indeed, following trauma the inability to reduce the $P_a\text{CO}_2$ may predict the need for tracheal intubation and ventilation [55]. The traditionally quoted compensatory adaptation is for the kidney to retain HCO_3^- over the ensuing 24–48 h and buffer the acidosis [56]. This model has, however, been challenged and a physicochemical explanation is of a reduction in plasma $[\text{Cl}^-]$, with elevated $[\text{HCO}_3^-]$ a secondary phenomenon [57].

In its clinical form, the Henderson–Hasselbach equation states:

$$\text{pH} = \text{pKa} + \log\frac{[\text{HCO}_3^-]}{[0.23\text{PaCO}_2]}$$

$$(\text{PaCO}_2 \text{ in kPa}).$$

As the pKa (6.1) is constant, for any given pH a ratio of $\text{HCO}_3^- : P_a\text{CO}_2$ is generated which demonstrates a fall in HCO_3^- with falling carbon dioxide. The isohydric principle dictates that the ratio of $\text{CO}_2 : \text{HCO}_3^-$ may 'define' a metabolic acidosis. Proponents of the physicochemical approach would suggest that these changes do not allow identification of mechanism, i.e. the HCO_3^- is a *dependent* variable and SID, A_{tot} and carbon dioxide will identify the cause. The application of physicochemical principles to patients with chronic obstructive pulmonary disease demonstrates that increasing $P_a\text{CO}_2$ is associated with increasing SID but that this represented a decrease in Cl^- which paralleled the HCO_3^- increase. The mechanism of metabolic compensation is a loss of chloride rather than a gain per se of HCO_3^- [58]. Other predictive rules of 'compensation' may be unreliable in chronic respiratory acidosis [59]. A variety of compensation relationships are described in the literature [60, 61] but we are increasingly being forced to challenge traditional concepts of HCO_3^- buffering as the predominant response to acid-base changes.

The reader is referred to the 'delta–delta gap', a bedside technique to identify mixed disorders. This is the arithmetic difference between the change in the AG and the $[\text{HCO}_3^-]$ (range -6 to $+6$ mmol.l^{-1}) or ratios of delta AG/delta HCO_3^- (ratio range 0.8–1.2, or more specifically absolute -8 to $+8$ mmol.l^{-1}) [62, 63]. Both techniques attempt to identify a discrepancy between a change in the AG (accumulation of acidic anion) and the $[\text{HCO}_3^-]$ (as an index of concurrent HCO_3^- retention). The validity of this technique is not assured and would be

rejected by physicochemical advocates as the $[\text{HCO}_3^-]$ is not independent.

Despite these developments there are accepted relationships between $P_a\text{CO}_2$ and HCO_3^- which attempt to distinguish between the expected degree of respiratory compensation ($P_a\text{CO}_2$) and a concurrent respiratory acid/alkalosis. One such relationship is [47]:

$$\text{PaCO}_2 = 0.2 \times [\text{HCO}_3^-] + 1 \pm 0.3 \text{ kPa}.$$

Diagnosis and classification of metabolic acidosis: putting it together

From the preceding discussion it is apparent that a variety of techniques may be used to evaluate acid-base disorders, and that we would regard these as different perspectives to view disorders rather than true or false. However, we would propose the following scheme for use 'at the bedside', and will adopt this approach when examining clinical aspects of metabolic acidosis in Part 2 of this review.

1 Identify metabolic acidosis through the pH, and the base excess.
2 Inspect the $P_a\text{CO}_2$ and whether it is appropriate for this level of acidosis [47].
3 Inspect the plasma [chloride] and the anion gap, and calculate the AG$_{corr}$ if hypoalbuminaemia is present [53].
4 Proceed to consider the clinical context, causes of high and low AG$_{corr}$ metabolic acidosis, and the additional calculations which may be made for unidentified acidic anions.

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