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A case-based review of a simplified quantitative approach to acid-base analysis

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Abstract

Objective – To present a simplified quantitative approach to acid-base analysis and to demonstrate its clinical utility.

Data Sources – Original research articles and textbooks.

Data Synthesis – A simplified quantitative approach to acid-base analysis is presented, which is derived from the Fencl-Stewart approach and calculates the magnitude of the effect on the standardized base excess (SBE) of 5 separate variables: (1) a free water effect (marked by sodium concentration), (2) an effect marked by the chloride concentration, (3) an albumin effect, (4) a lactate effect, and (5) a phosphate effect. Six clinical cases with acid-base abnormalities are presented in which the quantitative approach provides information that is not apparent from the traditional approach.

Conclusion – This simplified quantitative approach provides a comprehensive evaluation of complex acid-base disorders, identifies individual processes and their relative influence on SBE, and aids in the development of an appropriate therapeutic plan.

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Keywords: hypoproteinemia, lactic acidosis, metabolic acidosis, metabolic alkalosis

Introduction

The hydrogen ion concentration ($[H^+]$) of a living organism has important effects on molecular function, and homeostatic mechanisms aim to maintain $[H^+]$ within narrow physiologic limits.[1] The $[H^+]$ is usually expressed as pH, the negative base 10 logarithm of $[H^+]$. The normal blood pH of most domestic mammals is approximately 7.4. An elevation in blood $[H^+]$ is an acidemia and is evidenced by a pH less than normal while a decrease in blood $[H^+]$ is an alkalemia and will be marked by increases in pH. The pH of a living system is the net result of many individual contributors to acid-base balance. These processes have been broadly divided into carbonic acid, which is designated as the respiratory component and defined by the partial pressure of carbon dioxide (PCO_2), and the non-carbonic acids, which are designated as the metabolic component and variably defined by several parameters.[1,2]

The metabolic contribution to acid-base balance is the cumulative effect of many individual physiologic processes. Conventional acid-base analysis recognizes and characterizes the magnitude of respiratory and metabolic abnormalities but the nature of the metabolic abnormality is not further characterized. A more comprehensive analysis could identify and quantitate many of the important individual contributors to the metabolic component of the acid-base balance. This approach could enable the development of a treatment plan that is more specifically tailored to the patient's problems. A simple, effective, quantitative approach, which we believe accomplishes this goal, is herein presented.

The carbonic acid/bicarbonate buffer system, as represented in the following equation, is quantitatively the most important in the body. This is because PCO_2 can be regulated independently of changes in bicarbonate concentration, via alveolar ventilation, which increases the efficiency of bicarbonate buffering dramatically.[2,3]

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

All buffer systems in the body are in equilibrium, and any acid with its conjugate base may be used to define

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Table 1: Expected compensatory changes to primary acid base disorders for dogs[5]

Primary disorder	Expected compensation
Metabolic acidosis	↓ $PaCO_2$ of 0.7 mm Hg per 1 mEq/L ↓ $HCO_3 \pm 3$
Metabolic alkalosis	↑ $PaCO_2$ of 0.7 mm Hg per 1 mEq/L ↑ $HCO_3 \pm 2$
Respiratory acidosis – acute	↑ HCO_3 of 0.15 mEq/L per 1 mm Hg ↑ $PaCO_2 \pm 2$
Respiratory acidosis – chronic	↑ HCO_3 of 0.35 mEq/L per 1 mm Hg ↑ $PaCO_2 \pm 2$
Respiratory alkalosis – acute	↓ HCO_3 of 0.25 mEq/L per 1 mm Hg ↓ $PaCO_2 \pm 2$
Respiratory alkalosis – chronic	↓ HCO_3 of 0.55 mEq/L per 1 mm Hg ↓ $PaCO_2 \pm 2$

pH; typically the carbonic acid/bicarbonate system has been used. There are 4 primary acid-base disturbances defined by the carbonic acid/bicarbonate buffer system. An increase in carbon dioxide drives the above carbonic acid equation to the right, leading to increased $[H^+]$ and hence has an acidotic effect; a respiratory acidosis. A decrease in carbon dioxide has the opposite effect, a respiratory alkalosis. Elevations in the concentration of bicarbonate will shift the carbonic acid equation to the left, $[H^+]$ will decrease; a metabolic alkalosis. A reduction in bicarbonate concentration will have the opposite effect, a metabolic acidosis.

When a primary acid-base disturbance occurs, a secondary compensatory response in the opposing system is expected to minimize the overall change in pH. For example, a primary metabolic acidosis should be compensated by a respiratory alkalosis. The respiratory response to a primary metabolic abnormality is rapid in onset and complete within hours (assuming a stable level of the metabolic abnormality).[4,5] In comparison, the metabolic compensatory response to a primary respiratory disorder takes hours to begin and 2–5 days to complete.[5,6] The degree of expected compensation in dogs is commonly estimated from guidelines derived from healthy experimental animals (Table 1).[5] If the change in the secondary system observed in a patient is of a magnitude similar to the calculated, expected response compensation is confirmed and the assessment is a simple acid-base disorder. In other words the change in the secondary system is completely attributed to compensation and no other acid-base abnormality is suspected.

A mixed acid-base disorder is diagnosed when there are abnormalities present in both the respiratory and metabolic systems that are not attributable solely to compensation. A mixed disorder is present when both systems have the same abnormality. For example, a coexisting respiratory and metabolic acidosis. In addition a mixed disorder is diagnosed when the changes in the secondary system are not within a range compatible with expected compensation for a primary disorder. The assumption is that there is some disturbance of the secondary system preventing appropriate compensation from occurring. Some caution is needed when interpreting the appropriateness of metabolic compensation to a primary respiratory disorder as it will depend on the chronicity of the respiratory abnormality, which may or may not be accurately determined. There are no published guidelines for the compensatory responses of cats. The canine values are commonly used as a guideline for evaluating acid-base status in cats but the accuracy of this approach is unknown. Cats may demonstrate similar metabolic compensation for respiratory disorders as dogs, although 2 of the 3 studies on this topic were performed in anesthetized cats.[7–9] There is a single study in the literature reporting that cats do not develop respiratory compensation in response to a metabolic acidosis and there are no studies evaluating the respiratory response of adult cats to a metabolic alkalosis.[10] Consequently extrapolation of the canine calculations of expected metabolic compensation to respiratory disorders should be performed with caution in cats. Extrapolation of the canine calculations of expected respiratory compensation to metabolic disorders cannot be recommended in cats.

When a primary acid-base abnormality is identified, a list of common possible causes should be considered (Table 2). Each potential cause is then ruled in or out, keeping in mind that the patient's current clinical status may be a combination of several processes and that it is quite acceptable to cite multiple causes for the respiratory or metabolic abnormality. The calculations used to determine expected compensation are derived from a small number of healthy, experimental dogs with stable primary acid-base abnormalities of known duration. The validity of these calculations in a broad population of unhealthy animals is unknown. As a consequence the authors suggest that when appropriate compensation is identified it should be considered a possible cause of the abnormality in question, not the definitive diagnosis. In other words, when appropriate compensation is identified, a simple acid-base disorder is not assumed. Rather the clinician adds compensation to the list of rule-outs for the changes in that system. The change in the secondary system should be considered compensation when there are no other identifiable causes for the deviation and the magnitude of the compensation is appropriate (Table 1).

Evaluation of the metabolic acid-base component

The Henderson-Hasselbalch equation provides a convenient way to represent the influence of the carbonic acid/bicarbonate system on pH and forms the basis of

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Table 2: Common causes of acid-base abnormalities

Normal anion gap (hyperchloremia)	Intestinal fluid loss
	Renal tubular acidosis
	Iatrogenic – 0.9% NaCl administration
	Carbonic anhydrase inhibitors
	Compensation for respiratory alkalosis
Elevated anion gap (Normochloremia)	Lactic acidosis
	Hyperphosphatemia
	Ketoacids
	Intoxications – ethylene glycol
	Salicylates
	Metaldehyde
Metabolic alkalosis	Gastric hydrogen ion loss
	vomiting
	gastric suctioning
	Renal hydrogen ion loss
	loop or thiazide diuretics
	mineralocorticoid excess
	high-dose penicillin derivative antibiotics
	Intracellular shifts of hydrogen ions
	hypokalemia
	refeeding syndrome
	Contraction alkalosis
	Posthypercapnic alkalosis
	Iatrogenic – alkali administration
	Compensation for respiratory acidosis
Respiratory acidosis	Rebreathing (mechanical deadspace)
	Airway obstruction
	Central respiratory depression
	Neuromuscular disease
	Malignant hyperthermia
	Carbohydrate-rich parenteral nutrition
	Compensation for metabolic alkalosis
Respiratory alkalosis	Hypotension
	Systemic inflammatory response syndrome
	Exercise, excitement, pain
	Pulmonary parenchymal disease
	Compensation for metabolic acidosis

Table 3: Acid-base formulas[5,22–24]

Parameter	Formula
Henderson–Hasselbalch	$pH = 6.1 + \log([HCO_3^-]/0.03 \times PCO_2)$
Anion gap	$([Na^+]+[K^+]) - ([HCO_3^-]+[Cl^-])$
Free water effect	
Dogs	0.25 ($[Na^+]$ – normal $[Na^+]$)
Cats	0.22 ($[Na^+]$ – normal $[Na^+]$)
Corrected chloride	Measured $[Cl^-] \times$ (normal $[Na^+]$/ measured $[Na^+]$)
Chloride effect	Normal $[Cl^-]$ – corrected $[Cl^-]$
Phosphate effect	0.58 (normal [phos mg/dL] – measured [phos mg/dL])
Phosphate effect (mmol/L)	1.8 (normal [phos mmol/L] – measured [phos mmol/L])
Albumin effect	3.7 (3.1-measured [albumin g/dL])
Albumin effect (g/L)	0.37 (31-measured [albumin g/L]
Lactate effect	$-1 \times$ [lactate]
Sum of effects	Free water effect + chloride effect + phosphate effect + albumin effect + lactate effect
Unmeasured anion effect	Standardized Base Excess – Sum

HCO_3-, bicarbonate concentration (mEq/L); PCO_2, partial pressure of carbon dioxide (mm Hg); $[Na^+]$, sodium concentration (mEq/L); $[K^+]$, potassium concentration (mEq/L); $[Cl^-]$, chloride concentration (mEq/L); [phos], phosphorus concentration; [albumin], albumin concentration; [lactate], lactate concentration (mmol/L).

the conventional approach to acid-base analysis (Table 3).[11] In this approach bicarbonate concentration has been used to mark the metabolic contribution to the pH. Total carbon dioxide concentration is a common alternative to bicarbonate since most of the plasma carbon dioxide is in the form of bicarbonate.[12] It has long been recognized that bicarbonate concentration varies with changes in PCO_2 due to the direct influence of PCO_2 on the carbonic acid equation. This introduces a small degree of error in the interpretation of the bicarbonate concentration when significant respiratory abnormalities exist. Using the Siggaard-Andersen alignment nomogram, the bicarbonate concentration decreases to 21 mEq/L at a PCO_2 of 20 mm Hg (standardized base excess [SBE] = 0 mEq/L) and increases to 27 mEq/L at a PCO_2 of 80 mm Hg (SBE = 0 mEq/L).[13] Standard bicarbonate represents the bicarbonate concentration of the plasma sample when the PCO_2 is adjusted to 40 mm Hg.

The SBE is the purest marker of the metabolic component because it is standardized to a PCO_2 of 40 mm Hg (like standard bicarbonate) and incorporates the effect of hemoglobin as a buffer. It reflects the titratable strong acid or base needed to restore the arterial plasma pH of 1 L of extracellular fluid with fully oxygenated hemoglobin to pH 7.4 at a PCO_2 of 40 mm Hg and a temperature of 37 °C.[14] It is usually calculated by formulas programmed into the blood gas analyzer. Normal SBE values are about zero in humans and dogs, and are slightly more negative in cats (Table 4).[2,15,16] A negative SBE (a deficit of base) is indicative of a metabolic acidosis while a positive SBE indicates a metabolic alkalosis.

Bicarbonate and total carbon dioxide concentrations and SBE represent the net metabolic contribution to hydrogen ion balance; they do not identify the relative contribution of individual metabolic processes. There are several analytical methods available that attempt to further characterize the metabolic component. Anion gap (Table 3) divides metabolic acidosis into 2 broad categories: elevated anion gap (normochloremic) metabolic acidosis and normal anion gap (hyperchloremic) metabolic acidosis.[17] As shown in Table 3, anion gap is calculated as the difference between the major cations

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Table 4: Reference ranges for acid base and biochemical parameters in dogs and cats [11,12]

Parameter	Canine	Feline
Arterial values		
pH	7.407 (7.351–7.463)	7.386 (7.310–7.462)
PCO_2 (mm Hg)	36.8 (30.8–42.8)	31.0 (25.2–36.8)
HCO_3- (mEq/L)	22.2 (18.8–25.6)	18 (14.4–21.6)
SBE (mEq/L)	-1.8 (-0.2 to $+3.4$)	-6 ± 4.8
Venous values		
pH	7.397 (7.351–7.443)	7.343 (7.277–7.409)
PCO_2 (mm Hg)	37.4 (33.6–41.2)	38.7 (32.7–44.7)
HCO_3 (mEq/L)	22.5 (20.8–24.2)	20.6 (18.0–23.2)
SBE (mEq/L)	-1.2 ± 1.1	-5 ± 4.2
Na^+ (mEq/L)	145–154 (146)	151–158 (156)
Cl^- (mEq/L)	105–116 (110)	113–121 (120)
K^+ (mEq/L)	4.1–5.3	3.6–4.9
Lactate (mmol/L)	<2	<1.46
Phosphorus (mg/dL)	3.0–6.2 (3.9)	3.2–6.3 (5.0)
Phosphorus (mmol/L)	0.96–2.0 (1.25)	1.0–2.0 (1.6)
Albumin (g/dL)	2.9–4.2 (3.1)	1.9–3.9 (3.1)
Albumin (g/L)	29–42 (31)	19–39 (31)
Anion gap	12–25	15–28

Table represents published reference values of common acid-base parameters. It is recommended that readers use reference values specific for their laboratory or instrument used when interpreting values for individual patients.
SBE, standardized base excess.

and the major anions measured in plasma. In reality the total number of cations always equals the total number of anions but because a greater proportion of cations are routinely measured, in comparison with anions, there is an apparent differential between the 2 (the anion gap). Accumulation of acids such as ketoacids or lactic acid will decrease the bicarbonate concentration and increase the concentration of ketone or lactate anions. Because these are not normally measured, the calculated anion gap will be increased. In contrast, the loss of sodium bicarbonate in gastrointestinal disease, for example, is associated with hydrogen chloride retention; producing a metabolic acidosis with hyperchloremia and no change in the calculated anion gap. Albumin is the major unmeasured anion in the normal state. Hypoalbuminemia decreases anion gap and obscures the presence of anions which would otherwise increase the anion gap.[18,19] For instance a hypoalbuminemic dog with a lactic acidosis may have a calculated anion gap within the normal range suggesting the absence of anions such as lactate. The anion gap provides only broad categorization of metabolic acid-base abnormalities and cannot be interpreted in hypoalbuminemic patients.

The Stewart principles of acid-base chemistry provide an alternative approach to acid-base analysis. According to the Stewart approach there are 3 independent determinants of acid-base balance: partial pressure of carbon dioxide, the difference between strong cations and strong anions (strong ion difference [SID]), and total weak acids (A_{TOT}). SID and A_{TOT} are proposed to affect $[H^+]$ directly by altering the dissociation of water via electrochemical forces. Metabolic acidosis is proposed to be caused by a decrease in SID or an increase in A_{TOT} while a metabolic alkalosis is caused by an increase in SID or a decrease in A_{TOT}.[20,21] Strong ions are considered to be any ion that is fully dissociated at physiologic pH. Quantitatively sodium and chloride are the most important strong ions in the body and SID is commonly simply calculated as the difference between serum sodium and chloride concentration. A_{TOT} is primarily composed of albumin and phosphorus, and formulas to calculate their contribution to acid-base balance can be found in the literature.[21–23]

Several misconceptions have arisen from the Stewart approach. The most common is that sodium and chloride ions cause changes in pH while bicarbonate does not. Sodium and chloride are aprote ions (neither donate nor accept H^+) and cannot, per se, cause a change in pH. All changes in pH are, by definition, due to a change in $[H^+]$. Although based on a misconception, the Stewart approach can be used to aid identification of processes that impact acid-base balance. In addition, SID and A_{TOT} are aggregate indices, much like anion gap, that may reflect general acid-base abnormalities, but they are not specific. We propose that because the individual parameters required to calculate SID and A_{TOT} have to be measured in the first place, it would be more useful to calculate the individual contribution to the acid-base balance each parameter represents. This approach would provide a more comprehensive appreciation of the magnitude of the individual contributions and would provide clinically relevant information. This is the tenet of the Fencl modification of the Stewart approach.[24–26]

The Fencl-Stewart approach uses equations to estimate the magnitude of effect on SBE represented by 5 individual parameters. These parameters are: (1) a free water effect (marked by sodium concentration), (2) an effect represented by changes in chloride concentration, (3) an albumin effect, (4) a lactate effect, and (5) a phosphate effect. Differences between the sum total of all these known calculated effects and the SBE are attributed to the presence of unmeasured (unknown) acids or alkalis. The formulas used to determine these effects were developed using the Stewart principles of acid-base chemistry (Table 3).[24,27] Quantitative acid-base analysis as presented here requires measurement of pH and PCO_2, calculation of SBE and measurement of as many of the following parameters as possible: sodium, chloride, albumin, lactate, and phosphorus. From these

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Table 5: Acid-base effect of individual abnormalities identified with the quantitative acid-base approach

Alkalinizing	Acidifying
Free water deficit (hypernatremia)	Free water excess (hyponatremia)
Hypochloremia	Hyperchloremia
Hypoalbuminemia	Hyperalbuminemia
Increased unmeasured cations	Hyperphosphatemia
	Hyperlactatemia
	Increased unmeasured anions

measured parameters 8 metabolic acid-base influences can be identified and the magnitude of their contribution to the overall SBE estimated (Table 5). Normal values for these parameters are given in Table 4.

The free water effect is due to a change in the water concentration. Clinically, the free water concentration is marked by sodium concentration; a deficit of free water causing hypernatremia and an excess of free water causing hyponatremia. An excess of free water (hyponatremia) will have an acidotic effect; a dilutional acidosis. A deficit of free water (hypernatremia) will have an alkalotic effect; a contraction alkalosis (Table 5).[28] To calculate the free water effect, the change in sodium concentration is multiplied by a constant (Table 3): 0.25 in dogs and 0.22 in cats.[24,27]

In many processes within the body, chloride and bicarbonate are reciprocally linked (ie, when a chloride ion is excreted, a bicarbonate ion is retained and vice versa). Such processes include gastric acid secretion, intestinal bicarbonate secretion, renal acid-base handling, and transcellular ion exchange. Evaluation of the change in chloride concentration can therefore be used to estimate the contribution to acid-base balance made by these processes. Because chloride concentration will also be altered by changes in free water concentration, this effect will have to be corrected before calculation of the chloride effect (Table 3). The difference between this corrected chloride concentration and the patient's normal chloride concentration estimates the contribution by processes associated with the change in chloride concentration (and thus estimates the associated change in bicarbonate) (Table 3). An increased chloride effect is associated with a process that decreases bicarbonate concentration and is indicative of an acidotic process; a decreased chloride effect marks an alkalotic process (Table 5). The quantitative change in the chloride effect seldom equals the change in bicarbonate concentration because bicarbonate concentration is in turn affected by all of the other buffer systems.

Albumin acts as a weak acid. It has many H^+ binding sites associated with the imidazole group of the amino acid histidine. Hypoalbuminemia is equivalent to the removal of a weak acid from the system and therefore has an alkalotic effect; conversely, hyperalbuminemia has an acidotic effect.[29,30] There are species differences in the net negative charge of albumin. Species specific equations for albumin's effect on SBE for dogs and cats have not been derived hence there maybe some degree of inaccuracy in this calculation.

Lactate is the byproduct of cytosolic glycolysis and is produced during anaerobic metabolism when pyruvate is not incorporated by the Kreb's cycle. Pyruvate is converted to lactate in order to regenerate nicotinamide adenine dinucleotide to allow ongoing glycolysis.[31,32] Lactate can also be produced in situations of increased glycolysis or mitochondrial dysfunction.[31,33] Concurrent with the anaerobic production of lactate is an equimolar production of H^+ as a consequence of the hydrolysis of ATP.[31,34] Lactate is the conjugate base of lactic acid and its plasma concentration is used as a marker of lactic acidosis, a common abnormality in critically ill patients. With the advent of affordable lactate analyzers it is now common practice to measure serum lactate concentration. Endogenously produced lactic acid has approximately an equimolar effect on SBE (Table 3). Meaning that for every mole of lactate produced 1 mole of H^+ is produced leading to a decrease in the SBE by approximately 1 mole. Although the relationship between lactate concentration and acidosis is true for conditions such as anaerobic metabolism, there are causes of hyperlactatemia that are associated with little or no acidosis. For example, hyperlactatemia can occur in the absence of acidosis as a result of cytokine-mediated increases in glucose metabolism, hyperventilation, β-adrenergic receptor agonists, and contamination of blood samples with lactated Ringer's solution.[33,35,36]

Phosphoric and sulfuric acids are products of protein metabolism and are normally excreted by the kidneys. Renal failure patients retain these acids, resulting in a metabolic acidosis.[1,2] There exists an equilibrium between inorganic phosphorus, as it is measured on a chemistry panel, and organic phosphorus, in phosphoric acid. This allows estimation of the phosphoric acid contribution from a given inorganic phosphorus concentration by use of the equation in Table 3. Hyperphosphatemia is an important cause of acidosis. However, because serum phosphorus concentration is normally low, hypophosphatemia does not cause clinically significant alkalosis. Sulfate is not usually measured and is therefore one of the unmeasured anions.

This quantitative approach identifies many of the relevant contributors to the metabolic acid-base component. The difference between the sum of these effects and the patient's SBE represents unidentified acids or alkalis contributing to the acid-base equilibrium (Table 3). Unmeasured acids include ketoacids, sulfuric acid, ethylene glycol, salicylic acid, propylene glycol,

Table 6: Measured acid-base, electrolyte, and biochemical values of venous blood for Cases 1–6

Parameter	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Species	Canine	Canine	Canine	Canine	Feline	Feline
pH	7.501	7.480	7.104	7.047	7.350	7.427
PCO_2 (mm Hg)	47.4	56.4	38.5	32.5	42.4	43.8
HCO_3^- (mEq/L)	36.3	41.5	10.8	8.3	23.9	27.8
SBE	12.4	16.7	− 16.9	− 19.9	− 1.2	4.0
Na^+ (mEq/L)	163	128	148	120	146	161
Cl^- (mEq/L)	113	71	120	75	99	111
K^+ (mEq/L)	3.5	2.1	4.0	3.3	2.3	4.9
Ca^{2+} (mmol/L)	1.19	1.09	1.0	0.54	1.06	1.1
Phosphorus (mg/dL)	9.4	3.9	11.6	14.3	10	17.8
Phosphorus (mmol/L)	3.0	1.25	3.7	4.6	3.2	5.7
Albumin (g/dL)	2.4	4.1	1.0	3.2	2.1	2.1
Albumin (g/L)	24	41	10	32	21	21
Anion gap (mEq/L)	17.2	17.6	21.2	40	25.4	27.1

SBE, standardized base excess.

metaldehyde, D-lactate, and ethanol.[37] This calculation is more meaningful than anion gap because it takes into consideration more of the identifiable factors.[38]

To demonstrate the clinical application of this simplified quantitative approach to acid-base analysis, we chose 6 clinical cases in which the approach enhanced our understanding of the case compared with the conventional approach (Tables 6 and 7).

Case 1

A 10-year-old, spayed female Boxer with a history of diabetes insipidus was presented for evaluation of vomiting.

Conventional analysis (Table 6)

This patient has a severe alkalemia (pH = 7.501), a metabolic alkalosis (SBE = 12.4 mEq/L) with a concurrent respiratory acidosis (PCO_2 = 47.4 mm Hg). The degree of respiratory acidosis is consistent with appropriate compensation. *Assessment*: metabolic alkalosis attributed to gastric fluid loss (Table 3).

Quantitative analysis (Table 7)

The significant alkalosis is due to the combined effects marked by hypochloremia most likely as a result of vomiting (renal mechanisms cannot be ruled out), loss of free water via the kidneys due to diabetes insipidus, and hypoalbuminemia. The severity of this alkalosis is reduced by the coexisting acidotic effect of hyperphosphatemia.

Although there is no doubt the loss of hydrochloric acid secondary to vomiting is a major contribution to this patient's acid-base disorder, it is an oversimplification to consider only this process. The quantitative approach identifies the additional contribution of the loss of free water and hypoalbuminemia. While correcting the hypochloremia with a chloride-rich crystalloid remains the mainstay of therapy, the acid-base

Table 7: Measured lactate concentration and calculated quantitative acid-base values of venous blood for Cases 1–6

Parameter	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Species	Canine	Canine	Canine	Canine	Feline	Feline
SBE (mEq/L)	12.4	16.7	− 16.9	− 19.9	− 1.2	4.0
Lactate (mmol/L)	0.6	2.0	1.5	8.7	9.54	0.93
Corrected chloride	101.2	81.0	118.4	91.3	105.8	107.6
Chloride effect	8.8	29.0	− 8.4	18.8	14.2	12.5
Free water effect	4.3	− 4.5	0.5	− 6.5	− 2.2	1.1
Phosphate effect	− 3.2	0	− 4.5	− 6.0	− 2.9	− 7.4
Albumin effect	2.6	− 3.7	7.8	− 0.4	3.7	3.7
Lactate effect	− 0.6	− 2.0	− 1.5	− 8.7	− 9.5	− 0.9
Sum	11.8	18.8	− 6.1	− 2.9	3.3	8.9
Unmeasured anion effect	0.6	− 2.1	− 10.8	− 17.0	− 4.5	− 4.9

SBE, standardized base excess.

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picture can be further improved by correcting the free water and albumin abnormalities.

Case 2

A 6-month-old castrated male Toy Poodle was presented for evaluation of vomiting.

Traditional analysis (Table 6)
This patient has an alkalemia (pH = 7.480) due to a primary metabolic alkalosis (SBE = 16.7 mEq/L); the respiratory response is within the range predicted for appropriate compensation. The anion gap is normal and so the accumulation of unmeasured anions is unlikely. *Assessment*: metabolic alkalosis secondary to loss of gastric acid.

Quantitative analysis (Table 7)
Quantitative analysis reveals several coexisting acid-base abnormalities in this patient. The large alkalotic effect on base excess marked by the hypochloremia is attributed to gastric acid (HCl) loss. The severity of this alkalinizing effect is somewhat offset by the acidotic effects of the excess in free water and the high albumin level. There is also a mild increase in blood lactate levels.

The focus of therapy of this case is to stop the vomiting. The electrolyte and albumin concentration abnormalities can be corrected by the administration of a high chloride, high sodium crystalloid. Increasing the sodium concentration (decreasing the water concentration) and decreasing the albumin concentration will have an alkalinizing effect that will be more than offset by the acidifying effect of correcting the hypochloremia.

Case 3

A 7-year-old castrated male Maltese with sepsis and multiple organ dysfunction syndrome.

Traditional analysis (Table 6)
This patient has a severe acidemia (pH = 7.104) and a metabolic acidosis (SBE = –16.9 mEq/L) with a normal PCO_2. The lack of a compensatory respiratory alkalosis suggests the presence of a separate disorder preventing appropriate hyperventilation, making this a mixed disorder. The anion gap is within the normal range, suggesting the absence of unmeasured anions. *Assessment*: A mixed acid-base disorder; a normal anion gap, hyperchloremic metabolic acidosis without respiratory compensation. Causes of a non-anion gap metabolic acidosis include intestinal bicarbonate loss, renal tubular acidosis, and prolonged administration of 0.9% sodium chloride (Table 3). Processes preventing appropriate hyperventilation include sedative or analgesic drug administration, preexisting or acquired neurological or respiratory muscular disease (Table 3).

Quantitative analysis (Table 7)
The acidosis in this patient is due to the combined effects marked by hyperchloremia and hyperphosphatemia. In addition there is a large, unmeasured acidotic effect. These processes are offset by a significant alkalinizing effect of hypoalbuminemia. The increased anion gap that would be expected given the hyperphosphatemia and potentially the presence of other unmeasured anions, is obscured by the concurrent hypoalbuminemia. This case is an example of a complex acid-base disorder that cannot be fully appreciated by traditional analysis. Substantial acidotic and alkalotic processes coexist in this patient, and hypoalbuminemia renders the anion gap uninterpretable. The hyperchloremia marks an acidosis that could be due to excessive administration of 0.9% sodium chloride, gastrointestinal losses of bicarbonate-rich fluids, or renal tubular acidosis, the hyperphosphatemia is attributed to renal disease, and the hypoalbuminemia is likely a consequence of increased losses, reduced hepatic production, and dilution by administration of albumin-free fluids.

Therapy of this case with the conventional knowledge might focus on a fluid plan designed to lower serum chloride concentration and potentially sodium bicarbonate administration. The quantitative analysis identifies hyperphosphatemia as an important contributor to the acidosis in this patient. Furthermore the quantitative approach identifies the profound acid-base impact of the hypoalbuminemia. Independently increasing the serum albumin concentration would worsen the metabolic acidosis. This case is also an example of the misleading nature of the anion gap calculation in patients with hypoalbuminemia.

Case 4

A 12-year-old spayed female Poodle was presented for evaluation of weakness and labored breathing. A severe hyperglycemia (> 55 mmol/L [1000 mg/dL]) was noted on the initial bloodwork and the urine was positive for ketones on a dipstick.

Traditional analysis (Table 6)
This is a severe acidemia (pH = 7.047) due to a primary metabolic acidosis (SBE = – 19.9 mEq/L); there is a concurrent respiratory alkalosis that is in the range predicted for appropriate compensation. The anion gap is elevated at 40 mEq/L suggesting the presence of unmeasured anions (Table 3). The concurrent hyperglycemia and ketonuria is diagnostic for diabetic

ketoacidosis. *Assessment*: high anion gap metabolic acidosis due to ketoacidosis.

Quantitative Analysis (Table 7)
The severe metabolic acidosis is due to a combination of lactic acidosis, excess free water, hyperphosphatemia, and an unmeasured acidotic effect (presumably ketones). The lactic acidosis is most likely due to anaerobic metabolism and evaluation of the patient's perfusion parameters, oxygenating ability, and hemoglobin concentration is warranted. The hyponatremia in this patient is due to the osmotic effects of hyperglycemia drawing free water from the intracellular space to the extracellular space. This extra free water would have an acidifying effect on the acid-base balance. The unmeasured acidotic effect is likely to be due to ketoacids and possibly other uremic toxins in addition to the hyperphosphatemia. The concurrent hypochloremia marks a significant alkalotic effect, reducing the overall severity of the apparent acidosis (without this chloride effect, the SBE could have been as low as -39 mEq/L) and may be due to gastric or renal hydrogen ion loss. This case is a good example of the importance of calculating the corrected chloride for abnormalities in free water concentration before assessing the acid-base effect. The measured chloride is 35 mEq/L lower than normal but when this number is corrected for the excess free water present in this patient (using the formula in Table 3) the corrected value is only 19 mEq/L lower than normal. It is this corrected value that most accurately represents the change in bicarbonate associated with chloride exchange. The quantitative approach in this patient is able to elucidate multiple, coexisting metabolic acid-base abnormalities.

Therapy based on the conventional analysis would have focused on resolution of the ketoacidotic state. The quantitative analysis reveals a significant lactic acidosis that emphasizes the requirement for fluid resuscitation in this patient before insulin therapy. The severe hyperphosphatemia could be due to prerenal or renal causes and requires further patient evaluation; the ultimate treatment plan will depend on the primary cause of the hyperphosphatemia. The excess extracellular free water will resolve with resolution of the hyperglycemia.

Case 5

A 17-year-old castrated male domestic shorthair cat was presented for evaluation of chronic renal failure.

Traditional analysis (Table 6)
This patient has a normal pH and a normal SBE. The venous PCO_2 (42.4 mm Hg) is within the normal range for a cat. *Assessment*: There are no acid-base abnormalities evident.

Quantitative analysis (Table 7)
Despite a normal overall metabolic acid-base balance, the quantitative evaluation reveals serious underlying abnormalities. There is a significant hyperlactatemia, hyperphosphatemia, and hyponatremia, all of which represent an acidifying effect on the SBE. This is counteracted by a significant alkalinizing effect marked by a severe hypochloremia and modest hypoalbuminemia. The net effect is a rather minor change to the overall pH and SBE.

There is no therapy indicated by the conventional acid-base analysis. The quantitative approach however identifies a significant lactic acidosis that warrants further assessment and resuscitation of the patient. In addition, an effective fluid therapy plan is warranted to reduce the severity of the uremia and resolve the electrolyte abnormalities. This case demonstrates the ability of the quantitative approach to identify many coexisting acid-base disorders that could not be appreciated by conventional acid-base analysis.

Case 6

A 6-year-old castrated male domestic shorthair cat was presented for evaluation of chronic renal failure.

Traditional analysis (Table 6)
This is an alkalemia (pH = 7.427) due to a metabolic alkalosis (SBE = 4 mEq/L) with a concurrent respiratory acidosis. *Assessment*: Mild metabolic alkalosis, possible causes include gastric fluid loss, diuretic administration, hyperaldosteronism, and hyperadrenocorticism (Table 3). The respiratory acidosis may be due to appropriate compensation but no guidelines are available to help support this conclusion. Other causes of a respiratory acidosis include central respiratory depression secondary to intracranial disease such as neoplasia or extracranial disease such as uremic encephalopathy. Muscular weakness secondary to chronic disease and cachexia or electrolyte abnormalities such as hypokalemia could also contribute.

Quantitative analysis (Table 7)
Despite what appears to be a relatively mild abnormality, there is a significant alkalinizing process present marked by the hypochloremia. In addition, there is a large hyperphosphatemic acidifying effect. The overall result is a mild change in pH despite the presence of severe underlying abnormalities.

Specific therapy for the alkalosis in this case would depend on its primary cause. Gastric (vomiting) or

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renal hydrogen ion loss is most likely. Administration of fluids with a high chloride concentration such as 0.9% sodium chloride may be beneficial as increased delivery of chloride to the renal tubule helps support renal resolution of metabolic alkalosis.[2] Both the conventional and quantitative approaches could direct the clinician to this therapeutic plan but the quantitative approach allows appreciation of the severity of the alkalotic process and the coexistence of the acidotic influence of uremic acids. An important part of the therapy for this cat would be resolution of the uremia and hyperphosphatemia in order to reestablish a normal acid-base balance.

Table 8: Suggested shorthand formulas for estimation of quantitative acid base effects

Effect	Shorthand formula
Free water effect	(Measured sodium – Normal sodium)/4
Corrected chloride	Measured chloride × (Normal sodium/Measured sodium)
Chloride effect	Normal chloride – corrected chloride
Albumin effect	(Normal albumin – Measured albumin) × 4
Phosphate effect	(Normal phosphate – Measured phosphate)/2
Lactate effect	Measured lactate × −1
Sum	Free water effect + chloride effect + albumin effect + phosphate effect + lactate effect
Unmeasured anion effect	Standardized base – excess sum

Discussion

While the traditional approach to acid-base analysis provides an excellent overview of the acid-base status of the patient it does not identify individual processes contributing to the metabolic acid-base balance. The quantitative approach described here is used as an adjunct to the traditional approach to help determine some common individual contributors to complex acid-base disorders. Perhaps the greatest benefit of the quantitative approach is to increase the awareness of common causes of acid-base abnormalities such as hyperphosphatemia, hypoalbuminemia, changes in free water content, and abnormalities in chloride/bicarbonate. In several of the cases presented here the calculation of the individual contributors to the SBE may not have changed the therapy, but provide for the clinician an expanded perspective of the complexity of the acid-base imbalance. In Case 3 the hypoalbuminemia explains why the anion gap is normal in the face of hyperphosphatemia, which independently would have increased it. In other situations, the calculation of individual contributions to the SBE may have therapeutic implications. In Case 4, the obvious diagnosis of diabetic ketoacidosis is further complicated by a coexisting lactic acidosis.

This simplified quantitative approach to acid-base analysis identifies the presence of 5 individual processes and estimates the contribution of each of these processes on the SBE. Although these 5 processes are evaluated by the measurement of sodium, chloride, albumin, phosphorus, and lactate concentrations it is important to recognize that sodium, chloride, and lactate do not affect acid-base balance per se. Rather they are markers of acid-base processes in the body. Changes in sodium concentration are used as a marker of changes in free water concentration, changes in chloride concentration are used as a marker of changes in bicarbonate concentration resulting from chloride-bicarbonate exchange in the body, and lactate is used as a marker of hydrogen ion production subsequent to anaerobic metabolism. This distinction is important to avoid misconceptions such as adding sodium ions to a patient will have an alkalinizing effect or that lactate in the form of sodium lactate as found in lactated Ringer's solution will have an acidifying effect.

In certain situations, as demonstrated by Case 5, the traditional approach may give an erroneous impression of a patient's acid-base status. In critical illness where complex acid-base abnormalities are common, a quantitative approach to acid-base analysis is more comprehensive and potentially provides for more therapeutic guidance. The simplified Fencl-Stewart approach used in this report utilizes several basic equations to quantitate the individual contribution of several measured parameters to metabolic acid-base balance and can be readily applied in the clinical setting. Although hand calculations of these effects can be performed, it is laborious. With the use of a spreadsheet, these calculations can be accomplished rapidly and accurately. Alternatively, cage-side approximations of these effects can be made (Table 8).

The accuracy of this quantitative approach has not been evaluated in veterinary medicine. In human clinical patients the comparison of these simplified equations with more complex Fencl-Stewart equations was found to have good agreement.[39] Although it is believed that these equations provide valuable insight to acid-base disorders in our patients, determination of species-specific formulae and future evaluation with appropriate clinical studies would be beneficial.

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