Practical Approach to Physical-Chemical Acid-Base Management

Stewart at the Bedside

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Abstract

The late Peter Stewart developed an approach to the analysis of acid-base disturbances in biological systems based on basic physical-chemical principles. His key argument was that the traditional carbon dioxide/bicarbonate analysis with just the use of the Henderson-Hasselbalch equation does not account for the important role in the regulation of H^+ concentration played by strong ions, weak acids and water itself. Acceptance of his analysis has been limited because it requires a complicated set of calculations to account for all the variables and it d oes not provide simple clinical guidance. However, the analysis can be made more pragmatic by using a series of simple equations to quantify the major processes in acid-base disturbances. These include the traditional PCO_2 component and the addition of four metabolic processes, which we classify as "water-effects," "chloride-effects," "albumin effects," and "others." Six values are required for the analysis: [Na^+], [Cl^-], pH, P_{CO_2}, albumin concentration, and base excess. The advantage of this approach is that it gives a better understanding of the mechanisms behind acid-base abnormalities and more readily leads to clinical actions that can prevent or correct the abnormalities. We have developed a simple free mobile app that can be used to input the necessary values to use this approach at the bedside (Physical/Chemical Acid Base Calculator).

Keywords: acid-base; strong ion difference; base excess; chloride

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Assessment of acid-base status is a central part of the management of critically ill patients. Three distinct approaches for the assessment acid-base disorders have been identified: the physiological approach, the physical-chemical approach, and the base excess (BE) approach (1, 2). In reality all three overlap, for they are based on similar underlying basic physical-chemistry principles and common clinical parameters. Differences arise from emphasis on the components of the solutions in the body. The most common approach is called the physiological approach by its proponents (1, 2). It is based solely on the P_{CO_2}/carbonic acid/bicarbonate (HCO_3^-) equilibrium. P_{CO_2} is used to describe the respiratory component and HCO_3^- the metabolic component of acid-base disturbances with use of the Henderson equation (2, 3). The rationale is based on the abundance, physiological importance, and homeostatic control of these three reaction components. In this approach, acid-base balance is considered to be determined by net influx and efflux of H^+ and HCO_3^- as independent variables. Deviations from predicted values are dealt with by empiric equations derived from clinical observations of acute and chronic changes. This actually makes this approach primarily phenomenological rather than physiological, and we prefer to call it the traditional approach, as recently used by Seifter (4).

An alternative approach was developed by the late Peter Stewart (Figure 1) (5–9). This approach has become more mainstream with a recent *New England Journal of Medicine* publication (4). Stewart emphasized the importance of the electrical charge produced by differences in the concentration of strong positive and negative ions (SID), the role of weak acids, and the conservation of mass. In Stewart's analysis, SID is considered to be an independent variable, and [H^+] and [HCO_3^-] (square brackets referring to concentrations) are dependent variables. Of interest, the importance of the strong anion chloride (Cl^-) was recognized by Henderson in 1921 (3). A likely reason for his not including Cl^- in subsequent analysis was the difficulty at that time of measuring it.

A third approach to acid-base analysis developed by Astrup and Siggaard-Andersen is close to the traditional approach. The main difference is that it uses the empirically derived BE instead of

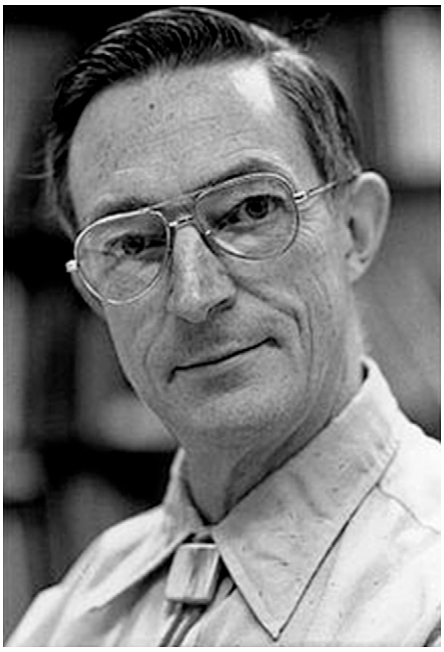

Figure 1. Peter Stewart, 1921–1993.

HCO_3^- to evaluate the metabolic component of acid-base disorders (10, 11). The BE approach in many ways bridges concepts in the traditional and Stewart approaches.

A criticism of the Stewart approach has been that a large number of variables are needed to perform the analysis (1). To address this issue, we have taken a pragmatic approach to the application of the basic principles in the Stewart approach, which we believe can lead to more rapid assessment of the primary clinical processes that produce deviations from normal. This potentially can lead to better treatment and prevention strategies, particularly in the choice of intravenous solutions (12). We have developed a phone app that allows quick calculations of the components of our analysis. This paper gives a brief introduction to the physical-chemical principles in Stewart's approach, the basis of the equations used in our app, and an introduction on how to use it. The online supplement gives four working examples.

Definition of Acidic and Basic Solutions

To begin, we need to define acidic and basic solutions with water as the solvent. The concentration of water molecules in water is 55.3 mol/L. This is 400 times the next most concentrated substance, Na^+, and 1,000 million times the concentration of H^+ (1×10^{-9} mol/L) (6). Water molecules dissociate, albeit to a very small extent, so that the pH of pure water at standard ambient temperature (25°C) and pressure (760 mm Hg) is 7.00, and $[H^+]$ and $[OH^-]$ equal 1×10^{-7} mol/L. An acid solution is one in which $[H^+]$ is greater than $[OH^-]$; a basic solution is one in which $[OH^-]$ is greater than $[H^+]$; and a neutral solution is one in which $[H^+]$ and $[OH^-]$ are equal. The dissociation of water molecules increases with an increase in temperature so that an increase in temperature of a solution reduces pH and increases $[H^+]$. However, the solution is not acidic, for $[H^+]$ still equals $[OH^-]$. All bodily fluids, with a few exceptions such as stomach contents when fasting and the contents of lysozymes, are alkaline, even under most extreme clinical conditions. This means that $[OH^-]$ in the body is almost always greater than $[H^+]$, and when we say that someone has an acidosis, what actually is happening is that the solution is becoming less alkaline. The key point from these definitions is that water itself presents a huge source of H^+, and the $[H^+]$ of pure water at standard temperature and pressure is actually more than double that of most bodily solutions.

Determinants of pH in Aqueous Solutions Based on the Physical-Chemical Approach

Stewart identified three determinants of $[H^+]$ in aqueous solutions including blood plasma: total CO_2 content (this incorporates P_{CO_2}, H_2CO_3, and HCO_3^-), the SID, and the concentration of weak nonvolatile acids. Of these three factors, changes in SID have the greatest effect on $[H^+]$.

Ions are charged substances, and strong ions are derived from substances that are almost completely dissociated in water-based solutions. In a macroscopic solution, the concentrations of all positive charges, including $[H^+]$, and all negative charges must be equal because any difference in charge produces a very strong electrical force that must be balanced to maintain thermodynamic equilibrium. The charge difference between strong anions and cations is called the SID, and it is measured in equivalents per liter (Eq/L). This electrical force distorts the dissociation equilibrium of weakly dissociating substances in the solution, including water itself. The charge also affects weak acids in the solution, including the weak volatile acid P_{CO_2}/carbonic acid and weak nonvolatile acids. The dominant nonvolatile weak acid in plasma is albumin, which dissociates into H^+ and albumin$^-$ (Alb^-). The carbonic acid/bicarbonate (HCO_3^-) equilibrium still has an important role, but it is total CO_2 that counts, not $[HCO_3^-]$, as long as there is sufficient carbonic anhydrase, circulating blood, and ventilation to regulate P_{CO_2}. When P_{CO_2} is regulated and total nonvolatile weak acids are relatively constant, only the movement of strong electrolytes into or out of a compartment can alter $[H^+]$. Importantly the analysis must be made at a quasi-steady state and is limited to a single compartment.

Determinants of pH in Aqueous Solutions

Stewart identified six equations to solve six unknowns that are needed to calculate $[H^+]$ in a water-based solution such as plasma with an SID, CO_2, and weak acids. This complicated analysis is intimidating, and it is not obvious how the system can be used at the bedside. Not surprisingly, uptake of Stewart's analysis by clinicians has been limited. However, in clinical practice $[H^+]$ does not need to be calculated, for it is measured (or its negative logarithm, pH). What clinicians want to know is what makes $[H^+]$ deviate from the standard value of pH 7.40 or $[H^+]$ of 40×10^{-9} mol/L.

An initial simplifying step proposed by Stewart and others (13, 14) was to only consider strong ions in plasma that have sufficient concentrations to have physiological roles and that are readily available in most patients. The positive strong ions are Na^+, K^+, Ca^{2+}, and Mg^{2+}, and negative ions are Cl^- and lactate$^-$. The only two substances in plasma that normally have sufficient concentrations to balance the normal SID are HCO_3^- and Alb^-. Thus, any difference between the measured SID and the charge accounted for by the concentrations of HCO_3^- and Alb^- must be due to unmeasured substances.

This has been called the strong ion gap (SIG) (13, 14). However, this approach still is cumbersome, for many values have to be acquired, and the SIG does not readily give insights into the actual components causing the acidemia or alkalemia.

We have taken a more practical and pragmatic approach that does not try to give an exact accounting of all factors, for many of them have minimal physiological significance (15–17). It derives from an approach presented by Fencl and Leith (9). Our approach quantifies the primary metabolic processes in an acidosis or alkalosis, which then can allow targeted therapy to these processes. What is lost in precision produces significant gains in accessibility of the concepts and considerably simplifies application in clinical practice. Using our simplified approach, entry of six values obtained from routine arterial blood gas and blood chemistry into a mobile app enables accurate identification of primary and secondary acid-base abnormalities and identifies the specific processes giving rise to the abnormalities (Figure 2).

Premises behind This Pragmatic Physical-Chemical Approach

The first premise is that physicians are primarily interested in deviations from normal.

The second premise is that although there are many strong electrolytes in blood, normal SID is dominated by the ionic concentrations of sodium [Na^+] and chloride [Cl^-]. The concentrations of other measurable ions are small and cannot deviate by more than 1 or 2 mEq/L without there being serious clinical consequences unrelated to their effect on pH. As a general principle, widening of the SID due to an increase in [Na^+] relative to [Cl^-] has an alkalinizing effect and can be considered to be like giving the equivalent of NaOH. In contrast, narrowing the SID by an increase in [Cl^-] relative to [Na^+] has an acidifying effect and can be considered to be like giving the equivalent of HCl.

The third premise is that there are four major types of metabolic acid-base disturbances in plasma. These are: (*1*) effects of dilutional changes on the SID, which we call "water effects"; (*2*) changes in the amount of [Cl^-] from its normal concentration, which we call "chloride effects"; (*3*) changes in the dominant weak acid, albumin, which we call "protein effects"; and (*4*) changes in "other" factors, most of which are not measured but include all the typical negative ions in the classic differential diagnosis of a wide anion gap acidosis (18). These are lactate, ketoacids, formate, oxalate, salicylate, sulfate, and phosphate (Table 1). The way each of these factors effects [H^+] is discussed below.

The fourth premise is that the BE as derived by Siggaard-Andersen, and available on all blood gas machines, provides a reasonable estimate of a patient's missing ions (11). To understand this point, it is necessary to understand what Astrup and Siggaard-Andersen did. They wanted to have a quantitative measure in a patient's arterial blood of the metabolic component of acid-base disorders that is independent of respiratory effects. To do so, they equilibrated blood samples from subjects to a P_{CO_2} of 40 mm Hg, thereby duplicating what happens to blood in pulmonary capillaries when the lung is functioning normally. If the pH of the sample at a P_{CO_2} of 40 mm Hg was greater than 7.40, they added the equivalent of an acid by using strong anions to bring the blood pH back to 7.40, and they called the amount of base that had to be countered BE (in meq/L). If the pH of the sample was less than 7.40, they added the equivalent of a base by using strong cations to bring the blood pH back to 7.40 and called this a base deficit. To avoid confusion, we only will use the term BE, and a base deficit will be indicated by a negative value of BE. Thus, in this usage, a negative BE is a metabolic acidosis. Because Siggaard-Andersen used strong ions to derive BE, it is not surprising that there is a tight relationship between the SIG and BE (15). Ironically, Siggaard-Andersen was vehemently opposed to Stewart's approach (19).

Siggaard-Andersen analysis treats the extracellular space as essentially one compartment. He also believed that hemoglobin in red blood cells directly acts as a classic buffer and effects acid–base balance in this compartment. He thus incorporated the hemoglobin concentration into his Van Slyke equation for calculating BE (20). Because hemoglobin is only in the vascular

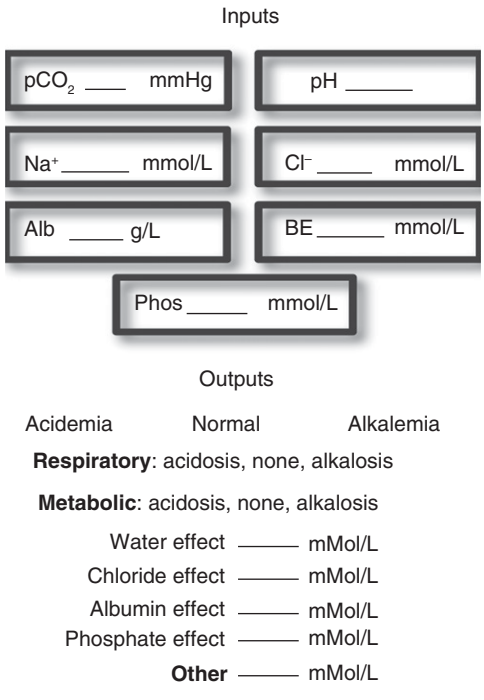

Figure 2. Schema of the front page of the phone app for the bedside approach to physical-chemical acid-base.

Table 1. Causes of wide anion gap acidosis

Wide Anion Gap Acidosis ("Other")
Production of unmeasured anions
Ketoacids
Lactate
Failure to clear unmeasured anions
Renal failure (SO_4^{2-})
Intake of strong anions
Salicylate
Acetate
Methanol (formate)
Ethylene glycol (oxalate)
Paraldehyde
Sulfate
Formaldehyde
Weak acids
Phosphate

compartment, and interstitial volume normally is approximately twice that of vascular volume, he concluded that the effect of hemoglobin on the acid-base balance of the extracellular space is diluted by one-third. This means that the titrations he did on isolated blood samples would be greater than seen in the whole body. Accordingly, he assumed a hemoglobin concentration of 50 g/L, one-third of normal, for his *ex vivo* experiments and called this standard BE. This is what is used on current blood gas machines. In this paper BE refers to standard BE.

Siggaard-Andersen's analysis, though, was based on the misconception that hemoglobin directly buffers blood. Hemoglobin in the cytoplasm of red blood cells is separated from plasma by cell membranes in the same way that the large intracellular space is separated from the interstitial space by cell membranes. The plasma space, too, is separated from the interstitial space by endothelial cells, and this produces differences between the concentrations of strong electrolytes and albumin in the plasma and interstitial space, but not that of total CO_2, for CO_2 is freely diffusible. A fundamental principle in Stewart's physical-chemical analysis is that electroneutrality and dissociation equilibrium must be satisfied by the components of the solution on both sides of membranes (9). Furthermore, dependent variables such as $[H^+]$ and $[HCO_3^-]$ on each side of adjacent membranes are determined by the values of the independent variables in that compartment (9). Thus, calculations of acid-base status must be made for each compartment in a quasi-steady state (8, 9). Red blood cells actually do alter plasma $[H^+]$, but this occurs primarily by their uptake or release of Cl^- when there is an increase in P_{CO_2} or oxygen saturation (21–23). For example small differences occur in the SID of the inflow and outflow of extracorporeal membrane oxygenation devices (22). *Ex vivo* changes in P_{CO_2} of blood samples also produces large changes in $[Cl^-]$ (23). However, hemoglobin concentration should have little effect on the pH and BE calculation in a sealed blood sample. The use of a fixed hemoglobin concentration in the standard BE equation means that the hemoglobin part of the equation becomes one of the constants and is irrelevant, which is why standard BE tracks the SID gap very well regardless of hemoglobin concentration or the size of the extracellular space. An important implication from this analysis is that it is not possible to obtain a whole body analysis of acid-base balance, as some have attempted (24–26), because the independent variables in each compartment, especially the diverse intracellular compartment, cannot be obtained. Of note, in Astrup's original experiments, hemoglobin did matter, for he lysed red cells, and the free hemoglobin in plasma then could act as a weak acid (27). Because SID, pH, and BE are not the same in venous and arterial samples, all values should be collected from the same site to be most accurate, but directional changes usually still can be approximated with samples from different sights.

Four Basic Mechanisms of Major Metabolic Alterations in pH

Water Effect

SID is measured in concentration units and as such it is determined by the difference in concentrations of strong positive and negative ions. Thus, a change in the amount of solvent, which is water, changes the SID by diluting or concentrating the components. Although values of electrolytes reported by hospital laboratories are given in mmol/L, it actually is "equivalents" (Eq/L) that determine reactivity in solutions, and this is what is measured by selective electrode systems (28). This distinction is made because not all of the mass of a substance is available to react due to interactions with other substances in the solution. However, under physiological conditions, values in equivalents and moles are close, and we use mmol/L for convenience and simplicity.

A beaker of water with $[Na^+]$ equal to 140 mmol/L and $[Cl^-]$ 100 mmol/L has an SID of 40 mmol/L. If 1 L of pure water is added, $[Na^+]$ decreases to 70 and $[Cl^-]$ to 50 mmol/L, and the SID is reduced by half to 20 mmol/L. Thus, simply adding water decreases pH. This occurs because less $[OH^-]$ from dissociated water is needed to balance $[Na^+]$, and the charge instead is balanced by the increase in $[Cl^-]$ relative to $[Na^+]$. Some of the OH^- can now reassociate with H^+, which thereby decreases the alkalinity (and increases the acidity) of the solution. Because $[H^+]$ increases, it has been asked where does the extra $[H^+]$ come from (29)? Conservation of mass is maintained simply because the added pure water had more H^+ than the original solution and allowed a new equilibrium value. This occurs in a beaker without kidneys or any other regulating mechanism, for it is a consequence of the law of electrical neutrality, the conservation of mass, and the dissociation constant of water. The same process changes blood pH when water content changes relative to solute and dilutes or concentrates blood electrolytes. Water effects can be recognized by observing deviations of $[Na^+]$ from a standard value, because $[Na^+]$ is a major determinant of plasma osmolarity (12). We use a standard $[Na^+]$ of 140 mmol/L and deviations from this value to indicate "water" effects. The magnitude in terms of mmol/L can be calculated by dividing the normal SID between Na^+ and Cl^- of almost 40 mmol/L by normal $[Na^+]$ to obtain the normal fraction of SID to $[Na^+]$, which is approximately 0.3. This is then multiplied by the difference between the measured $[Na^+]$ and the standard value:

$$\text{Water effect} = 0.3 \times ([Na^+ \text{meas}] - 140) \times \text{mmol/L} \quad (Eq.\ 1)$$

Water effects are common but usually small; a decrease of $[Na^+]$ to 130 mmol/L only contributes a −3.3 mmol/L effect on BE.

Chloride Effect

Change in $[Cl^-]$ is the major physiological nonrespiratory mechanism regulating

[H^+]. To measure the effect of deviations of [Cl^-] from normal, one must first correct for the dilutional effect on [Cl^-] that was already accounted for in Equation 1 and the water effect. This is done by multiplying measured [Cl^-] by the standard [Na^+] of 140 and dividing by measured [Na^+]. The way to think of this is that effective [Cl^-] should be higher after correcting for a dilution effect or lower if there was a concentrating process. Next, the corrected [Cl^-] is subtracted from the standard value, which we have set at 102 mmol/L:

$$\text{Chloride effect} = 102 - [Cl^- \text{effective}] \times (\text{mmol/L}) \quad (Eq.\ 2)$$

What becomes evident when using the physical-chemical approach is that changes in [Cl^-] give a lot of information about acid-base processes (12, 30).

Protein Effect

Alb is the major contributor to the protein effect by its dissociation into H^+ and Alb^- and acts as a weak acid. The effect of weak acids on solutions depends on the concentration of all of its components, the dissociation constant of the intact molecule, and ionic activity of the anion, in this case Alb^-. The ionic activity of Alb^- was established empirically by Figge and coworkers (31), who measured the change in plasma pH that occurs with a change in the concentration of albumin and also by analyzing in detail the dissociation constants of the major histidine groups on the albumin molecule. The empiric equation they derived can be used to determine the effect on the solution of changes in albumin from a standard concentration. The standard we have chosen is 42 g/L (or 4.2 g/dL). The equation is:

$$\text{Protein effect} = (42 - [\text{Alb} - \text{meas}]) \times (0.148 \times \text{pH} - 0.818) \times \text{mmol/L} \quad (Eq.\ 3)$$

Other

The last step is to identify ions that were not measured. These are usually anions, but chronically hypercapnic patients often have unidentified cations. This task is accomplished by subtracting the charge attributed to the water effect, chloride effect, and protein effect in Equations 1 to 3 from the calculated BE on the blood gas report. The rationale is that BE is a measure of all metabolic factors that account for deviations of the pH from normal after accounting for changes in pH due to deviations of CO_2 from normal. A curious observation from our own work (15) and that of Kellum and colleagues (13) is that patients with liver disease often have unexplained anions. At least some of these anions are associated with the anions in the tricarboxylic acid cycle (32).

Use of This Simplified Approach in Clinical Management

The analysis begins in the same way as in the traditional approach (Table 2). For simplicity we have defined an abnormality as any deviation from the mean value accepted as normal. Thus, a blood or plasma pH greater than 7.41 is considered an alkalemia and a pH less than 7.39 an acidemia, where "-emia" refers to the state of the blood. The next step is to assess the respiratory and metabolic components. The respiratory component, too, is analyzed as in the traditional approach, with some simplifications. A P_{CO_2} greater than 42 mm Hg is considered a respiratory acidosis, and a P_{CO_2} less than 38 mm Hg is considered a respiratory alkalosis, where "-osis" refers to a process driving deviations of pH from the normal value. The terms "acute" and "compensated" are dealt with under metabolic disorders and generally are due to changes in [Cl^-]. As in the Siggaard-Andersen approach (33), the presence of a metabolic disorder is defined by the BE. A BE greater than 1 indicates a metabolic alkalosis and a BE less than −1 indicates a metabolic acidosis. Although deviations of HCO_3^- are similar to changes in BE, the relationship is not exact, because BE eliminates the effect of changes in P_{CO_2} on HCO_3^-. This was the rationale for the original BE approach (10, 11). From this point on, the traditional and physical-chemical approaches differ.

The metabolic component is first evaluated by measuring the water effect, Cl^- effect, and protein effect as described in the equations above. The millimolar effects of these three processes are then subtracted from the reported BE to determine what is not accounted for, which we have called "other." Increase in negative other is acidifying, whereas an increase in positive other is alkalinizing. Negative other are essentially substances that produce wide anion gap acidosis (Table 1) (18). The advantage of the term other over the anion gap is that other excludes the effects of changes in [HCO_3^-] due to changes in P_{CO_2} and deviations of [albumin] from normal. Most of other factors are strong anions and narrow the SID in direct proportion to their molar quantities. An exception is phosphate, which has different dissociation constants for each of its oxidative states. The first acts as a strong ion and the other two are weaker. Figge and colleagues also provided an empiric equation for the ionic effect of phosphate (Phos) (31), which we have modified to calculate a phosphate effect. To do so, we subtract the measured phosphate from a normal value of phosphate of 0.8 mmol/L and multiply this by the equation of Figge and colleagues:

$$\text{Phos effect} = (0.309 \times (\text{pH} - 0.46)) \times (0.8 - [\text{Phos measured}]) \quad (Eq.\ 4)$$

We have not included Phos effect in the calculation of other in our routine analysis,

Table 2. Steps for assessing acid-base disorders using base excess

1. Is there an acidemia or alkalemia based on deviation of pH from 7.4?
2. Is there a respiratory acidosis or alkalosis based on deviation of P_{CO_2} from 40 mm Hg?
3. Are there metabolic abnormalities in acid-base balance (i.e., is there a positive or negative [BE] in mmol/L)?
4. What are the specific defects
   a. Free water \boldequals 0.3 ([Na+] − 140); [Na+] in mmol/L
   b. Chloride effect: first correct the [Cl^-] for water effects
      Corrected [Cl^-] ([Cl^-]$_c$) \boldequals [Cl^-] × (140/[Na^+]); in mmol/L;
      Then chloride effect \boldequals 102 − [Cl^-]$_c$
   c. Albumin effect \boldequals (0.148 × pH − 0.818) × (42 − [albumin]); [albumin in g/L)
5. What is the concentration of "other species" (unmeasured anions)?
   Other \boldequals BE − (water effect + [Cl^-]$_c$ + albumin effect + other) in mmol/L
6. What is the effect of change in phosphate?
   Phos effect \boldequals (0.309 × (pH − 0.46) × (0.8 − [Phos measured])

Definition of abbreviation: BE = base excess.

for phosphate is not always available. However, the calculation is included in the output of the app for consideration and can be taken into account by subtracting it from the other to determine how many negative other are still missing. We also do not include lactate, for it is our preference that when other are present the lactate should always be directly looked at to determine how much it is contributing, for lactate concentration has direct clinical implications in the management of patients in shock.

Introduction to Clinical Conditions That Alter the Four Factors

Water effects are produced by interaction of intake of free water, either orally or by the composition of intravenous infusions. Water balance also can be altered by hormonal, renal, and gastrointestinal regulatory mechanisms in disease states. Dilution of blood by an increase in water relative to solute narrows the SID, which is an acidifying effect. This can be managed by reducing free water administration. Decreased water relative to solute increases $[Na^+]$ relative to $[Cl^-]$ and widens the SID, which is an alkalinizing effect. This can be resolved by increasing free water.

Acidification from increased $[Cl^-]$ is commonly caused by the administration of normal saline solutions, for the high $[Cl^-]$ relative to normal blood narrows the SID (12). Excretion of excess Na^+ and Cl^- occurs quickly (34), but restoration of the normal plasma SID requires more Cl^- be excreted than Na^+. A nonessential cation is needed to accompany Cl^- and to maintain electrical neutrality in the renal tubules. This is accomplished by production of the positive cation ammonium (NH_4^+) in renal tubular cells, but this takes time (34, 35). Excretion of Cl^- is prolonged in patients with renal tubular acidosis, for they cannot produce adequate NH_4^+ to excrete with the Cl^- and have to use Na^+ or K^+ for this purpose. It is worth noting that $[Cl^-]$ in standard renal replacement solutions is ~110 mmol/L, and thus continuous renal replacement therapy with these solutions does not allow correction of the acidosis associated with hypercapnia, because metabolic "compensation" requires lowering $[Cl^-]$.

Negatively charged other indicates the presence of the well-known causes of a wide anion gap acidosis (18), and, as in the common approach, these disorders are corrected by stopping the underlying process such as ketoacid or lactic acid production or by removal of the causative anion.

Summary

This pragmatic physical-chemical approach to acid-base analysis starts the same way as the traditional approach by determining if there is an acidemia or alkalemia and then by determining whether there is a respiratory or metabolic process. These can be present even with a normal pH, depending on the balance of the processes involved. The new aspect is consideration of the role in the metabolic component of water effect, chloride effect, and protein effect by determining how well these three factors account for the BE. It becomes evident that $[Cl^-]$ is a much more important player than previously considered, for it is the only strong anion that can be easily manipulated by normal physiological mechanisms (30). Use of this approach can lead to a clearer understanding of processes regulating blood $[H^+]$ and allow more targeted management. The equations involved are not complicated (Table 2), and can be readily used at the bedside with the mobile app that we have developed. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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Practical Approach to Physical-Chemical Acid-Base Management: Stewart at the Bedside

Sheldon Magder and Ali Emami

ONLINE DATA SUPPLEMENT

Appendix 1:

Case examples

Case 1.

A 64 year old woman was found unconscious and lying in feces in her apartment. She had a three day history of abdominal pain, diarrhoea, confusion and hypotension. Her past history included diabetes mellitus, hypertension, hypothyroidism (treated), chronic renal disease due to neurogenic bladder and ureteral obstruction, and chronic obstructive lung disease. An abdominal CT scan suggested a sigmoid perforation. She also had bilateral hydronephrosis which was unchanged from previous imaging. Table 1 gives the initial laboratory finding and analysis. The working clinical hypothesis was urosepsis or peritonitis and lactic acidosis. The nephrologist urged aggressive infusion of 0.9% saline. The physical-chemical analysis indicated a mild acidemia (pH 7.33), respiratory alkalosis (PCO_2 25 mmHg) and a metabolic acidosis (BE -11.2 mmol/L). The decreased [Na+] ("water" effect) produced a mild acidifying effect of -1.2 mmol/L and there was a marked "chloride" effect of -13.3 mmol/L. The low albumin had an alkalinizing effect of 5.9 mmol/L. The sum of the "water", "chloride" and "albumin" effects left -2.6 mmol/L of BE, which were largely accounted for by the elevated phosphate. Surprisingly to the clinicians her lactate was normal but this was consistent with the measured "others". The primary process thus was hyperchloremic acidosis, which was likely related to renal tubular dysfunction and a possible colonic vesicular fistula. Instead of using a saline solution her volume support was managed with three ampoules of $NaHCO_3$ (total of 132 mmol/L of Na^+ in 5% dextrose in water) which reduced but did not correct her acidemia.

Elements	**Values**		
Na	136 mmol/L	Acidemia	
Cl	112 mmol/L	**Respiratory alkalosis**	**Metabolic acidosis**

Alb	20 mg/L		
pH	7.33		
Phosphate	1.96 mmol/L		
PCO2	25 mmHg	**Metabolic Analysis**	
HCO3	13.5	Water effect	-1.2
BE	-11.2 mmol/L	Chloride	-13.3
Lactate	0.9 mmol/L	Albumin	+5.9
		Other	-2.6
		Phosphate	-2.46

Case 2

58 year old man with cirrhosis, acute hepatic decompensation, and respiratory failure.

Elements	**Values**		
Na	128	Acidemia	
Cl	115	**Respiratory acidosis**	**Metabolic acidosis**
Alb	18	**Metabolic Analysis**	
pH	6.95	Water effect	-3.6
Phosphate	1.74	Chloride	-23.8
PCO2	47	Albumin	+5
HCO3	10	Other	+0.3
BE	-22	Phosphate	-1.9
Lactate	0.8		

The severe acidemia was due to a combination of respiratory acidosis and a marked metabolic acidosis. Given his hepatic decompensation an important possibility was lactic acidemia but the lactate was normal and the metabolic acidosis could be explained almost completely by hyperchloremia with some contribution from the hyponatremia. It was important to not use more chloride containing solutions for maintaining his volume status.

Case 3

39 year old diabetic male treated with glyburide presented to emergency with marked shortness of breath and obtundation. Ketones were not quantified but were strongly positive in blood and urine. He was treated with fluids and insulin. The first column shows laboratory results from the emergency department and the second column results the morning after.

Elements	**ER**	**Next morning**			
Na	140	152		**ER**	**Next morning**
Cl	103	130		**Acidemia**	**Acidemia**
Alb	42	40	**Metabolic Analysis**	**Respiratory alkalosis, Metabolic acidosis**	**Respiratory alkalosis, Metabolic acidosis**
pH	6.8	7.23			
Phosphate	0.6	0.8	Water effect	0	+3.6
PCO2	12	28	Chloride	-1	-17.7
HCO3	1.8	11.7	Albumin	0	+0.5
BE	-33.1	-13.4	Other	-32	+0.2
Lactate	0.6	0.8	Phosphate	+0.4	0

In the emergency department the severe acidosis could be accounted for primarily by “others” which were likely ketoacids. The next morning he was still acidemic which made his clinicians wonder if he still had a ketoacidosis. The analysis indicated that the acidosis could be completely explained from his elevated chloride which was likely due to his saline load during the resuscitation and delayed clearance

of chloride by his kidney. The high sodium, likely due to an osmotic diuresis and inadequate free water, had a moderating effect on the acidemia.

Case 4

A 39 year old woman was transferred from a rural hospital by air transit with pancreatitis, pulmonary edema and severe hypoxemia (Oxygen saturation 78% on arrival). The pancreatitis was likely due to biliary stones for the initial bilirubin was 62 umol/L. She was in renal failure (serum creatinine 305 umol/L) and her initial triglyceride was markedly elevated at 15.6 mmol/L. She was mechanically ventilated and renal replacement therapy was started. The laboratory results and analysis are below. The severe initial acidemia was due to a metabolic acidosis primarily related to hypercholremia, but with some unexplained anions ("other"), possibly related to the renal failure but not lactate. There also was an important respiratory acidosis which was likely worsened during the air-transfer. On the second day the hyperchloremia decreased and to a lesser extent so did the unexplained anions because of renal replacement therapy. The respiratory acidosis improved with ventilation but her oxygenation only improved when she went to the operating room to relieve an abdominal compartment syndrome. Lactates were at all times in the normal range.

Elements	**Arrival**	**Next morning**			
Na	137	138		**ER**	**Next morning**
Cl	115	109		**Acidemia**	**Acidemia**
Alb	27	27	**Metabolic Analysis**	**Respiratory acidosis, Metabolic acidosis**	**Respiratory acidosis, Metabolic acidosis**
pH	6.92	7.20			
Phosphate	0.80	0.82	Water effect	-0.9	-0.6
PCO2	64	47	Chloride	-15.5	-8.6
HCO3	12.4	17.6	Albumin	+3.1	+3.7
BE	-18	-9.3	Other	-4.7	-3.8
Lactate	1.5	1.3	Phosphate	0	0.1