Acid–Base

5

Victor A. van Bochove, Heleen M. Oudemans-van Straaten, and Paul W.G. Elbers

5.1 Introduction

A thorough understanding of acid–base balance is a prerequisite for practicing medicine and pivotal for those treating the critically ill. Acidity of fluids including that of plasma is determined by their hydrogen concentration or $[H^+]$, often confusingly expressed as its negative logarithm or pH. Plasma $[H^+]$ is tightly regulated around 40 nM (pH 7.4) and influences most physiological processes. Acid–base analysis often yields important diagnostic information, and its physiology represents the crossroads between electrolyte balance and the respiratory system.

The last century gave rise to three commonly used approaches to acid–base problems in clinical medicine. In 1908, Henderson described his equation for carbonic acid equilibrium, which was rewritten in logarithmic form by Hasselbalch in 1917. Ole Siggaard-Andersen introduced Base Excess in 1964. Finally, in 1981, Peter Stewart published his quantitative approach. Recently, the Stewart approach has become increasingly popular, especially in the setting of critical care medicine. This chapter will discuss all of these approaches and use their context to consider renal acid–base handling.

V.A. van Bochove • H.M. Oudemans-van Straaten • P.W.G. Elbers (✉)
Department of Intensive Care Medicine,
VU University Medical Center Amsterdam,
De Boelelaan 1117, Amsterdam 1081 HV, The Netherlands
e-mail: p.elbers@vumc.nl

H.M. Oudemans-van Straaten et al. (eds.), *Acute Nephrology for the Critical Care Physician*, DOI 10.1007/978-3-319-17389-4_5

5.2 The Stewart Approach

Often referred to as the physicochemical or quantitative approach, the basis of Stewart method is that all chemical equilibrium equations in which $[H^+]$ takes part must be satisfied simultaneously (Table 5.1). Water dissociation plays a pivotal role as a reservoir for H^+ ions. The key message of the Stewart approach is that $[H^+]$ is only dependent on three independent variables: the strong ion difference (SID), the total amount of weak acids (A_{TOT}) and the partial pressure of carbon dioxide PCO_2.

$$\left[H^+\right] = f\left(SID, A_{TOT}, PCO_2\right)$$

These three independent parameters can all be normal, decreased or increased and thus six major acid base disturbances can be distinguished. This also implies that bicarbonate does not play any role in determining $[H^+]$. Instead, $[HCO_3^-]$ is also determined by the three independent parameters.

5.2.1 Strong Ion Difference (SID)

Strong ions are always fully dissociated. Na^+, K^+ and Cl^- are the most important examples, but others include Mg^+, Ca^{2+}, sulfate and lactate. SID is the sum of strong cations minus the sum of strong anions. Its normal plasma value is about 40 mEq/L.

When SID increases, physicochemistry dictates that $[H^+]$ must decrease. An example is prolonged vomiting causing plasma $[Cl^-]$ to decrease and therefore [SID] to increase. When SID decreases, physicochemistry dictates that $[H^+]$ must increase. Examples include lactic acidosis and ketoacidosis. Ketones and lactate are also strong negative ions that decrease [SID] directly and therefore cause $[H^+]$ to rise.

5.2.2 Total Amount of Weak Acids (A_{TOT})

The total amount of weak acids is expressed as A_{TOT}. It mainly consists of albumin and to a lesser extent of phosphate. By definition, weak acids are only partially

Table 5.1 The Stewart equations

1. Water dissociation equilibrium: $\left[H^*\right]\times\left[OH^-\right] = K_w'$
2. Electrical neutrality equation: $[SID]+\left[H^*\right]=\left[HCO_3^-\right]+\left[A^-\right]+\left[CO_3^{2-}\right]+\left[OH^-\right]$
3. Weak acid dissociation equilibrium: $\left[K_A\right]\times[HA]\leftrightarrow\left[H^+\right]\times\left[A^-\right]$
4. Conservation of mass for "A": $\left[A_{TOT}\right]\leftrightarrow\left[A^-\right]+[HA]$
5. Bicarbonate ion formation equilibrium: $\left[PCO_2\right]\times\left[K_C\right]=\left[H^+\right]\times\left[HCO_3^-\right]$
6. Carbonate ion formation equilibrium: $\left[K_3\right]\times\left[HCO_3^-\right]=\left[H^+\right]\times\left[CO_3^{2-}\right]$

dissociated. When A_{TOT} increases, physicochemistry dictates that $[H^+]$ must increase, for example in the case of hyperphosphatemia in renal failure. When A_{TOT} decreases, $[H^+]$ must also decrease, as is the case in hypoalbuminemia, a common problem in critically ill patients.

5.2.3 The Partial Pressure of Carbon Dioxide (PCO_2)

Tissues produce CO_2. All approaches to acid–base treat PCO_2 similarly. Physicochemistry dictates that if PCO_2 rises, for example due to increased dead space ventilation, $[H^+]$ must rise too. If PCO_2 decreases, $[H^+]$ must also decrease. An example would be psychogenic hyperventilation.

5.2.4 Strong Ion Gap (SIG) and Urine SID

Both SIG and Urine SID may be used to further differentiate between causes of acid–base abnormalities (Tables 5.2 and 5.3). Urine SID is defined as urine $[Na^+]+[K^+]-[Cl^-]$. In metabolic acidosis, a positive urine SID may suggest renal tubular acidosis.

SIG is the difference between the apparent SID (SID_a) and the effective SID (SID_e). SID_a consists of the sum of the measured strong ions:

$$SID_a = \left[Na^+\right]+\left[K^+\right]+\left[Ca^{2+}\right]+\left[Mg^{2+}\right]-\left[Cl^-\right]$$

SID_e is an approximation of the true SID, calculating the remaining ion space after accounting for the negative charge on albumin and bicarbonate, and can be calculated from the other independent variables using the following formula, where albumin (Alb) is expressed in g/L and phosphate (P_i) in mM:

Table 5.2 Differential diagnosis of metabolic acidosis

Adjusted AG >8–12 mEq/L Low SID with SIG >0–2 mEq/L	Normal adjusted AG; Low SID with normal SIG
Lactate	NaCl 0.9 % infusion
Ketones	Diarrhea
End-stage renal failure	Early renal insufficiency
Salicylate intoxication	Acetazolamide
Methanol intoxication	Ureteroenterostomy
Ethylene glycol intoxication	Parenteral nutrition
	Anion exchange resins
	Small bowel/pancreatic drainage
	Renal tubular acidosis (Urine SID >0)
	Type I: Urine pH >5.5
	Type II: Urine pH <5.5/low serum K^+
	Type IV: Urine pH <5.5/high serum K^+

Table 5.3 Differential diagnosis for increased SID metabolic alkalosis

Chloride loss <sodium loss (urine $[Cl^-]$ <10 mmol/L)	Vomiting, gastric drainage, chloride wasting diarrhea, postdiuretic use, posthypercapnea
Chloride loss <sodium loss (urine $[Cl^-]$ >10 mmol/L)	Mineralocorticoid excess (Conn's syndrome, Cushing syndrome, Liddle syndrome, Bartter syndrome, exogenous corticoids, excessive licorice intake), ongoing diuretic use
Exogenous sodium load	Massive blood transfusions, parenteral nutrition, plasma volume expanders, sodium lactate, sodium citrate
Other	Severe deficiency of Mg^{2+} or K^+

$$SID_e = \left[HCO_3^-\right] + \left(0.123 * pH - 0.631\right) * \left[Alb\right] + \left(pH - 0.469\right) * \left[P_i\right]$$

Thus SIG represents the sum of any unmeasured strong positive and negative ions. Its normal value is 0 ± 2 mEq/L. When positive, unmeasured anions exceed unmeasured cations.

5.2.5 Osmol Gap

This is the gap between the measured osmolality and the calculated osmolality.

$$\text{Calculated osmolaity} = 2 \times \left[Na^+\right] + \left[\text{glucose}\right] + \left[\text{urea}\right]$$

where glucose and urea are expressed in mM. The normal value of the osmol gap is 10–15 mM. A high osmol gap suggests the presence of ethanol, ethylene glycol or methanol.

5.2.6 Effect of Resuscitation Fluids

Normal plasma has a SID of approximately 40 mEq/L. Thus, if fluids with a different SID are given, SID will change. Examples include 0.9 or 0.45 % saline with equal amounts of sodium and chloride thus a SID of 0 mM. The same is true for glucose 5 %, which does not contain any strong ions and hence also has a SID of 0 mM.

Balanced salt solutions contain variable amounts of negative ions that are metabolized, such as lactate or acetate. This explains their increased SID, which is about 28 mM for lactated Ringer's for example. Similarly, 8.4 % $NaHCO_3$ is essentially sodium without strong anions, resulting in a high SID of 1,000 mM. In clinical medicine, the effect of resuscitation fluids on SID is counterbalanced by simultaneous dilution of A_{TOT} and renal SID handling.

5.3 The Henderson-Hasselbalch Approach

As can be seen from Table 5.1, the Henderson-Hasselbalch equation is actually one of the Stewart equations:

$$\left[H^{+}\right] \sim PCO_2 / \left[HCO_3^{-}\right]$$

The ratio of $[HCO_3^-]$ and PCO_2 has a fixed relationship to $[H^+]$. All acid–base disturbances are thus explained by changes in either $[HCO_3^-]$ or PCO_2. Singling out this equation is attractive as it facilitates dividing acid–base abnormalities in respiratory and non-respiratory or metabolic disorders. However, it should be noted that because PCO_2 and HCO_3^- are interdependent, relying solely on this equation might lead to circular reasoning.

Compensatory changes to acid–base disturbances may also be respiratory or metabolic and reflected in same direction changes in PCO_2 of $[HCO_3^-]$. Respiratory compensation, either spontaneously or by altering the settings of mechanical ventilation may occur within minutes. Metabolic compensation is slower and may take hours to days, and is mainly regulated by the kidney. To determine whether the compensation is sufficient and to identify mixed acid–base disorders, rules of thumb have been proposed (Table 5.4).

Table 5.4 Rules of thumb for compensation

Primary acid–base disturbance	Compensation rule
Metabolic acidosis	$\Delta PaCO_2 / \Delta\left[HCO_3^{-}\right] = 1.2$ mEq/L $\Delta PaCO_2 = \Delta SBE$
Metabolic alkalosis	$\Delta PaCO_2 / \Delta\left[HCO_3^{-}\right] = 0.7$ mEq/L $\Delta PaCO_2 = 0.6 \times \Delta SBE$
Acute respiratory acidosis	$\Delta\left[HCO_3^{-}\right] / \Delta PaCO_2 = 0.1$ mEq/L $\Delta SBE = 0$
Chronic respiratory acidosis	$\Delta\left[HCO_3^{-}\right] / \Delta PaCO_2 = 0.3$ mEq/L $\Delta SBE = 0.4 \times \Delta PaCO_2$
Acute respiratory alkalosis	$\Delta\left[HCO_3^{-}\right] / \Delta PaCO_2 = 0.2$ mEq/L $\Delta SBE = 0$
Chronic respiratory alkalosis	$\Delta\left[HCO_3^{-}\right] / \Delta PaCO_2 = 0.4$ mEq/L $\Delta SBE = 0.4 \times \Delta PaCO_2$

5.3.1 Anion Gap and Urine Anion Gap

The anion gap (AG) should be calculated to differentiate between causes of metabolic acidosis and to assess the presence of mixed acid–base disorders. AG is an estimate of the relative abundance of unmeasured anions and is used to determine if a metabolic acidosis is due to an accumulation of nonvolatile acids or a HCO_3^- loss:

$$\mathrm{AG} = \left[\mathrm{Na}^+\right] - \left[\mathrm{Cl}^-\right] - \left[\mathrm{HCO}_3^-\right]$$

Its normal value is 3–11 mEq/L. This is mainly due to albumin, which is partially ionized. Therefore, the anion gap should be adjusted as follows:

$$\text{Adjusted AG} = \text{observed AG} + 0.25 \times \left(42 - \left[\text{Albumin}\right]\right)$$

where albumin is given in g/L. Values above 11 m Eq/L for the adjusted anion gap suggest a metabolic acidosis due to nonvolatile acids (Table 5.2). A normal adjusted anion gap metabolic acidosis is sometimes confusingly referred to as hyperchloremic metabolic acidosis. The urine anion gap is the same as the urine strong ion difference and can be used to further differentiate between causes of metabolic acidosis.

5.3.2 Delta Ratio

In high anion gap metabolic acidosis the delta ratio may be used to detect the possible coexistence of a normal anion gap acidosis.

$$\text{Delta ratio} = \Delta\mathrm{AG} / \Delta\mathrm{HCO}_3^- = \left(\text{measured AG} - 12\right) / \left(24 - \text{measured } \mathrm{HCO}_3^-\right)$$

Interpretation of the delta ratio (Table 5.5) should be done with caution due to possible inaccuracies.

5.4 Base Excess and Standard Base Excess

The third approach to acid–base is the base excess (BE) method. The base excess is defined as the concentration of strong acid or base required to return the pH of an in vitro specimen of whole blood with a PCO_2 of 40 mmHg and a temperature of

Table 5.5 Delta gap

Delta ratio <0.4	Hyperchloremic normal anion gap acidosis
Delta ratio 0.4–0.8	Combined high AG and normal AG acidosis
Delta ratio 1–2	Uncomplicated high AG acidosis
Delta ratio >2	Preexisting elevated HCO_3^- (examples: concurrent metabolic alkalosis, preexisting compensated respiratory acidosis)

37 °C to 7.4. A negative BE is also referred to as base deficit. The BE is based on the Van Slyke equation:

$$BE = \left(\left[HCO_3^-\right] - 24.4 + \left(2.3 \times Hb + 7.7\right) \times \left(pH - 7.4\right)\right) \times \left(1 - 0.023 \times Hb\right)$$

with Hb and HCO_3^- in mM. However, this formula proves not to be PCO_2 invariant in vivo. This is because in vivo CO_2 equilibration occurs throughout the total extracellular compartment, including interstitial fluid. To adjust for this the standard base excess (SBE) was developed, in which Hb is fixed at its approximate mean extracellular concentration of 5 mg/dL:

$$SBE = 0.93 \times \left[HCO_3^-\right] - 24.4 + 14.8 \times \left(pH - 7.4\right)$$

SBE is used to assess the metabolic component of an acid–base disturbance and to assess the compensatory regulation (Table 5.4). The primary acid–base disturbance is detected by comparing pH and PCO_2. Then, the SBE formulae are used to determine the metabolic component and compensatory response. If the measured response is different, a mixed acid base disturbance may be present.

5.5 Stewart at the Bedside: A Unifying Approach

Although its principles may be simple, using the Stewart approach at the bedside may be somewhat intimidating. One possibility is to use the online analysis module on acidbase.org. Alternatively, Story has proposed a unified and simplified approach to acid base. Focusing on the effect of SID, A_{TOT} and unmeasured anions on base excess (BE), this approach only requires three easy to remember formulas (Table 5.6).

1. Determine the problem and its severity by assessing the pH. Remember that acidosis and alkalosis refer to processes that influence $[H^+]$ or pH. A normal pH does not rule out acid–base pathology.
2. Assess the relative contribution of respiratory versus non-respiratory components using PCO_2 and BE. Remember that normal values do not rule out acid–base pathology.

Table 5.6 Formulas for the simplified Stewart approach

SID effect on BE	$\left(\left[Na^+\right] - \left[Cl^-\right]\right) - 40$
A_{TOT} effect on BE	0.25 * (42- [alb])
Unmeasured ions effect on BE	SBE-SID effect – A_{TOT} effect

Please note that the normal value for $[Na^+] - [Cl^-]$ may differ between laboratories. Albumin (alb) in g/L

3. Use Stewart derived BE partitioning to quantify contribution of various non-respiratory acid–base disorders.
   (a) Calculate the approximate influence of SID on BE.
   (b) Calculate the approximate influence of A_{TOT} on BE.
   (c) If measured BE differs from the sum of 3a and 3b, unmeasured ions must be present.

5.6 When and How to Treat Acid–Base Disorders

There is no consensus on treatment of acid–base disorders apart from addressing its cause. As acid–base disturbances influences every aspect of physiology including the cardiovascular, respiratory and immune systems, it is reasonable to start symptomatic treatment in the critically ill with severe deviations of pH from normal. These may arbitrarily be defined as pH <7.1 or pH >7.6. Ventilator settings and sedative infusions may be adjusted to modify PCO_2, although trade-offs need to be made clinically because of the adverse effects of overzealous sedation and ventilator induced lung injury at high tidal volumes or plateau pressures. When using a buffer, it should be remembered that administering sodium bicarbonate may transiently decrease intracellular pH, if ventilator settings are not changed simultaneously. In addition, there is no trial that has shown a benefit in terms of mortality when using sodium bicarbonate to attenuate acidosis. In this respect, tromethamine (THAM) may be better suited, as it does not induce intracellular acidosis. However, its clinical benefit is yet to be confirmed.

5.7 Renal Acid–Base Handling

In acid–base homeostasis, the kidneys are pivotal. In critical care medicine, their role is often compensatory, by regulating plasma electrolyte concentrations. However, the kidneys may also cause acid–base disturbances, for example in acute kidney injury or various types of renal tubular acidosis.

When discussing renal acid–base handling, it is important to point out that different explanations for observed cellular mechanisms exist depending on which approach to acid–base medicine is adhered to. For example, the Stewart approach may view sodium bicarbonate transporters as SID regulator, whereas the other approaches may relate its effect to bicarbonate transport itself. Interestingly, most of the physiological concepts dealing with renal transporters have been developed before the Stewart approach became popular. Thus, it may prove necessary to revise these concepts. A detailed discussion of controversies in this is beyond the scope of this book.

Renal acid–base handling is mainly dependent on SID and PCO_2. In the proximal convoluted tubule hydrogen ions are excreted into the tubular lumen through a Na^+-H^+ exchanger. There, mediated by carbonic anhydrase, the hydrogen ions react with the filtered bicarbonate to form H_2CO_3, which dissociates into CO_2 and H_2O. These

diffuse through the aquaporin channels into the cytosol. There, again mediated by carbonic anhydrase, the reaction is reversed and hydrogen and bicarbonate ions are formed again. Bicarbonate is then absorbed into the circulation together with Na^+ by a Na^+-HCO_3^- cotransporter. Chloride reabsorption has three main routes: (1) passive due to the electrochemical concentration gradient, (2) active by chloride channels and (3) coupled through various chloride-anion exchangers.

In the distal convoluted tubule, chloride, hydrogen and bicarbonate are handled by H^+-ATPase, H^+-K^+-ATPase and Cl^--HCO_3^- exchangers, situated within the cell membrane of type A-cells and type B-cells respectively. Depending on the acid–base status, the different components are either up regulated or down regulated. For example in acidosis hydrogen is excreted through the H^+-ATPase and H^+-K^+-ATPase and chloride is excreted through pendrin and band 3 protein. In alkalosis, chloride excretion is less due to down regulation of pendrin and band 3 protein.

5.7.1 Renal Tubular Acidosis (RTA)

In type 1 renal tubular acidosis (RTA) or distal RTA, there is a defect in the ability to secret hydrogen and chloride ions in the distal tubules due to for example mutations in the anion exchangers. As a reaction type B-cells will change and become type-A cells in order to try to increase the hydrogen secretion. As a reaction bicarbonate reabsorption is decreased. Therefore plasma bicarbonate is low and urine pH is increased.

In type 2 RTA or proximal RTA, a reduced capacity in the reabsorption of bicarbonate exists, due to inherited or acquired causes. In inherited RTA 2 a defect in transporters, such as Na/H exchanger (NHE), kNBC1 or NHE3 can exist. The causes are not fully known yet. Further RTA 2 can occur as part of a syndrome such as Fanconi's. Acquired causes include heavy metal poisoning and drugs related RTA. Since distal bicarbonate reabsorption is still possible, plasma bicarbonate is normally slightly decreased and blood pH low normal.

Type 3 RTA or mixed RTA is based on inhibition of carbonic anhydrase (CA). CA-II and CA-IV both play a role in the reabsorption of bicarbonate in the proximal tubule. CA-II also plays a role in the hydrogen excretion in the distal tubule. Inhibition of CA, due to treatment with acetazolamide, or autoimmune diseases such as Sjögren's disease cause a combination of proximal and distal RTA and is therefore named mixed RTA.

Type 4 RTA is characterized by a decreased renal excretion of ammonium and inhibition of H^+/ATPase in type-A cells caused by an aldosterone deficiency or resistance. Ammonium is normally used as a buffer for the excreted hydrogen ions. In the absence of ammonium, less hydrogen can be buffered and thus less hydrogen can be excreted, causing an acidosis. Causes of aldosterone deficiency include Addison's disease, congenital adrenal hyperplasia and drugs inhibiting aldosterone synthesis. Causes of aldosterone resistance include congenital causes, such as pseudohypoaldosteronism type 1 and 2 and acquired causes, such as interstitial nephropathies and drugs. RTA type 4 is commonly associated with a hyperkalemia.

5.7.2 Acute Kidney Injury (AKI)

Acute kidney injury (AKI) is a leading contributor of acid–base disturbances in the critically ill patient and often complex due to the coexistence of acidotic and alkalotic factors. Due to lowered chloride excretion by the kidneys, hyperchloremia may develop, leading to a decreased SID and therefore acidosis. In later stages of AKI in the critically ill, other causes of acidosis may develop, some only partially related to AKI. These include unmeasured anions, hyperlactatemia, hypocalcemia (decreasing SID) and hyperphosphatemia (increasing A_{TOT}). Two main causes of alkalosis may be present: hypoalbuminemia (lowering A_{TOT}) and hyperkalemia (increasing SID). The combination of coexisting acidosis and alkalosis can make the understanding of acid–base balance particularly difficult in the critically ill patient with AKI.

5.7.3 Chronic Kidney Disease (CKD)

The acid–base disturbances in chronic kidney disease (CKD) are similar to AKI. These start to develop when the glomerular filtration rate is less than 20–25 % of normal. Again, mechanisms include both impairment of SID handling and accumulation of A_{TOT}. The extent and relative contribution of each depends on the underlying cause of CKD, medication and renal replacement therapy.

5.7.4 Renal Replacement Therapy (RRT)

The best and fastest way to correct AKI or CKD induced acidosis is renal replacement therapy (RRT). The correction of metabolic acidosis is based on substituting the ultrafiltrate with a SID generator. These include bicarbonate-, lactate- and citrate based substitution fluids. Their effect is based on the metabolisation of the anions and therefore increasing SID and correcting the metabolic acidosis. However, when the metabolisation of the lactate or citrate is impaired, for example in the case of liver failure, the increasing strong anion load can lead to a decreased SID and therefore cause worsening of the metabolic acidosis.

Conclusion

Stewart's strong ion approach, Siggaard-Andersen's standard base excess approach and the Henderson-Hasselbalch based bicarbonate centered approach are popular frameworks for understanding acid–base disorders in the critically ill. Basic concepts, views of renal acid–base handling and clinical application of these methods were discussed in this chapter. Provided that hypoalbuminemia is corrected for in the latter two, all methods are mathematically compatible and may perform equally well in clinical practice, especially in uncomplicated acid–base disorders.

However, if acid–base disorders become increasingly complex, which is the case in many critically ill patients, Stewart's approach may be superior. Although

considered difficult, this method disentangles and quantifies the various factors responsible for complex mixed acid–base disorders, thus arguably providing the best overview. In addition, by explicitly clarifying the relationship between electrolyte disorders and acid–base physiology, the Stewart approach helps to demystify the effects of resuscitation fluids on acid–base balance.

The kidney is pivotal in acid–base physiology, mostly by modifying SID. Our understanding of renal electrolyte handling may need to be revised as a result of the principles of the physiochemical approach. Both in acute and chronic kidney injury, accumulation of weak acids and impaired SID handling may give rise to complex acid base disorders, especially if complicated by hypoalbuminemia.

Key Messages

- Three approaches to acid–base disorders are in common use: The bicarbonate centered, base excess and the Stewart approach. All methods are mathematically compatible provided that appropriate corrections are used for the first two. However, the Stewart approach may be superior in terms of versatility and improved understanding of complex acid–base disturbances.
- The Stewart approach states that only three independent parameters determine [H+]. These parameters are the Strong Ion Difference (SID), the total amount of weak acids (A_{TOT}) and the partial pressure of carbon dioxide (PCO_2).
- SID is the sum strong cations minus the sum of strong anions. Strong ions are always fully dissociated. Na^+ and Cl^- are the most important examples. A_{TOT} is mainly represented by albumin and to a lesser extent by phosphate. If SID decreases, or if PCO_2 increases or if A_{TOT} increases, physicochemistry dictates that $[H^+]$ must increase and vice versa.
- The kidney is pivotal in regulating non-respiratory acid–base physiology, mainly by modulating SID. Acidosis in kidney failure is complex and also includes accumulation of weak acids such as phosphate. Our understanding of renal electrolyte handling may need to be revised in the context of the Stewart approach.

Further Reading

Fencl V, Jabor A, Kazda A, Figge J. Diagnosis of metabolic acid–base disturbances in critically ill patients. Am J Respir Crit Care Med. 2000;162(6):2246–51.

Elbers PWG, Gatz R, AcidBase.org, online community and decision support for quantitative acid-base medicine. http://www.acidbase.org.

Kerry Brandis. Anesthesia Education Website. http://www.anaesthesiamcq.com.

James Figge. Human acid base physiology. http://www.figge-fencl.org.

Kellum JA. Determinants of plasma acid–base balance. Crit Care Clin. 2005;21(2):329–46.

Kellum JA, Elbers PWG, editors. Stewarts textbook of acid–base. Amsterdam: 2009. www.acid-base.org.

Ring T, Frische S, Nielsen S. Clinical review: renal tubular acidosis–a physicochemical approach. Crit Care. 2005;9(6):573–80.

Rodríguez Soriano J. Renal tubular acidosis: the clinical entity. J Am Soc Nephrol. 2002;13:2160.

Rose B, Post T, editors. Clinical physiology of acid–base and electrolyte disorders. New York: McGraw-Hill; 2000.

Stewart PA. How to understand acid base balance. A quantitative acid–base primer for biology and medicine. New York: Elsevier; 1981.

Stewart PA. Modern quantitative acid–base chemistry. Can J Physiol Pharmacol. 1983;61:1444–61.

Story DA. Bench-to-bedside review: a brief history of clinical acid–base. Crit Care. 2004;8(4):253–8.

Story DA, Morimatsu H, Bellomo R. Strong ions, weak acids and base excess: a simplified Fencl-Stewart approach to clinical acid–base disorders. Br J Anaesth. 2004;92(1):54–60.