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Acid–base balance: a review of normal physiology

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Learning objectives

By reading this article you should be able to:

- Explain the development of critical care services enabled by advances in technology.
- Define an acidosis and how this affects normal physiology.
- Describe the major buffer systems in the body and the difference between 'open' and 'closed' systems.
- Discuss the role of the kidney and liver in dealing with an acid load.

Key points

- Alterations in pH have a profound effect on physiological function.
- The body uses buffer systems to reduce the impact of an acute acid load.
- Bicarbonate is the most important buffer and functions in an open system.
- Fine control of acid–base status is brought about by the kidneys and liver.

It is quite apt that this article, reviewing the normal physiology of acid–base balance, was written during the COVID-19 epidemic of 2020–22: the importance of acid–base became clear during the polio epidemic of the early 1950s that centred in Blegdamshospital, Copenhagen. At this time new technology and knowledge came together to achieve medical advances.

The onset of the epidemic saw a high number of patients developing severe respiratory paralysis with bulbar poliomyelitis. Management strategies focused on supporting the patient's breathing, using negative pressure ventilators and adding supplementary oxygen guided by the presence of cyanosis. The mortality was initially more than 90%. It was noted that patients died with an increased total carbon dioxide in their blood. At the time this was thought to indicate that the patients had a metabolic alkalosis. Bjorn Ibsen, a Danish anaesthetist, suggested that in fact the patients died of lack of ventilation, this was confirmed with the assistance of Poul Astrup, director of the clinical laboratory, who using the recently developed pH electrode was able to prove that patients were acidaemic.

Working with Henry Lassen chief physician at the hospital, Ibsen built a team including anaesthetists, surgeons, clinical physiologists, nurses and medical students. Patients had a tracheostomy performed and were hand bagged by the students, sometimes for weeks. For the first time blood gas analysis of pH and P_{CO_2} were used clinically to guide care. The modern Critical Care was born.[1]

Today, the assessment of acid–base status continues to be pivotal in our management of critically ill patients. Measurement of lactate is an essential part of assessing patients with sepsis. Although lactate is not a direct measure of tissue perfusion, it may be an indicator of anaerobic respiration within hypoxic tissues; or a result of accelerated glycolysis driven by β-adrenergic stimulation or from hepatic dysfunction. Regardless of the aetiology, RCTs evaluating lactate-guided resuscitation have shown a reduced mortality.[2]

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What is acidosis and what is its relevance?

$pH = -\log_{10}[H^+]$

The normal blood pH is 7.35–7.45; this relates to a hydrogen ion concentration $[H^+]$ of 35–45 nmol L^{-1}. An acidosis is defined as a pH below 7.35. pH above 7.45 is an alkalosis. Although the $[H^+]$ (in nmol L^{-1}) has a concentration 1/1,000,000 of other common ions (Na^+ 135 mmol L^{-1}, Cl^- 105 mmol L^{-1}), it gains a major significance as the chemical reactions of many biological processes, enabled by enzymatic proteins, are highly dependent on pH.

For example during strenuous exercise, lactic acid accumulates in skeletal muscle. This is a strong acid, with a pK_a of 3.8, that rapidly dissociates to lactate$^-$ and H^+ ions, leading to a reduction in the intracellular pH. This lowers the concentration of free Ca^{2+} within the sarcomere available to react with troponin and reduces the number of actin–myosin interactions. This, in turn, leads to a reduction in the force of contraction of the muscle. There is a matching decrease on cardiac muscle contractility in laboratory studies; however, this is not replicated in all clinical studies and this is thought to be attributable to masking of this effect by the increase in catecholamines seen in acidotic states.[3,4]

The body uses alterations in pH to its advantage, as demonstrated by the function of the haemoglobin–oxygen dissociation curve. Haemoglobin is constructed of 4 haem units (2α, 2β). There is a degree of flexibility in how they are joined, and the spatial arrangement alters the availability of the binding points for oxygen. There are two conformations, a relaxed (R) high O_2 affinity form and a taut (T) low affinity form. An increase in $[H^+]$ causes protonation of the N-terminal amino group of the α-subunit and the C-terminal histidine of the β-subunit, thereby stabilising the T form and reducing the oxygen affinity of haemoglobin sot that the dissociation curve moves to the right. This is the Bohr effect.

The O_2 content of blood (Cao_2) can be quantified as

$$Cao_2 = 1.34 \times Hb \times Sao_2 + (0.025 \times Po_2) \text{ ml } L^{-1} \text{ (normally 200 ml } L^{-1} \text{ blood)}$$

The venous point of O_2 is 5.3 kPa and 70% saturated at pH 7.4. This relates to an arterio-venous (a-v) difference of 60 ml L^{-1}. In metabolically active tissues (such as exercising muscles), there is a reduced pH closer to 7.2; here the saturation approaches 55%, and the a-v difference is now 90 ml L^{-1}. In essence there is an extra 30 ml O_2 per litre cardiac output delivered to the tissues (Fig. 1).

Balance between acid–base production and clearance

The body produces approximately 13 mol day^{-1} of acid. This is made up of volatile acids from the production of CO_2 (13,000 mmol day^{-1} or 0.5 kg for those who want to carbon offset) and non-volatile acids (80 mmol day^{-1}). The non-volatile acids are subclassified as organic acids (lactate, free fatty acids and β-hydroxybutyrate) and inorganic acids (sulphuric, phosphoric acid).

In normal homeostasis there is an impetus to remove acid from the active tissues as soon as it is produced, and this is achieved through three main mechanisms whose effect varies in timescale:

(i) Neutralisation via buffer systems (seconds to minutes)
(ii) Exhalation by the respiratory system (minutes to hours)
(iii) Clearance by the renal system (hours to days)

Buffer systems

A buffer is a system that resists a change in pH. It consists of a solution of a weak acid and its conjugate base. Although buffers do not actually add or remove acid, they act to neutralise the harmful effects of an increased $[H^+]$ whilst other mechanisms act.

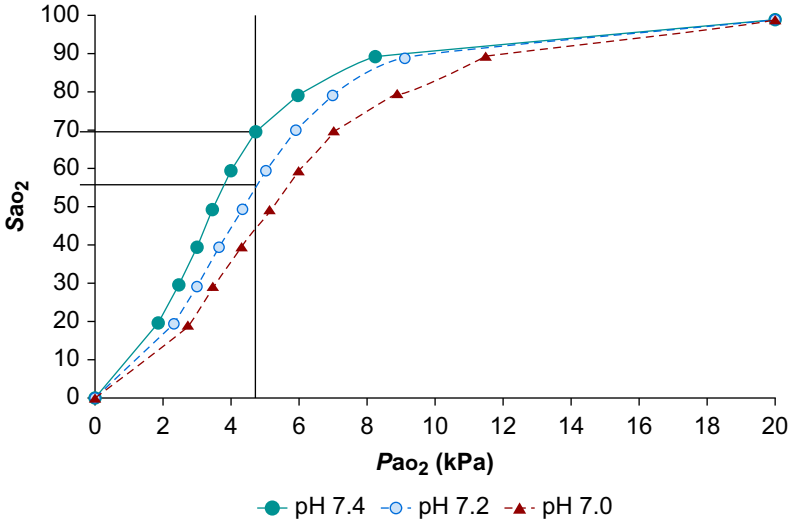

Fig 1 Alteration in oxygen carriage by haemoglobin with varying pH.[4] Reproduced with permission.

$$H^+ + A^- \rightleftharpoons HA$$

There is an equilibrium that is established between the ionised and non-ionised forms that can be defined by the rate constant K.

$$K_a = \frac{[H+][A-]}{[HA]}$$

We can rearrange this as:

$$[H^+] = K_a \frac{[HA]}{[A^-]} \text{(Henderson equation)}$$

Taking logarithms:

$$pH = pK_a + \log \frac{[HA]}{[A-]} \text{(Henderson} - \text{Hasselbalch equation)}$$

The addition of H^+ to a solution increases the rate of bonding to A^- and forms HA. The pK_a is the pH at which $[A^-] = [HA]$. The power of a buffer is greatest when it is working at a pH around its pK_a. The buffering capacity of blood is dependent on (i) the concentration of the buffer and (ii) the pH. The buffering capacity of the body is normally approximately 75 mmol L^{-1} at pH 7.4.

Buffer systems occur throughout the body, both intracellular and extracellular (Table 1).

The predominant acid produced is carbonic acid, a by-product of aerobic respiration in the breakdown of carbohydrates within the mitochondria.

$$C_6H_{12}O_6 + 6O_2 \Rightarrow 6CO_2 + 6H_2O \text{ with the production of ATP.}$$

Although ≈10% of the CO_2 is transported to the lungs dissolved in plasma, the majority is transported as either HCO_3^- (≈60%) or carbamino compounds (≈30%).

$$CO_2 + H_2O \overset{ca}{\leftrightarrows} H_2CO_3 \leftrightarrows HCO_3^- + H^+$$

When CO_2 combines with water it forms carbonic acid. This reaction is slow with an equilibration time of several minutes, but this is reduced to a fraction of a second by the catalytic enzyme carbonic anhydrase (ca). This enzyme, although not present within plasma, is widespread throughout the body — in particular within red blood cells, the nephron and the gastrointestinal tract. Dissolved CO_2 rapidly moves into red blood cells and reacts with H_2O producing carbonic acid, which because of its low pK_a rapidly dissociates.

The bicarbonate/carbonic acid system

Table 1 Buffer systems in the body.

Extracellular	Intracellular
Bicarbonate/carbonic acid buffer system	Haemoglobin buffer ($Hb{\cdot}H/Hb^-$ and $OxyHb{\cdot}H/OxyHb^-$)
Plasma proteins	Phosphate (H_2PO_4/HPO_4^-)
	Intracellular proteins

$$H_2CO_3 \leftrightarrows HCO_3^- + H^+$$

The pK_a of this reaction is 6.1, the pH at which the ratio of HCO_3^- to H_2CO_3 is 1:1. This is the pH at which the system has the greatest ability to resist a change caused by additional acid or base. From the buffer titration curve, we see that this is well below the physiological pH; at pH 7.4 the ratio of HCO_3^- to H_2CO_3 is 5000:1.[5] Theoretically this is at the weakest point for the buffer lying on the flat part of the sigmoid curve (Fig. 2).

The bicarbonate system is important for two reasons. Firstly, it is the most plentiful buffer within the body; secondly, it acts as an open buffer system. The classical buffer describes a closed system, the acid and its conjugate base are dependent only on each other, unaffected by other reactions. However, the bicarbonate buffer acts as part of an open equilibrium. The respiratory system is able to remove CO_2 from the body, adjusting the equilibrium towards carbonic acid removing an increased amount of H^+.

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

Applying the Henderson–Hasselbalch equation to the HCO_3/H_2CO_3 system:

$$pH = pK_a + \log \frac{[HCO_3]}{[CO_2]} \text{ or } pH = pK_a + \log \frac{[HCO_3]}{aPCO_2}$$

where a is the solubility of CO_2 in blood; using Henry's law $[H_2CO_3] = aP_{CO_2}$.

Consider a *closed* system scenario and the normal values for $[HCO_3^-]$ (24 mmol L^{-1}) and $[CO_2]$ (1.2 mmol L^{-1}).

$$pH(7.4) = pK_a(6.1) + \log \frac{24}{1.2}$$

If there is an increase in CO_2 of 1 mmol L^{-1} this would alter the $[HCO_3]/[CO_2]$ ratio to 23/2.2 and the pH would change to 7.2. A step of 2 mmol L^{-1} would leave a $[HCO_3]/[CO_2]$ ratio 22/3.2 and the pH would move to 6.9.

Now consider an *open* system. Should there be a change of 2 mmol L^{-1} in CO_2 there would be a corresponding decrease in the HCO_3^-. However, in reality there would be accommodation by the respiratory system and the extra CO_2 would be exhaled and return it to near 1.2 mmol L^{-1}; thus this would leave a $[HCO_3^-]/[CO_2]$ ratio at 22/1.2 and have a pH of 7.36.

Carbamino compounds

Carbamino compounds are produced by the combination of CO_2 with the terminal amine groups of proteins. This reaction occurs with both intracellular and extracellular proteins, the most significant one being haemoglobin. Both haemoglobin and oxyhaemoglobin can combine with CO_2. Hb^- is less acidic than $OxyHb^-$ and is able to combine with more H^+ (3.5 times greater affinity).[6] This is the Haldane effect.

Effect of acid–base control on respiration

Carbon dioxide is released and exhaled within the lungs. By the law of mass action H^+ clearance matches that of CO_2. The partial pressure of CO_2 or H^+ concentration in the blood has an indirect effect on the respiratory centre of the brainstem via signals from the chemosensitive area of the ventral surface of the medulla. This lies within the blood–brain barrier (BBB). H^+ cannot cross the BBB under normal conditions, but CO_2 can.

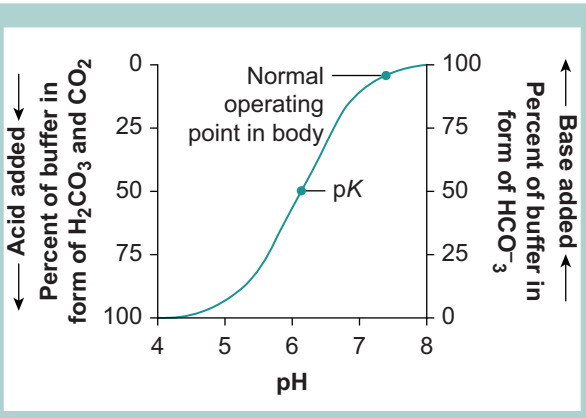

Fig 2 Titration buffer curve for the bicarbonate buffer system.[5] Reproduced with permission.

Paradoxically the effect of CO_2 on respiration is probably caused by alterations in H^+ concentration. The buffering of the CSF is less than in the plasma, and so CO_2 crossing the BBB rapidly reacts with H_2O to form H^+ and HCO_3^-. The H^+ then elicits the response from the chemosensitive area.

There is a steep linear respiratory response to an increase in P_{CO_2} throughout the normal physiological range (P_{CO_2} 4–13 kPa). Alveolar ventilation increases by 1–2 L min^{-1} for each 0.1 kPa increase P_{CO_2}. In contrast, the response to a change in the normal range of pH 7.3–7.5 in only one tenth as great.[5] Respiratory adaptation is a constant process, not just in disease. Any metabolic activity such as exercise is associated with an increase in CO_2 production and this increases ventilation.

Renal regulation of acid–base control

The kidneys are responsible for the excretion of non-volatile acids. These are produced by the metabolism of amino acids. A normal dietary intake of 70 g day^{-1} produces 190 mmol acids: hydrochloric acid (HCl) from the breakdown of arginine, lysine and histidine; sulphuric acid (H_2SO_4) from methionine and cystine. Most of this acid is used in the breakdown and recycling of organic anions (glutamate, aspartate and lactate), and the remaining 40–80 mmol day^{-1} must be excreted by the kidneys.

Quantitively, of more significance to the body is the reabsorption of HCO_3^-. Each day more than 4000 mmol are filtered into the glomerular lumen of which 80–90% is reabsorbed in the proximal convoluted tubule (PCT). HCO_3^- is not readily reabsorbed across the cell membrane; however, the cells of the PCT excrete H^+ into the lumen (via a Na^+/H^+ cotransporter) where, under the action of a membrane bound carbonic anhydrase, they react to form CO_2 and H_2O. CO_2, driven down a concentration gradient, readily crosses into the cell through aquaporins where the reaction is reversed. H^+ is recycled into the lumen

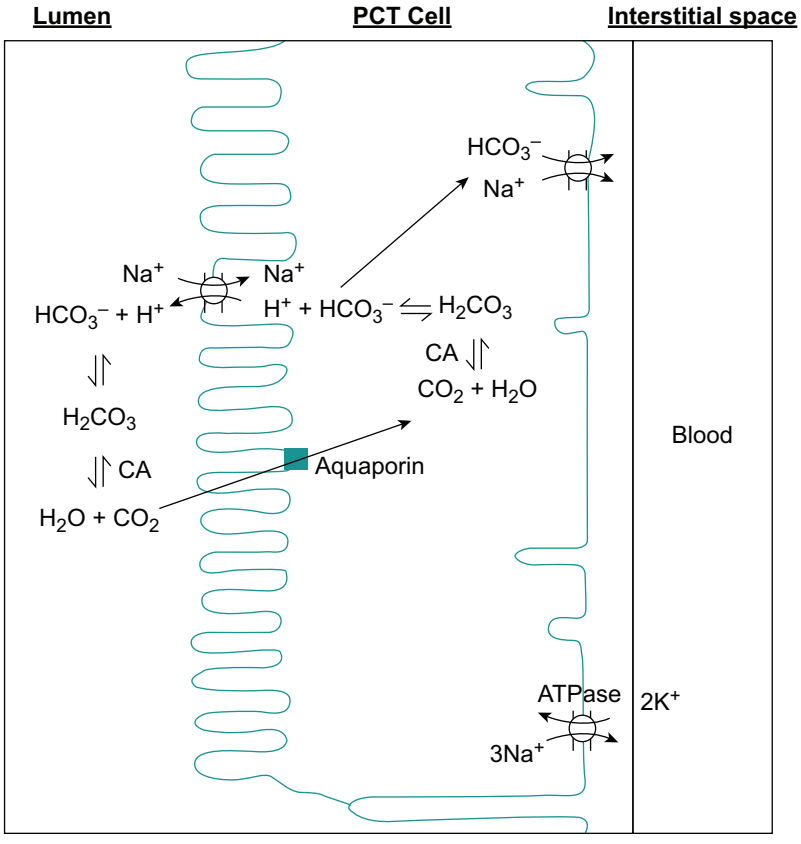

Fig 3 Acid–base control in the proximal convoluted tubule.

whereas HCO_3^- is moved by a Na^+/HCO_3^- co-transporter into the interstitial fluid and returned to the blood (Fig. 3).

The remaining HCO_3 passes through the loop of Henle to the distal convoluted tubule (DCT) where most is reabsorbed. Here the cellular excretion of H^+ is driven by H^+/K^+-ATPase and an aldosterone dependent Na^+/H^+ exchange.

The body is able to modify the pH of urine from pH 8 to pH 4.5. However, even at maximum acidification (0.003 mmol L^{-1} H^+), only a small proportion of the H^+ can be cleared in its free form; the remaining is cleared fixed to the titratable acids (phosphoric acid ≈ 80%, uric acid ≈20% and citric acid) or to ammonium.

$$HPO_4^{2-} + H^+ \leftrightharpoons H_2PO_4^-$$

$$NH_3 + H^+ \leftrightharpoons NH_4^+$$

Phosphate is filtered into the glomerular lumen; it is reabsorbed to a lesser extent than H_2O in the PCT and becomes concentrated. Tubular fluid tends to be acidic as phosphate, with a $pK_a = 6.8$, and takes on a more important buffer role than in the plasma. Once formed H_2PO_4 is excreted as a sodium salt. Overall, 5–10% of the filtered phosphate is excreted in this way and accounts for 30–40 mEq of H^+ excretion. The presence of the titratable acids in the filtrate, binds free H^+ and maintains the concentration gradient for H^+ across the cellular membrane, enabling further HCO_3^- production and transfer back into the body.

Ammonium is responsible for the remaining non-volatile acid clearance at ~40–50 mmol day^{-1}. NH_3/NH_4^+ is not a useful buffer as its $pK_a = 9.2$ is too far away from physiological pH. Instead, there is a combined role of the kidney and liver. Through the metabolism of amino acids in normal dietary protein, approximately 7000–1000 mmol NH_4^+ are produced. About 95% of NH_4^+ is combined in equal amounts with HCO_3^- to form urea and excreted in the urine, with no net acid–base effect. The activity of the urea cycle in the liver is dependent on the amino acid load of the diet (Fig. 4).

The proportion of NH_4^- not combined with HCO_3^- in the formation of urea is used to affect the acid–base equilibrium. Free ammonium ions are toxic in high levels and so are combined with glutamate in the liver to form glutamine; this absorbs one NH_4^+ ion without using a HCO_3^-.

Glutamine passes to the kidneys into the cells of the PCT; here it is cleaved first by mitochondrial glutaminase then by cytosol glutamate dehydrogenase to release 2 NH_4^+ and α-

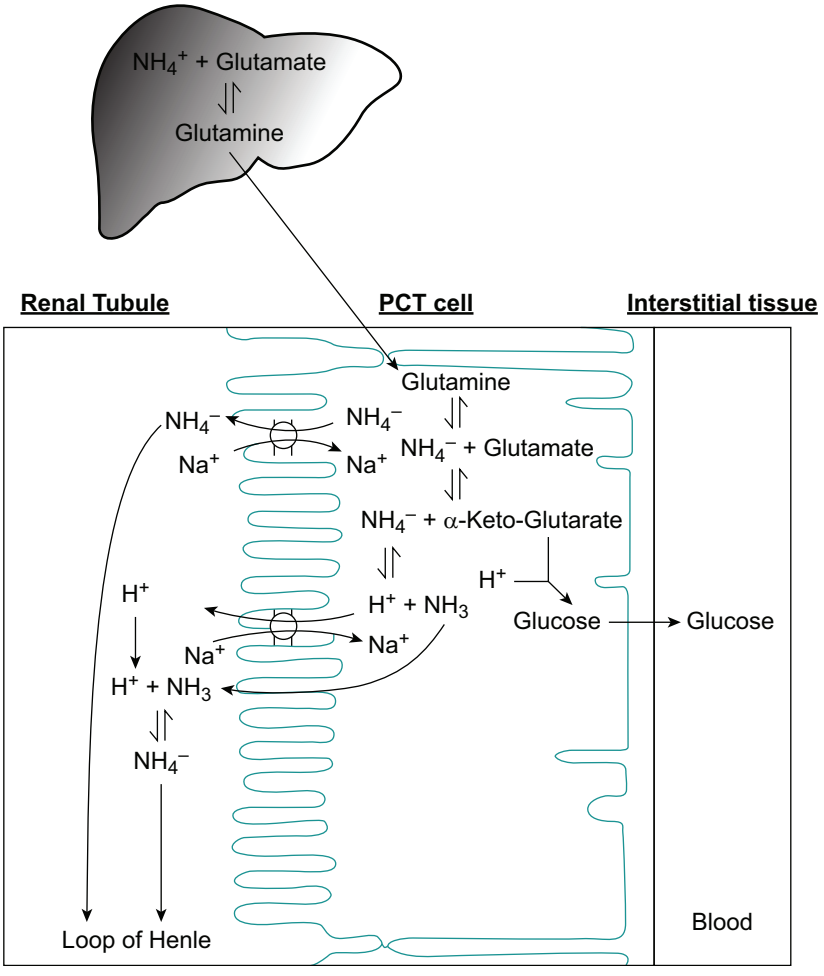

Fig 4 Renal and hepatic cooperation in acid–base control. PCT, proximal convoluted tubule.

ketoglutarate; the latter is converted to glucose within the cell and returned to the body. Conversion to glucose requires one H^+ so the net effect is 1 H^+ (as NH_4^+) per molecule of glutamine. NH_4^+ is either moved into the tubular fluid co-transported directly with Na^+ or dissociates to NH_3 and H^+. NH_3 can pass through the cell membrane down a concentration gradient and H^+ is co-transported with Na^+.

Once in the tubular fluid, NH_4^+ is reformed and moved into the loop of Henlé. In the interstitium there is significant reabsorption and concentration of NH_4^+. This contributes to the hyperosmolarity of the renal medulla. However, in the collecting duct H^+ ions are actively pumped into the tubular fluid and recombine with NH_3, moving by passive diffusion, to reform NH_4^+ and are thus removed from the body.

The consumption and clearance of NH_4^+ via either the urea cycle or the glutamate/glutamine system is controlled by feedback mechanisms affected by pH status. Within 1–2 days of the development of a metabolic acidosis there is increased hepatic glutamine production (at the expense of urea production) and renal glutaminase activity enabling a three-fold increase in clearance of NH_4. Thus, the liver has a direct effect on the acid–base status of the body.

Summary

In summary, the body requires close control of pH for normal function of many metabolic processes. The buffer systems are essential for rapid, local accommodation whereas long-term control is through the respiratory, renal and hepatic systems.

Declaration of interests

The authors declare that they have no conflicts of interest.

MCQs

The associated MCQs (to support CME/CPD activity) will be accessible at www.bjaed.org/cme/home by subscribers to *BJA Education*.

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