

## Acid-base homeostasis

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Acid-base homeostasis is critical to normal health and development. Protons are extremely reactive molecules that damage cellular function, and can lead to death, despite existing at very low concentrations. Normal proton concentration is 40 nM ( $40 \times 10^{-9}$  M).

Because protons are present at such low concentrations, we typically refer to their concentration as pH. Equation 1 shows this formula.

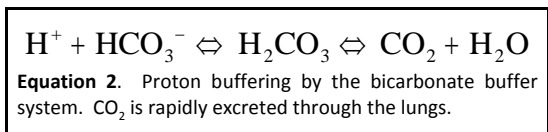
$$\text{pH} = -\log [\text{H}^+]$$

**Equation 1.** Relationship of pH to proton concentration.

The normal metabolism of amino acids leads to  $\sim 0.8$  mEq/kg/d of hydrochloric, sulfuric and phosphoric acid production. For the average 70 kg individual this leads to  $\sim 56$  mEq of strong acid production per day (equal to almost  $1\frac{1}{2}$  gallons of pH 2 hydrochloric acid).

The daily production of acids does not lead to overwhelming acidosis and death because the protons are buffered rapidly by the body. Both intracellular and extracellular buffers are involved in this process. For simplicity sake, we will consider only the bicarbonate buffer system. Equation 2 shows how this system buffers proton production.

This system is effective because bicarbonate ( $\text{HCO}_3^-$ ) is a strong base and is present at a concentration of  $\sim 24$  mM, an almost  $10^6$ -fold greater concentration than protons. The net result of proton addition to the system is consumption of bicarbonate, and production of  $\text{H}_2\text{O}$  and  $\text{CO}_2$ . The  $\text{CO}_2$  is then excreted through normal respiration.



Because of the interrelationship between  $\text{H}^+$ ,  $\text{HCO}_3^-$  and  $\text{CO}_2$  shown in Equation 2, it is possible to determine pH from the blood  $\text{HCO}_3^-$  and  $\text{pCO}_2$ . This is shown in Equation 3.

$$\text{pH} = 6.1 + \log\left(\frac{[\text{HCO}_3^-]}{0.03 \times \text{pCO}_2}\right)$$

**Equation 3.** Henderson-Hasselbach equation. Blood pH is determined by the relative concentrations of  $\text{HCO}_3^-$  and  $\text{CO}_2$ . Blood  $\text{HCO}_3^-$  concentrations are determined by acid and/or alkali intake, cellular acid production rates and renal  $\text{HCO}_3^-$  transport. Blood  $\text{pCO}_2$  is determined by pulmonary respiration.

### Clinical acid-base disturbances

All acid-base disturbances occur as a result of either inappropriate concentrations of  $\text{CO}_2$  or  $\text{HCO}_3^-$  in the blood (see Equation 3). Thus, there are four “simple” types of acid-base disturbances. They are shown in Table 1.

These are termed “simple” because most acid-base disturbances are more complicated. In particular, the body uses the duality of  $\text{HCO}_3^-$  and  $\text{pCO}_2$  effects on pH to try to maintain acid-base homeostasis.

If pH is abnormal due to either metabolic acidosis or alkalosis,

Arterial pH	Abnormality	Name of disorder
Low ( $\leq 7.35$ )	Low $\text{HCO}_3^-$	Metabolic acidosis
	High $\text{pCO}_2$	Respiratory acidosis
High ( $\geq 7.45$ )	High $\text{HCO}_3^-$	Metabolic alkalosis
	Low $\text{pCO}_2$	Respiratory alkalosis

chemoreceptors in the midbrain and medulla oblongata sense extracellular  $H^+$  concentration abnormality and regulate respiration to alter  $pCO_2$  to restore pH towards normal. This response requires only seconds to occur.

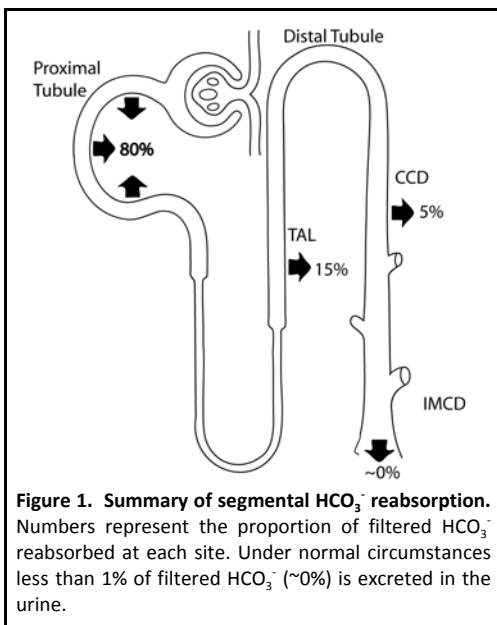
If pH is abnormal due to respiratory acidosis or alkalosis, the kidney recognizes this abnormality and alters net acid excretion to alter blood  $HCO_3^-$  concentrations. The kidney response, in contrast to the respiratory response, requires several days.

Thus, there are six fundamental mixed acid-base disorders. Table 2 shows these.

It is also possible to have combined or "mixed" acid-base disorders. Examples include simultaneous metabolic acidosis and respiratory acidosis. This, obviously, results in much more severe pH disturbances since no compensatory mechanisms are available to minimize the pH changes.

**Table 2.** The six mixed acid-base disturbances.

Arterial pH	Abnormality	Compensatory response	Name of disorder
Low ( $\leq 7.35$ )	Low $HCO_3^-$	Low $pCO_2$	Metabolic acidosis with secondary respiratory alkalosis
	High $pCO_2$ , short-term	None-to-very little	Acute respiratory acidosis
	High $pCO_2$ , 3-5 days or longer	Elevated $HCO_3^-$	Chronic respiratory acidosis
High ( $\geq 7.45$ )	High $HCO_3^-$	High $pCO_2$	Metabolic alkalosis with secondary respiratory acidosis
	Low $pCO_2$ , short-term	None-to-very little	Acute Respiratory alkalosis
	Low $pCO_2$ , 3-5 days or longer	Decreased $HCO_3^-$	Chronic respiratory alkalosis



**Figure 1. Summary of segmental  $HCO_3^-$  reabsorption.** Numbers represent the proportion of filtered  $HCO_3^-$  reabsorbed at each site. Under normal circumstances less than 1% of filtered  $HCO_3^-$  (~0%) is excreted in the urine.

**RENAL REGULATION OF ACID-BASE HOMEOSTASIS**

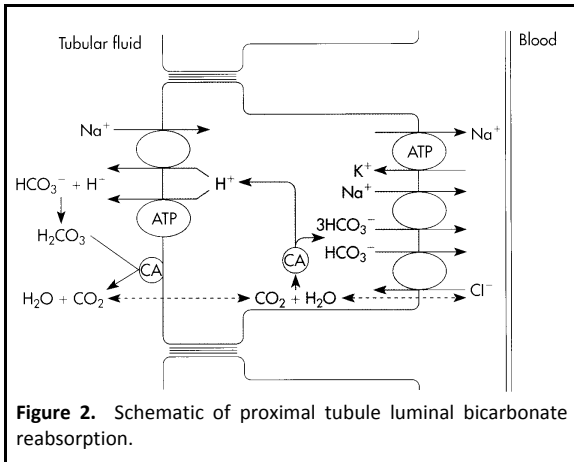
Bicarbonate is consumed in the buffering of acid produced by normal and abnormal cellular metabolism, and it is almost 100% filtered at the glomerulus. As a result, renal tubules must both generate new bicarbonate to replenish that lost in buffering protons and must reabsorb the bicarbonate filtered at the glomerulus. Because different cellular mechanisms are used for these two processes, they will be discussed separately.

**REABSORPTION OF FILTERED BICARBONATE**

First, we will consider the reabsorption of filtered bicarbonate. Figure 1 summarizes the relative amounts of filtered bicarbonate reabsorption in the different nephron segments. Once again, the proximal tubule mediates the majority of solute reabsorption, the thick ascending limb of the loop of Henle

provides second-stage functions, and the collecting duct mediates the tight, final regulation of reabsorption and urinary excretion. Physiologic stimuli regulate bicarbonate transport in each nephron region.

The proximal tubule mediates the majority of filtered bicarbonate reabsorption (~80%). Figure 2 shows a schematic of proximal tubule bicarbonate reabsorption. The apical  $\text{Na}^+/\text{H}^+$

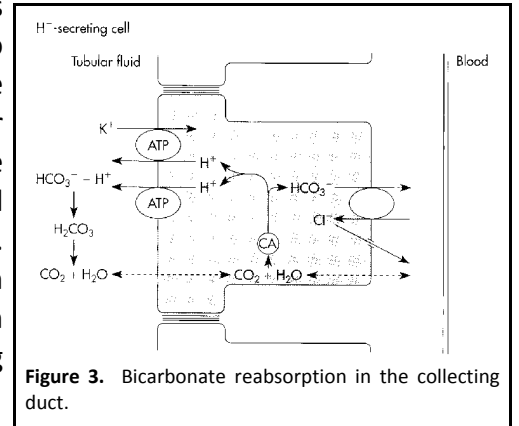


exchanger mediates the majority of proton secretion and bicarbonate reabsorption.

The medullary thick ascending limb of the loop of Henle reabsorbs ~15% of filtered bicarbonate using mechanisms very similar to those used by the proximal tubule.

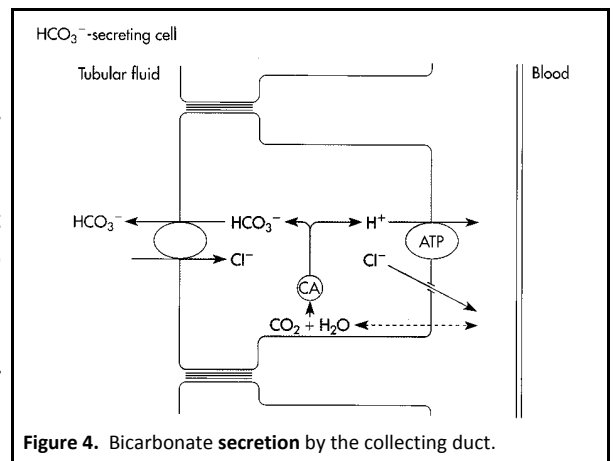
The collecting duct reabsorbs the remaining 5% of filtered bicarbonate. A specific cell in the collecting duct, the intercalated cell, mediates bicarbonate transport. Figure 3 summarizes the mechanisms by which the collecting duct reabsorbs luminal bicarbonate. Two

apical proton pumps secrete protons into the luminal fluid, one secretes protons and transports no other ions, whereas the other secretes protons and reabsorbs luminal potassium. The potassium that is reabsorbed can either recycle across the apical membrane (not shown) or exit across the basolateral membrane. The disposition of the potassium molecule depends, at least in part, on the potassium balance. In states of potassium depletion it preferentially exits across the basolateral membrane, resulting in net potassium reabsorption.



Both  $\text{H}^+$ -ATPase and  $\text{H}^+$ - $\text{K}^+$ -ATPase use ATP hydrolysis as an energy source that enables  $\text{H}^+$  secretion against steep pH gradients. As a result, proton secretion by the collecting duct can decrease luminal pH to as low as 4.4, indicating generation of a 1000:1 proton gradient.

In states of bicarbonate excess, e.g., metabolic alkalosis, the collecting duct must secrete bicarbonate into the urine in order to excrete the excess bicarbonate. Figure 4 shows a schematic of this mechanism. Emphasizing the necessity of luminal chloride for



collecting duct bicarbonate secretion is important. Bicarbonate secretion can increase urinary pH to ~8 in states of metabolic alkalosis.

**GENERATION OF “NEW” BICARBONATE.**

The second function of the kidney in acid-base homeostasis is to generate “new” bicarbonate molecules to replace those consumed in buffering protons (see Formula 2). There are two major mechanisms through which the kidney generates “new” bicarbonate. They are through ammonia excretion and through excretion of titratable acids. Ammonia excretion accounts for ~ 2/3 of basal new bicarbonate generation, and is the predominant mechanism through which the kidney increases new bicarbonate generation. Titratable acid excretion accounts for the remaining 1/3 of basal new bicarbonate generation.

Ammonia excretion requires the integrated activity of several nephron segments. Figure 5 summarizes this process. Proximal tubule cells metabolize glutamine to form equimolar amounts of ammonium (NH<sub>4</sub><sup>+</sup>) and bicarbonate. This bicarbonate molecule is a “new” bicarbonate molecule, and is returned to the systemic circulation via the renal veins. Ammonium is reabsorbed in the medullary thick ascending limb of the loop of Henle and diffuses through the interstitial space to the collecting duct. NH<sub>3</sub> is secreted into the luminal fluid, where proton secretion by collecting duct cells (see Figure 3) leads to formation of NH<sub>4</sub><sup>+</sup>, which remains “trapped” in the luminal fluid.

Titratable acid excretion plays an important, but quantitatively smaller, role in new bicarbonate generation. Proton buffers present in the luminal fluid are able to bind protons secreted in the collecting duct, enabling excretion of protons with less change in luminal fluid pH (see equation 4). The primary buffer in titratable acid excretion is phosphate, but other buffers also participate.

**REGULATION OF ACID-BASE HOMEOSTASIS**

The integrated renal response to acid-base homeostasis comprises three components. The first is reabsorption of filtered bicarbonate, second is excretion of titratable acids and the third is excretion of

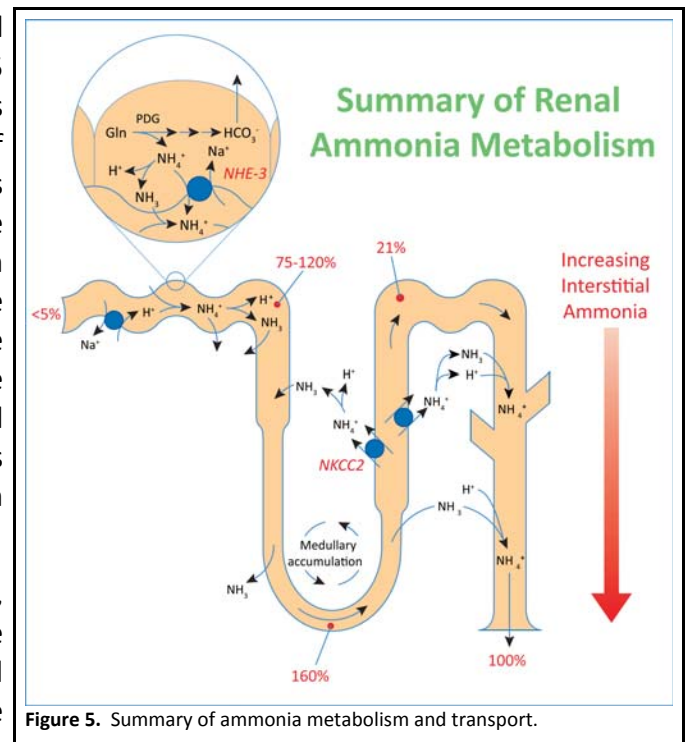
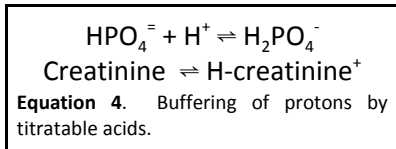


Figure 5. Summary of ammonia metabolism and transport.



$$\text{NAE} = (\text{U}_{\text{TA}} \times \text{V}) + (\text{U}_{\text{Amm}} \times \text{V}) - (\text{U}_{\text{HCO}_3^-} \times \text{V})$$

**Equation 5.** Calculation of net acid excretion, where U<sub>TA</sub>, U<sub>Amm</sub> and U<sub>HCO<sub>3</sub><sup>-</sup></sub> are the urinary concentrations of titratable acids, ammonia and bicarbonate, respectively, and V is the urine volume.

ammonium. These are assessed quantitatively as net acid excretion (NAE), using the formula in Equation 5.

Many factors regulate renal acid-base transport. Table 3 summarizes the factors that increase reabsorption of filtered bicarbonate. ECV contraction, acidosis and aldosterone also stimulate urinary acidification. By stimulating urinary acidification they also increase proton excretion via titratable acids.

**Table 3.** Factors that increase filtered bicarbonate reabsorption and increase urinary acidification.

<b>Factor</b>	<b>Site of action</b>
ECV contraction	Proximal tubule
Acidosis	Proximal tubule, medullary thick ascending limb of the loop of Henle and collecting duct
Aldosterone	Collecting duct

However, the excretion rate of buffers that function as titratable acids is limited, and generally poorly regulated by acid-base disturbances. Consequently, the extent to which titratable acid excretion contributes to acid-base homeostasis is limited.

Ammonia production and excretion are regulated by the same factors as regulate bicarbonate reabsorption. In addition, potassium balance also regulates ammonia handling. In particular, hypokalemia (potassium depletion) stimulates ammonia production and excretion, thereby increasing new bicarbonate generation. Hyperkalemia has the opposite effect.

The response of the kidney to acid-base disturbances may take days to develop. As a result, it is possible to differentiate between acute, recent disturbances, which stimulate little-to-no increase in net acid excretion, whereas longer-term, chronic disturbances stimulate a marked increase in net acid excretion.