



## Acid-Base Homeostasis

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### Abstract

Acid-base homeostasis and pH regulation are critical for both normal physiology and cell metabolism and function. The importance of this regulation is evidenced by a variety of physiologic derangements that occur when plasma pH is either high or low. The kidneys have the predominant role in regulating the systemic bicarbonate concentration and hence, the metabolic component of acid-base balance. This function of the kidneys has two components: reabsorption of virtually all of the filtered  $\text{HCO}_3^-$  and production of new bicarbonate to replace that consumed by normal or pathologic acids. This production or generation of new  $\text{HCO}_3^-$  is done by net acid excretion. Under normal conditions, approximately one-third to one-half of net acid excretion by the kidneys is in the form of titratable acid. The other one-half to two-thirds is the excretion of ammonium. The capacity to excrete ammonium under conditions of acid loads is quantitatively much greater than the capacity to increase titratable acid. Multiple, often redundant pathways and processes exist to regulate these renal functions. Derangements in acid-base homeostasis, however, are common in clinical medicine and can often be related to the systems involved in acid-base transport in the kidneys.

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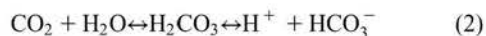
Acid-base homeostasis and pH regulation are critical for both normal physiology and cell metabolism and function. Normally, systemic acid-base balance is well regulated with arterial pH between 7.36 and 7.44; intracellular pH is usually approximately 7.2. For instance, chronic metabolic acidosis can be associated with decreased bone density, nephrolithiasis, muscle wasting, and progression of CKD (1–3). On a cellular level, many essential cellular processes, metabolic enzymes, and transmembrane transport processes are highly pH sensitive. Although this review will address systemic pH regulation and the role of the kidneys, individual cells also have a variety of mechanisms to regulate their intracellular pH (4). Overall concepts will be emphasized rather than specific pathways or processes, which are well covered elsewhere; references are selective.

### Basic Concepts

Intracellular and extracellular buffers are the most immediate mechanism of defense against changes in systemic pH. Bone and proteins constitute a substantial proportion of these buffers. However, the most important buffer system is the  $\text{HCO}_3^-/\text{CO}_2$  buffer system. The Henderson–Hasselbach equation (Equation 1) describes the relationship of pH, bicarbonate ( $\text{HCO}_3^-$ ), and  $P_{\text{CO}_2}$ :

$$\text{pH} = 6.1 + \log \frac{[\text{HCO}_3^-]}{0.03 \times P_{\text{CO}_2}} \quad (1)$$

where  $\text{HCO}_3^-$  is in milliequivalents per liter and  $P_{\text{CO}_2}$  is in millimeters of mercury. Equation 2 represents the reaction (water  $[\text{H}_2\text{O}]$ ):



This buffer system is physiologically most important because of its quantitative capacity to buffer acid or alkali loads and because of the capacity for independent regulation of  $\text{HCO}_3^-$  and  $P_{\text{CO}_2}$  by the kidneys and lungs, respectively. In fact, this latter aspect of independent regulation is the most powerful aspect of this system. Although the lungs and kidneys can compensate for disorders of the other, normal homeostasis requires that both  $\text{CO}_2$  and  $\text{HCO}_3^-$  be normal. Disorders of  $\text{CO}_2$  are usually referred to as respiratory disorders, and disorders of  $\text{HCO}_3^-$  or fixed acids are referred to as metabolic disorders.

Arterial  $\text{CO}_2$  is predominantly regulated by alveolar ventilation after production in peripheral tissues;  $\text{CO}_2$  is often referred to as a gaseous acid, because its addition to aqueous solutions produces carbonic acid, which then releases  $\text{H}^+$  and  $\text{HCO}_3^-$  (Equation 2 driven to the right). Plasma  $\text{HCO}_3^-$  is predominantly regulated by renal acid-base handling, and it will be discussed extensively below. The kidneys reabsorb, produce, and in some circumstances, excrete  $\text{HCO}_3^-$ . Plasma  $\text{HCO}_3^-$  is normally consumed daily by dietary acids and metabolic acids. As expressed by Equation 1, raising  $\text{HCO}_3^-$  or lowering  $P_{\text{CO}_2}$  will raise systemic pH, and lowering  $\text{HCO}_3^-$  or raising  $P_{\text{CO}_2}$  will lower pH.

In physiologic systems, the addition of an acid and the loss of alkali are essentially equivalent; for instance, as obvious in Equation 2, loss of  $\text{HCO}_3^-$  will pull the equation to the right, producing more  $\text{H}^+$ . A frequent example of this is the loss of  $\text{HCO}_3^-$  with diarrhea or proximal renal tubular acidosis. Conversely, the physiologic addition of alkali and the loss of acid are

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essentially equivalent. Therefore, the excretion of acid by the kidneys is equivalent to the production of base or  $\text{HCO}_3^-$ ; this point becomes important in considering below how the kidneys produce more  $\text{HCO}_3^-$ .

Typical high-animal protein Western diets and endogenous metabolism produce acid, typically on the order of 1 mEq/kg body wt per day or approximately 70 mEq/d for a 70-kg person. Phosphoric acid and sulfuric acid are significant products of this normal metabolism of dietary nutrients, such as proteins and phospholipids. To maintain acid-base homeostasis, these nonvolatile acids must be excreted by the kidney. Other nonvolatile acids, such as ketoacids and lactic acids, are produced in pathologic conditions. Nonvolatile acid loads (or loss of  $\text{HCO}_3^-$ , which is an equivalent process) in excess of the excretory capacity of the kidneys cause metabolic acidosis. Of note, vegetarian diets with high fruit and vegetable content are not acid producing and may produce a net alkali load (5); this may be an important consideration in the progression or treatment of CKD (6). Although the kidneys normally control plasma  $\text{HCO}_3^-$ , a few other factors have been considered. Endogenous acid production may be regulated, at least under certain circumstances (7); for instance, lactic acid and ketoacid production are decreased by a low pH. Also, hepatic production of  $\text{HCO}_3^-$  in the metabolism of proteins and amino acids is altered by systemic acid-base balance. Therefore, a role for hepatic contribution to the control of plasma  $\text{HCO}_3^-$  has been hypothesized (8).

### Respiratory Control of $P_{\text{CO}_2}$

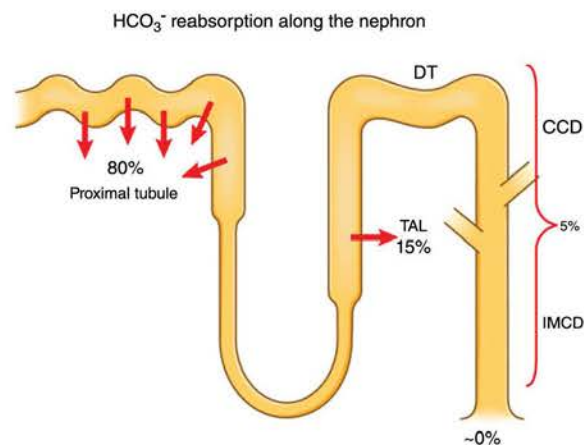
Alveolar ventilation normally eliminates approximately 15 mol  $\text{CO}_2$  per day produced from normal cellular oxidative metabolism and maintains arterial  $P_{\text{CO}_2}$  around 40 mmHg. Normally, with increases (or decreases) in  $\text{CO}_2$  production, alveolar ventilation increases (or decreases) to maintain  $P_{\text{CO}_2}$  and keep pH constant. Alveolar ventilation is controlled by chemoreceptor cells located in the medulla oblongata (and to a lesser extent, those in the carotid bodies), which are sensitive to pH and  $P_{\text{CO}_2}$  (4). Chemoreceptors respond to a decrease in cerebral interstitial pH by increasing ventilation and hence, lowering  $P_{\text{CO}_2}$ . Therefore, small increases in plasma  $\text{CO}_2$ , which decrease pH, will result in stimulation of ventilation, which will normally rapidly return  $P_{\text{CO}_2}$  toward normal. Metabolic acidosis and the resulting acidemia will also result in an increase in ventilation (and lowering of  $P_{\text{CO}_2}$ ) in response to decreases in cerebral interstitial pH. However, in contrast to the rapid response to changes in  $\text{CO}_2$ , the response to nonvolatile acids or a change in plasma  $\text{HCO}_3^-$  is slower, because the central chemoreceptors are relatively insulated by the blood-brain barrier. Hence, acute changes in plasma  $\text{HCO}_3^-$  have a slower effect on cerebral interstitial pH and hence, stimulation of central chemoreceptors. This likely accounts for the 12- to 24-hour delay in the maximal ventilatory response to metabolic acid-base disturbances. The maximal ventilation response cannot usually reduce  $P_{\text{CO}_2}$  <10–12 mmHg (9–12). Decreases in ventilation may be limited because of a variety of clinical circumstances, such as lung disease, fluid overload, and central nervous system derangements. Also, decreases in  $P_{\text{O}_2}$  may limit the extent to which decreased ventilation can raise  $P_{\text{CO}_2}$ .

### Renal Control of Plasma $\text{HCO}_3^-$

The kidneys have the predominant role of regulating the systemic  $\text{HCO}_3^-$  concentration and hence, the metabolic component of acid-base balance. This function of the kidneys has two components: reabsorption of virtually all of the filtered  $\text{HCO}_3^-$  and production of new  $\text{HCO}_3^-$  to replace that consumed by normal or pathologic acids. This production or generation of new  $\text{HCO}_3^-$  is done by net acid excretion. In other words, the kidneys make new  $\text{HCO}_3^-$  by excreting acid.

Because  $\text{HCO}_3^-$  is freely filtered at the glomerulus, approximately 4.5 mol  $\text{HCO}_3^-$  is normally filtered per day ( $\text{HCO}_3^-$  concentration of 25 mM/L  $\times$  GFR of 0.120 L/min  $\times$  1440 min/d). Virtually all of this filtered  $\text{HCO}_3^-$  is reabsorbed, with the urine normally essentially free of  $\text{HCO}_3^-$ . Seventy to eighty percent of this filtered  $\text{HCO}_3^-$  is reabsorbed in the proximal tubule; the rest is reabsorbed along more distal segments of the nephron (Figure 1).

In addition to reabsorption of filtered  $\text{HCO}_3^-$ , the kidneys also produce additional  $\text{HCO}_3^-$  beyond that which has been filtered at the glomerulus. This process occurs by the excretion of acid into urine. (As indicated above, the excretion of acid is equivalent to the production of alkali.) The net acid excretion of the kidneys is quantitatively equivalent to the amount of  $\text{HCO}_3^-$  generation by the kidneys. Generation of new  $\text{HCO}_3^-$  by the kidneys is usually approximately 1 mEq/kg body wt per day (or about 70 mEq/d) and replaces that  $\text{HCO}_3^-$  that has been consumed by usual endogenous acid production (also about 70 mEq/d) as discussed above. During additional acid loads and in certain pathologic conditions, the kidneys increase the amount of acid excretion and the resulting new  $\text{HCO}_3^-$  generation. Net acid excretion by the kidneys occurs by two processes: the excretion of titratable acid and the excretion of ammonium ( $\text{NH}_4^+$ ). Titratable acid refers to the excretion of protons with urinary buffers. The capacity of the nephron to excrete acid as free protons is limited as illustrated by the fact that the concentration of protons ( $\text{H}^+$ ), even at a urine pH 4.5, is <0.1 mEq. However, the availability of urine



**Figure 1. | Relative  $\text{HCO}_3^-$  transport along the nephron.** Most of the filtered  $\text{HCO}_3^-$  is reabsorbed in the proximal tubule. Virtually no  $\text{HCO}_3^-$  remains in the final urine. CCD, cortical collecting duct; DT, distal convoluted tubule; IMCD, inner medullary collecting duct; TAL, thick ascending limb.



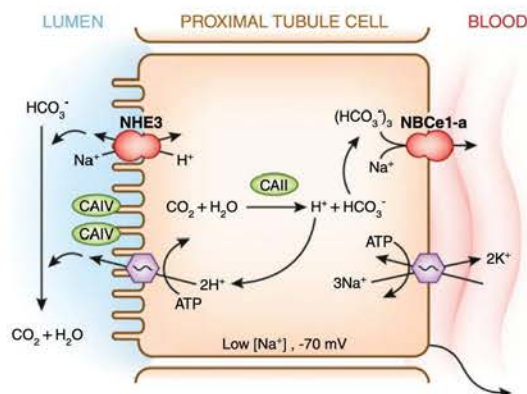
buffers (chiefly phosphate) results in the excretion of acid coupled to these urine buffers (13). Under normal conditions, approximately one-third to one-half of net acid excretion by the kidneys is in the form of titratable acid. The other one-half to two-thirds is the excretion of  $\text{NH}_4^+$ . The mechanism whereby the excretion of  $\text{NH}_4^+$  results in net acid excretion will be discussed below. The capacity to excrete  $\text{NH}_4^+$  under conditions of acid loads is quantitatively much greater than the capacity to increase titratable acid (Figure 2) (14,15). Net acid excretion in the urine is, therefore, calculated as

$$\text{net acid excretion} = \text{titratable acid} + \text{ammonium} - \text{urinary } \text{HCO}_3^- \quad (3)$$

Loss of alkali in the urine in the form of  $\text{HCO}_3^-$  decreases the amount of net acid excretion or new  $\text{HCO}_3^-$  generation. Loss of organic anions, such as citrate, in the urine represents the loss of potential alkali or  $\text{HCO}_3^-$ . However, in humans, the loss of these organic anions is not usually quantitatively significant in whole-body acid-base balance (15).

### Proximal Tubule $\text{HCO}_3^-$ Reabsorption

The proximal tubule reabsorbs at least 70%–80% of the approximately 4500 mEq/d filtered  $\text{HCO}_3^-$ . The proximal tubule, therefore, has a high capacity for  $\text{HCO}_3^-$  reabsorption. The mechanisms of this reabsorption are illustrated in Figure 3. Most (probably >70%) of this  $\text{HCO}_3^-$  reabsorption occurs by proton secretion at the apical membrane by sodium-hydrogen exchanger NHE3 (16) (Figure 3). This protein exchanges one  $\text{Na}^+$  ion for one  $\text{H}^+$  ion, driven by the lumen to cell  $\text{Na}^+$  gradient (approximately 140 mEq/L in the lumen and 15–20 mEq/L in the cell). The low intracellular  $\text{Na}^+$  is maintained by the basolateral  $\text{Na}^+/\text{K}^+$ -ATPase. An apical  $\text{H}^+$ -ATPase and possibly, NHE8 under some circumstances account



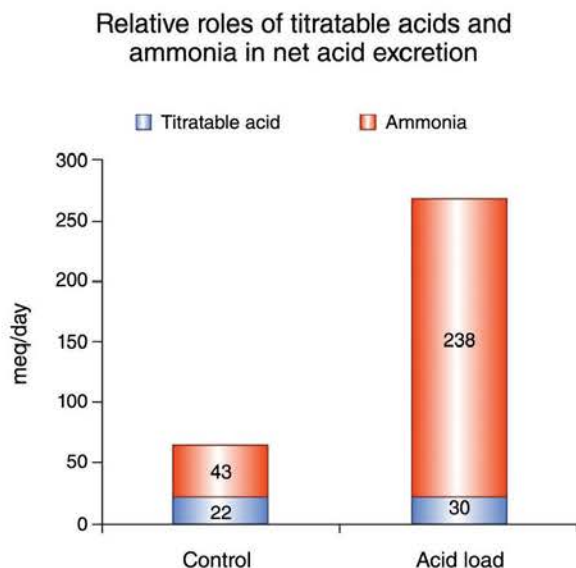
**Figure 3.** | Schematic representation of  $\text{HCO}_3^-$  reabsorption in the proximal tubule. Most  $\text{H}^+$  secretion occurs through  $\text{Na}^+/\text{H}^+$  exchange, although a component of an  $\text{H}^+$  pump is also present. Carbonic anhydrase (CA), both intracellular and luminal, is important for  $\text{HCO}_3^-$  reabsorption.  $\text{HCO}_3^-$  exits the cell by NBCe1-A.

for the remaining portion of proximal tubule  $\text{H}^+$  secretion and  $\text{HCO}_3^-$  reabsorption (17–19). This  $\text{H}^+$ -ATPase shares most subunits with the distal tubule  $\text{H}^+$ -ATPase described below.

In the lumen of the proximal tubule, the secreted  $\text{H}^+$  reacts with luminal  $\text{HCO}_3^-$  to generate  $\text{CO}_2$  and  $\text{H}_2\text{O}$ , which for the purposes here, can be considered to be freely permeable across the proximal tubule and reabsorbed. This reaction in the lumen (Equation 2 going from right to left) is relatively slow unless catalyzed, which occurs normally, by carbonic anhydrase (CA; in this case, membrane-bound CAIV tethered in the lumen). There are multiple isoforms of CA, but membrane-bound CAIV and cytosolic CAII are most important in renal acid-base transport (20,21). Mutations in CAII are known to cause a form of mixed proximal and distal renal tubular acidosis with osteopetrosis (22).

The source of the  $\text{H}^+$  in the cells is the generation of  $\text{H}^+$  and  $\text{HCO}_3^-$  from  $\text{CO}_2$  and  $\text{H}_2\text{O}$  (Equation 2) catalyzed in the cell by intracellular CA, predominantly cytosolic CAII. The  $\text{HCO}_3^-$  generated within the proximal tubule cell by apical  $\text{H}^+$  secretion exits across the basolateral membrane. Most of this  $\text{HCO}_3^-$  exit occurs by sodium  $\text{HCO}_3^-$  co-transport, NBCe1-A, or SLC4A4 (23). The stoichiometry and transported ionic species have been active areas of investigation, but studies suggest that 3  $\text{HCO}_3^-$  Eq or 1  $\text{HCO}_3^-$  Eq and 1  $\text{CO}_3^{2-}$  Eq are transported with each  $\text{Na}^+$ ; this electrogenic stoichiometry results in  $\text{Na}^+$  and  $\text{HCO}_3^-$  being driven out of the cell by the cell-negative membrane voltage. Mutations in this (NBC-e1) protein cause proximal renal tubular acidosis (24). Chloride-bicarbonate exchange may also be present on the basolateral membrane of the proximal tubule but is not the main mechanism of  $\text{HCO}_3^-$  reabsorption.

The proximal tubule is a leaky epithelium on the basis of its particular tight junction proteins and therefore, unable to generate large transepithelial solute or electrical gradients; the minimal luminal pH and  $\text{HCO}_3^-$  obtained at the end of the proximal tubule are approximately pH 6.5–6.8 and 5 mM, respectively. The inability of the proximal tubule to lower pH further may also result from the



**Figure 2.** | Relative urinary titratable acid and ammonia in adults on a control or acid loading diet (with  $\text{NH}_4\text{Cl}$ ). Reference 15.



dependence on the  $\text{Na}^+$  gradient (140:15–20) driving the  $\text{H}^+$  (pH) gradient. In the late proximal tubule, ongoing reabsorption of the low concentrations of luminal  $\text{HCO}_3^-$  may be countered and balanced by passive backleak of plasma or peritubular  $\text{HCO}_3^-$  into the lumen; however, continued  $\text{Na}^+/\text{H}^+$  exchange activity will result in continued  $\text{Na}^+$  reabsorption.

### Regulation of $\text{HCO}_3^-$ Reabsorption in the Proximal Tubule

A number of processes regulate proximal tubule  $\text{HCO}_3^-$  reabsorption both acutely and chronically. Many of these regulatory processes function to maintain acid-base homeostasis and are seemingly quite redundant; this is true in both the proximal and distal nephron segments. However, other processes overlap with volume or sodium regulatory processes, and the acid-base effects seem secondary and at times, dysfunctional for pH *per se*; for instance, during metabolic alkalosis induced by vomiting and volume depletion, various hormones are activated (catecholamines, angiotensin II, and aldosterone) that restore volume status but secondarily maintain high plasma  $\text{HCO}_3^-$  and alkalemia.

To maintain or restore acid-base balance, the proximal tubule increases  $\text{HCO}_3^-$  reabsorption during acidemia or acid loads and decreases  $\text{HCO}_3^-$  reabsorption during alkalemia or alkali loads (such that  $\text{HCO}_3^-$  might be excreted into the urine). Because this has been recently reviewed in this series (18), only a few comments will be made. The signals for these changes are often thought to be pH *per se*, either intracellular or extracellular. A variety of pH sensors have also been proposed (25), most notably including nonreceptor tyrosine kinase Pyk2, endothelin B receptor (activated by endogenous renal endothelin) (26,27), and  $\text{CO}_2$  activation of ErbB1/2, ERK, and the apical angiotensin I receptor (28). More directly, decreased intracellular pH will increase the availability of protons for  $\text{H}^+$  secretion and also, allosterically enhance the  $\text{Na}^+/\text{H}^+$  exchanger (29). In addition to allosteric modulation of acid-base transporters, acute acidosis will cause insertion of additional transport proteins into the apical membrane, probably through the mechanisms immediately above; this has been best studied for NHE3. Chronic acidosis induces the production of additional transport proteins by increased transcription and production of mRNA; this is activated through a variety of signal transduction processes that are still being actively investigated. Both apical transport proteins (e.g., NHE3) and basolateral transporters (e.g., NBCe1-A) are often activated and increased in abundance in parallel, although the specifics may vary (30). Chronic potassium depletion also increases  $\text{H}^+$  secretion, probably in response to changes in intracellular pH (31). In fact, hypokalemia has many effects on the kidney that parallel chronic acidosis, including effects on  $\text{NH}_4^+$  excretion discussed below.

Extracellular fluid volume status is also an important determinant of proximal  $\text{HCO}_3^-$  reabsorption. Decreasing extracellular causes increased reabsorption of not only sodium but also,  $\text{HCO}_3^-$ , both in large part through increased Na-H exchange. Increases in volume status inhibit reabsorption of sodium and  $\text{HCO}_3^-$ , other factors being

unchanged. As mentioned above and discussed more below, clinically, this relates to the association of metabolic alkalosis with both volume contraction and edematous states (because these have decreased effective arterial volume). Volume expansion can be associated with decreased plasma  $\text{HCO}_3^-$  and metabolic acidosis, usually mild. An important additional component of the change in net  $\text{HCO}_3^-$  reabsorption with volume overload is an increased backleak of  $\text{HCO}_3^-$  into the tubule lumen. In contrast to the effects of volume, increasing delivery of  $\text{HCO}_3^-$  to the proximal tubule with constant extracellular volume results in a proportional increase in  $\text{HCO}_3^-$  reabsorption; this can be conceptualized as an increase in delivery to a reabsorptive system that is not saturated (*i.e.*, below the transport  $K_m$ , the Michaelis–Menten constant [the substrate concentration that gives half-maximal velocity of an enzymatic reaction and also, is used to model transport kinetics]).

A variety of hormones, some as above, affect proximal  $\text{HCO}_3^-$  reabsorption (32,33). Some of these hormones act on a short-term basis (response in minutes to hours), and others act over longer periods (days). On an acute basis, for instance, adrenergic agonists and angiotensin II stimulate  $\text{HCO}_3^-$  reabsorption (32). Parathyroid hormone acting through cAMP inhibits but hypercalcemia stimulates proximal  $\text{HCO}_3^-$  reabsorption. With these hormones and others, many studies have addressed the specific processes and signal transduction events (32). With chronic acid loads or acidosis, intrarenal endothelin-1 acting through the endothelin B receptor has been identified as a crucial element in the upregulation of  $\text{Na}^+/\text{H}^+$  exchange (26,27). Glucocorticoids also are important in the development of proximal  $\text{HCO}_3^-$  transport and may be important in the chronic response to acidosis (34). In clinical circumstances, various regulatory factors may interact and be simultaneously operative. The net effect of these combined influences would vary depending on the exact circumstance. For instance, in metabolic alkalosis, volume contraction (and the associated hormonal changes and frequent fall in GFR) and high filtered loads of  $\text{HCO}_3^-$  increase proximal tubule  $\text{HCO}_3^-$  reabsorption, whereas increases in peritubular  $\text{HCO}_3^-$  and increased intracellular pH may be inhibiting  $\text{HCO}_3^-$  reabsorption—the net effect is maintenance of metabolic alkalosis until the volume status is corrected.

Despite the regulation mentioned above, changes in proximal  $\text{HCO}_3^-$  reabsorption may not be directly reflected in changes in whole-kidney net acid excretion or urinary  $\text{HCO}_3^-$  excretion, because additional  $\text{HCO}_3^-$  reabsorption and acid secretion occur in the distal nephron. Also, because virtually all of filtered  $\text{HCO}_3^-$  is normally reabsorbed by the kidneys, increases in  $\text{HCO}_3^-$  reabsorption *per se* cannot compensate for increased systemic acid loads. This compensation can only occur with increased acid excretion as titratable acids or  $\text{NH}_4^+$ .

### Distal Tubule Acidification

Several segments after the proximal tubule contribute substantially to acid-base homeostasis. First, the thick ascending limb (TAL) reabsorbs a significant amount of  $\text{HCO}_3^-$ , approximately 15% of the filtered load, predominantly through an apical  $\text{Na}^+/\text{H}^+$  exchanger (35). TAL acid-base transport is regulated by a variety of factors



(e.g., Toll-like receptors, dietary salt, aldosterone, angiotensin II, *etc.* [36–38]), but the integrated role of the thick limb acid-base transport in various acid-base disorders has not been well clarified.

Beyond the TAL, the distal tubule compared with the proximal tubule has a limited capacity to secrete  $H^+$  and thereby, reabsorb  $HCO_3^-$ . During inhibition of proximal tubule  $HCO_3^-$  reabsorption, increased distal delivery of  $HCO_3^-$  can overwhelm this limited reabsorptive capacity. However, the collecting tubule is able to generate a large transepithelial pH gradient (urine pH <5 with blood pH approximately 7.4). This large pH gradient is achievable because of the primary active pumps responsible for distal nephron  $H^+$  secretion (discussed below) and because of the relative impermeability of the distal tubule to ions (*i.e.*, a tight epithelial membrane). The large pH gradient ensures the generation of titratable acid and the entrapment of  $NH_4^+$ . The limitation in  $HCO_3^-$  reabsorption is likely, in part, caused by the absence of luminal CA discussed below, but there may be other factors as well, such as a limited number of  $H^+$  pumps.

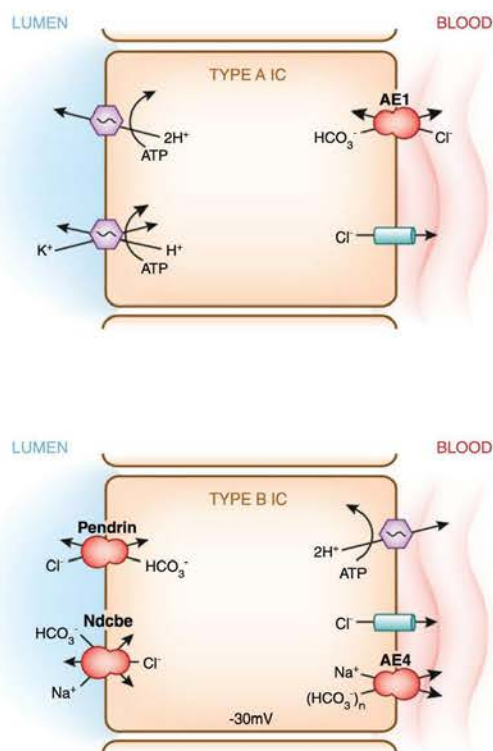
The distal tubule beyond the TAL consists of several distinct morphologic and functional segments, including the distal convoluted tubule, the connecting segment, and several distinct collecting duct segments, each with several cell types. Although several of these cell types can secrete  $H^+$ , the CA-containing (and mitochondrial-rich) intercalated cells (ICs) are chiefly responsible for acid-base transport. There are at least three types of ICs: type A or  $\alpha$  ICs, which secrete  $H^+$ ; type B or  $\beta$  ICs, which secrete  $HCO_3^-$ ; and non-A, non-B ICs, with a range of function that

remains under investigation. These have been recently reviewed in this series (39) (Figure 4).

Conceptually,  $H^+$  secretion in the type A ICs will result in  $HCO_3^-$  reabsorption in the presence of luminal  $HCO_3^-$  but will acidify the urine and generate new  $HCO_3^-$  in the absence of luminal  $HCO_3^-$  (*i.e.*, if virtually all of the filtered  $HCO_3^-$  has been reabsorbed upstream). The mechanism of this  $H^+$  secretion involves primarily an apical  $H^+$ -ATPase as illustrated in Figure 4. The apical  $H^+$ -ATPase is an electrogenic active pump (vacuolar ATPase) able to secrete  $H^+$  down to a urine pH of approximately 4.5. This is a multisubunit ATPase resembling that in intracellular organelles. The subunits are in two domains: a  $V_0$  transmembrane domain and a  $V_1$  cytosolic domain. Mutations in certain subunits are a known cause of distal renal tubular acidosis (40). Regulation of this pump is primarily by recycling between subapical vesicles and the plasma membrane involving the actin cytoskeleton and microtubules (41). Regulation may also be accomplished, in certain situations by assembly or disassembly of the two domains and phosphorylation of subunits.  $H^+$  secretion also occurs through another set of pump(s): apical  $H^+/K^+$ -ATPases.  $H^+/K^+$ -ATPases in the collecting duct include both the gastric form of  $H^+/K^+$ -ATPase and the colonic form of  $H^+/K^+$ -ATPase (42). On the basis of inhibitor studies, there may also be a third type of  $H^+/K^+$ -ATPase in the collecting duct (43,44). These transporters likely contribute to urine acidification under normal conditions but particularly during states of potassium depletion (42,44).

Conceptually,  $HCO_3^-$  reabsorption (or new  $HCO_3^-$  generation) as in the proximal tubule is a two-part process: secretion of  $H^+$  into the lumen and  $HCO_3^-$  exit from the cell across the basolateral membrane. Therefore, to complete the process of  $HCO_3^-$  reabsorption or new  $HCO_3^-$  generation,  $HCO_3^-$  produced in the cell from  $CO_2$  and  $H_2O$  exits across the basolateral membrane (Equation 2 as in the proximal tubule, with  $H^+$  being secreted across the apical membrane). In other words, the  $HCO_3^-$  generated intracellularly by any of these pumps exits the basolateral membrane. This exit into the blood occurs through a chloride-bicarbonate exchanger, a truncated version of the anion exchanger 1 (AE1; band 3 protein), which is the  $Cl^-/HCO_3^-$  exchanger in red blood cells that facilitates  $CO_2$  transport (45). This is an electroneutral exchanger driven by the ion concentrations of chloride and  $HCO_3^-$ . Mutations in AE1 can also cause distal renal tubular acidosis (40,46). Two other transporters SLC26a7 (a  $Cl^-/HCO_3^-$  exchanger) and KCC4 (a  $KCl$  cotransporter) are also in the basolateral membrane of some acid secreting cells in the collecting duct and likely contribute to urine acidification in certain conditions (47–49).

In the cortical collecting duct, in addition to  $HCO_3^-$  reabsorption by type A ICs, simultaneous  $HCO_3^-$  secretion occurs in separate cells, the type B ICs (39,50). This process involves an apical chloride-bicarbonate exchanger and a basolateral  $H^+$ -ATPase (51). In animal studies,  $HCO_3^-$  secretion is stimulated by alkali loading and inhibited by low luminal chloride. The basolateral  $H^+$ -ATPase is the same pump as in the apical membrane of type A IC, but the apical  $Cl^-/HCO_3^-$  exchanger has been identified as pendrin, a protein first identified as being abnormal in



**Figure 4.** | Schematic of  $H^+$  and  $HCO_3^-$  transport in the types A and B intercalated cells (ICs) in the collecting tubule (details are in the text). AE, anion exchanger.



some patients with hereditary deafness (39,52,53). The importance of  $\text{HCO}_3^-$  secretion in human pathophysiologic circumstances is not well characterized but may be important in the maintenance and/or repair of metabolic alkalosis.

The type B ICs, non-A, non-B ICs, and pendrin have now also been implicated in  $\text{NaCl}$  transport/balance and hypertension (53). This involves transport of  $\text{Cl}^-$  and  $\text{HCO}_3^-$  on pendrin and also, a sodium-driven chloride/ $\text{HCO}_3^-$  exchanger (NDCBE or SLC4A8);  $\text{Cl}^-$  exits the cell on AE4 (54–57).

Cytosolic CA, CAII, is present in all ICs of the collecting tubule, and it facilitates provision of  $\text{H}^+$  to be secreted into the lumen and  $\text{HCO}_3^-$  to be released into the basolateral aspect and blood. However, several segments of the distal nephron do not have luminal CA (*i.e.*, CAIV). The implications of this are that, as  $\text{H}^+$  is secreted into the lumen, luminal pH may be below equilibrium pH, with pH,  $\text{CO}_2$ , and  $\text{HCO}_3^-$  only coming to equilibrium later downstream in the final urine. Final urine  $P_{\text{CO}_2}$  may, therefore, rise above blood  $P_{\text{CO}_2}$  (as  $\text{H}^+$  and  $\text{HCO}_3^-$  react and come to equilibrium with  $\text{CO}_2$ ) and be an index of distal nephron  $\text{H}^+$  secretion.

### Regulation of Acid-Base Transporters in the Distal Nephron

Regulation of distal nephron acid-base transport is crucial, because this is the final site of control of urine composition. The distal tubule responds to systemic acidosis in a teleologically appropriate direction of increased  $\text{H}^+$  secretion and new  $\text{HCO}_3^-$  generation. As in the proximal tubule, changes in intracellular pH and plasma  $P_{\text{CO}_2}$  affect proton secretion in the distal nephron. A significant portion of this increased  $\text{H}^+$  secretion is through insertion of additional  $\text{H}^+$ -ATPase by fusion of subapical vesicles (containing  $\text{H}^+$ -ATPase) with the plasma membrane. These processes are mediated, in part, by a variety of signal transduction systems (cAMP, cGMP, and PLC/protein kinase C) (39,41). A role for soluble adenylyl cyclase, G protein-coupled receptor 4, and other mechanisms in sensing pH changes or acid-base loads has also been proposed in type A ICs and previously discussed in this series (39,41). Although the response to acidosis begins with these fairly rapid changes, chronic acidosis leads to a variety of changes in mRNA and protein levels of various transporters. Potassium depletion also increases  $\text{H}^+$  secretion in the distal tubule, similar to changes in the proximal tubule.

The electrogenic nature of the apical  $\text{H}^+$ -ATPase makes this process sensitive to transepithelial voltage. Therefore, an increased lumen-negative voltage (*e.g.*, more  $\text{Na}^+$  reabsorption) will increase  $\text{H}^+$  secretion. Increased  $\text{Na}^+$  reabsorption, such as with increased mineralocorticoids, will, therefore, be accompanied by increased  $\text{H}^+$  secretion. Interestingly, the cell voltages of ICs are strikingly different from most cells, including principal cells: first, although there is little data, the cell-negative voltages as shown in Figure 4 are much less (less negative), and second, the cells are energized by the  $\text{H}^+$  pump rather than by  $\text{Na-K-ATPase}$  as in most cells (54,57,58).  $\text{H}^+$  secretion, including in the medullary collecting tubule, is also directly stimulated by mineralocorticoids, not just by secondary electrical effects (59,60). Distal tubule acidification may be strongly

influenced by chloride concentration gradients between tubular lumen and peritubular blood; this may result both from voltage changes and by direct lumen to cell concentration gradients driving pendrin and other transporters.

In addition to aldosterone, other hormones and receptors, including angiotensin II and the calcium-sensing receptor, stimulate distal acidification (61). An important role for intrarenal endothelin has also been found (27,62,63).

Remodeling of IC morphology, number (relative numbers of A, B, and non-A, non-B ICs), and distribution of various transporters has also been characterized (64,65). The matrix protein hensen is a key mediator of this remodeling.

### Ammonia Excretion

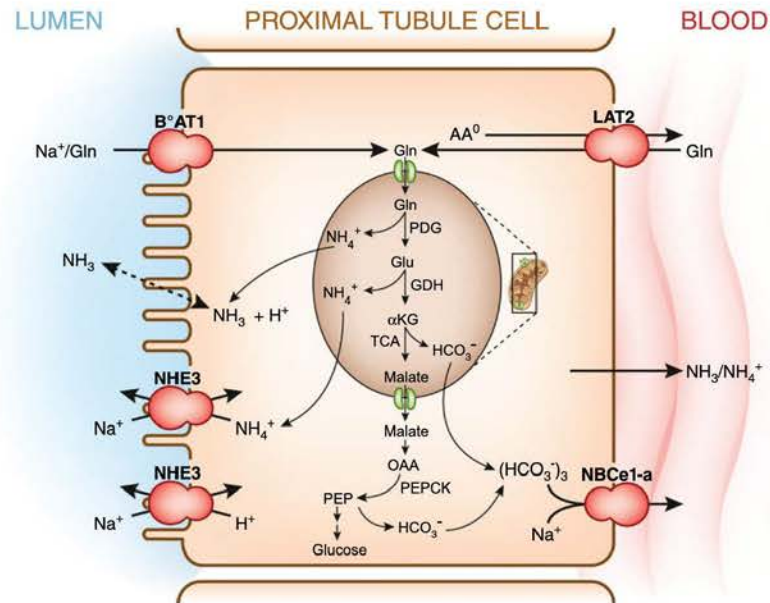
$\text{NH}_4^+$  excretion represents the other major mechanism whereby the kidneys excrete acid (66). Of the net acid excreted (or new  $\text{HCO}_3^-$  generated) by the kidneys, approximately one-half to two-thirds (approximately 40–50 mmol/d) is because of  $\text{NH}_4^+$  excretion in the urine. Additionally, during acid loading or acidosis,  $\text{NH}_4^+$  excretion can increase several fold, in contrast to a more limited increase in titratable acidity (15) (Figure 2).

Traditionally,  $\text{NH}_4^+$  excretion was viewed as the excretion of protons in conjunction with a buffer (ammonia [ $\text{NH}_3$ ]):

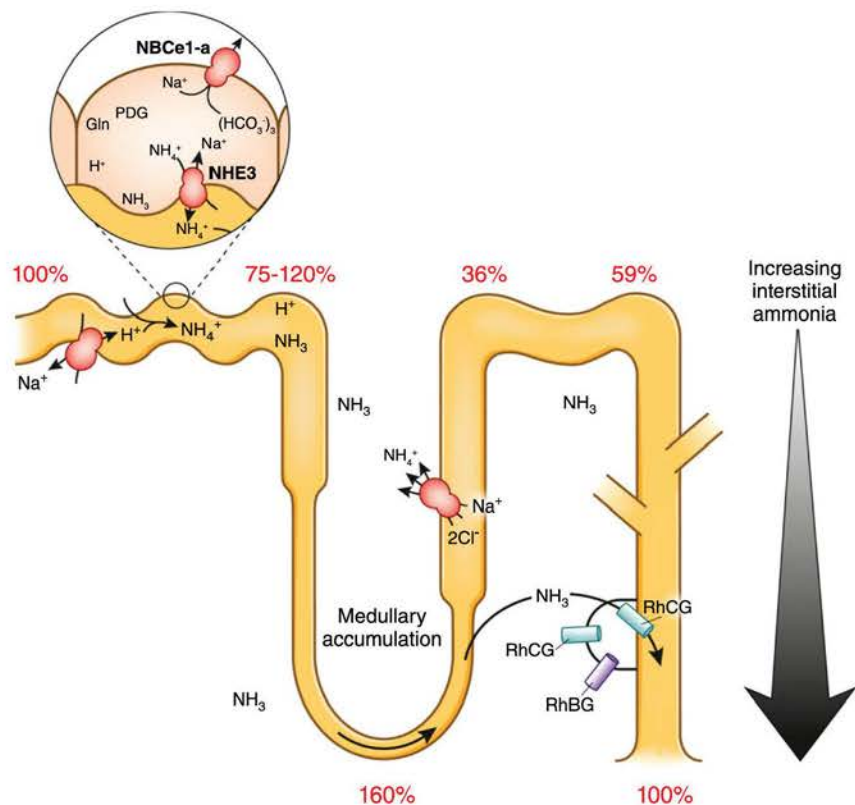


However,  $\text{NH}_3/\text{NH}_4^+$  is not an effective physiologic buffer, because its  $\text{pK}_a$  is too high (approximately 9.2), and most of total ammonia (>98%) at physiologic pH is  $\text{NH}_4^+$  on the basis of the  $\text{pK}_a$ . Furthermore,  $\text{NH}_4^+$ , not  $\text{NH}_3$ , is produced within the kidneys. However, total ammonia excretion in the urine does represent acid excretion (or the production of new  $\text{HCO}_3^-$ ) when considered in conjunction with the metabolism of the deamidated carbon skeleton of glutamine. Glutamine is the predominant precursor of  $\text{NH}_3$  in the kidney (Figure 5). Conceptually, the metabolism of the carbon skeleton of glutamine can result in the formation of one  $\text{HCO}_3^-$  formed for every  $\text{NH}_4^+$  excreted. Other amino acids can also be used to some extent. The predominant enzymatic pathway for  $\text{NH}_3$  formation is mitochondrial phosphate-dependent glutaminase in the proximal tubule, which produces one  $\text{NH}_4^+$  and glutamate. Glutamate dehydrogenase can then convert glutamate into  $\alpha$ -ketoglutarate and a second  $\text{NH}_4^+$ . The  $\alpha$ -ketoglutarate produced can be converted to glucose or completely metabolized to  $\text{HCO}_3^-$ . Other pathways for  $\text{NH}_3$  production also exist but are thought to be less important. Other nephron segments other than the proximal tubule can produce  $\text{NH}_3$  but not to the same extent, and the other segments do not have the same significant adaptive increases in ammoniogenesis with sustained acidosis as the proximal tubule. A variety of conditions affect the renal production of  $\text{NH}_3$ , but the most important is that of acid-base status. Chronic metabolic acidosis can increase  $\text{NH}_3$  production several fold in the kidneys. Potassium balance also alters  $\text{NH}_3$  production, such that hyperkalemia suppresses  $\text{NH}_3$  formation (and transport in both the proximal tubule and thick limb), and hypokalemia increases  $\text{NH}_3$  production by the kidneys. Each of these changes has clinical correlates in overall acid-base balance. A variety





**Figure 5. | Schematic of ammonia ( $\text{NH}_3$ ) production in the proximal tubule.** A proximal tubule cell is enlarged to show that glutamine (Gln) is metabolized to ammonium ( $\text{NH}_4^+$ ) by phosphate-dependent glutaminase (PDG); through a series of steps, the carbon skeleton of glutamine can be metabolized to  $\text{HCO}_3^-$ .  $\text{NH}_3$  can enter the proximal tubule lumen by either  $\text{NH}_3$  diffusion or  $\text{NH}_4^+$  movement on the  $\text{Na}^+$ - $\text{H}^+$  exchanger.  $\text{AA}^0$ , neutral amino acids; B\*AT1, B-type neutral amino acids transporter; GDH, glutamate dehydrogenase;  $\alpha\text{KG}$ ,  $\alpha$  keto-glutarate; LAT2, L-type amino acids transporter-2; OAA, oxalo-acetate; PEP, phospho enol-pyruvate; PEPCK, phospho enol-pyruvate carboxy kinase; TCA, XXX.



**Figure 6. | Ammonium ( $\text{NH}_4^+$ ) transport along the nephron.** In the thick ascending limb,  $\text{NH}_4^+$  is reabsorbed by the  $\text{Na}^+\text{K}^+\text{2Cl}^-$  transporter. In the collecting duct, Rh proteins mediate ammonia ( $\text{NH}_3$ )/ $\text{NH}_4^+$  transport. The numbers depict the percentages of urinary total  $\text{NH}_3$  at each site. Total  $\text{NH}_3$  is concentrated in the medulla (details are in the text). Gln, glutamine; PDG, phosphate-dependent glutaminase.



of hormones (angiotensin II, prostaglandins, *etc.*) have also been shown to alter  $\text{NH}_3$  production. The enzymatic and transporter changes that facilitate enhanced ammoniogenesis during acidosis have recently been reviewed in this series (18).

The transport of the produced  $\text{NH}_4^+$  along the nephron and into the urine is a complex process that is still a topic of intense study (Figure 6). Most of the  $\text{NH}_4^+$  produced is excreted into the urine rather than added to the venous blood; this is particularly true with acidosis—the proportions into urine and blood are almost even in normal conditions (13,67). Therefore, during acidosis, both total  $\text{NH}_3$  production and secretion into urine are increased. The overall picture of  $\text{NH}_3/\text{NH}_4^+$  transport is summarized as follows. In the proximal tubular,  $\text{NH}_4^+$  is produced from glutamine as discussed above and then, secreted into the lumen. This secretion occurs by both  $\text{Na}^+/\text{NH}_4^+$  exchange on the  $\text{Na}^+/\text{H}^+$  exchanger and  $\text{NH}_3$  diffusion across the apical membrane (68–70). Interestingly, the secretion of  $\text{NH}_4^+$  across the apical membrane is augmented by angiotensin II (71). Whether the diffusion of  $\text{NH}_3$  across the apical membrane of the proximal tubule is lipid-phase diffusion as long thought or facilitated by certain gas channels has not been determined. In the loop of Henle,  $\text{NH}_4^+$  ion is reabsorbed into the interstitium, where it accumulates in the medulla. In the TAL,  $\text{NH}_4^+$  is transported across the apical membrane predominantly on the  $\text{Na}^+-\text{K}^+-2\text{Cl}$  cotransporter, with perhaps some entry on  $\text{K}^+$  channels (72).  $\text{NH}_4^+$  has a similar hydrated size as  $\text{K}^+$  and therefore, can often be transported through many  $\text{K}^+$  pathways (73). Remarkably, the apical membrane of the TAL is virtually impermeable to  $\text{NH}_3$  in contrast to most cell membranes (74).  $\text{NH}_3$  probably leaves the TAL cell across the basolateral membrane by  $\text{NH}_3$  diffusion and  $\text{NH}_4^+$  movement by NHE4 (72). One fraction of this medullary  $\text{NH}_4^+$  is secreted back into the late proximal tubule as  $\text{NH}_3$  diffusion coupled to  $\text{H}^+$  secretion, and therefore, it is partially recycled. Another fraction of medullary  $\text{NH}_4^+$  enters the lumen of the cortical and medullary collecting ducts and as such, bypasses the superficial/cortical distal segment of the nephron. A small fraction of interstitial  $\text{NH}_4^+$  is shunted to the systemic circulation for eventual detoxification by the liver.

In the cortical and medullary collecting ducts, interstitial  $\text{NH}_3/\text{NH}_4^+$  is secreted into the lumen by several mechanisms, most identified only in recent years. The classic mechanism involves diffusion of medullary  $\text{NH}_3$  across the basolateral and apical membranes into the lumen, where secreted  $\text{H}^+$  titrates  $\text{NH}_3$  to  $\text{NH}_4^+$ . Another fraction of transcellular  $\text{NH}_4^+$  secretion involves the  $\text{Na}^+-\text{K}^+-\text{ATPase}$  that carries  $\text{NH}_4^+$  into the cell by substituting  $\text{NH}_4^+$  for  $\text{K}^+$ .  $\text{NH}_4^+$  can also be transported by  $\text{H}^+-\text{K}^+-\text{ATPases}$  in the collecting duct. Another critical mechanism of  $\text{NH}_3/\text{NH}_4^+$  transport is Rh proteins, specifically RhBG and RhCG. These were only identified as  $\text{NH}_3/\text{NH}_4^+$  transporters in recent years (75,76). These proteins function as  $\text{NH}_3/\text{NH}_4^+$  transporters, clearly facilitating diffusion of  $\text{NH}_3$  but also, probably including (at least for RhBG) electrogenic transport of  $\text{NH}_4^+$  (77,78). RhBG is present in the basolateral membrane of type A ICs and can transport  $\text{NH}_4^+$  and  $\text{NH}_3$  into the cell, whereas RhCG, present at the apical membrane of several cell types (and in some

circumstances, basolateral membrane), transports  $\text{NH}_3$  into the lumen. Luminal  $\text{NH}_3$  is then titrated by secreted  $\text{H}^+$  to  $\text{NH}_4^+$  as described above.

### Acid and Alkali Loads

With this background, what are the pathologic challenges to normal acid-base homeostasis? Table 1 provides a basic conceptual classification of pathophysiologic types of acid and alkali loads. This differs from the usual classifications of acid-base disorders *per se*, which focus only on clinical diagnostic algorithms or dive deeper into mechanisms. Acid loads can be in the form of either  $\text{CO}_2$  or non-volatile acids. Both types of acid loads occur normally on a daily basis and must be excreted. Primary ventilatory disorders resulting in increased arterial  $\text{P}_{\text{CO}_2}$  are referred to by the term respiratory acidosis. Nonvolatile acids, such as phosphoric acid and sulfuric acid, are also normal by-products of metabolism of dietary nutrients, proteins, and phospholipids. Nonvolatile acid loads in excess of the excretory capacity of the kidneys produce conditions termed metabolic acidosis. In other words, with normal acid loads or some increased acid loads that develop slowly, the kidneys can adapt, increasing acid excretion by both titratable acid and  $\text{NH}_4^+$  excretion, and maintain normal systemic acid-base homeostasis and pH. With larger acid loads (or base losses; for example, through severe diarrhea), the kidneys cannot keep up (*i.e.*, cannot excrete sufficient acid into the urine), and metabolic acidosis ensues. Metabolic acidosis is reflected predominantly by lowering of plasma or systemic  $\text{HCO}_3^-$ . Also, the loss of alkali from the body is equivalent to the addition of acid, and therefore, it represents metabolic acidosis; such loss of alkali might occur from excess stool  $\text{HCO}_3^-$  losses or loss of  $\text{HCO}_3^-$  in the urine.

Alkali loads, in contrast to acid loads, are not the result of normal physiology in persons on most diets, which provide net dietary acid. Alkali loads can be either respiratory or metabolic. Primary increases in ventilation and lowering of  $\text{P}_{\text{CO}_2}$  are referred to as respiratory alkalosis. Metabolic alkali loads can result from excess excretion of urinary acid, loss of other acids (such as gastric acid), or administration of exogenous alkali, and they can result in metabolic alkalosis. Metabolic alkalosis is reflected primarily by an increased plasma or systemic  $\text{HCO}_3^-$ .

Usually, however, as briefly discussed below, such metabolic alkali loads can be quickly excreted, so that the focus in understanding metabolic alkalosis is more on the factors that maintain the high plasma  $\text{HCO}_3^-$  and not the original generation by alkali load (79). Clinically, the factors that often maintain high plasma  $\text{HCO}_3^-$  include extracellular volume and chloride depletion, which may decrease GFR, increase proximal tubule  $\text{HCO}_3^-$  reabsorption, and increase angiotensin and mineralocorticoids, potent stimuli for  $\text{H}^+$  secretion in the proximal and distal tubules, respectively, as discussed above. The intermediaries in volume depletion include increased sympathetic activity and increased catecholamines, angiotensin II, and aldosterone, all of which increase  $\text{H}^+$  secretion,  $\text{HCO}_3^-$  reabsorption, and/or  $\text{NH}_4^+$  excretion as discussed above. The classic edematous disorders of congestive heart failure and cirrhosis and some nephrotic syndrome also have effective extracellular volume depletion because of low



**Table 1. Acid and alkali loads****Acid loads**CO<sub>2</sub>: Respiratory acidosis

Nonvolatile acids: Metabolic acidosis

*Exogenous acids (e.g., salicylate, methanol, and ethylene glycol)**Pathologic endogenous acids (e.g., ketoacids and lactic acid)**Decreased renal acid excretion (e.g., renal failure and distal renal tubular acidosis)**Loss of alkali, equivalent to acid load**Gastrointestinal losses (e.g., diarrhea)**Urine losses (e.g., proximal renal tubular acidosis)***Alkali loads**Excess CO<sub>2</sub> exhalation: Respiratory alkalosis

Nonvolatile alkali: Metabolic alkalosis

*Exogenous alkali (e.g., NaHCO<sub>3</sub> administration)**Loss of acid, equivalent to alkali load**Gastrointestinal losses (e.g., gastric fluid)**Excess urine H<sup>+</sup> losses and renal production of new HCO<sub>3</sub><sup>-</sup> (most classic causes of metabolic alkalosis, including chloride depletion metabolic alkalosis and mineralocorticoid excess)*

cardiac output or arterial underfilling (80); these conditions, thus, have sodium and H<sub>2</sub>O retention but also, can have increased HCO<sub>3</sub><sup>-</sup> reabsorption, H<sup>+</sup> secretion, and/or NH<sub>4</sub><sup>+</sup> excretion caused by the factors discussed above. Therefore, both volume depletion (e.g., vomiting and diuretics) and edematous disorders (primarily heart failure and cirrhosis) can and often are associated with metabolic alkalosis. Chloride depletion alone through a variety of mechanisms may also maintain metabolic alkalosis. Excess mineralocorticoids from any condition can also stimulate H<sup>+</sup> secretion and maintain metabolic alkalosis. Potassium depletion contributes to the maintenance of metabolic alkalosis by stimulating continued H<sup>+</sup> secretion.

### Compensation for Acid-Base Disorders

The mechanisms of physiologic responses to acid or base loads can be expected on the basis of the understanding of the mechanisms of usual physiology described above. The predicted extent of clinical response, however, is on the basis of empirical observations and not just mechanisms. On the basis of the chemistry, acute changes in P<sub>CO2</sub> alter plasma HCO<sub>3</sub><sup>-</sup> slightly, because nonbicarbonate body buffers are titrated. With chronic changes in P<sub>CO2</sub> (respiratory acid-base disorders), the kidneys respond to the change in pH by altering plasma HCO<sub>3</sub><sup>-</sup> in a direction to lessen the change in systemic pH through the mechanisms described above. These changes within the kidney take several days for completion and in general, do not return systemic pH completely back to normal. With chronic hypocapnia and the resultant increase in systemic pH, decreases in reabsorption of HCO<sub>3</sub><sup>-</sup> in the proximal tubule and distal tubule H<sup>+</sup> secretion result in a fall in plasma HCO<sub>3</sub><sup>-</sup>; these changes can begin within a very few hours (81). With chronic hypercapnia, increased proximal and distal H<sup>+</sup> secretion results in increased HCO<sub>3</sub><sup>-</sup> reabsorption and increased production of new HCO<sub>3</sub><sup>-</sup>, resulting in a higher level of plasma HCO<sub>3</sub><sup>-</sup>; most of the cell and molecular mechanisms parallel the response to metabolic acid loads, where these have been studied (82). Increased NH<sub>4</sub><sup>+</sup> excretion is expected as well with chronic respiratory acidosis (83). With the ubiquitous changes that occur in response to acidosis or acid loads, many investigators have looked for acid

sensors; a variety of proteins seem to serve some of this function, but no single sensor can be proposed (25).

Increased metabolic acid production or ingestion will initially result in increased new HCO<sub>3</sub><sup>-</sup> generation, such that plasma HCO<sub>3</sub><sup>-</sup> does not change. With larger acid loads, the capacity of the kidneys to generate new HCO<sub>3</sub><sup>-</sup> is overwhelmed, and plasma HCO<sub>3</sub><sup>-</sup> decreases. Metabolic acid loads or metabolic acidosis results in increased fractional proximal tubule HCO<sub>3</sub><sup>-</sup> reabsorption, increases in distal H<sup>+</sup> secretion (resulting in lower urine pH), and increased NH<sub>4</sub><sup>+</sup> excretion. (However, the lower plasma HCO<sub>3</sub><sup>-</sup> during metabolic acidosis decreases filtered HCO<sub>3</sub><sup>-</sup> and hence, decreases absolute proximal HCO<sub>3</sub><sup>-</sup> reabsorption.) Increased H<sup>+</sup> excretion may result not only from adaptive changes in response to systemic pH *per se* but also, secondary to increases in systemic glucocorticoids and mineralocorticoids with chronic acidosis and potassium depletion. The adaptive changes within the kidney include various factors discussed in the sections above, including endogenous endothelin. The increased H<sup>+</sup> secretion can result in increased titratable acid excretion up to 2- to 3-fold in certain situations. Urinary NH<sub>4</sub><sup>+</sup> excretion (a result of both increased production and increased secretion of produced NH<sub>4</sub><sup>+</sup>) can increase several fold (Figure 2). The maximum renal compensation for acid loading requires 3–5 days. Metabolic acid loads sufficient to lower plasma pH result in increased ventilation, resulting in a decrease in P<sub>CO2</sub> sufficient to raise the systemic pH toward but not to normal. The full respiratory compensation requires 12–24 hours. Paradoxically, the compensatory hypocapnia during metabolic acidosis may actually decrease somewhat the renal response to metabolic acidosis (84).

Metabolic alkali loads can normally be quickly eliminated in the urine, because the filtration rate of HCO<sub>3</sub><sup>-</sup> is high, and a small reduction in proximal tubule HCO<sub>3</sub><sup>-</sup> reabsorption can result in spillage of HCO<sub>3</sub><sup>-</sup> in the urine and prompt correction of the metabolic alkalosis. Frequently, however, in states of metabolic alkalosis, other factors prevent the excretion of HCO<sub>3</sub><sup>-</sup> and maintain the metabolic alkalosis as described above. Metabolic alkalosis also results in some hypoventilation and increase in P<sub>CO2</sub> to compensate for the alkalemia.



## Summary

Acid-base homeostasis is critical for normal physiology and health. Hence, multiple, often redundant pathways and processes exist to control systemic pH. Derangements in acid-base homeostasis, however, are common in clinical medicine and can often be related to the systems involved in acid-base transport in the kidneys. These have been studied for decades, but a variety of new pathways, such as pendrin and Rh proteins, have illustrated that our understanding is still far from complete.

## Disclosures

None.

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