

The kidney has two main targets; the most important one is to reabsorb the filtered bicarbonate.

****How much is the filtered load of bicarbonate?**

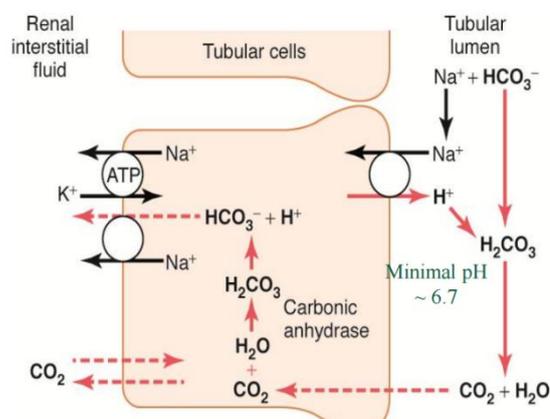
Filtered load of $\text{HCO}_3^- = 180\text{L/day} * 24 \text{ mEq/L} = 4320 \text{ mEq/day}$.

Normally We cannot tolerate losing one single bicarbonate daily, so the kidneys absorb almost all of it (only one or two might escape).

Bicarbonate in the proximal tubule:

Inside proximal tubular cell we have CO_2 which comes from three different sources; tubular fluid, delta cell, and interstitium. CO_2 binds with H_2O forming H_2CO_3 (by carbonic anhydrase enzyme), H_2CO_3 then dissociates to H^+ and bicarbonate. Bicarbonate is reabsorbed to the blood, while H^+ is secreted.

Mechanisms for HCO_3^- reabsorption and $\text{Na}^+ - \text{H}^+$ exchange in proximal tubule and thick loop of Henle



We are going to secrete H^+ in exchange with sodium, this H^+ is going to bind with bicarbonate in the tubular fluid forming carbonic acid which dissociates to H_2O and CO_2 , and this CO_2 re-enters the cell parenchyma, so H^+ that was secreted, re-entered in different form; CO_2 (masked hydrogen). This CO_2 that entered will get converted into carbonic acid again, then bicarbonate and H^+ , as you can see above.

So far there was no net secretion of hydrogen and no extra bicarbonate is added to the total bicarbonate in the cell (one left the cell to the blood, another entered from the lumen).

So by doing this we are just reabsorbing the filtered bicarbonate. 90% of bicarbonate is reabsorbed in this scenario in the proximal tubule. The remaining is reabsorbed in the thick ascending and collecting duct.

****No bicarbonate gain so far.**

What we give to the kidney through the renal artery is 4320 mMol/day of HCO_3^- , as we said, almost all of this amount is going to be reabsorbed. There will also be a production of 80 mMol/day of HCO_3^- by the kidney. So, you can consider the clearance of bicarbonate to be negative here; more bicarbonate leaving the kidney than entering (because of bicarbonate production).

****How can the kidney make new bicarbonate?**

We have H^+ secreted, the H^+ secreted here (in the tubular fluid) only can accumulate 5-6 times more than inside the cells of proximal tubule, so it is not enough unless this H^+ is buffered in the tubular fluid. For example if we have HPO_4 and H^+ it gives H_2PO_4 , so if I have 80 mMol of phosphate (but it is actually less) then this equals the net secretion of H^+ ; bicarbonate reabsorption is done and any additional bicarbonate goes to the blood is new bicarbonate.

So to make bicarbonate you have to secrete H^+ , H^+ secretion is limited unless you buffer it, you can buffer it by phosphate, but most of phosphate is reabsorbed, so what is buffered by phosphate is maximally 30mMol, (filtered load of phosphate is 200 L/day, 90% is reabsorbed, and those 10% remaining can work as buffers).

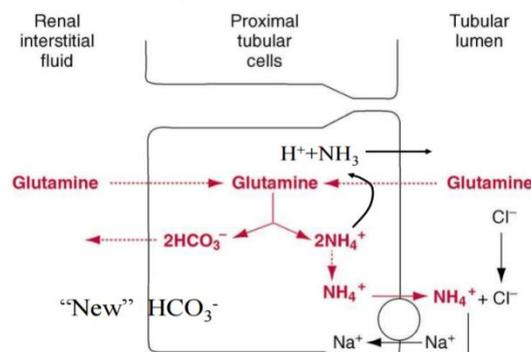
SO If we excrete 80 mMole/Day of phosphate then we gain 80 mMole/Day of HCO_3^- → → → Thus we solved the problem.

Unfortunately, we excrete only 30 mMole of phosphate. We still need additional 50 mMole of new HCO_3^- through other source → This is achieved by ammonium production through the following pathway:

Inside the proximal cell we have glutamine. Glutamine in presence of glutaminase inside the cell dissociates to alpha ketoglutarate which forms $2NH_4^+$ and 2 bicarbonate. **Ammonium** is secreted into the lumen by counter-transport mechanism in exchange of sodium in proximal tubules, thick ascending loop of Henley and distal tubules, while the bicarbonate is reabsorbed. So if I can secrete 50 mMol of ammonium then I gain 50 mMol of bicarbonate (they were produced in the same amounts).

If you have acidosis and your body is making for example 200 mMol of H^+ , to fix this, we need to increase bicarbonate production, the bicarbonate made through phosphate is fixed, any extra bicarbonate gain is through the ammonium. Acidosis stimulates glutaminase which makes this conversion towards ammonium. The kidney can make daily more than 500 mMol ammonium which means more than 500 mMol bicarbonate gain, so each mMol ammonium in urine correspond to same mMols of new bicarbonate additions in the plasma. Therefore, chronic acidosis increases NH_4^+ excretion.

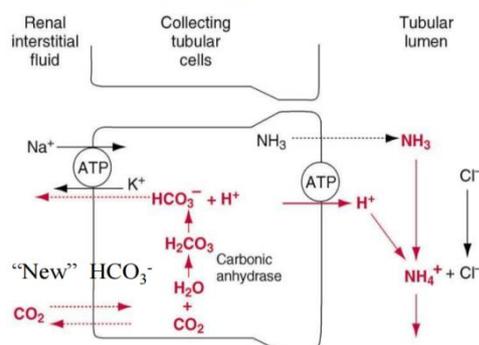
Production and secretion of NH_4^+ and HCO_3^- by proximal, thick loop of Henle, and distal tubules



This occurs in proximal, thick ascending and distal tubule and collecting ducts but with one thing different in collecting ducts:

In the collecting duct: here the cells secrete ammonia and H^+ (not ammonium), each time you secrete H^+ you make new bicarbonate that enters the blood. This binds with ammonia forming ammonium. Ammonium is charged it cannot go back to the cell, so ammonia is trapped in form of ammonium. This is called ammonia trapping.

Buffering of hydrogen ion secretion by ammonia (NH_3) in the collecting tubules.



Ammonia is secreted as NH_4Cl in the urine. Ammonia in the urine comes either from ammonia trapping from distal parts or from ammonium production in the other parts through glutamine.

Summary: the filtered load of HCO_3^- is 4320 mEq/day, we need to absorb them, for that we need 4320 H^+ to be secreted, but we have 4400 mEq/day H^+ secretion, 4320 of them will be titrated with the 4320 filtered bicarbonate in the tubule lumen (forming CO_2 which will diffuse into the tubular cell to be reabsorbed into the blood later as HCO_3^-), leading to the reabsorption of the filtered 4320 HCO_3^- without any production of new HCO_3^- yet. The excess 80 mEq H^+ secreted will be excreted, only a small amount in the form of H^+ , most of it will be titrated by 2 systems: 30mEq titrated by the phosphate buffer system, the 50 mEq left are titrated by ammonia buffer system as explained above, so the excess H^+ will be excreted as NH_4^+ and H_2PO_4^- . This process (titration) of the 80 excess H^+ in the lumen results in the production of 80 mEq HCO_3^- (in the cell) that will enter the circulation; 1 HCO_3^- for each H^+ secreted.

Now we can calculate the bicarbonate gain (new bicarbonate) per day:

We come to the urine, titrate it with OH^- to bring the pH to 7.4. The acids in the urine that we titrate are called titratable acids. So assuming we add 30 mMol of OH^- it means that we have 30 mMol of acids excreted in the form of phosphate, sulfate,... so these are 30 mMol of bicarbonate gain.

While for ammonia buffer we calculate the concentration of NH_4Cl in urine: $\text{pH} = 9.2 + \log [\text{NH}_3/\text{NH}_4^+]$. We want to reach 7.4, we add a little OH^- , so we are not going to affect total concentration of ammonium.

so bicarbonate gain = Titratable acid + ammonium excretion - bicarbonate in the urine (very little).

So far we have an idea about buffers in kidney.

Acid-Base disturbances:

It means a shift in pH; low pH: acidosis, high pH: alkalosis. Normal pH 7.38-7.42, but we use this range: 7.35-7.45, below it acidosis, above it alkalosis.

$$\text{pH} = 6.1 + \log [\text{HCO}_3^-/\text{CO}_2] = 6.1 + \log 24/1.2 = 6.1 + \log 20 = 7.4$$

*If we have Less bicarbonate, so in the previous equation instead of 24 we have 10, so $\text{pH} = 7.1$. The change in pH is caused by low bicarbonate, it's called metabolic acidosis.

*If it is caused by high CO_2 then it is respiratory acidosis.

*If we have high bicarbonate it's called metabolic alkalosis, while low CO_2 then we have respiratory alkalosis as in ascending to high altitude.

So these are the most common acid base disturbances. Sometime we have two of them together (metabolic and respiratory), this is called mixed or complex disturbance.

**Acidosis in clinical practice is more common than alkalosis.

**Metabolic acidosis is more common than respiratory acidosis.

Metabolic Acidosis:

Low pH. The change in pH is caused by low bicarbonate.

***Causes of metabolic acidosis (low bicarbonate HCO_3^-):**

- Diarrhea (losing bicarbonate).
- Vomiting containing pancreatic juice full of bicarbonate.

- Ingesting acids like aspirin which will be attacked by bicarbonate.
- ketoacidosis (body is producing too much acids, as in Diabetes mellitus 1))
- The kidney cannot make bicarbonate (renal tubular acidosis).
- Renal failure (we cannot reabsorb bicarbonate and cannot secrete H⁺)
- Any case of anaerobic glycolysis where lactic acid forms.

**Note: Diabetes type 1 which is less common is complicated with ketoacidosis. Diabetes type 2 which is more common is not complicated with ketoacidosis.

*The pH affects respiratory system to cause more hyperventilation, so you are trying to make the composition of alveolar air gases closer to outside air gases; CO₂ less and O₂ more. Hyperventilation is going to washout CO₂, this means the respiratory system has compensated with this response.

So in metabolic acidosis, you look at pH, it is low, to know whether metabolic or respiratory you look at bicarbonate and CO₂ as mentioned before, so here bicarbonate is low.

If you find CO₂ going down then there is compensation.

Metabolic Alkalosis:

pH is high, bicarbonate is high, CO₂ always goes in the same direction of bicarbonate to make compensation, if it remains constant, there is no or partial compensation.

Respiratory system cannot bring pH back to normal; 75% only (by reduction in the respiration rate). And don't expect both to be going up or down in the same amount. If the cause is metabolic the help comes from the lung but the kidney can do the job fully.

Causes of metabolic alkalosis:

- People with ulcers and take sodium bicarbonate to neutralize HCL.
- Diuretics with exception of carbonic anhydrase inhibitors (they were given before as diuretics, but now are only used for glaucoma). Diuretics increase the tubular fluid flow, so they are going to washout H⁺ (work like buffers) so you end up secreting more H⁺, this leads to metabolic alkalosis. carbonic anhydrase inhibitors inhibit the production of H⁺, you retain Hydrogen in the body and you end up having acidosis, but all other diuretics cause alkalosis.
- Excess aldosterone (as we know it causes H⁺ secretion).
- Loss of acid HCL ; as in pyloric stenosis, which leads to vomiting of the gastric HCL, here the vomiting is not deep (doesn't include pancreatic juice).

Respiratory acidosis:

pH is low, CO₂ is high, sometimes they have pH almost normal in chronic conditions like COPD , because bicarbonate is high as well.

Causes of Respiratory acidosis:

CO₂ is high, $pH = 6.1 + \log [HCO_3^-/CO_2]$, when CO₂ increases we expect HCO₃ to increase. How? The kidney reabsorbs the entire bicarbonate from urine, and the kidney activates glutaminase, so this is positive work in the kidney (increasing bicarbonate in the body), and the urine is full of ammonium.

Usually results from pathological conditions interfering with gas exchange (decrease the rate of ventilation) like COPD, respiratory center trauma, infections, drugs, tumors, diaphragmatic fatigue, phrenic paralysis, pneumonia, interference with mechanical ventilation.

**The name "respiratory" is not accurate, because it means a problem in the lung; but actually it is caused by any condition that can cause retention of CO₂ like the conditions mentioned above. So we shouldn't have called it respiratory, sometimes the whole respiratory system is intact and the problem is in CO₂.

For example, in hemodialysis, CO₂ diffuses more → respiratory alkalosis. The problem is not in the lung.

Respiratory alkalosis:

pH is high, CO₂ is low, bicarbonate is low.

Causes of respiratory alkalosis:

- CO₂ is low, this is caused by hysterical hyperventilation, high altitude hyperventilation, central trauma to the head causing hyperventilation. So Hyperventilation causes alkalosis.

- Rarely pathological, usually voluntary (hyperventilation)

- encephalitis (rare).

If someone ascended to high altitude, PO₂ is going to be low, the person will hyperventilate (Ventilation keeps increasing because of hypoxia. Hypoxia drives ventilation), which will decrease PCO₂, leading to respiratory alkalosis. The main compensatory mechanism for this is the increased excretion of bicarbonate by the kidneys, so now the kidney is not going to reabsorb or make new bicarbonate, the urine doesn't contain ammonium chloride (the H⁺ secretion decreased, along with bicarbonate absorption), and this is to bring the pH to suitable value. After a while pH will go back to normal. Alkalosis is removed by decreasing bicarbonate so we bring pH to normal. When we go down we hyperventilate for 3 days.

pH is high, free Calcium becomes less, and bound calcium increases (total calcium is the same) Here we will have Hypocalcaemia -even if the total is the same- we care about the free calcium. Hypocalcaemia stimulates motor neurons in spinal cord causing contraction of the peripheral muscles starting from the hands (carpopedal spasm), then it goes to respiratory muscles causing respiratory arrest, so here it becomes serious. The only way to help is to ask the person to breath from a closed bag so CO₂ comes back increasing CO₂, so pH is back to normal, so ionized (free) calcium is back to normal → relaxing the muscles.

*Note: For each 10 mmHg increase in CO₂ (in chronic respiratory acidosis) we expect 3.5 ml equivalent increase in bicarbonate, if less then there might be some metabolic problems. For each 10 mmHg decrease in CO₂ (in chronic respiratory alkalosis) I Have 5 ml equivalent decrease in bicarbonate. Here it is easier for the kidney to decrease bicarbonate (not much work) that's why it's 5 (more than 3.5)

Associations with other abnormalities:

When a patient with acidosis comes to you, it's not the main problem (with few exceptions), even in ketoacidosis, if you correct the glucose level, the acid base level is corrected by itself, and in diarrhea when hydrate the patient and you correct the electrolyte balance the acid base is corrected by itself. So it's most probably not the main problem, even though, if we don't care about acid base status we might lose the patient.

**In metabolic acidosis: Low bicarbonate, so low CO₂. For each 1mEq decrease in bicarbonate we expect to have a 1.2 mmHg decrease in arterial CO₂. If CO₂ falls more then we think of respiratory alkalosis too

**in metabolic alkalosis: for every 1 mEq increase in bicarbonate, there will be 0.7 mmHg increase in PCO₂.

**Respiratory acidosis is either acute or chronic; if it lasts for 4 or 5 days you expect to have full compensation from the kidney, but if it lasts for 1 or 2 days you don't expect that. That's why For every 10 mmHg increase in PCO_2 we expect 1 ml equivalent increase in bicarbonate in acute type, but in chronic we expect 3.5 ml equivalent increase (full compensation).

**In respiratory alkalosis the same thing; in acute we expect bicarbonate to decrease 2 ml equivalent and we expect it to decrease more in chronic (5 ml equivalent).

Anionic gap:

A patient comes to me having acidosis, how to know its cause?

Number of anions = number of cations (In all conditions even in alkalosis or acidosis)

Cations mainly sodium and potassium. Anions mainly Chloride and bicarbonate and all unmeasured anions (phosphate, citrate, lactate,...). If we considered all cations and anions we will find that they are equal in number (normally about 155 each)

The **anion gap** is the difference in the measured cations (positively charged ions) and the measured anions (negatively charged ions) in urine.

Normal anion gap is 8-16 mEq/L; more than 16 → increased anion gap; which means decreased anions.

*Usually the anion gap is measured without the potassium.

$Na^+ = Cl^- + HCO_3^- + \text{unmeasured anions}$

Anion gap = $Na^+ - (Cl^- + HCO_3^-) = \text{unmeasured anions}$

for example if we considered:

Cl = 110, Bicarbonate = 24, Na = 145, Anion gap = $145 - (110 + 24) = 11$.

In metabolic acidosis (decreased bicarbonate), it can be normochloremic (no change on Cl, only bicarbonate decreases) and in this case the anionic gap is high (>16) and it's called **normochloremic metabolic acidosis. It can be caused by diabetes mellitus (ketoacidosis), aspirin, methanol poisoning, starvation and lactic acidosis

Metabolic acidosis also can be hyperchloremic (here Cl increases besides the decrease in bicarbonate), in this case, the anionic gap is normal, and it's called **hyperchloremic metabolic acidosis**. It can be caused by diarrhea (loss of bicarbonate and sodium), renal tubular acidosis, Addison's disease and carbonic anhydrase inhibitors.

*It is very rare to have low anion gap (A low anion gap is frequently caused by hypoalbuminemia. Albumin is a negatively charged protein and its loss from the serum results in the retention of other negatively charged ions such as chloride and bicarbonate. As bicarbonate and chloride anions are used to calculate the anion gap, there is a subsequent decrease in the gap.).

*If bicarbonate and sodium decreased then anion gap remains normal.

The clinical picture should tell you which anionic gap to expect, for example, in diarrhea we expect normal anion gap. Patient took aspirin we expect high anion gap because bicarbonate will be decreased.

When the patient comes you make CBC test and electrolyte test most important for sodium, potassium and chloride, and arterial blood gases ($PO_2, PCO_2, PAH, \text{Bicarbonate}$). So from this data you can measure the anion gap. Check the slides they contain further explanation and questions.

“اللهم اني استودعك ما قرأت وما حفظت وما تعلمت فرده الي عند حاجتي اليه إنك على كل شيء قدير”