1. The Kidney reabsorbs HCO3- (in the Proximal Convoluted Tubule)
(Image credit: Dr. McLaughlin May 4th 2012 lecture)

1. Na+/H+ exchanger (NHE3):
   - Found only in the PCT
   - Reabsorbs 1 Na+ while secreting 1 H+ into tubule
   - This is how HCO3- reabsorption is linked to Na+ reabsorption. HCO3- wasting (i.e. in vomiting) also means Na+ will be wasted, ↑ urine [Na+]

2. The secreted H+ binds to the HCO3- that was filtered into the tubule; an extracellular Carbonic Anhydrase (CA) converts them into water and CO2.
   → As a gas, CO2 easily diffuses back into the cell.

3. In the cell, an intracellular Carbonic anhydrase converts CO2 and H2O back into HCO3- and H+.
   - The H+ is re-secreted back into the lumen by NHE3 to facilitate Na+ reabsorption.

4. An HCO3/Na+ symporter reabsorbs both HCO3- and Na+ from the ICF into the peritubular capillary (back into the ECF).

ICF pH:
Lower ICF pH = ↑ NHE3 activity (pump more H+ out of cell)

Type 2 Renal Tubular Acidosis:
- Metabolic acidosis due to the failure to reabsorb HCO3- in the PCT
- Can be due to dysfunctional NHE3-antiporters, CA, or Na/HCO3-symporters. Results in a lower threshold for proximal HCO3- reabsorption (PCT can maximally reabsorb less HCO3-)
- Results in a high HCO3- fractional excretion (FE_{HCO3} > 15%): HCO3-wasting
- RTA type 2 can be isolated, or as part of Fanconi’s syndrome (reduced PCT reabsorption of glucose, amino acids, uric acid, and phosphate, as well as bicarb)
Kidney control of Acid-base balance

2. **The Kidney secretes H+ as NaH₂PO₄ and NH₄Cl** (and generates HCO₃⁻ for the ECF)

(Image credit: Dr. McLaughlin May 4th 2012 lecture)

**Rationale:**
- Metabolism in the body is constantly producing excess H+, so these H+ need to be excreted to prevent acidosis.

1. HPO₄²⁻ is filtered into the tubule
   Since the filtrate pH is relatively high compared to the pKa of H₂PO₄⁻, the species remains in its deprotonated HPO₄²⁻ form.

2. As HCO₃⁻ is reabsorbed throughout the length of the tubule, the pH of the tubule ↓ the more distal to the bowman’s capsule.

3. In the collecting duct, H+ is actively secreted into the tubule lumen, ↓ lumen pH:
   - CO₂ diffuses from the blood into the tubule epithelial cells
   - Carbonic anhydrase in the tubule epithelium ICF converts the CO₂ into HCO₃⁻ (reabsorbed) and H+ (secreted)

4. The Lower pH of the tubule lumen converts HPO₄²⁻ into H₂PO₄⁻:
   - H+ is thus secreted as H₂PO₄⁻
   - Secretion of 1 H+ means the reabsorption/gain of 1 HCO₃⁻

**Acidosis can arise when this HCO₃⁻ regeneration/reabsorption process fails! (Indirect loss of HCO₃⁻):**
- Occurs when H+ is not secreted as H₂PO₄⁻, thus no HCO₃⁻ is reabsorbed.
- The H+ secreting capacity of this mechanism cannot increase! It’s limited by the amt HPO₄²⁻ originally filtered!
- Another process is needed to ramp up H+ secretion in case the body produces excess H+
Kidney control of Acid-base balance

2. The Kidney secretes H+ as NaH₂PO₄ and NH₄Cl
(and generates HCO₃⁻ for the ECF)
(Image credit: Dr. McLaughlin May 4th 2012 lecture)

Rationale:
→ Metabolism in the body is constantly producing excess H+, so these H+ need to be excreted to prevent acidosis.

1. PCT cells contain glutaminase (activated by low pH)
→ During ECF acidosis, more CO₂ is delivered to the PCT cell, and converted into HCO₃⁻ and H+. The HCO₃⁻ is pumped out, the H+ remains to ↓ intracellular pH, activating glutaminase.

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2. Glutaminase breakdown of 1 glutamine produces 1 HCO₃⁻, which is reabsorbed to help counter ECF acidosis.

3. The glutaminase breakdown of glutamine also produces an NH₄⁺, which is pumped into the tubule via NHE3
• Since it is charged, NH₄⁺ cannot diffuse back into cells in its own; it traverses the length of the tubule until the LoH.

4. In the thick ascending limb, NH₄⁺ is reabsorbed via a channel, & dissociates in the interstitium into NH₃ and H⁺.
• NH₃ thus accumulates in the interstitium.
• The H⁺ is re-secreted into the tubule to bind HCO₃⁻ & assist w/ its reabsorption.

5. In the collecting duct, α-intercalated cells have a proton-pump on their apical membrane, pumping excess intracellular H⁺ into the tubule
• ECF H⁺ are brought to the CCD cells by CO₂, converted into H⁺ & HCO₃⁻ by Carbonic anhydrase.
• W/out NH₃: H⁺ secreted w/ Cl⁻: very acidic (bad)!
• With NH₃: acid is secreted as NH₄⁺Cl⁻, much less dangerous to tubule.
• Secreting acids as NH₄⁺ allows for fine-tuning of H⁺ secretion with virtually unlimited capacity.
2. The Kidney secretes H+ as NaH₂PO₄ and NH₄Cl (and generates HCO₃⁻ for the ECF)

(Image credit: Dr. McLaughlin May 4th 2012 lecture)

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3 requirements for acid to be secreted as NH₄⁺:

1. A functional proton-pump on the apical membrane of the Alpha-intercalated cell
   → If this H⁺ pump fails, Type 1 RTA

2. Negative luminal charge, facilitating H⁺ export down its charge gradient.
   → Negative luminal charge is created by a functional principal cell (Reabsorbing Na⁺ makes lumen relatively -ve)
   → If principal cells fail (insensitive to aldosterone, etc) → lumen less negative, less H⁺ secreted → H⁺ builds up in ECF (acidosis) → Type 4 RTA

3. NH₃ in the lumen
   → A supply of NH₃ is essential to bind to H⁺ and get rid of it as NH₄⁺
   → No NH₃ can be due to 1) bad kidney damage to PCT, to glomeruli (↓ GFR), etc, 2) malnourished; no glutamine in diet.

High K⁺ secretion (↓ TTKG)
(Less H⁺ in tubule to counter-balance its negative charges, drawing out more K⁺)

Low K⁺ secretion (↑ TTKG)
(b/c of principal cell failure, for many reasons: less K⁺ channels in membrane, less Na⁺ reabsorbed, etc)