Acidosis & Alkalosis (5)

Non–Anion Gap Metabolic Acidoses

- Alkali can be lost from the gastrointestinal tract in diarrhea or from the kidneys (renal tubular acidosis, RTA).
- In these disorders reciprocal changes in [Cl–] and [HCO3–] result in a normal AG.

- In pure non–AG acidosis, therefore, the increase in [Cl–] above the normal value approximates the decrease in [HCO3–].
- The absence of such a relationship suggests a mixed disturbance.

Causes of Non-Anion Gap Acidosis

TABLE 51-5 Causes of Non–Anion Gap Acidosis

I. Gastrointestinal bicarbonate loss
   A. Diarrhea
   B. External pancreatic or small-bowel drainage
   C. Ureterosigmoidostomy, jejunal loop, ileal loop
   D. Drugs
      1. Calcium chloride (acidifying agent)
      2. Magnesium sulfate (diarrhea)
      3. Cholestyramine (bile acid diarrhea)

II. Renal acidosis
    A. Hypokalemia
        1. Proximal RTA (type 2)
            Drug-induced: acetazolamide, topiramate
        2. Distal (classic) RTA (type 1)
            Drug-induced: amphotericin B, ifosfamide
    B. Hyperkalemia
        1. Generalized distal nephron dysfunction (type 4 RTA)
            a. Mineralocorticoid deficiency
            b. Mineralocorticoid resistance (PHA I, autosomal dominant)
            c. Voltage defect (PHA I, autosomal recessive, and PHA II)
            d. Tubulointerstitial disease
    C. Normokalemia
        1. Chronic progressive kidney disease

III. Drug-induced hyperkalemia (with renal insufficiency)

A. Potassium-sparing diuretics (amiloride, triamterene, spironolactone, eplerenone)

B. Trimethoprim

C. Pentamidine

D. ACE-Is and ARBs

E. Nonsteroidal anti-inflammatory drugs

F. Calcineurin inhibitors

G. Heparin in critically ill patients

IV. Other

A. Acid loads (ammonium chloride, hyperalimentation)

B. Loss of potential bicarbonate: ketosis with ketone excretion

C. Expansion acidosis (rapid saline administration)

D. Hippurate

E. Cation exchange resins

TREATMENT: NON–ANION GAP METABOLIC ACIDOSES

- In diarrhea, stools contain a higher [HCO_3^-] and decomposed HCO_3^- than plasma so that metabolic acidosis develops along with volume depletion.
- Instead of an acid urine pH (as anticipated with systemic acidosis), urine pH is usually around 6 because metabolic acidosis and hypokalemia increase renal synthesis and excretion of NH_4^+, thus providing a urinary buffer that increases urine pH.
- Metabolic acidosis due to gastrointestinal losses with a high urine pH can be differentiated from RTA because urinary NH_4^+ excretion is typically low in RTA and high with diarrhea.

Urine anion gap (UAG)

- Urinary NH_4^+ levels can be estimated by calculating the urine anion gap (UAG): UAG = $[Na^+ + K^+]u - [Cl^-]u$.
- When $[Cl^-]u > [Na^+ + K^+]u$, the UAG is negative by definition.
- This indicates that the urine ammonium level is appropriately increased, suggesting an extrarenal cause of the acidosis.
- Conversely, when the UAG is positive, the urine ammonium level is low, suggesting a renal cause of the acidosis.

- Loss of functioning renal parenchyma by progressive renal disease leads to
  - hyperchloremic acidosis when the glomerular filtration rate (GFR) is between 20 and 50 mL/min
  - and to uremic acidosis with a high AG when the GFR falls to <20 mL/min.
- In advanced renal failure, ammoniagenesis is reduced in proportion to the loss of functional renal mass, and ammonium accumulation and trapping in the outer medullary collecting tubule may also be impaired.

- Because of adaptive increases in K+ secretion by the collecting duct and colon, the **acidosis of chronic renal insufficiency is typically normokalemic.**

- Proximal RTA (type 2 RTA) (Chap. 284) is most often due to generalized proximal tubular dysfunction
- manifested by glycosuria, generalized aminoaciduria, and phosphaturia (Fanconi syndrome).
- With a low plasma [HCO_3^-], the urine pH is acid (pH < 5.5).
- The fractional excretion of [HCO_3^-] may exceed 10–15% when the serum HCO_3^- > 20 mmol/L.

- Because HCO_3^- is not reabsorbed normally in the proximal tubule, therapy with $NaHCO_3$ will enhance renal potassium wasting and hypokalemia.

- The typical findings in acquired or inherited forms of classic distal RTA (type 1 RTA) include
  - hypokalemia,
  - non-AG metabolic acidosis,
  - low urinary NH_4^+ excretion (positive UAG, low urine $[NH_4^+]$),
  - and inappropriately high urine pH (pH > 5.5).
  - Most patients have hypocitraturia and hypercalciuria, so nephrolithiasis, nephrocalcinosis, and bone disease are common. I

- in generalized distal nephron dysfunction (type 4 RTA), hyperkalemia is disproportionate to the reduction in GFR because of coexisting dysfunction of potassium and acid secretion.
- Urinary ammonium excretion is invariably depressed, and renal function may be compromised, for example, due to
  - Diabetic nephropathy,
  - obstructive uropathy,
  - or chronic tubulointerstitial disease.

- Hyporeninemic hypoaldosteronism typically causes non-AG metabolic acidosis, most commonly in older adults with diabetes mellitus or tubulointerstitial disease and renal insufficiency.
- Patients usually have
  - mild to moderate CKD (GFR, 20–50 mL/min)
  - and acidosis,
  - with elevation in serum [K+] (5.2–6.0 mmol/L),
  - concurrent hypertension,
  - and congestive heart failure.
- **Both the metabolic acidosis and the hyperkalemia are out of proportion to impairment in GFR.**
- Nonsteroidal anti-inflammatory drugs, trimethoprim, pentamidine, and angiotensin-converting enzyme (ACE) inhibitors can also cause non- AG metabolic acidosis in patients with renal insufficiency

Urine Anion Gap

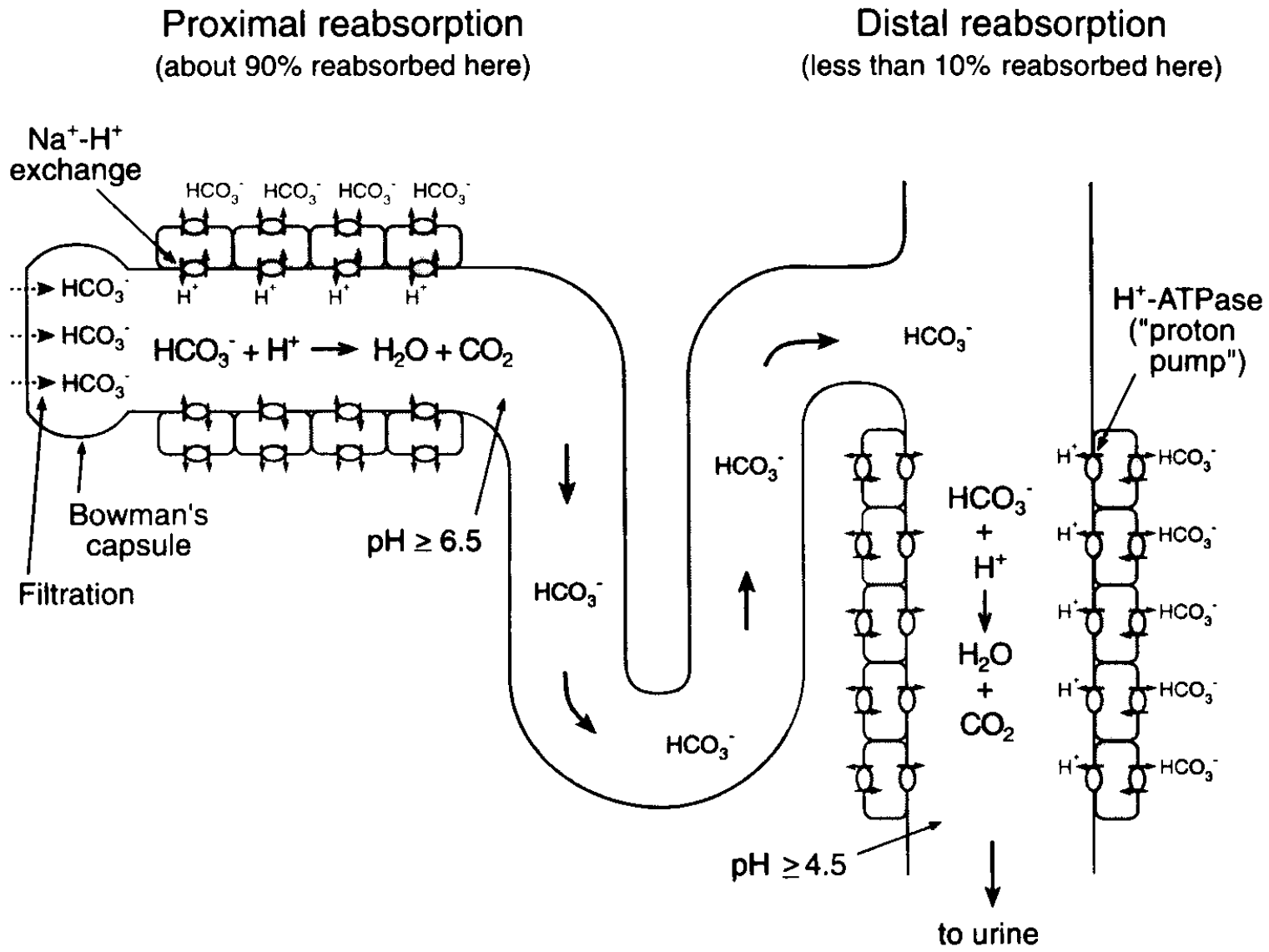
- Urine AG : Urine (Na + K – Cl)
- Negative value : most patients, diarrhea (normal AG Acidosis)
- Positive value : renal failure, distal RTA, hypoaldosteronism

Characteristics of different types of RTA

Characteristics of the different types of renal tubular acidosis

	Type 1 RTA	Type 2 RTA	Type 4 RTA
Primary defect	Impaired distal acidification	Reduced proximal bicarbonate reabsorption	Decreased aldosterone secretio or effect
Plasma bicarbonate	Variable, may be below 10 meq/L	Usually 12 to 20 meq/L	Greater than 17 meq/L
Urine pH	Greater than 5.3	Variable, greater than 5.3 if above bicarbonate reabsorptive threshold	Usually less than 5.3
Plasma potassium	Usually reduced but hyperkalemic forms exist; hypokalemia largely corrects with alkali therapy	Reduced, made worse by bicarbonaturia induced by alkali therapy	Increased

Renal bicarbonate reabsorption



Abelow, Understanding Acid-Base, Williams & Wilkins 1998

Potassium balance in RTA type4

- Hyperkalemia
  - Aldosterone deficiency
  - Aldosterone resistance
- Suppression of ammonia excretion (by hyperkalemia)
- Treatment
  - Fludrocortisone
  - Diuretics